R. Lor Randall
Editor

Metastatic Bone Disease

An Integrated Approach to Patient Care

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Preface/Acknowledgements: 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 who 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.

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Part I

The Problem

Bone Metastases: Epidemiology and Societal Effect

1

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 1.67 million people will be diagnosed with cancer in 2014. The incidence of cancer continues to increase [2]. Accurate figures are not readily available for how many of these 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.

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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 is often underestimated. The majority of patients with bone metastases do not require orthopedic intervention. That said, orthopedic opinions are often sought far too late and earlier referral may offer the opportunity for either less complex surgery or indeed any surgery. 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 1.4 million people are diagnosed with cancer every year. Of these, half of patients suffer a cancer that frequently metastasizes to bone [6]. In fact, bone is the third most common site of metastatic malignancy after lung and liver. Over 400,000 Americans are estimated to develop skeletal metastases annually [5].

Carcinoma is the most common skeletal malignancy. Bone metastases can occur in just about any primary malignancy. The most common cancers to metastasize to bone are breast, prostate,

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thyroid, lung, and kidney. In autopsy studies the incidence in breast and prostate cancers is as high as 73 % [7]. Lytic metastases are more likely to fracture. The most common sites of bone metastases are spine, pelvis, femur, and rib [8, 9]. A quarter of patients with skeletally metastatic renal cell cancer will have proximal femoral metastases [8]. 20 % of patients with bone metastases will have an upper extremity metastasis (in over half of these it is in the humerus) [10].

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 [11]. 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 % [15]. 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 in renal cancer. Most patients have multiple skeletal metastases [16] 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. 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 [17]. 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.

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 [12]	Cetin [13]	Jensen [11] and Yong [14]

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 [8]. A similar distribution was seen by Lipton [18] 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 [19].

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 [20].

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 [25].

In 1995 Bauer reported that after surgical treatment of skeletal metastases the 1-year survival was 30 % and the 3-year survival was 8 % [26]. 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 % [27]. 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) [16].

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. [20]

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 [21]	Saad [22]	Rosen [23]	Berenson [24]

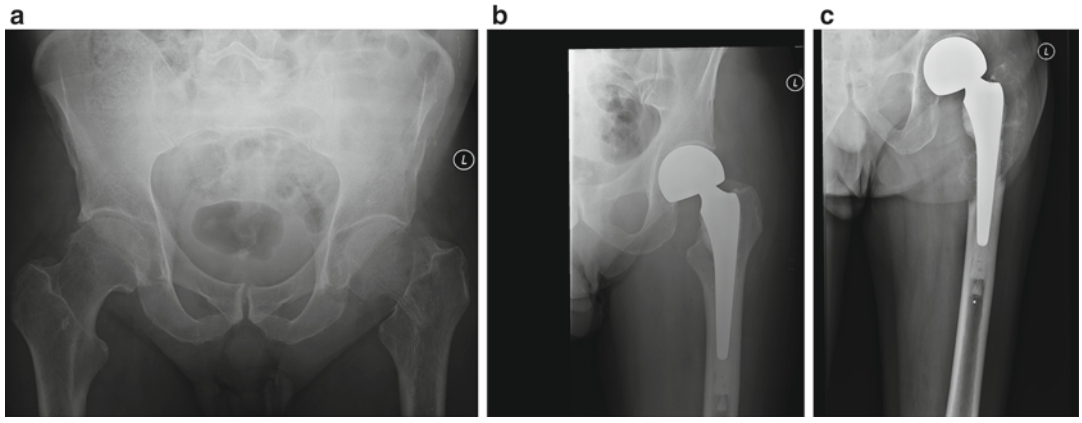

Fig. 1.1 Seventy-six male with known diffuse large B-cell lymphoma sustained a pathological femoral neck fracture (**a**) treated by hemiarthroplasty (**b**). Adjuvant radiotherapy was not given resulting in bone loss around the implant (**c**). The hemiarthroplasty was converted to a proximal femoral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

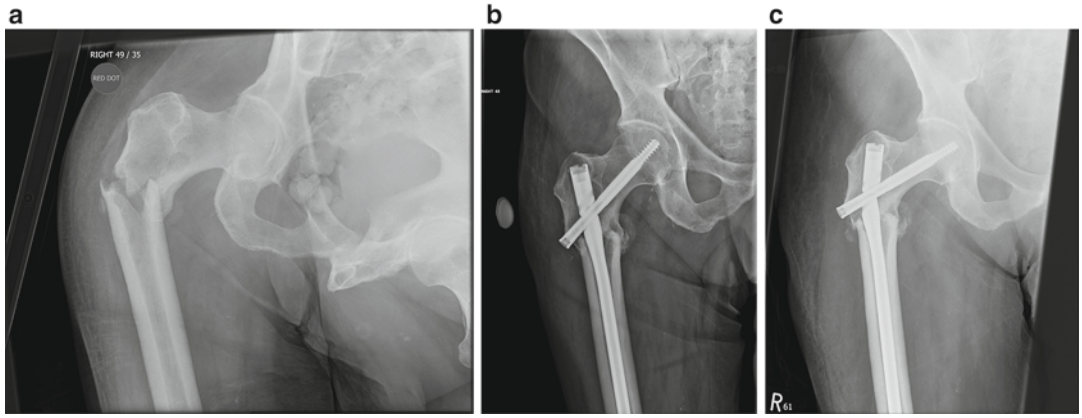

Fig. 1.2 Male with multiple myeloma. Pathological fracture proximal femur (**a**) treated by long Affixus nail (Biomet) (**b**). The nail failed (**c**) and was revised to a proximal femoral replacement

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.

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

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 [28]	Breast cancer with bone metastases	78/498 (16 %)
Prostate cancer	Saad [29]	Prostate cancer with bone metastases	46/208 (22.1 %)
Lung cancer	Joshi [30]	Lung cancer with bone metastases	21.6 %
Renal cancer	Lipton [18] Swanson [8] Forbes [31]	Renal cancer with bone metastases Newly diagnosed renal cell cancer	42 % 15 % 12 %
Other solid tumors (see description)	Rosen [23]	Bone metastases from non-breast/ prostate cancers	55/250 (22 %)

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 [16]

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.

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 [16] (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 [32].

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 [33] (Table 1.6).

Vertebral fractures have been reported as increasing in mortality ranging from 23 to 90 % [34].

Quality of Life and Bone Metastases

It is well documented that SREs have a negative effect on quality of life [35–41] 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

Table 1.6 Incidence of pathological fracture and implications on survival: data based on Saad et al. [33]. 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 non-vertebral 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

as return to activity [5]. Bone complications further diminish quality of life by increasing medical costs (discussed further later on in this chapter) [42], having a negative impact on survival [43] and impairing mobility [44].

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 [45]. Schulman and Kohles estimated that $12.6 billion (17 %) of the total direct medical cost of cancer was due to metastatic bone disease [46]. 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) [47]. 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 [48, 49]. 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 [50]. However, earlier work from the USA demonstrated that radiotherapy was more costly [41]. The mean cost incurred by cancer patients in the last 6 months before death is $75,000 largely because of increased inpatient costs [51]. 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 [52]	Barlev [53]

Authors have looked at the costs of SREs in individual cancers. From a US insurance database, Lage et al. 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 [41].

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 [46].

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 [54].

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) [55].

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 [56]. Caregivers have also been shown to have a mean of 2.2 absence days per month [2] 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 [57].

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. [58] 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 [59].

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. All of these need to be considered when managing the orthopedic patient with skeletal metastases.

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Part II

Biology of Metastases and Tissue of Origin Considerations

Pathobiology of Osteolytic and Osteoblastic Bone Metastases

2

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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
SDF-1	Stromal cell-derived factor 1
sFRP	Secreted frizzled-related protein
SMAD	Mothers against decapentaplegic homolog

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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 and to cause osteolysis and abnormal new 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].

Each of the three most common human neoplasms, breast, prostate, and lung, is strongly associated with skeletal morbidity of pain, fracture, hypercalcemia, and nerve compression syndromes. The American Cancer Society estimated that in 2014, in the USA alone, there were 232,570 new cases of invasive breast cancer, 233,000 new cases of prostate cancer, and 224,210 cases of lung cancer. The number of estimated deaths is 40,000 from breast cancer, 29,480 from prostate cancer, and 159,260 from lung cancer (American Cancer Society, Inc., www.cancer.org). The majority of patients dying from these cancers will have bone metastases. Clearly, cancer-associated bone morbidity remains a major public health problem. To improve therapy and prevention it is important to understand the pathophysiology of the effects of cancer on bone.

The molecular basis of this preferential growth of cancer cells in the bone microenvironment has been an area of active investigation for many years. Although the precise molecular mechanisms underlying this process remain to be 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. Concomitantly, cancer cells release several regulatory factors that result in abnormal bone destruction and/or formation. This complex bidirectional interplay between tumor cells and bone microenvironment establishes a feed-forward "vicious cycle" that leads to a selective growth advantage for the cancer cells [2]. 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.

Physiology of Normal Bone Remodeling and Calcium Homeostasis

In order to appreciate how perturbations in the normal mechanisms of bone and calcium homeostasis can cause osteolytic and osteoblastic lesions, it is necessary to understand these mechanisms in detail.

Bone Remodeling

Bone is unique among the cancer-affected tissues, because of its characteristic constant remodeling, resulting from the coupled and sequential actions of osteoblasts depositing new bone and osteoclasts resorbing bone. This remodeling is highly influenced by both circulating systemic hormones and local bone-derived growth factors, and it is tightly regulated under normal conditions to maintain a balance between bone destruction and new bone formation.

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.

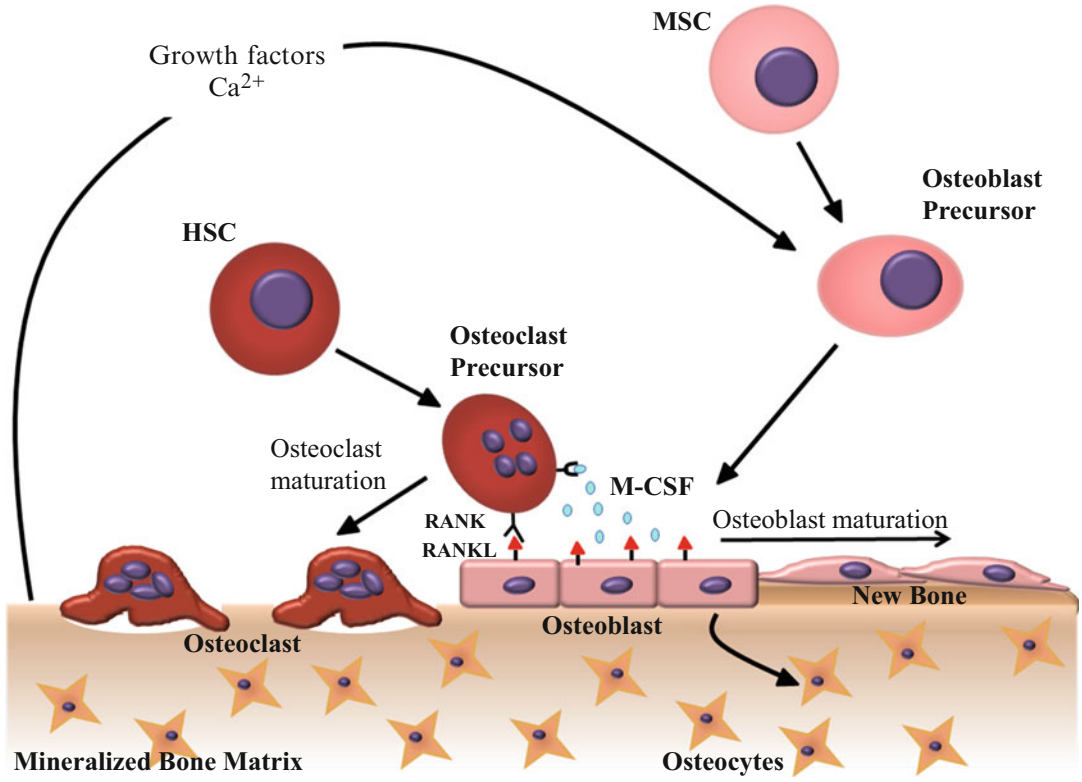

Fig. 2.1 Normal bone remodeling

The cavities created by the trabecular bone are home for the bone marrow, where stromal and hematopoietic stem cells are stored. Following differentiation, stromal stem cells form osteoblasts and hematopoietic stem cells form osteoclasts. These cells secrete cytokines and growth factors that will directly act on the surrounding cells or be included and become part of the mineralized bone matrix [3]. 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) [4, 5]. However, these osteoblast-secreted 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 [6]. 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 ($1,25\text{-}(OH)_2D_3$), 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 [7–9]. This complex balance between bone formation and bone resorption is profoundly compromised under pathologic conditions, including rheumatoid arthritis, osteoporosis, and bone metastases (Fig. 2.1).

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 [10, 11]. 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) [12, 13]. 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 pathway [9]. 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 [14, 15]. 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) [16]. 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 [17]. Other regulators of Wnt signaling pathway in bone 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: it binds LRP5/6 causing the internalization and degradation of the two co-receptors [18]. 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 inactive 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 [19]. An important protein in balancing RANKL function is its decoy receptor OPG, normally expressed in the bone marrow [9, 20]. Overexpression of OPG leads to severe osteopetrosis in mice, while mice that lack OPG show osteopenia [20]. 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 [21]. 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 [22].

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 [23]. 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) [24]. Active osteoclastic bone resorption causes extracellular calcium (Ca^{2+}) levels to rise up to 8–40 mmol/L [25].

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) [26]. 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 [27, 28].

Parathyroid Hormone

PTH is an 84 amino acid polypeptide that is secreted by the chief cells of the parathyroid glands. Secretion of PTH is highly regulated by Ca^{2+} concentration in the extracellular fluid. PTH secretion decreases as Ca^{2+} concentration increases, in a simple negative-feedback loop [27]. Activation of CaSR leads to the downregulation of PTH at the posttranscriptional level [29]. Another potent inhibitor of PTH secretion is calcitriol, while hyperphosphatemia increases PTH secretion [29–32].

PTH is active in bone, stimulating osteoclastic bone resorption, via osteoblast production of RANKL. In the kidney, instead, PTH stimulates calcium reabsorption and inhibits phosphate reabsorption from renal tubules, and it stimulates renal 1α-hydroxylase, resulting in calcitriol production, which, in turn, increases intestinal absorption of calcium and phosphate. Therefore, PTH biological actions result in increased serum calcium and increased urinary phosphate excretion. PTH signaling is mediated by its receptor, a G-protein-coupled receptor [33]. Following PTH binding, the receptor activates adenylate cyclase, which leads to production of cAMP and activation of protein kinase A (PKA). Although this seems to be the dominant pathway, PTH signal transduction also travels through the PLC/protein kinase C (PKC) route [34, 35].

1,25-$(OH)_2D_3$

One of the other important hormones participating in calcium homeostasis is 1,25-$(OH)_2D_3$ or calcitriol. 1,25-$(OH)_2D_3$ is a biologically active metabolite of the vitamin D sterol family. Vitamin D precursor can be synthesized from 7-dehydrocholesterol inside the skin via exposure to sunlight, or it can be introduced by diet.

In the liver, the precursor undergoes hydroxylation at the C-25 position and it is successively hydroxylated at the C-1 position in the kidney, forming 1,25-$(OH)_2D_3$ [36–38]. The most important control point of vitamin D metabolism is the renal 1α-hydroxylation of 25-$(OH)D_3$, regulated by phosphate, PTH, and calcitriol concentrations. Low serum phosphate level and PTH increase 1,25-$(OH)_2D_3$ production in an independent fashion [39, 40]. Increased levels of calcitriol, instead, downregulate calcitriol production via an autocrine negative-feedback loop that signals through vitamin D receptors in cells of the proximal convoluted tubule in the kidney [41]. The placenta and the granulomatous tissue are other known important sites of calcitriol production [42–44].

1,25-$(OH)_2D_3$ increases calcium and phosphate absorption in the gastrointestinal tract, increasing plasma concentration of calcium and phosphate. Moreover, it stimulates PTH ability to promote calcium resorption in the renal tubules, and increases bone resorption [45]. 1,25-$(OH)_2D_3$ functions as a differentiation agent for committed osteoclast precursors, which become mature multinucleated cells capable of bone resorption [46, 47]. In all, 1,25-$(OH)_2D_3$ function is to guarantee a sufficient amount of calcium and phosphate available for bone matrix mineralization at the bone surface.

Calcitonin

Calcitonin has an uncertain biological role in calcium homeostasis. It directly inhibits osteoclast bone resorption, with a rapid effect within minutes of administration [48]. Calcitonin causes production of cAMP and increase of cytosolic calcium in osteoclasts, resulting in the contraction of the cellular membrane [49–51]. These effects are transient and probably do not play a significant role in chronic calcium homeostasis.

Hypercalcemia of Malignancy

Hypercalcemia is defined as total serum calcium adjusted for protein concentration above 10.2 mg/dl. The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy, and the most common clinical manifestations are neuromuscular, gastrointestinal, and renal symptoms [52]. Hypercalcemia of malignancy is one of the most common paraneoplastic syndromes, with lung, breast, and hematologic tumors being the most frequently associated malignancies [53]. Tumors can secrete humoral factors that unbalance calcium homeostasis acting on bone, kidney, and intestine, and/or local factors in bone, in the case of metastases or hematological tumors, which directly stimulate bone resorption by osteoclasts [52].

Humoral hypercalcemia of malignancy is mostly due to increased PTHrP levels. PTHrP is expressed in many tumors and in normal tissue [54–57]. In addition to mediating hypercalcemia, PTHrP also plays a role in the development and progression of osteolytic bone metastases and tumor cell growth and survival [58–61]. In hematological tumors 1,25-$(OH)_2D_3$ mediates hypercalcemia together with PTHrP [62–65]. Increased production of PTH is instead only rarely associated with hypercalcemia of malignancy [52]. Other tumor-secreted humoral factors that contribute to the development of hypercalcemia are IL1, IL6, TGFα, TNF, and granulocyte colony-stimulating factor (G-CSF) [66–73].

Bone Metastases

Certain types of cancer, such as breast, prostate, and lung, have a higher propensity to metastasize to bone. Bone is the third most frequent site of tumor metastasis after the liver and the lung and almost all the patients with advanced breast or prostate cancer present with bone metastases. The spread and metastasis of tumor cells to the skeleton is a complex multistep process highly dependent on the properties and characteristics of tumor cells and bone microenvironment. A tumor cell needs to successfully complete each step of this process in order to establish a secondary tumor in bone. The metastatic process follows sequential events: detachment of cancer cells from the primary tumor, invasion of the adjacent tissues, entry into the circulatory system via the

neo-vasculature of the tumor, survival of host immune response and physical forces in the circulation, arrest in the distant capillary bed, and extravasation and growth into the bone [74].

The "Seed and Soil" Model and the Pre-metastatic Niche

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 [75]. 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 evidence that the bone microenvironment plays an important role in this process. 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" [76]. 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 [77]. 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 has been formulated. This model proposes that a primary tumor is capable to prepare a conducive microenvironment at a distant site before the disseminated tumor cells arrive at the site and establish metastases [78]. The concept of pre-metastatic niche, hence, involves the action of the primary tumor on the destination site of metastasis through production of tumor-derived growth factors, such as TGFβ, vascular endothelial growth factor A (VEGFA), and placental growth factor (PGF). In response to these factors, hematopoietic progenitor cells (HPCs), macrophages, and other tumor-associated immune cells gather at the metastatic site and prime the "soil" for the arrival of the tumor cells, helping adhesion and invasion [2, 79]. Recent data show that, in preclinical models of melanoma and lung cancer, bone marrow-derived hematopoietic cells expressing vascular endothelial growth factor receptor 1 (VEGFR1) home to the future metastatic site to form cellular clusters that increase fibronectin production in tumor target sites previous to the arrival of the tumor cells [80]. Further evidence of the existence of a pre-metastatic niche is the production of inflammatory chemo-attractants in pulmonary sites in a model of lung metastasis [81]. Although the molecular factors mediating the initial engraftment are still to be completely explained, it seems that the accumulation of myeloid cells, fibronectin, growth factors, and matrix remodeling proteins accelerate the micrometastatic process. Recently, in a model of breast cancer bone metastases, myeloid-derived suppressor cells (MDSCs) isolated from the tumor microenvironment have been shown to differentiate into osteoclasts [82]. Moreover, the recruitment of endothelial progenitor cells contributes to the switch from micrometastatic to macrometastatic phenotype. However, a lack of effects of bone marrow-derived circulating endothelial precursor cells on tumor growth has been reported [83]. The primary tumor determines the site of metastases also through the production of stroma-derived factors [84]. Zhang et al. showed that cancer-associated fibroblasts (CAF) in triple-negative breast carcinoma select cell clones within the primary tumor that thrive on CAF-derived factors CXCL12 and IGF-1. These clones showed high Src activity, which is related to increased Akt/PI3K signaling and bone relapse, and are primed for metastasis in the bone marrow microenvironment, rich of CXCL12 [85].

In the bone microenvironment, the primary tumor conditioning may take place through

endocrine-like actions, such as the production of circulating factors that target bone marrow cells and cells in the bone microenvironment, rendering it conducive to tumor colonization. It has been shown that breast cancer cells produce heparanase to increase bone resorption [86]. Other examples are tumor cells and senescent fibroblasts secreting osteopontin (OPN) to promote bone marrow cell recruitment and tumor formation, and osteoclasts producing matrix metalloproteinases (MMPs) to support prostate cancer bone metastasis formation [87–90]. Also, several tumors produce PTHrP, which can promote bone resorption and increase the production of local factors, such as chemokine (C-C motif) ligand 2 (CCL2), in the bone marrow [91–93]. In general, the bone microenvironment is a very fertile "soil" for metastatic cancer cell growth and proliferation because of the abundance of immobilized growth factors, such as TGFβ, IGF1, FGF, PDGF, and BMPs, cytokines, chemokines, calcium ions, and cell adhesion molecules [7, 9]. Many of these molecules are released mostly as a consequence of osteoclastic bone resorption, but also can be produced by stromal and immune cells in the bone marrow. In addition to molecular factors, also physical characteristics of the bone microenvironment, such as hypoxia, acidic pH, and high extracellular calcium concentration, facilitate tumor growth. Unlike in normal calcium homeostasis, in prostate and breast cancer cells PTHrP synthesis is increased by high levels of extracellular calcium. In turn, PTHrP stimulates bone resorption, which increases extracellular calcium concentration, creating a feedback loop [94–97]. Moreover, the bone marrow stromal cells might cross talk and collaborate with the tumor cells in the homing, differentiation, and proliferation processes, through the production of vascular cellular adhesion molecule 1 (VCAM1), cadherin 11, and fibronectin [98]. When tumor cells establish themselves in the bone microenvironment they start producing cytokines and growth factors that stimulate osteoclastic bone resorption both directly and indirectly. This creates a symbiotic relationship between tumor and bone microenvironment alimented by a molecular cross talk that sustains a feed-forward "vicious cycle" of increased bone destruction and tumor growth, leading to the formation of cancer bone metastases.

Bone Colonization

To escape from the primary neoplasm tumor cells first need to adhere to the basement membranes and other surrounding cells through cell adhesion molecules such as E-cadherin and laminin. Then they produce proteolytic enzymes that degrade the basement membrane and the proteins in the extracellular matrix, allowing the tumor cells to invade the surrounding tissues [99]. Among these enzymes are MMPs, a family of zinc-dependent proteinases that degrade extracellular matrix proteins. Clinical evidence indicates that platelets may physically shield tumor cells from the action of the immune system, thus promoting the metastatic process [99].

Tumor cells adhere preferentially to the bone marrow endothelium. Tumor cells homing to bone can use the same physiological mechanism used by hematopoietic stem cells (HSCs) [79, 100–102]. HSCs are attracted and regulated by osteoblasts and bone marrow stromal cells through integrins, such as α4β1, αvβ3 and VCAM1, chemokines, such as chemokine (C-X-C motif) receptor 4 (CXCR4) and chemokine (C-X-C motif) ligand 12 (CXCL12) (also known as stromal cell derived factor (SDF-1)), BMPs, Notch, OPN, and nestin [103–111]. HSC homing is also regulated by bone resorption, as proved in preclinical study. Metastatic prostate cancer cells and probably other cancer cells directly compete with the HSCs for the occupancy of the bone marrow niche [112–114].

Expression of CXCR4 on cancer cells has a major role in tumor cell homing to bone, and its ligand, SDF-1 or CXCL12, is expressed at high levels by osteoblasts and bone marrow stromal cells [100, 115–118]. Several groups have demonstrated a direct role of CXCR4/CXCL12 in breast and prostate cancer cell proliferation, sug-

gesting a role for this pathway in breast and prostate cancer cell homing to bone and establishment of bone metastasis [118–121]. CXCL12 expression by bone marrow stromal cells also upregulates expression of MMP9 and αvβ3 integrin on prostate cancer cells [116–118, 122]. CXCR4 overexpression, along with other bone metastasis signature genes, such as IL11, MMP1, and connective tissue growth factor (CTGF), in breast cancer cell lines increased their ability to metastasize to bone [100].

Integrins expressed on the cancer cell surface interact with proteins of the extracellular matrix that are expressed in the bone microenvironment. VCAM1 is normally expressed by bone marrow stromal cells and constitutes a ligand for α4β1 integrin [123]. Therefore, tumor cells expressing α4β1 integrin are expected to preferentially adhere to bone marrow stromal cells during the metastatic process. In fact, Chinese hamster ovary (CHO) cells transfected with α4β1 integrin were capable to establish bone and lung metastases after intravenous inoculation in nude mice, while non-transfected CHO cells only generated lung metastases [124]. In addition, antibodies against α4β1 integrin or against VCAM1 were able to inhibit the development of bone metastases. Expression on tumor cells of the α2β1, α5β1, and α4β1 integrins, respectively, receptors for collagen I, fibronectin, and VCAM1, has been shown to be involved in the interaction between cancer cells and bone marrow stroma in leukemia, breast cancer, prostate cancer, and myeloma [123–130]. The αvβ3 integrin interacts with fibronectin, vitronectin, OPN, and bone sialoprotein, and its expression in tumor cells is associated with increased bone metastasis, tumor-associated osteolysis, and bone endosteum colonization in breast and prostate cancer [131–134].

CXCR4 activation increases αvβ3 expression on prostate cancer cells and αvβ1 on myeloma cells, suggesting a cross talk between CXCR4 and integrin expression that could promote cancer cell recruitment to bone and bone colonization [116, 117, 135]. Bone-derived growth factors as TGFβ released during bone resorption might also enhance the metastatic potential of cancer cells with a mechanism involving integrin interactions [136].

The bone microenvironment constitutes a very favorable "soil" enriched with numerous factors promoting tumor growth, and the interaction between cancer cells and bone microenvironment can be studied in the different models of metastatic tumor and it represents the basis for cancer bone metastasis development.

Osteolytic and Osteoblastic Metastases

Conventionally bone metastases are classified into two different types: osteolytic bone metastases and osteoblastic bone metastases. However, most bone metastasis patients exhibit both the osteolytic and the osteoblastic component in different degrees, due to the general dysregulation of bone metabolism caused by the tumor affecting bone formation and bone resorption [7].

Osteolytic metastases are more common than the osteoblastic ones. Patients with osteolytic bone metastases suffer severe bone pain, spinal cord compression, pathologic fractures, and hypercalcemia. Breast, lung, renal, and thyroid carcinomas are some examples of cancer that produce osteolytic bone metastases [137]. Different primary tumors may use different mechanisms to activate osteoclasts and cause bone resorption.

Osteoblastic metastases are commonly associated with prostate cancer, but they have been described also in other tumors. Osteoblastic metastases result from increased osteoblast differentiation, proliferation, and activity, leading to excess bone deposition [74]. In patients, osteoblastic metastases lead to bone pain and pathological fractures due to the fragility of the disorganized new bone produced by overstimulated osteoblasts [9].

Osteolytic Metastases: Breast Cancer as the Prototype

The majority of the patients with breast cancer bone metastases present with osteolytic lesions.

Breast cancer bone metastases are associated with increased production of factors such as TGFβ, RANKL, PTHrP, IL11, IL8, IL6, and IGF1, which stimulate osteoclastogenesis, tumor growth, and bone resorption [99].

In breast cancer, PTHrP is expressed in 90 % of cases at the bone metastatic site and only in less than 20 % of cases at other metastatic sites [92, 138–140]. These data suggest a crucial role for PTHrP as a determinant for bone metastasis development in breast cancer. Blockade of PTHrP in a mouse model of MDA-MB-231 breast cancer bone metastases decreases size and number of osteolytic lesions and osteoclast number at the bone/tumor interface [92, 141]. MCF-7 is a breast cancer cell line that does not express PTHrP and does not cause bone metastases in vivo. When MCF-7 cells are engineered to overexpress PTHrP, they cause increased osteoclastogenesis and marked bone destruction [142]. PTHrP signals through its receptor, PTHR1, and stimulates RANKL expression by the osteoblasts and inhibits expression of OPG, the decoy receptor for RANKL, by stromal cells, resulting in an increase in osteoclastogenesis and bone resorption [99, 142].

Another important mediator of breast cancer osteolytic bone metastases is TGFβ. TGFβ is released from the mineralized bone matrix in its active form and it increases breast cancer bone metastases via stimulation of PTHrP secretion by tumor cells [6, 143]. TGFβ signaling is mediated through the interaction with the type II receptor, which in turn recruits and phosphorylates the type I receptor [144]. Interference with the expression of these receptors in animal models affects tumor burden and osteolytic lesions [143, 145]. TGFβ stimulates PTHrP secretion mainly via SMAD (mother against decapentaplegic homolog)-dependent signaling pathways, involving SMAD2, 3, and 4, in breast cancer bone metastases. However, PTHrP production can also be enhanced by TGFβ through the p38 mitogen-activated protein kinase (MAPK) signaling pathway [146].

Breast cancer cells commonly express Runt-related transcription factor 2 (RUNX-2), a transcription factor that regulates osteoblastogenesis. Blockade of RUNX-2 in a mouse model of breast cancer bone metastases reduces tumor burden and decreases bone resorption [147]. Wnt and DKK1 have also been found implicated in osteolytic bone metastases and their role has been extensively investigated [16]. DKK1 expression is higher in patients with breast cancer bone metastases compared to healthy women, breast cancer patients in complete remission, and patients with breast cancer metastases in sites other than bone [148]. Elevated expression of DKK1 is detected in cell lines producing osteolytic or mixed osteoblastic/osteolytic metastases. Conversely, in cell lines associated with osteoblastic metastases, DKK1 expression is not detectable [149].

Several growth factors, such as IL11, IL6, prostaglandin E2 (PGE2), and M-CSF, are produced by breast cancer cells. These growth factors play an important role in osteolytic lesions, inducing osteoclastogenesis and inhibiting osteoblast formation and activity [150, 151]. PGE2 stimulates RANKL expression, resulting in increased osteoclastogenesis [151]. IL11 is commonly expressed in stromal and immune cells, such as epithelial cells and fibroblasts, and its expression is stimulated by both PTHrP and TGFβ [152]. IL11 increased expression is associated with augmented tumor burden, bone resorption, and osteolytic lesions in mouse models of bone metastases [152]. A recent study shows that Jagged1 mediates breast cancer bone metastases by activating the Notch signaling pathway in stromal bone cells, stimulating IL6 release from osteoblasts, and activating osteoclast differentiation. Jagged1 is also a downstream mediator of TGFβ signaling and the use of a γ-secretase inhibitor reduces Jagged1-mediated bone metastases [153].

In the bone microenvironment, osteogenic cells secrete placental growth factor (PlGF), which expression is enhanced by the presence of metastatic breast tumor cells. Inhibition of host-derived PlGF in a mouse model of breast cancer bone metastases reduces incidence, number, and size of bone metastases. PlGF blockade inhibits

osteoclastogenesis by preventing upregulation of RANKL and the autocrine osteoclastogenic activity of PlGF, and reduces the engraftment of tumor cells in the bone microenvironment by inhibiting their interaction with the matrix components [154].

IGFs are also released in the tumor microenvironment during osteolysis and appear involved in breast cancer cell proliferation in bone [155, 156]. IGF-1 and IGF-2 are the most abundant factors in the bone matrix, followed by TGFβ [4]. Neutralizing antibodies against IGF-1 receptor abrogate the ability of bone-resorbing cell-conditioned medium to stimulate breast cancer cell proliferation [3, 156]. This indicates that IGF-1 signaling pathway has a role in osteolytic bone metastasis formation.

Recently, microRNAs have also been identified as mediators of osteolytic bone metastases, and they have been proposed as both prognostic biomarkers and therapeutic targets [157, 158]. Ell et al. identified a microRNA expression signature in differentiating osteoclasts exposed to metastatic tumor cell-conditioned media, partially determined by activation of NFkB signaling by metastatic tumor cell-secreted intracellular adhesion molecule (sICAM1). In vivo, intravenous injection of microRNAs downregulated during osteoclastogenesis, miR-141 and miR-219, reduced bone metastases inhibiting osteoclast activity. Serum levels of microRNAs that are upregulated during osteoclastogenesis, miR-16 and miR-378, and sICAM1 were correlated with bone metastasis burden [157] (Fig. 2.2).

Osteoblastic Metastases: Prostate Cancer as the Prototype

Osteoblastic metastases, unlike osteolytic metastases, are generated by tumor cell production of factors stimulating osteoblastogenesis, osteoblast

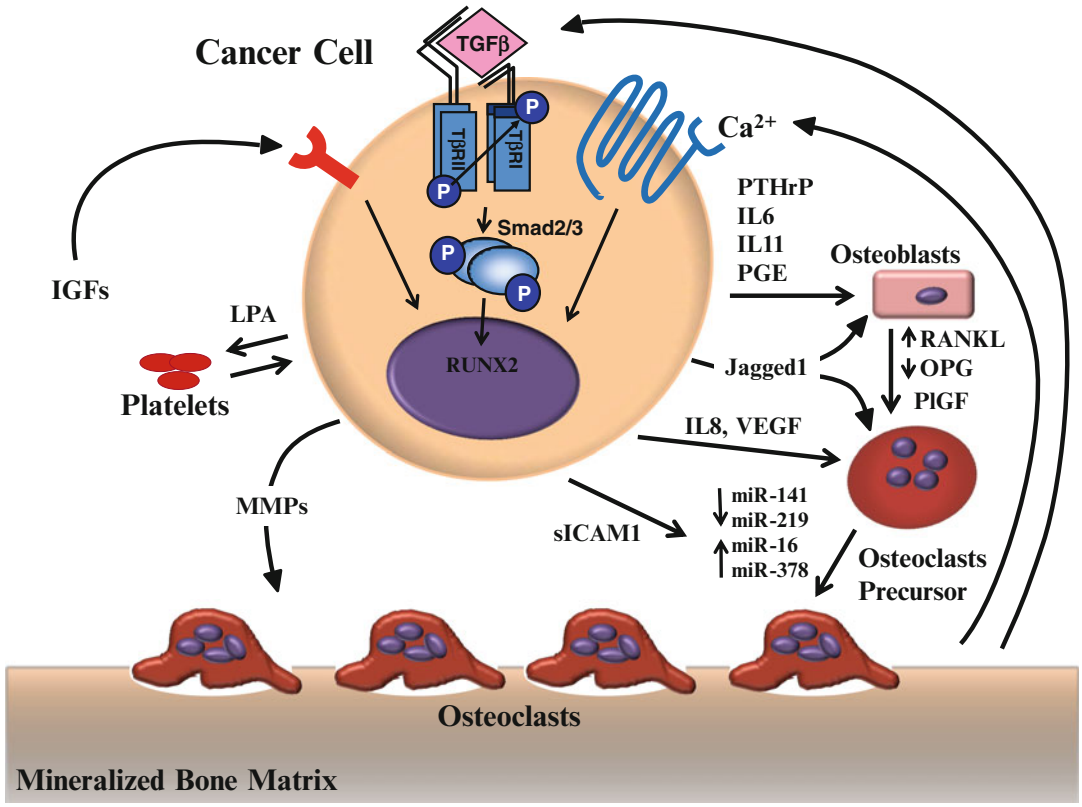

Fig. 2.2 Osteolytic bone metastases

proliferation, and new bone deposition [74, 159, 160]. Prostate cancer is the prototype of cancer, which shows predilection to form osteoblastic bone metastases. However, osteoclast activity is still an important driver of this process as bisphosphonates reduce skeletal-related events in prostate cancer [161].

One important determinant of prostate cancer osteoblastic metastases is endothelin 1 (ET-1). ET-1 is a potent vasoconstrictor and a potent osteoblast stimulatory factor via endothelin A receptor (ETAR) activation [162, 163]. Use of the ETAR antagonist, atrasentan, prevented osteoblastic lesions and reduced skeletal morbidity in patients with advanced prostate cancer [164]. Atrasentan also decreases osteoclastic bone resorption in patient trials [165]. However, in phase III clinical trials in patients with metastatic castration-resistant prostate cancer, atrasentan alone or in combination with docetaxel failed in delaying disease progression and improve overall survival [166–168]. Downstream of ET-1 signaling pathway there are important factors, such as IL6, Wnt5a, CTGF, and RANKL [99]. ET-1 inhibits DKK1, which works as a suppressor of the Wnt signaling pathway, and DKK1 overexpression in prostate cancer cells reduces Wnt signaling and leads to osteolytic lesions in the bone [169, 170]. However, DKK1 overexpression does not cause reduction of the basal osteoclast activity [169]. Overexpression of Wnt-1 and β-catenin has also been described in patients with advanced prostate cancer. This observation indicates a role for the Wnt signaling pathway in the pathogenesis of prostate cancer bone metastases [171].

Paradoxically, osteoblastic bone metastases nearly always express PTHrP. A partial explanation to this is that the prostate-specific antigen (PSA), which induces an osteoblastic phenotype in animal models [172], is a serine proteinase able to cleave PTHrP [173, 174]. The cleaved NH2-terminal fragment of PTHrP fails to activate the PTH/PTHrP signaling pathway, but can bind and activate ETAR [91, 175]. In experimental models, PTHrP fragment 1-16 enhances osteoblast proliferation and new bone deposition at similar levels to ET-1. Moreover, other two fragments, 1-20 and 1-23, of PTHrP had a marked bone anabolic effect, which was suppressed by the ETAR antagonist, atrasentan [91]. Evidence suggests that PSA might play a similar role in breast cancer bone metastases. PSA is commonly expressed in breast cancer [176]. IGF cleavage from its binding protein and TGFβ cleavage to its active form operated by PSA might contribute to osteoblastogenesis stimulation in breast cancer [177, 178].

There are other factors that have been found implicated in osteoblastic bone metastasis, such as TGFβ, BMPs, PDGF, FGF, IGF-1, adrenomedullin, and several proteases [99]. The serine protease urokinase (uPA) has been shown to be involved in prostate cancer bone metastasis formation in mouse models [179]. Experimental data suggest a dual role for uPA, where the carboxy-terminal domain might participate in tumor invasiveness and growth factor activation, while the amino-terminal domain might stimulate tumor growth [74]. BMP-7, instead, preserves the epithelial phenotype of prostate cancer cells, preventing the epithelial/mesenchymal transition, and its expression is decreased in more invasive and metastatic cells [180]. Other examples are FGF-1 and FGF-2 produced by prostate cancer cells, which could function as factor stimulating osteoblast proliferation [74]. Moreover, CTGF and adrenomedullin are both osteoblast-stimulating factors and are produced by several tumors [181, 182].

Clinical evidence indicates the presence of osteolytic components in osteoblastic bone metastases that could either precede the bone formation or follow it as a consequence of the excessive bone deposition [9] (Fig. 2.3).

The Vicious Cycle

Bone metastases thrive in bone by promoting a feed-forward vicious cycle involving tumor cells and the bone microenvironment components

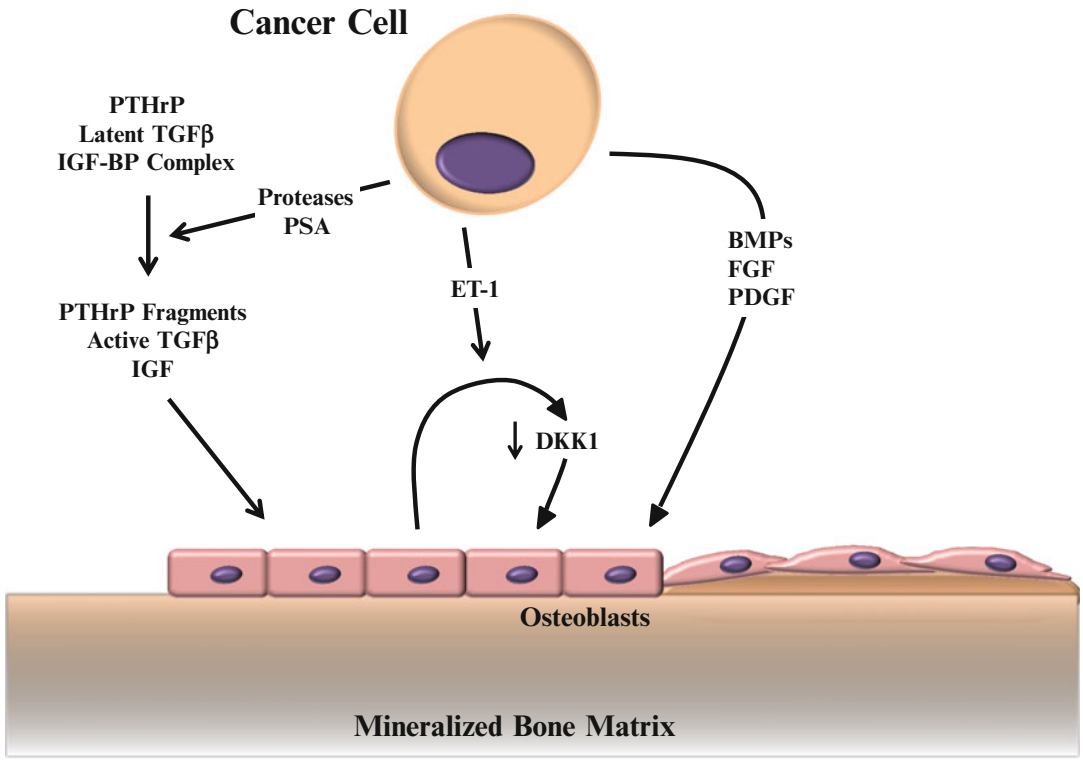

Fig. 2.3 Osteoblastic bone metastases

(osteoblasts, osteoclasts, and bone matrix) [183]. The mineralized bone matrix is a rich source of physical factors, such as hypoxia, acidosis, and calcium, and several growth factors. In osteolytic bone metastases, bone resorption by osteoclasts releases growth factors and calcium from the mineralized bone matrix [4]. These factors act on the tumor cells stimulating proliferation and tumor growth. Stimulated tumor cells produce high levels of PTHrP, further inducing osteoclastogenesis and bone resorption. Growth factors released from the bone matrix, such as TGFβ, type I collagen, osteocalcin, and IGFs, function as chemotactic factors for tumor cells in a integrin-dependent fashion [184, 185]. In osteoblastic bone metastases, tumor cells produce factors that stimulate osteoblast proliferation and differentiation, and new bone deposition, such as ET-1. Osteoblasts, in turn, express and secrete growth factors that enhance tumor growth in bone [52, 159, 160]. Recent studies unveil the implication of several microRNAs expressed by tumor cells and bone microenvironment cells in the vicious cycle, and their role in invasion and homing of cancer to bone [157, 186, 187]. Understanding of the mechanisms responsible for bone metastases will lead to better therapy of established disease and prevention of new disease. Most current bone-targeted therapies inhibit osteoclastic bone resorption (bisphosphonates and RANKL antibody), the main cellular driver of the tumor-bone interactions responsible for the morbidity associated with bone metastases (Fig. 2.4).

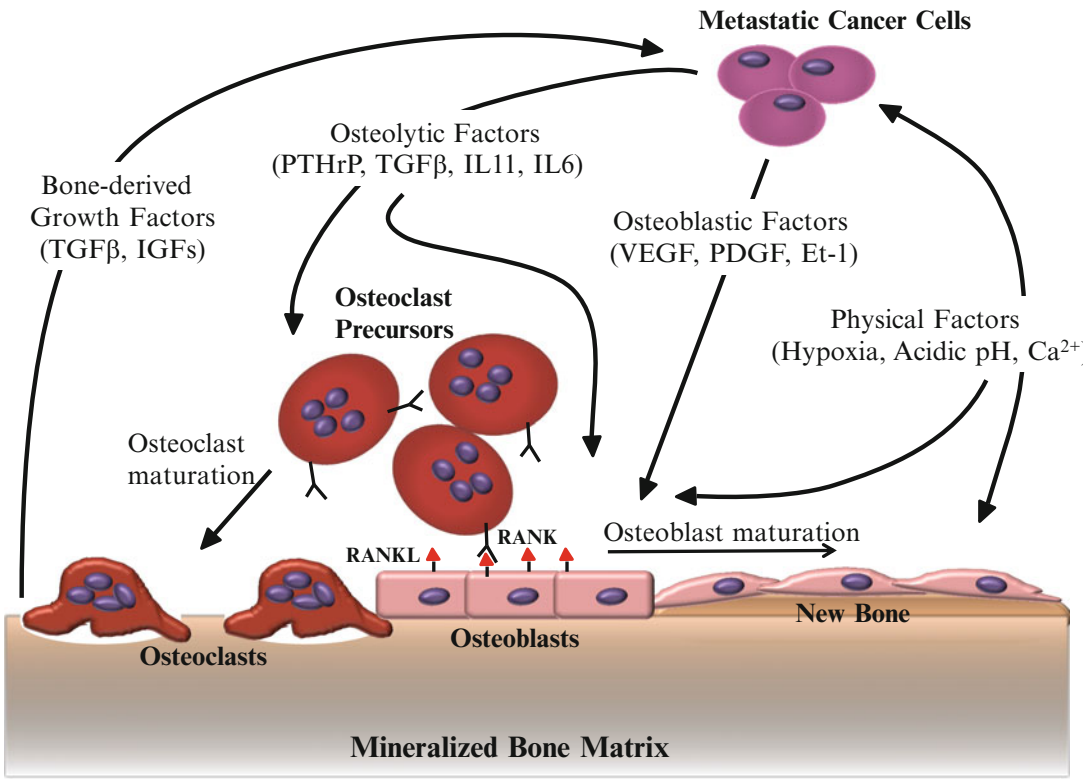

Fig. 2.4 The vicious cycle

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Biology of Bone Cancer Pain

3

Patrick W. O'Donnell and Denis R. Clohisy

Introduction

Pain is the most common presenting symptom in patients with skeletal metastases and is directly proportional to the patient's quality of life [1]. Two types of cancer pain exist: (1) ongoing pain and (2) incident or breakthrough pain. Ongoing pain is described as a dull and aching pain that is constant in nature and progresses according to overall disease process. Incident or breakthrough pain is most commonly associated with bone metastases and is characterized by sharp pain, intermittent in nature, exacerbated by movement. Breakthrough pain is difficult to treat, but can be found in as high as 80 % of patients with advanced disease [2]. Significant insight into understanding bone cancer pain and the development of new therapeutic strategies for bone cancer pain are due to the development of novel models of bone cancer pain and recent clinical trials [3]. Despite differences in these models, a wealth of information has been generated from animal research regarding the pathophysiologic mechanisms that drive bone cancer pain. Ultimately, bone cancer pain is a multifactorial process that is initiated by a complex interaction between the host cells within the affected bone and the tumor cells.

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Biology of Cancer Pain

Pain occurs during tissue damage as the result of release of neurotransmitters, cytokines, and other factors from damaged cells, reactive or activated inflammatory cells, adjacent blood vessels, and nociceptive terminals. Pain stimulus is transduced at the level of the primary afferent nerve fiber that innervates peripheral tissue. Bone is densely innervated by sensory nerve fibers within the bone marrow, mineralized bone, and periosteum (Fig. 3.1) [4]. Sensory and sympathetic neurons form a mesh-like network throughout the periosteum in association with blood vessels that can detect small distortions of skeletal integrity (Fig. 3.2) [5]. Tumor-derived cytokines, growth factors, and peptides have been shown to stimulate primary afferent nerve fibers that innervate bone. Prostaglandins, interleukins, protons, bradykinin, chemokines, tumor-necrosis factor-α, nerve growth factor (NGF), and endothelins are all examples of chemical mediators released from tumor cells, or the host inflammatory response, that sensitize nerve terminals resulting in cancer pain [6, 7].

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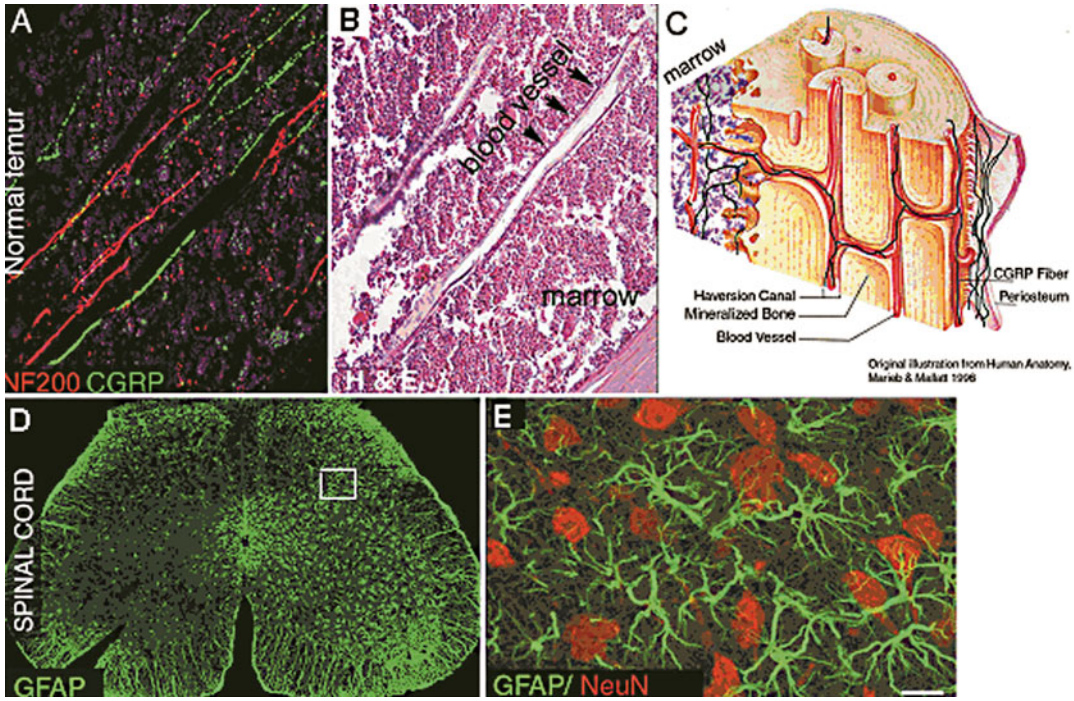

Fig.3.1 Mechanisms of bone cancer: Histophotomicrographs of confocal (**a**) and histologic (**b**) serial images of normal bone and confocal images of spinal cord of tumor-bearing mice (**d** and **e**). Note the extensive myelinated (*red*, NF 200) and unmyelinated (*green*, CGRP) nerve fibers within bone marrow that appear to course along blood vessels (*arrowheads*, **b**). (**c**) Schematic diagram demonstrating the innervation within periosteum, mineralized bone, and bone marrow. All three tissues may be sensitized during the various stages of bone cancer pain. (**d**) Confocal imaging of glial fibrillary acidic protein (GFAP) expressed by astrocytes in a spinal cord of a tumor-bearing mouse. Note the increased expression only on side ipsilateral to tumorous limb. (**e**) High-power magnification of spinal cord showing hypertrophy of astrocytes (*green*) without changes in neuronal numbers (*red*, stained with neuronal marker, NeuN). NF200, neurofilament 200; CGRP, calcitonin gene-related peptide; GFAP, glial fibrillary acidic protein; NeuN, neuronal marker

In chronic pain states, sensitization of the individual nerve fibers can create sensitization leading to decreased excitation thresholds, up-regulation of receptors in nerve terminals, or recruitment of previously silent pain receptors [8, 9]. Sustained neural signaling causes heightened reactivity of the nervous system (central sensitization) and can lead to allodynia, a painful condition where mechanical stimuli not normally perceived as noxious are painful. While central sensitization may occur anywhere along the central or peripheral nervous system, it is most commonly seen in the dorsal horn of the spinal cord, leading to a change in the activity and responsiveness of dorsal horn neurons occurs in response to persistent painful stimulation. Central sensitization may be mediated by glutamate, substance P, prostaglandins, and/or growth factors [10].

Several other nerve sensitization mechanisms exist in chronic pain conditions like cancer. Specifically, persistent stimulation of unmyelinated C fibers results in increased neural responsiveness of spinal neurons [11]. Sensitization can also occur when persistent stimulation results in phenotypic changes in neurons that are adjacent to neurons receiving the persistent painful stimulation. Typically this adjacent sensitization occurs in A-beta fibers that normally do not transmit painful stimuli. Once sensitized, A-beta neurons are capable of transmitting both non-painful and painful information. In addition, phenotypic alterations with neurochemical reorganization of tumor-bearing bones occur during the sensitization of peripheral nerves. Specific changes that may mediate pain include astrocyte hypertrophy and decreased expression of glutamate reuptake

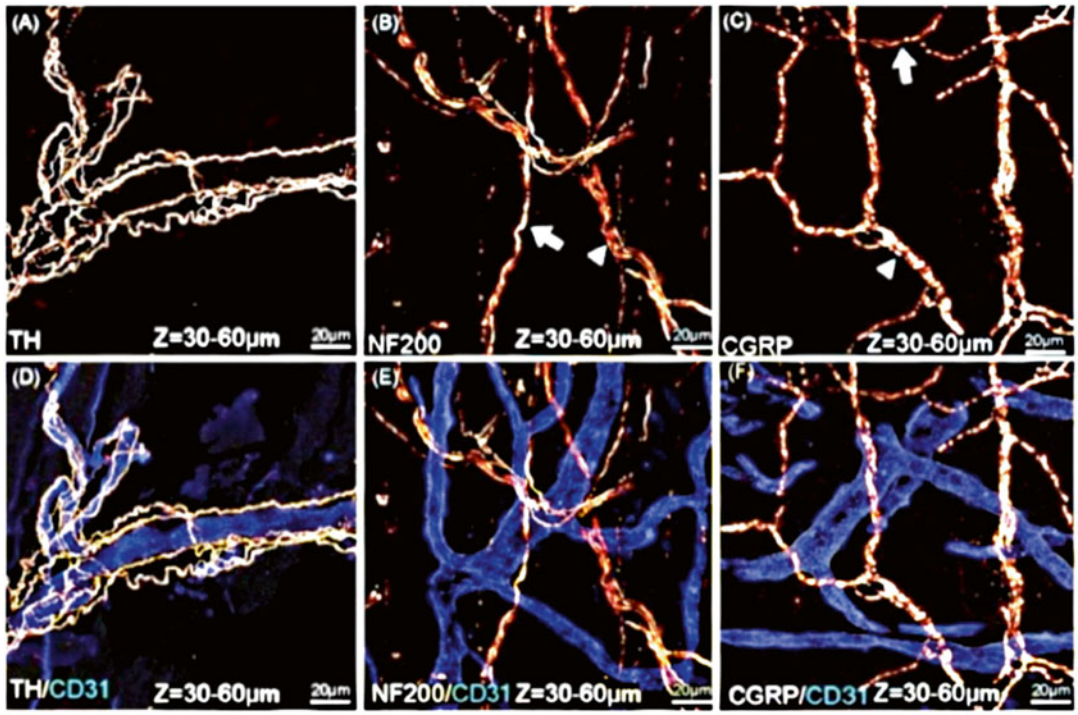

Fig. 3.2 Close association of sensory and sympathetic nerve fibers with blood vessels in the bone periosteum: High-power computed tomography scans of bone in cross section overlaid by confocal images. (**a**) Sympathetic nerve fibers wrapping around CD31-positive blood vessels of the periosteum (**d**). (**b**) NF200+ neurofilament-positive and CGRP+ calcitonin gene-related peptide-positive sensory nerve fibers (**c**) do not associate with CD31+ blood vessels

transporters. The increased extracellular glutamate levels result in central nervous system excitotoxicity and prolonged pain induces central sensitization, which leads to increased transmission of nociceptive information and allodynia [12, 13].

Multiple animal models of neural sensitization in bone cancer models exist [3]. In normal mice, the neurotransmitter substance P is synthesized by nociceptors and released in the spinal cord when noxious mechanical stress is applied to the femur. Substance P, in turn, binds to and activates the neurokinin-1 receptor that is expressed by a subset of spinal cord neurons, eliciting a response. In mice with bone cancer, the reorganization of nociceptive nerve fibers causes mechanical allodynia where non-painful level of mechanical stress induces the release of substance P, making the stimuli noxious [14].

Progress has been made in understanding the pathophysiology of nociceptive nerve sprouting in prostate cancer [15]. Using a mouse model, fluorescently labeled prostate cancer cells were injected into the bone marrow of naive mice. Twenty-six days after injection, nociceptive nerve fibers showed significant new sprouting with increased fiber density and appearance, forming a network of pathological nerve fibers (Fig. 3.3). These data suggest that pathological tumoral sprouting of nociceptive nerve fibers occurs early in the metastatic prostate disease process. To further evaluate the driving force for the new nociceptive fibers, RT-PCR analysis for NGF showed that the surrounding tumor-associated inflammatory, immune, and stromal cells are the major source of NGF in these painful tumors [15].

Targeting Bone Cancer Pain

Pain research highlighting key molecular mechanisms involved in pain transmission has allowed for investigation of novel therapies. Opioids are fraught with side effects that limit their clinical

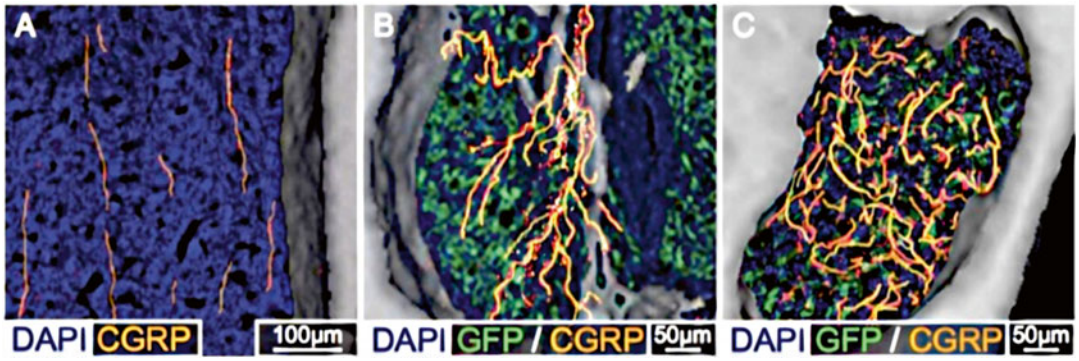

Fig. 3.3 Prostate cancer cells cause sprouting of sensory nerve fibers in bone. High-power computed tomography scans of bone in cross section overlaid by confocal images. DAPI-stained nuclei appear *blue*, GFP-expressing prostate cancer cells appear *green*, and CGRP+ sensory nerve fibers appear *yellow/red*. (**a**) Sham femur showing control level of nerve sprouting seen in characteristic linear morphology. (**b**) Prostate tumor-bearing femur from mice killed at early stage of metastatic disease showing tumor colonies and marked highly branched sensory nerve sprouting. (**c**) Prostate tumor-bearing femur from mice killed at advanced stage of metastatic disease with high density of sensory nerve fibers

efficacy. As cancer-related bone pain is partially related to neural changes such as those that are seen with central sensitization, the molecular understanding of the specific neural pathways involved in central sensitization is currently being investigated as a potential therapeutic option [16, 17]. Focused research targeting blockade of nerve sprouting, like during circumstances of chronic bone cancer pain, has shown significant promise and has resulted in multiple potential clinical interventions for pain management [18, 19]. In addition, many researchers now focus on targeting pain at sites of the initiating event/location with hope to inhibit neural sensitization pathways.

Cytokines

Multiple cytokines have been implicated in the causation, development, or neural sensitization of bone cancer pain. Nerve growth factor (NGF) modulates inflammatory and neuropathic pain states. In chronic pain, NGF levels are elevated in peripheral tissues and neutralizing antibodies against NGF are effective in reducing or preventing cancer-related bone pain [20]. In vitro studies have shown that neutralizing antibodies can inhibit growth and differentiation of NGF-dependent sensory nerve cell lines. More recently, these same antibodies have been shown to inhibit the in vitro migration and metastasis of prostate cancer cells [21]. In addition, pathological sprouting of nerve fibers in a prostate cancer model is modulated in an NGF-dependent fashion (Fig. 3.4) [15]. In animal models, anti-NGF antibodies reduce continuous and breakthrough pain by blocking the nociceptive stimuli associated with the sensitization in the peripheral or central nervous system [22].

Endothelins are a family of vasoactive peptides that are expressed by several tumors, with levels that appear to correlate with pain severity. Direct application of endothelin to peripheral nerves induces activation of primary afferent fibers and pain-specific behaviors. It is hypothesized that endothelins contribute to cancer pain by directly sensitizing nociceptors [23]. Selective blockade of endothelin receptors blocks bone cancer pain-related behaviors and spinal changes indicative of peripheral and central sensitization [24]. Brain-derived growth factor (BDNF) is involved in central sensitization as its expression is increased in nociceptive neurons in models of chronic neuropathy. BNDF sensitizes C fiber activity resulting in hyperalgesia and allodynia.

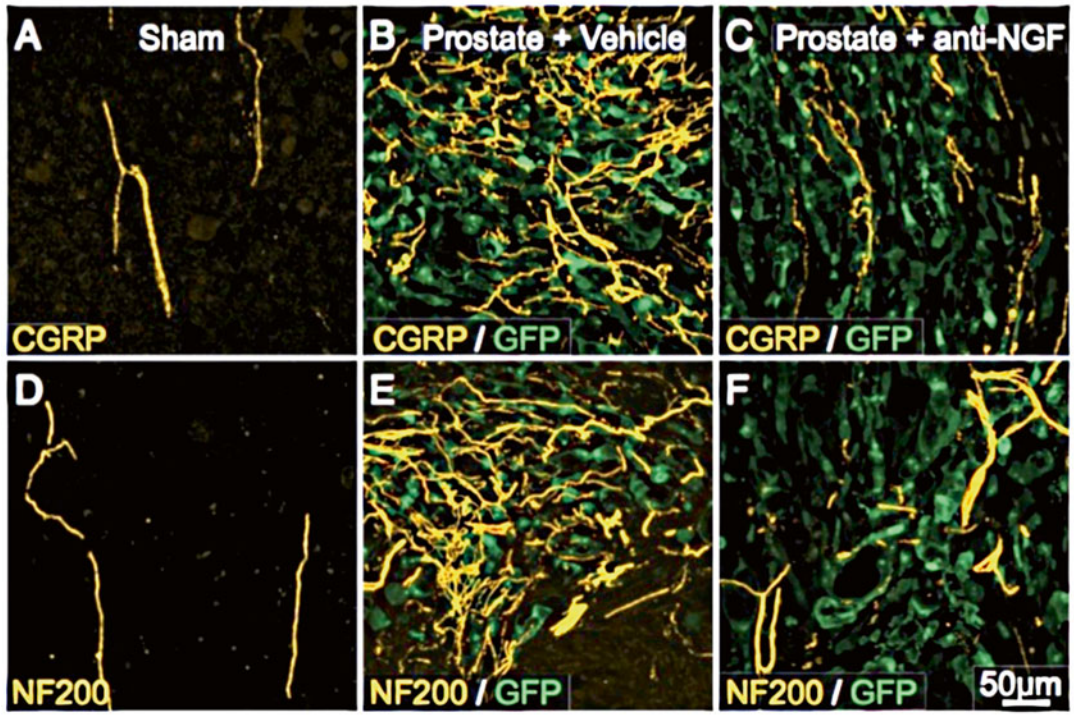

Fig. 3.4 The mesh-like network of nociceptive nerve sprouting in prostate cancer is inhibited by anti-NGF therapy. High-power computed tomography scans of bone in cross section overlaid by confocal images. CGRP+ and NF200+ nerve fibers appear *orange* and *yellow*, respectively, GFP-expressing prostate cancer cells appear *green*. (**a**, **b**) Sham-operated mice show regular innervation of bone by two types of nerve fibers: (**a**) CGRP+ and D NF200+. (**b**, **e**) GFP-transfected prostate cancer cells growing in bone after 26 days, with the CGRP+ and NF200+ nerve fibers. (**c**, **f**) Prevention of CGRP+ and NF200+ nerve fiber sprouting due to anti-NGF antibody therapy

Inhibition of BNDF and its cognate receptor, TrkB, results in decreased C fiber firing and a reduction in pain behaviors [25]. Glial-derived growth factor (GDNF) is important in the survival of sensory neurons and supporting neural cells. Neuropathic pain behaviors commonly observed in animal models of chronic pain are prevented or reversed following GDNF administration and these analgesic effects of GDNF show strong temporal and molecular regulation. Specifically the timing of administration of GDNF directly determines whether analgesia effects are observed [25, 26].

Ion Channels

The transient receptor potential V1 (TRPV1) family of ion channels is located on unmyelinated C fibers and spinal nociceptive neurons that mediate pain transmission. TRPV1 channels can be activated by heat, capsaicin, and acid. Activation of TRPV1 initially provokes a powerful afferent nerve irritant effect, followed by desensitization and long-term analgesia. As TRPV1 is only expressed on nociceptive peripheral terminals, selective blockade of TRPV1 may provide analgesia with a limited side effect profile [27]. Mice that lack the channel are unable to develop chronic pain states while antagonists to TRPV1 significantly decrease chronic pain [28]. In a canine model of bone cancer, intrathecal administration of TRPV1 antagonist resulted in pain reduction and selective destruction of small sensory neurons [29]. Recent work has focused on the role of TRPV1 in the acidic microenvironment of bone metastasis that mediates pain. Specifically, acid signals received by the sensory

nociceptive neurons innervating bone stimulate intracellular signaling pathways of sensory neurons. Molecular blockade of the activated intracellular transcription factors in these signaling pathways has served as a method to inhibit pain transmission [7, 30].

Osteoclast

Most metastatic skeletal malignancies are destructive in nature and produce regions of significant osteolysis via activation, recruitment, and proliferation of osteoclasts at tumor-bearing sites [31]. This activation and proliferation of osteoclasts are mediated by the interaction between receptor activator for nuclear factor κB (RANK) expressed on osteoclasts with RANK ligand (RANKL) expressed on osteoblasts. Increased expression of both RANK and RANKL has been found in tumor-bearing sites. Selective inhibition of osteoclasts using either bisphosphonates or the soluble decoy receptor for RANKL, osteoprotegerin (OPG), results in inhibition of cancer-induced osteolysis, cancer pain behaviors, and neurochemical markers of peripheral and central sensitization [32, 33].

Bisphosphonates have shown clinical success in treatment of both osteoporosis and tumor-induced osteolysis. Administration of bisphosphonates has shown a positive impact on overall skeletal health and quality of life in patients with breast and prostate skeletal metastasis [34, 35]. The long-term beneficial effects of bisphosphonate treatment in reducing bone pain and skeletal related events (e.g., pathologic fractures) and the patient-reported improvement in overall quality of life are clear from clinical trials in lung, breast, and prostate cancer [36–38]. In addition, one recent meta-analysis has shown that initiation of therapy with the bisphosphonates prior to the development of skeletal metastasis improves quality-of-life scores and decreases clinical pain and skeletal events in patients with prostate cancer [39].

Tumor-induced osteolysis is a multifactorial process but is stimulated by RANKL, and inhibited by osteoprotegerin (OPG). RANKL inhibition has shown success in treating bone cancer pain and pathological fracture-related complications. Specifically, denosumab (human monoclonal antibody against RANKL) was evaluated against zoledronic acid (bisphosphonate) in a randomized clinical trial evaluating the prevention of skeletal related events in breast cancer patients with bone metastases. While both therapies were well tolerated and delayed or prevented skeletal related events, denosumab trended towards superior reductions in patient-reported pain and improved patient quality of life [40]. In addition to being effective in patients with breast cancer, denosumab was compared to zoledronic acid in a phase III clinical trial for patients with metastatic prostate cancer. The results showed a greater decrease in skeletal related events such as pathological fracture in patients taking denosumab than those patients taking zoledronic acid [41]. A recent systematic review has shown that while denosumab is very effective in preventing skeletally related events, its effect on pain and quality of life in cancer patients is less clear [42].

Conclusion

Bone cancer pain is a multifactorial process with many potential targets for therapeutic intervention. As pain is the most common presenting symptom in patients with skeletal metastases and is directly proportional to the patient's quality of life, clinical improvements in the treatment of bone cancer pain are of the utmost importance. Research targeting pain-related cytokines, anti-osteoclastic medications, and ion channels has shown significant clinical progress in the treatment of cancer-related bone pain. With continued efforts into these and other therapeutic strategies, we hope to continue to improve the quality of life of those patients suffering with bone cancer pain.

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Breast Cancer Bone Metastases

4

Sarah Colonna and Theresa L. Werner

Background

Breast cancer is the most common cancer diagnosed among women, with 1.3 million cases diagnosed each year worldwide and is the leading cause of cancer death among women [1]. Further, for women aged 40–59, breast cancer is the leading cause of death from any cause. Most initial diagnoses of breast cancer are made during the early and curable stages of the disease, and women typically discern a breast tumor either by personal breast awareness or it is discovered by screening mammography (Table 4.1).

At the time of diagnosis, about 5 % of all breast cancers are metastatic, with bone being the most common location of distant spread. Thirty percent of women with early-stage breast cancer will eventually experience a recurrence of their breast cancer and subsequently develop metastatic disease [2]. Compared to bone metastases from other malignancies, breast cancer is most likely to become metastatic to the bone years after the initial cancer diagnosis. This is a result of recurrence of a localized breast cancer that spreads to the bone as opposed to having bony metastases at initial presentation.

Breast cancer demonstrates a particular predilection for spread to the bone, with 35 % of women whose only burden of metastatic disease is bony metastases. During the clinical course of metastatic breast cancer, the majority of women, estimated at 71 %, will eventually develop bone metastases [3]. Importantly, women with bone-only metastatic breast cancer have a significantly better prognosis compared to women with visceral metastases. Studies demonstrate a median overall survival of 71 months for women with metastatic bone disease only from breast cancer compared to women who have concomitant bone and liver metastases, whose median survival is 5.5 months [3, 4]. Furthermore, a significant portion of women with bone metastases from breast cancer, estimated at 41 %, have a solitary metastatic lesion, which is associated with increased survival compared to women with multiple bone metastases [5].

Breast Cancer Subtypes

Historically, breast tumors were defined according to the histologic subtypes of invasive ductal carcinoma, which are most common at 80 %, invasive lobular carcinoma at 15 %, or other less

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Table 4.1 Breast cancer staging, American Joint Committee on Cancer (AJCC) [52]

Stage	Tumor (T)	Node (N)	Metastatic (M)
Stage 0	Tis (carcinoma in situ)	N0	M0
Stage IA	T1 (≤20 mm)	N0	M0
Stage IB	T0 or T1 (≤20 mm)	N1mi (nodal micrometastasis, >0.2 mm but ≤2 mm in lymph node)	
Stage IIA	T0 or T1 (≤20 mm)	N1 (1–3 nodes)	M0
	T2 (>20 mm but ≤50 mm)	N0	M0
Stage IIB	T2 (>20 mm but ≤50 mm)	N1 (1–3 nodes)	M0
	T3 (>50 mm)	N0	M0
Stage IIIA	T0, T1,T2, T3 (any tumor not invading skin or chest wall)	N2 (4–9 nodes)	M0
	T3 (>50 mm)	N1 (1–3 nodes)	M0
Stage IIIB	T4 (tumor invading chest wall or skin)	N0, N1, N2 (0–9 nodes)	M0
Stage IIIC	Any T	N3 (≥10 nodes)	M0
Stage IV	Any T	Any N	M1 (distant metastasis)

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frequent subtypes [6]. Mixed ductal and lobular carcinoma is an infrequent pathologic subtype of breast tumor though it is more likely to become metastatic to the bone compared to either ductal or lobular breast cancer [7]. Breast tumors that recur in the skeletal system only are more likely to be clinically less aggressive, as determined by the pathologist as these tumors tend to be of low or intermediate grade (grade I or II, respectively) and thus have a slower rate of cell turnover [3].

The subclassification of breast cancer has become much more complicated though prognostically more meaningful due to the discovery of specific receptors on tumor cells. Breast cancer is increasingly being recognized as a very heterogeneous disease, with several different subtypes of cancer that are located within the same organ of the breast. These different subtypes are biologically and behaviorally distinct and microarray analyses have defined discrete patterns of gene expression [8]. Clinically, pathologists utilize three proteins on the surface of breast cancer tumor cells to categorize breast cancer into separate categories that carry both prognostic and predictive importance. These include estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2 or HER2/neu).

ER, PR, and HER2 receptor status are initially pathologically defined by immunohistochemistry (IHC) with ER and PR receptors defined by percent of cells expressing the receptor from 0 to 100 %. Tumors with a higher percentage of ER or PR positivity carry a better prognosis that correlates to the higher likelihood of tumor response to endocrine-based therapy. If either the ER or PR receptor status of a breast tumor is negative (or 0 % positivity) this portends a worse prognosis compared to cases where ER and PR status are both positive. However, ER and PR receptor status is typically concurrently either both positive or both negative.

ER negative tumors represent a more biologically aggressive subtype of breast cancer with a higher risk of recurrent disease, and typically with rapid relapse of local disease. Unfortunately there are limited effective treatment options available for patients with recurrent metastatic ER-negative breast cancer.

About 20 % of breast cancers over-express the HER2 protein and are classified as HER2-positive (HER2+) breast cancer. These tumors

also represent a biologically aggressive subtype of breast cancer with higher risk of recurrent metastatic disease. Common sites of metastases of HER2+ disease include the brain, liver, and lung [8]. In the past decade, specific targeted therapies, such as trastuzumab, have been designed to target HER2+ breast cancer and have dramatically improved the outcomes of women with this type of breast cancer [9].

Breast cancers that are both ER+ and HER2− comprise the majority of breast cancer diagnoses at 75 % of cases. These tumors occur more commonly among older postmenopausal women and have a lower risk of relapse following initial therapy when compared to ER− breast tumors [10].

There are two distinct groups of ER+ and HER2− breast cancer based on their tumor genomic profiles, termed luminal A and luminal B subtypes. These subtypes express genes associated with luminal epithelial cells of normal breast tissue and ER+ breast cancers, including ER, PR, and other genes associated with ER activation. Luminal A tumors, which make up about 40 % of all breast cancers, are the most common subtype and carry the best prognosis as they tend to have high expression of ER-related genes and low expression of proliferation-related genes. Luminal B tumors, which comprise about 20 % of all breast cancers, carry a worse prognosis compared to luminal A tumors due to lower expression of ER-related genes and higher expression of proliferation-related genes [11, 12] (Table 4.2).

ER+ breast cancers harbor the unusual proclivity to recur up to 20 or more years after a woman's initial breast cancer diagnosis. Notably, in cases of ER+ breast cancer that recur decades after initial presentation, nearly all of these women experience bone metastases [13]. There is a special symbiotic relationship between ER+ breast cancers and the milieu of the bone, with one review demonstrating that up to 90 % of women who have bone-only metastatic breast cancer had ER+ breast cancer [14].

When ER+ breast cancers recur and metastasize, they typically follow a more indolent course. Women with ER+ breast cancer also have more treatment options available as we are able to take advantage of the dependence of these tumors on estrogen. In these cases we utilize targeted biologic therapies, specifically estrogen blockade with oral agents such as selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs). These are oral therapies that are well tolerated with low side effect profiles. Unfortunately most metastatic ER+ breast cancer will become resistant to endocrine therapy over time, and women eventually require cytotoxic chemotherapy agents, which have more side effects (Table 4.2).

Table 4.2 Clinical features of breast cancer subtypes, 1986–1992

Clinical feature	Luminal A (ER+/HER2−)	Luminal B (ER+/HER2−)	Her2 positive (HER2+/either ER)	Triple negative (ER−/PR−/HER2−)
Age at diagnosis (median)	62	60	57	55
Overall survival from diagnosis at 10 years	70 %	54 %	47 %	56 %
If metastatic, % of women with bone metastases	66 %	71 %	62 %	41 %
Time from metastases to death	2.2 years	1.6 years	1 year	7 months
Available medical treatment options				
Hormone therapy (tamoxifen, aromatase inhibitor, fulvestrant)	Yes	Yes	Yes/No	No
Trastuzumab (HER2-directed therapy)	No	No	Yes	No
Chemotherapy	Yes	Yes	Yes	Yes

Data from Voduc et al. [13]

Bone metastases are disproportionately common among ER+ breast tumors and it is important to note that women with ER+ bone-only metastatic breast cancer can live many years with good quality of life, typically treated for years with only oral endocrine therapy. Thus, aggressive management of bony metastases and attention to the prevention of skeletal complications within this group of women are imperative.

Biology and Pathophysiology of Breast Cancer Metastases

The most common type of metastatic bone disease from breast cancer is generally classified as osteolytic, estimated at 80–90 %, which causes bone destruction. Osteoblastic lesions which cause bone formation can occur, although less commonly [15]. Breast cancer cells are thought to activate mature osteoclast formation and to influence the differentiation of hematopoietic cells into osteoclasts that create the destructive osteolytic lesions [16]. Importantly, osteoblastic and osteolytic categories are determined by crude radiologic criteria, and in reality, most breast cancer metastases to the bone are both osteoblastic and osteolytic, and the term "mixed lesion" is sometimes used to describe this phenomenon [17].

Clinical Presentation of Breast Cancer Bone Metastases

Bone metastases among women diagnosed with breast cancer are very common and present the greatest morbidity for women with breast cancer. The most common sites of bone metastases from breast cancer are vertebrae and pelvis followed by ribs, skull, and femur. The lymph and venous drainage from breast tumors proceed not only into the vena cavae but also through the epidural and perivertebral veins, which may partially explain why breast cancer tends to spread to the axial skeleton and limb girdles predominantly [18].

Bone pain is experienced by the majority of women, about 80 %, with bone metastases from breast cancer and is one of the key features that determine a patient's ability to retain good quality of life. Many women describe the pain from bony metastases as deep and aching, with occasional episodes of more acute or sharp pain, and pain that is often worse at night. Narcotic and other analgesic use for pain control from bony metastasis is a significant psychological burden on patients and presents increased costs to the overall healthcare system. Additionally, 37 % of women with bone metastases ultimately require palliative radiation for pain relief alone [19]. While the intensity of pain does not clearly dictate which women are at highest risk of fracture, pain that is worsened by movement can be a sign of an impending pathologic fracture [17]. Pain reduction should be a primary endpoint for any intervention for bone metastases.

Nearly two-thirds of women diagnosed with bone metastases from breast cancer will undergo a skeletal-related event (SRE), which are defined as a pathologic fracture, spinal cord compression, hypercalcemia, or pain requiring hospitalization or a procedure [20, 21]. SREs occur every 3–4 months among women with bony metastases from breast cancer [17]. For 22 % of women, an SRE is the clinical event that uncovers the diagnosis of metastatic breast cancer [22]. There is evidence that SREs occur disproportionately more commonly during the year immediately following a woman's diagnosis with metastatic breast cancer than during the subsequent years [23].

A compilation of two placebo-controlled multicenter randomized trials evaluating pamidronate, an intravenous bisphosphonate, published in 2000, offers the following insights into the frequency of particular SREs among women with metastatic breast cancer to the bone: within the placebo group, hypercalcemia was diagnosed among 13 % of women, 43 % of women received radiation to the bone for various indications, pathologic fracture occurred in 52 % of women, overall 11 % of women required surgery for a pathologic fracture, and lastly 3 % of women incurred spinal cord compression from bony

metastases. These statistics underscore the clinical burden of bone metastases upon women with breast cancer [19]. The risk of pathologic fracture can increase with the duration of metastatic involvement. Thus, women with metastatic ER+ breast cancer, who overall have a better prognosis and potentially live longer, have a relatively increased risk of pathologic fracture.

Sternal metastases from breast cancer represent a unique site of spread in terms of prognosis and treatment. This is a relatively frequent site of local metastases because breast cancer can directly spread from intra-mammary nodes of the breast, and sternal metastases may remain isolated due to lack of communication with the paravertebral venous plexus. Therefore, women with isolated sternal metastases from breast cancer should be considered for surgical resection, particularly since cancer in the sternum can be very painful and psychologically distressing [24].

Treatment of bone metastases among women with breast cancer represents a very important part of their overall oncologic care and represents an expensive challenge to the overall healthcare system. Women with bone metastases from breast cancer, who proceed to have an SRE, incur an increased $50,000 in healthcare costs compared to women of a similar health profile who do not have an SRE [25, 26, 27].

Imaging of Breast Cancer Bone Metastases

Since breast cancer frequently metastasizes to the bone, nuclear medicine bone scan or positron emission tomography (PET) is routinely performed for staging purposes among women who are at high risk of metastatic disease. The National Comprehensive Cancer Network (NCCN) recommends consideration of staging imaging for bone metastases among women who are diagnosed with either a locally advanced primary tumor (T3 or T4 lesion) or positive lymph nodes (N1 or N2 disease) (Table 4.1) [28]. If a woman is diagnosed with recurrent breast cancer, either locally or distally, women are typically restaged with imaging to evaluate specifically for bony metastases [27]. For this reason, many bone metastases are not detected from symptoms but from discovery from staging imaging.

Bone scans utilize radionuclides to measure increased osteoblastic activity and skeletal vascularity. It is the favored screening test for bony metastases in women with breast cancer since it is widely available and affordable. Additionally, bone scan has good sensitivity and specificity, at 62–100 % and 78–100 %, respectively, for detecting breast cancer in the bones. False positives do occur and can be caused by trauma, inflammation, or other hypermetabolic processes within the bones. In contrast, false negatives can occur when bone metastases are very indolent or when blood flow is absent from the metastatic site [28].

Typically, tumor response to therapy is visualized as decreased tracer uptake and progressive cancer demonstrate increased tracer uptake. "Tumor flare" is an important and confusing phenomenon that frequently occurs when interpreting bone scans. Patients with known bony metastases who have recently initiated medical therapy can appear to have progressive disease on bone scan due to increased radionuclide uptake in the metastatic lesion as the bone is actually healing. Therefore, it is key to implement caution when interpreting a bone scan soon after the onset of a new therapy. After about 6 months of therapy, the bone scan may again become an accurate tool to assess the status of the cancer in the bones [29]. A less common but equally confusing situation can occur when tumors are growing rapidly and do not demonstrate increased tracer uptake on bone scan because the large amount of bone destruction from cancer does not allow formation of new bone. If new bone formation is not occurring, no tracer uptake occurs and the bone scan does not demonstrate an abnormality despite the fact that a metastatic lesion does exist [30].

Radiographs can be a useful tool for evaluating skeletal metastases from breast cancer. X-ray pictures are less sensitive than bone scans, at 44–50 %, so they should remain only an accessory tool and not a replacement for bone scans for screening purposes. When bony lesions are deemed to be "suspicious" for metastases on bone scan, radiographs can then be used to fur-

ther characterize the lesion, particularly since X-ray pictures are very inexpensive and easily accessible [31]. Radiographs, however, provide a poor tool to assess the response of bony metastases to medical therapy, since the appearance of the lesions on plain films changes slowly and may not appear changed even when patients have clear clinical evidence that they are responding to therapy.

Computed tomography (CT) scans offer a very useful tool for detecting bony metastases among patients with breast cancer, with a sensitivity of 71–100 % when the bone window settings are utilized [32]. Accuracy of CT to detect bony lesions is attributable to its ability to distinguish between different densities and its ability to determine anatomic detail and thus CT is one of the best modalities to detect bone metastases within the spine and calvarium particularly [32, 33]. CT imaging is also a useful tool for assessing the response of bone metastases to medical therapy, since progression of cancer will appear more lytic in nature and improvement of cancer will appear as sclerosis on imaging [34]. CT imaging is not routinely used for screening for bony metastases since it is difficult to image a woman's entire body in a timely manner, but CT imaging is routinely used to better characterize known bony metastases with better accuracy and detail than other imaging modalities.

Magnetic resonance imaging (MRI) is another imaging modality that can be used to visualize bone metastases from breast cancer, with similar sensitivity and specificity to CT scan, at 82–100 % and 73–100 %, respectively [35]. MRI is distinctly useful in characterizing spinal cord compression from bony metastases but is inferior to CT when trying to understand the cortical integrity of bones or attempting to measure response to medical therapies [36]. Currently, outside of spinal cord compression, MRI has limited use in assessing bony metastases form breast cancer.

PET is a frequently utilized imaging tool for both staging and surveillance of metastatic breast cancer. Breast cancer typically displays a decreased metabolism when contrasted with other cancer types, but PET still has excellent sensitivity and specificity at 84–100 % and 98–100 %, respectively [37]. PET imaging is more sensitive than bone scan for detecting skeletal metastases, particularly osteolytic lesions, but the cost and limited availability of PET make bone scan the more commonly utilized modality [30]. As previously described with bone scan, one must utilize caution when interpreting PET scans to assess response because of the tumor flare phenomenon that can appear as worsening disease on PET after patients have recently started medical therapy, as tumors within the bone that are responding to therapy and bone healing appear as increased avidity of PET scan [38].

Nonsurgical Treatments

Treatment for bone metastases from breast cancer must be multidisciplinary, involving the medical oncologist, radiation oncologist, and orthopedic surgeon for optimal outcomes. Bisphosphonates have significantly impacted care and outcomes for women with bone metastases from breast cancer and are also effective therapy for hypercalcemia of malignancy. These drugs induce apoptosis of osteoclasts and thus inhibit osteoclast-mediated bone resorption. Bisphosphonates prevent and reduce bony pain and reduce further SREs by about 15 %. The Food and Drug Administration (FDA) approved the first bisphosphonate, pamidronate, for use in metastatic cancer in 1996 when this agent demonstrated that women treated with pamidronate experienced a longer time to an SRE, 13.9 months versus 9 months, compared to women who received placebo [39]. Zolendronic acid, another intravenous bisphosphonate, was approved in 2001 and demonstrated overall non-inferiority to pamidronate, but zoledronic acid demonstrated a longer time to first skeletal event in women with breast cancer with osteolytic bony metastases (310 days compared to 174 days) [40]. Zolendronic acid is more potent than pamidronate and can be administered over 15–30 min compared to 2 h for pamidronate.

Denosumab, a monoclonal antibody to RANK ligand, was approved for use in the treatment of bony metastases from cancer in 2011. RANK ligand is a key component in the pathway for osteoclast formation and activation. The conclusion of several clinical trials is that denosumab is more effective than bisphosphonates at reducing SREs with an RR of 0.78, but is more costly, causing practice patterns to vary nationwide [41].

Bisphosphonates and denosumab do pose some risk to patients. A viral-like infusion reaction is common but not life threatening. Hypocalcemia occurs in about 35 % of women, but is usually not severe, and the more concerning side effect of osteonecrosis of the jaw occurs rarely at 1.4 % [42]. Because of the possibility of osteonecrosis of the jaw, patients should be cautioned about dental interventions while on these therapies and encouraged to continue their regular dental maintenance. Additionally, bisphosphonates can cause renal toxicity, documented at 8.5 % in clinical trials, while denosumab does not impact renal function [43]. Since women with bony disease from breast cancer can live with their metastatic disease for many years, the question of how long to continue these agents is currently being considered in clinical trials and is yet uncertain.

Systemic endocrine therapy, including oral agents like tamoxifen or aromatase inhibitors, or fulvestrant which is a monthly injection, is very important in the management of metastatic breast cancer to the bones that is ER+. These agents are relatively well tolerated with minimal side effects, but they can take 6 weeks or longer to demonstrate a response either clinically or radiologically. Therefore, the patient being offered endocrine therapy alone should not have life-threatening disease or a visceral crisis requiring prompt tumor shrinkage (Table 4.2).

Notably, tamoxifen causes an increased risk for deep vein thrombosis (DVT) and pulmonary embolism (PE), so patients on tamoxifen undergoing surgery are at higher risk of thrombotic complications. For that reason, it is recommended that tamoxifen be discontinued around the time of surgery until her risk of blood clots decreases. Aromatase inhibitors (AIs) do not place women at increased risk of DVT or PE, but can slightly increase a woman's risk of metabolic syndrome and osteoporosis. For many women with bone-only metastatic breast cancer, they may be on endocrine therapy alone for many years.

There are many types of chemotherapy that have demonstrated response rates among women with breast cancer, with taxanes and anthracyclines being drugs with historically high response rates. Because there are so many active cytotoxic agents for women with breast cancer, clinicians typically use the side effect profile of each drug, such as hair loss or risk of cytopenias, to personalize which drug is best for a particular woman with metastatic disease. Chemotherapy can also produce response rates in bony disease, although once a woman has initiated chemotherapy, her overall survival is typically measured in months and no longer in years (Table 4.2).

External beam radiation is an effective therapy for bone metastases and usually has very limited toxicity if vital organs can be avoided. Clinical trials have evaluated single fractionation at 8 Gy, which provides similar pain control but may result in the need for retreatment when radiation given over multiple days of therapy [44]. It is important to note that healing of bone lesions can be inhibited by radiation of particularly large bony metastases since there may be inadequate bone matrix as radiation inhibits chondrogenesis [17].

Radiopharmaceuticals that were developed to target cancer in the bone for treatment of pain have most commonly been used in prostate cancer, but have shown promise for women with breast cancer who have refractory bony pain from metastatic disease. A majority of patients treated with this modality received a decrease in their pain level and the hematologic toxicity that can be incurred was mild [45].

As breast cancer subtypes have been better characterized in the past decades and as breast cancer therapy has increasingly become personalized, oncologists have learned that breast cancer can transform from being one receptor subtype to another receptor subtype within the same woman. For that reason, obtaining a new tumor biopsy at the time of recurrence and repeat

testing of the tumor for ER, PR, and HER2 status are very important. Reviews comparing IHC patterns of primary breast tumor compared to metastatic disease cite up to a 25 % chance that the tumor receptor status can transform, and usually the tumor loses surface protein expression, which also portends a poorer prognosis for the woman [46–47]. Knowing the profile of breast cancer greatly aids the medical oncologists in prognosticating accurately and choosing the most effective and the least toxic therapy for each woman.

Future Directions

Many signaling pathways are being investigated to better characterize druggable targets for therapy for bone metastases from breast cancer. TGF-Beta, Src, and Wnt are a few of the pathways that drugs are being designed to target. These therapies are either in the preclinical phases or early-phase human clinical trials and need further investigation before their clinical use is understood in women with bony metastases from breast cancer [48–51].

Summary

In summary, bone metastases from breast cancer are very common and are the most significant cause of morbidity for breast cancer patients. Bony metastases are likely to cause pain, may cause hypercalcemia, and lead to fracture or rarely spinal cord compression. A majority of women present with bony metastases at the time of cancer recurrence. There are several distinct immunohistochemical subtypes of breast cancer that behave differently and have different treatment options available. ER+ breast cancer is disproportionately likely to metastasize to the bone and oftentimes the bone is the only site of metastatic disease. These patients are likely to live years with good quality of life as ER+ tumors have a better prognosis; thus aggressive management of their bony metastases is important.

There are many imaging modalities available with bone scan being the best screening modality and CT scan being superior when attempting to characterize a bony lesion. A multimodality treatment approach is best for women with breast cancer metastatic to the bones and should include consideration of bisphosphonates or denosumab, radiation therapy, hormone therapy, and/or chemotherapy and orthopedic surgery.

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Prostate Cancer Bone Metastasis

5

Jonathan D. Tward

Introduction

Prostate cancer is the leading cancer diagnosis in American men, with 1 in 8 persons being diagnosed within their lifetimes. In 2014, it is estimated that about 233,000 persons will be diagnosed with prostate cancer, and that 29,480 will die of the disease [1]. There is controversy regarding the benefits of both screening and treatment of prostate cancer, as many prostate cancers currently diagnosed by prostate-specific-antigen (PSA) serum testing would have remained clinically occult throughout a man's lifetime. Nevertheless, prostate cancer remains the second-leading cause of cancer-related death in Western countries [2]. Although serum PSA levels are a controversial when used as a screening test, this tumor marker is an outstanding test at evaluating the treatment response of men undergoing various oncologic therapies.

The consequences of therapy and the direct impact of bone metastases on quality of life are significant for men living with prostate cancer. "Skeletal-related events" (SREs) is a defined term that has been adopted by the oncologic community, and is useful in comparing the efficacy of therapies on progression and impact on patient quality of life in research studies. The National Comprehensive Cancer Network (NCCN) task force defined SREs as "a constellation of skeletal complications, including fracture, need for surgery on bone, need for radiation to bone, spinal cord compression, and in some situations, hypercalcemia of malignancy" [3].

One universally accepted care standard in men diagnosed with metastatic disease of bone is the initiation of androgen deprivation therapy (ADT). By robbing the cancer of its growth factor, testosterone, one can reliably delay the progression of the cancer for what is typically several years. However, the concomitant effects of ADT on bone density and general skeletal health can compound the risk of SREs in men with metastatic tumor in bone.

Because prostate cancer is the most common malignancy diagnosed in men, it serves as one of the model systems to study how bone metastases influence survival, therapeutic decision making, and quality of life. This chapter does not attempt to reiterate the general management of bone tumors explained elsewhere in the book. It focuses on the elements that are specific to prostate cancer, with an emphasis on adenocarcinoma, which accounts for over 95 % of diagnoses.

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Biological Aspects Particular to Prostate Bone Metastases

Blastic Appearance

Prostate cancer bone metastases usually appear on X-rays as dense structures, suggesting osteoblastic reactions around tumor. Nevertheless, studies have also demonstrated that prostate bone metastases also have osteolytic properties, which in turn weaken and destroy the bone and are the presumed cause of the morbidity related to fractures [4].

Histologies

Adenocarcinoma accounts for 95 % of all prostate cancer diagnoses. Rarer histologies include sarcoma, mucinous or signet-ring cell carcinomas, adenoid cystic carcinomas, carcinoid tumors, large prostatic duct carcinomas (including the endometriod-type adenocarcinomas), melanomas, and small-cell undifferentiated cancers. Amongst these rarer histologies small-cell cancer may be the next most prevalent diagnosis at around 1 % of subjects. Unlike the adenocarcinomas, the neuroendocrine variants have a high incidence of bone metastases which are predominantly lytic.

Demographics and Prognosis of Men with Metastatic Prostate Cancer

Prostate cancer accounts for the majority of bone metastases diagnosed in men in the USA [5]. In a contemporary study utilizing the large SEER-MEDICARE claims database, 7.7 % of men with prostate cancer had evidence of bone metastasis at diagnosis. These men were more likely to be older than a matched cohort of men without bone metastasis (median age of 76 versus 74). Race and comorbidity do not appear to influence the risk of presenting with bone metastasis at diagnosis, and the hazard ratio of death is 6.6-fold for those with bone metastasis and no evidence of SREs at presentation compared to those without bone metastases [6]. When both bone metastasis and SREs are present at diagnosis, the hazard ratio for death climbs to 10.2.

Detection of Bone Metastasis

Occult Disease and Proposed Mechanism of Spread

Clinically occult prostate cancer bone metastases are discovered in a relatively large proportion of men with either known or unknown primary cancers at the time of autopsy. In a Swiss autopsy series of over 19,000 men who died of various causes between 1965 and 1995 (most prior to the era of PSA-screen detection), macroscopic localized prostate cancer was detected in 8.2 % of subjects [7]. Roughly half of these men had been diagnosed with prostate cancer during their lifetimes. Bone metastasis was identified in about 30 % of these men. The spine had bone metastasis in 90 % of the cases. In men with spinal disease, the lumbar vertebra were involved 97 % of the time, followed by thoracic spine at 66 %, and cervical spine at 38 %. Isolated metastases to the thoracic and cervical spine only occurred in 2 % and 1 % of men, respectively. Other bony sites outside the spine were not meticulously examined in this particular autopsy series.

The presence of bone metastasis in this autopsy series was strongly correlated with the presence of lymphatic metastasis. Bone metastases were identified in approximately 80 % of persons with lymphatic metastasis, but in only about 16 % of persons without evidence of lymphogenous spread. Para-aortic lymph node metastases were identified in ~58 % of persons with spine metastasis, but in only about 39 % of those without spinal metastasis. Taking these distributions into account, the authors propose that the route of bone metastases for prostate cancer follows two pathways: the first supporting the concept first proposed by Batson via a “backward spread” of metastasis from the prostatic veins into the lower lumbar spine followed by subsequent upward spread along spinal veins, and the second pathway via the usual hematogenous route of circulating tumor cells pumped through the lungs on their way to other bony sites [8].

Clinical Detection of Bone Metastasis

A clinical risk grouping system first proposed by D'Amico and then adopted and modified by the NCCN is typically used to determine who should be screened for prostate bone metastasis in men without symptoms of bony disease. Most treatment guidelines, such as those of the NCCN, recommend obtaining scans in men with "high-risk" prostate cancers, defined as men with a biopsy Gleason score of 8–10, a clinical T-stage of T3 or greater, or a PSA exceeding 20. For those with "low-risk" cancers (Gleason score <7, PSA < 10, no significant palpable disease on digital rectal exam), screening for bone metastasis is not indicated due to the low likelihood of detecting bone metastasis [9, 10]. The guidelines vary slightly from one another on criteria for obtaining scans in intermediate-risk patients and are summarized in Table 5.1.

The most common diagnostic test used to screen for bone metastases in newly diagnosed prostate cancer patients is the technetium bone scan (Fig. 5.1). Numerous studies evaluating how PSA values correlate with the likelihood of detecting bone metastasis have been performed. In men with serum PSA values of at least 10 ng/dl, Tc bone scan has reportedly detected bone metastasis in between 0.6 and 45.8 % of subjects. However, in studies evaluating a cutoff of 20 ng/ml, the detection range is reported to be between 14 and 26.5 % of persons [9].

In a contemporary series of over 800 newly diagnosed prostate cancer patients with Gleason 8–10 (high-risk) cancers, bone metastases were detected in 17 % of men. In men with palpable disease on digital rectal examination having lower Gleason scores, bone metastasis was discovered in 8 % of men [9].

