Chapter 49
Bone Metastasis

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Abstract Bone is a common site of distant involvement in advanced cancers. About 70% of patients with advanced breast and prostate cancers and up to 30–40% of patients with advanced lung, thyroid and kidney cancers develop metastatic bone disease.

Cancer-bone cell interactions are complex and can lead to altered bone metabolism and increased bone fragility. Metastatic bone disease is associated with significant morbidity and can have a substantial survival impact. Typically, skeletal complications of bone metastasis include pathological fracture, spinal cord compression, the need for surgery or radiotherapy for a symptomatic bone metastases, and hypercalcemia, collectively referred as skeletal-related events (SREs).

The treatment landscape of bone metastasis is multimodal and has evolved over the last decade. It includes both medical, radiation and surgical management.

In this chapter we will review the epidemiology, pathophysiology, clinical evaluation and management of metastatic bone disease from solid tumors.

Keywords Bone metastasis · Solid tumors · Bone-targeted agents

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Abbreviations

ALP	Alkaline phosphatase
BMPs	Bone morphogenetic proteins
BP	Bisphosphonate
BS	Bone scintigraphy
BTA	Bone-targeted agents
CRT	Convential radiotherapy
CT	Computerized tomography
CXCL12	C-X-C motif chemokine 12
CXCR4	C-X-C chemokine receptor type 4
CXCR7	C-X-C chemokine receptor type 7
IGF	Insulin like growth factor
IL	Interleukin
ISUP	International Society of Urological Pathology
IV	Intravenous
LHRH	Luteinizing hormone releasing hormone
MRI	Magnetic resonance imaging
NTX	N-terminal cross-linked telopeptide of type I collagen
PET	Positron emission tomography
PO	*Per Os*
PTHrp	Parathyroid hormone-related peptide
RANKL	Receptor activator of nuclear factor κ B ligand
RT	Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SC	Subcutaneous
SRE	Skeletal related event
TGF- β	Transforming growth factor-β
TNF-α	Tumor necrosis factor α
XR	Plain radiograph
ZA	Zoledronic acid

49.1 Introduction

Bone metastases are a significant hazard for patients with cancer, with differences by cancer type. In this chapter we will review the epidemiology, pathophysiology, clinical evaluation and management of metastatic bone disease from solid tumors.

49.2 Epidemiology

Patients with prostate and breast cancers are the most commonly affected by bone metastasis, with 5-year incidence of 17% and 5%, respectively, and, among patients with advanced cancer, a prevalence of 90% and 70%, respectively [1–4]. For patients

with advanced lung, thyroid and kidney cancers, bone involvement is reported in up to 30–40% of the cases [5]. In the other extreme, patients with gastro-intestinal tract tumors only rarely have bone metastatic disease [5]. This heterogeneous incidence and prevalence is driven by differences in bone tropism, both due to anatomic characteristics (such as blood drainage of the breasts following the Batson venous plexus), but also related with intrinsic biologic and molecular features [6, 7].

Regardless of the primary cancer, bone involvement has the potential to significantly negatively impact patients' quality of life metrics and/or survival, as well as to increase health care resources consumption [8]. This is mostly due to adverse bone outcomes, collectively referred as skeletal related events (SRE; pathological fracture, spinal cord compression, the need for surgery or radiotherapy for symptomatic bone metastasis and hypercalcemia of malignancy). In a population-based study, the 3-years incidence rate of pathological fracture, spinal cord compression and the need for surgery or radiotherapy for symptomatic bone metastasis was 211 per 1000 patients for breast cancer, 260 per 1000 patients for lung cancer and 150 per 1000 patients for prostate cancer, with the incidence of hospital admissions due to bone metastases ranging from 95 per 1000 for breast cancer, 156 per 1000 for lung cancer and 163 per 1000 for prostate cancer [9].

49.3 Molecular Mechanisms

The interaction between cancer cells and bone is a complex and incompletely understood process. Chemoattractant factors released from the bone marrow, such as CXCL12, contribute partially for the tropism of cancer cells to the bone; tumor expression of chemokine receptors, specifically CXCR4 and CXCR7, interact with the bone chemoattractant stimulus CXCL12 and induce bone homing [6, 10]. The process is further completed with the adhesion of tumor cells to the bone matrix through, e.g., the expression of integrins, such as α4β1 or α2β1 [6].

Bone is under permanent remodeling through the coupled activity of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells). Cancer cells disturb bone turnover equilibrium by affecting bone cells and benefiting from the release of agents entrapped in the bone matrix. These agents enhance tumor growth and lead to increased bone fragility [11, 12]. An interdependent cycle of a) bone turnover activation by tumor cells and b) tumor cell growth stimulation by factors entrapped in the bone matrix is established, thus generating a positive reinforcement loop known as the viscious cycle [13].

When in the bone, cancer cells activate osteoblasts through the release of parathyroid hormone-related peptide (PTHrp), tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8 and IL-11 [14]. Activated osteoblasts produce receptor activator of nuclear factor κ B ligand (RANKL) that ultimately activates osteoclasts and hence induces bone resorption [14]. Finally, growth factors entrapped in the bone matrix, such as transforming growth factor-β (TGF- β), bone morphogenetic proteins (BMPs), insulin like growth factor (IGF) and fibroblast growth factor are released inducing tumor growth [15]. The sum of these steps allows the generation of the previous referred self-perpetuating cycle known as the vicious cycle (Fig. 49.1).

