Metastasis

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Overview

Bone is the third most common site for metastasis in cancer. Bone metastasis occurs in most tumor types but is most prevalent in cancers of the breast, prostate, and lungs. The main purpose of the treatment for bone metastasis is to improve symptoms and prevent symptomatic skeletal events.

26.1 Introduction

Bone is the third most common site for metastasis in cancer. Bone metastasis occurs in most tumor types but is most prevalent in cancers of the breast, prostate, and lungs. The incidence of bone metastasis in prostate cancer is 65–90%, in breast cancer 65–75%, and in lung cancer 17–64%, and it is less frequent in thyroid, renal, and colorectal (10%) cancers. The prevalence of bone metastasis is estimated to be approximately 280,000 new cases per year in the USA and is expected to increase as medical management and surgery improve overall survival. Patients with bone metastasis may experience skeletal complications including bone pain, pathological fractures, spinal cord or nerve root compression, and hypercalcemia requiring orthopedic surgery and/or adjuvant treatments such as radiotherapy and chemotherapy. These events associated with an exacerbation of cancer-related pain have been described as "symptomatic skeletal events" (SSEs). The main purpose of the treatment for bone metastasis is to improve symptoms and prevent symptomatic skeletal events. The decision for surgical and/or medical treatments depends on the prognosis and expected survival for the cancer patients with bone metastasis. Less invasive and palliative procedures are performed for patients with poorer prognosis.

26.2 Pathogenesis

Paget's "seed and soil" hypothesis and Ewing's anatomical hypothesis have described the possible routes of migration and proliferation of cancer cells to bone. According to this hypothesis, cancer cells metastasize towards a favorable microenvironment or via the vessels. Bone is a rich source of laminin, collagen type I, osteopontin, and fibronectin; certain integrins expressed by malignant cells have specific receptors for these mole-

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cules. The bone-homing capacity of tumor cells is increased by the adhesive interaction between tumor cells and bone (mediated by the integrins). Once the surrounding environment becomes suitable for cancer cell proliferation, bone metastasis may arise. The type of interaction between the bone microenvironment and the tumor cells can potentially give rise to osteolytic or osteoblastic metastases. Osteoclastic activity is stimulated by factors secreted by malignant cells.

26.3 Long Bone Metastasis

Pathological long-bone fractures in bone metastasis cause difficulties to the most experienced orthopedic oncology surgeons. Prognosis, quality of life, and survival of the patients depend on their management. The incidence of a long-bone pathological fracture in bone metastasis has been reported to be between 10% and 29%. The most common primary tumor in long-bone metastasis is breast followed by lung, prostate, renal, and thyroid cancers, and the most commonly affected site is the femur. The surgical treatment is described in Chap. 26.