In men with androgen-insensitive prostate care without evidence of bone metastases (i.e., those with rising PSA values despite the use of therapies designed to remove or block testosterone

Table 5.1 Summary of guidelines for staging imaging studies in men with prostate cancer

Guideline	Recommendation for bone scan	Recommendation for CT/MRI
National Comprehensive Cancer Network (NCCN) [10]	Symptomatic patients Those with a life expectancy >5 years and … PSA >20 T2 disease with PSA >10 T3–T4 disease Gleason score 8–10	T3–T4 T1–T2 and nomogram-predicted probability of lymph node metastasis >10 %
European Association of Urology (EAU) [11]	Bone pain Poorly differentiated tumors and locally advanced disease irrespective of the serum PSA level	
American Urology Association (AUA) [12]	PSA >20	PSA >20 Locally advanced disease Gleason 8–10
European Society for Medical Oncology (ESMO) [13]	T3–T4 Gleason score 8–10 PSA > 20 Intermediate risk and … Clinical suspicion of bone metastases Gleason 4 + 3 PSA greater than 10	Consider in high-risk patients
European Society of Urogenital Radiology (ESUR) [14]	High-risk patients	Active surveillance patients Intermediate-risk patients to plan curative intent therapy approaches High-risk patients

Adapted and modified from Briganti et al. [2]

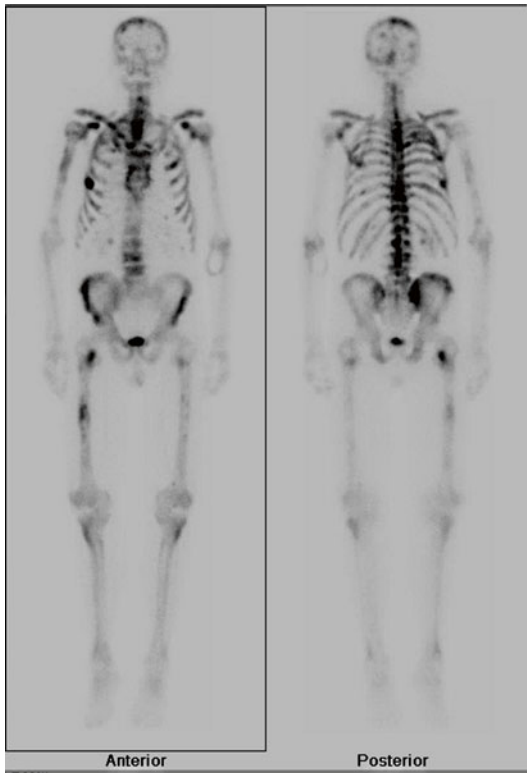

Fig. 5.1 Technetium bone scan: Numerous bone lesions throughout the axial and appendicular skeleton in a man with metastatic prostate cancer are shown. Note the heavy involvement of the spine, which is typical

to castrate levels in the serum), bone metastases developed by 2 years in approximately 40 % of subjects [2, 15, 16]. In subgroup analyses of a randomized trial in patients who had androgen-insensitive prostate cancer, a baseline PSA level of >24 ng/dl or a PSA doubling time of less than 6 months was correlated with the highest risk of developing bone metastases, with a reported rate exceeding 70 % by 3 years [2, 16].

Therapy

Prevention of Bone Metastases

Role of Surgical Treatment of the Primary Cancer

Approximately 85 % of men with newly diagnosed prostate cancer have disease clinically localized to the prostate alone. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial [17], which studied a mostly PSA-screened population randomized to radical prostatectomy or observation, reported on some nonmortality endpoints. They found an absolute risk reduction of 6 % in the prostatectomy group over the watch-and-wait group (number needed to treat of 17) to prevent bone metastasis. Notably, this change in development of bone metastases was realized almost exclusively within the first 8 years following diagnosis and treatment.

Role of Androgen Deprivation Therapy Plus or Minus Radiation Therapy

There have been three randomized trials completed comparing the efficacy of the addition or radiotherapy to androgen deprivation therapy alone in men with high-risk but clinically localized prostate cancer. All of the studies showed a significant disease-specific and overall survival benefit by the addition of radiation to the primary site [18–20]. One of the trials specifically reported on metastasis-free survival, which implies a delay in the development of bone metastases specifically. After 8 years of follow-up, 11 % of subjects on androgen deprivation alone (continuous leuprolide with flutamide) developed bone metastases, as opposed to only 3 % of those persons who had combined ADT and radiotherapy [18].

Treatment of Bone Metastases

Role of Bisphosphonates

There have been numerous randomized trials evaluating the efficacy of bisphosphonates versus placebo in the treatment of bone metastases for various malignancies. The majority of the studies included subjects with any histologies, most commonly those with breast prostate multiple myeloma and lung cancer [21]. There are several randomized trials that have restricted their subjects to those with prostate cancer [22–25]. The Cochrane Collaboration has performed a systematic review of these randomized trials as it pertains to pain relief. When restricting the analysis to prostate-only studies, and pain relief at 12 weeks as the endpoint, the Cochrane group reported an odds ratio of 1.81 favoring bisphosphonate

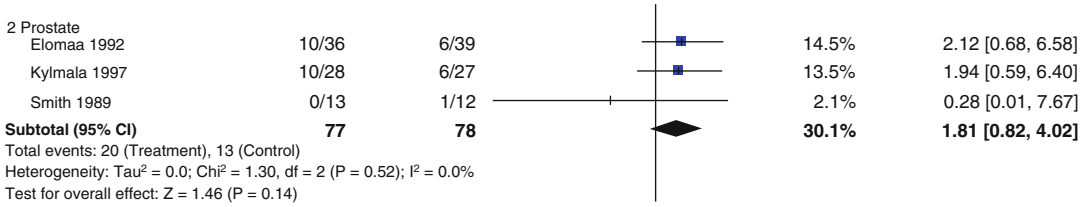

Fig. 5.2 Meta-analysis of bisphosphonates on alleviating prostate cancer bone pain. From Wong, R. and P.J. Wiffen, Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev, 2002(2): p. CD002068. Reprinted with permission from John Wiley and Sons

treatment over control. The 95 % confidence interval ranged from 0.82 to 4.02 (Fig. 5.2). Technically, this can be interpreted as not reaching "statistical significance." The conclusion of the reviewers as it specifically pertained to primary disease sites was that "The small numbers of studies meant conclusions could not be made regarding the relative effectiveness of bisphosphonates on patients with different primary disease sites." Overall, however, in pooled analyses of all disease sites, the number needed to treat to achieve pain relief with bisphosphonates at 4 weeks was 11 and at 12 weeks 7 [21]. A more detailed overview of bisphosphonates in the treatment of bone metastases will be addressed elsewhere in this book.

Role of External Beam Radiation Therapy

Randomized trials of treatment with conventional radiotherapy have shown complete pain relief rates ranging from 15 to 54 %, and partial pain relief rates ranging from 28 to 89 % for persons with bone metastases [26–38]. These trials did not restrict subjects to those with prostate cancer, although breast and prostate patients accounted for the majority of subjects. The Bone Pain Trial Working Party Group showed a median time to pain relief in all patients of approximately 1 month, and a median time to complete pain response of 3–4 months, whereas median time to first increase in pain was approximately 12 months or longer [26]. Stereotactic body radiotherapy (SBRT) is an emerging treatment modality delivering five or fewer highly conformal, high-dose radiation treatments to bone metastases. Early outcomes claim superior pain relief and control over conventionally fractionated radiations, but randomized trials are currently ongoing. A complete overview of radiotherapy as it applies to the treatment and efficacy of bone metastases is discussed in the chapter on radiotherapy elsewhere in this book.

Role of Parenteral Radionuclides

Radionuclides can be used in patients with widespread prostate cancer bone metastases where focal therapies such as surgery or radiation will not be expected to palliate the symptoms. Radionuclide therapy is generally aimed at persons with osteoblastic or mixed-type lesions, as the mechanisms of action are particularly targeted to blastic/sclerotic processes. The isotopes currently in use are strontium-89, samarium-153, and more recently radium-223. Both radium and strontium are in the same column of the periodic table of the elements as calcium, and therefore act as calcium mimetics. They emit beta-particles which exert their tumoricidal properties. As such, they intercalate into bone where calcium would otherwise be deposited and effectively act as very targeted radiotherapies. Likewise, samarium-153 is a chelated tetraphosphonian compound that selectively accumulates in places of bone transformation by binding to hydroxyapatite.

Strontium-89 and Samarium-153

Two systematic reviews evaluating the role of strontium or samarium for the palliation of painful bone metastases have been completed [39, 40]. In the most complete and contemporary review by the Cochrane Collaboration, the conclusion

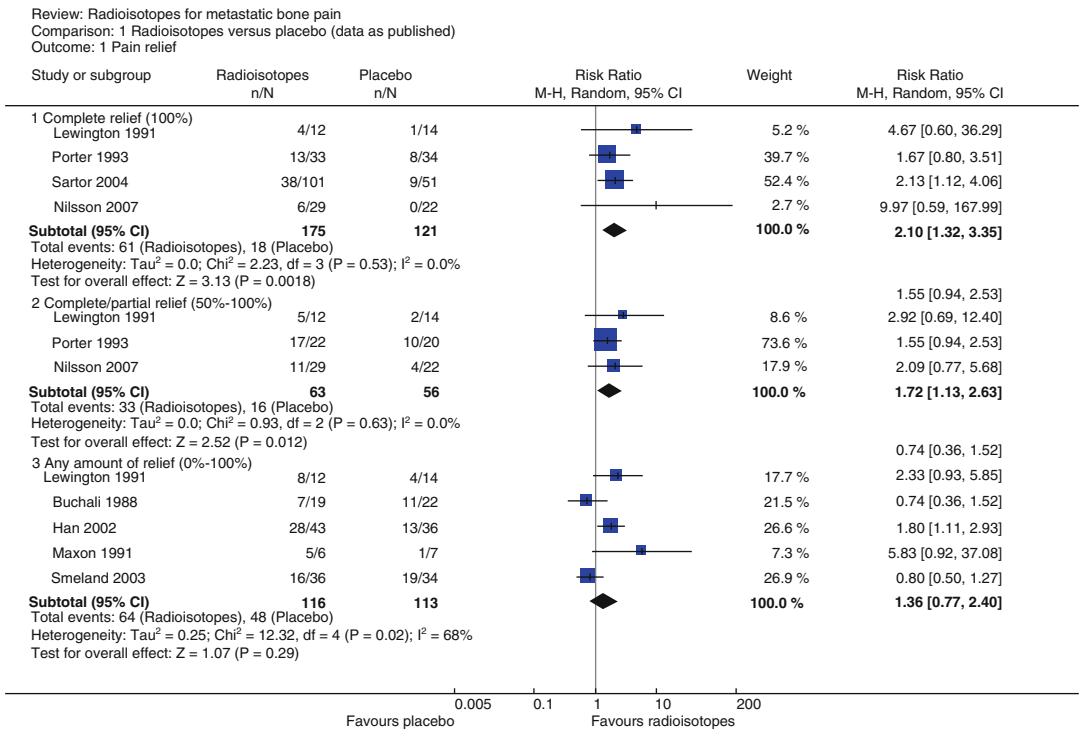

Fig. 5.3 Beta-emitting radionuclides for bone pain meta-analysis. From Roque, I.F.M., et al., Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev, 2011(7): p. Cd003347. Reprinted with permission from John Wiley and Sons

was that there was a "small benefit" of these isotopes in providing "complete" or "complete/partial" pain relief over 1–6 months (NNT = 5 and 4, respectively). Nevertheless, the review also reported that there was "no conclusive evidence to demonstrate that radioisotopes modify the use of analgesia with respect to placebo" (hazard ratio 1.36 favoring isotopes, 95 % CI 0.77–2.40) (Fig. 5.3). Furthermore, radioisotopes did not reduce the risk of spinal cord compression (HR = 1.10, 95 % CI 0.39–3.07) [40]. Neither strontium nor samarium treatment has been shown to impact overall survival.

Radium-223

Recently, radium-223 has been FDA approved for the treatment of prostate cancer bone metastases in men with castration-resistant disease. Radium-223 is an alpha particle emitter, which means that it will selectively destroy cells within only a few cell diameters (less than 100 μm) of where it is intercalated into bone as a calcium mimetic. This short path of the alpha particles results in a minimization of toxic effects to the bone marrow and adjacent healthy tissues. The landmark ALSYMPCA trial (Alpharadin in Symptomatic Prostate Cancer Patients) is a phase 3, randomized, double-bind, placebo-controlled trial with mature results [41]. Unlike other parenteral radioisotopes, the use of radium-223 showed a significant overall survival benefit in men with castration resistant prostate cancer (HR = 0.7, 95 % CI 0.58–0.83; median survival 14.9 months versus 11.3 for placebo). Secondary endpoints of the study all significantly favored radium-223 including time to first symptomatic skeletal event (HR 0.66, 95 % CI 0.52–0.83—median time 15.6 months versus 9.8 months placebo); and time to increase in PSA level (HR 0.64, 95 % CI 0.54–0.77—median time 3.6 months versus 3.4 months

placebo). Most notably, there were *fewer* adverse events in the radium-223 cohort than the placebo group. Given the overall survival benefit, decrease in SREs, and low side effect profile of radium-223, there is much excitement within the oncologic community about using this therapy in combination with other therapies such as chemotherapy, newer generation androgen deprivation therapy agents, and focal radiotherapies in men with metastatic prostate cancer.

Role of Androgen Deprivation Therapy

The 1966 Nobel Prize for Physiology or Medicine was awarded to Charles Huggins for the discovery that androgen ablation therapy causes regression of primary and metastatic prostate cancer [42]. The production of serum testosterone is primarily controlled by the hypothalamus via its production of luteinizing hormone-releasing hormone (LHRH) which acts on the anterior pituitary gland to release luteinizing hormone (LH). Within the testicle the LH is recognized by the Leydig cells within the testes signaling the production of testosterone. This pathway accounts for about 90 % of the production of serum testosterone. The remaining 10 % is peripherally produced by adrenal steroid conversion into testosterone (Fig. 5.4). Numerous drugs have been developed that target various points along these pathways, which ultimately interfere with testosterone signaling within the cancer cell. These include LHRH agonists (leuprolide, goserelin, triptorelin), LHRH antagonists (degarelix acetate), nonsteroidal antiandrogens that bind the androgen receptor (bicalutamide, flutamide, enzalutamide), and 17 α-hydroxylase/C17,20 lyase inhibitors (abiraterone). In men with metastatic disease, initial androgen deprivation therapy results in a median progression-free survival of 12–33 months [43, 44]. However, one can use the serum PSA value after initiation of ADT to prognosticate life expectancy. The Southwest Oncology Group (SWOG) performed a randomized trial evaluating the effect of immediate and continuous androgen deprivation therapy versus intermittent androgen deprivation for men with metastatic prostate cancer. All men in this trial had 7 months of induction ADT. The median survival was 13 months for patients with a PSA of more than 4 ng/ml after induction therapy, 44 months for patients with a PSA of more than 0.2–4 ng/ml or less, and 75 months for patients with PSA of 0.2 ng/ml or less [45]. In subjects with bone pain enrolled on the trial, there was a trend towards improved overall survival for continuous androgen deprivation therapy, but overall the results of for non-inferiority of intermittent versus continuous ADT were inconclusive for the trial [46].

Role of Surgical Therapy

Surgery for prostate cancer bone metastases is indicated to prevent or stabilize pathologic fractures, decompress spinal cord or nerve root compression, and palliate pain if other modalities fail to do so. The details of surgical management and indications will be addressed elsewhere in this textbook.

Role of Chemotherapy for Bone Metastasis

Chemotherapy for metastatic prostate cancer is generally reserved for the treatment of prostate cancer in symptomatic men who are no longer responding to therapies directed at disruption of androgen signaling (sometimes referred to as "castration resistant" or "androgen insensitive"). Contemporary agents routinely used include mitoxantrone, docetaxel, and cabazitaxel. One randomized trial assessed pain response in men with androgen-insensitive prostate cancer randomized to mitoxantrone plus prednisone versus prednisone alone. Those receiving mitoxantrone had a better palliative response (29 % versus 12 %), and the duration of palliation was longer in the chemotherapy group (43 weeks versus 18) [47]. In another randomized trial, mitoxantrone was randomized against cabazitaxel and although cabazitaxel did have a survival advantage over mitoxantrone, the palliation benefits were similar between the two drugs [48].

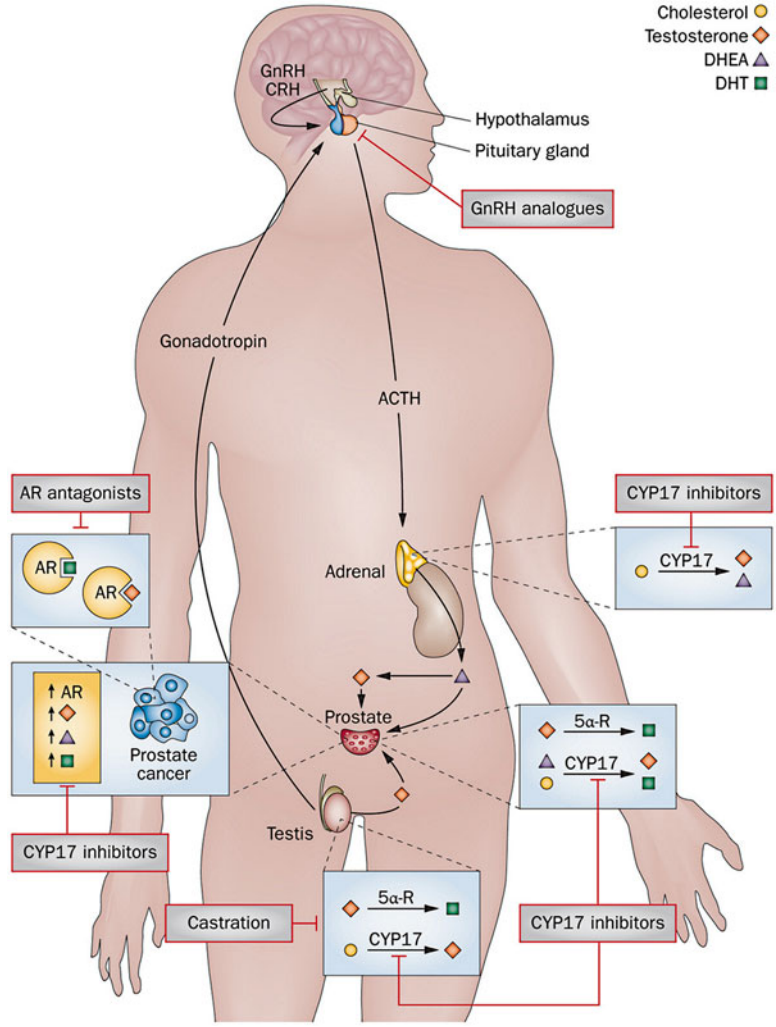

Fig. 5.4 The androgen axis and its targets. From Yin L, Hu Q. CYP17 inhibitors—abiraterone, C17,20-lyase inhibitors and multi-targeting agents. Nat Rev Urol. 2014 Jan;11(1):32–42. Reprinted by permission from Macmillan Publishers Ltd. Copyright 2014

Conclusion

Because prostate cancer bone metastases are common, much is known about its prognosis and treatment. Because the disease is sensitive to hormone manipulation, radiation, chemotherapeutic, and surgical therapies, it serves as an excellent model system for research. It is one of the only cancers where treatment of the bone metastases specifically has resulted in a survival benefit for the patients [41]. Ongoing prospective studies are investigating whether treatment of oligometastatic bone-only disease will result in potential cure or survival benefit. Furthermore, interventional ablative therapies are also emerging as a possible treatment of prostate bone metastases. Because skeletal-related events (SREs) are an important source of morbidity and decreased quality of life for prostate cancer patients, frequent surveillance and treatments to prevent progression of metastatic bone disease are the care standard.

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Lung

6

Shamus R. Carr

Introduction

Lung cancer is the second most common cancer in both men and women [1]. It was estimated to account for 224,210 cases in 2014 in the USA with the majority of patients at a non-operative advanced stage for the primary tumor. Estimates between 30 and 40 % of patients are initially found to be stage 4, with nearly 40 % of these patients with bone metastases [2]. Bone metastases are more common with non-small-cell lung cancer (NSCLC) and then with small-cell lung cancer (SCLC).

Patients, in general, with widely metastatic disease have no current curative options of the primary tumor. However some have reported improved survival in a hyper-select group of stage 4 patients that undergo surgery on both the primary tumor and the metastatic site [3, 4]. This is the exception and not the rule and these patients should be evaluated, managed, and treated on protocol. Management and treatment of the vast majority of patients with stage 4 disease are focused upon palliation of symptoms. These treatments include radiation to brain metastasis, radiation to bone metastasis for pain palliation, cytotoxic chemotherapy, or more recently target therapies towards mutations that are carried by the primary lung cancer. These targeted therapies have ushered in an era of tumor genotyping that has resulted in therapeutic decision making for lung cancer patients.

These mutations are oncogenic drivers and are detected in 64 % of patients with adenocarcinoma [5]. They are rarely detected in squamous cell carcinomas. The most common is the *KRAS* driver. However, there are multiple other ones: *EGFR, ALK* rearrangements*, BRAF, PIK3CA, MEK1, MET* amplification, *and HER2* (now *ERBB2*). These alterations are usually single mutations, but there are a small percentage of patients with mutations that carry oncogenic drivers in two genes. Other than *KRAS*, these genomic alterations are found in between 1 and 21 % of tumors (Fig. 6.1).

Work-Up

The work-up of patients is dependent on when the diagnosis of lung cancer is made. If a patient is found to have a nodule or mass in the lung by chest radiograph or CT scan, then this can be worked up appropriately in a multidisciplinary format with input from a dedicated thoracic surgeon. This scenario and the accompanying complete work-up are beyond the scope of this chapter and are readily found in both thoracic surgery and pulmonary medicine textbooks.

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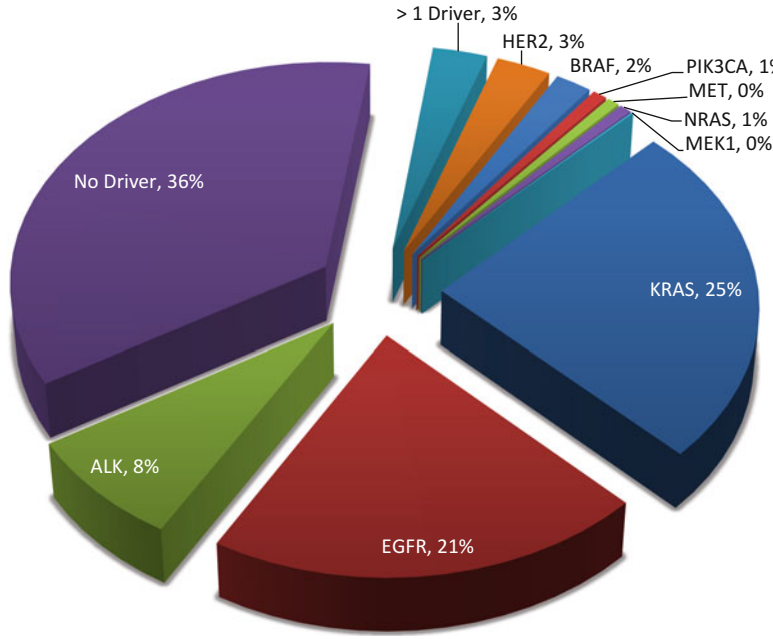

Fig. 6.1 Frequency of oncogenic drivers detected. Data from Kris et al. [5]

It should be noted that a standard part of the work-up is a positron emission tomography (PET) scan. This test has excellent sensitivity and specificity in determining if a patient is stage 4 [6]. If a patient is found with stage 4 disease, then a non-bone site that can be biopsied in the least invasive fashion in the most reliable way of obtaining adequate tissue is determined. This point, not performing a biopsy of a bone lesion, is critical as the processing of bone biopsies by pathology renders the tissue inadequate for mutational analysis. Other than bone, all other sites of disease show equal efficacy for determination of the presence of oncogenic drivers [7]. Once tissue is obtained, it should be processed in the standard fashion along with immunohistochemistry to confirm that the tumor is of lung origin and that it is an adenocarcinoma. Once this is done, testing for oncogenic divers should be mandatory. Currently, only adenocarcinomas undergo testing for oncogenic drivers, but early data demonstrates that a small percentage of squamous cell lung cancers do contain targetable oncogenic drivers [8].

There is variety in individual institutional practices on when testing for oncogenic drivers should be performed. Some institutions do not currently recommend testing for every lung cancer specimen. Other institutions routinely test all lung cancer cases regardless of stage. Others perform this testing only at the request of a treating physician. Despite these institutional practices most oncologists uniformly recommend it for all advanced-stage lung cancer patients and then will not proceed with chemotherapy until the results of these tests are available [9].

The other scenario that occurs commonly is when the diagnosis of lung cancer is returned on a bone biopsy that is obtained during open treatment of a fracture. In these scenarios the patient should be immediately referred to a medical oncologist for further evaluation and work-up. The reason for this referral is as stated above regarding the processing by pathology of the specimen obtained during the fracture surgery makes it unusable for mutation analysis testing. As part of this referral, an oncologist will obtain a PET scan and MRI of the brain to complete staging and determine the extent of disease. They will then coordinate a biopsy to obtain enough tissue for mutational analysis. Normally, an endobronchial ultrasound and biopsy of a medi-

astinal lymph node will be all that is required to obtain enough tissue for appropriate analysis. However, there are times when a biopsy of the primary tumor is required. This can be done under image guidance with a core needle biopsy; rarely is a thoracoscopic approach required to obtain tissue.

Endobronchial ultrasound is routinely done by both pulmonologists and thoracic surgeons and is an outpatient procedure. Other options to biopsy lymph nodes include mediastinoscopy, which is generally only performed by a thoracic surgeon. This procedure is performed as an outpatient and is considered safe [10]. The advantage that it may have over endobronchial ultrasound is that more tissue is obtained for pathological testing. Discussion with pathology and the treating medical oncologist can be beneficial to determine how much tissue is required and what procedure can provide enough tissue in the safest manner for the patient.

Prognosis

Identifying mutations and drug development has redefined both how we describe the disease and treat the patient. There are currently 11 oncological drugs that are approved for other indications that target 7 of the oncological drivers found in lung cancer. Both the number of drugs and the targets are expected to increase in the coming years.

There are two interesting findings that are being seen with patients that have oncogenic drivers identified. One deals with the survival of these patients compared to those that do not have oncogenic drivers. The other deals with survival based upon appropriate targeted therapy in those with oncogenic drivers. In patients with an oncogenic driver not treated with a targeted therapy who are compared to those with no identifiable oncogenic driver, there is an increase of median overall survival of 6 months. In all patients with an identified oncogenic driver, those treated with an appropriate targeted therapy have a median survival 12 months longer than similar patients who did not receive an appropriate targeted therapy [5]. Thus, patients undergoing appropriate targeted therapy for an oncogenic driver that is identified in their tumor have an increase in median overall survival over those that do not have an oncogenic driver of nearly 18 months.

One major issue that occurs with nearly all targeted therapies is that, over time, the tumor either secondarily mutates or develops an acquired resistance to the drug. This, in general, occurs within 2 years after starting the drug, regardless of the drug or the mutation [11]. Once this occurs, the patients again begin to experience progression of their disease. Attempts to change to newer drugs, that also target the identifiable oncogenic driver, have been studied with some positive results [12]. Others have tried combining cytotoxic drugs with targeted therapies after failure of first-line chemotherapy [13]. These studies with wild-type tumors do not show a benefit to adding a targeted therapy when an oncogenic driver was not identified.

Still others have tried using cytotoxic chemotherapy once the tumor develops resistance and then retrying the original targeted chemotherapy that the patient was previously taking after completion of a number of cycles of cytotoxic chemotherapy [14]. This management plan is known as a second-line therapy or regiment. Unfortunately, results using second-line therapies are diminished when compared to results of primary therapy.

A new frontier that is just starting to be investigated for advanced-stage lung cancer is the use of immunotherapies. Drugs such as ipilimumab and PD-1 ligand are being utilized and investigated in patients with non-small-cell lung cancer [15, 16]. While these drugs have shown promise in early studies in the non-small-cell lung cancer setting, further studies are warranted. An increasing number of trials nationally and internationally using combination of standard and targeted therapies with or without immunotherapies in appropriate patients are under way.

In patients where no oncogenic driver is identified, or in cases where there are no current drugs available, standard cytotoxic chemotherapy is the standard. Most commonly a platinum-based chemotherapy doublet is utilized. However, what is

paired with it varies and some appear to show better progression-free and overall survival than others [17]. Despite which doublet is utilized, in general, the median overall survival remains about 12 months or less for patients with advanced-stage non-small-cell lung cancer without an identifiable oncogenic driver.

Conclusions

Lung cancer commonly metastasizes to the bone. Once this occurs, general treatment options are limited to chemotherapies or radiation for palliation of symptoms. The two major options for chemotherapy are either standard cytotoxic agents or targeted therapies against identified oncogenic drivers. Attempts to identify an oncogenic driver should be mandatory for all advanced-stage adenocarcinoma lung cancer patients, regardless of sex, race, or smoking history. If multiplex testing is not available, then epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitor should be prioritized over other molecular testing [9]. This requires an adequate tissue biopsy from a site other than bone, due to how the tissue is processed, to be able to do next-generational sequencing to look for mutations that act as an oncogenic driver. Targeted therapies have shown promise in extending survival when used in only those patients that have identified oncogenic drivers. However, the effect is not permanent and eventually the tumor becomes resistance to the drug. Newer generational drugs, further identification and the role of oncogenic drivers, and use of immunotherapies provide hope in the treatment of an otherwise uniformly fatal disease.

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Kidney Metastatic Bone Disease

7

Patrik Luzny and Christopher Dechet

Introduction

Kidney cancer is one of the top ten newly diagnosed forms of cancer. According to data published by the American Cancer Society, an estimated 63,920 new cases of kidney cancer, representing 3.8 % of all new cancer cases, will be diagnosed in 2014 leading to estimated 13,860 deaths (2.4 % of all cancer deaths). Males appear to be affected by kidney cancer more commonly than females (1.58:1) and are also more likely to die from the disease (1.79:1). The median age at the time of diagnosis is currently 64 and the average 5-year relative survival is 73.5 %. Survival rates continue to improve and remain significantly higher than 52.1 % noted in 1975 [1]. Unfortunately, at the time of diagnosis, approximately one third of the newly diagnosed cases have evidence of local or distal metastases. Additionally, 20–40 % patients who are treated surgically for clinically localized renal cell carcinoma will develop metastases. Despite advances in immunotherapy and molecular targeted therapies, the nonsurgical response rates in patients with metastatic disease remain quite low at 15–25 % [2]. Renal cell tumors are known to be poorly responsive to radiation treatments as well as conventional chemotherapies mostly due to the expression of multidrug resistance (MDR) proteins, making surgical management of the primary tumor and selected metastatic tumors the mainstay in the treatment of kidney cancer.

The first nephrectomy was performed in 1869 by Gustav Simon and by 1900, more than 300 nephrectomies (mostly for benign indications) were performed annually in Europe and the USA combined [3]. Open nephrectomy remained the standard surgical approach to kidney tumors for the following 100 years. While the first partial (nephron sparing) nephrectomy was performed by Simon in 1870 as well, its use in the treatment of kidney cancer did not become widely utilized until the 1980s. Within the last decade, partial nephrectomy has become the standard surgical approach, accounting for nearly one half of all kidney tumor surgeries. This can be explained by advancements in imaging techniques as well as more frequent use of CT and MR imaging that has led to the earlier diagnosis of smaller, asymptomatic tumors that are confined to the kidney and amendable to treatment with partial nephrectomy. This trend toward earlier detection is also

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reflected in the declining death rates from kidney cancer by 0.6 % per year over the last decade seen in the SEER data. However, the incidence of renal cell carcinomas has been rising at a rate of 3 % since the 1970s, possibly due to a similar increase in prevalence of obesity, a recognized risk factor for RCC [4]. Unfortunately, despite trends toward earlier detection and advancements of surgical techniques as well as immunotherapy, the mortality rates remain high for patients with metastatic disease.

Classification and Staging

Advancements in the fields of histopathology, genetics, and molecular biology have revealed that renal cell carcinoma is not a single entity, rather a collection of several histopathologically different neoplasms arising from different types of epithelial cells of the renal tubules and displaying different genetic abnormalities. The Heidelberg Classification System of renal tumors was proposed in 1996. Its classification of malignant renal cell tumors divides tumors into five distinct groups [5]. Continuous improvement in the field of molecular genetics is reflected in the 2004 World Health Organization (WHO) classification of renal neoplasms, which now contains 10 malignant renal cell tumor subtypes [6].

1. Clear cell (conventional) renal cell carcinoma is the most common subtype of RCC representing 70–80 % of all renal cell carcinomas [7]. Clear cell RCC tumors are typically yellow, unilateral (96–98 % cases), unicentric (multicentricity occurs in 10–20 % cases and is usually associated with familial forms of RCC), and grossly vascular. They originate from the epithelial cells of the proximal convoluted tubules. This type of RCC owes its name to the microscopic appearance of the tumor cells. Abundant cytoplasm of these cells is rich in lipid compounds that are removed by solvents used during the histologic preparations, leaving clear appearing cytoplasm. There are several genetic abnormalities associated with clear cell RCC. Arguably the most studied one is the VHL gene dysfunction due to mutation, hypermethylation, or loss of the entire short arm of chromosome 3 (VHL gene is located on 3p25-26). Several gene products of the VHL / hypoxemia inducible factor pathway have become targets of novel pharmaceutical agents. Other genetic defects include gain of chromosome 5q and a loss of chromosome 8p, 9p, or 14q. While the overall prognosis is slightly worse for clear cell RCC compared to chromophobe or papillary subtypes, several steps starting with the loss of VHL function and subsequent dysregulation of normal cell processes have been identified as targets for new types of targeted therapies making clear cell RCC now more responsive to adjuvant therapy. Consequently, patients with advanced clear cell RCC currently have a better prognosis compared to other RCC types presenting at an advanced stage.
2. Papillary renal cell carcinoma is the second most common histologic RCC subtype accounting for 10–15 % of all renal cell carcinomas. Unlike clear cell RCC, papillary RCC is frequently associated with end stage renal disease and acquired renal cystic disease. Furthermore, papillary RCC is frequently (up to 40 %) multifocal, making partial nephrectomy a more desirable surgical approach. There are 2 subtypes of papillary RCC that are associated with a unique familial syndrome and genetic abnormalities. Type I is the most common with characteristic mutations in the *c-MET* proto-oncogene. Type II is more aggressive and frequently seen with hereditary leiomyomatosis associated with disruptions of the fumarate hydratase gene. Genetic abnormalities in sporadic cases of papillary RCC include trisomy 7 and 17 as well as loss of the Y chromosome. VHL mutations are quite rare. Several studies have shown a better cancer specific survival rate for the papillary subtype compared to clear cell when adjusted for stage [7, 8].
3. Chromophobe renal cell carcinoma accounts for 3–5 % of all RCC. Unlike papillary and clear cell RCC, the chromophobe RCC tumors originate from the epithelial cells of

the medullary portion of the collecting duct. Chromophobe RCC cells have a characteristic perinuclear halo due to the presence of many microvesicles that stain positive with Hale colloidal iron. Most chromophobe tumors show hypodiploidy with complete loss of chromosomes 1, 2, 6, 10, 13, 17, and 21. With the exception of those with metastatic disease, patients with the chromophobe subtype have the best prognosis of all RCC, with cancer specific survival approaching 100 % at 10 years with surgically treated pT1 tumors [8].

4. Collecting duct carcinoma and medullary carcinoma of the kidney are both rare forms of RCC accounting for <1 % of all RCCs. Under the WHO classification, renal medullary carcinoma represents a separate entity while previous classifications have considered it a form of collecting duct carcinoma. It affects almost exclusively African-American adults with sickle cell trait. Unfortunately, patients are usually diagnosed with metastases and the mean survival from diagnosis is 17 months [9]. Collecting duct carcinoma is also an aggressive subtype of RCC affecting younger patients and frequently (up to 40 %) presenting with metastases at the time of diagnosis. Prognosis is poor with a median survival of 11 months [10].
5. Unclassified renal cell carcinoma represents 1–3 % of RCCs not clearly matching any of the previously listed subtypes. In general, these represent higher grade tumors poorly responsive to treatment, and, consequently, unfavorable prognosis with median survival of 36 months [11].

Sarcomatoid transformation can be seen with all subtypes of RCC and carries a significantly worse prognosis. It has been reported in up to 9 % of chromophobe RCC, 8 % of clear cell RCC, and 3–5 % of papillary RCC tumors [8].

In addition to staging, tumor grading is also important in predicting the clinical course of RCC. The Fuhrman grade assigns a nuclear grade 1–4 in order of increasing nuclear size, irregularity, and nucleolar prominence. Several studies have identified the Fuhrman grade as an independent prognostic factor for papillary and in particular, clear cell RCC [7, 8, 12]. The latest TNM staging scheme for RCC as published in Seventh Edition of the AJJC Cancer Staging Manual is outlined in Table 7.1.

Table 7.1 AJCC staging of renal cancers

Primary tumor (T)			
TX: Primary tumor cannot be assessed			
T0: No evidence of primary tumor			
T1: Tumor ≤7 cm in greatest dimension, limited to the kidney			
T1a: Tumor ≤4 cm in greatest dimension, limited to the kidney			
T1b: Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney			
T2: Tumor >7 cm in greatest dimension, limited to the kidney			
T2a: Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney			
T2b: Tumor >10 cm, limited to the kidney			
T3: Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia			
T3a: Tumors spreads into renal vein or its muscles or perirenal and/or renal sinus fat, but not beyond Gerota's fascia			
T3b: Tumor extends into vena cava below the diaphragm			
T3c: Tumor extends into the vena cava above the diaphragm or invades the wall of vena cava			
T4: Tumor invades beyond Gerota's fascia and extends into the contiguous adrenal gland			
Regional lymph nodes (N)			
NX: Regional lymph nodes cannot be assessed			
N0: No regional lymph node metastasis			
N1: Metastasis to regional lymph nodes			
Distant metastasis (M)			
M0: No distant metastasis			
M1: Distant metastasis			
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1–T2	N1	M0
T3	N0–N1	M0	
Stage IV	T4	Any N	M0
Any T	Any N	M1	

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Biology of RCC, Targeted Therapy, and Immunotherapy

Renal cell carcinoma tumors are significantly different with respect to their cell type origin, type of genetic mutation, and in turn, responsiveness to different modes of therapy and clinical course. Four hereditary forms of RCC have been identified with specific genetic components: Birt-Hogg-Dube (*BHD1* aka *Folliculin* gene), familial leiomyomatosis and RCC (fumarate hydratase gene), hereditary papillary RCC (*c-MET* proto-oncogene), and von Hippel–Lindau (*VHL* gene). The role of *VHL* gene in RCC has been studied extensively and has resulted in the identification of several new targets for molecular therapies.

Von Hippel–Lindau disease was first described in the medical literature in 1894 in a report describing two siblings with abnormal, bilateral vascular retinal growths [13]. Eugene von Hippel described similar blood vessel tumors in members of one family in 1904 [14]. Arvid Lindau, a Swedish pathologist, described the presence of vascular tumors within the CNS associated with retinal tumors [15]. Since then, additional tumors have been described in the setting of VHL disease, namely clear cell renal cell carcinomas, pheochromocytomas, and pancreatic tumors of the islet cells. Approximately 50 % of patients with VHL disease will develop RCC, commonly after the third decade of life. Elegant genetic mapping studies performed on DNA of von Hippel–Lindau disease patients led to localization of the *VHL* gene to the short arm of chromosome 3 in 1988 by Seizinger et al. [16]. Analyses of DNA from RCC tumors of patients without VHL disease showed that 33–66 % of sporadic RCC tumors, predominantly clear cell RCC, contain the *VHL* mutation [17, 18]. The VHL tumor suppressor, VHL protein (pVHL), has been identified as a regulator of hypoxia-inducible genes based on observation that cells lacking pVHL have abnormally high amounts of hypoxia-inducible mRNA in the presence of normal oxygen levels [19]. It is an indirect regulation by a protein complex containing pVHL that marks hypoxia inducible factor (HIF) with ubiquitin for destruction by proteasomes. Absent or nonfunctional pVHL then leads to over-accumulation of HIF which, in turn, greatly increases transcription of HIF target genes including genes coding for various growth factors [20]. Additionally, HIF has been implemented in facilitating metastatic process through upregulation of the transcription factor TWIST, a master regulator of gastrulation and mesoderm-specification implicated in metastasis of hepatocellular carcinomas [21] as well as downregulation of intercellular adhesion molecules (integrins, E-cadherin) and upregulation of matrix metalloproteinases (MMP2, MMP9) [22]. Understanding of these pathways was crucial for the development of targeted therapy.

As of 2014, there are seven FDA-approved drugs for use in mRCC utilizing four different mechanisms of action. Bevacizumab (Avastin) is a IgG_1 monoclonal antibody able to recognize and bind circulating extracellular vascular endothelial growth factor (VEGF) molecules and thus preventing them from binding to the VEGF receptor on endothelial cells and pericytes. Activation of VEGF receptors initiates a signaling cascade leading to angiogenesis necessary to support tumor cells growth. Axitinib (Inlyta) and Pazopanib (Votrient) are both kinase inhibitors effective against tyrosine kinases associated with VEGF receptors. Sunitinib (Sutent) and Sorafenib (Nexavar) are also kinase inhibitors, but unlike Axitinib and Pazopanib, they have activity against intracellular kinase Raf-1 in addition to activity against tyrosine kinases associated with VEGF and platelet derived growth factor (PDGF) receptors [23]. Temsirolimus (Torisel) and Everolimus (Afinitor) are inhibitors of the mammalian target of rapamycin (mTOR), a kinase involved in regulation of cell proliferation, survival, and transcription of HIF [24]. In general, targeted therapies are well tolerated with relatively mild side-effects: rashes, hypertension, hand/foot syndrome, and diarrhea [25]. Summary of the seven currently available and FDA approved agents for targeted therapy in mRCC and their performance in initial trials can be found in Table 7.2. Figure 7.1 shows the molecular targets of targeted therapy.

Immunotherapy with cytokines interferon-α and interleukin-2 has been utilized in the treatment

Table 7.2 Comparison of targeted therapy agents' performances in clinical trials

Agent	Type	Line of therapy	Route	FDA approved	Study	Results	Results 2	Notes
Sunitinib Sutent	TKI (VEGFR and PDGFR)	1st	PO	January 2006	Sunitinib vs. IFN	mPFS (mo) 11 vs. 5 [58]	OS (mo) 26.4 vs. 21.8 [58]	
					Sunitinib vs. Pazopanib	Pazopanib noninferior HR 1.05 (95 % CI 0.9–1.22) [59]		QOL and safety better with Pazopanib
					Sunitinib vs. Pazopanib	70 % Patients preferred Pazopanib [60]		Double blind crossover study
Sorafenib Nexavar	TKI (VEGFR and PDGFR)	2nd	PO	December 2005	Sorafenib vs. placebo	mPFS (mo) 17.8(17.8) vs. 15.2(14.3) $P=0.146(0.029)$ [61]		() After censoring post-cross over placebo survival data
					Sorafinib vs. Axinitib	See under Axinitib		
Pazopanib Votrient	TKI (VEGFR)	1st	PO	October 2009	Pazopanib vs. placebo	mPFS (mo) 9.2 vs. 4.2 [62] (HR 0.46, $P<0.001$)		
					Pazopanib vs. Sunitinib	See under Sunitinib		
Axitinib Inlyta	TKI (VEGFR)	2nd	PO	January 2012	Axinitib vs. Sorafenib	mPFS (mo) 6.7 vs. 4.7 [63]		
					Axinitib vs. Sorafenib	mPFS (mo) 8.3 vs. 5.7 (HR 0.656, 95 % CI 0.55–0.78) [64]	OS (mo) 20.1 vs. 19.2 (HR 0.969, 95 % CI 0.8–1.174) [64]	
					Axinitib vs. Sorafenib	mPFS (mo) 13.7 vs. 6.6 [65]		ECOG score 0
						mPFS (mo) 6.5 vs. 6.4 [65]		ECOG score 1
Temsirolimus Torisel	mTOR inhibitor	1st	IV	May 2007	Temsirolimus vs. IFNα	mPFS (mo) 5.5 vs. 3.1 (HR 0.66, 95 % CI 0.53–0.81) [66]	OS (mo) 10.9 vs. 7.3 (HR 0.73, 95 % CI 0.58–0.92) [66]	
Everolimus Afinitor	mTOR inhibitor	2nd	PO	March 2009	Everolimus vs. placebo	mPFS (mo) 4.0 vs. 1.9 [67]		FDA approved for use after failure of Sunitinib or Sorafenib
Bevacizumab Avastin	Monoclonal antibody to VEGF	1st	IV	July 2009	Bevacizumab + IFN vs. IFN	mPFS (mo) 10.2 vs. 5.4 [68]	OS (mo) 22.9 vs. 20.6 [68]	FDA approved only for use in combination with IFNα-2a
					Bevacizumab + IFN vs. IFN	mPFS (mo) 8.5 vs. 5.1 [34]	OS (mo) 18.3 vs. 17.4 [34]	

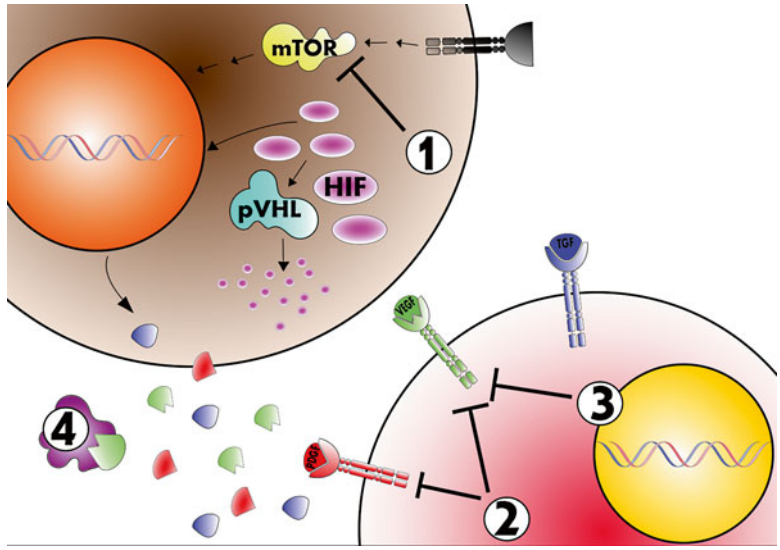

Fig. 7.1 Interaction between *RCC tumor cell* (*brown*) and *endothelial cell* (*red*). Temsirolimus and *Everolimus* (1) are inhibitors of the *mammalian target of Rapamycin* (*mTOR*) which is a part of the signaling cascade from *growth receptor* (*black*) leading to increased cell growth, motility, survival, and upregulation of *hypoxia-inducible factors* (HIF). *Von Hippel–Lindau tumor suppressor* (*pVHL*) degrades *HIF*. High levels of *HIF* increase secretion of *platelet derived growth factor* (*PDGF*), *vascular endothelial growth factor* (*VEGF*), and *tumor growth factor* (*TGF*). *Sunitinib* and *Sorafenib* (2) are receptor kinase inhibitors with activity against both vascular *endothelial growth factor receptors* (*VEGFR*, *green*) and *platelet derived growth factor receptors* (*PDGFR*, *red*). *Axitinib* and *Pazopanib* (3) are tyrosine kinase inhibitors with specific activity against *VEGFR*. Signaling from *PDGFR*, *VEGFR*, and *epidermal growth factor receptors* (*EGFR*, *blue*) increases growth and proliferation of endothelial cells as well as pericytes leading to increased tumor neovascularization. *Bevacizumab* (4) is a monoclonal antibody against VEGF-A and prevents it from binding to the *VEGFR*

of advanced RCC since their clinical trials in early 1980s. The exact mechanism of either of these agents is not fully understood. While IFN-α has some antiproliferative and direct antitumor properties [26], IL-2 has a wide-ranging stimulatory effect on the immune system including both T and B cells, monocytes, macrophages, and natural killer cells leading to tumor cell cytotoxicity [27].

Initial clinical trials of IL-2 showed response rates of over 30 %, but subsequent studies had lower response rates between 15 and 23 % [28, 29]. Most importantly, 7–9 % of patients treated with HD IL-2 had a durable complete response. Median duration of completed responses was not reached at the time of analysis, but have been estimated to be >80 months with 20 % patients surviving for 10 years following their treatment [28]. The efficacy of Il-2 appears to be dose-related as suggested by the results of a three arm trial with high IV dose, low IV dose, and SQ dose of IL-2 with response rates of 15, 10, and 8 %, respectively [30]. Unfortunately, IL-2 in high doses is very poorly tolerated and needs to be administered in an inpatient setting, preventing its wide spread use in all patients with mRCC despite its ability to induce a durable complete response. Such a response has not been seen with any targeted agent yet developed.

Until the advent of targeted therapy, IFN-α had been the agent of choice in the initial treatment of mRCC. Its response rates are generally lower (10–15 %) than those of IL-2 and durable complete responses are quite rare at less than 2 % [31, 32]. Unlike IL-2, IFN-α is relatively well tolerated and easily administered in the outpatient setting. Even though it has been shown to be inferior in terms of survival to the new mTOR and tyrosine kinase inhibitors in several comparative trials, it is still used in combination with VEGF monoclonal antibodies (Bevacizumab) [33, 34].

Prognostic Factors of Metastatic Renal Cell Carcinoma's Clinical Behavior

Renal cell carcinoma remains the deadliest of all genitourinary cancers. It is a complex disease with highly variable natural history and biological behavior. Approximately 30–40 % of newly diagnosed patients with RCC have evidence of metastatic disease. Additionally, 20–40 % of patients who initially presented with localized disease will develop metastases, frequently within 2 years. The majority of metastatic cases (up to 90 %) develop in the setting of clear cell RCC [35].

Prior to the advent of immunotherapy in early 1990s, the prognosis of patients with metastatic renal cell carcinoma (mRCC) was abysmal with a 10-year survival being virtually nonexistent. Introduction of high dose interleukin-2 therapy (FDA approved for treatment of advanced RCC in 1992) created a breakthrough in the management of advanced RCC. The overall response rates were between 21 and 23 % with durable complete responses seen in only 5–7 % of patients. Historically, the role of surgery in the form of either a cytoreductive nephrectomy or metastasectomy in this setting was purely palliative for cases of persistent hematuria, intractable pain, paraneoplastic manifestations, or constitutional symptoms. With the advent of immunotherapy, debulking of the primary tumor with cytoreductive nephrectomy has been shown to offer a survival benefit in a selected patient population and is now considered the standard of care [36]. However, high dose IL-2 therapy has a long list of specific toxicities related to hyperstimulation of the immune system ranging from relatively mild flu-like symptoms to life-threatening cardiovascular toxicities. These are similar to those seen in sepsis and septic shock [37]. There is a predominate vascular leak syndrome characterized by a widespread capillary leakage leading to a drop in systemic vascular resistance and intravascular volume. This can lead to a decrease in end-organ perfusion, renal insufficiency with oligouria and pulmonary edema [38]. Admission to an intensive care unit is common practice when administering IL-2.

The toxicities of high dose IL-2 treatment created a need for a prognostic model that would identify patients able to withstand the treatment and benefit from it based on clinical features of their disease. One such model was developed and published in 1999 from the Memorial Sloan-Kettering Cancer Center based on data obtained from 24 clinical trials totaling 670 patients with mRCC treated between 1975 and 1996. Multivariate analysis of numerous patient characteristics identified five pretreatment clinical features of mRCC associated with shorter survival: Karnofsky performance status <80 %, high serum lactate dehydrogenase (>1.5 times the upper limit of normal), low hemoglobin (below the lower limit of normal), elevated corrected plasma calcium levels (>10 mg/dl), and absence of prior nephrectomy. The mean overall survival was found to correlate strongly with the number of adverse prognostic factors [39]. The MSKCC model was later found to be predictive of survival in a dataset of 353 patients from Cleveland Clinic [40] and remains widely used in clinical practice today, helping to guide clinical decisions in the treatment of mRCC patients.

Metastatic lesions are quite common in RCC. Immunotherapy and chemotherapy has historically had only limited response rates, which has led to investigations into the role of metastasectomy in the treatment of mRCC. Kavolius et al. focused on the identification of disease features predictive of a post-metastasectomy clinical response. Their retrospective cohort study of 278 patients with recurrent and/or metastatic disease treated at MSKCC with metastasectomy between 1980 and 1993 included patients with both solitary and multiple lesions. Lung was found to be the most common metastatic site (57 %), followed by bone (19 %), lymph nodes (11 %), and brain (8 %). Significantly improved 5-year survival was associated with complete resections (44 %) compared to incomplete resection (14 %) and nonsurgical management (11 %). Disease free interval (DFI) >12 months, solitary site of

recurrence, and age <60 years were found to be predictive of improved survival [41].

A retrospective review of 297 mRCC patients treated at UCLA between 1989 and 2000 determined that the number of metastatic sites rather that their location predicts overall survival of patients with node-negative mRCC. Pulmonary metastases only were found in 120 patients, 33 patients had bone only involvement, and 144 had multi-organ involvement. The median survival was the same at 27 months for the lung and bone only mRCC patients compared to 11 months for multi-site metastases. Nephrectomy was shown to improve the median survival in all groups: 31 months for the lung and bone only groups, 13 months for the multiple organs group. Multivariate analyses have shown that metastases to multiple organs are associated with a poor prognosis (2.05 risk ratio, $P<0.01$) [42].

Evidence of osseous metastatic lesions has been reported in 15–34 % of all cases of mRCC [43, 44], with only the lung being a more frequently involved organ. A retrospective study by Toyoda et al. focused on survival and prognostic factors in patients with RRC metastatic to bone. Fifty patients with osseous mRCC (18 with synchronous, 32 with asynchronous metastases) were treated in a single institution between 1980 and 2004. Forty three patients underwent nephrectomy and 29 patients had osseous as well as extraosseous metastases. Median survival was 12 months and 2-year overall survival was 37 %. A longer period (>24 months) between diagnosis of RCC and the development of bone metastases and the absence of extraosseous metastases were identified as predictors of longer survival on multivariate analysis (5 months vs. 30 months) [45].

Advancements in the fields of molecular biology and genetics continue to improve our understanding of the processes leading to development and spread of RCC. New molecular tumor markers are being currently investigated and likely will improve our current predictive models for survival and response to therapy in the era of targeted therapies against components of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and mammalian target of rapamycin (mTOR) signaling pathways.

Impact of Surgery on Clinical Behavior of Metastatic Renal Cell Carcinoma

The first reported case of concurrent nephrectomy and resection of a solitary metastasis in the lung was performed and published by Barney and Churchill in 1939. The surgery proved to be a success and the patient died of cardiovascular disease 23 years later [46]. While most patients do not achieve such results, the role of surgery as a part of a multimodal approach to treatment of mRCC has been established in multiple retrospective and prospective studies and is considered to be the standard of care in many cases [47].

Cytoreductive nephrectomy in the absence of additional treatment mechanisms (immunotherapy, targeted therapy) does not usually lead to an increased survival [48] with rare exceptions of cases of spontaneous resolution of metastatic lesions following the removal of the primary tumor [49, 50]. Renal cell tumors are known to be immunogenic through secretion of proinflammatory cytokines (such as MCP-1, IL-6, and IL-8) and presence of immunogenic surface protein such as CAIX [51]. This finding has led to the development of immunotherapeutic agents (cytokines IL-2 and IFN-α) taking advantage of the host's immune system's ability to recognize RCC tumor cells as foreign and destroy them. Unfortunately, RCC tumors are also immunosuppressive and have a unique ability to downregulate the host's immune system's response. Analyses of peripheral blood samples taken from patients with clear cell tumors have shown increased concentration of "exhausted" CD8+ T cells with a sustained expression of inhibitory receptors as well as elevated concentrations of myeloid-derived suppressor cells (MDSC) that inhibit T cell proliferation and activation. Subjects with higher stage tumors (T3) were shown to have a unique pro-tumorigenic and inflammatory profile of cytokines and chemokines [52].

Termination of this immunosuppressive effect has been the main argument behind performing cytoreductive nephrectomies in the setting of mRCC. While the exact mechanisms through

which RCC tumors downregulate the host's immune system may not be fully understood, there is a significant body of evidence in the form of randomized prospective trials showing survival benefit in patients who had their primary tumors resected as part of a multimodal treatment approach.

SWOG trial 8949 included 241 patients (SWOG performance status 0–1, immunotherapy naïve, no prior or concurrent radiation treatment) from 80 institutions and were randomized to receive either interferon alfa-2b alone or radical nephrectomy followed by interferon therapy. The median survival of patients treated with surgery and interferon was 11.1 months compared to 8.1 months in patients treated only with interferon ($P=0.05$). These results were reported to be independent of SWOG performance status, metastatic site, and presence or absence of a measurable metastatic lesion [53]. Results of a similar, but smaller EORTC trial were reported in the same year with even more compelling results in support of cytoreductive nephrectomy. Eighty three patients with mRCC were randomized to interferon alone or surgery followed by interferon therapy. Inclusion and exclusion criteria were very similar to those in SWOG 8949 trial. Median overall survival was significantly better in the surgery + interferon group at 17 months compared to 7 months in the interferon only group [47].

The main drawbacks of performing cytoreductive nephrectomy are related to the possible delay in treatment with immunotherapy. There is a risk of systemic disease progression as well as postoperative morbidity that may prevent administration of adjuvant therapy or make patients ineligible for enrollment in clinical trial due to low performance status. In a National Cancer Institute study of 195 patients with mRCC undergoing radical nephrectomy followed by IL-2 therapy, only 121 patients (62 %) following their recovery from surgery were eligible for the IL-2 treatment. The majority of the patients ($n=45$, 51 %) ineligible for IL-2 treatment had disease progression, most commonly in lung ($n=16$, 22.6 %). Additionally, there were 26 (13 %) intraoperative and postoperative complications including 2 (1 %) deaths [54].

Metastasectomy for RCC

Metastasectomy has been found to provide a survival benefit in a carefully selected group of patients, but no prospective randomized trials exist to support this claim. However, there are several retrospective studies providing evidence to support the role of metastasectomy of both solitary and multiple metastatic lesions in the management of mRCC. Five-year survival rates between 30 and 71 % following metastasectomy have been reported [41, 55].

One of the largest studies focusing on this issue is the previously mentioned study of 278 patients with mRCC by Kavolius et al. [41]. Of 94 patients with a solitary metastasis, resection of lung metastases was associated with better 5-year overall survival when compared to bone and brain (54 % vs. 40 % and 18 %, respectively). Interestingly, 5-year survival rates after second and third complete resections were not different when compared to the initial resection (46 and 44 %, respectively, compared to 43 %). Solitary site of first recurrence, complete resection, long disease free intervals, and metachronous presentation of the metastatic lesions were found to be positive predictors of longer overall survival [41].

The impact of metastasectomy in the setting of multiple metastases was examined by Alt et al. Eight hundred eighty seven patients with a history of radical nephrectomy for RCC and resection of multiple metastatic lesions were included in the study. Only 127 patients (14 %) were able to obtain a complete resection of their metastatic lesions, but their median cancer specific survival was significantly higher at 4.8 years compared to those without a complete resection (1.3 years). Patients with metachronous metastases, fewer than three metastatic lesions, and pulmonary only metastases were more likely to have a complete resection. Absence of complete metastasectomy was associated with an increased risk of death (HR 2.91) on a multivariate analysis [56].

The most compelling evidence supporting the role of metastasectomy has been published by Eggener et al. In their retrospective study of 129 patients with a history of partial or radical nephrectomy for RCC and subsequent metachronous metastases, they risk stratified their cohort

into three categories based on the number of adverse disease characteristics. These included time from nephrectomy to recurrence <12 months, Hb <13 in males and 11.5 g/dl in females, corrected serum calcium >10 mg/dl, Karnofsky performance status <80 %, and serum LDH >300 U/l. Patients were classified as: favorable risk (0), intermediate (1–2), and poor risk (3–5). Patients treated with metastasectomy had a significantly better survival rate in all three risk-stratified groups. Their 5-year survival was 71, 38, and 0 % for favorable, intermediate, and poor risk groups, respectively. For the poor risk metastasectomy group, the reported 2-year survival was 50 % compared to no patient surviving at 2 years in the absence of metastasectomy. On multivariate Cox regression analysis, the lack of metastasectomy had a hazard ratio of 2.7 [55].

The role of metastasectomy continues to evolve in the era of targeted therapy. Although the overall reported response rates with targeted therapy are quite high (up to 47 % with the tyrosine kinase inhibitor Sunitinib), most of the responders had only stabilization or partial resolution of the tumor burden. Complete responses remain quite rare at 3 % [57]. Surgical resection of the primary tumor and certain metastatic sites therefore continues to play an important role in treating metastatic RCC.

Summary

Patients with metastatic renal cell carcinoma represent a therapeutic challenge. They benefit from a multimodal treatment approach and close cooperation between surgical and medical specialists. Patients presenting with metastatic lesions need to be referred to an urologist for staging and evaluation. In most cases, cytoreductive nephrectomy should be performed prior to initiation of medical therapy to decrease the immunosuppressive effect of the primary tumor. In a carefully selected patient population, metastasectomy has been proven to increase overall survival and should be performed by a surgical specialist based on the location of the lesion. Due to their favorable side effect profile, targeted therapy agents are now a widely used form of adjuvant treatment. The search for new treatment agents and modalities is ongoing. Currently, there are almost a hundred active clinical trials for stage IV renal cell all seeking to continue to improve the survival of patients with advanced RCC.

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Thyroid

8

Elie Klam and Dev Abraham

Introduction

Distant metastases in thyroid cancer including bone metastases are extremely rare. Most patients with bone metastases present with bone pain or fracture. The presence of distant metastasis reduces survival rate in thyroid cancer patients. Treatment of these patients involves a multidisciplinary approach consisting of medical treatment, radiotherapy, and surgery.

Epidemiology of Thyroid Cancer

Thyroid cancer accounts for 3.6 % of all new cancer cases, with an ever-increasing incidence and female preponderance. The median age is 50 years, with an incidence of 12.2 per 100,000 populations. This increase follows improvements and easy availability of ultrasound imaging [1].

The prognosis of most thyroid cancer patients is excellent, with 5-year survival rate of 97.7 %. Death rates from thyroid cancer have not significantly changed over the past decade despite the increased incidence of the disease. The most widely used staging system is based on the AJCC Cancer Staging Manual, 7th ed. Prognosis depends on the stage of disease at diagnosis (Table 8.1).

Risk Factors

Radiation exposure, either therapeutic such as for the treatment of Hodgkin's disease or environmental (e.g., Chernobyl disaster), increases the risk of thyroid cancer. Family history of thyroid cancer in a first-degree relative or history of familial syndromes such as MEN-2 and Li-Fraumeni syndrome is an intrinsic risk factor.

Classification

World Health Organization (WHO) and Armed Forces Institute of Pathology (AFIP) classified thyroid cancer into three main categories (Table 8.2). Epithelial tumors constitute of more than 95 % of cases with majority being papillary thyroid carcinomas.

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Table 8.1 Percent of case by stage and 5-year survival

Stage	Definition	5-Year survival (%)
Localized (68 %)	Confined to primary site	99.9
Regional (25 %)	Spread to regional lymph nodes	97.4
Distant (4 %)	Cancer has metastasized	55
Unknown (2 %)	Unstaged	87.4

Table 8.2 Classification of primary thyroid cancers

Epithelial tumors	Non-epithelial tumors
Differentiated	Malignant lymphomas
Papillary carcinoma	Sarcomas
Follicular carcinoma	Others
Poorly differentiated	
Undifferentiated (anaplastic)	
C-cell tumors	
Medullary carcinoma	

Distant Metastasis

Most commonly encountered distant metastasis sites include lungs, brain, bones, and liver. The vertebrae, pelvis, ribs, long bones (e.g., femur), and skull are the skeletal sites commonly involved. About 2–10 % of patients with papillary thyroid cancer and 15–20 % of patients with follicular cancers have distant metastases. Two-thirds of these patients have pulmonary and one-fourth has skeletal metastases. Bony metastasis occurs more frequently in subjects with follicular cancer due to hematogenous dissemination [3].

Distant Metastasis and Primary Tumor Characteristics

Follicular thyroid tumors can have a higher prevalence of distant metastasis than papillary thyroid cancers. The risk of distant metastasis is higher when the primary tumor size is >20 mm [4]. However, even smaller tumors have been reported to cause distant metastasis. Morbidity and mortality increase in patients with distant metastasis. Prognosis in distant metastasis depends upon the histology of the primary tumor, the number of metastasis, the age at diagnosis, and the avidity of radioactive iodine (RAI). The overall 10-year survival rate is 40 % when distant or skeletal metastases are present. In addition, age >45 years at the time of diagnosis and symptomatic metastasis are associated with worse prognosis [5, 6].

Diagnosis of Bone Metastasis

X-Ray Imaging

Plain films can show bone destruction. However, it may take several months before the lesions can be detected on simple imaging. Furthermore, plain X-rays may fail to show lesions that are <1 cm in size.

Computed Tomography (CT) and Magnetic Resonance Imaging

Computed tomography can be used to evaluate the extent of metastatic lesions, and is especially useful to evaluate the spine and pelvis (Fig. 8.1).

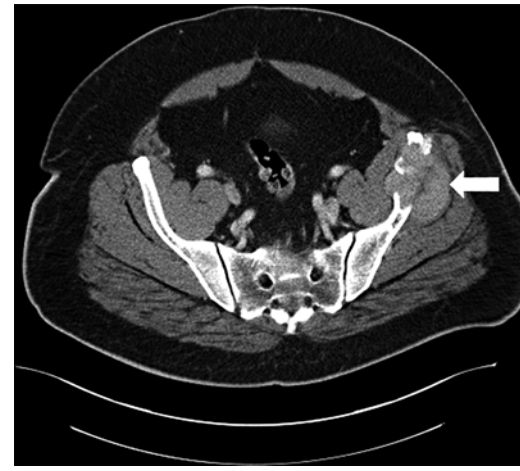

Fig. 8.1 CT pelvis showing 6.2×8.1 cm left pelvic distant metastasis (*arrow*) of a papillary thyroid cancer in a 57-year-old male. Patient had total thyroidectomy revealing a 4 mm follicular variant papillary thyroid cancer

Magnetic resonance imaging (MRI) images are useful to identify early spinal cord compression. MRI is highly sensitive (94 %) and can detect lesions as small as 2 mm.

Iodine-131 (I-131) Whole-Body Scan

I-131 whole-body scan (WBS) plays an important role in treatment and detection of metastatic thyroid cancer. It provides information on the presence of iodine-avid thyroid tissues including postoperative thyroid remnant. In the presence of a large thyroid remnant, the scan can be falsely negative as the remnant uptake can mask extrathyroidal disease, lymph nodes, or distant metastases. Also WBS can be falsely negative in distant metastases that are not avid to iodine. The WBS is most used following therapy, as post-therapy scan. WBS is done usually with either recombinant human TSH stimulation (rhTSH) or thyroid hormone withdrawal (Fig. 8.2).

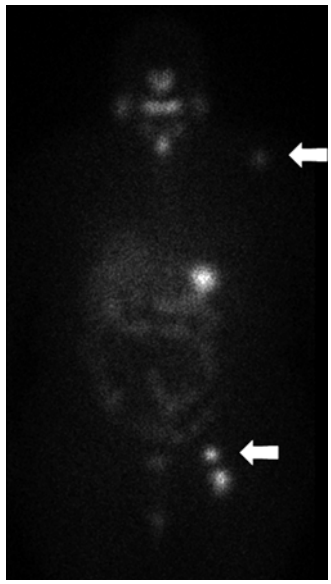

Fig. 8.2 I-131 Whole-body scan showing iodine-avid thyroid metastases involving the proximal left humerus, left sacrum, and proximal left femur (*arrows*) in a 74-year-old male with a 2.4 cm follicular variant papillary thyroid cancer

^{18}FDG-PET Scanning

^{18}FDG-PET scanning may provide superior localization after ablation than I-131 WBS in subjects with poorly differentiated thyroid cancers [7]. It is useful for the initial staging and follow-up surveillance of metastatic Hurthle cell carcinoma. False-positive results have been seen in subjects with inflammatory lymph nodes, suture granulomas, and increased muscle activity. Therefore, biopsy and histologic confirmation are required to confirm metastatic disease.

Treatment of Bone Metastasis

Treatment of thyroid cancers involves surgery, radioactive iodine ablation, and thyroid hormone suppression. The major indications for treating thyroid cancer bone metastases are the presence of or the risk for pathologic fractures, risk of spinal cord compression; the presence of pain, and avidity of RAI uptake. The main indications for surgery are persistent pain refractory to medical therapy, tumors with poor radioactive uptake, and spinal instability with or without neural compression. Improved survival has been noted in complete resection of isolated symptomatic bone metastases especially in patients <45 years old with slowly progressive disease [8]. RAI therapy of iodine-avid bone metastases, although rarely curative, has also been associated with improved survival. Multiple rounds of RAI therapies have been associated with pancytopenia or marrow dysplasia. External beam radiation therapy (EBRT) can be used to palliate painful bone metastasis, risk for fracture, and compressive neurologic symptoms with or without high-dose dexamethasone therapy. Complete or partial pain relief is obtained for at least 6 months in 50 % of cases. Chemotherapy regimens have limited effect on bony metastasis. The use of bisphosphonates has been shown to have antitumor activity and can decrease bone pain, improving quality of life.

TSH suppression should continue in the presence of distant metastasis with goal TSH levels of <0.5 mU/L as higher level (>1.0 mU/L) is associated with poor survival.

Conclusion

Bony metastasis from differentiated thyroid cancer is rare and carries an adverse prognosis. In the vast majority of subjects with bony metastasis, the presence of the metastasis is apparent readily. Management of these patients should include a multidisciplinary approach, involving surgery, radiation, and medical therapy.

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Myeloma

9

Srinivas K. Tantravahi and Tibor Kovacsovics

Introduction: Epidemiology and Etiology of Multiple Myeloma

Multiple myeloma (MM) is a clonal plasma cell disorder characterized by proliferation and accumulation of plasma cells in the bone marrow with secretion of a monoclonal immunoglobulin or light chain in the serum or urine or both and end organ damage attributable to the underlying plasma cell dyscrasia [1]. MM accounts for approximately 10 % of hematologic malignancies and 1 % of all cancers [2]. An estimated 24,050 new cases of MM will be diagnosed in the USA in the year 2014 and 11,090 will die of the disease [3]. The incidence of MM has been stable over the last few decades with an age adjusted annual incidence of approximately 4–5 cases per 100,000 in the USA [4, 5]. The exact etiology of myeloma is unknown despite the identification of several potential risk factors. In addition to the history of MGUS, age is an important risk factor and myeloma is a disease of predominantly older patients with a median age of 65–70 years. The disease affects African Americans twice more commonly in comparison to Caucasians for reason unclear and men are more frequently affected than women [6, 7]. Exposure to environmental agents such as pesticides, and herbicides are postulated to increase the risk of myeloma. In population-based studies, the prevalence of MGUS is twice higher among pesticide applicators suggesting a potential causal link [8]. Moreover, the incidence of myeloma is high among patients with repeated exposure to ionizing radiation. Epidemiological studies indicate an increased risk of MGUS and MM in first-degree relatives of patients with MM or MGUS. This is further supported by the fact that recent genome-wide association studies identified single-nucleotide polymorphisms localizing to several genes that are robustly associated with increased MM risk [9].

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Pathogenesis of Multiple Myeloma

Spectrum of Plasma Cell Dyscrasias: MGUS, SMM, and MM

Myeloma is an advanced disorder in the spectrum of plasma cell dyscrasias preceded by an asymptomatic premalignant disorder, monoclonal gammopathy of undetermined significance (MGUS) in almost all patients [10, 11]. MGUS is diagnosed based on the presence of monoclonal paraprotein in the serum (<3 g/dL) along with the absence of bone marrow plasmacytosis (<10 %)

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and lack of end organ damage attributable to the underlying plasma cell disorder [12] (Table 9.1). It occurs at a frequency of approximately 3 % in patients over the age of 50 years and the incidence increases with advancing age with an approximately 1 % risk of progression to MM per year [13]. Smoldering multiple myeloma (SMM), an intermediate stage between MGUS and MM, is defined by higher levels of monoclonal paraprotein (≥3 g/dl) or urinary monoclonal protein secretion (≥500 mg/24 h), or bone marrow plasma cell percentage (≥10 %) in the absence of end organ damage (Table 9.1). The risk of progression of SMM to MM is the highest in the first 5 years, approximately 10 % per year, and subsequently declines [14]. Recently, a high-risk group SMM has been identified based on the presence in the marrow of more than 60 % plasma cells, of an involved to uninvolved kappa to lambda free light chain ratio higher than 100 and of the presence of >1 focal lesion by MRI [15]. This group is associated with a risk of progression to MM of 80 % over the two years and is now considered an indication to initiate therapy.

Table 9.1 Diagnostic criteria for plasma cell disorders [40, 74]

Monoclonal gammopathy of undetermined significance (MGUS)[a]	(a) Serum monoclonal protein <3 g/dL And (b) Bone marrow clonal plasma cells <10 % And (c) Absence of end-organ damage attributable to the underlying plasma cell disorder (CRAB criteria, hyperCalcemia, Renal insufficiency, Anemia, and Bone lesions)
Smoldering multiple myeloma (SMM)	(a) Serum monoclonal protein (IgG or IgA)[a] ≥3 g/dL And/or (b) Bone marrow clonal plasma cells ≥10 %, And (c) Absence of end-organ damage attributable to the underlying plasma cell disorder (CRAB criteria, hyperCalcemia, Renal insufficiency, Anemia, and Bone lesions)
Multiple myeloma (MM)	(a) Bone marrow clonal plasma cells ≥10 % or biopsy proven plasmacytoma And (b) Evidence of end-organ damage attributable to the underlying plasma cell disorder specifically Hypercalcemia (serum calcium >11.5 mg/dL) Or Renal insufficiency (serum creatinine >2 mg/dL or estimated creatinine clearance less than 40 mL/min) Or Anemia (normochromic, normocytic anemia with hemoglobin >2 g/dL below the lower limit of normal or <10 g/dL) Or Bone lesions, lytic lesions, severe osteopenia, or pathologic fractures

g grams, *dL* deciliter, *Ig* immunoglobulin, *mg* milligrams
[a]Excluding IgM paraprotein as IgM MGUS progresses to symptomatic Waldenstrom's macroglobulinemia, not to SMM or MM

Pathogenesis of Bone Disease in MGUS and MM

Altered Cortical Bone Architecture and Reduced Strength Increases Fracture Risk in MGUS

Although by definition patients with MGUS have no osteolytic lesions, population based studies demonstrate an increased fracture risk in MGUS patients compared to their matched controls [16, 17]. Low lumbar bone mineral density is a major risk factor associated with significantly high fracture risk in this patient population [18]. The exact pathophysiology of increased fracture risk in MGUS patients is not well established. Intriguingly, using a high-resolution peripheral quantitative computed tomography imaging of the distal radius, patients with MGUS were shown to have significantly increased cortical bone porosity and reduced bone strength [19, 20]. In addition, serum markers for both increased osteoclastic and decreased osteoblastic activities were significantly elevated in patients with MGUS. Dickkopf-related protein (DKK1), a secreted Wnt pathway inhibitor is a critical medi-

ator of bone disease in myeloma through inhibition of Wnt-regulated osteoblastic differentiation [21]. Importantly, DKK1 is also implicated in increased osteoclastic activity through upregulation of RANKL and inhibition of OPG secretion [22]. Notably, one study showed significantly elevated serum DKK1 levels in MGUS patients compared to matched control subjects [20], although the increase was statistically insignificant in another study [23]. Finally, patients MGUS have significantly high serum level of osteoclast stimulating cytokine, macrophage inflammatory protein-1α (MPP-1α), when compared to matched healthy controls [20]. In conclusion, the altered bone microstructure and an imbalance between bone resorption and formation seem to be responsible for increased fracture risk even in patients with MGUS.

Altered Bone Remodeling Explains the Osteolytic Bone Disease in MM

Bone disease in MM is a major cause of morbidity leading to poor quality of life. Hypercalcemia and skeletal related events such as bone pain, vertebral compression fractures, and pathologic fractures occur due to osteolytic bone disease in a large proportion of patients. Notably, pathologic fractures negatively impact the survival with 20 % increase in the risk of death compared to patients without fractures [24, 25]. Under normal circumstances, continuous turn over and remodeling of adult skeletal occurs through a highly regulated network of interactions between bone microenvironment and the bone cells creating a balance between bone resorption by osteoclasts and formation by osteoblasts. Deregulated bone remodeling due to increased osteoclastic activity and decreased osteoblastic differentiation is the principle cause of excessive bone resorption in MM. The increased osteoclastic activity and the resultant bone resorption typically occur in the areas adjacent to the malignant plasma cells [26]. Moreover, histomorphometric studies also demonstrated an increase in the number of osteoclasts and osteoblasts early in the course of myeloma development [27]. Clonal plasma cells and other elements of bone marrow (BM) microenvironment cooperate with each other through a complex network of signaling factors and cytokines that ultimately result in uncoupling of osteoclastic and osteoblastic activities. A variety of cellular and non-cellular components of BM microenvironment including BM cells (clonal plasma cells, stromal cells, immune cells); extracellular matrix containing collagen, laminin, fibronectin, and extracellular fluid rich in cytokines and other growth factors contribute to the pathogenesis of osteolytic bone disease [28].

Osteoclasts are hematopoietic in origin derived from differentiation and fusion of the monocyte-macrophage lineage precursor cells to form inactive osteoclasts. Activated osteoclasts are responsible for bone resorption and eventually undergo apoptosis [29]. In contrast, osteoblasts arise from mesenchymal stem cells and factors such as platelet-derived growth factor, fibroblast growth factor, and transforming growth factor B enhance their growth and differentiation. Bone microenvironment plays a critical role in the formation of osteoclasts through macrophage colony-stimulating factor and receptor activator of nuclear factor-kB (RANK) ligand (RANKL) produced by the osteoblasts and stromal cells [30]. Osteoblasts and stromal cells have surface expression of RANKL, which bind to the RANK receptor on the osteoclast precursor cells and induce the osteoclast formation [31]. In contrast, osteoprotegerin (OPG), a decoy soluble receptor of RANKL, normally present in the bone marrow binds to the RANKL inhibiting the RANK-RANKL interactions, thereby limiting osteoclastogenesis [32]. The ratio of OPG/RANKL regulates the osteoclast development, and the unbalance of this ratio is associated with bone disease in MM.

The other unique feature of bone disease in MM is the absence of new bone formation in the areas of osteolysis unlike any other tumor metastasis. Importantly, lack of new bone formation due to decreased osteoblastic differentiation and activity explain the pure lytic bone lesions, a typical finding in MM unlike other solid tumor metastases [31]. The key factor involved in this mechanism is DKK1 produced by clonal plasma

cells which inhibits Wnt regulated osteoblastic differentiation [21]. This would also explain the persistence of lytic lesions in MM patients in remission despite the absence of increased plasma cells in the bone marrow. In addition to RANKL and DKK-1, several other key factors are involved in uncoupling of osteoclastic and osteoblastic activities including interleukin-3 (IL-3), Interleukin-6 (IL-6), MIP-1a, MIP-1B, BAFF, and activin A, and a detailed discussion is beyond the scope of this chapter. In conclusion, uncoupling of osteoclastic and osteoblastic activities is responsible for the formation of bone lytic lesions that are typical of MM. Understanding the mechanisms involved in this process has led to the development of several therapeutic targets for myeloma bone disease.

Clinical Presentation and Diagnostic Work Up

The clinical manifestations of MM occur due to bone marrow infiltration by clonal plasma cells, and the related monoclonal paraprotein resulting in end organ damage. It is important to distinguish MM from its preceding disorders such as MGUS or SMM. The hallmark of MM and other plasma cell dyscrasias is the presence of monoclonal protein (M-protein) produced by the clonal plasma cells. The key distinguishing feature of MM from MGUS and SMM, is the presence of end organ damage, commonly referred to as CRAB, which include hyperCalcemia, Renal insufficiency, Anemia and Bone lesions [12] (Table 9.1). Most commonly MM patients present with fatigue due to anemia, bone pain, elevated creatinine, symptoms related to hypercalcemia, and weight loss [6]. Recurrent infections due to impaired cellular immunity and hypogammaglobulinemia are a common feature. Extramedullary plasmacytomas (EMP) can be seen in 7 % of patients at diagnosis and an additional 6 % during the course of the disease, and are associated with overall poor survival [33].

In addition to the routine laboratory studies including complete blood count, differential count, evaluation of blood smear, and comprehensive metabolic profile, initial evaluation for suspected MM should include serum and urine protein electrophoresis and immunofixation (Fig. 9.1). Urine 24-h collection is necessary for identification and quantification of monoclonal immunoglobulin or free light chains, referred to as Bence Jones proteins. A small percentage (~3 %) of patients does not have a detectable M-protein either in the serum or urine, and are referred to as non-secretory myeloma. However, the majority of these patients have elevated serum free kappa or lambda light chains that can be measured with serum free light chain assays [34]. Therefore, the incidence of truly non-secretory myeloma, as defined by the absence of M-protein in the serum, and urine with normal serum free light chain ratio, is quite low.

Bone marrow evaluation is indicated in all patients with suspected MM including immunophenotyping, karyotype, and fluorescent in situ hybridization (FISH) using probes for chromosomal abnormalities of prognostic significance. A gene expression profile testing is also of prognostic significance and may identify high-risk patients [35].

The current International Myeloma Working Group (IMWG) guidelines recommend whole body X-ray skeletal survey as the gold standard test for evaluation of MM bone disease [36]. However, PET/CT and MRI scans are much more sensitive in detection of the number of bone lesions in MM with an ability to identify extramedullary plasmacytomas, the identification of which has a significant prognostic impact [37]. Advanced imaging studies should be considered in all patients with bone pain and normal skeletal survey or neurological symptoms suggestive of cord compression (Table 9.2). Routine use of PET/CT and MRI scan in MM is not currently recommended, although these advanced imaging modalities are being incorporated in management of MM.

Staging and Risk Stratification

The clinical course of MM is widely heterogeneous with a long indolent course in some patients while others have a rapidly progressive

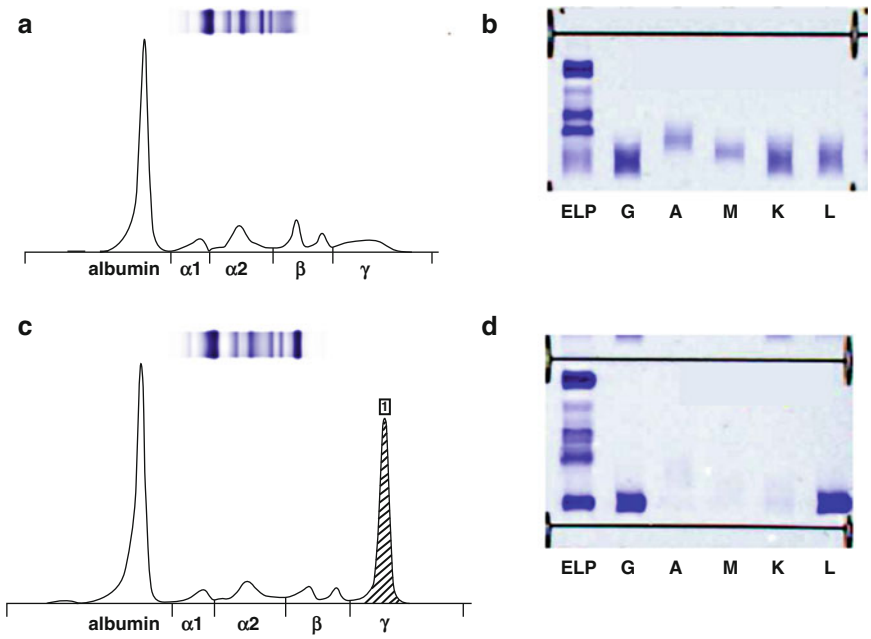

Fig. 9.1 (**a**) Normal serum protein electrophoresis. (**b**) Immunofixation electrophoresis shows polyclonal immunoglobulins with and monoclonal paraprotein. (**c**) Serum protein electrophoresis from a patient with multiple myeloma shows a monoclonal spike in the gamma region (*dashed area*). (**d**) Immunofixation electrophoresis identified the monoclonal protein as immunoglobulin G, lambda type. (*G* immunoglobulin G, *A* immunoglobulin A, *M* Immunoglobulin M, *K* kappa light chain, *L* lambda light chain)

Table 9.2 Initial diagnostic work up for suspected plasma cell dyscrasia

• Complete blood count with differential count
• Peripheral blood smear evaluation
• Complete metabolic profile
• Serum protein electrophoresis with immunofixation
• Urine protein electrophoresis with immunofixation
• Serum free kappa and lambda light chains[a]
• Serum beta-2 microglobulin
• Bone marrow aspirate and biopsy
• Chromosome analysis (karyotyping), bone marrow
• Fluorescent in situ hybridization (FISH), bone marrow
• Plain X-ray skeletal survey

[a]Consider in patients with no measurable M-spike

fatal disease. A variety of host factors, including the age, disease burden, severity of end organ damage and biological characteristics, influence the clinical course of MM. There are two staging systems that are widely accepted for staging and assessment of tumor burden in MM (Table 9.3). The Durie–Salmon staging system (DSS), developed many years ago based on mathematical calculation of plasma cell tumor mass in association with the severity of the end organ damage (Calcium level, Renal insufficiency, Anemia and Bone lesions) and immunoglobulin level is still widely used [38]. The main limitation of this system is the potential for subjective errors in evaluating lytic bone lesions and also the lack of prognostic significance. The International staging system (ISS), a simple and more practical system was developed based on retrospective analysis of a large number of previously untreated MM patients utilizing two widely available laboratory tests, serum β-2 microglobulin and albumin levels. The ISS has prognostic significance with a median survival of 62, 44, 29 months in patients with stages I, II, and III respectively [39]. Although the ISS is more easily reproducible in clinical trials, it does not effectively reflect the tumor burden as the level of albumin and β-2 microglobulin can be affected by the renal function and other comorbidities. In addition, the

Table 9.3 Staging for multiple myeloma

Durie–Salmon staging [38]	*Stage I*: Low cell mass: $<0.6\times10^{12}$ cells/m^2*and* all of the following: (a) Hemoglobin >10 g/dL (b) Serum IgG <5 g/dL and (c) Serum IgA <3 g/dL (d) Normal serum calcium (e) Urine monoclonal protein excretion <4 g/day (f) No generalized lytic bone lesions *Stage II*: Intermediate cell mass: neither stage I nor stage III *Stage III*: High cell mass: $>1.2\times10^{12}$ cells/m^2*and* one or more of the following: (a) Hemoglobin <8.5 g/dL (b) Serum IgG >7 g/dL and (c) Serum IgA >5 g/dL (d) Serum calcium >12 mg/dL (e) Urine monoclonal protein excretion >12 g/day (f) Advanced lytic bone lesion [a]*Stage IIIA* Serum creatinine <2 mg/dL and *IIIB* with serum creatinine ≥2 mg/dL
International staging system (*ISS*) [39]	*Stage I*: B2M <3.5 mg/L and serum albumin ≥3 g/dL *Stage II*: neither stage I nor stage III *Stage III*: B2M ≥5.5 mg/L

g grams, *dL* deciliter, m^2 meter square, *Ig* immunoglobulin, *mg* milligrams, *B2M* beta-2 microglobulin

prognostic role of ISS has not been validated in the era of novel biological therapeutic agents [40]. Neither staging systems are currently utilized in treatment decision-making.

In addition to the tumor burden as indicated by ISS and the DSS systems, host factors such as advanced age, ECOG performance status of 3 or 4 and renal failure (serum creatinine >2 mg/dL) are associated with adverse prognosis and less intensive treatment is recommended for those patients [41]. Finally disease biological characteristics play a critical role in determining patient prognosis and therapeutic strategies. Foremost are chromosomal abnormalities identified by conventional cytogenetics and by FISH, which allow risk stratification into standard-risk, intermediate risk and high-risk disease according to the Mayo stratification for myeloma and risk-adapted therapy classification (mSMART) [42]. Chromosomal translocations, t(14;16), t(14;20), and 17p deletion, typically identified by FISH, impart poor prognosis and are considered high-risk. The adverse prognostic impact of t(4;14) can be overcome by incorporating Bortezomib in the frontline treatment regimen, and therefore considered as intermediate risk category. All other chromosomal abnormalities, including hyperdiploidy and translocations t(11;14), t(6;14), are considered standard risk. The median overall survival in high risk MM is approximately 3 years in comparison to 8–10 years in standard risk patients. Treatment should be tailored to the individual risk category to minimize the toxicity and improve the overall clinical outcomes.

Risk-Adapted Therapy for Newly Diagnosed Patients

The first question to consider for newly diagnosed is whether patients are candidates or not for intensive chemotherapy followed by autologous stem cell transplantation (ASCT). Age and concomitant comorbidities should be taken in to account in determining transplant eligibility. In the USA, patients with physiologic age <70 years are considered ASCT eligible [42]. Active agents in MM available for treatment of frontline and relapsed myeloma patients belong to five different classes: corticosteroids (dexamethasone and prednisone), alkylating agents (Melphalan, and Cyclophosphamide), anthracyclines (Doxorubicin, and liposomal Doxorubicin), immunomodulatory derivatives or IMiDs (Thalidomide, Lenalidomide, and Pomalidomide), and proteasome inhibitors (Bortezomib and Carfilzomib), which are administered in multiple combinations.

Initial Therapy for Transplantation Eligible Patients

Patients eligible for ASCT are typically treated with two to four cycles of an induction regimen prior to stem cell harvest. Many treatment options are available and the choice of the regimen is based on risk stratification, on patient comorbidities and on physician preference. Stem cell dam-

aging agents such as Melphalan should be avoided in patients eligible for ASCT. Standard risk patients can be treated with an oral combination of Lenalidomide and low dose Dexamethasone [43]. Lenalidomide is currently preferred to Thalidomide due to superior activity and better toxicity profile [44]. Importantly, patients treated with Lenalidomide and Thalidomide should receive aspirin for thromboprophylaxis with consideration to warfarin and low molecular weight heparin in certain high-risk patients [45]. Bortezomib-containing regimens are given to intermediate and high-risk patients in combination with two additional agents, in so-called triplets. Popular combinations include VCD or CyBorD (Cyclophosphamide, Bortezomib, and Dexamethasone), VRD (Bortezomib, Lenalidomide, and Dexamethasone) and VTD (Bortezomib, Thalidomide, and Dexamethasone) [46–48]. Although VCD and VRD have not been compared in a randomized trial, the EVOLUTION trial has shown no difference between them in a small-size phase 2 study [49]. VRD is the preferred combination in patients with high-risk disease. Cisplatin and Etoposide combinations are a part of more aggressive treatment regimens (e.g., DT-PACE), typically reserved for patients with plasma cell leukemia and extramedullary disease at diagnosis [50].

Initial Therapy for Transplantation Ineligible Patients

The initial treatment regimens for newly diagnosed myeloma patients not eligible for ASCT due to age or comorbidities are the same as discussed for transplantation eligible patients. However, they are given for a total of 12–18 months. Addition of novel agents to the Melphalan-Prednisone (MP) backbone is associated to good clinical outcome, but the popularity of these regimens is limited in the USA in favor of the Lenalidomide–Dexamethasone combination. A meta-analysis of six randomized clinical trials showed that addition of thalidomide to MP (MPT) resulted in improvement in PFS and overall survival at the expense of increased toxicity, particularly peripheral neuropathy, and thrombosis [51]. A recent trial by the IFM group showed that a Lenalidomide–Dexamethasone combination, with Lenalidomide given continuously until progression, was superior to MPT [52]. Velcade-based regimens should also be considered in elderly patients, especially in high-risk group [46, 53].

High Dose Chemotherapy/ Autologous Stem Cell Transplantation (HDT/ASCT)

High dose chemotherapy with autologous stem cell transplantation remains the mainstay of MM with improvement in CR rates, event free survival (EFS) and median overall survival (OS) by approximately 12 months [54, 55]. The transplant related mortality is less than 3 % [56]. Age and concomitant comorbidities should be taken in to account in determining transplant eligibility. In the USA, patients with physiologic age >70 years are considered ASCT eligible [42]. Melphalan 200 mg/m^2 is the standard preparatory regimen followed by stem cell rescue. However, a reduced intensity regimen with Melphalan 100 mg/m^2 may be considered in older patients or with comorbidities [57]. The benefit of HDT/ASCT in the current era of novel biologic agents, which induce deeper and sustained responses, is unclear. Another important question is the timing of HDT/ASCT, early with frontline therapy or delayed at the time relapse. Delayed ASCT at the time relapse is acceptable for some patients as randomized controlled trials showed no difference in overall survival between early versus delayed transplantation strategies [58, 59]. However, most clinicians prefer to use early HDT/ASCT in all eligible patients due to improved quality of life. If delayed ASCT strategy is adopted, patients should have their stem cells collected and cryopreserved typically after four cycles of induction therapy, which should be continued until disease progression or relapse. Finally, the attempts to improve outcomes of ASCT in MM have been largely been unsuccessful so far, except that double or tandem transplan-

tation may offer some benefit in a subset of patients who fail to achieve a complete response or very good partial response after the first transplant [2, 60]. Therefore many centers prefer to collect stem cells adequate for two transplants. In conclusion, HDT/ASCT remains a key modality of therapy for MM until further data is available from prospective randomized trials incorporating novel agents up front.

Post-transplant Maintenance Therapy

The role of maintenance therapy in MM remains controversial. Optimal agent, patient population and duration of maintenance therapy are currently unknown. Two randomized has shown improvement in PFS with thalidomide maintenance without any OS benefit [61, 62]. Lenalidomide is emerging as the most promising agent for maintenance therapy due to better tolerance than thalidomide. Lenalidomide maintenance post ASCT has been shown to improve PFS in two separate with some OS benefit in one of the studies [63, 64]. Moreover, continuation of Lenalidomide after initial treatment with Melphalan-based regimens resulted in better PFS in elderly myeloma patients [65]. However, the emergence of late toxicities, particularly second primary malignancies, remains a concern with prolonged Lenalidomide maintenance. Finally, Bortezomib based maintenance post ASCT in high-risk patients is currently under investigation with promising preliminary data [66]. Currently Lenalidomide maintenance therapy could be considered post ASCT limiting to 2 years due to the risk of second primary malignancies. The role of Bortezomib-based maintenance in standard risk patient is currently unknown.

Treatment of Relapsed Myeloma

Most patients with multiple myeloma eventually relapse. The prognosis of patients relapsed with Bortezomib and Lenalidomide refractory disease is extremely poor. If relapse occurs late after 6 months of stopping treatment, reinstitution of prior treatment is acceptable. Several drugs have been FDA-approved over the past years for relapsed and refractory MM. They include Carfilzomib [67], Pomalidomide [68] and Panabinostat [69]. The combination of Carfilzomib to Revlimid and Dexamethasone has proven particularly active and may represent a new standard [70]. Patients who have undergone a previous ASCT are candidates for a second transplant provided the duration of their initial response is greater than 1 year [71].

Conclusion

Although multiple myeloma remains an incurable hematopoietic malignancy, novel agents in combination with autologous stem cell transplantation have improved the outcomes over the past decade [72, 73].

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Part III

Work-Up for Patients with Suspected Metastatic Bone Disease

Evaluation of the Patient with Carcinoma of Unknown Origin Metastatic to Bone

10

Bruce T. Rougraff and Terence J. Cudahy

Introduction

The skeleton is a common metastatic site for several visceral carcinomas, lymphoma, and melanoma. In patients who have a known primary carcinoma site, the breast and prostate are the most common malignancies that metastasize to bone. Metastatic disease in these patients usually occurs late in the disease process, long after the primary disease has been identified. However, 3–4 % of patients with metastatic carcinoma have an unknown primary site at the time of presentation [1]. Ten to 15 % of these patients have skeletal involvement as the cause of their presenting symptoms. In the patient older than 40 years with a poorly marginated bone lesion on plain radiographs, the diagnosis of a skeletal metastasis of unknown origin is more likely than a primary bone malignancy. Because these patients typically are evaluated initially by an orthopedic surgeon for musculoskeletal complaints, it is imperative that the treating physician have a rational and effective approach to the diagnostic evaluation and treatment of these patients [1].

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This review attempts to revisit the diagnostic issues in evaluating patients who present as a metastatic carcinoma to bone in light of newer diagnostic and staging methods. Expanding on this issue, the appropriate clinical approach to patients who initially present with pathologic fracture through a metastatic carcinoma of unknown origin requires discussion as very little direction is offered in the current literature.

Discussion

Metastatic carcinoma of bone must be considered in patients over the age 40 years who present with a poorly marginated bone lesion in the proximal skeleton and spine. Metastatic carcinoma is more likely than a primary bone sarcoma in this group of patients [2]. The most likely visceral primary carcinomas that spread to bone include the lung, kidney, prostate, breast, and thyroid. However, many other malignancies can spread to bone and may include melanoma, liver carcinoma, gastrointestinal carcinoma, metastatic lymphoma, and uterine carcinoma [3]. Primary malignancies of bone that occur in this older age group of patients include malignant fibrous histiocytoma of bone, primary lymphoma of bone, chondrosarcoma, and plasmacytoma. The first and most important part of the diagnostic strategy to evaluate these patients includes a thorough clinical patient history [1]. Patients who have had a previous malignancy in the distant past

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may not volunteer that information on a cursory medical history. Despite a long disease-free interval, any patient with the history of a previous carcinoma and a new skeletal lesion must be considered to have metastatic carcinoma until proven otherwise.

The second part of the diagnostic strategy involves a physical examination, which includes a breast examination in female patients, and a prostate examination in male patients. The thyroid and abdomen were examined in all patients. Unfortunately, these patients typically have small primary tumors that are not easily identifiable on physical examination. Rougraff et al. [1] reported that only 8 % of the patients had a primary carcinoma found on physical examination.

The third part of this evaluation should include a laboratory analysis to accomplish two goals: to assess the medical condition of the patient before surgical intervention, if needed; and to exclude the diagnostic possibility of multiple myeloma, which usually does not need a biopsy for diagnosis. The laboratory analysis should consist of the determination of a complete blood cell count, ESR, levels of electrolytes, liver enzymes, prostate-specific antigen, and ALP and serum and urine protein electrophoresis. Laboratory findings usually are non-diagnostic in patients who have a normal prostate specific antigen, and serum and urine protein electrophoresis.

The next part of the diagnostic strategy should involve a radiographic evaluation. A plain radiograph of the chest and involved skeleton should be obtained. Any painful extremity should be evaluated, and any radiographs of the skeleton should include the entire bone, with adequate markers to be able to plan skeletal reconstructive procedure if necessary. Radiographs of the chest identified the lung as the primary site in 43 % of the patients in the study by Rougraff et al. [1]. The typical radiographic appearance of a metastasis is a lytic, permeative lesion of the diaphysis or metadiaphysis of a proximal long bone or bone of the axial skeleton. If the lesion seems to involve mostly the cortex of a bone or is located distal to the knee or elbow, it is more likely to be from an occult lung primary carcinoma than other sites. A bone scan of the entire skeleton (technetium 99 m-phosphonate scintigraphy) should be obtained to identify whether there are multiple skeletal lesions. A patient with multiple skeletal lesions is unlikely to have a primary bone malignancy. In addition, another skeletal lesion may be found with bone scintigraphy that is more amenable to a biopsy or that may require prophylactic skeletal fixation.