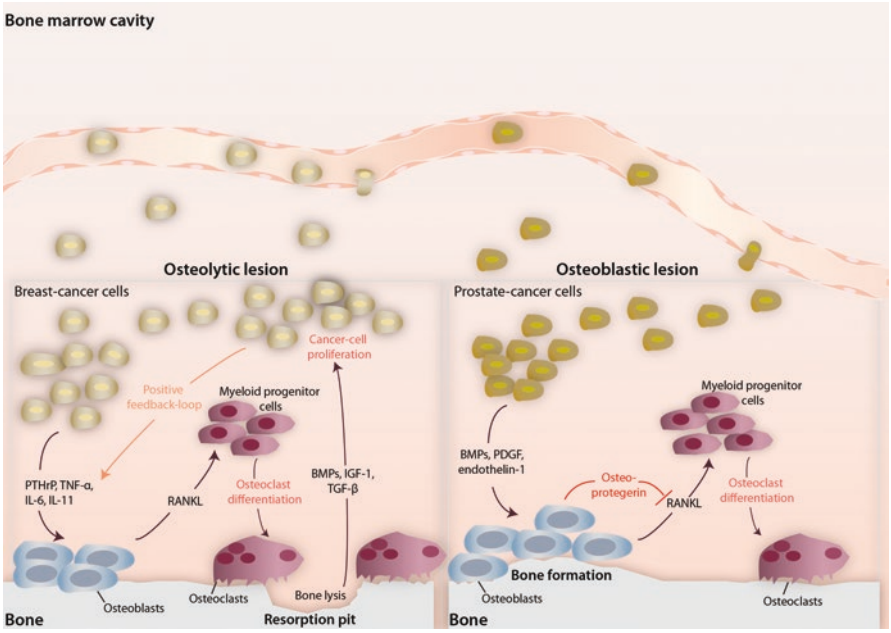

Fig. 49.1 Interactions between bone and cancer cells in paradigmatic examples of osteolytic (breast cancer) and osteoblastic (prostate cancer) bone metastases. In both examples bone metabolism with resorption and formation ocurrs. The depicted mediators emphasize the predominant pathways

49.4 Diagnosis

49.4.1 Clinical Findings

Metastatic bone disease affects more commonly the axial skeleton (pelvis, spine and ribs) and femurs. Approximately one third of the bone lesions are asymptomatic [16]. When symptoms are present, pain is the most common (50%) [17]. In addition to pain, bone fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases, frequently referred as SREs, are also a common manifestation of metastatic bone disease, more often in patients with lytic disease [8].

49.4.2 Laboratory Findings

Alkaline phosphatase (ALP; a marker of bone formation) and N-terminal cross-linked telopeptide of type I collagen (NTX; a marker of bone degradation) are commonly elevated in patients with bone metastases. Although informative, neither of these markers are recommended to guide clinical decisions [18].

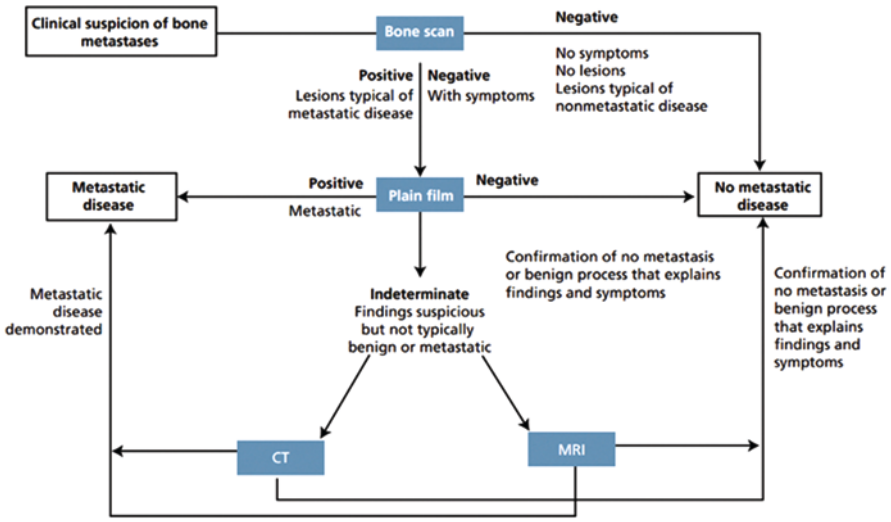

Fig. 49.2 Algorithm for imagological evaluation of patients with clinical suspicion of bone metastases. (Adapted from Ref. [19])

49.4.3 Radiologic Assessment

The radiologic assessment of metastatic bone disease can involve different imaging options, which provide complementary information (see diagnostic algorithm in Fig. 49.2). These include plain radiographs (XR), bone scintigraphy (BS), computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. Usually, when metastatic bone disease is suspected, BS and XR are the first exams to be requested. XR is widely available and is relatively inexpensive. However, 30–75% of normal bone mineralization must be degraded before osteolytic findings in the lumbar vertebrae become apparent on XR, delaying the diagnosis of metastatic lesions for several months [19]. BS is more sensitive than XR for the diagnosis of metastatic bone disease (62–100% vs. 44–50%). However, BS has lower specificity and therefore a higher false-positive rate. BS findings reflect the osteoblastic activity and skeletal vascularity (not the tumor cells themselves), therefore other bone insults, such as trauma or inflammation, can lead to false positive results. On the other hand, rapidly growing pure osteolytic metastasis, when bone turnover is slow, or when the site is avascular can lead to false-negative results. In clinical practice, XR and BS are complementary methods, with XR helping to clarify nonspecific or atypical findings.