26.4 Acrometastasis

Acrometastasis is defined as bone metastasis distal to the elbow and the knee and accounts for approximately 0.1% of bone metastasis. Acrometastasis usually arises from lung (>50%) or renal cancer, followed by cancers of the colon, breast, and genitourinary tract. It may appear in patients of every age, with men being twice as likely as women to be affected. The prognosis of patients with acrometastasis is generally poor since it indicates a widespread disseminated disease in most cases. Acrometastasis may also appear as the first presentation of occult silent cancer in 10% of the cases and can mimic other benign conditions such as inflammatory lesions, cysts, gout, ganglia, osteomyelitis, tuberculous dactylitis, pyogenic granuloma, and primary skin tumors. As a result, it is essential not to misdiagnose such a lesion. Lung cancer is the main cause of hand acrometastasis. More specifically, the distal phalanx of the thumb in the dominant hand is more commonly affected while acrometastasis in the middle phalanx and the carpus is extremely rare. The tarsal bones are most commonly involved in foot acrometastasis. Lower circulatory flow in distal regions of the body such as the hand phalanges is beneficial for secondary tumor growth. It is also worth mentioning that foot acrometastasis is usually associated with subdiaphragmatic tumors most commonly originating in the gastrointestinal, vesicle, renal, and uterus areas. Clinical examination shows deep and intermittent pain, refractory to common analgesics, along with a palpable mass, an enlarging digit, or a mechanical dysfunction impairing daily activities. Pain is a result of the inflammatory process, which leads to swelling, erythema, ulceration, and bleeding. Differential diagnosis should include benign conditions such as osteomyelitis, rheumatoid arthritis, tenosynovitis, and gout. A destructive permeative lesion is usually shown in radiographs. Lytic solitary lesions in a single bone in the hand are usually due to lung and renal cell carcinomas, while breast cancer acrometastasis is mainly sclerotic, lytic or mixed, and often multiple. CT in distal extremities has a limited value due to the decreased resolution in these areas. However, MRI consists of a useful imaging study in evaluating marrow disease and extraosseous extension of the tumor. Radiographs of the lesion, chest, and abdomen CT along with bone scan are essential for complete staging of the patients with acrometastatic cancer since the extent of spread is the most important factor for the treatment approach and prognosis. Bone scan assesses possible multiplicity and leads to either false-negative or -positive results due to very aggressive tumors or previous trauma, respectively. Positron-emission tomography scan has increased sensitivity. Trocar biopsy tissue sampling is paramount for histological diagnosis and documentation of the acrometastasis, while incisional biopsy should be avoided. The surgical treatment is described in Chap. 26.

26.5 Spine Metastasis

The spinal column is the third most common site for bone metastasis (after the lungs and the liver) and the most common site for bone metastasis (especially the thoracic spine). More specifically,

10–15% of spine metastasis occurs in the cervical spine, 60–70% in the thoracic spine, and 20–25% in the lumbosacral spine. Multiple lesions occur in 17–30% of patients. It is estimated that 10% of patients with cancer develop symptomatic spinal metastases, while this percentage increases to 40% in those with actual metastatic bone disease. Interestingly, in postmortem cadaveric studies, the actual incidence of spine metastasis in cancer patients regardless of symptomatology has been up to 90%. The most common primary cancers are breast (16–37%), lung (12–15%), and prostate cancer (9–15%), while non-Hodgkin's lymphoma and renal cell cancer account for 5–10%; the remaining cases are due to gastrointestinal carcinomas, sarcomas, and unknown primary tumors. Batson's vertebral plexus, a valveless venous plexus of the spine, provides a route of metastasis from organs to axial structures. Bone lysis or sclerosis leads to cortical bone destruction that causes vertebral body collapse. Epidural spinal cord compression, an emergency complication of spine metastasis, may occur through epidural spread by an initial hematogenous metastasis to the vertebral body or less commonly from direct growth of a paravertebral tumor such as lymphomas into the spinal canal through an intervertebral foramen. Before establishment of the diagnosis, 83–95% of the patients experience back or neck pain that may be mechanical due to bone destruction or tumorigenicity (mostly nocturnal). Pain may be unilateral or bilateral in the spine; it is localized to the region of the spine that is affected by the metastasis; it is worse when the patients are recumbent due to lengthening of the spine and distension of the spinal epidural venous plexus and progressively increases in intensity over time. Metastatic epidural spinal pain is caused when the periosteum, paravertebral soft tissues, or nerves are invaded by the enlarging mass and also by spinal instability, pathological fractures, and inflammatory and nociceptor stimulating substances secreted by the cancer cells. Interestingly, pain may be absent with intradural or intramedullary metastasis. Radicular pain due to nerve invasion and compression is less common than mechanical pain and may be accompanied by depression of tendon reflexes, weakness, and sensory changes in the distribution of the roots injured by epidural metastasis along with bowel or bladder disorders. New onset of back or neck pain in cancer patients should be always evaluated in order to rule out spine metastasis. A detailed medical history and physical examination should be the first steps prior to any imaging studies. Vertebral abnormalities such as pedicle erosion, vertebral collapse, and bone dislocation are seen in radiographs in 70–80% of patients with spine metastasis. However, decreased sensitivity and specificity are a major drawback. Treatment of spine metastasis requires a multidisciplinary team approach by a neurologist, radiologist, oncologist, and orthopedic surgeon. The goals of treatment are the ability to walk, pain relief, spinal stability, and improved survival. However, in most cases, treatment is aimed for palliation.