Next, a biopsy is required if the diagnostic strategy fails to identify a primary carcinoma, or before internal fixation if indicated. The placement of the biopsy incision is critical in case the final diagnosis is a primary malignancy of bone, which may require a subsequent resection and reconstruction. A poorly planned and executed biopsy in a patient with a primary bone malignancy could result in an amputation for a patient who might otherwise be a candidate for limb salvage surgery. The biopsy may be accomplished by needle biopsy if there is an accessible soft tissue mass, or an incisional biopsy. Good communication with the pathologist before the biopsy is critical so that enough tissue is obtained for special testing and so that the tissue is processed appropriately. The pathologist may be able to gain information concerning the primary site by using immunohistochemical tests or monoclonal antibodies as markers [4]. Occasionally, a bone lesion such as lymphoma can be misdiagnosed as an undifferentiated adenocarcinoma, resulting in significant mistreatment of the patient. If the pathologist is informed as to the pre-biopsy information and the remaining questions that are to be addressed, this type of mistake can be avoided.

The biopsy material itself, while confirming the diagnosis of metastatic disease, only infrequently identifies the primary site of malignancy. When a suspected metastatic lesion is encountered within bone, the initial step in the pathologic analysis is to confirm that the lesion in fact represents metastatic carcinoma. Positive reactions for cytokeratins (pancytokeratin, Cam 5.2, or AE1/3) will serve to confirm the diagnosis of metastatic carcinoma. A variety of antibodies may then be applied which can point to specific primary sites, including prostate-specific antigen, TTF-1 (lung and thyroid), CDX-2 (gastrointestinal tract) [4–6], and gross cystic

disease fluid protein (breast). Differential cytokeratin reactivity (typically utilizing CK7 and CK20) is also quite useful in pointing toward specific primary sites (e.g., the relatively unique CK7-negative/CK20-positive immunoprofile of colonic adenocarcinoma). Metastatic melanoma may closely mimic carcinoma, but exhibits a different immunoprofile (cytokeratin negative, but positive for S100, HMB-45, and Melan-A). Novel strategies using expression microarrays and serial analysis of gene expression have also been described [7–9].

This simple diagnostic strategy using CT scanning (Fig. 10.1) is able to identify the primary site of malignancy in most patients at the time of presentation. Clinical judgment should be used to decide whether additional testing is warranted in those patients with an unidentifiable primary malignancy. FDG-PET scanning combined with CT has had some success in finding occult primary sites [10]. Two recent reports have shown that postmortem examinations were able to identify the primary site in 51–55 % patients whose carcinoma was not identified before death [11, 12].

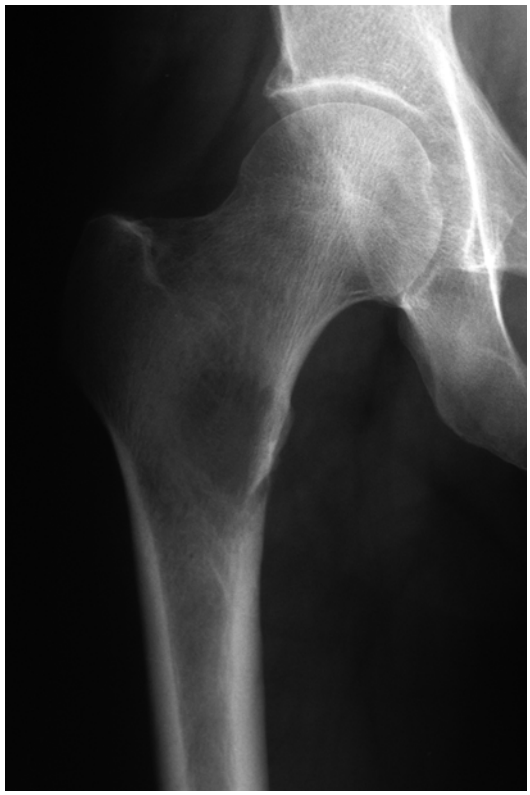

Fig. 10.1 This an anteroposterior radiograph of a 57-year-old male with a prior history of renal carcinoma and new right hip pain. He had no prior history of metastatic disease. A large lytic lesion of the proximal femur is seen that most likely represents a metastatic carcinoma

Unlike skeletal metastasis of known origin (most often of the breast or prostate), a metastasis of unknown origin usually originates from the lung or kidney (although almost any visceral carcinoma can be the source of an occult malignancy). This could be attributed to the inaccessibility of these organs to physical examination, to the large size to which tumors in the kidney or lung can grow before becoming symptomatic, or to the tendency of these tumors to metastasize to bone earlier than breast or prostate carcinoma. Because the breast is a distinctly uncommon site for a metastatic malignant tumor when the patient has a skeletal metastasis of uncertain origin, a mammography should not be included as part of the evaluation unless the history or physical examination reveals an abnormality in the breast, or in those women who, after the diagnostic strategy has been completed, still have an unknown primary site [13].

A difficult clinical scenario is the occasional patient who presents to the orthopedist with a fracture that seems to be pathologic, yet the patient has no prior cancer history [14]. The problem here is to provide skeletal fixation, identify the tumor type, and not eliminate a limb-sparing operation if the tumor is a primary bone sarcoma. Working the patient up with CT of the chest, abdomen and pelvis and obtaining a whole body bone scan is challenging due to patient's pain and difficulty in transferring. Depending on the fracture location and pain level of the patient at the time of presentation, blood testing and CT scans may be obtained prior to surgical intervention. A biopsy is needed at this point to rule out a primary sarcoma. It is much less important to identify the primary site in this scenario. Usually a needle biopsy of the lesion can be obtained either intraoperatively (before attempted fixation) or under radiographic guidance. If the needle biopsy is not diagnostic, an open or incisional biopsy is necessary. It is not appropriate to place

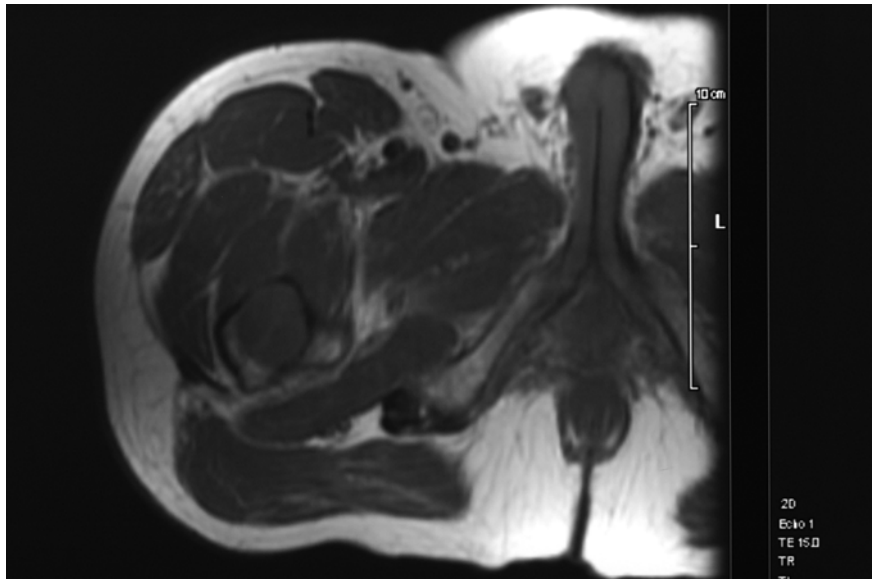

Fig. 10.2 This is a T1 magnetic resonance image showing marrow replacement of the proximal femur with cortical destruction

internal fixation before a primary bone sarcoma is ruled out by biopsy. Sending reamings from the surgery after placing an intramedullary rod for skeletal fixation as the initial biopsy is inappropriate. Obviously if the lesion is a primary sarcoma of bone, limb salvage has been eliminated as an adequate local control measure in this patient. In addition, contamination of the buttocks with the entry site for a femoral intramedullary nail complicates the possible amputation level further. Referral to an orthopedic oncologist prior to biopsy is an appropriate consideration.

A second challenging scenario is a patient with a history of cancer presenting with a bone lesion and no prior history of metastases (see Figs. 10.1, 10.2, 10.3, and 10.4). Although this patient most likely has a metastatic lesion from their previous primary carcinoma, occasionally the bone lesion is either a second malignancy or a primary benign bone lesion (see Figs. 10.5 and 10.6). Assuming the bone lesion is malignant, this patient should be evaluated first with a bone scan (total body) to assess for other lesions. Multiple positive lesions will increase the likelihood that the lesions represent metastatic disease from the known primary site. CT of the chest/abdomen/pelvis should be taken to assess for

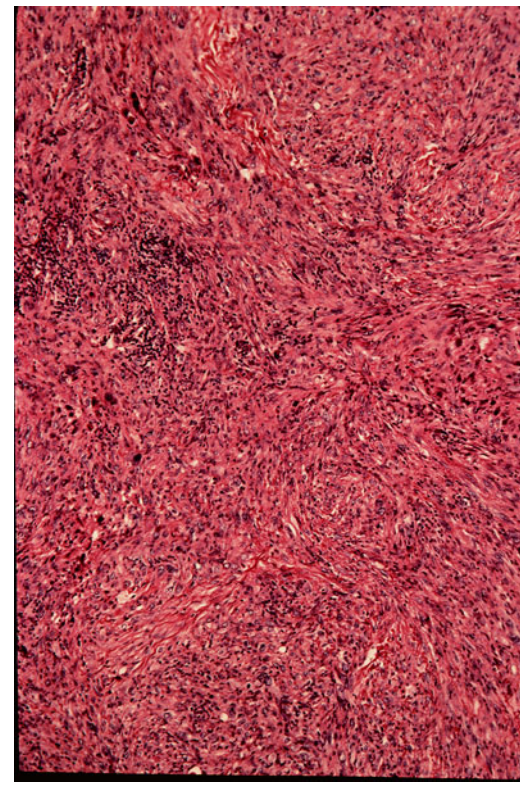

Fig. 10.3 A needle biopsy was performed which showed that the lesion was NOT carcinoma but a primary pleomorphic sarcoma of bone

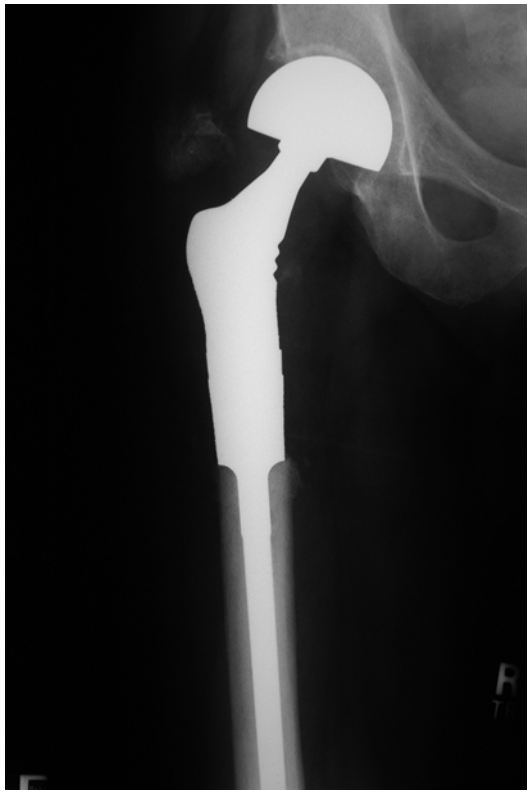

Fig. 10.4 The patient was treated with resection, metal reconstruction and chemotherapy and has remained disease-free. A prophylactic internal fixation with a simultaneous biopsy would have resulted in an amputation of the leg and a compromised oncologic outcome

other sites of metastatic disease or other initiating cancers. Needle or core biopsy generally should be done before treating the lesion to confirm the diagnosis of metastatic disease and to rule out a second primary cancer. It is inappropriate to begin any treatment of the first bone lesion without confirmatory biopsy. A biopsy specimen must be obtained before fixation in patients with an impending fracture.

Because many patients with skeletal metastasis of unknown primary site have a short life expectancy, it is tempting to limit the number of diagnostic tests, thereby limiting the cost to these patients. It may seem logical to proceed directly to a biopsy in these patients, without a pre-biopsy evaluation. There are at least six reasons for not starting the evaluation with a biopsy in these patients: (1) The lesion may be a sarcoma of bone, and an ill planned biopsy compromises the ability to do a limb salvage procedure and obtain high-quality imaging studies of the osseous lesion; (2) Another lesion may be identified that would be easier and safer to sample; (3) Renal cell metastasis can be very vascular, and it is helpful to know before the biopsy whether the osseous lesion is most likely to be renal in origin. This allows the surgeon to consider embolization before the biopsy, or to consider the use of a needle

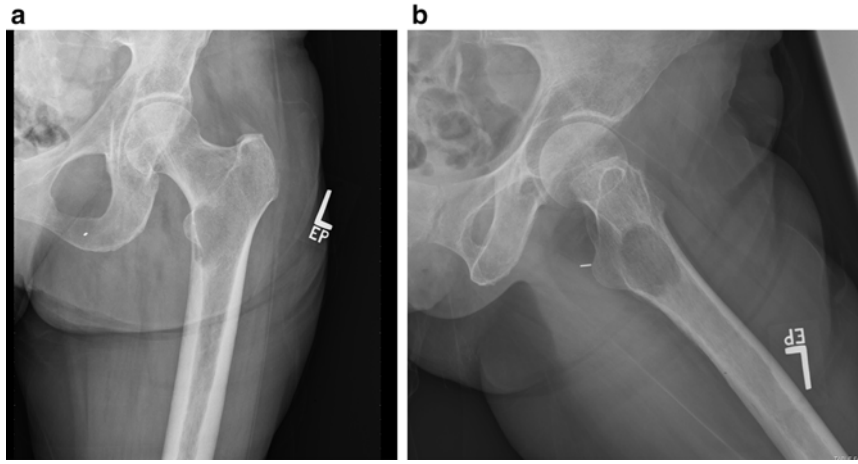

Fig. 10.5 This is a 64-year-old lady who had an isolated breast malignancy 12 years ago and no recurrence since treatment. She started having left hip and thigh pain and these two radiographs revealed a poorly marginated, lytic lesion of the left proximal femur

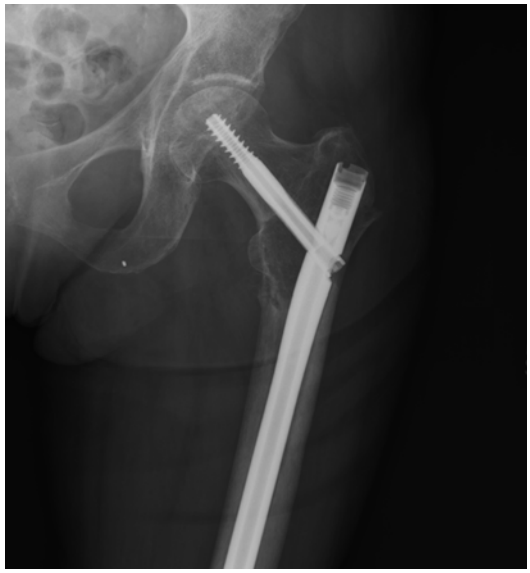

Fig. 10.6 The lesion was assumed to be metastatic breast carcinoma and a prophylactic intramedullary rod was placed through a trochanteric approach of the left femur. Reamings from the surgery were sent for pathologic evaluation and were consistent with primary high-grade bone sarcoma. The patient refused hemipelvectomy, was treated with radiation and chemotherapy and died 2 years later of metastatic sarcoma

biopsy to limit the blood loss from the procedure; (4) An unnecessary biopsy of a patient who has multiple myeloma can be avoided by obtaining the appropriate laboratory test; (5) The histologic analysis alone identifies the primary site in only a small percentage of patients. It is unlikely that a biopsy alone would identify the primary site without an appropriate prebiopsy evaluation; and (6) The surgeon and the pathologist will be more confident in making a histologic diagnosis based on frozen section if a primary malignant site is identified before the biopsy. This allows internal fixation of impending fractures to be done more often at the time of biopsy, and can eliminate the need for a second operation after a final histopathologic diagnosis has been obtained.

The prognosis of these patients is related to the primary site that was identified. Those patients with lung primaries usually have a very poor prognosis, with few of these patients surviving more than 12 months after the diagnosis [15]. Likewise, patients whose primary site cannot be identified survived an average of 11 months. However, those patients with kidney and thyroid carcinomas may have a very long survival, especially if they have isolated skeletal metastasis at the time of presentation. The technique of skeletal reconstruction used for these patients should be durable capable of several years of fixation in bone that may never be completely competent.

Skeletal metastases of unknown origin usually are painful, poorly marginated lesions of the proximal part of the skeleton. Ninety percent of these patients are older than 40 years at the time of their diagnosis. Using a simple diagnostic strategy, almost all occult primary carcinomas can be identified. Careful attention to the details to the approach and care of these patients can prevent an irreversible error in their treatment.

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Biopsy Considerations

11

Daniel M. Lerman

Introduction

Prior to surgical intervention for metastatic bone disease, it is appropriate to obtain a tissue specimen for histological confirmation of metastatic carcinoma. Failure to rule out other potential etiologies of osseous lesions creates the potential for misdiagnosis and mismanagement. While there is variation in the biopsy methods utilized to obtain a diagnostic specimen, the goals, indications, and procedural techniques are consistent and well established.

The goals of a diagnostic biopsy are to (1) obtain a sufficient amount of specimen, (2) minimize patient morbidity, (3) prevent local dissemination of malignant disease, and (4) avoid interference with future procedures [1]. A diagnostic biopsy should be considered the final preoperative study for a patient with metastatic bone disease and should not be relied upon to establish a definitive diagnosis in isolation. A complete clinical and imaging evaluation should precede the biopsy, as this information is critical for histological interpretation.

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Indications for Biopsy

A confirmatory diagnostic biopsy should be obtained prior to surgical intervention for presumed bony metastases, unless the patient has a previously confirmed diagnosis of metastatic bone disease. Apart from this exception, every patient should undergo a preoperative or intraoperative biopsy to evaluate the osseous lesion of interest prior to definitive surgical management.

A preoperative biopsy for presumed metastatic bone disease can prevent the devastating consequences of inadvertently treating a primary bone malignancy as if it were metastatic carcinoma. Even in patients with a history of cancer, it is neither safe nor accurate to automatically attribute a newly identified osseous lesion to a metastatic process [2]. Biopsies of skeletal lesions in patients with a known history of carcinoma reveal a different neoplastic process as often as 15 % of the time [3]. Concerning bony abnormalities may represent a wide range of alternate pathology from benign processes to primary malignancies of bone.

Establishing a diagnosis and treatment plan based solely upon patient history, physical examination and diagnostic imaging are fraught with the potential for error. Primary and metastatic osseous processes have a broad and nonspecific pattern of presentation. The potential for long periods of latency between the diagnosis of primary carcinomas and the development

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of bony metastasis introduces ambiguity when trying to empirically determine the etiology of newly identified osseous lesions. Even in the context of multifocal bony disease, a presumptive diagnosis of metastasis may be inaccurate. While the clinical suspicion for metastatic bone disease is very high in patients with multiple osseous lesions, the differential diagnosis also includes multiple myeloma, lymphoma, hyperthyroidism, and rare but identified cases of multifocal bone sarcomas [4–8].

For patients presenting with metastatic bone disease of unknown origin, a biopsy is critical but rarely sufficient for a definitive diagnosis. A biopsy alone can often confirm the presence of metastatic carcinoma in general [9, 10], but is ineffective in determining the tissue of origin [11]. Therefore, obtaining a biopsy of a presumed metastatic lesion does not obviate the need for a thorough diagnostic work-up. Determination of the tissue type from which the metastatic process originated is critical for optimal patient care as it helps to inform patient prognosis, perioperative, and surgical management [12–17].

Procedural Techniques

Regardless of whether a diagnostic biopsy is performed in a percutaneous or open fashion, the principles of a safe and effective musculoskeletal biopsy remain the same. An osseous lesion of unknown etiology should be presumed to be a primary musculoskeletal malignancy until proven otherwise. Therefore, biopsies of presumed metastatic disease should be performed in a manner consistent with the treatment of primary bone malignancies.

In approaching the lesion of interest as if it were a primary bone sarcoma, one must be cognizant that violation of the lesion imparts the risk of iatrogenic local disease dissemination. Any instrument or tissue that communicates with the lesion should be considered to be contaminated with cancerous cells. Therefore, whether open or percutaneous, the soft tissue tract through which a biopsy is performed is considered to be contaminated with potentially malignant cells and needs to be positioned in a manner that will facilitate its ultimate excision. To that end, biopsy incisions should be minimized while providing access to diagnostic tissue and oriented longitudinally, in line with an extensile surgical approach (Fig. 11.1). Oriented in this manner, biopsy tracts can be excised in an elliptical fashion in continuity with the final specimen if an en bloc resection is indicated. Complete excision of a transverse biopsy incision on an extremity necessitates the resection of a much larger area of soft tissue, often requiring complex reconstruction for dermal coverage.

The biopsy tract should be planned to span the shortest possible distance from the skin to the lesion while being located within a single muscular compartment and away from critical neurovascular structures. In this manner, potential disease dissemination is limited to a single compartment and spares vital structures, the contamination of which compromises limb-sparing surgery. Following the procurement of a specimen, absolute hemostasis is the goal. A hematoma arising from a biopsied malignancy contains cancerous cells. An expanding hematoma may dissect through tissue planes, introducing malignant cells throughout the extremity, increasing the risk of disease dissemination and complicating limb-sparing procedures.

A bone scan may further aid in the determination of the optimal biopsy location. By identifying multifocal osseous disease, a bone scan may reveal the presence of a readily accessible osseous lesion. The histologic diagnosis of one lesion in multifocal disease is considered representative of the other lesions, assuming that they have a similar morphology [2].

When an extraosseous soft tissue mass is present, it should be biopsied preferentially in order to avoid violating cortical bone and further weakening a bone at risk of fracture. However, in the absence of tumor soft tissue extension a cortical window osteotomy may be required to access the lesion of interest. In order to minimize the structural derangement resulting from a cortical window, the osteotomy should be longitudinally oriented, be oblong in shape, and have

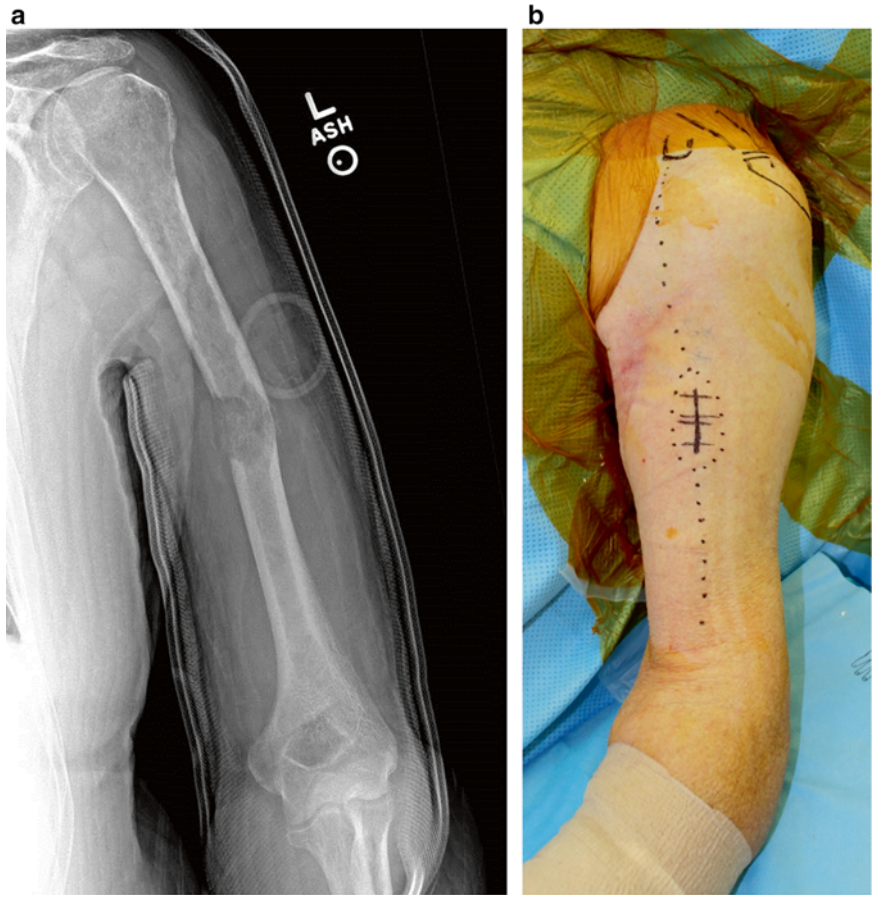

Fig. 11.1 (**a**) An anteroposterior radiograph of a suspected metastatic lesion in the humeral diaphysis. (**b**) The *solid line* indicates the planed open biopsy incision, longitudinally oriented within an extensile approach, indicated by the *dotted line* extending proximally and distally. The *dotted ellipse* around the planned biopsy incision indicates an appropriate biopsy tract excision if the biopsy reveals a primary musculoskeletal malignancy

rounded edges. The osteotomy should be narrow and enlarged longitudinally as needed. Increasing the osteotomy transversely, around the circumference of the bone, has been shown to significantly weaken a long bone, predisposing it to fracture. Cortical windowing performed in this manner is believed to preserve the structural integrity of long bones better than that of other geometries [18].

Prior to performing a biopsy, careful planning is essential. Considerations ranging from compartmental anatomy to lesion accessibility and surgical approaches for definitive management must be considered. Improperly placed biopsy tracts alter future procedures in 5 % of bone sarcomas [19]. Even when planning an intraoperative frozen section for the confirmation of metastatic disease, the initial approach should be planned with the aforementioned considerations in mind just in case the intraoperative biopsy reveals an unexpected malignant process.

Biopsy Methods

Whether an open or percutaneous biopsy is performed, appreciation for the general principles of musculoskeletal biopsies is essential. These considerations should be clearly communicated if someone other than the managing surgeon is per-

forming the biopsy. Of equal importance is communication with the pathologist. A patient's clinical history and diagnostic imaging provide important context, facilitating the evaluation of the histopathological specimen.

Incisional Biopsy

With diagnostic accuracy rates up to 98 %, an open incisional biopsy is considered the gold standard for obtaining a histologic diagnosis [20]. If there is a high index of suspicion for metastatic carcinoma to the bone, an incisional biopsy may be performed intraoperatively to obtain histological confirmation prior to the definitive operative procedure [21]. Alternatively, an open biopsy performed as an isolated procedure is rarely warranted as a first-line test due to increased cost, time, and risk of complications associated with the procedure compared to percutaneous options.

The principles of biopsy placement, orientation, and hemostasis are most relevant for incisional biopsies. Following open biopsies, complication rates up to 15 % have been reported in this high-risk patient population, made vulnerable by their underlying malignant pathology and their resultant therapies [19, 22, 23].

Core Needle Biopsy

Compared to open biopsies, image-guided core needle biopsies (CNB) have the advantage of being percutaneous and safe to perform [9, 24, 25]. Procedure-related sedation, recovery, cost, and complications are all lower compared to an open technique [9, 10, 25, 26]. When facilitated by image guidance, diagnostic accuracy rates for CNB have been reported between 74 and 93 % (Fig. 11.2) [9, 24–27]. These rates are predominately a reflection of the techniques' ability to distinguish between different types of primary bone malignancies. However, for confirming the presence of metastatic carcinoma in bone, a less nuanced diagnosis, accuracy rates for CNB have been reported as high as 97 % [9, 10].

The main advantage of a CNB over fine-needle aspiration (FNA), an alternate percutane-

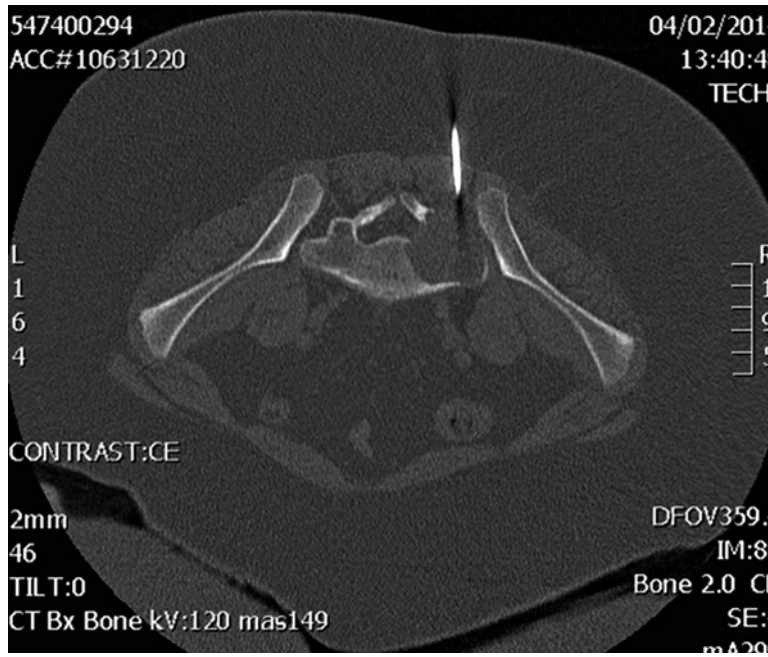

Fig. 11.2 An image-guided CNB enables tissue sampling deep structures with relatively minimal morbidity

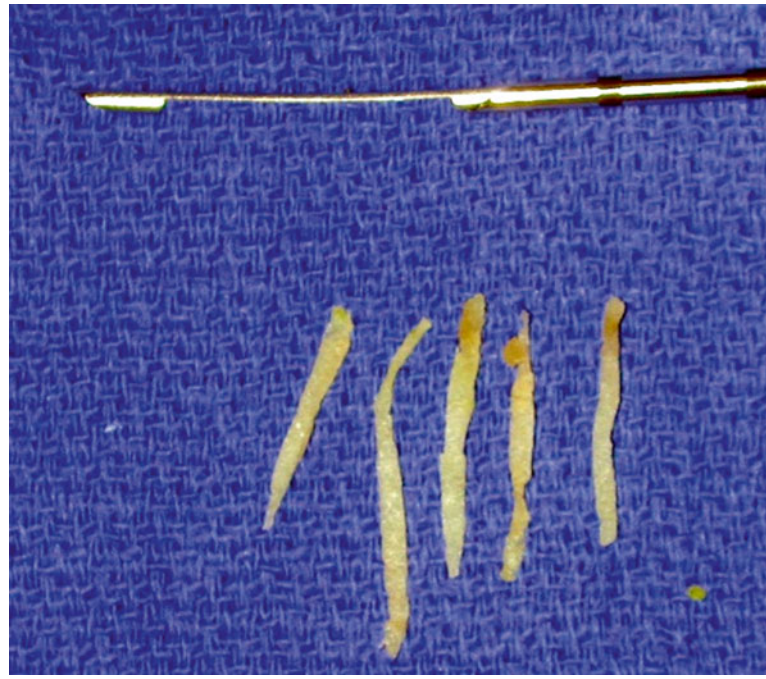

Fig. 11.3 The core biopsy needle with representative specimens. Obtaining a contiguous core of tissue allows maintenance of microscopic tissue architecture to facility histologic diagnosis compared to needle aspirations

ous modality, is its ability to retain normal tissue architecture which greatly facilitates histologic evaluation (Fig. 11.3).

Fine-Needle Aspiration

Similar to a CNB, FNA has the advantages inherent with a percutaneous procedure. The disadvantages to FNA compared to other modalities are a relatively low rate of accuracy and the requirement of an experienced cytopathologist for specimen review. The literature reports accuracy rates between 63 and 85 % for image-guided aspirations of bone lesions [26, 28]. For each non-diagnostic sampling a repeat biopsy must be performed, causing significant increases in time, cost, and patient anxiety. Proponents of FNA report a cost saving compared to open procedures; however the additive cost of FNA and the request repeat biopsies have a greater expense than CNB or intraoperative frozen specimen evaluation [24, 29].

Summary

A confirmatory histologic diagnosis of metastatic bone disease should be obtained prior to surgical intervention for an osseous abnormality presumptively attributed to metastatic carcinoma. The cost, time, and risks associated with a biopsy are negligible compared to the catastrophic consequences of inadvertently treating a primary bone malignancy as if it were metastatic disease.

Whether an image-guided percutaneous or open incisional biopsy is performed, the same principles of musculoskeletal biopsies must be respected and the lesion should be treated as if it were a sarcoma until proven otherwise. To this end, biopsy tracks should be positioned within a single muscular compartment while avoiding contamination of neurovascular structures. Any incision should be minimized in size and oriented longitudinally within an extensile approach to facilitate its ultimate excision should the need arise.

Both CNB and intraoperative frozen sections are reliable, safe, and cost-effective means to confirm, or exclude, the presence of metastatic carcinoma in an impending or realized pathologic fracture.

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Part IV

Medical Therapy

12 Bisphosphonates, Denosumab, and Anabolic Agents in the Treatment of Metastatic Bone Disease

Z. Deniz Olgun, Arianna Gianakos, Jonathan E. Jo, and Joseph M. Lane

Metastatic bone disease represents invasion of the skeleton by tumor from a distant site that leads to lesional growth and ultimately a weakening of the structural skeleton to the point of spontaneous fractures. A malignant tumor per se lacks the potential to cause direct bone loss and therefore must rely on the recruitment of osteoclasts to create the cavity where it can grow. These osteoclasts derive from monocytes and are stimulated in part by the production of receptor activator of nuclear factor kappa-B ligand (RANKL) by the tumor cells and a series of other factors. These and other factors cause the recruitment of monocytes to the site adjacent to the tumor and the conversion of pre-osteoclast to osteoclast, which will in turn create the cavity to hold the expanding metastasis. As consequence of this phenomenon, medical management has aimed at preventing recruitment and activation of osteoclasts in association with metastatic tumor.

Two classes of drugs are currently used to regulate osteoclast activity, each targeting a different component of the activation pathway (Fig. 12.1). One family consists of the bisphosphonates, which alter bone mineralization via a multitude of mechanisms. These drugs, discovered over 40 years ago, are analogs of inorganic phosphate that are specifically drawn to bone due to their inherent chemical structure [1]. They bind directly to hydroxyapatite minerals, and differing adsorption affinities contribute to the pharmacokinetic variations amongst the bisphosphonates [2]. Once localized to mineral surfaces, they are subsequently taken up by surrounding osteoclasts. The non-nitrogen-containing bisphosphonates are metabolically incorporated into non-hydrolysable analogs of adenosine triphosphate (ATP). These analogs interfere with ATP utilization and mitochondrial activity, which may ultimately trigger osteoclast apoptosis. Alternatively, nitrogen-containing bisphosphonates inhibit the mevalonate synthesis pathway, causing an accumulation of intermediate substrates that disrupts intracellular signaling and osteoclast activity [3, 4]. Bisphosphonates may also have a protective role for osteocytes, an attribute contributing to their overall antiresorptive properties [5].

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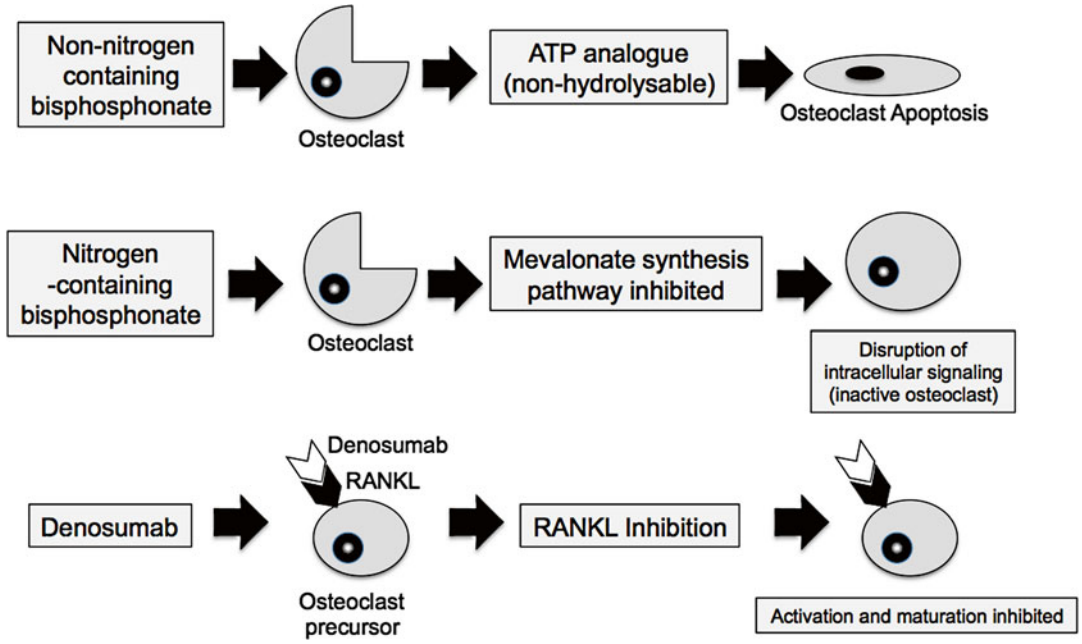

Fig. 12.1 The mechanisms of action of bisphosphonates and denosumab with relation to the osteoclast. *RANKL: receptor activator of nuclear factor kappa-B ligand*

Because these drugs are retained in the bone, they characteristically have a half-life spanning multiple years and may have effects lasting for years after administration [2–4].

The second class of medication consists of the denosumab family. These antiresorptive drugs are fully human monoclonal antibodies against RANKL, which is a key cytokine in recruiting osteoclasts for bone resorption. Denosumab binds to and inhibits RANKL, which inhibits osteoclast maturation and activation [5, 6]. The biochemical structure does not lend itself to the skeletal retention seen with bisphosphonates, and thus the half-life is only several weeks with effects lasting several months [6, 7].

Bisphosphonates have been used initially to prevent the hypercalcemia of malignancy and have been quite effective in that function [8–15]. Most have been used extensively to prevent bone penetration and growth of malignancy by inhibiting the ability of the resident tumor to expand its foothold in the skeleton. A number of outstanding studies, including multiple meta-analyses, have consistently demonstrated that the bisphosphonates are effective in markedly decreasing skeletal events, complications of which are always a cause for concern when treating patients with metastatic bone disease. Various clinical trials have evaluated the efficacy of different bisphosphonates in the treatment of hypercalcemia of malignancy [8–15]. A meta-analysis of randomized clinical trials by Machado et al. found that clodronate, pamidronate, and zoledronate were associated with reductions in morbidity in cancer patients with metastatic bone disease [8]. Phase III clinical trials of bisphosphonates have established their efficacy against bone complications in patients with breast cancer [9] while randomized control trials have shown skeletal-related event reductions with zoledronic acid in patients with breast cancer, prostate cancer, and multiple myeloma [10–12]. In addition, zoledronate was found superior in initial efficacy in a head-to-head comparison of pamidronate and zoledronate, which was performed in two randomized control trials [13]. These bisphosphonates also have been shown to have some analgesic effect on metastatic bone pain [14]. In a systemic review of the role of bisphosphonates on skeletal morbidity in bone metastasis, bisphosphonates were shown to significantly increase the time to

first skeletal-related event suggesting that treatment with them should be initiated when bone metastases are diagnosed [15].

Denosumab similarly will lower hypercalcemia by inhibiting the osteoclast pathway. Its main action is to prevent the development of newly formed osteoclasts but it will not limit the activity of pre-existing osteoclasts. In most comparisons it appears to be more effective than bisphosphonates with the exception of multiple myeloma [16–22]. Denosumab does not bind to bone and requires constant dosing. Several studies have tested its efficacy. An evaluation of subjects undergoing denosumab treatment for 5 years found normal bone quality with reduced bone turnover, consistent with its mechanism of action, continued bone mineral density increases, and low fracture incidence [16]. Treatment with denosumab has been proven to increase hip and spine strength as well as bone mineral density, volumetric bone mineral content, and density-weighted polar moment of inertia along the radius compared with both baseline and placebo, suggesting positive treatment effects in both the trabecular and cortical bone compartments [17, 18]. Direct comparisons of denosumab and bisphosphonates appear to favor denosumab. Denosumab was compared to zoledronate in two double-blind, randomized, controlled trials which showed either non-inferiority or superiority of denosumab to zoledronate with regard to skeletal-related events [19–21]. Lastly, even in situations of soft tissue involvement there appears to be some data to suggest that these agents may affect non-osseous metastases as well. In a randomized phase III study, denosumab was also more effective in delaying or preventing skeletal-related events in patients with bone metastasis from solid tumors and also prevented pain progression compared to zoledronate [22].

By lowering bone turnover, bisphosphonates and denosumab result in a loss of heterogeneity of the skeleton and accumulation of aged, non-replaced bone. Accumulation of microdamage has been established in older bone, but more recently studies have demonstrated that cancellous bone is susceptible to post-translational modifications of collagen, such as non-enzymatic glycation [23]. This occurs through the presence of extracellular sugars and causes the formation of advanced glycation end-products (AGEs). The accumulation of AGEs in bone leads to abnormal cross-linking of collagen resulting in an increase in its propensity to fracture [23]. Several consequences have been noted clinically in the use of these agents. Most notably osteonecrosis of the jaw has occurred in the long-term use of bisphosphonates particularly accompanying simultaneous use of chemotherapy and immunosuppressive agents (e.g. corticosteroids) [24–27]. Bi et al. demonstrated that the development of necrotic bone and impaired soft tissue healing was dependent on long-term use of high-dose bisphosphonates, immunosuppressive and chemotherapy drugs, as well as mechanical trauma [28]. It is highlighted by infections and bareness of the bone. Patients should improve their oral hygiene while oncologists and dentists should be aware of this complication and its management [28]. There has been reported a slightly but significantly increased risk of osteonecrosis of the jaw with denosumab [29].

A second observation is the development of atypical femoral fractures. In these often transverse fractures, there is also a beak, evidence of a pre-existing stress fracture, which also manifests itself as a long prodromal period of pain before the fracture takes place (Fig. 12.2). Bilaterality is common and when that does occur usually it is in the exact same anatomic location (Fig. 12.3). This has been particularly the case with bisphosphonates and when dosed over a long period of time. A special notice is seen when associated with treatment of myeloma. Most recently, this has occurred in the setting of long-term survival of breast cancer patients using these agents.

By the definition submitted by the Task Force of the American Society for Bone and Mineral Research, to be considered atypical, femoral fractures must demonstrate certain major features and may or may not display minor features (see Table 12.1) [30]. Although atypical femoral fractures have initially been defined in osteoporotic patients on long-term bisphosphonate treatment with no evidence of malignancy, the common utilization of these agents as bone-protective drugs

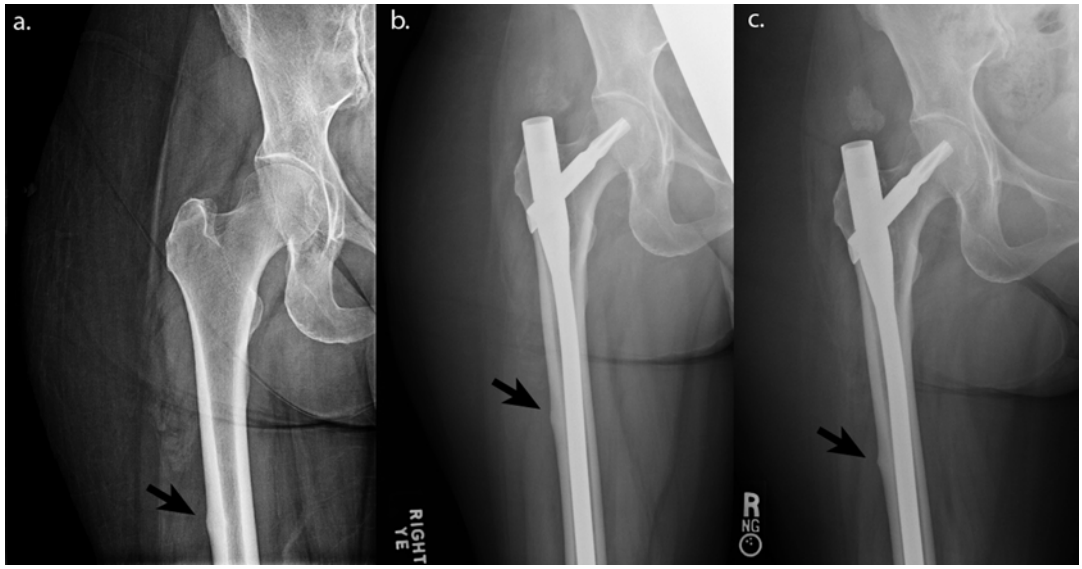

Fig. 12.2 Fifty-five year-old female patient diagnosed with metastatic breast cancer 6 years ago for which she had been on chronic zoledronic acid treatment. Patient presented to the office with insidious onset right thigh pain of 3 months' duration (**a**). Note thickening of the lateral cortex (*black arrow*), a component of atypical femoral fractures. As pain was the presenting symptom, patient was diagnosed with impending atypical femoral fracture of the right femur and treated with prophylactic intramedullary nailing. (**b**) Zoledronic acid was also discontinued and teriparatide treatment initiated. Pathology report of canal reamings was negative for metastatic disease. (**c**) Eighteen months after fixation, stress reaction has remodeled considerably. Patient remained cancer-free during the treatment of her impending fracture

in metastatic cancer and these patients' relative longevity with modern treatment may have left them vulnerable to this entity as well. Puhaindran et al. studied the incidence of atypical femoral fractures in a retrospective cohort of 327 patients with malignancy receiving bisphosphonate treatment and identified four patients (1.2 %), three with breast cancer and one with multiple myeloma, that sustained an atypical femoral fracture out of 14 femoral fractures altogether [31]. Chang et al. reported six atypical fractures out of 62 femoral fractures in a mixed cohort of breast cancer and multiple myeloma patients and also demonstrated patients with atypical fractures received more intravenous bisphosphonates, zoledronic acid particularly, and were more likely to develop osteonecrosis of the jaw [32]. Many independent case reports have also been published.

Denosumab, which is a drug more recently developed, has been associated with the rare occurrence of these atypical fractures but often in the setting of prior long-term bisphosphonate therapy. Literature of atypical femoral fractures associated with denosumab therapy is as yet limited to case reports only [33–35].

As a consequence of these adverse events there is controversy as to how long the bisphosphonates and denosumab should be administered to cancer patients. Questions have arisen whether a loading form can take place, followed by a bone holiday akin to the method now utilized in osteoporosis. Denosumab does not bind irreversibly to bone and will undergo a recovery phase in which there is a hyper-metabolic state compared to the bisphosphonates. All may offer a lower risk for these adverse events. At the time of the writing of this chapter, the actual dosing process for both bisphosphonates and denosumab had not been established as an area of question.

The bisphosphonates appear to have some efficacy when used locally during surgical treatment of bony metastases as well. Bobyn et al. have demonstrated that porous prostheses that have had bisphosphonate surface treatment have improved

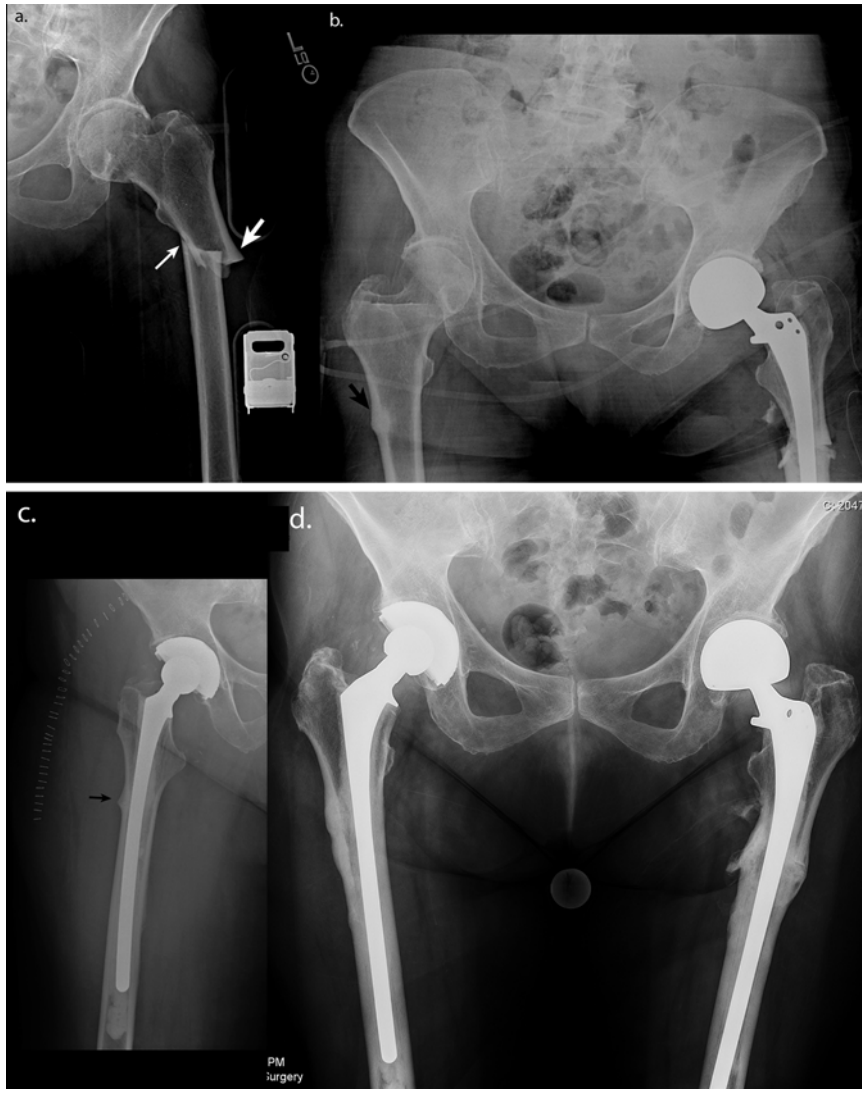

Fig. 12.3 Seventy-four year-old female patient with a diagnosis of multiple myeloma on long-term (8 years) zoledronic acid therapy, presenting to the emergency department with subtrochanteric femoral fracture displaying atypical features incurred with minimal trauma (ground-level fall) (**a**). Note thickening of lateral cortex (large *white arrow*) and medial beaking (small *white arrow*), two major features of atypical femoral fractures. At the time of presentation, patient had no active myelomatous lesions. (**b**) Patient was treated emergently with long-stemmed hemiarthroplasty. Note lateral cortical thickening on the contralateral side (*black arrow*). Patient was asymptomatic on this side at this time. (**c**) Nine months after surgery, while under close follow-up for possible atypical fracture of the contralateral femur, patient developed symptoms of groin and thigh pain on this side. She was indicated for a total hip arthroplasty in the setting of primary osteoarthrosis of this hip. (**d**) At final follow-up, 10 years after initial surgery, patient's stress reaction on the *right side* and fracture on the *left* have completely healed. Patient remains cancer-free

bone ingrowth and a greater pull-out strength [36]. The elution characteristics of locally delivered bisphosphonate have been described previously in the literature. Using this same delivery system in their 2005 paper, Tanzer et al. analyzed the amount of peri-implant bone formed around a cylindrical porous implant dosed with zoledronic acid and placed in the intramedullary canal of canine ulnae. Compared to the control group, bone in the zoledronic acid-dosed animals

Table 12.1 2010 American Society for bone and mineral research task force case definition of atypical femoral fractures [30]

Major features[a]:
• Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
• Associated with no trauma or minimal trauma, as in a fall from a standing height or less
• Transverse or short oblique configuration
• Non-comminuted
• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor features:
• Localized periosteal reaction of the lateral cortex[b]
• Generalized increase in cortical thickness in the diaphysis
• Prodromal symptoms such as dull or aching pain in the groin or thigh
• Bilateral fractures and symptoms
• Delayed healing
• Comorbid conditions (e.g. vitamin D deficiency, RA, hypophosphatasia)
• Use of pharmaceutical agents (e.g. bisphosphonates, glucorticoids, proton pump inhibitors)
Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures

From Shane, E., et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res, 2014. 29(1): p. 1–23. Reprinted with permission from John Wiley and Sons

[a]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures

[b]Often referred to in the literature as "beaking" or "flaring"

occupied 2.34-fold more space in the intramedullary canal, demonstrated greater than 58 % more ingrowth into the implant and individual bone islands, while of equivalent number, were 71 % larger [37]. This improved ingrowth was found to be long-lasting as well, as reported by Bobyn et al. in 2009 [36]. These authors also demonstrated that very small doses of zoledronic acid appear to be as effective [36]. Similar improvements in bone ingrowth were demonstrated for alendronic acid-coated implants as well [38].

For implant choice during total hip arthroplasty in the metastatic setting, porous ingrowth prostheses have been rarely used and most orthopedic surgeons prefer cemented implants in this setting. Recent studies have demonstrated long stem prostheses with porous ingrowth appear to have the same clinical efficacy as the cemented prostheses without the pulmonary challenge caused by polymethymethacrylate (PMMA); therefore, bisphosphonates may have a role in these prostheses in the setting of metastatic disease. An alternative approach is to mix bisphosphonates into the PMMA, allowing the drug to migrate out of the cement to the adjacent bone and develop a shield to protect the bone from tumor growth. Healey and his co-workers have demonstrated that up to ten percent replacement with bisphosphonates does not alter the mechanical properties of the cement, which represents a potential method for supporting prostheses set in bone with large tumor burden [39]. Randomized control studies testing out the efficacy of these agents are lacking at this time.

Another problem associated with the treatment of metastatic disease relates to osteolysis, which may cause loosening of prostheses independent of tumor. This could be troublesome particularly with long-term survivors. Patients who frequently receive chemotherapy become malnourished and this may result in a weakening of the bone-prosthesis attachment. In addition, some patients may develop cancer in the setting of an established diagnosis of osteoporosis while others develop osteoporosis secondary to the drug therapy they are receiving for it (i.e. steroids and chemotherapy). Samples of therapies that may in fact encourage osteoporosis are particularly related to multiple myeloma where steroids are often used and breast cancer where aromatase inhibitors have been developed to compromise the estrogen pathway [40]. In the absence of estrogen, the skeleton will rapidly lose bone mass and osteoporosis has been documented with these agents [40–42]. Therefore, antiresorptive agents may play a role in preventing osteoporotic weakening of the skeleton and offsetting a potential fracture risk in terms of minor metastatic penetration. The osteoporosis doses for the bisphos-

phonates and denosumab are far lower than those used for the treatment of hypercalcemia associated with cancer and therefore may be safer. In fact there is no clear indication whether the cancer dose itself may represent over-treatment of osteoporosis.

Patients with metastatic disease often receive radiotherapy during the course of their treatment. Combined with relative physical inactivity, this may preclude them to stress fractures when activity does occur. Bisphosphonates have been utilized previously in the prophylaxis for stress fractures. In a study where young, healthy military recruits were randomized to prophylactic treatment with risedronate versus placebo, with the intention to lower rates of stress fracture in this high-risk group, it was concluded that prophylactic treatment with risedronate in a training population at high risk for stress fracture using a maintenance dosage for the treatment of osteoporosis does not lower stress fracture risk or severity [43]. The effect of bisphosphonates on bone healing has also been investigated. In a recent animal study, mature rats received ibandronic acid for 3 weeks before undergoing a standardized tibial osteotomy treated with compression plates. Mechanical and histologic markers of bone healing were significantly reduced in the ibandronate group. The authors concluded that bisphosphonate therapy had detrimental effects on primary bone healing [44].

While there is conflicting evidence regarding the effect of bisphosphonates on bone healing, it is an established fact that atypical fractures occur during protracted bisphosphonate treatment and, compared to "typical" fractures, generally require a longer time to heal. Therefore, it is imperative that bisphosphonates be discontinued when clinical signs/symptoms or radiographic markings of a possible stress fracture appear until such a time that there is evidence that the fracture has healed completely. This is critical for the management of these patients.

Increasing reports of atypical fractures related to protracted bisphosphonate treatment in the setting of osteoporosis have led to the introduction of the "drug holiday," a scheduled period of time during which the bisphosphonate is discontinued, usually after 3–5 years of treatment. Even in the more prolific osteoporosis literature, the details of whether or not this drug holiday should occur, when it should take place or how long it should last have not yet been agreed upon, much less standardized [45–49]. The logic behind the drug holiday is sound and may be a good idea to harness the beneficial effects of bisphosphonates while avoiding the adverse effects of long-term therapy. It is therefore a natural extension of this logic that patients on bisphosphonate therapy for metastatic disease or myeloma be offered a similar drug holiday. However, one of the reasons for bisphosphonate utilization in these patients is the protective effect of these medications against bone metastases. It is unclear whether a drug holiday in this setting would be beneficial to the patient and there exists no literature on the subject. Furthermore, physicians should take into consideration the variable nature of these patients' malignancy and survival expectations. Drug holidays for these patients are not part of our routine practice and should be considered on a case-by-case basis. Rather than scheduled drug holidays, in the case where a malignancy patient presents with an adverse effect related to protracted bisphosphonate use, our practice is to discontinue the bisphosphonate and initiate treatment with a different anabolic agent, as detailed below.

If an atypical fracture does occur, it may require interventions in addition to operative reduction and fixation to heal. As an alternative to fortify bone healing in these fractures, an anabolic agent such as recombinant parathyroid hormone (PTH) should be considered. PTH 1–34, commonly known as teriparatide, inhibits the apoptosis of osteoblastic precursor cells and promotes their maturation and activation [50]. The net result is enhanced osteoblastic activity and increased bone formation [50, 51]. Randomized control studies suggest PTH may augment fracture healing in pelvic fractures and Colles' fractures, accelerate spine fusion, and decrease pedicle screw loosening after spine surgery [52–55]. Therefore, anabolic agents may be useful second-line medications in patients with stress fractures or adverse events from bisphosphonates, such as atypical fractures or osteonecrosis of the jaw.

Newer agents are undergoing clinical trials and are more specific. A cathepsin-K inhibiting agent has been quite efficacious in osteoporosis, largely affecting resorption while formation is only marginally affected. Finally, there are new anabolic agents such as anti-sclerostin antibody and anti-DKK antibody. These agents block the inhibitors of the WNT pathway. The WNT pathway is activated during bone formation and prolonged functioning of this pathway has been shown in animal models and now in clinical trials to augment bone mass and may play a role in rebuilding the skeleton.

This chapter summarizes the role of drugs that were originally developed for cancer and then moved into the osteoporosis world. They may in fact be quite helpful in preventing metastatic disease from growing in the skeleton, for correcting any bone loss or deficiencies within it and decreasing the likelihood of pathologic fractures. As these osteoporotic drugs become more specific to particular molecular pathways in bone resorption, the number of their safety issues decreases and they can be directed toward specific deficiencies that occur in the skeleton secondary to cancer.

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Biotargeting in Metastatic Bone Disease

13

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Over one million cases of cancer are diagnosed each year in the USA, and more than half of these will go on to involve the skeleton [1]. Bone metastases can be the presenting symptoms of previously undiagnosed malignancy; and, it can also be the harbinger of death in the form of end-stage oncologic disease. The two most common etiologies of metastatic bone disease (MBD) are breast and prostate cancer, which account for 80 % of cases. This association is logical as these two diseases are the most prevalent primary tumors. Additional sources of MBD include lung, kidney, colon, and thyroid cancers. Multiple myeloma and lymphoma/leukemia account for fewer cases but also have a tendency to develop bony lesions.

Several important principles of metastatic disease have been elucidated and accepted as fairly universal across pathologies. The mechanism of metastasis involves four key steps: (1) primary tumor growth and angiogenesis; (2) intravasation and dissemination through the vasculature and/or lymphatic system; (3) tumor cell arrest and extravasation at the secondary site (bone, in our focus); and (4) metastatic tumor cell survival and proliferation.

Animal model studies have shown that millions of tumor cells are released into the circulation by a primary tumor; however, only a few micrometastases are produced. There are many theories for this seemingly inefficient process. One theory suggests that a subset of tumor subclones are responsible for navigating through all of the steps of metastasis and, if they are not present, the cell will undergo apoptosis. Another theory suggests that most of the primary tumor cells have to develop multiple genetic abnormalities, a so-called metastatic signature, before obtaining metastatic potential. Whether it is a small subset or more universal change, research strongly suggests genetic alterations that act primarily on tumor dissemination. For example, increased activation of *Ras* initiates the Raf-MEK-ERK-MARK pathway, which leads to uncontrolled cell proliferation. Another feature of tumor cell survival is the ability to avoid immunological detection. Acquiring cell properties similar to osteoblasts, osteomimicry, or endothelial cells, vasculogenic mimicry can make tumor cells more invasive and resistant to local host defenses.

The interaction between the tumor cells and the extracellular matrix (ECM) is a critical step in the metastatic process. Invasion of the requires primary tumor cells to detach from each other,

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interact with the matrix proteins, degrade the matrix, and migrate through it to reach a blood vessel or lymphatic channel.

Bone has high potential for metastatic nesting partly due to its high vascular flow through red bone marrow. Furthermore, bone contains a proliferative quantity of growth factors, especially during bone turnover phases. Transforming growth factor-beta (TGF-b), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), and bone morphogenic proteins (BMPs) can aid in tumor cell proliferation, chemotaxis, and avoidance of apoptosis. Multiple chemokines are intricately involved in this process. Chemokine ligand 12 (CXCL12), known as stromal cell-derived factor 1, is produced by bone marrow stromal cells, as the name suggests. When CXCL12 binds chemokine receptor 4 (CXCR4) on tumor cells, it directs the tumor cell to "home-in" and seed to bone. When CXCR4 is neutralized by a monoclonal antibody, metastasis decreases; this is an example of the therapeutic potential in elucidating the specific molecular pathways of the metastatic process.

Similarly to the process of detaching from the primary tumor, metastatic tumor cells must regulate the expression of cell adhesion molecules (CAMs) to attach to the host organ's vascular endothelial cells in preparation for invasion and seeding. Cadherins, selectins, and integrins are classes of CAMs shown to be involved in this process. Once into the secondary organ, metastatic tumor cells cause dysregulation with matrix-degrading enzymes called matrix metalloproteinases (MMPs). Increasing the basement membrane permeability, this process in addition to activation of motility factors, such as IGF-1 and interleukin-8 (IL-8), permits tumor cell migration. Lastly, the metastatic tumor cells require a vascular supply and activate unregulated angiogenesis.

Biotargeting in Breast Cancer

A novel and promising target in the prevention of breast cancer metastasis to bone is IL-8. Elevated levels of IL-8 have been observed in a variety of breast cancer cell lines in vitro, as well as the plasma of patients with bone metastases [2–4]. Breast cancer cell lines that express high levels of IL-8 have been shown to grow aggressive bone tumors in vivo, while lines with reduced levels of IL-8 expression do not. In addition, patients with high serum levels of IL-8 have been shown to have a poorer relapse survival [5]. IL-8 has also been shown to be a direct stimulator of osteoclastogenesis and bone resorption [6], and this mechanism is independent of the RANKL pathway. IL-8 directly stimulates osteoclasts, as well as their precursor cells via activation of CXCR1 an IL-8 receptor located on mature osteoclasts and osteoclast precursor cells [3]. Therefore, anti-IL-8 therapy may prove to be of benefit in prevention of breast cancer metastasis to bone.

Another promising target in the prevention of breast cancer to bone, especially in patients with concomitant inflammatory conditions, such as rheumatoid arthritis, is interleukin-17A (IL-17A). Studies have shown that chronic inflammation can lead to the development of various types of malignancies [7, 8] and in fact patients with breast cancer and inflammatory arthritis have a poorer prognosis and decreased survival when compared to patients without concomitant autoimmune disease [9, 10]. IL-17A is a pro-inflammatory cytokine, which can in turn stimulate the release of several other cytokines including interleukin-6 (IL-6) and IL-8 to help mediate, its pro-inflammatory effects [11]. IL-17A has been linked to an increased incidence in metastasis in breast cancer as well as other cancers. Antibodies directed at IL-17A have been shown to decrease the incidence of breast cancer metastasis to bone in vivo, as well as invasiveness of breast cancer cell lines in vitro [12–15]. This is thought to be due to the downregulation of CXCL12/SDF-1, which is known to be involved in cancer metastasis [15–17], and is actively being targeted as a treatment strategy for a variety of cancers [18, 19].

A final promising new treatment strategy for the treatment of metastatic breast cancer to bone is recombinant Apo2 ligand/TNF-related apoptosis-inducing ligand (Apo2L/TRAIL). This treatment strategy targets tumor cells themselves instead of targeting components of the bone

microenvironment that make up a bone metastasis niche which is thought to regulate a cancer's ability to metastasize. Apo2L/TRAIL is a member of the TNF family that induces apoptosis in a variety of cancer cell lines, and appears to preferentially target tumor cells as opposed to normal cells, making it a more tumor-specific treatment, as opposed to a treatment with many systemic side effects [20–23]. Recombinant human apoptosis ligand 2/tumor necrosis factor-related apoptosis-inducing ligand (rhApo2L/TRAIL) is an optimized soluble form of an endogenous apoptosis-inducing ligand, which has been found to have antitumor activity in both in vitro and in vivo models. In addition it has been shown to be effective when used alone and in combination with more conventional therapies [24]. Clinical trials have shown that rhApo2L/TRAIL is generally well tolerated and safe both alone and in combination with other agents [25–27]. A recent study examined the effect of rhApoL2/TRAIL treatment both alone and in combination with a RANKL inhibitor, a more conventional treatment for bone metastasis. They found that treatment with rhApoL2/TRAIL in an animal model of breast cancer rapidly reduced the skeletal tumor burden in their animal model. In addition, addition of a RANKL inhibitor further reduced the skeletal burden of disease [28]. This is an exciting new potential therapeutic option for patients with skeletal metastasis, and could potentially augment the more traditional treatment approaches we have now for these patients.

Biotargeting in Prostate Cancer

Bone morphogenetic proteins (BMPs) belong to the TGF-beta superfamily and play an important role in skeletal growth and development. BMPs are also detected in both primary tumors and metastatic bone tumors in prostate cancer [29, 30]. Thus, BMP-mediated pathways are assumed to be involved in the osteoblastic metastasis of prostate cancer. BMPs are thought to be promoters of prostate cancer metastases to bone by stimulating cellular migration and invasiveness of prostate cancer cells. In addition, the overexpression of the BMP antagonist, noggin, in prostate cancer cell lines has also been shown to inhibit bone metastasis in a mouse model [31, 32]. Therefore, targeting BMPs may play a crucial role in the prevention of prostate metastasis to bone.

The Wnt signaling pathway has been implicated in a variety of cancers including a number of GI and GU cancers, including prostate cancer [33]. The Wnt proteins bind to a number of receptor complexes and ultimately induce β-catenin activity. Wnt signaling is essential for skeletal growth [34, 35] and has been shown to be involved in prostate cancer bone metastasis [36]. Wnt proteins have been shown to increase expression of bone morphogenetic protein-4 (BMP-4) and bone morphogenetic protein-6 (BMP-6) in prostate cancer cell lines, and this BMP expression contributes to the pro-osteobastic activity of the Wnt proteins. However, Wnt proteins also mediate osteoblastic activity through BMP-independent pathways, indicating that the Wnt proteins may be a potential target in treating prostate cancer bone metastasis [37].

Biotargeting in Thyroid Cancer

Angiogenesis plays an important role in the ability of tumor cells to grow and metastasize, and is thought to be quite important in the development of more aggressive thyroid cancers. Vascular endothelial growth factor (VEGF) is an endothelial-specific mitogen and plays a key role in tumor angiogenesis in thyroid carcinoma, as well as tumor cell proliferation through downstream activation of tyrosine kinase [38–40]. In general, tyrosine kinases function to stimulate tumor proliferation, angiogenesis, tumor invasiveness, and metastasis. There has been an interest in using tyrosine kinase inhibitors in the treatment of thyroid cancer since the discovery of mutations in tyrosine kinases RET and RAS that play a role in oncogenesis, in addition to their ability to inhibit growth factor receptors such as VEGF receptor [41, 42]. Tyrosine kinases affect regulation of both cancer cells and noncancerous cells, and therefore, targeting downstream targets may provide more tumor-specific effects, and help to limit systemic toxicity. VEGF mRNA and protein levels are associated with high mitogenic

activity and increased growth in thyroid cancer cell lines. The overexpression of VEGF in differentiated thyroid cancer has been correlated with poor prognosis, increased risk of recurrence, and greater probability of metastasis [43, 44]. Inhibition of VEGF production or VEGFR phosphorylation has been shown to reduce the growth of thyroid cancer cell lines as well as growth of these cell lines in animal model [45–47]. Studies have also shown stabilization of disease progression, as well as prolonged progression-free survival in thyroid cancer patients treated with anti-VEGF therapy [48, 49]. VEGF inhibitors are currently being used in the management of renal cell carcinoma, as well as gastrointestinal stromal tumors (GIST), among others, and may offer a promising new target in the management of thyroid cancer metastases to bone.

Epidermal growth factor receptor (EGFR) is a growth factor that stimulates cell growth, proliferation, and differentiation. Mutations that lead to EGFR overexpression have been associated with a number of cancers [50]. Binding of EGFR to its cell surface receptor initiates several signal transduction cascades, principally the MAPK, Akt, and JNK pathways, leading to DNA synthesis and cell proliferation [51]. EGFR overexpression is implicated in the progression of aggressive thyroid carcinoma [52] and EGFR has been found to be significantly overexpressed in metastatic thyroid tumors compared with primary tumors [53]. In addition, co-expression of EGF and EGFR is also associated with bone metastasis thyroid cancer [54]. Disruption of EGFR signaling decreases the growth and invasion of thyroid cancer cells in vitro [55].

Given the importance of both EGFR and VEGF in the progression of metastatic thyroid cancer, blockade of both EGFR and VEGFR tyrosine kinase activity may offer an important approach for the treatment of bone metastasis in the setting of thyroid cancer. Suppression of both EGFR and VEGFR signaling significantly reduces thyroid cancer tumor volume in nude mice by both direct antitumor and antiangiogenic effects [56]. A phase II multicenter study in France was recently completed to examine the safety of sunitinib, a multiple receptor tyrosine kinase inhibitor, in the treatment of thyroid cancer. Results of the study are not yet available, but will hopefully lead to phase III clinical trials to examine the drug's efficacy in the treatment of thyroid cancer. However, targeting of tyrosine kinase inhibitors effects both cancerous and non-cancerous cells, so blockade of downstream targets may provide more tumor-specific advantages, and limit systemic toxicity.

Biotargeting in Lung Cancer

Lung cancer originates in a highly vascular and well-oxygenated environment with tremendous exposure to toxic elements. Cigarette smoking is a very-well-established major risk factor for lung cancer development. For many cancers, there is an extensive latency period between primary tumor diagnosis and development of metastatic disease. Lung cancer, however, frequently does not display this latency period, suggesting that primary tumor cells are sufficiently adapted to survive at distant sites more readily than other carcinomas. Several features of lung cancer may be responsible: (1) the toxic insults responsible for the initial tumor development may confer additional pro-metastatic mutations; (2) many lung cancers are diagnosed at a late stage.

With medial overall survival of less than 6 months, NSCLC management algorithms do not include a standard prospective screening strategy to detect BMD. The European Society for Medical Oncology (ESMO) recommends a bone scan when there is bone pain, hypercalcemia, or elevated alkaline phosphatase. Skeletal-related events, defined as pathologic fracture, spinal cord compression, palliative radiotherapy, or surgery to bone, consistently predict life expectancy for NSCLC patients [57].

Like many other solid organ tumors, lung cancer cells have distinct preferences for the tissues to which they metastasize, the so-called tissue tropism. The ability of primary tumor cells to direct adaptation at distant sites for future colonization has been termed developing a "pre-metastatic niche" [58]. Evidence suggests that tumor cells navigate through the aforementioned

stages of metastasis via interactions with stromal environments both at the primary site and metastatic site. The role of mesenchymal stem cells (MSCs) in tumor-stromal interaction is an important area of study. Patients with untreated lung cancer without bony metastasis exhibit changes in MSC plasticity that predisposes the bone to osteolysis [59]. These tumor-stromal interactions are critical in the metastatic process and an important potential area of therapeutic intervention.

While there is some evidence to suggest pre-metastatic conditioning in the bone marrow, the bone marrow environment has several molecular features favorable for lung cancer micrometastases [60]. The interaction between osteoclasts and osteoblasts promotes bone degradation, which releases extracellular matrix-bound growth factors. These, in turn, promote the growth of tumor cells. Examples of tumor-secreted factors that stimulate osteoblast and osteoclast activity are interleukins (IL-1, IL-6), receptor-activator-of-nuclear-factor-Kappa-B-ligand (RANKL), parathyroid hormone-related protein (PTHrP), and macrophage inflammatory protein-1-alpha (MIP-1a). Tumor-induced secretion of osteoclastic factors trips a vicious cycle of osteoclast-mediated bone resorption. In addition, proteolytic degradation of bone matrix occurs through tumor secretion of MMP and other proteases released at the tumor-stromal interphase [61]. In turn, osteoclasts then release TFG-beta and IGF-1 from bone matrix which stimulate PTHrP production and, therefore, promotes tumor growth. PTHrP stimulates osteoclast activity, prevents osteoclastic apoptosis, and enhances renal tubular reabsorption of calcium.

Tumor cells achieve local bone resorption by activating osteoclast precursors. The osteoclastogenesis process is regulated by the receptor-activator-of-nuclear-factor-Kappa-B-ligand (RANKL)/RANK/osteoprotegerin (OPG) pathway. RANKL, a member of the tumor necrosis factor (TNF) family, is expressed on the surface of osteoblasts and osteocytes and released by activated T cells. RANKL binds RANK, which is present on osteoclasts and osteoclast-precursors, and activates NF-kB, a transcription factor that is also activated within lung cancer cells by EGFR/oncogenic K-ras [62]. Increased expression of RANKL induces osteoclast formation and activation, which increases bone resorption and local bone destruction. OPG is a soluble glycoprotein that binds RANKL and competitively inhibits the RANK-RANKL interaction.

Targeting this pathway has been the focus of intense research interest in all MBD in solid tumors. Bisphosphonates, synthetic analogues of pyrophosphate, are anti-osteoclastic agents by inhibiting osteoclast-mediated bone resorption. Zoledronic acid has been shown to decrease the number of SREs [63]. More recently, investigations are targeting the RANKL/RANK/OPG pathway directly. Denosumab, a monoclonal antibody that binds and neutralizes RANKL and thereby inhibits osteoclast function, has been approved for use to help prevent SREs in patients with BMD from solid tumors [64]. A phase III trial compared zoledronic acid with denosumab in patients with multiple myeloma or solid tumors (40 % of which were NSCLC); when stratified by tumor type, there was no statistically significant difference between the two therapies for time to first SRE [65, 66]. Bisphosphonate use has been limited in NSCLC as compared with other solid organ cancers; in part, this may be attributable to intrinsic nephrotoxicity of this drug class. Furthermore, previous cisplatin nephrotoxicity and smoking-related arteriosclerosis may limit the therapeutic risk-benefit ratio.

Another potential important mediator in the tumor-stromal interaction is epidermal growth factor (EGF), which directly stimulates tumor cell proliferation and indirectly increases bone stromal favorable for metastasis [67]. Gefitinib, an EGFR inhibitor, may block osteoclast activation by inhibiting EGF signaling in bone stromal cells. Tumor cells release three EGF-like factors: heparin-binding EGF, amphiregulin (AREG), and TGF-alpha; these activate the EGFR pathway in osteoblasts and downregulate OPG expression [68, 69]. Therefore, the disinhibition of this competitive inhibitor of RANK-RANKL osteoclastogenesis should theoretically diminish this vicious cycle. Moreover, there is evidence of osteoblastic reactions in patients treated with

EGF tyrosine kinase inhibitors (TKI); however the mechanism and implications are not well understood.

Biotargeting in Renal Cancer

Because of RCC's poor response to standard chemotherapies, alternative treatment options have been the standard of care for systemic disease. The primary treatment for non-metastatic disease is surgery alone. Until recently, very few systemic treatments have been approved for first-line therapy of isolated renal disease. Prior to 2005, immunotherapy with high-dose interleukin-2 (IL2) and interferon-α (INFα) were the standard therapies available for advanced or systemic RCC. These treatments are not well tolerated by patients due to side effects and have shown only a modest improvement in survival of around 3 months compared to placebo. Starting in 2005, targeted therapies for RCC began to become available. Most of these therapies were believed to be working through inhibition of the VEGF-mediated pathway, which is thought to be deregulated as a result of VHL gene dysfunction. Bevacizumab, an anti-VEGF antibody, was first approved for use in colon cancer patients in 2004. It was found to have a modest response in patients with RCC and was approved for combination use with INFα in 2009 for patients with RCC. It is one of the few treatments now approved for first-line treatment of non-metastatic RCC [79]. The major side effect of this antibody is increased risk of thromboembolic events.

The most recent round of molecular targeted therapies for RCC has focused on the mammalian target of rapamycin (mTOR) pathway. This pathway is involved in the regulation of cell growth and cell proliferation. It has been the focus of research recently in cancer therapy as this pathway appears to be integral to cell proliferation in several cancers [80]. It is thought to work in part by regulating flow of nutrients in and around the cell and may be bringing in new blood supply via angiogenesis by increasing translation of HIF1α and HIF2α. The first intravenous form of an mTOR inhibitor, temsirolimus, was approved in 2007 for metastatic RCC, followed by approval of the oral mTOR inhibitor, everolimus, in 2009. In a randomized clinical trial, temsirolimus was found to improve survival by approximately 3.5 months compared to INFα alone [81]. The side effect profile was also well tolerated by patients. This agent is now being used for patients with poor prognostic risk factors or metastatic RCC.

There are several upcoming targeted therapies that have some promise in the treatment of metastatic RCC. Several new RTK inhibitors that are more directed towards the tyrosine kinase receptors involved in RCC are under development and in early clinical trial. Similarly, there has been work done in the development of more selective VEGF inhibitors. These newer molecules are hoped to reduce the side effect profile compared to the currently available treatments, which may allow for combination therapies and higher dose treatment. This could ultimately help improve survival and decrease metastatic bone disease morbidity.

Unfortunately, all of the agents available to date and even some of the newer therapies on the horizon are cytostatic agents and not cytotoxic [70–75]. As a result, ultimately the RCC cancer cells develop resistance with inevitable disease progression. What is needed now for metastatic RCC are agents that induce cell death. There is some hope in this area. Naptumomab estafenatox is a fusion protein that binds cancer cells and leads to T-cell-activated cell destruction [75]. There is some hope that this could be an effective treatment for RCC and other cancers as well. There has also been work looking at the induction of apoptosis in RCC. Inhibition of the mTOR pathway is thought to partially work through this mechanism [76]. Similarly, targeted therapies looking at inhibition of EGF receptor may be working through induction of cell apoptosis [77, 78].

Recent evidence suggests that the calcium-sensing receptor present in normal renal tissue is up-regulated in metastatic RCC to bone compared to non-metastatic RCC or metastatic lung RCC. In these same cells that showed up-regulation of the calcium-sensing receptor there

was increased RCC cell migration in the setting of a high-calcium substrate [79]. These findings strongly suggest that there are molecular differences in RCC tumors that spread to bone and that there could be potential targets that specifically prevent bone metastasis, such as blockage of the calcium-sensing receptor in high-risk patients. Other targeted therapies that specifically look at the bone environment have focused on proteins that are involved in the angiogenesis pathway. The rationale for studying this pathway goes back to our understanding that RCC is a very vascular tumor and appears to be dependent on that vascularity for growth. The angiopoietin family is a set of proteins that have been studied as potential targets in metastatic RCC. Like the VEGF family, they are involved in vessel development and have shown increased expression in RCC to varying degrees. There is evidence to suggest that decreasing angiopoietin-1 and increasing angiopoietin-2 are linked to a poorer prognosis [80–82]. Molecular studies of cell lines have confirmed that RCC with bone affinity seems to have increased expression of Ang-2 and decreased expression of Ang-1 [83].

Another protein that has been linked to prognosis and pathogenesis of metastatic RCC to bone is semaphorin-4D and its receptor Plexin-B1. Semaphorin-4D (Sema4D) is a membrane-bound and -secreted protein initially identified as a cell signaling molecule present on activated T-cells. Activation of Plexin-B1 through binding of Sema4D is thought to be coupled with c-Met activation, which in turn leads to downstream endothelial cell migration and capillary formation. This pathway appears to be independent of the VEGF-mediated pathway [84, 85, 87]. Newer evidence has also shown that this diverse molecule is implemented in the signaling pathway between osteoclasts and osteoblasts. Most notably, it has been shown to be expressed in high levels on the surface of osteoclasts as well as present in the supernatant of cultured osteoclasts, while its receptor Plexin-B1 has been found on the surface of osteoblasts. Sema4D has been shown to reduce osteoblast differentiation and thereby bone formation. Sema4D knockout mouse models have a higher bone mass phenotype with a higher rate of bone formation [86]. Therefore, this molecule is a potential ideal target for therapy specific for preventing RCC-mediated bone destruction and tumor growth within bone.

Finally, there has also been some headway made in using biomarkers to help predict a patient's response to therapy. This may greatly help treat patients with RCC because there are so many agents available and it is difficult to predict which will be most effective in slowing tumor growth. Work in this area is still ongoing, but the potential for helping treat patients with RCC is high.

Biotargeting in Multiple Myeloma

One of the hallmarks of multiple myeloma, and perhaps the primary concern for orthopedic surgeons, is the extensive destruction of bone. In skeletal lesions, increased production of multiple cytokines (IL-1β, IL-3, and IL-6) helps promote osteoclastic differentiation, while additional factors (TNFα, hepatocyte growth factor [HGF], and VEGF) further support osteoclast survival and bone resorption [89]. Myeloma cells produce macrophage inflammatory protein-1α (MIP-1α), a chemokine involved in cell adhesion and migration, which stimulates survival, proliferation, and migration of myeloma cells [90]. MIP-1α-induced expression of IL-6 and RANKL by local marrow cells may play a significant role in osteoclastogenesis and the development of skeletal lesions [88, 91].

One of the key features that appear to help propagate the survival of myeloma cells is the ability of the cells to create a symbiotic relationship between themselves and the surrounding bone marrow environment. Several novel therapies are now emerging that specifically target that interaction. There has been evidence to suggest that targeting the bone can not only reduce skeletal events in myeloma, but also improve survival. This has been seen in the use of bisphosphonates in myeloma with evidence of improved survival seen in patients placed on

bisphosphonates [92, 93]. Bisphosphonates are currently the standard of care for myeloma-induced lytic bone disease. Bisphosphonates have been found to reduce skeletal events in myeloma patients, but have not been found to reverse the osteolytic process once established. One clinically available option that has strong potential therapeutic benefit in myeloma bone disease is the RANKL inhibitor denosumab. The RANKL, OPG, and Rank pathway is integral to the lytic bone disease seen in all metastatic bone disease and myeloma is no exception [94]. Phase II and III clinical trials are under way for use of denosumab in myeloma patients as an alternative to bisphosphonates.

Some other potential targets that are being looked at as options for directly inhibiting myeloma-induced bone disease include Dickkopf-1 (Dkk-1) and sclerostin [95]. Dkk-1 inhibits the Wnt/beta-catenin pathway by binding to LRP5/6 receptors. Inhibition of Wnt leads to increased bone destruction via osteoclastogenesis and decreased bone formation via reduced osteoblastogenesis. Antibodies directed at Dkk-1 have been shown to reduce osteolysis and increase bone density in myeloma mouse models. Currently, clinical trials are under way looking at potential antibody inhibition of Dkk-1 in metastatic disease and myeloma. Sclerostin is another Wnt/beta-catenin pathway inhibitor that is under investigation as a target to prevent and reverse bone loss in patients with osteoporosis [96]. Although not utilized yet in cancer patients, it also has much potential as a targeted therapy to prevent neoplastic cell-induced bone destruction in multiple myeloma and other malignancies.

Macrophage inflammatory protein 1α (MIP1α) has also emerged as a potential target for treatment of myeloma bone disease. It is found to have increased expression in myeloma cells and in patients with high tumor burden and osteolytic disease. It has also been associated with myeloma cell survival. Antibodies targeting MIP1α were shown to reduce tumor burden and osteolytic disease in animal models [97]. Further studies are under way as to the efficacy of antibody-induced inhibition in patients with myeloma-induced lytic bone disease.

Biotargeting in Lymphoma

Lymphoma is the terminology used to describe a broad category of malignancies that are thought to be derived from the lymphocytes of the normal human immune system. There are many subclassifications within this diverse family of neoplasias, but the two broad categories include Hodgkin's and non-Hodgkin's lymphoma. Lymphoma in many cases originates in the lymph node tissues, but can also develop de novo in bone and solid organs, like the liver. Much like multiple myeloma, lymphoma is known for its propensity to involve bone marrow. Once present in the bone marrow, the neoplastic white blood cells can activate osteoclast-induced bone resorption via the RANKL/Rank pathway. Currently, the most useful targeted therapy in the treatment of lymphoma (especially B-cell type) is the anti-CD20 antibody rituximab. There have been good clinical responses to this medication both at the bone and non-bone sites of lymphoma involvement. Unfortunately, in many cases, the lymphoma cells ultimately develop resistance to this antibody and can progress after years of quiescence.

One of the mechanisms that seems to be involved in lymphoma cell resistance to rituximab is the interaction between the bone marrow stromal cell (BMSC) and the neoplastic B-cells [98]. Recent analysis has shown that BMSC are capable of enhancing the resistance of B-cells to anti-CD20 therapy. This interplay between the bone microenvironment and the neoplastic B-cells has been the focus of emerging research. The signaling pathway between CXCL12 (also known as stromal cell-derived factor-1, SDF1) and its transmembrane receptor CXCR4 has been implicated as a major component involved in lymphocyte cell homing and retention in the bone marrow as well as BMSC-induced chemoresistance of neoplastic lymphocytic cells [100, 101]. Several studies have now looked at targeting this signaling pathway as a means of reducing chemoresistance and improving neoplastic lymphocyte apoptosis. Both in vitro and in vivo studies have confirmed that inhibition of this signaling pathway can induce lymphoma cell death and

prolong survival in animal models of B-cell lymphoma [98, 99]. This is one good example of how bone microenvironment targets in hematopoietic neoplastic diseases are becoming major areas of targeted therapy.

Much work on targeted therapies in lymphoma is still under way and includes targets of non-bone microenvironment, such as BCL2. There is also headway being made for both lymphoma and myeloma looking microRNAs and the role that they are playing in the pathogenesis of these malignant conditions. Evidence that microRNAs are also involved in signaling between hematopoietic neoplastic cells and the BMSC in the bone microenvironment has fueled an interest in these microRNAs as also potential therapeutic targets in the future [100, 101].

Metastatic disease to bone is a common occurrence in the setting of carcinoma, especially breast and prostate cancer. Although the addition of bone-targeting agents such as Zometa and Xgeva, to the treatment regimen of these patients, has improved morbidity and mortality, many patients still develop progressive skeletal disease while on these medications. Additional targets for the prevention of metastatic disease to the skeleton are needed. Research is focused on the identification of multiple additional pathways that can be targeted, including cytokines, proteins that promote angiogenesis, and a variety of other factors. Identification of new biotargets will increase the agents we have in our armamentarium to help prevent metastatic disease to bone.

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Part V

Supportive Oncology

14 Psychosocial Considerations for Patients with Metastatic Bone Disease

Amy Horyna

Psychosocial care, a critical component to supportive oncology, needs to be an integral part of quality cancer care for patients with metastatic bone disease. The Institute of Medicine (IOM) report (2008) [1] defined psychosocial health services as "psychological and social services that enable patients, their families and health care providers to optimize biomedical healthcare and to manage the psychological/behavioral and social aspects of illness and its consequences so as to promote better healthcare."

Patients with bone metastases represent as much as 40 % of an oncology practice and at least half of these patients have uncontrolled pain [2–4], poor quality of life [2–10] and increased care costs [11]. Carcinoma bone metastases occur 15 times more often than primary bone tumors [12]. The most common carcinomas to develop bone metastases are prostate and breast, followed by lung, renal cell, and thyroid. The life expectancy of these patients varies greatly depending upon disease type [13]. As many as one third of carcinomas include bone metastases. Lymphomas account for 7 % [12] of malignant bone tumors and more than 80 % of multiple myeloma patients develop symptomatic bone lesions [13, 14]. Alone, myelomas account for 45 % of all bone tumors [12].

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Supportive oncology which should include symptom and pain management as well as psychosocial services for patients with bone metastases is vital. These patients respond positively to nonpharmacological interventions [15] such as psychotherapy which can be used in conjunction with analgesia regimens. These advanced cancer patients also experience significant psychiatric disorders at the same rate as the general population but tend to access and utilize mental health services at a much lower rate [16]. Although efficacy of psychosocial support on survival is unclear [17–19]; it does have a positive impact on quality of life, treatment compliance [17, 20] and decreases utilization of unnecessary care [21, 22]. Patients who have coping responses of hopelessness and helplessness combined with limited social support have been shown to have decreased life expectancy [17, 23–26]. It is paramount that medical providers refer patients and caregivers to oncology mental health providers to address psychosocial needs beyond their medical treatments.

Psychosocial Screening, Assessment and Treatment

Psychosocial distress screening is an effective first step and an integral component to assessing and treating psychosocial needs of patients with bone metastases. Distress, as defined by the National Comprehensive Cancer Network (NCCN), is "an

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unpleasant emotional experience of a psychological, social and/or spiritual nature that interferes with the ability to cope effectively with cancer and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability and sadness, to problems that can be disabling, such as depression, anxiety and social isolation" [27]. The IOM and NCCN have emphasized the need for distress screening for several years [1, 27]. The American College of Surgeons (ACoS) Commission on Cancer (CoC) has set distress screening standards for accreditation starting in 2015 [28]. The distress screening standard set by the CoC (3.2) have five components that should be addressed when implementing a screening process:

1. Timed distress screening of patients at key or "pivotal" medical visit(s), one screen minimum.
2. The method of screening (paper and pencil, computer generated, interview with provider) to be determined by the program.
3. The tool(s) for screening is also to be determined by the program. Tools are encouraged to be standardized and validated with established clinical cutoffs, but this is not required.
4. Assessment and referral for those who demonstrate "moderate or severe distress." This process should include evaluation of psychological, behavioral, and/or social problems that interfere with the patient's ability to participate in or manage their health care needs and/or the consequences of the illness.
5. Documentation of the screening, referral, and care needs, including follow-up care, should be clearly detailed in the patient's medical record [28].

Screening for distress provides an opportunity to identify and address the most at-risk patients with newly diagnosed bone disease. Highly distressed patients require more medical care than their less distressed counterparts. They have increased difficulty making decisions, often miss more medical appointments, are less likely to follow treatment regimens and tend to have decreased patient satisfaction with their medical care [21, 27, 29–31]. Unaddressed emotional needs may result in increased somatic complaints including poor memory, decreased concentration, and increased fatigue and pain [11], which can result in increased and unnecessary evaluations, tests, medications, and treatment [11, 21, 22].

Significant research has been done comparing various tools to assist programs in determining which might best fit their organization or system [21, 32–37]. Several tools have been developed that are both valid and reliable. Cost varies, but some are available at no charge. Operationalized tools and screening systems that provide structure and a process for implementing distress screening components have been developed by various institutions and companies. These systems are customizable to meet provider and/or organizational needs. Choosing the right tool and developing a standardized screening process or investing in an existing electronic screening system should be done with thoughtful consideration from a multidisciplinary team. Oncology trained mental health providers who can skillfully screen, assess, and address the unique emotional and practical needs of patients can significantly reduce provider time [11, 21, 27, 29–31] by addressing psychosocial issues.

Distress screening, when viewed from a theoretical framework such as Stress Model Theory (SMT), as suggested by Dr. James Zabora, demonstrates how screening works and why it is beneficial to identify those at moderate and high risk [38]. According to SMT, stress (or distress) comes from an imbalance of internal and external resources in relation to the perception of demands being made of the individual. It is the perception of the stressor combined with the individual's coping skills and his/her external resources that mediates the stress response. This suggests individuals control distress via their coping skills and support system(s) [39, 40]. This can also explain why some patients struggle and others are able to complete treatment and even end-of-life with little need for additional support [39, 40]. This concept is significant for patients with bone metastases because the disease has shifted from a potentially curable to a terminal process. The

demand on their coping resources (internal and external) has and will increase. Patients with limited or dysfunctional internal coping skills and external resources may have increased distress and will require more external supports [41] from their providers, the medical system, and their community.

Providing a timely psychosocial assessment for moderately and highly distress patients by a licensed mental health provider with expertise in oncology reduces the risk of overlooked needs, decreases medical staff's responsibilities to those needs, and leads to a more equitable delivery of care for all patients [42]. As disease progresses, so does pain, distress, and other psychosocial needs of patients and their caregivers. Rescreening and reassessing of patients ensures that needs are consistently identified and addressed. A thorough psychosocial assessment should include physical, psychological, social, financial, legal, spiritual, and existential inquiry. Obtaining histories from patients and from family members and/or primary caregivers regarding psychological and behavioral health, substance use, suicide ideation, body image concerns, and sexuality are also critical to effectively treating psychosocial needs of patients [27, 42, 43]. Despite time and resource limitations, assessing and treating the psychosocial needs of patients with metastatic bone disease is effective and provides overall cost savings [11] to providers and healthcare systems. Employing the support of oncology trained mental health clinicians and utilizing other screening tools facilitates an effective assessment process. Several valid and reliable tools such as the Patient Health Questionnaire-9 (PHQ-9), Hospital Anxiety and Depression Scale (HADS), Generalized Anxiety Disorder 7 (GAD-7), Functional Assessment of Cancer Therapy General (FACT-G or FACT-G7), and Functional Assessment of Cancer Therapy Bone Pain (FACT-BP) provide a quick and efficient method to screen and assess specific concerns such as anxiety, depression, quality of life, and pain.

Once a patient and the family or caregiver(s) have been assessed and the needs have been identified, appropriate interventions should be provided. Managing the complexity of mood and behavioral disturbances associated with cancer or exacerbated by diagnosis and/or treatment requires trained mental health providers to utilize a unique skill set. Modes of intervention may include (but are not limited to): individual, couple, family, and group psychotherapy, emotional support for individuals or groups, patient and family education, cognitive behavioral interventions, skill development such as mindfulness based practice or problem solving, and existential and meaning based therapies. Problem solving and connecting patients and caregivers to medical and community resources can be an effective method for building rapport and can also be an avenue to address the emotional and psychological impact a cancer diagnosis, especially a terminal one, has on an individual and/or family system. Goals of care discussions should be facilitated throughout the continuum of the patient's care and are best done in the context of a family meeting. Often these discussions will need to be with patients and their families more than once. Patients and families need time to process information about illness and prognosis, both cognitively and emotionally. These two processes, which can often appear from the outside to be misaligned, even through end-of-life, can be understood within the framework of the family system. Social workers provide support, education, and therapeutic interventions for patients and families within the context of their system. Attempts to forcibly change a dysfunctional system amidst a significant life-changing event such as a terminal diagnosis often results in decreased quality of life, poor patient and family satisfaction with their provider and often results in increased utilization of medical services [11]. Oncology social workers are skilled to assist health care providers understand these complex patient and family behaviors and decisions [44] within their context. When mental health providers are able to intervene with complicated family dynamics (fixed patterns of behavior that are often more apparent during crisis) with providers, the patient's decisions and/or behaviors either may no longer appear maladaptive or may, at least, be managed. Managing complicated family dynamics ensures conversations about goals of care remain patient-centered.

Depression and Anxiety

Interventions for depression and anxiety are effective with both newly diagnosed patients and those with metastatic disease. Stigma around mental health and emotionally supportive services continues to be one of several barriers to distressed and emotionally compromised patients. Depression, anxiety, and adjustment disorder with depressed mood can be diagnosed in 16–25 % [45–47] of newly diagnosed cancer patients, and is higher with metastatic and terminal patients [11]. Receptivity to services and interventions will vary. It is estimated by some studies that oncology psychosocial services continue be severely underutilized at a mere 14 % acceptance rate, when moderate to high distress accounts for somewhere between 30 to 40 % of all cancer patients [18, 48–50]. Psychological and psychosocial distress varies among disease type, but is consistently high with those who have a poor prognosis and a significant symptom burden, which is often the case for those with metastatic disease to the bone [11, 50]. Cognitive behavioral and existential therapeutic interventions that provide hope and reduce a sense of helplessness and worthlessness can improve quality of life, as long as physical symptoms are adequately managed [51, 52].

Depression and anxiety develop in cancer patients at a higher rate compared to the general population. However, these disorders manifest differently. The oncology trained mental health provider can assess whether the disorder(s): predates the cancer diagnosis; is a result of the illness or the treatment; is a medication reaction; or is a reactive response to the diagnosis or prognosis. Distinctions like these help determine what interventions are needed. For example, a patient with preexisting psychiatric disorders may require more care coordination with his or her community providers and closer monitoring by the multidisciplinary team. Some medications, such as steroid use, can exacerbate anxiety, and may require a multidisciplinary discussion to consider adjusting the treatment regimen. Another patient may have an adjustment disorder as a result of receiving news he/she has metastatic disease and may require ongoing individual support to process the difficult emotions and may benefit from referrals for practical resources to assist with day to day functioning. These patients may present with similar needs, but the necessary interventions are not. Depression [53] is an emotional disruption with persistent and pervasive low mood and loss of interest in usual activities over a period of time. Patients with cancer are at two to four times higher risk [54] of developing depressive symptoms throughout the course of their care. One study found 29 % of their pain and palliative care patients [55] met criteria for clinical depression. Anxiety is also a normal psychological and emotional reaction to a real or perceived threat. Anxiety disorders are problematic for patients because they may interfere with functioning and, for some, can be debilitating. Depression and anxiety are treatable with a variety of interventions including medication, individual, group and/or family psychotherapy, cognitive behavioral therapy, existential therapy, and skill development such as mindfulness based practices, meditation, progressive muscle relaxation, or guided imagery.

Post-traumatic Stress Disorder

A cancer diagnosis, especially with metastases, and the subsequent treatment can be traumatic both physically and psychologically [56] for patients as well as caregivers. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [53] describes PTSD as the exposure to actual or threatened death, serious injury, or violence, and can develop by either direct exposure or witnessing others' trauma. Symptoms of PTSD include persistent, involuntary reexperiencing of traumatic events, emotional numbing and detachment from others [53]. Patients with preexisting PTSD may have exacerbated symptoms as a result of cancer treatment. Reports of post-traumatic stress symptoms and PTSD as a result of cancer care, vary greatly and requires additional research and attention. Therapeutic interventions, specifically cognitive behavioral and skill development of relaxation

techniques and anger management are effective for those with PTSD symptoms and should be addressed by mental health providers throughout the course of the patient's care.