CT scans and MRI are usually used to further characterize bone disease. CT scan is very sensitive when detecting small cortical erosions and fractures (71–100%) [19]. Bone MRI has a reported sensitivity of 82–100% and specificity from 73% to 100% for the diagnosis of bone metastasis. MRI is commonly used to assess pathologic fractures of the hip and pelvis, as well as spinal cord compression [20].

Finally, the emergence of PET scan, and particularly of the combination of PET scan with CT (PET/CT) led to a more widespread use of this method as an option to evaluate bone disease. Nevertheless, PET without the CT component is not an ideal method for the diagnosis of osteoblastic lesions [21]. While for most tumors ^{18}F-fluorodeoxyglucose is the label of choice for PET/CT, for prostate cancer ^{11}C-choline and ^{68}Ga-PSMA were more recently established as the preferred labels [22].

49.4.4 Longitudinal Assessment of Bone Disease

The longitudinal assessment of bone disease is challenging. In fact, the Response Evaluation Criteria in Solid Tumors (RECIST) only considers bone lesions as "measurable" if associated to a soft tissue component ≥10 mm. To overcome RECIST limitations, bone-specific (MD Anderson [MDA]) and metabolic-specific (Positron Emission Tomography Response Criteria in Solid Tumors [PERCIST]) response criteria were developed, however the uptake of these criteria has been minor. In prostate cancer, the Prostate Cancer Clinical Trials Working Group (PCWG) developed guidelines to standardize disease assessment, also when affecting the bone [23]. Overall, a combination of clinical symptoms, laboratory findings and imaging data is necessary to interpret bone disease.

49.5 Treatment Approaches

The treatment goals of metastatic bone disease are symptoms control, as well as the improvement in quality of life and survival. Both systemic (anti-tumor and bone targeted agents) and local treatments (radiotherapy and surgery) are available. These approaches may be used sequentially or in combination.

49.5.1 Systemic Management

The systemic management of metastatic bone disease has evolved over the last decade to include therapies directed to the tumor and bone environment.

1. Tumor directed therapy

1.1. Medical management

Tumor directed therapies (chemotherapy, hormonal therapy and biologics) are useful for the management of metastatic disease in tumors known to respond to these modalities. Tumor directed therapy should follow the appropriate metastatic

treatment guidelines for each primary tumor. Cancer medullar involvement and chemotherapy can induce an additive hematologic toxicity.

1.2. Bone-targeted radioisotopes

Bone-targeted radioisotopes are a group of bone-seeking radioactive elements that emit α or β radiation. Examples of such agents include radium-223, strontium-89 and samarium-153 [24]. Despite their theoretical applicability to a broad range of tumors, current clinical use is mostly restricted to radium-223 (an α particles emitting radioisotope) in adults with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. This label of radium-223 was obtained after the results of the pivotal ALSYMPCA study, a phase III trial of Radium-223 against placebo in 921 patients with castration-resistant prostate cancer and bone metastases that were not eligible or refused docetaxel. In this study, radium-223 extended survival (14.0 vs. 11.2 months; HR 0.70; 95% CI 0.55–0.88, $p = 0.002$) and time to first symptomatic SRE (15.6 months vs. 9.8 months) [25]. No other radiopharmaceuticals showed a survival impact in the management of solid tumors with bone metastases, but methodological limitations might limit the interpretation of those studies [24].

2. Bone targeted agents (BTA)

Bisphosphonates (BP) and denosumab are the two class of drugs approved for the prevention of SREs in patients with advanced malignancies affecting the bone. As of January 2019, denosumab is indicated for solid tumors and multiple myeloma both in the EU and in the US.

2.1. Available BTAs, Administration and Efficacy

Bisphosphonates are incorporated in the bone matrix and absorbed by osteoclasts during bone remodeling. Inside osteoclasts, BPs block the osteoclast activity and ultimately bone resorption, thus, in patients with bone metastases, BPs halt the vicious cycle of bone metastases and the rate of SREs. BPs are a class of agents that include, among others, zoledronic acid (4 mg IV over 15 min every 3–4 weeks), and ibandronate (50 mg PO daily).

Pamidronate (another BP) was compared to placebo showing an improvement in skeletal morbidity rate and median time to SRE (12.7 vs 7 months, $P < 0.001$) [26]. Pamidronate was subsequently compared to ZA in a phase III study involving 1648 patients with bone metastases from breast cancer and multiple myeloma that showed a 16% reduction in the overall risk of SREs in those treated with ZA and with a similar safety profile [27]. Favorable results for ZA were also reported for patients with castration-resistant prostate cancer (36% reduction of SREs risk when compared to placebo), lung (31% reduction of SREs risk when compared to placebo) and renal cell (58% reduction of SREs risk when compared to placebo) cancers [28, 29]. A weaker but clinical significant evidence of efficacy was also documented for other solid tumors, as thyroid and bladder cancer [28]. Oral formulations of BPs, as ibandronate, are also available. These formulations, despite less efficacious in terms of skeletal morbidity, have a comparable safety profile and for some patients are

viewed as having a more convenient mode of administration [30]. In this setting, no overall survival differences were found. Therefore, oral options can be discussed with the patient if a strong preference is present or if difficulties with intravenous formulations occur.