Nonsurgical or minimally invasive palliative management is usually recommended for patients with very poor prognosis; radiotherapy, chemotherapy, vertebroplasty, and kyphoplasty have yielded satisfactory results for pain relief. If symptomatic metastatic spinal cord compression is confirmed, external beam radiation therapy and prompt administration of corticosteroids are standard options along with several analgesics and other supportive measures such as opioids controlled through a patient-controlled analgesia device, bisphosphonates, and spinal braces. Embolization should also be considered for pain palliation of patients with spine metastasis. Thorough patient evaluation should be performed prior to any treatment to minimize morbidity and increase therapy efficiency. Recently, a decision framework has been introduced which incorporates the basic principles that should be considered prior to the treatment of spine metastasis. These include the location of disease, with respect to the anterior and/or posterior columns of the spine and number of spinal levels involved (contiguous or noncontiguous), mechanical instability (as graded by Spine Instability Neoplastic Score—SINS), neurological manifestations and symptomatic epidural spinal cord compression, oncological properties and histopathologic diagnosis particularly with respect to radiosensitivity, and patient fitness, patient wishes, prognosis, and response to prior therapy. The surgical treatment is described in Chap. 26.

26.6 Pelvic Metastasis

The pelvis is the second most common site of bone metastasis after the spine. Clinical manifestations include pain, bone destruction causing mechanical instability, and pathological fractures. Metastatic lesions are always progressive and cause bone failure due to the tumor cell adhesive molecules that bind the tumor cells to the marrow stromal cells and bone matrix, allowing them to grow and produce angiogenic and bone-resorbing factors. In most cases, treatment is aimed at palliation since complete cure of the disease is not possible. Nevertheless, pelvic metastasis substantially decreases the quality of life of the patients and necessitates further treatment. The overall prognosis of the patients with pelvic metastasis extremely varies depending on the site of the lesion, type of primary cancer, and existence of associated metastases. Highly stressed anatomical sites are predisposed for pathological fractures. Enneking's classification divides the pelvic girdle into four different zones. Zones 1 and 3 are non-weight-bearing, while zone 2 is the periacetabular area. Periacetabular metastasis is at greater risk for mechanical failure with progressive destruction of the hip joint, while metastasis in zones 1 and 3 does not compromise the mechanical stability of the pelvic ring. Moreover, osteolytic lesions are considered more at risk for pathological fracture compared to osteoblastic or mixed lesions. Permeative pattern of osteolysis indicates the same risk of fracture as the more classic types that show a discrete area of osteolysis. Radiographs do not always reveal this permeative osteolysis; therefore, MRI is more sensitive to show the real extent of the disease. A prospective protocol containing guidelines on the indications for surgery and the type of procedure that should be undertaken was reported in 2001. Expected survival, type and stage of the tumor, visceral spread, time since detection of the primary tumor, risk for pathological fracture, and predictive sensitivity to chemotherapy, hormonal therapy, and radiotherapy were the accounted factors. According to this protocol, patients were categorized in four classes: class 1: patients with a single metastasis of a primary tumor with a good prognosis and an interval of >3 years from detection of the primary lesion to the development of bone metastasis: primary tumors with a favorable prognosis include well-differentiated thyroid, prostate, breast when sensitive to hormonal treatment or chemotherapy, clear-cell renal, and colorectal carcinoma; class 2: patients with a pathological fracture in a major long bone; class 3: patients with radiological and/or clinical signs of impending fracture in a major long bone or the periacetabular area; and class 4: patients with (a) osteoblastic lesions at all sites; (b) osteolytic or mixed lesions in non-weight-bearing bones such as the fibula, ribs, sternum, or clavicle; (c) osteolytic lesions in major bones with no impending fractures; and (d) lesions in the wing of the ilium, anterior pelvis, or scapula (excluding patients included in class 1). In addition, Harrington's classification has been used to indicate the acetabular destruction for patients in classes 2 and 3: Harrington group 1: integrity of medial and superior periacetabular bone; Harrington group 2: medial acetabular wall insufficiency; Harrington group 3: medial wall and supra-acetabular destruction; and Harrington group 4: total collapse of acetabulum. The surgical treatment is described in Chap. 26.