Suicide Ideation

Patients with metastatic bone tumors, due to the disease process, have several risk factors for suicide ideation and this should be regularly assessed. A terminal illness, significant symptom burden, and poorly controlled pain are all risk factors; therefore, suicide assessment is a vital component to cancer treatment, psychosocial services, and overarching supportive care services [57, 58]. Additional risk factors for suicide include depression, previous attempt(s), age, sex, substance abuse and limited social support. Hopelessness is also a risk for suicide completion. Active suicide ideation should be address immediately by a mental health professional. Three large Scandinavian studies have identified certain anatomic cancer sites which may increase suicide risk in some patients. A Denmark study found those with breast and lung cancers complete suicide at higher rates [59]. A Norway study found lung and oropharyngeal cancer [60] were at higher risk, while a Swedish study identified esophageal, pancreatic and lung cancers [61] completed suicide at higher rates than the general population. Another study took tumor registry data from Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute and analyzed data submitted from 1973 to 2002 and compared it to national US mortality data on non-cancer suicides. This study suggested the rate of suicide was twice as high with cancer patients as compared to the general population and remained higher for as much as 15 years after diagnosis. This study, like the Scandinavian studies, also identified lung, as well as stomach and head and neck cancers at a higher risk for suicide in the USA [62].

Suicide assessment and intervention is another critical component to supportive oncology psychosocial care. It is estimated that as many as 45 % of those who complete suicide have seen their primary care physician within the 30 days prior to their death [63]. Assessing and exploring "desire to die" [57] statements by patients are vital parts of the assessment process. Desire to die statements [57] can be classified into three categories: suicidal intention, an expression of suffering, or as a means to cope. Statements about suicide or hastened death should be evaluated by a mental health provider to differentiate the patient's meaning and intention. An appropriate multidisciplinary treatment plan should be developed with the patient to address the cause, whether this is a psychiatric disorder; distress and suffering; or despair and hopelessness [58]. Desire to die [57] statements as either expressions of suffering and as a means to cope should also be addressed by psychosocial services. Interventions will vary depending on the suicide assessment. Although rare, some patients may require hospitalization. A thorough assessment by a trained mental health provider can distinguish between those who are actively suicidal with a clear plan and intention from those who are suffering and may use this type of ideation as a coping strategy. This distinction is critical to effectively manage resources and to minimize unnecessary emergency room visits or hospitalizations. Medications to manage mood, in conjunction with cognitive behavioral therapy and existential/meaning based therapies, are effective interventions for patients who express feelings of worthlessness and hopelessness which can exacerbate thoughts of suicide. Developing a clear safety plan with the patient's support system should also be initiated and then clearly documented.

Substance Abuse

Patients with substance abuse disorders who required pain medication during any course of their care will also require a psychosocial assessment. These patients will need a detailed treatment plan specifically outlining the expected use of prescribed controlled substances and the provider

policies around use of non-legal substances. Family members may also have increased needs for support as it may be increasingly difficult for them to set limits for the substance abusing patient, while others may need reassurance that the patient does, in fact, have valid pain concerns that require medication. This becomes increasingly more complicated to manage for patients, caregivers, and the medical providers as pain control issues escalate, which often happens with those who have a terminal illness with bone metastases. Patients with a substance abuse history are also at increased risk for relapse due the distress associated with the diagnosis and for those with poor prognosis. These patients may require more visits with providers to adequately manage the medications and may require a behavioral treatment agreement in order to receive prescription medication. Multidisciplinary support for patients throughout their care is essential to ensure that they receive both adequate pain control and the needed emotional support. For some, substance abuse treatment may be needed as part of their treatment plan.

Psychiatry

Psychiatry is also a necessary component to psychosocial services for those with metastatic bone disease. Psychiatry, whether a physician or advanced practice provider with expertise in psychiatric disorders and skill with mediation management, significantly enhances supportive care services. These providers can facilitate evaluations for complicated treatment, medication or disease induced psychiatric disorders. They can also manage patients' moods more effectively in conjunction their cancer regimens. In close collaboration with mental health providers, psychiatry significantly enhances care for patients by focusing on quality of life and emotional well-being. Patients with preexisting psychiatric disorders such as bipolar disorder or schizophrenia, require increased coordination of care with their treatment providers in the community. While some institutions may have adequate resources to manage these patients' needs, others do not. Regular communication with patients' psychiatrists and therapists in the community is of the utmost importance throughout cancer treatment. These patients also benefit from ongoing psychiatric support at end-of-life. These patients can also be more sensitive to distress and easily overwhelmed by both treatments and the day to day demands required for their cancer care. The availability of an oncology trained mental health provider enables these patients to navigate a complicated medical system in addition to attending to their ongoing psychiatric needs.

Spirituality and Religion

Spirituality, as defined by the Consensus Conference in 2009, is "the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to the self, to others, to nature and to the significant or sacred" [64]. Culturally sensitive spiritual screening should be conducted throughout the course of a patient's care. Licensed mental health providers can screen and assess for unmet spiritual needs and can provide existential and meaning based therapeutic interventions, but should know the limits of their scope of practice and refer to an appropriate spiritual care provider such as a board certified chaplain when indicated. Other patients and families will find comfort in receiving this support from their religious community, and coordination for this support should be facilitated. Spiritual and religious beliefs and preferences can also drive decision making and end-of-life decisions and is integral to patient and family care plans. For many, religions or spiritual beliefs are a means of coping both psychologically and practically to a cancer diagnosis. Spirituality may be beneficial as another supportive care resource to patients with bone metastases as deal they with pain, grief, and end-of-life decision making.

Diversity

Although this is only briefly addressed in this chapter, special consideration to race, ethnicity, culture, and diversity is also a critical component of psychosocial and supportive care programs and should not be minimized. Addressing the needs of marginalized and underserved populations is a basic tenant of social work practice. Fear of persecution, lack of understanding, language barriers, inadequate resources, and/or disenfranchisement with the medical system are a few of the reasons why certain populations delay or avoid seeking appropriate medical care. Cultural differences related to healthcare, accessing (or access to) resources and views regarding end-of-life can vary significantly depending on a patient's ethnicity, culture, and background. Communication regarding the disease status and the prognosis can vary greatly by culture. Treatment decisions may differ based on a patients religious beliefs or culture. Religious views can also influence patient and family needs throughout their care. Assessing cultural background, needs, and preferences of patients and families throughout their care is vital and should also be included in the psychosocial care, assessment, and treatment planning.

The needs of lesbian, gay, bisexual and transgender (LGBT) persons should also be thoughtfully considered and addressed. The LGBT patient experiences discrimination and health care disparities at a much higher rate than the general population. Until recently, state and federal laws vary significantly with regard to partner rights. Oncology trained mental health providers can assist LGBT patients in navigating these complicated issues. LGBT individuals are also at higher risk for certain cancers compared to the general population including cervical, breast, Hodgkin and non-Hodgkin lymphoma, Kaposi sarcoma, liver, lung, and anal cancers [65]. LGBT patients are also less likely to seek health care for fear of discrimination [66, 67], are at higher risk to attempt suicide than their non-LGBT peers [68], and have increased risk for stress related mental health and substance abuse problems [69]. Identifying and intervening with issues related to communication, family of birth vs. family of choice, disclosure, and legal and financial concerns for the LGBT community are imperative. The goal of high quality care is the provision of services by licensed mental health providers who have a high level of expertise and knowledge to diverse populations.

Integrated and Complementary Medicine

Integrated medicine that complements both the physical and psychosocial needs of patients with bone metastases may also be helpful in providing supportive services to patients. Encouraging patients with incurable metastatic disease to explore complementary and alternative medicine, either in addition to, or in place of conventional medicine can enhance quality of life. Qualitative research on integrated medicine is growing and suggests that supportive care services such as massage [70] can be an effective intervention for some and can help with anxiety, distress, nausea, and pain [71]. Acupuncture can be an effective intervention for some to manage pain, anxiety [72], nausea, and even neuropathy [73]. While some patients may not be open to these types of interventions, others may appreciate the benefits from these treatment approaches, especially when conventional methods are no longer viable options.

End-of-Life Care Planning and Decision Making

Assisting patients with end-of-life care planning is another critical component to psychosocial care. Facilitating thoughtful discussions with patients and families throughout the continuum of care is an essential component to supportive oncology. End-of-life decision making is a process that changes as the disease process changes. Goals of care discussions should be revisited with patients and their families or caregivers regularly to address concerns, modify treatments, and continually reevaluate palliative

care needs as the disease progresses. Identifying and documenting surrogates by completing the appropriately legal documents such as a living will, advance directive, and/or power of attorney should also be done. Patient and family centered discussions can be facilitated by any member of a multidisciplinary team. It can be beneficial to have a provider who can address medical questions while a licensed mental health provider addresses the emotional and practical psychosocial concerns.

Conclusion

Comprehensive cancer treatment for patients with bone metastasis should include all aspects of supportive care services including assessing and addressing psychosocial needs. This is a broad area of care that can be well addressed by a multidisciplinary team approach and should include an oncology trained mental health provider. Appropriately addressing psychosocial needs of patients with bone metastases enhances quality of life, reduces distress, improves treatment compliance, decreases unnecessary care, and may reduce time and costs of patient care for providers.

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Pain Management in Metastatic Bone Disease

15

Shane E. Brogan and Daniel W. Odell

Introduction

Pain is one of the most common and debilitating symptoms of cancer. Epidemiologic studies indicate that pain occurs in 53 % of all cancer patients including 59 % of patients undergoing anticancer treatment and 64 % in advanced disease. Furthermore, greater than one third of these patients rate their pain as moderate to severe [1].

Metastatic bone disease is a leading cause of cancer related pain and is associated with significant morbidity. Bone is the most common site of metastases after liver and lung. Three of the most common cancers—prostate, breast, and lung—have a high incidence of metastasis to bone and therefore metastatic bone pain is very prevalent in contemporary oncologic practice [2]. Metastatic pain is often multifactorial including both nociceptive and neuropathic components. The former is characterized by somatic pain from the invasion of bony structures and soft tissues, increased pressure on the endosteum and periosteum, and pathologic fractures [3]. Neuropathic pain arises when tumor compresses or invades local neural structures including spinal elements, plexi, and peripheral nerves [4]. Furthermore, regional muscle pain and spasm may develop as a secondary phenomenon due to underlying bone pain and loss of normal musculoskeletal function. Consequently, pain management in metastatic bone disease may require a multifaceted approach combining several drug classes, interventional pain procedures, complementary techniques, in addition to more specific oncologic and surgical therapies [4].

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An Approach to the Patient with Cancer Pain

In the 1980s the World Health Organization introduced a practical step-wise guide to treating pain, starting with simple analgesics and escalating to "strong" opioids. While this approach has been extraordinarily successful globally, more contemporary guidelines are now available that encompass more than just pharmacologic management [5, 6] (Fig. 15.1).

A careful history will help the practitioner tailor the treatment plan to offer the best chance of clinical success. It is important to correlate symptoms and what is known about disease extent and location. For example, a solitary, painful metastatic lesion may be best treated with radiation therapy, whereas more extensive disease will require systemic therapy with analgesics.

It is also important to distinguish between nociceptive versus neuropathic, described above, as the treatments are quite different.

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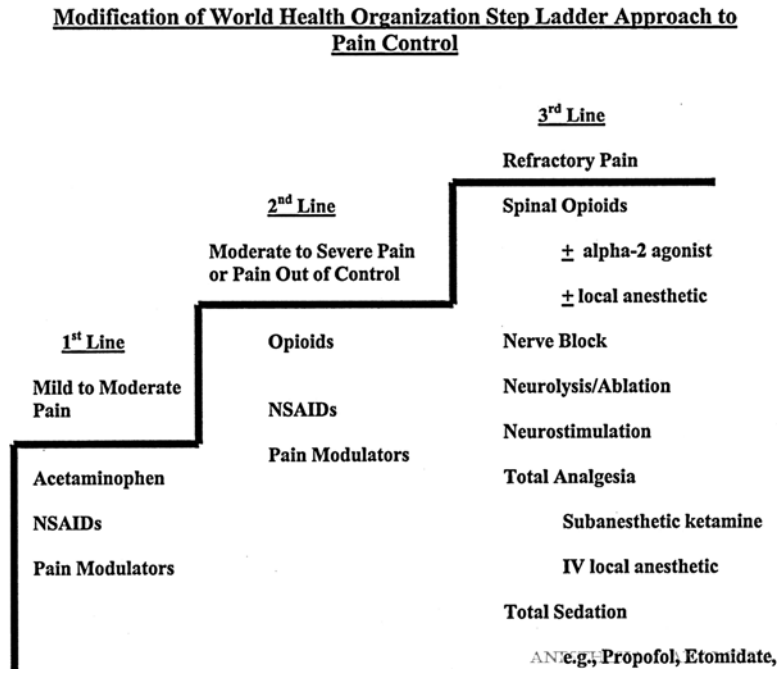

Fig. 15.1 A modification of the World Health Organization ladder of pain management showing contemporary pain management techniques. From Fine PG. The evolving and important role of anesthesiology in palliative care. Anesth Analg 2005; 100:183–188. Reprinted with permission from Wolters Kluwer Health

Neuropathic pain is characterized by features such as a burning, tingling, and associated neurologic dysfunction. Nociceptive pain is most often characterized as "aching," more localizable, and exacerbated by movement.

If the history supports an acute onset of pain, a pathologic fracture must be considered, and therapy will depend on the clinical and imaging findings. For example, select acute vertebral compression fractures will respond well to percutaneous vertebral augmentation techniques such as kyphoplasty or vertebroplasty.

When considering initiation or modification of an analgesic regimen, it is important to consider what medications have already been tried and whether a therapeutic response was obtained. A historical benefit with NSAIDs should be noted, including screening for side effects and contraindications.

It is also imperative that prior to initiating therapy with opioids, screening is performed for a patient history of substance abuse—a positive history will obviously complicate management and obtaining additional help from a palliative care, or pain, specialist should be considered.

Pharmacology

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The use of nonsteroidal anti-inflammatory agents (NSAIDs) or acetaminophen has been established as the initial step in cancer pain management by the World Health Organization [7]. While the WHO algorithm has been greatly expounded upon since its inception, the use of NSAIDs and acetaminophen endure as mainstays of initial cancer pain treatment. Patient familiarity, widespread access, low cost, and ease of use all contribute to the advantageous nature of NSAID use in cancer pain management.

Pharmacology

NSAIDs are a diverse group of drugs broadly categorized into salicylates (e.g., aspirin), propionic acid derivatives (e.g., ibuprofen), acetic acid derivatives (e.g., ketorolac), oxicam derivatives (e.g., piroxicam), and the heterocyclics (e.g., celecoxib). See Table 15.1 for a list of common NSAIDs and their properties.

Table 15.1 Summary table of nonsteroidal anti-inflammatory drugs and acetaminophen

DRUG	Common trade name	Half-Life (h)	Typical daily dose range	Typical dosing schedule	Typical pediatric dosing, mg/kg/24 h	Notes
Acetaminophen/paracetamol	Tylenol, Panadol	2	2–4 g	325–650 mg Q4 h	10–15 mg/kg q6–8 h prn	
Propionic acid derivatives						
Fenoprofen	Nalfon	2–3	1.2–2.4 g	300–600 mg QID	900–1800 mg per body surface area in M2	
Flurbiprofen	Ansaid	2	200 mg	100 mg BID	NA	
Ibuprofen	Motrin, Advil, Brufen Caldolor (iv) , others	6	1.2–2.4 g	400–800 mg QID	7.5–10 mg/kg QID	Higher doses sometimes used for inflammatory conditions; max dose 3200 mg/day
Ketoprofen	Orudis	2–4	225 mg	75 mg TID	NA	
Naproxen	Naprosyn	14	750–1000 mg	250–375 mg BID	5–10 mg/kg BID	
Naproxen Sodium	Alleve, Anaprox	14	550–1100 mg	275–550 mg BID	5–10 mg/kg BID	
Fenamates						
Diclofenac	Voltaren	1–2	150–200	50 mg TID 75 mg BID	2–3 mg/kg/24 h	
Tolmetin	Tolectin	5	800–2400 mg	400–800 mg TID	20–30 mg/kg/24 h as 3–4 doses	
Ketorolac	Toradol	4–6	IV: 60 mg/day[a]	30 mg first dose; then 15 mg q6 h[a]	IV: 0.5 mg/kg/day, single dose only.	Only parenteral agent available
Enolic acid derivatives (oxicams)						
Meloxicam	Mobic	15–20	7.5–15	7.5–15 mg QD.	NA	Higher dose typically used for rheumatoid arthritis.
Piroxicam	Feldene	40–50	20 mg	10–20 mg QD	NA	
Nabumetone	Relafen	24	1000–1500 mg	500–750 mg BID	NA	
Acetic acid derivatives						
Etodolac	Lodine	7	400–1200 mg	200–400 mg TID/QID	15–20 mg/kg/24 h	

iv intravenous

[a]Half the dose if age >65 years or <50 kg

Mechanism of Action

All NSAIDs act by inhibition of prostaglandin synthesis. Prostaglandins have important physiologic functions including the mediation of the inflammatory response, the transduction of pain signals, as well as a central antipyretic effect. Prostaglandins are derived from arachidonic acid via a reaction catalyzed by cyclooxygenase (COX) enzymes. By inhibiting COX enzymes NSAIDs block production of prostaglandins from arachidonic acid.

The COX enzymes are known to exist as three isoforms: COX-1, COX-2, and COX-3. COX-1 and COX-2 are the isoforms nonspecifically targeted by the traditional NSAIDs, while the more selective COX-2 inhibitors preferentially block COX-2. COX-1 is involved in normal physiologic functioning such gastrointestinal mucosal protection and hemostasis. COX-2, on the other hand, is inducible during physiologic stress by agents including pro-inflammatory cytokines, neurotransmitters, and growth factors. Although both enzymes are structurally similar and act in the same fashion, their respective gene expression profiles and selective inhibition can determine NSAID side-effects and toxicity.

Evidence for NSAID Use in Cancer Pain

Studies investigating short term NSAID use in cancer pain management consistently demonstrate a dose-related improvement in pain relief compared to placebo with no increase in side effects. However, the longer-term efficacy and tolerability of NSAIDs is not well established. In modern oncology practice, with often-prolonged survivorship, the sequelae of longer-term NSAID use, such as renal toxicity, gastric ulceration, and increased cardiovascular risk, should be considered [8].

Side by side comparison of NSAIDs, including the COX-2 inhibitors, fails to demonstrate superiority of pain relief from any one formulation. These studies also fail to show significant difference in side effects across the NSAID spectrum. Assuming there are no contraindications to NSAID use, including renal insufficiency or active gastrointestinal ulceration, NSAIDs should be trialed in most cancer pain patients. After initiating an NSAID, regular screening for efficacy and toxicity should be implemented, with discontinuation of the drug if inefficacy or toxicity is observed. Celecoxib, the only remaining COX-2 inhibitor on the US market, has less gastrointestinal toxicity during short term use, yet controversy remains about whether there is any difference, compared to nonselective NSAIDs, beyond 6 months. Finally, celecoxib enjoys the advantage of lacking an antiplatelet effect, but does have similar renal toxicity compared to nonselective NSAIDs.

Toxicities and Risks

The use of NSAIDs in management of cancer pain may be precluded by comorbidities or concurrent treatments such as chemotherapy. Side effects and toxicities of NSAIDs present in the general population are often augmented in patients being treated for cancer due to additional treatments or overall poor state of health. In particular, NSAIDs should be prescribed with caution in patients at increased risk for renal, gastrointestinal, or cardiac toxicities as well as those with bleeding disorders or thrombocytopenia [9].

Renal Toxicity

All NSAIDs can transiently decrease renal function in selected patients, resulting in hypertension, edema, and even acute renal failure. Patients at elevated risk for renal toxicities from NSAID treatment include: age greater than 60 years old, compromised fluid status, interstitial nephritis, papillary necrosis, and concurrent administration of nephrotoxic drugs, including cyclosporine and cisplatin. Further, any chemotherapy drugs excreted renally elevate the risk for toxicity.

If the patient's serum creatinine is elevated or shows a trend towards elevation, the NSAID should be discontinued.

GI Toxicity

The chronic use of NSAIDs inhibits production of prostaglandins that maintain normal gastrointestinal mucosal integrity, and results in gastric

and colonic mucosal damage including erosion and ulceration. Patients at increased risk for GI toxicity include: age greater than 60 years old, history of peptic ulcer disease or significant alcohol use, major organ dysfunction (including hepatic), and use of high-dose NSAIDs for a long duration.

If a patient develops mild to moderate gastric symptoms (dyspepsia, abdominal pain, nausea) discontinuation of NSAIDs should be considered. Alternatively, the patient could be switched to a COX-2 inhibitor due to their lower incidence of GI side effects. Drugs that decrease gastric acidity including antacids, H2 receptor antagonists, or proton pump inhibitors may ameliorate GI side effects.

Certain gastrointestinal conditions should prompt immediate discontinuation of NSAIDs. These include presence of gastrointestinal peptic ulcers, gastrointestinal hemorrhage, and an increase in liver function studies 1.5 times the upper limit of normal.

Cardiovascular Toxicity

All NSAIDs, including COX-2 specific agents, can increase the risk of serious cardiovascular thrombotic events such as myocardial infarction and stroke. In addition, NSAIDs may increase blood pressure, and this is likely linked to the increased cardiovascular risks associated with their use. Patients at increased risk for cardiac toxicities include: prior history of cardiovascular disease or those at increased risk for cardiovascular disease or complications due to factors such as a history of smoking or known family history. Further, patients currently using anticoagulants are at significantly increased risk for bleeding complications when placed on concurrent NSAID therapy—NSAID use should be avoided in these patients.

Bone Healing

Bone healing is dependent upon an inflammatory response involving numerous cytokines and fibroblast growth factor, so it should not be surprising that an agent that disrupts normal cytokine function may impair bone homeostasis and repair [10]. In fact, this inhibitory healing response has been used therapeutically to prevent heterotrophic bone formation after arthroplasty [11].

However, data on detrimental effects of NSAID use in the perioperative period is somewhat conflicted and controversial [12]. The issue of bone healing and NSAIDs has been addressed most thoroughly in the spinal fusion literature. A retrospective analysis of 288 patients who underwent instrumented spinal fusion from L4 to the sacrum demonstrated a fivefold higher nonunion rate when ketorolac was used in the immediate postoperative period [13]. In direct contrast to this, another retrospective study was performed in which 405 consecutive patients who underwent primary lumbar spinal fusion—a subset of these patients who received ketorolac 30 mg intravenously every 6 h for 2 days had similar fusion rates to a group that had no NSAIDs [14]. A metanalysis of 5 retrospective studies explored the relation of ketorolac dose and successful spinal fusion rates, and concluded that high dose ketorolac (dose > 120 mg/day) may be associated with poor outcomes, whereas standard dose ketorolac (<120 mg/day) was not [15]. Considering the absence of any prospective or randomized studies as well as the high morbidity associated with bony nonunion, use of perioperative nonselective NSAIDs in spinal fusion cases should be considered carefully, particularly when other risk factors for poor bone healing (i.e., smoking) exist. In non-spine orthopedic surgery there is good evidence of NSAID analgesic efficacy without significant compromise of bone healing [12, 16].

Opioids

Opioid-based analgesia remains the cornerstone of pain management in cancer patients and postoperative pain. Opioids are indicated when NSAIDs are insufficient for adequate pain relief or when patients have contraindications to NSAIDs. Ideal opioid regimens are individualized to each patient. The prescriber should recognize the wide dosing variability that exists in the

population rather than adhering to a standard dosing protocol. Careful titration of opioids optimizes pain relief while minimizing adverse side effects such as constipation, nausea, respiratory depression, and sedation.

A Practical Approach to Opioid Management in Cancer Pain

Before initiating opioid therapy in any patient it is important to establish goals of care, i.e., short-term postoperative use versus longer-term management for chronic, cancer-related, pain. Patients must be screened for a personal history of drug abuse and serious mood problems. Urine drug toxicology should be considered if there is a suspicion for illicit drug use. Patients must be educated on the safe use, storage, and disposal of their medication [17].

Typically, short-acting opioids are prescribed first, on an as-needed basis. In many countries the short-acting opioids, such as hydrocodone and oxycodone, are formulated with acetaminophen so it is imperative that the total daily dose of acetaminophen does not exceed 4000 mg/day (see Table 15.2). If the acetaminophen dose ceiling is approached, changing to a non-acetaminophen containing product is advised.

Within a few days, if sufficient pain relief is not obtained with as-needed medication, a long-acting (or "around-the-clock"—ATC) medication is added to provide more continuous pain relief. Frequent reassessment for both side effects and efficacy should be performed, with dose adjustments every few days if necessary. If the patient is having side effects with an opioid, consider switching to another opioid at an equivalent dose.

Choosing an appropriate ATC (long-acting) opioid and its dosage is the subject of a lot of commentary but need not be complicated. The most practical approach is to choose the long-acting formulation of the short-acting drug the patient is using, rather than introducing a new drug for which the efficacy and tolerability are unknown. For example, a patient taking frequent immediate release morphine could be switched to long acting morphine without concern for idiosyncratic side effects of a new agent. First, calculate the total daily dose of the short-acting opioid, and then administer 50–75 % of this dose as the daily dose of ATC opioid. For example, if a patient takes 60 mg of short-acting morphine per day, a conservative starting dose of long-acting morphine would be 15 mg twice daily, with the short acting formulation continued as needed until efficacy is established. Transdermal fentanyl is a popular ATC opioid due to its convenient, three-daily application, and its suitability when the oral route is not possible due to fasting or inability to take pills.

The dose of ATC can be increased every few days by up to 50 % provided there are no side effect limitations, including respiratory depression. After optimal dose adjustment, the patient should rely primarily on the ATC opioid, using short acting opioids only for breakthrough pain (see case example below).

At each visit screen for opioid related side effects and treat accordingly.

Screening for efficacy is also important—if there is no improvement with each successive dose increase, the patient's pain may not be opioid responsive, and it is inappropriate to continue dose escalation. If pain seems refractory to management with one opioid, it is appropriate to switch to an alternative opioid on a trial basis [18].

Breakthrough Pain

Breakthrough pain occurs when a patient with otherwise stable pain management experiences transient superimposed pain [19]. Metastatic bone disease presents a unique challenge in cancer pain treatment due to the high rate of breakthrough pain, which is particularly common with movement. The traditional treatment approach involves administration of a rescue medication, typically supplemental short-acting opioids such as hydrocodone, oxycodone, morphine, or hydromorphone. Recent attention to the inadequacy of this paradigm has prompted development of alternatives. For example, simply increasing the patient's ATC dose has been shown to decrease the severity of breakthrough pain [20]. Alternatively, there are now numerous forms of oral and nasal transmucosal fentanyl citrate available that are both safe and effective in the treatment of breakthrough pain.

Table 15.2 Commonly used opioids

DRUG	Common formulations	Common trade names	Typical starting dose	Approximate dose equivalence[a]	Comments
Hydrocodone	5, 7.5, 10 mg acetaminophen 325 or 500 mg/pill	Norco® Vicodin® Lortab®	5/325 mg, 1–2 pills q4 h prn, max 10 pills/day	10 mg	Caution with acetaminophen containing products: keep total daily dose <4000 mg/day
Oxycodone	IR: 5, 10, 15, 30 mg ER: 10, 15, 20, 30, 40, 60, 80 mg	Percodan® (APAP) Percocet® (APAP) Roxicodone® Oxycontin®	Immediate release: 5 mg, 1–2 pills q4 h prn. Extended release: 10 mg BID	7.5 mg	See acetaminophen comment above
Morphine	IR: 15, 30, 60 mg ER: 15, 30, 60, 100, 200 mg	ER: MsContin ®, Kadian ®	IR: 15 mg q4 h prn. ER: 15 mg po BID	10 mg	Caution in advanced renal insufficieny—metabolites may accumulate
Hydromorphone	IR: 2, 4, 8 mg ER: 8, 12, 16, 32 mg	ER: Exalgo ®	IR: 2 mg po q4 h prn ER: 8 mg po QD	2 mg	
Fentanyl	ER: 12, 25, 50, 75, 100 mcg/h	ER: Duragesic ®	ER: 25 mcg/h, changed q3 days	See manufacturer's prescribing information	Only for use in opioid tolerant patients IR products such as Actiq® available, but probably best prescribed by a pain or palliative care specialist
Tramadol	IR: 50 mg ER: 100, 200, 300 mg	IR: Ultram ® ER: Ultram ER ®	IR: 50–100 mg q6 h prn ER: 100 mg po QD	100 mg	Mu receptor agonist. Max dose 400 mg/day due to risk of seizure

IR immediate release, *ER* extended release, *APAP* acetaminophen, *QD* once daily, *BID* twice daily

[a]Approximate dose equivalence is described using the approximated oral dose that would provide similar analgesia to morphine 10 mg orally. Note that there is great inter-patient and inter-drug variability, and the described approximations should be used as a conservative guide only

These formulations include a buccal tablet, a buccal soluble film, nasal spray, a sublingual orally disintegrating tablet, a transmucosal lozenge, and most recently a sublingual spray. Unfortunately, all the transmucosal products are expensive, and in the USA require special physician registration process before prescribing, so these drugs are unlikely to be of practical value to the orthopedic surgeon.

Opioid Pharmacology

Although chemically diverse, all opioids share the ability to bind to various opioid receptors found throughout the central nervous system as well as other tissues. The structure of opioids can be broadly categorized into two groups based on the molecule from which they are derived.

Morphine is the prototypical benzylisoquinoline alkaloid and many of the clinically used opioids are derived by simple modifications of its structure. Codeine, oxycodone, hydrocodone, and hydromorphone are all derived from alterations of morphine. The second group of opioids is structurally related to meperidine, a phenylpiperidine, and the first completely synthetic opioid. Fentanyl, alfentanil, remifentanil, and sufentanil are examples of clinically used opioids that are based on the phenylpiperidine structure.

Mechanism of Action

There are three classic opioid receptors: mu, kappa, and delta. Different opioids interact with these receptors to varying degrees including both agonist and antagonist properties. The opioid ligand binds to the opioid receptor, which is coupled to G proteins. Activation of the G protein sets off multiple effects including inhibition of adenylate cyclase with subsequent decreased levels of cyclic AMP. Other effects include inhibition of voltage-gated calcium channels and activation of inward rectifying potassium channels. The net effect is hyperpolarization of the cell membrane and decreased neuronal excitability.

Modulation of neuronal excitability by activation of opioid receptors has widespread effects in different locations and tissues in the body. Therapeutic effects take place in the dorsal horn of the spinal cord where nociceptive neurons are inhibited from releasing substance P. As a result, transmission of painful sensations to the brain is blocked. Furthermore, opioids amplify inhibitory pathways from the midbrain periaqueductal gray area to the dorsal horn of the spinal cord enhancing the analgesic effect.

While most of the therapeutic effects of opioids take place in the central nervous system, some opioid side effects are largely due to the presence of opioid receptors in peripheral tissues. For example, activation of mu receptors located in the enteric plexus leads to decreased gastrointestinal motility and constipation.

Evidence for Opioid Use on Cancer and Metastatic Bone Disease

While comprehensive, randomized, studies of opioid therapy for cancer pain are lacking due to ethical concerns, there is evidence to suggest that the WHO algorithm combining opioids and NSAIDs produces the most optimal pain therapy for control of baseline cancer pain [8, 21]. Additional components of the multimodal approach continue to progress in cancer pain management, but in modern practice opioids endure as the mainstay of treatment [22].

Opioid Side Effect Management

Constipation

Constipation is perhaps the most ubiquitous side effect of opioid therapy, and unlike other side effects, is not subject to tolerance. Management should consist of a multifaceted approach including a prophylactic bowel regimen, fluid intake, and exercise if possible. The initial pharmacologic management of constipation should include a stimulant laxative (e.g., senna or polyethylene glycol (Miralax®)) with or without the addition of a stool softener (e.g., docusate). Persistent constipation should prompt a thorough evaluation for other causes such as bowel obstruction or impaction. Having ruled out these causes additional agents to consider include magnesium hydroxide, bisacodyl, or a prokinetic agent (e.g., metoclopramide), among others. When these measures have failed neuraxial analgesics or neuroablative

techniques could be used to reduce the opioid dose. Methylnaltrexone, a subcutaneously administered opioid antagonist that does not cross the blood–brain barrier and therefore does not antagonize analgesia, may also be used in refractory opioid-induced constipation.

Nausea

Nausea in cancer patients is often multifactorial in etiology including chemotherapy and radiation therapy, constipation, breakthrough pain, drugs, or central nervous system pathology. Therefore, it is important to perform frequent reassessment of potential causes of nausea so that appropriate treatment can be delivered. For the first line treatment of nausea, consider using a phenothiazine (e.g., prochlorperazine) as needed. With persistent nausea sequential addition of a serotonin antagonist (e.g., ondansetron), dopaminergic antagonist (e.g., metoclopramide), and dexamethasone can be considered. As is the case with constipation, the ultimate solution may be a decrease in opioid dose by providing neuraxial analgesia or neuroablative techniques.

Respiratory Depression

Respiratory depression occurs as a result of opioid activation of neurons located in the respiratory centers of the brainstem. Any reversal of respiratory depression could also result in reversal of analgesia and should be done with caution. With life-threatening respiratory depression, naloxone can be titrated with repeated doses every 30–60 s until improvement is noted. The process will likely need to be repeated in the intensive care unit as naloxone has a short half-life relative to most opioids.

Sedation

Sedation is a recognized side effect of opioids and cancer patients in particular may demonstrate a greater propensity toward altered mental status as a result of concurrent treatment regimens or central nervous system pathology. Initially, the patient's pain level should be evaluated to determine if a simple decrease in opioid dose would resolve the issue. If acceptable pain relief with lower doses of opioids is not possible consider switching to a different class of opioid or adding a non-opioid to supplement the pain regimen. Careful screening for non-opioid sedatives such as benzodiazepines and sleep aids should be performed, with rationalization of the regimen if possible. If these interventions are unsuccessful stimulant medications can be considered including caffeine, methylphenidate, dextroamphetamine, or modafinil. Frequent reassessment of sedation etiology should be performed with appropriate intervention as needed.

Neuropathic Pain

Neuropathic pain is relatively common in metastatic bone disease as a result of compression of neural structures by bony abnormalities or pathologic fractures, local invasion of neural structures, postsurgical sequelae, and preexisting chemotherapy induced neuropathy. Neuropathic pain results from nerve sensitization and ectopic transmission of noxious stimuli resembling the abnormal hyperexcitability of neuronal transmission seen in epileptic disorders. Phantom limb pain can be considered as a neuropathic pain condition and should be treated as such, though simultaneous musculoskeletal stump pain is common and should also be addressed. Phantom symptoms may also respond well to cognitive techniques such as mirror therapy.

Historically, numerous anticonvulsants have been used in the treatment of neuropathic pain including phenytoin, topiramate, carbamazepine, and sodium valproate. While some of these agents continue to be used for certain conditions the newer anticonvulsants with FDA approval for the management of pain, gabapentin and pregabalin have largely supplanted their role. These second generation antiepileptic medications, referred to as "gabapentinoids," provide much better tolerability in terms of side effects and toxicity and offer greater receptor selectivity than first generation drugs [23].

The selective serotonin and norepinephrine reuptake inhibitor, duloxetine (Cymbalta®), also has utility in the treatment of neuropathic pain.

Topical Agents

Topical agents may also be helpful in smaller, discrete, neuropathic pain areas. Topical lidocaine in a 5 % patch (Lidoderm®) is FDA-approved for post-herpetic neuralgia, but may also be trialed for other localized neuropathic pain syndromes. A less expensive, but less well-studied, alternative is lidocaine 2 % ointment or cream, applied several times a day.

Gabapentin and Pregabalin

Mechanism

Gabapentin and pregabalin are branched-chain amino acids and chemical analogues of the neurotransmitter γ-aminobutyric acid (GABA). Despite their name, neither drug has activity in the GABAergic neuronal system. They are functionally similar to the essential amino acid leucine in that they competitively bind α_2 σ calcium channels [24]. Their analgesic effects may be related to calcium influx inhibition as well as inhibition of the release of excitatory neurotransmitters in spinal and supraspinal pathways [23].

Pharmacology

The metabolic profiles of gabapentin and pregabalin are very similar. Both drugs are metabolized to their corresponding N-methyl metabolite in dogs but undergo minimal metabolism in humans. There are no known drug–drug interactions.

Adverse Effects

With careful dosing, gabapentin and pregabalin are typically well tolerated. Dizziness and somnolence are the most commonly reported adverse effect of both drugs, and the latter is the most frequent reason for discontinuation. Other reported side effects include xerostomia, peripheral edema, angioedema, blurred vision, ataxia, dysarthria, tremor, lethargy, memory impairment, euphoria, constipation, decrease or loss of libido, and weight gain. The adverse effects of gabapentinoids are reversible and dose dependent.

Common Clinical Indications

Gabapentin is currently FDA approved for post-herpetic neuralgia and partial seizures, while pregabalin is FDA approved for partial seizures, painful diabetic peripheral neuropathy, post-herpetic neuralgia, and fibromyalgia. Furthermore, recent guidelines published by the International Association for the Study of Pain (IASP) recommend both drugs as first-line therapy for these conditions as well as central pain syndromes such as central post-stroke pain and pain related to spinal cord injury and multiple sclerosis [25].

Studies that have investigated the role of gabapentinoids in managing postoperative pain have yielded mixed results. While some studies that looked at the administration of gabapentin to patients undergoing craniotomies, thoracotomies, and thyroidectomies showed favorable results in terms of controlling acute pain as well as preventing chronic pain, others show that it is an inferior as a single agent compared to numerous other drugs used in this setting [26].

The same holds true for pregabalin as there are some studies that show it may decrease perioperative opioid and epidural use in patients with more acute neuropathic pain compared to acute inflammatory pain, and it may also decrease the incidence of chronic pain if the surgery involves a more neuropathic-type acute pain process [27]. A large meta-analysis of numerous randomized controlled trials showed no clear beneficial effect of pregabalin in acute postoperative pain [28].

Gabapentin and Pregabalin in Cancer Pain

Evidence is lacking with respect to the use of pregabalin and gabapentin in neuropathic cancer pain. One study did show a modest benefit in patients randomized to pregabalin, gabapentin, or amitriptyline [29]. Otherwise, the use of gabapentin-type drugs in cancer pain is based upon anecdotal reports.

Dosing

Gabapentin can be started at 300 mg PO three times daily, and escalated every few days—doses up to 2700 mg/day may be required. Pregabalin is often started at 50 mg PO twice daily, and escalated to 150 mg PO twice daily as tolerated.

In the elderly, it is advisable to start at half the doses described above.

Clinical Vignette *A 39-year old woman with widely metastatic chondrosarcoma complains of severe pain in her sacrum due to known disease in her bony pelvis. She also has lumbosacral plexus invasion with associated "burning" pain in her entire left lower extremity. She is taking oxycodone/APAP 5/325, about 16 pills a day. She complains of mild constipation but no other side effects. How do you proceed?*

Treatment Considerations:

- Consider all treatment options including radiation therapy
- She is taking a potentially toxic dose of acetaminophen
- The total daily dose of oxycodone is 80 mg/day—consider prescribing an ATC opioid at 50 % of the daily dose—i.e., oxycodone sustained release 20 mg BID.
- Continue oxycodone/APAP but limit to 8–12/day, reassess next visit
- Consider adjuncts such as gabapentin for neuropathic extremity pain
- Consider NSAID unless contraindication.
- Reassess in 1–2 weeks and titrate medications as appropriate and screen for side effects.

Advanced Pain Management Options

Consultation with a pain specialist may be indicated under certain circumstances. If the standard approach to pain and symptom management is inadequate and escalating doses of opioids are either failing to offer sufficient relief or further dose adjustment is limited by side effects, referral is indicated. Musculoskeletal pain after complex orthopedic surgeries may respond best to rehabilitative strategies, including physical therapy, and possible trigger point injections. The psychosocial impact of pain must not be ignored, and the involvement of an interdisciplinary team including a psychiatrist, psychologist, and social worker may be very advantageous.

Intrathecal Analgesia

Metastatic bone pain or neuropathic pain refractory to treatment with opioids can be especially challenging, and these patients often do best with advanced techniques such as intrathecal therapy (ITT). ITT involves the delivery of medication, via an implanted electronic pump and catheter and system, directly into the cerebrospinal fluid. Because medications are deposited adjacent to the spinal cord and emerging nerve roots, tiny doses cause profound analgesia without having significant systemic absorption that could lead to side effects. Additionally, intrathecal therapy offers a wider armamentarium of therapeutic agents including opioids, local anesthetics, clonidine, and other novel agents such as the snail toxin, ziconotide. There is ample evidence that ITT provides higher clinical success and improved patient satisfaction compared to conventional pain management with opioids [30, 31].

Peripheral Nerve Blocks

Extremity pain can be relatively easily treated using peripheral nerve blocks, typically performed under ultrasound guidance in modern practice. The duration of effect is limited by the pharmacokinetics of the local anesthetic used. For example, an interscalene brachial plexus block with bupivacaine can offer excellent analgesia of the upper extremity, but typically only for a maximum of 12–16 h. Increased duration of effect can be obtained by placing a perineural catheter and continuous infusion, but these catheters are seldom left in place for more than 3 days. Therefore, peripheral nerve blocks are very useful for the management of perioperative pain, or as a palliative technique in a patient whose life expectancy is measured in days.

Neurolytic Nerve Blocks

The chemicals phenol and alcohol may be used to disrupt nerve conduction for up to 3–4 months. The primary problems with neurolytics are the

indiscriminate loss of neural function including motor fibers, and the possibility of developing abnormal sensations (dysesthesia, allodynia) that may end up being more distressing than the pain being treated.

Given the clinical success of intrathecal therapy, neurolytic blocks are rarely indicated, but still hold a role in the management of particularly difficult situations. An exception to this is the use of intercostal neurolysis for the management of rib pain secondary to metastasis. Intercostal neurolysis can easily be performed in the office setting under ultrasound guidance and offers excellent outcomes with minimal risk.

Less commonly, a brachial plexus neurolysis can be performed under ultrasound guidance for the management of truly refractory upper extremity pain. Brachial plexus neurolysis can result in significant motor loss, so is best considered only in patients who already have full functional loss of the extremity, and after a careful consent process. Other nerves/plexi that can be targeted for neurolysis include the femoral, sciatic, trigeminal, celiac (for upper abdominal visceral pain), and superior hypogastric plexus (for pelvic pain).

Kyphoplasty and Vertebroplasty

Vertebral compression fractures secondary to metastatic deposits are typically very painful and associated with major functional impairment. Vertebral augmentation procedures such as kyphoplasty and vertebroplasty are percutaneous procedures performed under fluoroscopy or computerized tomography guidance, and involve the deposition of cement into the fractured vertebral body. Kyphoplasty involves an initial cavity creation with a balloon which allows for lower pressure, and possibly safer, injection of cement. Vertebroplasty involves injection of cement only, and is typically only performed for higher thoracic or cervical levels where balloon inflation is limited by the smaller size of the vertebrae. The specific indications and contraindications of vertebral augmentation are beyond the scope of this text.

While conservative management of compression fractures may show spontaneous recovery over several months, the short-term impairment can be considered unacceptable in a patient with limited life expectancy, so kyphoplasty or vertebroplasty for acute or subacute fractures is indicated [32].

Postoperative Analgesia

Postoperative pain continues to be a significant clinical challenge and a major driver of patient satisfaction. Much of the dissatisfaction is driven by a patient perception that their providers often ask about their pain but seldom do anything about it. It is important to remember simple approaches like the application of ice-packs and reassurance.

While opioids continue to be the mainstay of analgesia during the perioperative period, NSAIDs and acetaminophen alone can be sufficient for the management of mild pain and are a very useful adjunct in the management of moderate to severe pain. The latest American Society of Anesthesiologists practice guidelines for acute pain management in the perioperative setting encourage the use of NSAIDs and other adjuncts whenever possible [33].

A meta-analysis examined the effect of adding acetaminophen, nonselective NSAIDs, or COX-2 selective NSAIDs to opioid patient-controlled analgesia. The results suggested that all three analgesic agents provided an opioid dose-sparing effect (25–55 %). Moreover, the addition of NSAIDs to morphine was associated with a decrease in the incidence of postoperative nausea and vomiting and sedation [16]. Clinical trials of COX-2 selective NSAIDs used preoperatively and into the postoperative period for patients undergoing both major surgery and minimally invasive surgery have demonstrated improved clinical outcomes including reduction in postoperative pain, opioid use, and nausea [16, 34, 35]. A meta-analysis of clinical studies evaluating COX-2 inhibitors compared to nonselective NSAIDs for postoperative pain showed that the analgesic efficacy of COX-2 inhibitors in the 6 h after surgery was similar to or better than ibuprofen [36].

Regional Anesthesia Techniques

For major orthopedic procedures of the extremities consideration should be given to using a nerve block technique. Either a single shot technique or perineural catheter may provide excellent postoperative analgesia and an opioid sparing effect that is associated with high patient satisfaction. Good postoperative analgesia also permits earlier initiation of physical therapy and discharge from the hospital [37, 38].

Patient Controlled Analgesia (PCA)

PCA allows the patient to self-administer dose of an opioid such as morphine or hydromorphone for the management of postoperative pain, but may also be used for the short-term management of cancer pain. PCA has the advantage of patient autonomy in titrating pain medication to his or her comfort level, and is characterized by higher satisfaction compared to the patient having to ask the nursing staff for pain medication. Relative safety with PCA is ensured by the fact that if the patient is overmedicated he/she is unlikely to further activate the PCA system. However, there is still risk associated with PCA use and all patients should be continuously monitored for signs of opioid toxicity including sedation and hypoventilation.

PCA is best utilized in scenarios where there is significant pain, a nerve block technique is not indicated, and the oral route is not possible (i.e., fasting, ileus, or nausea and vomiting) until transition to the oral route is possible.

Typical starting PCA dosing parameters in adults are morphine 1 mg every 10 min as needed, or hydromorphone 0.2 mg every 10 min as needed. Loading doses and basal infusions are generally not indicated and may add substantially to risk. If standard doses are insufficient, and there is no evidence of overmedication, AND the patient is using all available PCA doses, the dose may be increased 50–100 %, keeping the dosing interval the same.

Perioperative Pain Management in the Opioid Tolerant Patient

In the field of sarcoma orthopedics, many patients will present to the surgeon already on opioids, presenting a challenge in terms of postoperative pain control.

In these patients, using adjunctive techniques including NSAIDs, gabapentin or pregabalin, and nerve block techniques, will be important. Certain intraoperative techniques may also be employed by the anesthesiologist, such as ketamine infusions, lidocaine infusions, alpha agonist infusions (like dexmedetomidine), or other modalities.

If the patient was already on opioids prior to surgery, the preexisting opioids should be continued perioperatively, with the addition of additional opioids as indicated—a good rule of thumb in the opioid tolerant patient is that the surgeon should continue the patient's current regimen, and simply add whatever analgesics he or she would normally prescribe for a given surgery.

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When Is Hospice Appropriate? The Role for Hospice in Palliating Patients with Bone Metastases

16

Andrew Badke and Anna C. Beck

Introduction to Hospice

The concept of Hospice dates back to the European Middles Ages. The Latin term *hospes*, meaning to host a guest or stranger, was applied to monasteries that would provide refuge for traveling crusaders and pilgrims. The travelers were often in ill health and would frequently spend their last days in the monasteries; it then was up to the entire community to help support and care for them [1]. The concept of community providing rest and refuge for others inspired hospice as we know it today.

Dame Cicely Saunders pioneered the modern day hospice movement in the late 1950s. Up until that point, patients had two options for spending their final days. One option was at home, devoid of medical attention, wherein patients were cared for by family and friends. The alternative was to remain in the hospital where further attempts to cure the underlying disease were continued. Saunders envisioned a different type of care at the end of life. She urged the medical field to not focus on the *disease* at the end of life, but to focus on the *patient* [2]. Her vision became the crux of modern hospice philosophy.

Today, hospice refers to a program of care and support for the terminally ill. For a patient enrolled in hospice care, the primary intent is comfort at the end of life. Rather than emphasizing cure for an illness, hospice embraces the notion of a comfortable death with dignity. Hospice does not aim to shorten or prolong life, but rather provides comfort and support services to help people live out the time they have remaining to the fullest extent possible. Hospice is not a place, but rather a philosophy of care that works to address goals and values of patients who are dealing with a terminal illness.

Hospice care has become well integrated into the US health care system today. The Medicare Hospice Benefit was adopted in 1982, and since this time, hospice has seen significant growth with dramatic increases in both patient utilization and provided services. As of 2010, Hospice was used by over 1.5 million people annually and approximately 42 % of deaths in the USA were under the care of a hospice program [3]. Interestingly, despite the increased popularity of hospice, it represents a small portion of the Medicare budget. For instance, in 2010 27 % of Medicare spending was used to care for patients in their last year of life [4]. However, only 2.8 % of this budget was spent on Hospice benefits [3, 5]. This indicates that there is still substantial room for growth regarding hospice awareness and need for further education on what hospice can accomplish.

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Structure and Services of Hospice Under Medicare Part A

Certain eligibility conditions must be met prior to enrolling into the Medicare Hospice Benefit. To begin with, a physician and a hospice medical director must certify that a patient is terminally ill and has a prognosis of 6 months or less if the illness runs its normal course. Patients and families should acknowledge that the goal of treatment is no longer curative. Instead, treatment is focused on symptom management while maintaining values, dignity, and quality of life for the patient.

For cancer patients, eligibility typically begins once the disease becomes metastatic. Eligibility can also include disease progression despite treatment, or if a patient has declined further curative-directed therapy. Because of their inherently aggressive natures and limited options for palliation, brain, pancreatic, and small cell lung cancers are eligible for hospice once there is a need for assistance with activities of daily living.

Once a patient is enrolled in hospice, their care is provided by a multidisciplinary team. Medicare will cover the cost of these services as well as provide medical supplies, equipment, and medications that are needed to help manage the progression of the terminal illness [6]. The team itself includes physicians, nurses, hospice aides, social workers, chaplains, volunteers, and therapists. Each team member addresses a specific role in caring for the terminally ill. The details of the interdisciplinary team will be briefly described below.

The registered nurse is the primary case manager and coordinator between the different team members. The nurse and the patient's family/caregivers will help formulate the plan of care and facilitate additional services that are needed. The nurse will typically visit the patient anywhere from daily to weekly depending on the needs of the patient. A nurse is also available on call 24 h a day in case of emergencies. The case manager acts as the liaison between the physician and the patient, provides symptom assessment, and with physician instruction, will help manage a variety of symptoms that are common at the end of life.

The hospice physician works in conjunction with the patient's chosen attending physician. The hospice physician oversees the care of all of the patients admitted to hospice. They are typically specialty trained in palliative or pain medicine and are very skilled in symptom management at the end of life. A hospice physician is also available on call 24 h a day to help coordinate care and address any urgent needs of the patient or family. Patients are also encouraged to continually meet with their chosen attending physician to provide supportive care and address symptoms.

Hospice also provides significant psychosocial and spiritual support. Each patient will have a social worker and a chaplain assigned to their care. The frequency of social and spiritual support visits are determined by the need of the patient. The social worker assists with counseling and bereavement for patient and families, while the chaplain can address spiritual and existential concerns. Hospice aspires to be a humanistic service that offers support to all people regardless of religious or cultural beliefs. Chaplains and social workers are specifically trained in this capacity [7].

Hospice aides and volunteers will also help with the day-to-day care of the patient. This may include personal care, food preparation, or limited respite for the primary caregiver. Hospice does not provide 24-h custodial care for the patient, but aides and volunteers can visit as often as once or twice daily. Some hospices will provide continual support in the last hours of a patient's life. In this situation, the team members will be able to assist at the bedside with symptom control and bereavement support with the family. Bereavement support is provided to families and caregivers for at least 13 months past a patient's death [6].

The last component of the hospice team, which has specific significance to the orthopedic patient, is therapy. It is a common misconception that physical, occupational, and speech therapy have little role in the hospice patient. However, their skill set can be valuable in enhancing quality of life for the patient and caregiver. For example, physical therapy can provide caregivers with training to assist with bed mobility, transfers, and safe positioning techniques. Occupational therapy offers training to assist

patients in self-care and home management, while speech therapy can provide training for patients in communication and oral-motor techniques [8]. In keeping with the goal to enhance quality of life and reduce caregiver burden, short episodes of therapy can play in integral part in hospice care.

This team approach is considered "routine home care" and makes up over 96 % of hospice cases [3]. Routine home care can take place in a private residence, an Assisted Living Facility or Skilled Nursing Facility depending on where the patient lives. The Medicare Hospice Benefit will also provide three additional levels of care if needed: inpatient respite care, continuous home care, and general inpatient care.

Respite care is a service that offers temporary inpatient nursing to provide respite for the primary caregiver. It can help relieve some of the burden on the caregiver while ensuring quality care for the hospice patient. Respite care is provided in a care facility that has sufficient nursing staff present on all shifts to guarantee that patient's needs are met. Respite care is provided for a maximum of 5 consecutive days, can occur as often as monthly, and may require a small co-pay.

Sometimes symptoms require more frequent attention than what routine home care can provide and continuous attention is necessary. In this situation, a licensed nurse will provide temporary continuous care at the patient's residence when the goal is to control symptoms and avoid transferring to an inpatient setting.

In the case of unmanageable symptoms, Medicare will cover inpatient treatment arranged by the hospice provider. This is a called General Inpatient Care or "GIP" care. GIP is intended to provide acute pain control or other complex symptom management that cannot feasibly be provided in any other setting. GIP can only be provided in a Medicare certified hospital or nursing facility that has a registered nurse available 24 h a day to provide direct patient care [7]. Once the patient's symptoms are effectively managed they will be discharged back home. In the case of an actively dying patient with uncontrolled symptoms, management will continue in the inpatient setting until the patient passes away.

Limitations of Hospice Services Under Medicare Part A

While Hospice covers a considerable amount of benefits, there are also limitations with hospice care. As alluded to earlier, hospice does not provide 24 h custodial care. Patients near the end of their life are usually fully dependent on the support of others. The hospice team is available to help support patients through their terminal illness, but the team is not intended to take the place of families or caregivers. This, at times, may place a heavy burden on the patient's family and friends. If a private caregiver is needed to assist with care beyond what hospice can provide, this will be an out of pocket expense for the patient.

Similarly, hospice will not cover long-term room and board. The hospice team will provide services in a patient's home or living facility, but the Medicare Hospice Benefit will not cover the actual living expenses if a patient is living in a nursing home for example. Short-term intermittent inpatient stays in the setting of respite and GIP level care are considered an exception and are covered by the Medicare Hospice Benefit.

The intent of Hospice is to provide maximal comfort measures in a residential setting. This means that transfer to an emergency room or an inpatient hospitalization may not be covered by Medicare part A unless arranged for by the hospice. Patients who seek emergency room, inpatient facility care, or ambulance transportation related to their terminal illness outside of their hospice plan of care may be liable for the entire cost of such care. Patients may seek the services described for medical conditions that are unrelated to their terminal illness. For example, a patient with metastatic cancer that falls and suffers from a facial laceration will still be able to receive Medicare benefits for further medical attention if the fall and laceration are unrelated to the patient's terminal illness. Alternatively, a patient receiving hospice care for end-stage cardiac disease, that seeks hospitalization for a CHF exacerbation, will likely be liable for the expenses. For this reason, coordinating care with the hospice team prior to receiving such services is recommended. In addition patients may stop hospice

care at any time and receive the Medicare coverage they had before they chose hospice care.

Medicare will cover medical expenses to help manage symptoms as the terminal illness progresses. However, Medicare will not pay for any therapies intended to cure or treat the terminal illness. In general, Medicare pays an aggregated capitated rate of approximately 150 dollars per patient per day. This is meant to cover staffing (nursing, aides, physicians, etc.), treatments, medications and medical equipment deemed necessary to palliate the terminal illness [9]. Some larger hospices can accommodate more expensive palliative therapies such as palliative chemotherapy and radiation, blood transfusions, etc. but this tends to be the exception more than the rule.

The Benefit of Hospice Model of Care

Several large survey studies including the National Hospice Study demonstrated that hospice patients have a higher quality of life. The surveys reported improved symptom control, quality of life at the end of life, and quality of death when compared to non-hospice patients [10, 11]. Families and caregivers have also reported improved satisfaction with hospice care. Families are less likely to experience prolonged grief or post-traumatic stress [12], and over 70 % of families rated their care through hospice as "excellent". Families gave this same excellent rating in less than 50 % of the time when the patient was in an institutional setting [13]. Families consistently report satisfaction with hospice care and 98 % are willing to recommend it to others in the end of life [14].

There remains a pervasive myth that hospice care hastens death. In reality hospice care actually has the opposite effect and tends to have a positive impact on patients' longevity. Survival trends across different diagnoses including heart failure, lung cancer, and pancreatic cancer have all showed a survival benefit for those who were enrolled with hospice as compared with those who were not [14]. Medicare data compiled over a 3-year period demonstrated that hospice patients lived on average 29 days longer than the non-hospice patient [15]. This may be in part due to forgoing certain aggressive curative treatments that may be of little benefit in severely frail patients at the end of life.

Finally, the hospice model of care offers tremendous cost savings. Hospice patients reduce emergency room visits, inpatient hospitalizations and ICU stays. A Robert Wood Johnson Foundation study conducted by Duke University found that hospice saves Medicare, on average, more than $2300 per patient compared to alternative sources of care for the same population [16]. Over 1.5 million patients are enrolled in hospice in the USA, yet only use roughly 3 % of the Medicare budget [5]. With this amount of cost savings, increasing hospice utilization may provide a successful avenue for controlling American healthcare costs in the future.

Discussing Hospice with Your Patients

Despite all of the benefits described above, hospice is still an underutilized service. The median length of hospice care for patients in 2012 was 19 days with over one-third of hospice patients dying within the first week of enrollment [3]. This indicates that patients are being referred to hospice far too late. Possible explanations for the late referrals include patient and cultural preferences and an increasing variety of curative therapy options. But, by far the most important factor is physician attitudes and understanding.

Physicians can often regard death as a personal failure and can push patients to continue to pursue every measure possible. Physicians also feel uncomfortable communicating terminal prognosis and will neglect having difficult conversations where they must deliver bad news and address goals of care. Most critical of all, physicians view hospice as appropriate only for the imminently dying [17]. A late referral to hospice limits quality of life for the patient and the family and can often lead to less satisfaction with end of life care [18]. Education amongst physicians

regarding what hospice is and does is critically important. It is also imperative to have a frank discussion of hospice early in the terminal disease to help plan and clarify the patient's wishes for the future.

Prognosis

Understanding a patient's prognosis is crucial for the orthopedic surgeon caring for cancer patients with newly diagnosed bone metastases. A surgical approach may differ considerably in a functional patient with a metastatic femur lesion from metastatic thyroid cancer, versus the same functional patient with a similar lesion but arising from metastatic lung cancer.

Ideally, the patient should have an understanding of their prognosis as well. For some patients, an aggressive approach will be consistent with their goals of care, even in the setting of incurable disease. For others, the goal of having symptoms managed rather than pursuing major surgery that provides little chance for improved functional status will be more appealing. When both the orthopedist and the patient share a true understanding of prognosis, the outcome will be more in line with goals of care. When determining prognosis, consultation with a palliative care physician and oncologist will be helpful in establishing potential for survival, the impact of surgical approach to bone lesions or pathologic fractures, and the expected course of the underlying malignancy [19].

Prognostic Indicators

Primary Tumor Origin

The vast majority of patients who succumb to metastatic cancer will have bone involvement; however, survival can vary significantly based on the tumor site of origin. For example, lung cancer patients with a skeletal related event (SRE) have an overall survival of approximately 6 months [20] versus an expected 33 months in women with metastatic breast cancer [21].

Breast Cancer

Breast cancer remains the most common cancer in women in the USA [22]. Roughly 20 % of women diagnosed with breast cancer will eventually develop metastatic disease [23], with bone involvement as a common initial manifestation of recurrence [24, 25]. Survival can vary widely (see Table 16.1) and reflects the heterogeneous nature of breast cancer. In addition to the histologic grade of the recurrent disease [25, 26], survival can be favorably influenced by a long disease free interval [25, 26], strong tumor expression of the estrogen and progesterone receptors [24–26], older age at diagnosis [25] and disease limited to bone [21, 39]. In contrast, the absence of both the hormone and the HER2 receptor (triple negative receptor expression), involvement of multiple organ sites, African American race [24, 39], and unresponsiveness to hormone therapy [39–41] predict a shorter survival. Of note, a skeletal related event (SRE) in addition to the presence of bone metastases confers a significantly higher mortality risk compared to women with bone metastases alone [42].

Prostate Cancer

Prostate cancer is the most common cancer in men in the USA. Fortunately, the majority of patients who are diagnosed will not succumb to the disease [22]. However, if metastases occur, approximately 90 % will involve the skeleton [43, 44], ultimately heralding a potentially terminal condition [45]. As with breast cancer, survival in metastatic prostate cancer can be measured in years [28, 29, 44, 46, 47], and has several prognostic indicators that are useful. For example, improved survival with recurrent disease has been linked to a long interval between diagnosis to relapse [44, 47], distribution of bone metastases exclusively within the pelvis and lumbar spine [28], oligometastatic disease with <6 sites at time of recurrence [47], lack of visceral involvement [47], a Gleason score of metastasis of less than 9 or 10 [29], and a low PSA doubling time [46]. Similar to other cancers, the development of a

Table 16.1 Estimated lengths of survival based on underlying cancer

Origin	Survival	Comments
Breast	Median 33 months [21]	Following diagnosis of bone metastases only
	Overall survival 30 months 10.6 months 27.3 months [26]	ER+/PR+ Triple negative Bone metastases only
Prostate	Median survival 19 months [27]	Castration resistant
	Median survival 43 months 20 months [28]	Androgen sensitive Castration resistant
	Median survival 1 year [29]	Following surgery for SRE
	Overall survival 19 months [30]	Castration resistant
Lung	Mean survival 9.7 months [31]	Survival following diagnosis of bone metastases
	Median survival with chemo 10.8 vs. 5.8 months [32]	Good performance status ECOG 0-2
	Median survival with chemo 4.8 vs. 2.4 months [32]	Poor performance status ECOG 3-4
	Overall survival 7.4 months [33]	Second line chemotherapy, good performance status
	Mean overall survival 9.2 months [34]	Review of 60 trials using first-line chemotherapy
Melanoma	Median survival 4–6 months	Following diagnosis of bone metastases
	Median survival 11.8 months [35]	Following wide excision of bone lesion
Thyroid	Median survival 5.8 years [36]	After the diagnosis of bone metastases, post 1990
	Median survival 15.2 years [37]	Age < 45 years
	Median survival 3.3 years [37]	Age >44 years
	Median survival 49.3 months [38]	Following metastasectomy +/− radioactive iodine in limited disease

SRE (skeletal related event) is ominous in prostate cancer [48]. Cheville et al. noted that in men who required surgery for a SRE in metastatic prostate cancer, the interval between diagnosis and surgical intervention was prognostic. A long interval between diagnosis and surgery was associated with a shorter survival and a transition to castration resistance [29].

More recently, there has been an explosion of new therapies for castration resistant prostate cancer resulting in an improvement in overall survival [49]. In a recent survey of trials examining the survival benefit seen with novel hormonal agents following chemotherapy, Stockler et al. noted that the median OS varied from a worst-case scenario of 5 months, to an upper-typical survival of 24 months—a welcome improvement for castration resistant disease which lacked viable treatment options less than 5 years ago [30].

Lung Cancer

Lung cancer has long been the most deadly cancer amongst men and women in the USA [27]. Although visceral involvement is common, metastatic disease occurs in 30–60 % of cases and has been associated with decreased quality of life, functional ability and overall survival [50–53]. Several observational studies suggest that of all the cancers that involve the skeleton, lung cancer is associated with the poorest survival [31].

There are a number of characteristics that predict a shorter survival in lung cancer: presence of bone metastases [20, 31, 33, 52–55], male gender [31–33], poor performance status [32, 33], more than solitary bone metastases, non-adenocarcinoma histology [31], and previous use of first line chemotherapy [31, 33, 55]. In contrast to both breast and prostate cancer, lung cancer has limited effective chemotherapy options; however, the use of second line therapy with epithelial growth factor receptor inhibitors in patients who maintain a good performance status may be associated with improved survival [31].

Melanoma

The prognosis for melanoma that has metastasized to bone is dismal, with a median survival of 6 months or less. However, in a retrospective analysis of 130 cases of patients with bony melanoma, Colman et al. identified a favorable prognostic group of patients with isolated metastases who were able to undergo wide resection of their disease. As with melanoma patients who present with resectable visceral disease, the survival was significantly higher in these patients compared to nonoperative patients (11.8 months vs. 4.8 months) [35].

Thyroid Cancer

Thyroid cancer is the fifth most common cancer in women [56], but fortunately enjoys a good prognosis with a relapse rate of approximately 10–15 % [36, 57–59], and a survival—even with metastatic disease—measured in years [36, 57, 60–63]. Good prognostic indicators include young age [36, 64], sensitivity to radioactive iodine [37, 57, 60–62], limited skeletal involvement [37, 57, 65]. Similar to melanoma, there is evidence to suggest that those patients who present with surgically resectable bone lesions may have improved survival [37, 60, 61, 63, 66].

Tools for Predicting Prognosis in Advanced Cancer

Performance Status

Besides considering the tumor origin in skeletal involvement with cancer, there are other clinical considerations that may be helpful in estimating prognosis. Clinical prediction of survival (CPS) refers to the clinician's best prediction of survival based on informal and subjective information. Unfortunately, physicians' are notoriously optimistic in their estimation of patient survival [67–70], which may explain a reluctance to refer patients to hospice at an earlier point in their illness trajectory.

Performance status intuitively makes sense as a predictor, given that a decline in function occurs as a result of progressive bone involvement. In oncology, both the Karnofsky Performance Status (KPS) and the Eastern Cooperative Oncology Group (ECOG) Performance Status are extensively used to assess eligibility for enrollment in clinical trial or aggressive therapy. The KPS also has demonstrated potential in predicting prognosis [67, 69]. For example, a majority of cancer patients with a KPS score of ≥50 % (i.e., requires considerable assistance and frequent medical care) live more than a month, while the majority of patients who score 10–20 % (very sick, hospitalization necessary, active supportive treatment necessary or Moribund) die within 18 days [71].

The Palliative Performance Scale (PPS) was subsequently developed as a modification of the Karnofsky Performance Status, with the goal of assessing the functional status and survival of patients appropriate for palliative care at end of life [72]. More complex than the KPS, the PPS ranks performance based on ambulation, activity/evidence of disease, ability to care for self, oral intake, and level of consciousness. As with KPS, PPS scores have been shown to correlate with survival, but have been validated primarily in patients who are already in the palliative care setting [62, 83].

Palliative Prognostic Score (PaP)

In an effort to create a scoring system that included both objective and subjective measures, the palliative prognostic score (PaP) was developed and externally validated in several trials with advanced cancer patients [73, 74]. Based on assessment of patients' symptoms of anorexia and dyspnea, the KPS, total WBC, presence of lymphopenia, and the clinician's prediction of survival, mathematical scores are generated and subsequently predict the chances for surviving 1 month. Limitations with the PaP include patients who may have survivals longer than this,

and the inclusion of the clinician's prediction of survival. The PaP also requires a blood sample for determination of the WBC and lymphocyte count, which may not always be desirable or practical at end of life.

Palliative Prognostic Index (PPI)

One model that relies on a scoring system based on less subjective measures is the palliative prognostic index (PPI). Based on the patient's palliative performance score (PPS), oral intake, presence of edema, dyspnea at rest, and delirium, patients are divided into one of three group, with survival subsequently estimated in terms of less than 3 or 6 weeks [75]. The PPI has been externally validated; and although the exclusion of the clinical prediction of survival improves the accuracy, its utility is limited to patients with a survival of only a few weeks.

Number of Risk Factors Model (NRF)

Another model that may have significant utility when predicting prognosis in patients with bone metastases is the number of risk factors (NRF) model. Unlike the other externally validated models discussed, the NRF model has several criteria that are unique to the orthopedic oncology patient population: (1) it was created based on patients referred for radiation, a commonly used palliative treatment option; (2) patients are characterized by the need for radiation to bone versus non-bone sites, and (3) they are further grouped based on breast versus non-breast cancer. The model is quite simple to use, with patients stratified into three prognostic categories based on primary cancer site, presence of bone metastases, and KPS of >60 vs. <60 [76]. Scoring leads to survival predictions of 60 weeks, 26 weeks, or 9 weeks based on the presence or absence of risks.

Normograms

A variety of normograms have been developed to aid in prognostication, although only the Spain normogram has been externally validated [34]. Unfortunately, its use in the USA is limited as it requires LDH value to be reported in U/L, which is not the typical reporting unit. Although not externally validated, an additional survival normogram based on the PPS, patient age, gender, and tumor origin has been published, is easy to use, and provides a range of best-case/worst-case predictions [77, 78] (Fig. 16.1).

Which Tool Is Best for My Patient?

Knowing which prognostic indicator to use when making decisions regarding appropriate therapy for patients with advanced cancer is not clear. For the orthopedic patient, functional status is intuitively predictive. While both the KPS and PPS provide prognostic information, both tests may be more accurate when combined with other measures, such as CPS or laboratory testing [75, 76, 79]. Assessing patients at more than one point in time, noting the rate of decline may also add to accuracy when using tools such as the PPI [78, 80] or the PPS [81, 82]. One multicenter observational study prospectively evaluated the Palliative Prognostic Score (PaP), the D-PaP Score (a modification of the PaP that included delirium as a measurement), the Palliative Performance Scale (PPS), and the Palliative Prognostic Index (PPI). All four models were found to be statistically significant predictive capacity, with the PaP and D-PaP scores being most accurate [38]. Of note, both the PaP and the PPI are predictive for very short survivals; other tools such as the PPS and the NRF model will be more accurate for patients with longer survivals. Finally, in cases where prognosis remains unclear, consultation with both the patient's oncologist and a primary care physician will be helpful in determining potential surgical interventions in the setting of metastatic cancer.

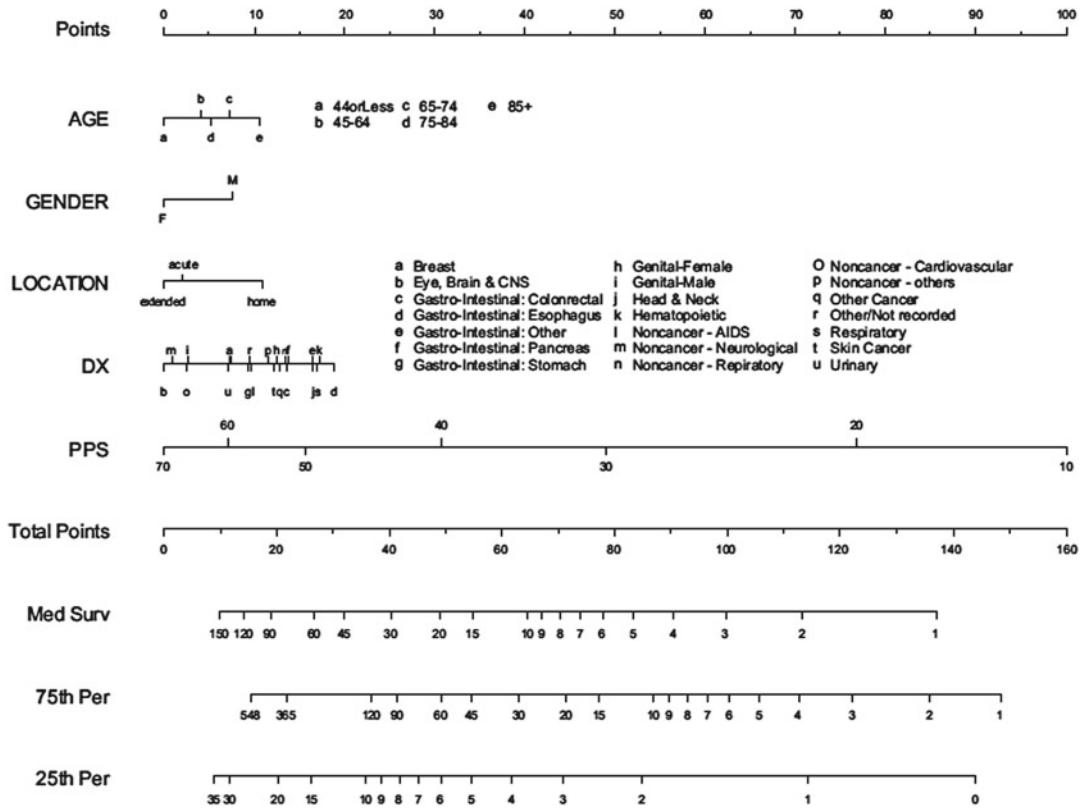

Fig. 16.1 A survival nomogram based on age, gender, location, diagnosis, and PPS. From Lau F, Downing M, Lesperance M, Karlson N, Kuziemsky C, Yang J. Using the Palliative Performance Scale to Provide Meaningful Survival Estimates. Journal of Pain and Symptom Management. 2009 Jul;38(1):134–44. Reprinted with permission from Elsevier Limited

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Part VI

Radiation Oncology

Current and Emerging Modalities 17

Hilary P. Bagshaw and Jonathan D. Tward

Radiotherapy

History

In 1895, Wilhelm Röntgen discovered what he termed "the X-ray," a high frequency, short wave with the ability to pass through dense material [1]. Beginning in the early 1900s, radiation therapy was used for the treatment of both benign and malignant diagnoses [2, 3] and advancements in the field allowed for treatment of deeper seated malignancies by the 1920s [2, 4]. There are case reports of intact bone metastases being treated with radiotherapy as early as 1925, with good analgesic effects [5, 6] and irradiation for pathologic fractures secondary to metastatic malignancies was utilized as early as the 1930s [6]. Early on, the analgesic effect of X-rays was hypothesized to be secondary to either the release of pressure on nerves from shrinking a large tumor, or direct effect on inflammatory cells in the treated region [3, 5]. As more patients were treated with radiotherapy for malignant bone metastases, case reports of resolution of metastatic lesions with recalcification of treated bone were published suggesting a direct therapeutic action on the disease and not merely an analgesic effect [6, 7]. Although technology and techniques have evolved over the years, radiotherapy for treatment of bony metastatic disease remains a mainstay of therapy today.

Basic Radiobiology and Physics

X-rays can be used for both diagnostic and therapeutic purposes. Diagnostic X-rays have a lower average energy than those used in the therapeutic setting. Linear Accelerators are used to produce high energy X-rays (photons), by accelerating electrons through an electric field after which they are decelerated by a target, creating X-rays of different energies. These X-rays are filtered, and a beam with an average energy is produced. The beams can be monoenergetic or polyenergetic, depending if the photons produced are all of the same energy or differing energies. Most photon beams used in therapeutic radiation are polyenergetic. As beam energies increase, the depth at which the maximal dose is deposited in tissues increases, but the dose to the skin and other superficial tissues decreases. This allows for a relative sparing of the skin over the target lesion. DNA damage is a function of radiation dose, expressed in Gray (Gy) or centigray (cGy), 1Gy being equal to 100 cGy and 1 cGy being

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equal to 1 "rad." The damage that can occur in various tissues at conventional doses of radiation can be modeled by a linear quadratic model of radiation damage. At lower doses, DNA damage is more likely to be caused by a single electron and is proportional to dose, whereas at higher doses damage is more likely due to two electrons and is proportional to the square of the dose. The effect of dose and fraction number on tissue is dependent on whether the tissue is an "early" or "late" responding tissue. For example, proliferating tissue such as intestinal crypt cells and tumor cells are "early" responding tissue, whereas skin cells are "late" responding tissue. Increasing the number of fractions allows for sublethal damage repair of DNA between treatments, and late responding tissues benefit more from fractionation than early responding tissues.

As a photon beam passes through matter, an ionization event occurs causing an orbital electron to be ejected from an atom [8]. DNA damage is then caused by two mechanisms; directly by damaging DNA, and indirectly by first interacting with a water molecule creating a radical, which then damages DNA. Most DNA damage caused by X-rays, or photons, is indirect damage. A constant proportion of cells are affected by radiation damage with each radiation treatment, caused by single or double stranded breaks in DNA or crosslinking events.

The therapeutic ratio, or the percent of tumor control achieved for a given level of normal tissue damage, is an important concept in radiation biology. As cells are damaged with exposure to radiation, the dose must be optimized to cause maximal tumoricidal effects while minimizing effect on normal tissue. Ideally, tumor cells would be much more radiosensitive than normal tissue cells. Fractionation, or dividing the total dose into multiple small treatments once daily, allows for an increased tumoricidal effect of radiation on tumor cells and increased sparing of normal tissue, taking advantage of the slower division of normal tissue compared to rapidly proliferating tumor cells [8, 9]. There are many other aspects of radiation therapy and different mechanisms by which radiation is delivered in the therapeutic setting, although these will not be explored further in this chapter, as they are beyond the scope of this work.

Radiotherapy for Bone Metastases

Indications

Radiation therapy is used as first line therapy for bone metastases as well as in the adjuvant setting following resection and stabilization. Indications for radiation for bone metastases include pain, tumors causing cortical destruction or concern for impending fracture, tumors eroding through bone creating a soft tissue mass causing symptoms, nerve impingement or spinal cord compression secondary to a vertebral body or soft tissue metastasis, or adjuvantly following surgical resection of a metastatic lesion with stabilization [10]. Table 17.1 displays indications for radiotherapy in the emergent setting as well as in asymptomatic patients. The Mirel's classification system is useful in predicting impending fracture and guiding when prophylactic pinning is required prior to radiotherapy [11, 12]. The scoring system and clinical recommendations are displayed in Tables 17.2 and 17.3.

Table 17.1 Indications for radiotherapy

General	Asymptomatic	Emergent
Pain	Paraspinal mass	Spinal cord compression
Bone erosion with soft tissue mass component	Large lytic lesion in weight-bearing bone[a]	Cauda equine compression
Cortical disruption		Radiculopathy
		Metastases to orbital region
		Base of skull metastasis with cranial nerve involvement
		Severe pain

[a]Requires pre-RT surgical consult for prophylactic stabilization
RT radiotherapy

Table 17.2 Mirels' scoring system for metastatic disease in long bones [11, 12]

Score	Site of lesion	Size of lesion	Nature of lesion	Pain
1	Upper limb	<1/3 of cortex	Blastic	Mild
2	Lower limb	1/3–2/3 of cortex	Mixed	Moderate
3	Trochanteric region	>1/3 of cortex	Lytic	Functional

Table 17.3 Mirel's clinical recommendations [11, 12]

Mirel's score sum	Clinical recommendation
≤7	Radiotherapy and observation
8	Use clinical judgement
≥9	Prophylactic fixation

Table 17.4 Pain from bone metastases

Possible mechanism of pain	Possible effects of radiotherapy
Release of chemical mediators	Tumor shrinkage
Increased pressure within bone	Osteoblastic repair
Microfractures	Reduction of inflammatory cells
Periosteal stretching	Inhibition of chemical mediators
Muscle spasm	Inhibition of osteoclastic activity
Nerve root infiltration	
Compression of nerve due to bone collapse	

Mechanism of Pain Relief with RT

As radiotherapy for bone metastases is a palliative treatment, the dose required to achieve the palliative effect is typically lower than in the definitive setting. Therefore, any bone in the body is a candidate for palliative radiotherapy because adjacent organ damage is unlikely to occur. The pathophysiology of pain relief after radiotherapy for bony metastatic disease remains somewhat unclear. Some hypothesize that relief is secondary to tumor cell killing, while others suspect radiotherapy causes a change in the local environment of the bone affecting osteoclasts, osteoblasts, and other cells activated in the region [13]. Table 17.4 outlines possible mechanisms for pain relief after radiotherapy.

For decades, tumor cell kill was thought to be the mechanism behind pain relief following radiotherapy for bone metastases. In the 1980s, a randomized trial of radiation with a single fraction compared to multiple fractions did not demonstrate a difference in pain relief between histologies [14]. Classically radiosensitive tumors, such as lymphoma, were no more sensitive to the treatment than other putative radioresistant histologies, and the authors hypothesized that factors other than tumor cell kill played a role in pain control, such as cytotoxic effect on cells secreting pain response mediators [14]. The Bone Pain trial Working Party similarly saw no difference in pain relief between different histologic subtypes, and hypothesized that pain relief may be secondary to death of radiosensitive host cells such as macrophages, which release mediators of pain response such as prostaglandin E2 [15]. There has not been a consistent dose response relationship for treatment of bone metastases in the literature [14, 16], suggesting that pain relief is not due to tumoricidal properties of radiotherapy but rather some other mechanism. Another proposed mechanism differentiates between short term and long term relief and describes the cause of pain from bone metastases as secondary to nerve stimulation in the endosteum due to release of chemical agents from destroyed bone, stretching of the periosteum by tumor growth, fracture, and growth of tumor into surrounding nerves [17]. Thus, in the short term, pain relief may be secondary to a cytotoxic effect on normal bone cells and inhibition of release of chemical pain mediators in the first 48 h following treatment, whereas pain relief achieved 2–8 weeks after treatment may be secondary to tumor cell kill [17]. Clinically, pain relief depends on the anatomy and stressors to the involved site, the histology of the primary tumor, as well as dose of radiation.

Preparation for Treatment Delivery

After consultation with a radiation oncologist, patients are scheduled for a "simulation" appointment. The simulation involves a non-contrast CT scan of the patient in the treatment position, determined by the treating physician. Permanent tattoos are placed on the patient's skin for alignment purposes when the patient is to receive multiple fractions. Immobilization devices are used to ensure the patient is in the same position at the time of simulation and when they return for their treatments. After simulation, the patient returns a few days later for the start of radiotherapy. In cases where an extreme degree of precision or dose escalation is required, additional imaging techniques, such as MRI, may be used to help discern the target anatomy from the avoidance structures.

The treating radiation oncologist works with a dosimetrist and physicist to plan the treatments. This entails outlining, or contouring, structures on the cross-sectional image sets obtained at the time of simulation, delineating the tumor volume, as well as normal structures, or "organs at risk," that would ideally be spared from radiation dose. The dosimetrist, working with the radiation oncologist, then creates a treatment plan using a computer program to model dose delivery to the target lesion and organs at risk. Once the plan is approved by the treating physician, it is transferred to the linear accelerator for treatment delivery. A medical physicist will ensure that the treatment plan modeled in the computer and the actual treatment delivered by the treatment machine are consistent by performing various quality assurance checks and calibrations prior to initiating actual treatment. Prior to the first treatment, an image guidance method, usually X-ray in nature, assures that the alignment of the patient on the treatment table is acceptable compared to the alignment at simulation. Other forms of image guidance can also be used, which include CT scans and ultrasound.

During treatment, patients are unlikely to experience any significant side effects. Acute side effects following treatment depend on the location irradiated, the total dose and the number of fractions. In some cases, however, patients can develop acute skin erythema, moist or dry desquamation of the skin, fatigue, esophagitis, diarrhea, or nausea. Incidence and severity of side effects are dependent on the normal tissues within the irradiation field, the total dose, as well as dose per fraction. Most patients treated for bone metastases experience little to none of these stated side effects, as the dose is quite low compared to curative radiation doses, and organs at risk are usually spared from the field.

Radiotherapy for Spinal Cord Compression

Spinal cord compression is a common diagnosis seen in the Radiation Oncology clinic, and is usually caused by a bony tumor in the vertebral body growing into the epidural space and compressing the spinal cord. Radiotherapy and surgery have both been utilized as definitive management in such cases, although due to the anterior location of most tumors causing cord compression, a laminectomy with a posterior approach does not always result in immediate decompression of the tumor. In 1992, Patchell et al. enrolled patients with spinal cord compression secondary to metastatic disease in a randomized trial comparing radiation therapy alone versus direct decompressive surgery with an anterior approach followed by postoperative radiation (PORT) within 14 days [18]. Patients in the surgery and PORT arm had better outcomes than those in the RT only arm, and thus the trial was stopped early. Patients who received combined modality treatment retained the ability to walk after surgery more often than those treated with RT alone, 84 % versus 57 %, and were able to walk longer, 122 days versus 13 days [18]. These results prompted the adoption of upfront surgery with PORT for cord compression, and provide a basis for the same sequence of therapy for patients with bone metastases in other locations.

Conventional Radiation Therapy for Bone Metastases

Since the early 1920s, case reports of patients treated with radiation for painful bone metastases reported good analgesic outcomes [3, 5, 7]. Historically radiation portals were designed using plain film X-rays and typically directed at the target volume, or tumor, from one or two angles. With the invention of three-dimensional imaging, radiotherapy has become more conformal and the term "three dimensional conformal radiation therapy" (3DCRT) is commonly used to describe these techniques. 3DCRT is used for all sites of disease, and involves multiple photon beams targeted at the tumor from different angles. A computer system is used to block areas containing organs at risk, to create a conformal cloud of dose targeted at the involved site, allowing for dose sparing of organs at risk. Figure 17.1 shows an example of a 3DCRT treatment plan.

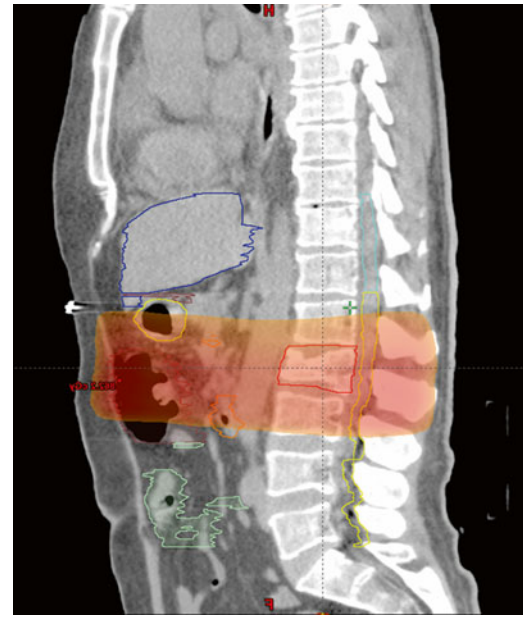

Fig. 17.1 3D conformal RT treatment for L2 spinal metastasis. This is a representation of what the dose in a 3D conformal plan would look like for the same patient treated on protocol in Fig. 17.2. L2 is the target, outlined in *red*. In a typical single fraction conventional treatment, the dose is 800 cGy, and the *red dose color* wash in the figure above represents 95 % of the prescribed dose, or 760 cGy. By convention, with conventional treatment, one vertebral body above and below the index lesion is also treated. As depicted, more of the bowel and spinal cord receives full dose compared to the stereotactic body radiation therapy (SBRT) plan shown in Fig. 17.2

Randomized trials of treatment with conventional radiotherapy have shown complete pain relief rates ranging from 15 to 54 %, and partial pain relief rates ranging from 28 to 89 % [14–16, 19–28]. The Bone Pain Trial Working Party Group showed a median time to pain relief in all patients of approximately 1 month, and a median time to complete pain response of 3–4 months, whereas median time to first increase in pain was approximately 12 months or longer [15]. In the Radiation Therapy Oncology Group (RTOG) Trial 9702, time to pain relief ranged from 3 to 7 weeks and time to pain relief was slower when metastases were irradiated in the pelvis compared to the long bones and spine, and the outcome was not dependent on histology of the primary tumor nor on the initial pain score [27]. Median duration of pain control was reported anywhere from 12 to 29 months [27]. For both single and multiple fraction treatments, Price et al. [14] demonstrated a median time to onset of pain relief of approximately 1–2 months, and for patients who achieved pain control in 1 month up to 49 % of patients reported pain control over 24 weeks. In a randomized trial of single fraction treatment compared to four fractions, approximately 20 % of patients in each cohort did not achieve pain relief [25]. Although the time to onset of pain control and the duration of pain response varies in the literature, patients should typically experience pain relief within 4 weeks of treatment, and be aware that if pain returns they may discuss retreatment with their physicians.

Complications following radiotherapy can include fracture, with an incidence ranging from 2 to 18 % depending on the total dose and fractionation scheme of treatment, although there has been controversy in the literature with regard to the incidence of fracture between treatment regimens [14–16, 19–28]. A randomized study from Berlin showed improved recalcification in patients after 30 Gy in ten fractions compared to a single fraction treatment, and recommended if there is concern about stabilization of the bone to choose a more fractionated regimen [26].

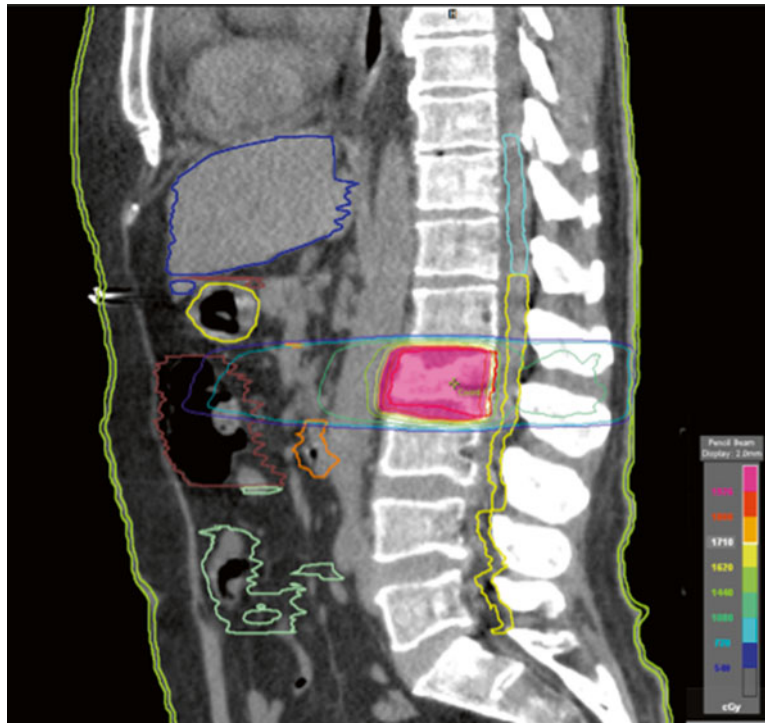

Fig. 17.2 SBRT treatment for L2 spinal metastasis. This patient was treated on RTOG protocol 0631, and received SBRT to an L2 spinal metastasis; 18 Gy (1800 cGy) in a single fraction. This is a representation of the radiation plan with the normal structures (such as liver, bowel, spinal cord, etc.) outlined, as well as the gross target volume (GTV), outlined in *red*, the L2 vertebral body in this case. The dose color wash (*pink*) represents the area that received 95 % of the dose (1710 cGy). The *yellow*, *blue* and *purple lines*, represented different dose ranges, as shown in the *lower right side bar*. As depicted, SBRT treatment allows for tighter dose delivery to the target volume, with less dose delivery to surrounding structures

The RTOG trial 7402 showed a significantly higher fracture rate in those that received 4050 rads in 3 weeks compared to 2000 rads in 1 week [27]. In a typical practice, many factors play a role in deciding how many fractions to deliver treatment in, such as the site of disease, histology, surrounding organs, patient discomfort level, and the role of surgery.

Although radiotherapy has been used for almost a century to treat bone metastases, the dose and fractionation has been an area of controversy. One of the first randomized trials comparing dose and fractionation for treatment of bone metastases started enrollment in 1974 by the RTOG. Patients with solitary or multiple osseous metastases were eligible and were randomized to different total doses and fractionation schemes depending on if they had solitary or multiple metastases [27]. Overall, 90 % of patients received some pain relief, and those with initial pain scores less than 9 out of 10 on the visual analog pain scale, and those with breast or prostate primary tumors were more likely to achieve pain relief. For patients with solitary metastases, there was a higher risk of fracture in patients who received a higher total dose of radiotherapy, although there was no difference in the courses of radiotherapy for symptomatic response. A reanalysis of this data by Blitzer, with different response definitions, showed that highly fractionated treatments to higher total dose (4050 cGy and 3000 cGy for solitary or multiple metastases respectively) were superior in all endpoints and outcomes [19]. In 1983 a randomized trial comparing

two fractionation schemes showed equivalent pain control of 48 % after either 20 Gy in 2 fractions or 24 Gy in 6 fractions [24]. A randomized trial from Germany also showed equivalence in all pain outcomes and survival with 20 Gy in 5 fractions compared to 30 Gy in 15 fractions, and the authors favored the shorter course therapy due to the poor prognosis of most patients with metastatic disease [28].

Single Versus Multiple Fractions

Many patients with painful bone metastases cannot tolerate a long course of treatment due to a poor performance status and inability to lie on the treatment table daily due to pain, and therefore single fraction treatment has been explored extensively, as shown in Table 17.5. A trial comparing 8 Gy in a single fraction to 30 Gy in 10 fractions showed equivalent duration and speed to onset of pain relief across all histologies [14]. Patients treated with a single fraction received retreatment more commonly, but there was no difference in toxicity and the authors hypothesized that treating physicians were more prone to deliver a second fraction to patients who had only received one treatment as opposed to those who had received ten [14]. A Danish trial showed equivalent pain relief with 8 Gy in a single fraction and 20 Gy in 5 fractions, with over half of patients reporting some pain relief at up to

Table 17.5 Randomized trials of radiotherapy regimens

Trial	Fractionation	Complete response	Partial response
RTOG 9702 Tong et al. [27]	*Solitary lesion* 4050 rad/3 weeks 2000 rad/3 weeks *Multiple lesions* 3000 rad/2 weeks 1500 rad/1 week 2000 rad/1 week 2500 rad/1 week	 61 % 53 % 57 % 49 % 56 % 49 %	 85 % 82 % 87 % 85 % 83 % 78 %
Price et al. [14]	8 Gy/1 fraction 30 Gy/10 fractions		45 % 28 % (ns)
Nielsen et al. [25]	8 Gy/1 fraction 20 Gy/5 fractions	25 % 25 % (ns)	>50 % >50 %
Bone Pain Trial Working Party [15]	8 Gy/1 fraction 20 Gy/5 fractions or 30 Gy/10 fractions	57 % (ns)	78 %
Gaze et al. [21]	10 Gy/1 fraction 22.5 Gy/5 fractions	33.4 % 32.3 % (ns)	83.7 % 89.2 % (ns)
RTOG 9714 Hartsell et al. [22]	8 Gy/1 fraction 30 Gy/10 fractions	15 % 18 % (ns)	50 % 48 % (ns)
Kaasa et al. [23]	8 Gy/1 fraction 30 Gy/10 fractions	ns	
Koswig et al. [26]	3 Gy/1 fraction 30 Gy/10 fractions	33 % 31 % (ns)	81 % 75 % (ns)
Chow et al. [20] (*meta analysis*)	SF MF	23 % 24 % (ns)	
Wu et al. [16] (*meta analysis*)	 SF MF	 33.4 % 32.3 % (ns)	**all patients* 62 % 58.7 % (ss) **evaluated patients* 72.7 % 72.5 % (ns)

Gy gray, *SF* single fraction, *MF* multiple fractions, *ns* non significant, *ss* statistically significant

6 months [25]. The Bone Pain Trail Working Party examined a single fraction of 8 Gy compared to multiple fractions; 20 Gy in 5 fractions or 30 Gy in 10 fractions, with the goal of examining long term outcomes and acute side effects [15]. In both groups, 78 % of patients had some pain relief, and 57 % experienced complete pain relief, with no difference between the regimens. After 12 months of follow up, the authors concluded that a single fraction regimen was no different in efficacy or toxicity to multi-fraction regimen, and the single fraction provided adequate durability of pain control. Jeremic & Hoskin [29, 30] both showed superior outcomes with single doses of 8 Gy compared to 4 Gy, and Gaze et al. [21] showed equivalence in all outcomes with a single fraction of 10 Gy compared to 22.5 Gy in 5 fractions. Three randomized trials showed equivalence in pain relief with 8 Gy compared to 30 Gy in 10 fractions [22, 23, 26]. Although one study reported higher rates of fracture with 8 Gy, they also found higher toxicity with the 30 Gy regimen [22]. A meta-analysis of multiple randomized trials demonstrated that when comparing single versus multiple fraction treatment, the complete response rate is 23 and 24 % respectively [20]. Using international consensus criteria to define response end points a study showed that 72 % of patient had an overall (or partial) response, and 14 % a complete response [31]. Overall, it appears radiotherapy for bone metastases results in a 60–70 % response [20]. The authors of many randomized trials urge the adoption of single fraction radiotherapy for pain relief from bony metastases as standard of care as it is more convenient for patients, provides similar outcomes, and is cost effective.

Meta-analyses of randomized trials have also shown equivalent outcomes with single and multi-fraction regimens, and no difference in outcomes when examined by biologic effective dose (BED) [16, 20]. A recent meta-analysis of 16 randomized controlled trials showed no difference in overall or complete response rates in single fraction compared to multi-fraction radiotherapy, with complete response rates of 23 % versus 24 % for single or multiple fractions respectively. There were significantly more re-treatments in the single fraction group (20 % versus 8 %), but no difference in fracture rates. The authors stress the higher retreatment in the single fraction group may be due to the fact physicians are more prepared to retreat after a single fraction than multiple fractions [20].

In 2004, Wu et al. published an evidence based guideline for radiotherapy fractionation recommending a single dose of 8 Gy for patients when the goal of therapy is pain relief for symptomatic and uncomplicated metastases [32]. The American Society for Radiation Oncology (ASTRO) recently published a list of treatments to question as part of a national "Choosing Wisely" campaign, and recommended against the use of fractionation schemes with more than 10 fractions for bone metastases [33]. A single fraction course is more commonly used for patients with uncomplicated bone metastases, whether in the postoperative setting or for those treated for intact tumors. The National Comprehensive Cancer Network (NCCN) Treatment Guideline for Prostate Cancer specifically recommends that a single fraction should be used to palliate a painful prostate cancer bone metastasis [34]. Despite these recommendations and numerous randomized trials, radiation oncologists have been reluctant to adopt the single fraction methods. In an patterns of care analysis published in the Journal of the American Medical Association in 2013, fewer than 5 % of patients received a single fraction treatment, and about 30 % of patients received more than 10 fractions [35]. A cynical view of this practice pattern indicates that increased reimbursement for additional fractions may be driving this overutilization.

Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) is a technique used to deliver high doses of radiation with high precision in a limited number of fractions. Immobilization devices are used that are more restrictive than those used for 3DCRT, and image guidance is used prior to each treatment to ensure precision of treatment delivery with

accuracy to the millimeter. SBRT allows for delivery of a higher dose of radiation in a shorter course and at the same time normal tissues can be spared due to the rapid dose fall off compared to 3DCRT [36]. This rapid dose fall off is displayed in Fig. 17.2, an example of an SBRT treatment plan to a vertebral body metastasis, as compared to the dose distribution in a 3DCRT treatment plan, shown in Fig. 17.1.

It has been hypothesized that since SBRT allows for significant dose-escalation, the time to pain control may be shorter and durability may be longer compared to 3DCRT [36]. In recent years, patients with primary tumors of histologic types thought to be "radioresistant," such as melanoma and renal cell carcinoma, have been treated with SBRT and higher doses per fraction in an attempt to improve treatment response and durability of pain control [36–39]. The disadvantages of SBRT include increased cost due to the additional quality assurance measures that must be performed to ensure patient safety, as well as longer total time on the treatment machine for positioning and image guidance. This can be difficult for patients with painful bony disease. The volume of disease can also be limiting, as it is preferable to treat smaller sized tumors with SBRT and therefore many times patients are not candidates for this modality.