Denosumab is a fully human monoclonal antibody with high affinity for RANKL. The interaction between denosumab and RANKL decreases the availability of RANKL, thus blocking its natural interaction with the osteoclast precursor surface receptor RANK and precluding osteoclast formation, bone resorption, and in patients with bone metastases SREs.

Denosumab (120 mg SC every 4 weeks) was compared to ZA in a phase III trial including 2046 patients with bone metastases from breast cancer [31]. Denosumab was superior in delaying time to first on-study SRE (26.4 months vs not reached; P = 0.01 for superiority) and time to first and subsequent (multiple) on-study SREs. A similar safety profile was documented. Denosumab has also demonstrated favorable results when compared to ZA in patients with castration-resistant prostate cancer (18% reduction on time to first SRE) [32]. Of note, hypocalcemia was more frequent in prostate cancer patients (13% vs. 6% in ZA group). For patients with other types of solid tumors and multiple myeloma denosumab was non-inferior to zolendronate [33]. A subsequent meta-analysis concluded that denosumab is superior to ZA in the prevention of bone complications from bone metastases, but no effect on survival was found [34]. Furthermore, the cost of denosumab is significantly higher than that of ZA, particularly where generic BPs are available.

This data is summarized in international guidelines that consider denosumab and ZA as equally valid options in the setting of bone metastases [35, 36].

2.2. Treatment Duration and Schedule

Pivotal trials have arbitrarly defined treatment duration for bisphosphonates of around 2 years, and for denosumab of up to 3 years. However, there is no rational to stop BTAs in patients with active bone metastasis. In this setting, international guidelines recommend treatment with BTAs until evidence of substantial decline in patient's general performance status or even indefinitely [35, 36].

Despite the approved scheduling of BTAs, several trials tested the administration of ZA every 12 weeks (instead of every 3–4-weeks) in patients with metastatic breast cancer, as a strategy to decrease treatment toxicity and hospital visits. In a recent meta-analysis, this schedule showed a similar SRE risk when compared to a every 4-weeks administration [37]. Subsequent individual study updates [38, 39], and recent guidelines support this approach [35]. Of note, ZA de-escalation should be done with caution in patients with extra-bone metastases, previous SREs, disease with aggressive behavior and time to BTA introduction ≥6 months (from the diagnosis of bone metastasis).

2.3. Side Effects

Osteonecrosis of the jaw (ONJ) is an uncommon (approximately 1.6% of those receiving ZA or denosumab) but serious side effect from parenteral BTAs [40]. ONJ is a persistent lesion in the oral cavity exposing bone despite adequate treatment for

at least 8 weeks and without local evidence of malignancy nor prior radiotherapy to the affected region [41]. The risk of ONJ increases with prolonged therapy duration (median time to ONJ in patients receiving ZA or denosumab of 15 months) [40]. Patients at higher risk include those with recent invasive dental procedures (extractions or implants), trauma, poor dental hygiene, and therapy with antiangiogenic agents and probably corticosteroids. Every invasive dental procedure should be done several months before treatment with bone modifying agents, and BPs discontinued for 3 months before and after elective invasive dental surgeries. Patients should be encouraged to maintain good oral hygiene and clinicians should assess in every visit jaw/tooth pain or exposed bone on clinical examination. A conservative management is recommended with limited debridement, antibiotics and oral rinses (as chlorhexidine) [41].

Other shared side effects from BTAs include:

1. Hypocalcemia. Patients should be encouraged to take supplemental calcium and vitamin D and serum calcium, magnesium and phosphate monitored during therapy.
2. Acute phase response. This reaction is characterized by fever and flu-like symptoms occurring in the first 3 days after therapy and shortly resolving. Paracetamol or NSAIDs improve symptoms. It generally does not recur after first or second administration.

BPs have specific side effects:

1. Nephrotoxicity. ZA induces tubular dysfunction, while pamidronate damages the glomeruli. Patients should maintain adequate hydration and clinicians need to monitor renal function during therapy. A dose reduction is recommended for patients with creatinine clearance <60 mL/min and BPs are contra-indicated for those with creatinine clearance <30 mL/min.
2. Ocular toxicity. Conjunctivitis, uveitis, scleritis and orbital inflammation were documented.
3. Bone joint or muscular pain.
4. Atypical femoral fractures (subtrochanteric or diaphysis regions) for patients treated for more than 3–5 years.

49.5.2 Local Treatments

The assessment for the best local treatment is based on the lesion localization (axial skeleton vs. extremities), lesion features and patient's fitness. A combination of localized treatments can be proposed (e.g., surgery followed by radiation). The NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is recommended as a decision tool in the management of axial/spine metastasis [42]. Other popular decision tool is the Mirels score for femoral lesions: in this system, axial cortical involvement >30 mm and/or circumferential cortical

involvement >50% were significant predictors of bone fracture and thus mandates prophylactic local treatment [43].

1. Radiation therapy

RT aims at (1) relieving localized pain, (2) treating spinal cord compression and (3) complementing primary surgical treatment [44, 45]. RT can be combined with other treatment modalities, as e.g. bisphosphonates [46]. Conventional RT (CRT) can relieve pain in 60–80% of cases, with complete pain resolution in 15–30% within 3–4 weeks of treatment [44, 47].

There are different hypofractionated schemes for CRT [44, 48]:

- 30 Gy in 10 fractions/daily (30Gy/10fx),
- 20 Gy in 5 fractions/daily (20Gy/5fx) and
- 8 Gy in a single fraction [8Gy/1fx]).