There has been less experience with SBRT for bone metastases, and unlike 3DCRT, mature randomized trials comparing dose and fractionation with this technique have not yet been reported. Currently, the RTOG is enrolling patients with painful vertebral body metastases to a randomized trial of a single fraction of 3DCRT to a dose of 8 Gy, compared to SBRT in a single fraction, either 16 Gy or 18 Gy [38]. There is no outcome data published to date, although a recent publication showed safety and feasibility to proceed with the phase III component of the trial [40]. Many institutions have published phase I data as well as retrospective series of their own experience using SBRT to treat bony metastases, with good pain control and minimal toxicity [36]. Table 17.6 summarizes much of the retrospective data published with regard to SBRT for bone metastases.

Treatment by Histology

Breast, prostate, and lung cancer primary tumors account for a high proportion of bone metastases [17]. Table 17.7 displays the incidence of bone metastases with different primary histologies. Randomized trials have not shown a difference in outcomes between different histologies of the primary cancer [14, 15, 17, 22, 27], although malignancies such as renal cell carcinoma and melanoma have been classically defined as "radioresistant" to conventionally fractionated radiation. With advancements in the field more research has examined how to improve control for these patients. SBRT, as discussed, allows for a higher dose of radiation to be delivered in fewer fractions with great precision. Renal cell carcinoma, a classically termed a radioresistant histology, has been shown in retrospective data to respond to conventionally fractionated palliative radiation courses, especially when disease is in the bones [39, 70]. Newer data suggest that metastatic disease responds better with a hypofractionated course, or higher doses per fraction in fewer fractions [37, 38, 52]. A recent retrospective analysis of 24 patients with metastatic bone disease from renal cell carcinoma were treated with SBRT, and those who received a higher total BED (biologic effective dose) of radiation had more durable pain relief and faster time to pain relief than those with a lower dose, with an average time to pain relief of 2 weeks [38]. Memorial Sloan Kettering also showed that the 3-year local progression free survival for patients receiving a high dose, single fraction treatment of 24 Gy or higher was significantly higher at 88 %, compared to patients who received a low dose single fraction treatment of less than 24 Gy, 21 %, and those with hypofractionated courses, 17 %, with no difference in complications [37]. Melanoma is another histology classically termed radioresistant. There have been many retrospective studies of melanoma bone metastases treated with radiotherapy, with response rates anywhere from 68 to 90 % [71]. Some data showed equivalent outcomes with high and low dose per fraction [71]. These histologies that have been taught for

Table 17.6 SBRT for spinal metastases

Authors	Type	Radiosurgery status/ indication	n	Dose	Results
Ahmed et al. [41]	Prospective case series	Primary and reRT for metastases	66 pts 85 lesions	24 Gy (10–40 Gy) (median 3 fx, range 1–5)	12 months OS 52.2 % 1 year LC 83.3 %, 91.2 % (with or without prior RT)
Amdur et al. [42]	Prospective case series	Primary and reRT for metastases	21 pts	15 Gy (no prior RT) 5 Gy (prior RT)	43 % pain relief 1 year PFS 5 %
Benzil et al. [43]	Case series	Primary and reRT for metastases and primary tumors	31 pts 26 mets 9 primaries	2.68 Gy mean single 6.89 Gy mean total dose	94 % pain relief
Chang et al. [44]	Case series	Primary for spinal metastases	63 pts	27–30 Gy (9 Gy×3 fx, 6 Gy×5 fx)	1 year PFS 84 %
Chang et al. [45]	Case series	Primary and reRT	54 pts reRT 131 pts initial	51.1 Gy mean reRT 50.7 Gy mean initial	PFS 23.9 months (18 months reRT, 26 months initial) 6 months LC 95 % 12 months LC 80 %
De Salles et al. [46]	Case series	Primary for spinal metastases and benign tumors	14 pts (11 pts metastases)	12 Gy mean (8–21 Gy range)	Mean FU 6 months 3 pts pain free 4 pts considerable relief 4 lesions decreased, 5 stable, 7 progressed, 6 no follow up
Garg et al. [47]	Prospective case series	Primary for spinal metastases	61 pts 63 lesions	16–24 Gy (single fx)	18 months LC 88 % by imaging 18 months OS 64 %
Levine et al. [48]	Case series	Primary for spinal sarcomas and metastases	24 pts	30 Gy	80 % pain relief mean survival 11.1 month
Martin et al. [49]	Case series	Primary for primary or spinal metastases	41 pts 53 lesions	8–30 Gy (1–3 fx)	Median FU 11.1 month LC 91 % OS 65 % 75 % of symptomatic pts had pain improvement at 6 months post RT
Ryu et al. [50]	Case series	Primary for spinal metastases	49 pts 61 lesions	10–16 Gy (single fx)	85 % complete/partial pain relief 7 % pain relapse

Authors	Type	Radiosurgery status/ indication	n	Dose	Results
Wang et al. [51]	Case series	Primary for spinal metastases	149 pts 166 lesions	27–30 Gy (3 fx)	26–54 % pain improvement at 6 months 1 year PFS 80.5 %
Gerszten et al. [52]	Case series	Primary and reRT for RCC metastases	48 pts 60 lesions	17.5–25 Gy (mean 20 Gy) in 1 fx	89 % pain improvement no RT toxicity in median FU of 37 months
Gerszten et al. [53]	Case series	Primary & reRT for melanoma spinal metastases	28 pts 36 lesions	17.5–25 Gy (mean 21.7 Gy) in 1 fx	96 % pain improvement no RT toxicity in median FU of 13 months
Choi et al. [54]	Case series	reRT for spinal metastases	42 pts 51 lesions	20 Gy median dose (range 10–30 Gy) in 1–5 fx (median 2 fx)	6, 12 months LC/OS 87 %/73 %, 81 %/68 %
Gagnon et al. [55]	Case series	reRT for breast cancer spinal metastases	18 pts reRT (compared to 18 with conventional)	21–28 Gy (3–5 fx)	Similar outcomes in both groups
Klish et al. [56]	Prospective case series	reRT for spinal metastases	58 pts		3 % failure (<5 % isolated failures of the unirradiated adjacent vertebral body)
Koyfman et al. [57]	Case series	reRT for spinal metastases	149 pts 208 lesions	14 Gy (median 10–16 Gy)	Median survival 12.8 months 12.5 % recurrence, median 7.7 months post RT Recurrence in pts <16 Gy was 16.3 %, versus 6.3 % in those >16 Gy (ns)
Mahadevan et al. [58]	Case series	reRT for spinal metastases	60 pts	24 Gy (3 fx) 25–30 Gy (5–6 fx) if near spinal cord	Median PFS 9 months 93 % stability 65 % pain relief 7 % progression
Nikolajek et al. [59]	Case series	reRT for spinal metastases	54 pts 70 lesions	18 Gy (10–28 Gy), 1 fx	FFLF 6, 12, 18 months was 93 %, 88 %, 85 %
Sahgal et al. [60]	Case series	Primary and reRT for spinal metastases	39 pts 69 lesions, 37 with prior RT	25 Gy (3 fx)	Median survival 21 months 1, 2 years PRP 85 %, 69 % salvage RT 1 year pFP 96 %

(continued)

Table 17.6 (continued)

Authors	Type	Radiosurgery status/ indication	n	Dose	Results
Sahgal et al.[61]	Case series	reRT for spinal metastases	19 pts 5 had RT myelopathy	20 Gy for no RT myelopathy 67.4 Gy (1–5 fx) for RT myelopathy	reRT 20–25 Gy safe
Sheehan et al. [62]	Case series	Spinal metastases	40 pts 110 lesions	17.3 Gy (10–24 Gy)	82 % decreased or stable tumor volume 85 % pain improvement
Shin et al. [63]	Case series	Spinal metastases	9 pts	13.8 Gy (10–16 Gy)	80 % improved symptoms
Jin et al. [64]	Case series	Epidural myeloma	24 pts	16 Gy (10–18 Gy)	81 % complete radiographic response 86 % pain control 71 % improvement in neurologic symptoms
Massicote et al. [65]	Case series	Primary postoperative	10 pts		Median time to SBRT treatment 7 days LC 70 % of patients
Moulding et al. [66]	Case series	Primary postoperative	21 pts 20 lesions	Median 24 Gy (18–24 Gy)	LC 81 % High dose (18 or 21 Gy) showed 93.8 % LC
Garg et al. [67]	Prospective case series	reRT for spinal metastases	59 pts 63 lesions	30 Gy (5 fx) 27 Gy (3 fx)	1 year LC 76 %
Gerszten et al. [68]	Prospective nonrandomized study	Primary and reRT for spinal metastases	500 cases	Mean 20 Gy (12.5–25 Gy), 1 fx	86 % long term pain improvement 90 % long-term LC for primary treatment, 88 % for reRT

reRT reirradiation, *pts* patients, *Gy* gray, *fx* fractions, *mo* month, *OS* overall survival, *yr* year, *LC* local control, *RT* radiotherapy, *PFS* progression free survival, *mets* metastases, *FU* follow up, *RCC* renal cell carcinoma, *FFLF* freedom from local failure

This table was adapted from tables previously published by Joaquim et al. [69] and Jhaveri et al. [36]

Table 17.7 Incidence of bone metastases by histology

Primary	Patients (number)	Percent with bone metastases (%)
Breast	6423	17
Prostate	144	16
Esophagus	451	6
Lung	589	5
Bladder	172	5
Rectum	274	4
Thyroid	107	4
Cervix	1981	3
Uterine	509	3
Head and neck	2860	2
Ovarian	586	1
Colon	153	1
Gastric	118	1

decades to be "radioresistant," actually respond well to radiotherapy, especially a course with SBRT, and radiotherapy should not be omitted in these cases. The classical teaching that certain tumors are "radioresistant" should be abandoned.

Timing of Surgery and Radiotherapy

There is little prospective data examining the timing of palliative radiotherapy with regard to surgery. In the randomized study for patients with spinal cord compression, patients were required to have postoperative radiotherapy within 14 days of surgery [18]. There has been minimal data examining a longer interval between surgery and radiotherapy. Retrospective data has been published focusing on other disease sites, for example breast cancer [72, 73], suggesting that a delay in radiotherapy is not necessarily associated with poorer outcomes, but the authors urge timely delivery of adjuvant radiotherapy due to the retrospective nature of the data. At our institution, we recommend completion of postoperative radiotherapy within 4 weeks of surgery, and a common practice is to deliver a single fraction of radiotherapy within 72 h immediately before, or following, surgical resection or stabilization. Although the sarcoma literature indicates that preoperative radiotherapy can lead to delayed wound healing compared to postoperative radiotherapy [74], this circumstance is different from that of palliative radiation for bone metastases due to the difference in dosing and field design. To our knowledge, there are no reports of a palliative course of postoperative radiotherapy, with conventional doses typical of palliative therapy, causing wound breakdown or serious wound complications. Single fraction radiotherapy with doses nearly identical to palliative regimens has been delivered in the perioperative setting to prevent heterotopic ossification for decades. There are no reports of delayed wound healing in the literature [75–78] for these heterotopic ossification patients.

Re-irradiation

Occasionally, patients treated for bony metastatic disease present with recurrence of tumor in a site previously irradiated, or a site adjacent to a radiation portal. Indications for re-irradiation include no pain relief after initial therapy or progression after initial therapy, partial response after initial therapy, or relapse after an initial response [79]. There is controversy in the literature with regard to whether the number of fractions affects the need for retreatment. Some prospective data has shown that with single fraction radiotherapy there is a higher rate of retreatment compared to a multiple fraction course upfront [14–16, 20, 22, 25], and other trials have shown no difference [19, 27, 28]. A hypothesis to explain the higher rate of retreatment with single fraction treatment upfront is that physicians may be more willing to retreat a patient if they only had one fraction initially as opposed to a longer initial course.

Cases of re-irradiation are more extensively reported in the literature today as it is more commonly used, even though second course treatment has been used by radiation oncologists for decades safely and effectively [14, 15, 29, 30, 80]. A retrospective study recently published included 12 patients with bone metastases who

were re-irradiated with conventional treatment and 82 % of patients overall had a good response, with no reported long term toxicities [81]. A meta-analysis reported a 58 % response rate for patients re-irradiated with painful bony metastases and most of these patients requiring repeat treatment had received a single fraction of radiation upfront [79]. A randomized trial published this year of single versus multiple fractions for re-irradiation of painful bone metastases showed equivalent pain response, toxicities and pathologic fracture rates with both regimens [82].

Re-irradiation of spinal metastases has also been shown to be safe and effective and is commonly practiced. The treating physician must use caution in such cases and consider duration of time between the two courses of treatment, the total dose and number of fractions for each course, as the data suggests specific parameters to avoid myelopathy [83, 84]. SBRT after conventional palliative radiotherapy to spinal metastases has also been shown to be safe and effective in certain cases [61].

Conclusions

Radiotherapy is an integral part of treatment for patients with metastatic disease to bone, both in the upfront and adjuvant setting. Patients should expect pain relief within 4–8 weeks following treatment, but they are unlikely to experience complete relief immediately. Repeat irradiation is considered in some situations, and referral to a radiation oncologist is important to assess prior treatment sites and if a second treatment would be appropriate. This treatment is safe and effective for patients with metastatic disease and can help palliate pain and improve stabilization. Radiotherapy is important in the adjuvant setting as well, and the number of treatments used can range from a single treatment to up to 10 or 15, depending on the patient and site of disease. Stereotactic Body Radiotherapy (SBRT) is an emerging treatment modality that holds great promise for increasing both pain control as well as durable local control.

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Part VII

Interventional Oncology

Ablation and Cementation Technologies

18

Aaron E. Frodsham and Laura B. Eisenmenger

Abbreviations

FDA	Food and Drug Administration
IMRT	Intensity modulated radiation therapy
KP	Kyphoplasty
PMMA	Polymethylmethacrylate
SBRT	Stereotactic body radiation therapy
VAS	Visual analog scale
VAT	Vertebral augmentation therapy
VCF	Vertebral compression fractures
VP	Vertebroplasty

Introduction

Approximately 965,000 new cancer cases are noted each year in the USA, with the skeletal system being the third most common site for metastatic disease following the lungs and liver. Approximately 30–70 % of these patients develop spinal metastases and up to 85 % of autopsy studies show evidence of bone metastases at the time of death [1, 2]. Musculoskeletal metastases often replace and compress normal healthy tissue, cause structural instability, elicit pain, and cause fractures often requiring treatment. Treatment options have historically focused on radiation, medical, and surgical treatments with interventional therapies providing a limited role.

Interventional therapies are growing alternatives or complementary treatment options for patients with these metastatic lesions. Musculoskeletal interventions for metastatic disease have historically focused on treatment of pathological fractures with vertebral augmentation therapies (VAT), including vertebroplasty and kyphoplasty. Despite some recent controversy (which is addressed later in this chapter), these therapies have proven to be effective in relieving acute pain and stabilizing metastatic spine lesions with numerous studies supporting their use [3–21]. In addition, prophylactic VAT post radiation therapy can reduce the risk of pathological fracture and ultimately prevent or reduce the associated clinical sequelae of time spent in bed, deep venous thrombosis, and possibly mortality [22].

The most recent development in interventional therapies is thermal ablation of bone tumors to control pain and to help with local tumor control. The two most commonly utilized technologies currently are radiofrequency ablation (RFA) and

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cryoablation. Radiofrequency and cryoablation technologies have also been used for soft tissue tumors for years, having been validated in numerous studies [23–34]. RFA has also been used for many years in the treatment of osteoid osteoma. Several recent studies have also shown these therapies to be effective at rapidly reducing or controlling acute back pain due to malignancies [2, 35–38]. These therapies can be performed alone although they are more frequently being done in combination with vertebroplasty or kyphoplasty to prevent or treat a pathological fracture.

The intent of this chapter is to provide an overview of interventional treatment options and to also discuss some of the more recent developments in this growing and evolving field. The first part of this chapter discusses the rationale for interventional therapies in the setting of current treatment options. This is followed by an overview and discussion of conventional vertebral augmentation therapies and newer thermal ablation therapies in the treatment of metastatic disease to the spine. The final portion discusses combination therapies for treatment of metastatic bone disease.

Rationale for Interventional Therapies

Spinal metastases are the most common cause of cancer-related pain [39]. Involvement of the spine not only leads to painful VCFs but also potential cord compression and painful bone lesions prior to fracture. With increasing life expectancy and improving therapies, spinal metastases can be expected to increase [40].

Tumor pain in the spine, however, is not completely understood. It is presumably multifactorial with mechanical and chemical factors. Possible causes include tumor ingrowth into neural structures, local tumor inflammatory response, mechanical instability, pressure effects on the periosteum, and fractures [41]. Nerve fibers in the spine are thought to primarily follow the vascular distribution, with nerve fibers entering the posterior vertebrae via the basivertebral foramen and following the course of the nutrient artery. These fibers cluster in the vertebral center after which they branch inferiorly and superiorly towards the endplates [42]. There are also nerves in the bone periosteum, also thought to be involved in the pain response to malignancy [43]. Intuitively, treatments for cancer related pain would target the nerve fibers and factors that stimulate these fibers such as structural instability, tumor mass effect, ingrowth into nerve fibers and healthy tissue, and tumor-related inflammation.

Radiation therapies have traditionally been the standard of care for painful metastatic spinal tumors, frequently providing durable pain relief within weeks and local control rates up to 84 % being reported [44–53]. The mechanism by which this works, however, is not well understood. Presumably radiation injury and necrosis of nerve fibers and tumor cells reduces the pain response and also tumor volume. However, pain control is not always complete or effective with radiation therapy, and at times it may take weeks for an adequate treatment response.

Newer advances in radiation therapy such as stereotactic body radiation therapy (SBRT) and intensity modulated radiation therapy (IMRT) have substantially improved the accuracy of radiation therapy to the spine and reduced the amount of scatter radiation. However, both SBRT and IMRT also use a greater number of beams than conventional external beam radiation, and there is also some scatter or leakage dose to normal healthy tissue. Unfortunately, spinal tissue has a relatively low tolerance for radiation in comparison to other tissues. Some tumors are also resistant to radiation, such as sarcomas and melanomas, which may require multiple treatments for local tumor control and pain response. To complicate matters further, some patients fail radiation therapy with local tumor recurrence.

Some studies have also shown a significant risk for compression fracture after radiation therapies [40, 54]. For example, Rose et al. found lesions treated with IG-IMRT between T10 and the sacrum were 4.6 times more likely to fracture than lesions above T10. Lytic lesions were also 6.8 times more likely to fracture than sclerotic or mixed lesions [40]. Similarly, Boehling et al.

found an overall 20 % risk of vertebral compression fracture after SBRT [54]. These risks are important to consider when treating spinal lesions.

Tumor size may also limit or affect treatment options. Lesions involving >50 % of the vertebral body in general carry a much higher risk of pathological fracture [54–57]. As previously mentioned, radiation therapy can actually increase the risk of fracture, which is worse for larger lesions. Medical therapies can also create a post-treatment necrotic tumor cavity, further destabilizing the bone and increasing the risk of fracture. While some of these larger lesions can be treated surgically, sometimes these patients are not surgical candidates.

Interventional therapies can provide additional options for patients when conventional therapies are not possible or may be less effective. These have the added benefit of providing structural stability through vertebral augmentation with bone cement. They may also be used in combination with surgical, radiation, and medical oncology therapies to reduce morbidity and mortality, frequently improving treatment effectiveness [36].

Vertebral Augmentation Therapies

As previously mentioned, vertebral compression fractures (VCFs) are an important cause of pain and disability, often with profound associated healthcare costs [58]. This type of fracture is most commonly due to osteoporosis although with increasing life expectancy and improved cancer treatments, compression fractures are becoming more common in the setting of malignancy [59–61]. Vertebral augmentation therapies (VAT), conventionally vertebroplasty and kyphoplasty, have become an integral treatment option for pain control and stabilization of compression fractures.

Vertebroplasty (VP) is an imaged guided procedure in which cement is injected into the vertebral body through a bone introducer needle to solidify the fracture and internally support the collapsed bone (Fig. 18.1). Kyphoplasty (KP) differs in that prior to cement injection, a balloon is inserted though the introducer needle into the vertebral body with the goal of creating a cavity within the vertebral body, and in some cases, mild restoration of vertebral body height to reduce kyphosis or angular deformity (Fig. 18.2).

VAT fell out of favor for a brief period of time shortly after studies in the New England Journal of Medicine published in 2009 by Buchbinder et al. and Kallmes et al. showed no benefit of VP over a sham procedure [62, 63]. This led the American Academy of Orthopaedic Surgeons to advise against the use of VP. There were, however, some important shortcomings of these studies. The patients were primarily outpatients, with pain scores as low as 3 out of 10. Additionally, patients with chronic fractures were included (>4 months old), which do not traditionally respond as favorably to VAT. Furthermore, the studies were not appropriately powered for subset analysis, which would have been necessary for evaluation of the subset of patients included in these studies with acute, severe pain. These are important factors in such studies as patients who typically benefit from these treatments are those with acute fractures associated with severe pain. Subsequent studies including the VERTOS I, VERTOS II, CAFE, and FREE trials have shown dramatic pain reduction after vertebral augmentation therapies using appropriately selected patients [64–67]. More specifically, patients having acute fractures with associated moderate to severe pain demonstrated a more dramatic, measurable benefit after VAT in these studies.

Although VAT are most commonly used in the case of painful osteoporotic fractures, there are several other indications. VP is used to treat painful primary bone tumors such as hemangiomas, treat painful fractures due to osteonecrosis (Kummel disease), reinforcement of the vertebrae prior to fixation surgery, and for treatment of painful vertebrae with malignant infiltration causing instability or fracture [59, 60]. The common malignancies that can affect the vertebral bodies include multiple myeloma, lymphoma and metastatic disease with breast, prostate, lung, bladder and thyroid cancers having a predilection to metastasize to the bone [58].

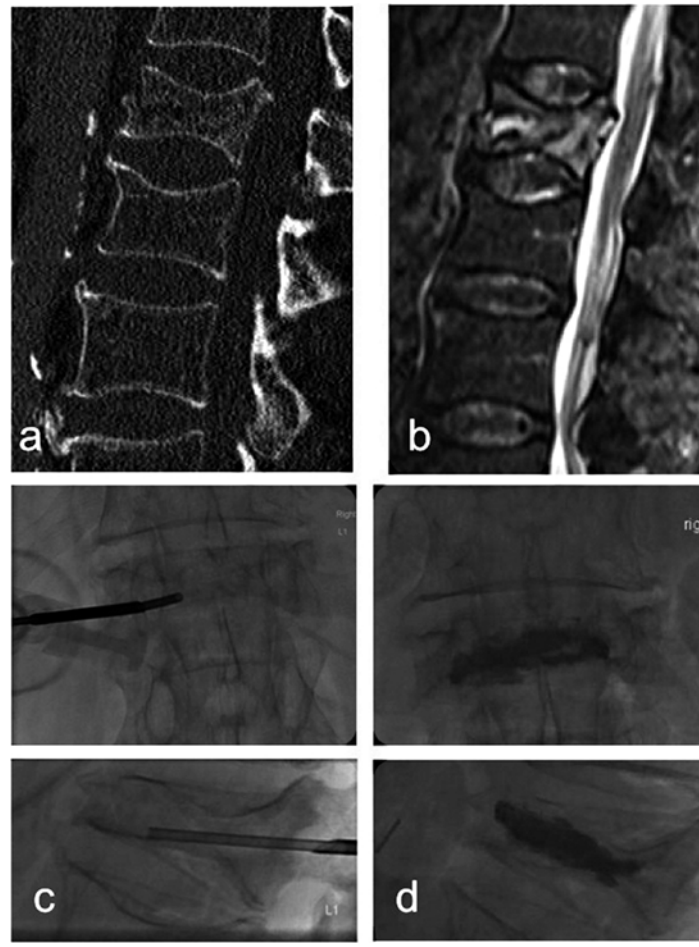

Fig. 18.1 66-year-old male with L1 compression fracture. (**a**) Sagittal CT and (**b**) sagittal STIR MRI demonstrating compression deformity with high T2 signal in L1 compatible with bone edema and acute fracture. (**c**) Unipedicular L1 vertebroplasty from a left transpedicular approach. (**d**) Post vertebroplasty with uniform cement distribution throughout the compressed vertebrae. (Courtesy of Perry Ng, M.D., University of Utah Health Sciences)

In the case of malignancy, indications for VAT are frequently tailored to the patient. The first and most obvious indication is pain associated with the VCFs with a common recommendation of at least 4 out of 10 on a base 10 visual analog scale (VAS) [15]. The second indication is edema on magnetic resonance imaging (MRI) or a positive bone scan (Fig. 18.3), indicating the acuity of the fracture. This indication is, however, occasionally flexible as good results have also been obtained in subacute or chronic VCFs refractory to conservative measures [67–69]. Bone scan can also indicate a recent neoplastic process at a compression fracture site [6, 15, 18, 21]. Imaging studies should also be used to rule out other possible causes of the patient's pain. In addition, clinical examination should correspond with imaging studies to confirm fracture as the primary cause of pain and exclude alternative etiologies [9].

Life expectancy of the patient is also an important consideration. Patients not expected to live for 6 months may not be good surgical candidates and in many cases may benefit from a VAT to improve their quality of life [70–72]. It should also be noted that when life expectancy is very short, VAT may be of limited value or in some cases may be an unacceptable risk. Ultimately this should be evaluated on a case-by-case basis balancing risks, benefits, patient values, and treatment goals.

Several absolute and relative contraindications exist for VP and KP. The most well established contraindications include overt instability and

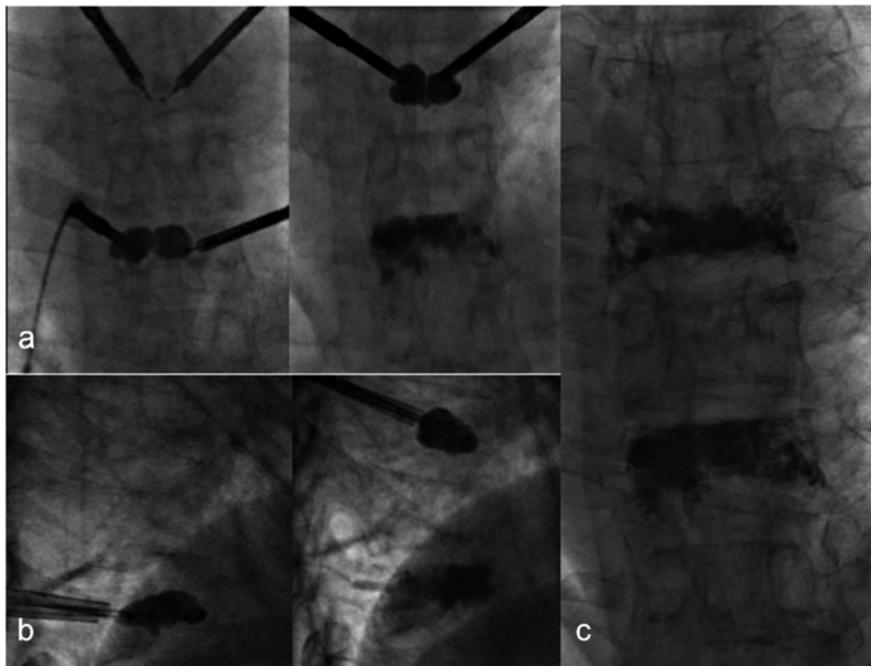

Fig. 18.2 51-year-old male with multiple myeloma and T7 and T9 compression fractures. (**a**) Frontal and (**b**) lateral fluoroscopic images with 15 mm Kyphon kyphoplasty balloons in the T7 and T9 vertebrae. (**c**) Magnified view demonstrating symmetrical cement deposition in the T7 and T9 vertebrae

cord compression [15]. Cord compression on imaging is considered a relative contraindication by some in the field with special precautions taken during VAT in this population of patients [11, 18, 73]. A combination of VAT with laminectomy with or without additional instrumentation can also be used in appropriately selected cases [74]. Infection at the fracture site, bleeding disorder, low platelet count, allergy to contrast, and contraindications to local or general anesthesia are also contraindications to VAT [15]. A full preoperative work up should always be performed.

Vertebroplasty is performed under sedation or general anesthesia with the guidance of biplane fluoroscopy or CT. Polymethylmethacrylate is the most common cement that is used. A needle is placed into the vertebral body prior to cement preparation. A transpedicular approach is typically used for the lumbar and thoracic levels due to inherent safety, but a parapedicular or infrapedicular route can be used if the pedicles are too small or destroyed. An anterolateral approach is often used in the cervical vertebrae. A bipedicular approach is frequently used, although in many cases, a unipedicular approach can just as effectively be utilized depending on the patient's anatomy (Fig. 18.1) [75]. The cement is injected in the polymerization phase to reduce risk of it entering the venous circulation or leaking outside of the vertebra. Injection is done under imaging, which allows early detection of epidural and lateral leaks. The anterior two-thirds of the vertebral body are filled evenly with cement, and the needle is removed prior to cement setting.

In kyphoplasty, bone needles are inserted into the vertebral body after which a balloon is inserted through the bone needle and inflated prior to cement injection (Fig. 18.2). A bipedicular approach is typically utilized. The goal is to create a cavity within the vertebral body and also to attempt to restore or improve vertebral body height. Cement is then injected to fill the cavity, typically starting from the anterior third of the vertebral body in a retrograde fashion as the

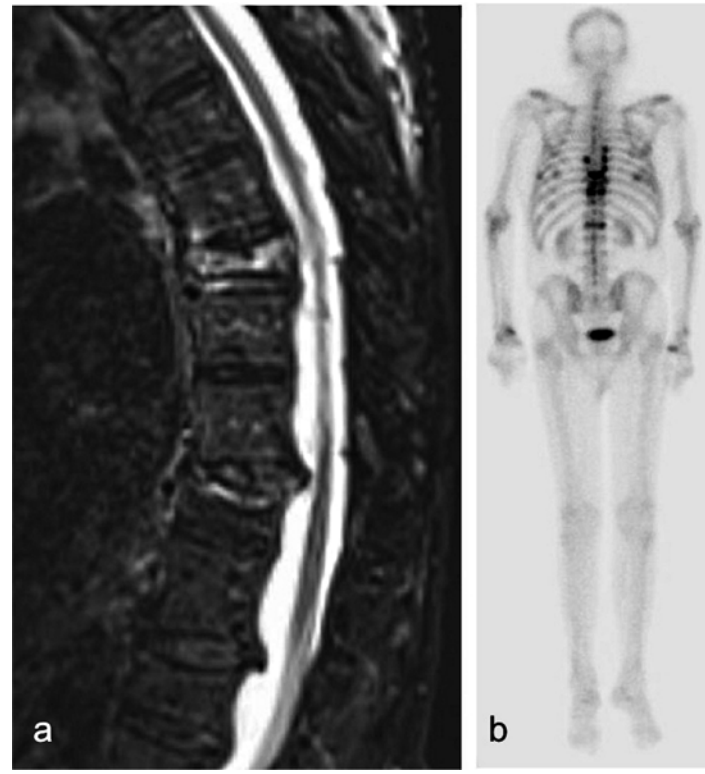

Fig. 18.3 (**a**) Sagittal STIR MRI of the thoracic spine with increased T2 signal in the T8 vertebra consistent with acute compression fracture. Also note chronic fracture at T11 with mild retropulsion. (**b**) Whole body Tc-99m MDP bone scan with posterior planar image demonstrating multiple compression fractures including T8, T9, and T10

needle is slowly retracted into the middle third of the vertebral body. Cement injection is stopped when it reaches the posterior third of the vertebral body. Because a cavity has been formed, injection of cement is under lower pressure than during injection with VP [18].

Significant pain relief has been described in many previous studies and can be expected in the appropriately selected patient population [20, 21, 65–67, 76]. Pain relief is more pronounced in VAT done in acute fractures although some improvement has been shown in more subacute and chronic fractures [67, 76]. Vertebral body height restoration of up to 34–36 % with 3–7.6° of improved sagittal alignment has been described [3, 6, 9, 15, 18, 19, 67, 75]. This has been shown to encourage upright posture, reduced future fractures, and reduced flexion movements of the involved vertebrae [77, 78]. Furthermore, multiple levels can be done simultaneously. No significant increase in operative time or morbidity rate has been seen with 3–4 levels augmented at one time [15]. The number of augmented levels per procedure should be planned on a patient-by-patient basis.

The most frequent complication of VP and KP is leakage of cement with the greater majority of cases being asymptomatic. This is particularly more risky into the posterior canal given tumors frequently involve or destroy the posterior cortex of the vertebra (Fig. 18.4). For hematogenously spread tumors, this is likely facilitated by the vascular anatomy, with blood supply entering through the basiverteral foramen posteriorly [42]. Extravasation of cement is less frequent in KP, likely due to the lower pressure during cement injection [15, 18, 76]. Many less frequent complications have been reported with the most notable being fatal penetration into vital structures; however, the rate of serious complication is very low [75, 79, 80]. Adjacent fractures can also occur although the incidence is similar or reduced compared to conservative treatment [16].

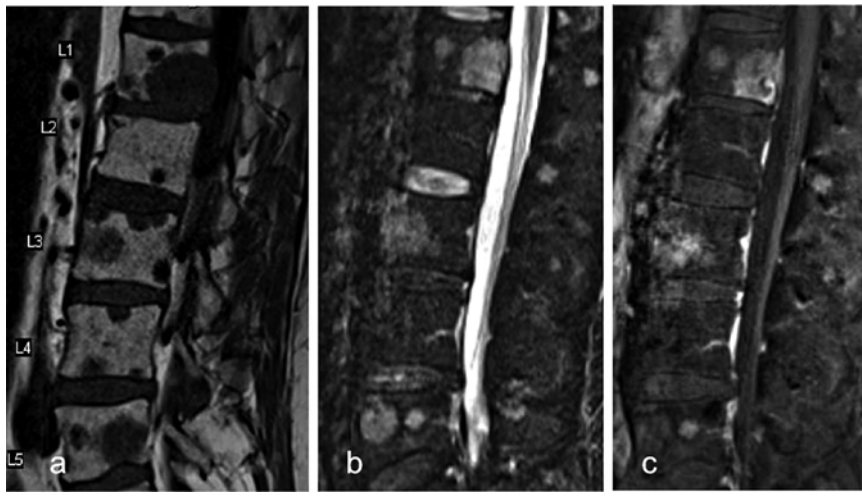

Fig. 18.4 40-year-old male with metastatic colon cancer to the spine. (**a**) Sagittal T1, (**b**) T2 STIR, and (**c**) gadolinium enhanced T1 fat-suppressed MRIs demonstrating innumerable spinal metastases with a larger lesion at L1 extending through the posterior cortex and compressing the ventral thecal sac (Courtesy of Roderick Willmore, M.D., University of Utah, HSC)

Initially it was hypothesized that pain resolution after VAT was that PMMA destroys pain fibers due to the exothermic effect of cement polymerization or direct toxicity from the monomer [81–84]. Other studies challenged this due to only minimal osteonecrosis, no evidence of intraosseous neural tissue necrosis, and similar pain reduction seen with calcium phosphate cement which crystallizes at room temperature [85–87]. PMMA may also simply affect vertebral body nerve fibers by mechanical disrupt during balloon inflation or the filling of the central vertebral body with cement. Cement may also simply provide internal fixation preventing pain fiber irritation [85, 86].

There is also some disagreement among experts in the field regarding the appropriate amount of cement used with no definitive amount established. Some studies suggest that smaller cement volumes may restore vertebral body strength and stiffness with adequate pain control [88]. Others propose larger amounts produce better biomechanical results. Larger volumes of cement have been shown to better correct deformities and maintain vertebral body height [89, 90]. One study specifically found that cement volume was the most important predictor for pain alleviation in a dose-dependent pattern [91]. The exact mechanism by which VP/KP provide pain relief remains somewhat controversial.

Appropriate prophylactic use of VP and KP is currently a point of disagreement. Prophylactic VP and KP have been used in vertebral bodies adjacent to the level augmented for fracture to reduce stress on those adjacent levels and prevent subsequent fractures [92]. A specific example of this is performing prophylactic augmentation in between two augmented vertebrae as this vertebra is exposed to increased forces on either side (Fig. 18.2).

Discussion more recently has been directed towards the treatment of metastatic disease prior to fracture. There is some controversy as to whether this will help reduce future fractures and patient morbidity or cause tumor spread. Combining VAT with conventional radiation is one approach, providing bone stabilization with additional local control [46]. Newer techniques such as radiofrequency ablation and cryotherapy combined with cement augmentation and radiation seem to be the next step in the treatment of metastatic spinal disease [10, 93, 94], which are discussed further in this chapter.

Thermal Ablative Therapies for Bone Tumors

Thermal ablation of bone tumors currently involves the use of radiofrequency or cryoablation probes to induce thermal necrosis in a bone tumor. Ablative technologies have been around for several years, primarily used for treatment of soft tissue tumors [24–28, 31–33]. Radiofrequency ablation has also been used for many years in the treatment of osteoid osteomas, with the first published study of this technology by a radiologist, Daniel Rosenthal, M.D. [95]. The treatment has since been performed extensively and has been shown to be effective with a good safety profile [96–100].

In the past several years, numerous studies have also evaluated thermal ablative treatments of metastatic bone tumors for patients with non-operative malignancies with favorable results [2, 35–38]. Technologies for this have primarily focused on radiofrequency ablation and cryoablation. The rationale for ablative therapies is primarily to relieve tumor pain and to also provide local tumor control. Cement augmentation can also be performed afterwards to stabilize the tumor/ablation cavity and reduce the risk of pathological fracture. As noted above, thermal ablation causes rapid local tissue necrosis, which kills tumor tissue as well as pain fibers simultaneously. Pain control is thought to be primarily due to thermal necrosis of nerve fibers. When ablation is followed by cement augmentation, pain control is also augmented by bone and/or fracture stabilization.

The goal of either ablation technology is to kill both neural pain fibers and tumor cells. This is achieved by creating a 5–10 mm treatment margin beyond the tumor borders based on the preoperative imaging. This can often be done with a single probe but at times may require multiple probes or single probe repositioning. Indications for this procedure are similar to those for VAT, with pain, local tumor control, and fracture prevention as the most common indications. Contraindications are similar to those for VAT. Additional risks to consider include integrity of the posterior wall of the vertebrae and pedicles, predicted ablation zone, and proximity to adjacent neural and vital structures.

Physicians performing these ablation procedures should also be exceptionally familiar with device placement under CT or fluoroscopic image guidance as precise probe placement within the tumor is crucial. Additional familiarity with cross-sectional imaging anatomy and interpretation is paramount for pre-procedure planning, intra-procedural evaluation and monitoring, and post-procedure interpretation. Clear knowledge of the neural anatomy is also critical when performing these therapies to reduce the associated risk of permanent neurological injuries. Appropriate training and experience in these ablative therapies is therefore critical to patient safety.

Radiofrequency Ablation Technology

Radiofrequency ablation uses high frequency alternating electrical current (200–1200 kHz) produced by the electrode. With earlier RF technology, radiofrequency ablation required grounding pads to complete the electrical circuit and prevent soft tissue burning. Many of the newer RFA devices utilize bipolar technology, eliminating the need for grounding pads. The alternating electrical current causes ionic agitation with subsequent frictional heat resulting in ionic agitation. The heat generated causes coagulative necrosis, with irreversible cell damage typically occurring between 60 and 100 °C. Above this temperature, charring and tissue vaporization occurs which can impede the flow of the current [101].

Some of the currently used RF devices for bone include OsteoCool RF Ablation System (Baylis Medical, Burlington, Massachusetts), Dfine STAR ablation (Dfine, San Jose, California), and UniBlate RFA (Angiodynamics, Latham, NY) (Fig. 18.5). Dfine STAR also has a unique tip deflection technology, facilitating directional guidance of the ablation tip into hard to reach places, such as the central or posterior portion of the vertebral body (Fig. 18.6) or other challenging locations such as the acetabulum (Fig. 18.7). OsteoCool and Dfine STAR are both

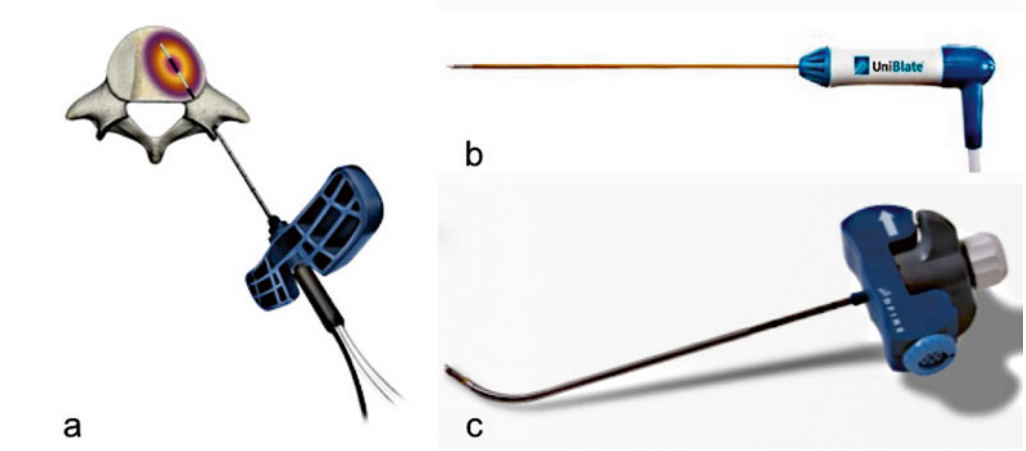

Fig. 18.5 Bone radiofrequency ablation systems. (**a**) Baylis Medical OsteoCool bipolar RFA instrument. (**b**) Angiodynamics Uniblate unipolar RFA instrument. (**c**) Dfine STAR bipolar RFA instrument (Images reprinted with the permissions of Baylis Medical, Inc.; Angiodynamics; and Dfine, Inc. 2014)

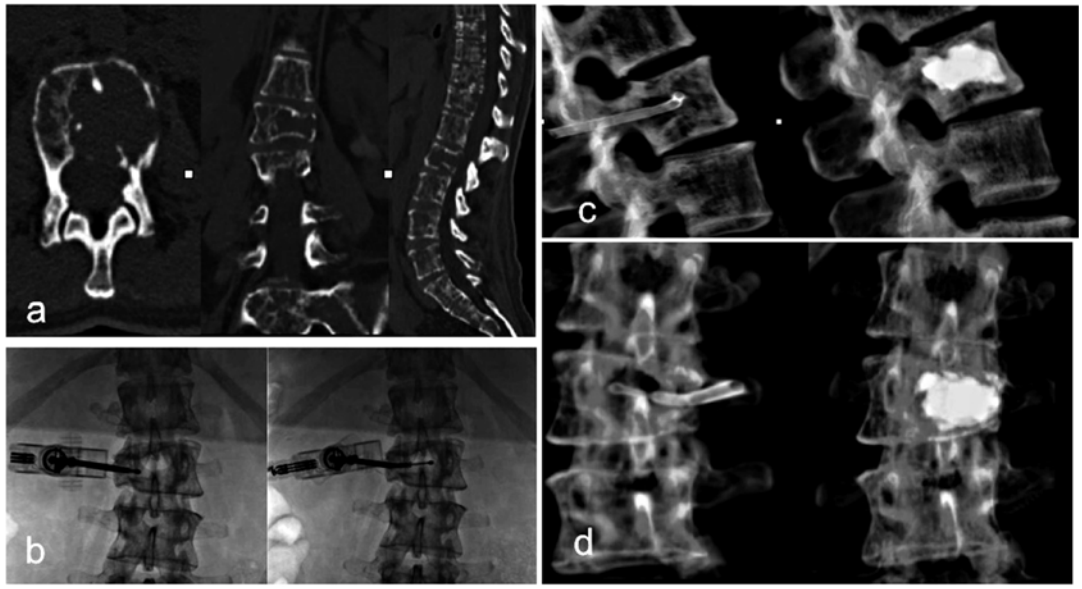

Fig. 18.6 47-year-old female with multiple myeloma with L2 compression fracture. (**a**) Axial, coronal, and sagittal CT images demonstrating lytic L2 lesion. (**b**) Dfine STAR RFA instrument via left unipedicular access of L2 with tip deflected into the central portion of the vertebrae. (**c**) Sagittal and (**d**) coronal intra-procedural spin DynaCT 3D reconstructed images demonstrating before and after cement deposition within the vertebrae to fill the ablation/tumor cavity

bipolar devices, which is a more recent technology essentially eliminating the need for grounding pads. UniBlate and Dfine STAR also have thermocouples built into the tip provide immediate temperature feedback, which can also be utilized for ablation zone prediction (Fig. 18.8).

Ablation cycles are typically for 10–15 min, depending on the size, shape, location, and intrinsic characteristics of the tumor. RFA also has a cauterizing effect which reduces the risk of bleeding. This quality is particularly advantageous for hyper vascular tumors or coagulopathic patients.

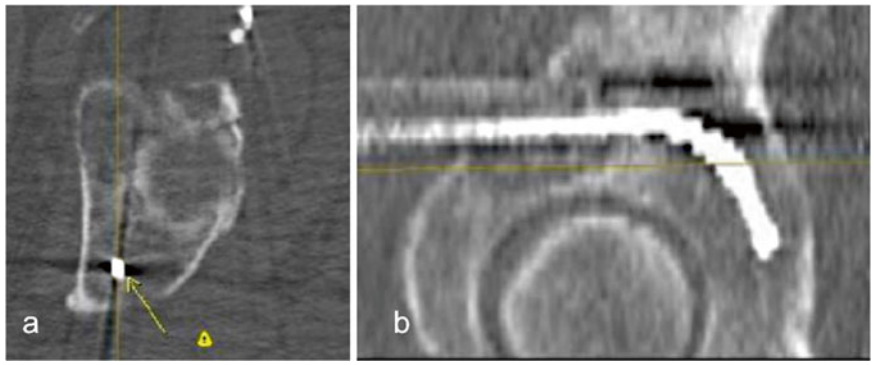

Fig. 18.7 (**a**) Axial and (**b**) sagittal oblique CT images of the hip demonstrating superior acetabular lesion with Dfine STAR ablation instrument directed into the lesion (Courtesy of Jack Jennings, M.D., Ph.D., Washington University)

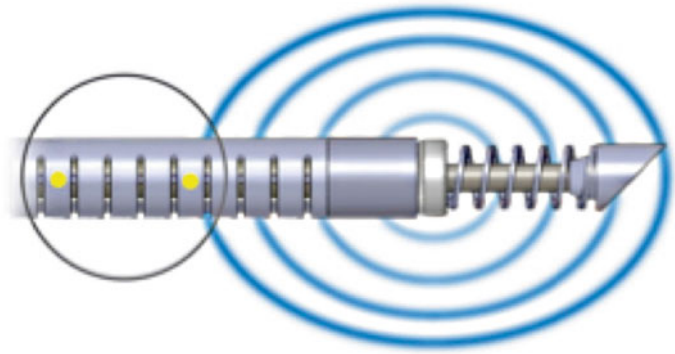

Fig. 18.8 Dfine STAR distal and proximal thermocouples (*circled*) for real-time monitoring of ablation zone

RFA has also been shown to have a synergistic effect with radiation therapy, thereby improving the therapeutic effect and potentially survival.

One of the challenges with RF ablation is the inability to clearly visualize the treatment zone during ablation. The exception to this is with ultrasound, where gas formation during ablation is clearly seen. However, the gas also creates posterior acoustic shadowing, which obscures visualization of the tumor. As mentioned above, some of the newer devices have thermocouples attached on the device (Dfine STAR, San Jose, California) to more accurately monitor the treatment zone by tracking the temperature during treatment rather than relying on imaging. Additionally, the active tips of the RF probes can be difficult to see on CT due to streak (beam hardening) artifact, which can make exact placement within the tumor challenging.

Cryoablation Technology

Cryoablation is another current technology that is being used more frequently for treatment of bone tumors with good reported outcomes [102–105]. It is actually an older technology, being first used to treat breast and uterine cancers in the 1840s. It gained more traction in the 1960s when trocar-type probes were designed, primarily for treatment of liver tumors [106, 107]. The technology takes advantage of the thermal properties of highly pressurized gases, typically argon or nitrous oxide. As the gas travels through the thermal probe to the tip, the gas expands at the applicator tip causing the temperature to rapidly drop. This is known as the Joule-Thompson effect, with temperatures of −80 °C to as low as −160 °C possible [101]. A temperature between −20 and −40 °C is necessary and needs to persist

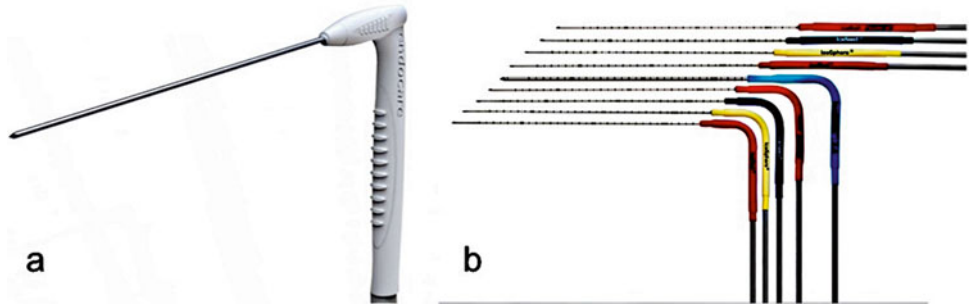

Fig. 18.9 (**a**) Endocare and (**b**) Galil Medical bone cryoablation instruments. (**a**) Provided with permission of Endocare, Inc. a wholly owned subsidiary of HealthTronics, Inc. © 2013 HealthTronics, Inc. All Rights Reserved. (**b**) Used with permission. ©2014 Galil Medical

1 cm beyond the tumor periphery [107–109]. Most current probes also use Helium to thaw the tip, which heats the probe tip when the gas expands. Freeze cycles are typically 10 min followed by an 8 min thaw cycle, with ablations frequently requiring two freeze/thaw cycles. Some of the cryoprobes currently used for cryoablation are produced by Endocare (Healthtronics/Endocare Incorporated, Irvine, Calif) and Galil Medical (Galil Medical, Arden Hills, Minnesota) (Fig. 18.9).

Cryoablation is thought to work through multiple mechanisms. Ice crystal formation disrupts cellular membranes and denatures intracellular proteins interrupting cellular metabolism. It also coagulates blood, interrupting blood flow to the tissue resulting in cell dehydration and ischemia. This cascade of events promotes apoptosis and subsequent cell death. Additionally, there is the potential for immunomodulation with stimulation of the immune system, leading to immunological targeting of tumor cells. This is believed to occur by an immune response against sub-lethally damaged or untreated tissue, being first seen in treatment of prostate cancer in the 1970s. This is currently a matter of debate as there is also evidence for a paradoxical immunosuppressive effect [106, 107, 110, 111].

Cryoablation has the advantage of smaller ablation probes, with probes as small as 17 gauge (Galil Medical, Arden Hills, Minnesota). It also has the added benefit of a clearly visible ablation zone (ice ball) during the ablation, which can be seen on CT, MR, or ultrasound. It is also thought to have less post-procedural pain. Caution, however, must be used near neurological structures as it can also cause permanent neurological injury, and patients may have no physical signs of this during the procedure. This is of particular concern in areas such as in the vertebral body pedicle with the adjacent nerve roots or in lesions abutting the spinal cord.

More recently, Callstrom et al. have measured neurological response during cryoablation to reduce the risk of neurological injury [105]. This is achieved by monitoring motor evoked potentials during stimulation of involved musculature during treatment. This method has helped to reduce this risk of neurological injury dramatically. Additionally, in contrast to RF ablation, cryoablation does not have a cauterizing effect on ablated tissue. Therefore, caution should also be used with hypervascular tumors or in patients with underlying coagulopathy due to the risk of bleeding post ablation. More recently, newer probes offer post-ablation cauterization (IceRod CX, Galil Medical, Arden Hills, Minnesota) to reduce the risk of post ablation bleeding. Another potential drawback of cryoablation is the amount of time it takes to perform the ablation, at time requiring upwards of 30–50 min depending on the size of the tumor and the number of freeze and thaw cycles.

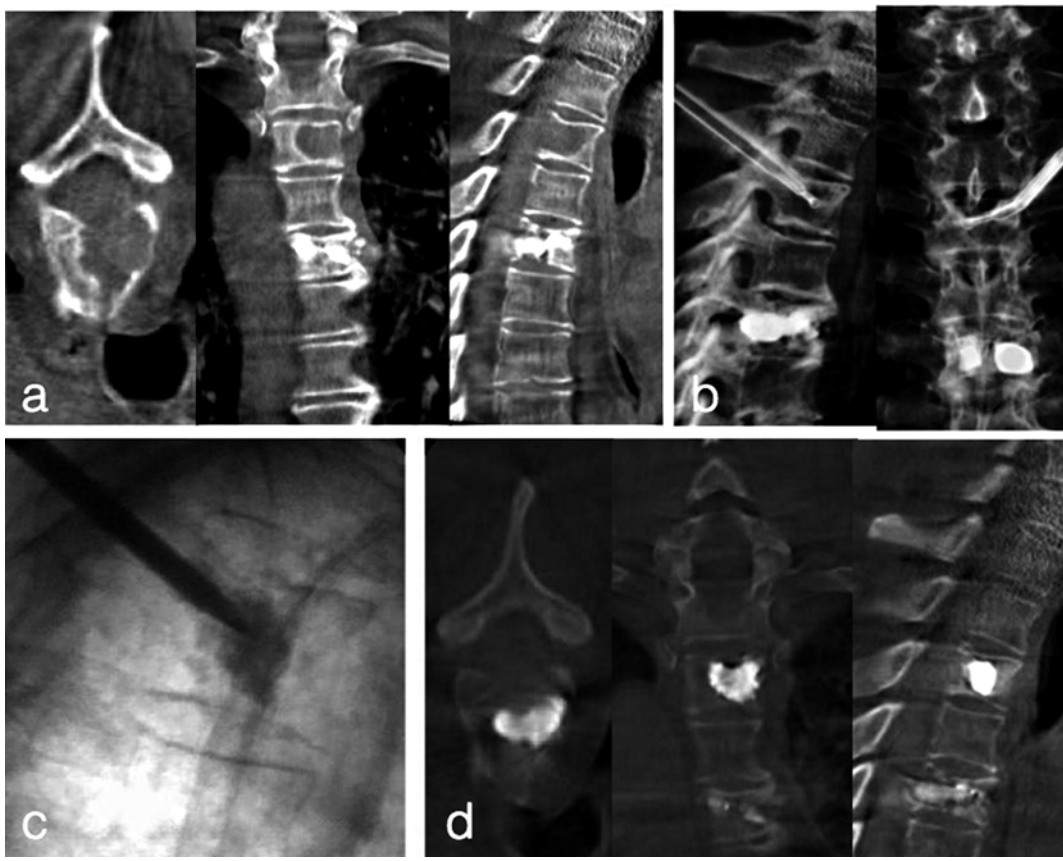

Fig. 18.10 72-year-old male with metastatic lung cancer to the thoracic spine. (**a**) Axial, coronal, and sagittal reconstructed DynaCT images demonstrating lytic T3 lesion as well as prior kyphoplasty changes at T5. (**b**) Sagittal and coronal 3D reconstructed images demonstrating Dfine STAR ablation device within T3. (**c**) Sagittal fluoroscopic images demonstrating polymethylmethacrylate (PMMA) cement injection into T3. (**d**) Axial, coronal, and sagittal reconstructed DynaCT images demonstrating PMMA cement within the ablation cavity

Post ablation Osteoplasty

After ablation, the residual necrotic cavity frequently benefits from cement augmentation to stabilize the necrotic bone cavity, thereby reducing the risk of future compression fracture (Fig. 18.10). This risk is particularly high for lesions involving >40 % of the vertebrae and below T10, especially for mixed or lytic lesions.

One of the potential drawbacks of VAT without pre-ablation is theoretical tumor displacement into adjacent normal/healthy tissue by either the kyphoplasty balloons or injected cement during vertebroplasty. One of the benefits of ablation prior to cement augmentation is the destruction of malignant tissue, which reduces the risk of local tumor displacement and possible extension into normal healthy tissues. Ablation also likely creates an ablation cavity due to tissue dehydration and vaporization, creating a potential space for bone cement deposition.

Because metastases frequently involve the posterior wall of the vertebrae, there is also the increased risk of cement leakage into the canal through the weakened or destroyed posterior cortex. During cement injection, the cement essentially follows the path of least resistance, which could potentially leak through a weakened or destroyed posterior cortex into the canal. Creating an ablation cavity prior to cement injection may

reduce the risk of leakage into these undesirable locations. Cavity creation can also be facilitated after ablation when necessary by balloon kyphoplasty.

Combination Therapies

Combination medical, surgical, and radiation therapies for metastatic disease are common with adjuvant and neoadjuvant therapies frequently being utilized to improve treatment efficacy. Adjuvant radiation therapy post metastatic bone ablation is frequently beneficial, particularly for larger lesions. Combining these therapies should theoretically improve local tumor control and pain response by killing any resistant or residual tumor cells with the additional therapy. In support of this concept, a recent study by Di Staso et al. showed more rapid and effective pain control by combining RF ablation with radiation therapy for spinal lesions in comparison to standard radiation therapy [36].

Pretreatment of the lesion with thermal ablation can also theoretically reduce the rate or local recurrence and the associated increased amount of radiation required for treatment. As previously mentioned, newer technologies such as SBRT and IMRT have substantially improved accuracy; however, there is still some dose to adjacent tissues, and spinal tissue has a relatively low radiation dose tolerance. Further complicating matters, some tumors are also resistant to radiation, such as sarcomas and melanomas, and treatment responses are not always complete. Performing thermal ablation prior to radiation therapy can potentially reduce the number of radiation treatments necessary for local tumor and pain control and the associated scatter/leakage dose to normal tissue. Aside from this, some patients may have severe positional pain and may not tolerate lying flat or in the same position for the appropriate amount of time for radiation treatments. Pretreating these patients with thermal ablative therapies prior to radiation treatments may allow them to be more comfortably immobilized and capable of tolerating further radiation therapy.

Medical and surgical therapies are also frequently warranted. In particular, multiple myeloma patients are frequently treated with chemotherapy at our institution prior to VATs. Although less common, we also perform VAT prior to or after surgery, particularly for bone stabilization, prior to hardware placement. Given the complexity of cases and various evolving treatment options, most (if not all) cases, are best served by a multidisciplinary treatment planning committee including radiation, medical, surgical, and interventional oncology services.

Conclusion

Historically, treatment of both benign and malignant tumors focused on radiation, medical, and surgical options; however, interventional therapies are taking a larger role in malignancy-related therapies providing alternate or complimentary therapies for patients in the appropriate clinical setting. Specifically, vertebroplasty, kyphoplasty, radiofrequency ablation, and cryoablation are now providing additional options for bone malignancy treatment, particularly of spinal tumors and their associated pathologies. Continued advances in the field of interventional therapy will hopeful continue to offer new and innovational advances in treatment.

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Part VIII

Principles of Orthopaedic Surgical Oncology

Issues Facing the Established Metastatic Bone Disease Patient, Timing/Indications for Surgery

19

George T. Calvert

Introduction

The established metastatic bone disease (MBD) patient presents a unique set of challenges for the surgeon. Medical and in particular orthopedic training appropriately places great emphasis upon the evaluation of patients presenting with bone lesions of undefined or indeterminate malignant potential. The consequences of misdiagnosis or delayed diagnosis may be grave, and a rational approach to clinical evaluation, diagnostic testing, and biopsy (as discussed in detail elsewhere in the text) is fundamental to sound MBD treatment. Fortunately, primary site diagnosis is not the challenge for most MBD patients as bone involvement is frequently identified with staging studies obtained after identification and diagnosis of the primary site. In these cases, the surgeon is posed a different but equally taxing challenge; determination of when and if surgical intervention may benefit the overall care and well-being of the MBD patient. The majority of orthopedic training and subsequent general orthopedic practice focus on preservation and restoration of musculoskeletal function. Palliative and end of life care are not at the forefront of daily practice for most orthopedists. A study of orthopedic surgeon ethical knowledge found end of life issues deficient relative to other aspects of medical ethics such as informed consent [1]. Skillful fixation of a MBD lesion done for inappropriate indications or at an inopportune time may be more harmful than no surgery at all. A recent American College of Surgeons editorial questioned whether modern surgeons are regressing back to their pre-nineteenth century medical role of mere technicians [2]. The MBD patient provides orthopedic surgeons the challenge and privilege of utilizing both the art and science of medicine to optimize musculoskeletal care in the context of an often complex multidisciplinary regimen.

Perioperative Risk Assessment of the Metastatic Bone Disease Patient

Inability to survive surgery is a clear contraindication to operative MBD intervention. Quantifying survival risk is often challenging as is relaying the information to patients and families in an intelligible fashion. Most cardiologists, pulmonologists, general internists, and anesthesiologists rely heavily upon the American College of Cardiology/American Heart Association (ACA/AHA) Guideline on Perioperative Cardiovascular Evaluation [3] which was recently updated in 2014. Some relevant points from the guidelines are summarized in Fig. 19.1.

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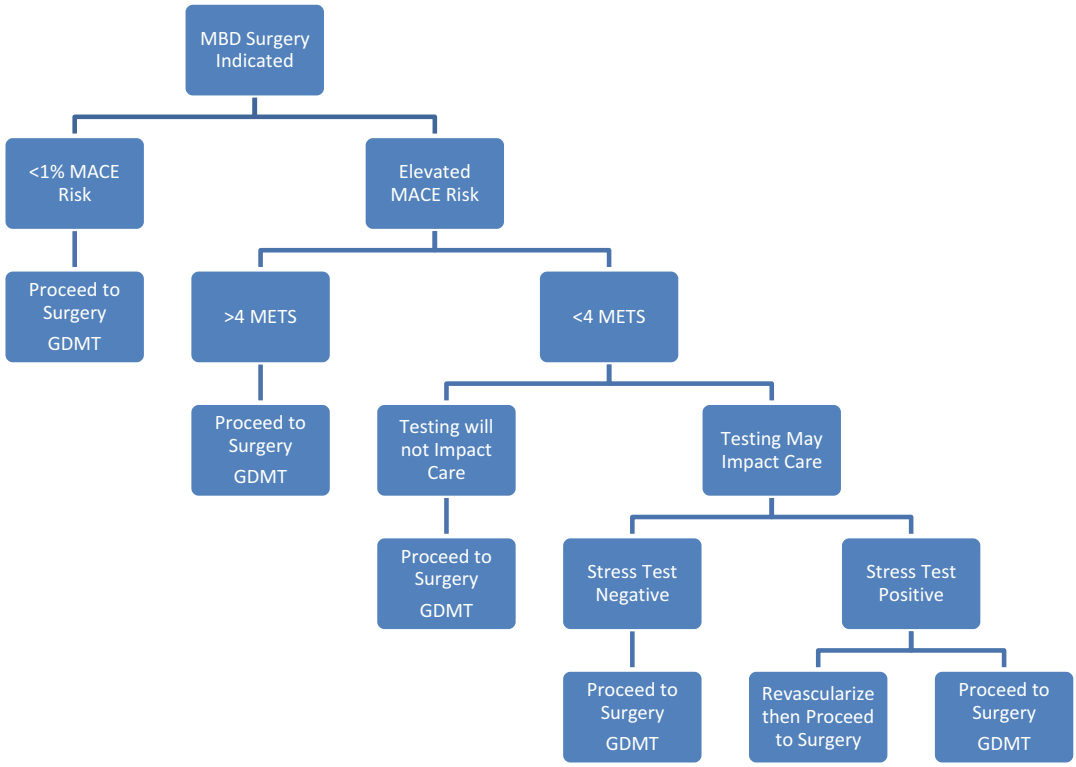

Fig. 19.1 Abbreviated ACA/AHA Peri0op evaluation schema [3]. *MACE* major adverse cardiac risk event, *GDMT* guideline directed medical therapy, *MET* metabolic equivalent

Urgency Definitions

Emergency: Likely loss of life or limb if surgical intervention delayed more than 6 h.

Urgent: Surgical intervention required between 6–24 h to avoid loss of life or limb; limited clinical evaluation is usually possible.

Time Sensitive: Delay of surgery >1–6 weeks to allow for evaluation or significant changes in management will result in patient harm; most oncology cases fall into this category.

Elective: Procedure can be delayed for up to 1 year.

Risk Definitions

Low Risk: Risk of death or myocardial infarction is <1 %.

Elevated Risk: Risk of death or myocardial infarction is 1 % or greater.

Percent risk is determined by both the procedure and the patient's risk factors.

Both the RCRI (below) and ACS NSQIP Risk Calculator may be used to calculate the risk.

Risks Addressed by the Guidelines

Coronary Artery Disease
Heart Failure
Cardiomyopathy
Valvular Heart Disease
Arrhythmias and Conduction Disorders
Pulmonary Vascular Disease
Adult Congenital Heart Disease

Revised Cardiac Risk Index (RCRI) Factors

High Risk Surgery
History of Ischemic Heart Disease
History of Heart Failure
History of Cerebrovascular Disease
Diabetes Mellitus Requiring Insulin
Serum Creatinine >2.0 mg/dl

1 factor entails a death or myocardial infarction risk of 1 %

Activities Requiring >4 METS

Climb 2 Flights of Stairs
Walk 4 Blocks
Heavy House Work
Walk 4 mph on Level Ground

A major revision to the definitions of urgency was made with creation of a "time sensitive" category for which delay of surgery >1–6 weeks will harm the patient. The guidelines specify that "most oncologic procedures would fall into this category." The new guidelines also eliminated the intermediate risk category because previous recommendations for intermediate and high risks were very similar. For even the highest cardiac risk patients, the ACA/AHA guidelines also specify that "if testing will not impact decision making or care, then proceed to surgery according to guideline directed medical therapy." The major limitation of these guidelines is scope as they address only cardiac risk. The ACA/AHA guidelines provide little guidance for the MBD patient with extensive liver, brain, or pulmonary metastases but completely normal cardiac anatomy and function. While the primary anesthesiology mandate is patient survival during surgery and the immediate postanesthesia recovery period for which cardiac assessment generally takes precedence, patients and surgeons are concerned with survival through the entire hospitalization during which cognitive, pulmonary, renal, hepatic, and infectious complications impact morbidity and mortality. A 2012 study of 40,919 total hip arthroplasty cases identified metastatic cancer, dementia, psychosis, renal disease, hemiplegia/paraplegia, and chronic pulmonary disease as independent risk factors for 90-day mortality [4]. Cerebrovascular disease and congestive heart failure were the only cardiovascular independent risk factors for mortality.

The American College of Surgeons (ACS) developed a universal surgical risk calculator based upon greater than 1 million cases collected in the National Surgery Quality Improvement Program (NSQIP) database [5]. The calculator is procedure specific, utilizes 21 patient variables, quantifies 1 month cumulative risk of 9 different complications including mortality, and is available online (www.riskcalaculator.facs.org). The general impact of comorbidities on mortality has been extensively studied. The Elixhauser Comorbidity Method was found to better predict mortality risk among orthopedic surgery patients than the more commonly used Charlson Index [6]. Poor functional capacity irrespective of comorbidities has long been recognized as a risk factor for perioperative complications and mortality [3]. The Karnofsky performance status (KPS) scale and Eastern Cooperative Oncology Group (ECOG) scores are frequently used for oncology clinical trials and by oncologists to assess patient fitness for chemotherapy treatment (Table 19.1) [7]. Neither has been validated for survival prediction in MBD surgery. However, a prospective study of 1157 patients treated with radiation for painful bone metastases determined that KPS combined with the primary tumor diagnosis predicted survival in a large multivariate model [8]. The Timed Up and Go (TUG) test was initially developed to evaluate fall risk and is perhaps the simplest assessment tool. The TUG test measures the time taken to rise from a chair, walk 3 m, turn around, walk back, and sit down [9]. A 2014 prospective, international, multicenter study of 280 patients undergoing solid tumor surgery demonstrated that TUG score of >20 s was an independent predictor of major postoperative complications and was superior to American Society of Anesthesiologist scoring for this purpose [10]. An obvious limitation of the TUG test is inability to ambulate due to a lower extremity fracture.

Surgeons rely upon their medical and anesthesia colleagues in assessing perioperative risk. Ultimately, the final decision must be made by the patient and surgeon. Very few of the palliative MBD procedures are truly elective by the ACA/AHA criteria. Surgeons should question expensive, potentially painful, and frequently palliation delaying testing if it will not result in preoperative intervention or alteration of perioperative management. The ACS risk calculator and the TUG test provide surgeons with simple, objective risk data that can be obtained rapidly and shared with patient. Physicians and patients should also clearly distinguish between mortality risks due to the surgery versus the prognosis of the cancer. The two issues are frequently but not always linked. For example, a patient may have limited painful MBD and severe coronary artery disease. In such a case, the perioperative risk is determined primarily by a non-oncologic issue.

Table 19.1 Functional assessment scales used to assess patients with cancer [20]

KPS	KPS variable	ECOG	ECOG variable	PPS	PPS activity/disease status
100	Normal, no complaints	0	Fully active	100	Normal, no evidence of disease
90	Normal activities, minor symptoms	1	Restricted in physically strenuous activities	90	Normal activity, some evidence of disease
80	Normal activity with effort	1		80	Normal activity with effort, some evidence of disease
70	Self-care, unable to do normal activity	2	Ambulatory, self-care, up >50 % of waking hours	70	Unable to do normal job, significant disease
60	Requires occasional assistance	2		60	Unable to hobby/housework, significant disease
50	Requires considerable assistance and frequent medical care	3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours	50	Unable to do any work, extensive disease
40	Diasbled, needs special care	3		40	Unable to do most activity, extensive disease
30	Severely disabled, hospitalization indicated	4	Completely disabled, no self-care, confined to bed or chair	30	Unable to do any activity, extensive disease
20	Very sick, hospitalization required	4		20	Unable to do any activity, extensive disease
10	Moribund	4		10	Unable to do any activity, extensive disease
0	Death	5	Death	0	Death

Maltoni et al. [20] *ECOG* Eastern Cooperative Oncology Group, *KPS* Karnofsky Performance Status, *PPS* Palliative Performance Scale

Patients and their care team should also be mindful of the risks of inaction when considering prophylactic stabilization. A review the Medicare database from 1999 to 2007 identified 14,400 patients admitted for hip fractures who had been receiving hospice services within 30 days prior to the admission. Despite hospice status, 83.4 % of these patients underwent surgery for their fracture [11]. Based upon these data, one may infer that patient and care provider perception of "unacceptable" risks and "over-aggressive" treatments alter based upon the presence or absence of fracture pain and immobility.

Survival Estimation: Useful Guidance or Exercise in Futility?

The more we, the medical community, learn about the biology and treatment of metastatic cancer, the less effective we appear to be at predicting the survival of patients afflicted with the disease. Prior to President Nixon's "War on Cancer" (launched in 1971), survival of patients with MBD was usually predictable. With few effective chemotherapy agents and no targeted therapies (with the exception of hormonal modulation/ablation), survival was predictably short for most patients [12]. Improved treatment has resulted in the fortuitously increased challenge of life expectancy prognostication for many types of metastatic cancer. A central component of informed consent is discussion of the risks, benefits, and alternatives of the proposed intervention [13]. Benefits of intervention depend upon at least two variables: the improvement gained from the intervention and the duration for which the improvement lasts. Patients with limited life expectancy may not benefit from well-intentioned MBD surgery if the requisite recovery period is longer than their remaining survival. It would appear logical that extensive clinical experience or the pooled expertise of multiple providers should improve prognostication. Unfortunately, a 2007 study found that an experienced clinician was no better than trainees (average 1.7 years experience) at prognostication (<1 month, 1–6 months, >6 months) in a prospectively evaluated cohort

of 216 metastatic cancer patients. Furthermore, a multidisciplinary tumor board was not better than the trainees or the individual experienced physician [14]. Survival was systematically overestimated among the 15 % of patients who died within one month. Another study analyzed 395 predictions made by 8 different disciplines within a radiation oncology unit. Overall, survival was overestimated 72.4 % of the time. Radiation oncologists, radiation therapist, and nurses had equivalent predictive accuracy in a study comparing physician, nursing, allied health professional predictions of survival [15]. Accuracy of prognostication varies with the time frame being predicted. A study of primarily general surgical oncology patients undergoing palliative procedures found that surgeons could accurately predict survival of less than or greater than one year. Surgeons also tended to underestimate the palliative benefit of surgery relative to validated patient self-reported questionnaires [16].

Due to the poor prognostic ability of physicians, investigators have sought to use patient derived data to make predictions. A study of 1636 patients with metastatic lung or colorectal cancer found that patients frequently self-report worse nutritional intake and a lower KPS than their oncologists. Patients had objectively worse survival when their self-reported KPS differed from that of their physician [17]. Another study of patient derived performance status showed good predictive ability of the patient derived data in three distinct cohorts: home hospice, inpatient, and ambulatory care [18]. While patient's self-assessment has shown utility for prognostication, caution is warranted in evaluating patients with high levels of psychosocial distress. A study of over 1000 terminal cancer patients failed to identify psychosocial distress as an accurate predictor of survival although its identification may impact the patients' treatment plan and overall well-being [19]. The Palliative Prognostic (PaP) score was created in an effort to objectively prognosticate survival of metastatic cancer patients. The PaP combines a clinician estimate of survival, KPS, presence or absence of dyspnea and anorexia, total white blood cell count, and lymphocyte percentage; it has been validated in several different cohorts [20]. A subsequent study found that inclusion of delirium improved the prognostic capability of the PaP [21].

Every patient does not seek an estimate of survival, nor do they always use the information in selecting a treatment plan. A 2005 Australian study found that only 61 % of patients wished to know their prognosis, and only 52 % of this subset wanted to know their exact (within weeks) prognosis [22]. Cultural differences exist with respect to the desire for prognostic information, and culturally competent approach can improve patient and family satisfaction [23]. The data summarized above suggests that patient derived data, and the use of a validated scoring system can improve prognostic accuracy. Regardless of the prognosis or its accuracy, survey data indicate that patients appreciate physicians who appear honest and competent and dislike the use of euphemisms and physicians who appear uncomfortable or nervous in discussing end of life issues [24].

Timing: All Surgeries Are Not Created Equal

The urgency of surgery is difficult to define as reflected by the updated ACA/AHA guidelines discussed above. Delay of 1 week versus 6 weeks (the range defining time sensitive cases by ACA/AHA) may be inconsequential for many solid organ tumors requiring surgery, but few orthopedic surgeons consider this time differential equivalent when addressing a fracture. Threats to life and limb, severe pain, and resource availability and allocation may all impact the timing of surgery. Most pathologic fractures are low energy, mildly displaced, and associated with less soft tissue injury than the fractures due to high energy polytrauma encountered commonly by the majority of orthopedic surgeons. Despite this fact, pathologic fractures may rarely cause hemorrhage, severe soft tissue damage, and systemic inflammatory response necessitating more of a "trauma" as opposed to an "oncologic" strategy. In reality, this bimodal view is myopic as patients present on a continuum necessitating the use of best practices from traumatologic and oncologic orthopedics.

A common timing dilemma occurs when an impending or non-displaced pathologic fracture occurs in a patient receiving chemotherapy. In such cases, acute surgical intervention may compromise their systemic treatment or place them at increased risk of postoperative complications such as infection. In these cases, the consequences of displacement of the fracture upon the surgical plan should be considered. Femoral head and neck lesions are typically treated with arthroplasty; furthermore, the complexity of the arthroplasty is generally not increased by displacement of a femoral neck fracture. In contrast, non-displaced fractures of the intertrochanteric and subtrochanteric femur may be treated with a simple intramedullary nail whereas their displaced counterparts may require complex primary arthroplasty or even proximal femoral replacement [25]. As such, the consequences of waiting are far more severe for the latter than the former despite the difference in location within the bone of mere centimeters. Upper extremity lesions may also be treated more expectantly as even displaced fractures are unlikely to result in a bed bound state or necessitate inpatient hospitalization [26]. Most upper extremity pathologic fractures may be temporized with sling or splint immobilization while the patient is optimized for surgery. Medical oncologists must rely upon their orthopedic colleagues for discernment of these subtle nuances. A true multidisciplinary team effort is frequently required to obtain the most satisfactory solution.

Coordination with Chemotherapy and Radiation

Most patients receiving cytotoxic chemotherapy experience neutropenia which is commonly defined as an absolute neutrophil count (ANC) of less than 1500 neutrophils per microliter with severe neutropenia defined as an ANC less than 500 [27]. Metastatic cancer is an independent risk factor for surgical site infection, and neutropenia further increases this risk [28]. Severe neutropenia increases the infection risk of even small implant procedures such as vascular access port placement [29]. The timing of the ANC nadir will vary with the specific agents being used and the patient's general condition and past response to chemotherapy. Close coordination with the medical oncologists is required to avoid scheduling surgical intervention during a period of neutropenia. There are no absolute guidelines for delaying surgery in the neutropenic patient. One study of intra-abdominal surgeries in neutropenic patients concluded that waiting for neutrophil recovery if at all possible was most prudent [30]. It is the author's preference to delay surgery until the ANC is >1000 unless the clinical scenario absolutely dictates otherwise.

Targeted therapies have revolutionized the treatment of many malignancies including those frequently metastasizing to bone (Table 19.2). While neutropenia is less frequent with these agents than cytotoxic therapy, the effects of targeted agents on wound and bone healing are largely unknown. Bevacizumab, a vascular endothelial growth factor (*VEGF*) inhibitor, has well-documented adverse effects on surgical wound healing [31]. *VEGF* is a key regulator of angiogenesis which is crucial for both tumor growth and wound healing. In addition to generalized wound complications, it has specifically been shown to impair bone healing after craniotomies for brain metastases [32]. The majority (60–80 %) of patients treated with epidermal growth factor receptor (*EGFR*) inhibitors develop skin toxicities, and 38 % of patients with skin pathology developed superficial infections in a study of 221 patients [33]. The majority of these infections were Staph Aureus with 5 % being methicillin resistant. Human epidermal growth factor receptor 2 (*HER2*) is EGFR family member particularly important in breast cancer. In addition to skin toxicities, the HER2 antagonists cause left ventricular dysfunction in up to 18 % of patients [34] which may be of particular relevance for planned surgical interventions. Knowledge of the risks of all selective therapies is unrealistic; however, orthopedic surgeons should be aware that significant perioperative risks which may not be identified with routine preoperative testing exist with these agents. Close communication with the treating medical oncologist is important to both fully inform patients of the attendant risks and to potentially mitigate the risks.

Table 19.2 FDA approved targeted therapies (as of 2014) for breast, lung, renal cell, prostate, and thyroid cancer

Drug (Trade Name)	Target	Indication	Selected adverse effects relevant to orthopedic surgery
Ado-trastuzumab emtansine (Kadcyla)	HER2	Breast	Hepatotoxicity, cardiotoxicity, neuropathy, thrombocytopenia
Afatanib (Gilotrif)	EGFR HER2	Lung	Skin rashes, paronychia, wound healing?
Aldesleukin (Proleukin)	IL-2 receptor	Renal	Increased infections
Axitinib (Inlyta)	Multi-kinase	Renal	Thromboembolic events, bleeding, GI perforations
Bevacizumab (Avastin)	VEGF Ligand	Lung Renal	Wound healing, bleeding, necrotizing fasciitis, GI perforations
Cabozantinib (Cometriq)	Multi-kinase	Thyroid	Wound healing, thromboembolic events, GI perforations, hypertension, bleeding
Ceritinib (Zykadia)	ALK	Lung	Little data as drug has been very recently approved
Crizotinib (Xalkori)	ALK MET	Lung	Sensory neuropathy, elevated liver enzymes
Erlotinib (Tarceva)	EGFR	Lung	Rash, increased infection risk
Everolimus (Afinitor)	mTOR	Renal Breast	Anemia, increased infection risk, rash
Gefitinib (Iressa)	EGFR	Lung	Rash
Lapatinib (Tykerb)	HER2 EGFR	Breast	Mucositis, generalized musculoskeletal pain
Pazopanib (Votrient)	Multi-kinase	Renal	Wound healing, bleeding, liver failure
Pertuzumab (Perjeta)	HER2	Breast	Neutropenia, skin and nail infection, rash
Sipuleucel-T (Provenge)	PAP antigen	Prostate	Back pain, myalgias
Sorafenib (Nexavar)	Multi-kinase	Renal Thyroid	Musculoskeletal pain, neutropenia
Temsirolimus (Torisel)	mTOR	Renal	Pancytopenia, bleeding, myalgias
Trastuzumab (Herceptin)	HER2	Breast	Hepatotoxicity, cardiotoxicity, neuropathy
Vandetanib (Caprelsa)	Multi-kinase	Thyroid	Rask, hypocalcemia

Adapted from Abramson, R.G. 2014. Overview of Targeted Therapies for Cancer. *My Cancer Genome*. http://www.mycancergenome.org/content/other/molecular-medicine/overview-of-targeted-therapies-for-cancer/ (Updated Nov. 18, 2014)

Radiation therapy coordination with surgery is thoroughly covered in Chapter 21. For the established MBD patient, reiteration of the recent findings of increased wound complications in patients treated with preoperative radiation is warranted. Review of 1195 surgeries for skeletal metastases by the Scandinavian Sarcoma Group identified preoperative radiation as a risk factor for surgical complications [35]. A more detailed analysis of 672 operated kidney, breast, lung, and prostate metastases again demonstrated higher complication and reoperation rates in patients who received preoperative radiation [36]. Detailed analysis of radiation timing, dose, and fractionation schedule were lacking in these analyses. A smaller series of spinal decompressions for metastatic disease reported a three-fold increase in wound complications with preoperative radiation [37]. Persistent pain despite local radiotherapy was an early criterion for prophylactic stabilization of MBD lesions [38]. Preoperative radiation is mandatory if this criterion is to be used; fortunately, the better validated Mirel criteria eliminate the need for radiotherapy "trialing." If a fracture is eminent, sequencing of surgery before radiation seems prudent both to minimize fracture risk and the risk of wound complications. If surgery is being contemplated for pain palliation in a patient judged to be at low risk of fracture, then preoperative radiotherapy remains a good option as it may obviate the need for surgery entirely.

Tissue Sampling: More than Just Diagnosis in the Age of Targeted Therapy

While biopsy for the diagnosis of metastatic bone disease has been extensively covered elsewhere in the text, the utility of tissue sampling of MBD lesions in patients with a well-established diagnosis is less well defined. Discovery and approval of targeted cancer therapies has accelerated over the past decade (Table 19.2) making molecular profiling of tumor tissue fundamental to the medical management of metastatic disease. Repeat sampling of tumor tissue plays a comparatively smaller role in decision making for cytotoxic chemotherapy as the efficacy of such agents does not depend on the presence of specific receptors. The importance of receptor status is well established for breast cancer, and discordance in receptor status between primary tumors and metastases has been documented. An analysis of 289 breast cancer patients who underwent biopsy of metastatic lesions demonstrated statistically significant discordance in ER (12.6 %), PgR (31.2 %), and HER2 (5.5 %) receptors status. Clinical management was altered in 14.2 % of cases, and the number of biopsies needed to change management was 7.1 [39]. Other authors have argued against routine repeat biopsy as some of the discordance may be explained by sampling error and technical limitations of the receptor measurement methodology [40]. Mutational analysis of lung cancer specimens to guide treatment is also well established with image guided needle biopsy of lung metastases being the most common approach. A study of 126 patients referred for repeat image guided lung cancer biopsy found that repeat biopsy was not technically feasible in 25 % and diagnostic tissue was obtained in only 80 % of patients in whom biopsy was possible [41]. Bone sampling in patients for whom repeat lung biopsy is not possible or fails may provide valuable diagnostic and prognostic information. Cost-effectiveness of mutational analysis and repeat lung cancer biopsy has been recently studied in a decision model. The incremental cost-effectiveness ratio of the re-biopsy strategy was $122,219 per quality adjusted life year which is generally considered acceptable for patients with advanced cancer [42]. Surgeons will note that large amounts of tissue are usually obtainable during palliative metastatic bone cases and the incremental cost of obtaining tissue is minimal for such procedures when compared with a separate image guided biopsy.

Personalized oncology is rapidly transitioning from theory to practice, and "palliative" metastatic procedures may provide life prolonging information. The breast and lung data discussed above may ultimately be refined and expanded for all cancer metastases. The recently announced National Cancer Institute Molecular Analysis for Therapy Choice (MATCH) trial will enroll approximately 3000 patients with any solid tumor or lymphoma diagnosis to undergo biopsy of a metastasis for the purpose of sequencing and mutational analysis. Approximately half of the patients are expected to have mutations amenable to targeted therapy; this cohort will then be enrolled into one of approximately 20 treatment "arms" determined by their molecular profile without regard to their primary diagnosis [43]. As bone is the second most common metastatic site, orthopedic surgeons will undoubtedly play a major role in future molecular diagnosis and treatment efforts.

Second malignancy is a less common but important reason to analyze tissue obtained from patients with established metastatic bone disease. Second primary malignancies now account for nearly 1 of every 6 new cancers reported in the USA, and the incidence is rising due to improved survival after primary cancer [44]. In a study of 482 consecutive bone biopsies performed in patients with a single known primary malignancy, 15 (3 %) identified a new second malignancy [45]. This relatively rare occurrence will almost always impact the medical treatment plan. A rarer but well-described entity is tumor to tumor metastasis (sometime called collision metastasis) in which metastatic disease spreads to the site of a different primary or metastatic cancer [46]. Considering the increasing frequency of second malignancies, routine submission of tissue with any MBD intervention is prudent.

Beyond Palliation: Surgery as a Means of Cancer Therapy

Fracture prevention, maintenance of function, and palliation of pain are well-established indications for surgical intervention in the established MBD patient. The systemic effects of MBD surgery have been generally considered adverse due to the requisite physiologic stress and its associated medical risks. Tumor extravasation and distant spread was also a major concern early in the evolution of MBD surgery [47], and many patients still question whether surgical manipulation of a bone tumor will cause dissemination. More recently, the potential for positive systemic effects of surgical intervention on MBD through immune modulation and systemic response has been described [48]. Early reports of spontaneous remission of prostate metastases after cryoablation of the primary tumor suggested a potential systemic immune response to the ablated tissue [49]. Subsequently, radiofrequency ablation, microwave ablation, and high intensity focused ultrasound have also been shown to induce immunologic responses (48), and regression of lung metastases after cryotreatment of a metastatic bone tumor has been reported [50]. Nishida et al. reported 24 bone tumor cases treated with liquid nitrogen freezing of the resected specimen which was then used as autograft to reconstruct the skeletal defect. They demonstrated significant increases of interferon γ and interleukin-12 levels at 1 and 3 months postoperatively suggestive of an immune response [51]. Murakami et al. subsequently reported 60 cases of total en bloc spondylectomy for which liquid nitrogen treated tumor autograft was used for reconstruction. They similarly noted a significant increase in immune cytokines at 1 and 3 months postoperatively [52].

Unfortunately, dramatic responses with use of ablation techniques alone are rare as anyone who routinely treats MBD patients can attest. In fact, isolated cryotherapy has both immune suppressive and stimulating effects which vary with the therapy technique as well as the tumor being treated [53]. Researchers are now focused on methods to enhance the immune response elicited by ablative techniques. One promising intervention is blockade of CTLA-4, a T cell co-receptor responsible for inhibition of self-reactive T cells. An anti-CTLA-4 antibody has already been approved for treatment of melanoma, and a recent animal study demonstrated that combining blockade of CTLA-4 with metastasis cryoablation resulted in dramatic tumor regression in a mouse model [54]. Other strategies to boost the immune response to tumor ablation include co-administration of GM-CSF and toll like receptor agonists [48] as well as injection of antigen primed autologous dendritic cells [51]. The results of in vivo experiments and early phase clinical trials are promising; however, these techniques remain investigational. It is highly likely that the demarcation between purely palliative bone metastasis interventions and the systemic treatment of metastatic cancer will diminish over the next decade. Surgeons may soon be able to positively impact patient survival in addition to quality of life.

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Questions to Ask Your Medical Oncology Colleagues

20

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Introduction

Oncology is the ultimate team sport. Diagnosis requires the collaboration of clinicians, pathologists, and radiologists. Treatment is multimodal, often requiring input from medical, surgical, and radiation experts. Improved patient outcomes are seen when multidisciplinary teams coordinate care and individual providers do not work in isolation [1, 2]. Misaligned priorities among specialists and between providers and patient are the most common source of suboptimal care. The solution to this problem is often simple: better communication.

Tumor boards are often used to facilitate this communication. Providers from different subspecialties are brought together to coordinate a consensus treatment plan, and optimally, to continue to refine this treatment plan throughout the patient's clinical course [3]. However, as tumor boards are often disease-specific, orthopedic surgeons often are far better at communicating with sarcoma medical oncologists with whom they regularly meet than medical oncologists from other fields. While the orthopedic oncologist would ideally attend breast, lung, thyroid, renal, and prostate tumor boards (among others) to ensure communication with these respective medical oncologists, this is often not practical and therefore alternative methods of communication must be employed when treating metastatic disease. Additionally, while the bulk of sarcoma care is provided by orthopedic oncologists, much of the surgical treatment for metastatic disease is performed by general orthopedic providers. These providers often do not have the same access to medical oncologists that orthopedic oncologists enjoy, leading to additional challenges to interdisciplinary care and good communication.

This chapter will address one aspect of this essential communication between providers: questions the orthopedic surgeon may want to ask his or her medical oncology colleagues. The chapter focuses on questions surrounding the treatment of metastatic lesions, and not questions relating to making the diagnosis, as this is covered in other chapters. Nonetheless, one cannot overstate the importance of good communication in formulating a diagnosis, as proper care is predicated on appropriate tissue diagnosis. No surgical plan should be made without a confirmation of tissue diagnosis with the medical oncology team, and if

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the diagnosis is in question, a discussion of biopsy prior to surgery should be thoroughly vetted.

This chapter lists a set of questions and topics that the orthopedic surgeon may want to raise with the medical oncologist prior to surgery. This chapter is not intended to be comprehensive, but hopefully will provide a framework from which the orthopedic surgeon can approach the medical oncologist. Most importantly, an open chain of communication, with regular updates and real-time flow of information is essential as patient health, expectations, and treatment priorities are often fluid.

The Patient

Orthopedic surgeons often meet patients with metastatic disease in times of crises. The patient has often just fractured through a pathologic lesion or developed debilitating pain, and the goal of care is often rapid return to function and pain relief. It is critical, however, that the orthopedic surgeon takes the necessary time to understand the larger framework in which this metastatic lesion exists. Specific questions for the medical oncologist about the patient are an efficient means to gaining this perspective.

Life Expectancy

What is the patient's life expectancy?

Assuming the diagnosis is well-established and the patient is under the care of a medical oncologist, that provider is often best suited to shed light on the overall health and life expectancy of the patient. While medical oncologists often shy away from "committing" to a mean or median survival, a gestalt or estimation of life expectancy is critical for assessing the risk-benefit ratio for a procedure [4]. While a dogma exists that fracture fixation should not be performed on someone with a life expectancy less than 1 month and an arthroplasty should not be performed on someone with less than 6 months [5], the authors believe that life expectancy should be used as one criterion of many, not as an absolute. Recent literature has shown significant quality of life benefits of orthopedic interventions in patients with short life expectancies [6]. Additionally, orthopedic surgeons often underestimate the symptom relief a surgery will achieve in palliative situations and therefore miscalculate a risk–benefit ratio in patients with short life expectancies [7].

Often definitive estimates of life expectancy are not provided to the patient and family because of their desires, or the discomfort of the discussion for the medical provider. While one need not be specific with a patient or family that does not want this information, it is critical to share the overall prognosis with a patient and family that is considering surgery [6, 7]. Paternalistic medicine of protecting patients from this information has given way to collaborative medicine in which the physician's role is to educate and guide a patient and family through difficult decisions so that they exercise their right to determine how they want to live [8, 9]. Nowhere is this more critical than in metastatic disease where quality of life and dignity in death are of the utmost importance.

Finally, life expectancy may influence the operating surgeon's choice among surgical options. If options of fixation versus arthroplasty are being considered, for example, a shorter life expectancy may push a surgeon toward a palliative fixation procedure if recovery from arthroplasty is more significant. This rationale, however, must be employed with extreme caution, as life expectancy is an estimation and is often wrong [5]. The surgeon has done a disservice to the patient, for whom he has selected a "short-term" palliation procedure that the patient has outlived, requiring a second, revision procedure. Therefore, it is the authors' practice to use life expectancy as a major consideration for whether surgery should be performed but a minor consideration in selecting the appropriate surgical procedure to perform.

Medical "Fitness"

Can this patient tolerate this surgery?

We in orthopedics pride ourselves as problem solvers. We hone in on an issue and fix it. It is one

of the most gratifying aspects of the field. The danger, however, with this focused (at best) or myopic (at worst) approach is that it can often gloss over other medical problems that can render our "fix" irrelevant.

In metastatic disease, it is essential to understand a *specific* patient's tolerance for this *specific* surgery. Unlike a generic "medical clearance," the medical oncologist needs to be educated on the specifics of a surgery—estimated blood loss, anesthetic needs, recovery time, etc.—so that they can weigh on the ability of that specific patient to tolerate that procedure. Remember that the medical oncologist may have only a cursory understanding of the invasiveness of a particular procedure. Educating the medical oncologist to the specifics of a proposed operation will allow them to evaluate the patient's lung, heart, kidney, and other organ capacity to withstand the stressors of surgery.

Perioperative Concerns

Are there specific perioperative concerns our team should know about?

Whether because of the specific patient, the specific tumor, or the specific medical therapies given, there may be increased perioperative risks that the medical oncologist can predict. A large burden of disease in the lung, for example, puts the patient at increased risk of pneumothorax from positive pressure ventilation under anesthesia, whereas concurrent doxorubicin treatment may put the patient at risk for a cardiac event. The medical oncologist has often been treating the patient for an extended period of time and therefore knows the issues around the pathology, the medications, and the patient. Having this information preoperatively can be the difference between life and death as predicted events are more rapidly recognized and treated than unexpected ones.

Expectations

Do you have a sense for the overall expectations and goals of the patient and family?

While this conversation should be had with the patient and family themselves, the medical oncologist can be an invaluable resource in gaining insight into their priorities, expectations, and goals. As the medical oncologist has often had weighty conversations with the patient about life expectancy, advance directives, and willingness to undergo chemotherapy, he or she may be able to provide a framework from which to approach the patient in discussion of surgical options. A patient who is adamant that they do not want resuscitation attempts made and has moved toward discussions of hospice may be less inclined to undergo an operation that has a lengthy recovery period. Nonetheless, it must be remembered that medical oncologists conversations are often focused on lengthy treatment protocols and just because a patient does not want to pursue a novel chemotherapy does not mean they will not elect to proceed with a surgery that could provide significant pain relief.

The Disease

In addition to knowing the patient, medical oncologists are experts in the biology, subspeciation, and clinical course of the different cancers that metastasize to bone. As science progresses and we identify more markers for prognosis, treatment response, and outcome, we rely on the expertise of our medical oncology colleagues to answer questions about the cancer as it pertains to our patient.

Efficacy of Medical Therapy

Can medical therapy prevent or augment this surgical procedure?

Over the past decades, our understanding of the biology of different cancers has dramatically improved, and our expectation is that it will continue to do so. The model of just "nailing" the lesion and ignoring the biology of the tumor is outdated, and we need to continue to keep up with the developing medical understanding of different cancers. As such, some lesions are extremely

responsive to medical therapy. A lymphoma lesion responds dramatically differently to medical therapy than a metastatic small cell lung carcinoma, which responds differently than a Her2+/ER+ breast carcinoma. As our medical oncologists are at the forefront of new medical therapies and longitudinal care for these patients, it is critical to discuss the expectations of lesional response to medical treatment. In highly responsive lesions that have not yet seen treatment, a more conservative surgical approach can often be undertaken. When considering the need to augment a intramedullary nailing with polymethymethacrylate, for example, knowledge of expected tumor response to treatment can be an important variable.

Availability of Clinical Trial

Does surgery affect availability of clinical trials?
Medical therapy with targeted agents, immunomodulators, and novel chemotherapeutics are rapidly advancing for patients with metastatic disease. Clinical trials studying new agents are opening and closing all of the time and eligibility criteria are varied. Some trials require measurable disease, while others require no imminent surgical intervention. Communication with the medical oncologist and the patient is essential if considering a trial. This is a classic case of losing the forest for the trees. Well-intentioned orthopedic surgeons often perform technically excellent operations for patients with metastatic disease that render the patient ineligible for a clinical trial. Knowing the oncologist's and patient's expectation and anticipation of clinical trial is therefore critical before embarking on a surgical procedure.

Tissue

Do you need tissue to better understand this patient's disease?
Advances in medical science and patient care are being driven by better understanding of the biology of tumors. The heterogeneity of cancers, among and within subtypes, is driving our knowledge base to predict responders to targeted therapies and develop novel therapeutics. Individual tumor tissue is therefore critical to both the care of the individual patient and to the field of oncology in general. It therefore cannot be ignored that the time of surgical management is an opportunity to obtain further tissue for study.

Tissue can be used for anything from developing research cell lines to better understanding the genomic makeup of the patient's tumor to establishing xenografts to assess a specific tumor's susceptibility to novel agents. While all of this work must be highly scrutinized by institutional review boards, understood and consented to by the patient, and performed in HIPAA-compliant manner by the surgical and pathology team, simply ignoring this facet of oncologic care and science is doing a disservice to our patients. The orthopedic surgeon plays a key role as, at the very least, a steward of this tissue. Considering whether the patient specifically or science as a whole may benefit from this tissue may be beyond the responsibility of the orthopedic surgeon, discussing a willingness to help coordinate tissue for study with the medical oncology colleagues acknowledges a support of science and will lessen the amount of "wasted" material that goes unstudied. This is especially true in the case of metastatic disease where the tissue diagnosis is already established.

The Medications

Wound Healing

Is this patient on cytotoxic therapy?
Orthopedic oncologists often have dogmatic rules about when they operate in relation to a patient receiving chemotherapy or steroid. Often surgeons will say, "The patient needs to be off chemo for *x* weeks" or "No chemo until the wound heals." These dogmatic statements were most likely formed in response to cytotoxic chemotherapies and do not take into consideration the vast arrays of therapeutics, immunomodulators,

and hormone therapies that currently make up the mainstay of cancer treatment. In this setting, different drugs have widely varied effects on wound healing, immune response to surgery, and risks for infection. A discussion of the cytotoxic effects of a specific patient's medication list, the possibility of delaying the more cytotoxic therapies around surgery, and the risk-benefit analysis of altering the timing of therapy is a discussion to be undertaken in conjunction with the medical oncologist.

Bisphosphonates or Rank-L Inhibitors

Is this patient on a anti-bone resorption medication?

It must be remembered that the osteoclast, not the tumor cell, is responsible for the resorption of bone noted in metastatic disease. It is now well-established that both bisphosphonates (inhibitors of osteoclastic activity) and denosumab (inhibitor of receptor activator of nuclear factor-κB [RANK]-ligand differentiation and activation) can decrease the frequency and severity of skeletal-related events from metastatic disease [10]. While most medical oncologists are current in the understanding of these medications and their pathways, it is important for the orthopedic surgeon to verify this with the medical oncologist to reduce the risk that the patient is returning for more surgery in the near future.

Logistics

Timing of Surgery

What is the schedule of medical therapy and where does surgery best fit in?

The medical treatment protocol for metastatic disease often includes intermittent therapies. These medical therapies can deplete the immune system and render the patient susceptible to infection, wound problems, or perioperative complications. Additionally, patients with metastatic disease are often evaluating how they want to spend their time. Sometimes a gap in therapy is an important time for the patient to spend time with family, reengage with work, or pursue other interests, and it is often a time he or she is not inclined to spend recovering from an operation. Depending on the medical therapies being used, concurrent medical and surgical care may be an option to decrease inpatient time for the patient. A discussion of surgical timing with the medical oncologist and the patient can lessen risks associated to surgery, improve outcomes, and increase patient satisfaction.

Perioperative Medical Care

Who will be the on-call person for oncologic questions for this patient?

While this may seem like a trivial question, it can play a critical role in minimizing perioperative complications. Medical oncologists, like so many fields of medicine, are moving toward "team" medicine and more shift-oriented hours. Having contact information for the patient's established medical oncologist is certainly ideal; however, at the very least, knowing who the covering "on-service" medical oncologist will be prior to surgery can prevent confusion and delayed care. Often questions emerge about restarting chemotherapeutics, steroids, or immunomodulators after surgery, and an open line of communication between the surgical and medical teams can resolve issues as they arise.

Follow Up

How often do you see this patient?

Patients with metastatic disease often spend a significant portion of their time at or traveling to their medical appointments. Patients often live far from medical centers and these regular visits are time-consuming, costly, and anxiety provoking. While orthopedic surgeons often have a "set schedule" to see their postoperative patients—i.e., 2 weeks, 6 weeks, 3 months, etc.—some flexibility in matching the patient's appointments with his or her medical oncologist with that of the orthopedic surgeon is an easy

way to improve the patients quality of life. Similarly, arranging to get follow-up radiographs at the same setting that the patient goes to get other oncologic surveillance imaging performed can save the patient time, money, and effort.

Conclusions

Communication between the orthopedic surgeon and the medical oncologist can improve the patient care, prevent complications, and enhance the patient's quality of life. Questions about the patient, the tumor, the medical therapy and the logistics of care posed to the medical oncologist preoperatively can help design a patient-specific treatment plan that meets the goals of patient and family and optimizes patient outcomes.

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Consideration of the Temporal Relationship Between Surgery and Radiation Therapy

21

Daniel M. Lerman

Introduction

Patients with impending or realized pathologic fractures from metastatic bone disease require multimodality therapy for optimal pain control and preservation of function. Indications for radiation therapy and surgery often overlap in the treatment of metastatic bone disease and outcomes are improved when both modalities are strategically used in combination [1]. Radiotherapy effectively decreases pain from bony metastasis and can inhibit local disease progression, with an acceptable side effect profile. Surgical intervention is indicated for most pathologic long bone fractures, certain impending fractures, and cases of severe bone pain refractory to nonoperative modalities [2–4].

Although the therapeutic benefits of surgery and radiation therapy are often additive, their concurrent implementation can increase the incidence of undesirable side effects [5–9]. The increased risk for postoperative complications, particularly affecting wound healing, in this already fragile patient population prompts inquiry into which treatment related factors can be altered in order to minimize postoperative complications and optimize patient outcomes.

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The administration of radiation therapy is as varied as surgical practice [10–12]. It is incumbent upon the operative surgeon to have an appreciation for variations in radiotherapy protocols and their implications for postoperative complications. Total radiation dose and the duration of time between irradiation and surgery have been proposed as the two most influential treatment variables; the alteration of which can significantly impact the incidence and severity of postoperative complications [6, 13–15].

The optimal sequence of, and time interval between, radiotherapy and surgery are common clinical questions which lack definitive answers. In the context of a long bone pathologic fracture, surgical stabilization is typically performed urgently, preceding radiation therapy without question [3, 16–18]. However, in consideration of impending fractures the ideal sequence of the procedures is ambiguous. Although there are no conclusive clinical studies regarding the procedure sequence (preoperative versus postoperative radiation) and safe time intervals between treatment modalities for patients with metastatic bone disease, treatment guidelines can be extrapolated from basic science research and a variety of clinical studies.

The Biology of Wound Healing

Normal wound healing follows a highly regulated sequence of events, commonly divided into three phases. These phases overlap one another,

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as each new phase builds upon the preceding one to create a mature scar.

Inflammatory Phase

The inflammatory phase is initiated upon wound closure and continues for 3–4 days. Its defining features are hemostasis, active cellular migration, and the formation of a temporary matrix, to which macrophages and fibroblasts are drawn [14].

Hemostasis is initially achieved by the activation and accumulation of platelets at the site of endothelial injury. Accumulating platelets form a platelet plug which is later replaced by a more robust fibrin-rich clot matrix, constituting a temporary scaffold for wound healing [19]. Platelets, activated by endothelial damage, release multiple proinflammatory factors (serotonin, bradykinin, prostaglandins, prostacyclins, thromboxane, and histamine) which cause vascular dilatation and increased permeability [20]. Increased vascular permeability allows plasma leakage from the intravascular space to the extravascular compartment. This facilitates the egress of fibroblasts and inflammatory cells from the circulation as they are recruited to the site of injury by transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF), chemotactic agents released by activated platelets [20].

Within hours of injury monocytes, neutrophils and lymphocytes migrate into the wound bed to remove necrotic tissue, foreign debris and bacteria. By 24–48 h polymorphonuclear leukocytes (PMNs) are the predominate cell type as they work to phagocytize debris and bacteria, in addition to releasing bactericidal agents, such as reactive oxygen species and free radicals [20]. By the end of the second day macrophages, derived from previously recruited monocytes, induce PMN apoptosis and become the predominant cell type. Wound macrophages have many roles, they release bactericidal agents, phagocytize debris and bacteria, degrade extracellular matrix to facilitate cellular migration and when stimulated by hypoxia induce angiogenesis [20]. Additionally, wound macrophages release multiple proinflammatory cytokines which coordinate later events, specifically the recruitment and proliferation of fibroblasts, keratinocytes, and endothelial cells.

Resolution of the inflammatory phase, signaled by decreasing PMN and macrophage populations, is essential for normal wound healing. At this point, the wound edges are held together by merely the fibrin matrix, resulting in a tensile strength less than 5 % of normal tissue [14].

Proliferative Phase

The proliferative phase begins prior to completion of the inflammatory phase, approximately 2–3 days following tissue damage and continues for a minimum of 3 weeks. The defining events are angiogenesis, fibroplasia, and epithelialization [20].

Cell disruption and hypoxia induce angiogenic growth factors, fibroblast growth factor, vascular endothelial growth factor, PDGF, and TGF-β which activate endothelial cells, causing basement membrane degradation in the preexisting vasculature [20]. This increases vascular permeability, facilitating the extravasation of endothelial cells that then contribute to neovascularization. Endothelial cells are drawn into the extravascular compartment and stimulated to proliferate by tumor necrosis factor α, which is released by activated macrophages [20].

Fibroblasts are drawn into the healing wound by macrophage and platelet derived cytokines. TGF-β and PDGF stimulate the proliferation of fibroblasts which become the predominant cell type at 1–2 weeks following wounding [19]. The fibroblasts primary function is collagen synthesis which increases with the fibroblast population and continues at a prolific pace until the fourth week, at which time wound strength has reached 30 % that of normal tissue [14]. After the fourth week collagen synthesis declines to match the rate of collagen degradation, signaling initiation of the *maturation phase*.

Newly synthesized collagen is deposited in the wound base in an immature, disorganized fashion. Immature collagen deposits reinforce the fibrin-rich clot matrix and form a temporary

scaffold upon which keratinocytes migrate from the basal level of the adjacent epidermis to re-epithelialize the wound [20].

Maturation Phase

The maturation phase commences around week three and continues for 2 years. This phase is relatively acellular as most endothelial cells, macrophages, and fibroblasts have undergone apoptosis or migration away from the healing wound [19]. Wound contraction is the defining feature of the maturation phase, achieved by myofibroblasts and collagen maturation. During this process type III collagen, deposited during early wound healing, is replaced by type I collagen which more readily aggregates to form organized collagen fibers. Collagen fiber formation and increased collagen cross-linking are primarily responsible for the increased tensile strength of the mature wound.

Effects of Radiation Therapy on Wound Healing

The deleterious effects of radiation therapy on the skin are well recognized with over 90 % of patients experiencing early skin reactions [8]. The highly orchestrated cellular interactions required for normal wound healing are disrupted by ionizing radiation. In a *dose-dependent manner* wound tensile strength is impaired and side effects develop [19]. Common early side effects include erythema, dry desquamation, hyperpigmentation and alopecia. These may resolve or progress to dermal atrophy, dyschromia, fibrosis, and ulceration [5].

Ionizing radiation induces apoptotic cell death due to extensive DNA damage [21]. Rapidly dividing cells are more susceptible than quiescent ones and therefore active biologic processes, such as wound healing, are disproportionately affected [20]. Additionally, radiation induced cytotoxicity damages vascular endothelium leading to thrombosis, decreased tissue perfusion and edema in the irradiated area [21].

Impaired wound healing following radiation therapy is primarily due to inhibition of neovascularization, aberrant collagen synthesis, and impaired collagen remodeling [7, 19]. These changes have been observed in patient histopathology and in vivo animal models. In a rat model, Doyle et al. demonstrated impaired neovascularization with radiation doses as low as 9 Gy when administered within 24 h of wounding. Neovascularization was decreased over 30 % with radiotherapy doses of 9–30 Gy in a dose-independent manner. Alternatively, when the same 9 Gy dose was administrated prior to wound generation neovascularization was unaffected [22].

The initial 48 h following wound closure appear to be the most sensitive to the detrimental effects of ionizing radiation [23]. Histology from wounds irradiated during this time interval demonstrates monocytes and fibroblasts in decreased number and altered morphology compared to unirradiated controls [5, 24, 25]. However, cell number and morphology were not altered when wounds received preoperative radiotherapy or delayed postoperative radiation administrated at a minimum of 5 days following surgery [24].

Compared to unirradiated wounds, collagen content and wound bursting strength (WBS) are decreased following radiation therapy [26]. In an animal model, Bernstein et al. found that both type 1 collagen gene expression and WBS were significantly decreased 7 days following an 18 Gy dose of radiation. Despite collagen gene expression returning to normal after 2 weeks, WBS continued to be limited—54 % compared to unirradiated controls [27]. This indicates a persistent disruption of normal collagen synthesis despite normal gene expression. Inhibition of collagen remodeling has been recognized as a source of long-term wound fragility [14].

Basic science research and animal models provide insight into the biologic effects of radiation on healing wounds. Consistent with the conclusions from those resources, significant clinical evidence demonstrates an association between perioperative radiation therapy and increased postoperative complications [6, 9, 14, 28–31]. However in clinical studies, details such as

treatment dose, interval, and specific complications are often lacking, preventing determination of the optimal timing and sequence of perioperative radiation.

Although there is extensive literature addressing the role radiotherapy and surgery in the treatment of metastatic spine disease, only a single article evaluated the significance of the time interval between radiation and surgery. Ghogawala et al. identified a trend towards higher rates of wound complications when surgery was performed within 7 days of preoperative radiotherapy [32]. Although their results were not statistically significant, the authors cited a wound complication rate of 46 % amongst patients who received urgent surgery following preoperative radiation compared to 20 % in patients who had a minimum interval of 7 days between preoperative radiation and surgery. In addition, the authors identified a significant difference in the rate of wound complications between patients who received preoperative radiotherapy (32 %) compared to patients who were irradiated postoperatively (12 %) [32]. A review by Itshayek et al. identified eight studies containing 122 patients that examined outcomes following surgical intervention and postoperative radiation therapy for spinal metastases. The combined wound complication rate was calculated to be 7.4 % [6]. The only study to report the time interval and radiation dose contained 29 patients who received a 30 Gy dose of radiation a minimum of 7 days postoperatively. In this series, no wound complications were identified, leading the authors to conclude that a 1 week interval between surgery and radiotherapy was sufficient to prevent major radiation induced wound complications [33].

In addition to often cited wound complications [5, 6, 8, 9, 19, 31, 32, 34], a Scandinavian registry study of 1195 operated skeletal metastasis revealed a higher rate of endoprosthetic complications amongst patients who received preoperative radiotherapy compared to unirradiated patients [28]. Alternatively, in a small retrospective review, Townsend et al. compared patients with metastatic bone disease who underwent orthopedic intervention followed by postoperative radiotherapy versus patients who received surgery alone. The addition of radiotherapy decreased the incidence of revision surgery and on multivariate analysis was associated with an improved functional status [1]. In this series the median radiation dose was 30 Gy, administered at a mean of 14 days postoperatively. The Scandinavian review did not address radiotherapy doses or intervals to surgery, preventing any reconciliation of these two studies.

A prospective randomized trial by O'Sullivan et al. evaluated the incidence of wound complications amongst patients with soft tissue sarcomas treated with preoperative versus postoperative radiation therapy. In both protocols an interval of 3–6 weeks was imposed between surgery and perioperative radiation. Wound complication rates were higher amongst patients who received preoperative compared to postoperative radiotherapy, 35 % versus 17 %, respectively. No differences were observed in local recurrence rates, regional or distant treatment failures [30]. While the results of this high-level study argue in favor of postoperative radiation, the findings may not be applicable to the treatment of metastatic bone disease where radiation doses (8–30 Gy) are considerably lower than those used for soft tissue sarcoma (50–66 Gy).

The impact of radiation therapy on surgical wound healing has also been evaluated extensively in colorectal surgery. Similar to the orthopedic literature there is consistent evidence demonstrating increased wound healing complications with perioperative radiation [35], and suggestions that an increased time interval is protective against radiation induced wound complications [36]. A Cochrane review of preoperative radiotherapy and surgical excision for rectal carcinoma concluded that preoperative radiation increases the risk of postoperative wound infections when compared to surgery alone [35]. This conclusion was based upon the pooling of 19 studies with resulting risk ratios for abdominal, perineal, and other wound infections of 0.90 (95 % CI 0.65–1.25), 1.36 (95 % CI 1.00–1.83), and 1.30 (95 % CI 0.87–1.94), respectively. The details of the data are less definitive than the resulting conclusion. This review demonstrates the limits of clinical knowledge distilled from heterogeneous studies containing of a wide range of radiation therapy protocols.

Summary

Although patients with an impending or realized pathologic fracture from metastatic bone disease have improved outcomes with radiation therapy and surgical intervention, there are no guidelines to indicate the optimal sequence or time interval between the two treatment modalities. One study that specifically examined outcomes in patients with appendicular metastatic bone disease who received surgical intervention with and without radiation therapy did not evaluate postoperative complications [1]. The large Scandinavian registry review identified an increased endoprosthetic complication rate with preoperative irradiation, but did not find any association between preoperative radiotherapy and wound complications [28]. Other studies evaluating the effects of perioperative radiation were performed in patients with metastatic spine disease and soft tissue sarcomas [6, 9, 29, 30, 32]. However, none conclusively establish a safe dose or time interval between radiotherapy and surgery.

General principles derived from basic wound healing mechanisms and in vivo animal models guide our interpretation of the sparse clinical data. From this we can conclude that dose and time intervals are significant treatment variables [6, 13–15]. Additionally, within a clinically relevant range, the intervals between radiation fractions have not been shown to impose a significant effect on wound complication rates [37].

The American Society for Radiation Oncology promotes either a signal dose of 8 Gy or 20–30 Gy radiation dose divided into multiple fractions as palliative treatment protocols for bone metastasis [12]. Evidence of the dose-dependent cytotoxic effect of radiation makes the single 8 Gy perioperative dose appealing due to a potentially lower the side effect profile. Despite the preference for a low dose radiation protocol, in vivo animal models indicate that even this can have a detrimental effect on wound healing [15]. Therefore, the time interval between procedures should still be respected even with low dose radiation therapy.

Clinical research suggests that a longer time interval between radiation and surgery decreases the risk for surgical site complications [32, 36]. While this is consistent with the biology of wound healing, a prolonged interval is often impractical clinically. Wound healing is a highly organized additive process, therefore the earlier it is disrupted by ionizing radiation, the more detrimental the effect. Due to this and the abundance of active cellular processes (migration, activation, and proliferation) that occur within the first 48 h after wounding, this time period is promoted as the most radiosensitive. Therefore, when clinically feasible, consideration should be given to avoiding the administration of radiation therapy during first 48 h postoperatively. Studies that evaluated the significance of a 7 days interval provide merely anecdotal evidence that this time point is meaningful.

Preoperative radiation is not a reasonable consideration in the treatment of long bone pathologic fractures as surgical stabilization takes priority. However, for the treatment of impending pathologic fractures preoperative radiation is an option. While animal models suggest a benefit to preoperative compared to postoperative radiotherapy, this has not been supported by clinical studies in which radiation preoperatively has been associated with a higher rate of wound complications and endoprosthetic failures.

In summation, in the setting of patients afflicted with metastatic bone disease, the optimal perioperative radiation therapy protocol appears to consist of a single 8 Gy dose administered at a minimum of 48 h. Other regimens determined by an experienced team of radiation and orthopedic oncologists are certainly acceptable however.

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Role of Surgery in Oligometastatic Disease

22

George T. Calvert

Definition and Historical Background

Oligometastatic disease defies simple definition despite its seemingly intuitive meaning. No precise number of lesions has been agreed upon as the upper limit for oligometastases. Furthermore, the involvement of more than one system does not necessarily preclude the use of the term. For example, do two lesions, one involving lung and the other bone, connote oligometastases more or less than four lesions involving solely lung? Historical review indicates that surgical management of "oligometastases" was undertaken prior to the use of the term and notably prior to many modern theories of cancer pathogenesis and spread. Alexander and Haight [1] reported 24 cases of pulmonary resections for solitary pulmonary metastases in 1947. Subsequently, pulmonary metastasectomy has gained widespread acceptance [2]. Woodington and Waugh [3] documented a series of 25 hepatic resections for metastases in 1963 with 20 % of the cohort achieving greater than 5-year survival. Resections of bone metastasis were not adopted as early or widely as those of lung and liver. Perhaps due to thoracic surgeons' experience with lung metastasectomy, case reports [4, 5] of sternal resections for metastases are among the earliest examples. In 1994, Stener et al. [6] reported 15 musculoskeletal resections for solitary renal cell carcinoma (RCC) metastases. They concluded that the musculoskeletal results compared favorably with pulmonary metastasectomies and advocated continued use of the technique.

Although surgical treatment of oligometastases dates to at least the 1940s and was well accepted by the 1980s, a theoretical framework for its use was first proposed by Hellman and Weichselbaum in 1995 [7]. Most contemporary thought suggested that metastases are systemic and widespread even if they cannot be accurately detected. Hellman and Weichselbaum termed this a binary or subsequently "leukemia-like" theory [8] of metastases. They argued that the multistep nature of cancer pathogenesis and spread strongly suggests a more continuous spectrum of metastatic disease and therefore proposed the "oligometastatic state." They theorized that cancer cells (due to their inherent biology) in some patients may achieve the capacity to spread to only a limited number of tissues or physical locations. At this intermediate stage of metastasis, patients may be amenable to curative local interventions. Decades of clinical evidence demonstrating long-term survival of patients with limited metastases treated with aggressive surgical resection was utilized as the main empiric evidence in support of the theory. Within this paradigm [8], oligometastases are defined not by the number of lesions.

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Instead, the biologic potential of the cancer cells and the potential for cure with local intervention define the oligometastatic state.

Basic Science and Clinical Rationale

Resection of metastatic bone lesions generally entails greater morbidity than other treatments (medication, radiation, and fixation) and should be reserved for patients who are likely to benefit from the more extensive intervention. The previously described definition of oligometastases is in some respects a temporally circular argument. The oligometastatic state is defined by its potential for cure with local measures; however, this potential may presently be determined only after attempted curative treatment is performed. The "Will Rogers phenomenon" [9] in which stage-specific survival rates are improved (without any true concomitant increase in overall patient-specific survival) due to stage migration has been described for multiple cancers. The contrarian may argue that "oligometastases" similarly represent a subgroup of metastatic patients predisposed to prolonged survival regardless of intervention. The counterargument is that current diagnostic technology limits our ability to define truly oligometastatic cases [7, 8], and abundant clinical evidence (reviewed later in the chapter) demonstrates that some patients do indeed benefit. One potential solution to this dilemma is provided by liver surgery in which a clinical scoring system [10, 11] was developed to determine which patients would benefit from resection of oligometastases. A similar scoring system is lacking for skeletal metastases.

Recent research elucidating the tropism of specific cancer types to bone [12], the role of circulating tumor cells (CTCs) in metastatic cancer [13, 14], and the phenomenon of tumor self-seeding [15] has provided further theoretical evidence in support the oligometastatic state. Bone provides a metastatic niche for particular cancers through the expression of surface proteins (integrins) and secretion of chemokines which attract circulating cancer cells to the bone marrow stroma and ultimately the bone tissue itself [12]. This homing specificity partially explains the relatively common occurrence of bone-only metastases in breast and prostate cancer. CTCs without overt evidence of metastatic disease have been identified in several types of cancer [13], and their presence has been correlated with overall survival in breast, prostate, and colon cancer [14]. While CTCs have entered clinical use in evaluating response to treatment, pharmacodynamics, and assessment of minimal residual disease [16], their potential use for differentiating oligometastatic from polymetastatic patients is apparent although not yet proven. The more recent discovery of tumor self-seeding has demonstrated that in addition to colonizing distant metastatic sites CTCs return to the primary tumor site [15]. Additionally, metastasis may self-seed or re-seed the primary site [15]. The biologic basis for this phenomenon is that the local environment or "soil" is most conducive to CTC adherence and growth at these sites. This intuitively supports the oligometastatic model in that only a select few sites may provide appropriate "soil" in which metastases may grow.

Additional theoretical support for bone metastasis resection is provided by general and gynecologic surgeons' collective experience with cytoreductive surgery. This technique is most commonly employed for peritoneal carcinomatosis and involves surgical resection of all visible macroscopic disease usually performed in combination with hyperthermic intraperitoneal chemotherapy. A prospective randomized controlled trial of this technique demonstrated statistically significant survival benefit (22.2 months versus 12.6 months with standard therapy) in colon cancer patients with peritoneal carcinomatosis [17, 18]. In ovarian cancer, the quality of cytoreductive surgery has been correlated with patient survival. A Gynecologic Oncology Group review of 360 patients identified median overall survival with microscopic 0.1 to 1.0 cm, minimal 1.1to 5 cm, and gross >5 cm residual disease to be 64, 39, and 19 months, respectively [19]. A European study of 573 ovarian cancer patients identified improved survival with complete resection of all macroscopic disease and noted that this was the only significant variable in their multifactorial analysis amenable to intervention [20]. Why should this

strategy work when multifocal micrometastases invariably remain after cytoreductive surgery? Theoretical benefits include: (1) removal of larger necrotic masses improves chemotherapy delivery to the microscopic deposits with better blood supply, (2) removal of resistant clones delays development of chemotherapy resistance, (3) residual microscopic implants have a higher growth fraction more responsive to chemotherapy, and (4) debulking may improve the patients' nutritional and functional status [21]. Similar evidence for bone metastasis cytoreduction is lacking; however, the same theoretical arguments may be applied.

Epidemiology of Bone Oligometastases

While Chapter 1 details the overall epidemiology of metastatic bone disease, high-quality population-based data regarding solitary and oligometastatic bone metastases is lacking. A few small studies of solitary metastasis among individual cancer types provide some limited insight. A study of all breast cancer patients ($n=5538$) treated from 1988 to 1998 at a single tertiary center in Japan found that 120 patients (2.2 %) developed solitary bone metastases [22]. A single-institution study from Turkey analyzed breast cancer patients with localized disease who subsequently developed metastases; 17 % (79/470) developed solitary bone metastases [23]. RCC likely has an even higher rate of solitary metastasis than breast. A US single-institution study of 231 RCC patients treated with initial curative intent nephrectomy who subsequently developed metastatic or recurrent disease found that 55.8 % had solitary metastasis with bone being the second most common site (19 %) after lung (57 %) [24]. The Scandinavian Sarcoma Group has maintained a prospective multi-institutional registry of all operatively treated skeletal metastases since 1999. Among patient with complete datasets for the time interval 1999–2009, 146 of 651 (22.4 %) operatively treated patients had solitary skeletal metastases [25]. From the data set, the authors created a prognostic scoring system for bone metastases in which solitary lesions portend longer survival. A subsequent study using the same registry focused on 672 operatively treated breast, kidney, lung, and prostate metastases. The rates of solitary metastases and survival after en bloc resection as opposed to other surgical procedures are listed in Table 22.1 [26]. Notable findings from the study include the impressive survival advantage of renal solitary metastasis patients treated with en bloc resection. Although rare, solitary skeletal metastases were identified in prostate and lung cancer patients in addition to the more common breast and renal cancer patients. No epidemiologic data on non-solitary oligometastases exists at present.

The perceived rarity of oligometastatic bone disease is diminished if one considers the vastly greater number of metastatic bone disease patients relative to those with primary bone cancer. Resection surgery is traditionally associated with and reserved for primary bone cancers. The Surveillance, Epidemiology, and End Results (SEER) Program database predicts 3020 (0.9 per 100,000) new primary bone sarcomas of all types for the United States in 2014 [27]. This estimate may even be higher as true population-based data from England identified a stable annual incidence

Table 22.1 Scandinavian Sarcoma Group study of surgical 672 consecutive cases of operatively treated skeletal metastasis revealed varying rates of solitary metastases among different cancer diagnoses [26]

Primary	Patients	Solitary (%)	Solitary survival (months)	Multiple survival (months)	En Bloc resection (%)	En Bloc survival (months)	Other surg. survival (months)
Breast	307	10.4	35[a]	12	3.9	17	13
Prostate	146	5.5	11	6	0.7	15	6
Kidney	122	45	19[a]	6	22	47[a]	9
Lung	97	22	4	3	3	6	3

[a]Denotes a statistically significant difference in survival

of 0.67–0.81 per 100,000 [28]. Among primary bone cancer patients, some are not candidates for resection due to advanced disease at presentation. In contrast, SEER predicts 816,780 combined new cases of breast, lung, kidney, prostate, and thyroid cancer in 2014 [27]. If only 1 % of these patients have resectable solitary or oligometastatic bone lesions, the number of bone resections for metastatic disease would more than double those of primary bone cancer (Fig. 22.1). The number of patients with resectable bone oligometastases is also likely to grow at a faster rate than those with primary bone sarcomas due to multiple reasons. First, metastatic carcinoma cases will likely continue to increase at a faster rate than primary bone sarcomas. Second, the detection rate of the oligometastatic state may increase with improved diagnostic tests. Finally, advances in treatment (chemotherapy) may render more patients amenable to oligometastatic resection surgery.

Indications for Oncologic Surgery for Oligometastases

The term "oncologic resection" generally implies at least local curative intent and typically involves procedures intended to remove or destroy all viable tumor cells; it is used in contrast to the far more common palliative orthopedic procedures intended to ameliorate symptoms without regard to tumor control at the site of intervention. Resection is the classic oncologic intervention and will be the focus of this section; however, other techniques with oncologic intent exist and are described later. High-level evidence supporting oncologic surgery in lieu of less aggressive interventions for bone metastases does not exist. As such, indications for resection are not absolute and should be tailored to patient goals, fitness for surgery, and surgeon experience and judgment. Potential indications for resection of bone metastases are provided in Table 22.2. The primary indication of surgery in the majority of cases is prolongation of survival or even cure. "Expendable" bones for which the morbidity of resection surgery is unlikely to be no worse than fixation or reconstruction constitute another relative indication [29].

"Expendable" bones generally not requiring reconstruction:

- Sternum (partial).
- Scapula (nonarticular).
- Clavicle.
- Rib.
- Spinal elements (if instability is avoided).
- Iliac wing.
- Pubic rami and symphysis.
- Fibula (diaphysis).

Small bones of the hands and feet, although not "expendable," are often so extensively destroyed by tumor that reconstruction is not feasible. Acral metastases from lung cancer are a classic example of this group [30].

Periarticular metastases of the shoulder and hip are relatively common and are frequently treated with arthroplasty [31]. Often, oncologic resection of these sites may be accomplished with little increased morbidity relative to palliative intralesional arthroplasty. For lesions of the femoral head and neck, there may be no increased morbidity if the abductor insertion to the greater trochanter can be maintained. Less common indications for resection as opposed to stabilization include bone lesions with large, symptomatic soft tissue masses or soft tissue masses impinging upon critical structures such as nerves or vessels. Palliation in such cases is unlikely to be achieved without tumor removal as the mass effect is the source of symptomatology. Finally, palliative amputation is occasionally the best option in advanced cases in which palliative stabilization and limb salvage would leave the patient with greater pain and less function than amputation [32].

Surgical Technique

Resection

The surgical technique required, and specifically the histologic margin necessary to achieve local control of bone metastases, is poorly defined. For the more extensively studied bone sarcomas, substantial debate exists within the orthopedic oncology

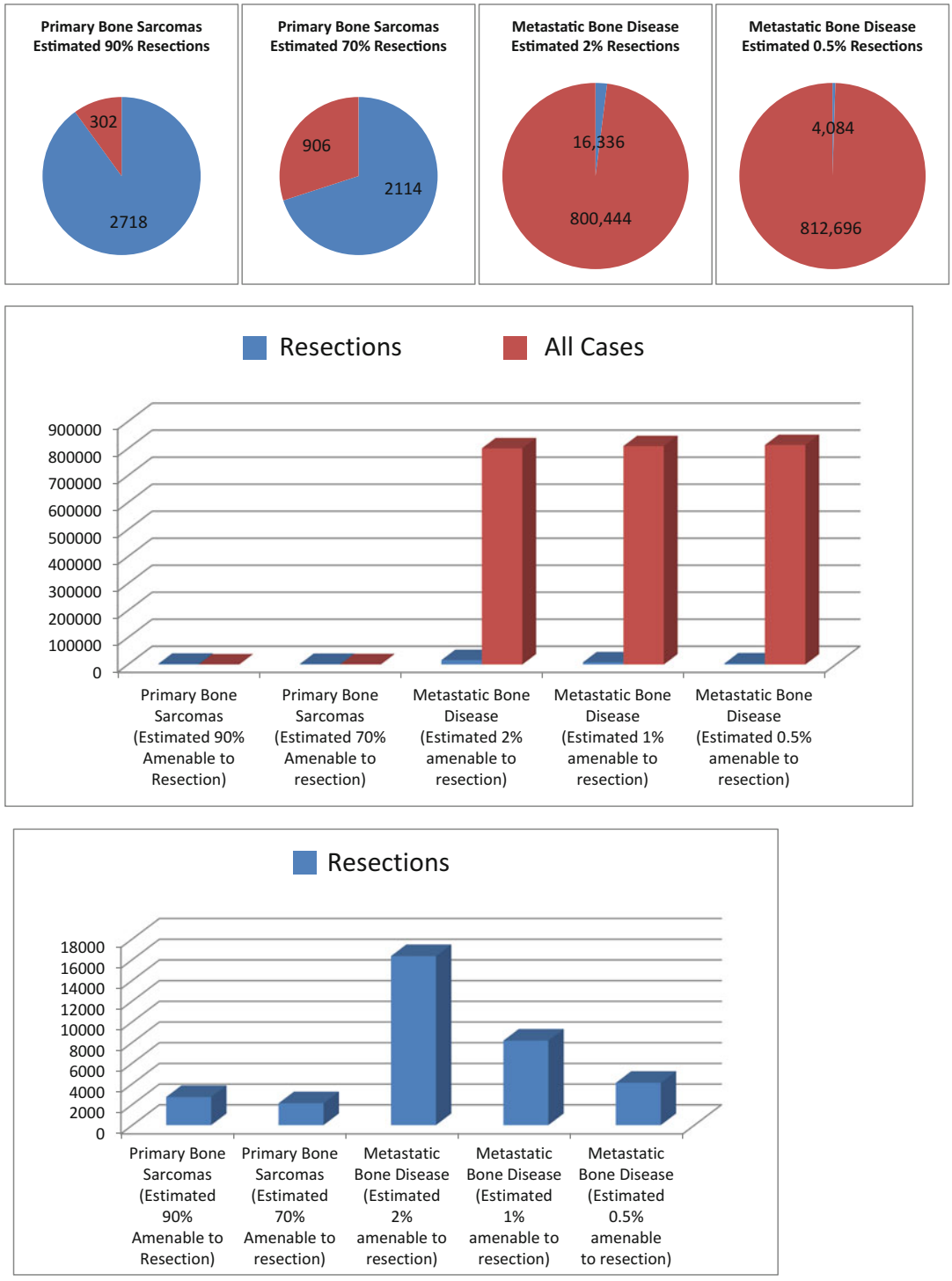

Fig. 22.1 Estimated primary bone sarcoma resections compared with estimated resectable oligometastatic bone disease in the United States 2014 (SEER Database)

Table 22.2 List of relative indications for bone metastasis resection

Indication	Rationale
Solitary or oligometastasis	Render the patient macroscopically disease free; Prolong life, possibly cure
Expendable bones	Morbidity of resection surgery no greater than fixation surgery
Periarticular metastases	Resection may not increase surgical complexity or patient morbidity if arthroplasty is required anyways
Small bones	Surgery other than resection not technically feasible
Highly vascular tumors	Resection may provide better hemostasis than fixation or curettage
Bone metastases with large associated soft tissue masses	Mass effect symptoms often cannot be addressed without resection
Fungating or infected masses	Resection may be required to enable wound healing
Functionless, painful limb	Amputation may be the best palliative option

community regarding the "adequate" surgical margin required. National Comprehensive Cancer Network (NCCN) guidelines for the treatment of primary bone sarcomas recommend wide excision providing histologically negative margins without defining any specific distance from the tumor to the margin [33]. A recent study of osteosarcoma resections found no difference in local recurrence or survival between close (<5 mm) and wide margins [34]. No similar studies are available for bone metastasis. A notable difference relative to osteosarcoma is the increased radiosensitivity of breast, lung, prostate, and thyroid metastases [35]. This increased sensitivity may permit closer margins relative to primary bone sarcomas when postoperative radiotherapy is added to the treatment regimen. Renal cell carcinoma is the potential exception as it is generally considered radioresistant although recent research questions this assumption [36].

Similar to other aspects of metastasectomy, evidence from the hepatic and thoracic surgery literature is more robust with respect to surgical margins. Positive surgical margins have been shown to increase the risk of local recurrence in patients undergoing both liver and pulmonary metastasis resections [37–39]. The residual disease classification (Table 22.3), as opposed to specific margin distances, is typically used for reporting margin status in both the thoracic and hepatobiliary literature [40]. Advantages of this classification include familiarity across disciplines and simplicity; however, all R0 resection may not be equivalent as recent study of liver metastasectomy demonstrated higher local recurrence with resection margin distance of <5 mm [37]. In addition to local disease control at the metastasectomy site, R0 margins have been correlated with improved overall survival for both lung [41] and liver [38] oligometastases. In the absence of bone-specific data, it appears prudent that surgeons pursue R0 resections of bone oligometastases (preferably of >5 mm) based upon the experience with lung and liver resections.

Table 22.3 Residual disease classification of oncologic tumor resections [40]

Type of resection	Pathologic outcome
R0	No tumor at margin
R1	Microscopic tumor at margin
R2	Gross tumor at margin

Extended Curettage

Curettage with the use of adjuvants is now a widely accepted treatment for low-grade chondrosarcoma [42]. Common adjuvants used to extend the zone of tumor necrosis around the curettage cavity include high-speed burring, liquid nitrogen, phenol, hydrogen peroxide, and argon beam coagulation. A combination of modalities such as high-speed burring, liquid nitrogen cryoablation, and hydrogen peroxide irrigation are often utilized. Little evidence exists to support one method in favor of the others and large variations in practice exist based upon surgeon experience, preference, and resource availability [43]. The use of curettage for bone oligometastases is controversial with limited evidence to guide surgeons as to when and how it should be used. Some retrospective studies support the use of curettage as an alternative to resection. A single-institution review of 295 consecutively treated renal cell metastases to bone showed no difference in overall survival or local

recurrence comparing en bloc resection and curettage [44]. This equivalence was evident even among patients with solitary metastases. Another retrospective study of solitary pelvic bone metastases compared en bloc resection with extended curettage with the use of adjuvants [45]. No difference in overall survival was identified. The previously referenced cytoreduction literature and the general principles of oligometastases treatment suggest that reduction of tumor burden by curettage when en bloc resection is not feasible may be of benefit. The use of adjuvants to improve local control also seems prudent in light of their known benefits in local control of benign aggressive bone tumors and low-grade chondrosarcoma.

Results of Treatment

Renal cell oligometastasis resections have the largest body of clinical literature (Table 22.4) [6, 24, 26, 44, 46–55]. Reasons for this include the comparatively high rate of renal cell oligometastases [26], radioresistance [36], and until recently the lack of effective chemotherapy [56]. For many years surgical resection was the only intervention available to this cohort. Surgical resection is presently considered standard therapy for oligometastatic renal cell carcinoma as outlined by both NCCN and European Society for Medical Oncology (ESMO) guidelines [57, 58]. An important consideration when considering longer and more extensive resection surgery (relative to stabilization) is patient safety. The acute mortality rate in all of the series collected over a period of three decades was low. Resection may in fact be safer than intramedullary nail fixation with respect to acute cardiopulmonary complications as intramedullary instrumentation is either avoided completely or performed only after tumor removal [59]. Another important factor in determining the overall clinical efficacy of resection versus fixation is durability of the fixation and the potential need for reoperation. Resections typically require more surgical dissection and longer operative times which may predispose to wound complications and infection in an already high-risk population (Fig. 22.2). These risks are counterbalanced by the improved local control and often stouter fixation obtained with resection surgery. A single-institution study of 298 consecutive pathologic proximal femur fractures reported failure rates of 3.1 % for endoprostheses ($n=197$), 6.1 % for nails ($n=82$), and 42 % for internal fixation ($n=19$) ($p=0.03$) [60]. Many of the endoprosthesis cases in the study were not resections and therefore are not directly applicable to the present discussion. The previously described SSG study of skeletal metastasis did specifically assess resection cases. SSG reported a lower overall complication rate and lower reoperation rate for resection surgery compared with other interventions for both solitary metastases (10 % vs. 14 %) and multiple metastases (7 % vs. 11 %) [26].

Thyroid cancer, specifically the differentiated subtypes, is the second most studied cancer with respect to bone oligometastases resection (Table 22.5) [26, 61–68]. Unlike renal cell carcinoma, radioactive iodine has provided differentiated metastatic thyroid patients an efficacious adjuvant treatment option for several decades. Whereas surgery was initially attempted (first series 1984) for renal cell cancer metastasis due to the lack of other options [6], it was initially (first series 1986) used for thyroid metastases to improve the efficacy of radioactive iodine treatment by reducing the requisite dose [61]. A subsequent French study of 1977 differentiated thyroid cancer patients treated with radioactive iodine from 1958 to 1999 identified complete bone metastasectomy as an independent predictor of survival ($p=0.04$) on multivariate analysis [63]. Surgical case series from Vienna, New York, and Houston have all demonstrated improved survival with resection of all macroscopic disease relative to other treatment approaches. Resections of as many as five separate sites have been reported. Figure 22.3 presents an 8-year metastatic thyroid cancer survivor who has undergone five separate resections (2 lung, 1 spine, 1 pelvis, 1 soft tissue) is macroscopically disease free at the time of writing.

Skeletal metastasectomy for diagnoses other than renal cell and thyroid carcinoma has been reported less frequently in the literature (Table 22.5). Metastatic melanoma has historically been treated with an aggressive surgical approach

Table 22.4 Results of metastasectomy for renal cell cancer

First author	Pub. year	Total cohort	Resection cases	OS	Notes
Stener [6]	1985	21	21	35.2 months mean	8 died of unrelated disease; 4 long term survivors (>5year)
Althausen [46]	1997	38	16	NR	55 % 5-year OS for the entire cohort (including non-resection cases)
Kavolius [24]	1998	278a	5	40 % 5 year	The 141 patients with resection of all macroscopic disease had improved survival relative to those receiving palliative resection or no surgery.
Durr [47]	1999	45	7	NR	15 % 5 year survival of the entire cohort; 28 % 5 year survival for those with solitary metastasis
Baloch [48]	2000	25	25	54 % 3 year 13 % 5 year	Low complication rate; authors advocated resection for solitary lesions
Kollender [49]	2000	45	31	NR	38 % 3 year survival for the entire cohort; 1 local recurrence with resection and 3 local recurrences with curettage
Jung [50]	2003	99	9	80 % 5 year	Wide resection associated with survival advantage on multi-variate analysis
Fuchs [51]	2005	60	13	NR	No survival advantage of wide resection was identified; a lower failure implant failure rate was seen with resection as opposed to fixation
Lin [44]	2007	295	33	38 % 5 year	Solitary metastases but not resections had better survival
Fottner [52]	2010	101	26	~50 % 3 year	Wide resection had statistically better survival; Combined bone and visceral metastasis resections (n = 16) also had survival advantage
Alt [53]	2011	887*	NR	NR	125 patients underwent complete resection of all macroscopic disease which strongly correlated with survival even when 3 or more separate lesions were resected
Evenski [54]	2012	69	NR	42.5 % 5 year	Survival difference was not statistically significant between wide and intralesional resection, but local recurrence was greater with (29 % vs. 5 %) intralesional resection
Hwang [55]	2014	135	135	45 % 3 year 28 % 5 year	Multivariate analysis demonstrated that multiple skeletal metastases, >1 visceral metastases, and local recurrences did worse
Ratasvuori [26]	2014	122	27	47 months Median	En bloc resection had significantly better survival than other surgical interventions

[a]Cohort consists of a mixed group of metastatic renal cell carcinoma patients, not just bone metastases

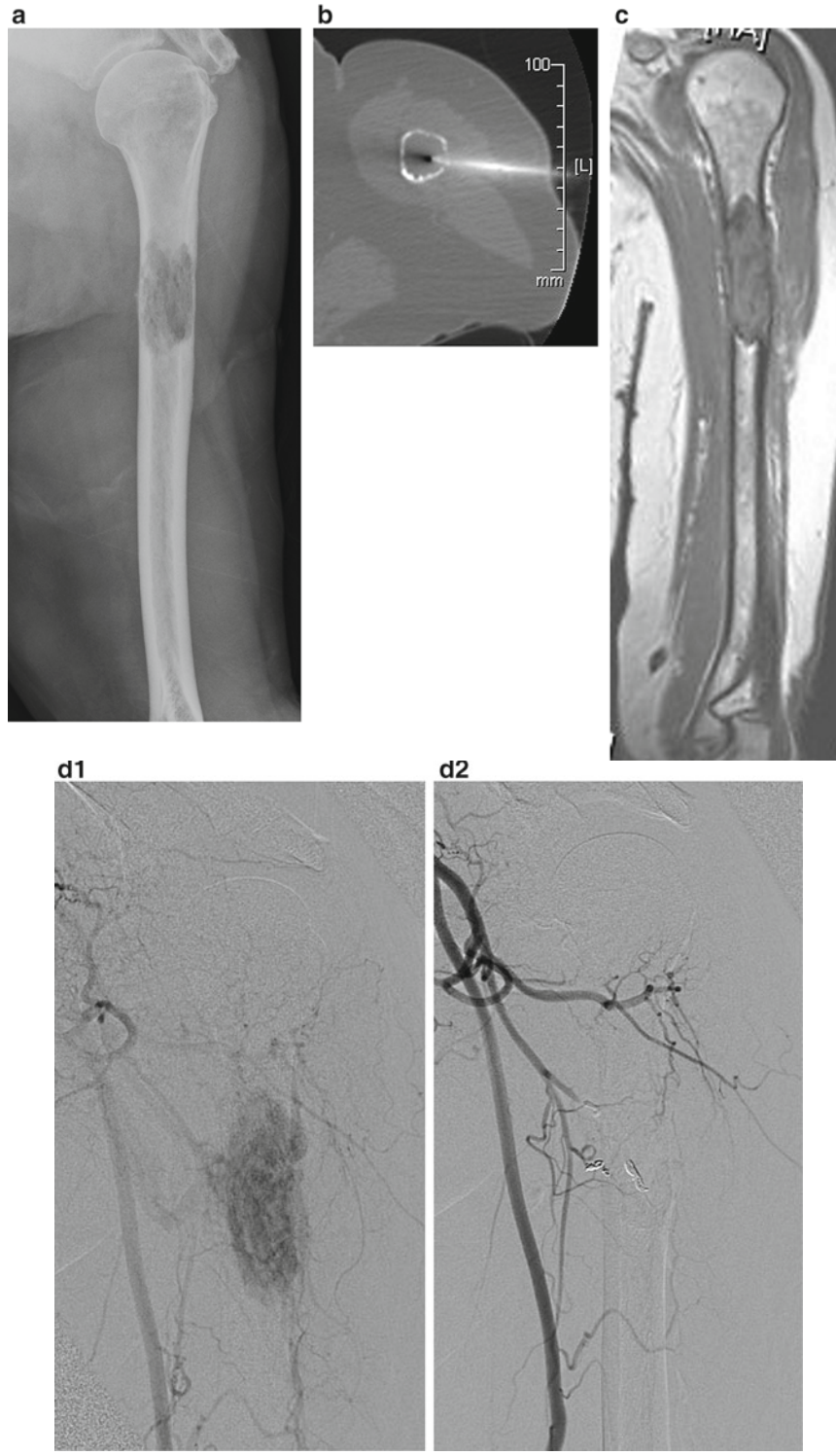

Fig. 22.2 A 69-year-old male with left shoulder pain and a remote history of scalp melanoma. (**a**) Radiographs demonstrated a destructive diaphyseal lesion of the proximal humerus. (**b**) CT-guided biopsy demonstrated clear cell carcinoma versus sarcoma and orthopedic oncology consultation was requested. CT chest/abdomen/pelvis revealed a large right renal mass. (**c**) MRI better demonstrated the intraosseous extent of the metastasis. Multidisciplinary

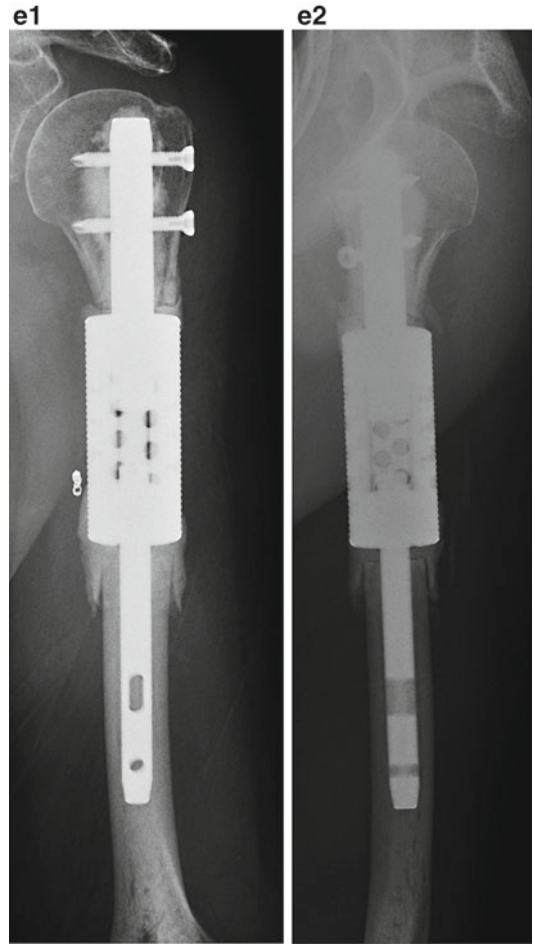

Fig. 22.2 (continued) tumor board recommended resection of the solitary renal cell metastasis followed by nephrectomy due to the risk of fracture if the primary tumor was treated first. (**d**) Preoperative embolization images demonstrating elimination of tumor blush after coil placement. (**e**) Radiographs 6 months after intercalary resection and reconstruction. The patient was treated with 1 year of sunitinib post-nephrectomy and is disease free with excellent left upper extremity function at 2 years post-metastasectomy

due to perceived radioresistance and until recently limited chemotherapy options [69]. Overall, surgical treatment of melanoma metastatic to bone has a poor prognosis with a reported median survival of 1.9 months [66]. However, complete resection of skeletal melanoma oligometastases improved survival in a series of 180 metastatic melanoma patients. Nonoperative ($N=80$), intralesional ($N=32$), and resection ($N=18$) had median survival of 4.8, 5.1, and 11.8 months, respectively. The authors of this study performed statistical analysis to correct for independent predictors of worse survival, and the 1-year survival of resection patients was still nearly double that of matched controls [68]. Lung, prostate, and breast cancer have few reports in the literature with respect to oligometastases treatment. The previously described SSG studies included small numbers of en bloc resection of these histologies. Statistical conclusions could not be derived for individual cancer types, but a statistically significant 20-month increase in survival was noted for all cancer types combined when treated with resection for solitary metastases [26].

Table 22.5 Non-renal bone metastasectomy series

First author	Primary disease	Pub. year	Total cohort	Resection cases	OS	Notes
Niederle [61]	Thyroid	1986	45	17	NR	45 % 5 years and 33 % 10-year survival after solitary metastasis resection
Kanthan [62]	Colon	1999	355[a]	NR	NR	Bone-only metastases ($n=60$) had better survival than patients with multisystem disease ($n=295$)
Bernier [63]	Thyroid	2001	109	24	6.2 years median	Complete bone metastasectomy was associated with improved survival on multivariate analysis
Zettinig [64]	Thyroid	2002	22	10	100 % 5 years	The 10 patients treated with surgical extirpation all survived 5 years; 50 % of nonsurgically treated patients survived 5 years ($p=.025$)
Durr [65]	Breast	2002	70	6	NR	Solitary bone metastasis patients ($n=19$) had better survival; resections were too few for statistical analysis although 4/6 died of disease
Wedin [66]	Melanoma	2012	31	1	41 months	One patient in this series of melanoma skeletal metastases had a misdiagnosis of sarcoma and was treated with curative resection. That patient was the longest survivor of the series
Ratasvuori [26]	Lung	2014	550	3	5.8 months	Multivariate analysis showed overall advantage of resection for all groups but not for individual subgroups
	Prostate			1	15.3 months	
	Breast			12	16.8 months	
Deberne [67]	Lung	2014	55[b]	2	>5 years	The two resection patients were the only members of this cohort to survive >5 years
Colman [68]	Melanoma	2014	130	18	12 months median	Multivariate analysis showed significant survival advantage of resection versus intralesional or nonoperative treatment

[a]Mixed cohort of all colon cancer patients with skeletal metastases
[b]Cohort consisted of 55 lung cancer patients whose initial diagnosis was made due to a skeletal complaint. Only 2/10 solitary bone metastasis patients were treated with resection

Future Directions

Percutaneous thermal ablation has historically been utilized for benign bone tumors, most notably osteoid osteoma [70]. Thermal ablation treatment of metastatic disease has generally been considered palliative. A prospective single-arm multicenter trial found statistically significant improvements of pain and patient mood after radiofrequency ablation (RFA) of bone metastases [71]. More recently, thermal ablation has been used to treat bone oligometastases with curative intent. Abundant laboratory and clinical evidence demonstrates that temperatures greater than 60 ° C or less than −40 ° C rapidly induce cancer cell death. In addition to local control of the ablated lesion, mounting evidence suggests that systemic oncologic benefit is obtained due to immunologic response of the patient to tumor antigens generated by the ablation. This response is greater for cryoablation as opposed to heat ablation presumably due to less protein denaturation induced by

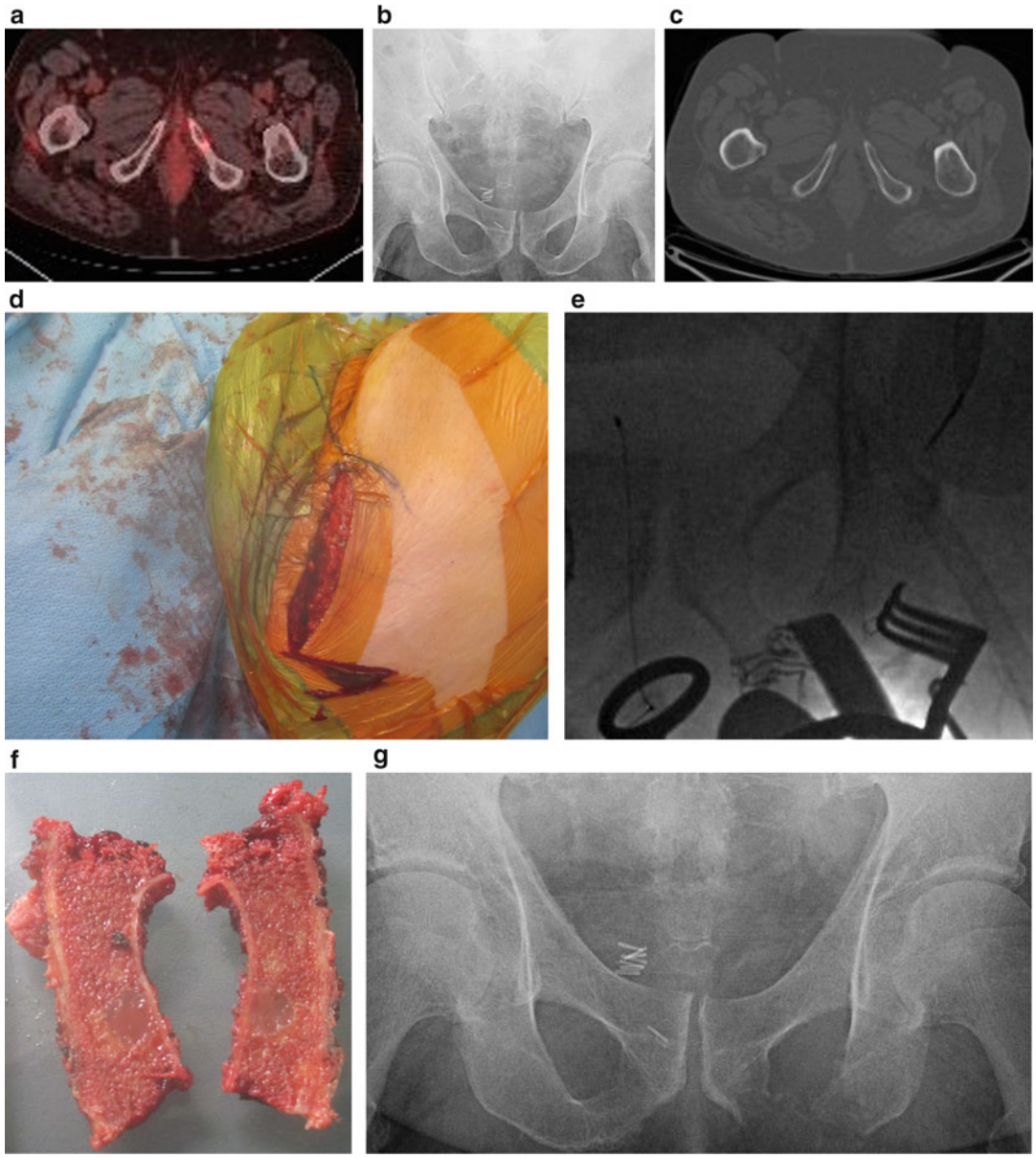

Fig. 22.3 A 75-year-old male with metastatic thyroid cancer underwent previous thyroidectomy (7 years prior), prostatectomy for localized prostate cancer (7 years prior), spine metastasectomy (5 years prior), lung metastasectomy (2 years prior), and soft tissue metastasectomy (6 months prior). PET/CT fusion scan (**a**) demonstrated a solitary left inferior pubic ramus lesion with PET avidity similar to previous thyroid metastases. Radiographs (**b**) and CT (**c**) of the involved area were normal. After multidisciplinary review, pelvic metastasectomy was recommended for disease control despite complete lack of symptoms. Surgery performed in lithotomy position (**d**) with use of fluoroscopy (**e**) to estimate the location of the metastasis and intraoperative sectioning of the bone (**f**) to confirm adequacy of the resection. The patient recovered without any functional deficits, pain, or evidence of local recurrence at 1 year (**g**). He underwent lung metastasectomy 2 years after the pelvis resection and has no macroscopic disease at the time of this writing

the former [72]. Smaller lesions are technically easier to ablate as existing technology permits uniform heating or cooling over limited physical areas. RFA has been most extensively studied for bone, but other thermal modalities include microwave ablation, cryoablation, lasers, irreversible electroporation, and high-intensity focused ultrasound. Each has distinct advantages and disadvantages with no modality having proven superiority over the others [73]. Similar to other oligometastasis treatments, thermal ablation has been best studied for hepatic metastases and subsequently adopted for bone and other tissues. Pooled analysis of two recent European Organisation for Research and Treatment of Cancer (EORTC) trials found equivalent local control rates between resection and RFA for colorectal liver metastases less than 3 cm [74].

A Mayo Clinic series of curative intent cryoablations of 52 bone and soft tissue tumors in 40 patients reported 87 % local control at a median follow-up of 21 months. Cryoablation local control was better for soft tissue (32/33, 97 %) than bone (13/19, 68 %). Two-year overall survival was 84 % [75]. A larger French study reported 122 curative intent bone ablations in 89 consecutive patients; 69 oligometastases in 56 patients and 53 impending fracture lesions in 33 patients were evaluated. Both RFA and cryotherapy were used at the interventionalists' discretion. Complete local control (defined by follow-up imaging) was 67 % at 12 months. Multivariate analysis identified metachronous presentation with the primary tumor ($p = .004$), oligometastatic disease ($p = .02$), small lesion size ($p = .001$), lack of cortical erosion ($p = .01$), and lack of nearby neurologic structures ($p = .002$) as favorable prognostic factors for success of the ablation [76]. Notably, the optimal lesion size in this study was 2 cm or less which differs from the 3 cm threshold identified in the liver oligometastasis studies. Based upon these preliminary data, curative thermal ablation should be considered for small bone oligometastases with intact cortices distant from neurovascular structures. This technique can be readily combined with open resection of a larger oligometastases in order to render a patient with multiple lesions macroscopically disease free.

Conclusions

Aggressive treatment of oligometastatic bone disease has a demonstrable positive impact on patient survival. The number of oligometastatic patients is likely to increase due to improved imaging resulting in earlier detection of metastatic disease, better systemic therapies increasing patient survival and decreasing the amount of metastatic disease burden, and greater awareness and acceptance of the oligometastatic concept by the medical community. A paradigm shift in surgeon perception will be required to optimize the treatment of bone oligometastases. Colon cancer metastatic to the liver was considered terminal until recently; now most patients are treated with curative intent. Instead of asking if the rare patient with a solitary bone metastasis may be a candidate for resection, one should question whether a combination of surgery and ablation may improve survival for every patient presenting with metastatic bone disease.

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Part IX

Specific Anatomic Considerations for Surgery

Metastatic Bone Disease: Pelvis

23

Vishal Hegde and Nicholas M. Bernthal

Introduction

The management of metastatic disease to the pelvis represents a significant challenge to the orthopedic surgeon. Although the vast majority of metastatic pelvic disease is treated nonoperatively with radiation and pain control due to the radiosensitivity of these tumors, occasionally surgery is indicated [2]. By the time that tumors cause symptoms in the pelvis, they have already reached a substantial size. In addition, the complex anatomy and critical structures in the pelvis make surgical management of disease all the more difficult. When considering surgical management, it is important that the orthopedic surgeon weigh the risks and benefits of the procedure, as extensive surgery may not ultimately benefit a patient whose survival is limited.

As with most bony metastasis, skeletal metastasis to the pelvis most commonly originates from cancers of the prostate, breast, lung, kidney and thyroid. Other sources include local malignancies such as uterus, colon, rectum, and endometrium, and hematologic malignancies such as lymphoma and myeloma [3]. Surgical management can be divided into intralesional interventions, including both percutaneous resections/ablations and open curettage with or without adjuvant therapy, and extralesional interventions, typically internal or external hemipelvectomies. In the authors' experience, most metastatic lesions that require surgery are treated with intralesional procedures, as the significant morbidity and prolonged recovery from a hemipelvectomy often outweighs the benefit if the surgery is not curative. Reconstruction options from intralesional procedures vary, and several will be discussed in this chapter. The mainstay of reconstruction in metastatic disease remains polymethylmethacrylate (PMMA) for its adjuvant thermal tumor kill, ability to deliver antibiotics locally, and the near-immediate structural support it lends.

Indications and Contraindications

With rare exception, oncologic cure is not the goal of surgery for metastatic disease to the pelvis. Goals of relieving pain, improving function, and providing structural stability are paramount. With this in mind, intralesional curettage with adjuvant therapy is the mainstay of treatment, followed by structural stabilization if needed. In patients with intractable pain associated with locally progressive disease that has not been controlled with narcotic pain medication and

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preoperative radiation, intralesional curettage can help reduce pain and promote comfort and mobility. Patients with compromised pelvic stability include those with tumors of the posterior ilium, which may affect lumbosacral integrity. Pathological fractures of the acetabulum, as well as tumors that extend into the acetabular roof and are associated with cortical destruction and pain on weight bearing, also compromise the stability of the pelvis. In these patients, curettage and reinforcement with a cement hardware construct can prevent continued erosion, and reestablish the structural support required for unrestricted weight bearing. Finally, curettage can be used to remove solitary metastasis in select patients with contained defects and prolonged survival in which a functional limb can be preserved. Reconstruction after intralesional resection is location specific. However, a general dogma in the surgical treatment of metastatic disease is that only reconstructions that will allow immediate weight bearing postoperatively should be considered. The idea of a prolonged "immobilization" period for patients with often limited life expectancy and unpredictable bone regeneration potential (from tumor and radiation) often drives orthopedic oncologists to demand immediate structural stability in the postoperative period as a prerequisite for surgery. As with all dogma, this may change over time as medical therapies improve, patient survival increases, and bone biology under therapy is more predictable. However, for the vast majority of cases, surgical management is undertaken only if postoperative stability in the form of unrestricted weight bearing is expected.

Extralesional resection with either internal or external hemipelvectomy is rarely indicated for metastatic disease. Indications include massive tumor burden with incapacitating pain or a nonfunctional lower extremity, significant neurovascular involvement of the tumor, and, very rarely, cases in which adequate negative margins may impact survival. While studies have not focused on pelvic metastatic disease specifically, it has recently been suggested that wide resection, rather than curettage, may increase survival in patients with an isolated bone metastasis from renal cell carcinoma [4, 5]. In considering internal versus external hemipelvectomy, three structures must be considered: the sciatic nerve, the femoral neurovascular bundle and the hip joint. Typically, if two out of three of these structures are involved and resection is required, amputation is indicated, as a functional limb cannot be preserved. Although internal hemipelvectomy can lead to improved hip and gait function, it is important to note the advantages of external hemipelvectomy: namely a lower incidence of complications and a faster recovery time [6–11]. When deciding between internal and external hemipelvectomy, internal hemipelvectomy must provide the same tumor free margins, a superior functional outcome and have acceptable morbidity. Regardless, if proceeding with hemipelvectomy, the morbidity and mortality of the resection as well as the lengthy rehabilitation process must always be weighed against the limited life expectancy of the patient.

Preoperative Imaging and Surgical Planning

A thorough evaluation of pelvic metastasis with preoperative imaging is critical prior to any surgical intervention. Plain radiographs and computed tomography (CT) of the pelvis and hip joints are required to evaluate the full extent of bony destruction and soft tissue extension of the tumor, as well as the integrity of the hip joints [12]. MRI typically does not add additional information, except in lesions with diffused intramedullary extension such as multiple myeloma, which can be underestimated by CT. Bone scintigraphy is done to detect other metastasis in the skeleton. If it is suspected that major vascular structures are involved, conventional or magnetic resonance angiography can be used to evaluate the extent of vessel involvement and plan for possible flap closure. Finally, it is essential that hypervascular lesions such as renal cell carcinoma or thyroid carcinomas undergo preoperative embolization to reduce what can potentially be profuse and life-threatening blood loss intraoperatively upon curettage of these lesions [13, 14].

After evaluating all of the appropriate imaging, the orthopedic surgeon should be able to answer these questions: Is the lesion an impending or completed pathologic fracture? What is the full extent of bony destruction and soft tissue extension? What approach will be required for optimal exposure? What type of intervention (intralesional vs. extralesional) and reconstruction technique is required? Are there additional bony metastases and do they require operative or nonoperative management?

Anatomic Considerations

When considering surgical intervention for metastatic pelvic tumors, a thorough knowledge of pelvic anatomy is required (Table 23.1). The bony pelvis is divided into three regions: the iliac wing, periacetabular region and obturator ring (Fig. 23.1). The gluteal muscles lie on the outer table of the lilac wing, and the iliac crest is the attachment site for the abdominal musculature. On the inner table lies the iliacus muscle, which joins the psoas major muscle originating on the vertebral bodies to form the iliopsoas tendon. This tendon crosses over the pelvic brim and inserts on the lesser trochanter. Between the iliacus and psoas major muscle bellies runs the femoral nerve. The obturator ring includes the pubic rami, which join anteriorly at the pubic symphysis and articulate with the sacrum through the sacrospinous and sacrotuberous ligaments. The common iliac artery crosses and bifurcates along the sacral ala, dividing into the internal and external iliac arteries. The external iliac vessels exit the pelvis medial to the iliopsoas tendon and become the femoral vessels, while the internal iliac vessels exit through the greater sciatic notch. In addition, the adductor muscles, anterior and posterior thigh muscles and pelvic floor muscles all originate from the pelvis and may require resection.

Other vital non-musculoskeletal structures in the pelvis may also be involved or require protection when addressing metastatic pelvic tumors. These include the urethra, prostate and corpus of the penis in males; uterus, ovaries and vagina in females; and rectum and bowel. This underscores the multidisciplinary approach, involving colleagues from urology, general surgery, vascular surgery, colorectal surgery, plastic surgery, neurosurgery, and spine surgery that may be required for these tumors.

Table 23.1 Common classifications of pelvic, hip, and spinopelvic resections [1]

Pelvic resection classification system	
Type I	Ilium
Type II	Periacetabular
Type III	Pubis
Type IV	Ilium
Resections including the femoral head	
H1	Femoral head
H2	Peritrochanteric area
H3	Subtrochanteric area
Spinopelvic resections	
Type 1	Total sacrectomy
Type 2	Hemisacrectomy
Type 3	Partial sacrectomy with hemipelvectomy
Type 4	Total sacrectomy with hemipelvectomy

Lesions in multiple areas named by combining numbers

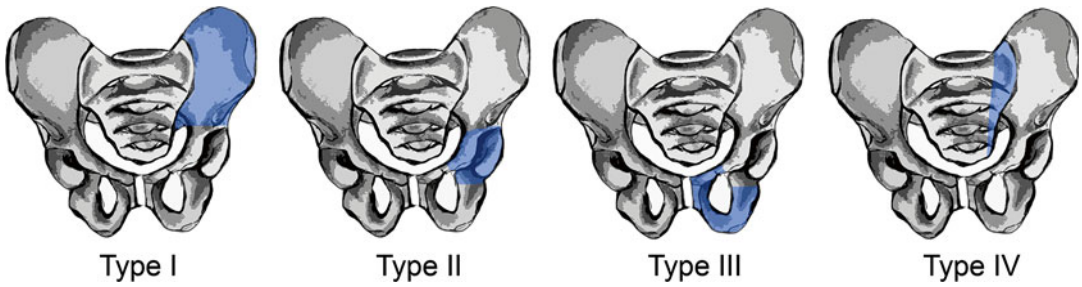

Fig. 23.1 Anatomic zones of the pelvis as described by Enneking [1]

Exposure

The incision commonly used for most types of pelvic metastatic disease is the ilioinguinal approach. This approach extends from the pubic tubercle along the inguinal ligament to the anterior superior iliac spine and along the iliac crest to the posterior superior iliac spine. Anterior lesions may require an extension to the contralateral pubic ramus and an additional perpendicular T-incision for good visualization. Posterior lesions may require extension to the midline of the spine with or without a perpendicular midline extension. For periacetabular lesions, the ilioinguinal approach can be extended laterally to the thigh. In addition, if the hip is involved, an anterolateral approach to the hip can be used and a supra-acetabular window can be made. A standard posterior approach to the hip can also be utilized, depending on the location and visualization requirements of the tumor being removed.

Curettage, Cementation, and Adjuvant Therapy

Multiple methods exist for the intralesional treatment of pelvic metastatic disease, including percutaneous cementoplasty and traditional open curettage and cementation. These intralesional procedures are much more commonly performed than extralesional resections in the pelvis due to the fact that they are less invasive and thus less morbid methods of treatment.

Percutaneous cementoplasty is the percutaneous, image-guided application of cement to treat or prevent pathologic fractures and pain. Cement is used to describe a wide variety of viscous materials that are injected for stabilization and consolidation of osteolytic lesions. The relief of pain is believed to be from the consolidation of weakened and pathological cancellous bone as well as a thermal and chemical cytotoxic effect produced during the polymerization of the cement. Polymethylmethacrylate (PMMA) is the most commonly used cement and polymerizes at a temperature of 80–120 °C [15]. This exothermic reaction has a penetration of 1.5–2 mm in cancellous bone and 0.5 mm in cortical bone [16]. Other materials, such as dimethacrylate resins and calcium phosphate based cements are also used. It is recommended that iodinated contrast be injected into the defect prior to cement injection to predict cement distribution and possible pathways of extravasation. Due to the high temperatures PMMA reaches during polymerization, extravasation adjacent to important neurovascular structures such as the obturator or pudendal nerves can cause substantial damage and should be avoided.

Open curettage and cementation requires the creation of a large cortical window corresponding to the location of the lesion. The tumor is then carefully and fully curetted out. A high-speed burr can then be used to create a single concentric cavity and remove any microscopic disease, as well as expand the margins of the cavity. After this is complete, adjuvants such as phenol, liquid nitrogen, or argon are often used to maximize tumor kill in the cavity. Phenol is a chemical agent that induces necrosis by protein coagulation with an infiltration depth estimated at 0.2 mm [16]. Cryoablation with liquid nitrogen induces necrosis through intracellular ice crystal formation and membrane disruption. Repetitive rapid freeze and slow thaw cycles can increase margins by up to 2 cm. Argon is a plasma gas that is ionized by a high voltage spark at the tip of a probe, distributing thermal energy on the cavity surface that penetrates roughly 2–3 mm [17]. Any adjuvant can be used to good effect, depending on surgeon preference, as none have proven to be superior in the literature. Finally, PMMA is inserted for consolidation and structural stabilization similar to percutaneous cementoplasty. In addition, cement will allow for easier determination of tumor extent on postoperative imaging and radiation field planning as well as early detection of local recurrence at the cement bone interface.

Type I Lesions

Type I metastatic pelvic lesions are those that involve the ilium. Positioning for surgical treatment of these lesions is typically supine with the ipsilateral hip slightly elevated. Exposure to the

appropriate area of the ilium can usually be obtained using the posterior aspect of the standard ilioinguinal approach. The glutei and iliacus muscles are detached and reflected from the outer and inner tables respectively. At the superomedial aspect of the posterior iliac crest, the iliolumbar ligament is identified. This ligament is a good landmark for the L5 nerve root, which runs just inferomedial to it. This ligament can also be released to enhance exposure if necessary.

Due to the fact that iliac resections generally do not impair sacroiliac or acetabular joint integrity, they rarely have an impact on function. This, combined with the difficulty of curettage of iliac tumors, makes resections for type I lesions the preferred treatment [13]. Osteotomies of the ilium around the lesion are performed. The anterior osteotomy is typically through the sciatic notch or just superior to the acetabulum, while the posterior osteotomy is through or adjacent to the sacroiliac joint. These resections are often left unreconstructed, except when the sciatic buttress is resected, which leads to disruption of pelvic ring continuity and resultant limb length discrepancy. This can be restored with autograft, allograft, or a metallic prosthesis. A small case control study looking at patients with either iliosacral repair or no reconstruction showed similar functional scores and survival rates in both groups. Yet patients who did not undergo reconstruction needed a lesser degree of chronic pain medication and assistive ambulatory devices, demonstrating that leaving these resections unreconstructed is a reasonable option [18]. The preference of the authors' is to leave Type I lesions unreconstructed.

Type II Lesions

Periacetabular lesions are called type II lesions, and are the lesions for which surgical intervention is most common. Positioning is dependent on the approach used. If the ilioinguinal approach will be utilized, the patient can be positioned supine with the ipsilateral hip slightly elevated. If the anterolateral or posterior approach to the hip is used, the patient should be positioned true lateral with the affected side facing up. With the ilioinguinal approach, the middle component of the incision is used. For lesions with medial cortical destruction, the incision can be extended 5 cm along the inguinal arm of the incision. The iliacus can then be detached and reflected from the inner table exposing the medial acetabulum. For lesions with lateral cortical destruction, a 5 cm extension is made along the lateral thigh. The glutei are then detached and reflected from the outer table, exposing the lateral acetabulum. For lesions with equivalent destruction, this lateral approach is used due to its ease. If reconstruction of the hip is required for weight bearing stability or there is concurrent femoral disease (the majority of surgical cases in the authors' practice), a standard posterior approach to the hip can be utilized and is preferred over an anterior approach because of its extensile nature.

Whenever feasible, a cortical window is then made above the lesion and curettage with high speed burr drilling, adjuvant therapy and cementation is performed. Metastatic disease typically does not invade cartilage, so these lesions normally spare acetabular cartilage [19]. When there are no cortices left to contain an internal fixation device, formal resection is done. This requires three osteotomies. The first is the superior osteotomy, made superior to the posterior iliac spine through the greater sciatic notch [12]. The second is the anterior osteotomy, through the anterior column of the acetabulum at the base of the superior pubic ramus. The final osteotomy is the posterior osteotomy, through the posterior acetabular column or ischium.

There are a large variety of reconstructive options for peri-acetabular lesions. The most commonly used reconstructive option in the authors' practice is the arthroplasty reconstruction. After initial reaming of the acetabulum, the periacetabular tumor is often encountered just deep to the cartilage. This lesion can be curetted and burred out, and adjuvant therapy used. If adequate ilium and pubis are remaining, implants can be attached and cement may be used to fill any residual defects and increase stability. Options for reconstruction include allograft or prosthetic composites such as cup-cage and porous tantalum reconstructions. The authors' preferred method of reconstruction is the Harrington reconstruction [20].

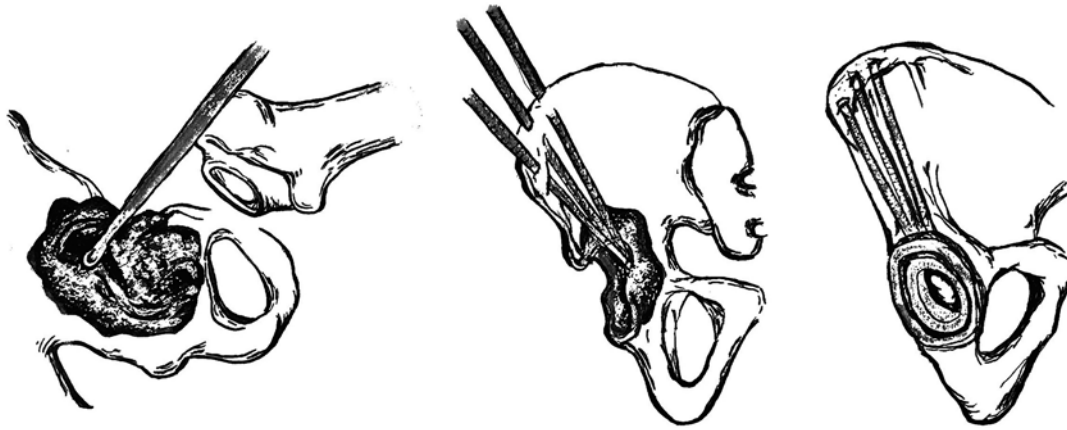

Fig. 23.2 Harrington technique with (**a**) antegrade Steinmann pins placed through the iliac wing proud into the defect, followed by (**b**) cementation to fill the defect and create a rebar receptor for the acetabular component, and (**c**) placement of the acetabular component

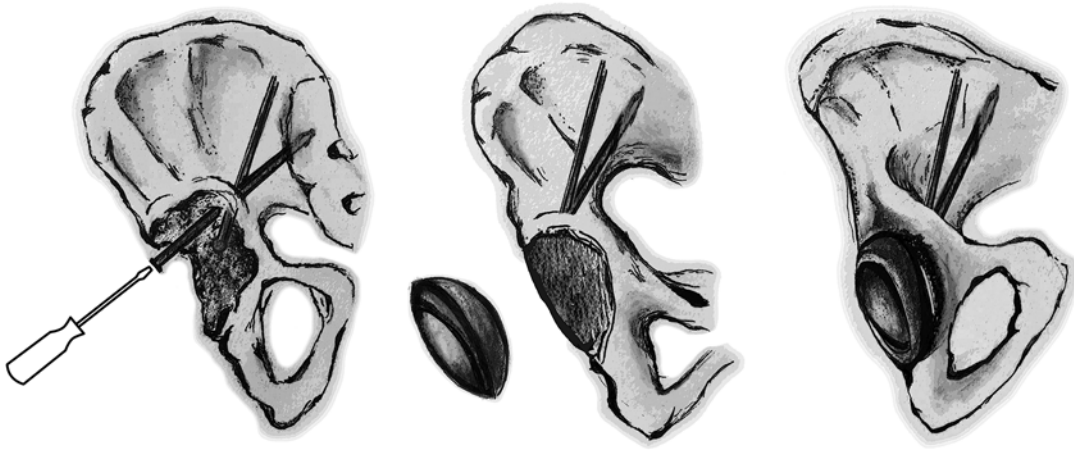

Fig. 23.3 Harrington technique with (**a**) retrograde screws placed from the defect in the posterior column (authors' preferred technique), followed by (**b**) cementation to fill the defect and create a rebar receptor for the acetabular component, and (**c**) placement of the acetabular component

This is a cement-rebar reconstruction technique that involves placing screws in either an antegrade or retrograde manner through the ilium and into the acetabular defect (Fig. 23.2 and 23.3). Bone cement is then placed into the defect to create the cement-rebar construct. The acetabular component is placed into the cement and the femur is prepared using a cemented long-stemmed implant. This reconstruction results in good cosmesis and limb length equality. A retrospective series from the author's institution showed good outcomes, including a failure rate of 9.6 %, and 96 % of patients able to ambulate after surgery. However, the authors have experienced higher than expected failure rates in patients with significant tumor burden in the ischium and prolonged life expectancy. In this patient population, the authors express caution.

Other reconstructive prosthetic options include pedestal cup endoprostheses, saddle prostheses, and custom implants. The saddle prosthesis was previously used due to its ease of

insertion, maintenance of limb length equality, and good cosmesis. This implant is anchored in the femur and hinges over an articulating notch made in the ilium. Yet due to an extremely high reported failure rate of 41.1 %, they are now off the market [21]. Failures were reported due to infection, nerve palsy, fracture, loosening, lateral shift, heterotopic ossification, and dislocation. In addition, the eccentric position of the new hip center resulted in reduced range of motion. Custom devices require Food and Drug Administration (FDA) approval prior to the procedure, limiting their use due to the lengthy approval process. Further details about the resection and reconstruction of tumors involving the femur can be found in the chapter about surgical management of metastatic disease to the femur.

When limited bone stock is available and anatomic hip reconstruction is not viable, alternatives include hip arthrodesis and leaving a non-reconstructed flail hip. The goal of a hip arthrodesis or pseudoarthrodesis is to establish a fibrous or solid union between the proximal femur and remaining pelvis (iliofemoral, ischiofemoral, or sacrofemoral), using hardware [22, 23]. This procedure is currently rarely used, as arthrodesis requires hip spica cast immobilization for 3 months to obtain potential union. Even then, union rates are less than 50 % and most patients end up developing a stable and painless pseudoarthrosis [24, 25]. In addition to the long consolidation time, which consequently requires prolonged rehabilitation, the disadvantages of arthrodesis include loss of hip joint function, limb length discrepancy, and lack of mobility.

A final option that should not be overlooked is the Friedman–Eilber resection arthroplasty, or flail hip, which requires only a soft tissue closure with a hip transposition. The hip transposition consists of anchoring or tying the proximal femur or femoral head to the remaining ilium or sacrum. The suspension and stabilization of the residual limb is important to maximize function and provide stability. This procedure can be performed without any prerequisite amount of bone available on the pelvic side and is used by the authors when resection includes an internal hemipelvectomy. The benefits of the Friedman–Eilber resection arthroplasty are its shorter surgical time, reduced blood loss, and decreased hospital stays in comparison to a more complex reconstruction, although it has a long recovery time of up to 2 years [26].

Type III Lesions

Lesions involving the pubis are considered type III metastatic pelvic lesions. Positioning for these lesions is supine with the ipsilateral hip slightly elevated. For exposure, the anterior aspect of the standard ilioinguinal approach is used, from the anterior superior iliac spine to 2 cm across the pubic symphysis. During the exposure, the femoral neurovascular bundle is isolated, marked with vessel loops and mobilized. The retropubic space is exposed, and a pad is inserted between the bladder and pubis. Lastly, the muscle attachments on the inferior aspect of the pubis can be removed if necessary.

Whenever possible, the preferred treatment of type III lesions is curettage with high speed burr drilling, adjuvant therapy and cementation through a cortical window above the lesion. Occasionally, the pubis will be destroyed, and no cortices will be left to permit curettage. In these situations, the incision should be extended to expose intact cortices on both sides of the lesion [12]. A medial osteotomy can then be done as far as the pubic symphysis or beyond at the opposite pubic ramus, and the lateral osteotomy just medial to or through the acetabulum, attempting to preserve as much intact bone as possible. It is important to be aware that the obturator neurovascular bundle may need to be sacrificed due to its proximity to the tumor. Aside from filling a defect created by curettage with cement, no formal bony reconstruction is required for these lesions. A critical component of these surgeries is the soft tissue reconstruction, to prevent bladder or soft tissue herniation into the soft tissue defect. These are typically reconstructed with a synthetic mesh or fascial allograft. The inguinal floor should also be reconstructed from the pubic tubercle to the lateral ilium to prevent peritoneal hernias. Care should be taken to appropriately reposition the femoral vessels, as well as the spermatic cord and its contents in men.

Type IV Lesions

Type IV metastatic pelvic lesions can be challenging to manage, as bleeding can be perfuse and exposure of the nerve roots is often difficult with anatomy distorted from the tumor. When positioning for surgical management, patients should lie true lateral with the affected side up, or prone, depending on the location of the tumor in the sagittal plane. If lateral positioning is selected, the operative table is bent with the apex just below the contralateral hip to widen the space between the iliac crest and the chest wall for better access. The posterior aspect of the ilioinguinal approach can be used. The glutei are detached and reflected to gain access to the posterior ilium and sacrum. If prone position is used, a similar approach of detaching the glutei is used for more lateral lesions, whereas a standard posterior approach to midline is used for more central lesions.

As with type II and III lesions, type IV lesions can typically be managed with curettage and high-speed burr drilling, with the resultant cavity filled with cement. When the defect is not contained and there are no cortices left due to destruction of the posterior ilium, resection of the posterior iliac segment is performed [12]. This typically involves resection of the adjacent sacroiliac joint, which can impair the stability of the pelvic girdle. Small sacroiliac joint resections involving less than 50 % of the joint do not require reinforcement. Defects involving greater than 50 % of the sacroiliac joint require reinforcement with a plate or spinal fixation construct to prevent joint dissociation. Dissociation can lead to an unstable pelvis and gradual upward migration of the ilium upon weight bearing, leading to limb length discrepancy. Eventually, the muscles and scar that form between the pelvis and spine will also form a biological sling, helping to stabilize the pelvis. Sacral resections below S1 are considered structurally stable and are thought to not require reconstruction. Further details about the resection and reconstruction of tumors involving the spine can be found in the chapter about surgical management of metastatic disease to the spine.

Soft Tissue Reconstruction and Wound Closure

Following resection, an oft overlooked but extremely important part of any surgery for pelvic metastatic lesions is the soft tissue reconstruction and wound closure. The correct attachment of the glutei, iliacus and abdominal musculature is critical to their function, including the restoration of the abdominal wall cavity to prevent herniation. If there is enough remaining bone and the muscles can be closed with acceptable tension, the glutei and iliacus are sutured onto the innominate bone using non-absorbable suture through drill holes. Alternatively, the authors have found the use of double-limbed suture anchors to be a convenient alternative method that can provide an advantage when tensioning the two limbs. This glutei-iliacus reconstruction is then sutured to the abdominal wall musculature. If there is a defect present between these muscles, this can be spanned with mesh to minimize herniation risk. A well-closed, tension-free layer is of the utmost importance.

If there is too much tension present, primary closure is avoided to prevent significant complications including wound dehiscence, hematoma formation and infection. In these situations, pedicled or free myocutaneous flaps can be used for closure. For a standard hemipelvectomy, the posterior gluteus myocutaneous flap is preferred. When using this flap, it is important to be aware of the potential for skin flap necrosis. Blood supply to this flap can be left intact by leaving the gluteus maximus attached, thus providing perfusion from arterial branches entering the gluteus maximus at its sacral origin [27–32]. In situations where the posterior flap is involved in the resection, the anterior thigh flap, which includes the skin, subcutaneous fat and quadriceps muscle, is a feasible alternative [33]. When both the buttock and anterolateral thigh are involved the medial thigh adductor myocutaneous flap can be used [34, 35]. In the closure of large sacral defects, the transabdominal rectus abdominis musculocutaneous flap is primarily utilized [36–38]. Finally, alternative flaps such as the axial thigh fillet flap or free fillet lower leg flap are also viable options.

The axial thigh fillet flap is based on the spare parts concept, where residual tissue from amputated limbs can be used for complex soft tissue reconstruction, thereby limiting donor site morbidity by not involving healthy structures. The free fillet lower leg flap is raised from the calf and supported by the popliteal artery, which is anastomosed to the internal iliac artery [39–42]. Regardless, it is important in these situations to involve a plastic or general surgeon to help plan and assist in the closure.

Postoperative Care

After the wound is closed over suction drains, an abduction pillow is typically used to minimize stress at the suture line during the healing process. Drains are typically left in until their output has decreased to an acceptable level, which typically takes between 3 and 5 days. While the drains are in, antibiotics are continued in the authors' practice, although the data behind this remains unclear. Rehabilitation with physical therapy is encouraged after surgery for ambulation and both active and passive hip range of motion.

Complications

Although the mortality rate associated with surgery for pelvic metastatic disease is relatively low, the complication rate is significant. A systematic review of seven published studies following open reduction and internal fixation (ORIF) of pelvic metastatic disease found a perioperative mortality and complication rate of 3.3 % and 19.5 % respectively [43]. Common complications cited in this study included intra-operative hemorrhage; contralateral sciatic and femoral nerve injuries; ureter, bladder, and bowel injuries; wound healing complications; prosthetic infections and dislocations; allograft infections and fractures; lower-quadrant hernias; bowel ischemia; and late deep vein thrombosis. In a series of 160 consecutive hemipelvectomies, it was found that increased surgical time and complexity was associated with increased rates of wound infection and flap necrosis [44]. Flap necrosis was most commonly associated with ligation of the common iliac vessels. Due to the myriad of complications associated with the surgical management of pelvic metastatic disease, it is important to thoroughly counsel patients on possible predictable complications and negative outcomes prior to surgery to ensure informed consent.

Outcomes

There is no validated scoring system to help assess function following pelvic resection, and few studies have been published examining outcomes. Intralesional procedures are widely varied in size and scope, and therefore, associated morbidity is as well. The rate of complications following hemipelvectomy (for primary and metastatic lesions) in the literature ranges from 20 to 50 % [9–12, 21, 32, 44]. In a retrospective review comparing internal and external hemipelvectomies, functional outcomes were similar. While patients with external hemipelvectomies had better transfer ability at hospital discharge, they also had increased pain and bladder dysfunction and follow-up [45]. Despite these morbidities and complications, surgery for metastatic disease to the pelvis can be extremely beneficial to the quality of life of the patient. In the systematic review of seven published studies following surgery for metastatic disease to the pelvis, 93 % of patients reported improvement in pain, and 94 % reported maintained or improved ambulatory status following surgery [43].

Conclusion

Pelvic metastatic disease rarely requires surgery, but in cases such as pathologic fracture, intractable pain, or certain solitary metastasis, surgery can be of benefit to the patient. Interventions can range from smaller intralesional surgeries such as percutaneous cementoplasty or curettage with or without adjuvant therapy and cementation, to extralesional wide resections such as internal or

external hemipelvectomies. Due to the complexity of pelvic anatomy, extensive preoperative imaging and planning is required, and consultation with other surgical specialties may be necessary. It is important that any surgery performed lead to immediate unrestricted weight bearing for the patient and be weighed against potential morbidity and limited life expectancy. In spite of significant potential complications associated with surgery, it has been shown that outcomes are generally quite good and that, when indicated, surgical management can lead to an improved quality of life for the patient.

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Metastatic Bone Disease: Femur

24

Shawn L. Price

Introduction

Symptomatic bone metastases occur in roughly 20 % of patients with known metastatic disease [1]. However, autopsy evaluations of those with cancer suggest that the incidence in this population encroaches 70 % [2]. The incidence of symptomatic metastatic bone disease has increased secondary to improvements in medical management and the positive effect this is having on cancer patient's survivorship [3]. While the exact incidence of metastatic bone disease of the femur is not known, the proximal femur remains a common location for bone metastasis. Half of metastatic lesions are located in the femoral neck, 20 % in the peritrochanteric region and 30 % in the subtrochanteric region [4]. In this chapter, we will discuss metastatic bone disease to the femur. By the end of this chapter you will be able to identify clinical signs and symptoms associated with metastatic bone disease to the femur, understand how to work-up patients who present with findings concerning for metastatic disease to femur, become familiar with patient-specific variables to determine a treatment plan and understand operative and non-operative techniques for symptom management and improving mobility status.

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Presentation

As with most patients with metastatic bone disease, those with disease in the femur usually present with pain that affects their ability to ambulate. Patients known to have cancer may present with a focal area of pain prompting further work-up. Patients recently diagnosed with cancer, may, during staging be found to have osseous metastasis. Finally, some may present with pain and no known diagnosis of cancer and be found to have a destructive bone lesion with an unknown primary source of malignancy [3].

Pain can be variable in presentation. Some patients may experience a dull ache, whereas others may present with severe constant pain, which is made worse with ambulating, weight bearing, or movement [5]. Rest may help their symptoms, but rarely does it provide complete symptom relief. The symptoms may be present for variable periods of time. Some medical professionals may attribute these symptoms to arthritis and provide treatment based upon this diagnosis. This often leads to a delay in diagnosis or pathologic fracture.

These patients will usually present to the orthopedic surgeon with radiographs of the affected area, which may demonstrate a destruction lesion. In the situation of the femur, they may present with hip radiographs or knee radiographs. Additionally, they may present with CT scan, which includes the pelvis. This scan may demonstrate a lesion in the proximal

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femur. It is important that work-up be performed in a systematic manner to avoid inappropriate treatment.

First, the treating surgeon should obtain orthogonal radiographs of the entire femur. In the situation of a realized fracture this may not be possible. Advanced imaging with a CT scan may be better in this situation. Imaging of the entire femur will allow the surgeon to further characterize the lesion and determine the extent of disease. This is important in deciding treatment modality. Imaging of the pelvis should also be performed to look for acetabular disease, if arthroplasty for the proximal femur is being considered.

Secondly, whole body bone scan (WBBS) may help determine if the other areas of disease are present on the femur or other areas of the skeleton. In the situation of a solitary bone lesion of the femur, one must use caution. It is estimated that 10 % of these bone lesions are not secondary to metastatic disease and may represent primary bone sarcoma [4]. Those with solitary osseous lesions, even with a known diagnosis of carcinoma, require a biopsy prior to definitive treatment, as treatment for metastatic carcinoma is different than that for primary bone sarcoma. The work-up described by Rougraff et al. for solitary bone lesions includes a thorough history and physical examination, radiographs of the involved bone, chest radiograph, bone scan, followed by CT scan of the chest, abdomen, and pelvis [6]. Biopsy may be accomplished in two manners: image guided by a radiologist or open biopsy. In situations where sarcoma is strongly suspected, biopsies should be performed by the surgeon who can perform the definitive resection [7]. Anecdotal experience has suggested the use of WBBS as a means to evaluate the upper extremity. If increased activity is noted on bone scan, radiographs should be obtained to determine whether operative treatment is warranted. Disease in the upper extremity may affect the patient's ability to ambulate following treatment of femoral metastasis, as these patients will often require assistive devices when ambulating and working with physical therapy.

Non-operative Treatment

In patients who have not sustained a pathologic fracture and not deemed to be at risk for pathologic fracture, non-operative treatment options may be entertained. Non-operative treatment options include hormonal therapy, bisphosphonates, receptor-activated nuclear factor kappa-B ligand (RANK-L) inhibitors, chemotherapy, targeted therapy, and radiation.

Although bisphosphonates continue to be used for pain control and to reduce the risk of skeletally related events secondary to metastatic bone disease, denosumab, a RANK-L inhibitor has gained acceptance in this patient population as well. Denosumab is a monoclonal antibody against RANK-L and serves to inhibit osteoclast activation. Some studies suggest that denosumab is more effective than zoledronic acid in reducing frequency of and time to skeletally related events [8, 9].

Protected weight bearing with crutches or a walker can also be considered for those who are able and can reliably adhere to these restrictions. One should avoid utilizing this form of treatment in those with impending pathologic fractures of the femur. Noble attempts at conservative treatment for impending pathologic fractures may lead to more extensive surgical procedures in the poorly selected patient. Non-operative treatment for impending or realized pathologic femur fractures should be restricted to those with contraindications to surgical intervention. Patients not considered ideal candidates for surgery are those whose life expectancy is very short, those who have infected wound or concerning skin lesions in the region of the surgical site, patients with current deep venous thrombosis, those who have extensive neurovascular involvement, and finally those with poor preoperative medical status, or severe malnutrition [3, 10]. The decision for operative intervention is individualized and the decision shared by the patient, the surgeon and medical oncologist.

Radiation therapy is often employed as a means of pain control. The treatment strategy is variable and may be administered as a single fraction of 8 Gray (Gy) to multiple fractions, i.e.,

10×3 Gy. Pain relief between the two groups is similar; however, the need from retreatment is higher for those who received single fraction therapy [3]. Radiation may be targeted to the site of disease alone in those not at risk for fracture. In those who have undergone surgical stabilization, the radiation field should include the full length of the implant, in most situations the entire femur [11]. Side effects of radiation include fatigue, skin irritation, bone marrow suppression, and stress fractures. It is important to inform patients that radiation delays bone healing, and that weight bearing restrictions should be in place for 2–3 months [3].

Operative Treatment

Surgical intervention is reserved for those patients with impending or actual pathologic fractures. While it is not always possible, it is most ideal to prophylactically stabilize an impending fracture as patients with realized fractures are shown to have a worse overall survival and longer hospitalizations [3, 12]. Additionally, patients who undego prophylactic stabilization are less likely to be discharged to skilled nursing facilities and nursing homes and more likely to be able to ambulate without assist devices in comparison to those who have realized fractures [3].

Prior to surgical intervention, it is important to determine the patient's anticipated survival and prognosis. For patients with a favorable prognosis in the setting of pathologic fracture, consideration should be given to reconstruction with durable construct that is not likely to be revised during the life of the patient.

Fixation Failure

During initial operative treatment of femoral metastasis, the surgeon must consider the durability of the implant, the mechanical requirements of the implant, and the patient's estimated survival. Implant failure rates have been shown to range from 3.1 to 42 % for those who live past one year [13]. It has been shown that plate fixation for pathologic fractures of the proximal femur is associated with higher failure rate than endoprosthesis and intramedullary nail. The superior salvage procedure was found to be endoprosthesis [14] (Figs. 24.1 and 24.2).

Minimally Invasive Procedures

In patients with impending fractures, minimally invasive procedures such as radiofrequency ablation and cementoplasty or a combination have been utilized to relieve pain and prevent fracture [3]. The exact indications for these treatment modalities are yet to be established.

The proximal femur has been thought to be a location for which cementoplasty was contraindicated. Recent data suggest that when utilized under specific parameters it can be considered. These parameters include, less than 30 mm of cortical involvement and no history of fracture of the lesser trochanter. If either of these scenarios is present, then the risk of fracture is too great and cementoplasty should not be attempted [15]. Plancarte-Sanchez et al. also reported a series of patients for which cementoplasty or as they call it femoroplasty was performed for symptomatic bone lesions of the head, neck, and proximal one-third of the femur. They reported pain reduction in the patients who underwent the procedure. They did not encounter any significant complications [16].

Intramedullary Nails

In patients with pain secondary to femoral metastatic disease, intramedullary nails (IMN) have utility in both patients with impending and realized pathologic fractures. IMN function as a load-sharing device that allows for early mobilization and weight bearing. It has been shown that patients who underwent reamed IMN for femoral metastatic bone disease had improvement in pain at rest and with activity [17] (Fig. 24.3). Preoperative radiofrequency ablation of painful osteolytic bone lesion has been suggested as an adjuvant to reduce

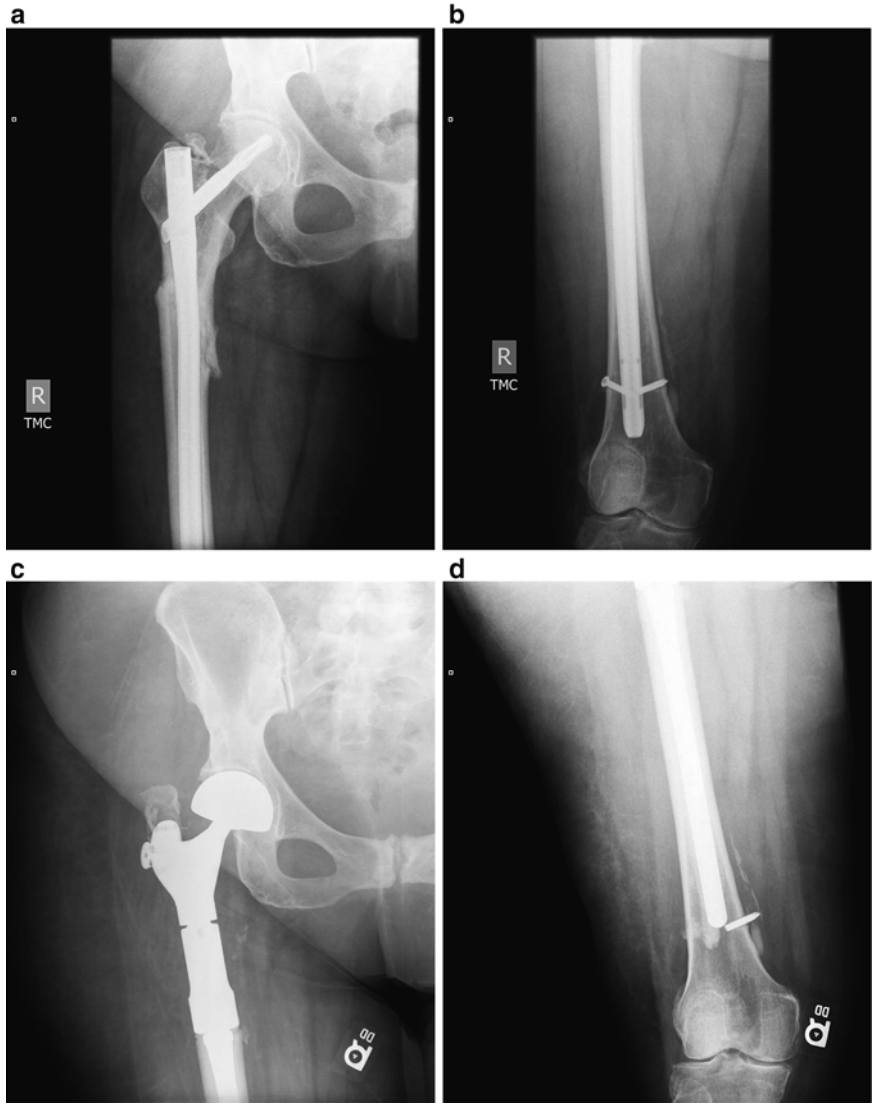

Fig. 24.1 (**a**, **b**) Sixty-one year-old woman with metastatic breast cancer who sustain a fracture after biopsy which was treated with cephallomedullary nail but failed to heal. She still had pain and presented with radiographic findings of failed hardware. (**c**, **d**) She underwent removal of hardware, proximal femoral resection, and endoprosthetic prosthetic reconstruction

tumor dissemination, intraoperative blood loss, and improve pain management [18].