Different fractionation schemes are determined by patient characteristics, tumor features, symptoms and previous treatments.

1.1. Localized non-complicated painful bone metastasis

For non-complicated/"uncomplicated" bone metastasis, defined as the "presence of painful bone metastasis unassociated with impeding or existing pathologic fracture, or presence of spinal cord or cauda equine compression" [49], CRT with 8Gy/1fx is feasible, easy to implement and cost-effective [48, 50]. A systematic review from Chow *et al* showed similar results between a single fraction versus non-single fractionation for pain control (overall pain response rates of 60% vs. 61% with a pooled odds ratio of 0.98 [95% CI 0.95–1.02]; and pain complete response rates of 23% vs. 24% for non-single fractionation with a pooled odds ratio of 0.97 [95% IC 0.89–1.06]) [51]. Another systematic review also failed to show significant differences in efficacy or in toxicity between non-single fractionated CRT schemes [52]. However, single fraction CRT requires re-treatment more frequently (20% vs. 8% for non-single fractionation) with a 2.6-fold higher likelihood for re-irradiation (95% CI 1.92–3.47; $p < 0.001$). In this setting, a minimum interval of 4 weeks between treatments is recommended for re-treatment [44, 48] and up to 2/3 of the patients (95% CI 0.49–0.67) will have pain relief after re-irradiation with CRT [53]. Moreover, similar rates of response to re-irradiation are expected between single and non-single fractionations [52]. The RTOG 0433/NCIC CTG SC 20 trial demonstrated that 8 Gy/1fx for re-irradiation is non-inferior and less toxic than 20 Gy/5fx [54].

A special attention should be given for patients with bone pain with neuropathic features. In these cases, beyond palliative radiotherapy, drugs known to be effective in neuropathic pain (e.g., gabapentin and opiates) should also be prescribed [55, 56]. Moreover, the use of single fractionation CRT is debatable, as highlighted by the TROG 96.05 results that favored the 20Gy/5fx scheme when compared with the 8Gy/1fx [57]. In specific, the 20Gy/5fx scheme had a trend for better overall response rate (61% vs. 53%), complete response rate (27% vs. 26%) and less consumption of analgesics and hospital admission costs.

1.2. Radiotherapy options in impeding bone fracture, bone fracture and in the post-operative setting

For impeding or pathological fractures, surgery should be the first approach when possible. There is no recommend fractionation or radiotherapy technique to treat an unstable spine, and isolated RT should be avoided whenever possible [58]. The same should be applied for appendicular bones with impeding fracture.

In the postoperative setting, metallic prosthesis and surgical hardware are not an absolute contraindication for radiation, but they can interfere with RT planning as imaging artifacts affect delineation and metal alters dosimetry planning. Therefore, unnecessary metal instruments on the patient's skin (e.g., staples) during the planning-CT scan should be avoided. RT should start within 2–3 weeks after surgery [59].

One of the pivotal studies of postoperative CRT included patients with spinal bone metastasis and initial signs of spinal cord compression [60]. In this study, patients were treated with surgery plus 30G/10fx starting within 15 days after surgery. Ability to walk, the study primary endpoint, was more frequent in the postoperative RT group (84% vs 57% in the RT only group; odds ratio 6.2, 95% CI 2.0–19.8; $p = 0.001$). Of note, this trial was performed before recent improvements in the systemic treatment for many tumors, and the advent of increasing aggressive management of oligometastasis. This further highlights the need for improved local control of bone metastasis in patients with increasing survival. In case of recurrent spinal compression, pre-treatment neurological status is an important decision and prognostic factor. Expert consensus suggest surgical decompression due to higher salvage rates, despite foreseeable complications [61].

In case of patients with appendicular bone lesions eligible for surgery, postoperative CRT is frequently used (either 30Gy/10fx or 20Gy/5fx). This is especially valid for long bone lesions, to promote bone remineralization, and to decrease the likelihood of second surgery, re-irradiation, tumor progression and/or prosthesis displacement [62]. Unfortunately, prospective evidence is lacking, and current approaches are based on retrospective data that disregards recent treatment innovations [63].

For the management of spinal cord compression, please refer to the corresponding chapter.

1.3. Toxicity associated with radiotherapy

Some of the acute side effects of CRT include [48, 64–68]:

- Fatigue, the most frequent side effect (80–90%).
- Pain flare, a sudden increase from basal pain within a week after the start of the treatment. It is identified up to 3–44% cases and it lasts for a median of 3 days.
- Acute gastrointestinal and hematological toxicities are expected on large radiation volumes. Prophylactic oral anti-emetics should be given and blood counts should be monitored.
- Pathological fractures are less frequent but can occur in stereotactic body radiotherapy (SBRT) (<10%) and data is still equivocal for single fraction CRT.

- Spinal cord injury risk is <0.2% with CRT technique if constrain dose is respected (maximum dose 50 Gy).

2. Surgical management and other invasive procedures

The surgical management of bone metastasis aims to achieve pain relief, skeletal stabilization and the prevention of impending fractures or spinal cord compression [59]. Elective interventions of impending fractures are associated with shorter intraoperative time and blood loss, shorter hospital stay, greater likelihood of discharge to home as opposed to an extended care facility and greater likelihood of resuming support-free ambulation [69].