Protecting the entire bone is often the recommendation when using IMN for femoral metastasis. Cephallomedullary devices are often used to protect the femoral neck (Fig. 24.1). Recent data from MD Anderson suggest that cephallomedullary nail may not be needed. Their data suggest that for those with diaphyseal disease, a standard nail is sufficient as there was no development of metastatic lesions in the femoral head and neck region after stabilization [19].

When using an intramedullary device, one must be aware of risks and complications associated with intramedullary nail placement in those with metastatic bone disease. Given that metastatic bone disease more frequently occurs in older adults, these patients may have compromised pul-

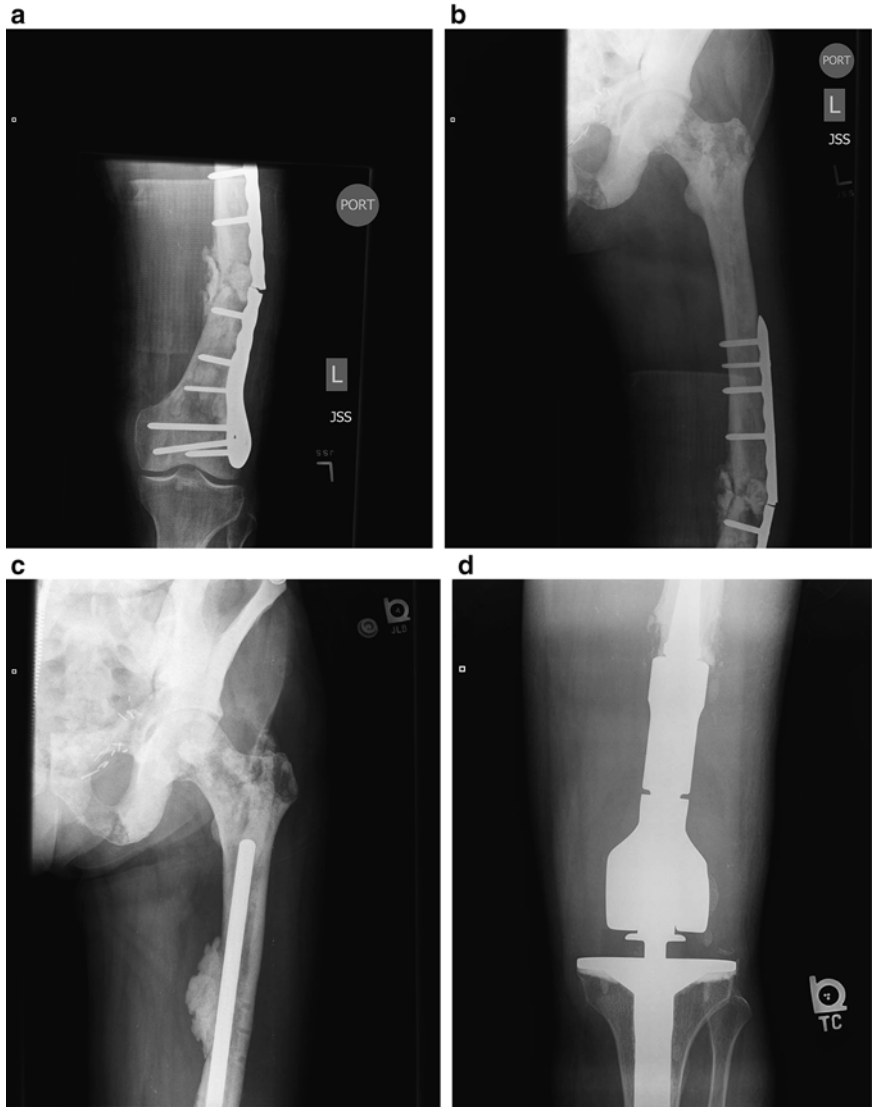

Fig. 24.2 (**a**, **b**) Seventy-seven year-old man with history of pathologic fracture secondary to metastatic prostate and renal cell carcinoma initially treated with plate fixation and cementation. He presented with pain and failure of fixation. (**c**, **d**) He underwent distal femoral resection and endoprosthetic reconstruction and ultimately died of disease approximately 5 months afterwards

monary function secondary primary lung disease such as chronic obstructive pulmonary disease. One must also take into account the effect malignancy may have on the lungs. These patients may have metastatic disease involving the lung, decreased pulmonary function or atelectasis secondary to prolonged immobilization, a history of prior radiation to the lungs, or toxicity associated with pharmacologic treatment for malignancy.

Additionally, complications are thought to be related to embolic phenomena; fat or malignant cells. There have been reports of intraoperative cardiac arrest and intraoperative deaths related to reaming and nail insertion [20]. Additionally, reaming the femur is thought to produce a release of inflammatory mediators, which may activate the coagulation cascade. Because of these potential complications, placing intramed-

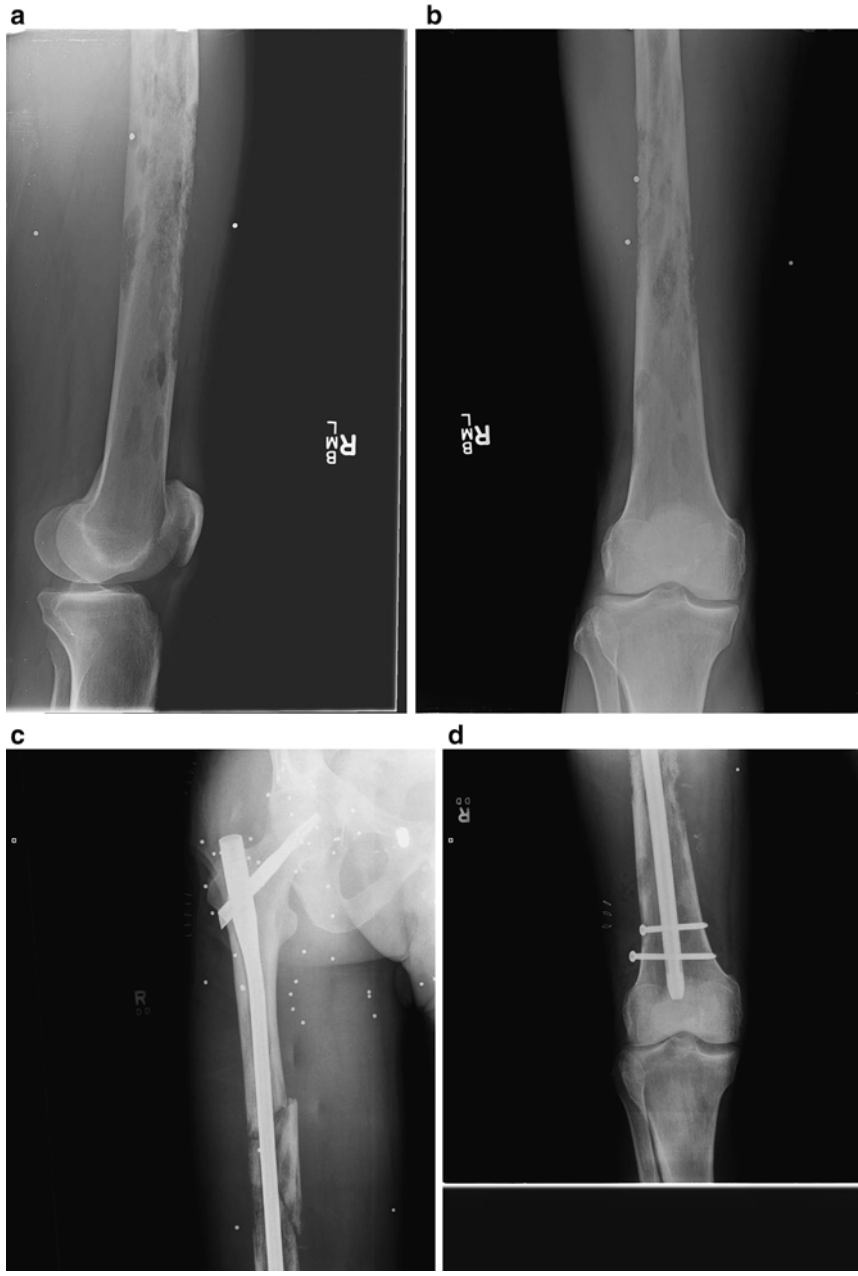

Fig. 24.3 (**a**, **b**) Fifty-seven year-old man presented with severe left lower extremity pain and abnormal femoral radiographic findings. He was found to have widespread metastasis, with unknown primary. (**c**, **d**) He underwent biopsy and stabilization with cephallomedullary nail as he refused hip disarticulation. He unfortunately continued to have severe pain and ultimately underwent palliative hip disarticulation and died of disease approximately 3 months afterwards

ullary devices into multiple long bones in one operative setting is not usually recommended. However, Moon et al. presented data showing that simultaneous intramedullary nailing had mortality rates similar to that for staged nailing; suggesting that while still associated with increased mortality, simultaneous nailing may be performed and that staging multiple

intramedullary nailing procedures is not absolutely necessary [21].

Data extrapolated from animal studies have demonstrated a reduction of embolic phenomena with the use of a reamer-irrigator aspirator (RIA) (Synthes, Paoli, PA) [22, 23]. The RIA is designed to remove intramedullary contents, to minimize heat generation and fat embolization. It has also been used to harvest bone graft. Cipriano et al. have demonstrated that the RIA is successful in retrieving intramedullary contents including tumor cells and they suggest that it may prevent systemic dissemination [24]. In this study, they did not have any canal perforations however, one must use extreme caution with this device in metastatic bone, as the reamers are sharper that conventional reamers and may create cortical breaches in already weak bone.

Open Reduction and Internal Fixation

Open reduction and internal fixation of proximal femoral metastatic bone lesions is associated with a high rate of failure secondary to nonunion, implant failure, and need for reoperation [14]. Its use is surgeon-dependent. Some favor plate fixation when dealing with osteoblastic metastasis, as the passage of intramedullary devices in this situation may be challenging [14]. Depending on the amount of bone destruction, cement augmentation may also be required to create a more durable construct and allow the patient to weight-bear in the postoperative period [3]. In the situation of impending pathologic fractures in solitary lesions, one can consider plate fixation augmented with polymethymethacrylate and postoperative radiation therapy. This surgical procedure can also be considered in those who are not expected with limited life expectancy [3] (Fig. 24.4).

Arthroplasty and Endoprosthetic Reconstruction

Extensive bone destruction, articular surface involvement, or loss of subchondral bone present challenges to conventional surgical treatment with or without cement augmentation. Arthroplasty is often required in these situations as lack of adequate bone stock presents unique challenges to conventional fixation techniques [10, 25]. Additionally, stronger consideration should be given to arthroplasty given that in open reduction internal fixation the nonunion rate encroaches 65 % [26].

For lesions of the femoral head, femoral neck or intertrochanteric lesions, cemented arthroplasty is usually performed. It is important to evaluate the acetabulum for disease as well. When the acetabulum is free of disease, hemiarthroplasty is preferred [10]. When arthroplasty is performed it is important that radiographic evaluation of the entire bone is performed prior to surgery. In some situations, medium or long-stemmed prosthesis may be warranted to reduce the risk of subsequent fracture.

As previously discussed, instrumenting the entire femoral canal is not without its risk in patients with metastatic bone disease. The addition of PMMA as a means of component fixation adds additional risk. An association between intraoperative death and cementation during standard total hip arthroplasty is known [27]. This risk is even greater in those with metastatic bone disease [28]. There have been proponents for both short-stem and long-stem femoral components. Those who advocate short-stem components do so because of reduced rated of embolic phenomenon and resultant sequelae. Supporters of long-stem femoral components have described techniques to reduce the risk of cement-associated perioperative complications. Randall et al. described a technique emphasizing aggressive medullary lavage, application of cement in its early cure state and slow placement of the femoral component to reduce the risk of embolic and cement-associated phenomenon [28]. With their technique, long-stem femoral components were cemented and there were no reports of intraoperative death [28]. Adding further support to their technique, Price et al. examined an additional 44 consecutive long-stemmed hip arthroplasty without an intraoperative death [29]. Advocates of long-stem femoral components often recommend their use to protect the entire bone in the event that disease develops distal to the end of a shorter femoral component. Xing et al.

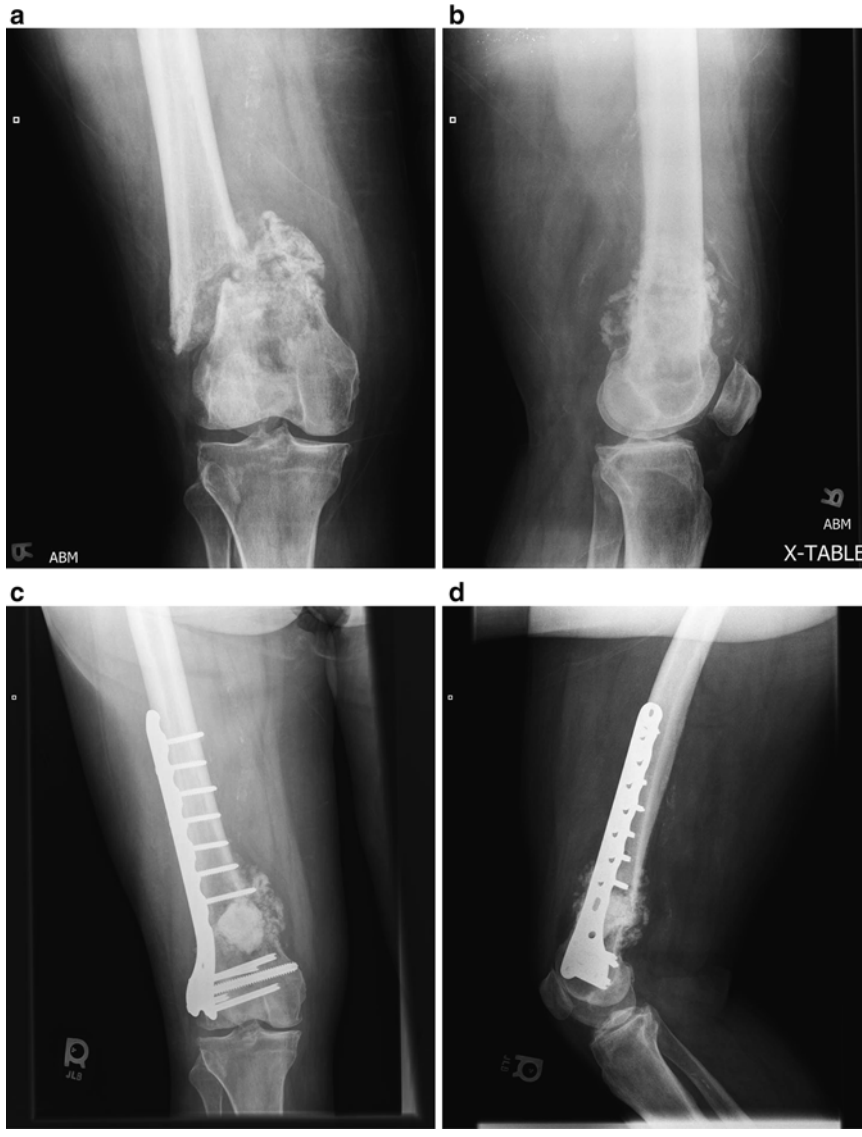

Fig. 24.4 (**a**, **b**) Sixty-one year-old woman with metastatic breast cancer who complain of right knee pain for over a year, thought to be secondary to arthritis. Presented with gross motion at the distal femur and the radiographic findings seen here. (**c**, **d**) The patient had a chronic non-healing breast wound and significant organ involvement with a poor prognosis. It was decided that plate fixation with cement augmentation would be best in this situation. Postoperatively, the patient had pain free motion and ambulation and died of disease 4 months after surgery

have shown in their series a low incidence of disease progression and development of disease distal to the stem suggesting that short components may used in patients with disease in the proximal femur and long stems are not always needed [30].

When disease is located in the distal femur alone, curettage, cementation and stabilization with a condylar plate, dynamic compression screw/plate construction or other fixed angle device has utility [5] (Figs. 24.1 and 24.2). When there is significant articular and or subchondral bone involvement total knee arthroplasty is usually not sufficient and reconstruction with an endoprosthesis should be considered.

Conclusion

Bone remains the third most common site of metastatic disease and two-thirds of pathologic fractures occur in the femur. Treatment of impending or realized pathologic fracture requires a systematic and multi-disciplinary approach and should be individualized. Non-operative treatment is rarely indicated in patients with impending or realized pathologic fractures. Operative intervention is based on the location and extent of bony destruction and can include plate fixation, intramedullary nails, arthroplasty, or endoprosthesis. The treating surgeon should be comfortable with caring for this population and should not hesitate in referring these patients to a musculoskeletal oncologist if experience and appropriate resources are lacking.

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Metastatic Bone Disease: Femur—Tibia

25

Nicholas P. Webber

Introduction

Metastatic adenocarcinoma is the most common source of cancer affecting the bones. There is a common misconception by the lay public that patients who are affected by metastatic adenocarcinoma to bone are affected by "bone cancer." In reality, metastatic disease to the bone is much more common than primary bone sarcoma with approximately 1000 cases of primary bone sarcoma diagnosed per year in the United States as opposed to nearly a million new cases of cancer, almost half of which will develop bony metastases at some point in their course [1]. With specific regard to the tibia, metastases are much less common than those to the axial skeleton, the proximal femur, and the humerus/shoulder girdle. There are many theories regarding the reason for this most of which include differential blood flow to the tibia, and that these metastases may later in the course of cancer, or become symptomatic at a more "end-stage," but nevertheless they are a source of significant morbidity [2].

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As in all metastases to bone, there are a number of key factors that must be taken into account with regard to appropriate treatment. The two major considerations of this review will focus on lesions of the tibia that are at risk of fracture, and those that have had realized fracture through them. These are treated with different methods but the basic tenants of reconstruction, stabilization, and palliation remain the same. Of paramount importance is the need to understand the susceptibility of the metastatic lesion(s) to other treatment modalities including chemotherapy, radiation, hormone therapy, or other local ablative techniques that are less potentially morbid to the patient. Furthermore, a thorough understanding of the biology of the disease and the type of lesion seen in the bone is critical. This understanding leads to appropriate type of procedure necessary to palliate the patient's symptoms, and can lead to a durable reinforcement or reconstruction. Furthermore, metastatic disease to long bones results in a pathologic fracture in approximately 25 % of patients, and when a pathologic fracture is realized, it can result in a more difficult situation than if treated prophylactically, especially when fixation of the fracture is unable to restore immediate return to weight bearing and system treatment [3].

As in all metastatic disease to the bone, appropriate communication and realistic expectations, and a shared goal with the patient and the treating surgeon are paramount. With rare exception, the

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goal of treatment of metastatic adenocarcinoma to the tibia is palliative in nature. With the exception of the oligometastatic disease in some specific disease histologies, long-term survival is not the goal, and understanding of the natural history of each of each of the histologies is key in the decision-making process. It is paramount that the disease process be well understood by the patient and treating orthopedist such that appropriately aggressive steps can be pursued [4].

Evaluation of a Metastatic Bone Lesion of the Tibia

It is rare that a boney metastatic disease to the tibia is the presenting symptom leading to the diagnosis of a primary adenocarcinoma. It has been reported that a pathologic fracture is the initial presentation of patients with metastatic disease in approximately 10 % [5]. Of those with metastases to the bone, realized fractures are found in approximately 25 % of patients [3]. Of patients with metastatic disease to bone, Leeson et al. found that less than 10 % of the boney metastases are found below the elbow and knee and less than 5 % involve the tibia [6]. This is most likely attributable to the Batson's venous plexus, which is the venous drainage system that drains the majority of primary sites of adenocarcinoma that commonly metastasize to bone. These include the breast, the prostate, the lung, and the kidney. This system is directly connected to the appendicular skeleton and proximal limb girdles [7]. Furthermore, the more robust blood supply both from a vascular standpoint of the more proximal limb girdles, as well as the soft tissue envelope that surrounds these parts of the skeleton may lead to the greater propensity of metastatic disease to these sites.

In the case that a patient does present with a lesion of the tibia and no known primary site of disease, the protocol of evaluation of a patient with a bone lesion of unknown primary is initiated. This evaluation is relatively well established and includes appropriate imaging and laboratory evaluation that has been discussed in other chapters. In brief, cross-sectional imaging of the chest, the abdomen, and the pelvis, along with standard laboratory draws, and scan of the entire skeleton will lead to diagnosis in 80 % of patients with a bone lesion with an unknown primary site of disease.

The Mirel's classification is often used by surgeons when deciding on prophylactic stabilization of a particular bone with a pathologic lesion [8]. However, with regard to the tibia specifically, there are more mechanical issues that should be taken into account. These include the specific location in the tibia given its morphologic difference with regard to the anatomy (when compared to the more commonly affected femur), the propensity of proximal tibial lesions to result in insufficiency fractures rather than frank displaced fracture as seen in the peritrochanteric/subtrochanteric areas of the femur, and the often tenuous surrounding soft tissues of the tibia that can make wounds less easily manageable. Specifically, in Mirel's scoring system, functional pain or pain with weight bearing may be the most concerning and demonstrative symptom of an impending fracture. As nonunion of a traumatic tibia fracture in patients without metastatic disease, who are not immunocompromised, remains a problem, this must be especially taken into account in those patients with metastatic disease. Preventing fracture by attempting to predict and identify impending fractures remains an important part of treating metastatic disease to the tibia [9]. Nevertheless, the role of the Mirel's classification can still be helpful in determining treatment of the specific lesion.

Modern imaging modalities can also play a major role in determining treatment. While Mirel's classification is based on a plain radiographic interpretation of predicting fracture, incorporating computed tomography, MRI, and bone scan can assist with establishing a treatment protocol. Many surgeons base their decision on type of prophylactic stabilization on location of the metastatic lesions. Cross-sectional imaging allows evaluation of the trabecular pattern of bone such that all affected parts of the bone can be stabilized. While most orthopedists understand the concept of stabilizing the entire bone in cases where the femur is affected, when the tibia

is affected, combined techniques may need to be utilized in order to reinforce the tibia, given the very proximal and very distal metaphyseal locations.

Nonoperative Treatment of Metastatic Disease to the Tibia

Whether operative or nonoperative treatment is recommended by the treating physician, the goals of treatment remain the same, while always taking into account the life expectancy, foreseeable complications, and expectations of recovery. Optimization of quality of life, reduction of events that would prevent systemic palliation, improvement in pain control, and facilitation of activities of daily living to the extent possible remain the goals of treatment. Adopting realistic goals from a systemic as well as a local standpoint is of paramount importance. Many of the procedures that are usually associated with low risk can be detrimental to patients who are in a compromised state and who have been extensively treated with various forms of systemic therapy.

When patients are at a low risk of having a pathologic fracture as per the Mirel's classification (or the method used by the treating physician), then a number of nonoperative treatments are available. Radiation may be the most commonly used non-medical adjuvant therapy. Radiation in the form of an external beam is often effective in recalcification of the lesion, especially in those tumor histologies that are historically more "radiation-sensitive" [10, 11]. However, if a pathologic fracture has already occurred, radiation can be detrimental to healing if internal fixation is not completed. Most orthopedic oncologists prefer to obtain rigid skeletal fixation and then proceed to adjuvant radiation therapy, as radiation may further weaken the already compromised area of the metastatic lesion. However, in patients where the risk of pathologic fracture is low, radiation may be the only modality necessary to maintain skeletal rigidity and palliate pain. In some situations in which there is bulky disease, physicians may choose to stabilize after curettage, and the radiation can theoretically have a more profound effect on microscopic disease rather than bulk tumor.

Bisphosphonates have been found, in some studies, to decrease the progression of metastases and may aid recalcification in some patients with lytic metastases. Particularly in metastatic breast cancer, the use of bisphosphonates can decrease the risk of new lesions, and can decrease the skeletal morbidity of metastatic lesions by 30 % [12, 13]. This literature has been used in other disease histologies and most patients are treated aggressively with a bisphosphonate by their medical oncologist, whether they have a lesion that is impending or not. In cases where patients develop an impending facture of the tibia, a bisphosphonate alone is usually not sufficient to appropriately treat the lesion, or relieve the pain to a sufficient degree [14–19].

Treatment Algorithm for Operative Treatment Metastatic Disease to the Tibia

Kelly et al. presented a treatment algorithm for treatment of metastatic disease to the tibia when surgery is indicated. This algorithm is based on the location of the metastases, and the material and method available to most reliably reconstruct and/or reinforce the weakened portion of bone in an aggressive, yet, reliable manner. Furthermore, they found that when this algorithm was followed, their reconstructions outlasted the life expectancy of the patient in greater than 95 % of their cohort. They proposed that surgical intervention, even in patients with end-stage disease, was warranted, and best treated in the hands of an orthopedic oncologist, improving quality of life, and assistance with maintenance of independence and nursing care.

The authors propose that patients with lesions in the proximal tibial metaphysis are best treated with curettage and cementation and plate fixation or interlocking intramedullary nail. A common tenant in tumor surgery is to stabilize the entire bone when a metastasis is present, or when there has been a fracture through a metastatic lesion in

one part of the long bone, even when no disease is present in other parts of that bone. However, with modern common imaging techniques, especially in the extremities distal to the knee and elbow, it is possible to evaluate how much of the bone is necessary to stabilize on a case-by-case basis. The basis of this is that if one technique may be more reliable, and beneficial to the patient on a short-term basis, it may be worth the very small risk of a metastasis developing in a site that is "unspanned" by the reconstruction. This is often the case in proximal tibial lesions, in the scenario that there is the sparing of the joint and articular cartilage though there is massive subarticular bone loss. In this case, plate fixation with screws placed as "rafting supports" or "rebar" may be superior to locking intramedullary nail fixation even though the locked intramedullary nail spans the entire bone and the locked plate usually does not extend to the distal metaphyseal flair.

There is general agreement regarding treatment as well, regarding diaphyseal lesions at risk of fracture and which are painful to the patient. Most surgeons choose to use prophylactic nail stabilization with or without curettage and cement replacement of the remaining deficit. The treatment of this is somewhat controversial, as some surgeons prefer to prophylactically stabilize without curettage and treat with adjuvant radiation only, depending on the likely longevity of the patient. Furthermore, given the often narrow diameter of the tibial diaphysis, supplementation of the canal or cortical deficit can be futile, and incisions in this site can be problematic, especially in patient with underlying vascular disease, or those that have been treated with radiation or other modalities prior to their operative procedure.

More controversial, however, is the use of mega prostheses or revision prosthetics supplemented with cement for the deficits created by the metastatic disease. The major challenge with reconstruction of the proximal tibia with a mega-endoprosthetic is the same as that of primary sarcoma resection, which relates to the reattachment of the patellar tendon. This is often unreliable in young, otherwise healthy patients. The challenges become more significant in patients who are at advanced age and are in the process of systemic treatment or who have had locally destructive therapy, which can make tissue healing very tenuous. Furthermore, the postoperative rehabilitation can be difficult as keeping the leg in full extension for an extended period of time can inhibit mobility, decrease weight bearing and other quality of life activities, and increase the risk of thromboembolic events in a population that is already at relative high risk of thromboembolic events. Methods of preserving the native attachment of the patellar tendon to the tibial tuberosity with the use of extended curettage of the lesion with cementation of the remaining tibia can reduce the complications associated with resection of the proximal tibia. As is the goal with most methods of reconstruction, it allows immediate weight bearing and can allow much earlier and more aggressive range of motion than that provided by proximal tibial reconstruction with a megaprosthesis requiring healing at the tibial tuberosity. In some scenarios, where there is limited subarticular disease with bone loss that mimics that of debris wear, or massive bone loss, the lesion can be treated with revision total knee arthroplasty components that are stabilized with a diaphyseal extension and replacement of the metastatic lesion with cement, or a more structural augment. Figure 25.1demonstrated a patient with widely metastatic non-small cell lung cancer with his main complaint being debilitating knee pain and inability to bear weight on that side. He was treated with neoadjuvant radiation, with minimal pain control and eventually elected a knee arthroplasty procedure. Figure 25.2 shows his reconstruction, with extended curettage and local adjuvant (argon beam, use of high speed burr) and a cemented primary total knee arthroplasty with a stem to provide stability. He was able to weight bear immediately. While this is a relatively rare scenario, the ability to have modular reconstructive techniques gives the ability to make durable reconstructions when the joint is involved. The extended rehabilitation, higher risk of infection and significant wound healing complications that result after radiation can certainly contribute to a higher complication

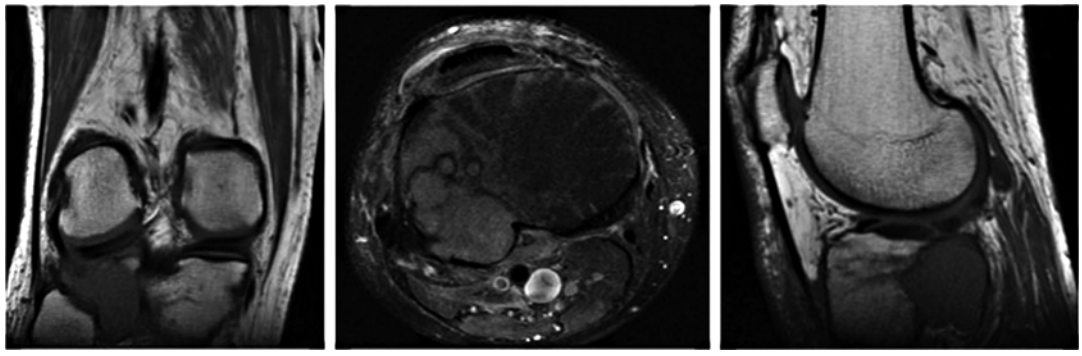

Fig. 25.1 Fifty-four year-old male with metastatic non-small cell lung adenocarcinoma. MRI demonstrating focal area in posterolateral tibial plateau, with involvement of the tibial articular cartilage

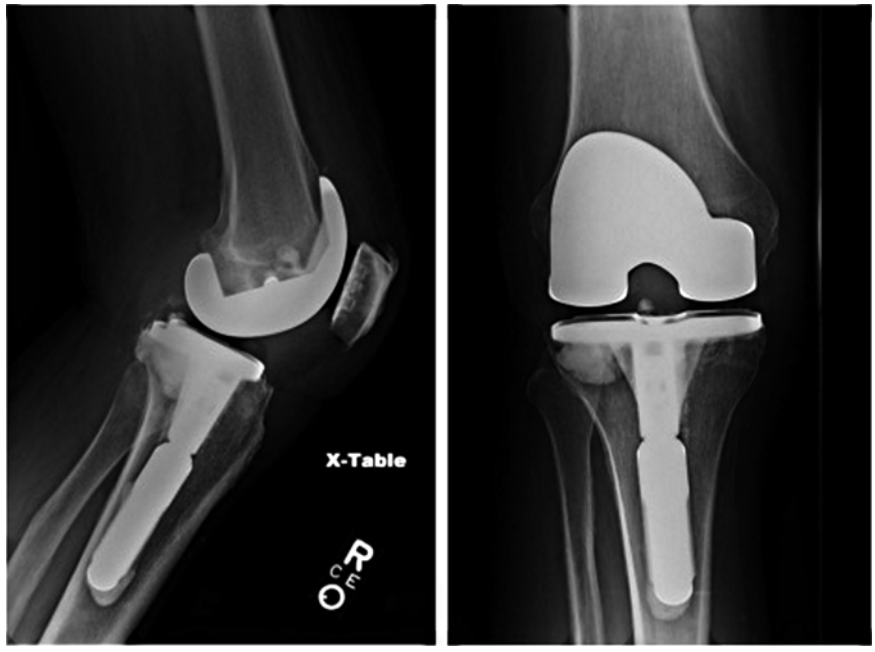

Fig. 25.2 Metastatic lesion treated with extended curettage, local adjuvants, and cementation of the remaining defect. The patient had complete relief of symptoms immediately

rate, though the relatively quick palliation of significant pain can give a very robust and rewarding result. Similarly, despite the proximal metaphyseal involvement, if there is articular destruction/disruption, and if the tibial tuberosity can be maintained, a cemented arthroplasty procedure with or without augments is a viable option to improve weight bearing and mobility.

With regard to distal tibial lesions that are non-articular, many surgeons choose to treat these with extended curettage and stabilization with plates or intramedullary nails or a combination of the two given the lack of stability provided by intramedullary nails alone in some scenarios. Distal tibial megaprosthetics can be used in rare circumstances, though with limited soft tissue coverage available and difficulties with wound healing in patients undergoing adjuvant systemic and local treatments, complications can be significant. In extreme cases, with severe osseous

destruction and no reasonable reconstruction, a below knee amputation can be utilized. In some cases, a retrograde fusion-type nail can be used in order to negate the need for below knee amputation if there is adequate bone above and below the metastatic lesion to maintain stability for the remainder of the patient's life, without the goal of actually obtaining an osseous union.

Patients who undergo below knee amputation can expect a significant decrease in pain with weight bearing [19, 20]. However even inpatients who are healthy and not immune-compromised, there is a very real likelihood of recovering fully for 2–4 months before reasonably comfortable weight bearing with a well fit prosthesis is possible. This can be a major deterrent to this historically successful procedure, given that this recovery may be longer than the expected lifespan of the patient. The long-term benefits seen in patients with mangled feet are mitigated in patients with limited life expectancy given the short-term problems with healing, and prosthetic fit in immune-compromised patients. In most patients at this stage in their disease, and with limited life expectancy, the possibility of prosthetic use may be significantly limited, and amputation likely leaves the patient dependent on a wheelchair.

Pathologic Fractures of the Tibia

When a fracture has been realized, and is no longer simply a lesion of the tibia at risk of fracture, the treatment algorithm is much like that of an impending fracture, and surgical intervention is usually warranted. Rigid internal fixation is paramount given the high likelihood of delayed and nonunion in the tibia given its inferior blood supply, relatively thin soft tissue envelope, and relatively smaller size when compared to its more proximal boney counterparts. For this reason, treating pathologic fractures of the tibia is to control pain and mobility rather than surgery with the goal of osseous union. Surgery is usually the treatment of choice in the case where the fracture causes pain and immobility in a patient who may otherwise benefit from pain control and mobility with surgical intervention. Clearly the challenge of obtaining osteosyntheses through diseased bone in the tibia is, historically, a loosing battle, though understanding reconstructive techniques that can mimic union for the remainder of the patient's lifespan can accomplish the goal at hand.

When possible, locked intramedullary, load sharing devices are superior in that they allow patients to bear immediate weight and remain mobile in the late stages of disease. The use of assistive devices in these patients may also be compromised given the fact that they may have other, more proximal sites of disease, and disease in their upper extremities. Also, the use of intramedullary devices can diminish the number of complications seen with plate fixation requiring larger incisions and longer time to adjuvant radiation, and inadvertent weight bearing through load bearing devices. Figure 25.3 demonstrates a locked, intramedullary nail for a patient with a non-displaced, insufficiency-type fracture through metastatic lung cancer. The patient was able to weight bear immediately on this, and started radiation 10 days postoperatively, given the very small incisions, and low risk of dehiscence and wound healing issues seen with plate and screw fixation. Pain was reduced immediately. Three months postoperatively, the patient continued to improve with boney remodeling. In this case, given microvascular disease and significant venous stasis, no curettage was performed given the risk associated with the soft issue envelope of the proximal tibia. Given the multiple proximal screw options, and the ability to span the entire bone with a load sharing device, it was considered to be a reasonable option and one that would more readily return him to his desired, normal activity.

When considering the aforementioned fractures, the common tenants of treating patients with metastatic adenocarcinoma should be followed. First, the recovery from treatment should not be longer than the expected survival. This is especially important when delineating which type of fixation to choose when a fracture has been realized. The key concept is understanding the biomechanical stability of the reconstruction

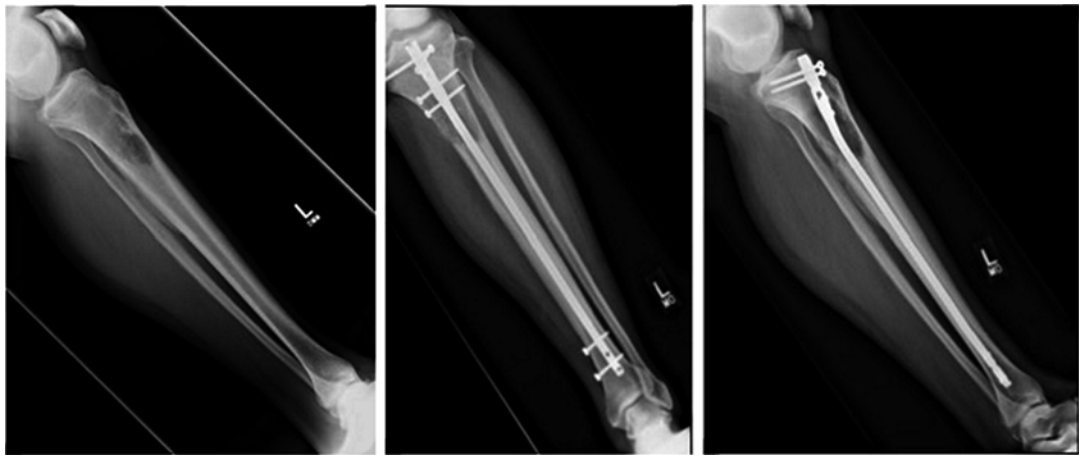

Fig. 25.3 Patient who presented with a pathologic fracture through lesion consistent with metastatic lung cancer. Patient went on to early post op radiation and had good resolution of symptoms

and the goals of fracture fixation. For example, when a fracture of the tibia occurs in a location that has a historic risk of nonunion, or delayed union, fixing that fracture with standard techniques of locked intramedullary nail is unlikely to result in fracture osteosynthesis. However, given the limited life expectancy of the majority of patients with a realized pathologic fracture of the tibia, the biomechanical nature of the reconstruction may be enough to allow early weight bearing, and pain control. The notion that a radical procedure is necessary given the high rate of nonunion of pathologic tibial fracture must be weighed against the long recovery that may result from overly aggressive procedures. For this reason, fixation of most fracture is limited to load sharing devices, or load bearing devices supplemented with load sharing supplements such as methylmethacrylate.

The treatment of metastatic disease to the tibia is a difficult undertaking, though should be simplified to the extent possible for the well being of the patient with the goal of palliation and optimization of function. While many reconstructive techniques have been proposed, the most important concept to reiterate is that there are many problems that can result when all factors are not taken into account including medical comorbidities, soft tissue coverage, known complications, and most importantly, the specific goals of the patient. Palliation of pain with the modality of treatment causing the least risk of morbidity while maintain a thorough understanding of the systemic disease is paramount. As in other chapters, the adage to "first, do no harm" is key in this very fragile patient population. As in most parts of this combined medical and surgical specialty, the key elements of treatment require a thorough understanding of the fracture, and impending fracture fixation, biology of the disease, psychology of the process, and most importantly, the goals of individual patient and the role of the surgeon in achieving those goals.

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Metastatic Bone Disease: Foot

26

Judd E. Cummings

Introduction

Metastatic bone disease involving the foot is extremely rare and often portends a poor prognosis [1, 2]. Reported rates of acrometastasis involving the foot vary between 0.01 and 0.003 % of patients with primary malignancies [3–6]. While any metastatic carcinoma can involve the foot, patients with a diagnosis of colorectal, genitourinary, lung, and breast sites of primary disease are most often affected [2, 6, 7]. Several factors are thought to contribute to the rarity of this condition including relative decreased blood flow, microcirculatory properties, immune system and platelet function, and limited communication between Batson's plexus and lower limb vasculature [2, 8, 9]. Because of the tremendous loads imparted to the foot, even small foci of disease can cause significant morbidity. Patients developing metastatic lesions in the foot often note pain and difficulty with weight bearing activities. Alternatively, a small focus of disease may be discovered incidentally on staging studies such as PET CT or conventional bone scan.

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When an osseous abnormality is discovered either clinically or radiographically, appropriate evaluation is needed as outlined in earlier chapters. Following the diagnosis of acrometastasis involving the foot, patients and physicians need to carefully consider treatment strategies that minimize morbidity associated with the metastatic lesion, while balancing the risks of surgical intervention and other adjuvant modalities. When surgical intervention is deemed necessary, focus should be placed on techniques that will allow early or immediate weight bearing activity, include appropriate management of the soft tissue envelope, and are commensurate with the patient's overall health status and prognosis.

General Considerations

When metastatic disease occupies the foot, symptoms may be at first misinterpreted as other more common foot ailments such as plantar fasciitis, gout, stress fracture, arthropathies, or tendinopathies [7]. Delayed diagnosis of foot metastasis has been reported up to 24 months [4]. Metastatic disease should be considered in any symptomatic patient with a current or remote history of malignancy, as these lesions can present years after initial diagnosis [4]. The presence of radiographic bony irregularities should also prompt an appropriate work-up. A majority of patients present with lytic lesions that generally respect the adjacent

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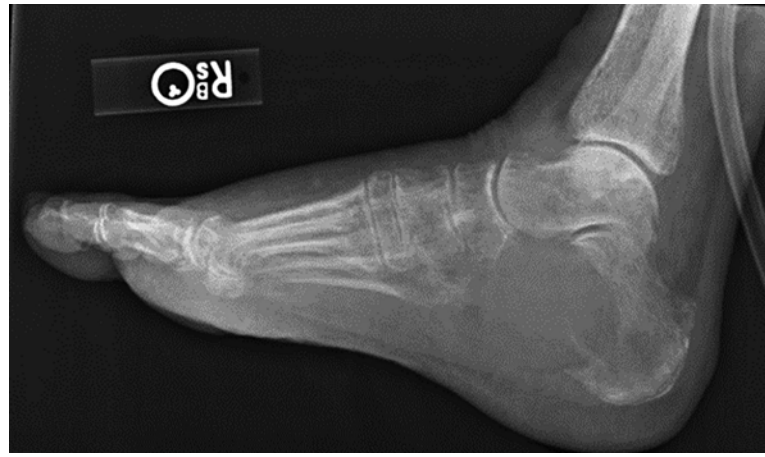

Fig. 26.1 Sixty-eight year-old female with history of endometrial carcinoma. Lateral radiograph of the right foot demonstrating and aggressive appearing lytic lesion involving the body of the calcaneus

bone or joint boundaries [2, 7]. Tissue sampling is the only definitive method of diagnosis.

Once a diagnosis of metastatic carcinoma is made, treatment options are considered. Non-operative measures such as systemic and medical therapies, external beam radiation, or percutaneous ablative treatments may be warranted. Surgical intervention is generally reserved for failure of non-operative management or when structural integrity of the host bone is compromised causing deformity, pain, and/or limited function (Figs. 26.1, 26.2, 26.3, and 26.4). Surgical treatment is considered palliative with emphasis placed on providing structural support and limiting morbidity. Secondary goals include tumor ablation and cosmesis. Radical surgical intervention such as attempted wide tumor resection with complex reconstruction is rarely indicated except in cases of isolated metastatic disease involving cancers that are not responsive to systemic or adjuvant therapies. Surgical treatment usually involves intra-lesional (ILR) tumor resection followed but cement augmentation including screw or pin fixation as needed. Toe or ray amputations are commonly employed for management of lesions involving the forefoot. These procedures are generally well tolerated and allow early functional weight bearing. In cases of widespread bony involvement and soft tissue extension, partial or complete foot amputation may be an option particularly if wound healing following surgery or radiation is a concern, and if the patient's life expectancy and overall prognosis is favorable. Use of a radiolucent table and fluoroscopy is particularly helpful to gauge adequacy of tumor resection and guide placement of hardware. Post-operative splinting and

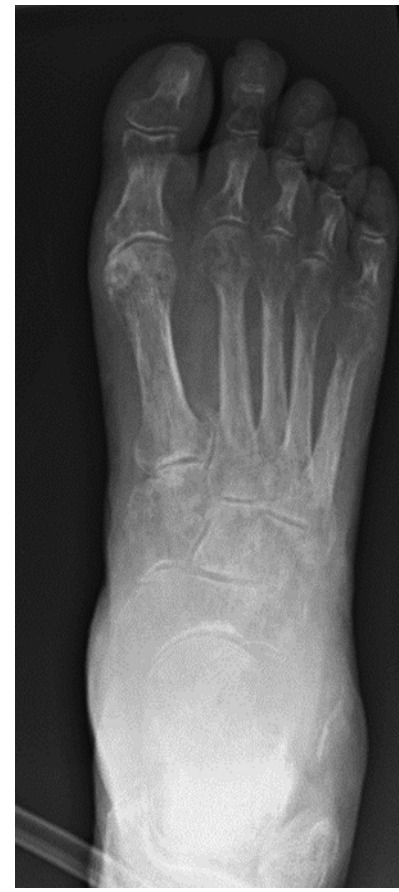

Fig. 26.2 AP radiograph of the right foot

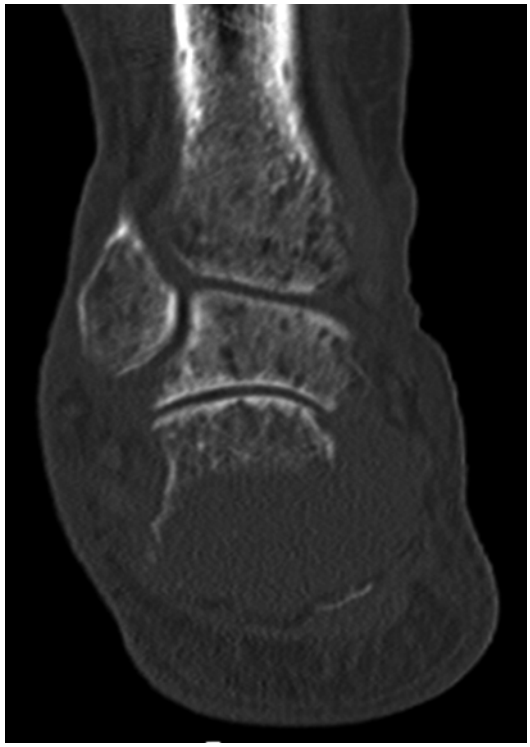

Fig. 26.3 Coronal CT image of the hindfoot demonstrating a lytic calcaneal lesion with disruption of the medial wall

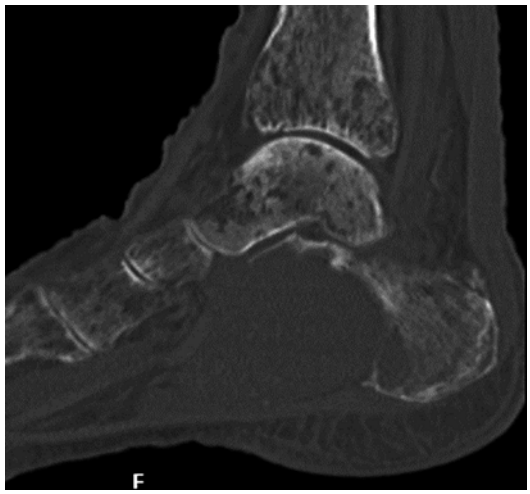

Fig. 26.4 Sagittal CT image of the hindfoot illustrating the anterior to posterior extent of the lesion

use of modalities to minimize soft tissue swelling or irritation (leg elevation, ice, compression stockings, orthotics) can facilitate and improve soft tissue healing rates and should be considered as appropriate for the individual patient. Surgical and post-surgical treatment should be tailored to allow immediate weight bearing activities as tolerated. Generally, patients with metastatic carcinoma have significant comorbidities and limited physiologic reserve precluding prolonged non-weight bearing or activity restriction. Full ambulatory status not only promotes general health but adds to quality of life and independence.

Anatomic Locations

Hindfoot

Surgical management is directed by several factors including size of the lesion, bone(s) affected, location within the bone, and health of the soft tissue envelope. The hindfoot can be safely approached from either the lateral or medial side depending on tumor location. Experience from the treatment of calcaneus fractures has highlighted the need for meticulous handling of the soft tissue envelope when utilizing a lateral-based approach. This is particularly true when external beam radiation has been used as an adjunct to local tumor control. In patients with poor tissue perfusion and limited potential for wound healing (vascular disease, diabetes, malnutrition, fluid imbalance), strong consideration for non-operative management should be given.

Intra-lesional resection or curettage is undertaken with margin expansion utilizing power burr and/or adjuvants, such as argon beam or liquid nitrogen, as deemed necessary. Excessive resection of adjacent cortical or cancellous bone is not indicated and can have a negative impact on subsequent reconstruction. Following tumor resection, bony reconstruction is generally achieved with bone cement augmented with screw or wire fixation when possible (Figs. 26.5 and 26.6). Non-contained defects (those that involve loss of the normal cortical boundaries) may be supplemented with low profile, specialized plating systems to prevent cement extrusion and re-establish normal cortical boundaries. These techniques generally allow for early weight bearing activities while avoiding complications inherent with bone graft use such as nonunion or infection.

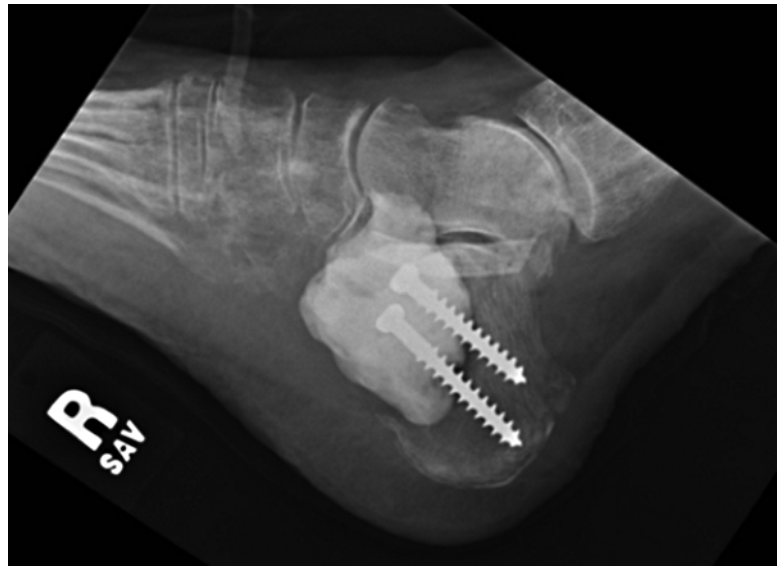

Fig. 26.5 Post-operative lateral radiograph of the hindfoot showing cement and screw reconstruction following intra-lesional resection of the metastatic lesion

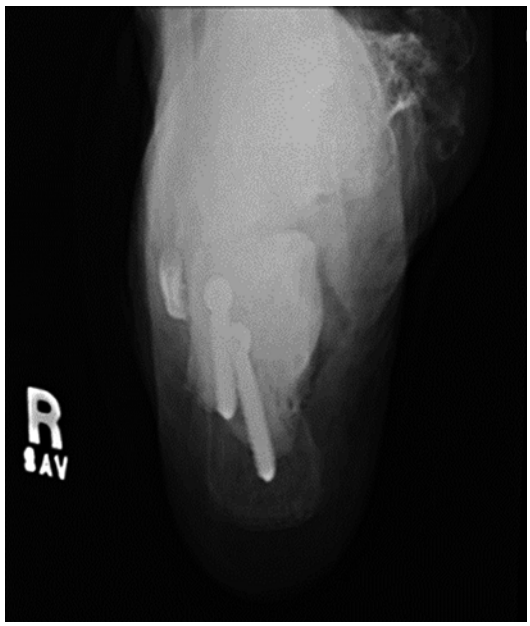

Fig. 26.6 Post-operative Harris view of the calcaneus

Because of the abnormal biologic environment and limited healing potential, large structural bone grafts or bone graft fillers are not generally recommended.

Midfoot

Metastatic lesions involving the tarsal bones or proximal metatarsals are treated similarly to lesions found in the hindfoot. Due to size and anatomic constraints, use of screw or pin augmentation within individual bones is limited. It may be necessary, however, to consider transtarsal or metatarsal fixation in cases of large, non-contained lesions with significant bone loss. Dorsal, medial, or lateral approaches can be used safely depending on the particular site of involvement. Again, meticulous handling of the soft tissue envelope is paramount to avoid wound healing complications, dehiscence, and infection.

Forefoot

Lesions involving the metatarsals and phalanges are less commonly seen and often require no surgical intervention. When surgery is deemed necessary (often due to nonunion of a pathologic fracture and/or recalcitrant pain), consideration for toe or ray amputation should be given. These procedures are generally well tolerated with little effect on patient function and reliably relieve

patient pain and discomfort. A notable exception would be amputations involving the first ray or great toe in which balance, walking, and foot alignment may be adversely affected.

Amputation

Amputation may be considered for several reasons in the patient with acrometastasis of the foot. Metastatic tumor lesions may become large and not amenable to tumor resection with anticipated satisfactory reconstruction. Prior attempts at limb salvage may prove unsuccessful and complicated by reconstruction failure, poor wound healing, or superimposed infection. Given the limited life expectancy of many patients with metastatic bone disease, amputation can provide an immediate surgical solution in carefully selected patients while avoiding prolonged hospitalizations, multiple surgical interventions, and protracted weight bearing restrictions. A patient's general health and comorbid conditions such as diabetes, vascular disease, and nutritional status must be considered when deciding on the appropriate amputation level. Objective measures such as ankle/brachial index (ABI), transcutaneous oximetry, and newer fluorescence angiography systems can help quantify tissue perfusion and predict successful wound healing at a particular amputation level [10]. Patient expectations, mobility requirements, and overall prognosis must be balanced with the expected functional and cosmetic results following amputation.

Toe or ray amputation is generally well tolerated and accepted by most patients with little morbidity. Weight bearing can begin commensurate with wound healing. Often, a specialized orthotic is used to accommodate shoe wear. This prevents soft tissue irritation, ulcers, and progressive deformity or malalignment of the remaining forefoot. As the level of amputation moves proximal, surgical morbidity and complication rates escalate. Transmetatarsal amputation may be indicated in cases of significant forefoot tumor burden with wound complications and/or superimposed infection. Chopart amputations involving the talonavicular joint provide an acceptable weight bearing surface with equal limb lengths, but is often complicated by gradual equinovarus foot deformity causing soft tissue irritation, exostosis, or other complication. Ankle fusion or revision to a more proximal amputation level may be necessary [11]. Ankle disarticulation, or Syme amputation, involves removal of the talus and calcaneus, malleolar osteotomy, and anchoring the heel pad to the weight bearing portion of the distal tibia. This procedure has a relatively high complication rate owing to wound complications and migration of the heel pad cushion making prosthetic use difficult [12]. Careful patient selection is mandatory. Below knee amputation (BKA) has been widely used for a multitude of problems involving the lower leg, ankle, or foot. Because the level of amputation is generally at the mid tibia region, wound healing is often favorable but does require a prosthetic limb for weight bearing activity.

Summary

Acrometastasis of the foot is rare. It should be considered in any patient with a symptomatic foot and a history of metastatic bone disease, or in the presence of abnormal imaging studies. Lung, breast, genito-urinary, and colorectal sites of primary disease are most often implicated. Treatment is often non-operative with surgical intervention reserved for those patients who fail non-operative therapies or who require osseous support of impending or realized pathologic fractures. Surgical intervention is palliative and should alleviate patient's symptoms, while allowing early return to independent weight bearing activities. Intra-lesional tumor resection is followed by durable reconstruction utilizing bone cement +/– screw or pin fixation. Amputation may be deemed necessary for select patients to salvage failed reconstruction attempts or when reliable reconstruction is not initially feasible. Patient selection is critical and appropriate surgical treatment begins with careful consideration of their general health, overall prognosis, prior or anticipated adjuvant therapies, and patient expectations for pain control, cosmesis, and functionality.

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Metastatic Bone Disease: Humerus and Scapula

27

Michael J. Monument and Shannon K.T. Puloski

Humeral Metastases

Burden of Disease

Metastatic and myelomatous lesions of the humerus are extremely common. The true incidence is hard to determine given that patients may be less likely to display symptoms with lesions of the upper extremity and variation in the primary source of disease to affect all bones of the skeleton equally. Among the long bones, the humerus is the second most common site for symptomatic metastatic lesions [1, 2]. Similar to the axial skeleton and femur, the most common primary histologies that metastasize to the humerus are breast (30 %), renal cell (20 %), lung (10 %), and prostate carcinomas (10 %). Other primaries such as thyroid, colorectal, bladder, and hepatocellular carcinoma represent less than 10 % of humeral disease [1, 3, 4]. Myeloma accounts for about 20–25 % of symptomatic humeral lesions [3, 5] and although myeloma is not considered a bone metastasis, these lesions can be managed using similar principles.

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The anatomic distribution of humeral metastases can be divided into lesions involving the diaphysis, distal third and proximal third. Lesions of the diaphysis are most common representing 50–60 % of cases, whereas lesions of the proximal third and distal third are less common (20–30 % and <10 % of cases, respectively) [1]. Similar to the traumatological approaches used to guide management of humerus fractures, surgical management of metastatic lesions and pathologic fractures of the humerus can be approached by dividing the humerus into these broad anatomic segments (see below). However, osseous involvement or resulting pathologic fracture(s) can span the virtual boundaries outlined above and hence may require a modified approach to management.

Over the past two decades, targeted therapies for a variety of metastatic carcinomas are becoming available to patients and the survival of patients with metastatic bone disease is anticipated to increase in the future. In addition, the functional capacity of patients with metastatic disease burden continues to improve which may necessitate a more aggressive approach to treatment in certain cases. Nonetheless, the prognosis for patients that develop a metastasis to the humerus remains guarded with 1- and 2-year survival for these patients reported as between 30–40 % and 10–25 %, respectively [3, 5]. With this in mind, and in the setting of failed nonsurgical measures, operative intervention for metastatic lesions of the humerus should provide limited

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morbidity and durable fixation in the absence of bone healing and permit immediate load-bearing and rapid rehabilitation.

Non-operative Care

Because the humerus is a non-weight-bearing bone there exists greater possibility to treat symptomatic metastatic and myelomatous lesions of the humerus with radiation therapy, splinting, and/or a temporary period of activity modification. The capacity of the underlying histology to respond to adjuvant therapy (either local or systemic) must be considered, as these variables will have an impact on the local outcome if the goal requires consolidation of bone loss or healing of a pathologic fracture. As the humerus is subjected to much lower forces than the bones of the lower extremity, it is not uncommon for patients to present with a pathologic fracture without any antecedent pain. Predicting which lesions are at risk for fracture, thereby warranting prophylactic stabilization, remains difficult and any criteria to do so are ill defined. Mirels criteria [6] remains the most commonly used scoring system to evaluate metastatic lesions of the long bones for fracture risk despite a relatively low specificity [7]. These criteria were developed in a population predominantly burdened with metastatic breast cancer involving the femur and therefore this scoring system may not be generalizable to all lesions within the humerus. However, in a study by Evans et al. [8], the authors were able to show that Mirels criteria remained reproducible, valid, and more effective than clinical judgment alone in the determination of prophylactic stabilization of the humerus. Although not easily rationalized, the authors of this study were able to show improved sensitivity and specificity when a threshold score of 7 was used (as opposed to a score of 9 for femoral lesions) to predict the need for prophylactic stabilization [8]. Preventing a pathologic fracture of the humerus remains an important dialogue, as postoperative complications are more commonly seen in surgically stabilized complete fractures versus prophylactic treatment of impending fractures [3].

In symptomatic lesions of the humerus deemed low risk for fracture or in patients who are unlikely to tolerate an anesthetic or have a limited life expectancy, treatment with external beam radiation would be considered the standard of care (please refer to Chaps. 17 and 21 for more detail). The optimal radiation treatment protocol for symptomatic bony metastases is controversial [9–11], although data from systemic reviews and meta-analyses would suggest that a single fraction dose of 8–10 Gy or mutlifractionated doses of 20–30 Gy over 5–10 treatments equally improve pain outcomes. Single-fraction therapy is associated with less local toxicity but higher rates of retreatment and posttreatment fractures compared to mutlifractionated doses [12, 13]. Roughly 30–40 % of lesions treated will demonstrate some radiographic evidence of bony reconstitution after radiation therapy [14, 15]. Systemic agents, including bisphosphonates, may also have an effect on overall success of treatment.

Although nonsurgical management of many traumatic humeral fractures is considered the standard of care, this same approach for established pathologic fractures needs to be cautiously considered given the low likelihood of achieving union in many tumor histologies (Fig. 27.1a–c). In the frequently cited study by Flemming and Beals [16], nonunion and inadequate pain control were observed in 50 % and 88 % of patients, respectively. Given the limited life expectancy of metastatic carcinoma patients, the prolonged physical impairment associated with nonoperative management of pathologic humerus fractures warrants prompt surgical care. Functional bracing can be used for patients that are not systemically fit for surgical care or in some tumor types whereby healing is considered to be likely if adjuvant treatment is known to have a positive effect on osseous disease. Patients with a diagnosis of multiple myeloma who have yet to receive systemic treatment or those currently receiving active treatment may be considered candidates for a trial of nonsurgical care (Fig. 27.1d–f). Functional status, activity expectations, hand dominance, and analgesic requirements may impact on the decision to treat conservatively.

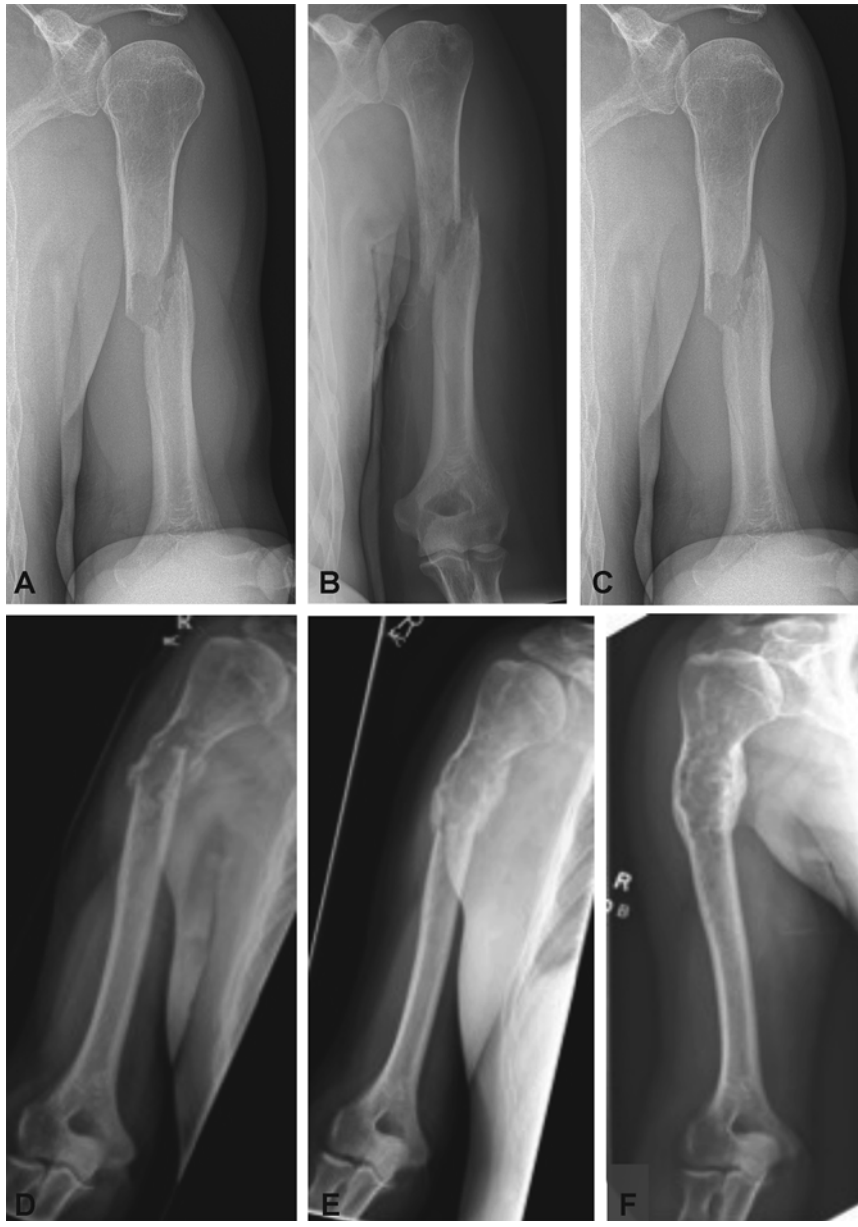

Fig. 27.1 Panels **a**–**c**: 65-year-old male patient with a metastatic adenocarcinoma lesion and associated pathologic fracture of the humeral diaphysis managed nonoperatively. Images of the fracture at presentation (**a**), 6 weeks (**b**), and 3-month follow-up (**c**) demonstrated persistent nonunion. Panels **d**–**f**: 51-year-old male patient with new diagnosis of multiple myeloma on active chemotherapy with 6-week history of upper arm and shoulder pain (**d**). 3 months following period of activity modification (**e**). 2 years after presentation having completed appropriate therapy and disease remission (**f**)

Operative Management

For the vast majority of cases, surgical management of metastatic bone disease is a palliative treatment. Therefore the primary goals of any surgical intervention in this patient population should be to provide a definitive procedure that controls local tumor burden, provide immediate and durable osseous stability, reduce pain, and enable a rapid return to activities of daily living.

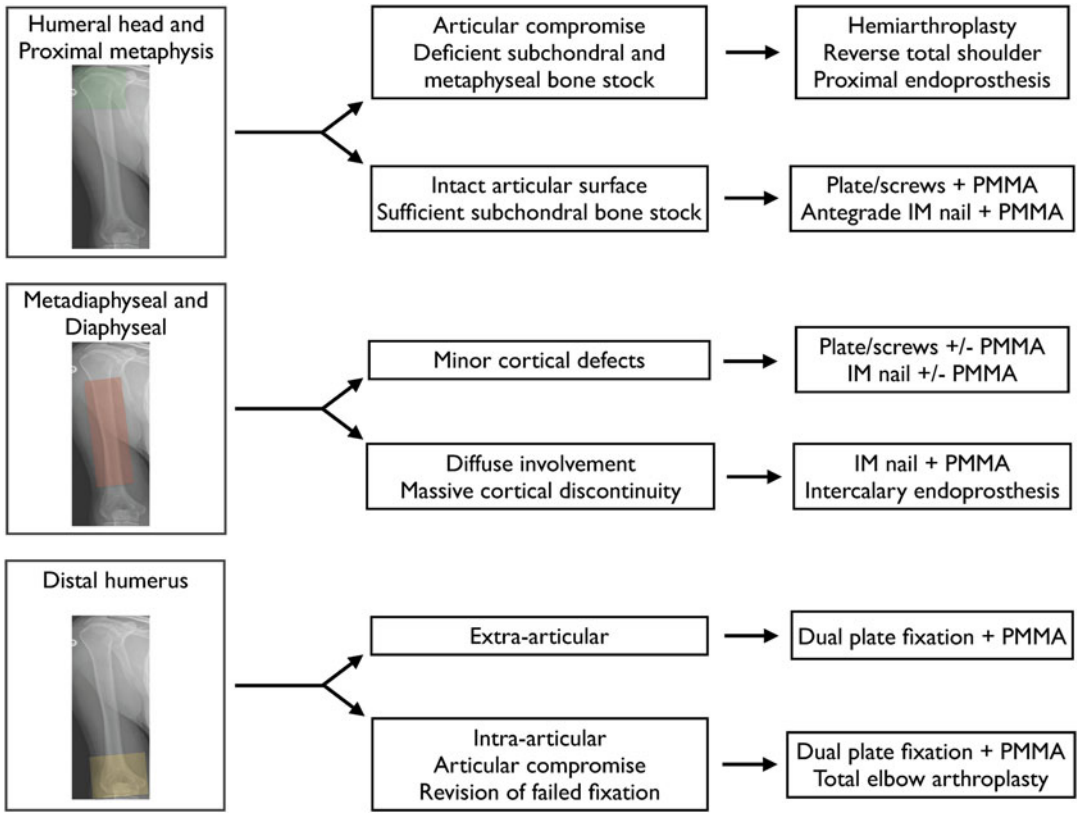

Fig. 27.2 Surgical treatment algorithm for lesions and/or pathologic fractures of the humerus based on anatomic factors

Failure to meet any one of these goals often necessitates revision surgery, prolonging recovery in individuals with an already compromised quality of life. These operative goals are no different for the humerus than for the long bones of the lower extremity. Pathologic and impending fractures of the humerus can be operatively stabilized using a variety of techniques and implants. Optimal implant and technique selection is based on a constellation of factors such as patient health status, anatomic location of the fracture and/or lesion(s), the extent of bone loss, histologic diagnosis, and surgeon preference.

To simplify these variables, surgical decision making can be stratified using anatomic landmarks. Lesions of the metaepiphyseal proximal humerus are managed using plate and screw constructs or endoprosthetic reconstructions. Diaphyseal and metadiaphyseal lesions are most amendable to intramedullary nail fixation or plate and screw fixation, while distal lesions of the humerus are best treated stabilized using orthogonal plating strategies or elbow arthroplasty techniques (Fig. 27.2). Alternatively, the indications and technical considerations for each reconstructive or stabilizing device can be evaluated in the context of pertinent patient and fracture-related variables.

Intramedullary Nail Fixation

Intramedullary nails are ideal load-sharing devices for stabilization of most impending and complete pathologic fractures of the humerus. Antegrade and retrograde interlocking humeral nails are widely available and technically simple to use. A major advantage of these devices is that the working length of the nail spans the entire bone, especially with diffuse disease (Fig. 27.3a, b). Plates can also be used to span the majority of humerus (Fig. 27.3c, d). However nails, unlike plate

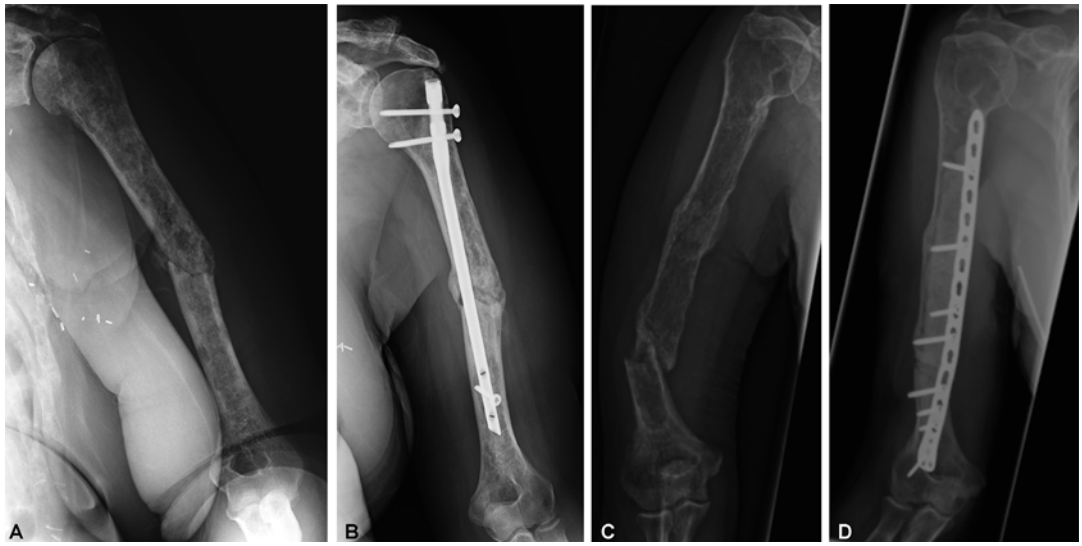

Fig. 27.3 Panels **a** and **b**: 61-year-old female with diffuse involvement of the humerus secondary to metastatic breast carcinoma (**a**). An intramedullary nail provides fixation for the entire diaphysis and proximal metaphysis with evidence of fracture healing at 3-month follow-up (**b**). Pain symptoms were dramatically improved in this patient, despite incomplete fracture union at 3 months. Panels **c** and **d**: 62-year-old female with multiple myeloma on maintenance chemotherapy and history of pathological humeral fracture(s). Patient presented with symptomatic nonunion of distal humeral diaphysis (**c**). Definitive stability achieved with long posterior locking plate augmented with cement (**d**)

constructs, are more amenable to a minimally invasive approach, which is advantageous in situations where the additional risk associated with exposure of the lesion or fracture (blood loss, nerve injury, etc.) is not warranted. Tumor debulking and cement augmentation of bone defects can still be accomplished simultaneously using additional exposures along with nailing procedures.

General indications for intramedullary nail fixation include lesions or fractures located within 2–3 cm distal of the greater tuberosity to roughly 5 cm proximal of the olecranon fossa [17]. In addition to the proximal-distal location of the lesion, 4–5 cm of intact cortical bone on either side of the nail is required for rigid fixation [18]. Proximal or distal metaphyseal defects do not preclude the use of an intramedullary nail although plate fixation or cement augmentation should be considered in these instances. Tumor debulking and cement augmentation should also complement nail fixation of diaphyseal defects >2–3 cm. Proximal and distal interlocking screws should be utilized whenever possible, especially for complete fractures [18]. When using cement augmentation, cement can be added in a more viscous state and packed around the nail after insertion or in a less mature state after reaming and immediately before the definitive device is inserted.

In appropriately selected patients, outcomes after intramedullary fixation are favorable. Durable pain relief and return to activities of daily living can be expected in >90 % of patients. Reoperation rates are less than 5 % and most commonly associated with tumor progression and prominent proximal hardware [4, 17–20] (Fig. 27.4). One retrospective case–control study demonstrated earlier functional gains and pain improvement when intramedullary fixation was augmented with cement [20], although the necessity of cement augmentation with IM nail fixation remains controversial.

There are nonetheless various pitfalls and complications associated with intramedullary humeral nails. Shoulder pain and/or decreased shoulder abduction and forward flexion is observed in 10–15 % of patients likely secondary

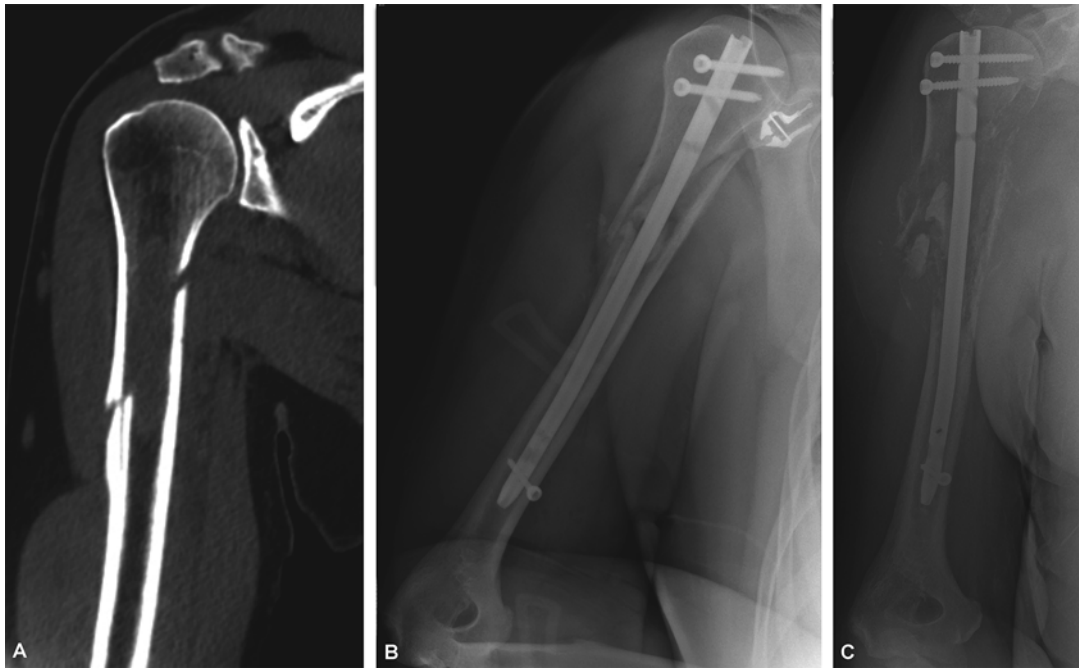

Fig. 27.4 A 59-year-old patient with metastatic renal carcinoma involving the proximal humeral diaphysis with an associated pathologic fracture as his presentation of disease (**a**). Despite tumor debulking, IM nail fixation, and postoperative radiation (**b**), the lesion and bone destruction progressed rapidly with extensive bone destruction at 6-week follow-up (**c**). Within 5 months of his fracture, this patient died of this aggressive systemic disease

to rotator cuff injury during insertion or a prominent proximal nail position [21–24]. This can be lessened by meticulous protection of the supraspinatus tendon during reaming and nail insertion. Ensuring the proximal nail or proximal locking bolts are not left proud will also minimize postoperative shoulder issues. In a recent systematic review comparing plate osteosynthesis and intramedullary nail fixation for non-pathologic fractures of the humerus, nail fixation was associated with a greater incidence of shoulder impingement (21/123 cases, 17 %), decreased range of motion, and hardware removal (9/69 cases, 13 %) [25]. These results may not be generalizable to patients with pathologic fractures and impending fractures given the lower functional demands and life expectancy of these patients. Regardless, patients should be counseled of the risk of shoulder impingement preoperatively.

Postoperative radial nerve palsies are also associated with intramedullary fixation of the humerus, with an incidence of 3–6 % reported in the literature [4, 24, 26]. Cadaveric studies have demonstrated a 30 % incidence of lateral-medial distal locking bolt abutment with the radial nerve after humeral nailing [27]. Although more commonly encountered reported during the treatment of femoral metastases, embolic pulmonary complications are associated with intramedullary preparation and nail insertion into the humerus [28]. Nail insertion after cement injection adds an additional risk for embolic debris and therefore low-viscosity cement combined with attentive cardiopulmonary monitoring should be employed in these cases [28, 29].

Plate Fixation

Plate fixation of humeral metastases is less commonly utilized than intramedullary nailing, mostly because these procedures are often more invasive and do not always protect the entire bone. Plate and screw constructs are ideal for joint preserving reconstructions of lesions involving

the proximal metaphysis/humeral head and distal humerus where intramedullary nail fixation is unlikely to provide adequate fixation in abnormal bone [30]. For these anatomic locations a preoperative CT scan is helpful to determine the extent of bone loss, aiding preoperative decision making between plate and screw or arthroplasty options. Plate fixation also affords direct exposure of the lesion for tumor debulking, avoids violation of the rotator cuff, and permits direct fracture reduction. Because of the limited working length of plate and screw constructs, judicious tumor debulking followed by cement augmentation should be considered in all cases. Cement augmentation provides additional mechanical stability and improves the pull-out strength of orthopedic screws inserted into abnormal bone [31, 32]. Both locking and non-locking screws can be placed across a mature cement mantle. Plate constructs should be cautiously used in cases with diffuse involvement of the bone, massive segmental cortical defects, and uncontained periarticular lesions with compromised articular integrity. Extensive disease involving the humeral diaphysis with extension into the distal metaphysis creates a challenging problem when deciding on the most appropriate implant given the challenges of obtaining distal fixation with intramedullary constructs (Fig. 27.3c, d).

For proximal lesions, a deltopectoral approach with a distal anterolateral extension provides adequate exposure while a triceps-sparring or -splitting posterior approach should be used for distal lesions. Distal lesions of the humerus have the highest incidence of mechanical failure and revision surgery (30 %); therefore dual plating with tumor debulking and cement augmentation is recommended to provide maximal stability and longevity [3]. Locking plates compared to non-locking fixation has been shown to provide superior screw fixation in the setting of poor bone quality, which has expanded the indications of these devices to include patients with metastatic bone lesions [30, 33, 34]. Contrary to this, satisfactory results using non-locking fixation and cement augmentation in the humerus are possible [5] and should not be abandoned, especially as government and hospital cost-containment pressures increase. In either setting, plates should span the defect by at least two cortical diameters, permit three bicortical screws on either side of the lesion, and, when possible, cover as much of the entire length of the bone permitted by the surgical approach [2, 5, 30]. Percutaneous fixation to limit surgical exposure can be used, when safe, in order to extend the length of the construct.

Like intramedullary fixation, outcomes after plate and screw fixation are favorable; pain relief can be expected in 85–95 % of patients, and the majority of patients will resume activities of daily living with the affected extremity [5, 18, 34, 35]. In patients surviving more than 1 year, revision surgery is required in about 10–15 % of patients for adverse events such as infection, mechanical failure, and tumor progression [3–5, 35]. In the context of humeral metastases, plate and screw reconstructions are associated with increased blood loss, longer operative times, and a higher incidence of iatrogenic radial nerve injuries compared to the results of IM nail fixation [18, 36, 37]. An iatrogenic radial nerve palsy, even if transient, can be a significant functional impairment in this patient population, especially when survival is limited. This limited data however should be interpreted with caution as high-quality, prospective, controlled studies directly comparing fixation techniques are lacking.

Endoprosthetic Reconstructions

Endoprosthetic reconstructions of the proximal and distal humerus using modular tumor prostheses are valuable treatment options and should be considered when traditional internal fixation methods are unlikely to achieve durable stability and pain reduction. Indications for prosthetic reconstruction of the humerus include lesions of the humeral head with joint destruction and articular compromise, large segmental cortical defects, revision of failed intramedullary nail and/or plate and screw stabilizations, and defects of the distal humerus. In this context, proximal humerus resections are reconstructed using an endoprosthetic hemiarthroplasty [3, 38, 39] whereas distal humerus resections are coupled to a total elbow arthroplasty [3, 40, 41]. Because of pre- and postoperative radiation, systemic chemotherapy, and

general poor bone quality, cemented fixation should be used whenever possible.

For proximal humerus reconstructions, a deltopectoral approach provides reliable access and visualization. Division of the rotator cuff insertion is frequently required and creative, although largely ineffective measures are often employed to reapproximate these tissues to the prosthesis. When possible, securing the native joint capsule around the prosthesis using a purse-string suture is thought to augment joint stability. Otherwise, a delicate balance of humeral head retroversion, head size selection, and rotator cuff tendon approximation are essential for long-term stability. Depending on the length of the bone resection needed, detachment of deltoid insertion is sometimes required. In these instances, the deltoid should be tenodesed to the pectoralis major tendon [38]. Deciding on whether to use a standard hemiarthroplasty implant, reverse shoulder or humeral megaprosthesis may depend on a number of factors including the amount of proximal bone loss, life expectancy, implant cost and access, and the potential for adequate soft tissue coverage and capture. To date, no literature has supported the use of one construct over another and shoulder stability can be adequately achieved with either. Proponents of a reverse total shoulder or allograft prosthetic composite argue improved shoulder function but the use of these somewhat more complicated reconstructions should be evaluated in the context of the patients' overall condition.

The ultimate goal of a proximal humerus endoprosthetic reconstruction is to obtain a stable shoulder, providing a platform for independent elbow and hand function. Preservation of elbow and hand function and pain reduction are principal advantages of these reconstructions. Consequently, patient satisfaction is generally favorable with these procedures. However, because the rotator cuff insertion is sacrificed with these resections, suboptimal shoulder function is common postoperatively. Despite deltoid and axillary nerve preservation, resultant forward flexion and abduction are unlikely to exceed 90 degrees. [38, 39, 42]. Patients should be counseled that a reasonable postoperative expectation is for the ipsilateral hand to reach the mouth and face [39]. Proximal migration of the prosthesis or glenohumeral instability is observed in a 20–30 % of cases [38, 39]. Because of the inherent instability of the glenohumeral articulation, most centers advocate 4–6 weeks of restricted motion in a shoulder immobilizer to allow sufficient time for soft tissue healing. Because of rotator cuff deficiency and limited overhead mobility following standard endoprosthetic reconstructions of the proximal humerus, some authors have advocated using a reverse total shoulder arthroplasty (RTSA) [43, 44]. With these implants, the center of joint rotation is moved inferior and medial, which improves deltoid biomechanics and enables greater potential for abduction and forward flexion beyond 90 degrees. Intraoperative and postoperative complications are more common with RTSA as compared to primary shoulder arthroplasties [45]; however outcomes in metastatic patients are lacking and warrant further investigation.

Metastatic lesions of the distal humerus are relatively uncommon, although complications and revisions are proportionately more common in these cases [3]. Distal humeral resections coupled to a hinged or semi-constrained total elbow prosthesis facilitate complete tumor removal and rapid restoration of elbow function [40, 41]. A total elbow arthroplasty is often sufficient for smaller lesions of the trochlea and capitellum, where larger, more destructive lesions of the distal humeral metaphysis should be reconstructed with a modular endoprosthesis or allograft prosthesis composite (Fig. 27.5). A midline posterior approach to the elbow can be used for the majority of these cases. The ulnar nerve should be dissected and mobilized prior to exposure of the joint. Joint exposure can be accomplished by a variety of techniques such as the Bryan-Morrey posteromedial approach [46], working on either side of the triceps [47], an osteo-anconeus flap [48], and triceps-splitting approach [47], depending on local anatomy and surgeon preference.

With these procedures, patients can expect a substantial improvement in pain and elbow motion. Postoperative elbow motion in the sagittal plane is sufficient for most activities of daily

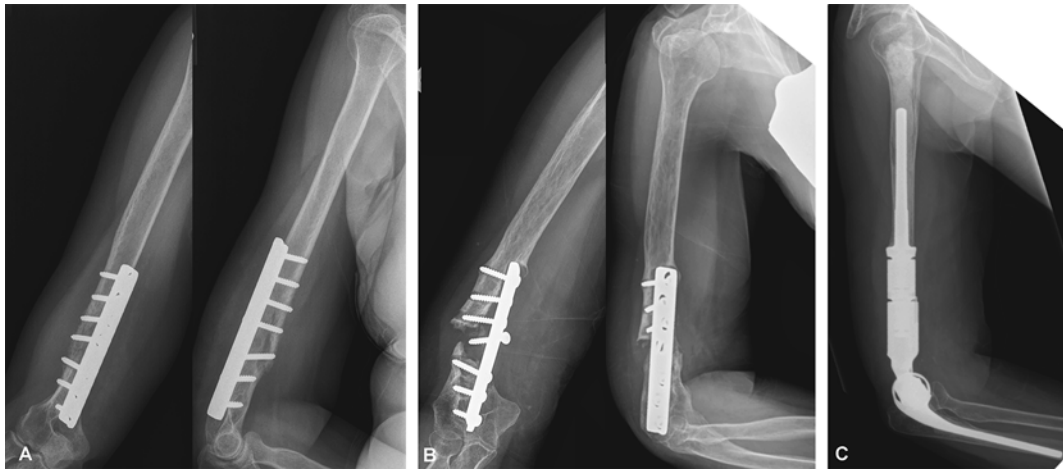

Fig. 27.5 A 65-year-old female with myeloma of the distal humerus and associated pathologic fracture was treated with plate fixation and postoperative radiation (**a**), although subsequently developed further bone resorption, atrophic bone ends, and hardware failure (**b**). As revision osteosynthesis was unlikely, a distal humerus resection was reconstructed with a distal humerus endoprosthesis coupled to a hinged total elbow arthroplasty (**c**)

living and coordinated positioning of the hand towards the mouth and face. A major limitation of total elbow arthroplasties is diminished lifting capabilities. Most surgeons advocate permanent lifting restrictions of 5–10 lbs. Early complications can be expected in 25–30 % of cases, the most common complication being iatrogenic injury to the ulnar nerve followed by infection [40, 41, 49]. Other causes of revision include triceps avulsion, local disease progression, and peri-prosthetic fractures. Implant instability is uncommon.

In situations where extensive diaphyseal bone loss is initially identified or can be expected after tumor debulking or resection, reconstruction using a cemented intercalary endoprosthesis may provide some appealing benefits (Fig. 27.6). The reconstruction allows for a limited exposure directly over the affected area of bone loss and intramedullary stem insertion. This mitigates the need for extensive exposure that may be required for long plate fixation or violation of the shoulder for proximal nail insertion. Early reports of these devices in the USA were complicated by a high rate of transient nerve palsies (likely secondary to distraction needed for implant coupling), peri-prosthetic fractures, and failure at the implant coupling interface [50]. Newer implant designs have mitigated some of these complications although aseptic loosening in one study was reported in 3/11 (27 %) patients [8]. In a separate report from Europe, the authors reported one case of aseptic loosening in eight patients at a mean follow-up of 29 months [51]. Based on these findings, the authors propose a narrow indication for these implants limited to patients with limited life expectancy and proximal or distal bone stock to allow for a minimum of 5 cm of intramedullary fixation [8].

As a general rule, relative to internal fixation strategies, functional outcomes for intra-articular proximal and distal endoprosthetic reconstructions of the humerus are inferior to conventional fixation strategies such as intramedullary nails and plate osteosynthesis [42]. With this in mind, if the joint can be saved using durable intramedullary nail or plate reconstruction, consideration of these strategies should be prioritized, although this is not always possible. Endoprosthetic implants are at higher risk for infectious complications (3–10 %), which can be disastrous in the immune-compromised host [52]. Endoprosthetic reconstructions are generally more costly than internal fixation options; however this is potentially

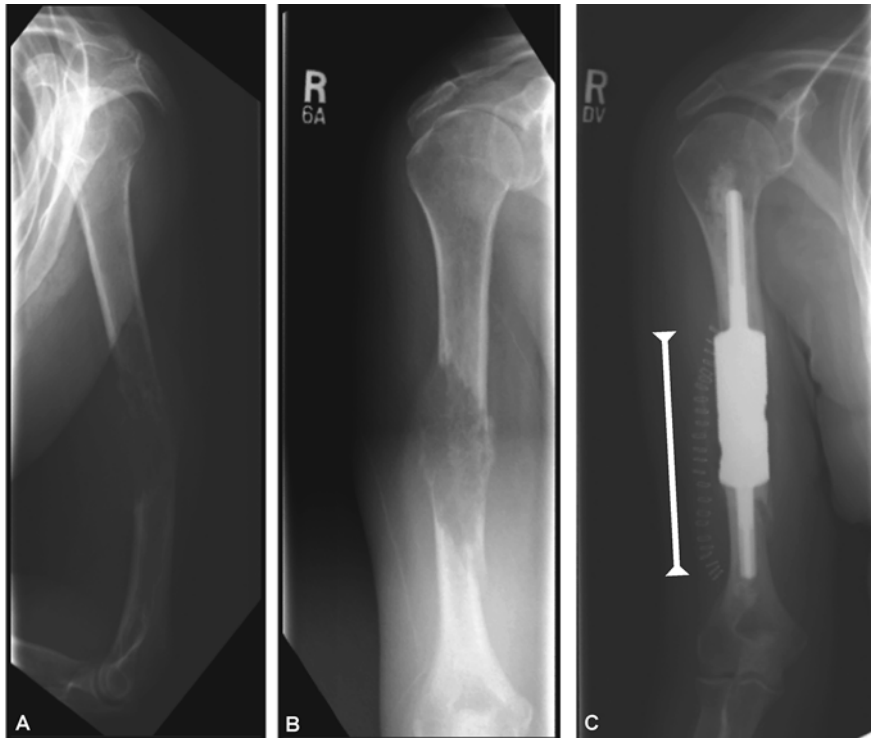

Fig. 27.6 50-year-old female with metastatic breast cancer and extensive diaphyseal bone loss (Panels **a** and **b**). Intercalary endoprosthesis was used to reconstruct the defect and allow for early motion and immediate load-bearing (**c**). Surgical exposure requires limited incision (white line) directly over osseous defect for tumor resection and intramedullary stem fixation

offset in particular lesions where alternate fixation is deemed to be high risk for failure and subsequent revision.

Scapular Metastases

Burden of Disease

Metastatic lesions of the scapula are uncommon (<3 % of all skeletal sites) [53] and reports detailing the management of these lesions in literature are scarce. In a recent report from the Scandinavian Sarcoma Group, registry data of 1195 surgically treated skeletal metastases identified 8 lesions involving the scapula [1]. This number certainly underestimates the true incidence of metastatic lesions involving the scapula but highlights the infrequency of surgical management at this anatomic location.

Non-operative Care

Given the deficiency of a standardized surgical approach for scapular metastases and the morbidity associated with surgical resection of the scapula, first-line treatment for symptomatic lesions irrespective of associated fracture status should involve radiation therapy and multimodal pain management. Failure to improve after radiation therapy or severe disability from involvement of the glenohumeral joint may justify surgical intervention.

Operative Care

Indications for the surgical management of scapular metastases include persistent debilitating symptoms after radiation, intolerable mass effect from large tumors, compromise of the

glenohumeral articulation, and in rare cases where a curative resection of an isolated scapular lesion is desired. Surgical options include partial or total scapulectomies, glenohumeral arthroplasties, intra-lesional curettage with cement augmentation (cementoplasty), and radiofrequency ablation. Rarely is forequarter amputation indicated unless there is a massively dysfunctional limb as in the setting of axillary radiation-induced lymphedema or secondary angiosarcoma.

Forequarter Amputation and Scapulectomy

Forequarter amputation for metastatic disease is technically simple, and affords the most definitive removal of local disease burden. Indications for this technique are *exceedingly rare* and should only be considered when there is extensive tumor burden involving a combination of the shoulder girdle, proximal arm, and particularly the axilla and neurovascular bundle. Surgical resection can be achieved using an anterior or posterior based approach; however an anterior based resection and closure using a posterior myocutaneous flap affords the most direct exposure of critical neurovascular structures in the shoulder girdle and axilla [54, 55]. Early complications are infrequent and include seroma/hematoma formation, wound dehiscence, and skin edge necrosis [54, 56]. The posterior flap is well vascularized and healing of the myocutaneous flap is usually not a concern, unless there has been extensive undermining of the subcutaneous layer. Prosthetic use postoperatively is uncommon, especially in the metastatic bone disease population. Cosmesis, phantom limb pain, neuropathic pain, and functional limitations are major long-term issues associated with this procedure.

Scapulectomy

Total or partial scapulectomy permits aggressive resection of scapular disease while retaining the upper extremity for preserved elbow and hand function. Like amputation, the surgical indications for these procedures in this patient population are *exceedingly rare*.

Resections of the shoulder girdle are classified based on anatomic zones of scapula and glenohumeral involvement. These resection types were described for sarcoma resections; however the general principles can be applied to resections for metastatic bone disease. Type I resections are an intra-articular resection of the proximal humerus; type II resections involve resection of the inferior, non-articular half of the scapula, where the entire scapula is resected in a type III resection; and type IV resections involve an extra-articular resection of the scapula, distal clavicle, and proximal humerus [57]. In type IV resections, also known as the Tikhoff–Linberg procedure (total shoulder girdle resection), the residual humerus is suspended from the residual clavicle or in modifications of this technique the residual humerus or a metallic proximal humerus spacer can be affixed to the ribs [58].

Depending on the type, extent of resection shoulder function and the ability to palliate are variable. Elbow and wrist function is comparable to other shoulder and proximal humerus reconstruction procedures [59–61]. Shoulder cosmesis remains a common complaint in patients after this procedure; however this can be improved using inserts and shoulder padding.

Debulking, Cementoplasty, and Radiofrequency Ablation

Forequarter amputations and scapulectomies are morbid procedures associated with poor functional results. In light of this, far less invasive procedures for metastatic lesions of the scapula are the norm. As oncologic cure is rarely the goal with these procedures, debulking procedures with or without cement augmentation can provide improved pain symptoms, restore shoulder girdle function, and be performed as outpatient surgery. This technique is especially helpful in smaller lesions around the glenoid where joint preservation is desired (Fig. 27.7).

Radiofrequency ablation of musculoskeletal lesions has gained increasing popularity over the past two decades. Using this minimally invasive technology, lesions are accurately targeted using intraoperative cross-sectional imaging modalities and heated to temperatures of 60–100 °C for approximately 1–4 min using a low-voltage, high-frequency current, which is transferred to

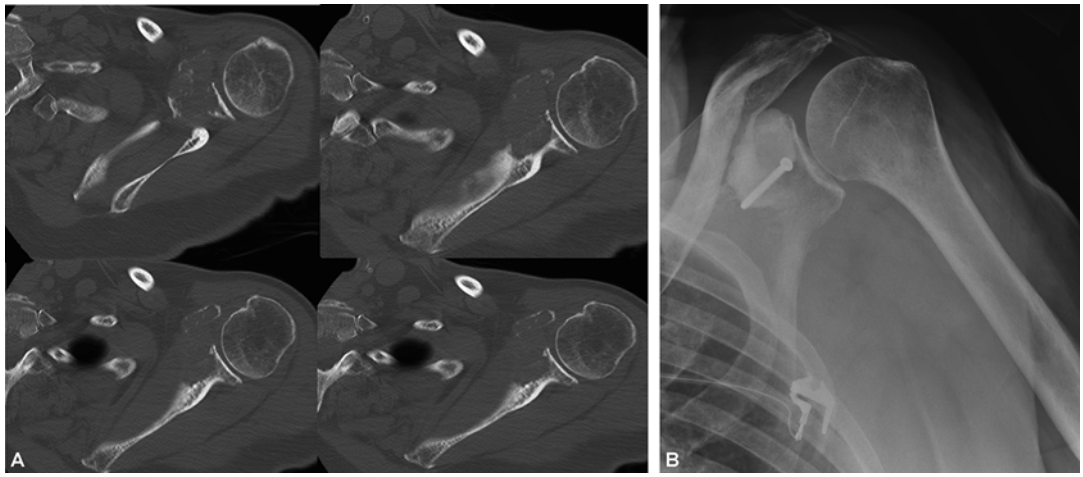

Fig. 27.7 69-year-old male presenting with severe shoulder pain secondary to a metastatic lesion of the glenoid and coracoid process (**a**). Given the limited residual glenoid bone stock available for a total shoulder arthroplasty, this lesion was treated by an open debulking procedure and cement augmentation using a screw-rebar technique (**b**)

surrounding tissues. Resistive heating around the electrodes causes immediate cell death, whereas more distal tissues are heated by thermal conduction [62]. It is generally accepted that temperatures greater than 50 °C lead to irreversible cell damage and death.