The selection of patients and type of intervention depends on the estimated life expectancy, the mental and motor status, pain control and general nutritional and metabolic status [59]. Relative contraindications for surgery are related to patient fitness, expected overall survival to benefit from the surgical treatment (ranging from 1 to 3 months), extensive neurovascular enclosure by tumor extension, malnutrition (which would preclude wound healing) and metastasis in other sites compromising function.

Major surgery complications include peri-operative death (from 6% to 15%), fixation failure, infection and thromboembolism [70].

2.1. Disease of the extremities

Femoral lesions are the most common lesions of the extremities. Surgery can be directed to (1) impending fractures or (2) established pathologic fractures. Commonly used surgical approaches in lesions of the extremities include bone reinforcement with or without removal of metastasis, reconstruction of the articular surface or amputation.

(1) The selection of patients with impending fractures is assessed by various scores, as, e.g. Harrington or Mirels score systems. Prophylactic surgery usually involves internal fixation followed by RT.
(2) Pathologic fractures of long bones diaphysis (femur or humerus) are usually treated with internal fixation with bone cement and interlocking screws followed by RT. Femoral head and neck fractures are better treated with hemiarthroplasty. Surgical technics for femur intertrochanteric, subtrochanteric and acetabular lesions as other bone site lesions are out of this chapter scope.

2.2. Disease of the axial skeleton

Indication for surgical intervention should be based on the NOMS decision framework and expected functional impairment after treatments. As a rule of thumb common indications include the presence of spinal instability, neurological deficit or functionally relevant deformity. Surgery is also indicated in symptomatic lesions from tumors that are radioresistant (e.g. renal cell carcinoma) or that continue to progress despite RT.

Common approaches to axial lesions include surgical anterior/posterolateral decompression with vertebrectomy and graft or cage reconstruction; laminectomy;

and percutaneous vertebroplasty or balloon kyphoplasty, both of which include de intra-vertebral injection of methyl methacrylate cement. Adjuvant RT and orthosis, as cervical/spinal collars, are frequently used.

49.6 Future Developments

Several points in the treatment of bone metastases are under active research. In prostate cancer, these include treatment combinations of the radiopharmaceutical radium-223 with other direct antitumor agents as abiraterone, enzalutamide, or docetaxel. To this regard, the randomized, double-blinded phase III ERA-223 trial (NCT02043678) of abiraterone plus prednisone with either radium-223 or placebo in chemotherapy-naive patients with asymptomatic or mildly symptomatic mCRPC with bone metastases was prematurely stopped due to the identification of more fractures and deaths in the combination arm.

At the same time, several studies are moving BTAs from the palliative setting to the adjuvant setting. To this end, ZA has already shown to be useful for the prevention of bone metastases in postmenopausal women with early breast cancer treated with curative intent. In the genomic era, several groups are also seeking to define gene signatures predicting for the risk of development of bone metastases. In addition, active research is also looking for the development of new classes of BTA.

In the CRT field, the Post-operative RadioTherapy for Patients With Metastases of the Long Bones (PORT) trial (NCT02705183) will update the evidence of delivering postoperative CRT to impending and pathological fractures.

Growing evidence supports the use of Stereotactic Body Radiotherapy (SBRT) as an ablative treatment for localized bone metastasis, while maintaining spinal cord dose constraints. Available data tested its use in fit patients with limited metastasis (oligometastatic) and expected to survive longer than 3–6 months. Other indications might include recurrent bone lesions after CRT, irradiation of radioresistant tumors and as a complementary post-operative treatment [58]. Expert consensus have been developed to standardize treatment and to define standards for the collection of outcomes for non-irradiated, previously irradiated and for complementary postoperative RT. [71, 72]

Key Points

- Bone metastases are a significant hazard for patients with cancer, especially in patients with prostate and breast cancers;
- The axial skeleton (pelvis, spine and ribs) and femurs are the most frequently affected sites and pain the most common symptom (50%) with a third of patients being asymptomatic;
- Bone targeted agents (as bisphosphonates and denosumab) are effective treatments to reduce the incidence of skeletal related events, a group of bone complications including pain, fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases;

- RT is used to relieve localized pain, treat spinal cord compression and as a complementary treatment after surgery; for patients with uncomplicated bone metastasis, CRT in a single fraction of 8 Gy is non-inferior to other non-single fractionated schemes.
- In case of unstable spine or neurological impairment, surgery should be the first approach when possible.

Clinical Case

An 80 years-old male, previously independent, was admitted to the emergency room with pain in the right thigh. Patient had medical history of osteoarthrosis affecting both hips and recently developed constipation, unusual generalized weakness and nausea, but could still performed his daily routine. Laboratory workup revealed an elevated ALP, hypercalcemia (13.5 mg/dL), no renal injury and an elevated PSA (172 ng/mL). A bone XR and subsequent CT scan revealed a low density lesion involving all circumference of the right femur diaphysis, thus compatible with impeding bone fracture. Patient was given analgesia and electrolytes were optimized. Afterwards, patient was submitted to orthopedic surgery with lesion removal, internal fixation and interlocking screw placement. Subsequent external radiotherapy was administered (20 Gy in 5 fractions). Pathological review confirmed prostate adenocarcinoma. Additional clinicopathological workup revealed a prostate adenocarcinoma, Gleason Score 8 (4+4)/ISUP grade group 4, T3b, with lumbar and right femoral bone metastasis but no visceral involvement. Patient was discussed at the urological tumor board and subsequently started on androgen deprivation therapy with an LHRH antagonist. Given the castration sensitive setting, he was not started on bone targeted agents.

Multiple-Choice Questions

1. Bone metastases are a systemic complication of solid tumors. Select the false:

   (a) Tumor cells reach the bone through a combination of mechanisms, including biochemical homing and anatomical characteristics of the primary;
   (b) The vicious cycle of bone metastases explains the mechanism by which tumor cells manipulate and derive benefit from the bone microenvironment;
   (c) In the vicious cycle of bone metastases, PTHrp is released by cancer cells to activate osteoblasts that subsequently produce RANK ligand that ultimately activates osteoclasts and hence induce bone resorption and the release of growth factors entrapped in the bone matrix;
   (d) The 3 tumors with the highest likelihood of metastization to the bone are prostate, breast and colon cancers;
   (e) Typical growth factors released by the bone matrix include TGF- β, BMP, IGF and FGF.

Correct answer: d

Comments: While patients with prostate, breast cancers, lung, thyroid and kidney cancers develop frequently bone metastases, those with gastro-intestinal cancers, as colon cancer, develop less frequently bone metastases.

2. Regarding clinical presentation of bone metastases:

   (a) Large bones, as e.g. the humerus, are the most commonly affected sites;
   (b) More than half of patients show no symptoms at presentation;
   (c) The N-terminal cross-linked telopeptide of type I collagen is a biochemical mediator of pain;
   (d) X-ray and bone scintigraphy are complementary imaging methods, with X-ray helping to clarify nonspecific or atypical findings of bone scintigraphy
   (e) MRI is better than CT-scan in detecting cortical bone erosion

Correct answer: d

Comments: Bone scintigraphy (BS) is more sensitive than X-ray for the diagnosis of metastatic bone disease, but BS has lower specificity, given that other bone insults, such as trauma or inflammation, can lead to false positive results; conversely, pure osteolytic metastases, when bone turnover is slow, or when the site is avascular can lead to false-negative results. Therefore, X-ray and BS are complementary methods.

3. What should be the first approach if you suspect a solitary painful bone metastasis?

   (a) Always request a bone biopsy to assess the nature of lesion;
   (b) Early treatment with surgery showed to universally improve survival;
   (c) Start with upfront denosumab, given that no other bone targeted agent showed to improve survival;
   (d) Request a bone MRI, given its superior sensitivity for the diagnosis of bone metastasis;
   (e) Characterize pain and other symptoms, exclude neuropathic pain and neurological impairment, as well as assess fracture risk before deciding next treatment steps.

Correct answer: e

Comments: the management of a new painful lesion in the bone should focus on characterizing patient's symptoms and risk of skeletal complications in order to act appropriately both in terms of symptoms palliation and avoidance of acute complications, as SREs.

4. Regarding the treatment of bone metastases, select the false:

   (a) Treatment goals include symptoms control, improvement in quality of life and extension of survival;
   (b) Combination of treatment options, such as surgery and radiotherapy, are experimental, and should only be performed in the setting of a clinical trial;
   (c) Despite the existence of several bone-targeted radioisotopes, only radium-223 showed to both impact bone outcomes and overall survival in prostate cancer;

(d) Radium-223 is an α particles emitting radioisotope, thus presenting less hematologic toxicity;
(e) Denosumab and bisphosphonates have slightly different approval indications.

Correct answer: b

Comments: the use of surgery and post-operative radiotherapy is the standard of care both for axial and appendicular lesions. This is based on randomized data for axial lesions, but only retrospective data for appendicular lesions, where most evidence reflects patients with lesions affecting the long bones.

5. Regarding the various options of bone-targeted agents, select the false:

(a) Denosumab is superior to zoledronic acid in all indications and should always be the preferred option;
(b) Bone-targeted agents do not improve survival, but contribute substantially to reduce morbidity;
(c) For the majority of patients with breast cancer and bone metastases, the scheduling of zoledronic acid can either be every 3 weeks, every 4 weeks or every 12 weeks;
(d) Ibandronate is an oral bisphosphonate and, despite being less efficacious in terms of reducing skeletal morbidity, is still a reasonable alternative in patients with strong preference for oral drugs or if difficulties with intravenous formulations occur.
(e) Denosumab is administered subcutaneously.

Correct answer: a

Comments: denosumab is superior to zoledronic acid (in terms of delaying time to first on-study SRE and time to first and subsequent SREs) in patients with castration resistant prostate cancer and breast cancer. For the remaining types of cancer, denosumab was non-inferior to zoledronic acid. Of note, differences in safety and tolerability profiles should also be taken into consideration.

6. Regarding the various options of bone-targeted agents, select the false:

(a) Zoledronic acid is a bisphosphonate administered intravenously and no faster than in 15 min;
(b) Treatment de-escalation of zoledronic acid for every 12-weeks is a reasonable alternative in all patients with bone metastases, regardless of symptoms, previous SREs and type of primary;
(c) Ibandronate is an oral bisphosphonate administered once daily;
(d) Denosumab is administered subcutaneously every 4 weeks.

Correct answer: b

Comments: most evidence around treatment de-escalation of zoledronic acid is available for patients with breast and prostate cancer. Of note, this should be done with caution in patients with extra-bone metastases, previous SREs, disease with aggressive behavior and time to BTA introduction ≥6 months.