Various studies have reported favorable outcomes using this technology for symptomatic metastatic bone lesions recalcitrant to conventional external beam radiation therapy [63–65]. In one multicenter study designed with a predetermined definition of a clinically significant patient benefit, 95 % of patients experienced a meaningful reduction in maximal pain scores and a significant reduction in opioid consumption [63]. These improvements can persist beyond 3 months. Furthermore, RFA procedures can be repeated multiple times on the same lesion. In cases where lesions are in close proximity to nerves, RFA can be performed under conscious sedation to monitor nerve symptoms. In the context of metastatic lesions of the scapula, RFA is usually reserved for lesions <8 cm [64, 65] and may not be a feasible option for larger mets of the scapular body. Lesions associated with a pathologic fracture will not benefit from this technique in isolation. Further details about these concepts in general can be found in Chap. 18.

Summary

Metastatic lesions of the humerus are common and a variety of non-operative and operative treatment options are available for these patients. Unlike the femur, greater opportunity exists to manage symptomatic lesions with radiation and activity modification. Numerous surgical options are available for pathologic fractures. Scapular lesions are less common and first-line therapy should include radiation therapy. For radiorefractory cases, scapular resections are highly morbid and minimally invasive procedures such as radiofrequency ablation and cementoplasty can provide good symptomatic control.

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Metastatic Bone Disease: Forearm, Hand

28

Russell Ward

Metastases to the distal upper limb are, fortunately, uncommon. Most metastases in this region are from primary lung carcinoma. The preference for acral disease spread, though widely recognized, is poorly understood. It has been postulated that there may be a factor of increased blood flow since the majority of acrometastases occur in the dominant hand. It is thought that trauma may be a predisposing event in this situation by the same mechanism [1]. Renal cell carcinoma seems to be the next most common malignancy involving the acral skeleton and can be seen in this location as well [1, 2]. Beyond these, the remainder of distal upper limb metastases reported are related to an array of primary malignancies. The surgical management of forearm, wrist and hand metastases as well as the role for radiation therapy and other treatment modalities will be reviewed.

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Surgical Management in the Forearm

General surgical principles for the treatment of metastatic disease discussed elsewhere in this text apply to the distal upper extremity as well. As in all anatomic locations, the primary goals are early pain relief and early return to function. Non-operative treatment of metastasis to the forearm in the setting of fracture yields poor functional results [3]. Most symptomatic metastases can be treated with intralesional excision and plate stabilization augmented with methyl methacrylate (Fig. 28.1). This technique is particularly useful in the setting of impending fracture of the olecranon, proximal or distal radius, and shaft lesions. Flexible nailing may also be useful to provide stabilization for impending fracture in a minimally invasive fashion.

In the setting of oligometastatic disease, occasionally radical excision is warranted. Reconstructive modalities are limited in this location, and often necessitate the use of bulk allograft, free vascularized fibula, or custom endoprostheses. These techniques apply only on a case-by-case basis and should be reserved for those with reasonably good anticipated longevity due to the increased healing requirements and protracted recovery.

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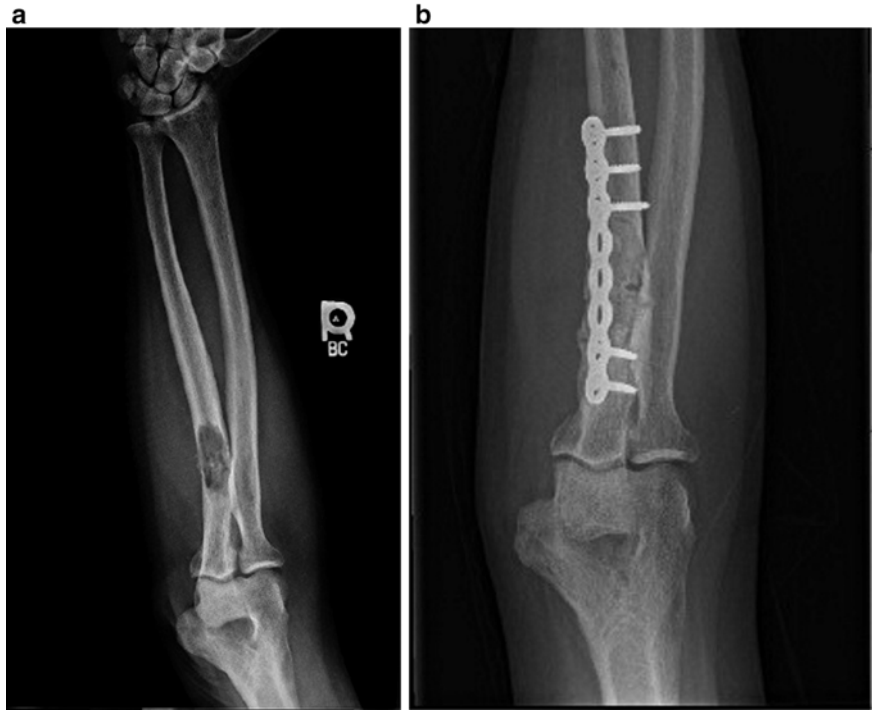

Fig. 28.1 Preoperative (**a**) and postoperative (**b**) radiographs of a 61-year-old man with metastatic lung carcinoma to the proximal ulna with minimally displaced pathologic fracture. Treatment consisted of curettage with adjuvants followed by plate stabilization augmented with cementation

Amputation is sometimes a better alternative than limb-salvage. If amputation is pursued, it should be at a level that has the best likelihood to heal without reoperation, while preserving as much function as possible, bearing in mind that nearly all of these patients will choose not to become prosthetic wearers. For distal forearm metastases requiring amputation, a trans-radial amputation can heal predictably. For proximal forearm metastases, a long trans-humeral amputation is preferred to a through elbow amputation.

Surgical Management in the Carpus and Hand

In an extensive review of the literature, the median survival of patients with metastasis to the hand was 6 months [2]. Acrometastasis is generally a finding of late-stage, disseminated metastatic carcinoma [4]. This should be borne in mind when undergoing surgical decision-making to avoid extensive periods of recovery, or disability associated with postoperative protocol. When metastasis presents in the hand, and is symptomatic enough to justify surgical treatment, ablative surgery is usually preferred (Fig. 28.2). Particularly with involvement of the phalanges, interphalangeal amputation can effectively relieve pain, heal predictably, and preserve function. With proximal phalangeal or metacarpal involvement, a ray amputation can usually be accomplished with good preservation of function as well. Ray amputation is preferred to metacarpophalangeal amputation for both functional and cosmetic reasons. For metastasis involving the thumb, interphalangeal amputation has been shown to have a better functional outcome than metacarpophalangeal amputation [5].

Metastasis to the carpus is rare, but is reported, and it has been reported to be the initial presentation of malignancy [6]. In most cases

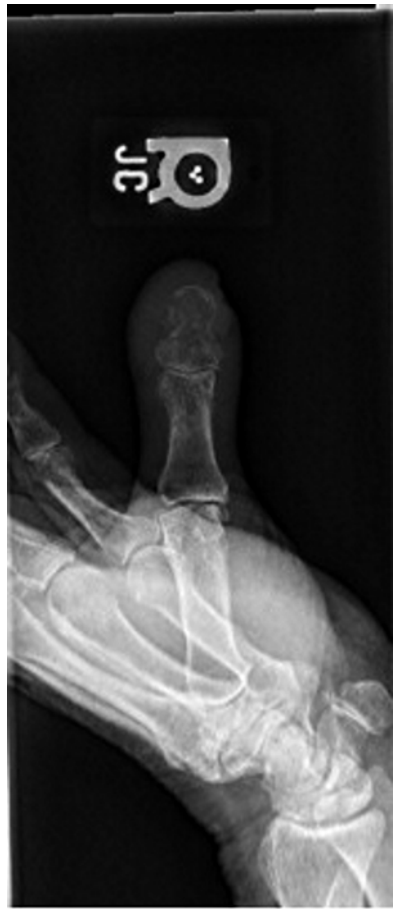

Fig. 28.2 Radiograph of a 74-year-old man with metastatic lung carcinoma to the distal phalanx of the thumb. He was treated with interphalangeal amputation

surgical treatment will be limited to excision alone, or amputation. Arthrodesis should only be considered if a radical excision is to be performed and there is no plan for adjuvant radiation therapy, as radiation can have an inhibitory effect on fusion.

Radiation Therapy for Distal Upper Extremity Metastasis

Radiation therapy applies to the palliative treatment of acrometastasis similarly to other locations of skeletal metastasis. Its use in the forearm is widely reported and mimics more common anatomic sites in both dose and fractionation. Though the tolerance of radiation in the hand is somewhat poor, its use in palliation has been reported in both fractionated treatment and single-fraction therapy [2, 7].

Alternative Therapeutic Modalities

Radiofrequency ablation and cryotherapy have both been reported in the treatment of symptomatic skeletal metastasis [8]. The role of these techniques has not been well established in the distal upper extremity. In many cases, these techniques have been utilized after prior radiation therapy. It is feasible, given the beneficial outcomes reported, that the use of these techniques may extend to distal skeletal sites, particularly when other treatment alternatives are limited.

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Metastatic Bone Disease: Spine

29

Matthew W. Colman and William Ryan Spiker

Introduction

Metastatic involvement of the spinal column is becoming more prevalent with each life-extending advance in the systemic treatment of metastatic disease. Proper care of metastatic disease of the spine demands a multidisciplinary approach taking into account the structural, neurologic, and systemic disease issues. Treatment modalities are varied, and nearly all facets of treatment have evolved considerably in the past decade. The purpose of this chapter is to review the work-up and treatment of common clinical presentations, and to critically examine the current evidence for best-practice care of metastatic bone disease to the spinal column.

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Background and Incidence

Up to 20 % of all patients with cancer will develop symptomatic metastases to the mobile spinal column [1–5]. The actual incidence of spinal disease in cancer patients, regardless of symptomatology, may be up to 90 % based on postmortem cadaveric studies [6, 7]. The skeletal system is the third most common organ site of metastatic disease behind the lung and liver and the spinal column is the most common skeletal site [8]. The majority of metastases are in the thoracic spine and extradural as opposed to intradural [9]. However, 5–10 % of all cancer patients and 40 % of those with known metastatic skeletal disease (total annual incidence of 25,000 patients in the USA) will develop epidural spinal cord compression due to progressive disease [6].

The incidence of specific tumor types metastatic to the spine roughly mirror those of other skeletal sites, with the most common histologies being breast, lung, thyroid, renal cell, prostate, and hematopoietic malignancy. According to several large studies, breast cancer appears to be both the most common metastatic spine tumor histology as well as the histology most likely to have spine metastases (Table 29.1) [10, 11].

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Table 29.1 Incidence data from two large series of metastatic carcinoma to the spine, demonstrating that breast carcinoma is both the most common of all histologies which metastasize to the spine, and also one of the most common primary histologies to later develop vertebral metastases

Histology	Percentage of all histologies in patients with spine metastases	By histology, percentage of patients with vertebral metastases on bone scintigraphy
Breast	26	60
Lung	12	43
Prostate	8	60
Thyroid	4	67
Renal cell	3	48
Unknown primary	11	NR
Sarcoma	7	NR
Hematological	6	50
Melanoma	1	35
Other	22	32
Number of patients	600	1355
Reference	Constans et al. [10]	Tofe et al. [11]

Anatomic Considerations

According to current understanding of the pathophysiology of metastatic disease, in order for metastasis to occur a complex multistep process must occur involving genetic instability, acquisition of malignant phenotype, growth of the tumor cell, extravasation from the local environment, dissemination in the circulation, adhesion in the new environment, angiogenesis, and new focal colonization. One early explanation for the relatively high frequency of prostate carcinoma metastatic to the thoracolumbar spine involves retrograde communication from the prostatic venous plexus through a valveless vertebral venous plexus which parallels the caval system, the so-called *Batson's plexus* [12]. Since the original description, this venous plexus has been invoked in explaining the pathophysiology of spinal metastasis for many different tumor types. However, if metastatic spread were predominantly along this pathway, one would expect metastatic tumor deposits to be along the course of the end venules in each vertebra, namely in the posterior and middle vertebral body. In fact, the metastatic distributions are considerably more varied, and no correlation has been found between the anatomy of vertebral venous drainage and vertebral metastatic deposits. Thus, other more complex distribution mechanisms likely exist which depend on both arterial and venous pathways, the primary tumor location, and molecular based adhesion and colonization properties [13, 14]. Other mechanisms for metastatic tumor invasion of the spine include direct local extension from organs such as the lung or kidney, or invasion via cerebrospinal fluid seeding.

The Weinstein-Boriani-Biagini system (Fig. 29.1) [15] was designed as an anatomic classification for primary tumors of the spine but is a useful descriptive scheme for any spinal lesion including metastatic foci. It allows for precise axial and radial localization of the lesion within the extra-osseus, intra-osseous, intra-canal/extradural, and intradural spaces. Although up to 95 % of metastatic spinal lesions occur extradurally [9], it is important to note that intradural or intramedullary metastases do occur [16, 17] and their treatment should involve a surgical team specifically trained in the care of intra-dural neoplasms.

Each segment of the mobile spine has unique anatomic properties and implications for the treatment of metastatic disease. For example, one should recognize that metastatic epidural compression at the spinal cord level in the zone of the cervical or thoracic spine has more serious implications for neurologic injury than nerve-root-level compression below the conus medullaris (typically caudal to L1 or L2). Different zones of the mobile spine also have different structural properties. In the cervical spine, the intrinsic mobility of each spinal motion segment may predispose to early instability-related myelopathic progression, whereas in the thoracic spine the stabilizing effect offered by the costosternal architecture may temporize instability-related pain and cord injury. In contrast, while the lower lumbar and lumbosacral spine may tolerate more spinal canal encroachment due to the root-level anatomy, bony destruction and instability may be

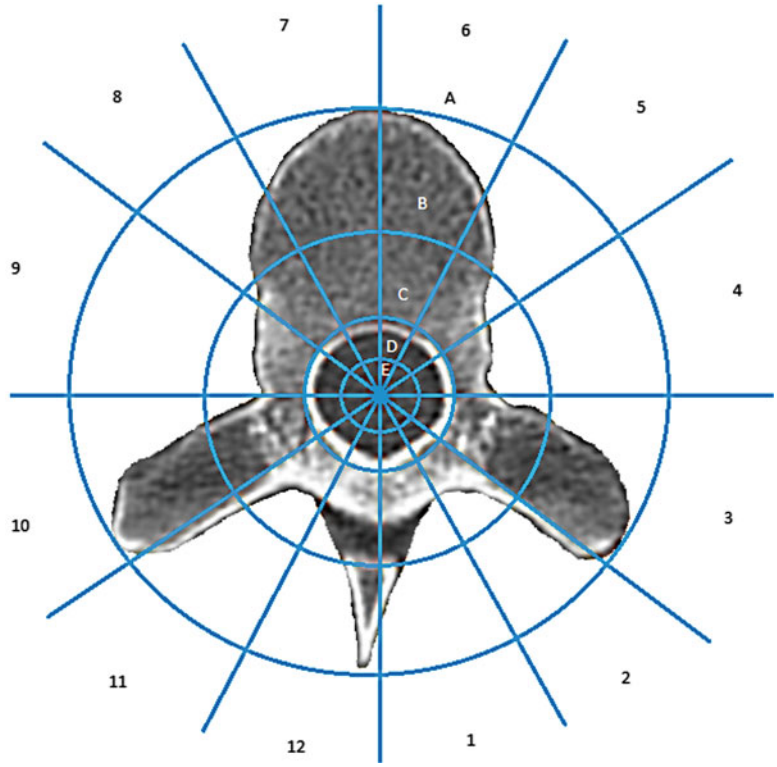

Fig. 29.1 Pictorial representation of the Weinstein-Boriani-Biagini as adapted from [15] demonstrating axial clock-face staging system of tumor involvement

particularly poorly tolerated from a pain standpoint given the high mechanical loads placed upon this region of the spine.

Another anatomic consideration is the surrounding vascular anatomy. The vertebral artery or great vessel architecture may dictate the laterality and orientation of the surgical approach. Also, one may consider preoperative angiographic mapping when planning possible sacrifice of key segmental or radiculomedullary vessels such as the Adamkiewicz artery, since their disruption could lead to spinal cord ischemia [18, 19].

Prognosis

Average life expectancy from the time of diagnosis with bony spinal metastases is short (often less than 12 months), with variation based on histology, extent of disease, neurologic status, performance status, and other factors [20–22]. Although many texts and expert opinions cite a 3-month predicted survival as a rough cutoff for surgical candidacy, no hard rules exist to define when and in whom a more aggressive approach should be pursued. In addition, there are many different surgical approaches now available, each with their own unique morbidity and mortality risks. Multiple authors have attempted to risk-stratify patients by predicted survival in order to identify a priori those who are not likely to survive for long periods of time and thus may not be appropriate for open surgical intervention. Several of the more popular scoring systems are listed in Table 29.2, along with their stratified survival data. A recent analysis of these scoring systems retrofit to a large, single center dataset identified the Bauer and modified Bauer prognostic scale as the best instruments for distinguishing between good, moderate, and poor survival prognoses [22]. While these scoring systems help predict survival for groups of patients, it should be stressed that they are merely tools to assist the

Table 29.2 Side-by-side comparison of six commonly cited prognostic scoring systems for survival after diagnosis with metastatic spine disease, along with their reported stratified survival data

System	Modified Tokuhashi	Bauer[a]	Tomita	Sioutos	Van der Linden
Patients	246	241	67	109	342
Factors	Performance status (2 for Karnofsky 80–100 %; 1 for 50–70 %; 0 for 10–40 %)	Absence of visceral metastases	Primary histology rapidity of growth (1 for slow, 2 for moderate, 4 for rapid)	Multiple vertebral body involvement	Performance status (2 for Karnofsky 80–100 %; 1 for 50–70 %; 0 for 10–40 %)
	Number of extraspinal foci (2 for 0; 1 for 1–2; 0 for >2)	Absence of lung primary	Visceral metastases (2 if treatable, 4 if untreatable)	Lung or colon histology	Histology (3 for breast; 2 for prostate; 1 for lung; 0 for other)
	Primary histology (5 for breast, prostate, thyroid, carcinoid; 4 for rectum; 3 for renal cell, uterine; 2 for tumors NOS, 1 for liver, gallbladder, and unidentified histology; 0 for lung, gastroesophogeal, bladder, pancreas)	Primary tumor "favorable" histology (renal cell, breast, lymphoma, myeloma)	Skeletal metastasis (1 for solitary, 2 for multiple)	Preoperative lower extremity motor grading of 3 or less out of 5	Visceral metastases (1 for no, 0 for yes)
	Number of metastases to spine (2 for 1; 1 for 2; 0 for >2)	Only one skeletal metastasis			
	Presence and resectability of visceral metastases (2 for none; 1 for resectable; 0 for unresectable)	Absence of pathologic fracture			
	Frankel neurologic grade (2 for normal; 1 for incomplete; 0 for complete)				
Survival Data	Score of 8 or less predicted OS <6 months	1 or less criteria had 0 % 6-month OS	Score of 2–3 had mean OS 50 months	0 negative predictors had mean OS of 18 months	6 points had mean OS of 18 months
	Score of 9–11 predicted OS >6 months	2–3 criteria had 25 % 12-month OS	Score of 4–5 had mean OS 24 months	1 negative predictor had mean OS of 11 months	4–5 points had mean OS of 13 months
	Score of 12–15 predicted OS >12 months	4–5 criteria had 50 % 12-month OS	Score of 6–7 had mean OS of 15 months	2 negative predictors had mean OS of 6 months	0–3 points had mean OS of 5 months
			Score of 8–10 had mean OS of 6 months	3 negative predictors had mean OS of 2 months	

[a]Modified Bauer does not include pathologic fracture scoring

care team in estimating survival and planning treatment. It is notoriously difficult to predict any individual patient's survival, and given the constant evolution of medical, surgical, and radiotherapies, each treatment plan should be highly individualized by the multidisciplinary care team.

Presentation and Diagnosis

Most patients with metastatic spine disease first experience back pain [23], but by the time they present for care, up to 85 % may have a true

neurologic complaint [24]. Factors which distinguish neoplastic pain from more common degenerative complaints include acuity of onset, progressive quality, night pain, accompanying constitutional symptoms, weight loss, or other suggestive disease-specific symptoms such as a breast mass, goiter, or hematuria. Carefully distinguishing rest or night pain from activity-related mechanical pain is especially important because the latter may indicate mechanical instability. A detailed neurologic exam should be performed by a qualified practitioner versed in care of the spine and should include examination of sharp, dull, and light touch sensation, motor grading, and reflex evaluation. Ambulatory status and a sensorimotor level should be established if applicable. Radiculopathy should be distinguished from myelopathy or frank spinal cord injury. Signs of myelopathy such as gait dysfunction, difficulty with fine motor coordination, hyperreflexia, and bowel or bladder dysfunction may be subtle and should be carefully investigated.

Since up to 20 % of *initial* presentations of metastatic disease will present with a spine-related complaint [25], physicians caring for the spine should be familiar with the general work-up of metastatic disease. In the presence of multiple skeletal metastases of unknown origin, history and physical exam along with computed tomography scans of the chest, abdomen, and pelvis identify nearly 80 % of primary tumors [26]. Further advanced imaging, specialized laboratory tests, and biopsy modalities may ensue if the diagnosis continues to be in doubt.

Great care must be taken when one encounters a solitary aggressive-appearing neoplastic lesion of the spine. Although metastatic disease is possible and is indeed amongst the more likely entities, one must also consider that the lesion could be a primary malignant tumor of bone. Intralesional excision or unplanned biopsy in this setting can have disastrous consequences and make future treatment difficult. Table 29.3 lists common entities in the differential diagnosis for a solitary neoplastic lesion of the bony spine.

Imaging

Initial imaging should consist of upright standing full-length scoliosis-style films of the spine in the coronal and sagittal planes. This allows for visualization of the symptomatic area in question, other abnormal areas which may be asymptomatic, and for an assessment of coronal and sagittal alignment. The latter become important when assessing tumor-related instability and in planning reconstructive surgery. If standing films are not obtainable due to patient intolerance, full length sitting films may substitute. It should be noted that plain films typically detect bony destruction only in the late, progressive state, for example when more than 50 % of the vertebral bone has been replaced [27]. For context, the classically described "winking owl" sign, or loss of the pedicular density on AP radiographs, usually can't be seen unless nearly the entire pedicle cortex had been replaced by tumor.

Technetium-99 scintigraphy and in some cases fluorodeoxyglucose positron emission tomography (FDG-PET) scanning may contribute to systemic disease staging, but are not usually first-line modalities in the work-up of metastatic disease to the spine. They are sensitive but not specific for metastatic disease. The most useful advanced imaging modalities in the spine are computed tomography (CT) and magnetic resonance (MR) imaging. The former is useful in demonstrating detailed bony architecture and as such is able to identify subtle pathologic fracture or corticocancellous destruction earlier than plain radiographs, bone scanning, or MR. In addition, CT may demonstrate intralesional calcifications in the case of chondrosarcoma or chordoma, phleboliths and normal intervening marrow architecture in the case of hemangioma, and other tumor-specific findings. For metastatic disease in general, it is best used to understand the extent of bony destruction. The main disadvantage is the relatively large amount of ionizing radiation exposure.

Conversely, MR is an excellent soft-tissue imaging modality which emits no ionizing radiation and should be used liberally to delineate

Table 29.3 Most common differential diagnoses when encountering a solitary neoplastic-appearing lesion in the spine, along with imaging hallmarks and other diagnostic aides

Entity	Imaging hallmark	Diagnostic aids
Malignant primary neoplasms		
Chordoma	Lobular T2 hyperintensity on MRI; intralesional calcifications on CT	Tissue confirmation
Osteosarcoma	Malignant osteoid matrix	Tissue confirmation
Chondrosarcoma	Intralesional calcification on CT	Tissue confirmation
Ewing Sarcoma	Permeative cortical bone destruction	Tissue confirmation
Systemic malignancies		
Myeloma	Purely lytic; systemic disease evident on skeletal survey; usually "cold" on bone scan	Protein electrophoresis
Lymphoma	Permeative cortical bone destruction	Peripheral blood smear; flow cytometry
Metastatic carcinoma	Lytic, blastic, or mixed appearance	History and physical exam; CT chest/abdomen/pelvis
Benign aggressive primary neoplasms		
Osteoblastoma	Diffuse inflammatory reaction; intense corticocancellous bone reaction; posterior element location	Tissue confirmation
Giant cell tumor of bone	Lytic destructive appearance; vertebral body location	Tissue confirmation
Aneurysmal bone cyst	Fluid-fluid levels on T2 weighted MRI; posterior element location	Tissue confirmation
Benign quiescent primary neoplasms		
Osteoid osteoma	Nidus sometimes evident on CT; intense corticocancellous bone reaction; posterior element location	Imaging; night pain relief with prostaglandin inhibitors
Hemangioma	Speckled appearance on MRI and CT with intermittent normal intralesional marrow signal	Imaging
Nonneoplastic entities		
Degenerative cyst	Endplate sclerosis and involvement of both sides of disc	Imaging
Bone island	Geographic cortical density on XR and CT	Imaging
Bacterial infection	Originates in or crosses disc space	Imaging; tissue culture

the extent of metastatic disease and its relation to the neural elements. We recommend MR imaging of the entire spinal column when confronted with a spinal neoplasm, as this is a sensitive and specific modality for identifying synchronous lesions [28], and helps with treatment planning. Generally speaking, it is advantageous to use intravenous gadolinium contrast to aid visualization of tumor vascularization and help differentiate solid vascularized tumor from cystic necrosis, scar, or fluid-filled cavities. MR can also be helpful in differentiating de novo or recurrent metastatic bone disease from osteoporotic compression fractures or radionecrosis [29–32].

Biopsy

If the diagnosis is in doubt after thorough noninvasive work-up or if the lesion is solitary, biopsy should be strongly considered. We and others [33] feel that the best outcomes occur when the biopsy is performed by experienced interventionalists or proceduralists at the final treating institution, as part of a multidisciplinary treatment plan that takes into account the expected histology and the likely surgical approach for resection.

While fine needle aspirate may demonstrate neoplastic cells, it does not offer preservation of tissue architecture and thus CT-guided core-needle

biopsy has become the standard modality. This is typically performed via a posterior transpedicular approach and is useful for most vertebral body tumor locations except for those posterior central locations where access is difficult. Cultures should be sent from most tumor biopsies to rule out infection, and depending on the expected histology, advanced histopathologic techniques can be employed such as with flow cytometry in lymphoma. Needle biopsy of the spine through hollow viscera or along tracts of tissue that cannot be readily excised during definitive surgery is discouraged given the theoretical concern for needle tract contamination and tumor cell implantation.

Open biopsy may be required in the case of equivocal needle biopsy results or progressive neurologic deficit requiring urgent concomitant decompression of the neural elements, but this procedure should be undertaken with great care given the potential for tumor contamination and compromised future treatment options.

Metastatic Epidural Spinal Cord Compression

Metastatic epidural cord compression is a clinical scenario that deserves separate commentary because of the propensity for permanent neurologic injury and disability. Compression of the neural elements can generally occur via three mechanisms: direct tumor compression, bony retropulsion or deformity due to pathologic fracture, or more rarely, impingement from osteoblastic bone response. The Spine Oncology Study Group [34] has laid out an anatomic classification system of metastatic epidural spinal cord compression (MESCC) based on axial T2 MRI that can be broken down into six categories: grade 0 (bone only), grade 1a (tumor in epidural space but no thecal sack compression), grade 1b (thecal sack compression but no touching cord), 1c (cord abutment without deformation), 2 (cord deformation with some surrounding cerebrospinal fluid (CSF) visible), and 3 (no remaining visible CSF). It is impossible to direct treatment based on this or any other one classification system alone because of the interaction of other factors such as the neurologic exam and mechanical instability, but the authors suggest tumors which fall into the latter two grades be considered "high grade" and require open surgical decompression prior to radiotherapy given the proximity of tumor to neural elements. Conversely, they suggest other grades be considered for radiotherapy prior to surgery in the absence of mechanical instability.

Treatment Overview

Since the life expectancy of patients with metastatic disease to the spine is short, the goals of treatment are typically palliation of pain, maintenance of ambulatory function via preservation of spinal stability, and optimization of quality of life. In certain settings, goals may also include optimization of neurologic recovery or local tumor control. Three patient specific factors should be considered when selecting the most appropriate treatment: the neurologic status, the mechanical stability of the spine, and the systemic status of disease. Aspects of this framework have been widely described, but a treatment algorithm based on the NOMS (neurologic, oncologic, mechanical, and systemic) framework was recently crystallized by Laufer et al. [35], and forms the basis for the adapted treatment framework we lay out in Fig. 29.2. Rather than presenting a rigid algorithm, we present positive prognostic factors in each of the three domains which help inform the invasiveness of intervention along the displayed hierarchy of possible treatments. As has been stated, treatment should be highly individualized, and many factors contribute to selecting the most appropriate course.

The neurologic status of the patient forms the basis of the acuity of treatment, and the presenting neurologic status is one of the best predictors of posttreatment neurologic status [36]. Although the optimal timing of treatment for vertebral metastases has yet to be defined, it intuitively follows that treatment is most advantageous prior to progressive neurologic involvement, when

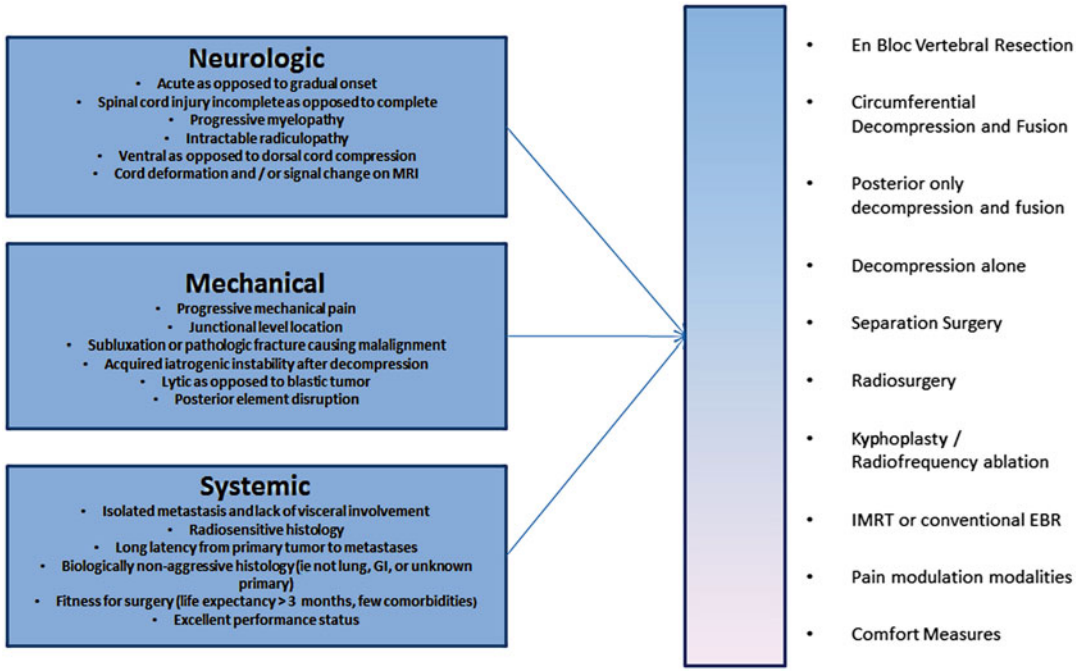

Fig. 29.2 Hierarchical representation of treatment options as dictated by neurologic, mechanical, and systemic disease factors. Sub-modifiers under each domain are positive prognosticators for more invasive surgical treatment, and move the patient higher on the hierarchy of treatment options. Final treatment planning should always be carried out between the individual patient and the multidisciplinary team

options become more limited. In a prospective audit by the Scottish Cord Compression Study Group of 319 patients who developed malignant cord compression, the median time interval between back pain in cancer patients and development of neurologic symptoms was 66 days [37]. Thus, the patient's neurologic condition should be carefully established. For those patients with an evolving or progressive neurologic deficit, urgent surgery within 48 h of the onset of symptoms [38] seems to result in the best neurologic outcomes. An urgent operative intervention in this clinical setting is also supported by various studies in the traumatic spinal cord injury literature [39]. In the case of an evolving, cord-level neurologic deficit it is our practice to intervene with surgical decompression immediately or as soon as the patient can be medically optimized for surgery.

The mechanical stability of the spine is also a major consideration in planning treatment, and it becomes the principle issue when no neurologic deficit exists. Clinical signs of impending or frank mechanical instability include abrupt new axial or radicular pain, especially that which worsens with activity. Severe cases may present with changes in clinical alignment such as with horizontal gaze in the cervical spine or ability to stand upright in the thoracolumbar spine. Multiple studies have attempted to identify risk factors for thoracolumbar instability using finite element, biomechanical, cadaveric, and clinical designs. These are outlined in Weber's recent systematic review [40]. Consistent factors which seem to predict higher risk for compression or burst fracture in the thoracolumbar spine include larger tumor volume, location of tumor in the pedicles and other posterior elements, loss of integrity of the ribcage or costovertebral junction, poor baseline bone mineral density, baseline sagittal imbalance, and high spinal loads such as with obesity and strenuous activity. Combining consensus expert opinion with published data, the Spine Oncology Study Group recently created a

Table 29.4 Spine Oncology Study Group scoring system for predicting mechanical instability due to metastatic disease in the spine, as adapted from [41]

Factor	Subcategory		Score
Tumor location	Junctional	Occiput–C2	3
		C7–T2	3
		T11–L1	3
		L5–S1	3
	Mobile	C3–C6	2
		L2–L4	2
	Semirigid	T3–T10	1
	Rigid	S2–S5	0
Alignment	Subluxation		4
	Baseline sagittal/coronal imbalance		2
	No deformity		0
Pain	Mechanical		3
	Occasional nonmechanical		1
	None		0
Vertebral collapse	>50 %		3
	<50 %		2
	Pre-collapse (>50 % of body involved)		1
	None of the above		0
Tumor type	Lytic		2
	Mixed		1
	Blastic		0
Posterior element involvement	Bilateral		3
	Unilateral		1
	None		0

Scores from 0 to 6 indicate stability, scores from 13 to 18 indicate instability, and scores from 7 to 12 are indeterminate

novel scoring system for predicting spinal instability (Table 29.4, adapted from [41]). While no prospective validation of this schema has been performed, it appears to be a reliable and retrospectively validated scoring system [42, 43], with scores from 0 to 6 predicting stability, scores from 13 to 18 predicting instability, and scores from 7 to 12 having indeterminate stability.

The systemic status of disease is a broad category that forms the third consideration when planning treatment. Tumor biology is a principal consideration. The categorical aggressiveness of the histology is one factor, with lung, gastrointestinal, and carcinoma of unknown primary typically cited as the most aggressive. However, for any histology, multiple studies have identified the presence of visceral and other skeletal metastases as risk factors for poor survival duration [44–48], while isolated spinal metastases are thought to portend a better prognosis and may be more appropriate for aggressive treatment. In addition, the latency of metastasis from primary tumor treatment is important because short latencies may indicate a biological aggressiveness which portends a poor survival duration regardless of the histology. Radiosensitivity of the tumor is another tumor biology factor which helps inform the contribution of various radiation modalities to treatment. Lastly, the medical comorbidities and overall performance status of the patient help guide treatment by changing the risk/benefit ratio of invasive or cytotoxic therapies.

Systemic Medical Treatment

Although metastatic spinal disease frequently causes *local* mechanical or neurologic issues, it is important to remember that metastatic disease is, oncologically speaking, a *systemic* problem. Systemic therapy is usually directed by the medical oncologist in conjunction with the multidisciplinary surgical team. The range of first and second-line therapeutics for stage IV carcinoma is protean, but can be generally classified into cytotoxic, targeted, and immunologic chemotherapy. There are other chemotherapy options, however, which are not themselves antitumor but instead address the secondary effects of disease. One subclass of these drugs includes bisphosphonates, which may temporize osteoclast-mediated bony destruction and improve tumor-related pain. Others include corticosteroids for their anti-inflammatory and neuroprotective properties, as well as opioids and nonsteroidal anti-inflammatory medications for their pain-modulatory effects.

Radiotherapy

Radiotherapy plays an important role in the treatment of metastatic spinal disease, and can be thought of in three contexts: as definitive therapy,

as combination therapy before surgery, and as combination therapy after surgery. There are a wide range of clinical contexts in which radiotherapy can be used, ranging from bone-only lesions which cause pain but no instability or neurologic symptoms, to lesions which cause instability and epidural spinal cord compression. There are also multiple different modalities which have clinical relevance, including conventional external beam radiotherapy (EBRT) and 3-D conformal modalities such as intensity modulated radiotherapy (IMRT) and stereotactic radiosurgery (SRS). These modalities differ primarily in their practical availability and their ability to control radiotoxicity to surrounding healthy tissues including the neural elements of the spinal cord. These toxicities are many and range in severity from mild mucositis or fatigue to radionecrosis-induced vertebral fracture or radiation-induced myelopathy.

A primary consideration is the relative radiosensitivity of the metastatic histology. While to some extent any tumor histology can be killed if the radiation dose is high enough, certain histologies are more responsive to ionizing radiation than others, and thus offer a better dose response-toxicity profile. Table 29.5 describes the relative radioresponsiveness of common metastatic histologies (adapted from [49]). Any favorable histology without neurologic deficit or instability can be considered for radiotherapy as a stand-alone treatment given the functional and pain-modulatory benefits [50]. However, in the presence of epidural cord compression or mechanical instability, unless the patient is medically unfit for surgery or the histology in question is exquisitely sensitive to radiation, a combined approach using surgery and radiation is preferable [51, 52].

Table 29.5 Relative radiosensitivities of common histologies which metastasize to the spine, as adapted from [49]

Histology	Relative radioresponsiveness
Lymphoma	+++
Myeloma	+++
Seminoma	+++
Small-cell lung	++
Breast	+
Prostate	+
Ovarian	+
Neuroendocrine	+
Renal	–
Thyroid	–
GI	–
Sarcoma	–
Non-small-cell lung	–
Melanoma	–

Conventional external beam radiotherapy is now most often delivered in 8–10 fractions to approximately 25–40 Gy in total dosing. Many different variations of this schedule have been reported, including single high-dose or two-dose scheduling without a major difference in functional outcome [53]. Although controversial, some studies suggest a more durable tumor control effect with longer course scheduling [54]. In addition, the temporary side effects of higher frequency/smaller dose scheduling such as mucositis or dermatitis may be less. However, patients with longer life expectancies and favorable histologies are more likely to be treated with an extended course, introducing a significant selection bias into the available studies.

Higher quality studies are available which examine conventional EBRT as a stand-alone treatment vs. EBRT in combination with surgery for spinal metastases causing spinal cord compression and instability. Outcomes have been disappointing with stand-alone treatment, with only 19–33 % of non-ambulatory patients regaining ambulatory ability, and only 60–74 % maintaining ambulatory ability after stand-alone conventional EBRT [51, 55, 56]. Pain palliation is also unpredictable, with only half of patients reporting an improvement in pain after stand-alone EBRT [53].

SRS is another radiotherapy modality which is an option as stand-alone therapy or for use in combination with open surgery. Reported data suggest very high levels of tumor control (up to 88 % with median 21-month follow-up) and improvement of tumor-related pain (85–100 %) [53]. Benefits include the ability to deliver high doses of radiation to very specific tissue volumes, which limits dose toxicity to surrounding

structures such as the spinal cord or adjacent non-involved vertebrae. Data show high levels of efficacy with single-dose administration, and less dependence on histology for therapeutic effect than conventional EBRT [49]. For example, some studies have shown long-term local tumor control for classically insensitive histologies such as melanoma or renal cell carcinoma as high as 75–87 %. Disadvantages include cost, availability, and the fact that for high-grade cord compression, even the accuracy of dose delivery SRS offers is usually not enough to preclude open surgical decompression.

Recent reports have described using SRS or IMRT in the adjuvant setting after limited open posterolateral decompression of the spinal cord [35]. The theory behind "separation surgery" is to perform a limited posterior and anterior decompression via a posterolateral approach to create a margin of tumor-free space around the spinal cord in preparation for postoperative cytotoxic radiosurgery. In separation surgery the intervertebral discs are usually not removed and the anterior column is typically not reconstructed. The surgical approach typically avoids an extended exposure, aggressive tumor resection, and excessive blood loss, and is thus thought to be less morbid than definitive anterior vertebral tumor resection and reconstruction. Laufer et al. describe a retrospective cohort of 186 patients who underwent separation surgery for high-grade metastatic spinal cord compression, and found a low cumulative incidence of tumor progression at 1 year (4.1 %) when high-dose (24–30 Gy) hypofractionated regimens were used [35]. Failure of posterior instrumentation appears to be low (2.8 %) despite not reconstructing the anterior column [57].

A final consideration is of the order of treatment when radiotherapy is used in conjunction with surgery. Conventional wisdom holds that preoperative radiation leads to more wound complications but involves a smaller radiated field and therefore lower cumulative dose [58–60]. For spine metastases specifically, there is a paucity of high-quality evidence to answer the question of whether or not to radiate pre- or postoperatively, and what time interval should lapse between the two modalities in either scenario. Based on weak evidence, one recent review recommends that radiation is delivered either before or after surgery but not within 1 week of the surgical date [58].

Percutaneous Interventions

Vertebroplasty (percutaneous transpedicular cement injection into the vertebral body midsubstance) and kyphoplasty (cement injection after percutaneous transpedicular balloon tamping of an intravertebral cavity) are minimally invasive options to restore substance and shape to vertebral bodies which have collapsed due to pathologic fracture. Kyphoplasty is largely reported to affect a lordotic change of 4–6° and a restoration of vertebral height around 4–5 mm [61]. These techniques also potentially offer adjuvant thermal necrosis of tumor cells during the cement curing process. They are predominantly indicated for mechanical pain due to acute fracture, and are contraindicated in the presence of spinal cord compression, as well as cortical destruction that could lead to cement extravasation or bone or tumor retropulsion into the neural elements such as with posterior body or pedicular tumor breach. This said, kyphoplasty offers a more controlled delivery of cement than vertebroplasty due to use of a balloon bone tamp. In a recent large prospective multicenter study, kyphoplasty compared with nonsurgical management for tumor-related acute vertebral compression fractures showed a significant benefit in multiple outcome measures such as Roland-Morris Disability Questionnaire, Karnofsky Performance Status, multiple SF-36 domains, and days spent in bed or with reduced activity [62]. Because of crossover from the nonsurgical group after 1 month, the 12-month endpoint analyses were as-treated in nature, but largely showed a durable benefit. It is important to note that these results were in patients with imaging and exam findings consistent with an acute fracture. These findings support previous work from single center institutions showing

durable pain reduction after vertebroplasty or kyphoplasty compared with nonoperative care, without a high risk of clinically significant adverse events [61]. Lastly, other authors have described percutaneous transpedicular radiofrequency ablation, which can be used with or without kypho/vertebroplasty [63].

Minimally Invasive Open Surgical Therapy

Less invasive posterolateral instrumentation techniques using percutaneous pedicle screw instrumentation were designed to take advantage of the biomechanical strength of segmental spine instrumentation without the attendant surgical trauma of the wide dissection typically used for their insertion. With lower rates of wound healing problems and infection, this technique has potential benefit in the metastatic disease setting because it may allow more patients to advance postoperatively along the therapeutic algorithm to adjuvant radiotherapy and/or systemic chemotherapy. Disadvantages include the inability to expose and decompress the neural elements and less ability to obtain a bony posterolateral fusion compared with open technique. Thus, this technique is most applicable as stand-alone instrumentation for mechanical pain or deformity without cord or root compression in patients who are not expected to survive on the order of years (since long-term nonunion inevitably leads to hardware failure). In addition, it can be used as a posterior tension band after anterior decompression, reconstruction, and fusion via a separate approach, either open or thoracoscopically [64, 65]. Kim et al. reported on 16 patients with 3–6-month life expectancy who underwent palliative percutaneous screw fixation across a single pathologically fractured vertebra. In this cohort of patients, pain scores were significantly improved, and 44 % had an improvement in their ECOG performance status postoperatively while 81 % did no worse. In addition, the instrumentation was able to correct a peri-fracture kyphotic angle by nearly 11° [66].

Open Surgical Intervention Overview

Open surgical decompression and stabilization has become the standard of care in medically fit patients who have MESCC with or without mechanical instability. In their landmark prospective multicenter study, Patchell et al. showed that patients with a heterogenous set of tumors undergoing direct surgical decompression followed by postoperative radiotherapy compared with radiotherapy and nonoperative care had a higher likelihood of regaining and maintaining the ability to walk, higher rates of maintaining urinary continence, higher rates of maintaining neurologic function scores, and even a slightly longer median survival time [51]. Since then, multiple other studies have confirmed this effect, the results of which are combined in a recent meta-analysis [67].

Generally, the goals of open surgery are decompression of the neural elements, deformity correction, and stabilization, with or without biopsy depending on the need for a tissue diagnosis. While the spine can be accessed and decompressed throughout its length via a standard posterior subperiosteal approach and midline laminectomy, there are a variety of specialized anterior and lateral approaches to the spine which may be used depending on the surgeon training as well as the level and axial location of pathology. In addition, while segmental pedicle screw fixation has become the standard of care for posterior instrumentation, there are a wide variety of vertebral body replacement techniques that can be used to reconstruct the anterior and middle columns of the spine. Generally speaking, for cord level lesions, all available intraoperative aides should be utilized including multimodal neuromonitoring, spinal traction, meticulous maintenance of tissue oxygenation, and maintenance of mean arterial pressures greater than 80 mm/Hg.

Vertebral body reconstruction may be accomplished using a variety of media, including PMMA alone or PMMA/Steinmann pin combinations, titanium expandable or mesh cages, other synthetic cages using materials such as PEEK,

or bone options such as structural autograft or allograft. Expandable cages are especially useful in situations where a relatively large defect must be reconstructed but access for insertion is limited, such as with costotransversectomy. Biologic reconstructions involving allograft or autograft are most appropriate for reconstruction in clinical settings where biologic fusion is possible, such as cases in which radiation will not be used and in nonsmoking patients with longer life expectancies. However, the fact remains that the evidence for superiority of any one technology or biologic is lacking, and most surgeons use a variety of implants based on many factors including surgical approach, life expectancy, chance of bone fusion, personal experience, training, cost, and other issues.

Margin of Tumor Resection

Since metastatic tumors by definition represent systemic disease which cannot be eliminated or cured by local methods, intralesional resection is commonly performed. However, gross total resection with adjuvant chemo- or radiotherapy is ideal around the neural elements since postoperative local disease progression may cause recurrent neurologic symptoms and need for revision surgery. The one exception to an intralesional margin goal may lie with those patients who present with isolated or few metastases. For histologies such as renal cell or melanoma, authors have reported improved survival rates with complete metastasectomy in carefully selected patients [68–70]. In the spine specifically, other authors have used wide resection techniques such as total en bloc spondylectomy for oligometastatic disease with success, although the potential for selection bias is high and the quality of evidence for using this technique over intralesional resection is low [71–73].

Occipital-Cervical Junction

The region from the occiput to C2 presents special challenges because of the unique structure of the occipito-atlanto-axial articulations and surrounding vascular anatomy. The posterior elements of the occiput, C1 ring, and C2 lamina can be easily removed in standard fashion if posterior compression occurs. However, in the case of compression or instability anterior to the spinal cord, the options are less routine. Subtotal curettage for tumor removal can be accomplished at the anterior aspects of C1 and C2 via a trans-oral approach with acceptable rates of morbidity [74]. For larger en bloc resections or spondylectomy of C1 or C2, mandible splitting or other mandibular osteotomy-type approaches may be necessary, however these approaches carry significant osseous, pharyngeal, and pulmonary morbidity. If an anterior approach is not desired but vertebral body access to C2 is required, a posterolateral transpedicular approach has been described [75].

Reconstruction of the occiput-C1-C2 junction largely relies on posterior instrumentation and few reconstructive configurations are based on stand-alone anterior fixation. To reconstruct the dens and C2 body, anterior options include polymethyl-methacrylate (PMMA) with or without Steinman pins, structural allograft, or metal cage reconstruction with or without plate fixation [76]. When the occiput-C1 articulations are disrupted by tumor, biomechanical stability is most dependent on the integrity of the transverse ligament and C1 lateral mass articulations, and thus reconstructive efforts are best performed along the lateral columns [77].

Subaxial Cervical Spine and Cervicothoracic Junction

In the subaxial spine to the level of T1, anterior cord compression is readily addressed using corpectomy, discectomy, or hybrid constructs via a standard Smith-Robinson approach. The zone from T2-T5 presents greater access challenges and may require formal midline sternotomy, partial sternotomy via the "trap door" exposure, or other alternatives, especially when concomitant pulmonary or mediastinal access is required [78, 79]. An alternative to the surgical morbidity of these approaches involves a posterior-only decompression via costotransversectomy, which provides excellent access to the anterior vertebral

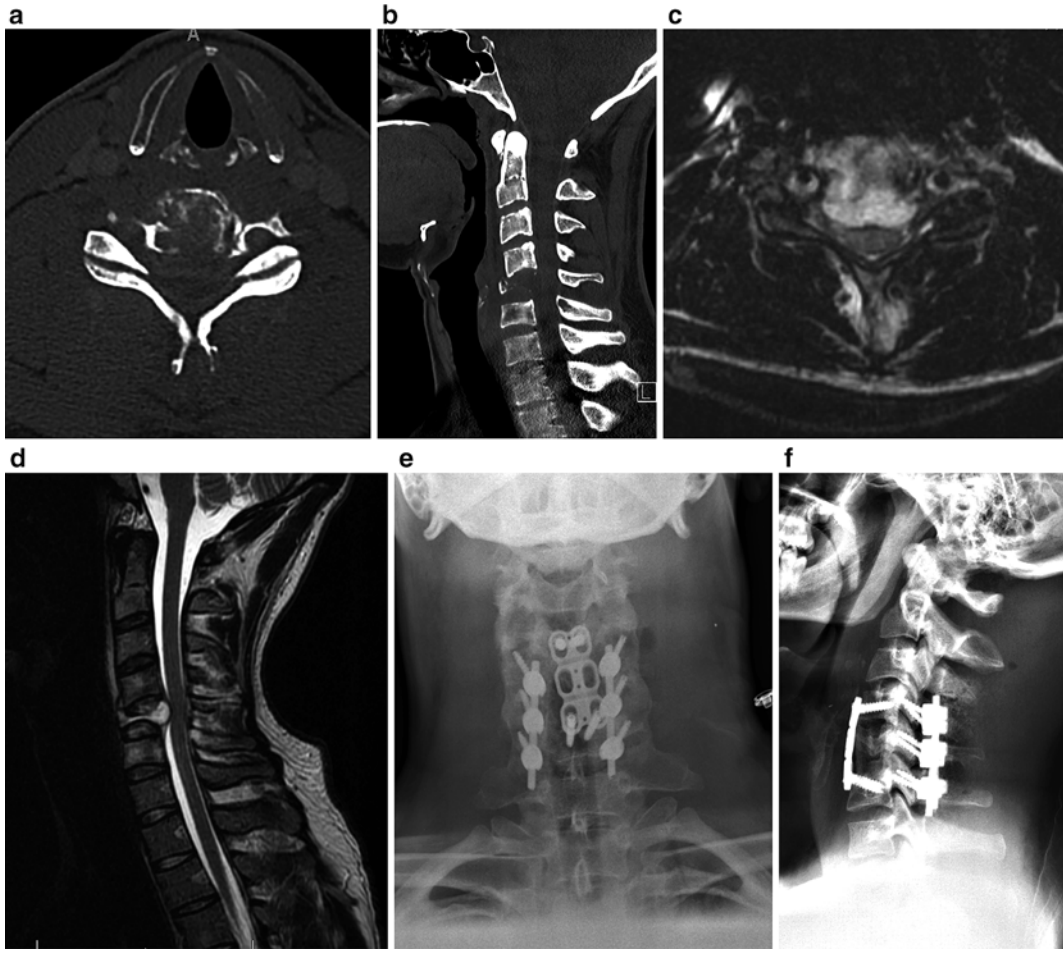

Fig. 29.3 Case example with preoperative axial (**a**) and sagittal (**b**) CT scan imaging showing nearly complete destruction of the C5 vertebral body by metastatic melanoma, with subluxation of C4 on C6. In addition, corresponding axial (**c**) and sagittal (**d**) T2-weighted MRI imaging showing spinal cord compression. Postoperative AP (**e**) and lateral (**f**) radiographs are also shown, with circumferential reconstruction involving tricortical iliac crest allograft

body but not necessarily to the lung, mediastinum, or great vessels when tumor involves extraosseous structures. When considering the costotransversectomy approach in the upper thoracic spine, consideration should be given to the rare but described postfixed brachial plexus, where the T2 nerve root contributes to hand intrinsic and upper extremity sensory function.

Figure 29.3a–d shows the presenting axial and sagittal computed tomography scans and T2-weighted MRI scans of a 24-year-old male patient who presented with neck pain and myelopathy 2 years after excision of a primary cutaneous melanoma. He had been treated for groin nodal metastases 6 months prior, but at the time of presentation had an ECOG performance status of 0 and no other known visceral or bony metastatic sites. Given his myelopathic symptoms, ISOSG grade 2 compressive cord-level lesion, and mechanical instability, he was indicated for surgical decompression and reconstruction. This consisted of anterior cervical corpectomy of C5, tricortical iliac crest allograft reconstruction, and anterior plating, with staged posterior cervical instrumented fusion from C4–C6 (Fig. 29.3e, f).

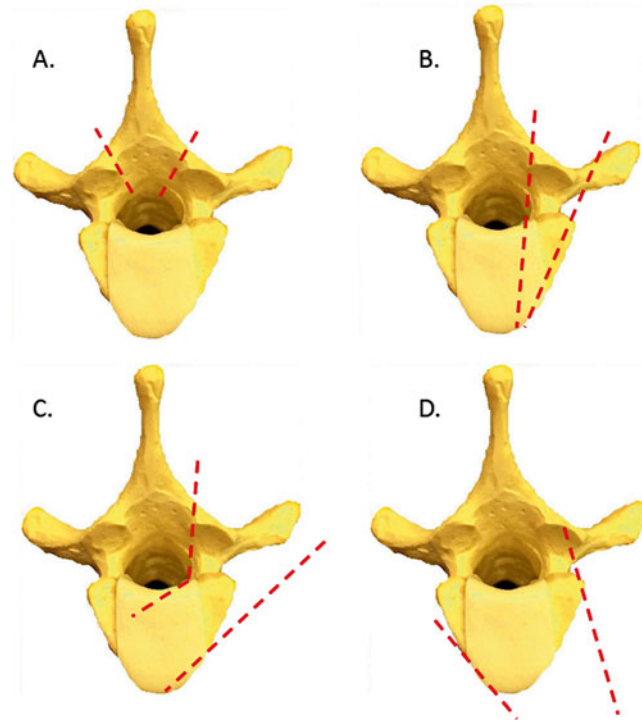

Fig. 29.4 Pictorial representation of a T7 vertebra with superimposed bony resection and visual fields (*red dashes*) provided by (**a**) midline laminectomy, (**b**) transpedicular decompression, (**c**) costotransversectomy, and (**d**) thoracotomy

Thoracic Spine

In the thoracic spine below T5, there are multiple posterior, lateral, and anterior approaches that allow decompression of epidural disease. Figure 29.4 demonstrates a schematic of posterior laminectomy access as compared with several extracavitary and transcavitary options. Advantages of posterior-only approaches include the convenience of single-stage, single-incision, and single-surgical team surgery, without major differences in reported complication rates. Advantages of trans-cavitary surgery via a formal anterolateral thoracotomy include better access to the entirety of the anterior vertebral body as well as intrathoracic extra-osseous structures. Reconstruction of the anterior thoracic spine may be accomplished using any of the previously described vertebral body replacement techniques. Posterior instrumentation is commonly added to restore the tension band properties of the posterior ligamentous complex, to support anterior column hardware, and to add overall construct stiffness in the setting of radiotherapy and anticipated bony nonunion.

Figure 29.5a–d demonstrates the preoperative axial and sagittal T2 weighted MRI and CT scans of a 70-year-old male who presented with 2 months of increasingly severe mechanical mid-thoracic back pain. Systemic imaging demonstrated multiple other sites of bony and visceral disease, including the suspected primary tumor site shown in Fig. 29.5e, and a biopsy was consistent with non-small cell carcinoma of the lung (squamous cell type). He was neurologically normal. After a frank discussion of the risks and benefits, the patient elected to undergo surgical decompression and stabilization consisting of a decompressive posterior hemilaminectomy and left sided costotransversectomy at T8 and T9, tumor curettage, and reconstruction with posterior instrumentation from T5–T12 and an anterior titanium expandable cage. An intraoperative photograph shown in Fig. 29.5f demonstrates the decompressed spinal cord (black arrow) and the anterior cage reconstruction (white arrow). Postoperative radiographs are shown in Fig. 29.5g, h.

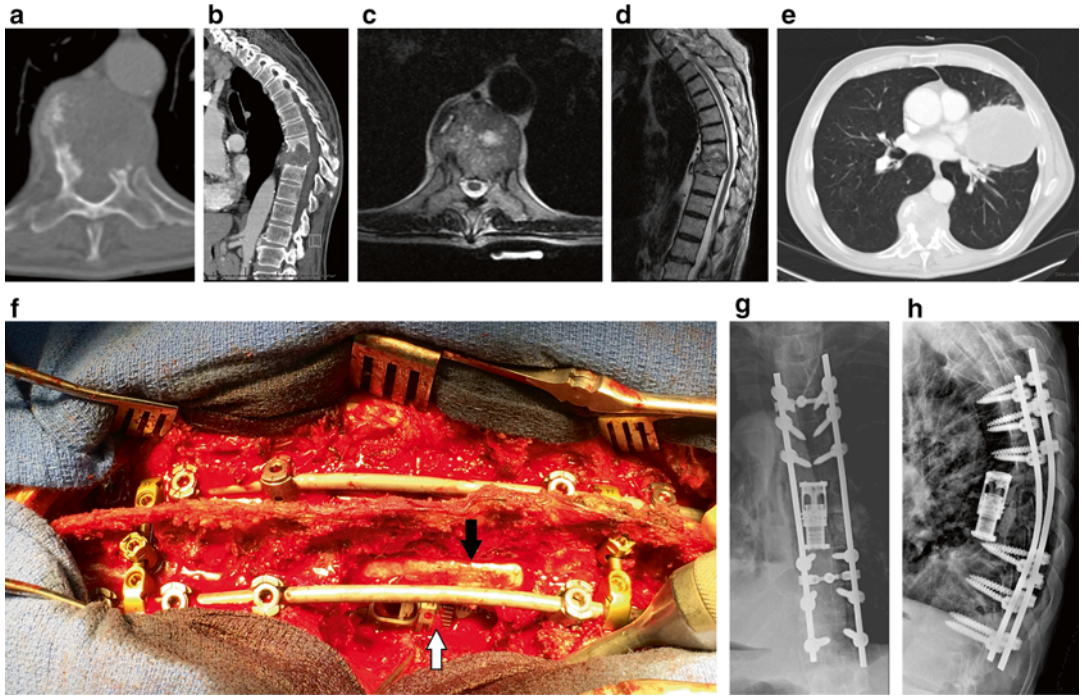

Fig. 29.5 Case example with preoperative axial (**a**) and sagittal (**b**) CT scan imaging showing nearly complete replacement of the T9 vertebral body by non-small-cell lung carcinoma, along with partial cavitary destruction of T8. In addition, corresponding axial (**c**) and sagittal (**d**) T2-weighted MRI imaging showing thecal sac compression without spinal cord deformation (SOSG 1b). CT scan of the chest is shown depicting the suspected lung primary (**e**). In addition, an intraoperative photograph (**f**) is shown along demonstrating the costotransversectomy exposure along with decompressed thecal sack (*black arrow*) and expandable titanium cage reconstruction (*white arrow*). Finally, postoperative AP (**g**) and lateral (**h**) radiographs are shown, with the final reconstructive hardware in place

Lumbar Spine

Factors which differentiate surgical decompression and stabilization procedures in the lumbar spine from other anatomic locations include the lack of a sternocostal complex for support, high mechanical loading conditions, and the need to preserve segmental nerve roots for preservation of lower extremity sensorimotor function. Although posterior-only circumferential decompression and reconstruction techniques have been described [80], they are less useful in the lumbar spine than in the thoracic spine given the technical challenges of exposure and hardware insertion around preserved nerve roots. Generally speaking, in addition to posterior approaches, standard anterior options include left sided retroperitoneal direct anterior or anterolateral exposures. Technical challenges change based on the level of pathology. For example, in the low lumbar spine from L4–S1, mobilization of the inferior vena cava and left common iliac vein often requires identification and ligation of the iliolumbar vein, while higher in the lumbar spine at L1–2 a diaphragmatic crus takedown and later repair must be accomplished.

Figure 29.6a, b demonstrates the preoperative axial and sagittal T2-weighted MRI scans of a 58 year-old patient who presented with several months of worsening mechanical low back pain and the acute onset of a conus medullaris syndrome manifesting with bladder dysfunction, decreased rectal tone, and saddle anesthesia. A CT scan of the abdomen demonstrated the previously undiagnosed primary tumor shown emanating from the right kidney (Fig. 29.6c). After tumor embolization via interventional

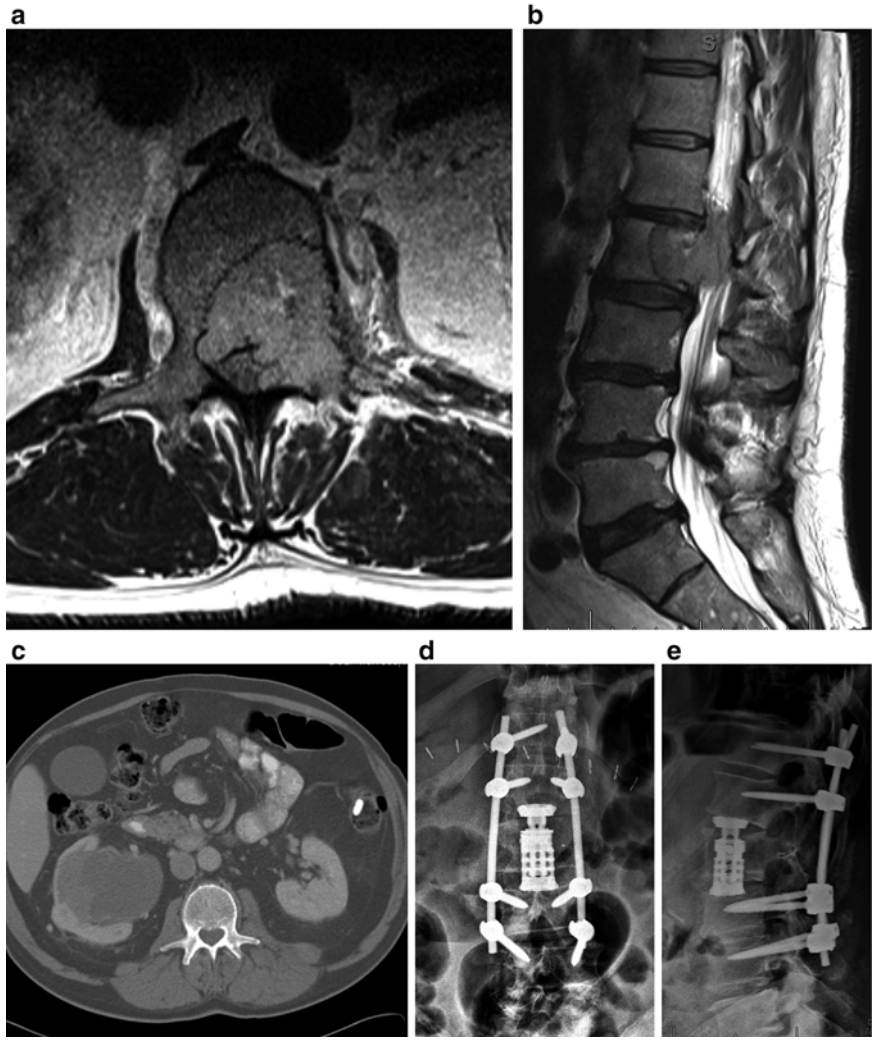

Fig. 29.6 Case example with preoperative axial (**a**) and sagittal (**b**) T2-weighted MRI imaging showing tumor replacement of the body and left pedicle of L2, along with high grade compression of the conus medullaris. The suspected renal cell carcinoma primary is demonstrated in (**c**). Postoperative AP (**d**) and lateral (**e**) radiographs demonstrate circumferential reconstruction with posterior instrumentation and anterior expandable titanium cage

radiology, the patient was taken urgently to the operating room for a two-stage decompression and fusion consisting of a left retroperitoneal approach, L2 corpectomy, and expandable cage reconstruction followed by a posterior laminectomy and segmental instrumentation from T12–L4 (Fig. 29.6d, e). Pathology was consistent with metastatic renal cell carcinoma. He regained sacral spinal neuron function postoperatively, and underwent conventional EBRT 2 weeks postoperatively to 800 cGy over one dose. Two months postoperatively, he underwent resection of the primary renal tumor and began temsirolimus chemotherapy.

Sacrum

Metastatic disease in the sacrum generally does not cause mechanical instability as this segment is rigidly fixed to the pelvis by the bilateral sacral-iliac joints and their stout accompanying

ligaments. In cases of massive tumor destruction of the S1 body and/or L5–S1 junction, fixation from the low lumbar spine into the sacrum and pelvis may be required to restore the spinopelvic continuity. Although the thecal sac typically ends at the upper section of S2, sacral epidural root compression can still occur and is typically treated, if nonoperative measures fail, with posterior midline sacral laminectomy without instrumentation. If instability does occur in the sacrum, reconstruction often includes low lumbar pedicle-based instrumentation along with sacral pedicle instrumentation and iliac bolts, with or without additional sacro-iliac screws.

Summary

Metastatic disease in the spine encompasses a heterogeneous group of tumors which cause a wide variety of clinical scenarios involving degrees of pain, mechanical instability, and neurologic injury. Ideal treatment plans are developed by a multidisciplinary team and are best tailored to the individual patient by consideration of spinal stability, neurologic status, and systemic status of disease. Future directions will involve combinatorial leverage of the latest advances in molecular systemic therapy, radiotherapy, and surgical techniques.

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Part X

Emerging Surgical Technologies

Intraoperative Imaging and Navigation

30

John A. Abraham and Christina J. Gutowski

Introduction

Prior to its introduction to orthopedic surgery, intraoperative computer guidance systems were used primarily in neurological surgery, to assist in the identification of the precise location of brain tumors. Once introduced into orthopedic surgery, several avenues of potential application were explored: total joint arthroplasty, spinal surgery, and trauma. During total hip replacement surgery, appropriate anteversion and abduction of the acetabular cup can be achieved more accurately and reproducibly with computer assistance [1]. In total knee replacement, improvements in coronal alignment [2], precision of mechanical axis realignment, and femoral component positioning (both rotation and flexion angle, specifically) have been associated with utilization of navigation [3]. Despite these advantages, routine utilization of navigation in primary arthroplasty has been limited for several reasons: it has been linked to periprosthetic fracture [4], increased cost, and increased surgical time [5]. Furthermore, the increased precision afforded by computer navigation in these applications may not have significant clinical benefit: while it has been shown that considerable misalignment leads to increased risk of revision arthroplasty surgery [6], no study to date has been able to demonstrate consistently improved clinical outcomes with the use of navigation for arthroplasty [2, 7]. Navigation has also been employed in orthopedic trauma surgery [8], and has been particularly useful in percutaneous sacroiliac screw insertion [9], pelvic and acetabular fracture fixation [10, 11], and the placement of screws in periarticular areas such as the tibial plateau. Specific difficulties relative to fractures, such as the mobility of the fracture fragments and the inability to register several bone fragments and their relationship to each other at one time, have limited the use of navigation in trauma surgery. In spinal surgery, the accuracy of screw placement correctly within the pedicles has been shown to improve when navigation is employed: in one study, 95 % of screws placed under navigation guidance were found on postoperative MRI to be appropriately placed, as compared to only 85 % of screws placed using conventional methods [12]. Subsequent rates of return to the operating room for screw revision were lower in the computer-assisted group [13]. Although utilization rates of navigation in spinal surgery are

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higher than in arthroplasty, it is still not considered to bring enough clinical benefit to have widespread use. Although detectable differences in accuracy can be shown in all these applications, the marginal clinical benefit afforded by the use of navigation in these fields limits its adoption by many surgeons.

The application of computer navigation in orthopedic oncology began primarily with case reports of its utilization in pelvis tumor excision. Initially the navigation systems were believed to afford a safer resection by allowing the surgeon improved visualization of the operative field, which is obscured in this region by not only the complex anatomy, but in many cases also the tumor itself. Initial literature focused on simply the ability to utilize navigation for this application and its safety [14, 15], but as the use of navigation in pelvic tumor resection expanded, the additional benefit of more precise resections was realized. Studies investigating the precision of osteotomies during tumor resection when compared to the planned resection found navigation-assisted resection to be more accurate [16]. Surgeons utilizing this technique were able to demonstrate case series with safe and accurate resection of technically challenging cases. As in the arthroplasty realm, however, the initial response among experienced surgeons who routinely perform these procedures without navigation was that tumors could be removed safely and precisely without the use of navigation, reasoning that the additional cost and operative time was not justified. In order to address these concerns, and to highlight the need for more precise resections in difficult anatomic areas such as the pelvis, Cartiaux et al. demonstrated the high baseline level of inaccuracy exhibited by even experienced surgeons when complex musculoskeletal resections were simulated on plastic models: only 52 % of the time were negative margins obtained in their simulation study [17]. This rate improved significantly with the use of navigation in performing the same simulated resections. Studies such as this one demonstrate that as opposed to other subspecialty applications, the utilization of navigation in orthopedic oncology surgery is warranted. Given the relationship between surgical resection margins and clinical outcome for malignant bone tumors, the clinical benefit of a more precise resection is undeniable. For example, pelvic tumors with sacral involvement have been shown to have higher rates of inadequate margins during resection than those that spare the sacrum [18], and so computer-assisted surgery holds specific promise in improving resections in this area and other complex anatomic regions.

Role of Navigation in Orthopedic Oncology

The application of navigation offers potential advantages to the surgeon in several different capacities. As discussed above, computer assistance is particularly useful for tumor resection in complex anatomic areas, such as the pelvis, spine, and periacetabular region. Navigation allows for joint-salvage resection and reconstruction for periarticular malignancies that, in the past, were treated with replacement. Navigation also potentially improves the safety of operating in poorly visualized areas, thereby providing the opportunity to resect tumors by way of nonstandard surgical approaches. It also facilitates reconstruction, both by improving the accuracy of hardware placement as well as allowing for prosthetic design or allograft fashioning that is patient-specific and precisely fitting with the defect created after resection.

Tumor Resection in Difficult Anatomic Areas

The increased utilization of computer navigation in oncology surgery is occurring within the context of surgeons taking on increasingly challenging cases, largely as result of enhanced imaging and diagnostic capabilities, as well as the improvements of limb-salvage implants, neoadjuvant chemotherapy, and radiation [19]. Despite these advances, patients with malignancies of the pelvic girdle are still at higher risk for treatment failure than are patients with similar tumors

located in an extremity [20]. This is largely due to the complexity of this anatomic area, and the resultant inadequacy of the surgical margin obtained; evidence presented above supports utilization of navigation for this reason. In the setting of metastatic disease, increasing evidence suggest that in certain tumors, complete resection of bone metastases (rather than simple mechanical fixation of impending fractures) may have not only recurrence advantages but in some cases even survival advantages [21]. This information significantly increases the number of patients who may have an appropriate indication for resection surgery, thereby expanding the potential role of navigation-assisted resections in orthopedic surgery.

Navigation allows for correlating preoperative mapping of the tumor's extent within the pelvis to intraoperative visualization of the tumor and important structures within the anticipated plane of resection. Three-dimensional surgical planning coupled with intraoperative visualization is thought to facilitate a safer and more accurate resection at the time of surgery. Recent studies performed by Cho et al. [22] and Wong and Kumta [23] found improvement in local recurrence rates in patients with pelvic or sacral tumors resected under navigation assistance: recurrence rates were 20 and 25 %, respectively, compared to a 70 % recurrence rate for pelvic osteosarcomas treated with traditional techniques, as reported by Ozaki et al. [24]. Jeys et al. achieved a reduction in intralesional resection rate from 29 to 8.7 % with adoption of navigation in pelvic tumors [25]. Ritacco et al. were able to demonstrate accuracy of pelvic/sacral tumor resection to within 2.82 mm of planned osteotomies with computer-assisted surgery, despite the complex anatomic location of these tumors [26] (Fig. 30.1).

In the case of metastatic disease, it is rare than an acetabular or pelvic lesion would require resection. However, in light of recent evidence that resection of certain solitary metastatic bone tumors may increase survival, it is possible that these types of resection may be increasingly performed.

Minimally Invasive Treatment of Tumors Not Requiring Resection

In addition to pelvic and sacral tumor resection, navigation is also useful in management of subchondral, periarticular, or periacetabular lesions that do not require wide resection. This may

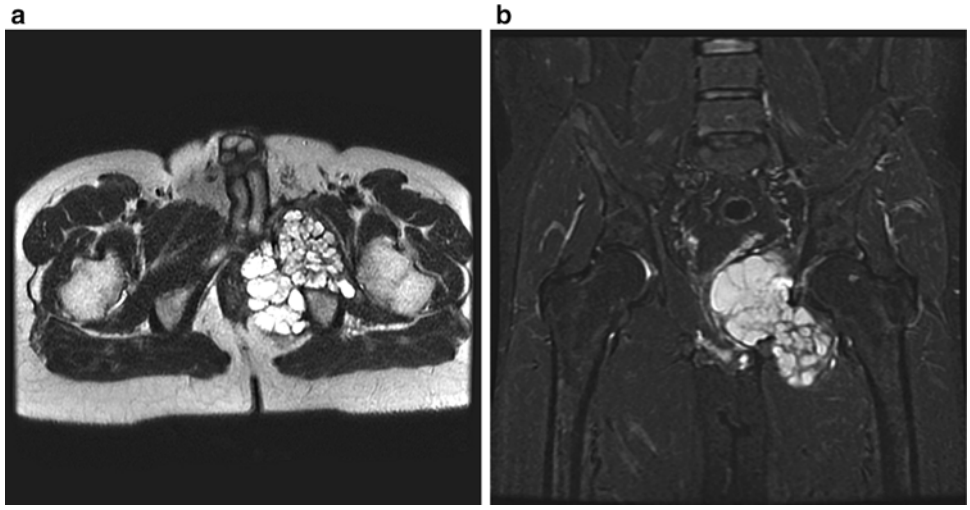

Fig. 30.1 (**a–b**) Axial T2 and coronal STIR magnetic resonance images of a large pelvic chondrosarcoma, displaying its difficult anatomic location that poses challenge to resection. Note the proximity to the rectum, vas deferens, prostate, and bladder

include certain metastatic lesions of bone. Wu et al. described computer-assisted curettage and radiofrequency ablation of a chondroblastoma located in the proximal humeral epiphysis of a child, with preservation of the articular surface and full return to painless shoulder range of motion within 1 month [27]. This group also described the application of navigation in cases of radiofrequency ablation of acetabular osteoid osteoma, curettage of ischial pheochromocytoma metastases, and curettage and cementation of supracetabular lytic lesions secondary to multiple myeloma. Cheng et al. also described the advantages of navigated radiofrequency ablation of osteoid osteomas [28]. By guiding precise approaches to these lesions, outcomes can be optimized with minimally invasive exposures and less perioperative morbidity (Fig. 30.2). In the case of metastatic disease, bone lesions that need to be treated without the need for mechanical stabilization may be good targets in which to consider the use of navigation technology.

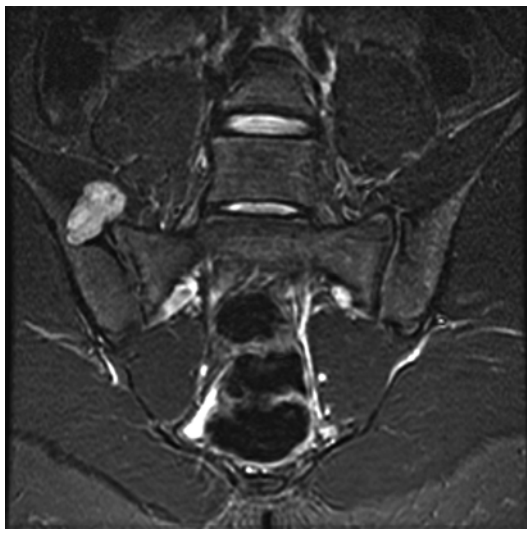

Fig. 30.2 Coronal STIR magnetic resonance imaging of a juxtacortical chondroma in a 19-year-old field hockey player with back pain. Note the nearby L5 nerve root. Navigation facilitated precise localization and a minimally invasive approach to the mass for resection through an incision of less than 5 cm in length, allowing for rapid return to sport

Alternative Resection Capabilities

Navigation also offers the ability to perform tumor resection via surgical approaches that are not possible or less safe with traditional techniques, due to visualization challenges or soft tissue concerns. In the author's experience, one case involving a large ischial mass requiring type III internal hemipelvectomy was approached surgically through an all-posterior buttock incision. The large posterior-based flap on the inferior gluteal pedicle that was created allowed excellent ability to maintain a margin on the most posterior and inferior portions of the mass, which would have been particularly challenging through a standard ilioinguinal hemipelvectomy incision. With navigation assistance, accurate osteotomies within the ischium and pubis were created through the posteriorly based incision. Without navigation, this surgical approach would have been less safe and likely less effective at achieving satisfactory tumor resection. The described surgical plan afforded a direct approach to the tumor, relatively short operative time, excellent visualization of the mass, negative surgical margins, and a rapid return to function following soft-tissue healing that may not have been achievable had a traditional approach been utilized. Likewise, for metastatic bone disease resections (when performed) it would be beneficial to minimize the scale and scope of surgery while still obtaining the desired resection. It is possible, in fact, to argue that patients with metastatic disease who require resection of bony metastases benefit even more than patients with primary disease from resections that heal faster and with less dissection, as the need for return to systemic therapy may be more pressing in these patients. For this reason, it is possible to speculate an important upcoming role for navigation in the treatment of these types of metastases.

Periarticular Resection

Seong et al. described the application of navigation to periarticular mass resection [20]. In the past, high-grade sarcomas involving the metaphyseal

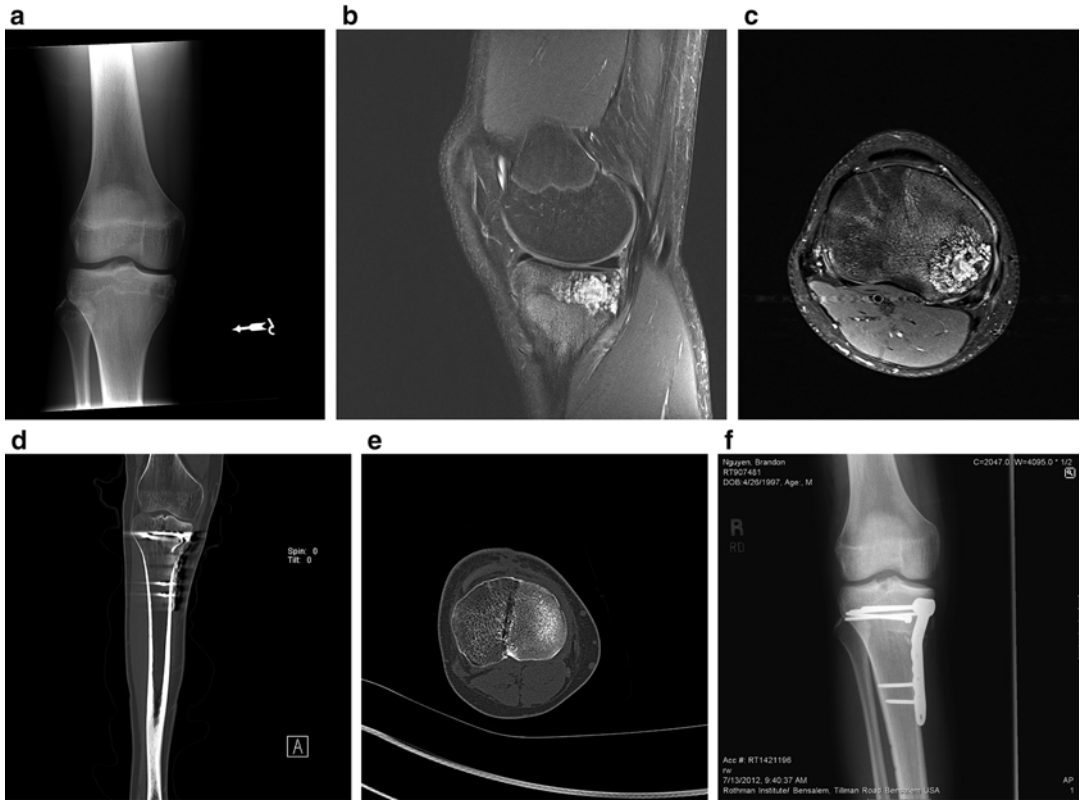

Fig. 30.3 (**a**–**f**) Preoperative X-ray and saggital STIR MRI images (**a**–**c**, respectively) of an 18-year-old male patient with clear cell chondrosarcoma of the proximal medial tibia. To preserve the joint, a navigation-assisted hemi-condylar resection and allograft reconstruction is performed. The system is used to replicate the bone cuts on both the host tibia and allograft, optimizing the allograft fit into the defect. (**d**–**f**) Display postoperative X-ray and CT images after reconstruction, demonstrating the level of precision that can be achieved with this technique. No visible gap can be appreciated between the host bone and allograft, which is difficult to achieve with free-hand methods and maximizes the healing potential at the allograft–host junction

or epiphyseal area of long bones often required sacrifice of the entire adjacent joint in order to achieve a negative margin [29]. In skeletally immature patients, the preservation of the adjacent epiphysis could sometimes be achieved thanks to the physis acting as an intraoperative landmark [30, 31]; however in skeletally mature patients lacking this physeal landmark, navigation now allows for precise localization and subsequent joint preservation. The authors showed that on pathological examination, the actual distances from the tumor to the resection margin were in accordance with their preoperative plan, and at their most recent postoperative follow-up their patients demonstrated healing at all periarticular osteotomy sites, with no evidence of recurrence, and satisfactory MSTS scores in all patients. It has been the author's experience that navigation provides considerable assistance with periarticular resections, where precisely defined margins of resection are critical and an allograft can be fashioned based of a pre-generated template. This has allowed for allograft–host junctions that can be more precisely mated, allowing for improved healing and future function [32] (Fig. 30.3). In the case of metastatic disease, periarticular lesions are seen more frequently with certain subtypes of primary cancers. For instance, lung metastases have a higher predilection for periarticular locations. In the event of this type of metastasis, resection and reconstruction is often necessary to limit pain, preserve function, and

maintain ambulation. The ability to perform improved periarticular resections and reconstructions using navigation is an important benefit of this type of technology.

Reconstruction

Navigation technology also has application in reconstruction after tumor resection, as it allows for precise planning of an implant or prosthesis after guided resection. Computer-aided design and computer-aided modeling (CAD/CAM) surgical jigs are patient-specific instruments that facilitate customized, preplanned bone resection, followed by reconstruction with a precisely designed prosthesis that has been created to match accurately to the skeletal defect [33]. One study testing customized CAD/CAM cutting jigs in a cadaver trial found the dimensional difference between the achieved and planned bone resection to be <1 mm, with the bone resections performed via the slots in the jig. After reporting their cadaveric results, they also described successful application of this technique to a patient with low-grade osteosarcoma of the femur. This system offers improved guidance and some extent of limitation to aberrant surgeon motion during bone cuts. CAD custom prostheses were also shown to achieve positions comparable to their planned positions based on postoperative CT scans, suggestive that this technique may facilitate not only planned resection with negative margins, but also planned reconstruction with custom implants [23].

Docquier et al. developed a novel reconstruction technique utilizing navigation to create a precisely replicated allograft specimen to fit within the pre-planned resection planes (illustrated in Fig. 30.3, above) [34]. In their report, they describe how the allograft was fashioned by a separate surgeon using navigation technology on the back table, simultaneously during resection of the pelvic sarcoma. They describe the surgical efficiency of this strategy, along with achievement of a highly precise reconstruction in a complex anatomical location, where fit of the allograft or implant is a challenge with traditional techniques. An additional advantage of this technique, the shortened surgical time has implications both clinically and financially.

The orthopedic spine literature supports the use of navigation as a means to improve accuracy and precision of hardware placement. In areas of the pelvis that are difficult to visualize, this can be an advantage during reconstruction. When anatomic landmarks are resected en bloc with the tumor, which are commonly used as touchstones for implant placement (for example, the transverse acetabular ligament for establishing the version of an acetabular cup), navigation allows for accurate estimation of component position. In cases where a megaprosthesis is utilized, navigation has served particularly useful in the author's experience at maximizing safety when placing lag screws between neural foramina during endoprosthetic hemipelvis reconstruction (Figs. 30.4 and 30.5).

When managing metastatic disease, reconstructive considerations are different than in the case of primary disease resections. It is critical to allow metastatic disease patients to bear weight right away, and to maximize immediate function, even at the risk of trading long-term durability or a particular reconstruction. In this regard, navigation may play less of a critical role than in bone resections for primary disease. However, navigation can still be an important adjunct tool in assessing appropriate length, rotation, or version of the reconstruction.

Robotics

Robotic surgery has also been utilized in orthopedics. Two main types of robotic systems exist: haptic and autonomous. Haptic or tactile systems still rely on the surgeon to control, or "drive," the robot to perform the surgery. On the contrary, autonomous systems can carry out the intended surgery independently once the approach has been performed and the instruments have been set up by the surgeon. The former has been applied most often in unicompartmental knee arthroplasty, where the machine allows the surgeon to perform bone resection with a

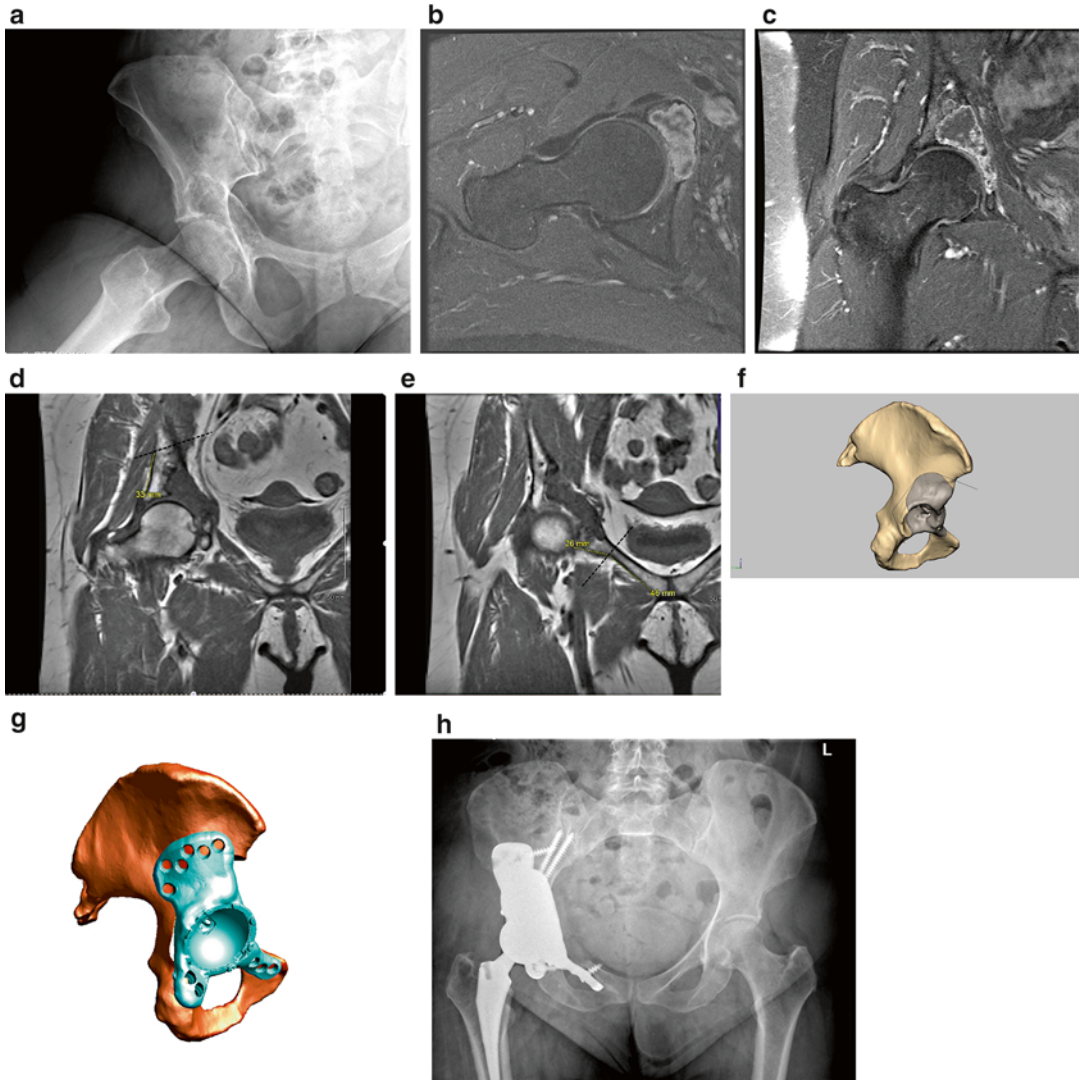

Fig. 30.4 (**a–h**) Example of a grade II chondrosarcoma of the right acetabulum. Preoperative X-ray and both axial and coronal STIR magnetic resonance images illustrate the periarticular location of this tumor (**a–c**). Preoperative planning of osteotomy planes on coronal T1 MRI images is shown in (**d**, **e**), with computer simulation of the planned resection illustrated in (**f**). The implant is designed by the surgeon and engineer, and the system generates a model of the prosthesis fitting into the planned resection defect, (**g**, **h**) display the postoperative X-ray, demonstrating the implant. This patient began walking with an assistive device 8 weeks from surgery

force-controlled burr [35]. This burr limits the surgeon to cuts within a certain pre-planned resection zone, and will prevent the surgeon from driving the burr outside of this field. Additionally, if the robot senses the surgeon is resecting more bone than necessary in any plane, a safety feature engages which stops the burr. These characteristics distinguish the robot from other "passive" navigation/computer-assisted surgical systems, which only monitor progress and provide surgeons with data during procedures but lack the robot's guidance and limitation capabilities.

While data on the application of robotics in tumor surgery are quite limited, there is great potential for application of this technology in this

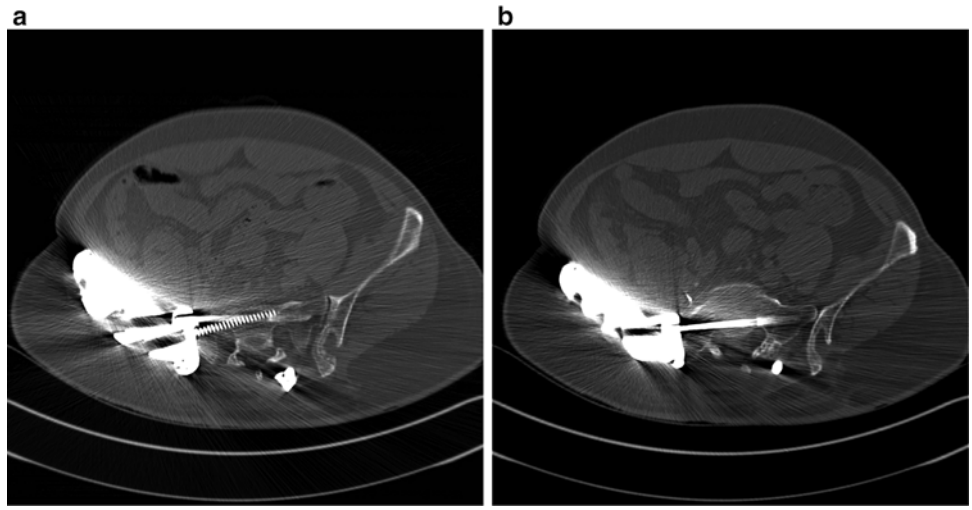

Fig. 30.5 (**a**, **b**) Sequential axial CT images illustrating an example of difficult screw placement. Insertion of these *trans*-sacral screws was facilitated by navigation guidance. Two screws were needed at both the S1 and S2 levels to provide secure fixation for a hemipelvis implant; this would be nearly impossible to perform safely without navigation guidance, even by the most experienced pelvic surgeon

field, especially in cases where surgical dissection and boney resection are adjacent to vital soft tissue structures (in the pelvis or spine, for example). Khan et al. have reported the feasibility, efficacy, and adequacy of resection margin when haptic robotic technology was used for distal femur resection in a sawbones lab; post-reduction images displayed more accurate resection with this technology over a manual technique [36]. It would be advantageous to set a limit to further resection as an instrument approaches one of these vital structures or the tumor itself, which would allow for optimization of safety and simultaneous maximization of the margins of resection.

One can envision a role for robotic surgery in metastatic disease in limiting the amount of tumor resection to only precisely the tissue that is affected. For instance, in the case of a curettage of a metastatic lesion, a robotic operation may allow the surgeon to remove precisely the diseased tissue without removal of any normal adjacent bone. Although in our current framework of treatment this would be an unusual necessity, it may be a more routine procedure in the future, in particular if control of primary disease improves and surgical procedures for metastatic lesions become more limited.

Pitfalls and Barriers to Development

Although the benefits of computer navigation in orthopedic oncology are increasingly demonstrated, significant barriers to the development of this technology to its full potential do exist. The rarity of sarcomas alone is a significant barrier to large-scale studies investigating resection techniques. Furthermore, relatively poor outcomes for pelvic sarcomas make long-term follow up data difficult to obtain. As a result, the majority of literature regarding this topic is comprised of individual case reports and small case series that describe outcomes. However, the expansion of the use of this technology to metastatic lesions, benign lesions in difficult locations, and other specialized applications as discussed in this chapter will undoubtedly help maximize the benefits of navigation in orthopedic oncology. Technical factors such as the learning curve for the utilization and mastery of the navigation systems may limit adoption of this technology, particularly among senior surgeons. The cost of the equipment, and potential increases in operative time must also be considered, although in many cases one navigation system may be shared

between several services within a department or hospital, sharing the burden of cost. In most cases, navigations systems are too expensive to be purchased for utilization by an orthopedic oncologist alone, so many surgeons have partnered with spinal surgical colleagues to ensure adequate utilization of the costly machinery to justify purchase. Another significant issue is the limited commitment by the industry in developing applications, software, and workflow systems specific for orthopedic oncology, due in part to the limited sales market. This is a barrier that will hopefully improve as utilization of navigation in orthopedic oncology increases, and as newer and more robust data are acquired demonstrating the significant clinical advantages that come from its use.

Conclusion

Although a relatively recent addition to the armamentarium of the orthopedic oncologist, computer navigation has already made a significant impact on how bone tumors are resected and reconstructed. The most significant impact has been in the realm of pelvic tumor excision, and customized patient-specific reconstructions. Navigation has allowed more periarticular tumors to be removed with joint sparing resections, and has been useful even in the treatment of metastatic and benign lesions, by providing a means of minimally invasive approach to deep seated lesions. As the investigations of this technology in orthopedic oncology continue to expand, new future applications and refinements of current applications are certain. With respect to treatment of metastatic bone lesions, many of the current applications of navigation-assisted surgery apply, and new and innovative uses of this important technology will undoubtedly surface in the future.

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Part XI

Putting It All Together

Integrative Approach with the Patient in Mind: A Glance Forward

31

R. Lor Randall

While the intended audience of this book has been the orthopedic surgeon, to paint a comprehensive picture of the problems, issues, and treatments facing patients afflicted with metastatic (nonprimary) cancer to bone, one must gain an appreciation of the perspectives of the other disciplines involved in care delivery. Each chapter has hopefully pushed the boundaries of knowledge such that the practicing orthopedic surgeon has a better appreciation of the true task at hand in optimally managing these patients facing the most dire of circumstances. To wax philosophic for a moment, I trust every student went into medicine because they had a heartfelt, earnest desire to help those afflicted with compromised health. However as I approach my twentieth year in practice, I interface with many surgeons that seem to have lost this direction on their compassion compass. Certainly this is not egregious. The training and practice processes, with ever waxing manacles of care delivery, harden us to what it feels like to be on the other end of the scalpel. Yet obviously we are as human as those we treat and if no other process takes us down, eventually cancer will in the end.

As an atticism, cancer is simply life unchecked; the symphony with a conductor no longer fit to orchestrate the complexity of the harmony. Many of us will develop carcinomas of the prostate, breast, or elsewhere. Others will present to their doctor with bone pain to be told they have myeloma. When our cancers have spread to the jurisdiction that we, as orthopedic surgeons are entrusted to shepherd, how will we want to be tended? I humbly submit that we would want a comprehensive and fully compassionate cohesive team of experts, only one or two of whom will be an orthopedic surgeon.

With this in mind, having hopefully read this book from "cover to cover" the orthopedic surgeon is better versed to interface with and contribute to this team. If one were to read *The Decline and Fall of the Roman Empire*, one would not become a Roman but one would certainly appreciate what empire is and how fragile it is to maintain its equilibrium. So in absorbing the material within this book, hopefully one is more able to integrate into the team involved in the end stages of life. The key is to assiduously communicate with the allied healthcare team in a constructive manner focusing on the mosaic of needs for patients afflicted with metastatic cancer to the musculoskeletal system.

Finally, in looking forward, how can we do a better job beyond embracing an integrative

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approach? As heath care reforms are upon us, we are charged with maximizing the quality of our work [1]. In the setting of patients with metastatic bone disease, this has generally been with level IV, retrospective analyses [2–5]. In one meta-analysis of the literature [6], it appears we are doing a reasonable good job. Overall, pain relief after intervention is reported in over 90 % of cases involving the humerus, femur, and pelvis. Maintained or improved function is also seen in about 90 % of the time. The authors however emphasize that we must remain vigilant in our pursuit of better metrics to definitively establish that we are indeed improving the quality of life in the terminal crisis period of these patients' lives.

What might these better metrics be? Patient-recorded outcomes such as the National Institutes of Health's PROMIS® are certainly one way by which we can know if we are satisfying our patients' needs. These types of tools are now being employed in a variety of orthopedic settings [7–9]. Given how important our interventions are in the short term for patients with metastatic bone disease (MBD), we must follow suit. In fact, as individuals with MBD are living longer and more productively than ever before, it truly is an obligation to those that we treat, as well as society, that we keep our promise and demonstrate that we are affording an improved quality of life; no matter how long someone has left to live.

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Index

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