7. Regarding the side effect osteonecrosis of the jaw, select the false:

   (a) Osteonecrosis of the jaw (ONJ) is an uncommon side effect of bone targeted gents occurring in less than 2% of cases;
   (b) A conservative management is recommended with limited debridement, antibiotics and oral rinses (as chlorhexidine);
   (c) The risk of ONJ increases with prolonged therapy duration;
   (d) Invasive dental procedures should be done several months before treatment with bone modifying agents, and BPs discontinued for 3 months before and after elective invasive dental surgeries are performed;
   (e) Dental hygiene is not related with the risk of ONJ.

Correct answer: e
Comments: Poor dental hygiene is an established risk factor for ONJ.

8. Side effects of bisphosphonates include all of the following, except:

   (a) Hypocalcemia
   (b) Flu-like symptoms
   (c) Minor alopecia
   (d) Nephrotoxicity
   (e) Uveitis

Correct answer: c
Comments: bisphosphonates are not associated with alopecia.

9. What is SRE?

   (a) A type of bone treatment for patients with bone metastases;
   (b) It is an acronym of typical sites of bone metastases in patients with lung tumors;
   (c) It is a common composite endpoint of adverse bone outcomes for clinical trials testing drugs targeting bone metastases and stands for skeletal-related events;
   (d) It is a special radiotherapy technique for the treatment of bone metastases;
   (e) The ultimate goal of treating patients with cancer and bone metastases is to reduce SREs, a composite endpoint including pain, bone fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases.

Correct answer: c
Comments: SRE stands for skeletal-related events, and is a common composite endpoint of adverse bone outcomes for clinical trials testing drugs targeting bone metastases. Its avoidance may positively impact patients' quality of life, but it does not improve survival.

10. Regarding radiotherapy for the treatment of bone metastases, select the correct option:

    (a) It is used to prevent bone fractures, especially if mechanically unstable;
    (b) It cannot be used to treat diffuse bone metastasis;
    (c) It should not be used in combination with other treatments;
    (d) Complete pain relief happens most of the time more than 3 months after treatment
    (e) If pain relief is not achieved after first treatment course or symptoms reappear, re-irradiation might still be a treatment option.

Correct answer: e

Comments: re-irradiation is a treatment alternative if pain resurges. A minimum interval of 4 weeks between treatments is recommended and up to 2/3 of the patients will have pain relief after re-irradiation.

11. Are there multiple options of dose fractionation for conventional radiotherapy?

    (a) No, there is only one type of fractionation scheme, which is 8 Gy in a single fraction;
    (b) Yes, but 30 Gy in 10 fractions is the best fractionation that confers best pain control regardless of patient's fitness for the treatment;
    (c) Yes, there are multiple fractionation schemes and the best option will dependent on patient characteristics, tumor features, symptoms and previous treatments.

Correct answer: c

Comments: There are different hypofractionated schemes: 1) 30 Gy in 10 fractions/daily, 2) 20 Gy in 5 fractions/daily, and 3) 8 Gy in a single fraction. Different fractionation schemes are determined by patient characteristics, tumor features, symptoms and previous treatments.

12. In patients with uncomplicated bone metastasis, what is the best evidence-based fractionation scheme of conventional radiotherapy (CRT)?

    (a) 30Gy in 10 fractions is the best fractionation scheme that confers best pain control regardless of patient's fitness for the treatment;
    (b) 20Gy in 5 fractions is the best fractionation scheme that confers best pain control regardless of patient's fitness for the treatment;
    (c) A single fraction of 8Gy is non-inferior to other non-single fractionated schemes, feasible, easy to implement and cost-effective;
    (d) Single fraction CRT requires less re-treatment.

Correct answer: c

Comments: In the setting of uncomplicated bone metastases, i.e. presence of painful bone metastases unassociated with impeding or existing pathologic fracture, or presence of spinal cord or cauda equine compression, CRT with 8Gy/1fx is

non-inferior to other CRT fractionated schemes, feasible, easy to implement and cost-effective.

13. What is the indication for radiotherapy in the postoperative setting?

    (a) It should never be performed because patient already received an effective treatment;
    (b) It is indicated in patients with either axial or appendicular bone lesions with high quality evidence;
    (c) The most well established evidence supports its application in patients with spinal cord compression that received surgery as first treatment approach;
    (d) Given the generalized access and high quality evidence, SBRT should be proposed in the postoperative setting for all patients regardless of the estimated survival;
    (e) Metal implants are an absolute contraindication for postoperative RT, thus other materials should be used in the setting of surgical stabilization of bones.

Correct answer: c

Comments: despite the evidence supporting the use of post-operative CRT in the majority of bone metastases managed surgically, only the setting of spinal cord compression treated with surgery as first treatment approach was formally tested in clinical trials. The management of appendicular lesions with surgery plus CRT derives from retrospective analysis.

14. Regarding the use of surgery for the management of bone metastases, select the correct option:

    (a) Patient only benefit from surgery when there is a bone fracture or in case of spinal cord compression;
    (b) In patients with axial/spine metastases, the NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is useful to decide if surgery is the best local treatment approach;
    (c) Risk of fracture is difficult to predict and besides physician experience there are no other tools to estimate this risk;
    (d) There are no other established invasive procedures to treat bone metastases besides surgery.

Correct answer: b

Comments: The NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is recommended as a decision tool in the management of axial/spine metastasis. Other popular decision tool is the Mirels score for femoral lesions. Besides these scores, indication for surgical intervention should also take in consideration the expected functional impairment after treatments.

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