26.7 Palliative Treatments

Palliative treatment of metastasis in any site of the skeleton includes radiotherapy, radiopharmaceuticals, chemotherapy, embolization, thermal ablation techniques, electrochemotherapy, and high-intensity focused ultrasound (HIFU).

26.7.1 Radiotherapy

The primary goal of radiotherapy is to palliate painful metastasis, achieve local tumor control, and improve quality of life. Metastasis usually starts to get ossified in 3–6 weeks after treatment delivery, reaching the highest degree within 6 months. It has been reported that high partial response rates are approximately 60% and complete response rates

range from 10 to 25%. Single-fraction treatments have higher rates of retreatment.

External Beam Radiation Therapy: The exact mechanism of external beam radiation therapy is unknown. However, it is believed that tumor regression and cell death are implicated. Patients with repeat symptoms after their initial palliative radiotherapy and patients who receive single-fraction radiotherapy may require repeat radiotherapy.

Stereotactic Body Radiation Therapy: Stereotactic body radiation therapy is a highly focused form of radiotherapy designed to deliver high doses to targets while sparing normal surrounding tissue. It is performed using daily image guidance to deliver radiation precisely to the target. The complete response rates for pain and local control are improved because the biologically effective dose can range from 4 to 8 times that of conventional palliative radiotherapy.

26.7.2 Radiopharmaceuticals

Radiopharmaceuticals are now available for the palliation of metastatic bone pain, especially in patients with diffuse bone metastases for which external beam radiation alone is not adequate. Radionuclides, including beta-emitters such as strontium-89 (89Sr) and samarium-153 (153Sa), and alpha-emitters such as radium-223 (223Ra) can be selectively delivered towards bone to areas of amplified osteoblastic activity, sparing healthy organs from irradiation. Once target cells have been reached, radionucleotides induce DNA damage and apoptosis.

26.7.3 Chemotherapy

Systemic approaches to bone metastasis include specific anti-tumor treatments that are necessary to control disease progression at skeletal sites. The pathological type of the tumor is most important in selecting systemic treatment. Anticancer agents are used to control tumor progression, and bisphosphonates are used to prevent skeletal complications.

Bisphosphonates: Bisphosphonates are pyrophosphate analogues whose chemical structure is characterized by a P–C–P-containing central structure. Bisphosphonates cause osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase, which is essential for osteoclast survival and activity. They also reduce osteoclast activity indirectly through an effect on osteoblasts. Current guidelines suggest treatment with bisphosphonates for patients with bone metastasis. More specifically, zoledronic acid is approved for bone metastasis management in both solid tumors and multiple myeloma, while pamidronate can be used for breast cancer and multiple myeloma patients. Ibandronate is effective in breast cancer patients in both intravenous and oral formulations. Oral clodronate is another therapeutic option for the management of lytic skeletal metastases.

Denosumab: Denosumab is a human monoclonal antibody designed to target RANKL (RANK ligand), a protein that acts as the primary signal to promote bone loss. It inhibits the interaction between RANKL and RANK, to reduce osteoclast maturation and activity. General guidelines for denosumab use in bone metastasis are almost identical to bisphosphonates. Nevertheless, denosumab is not nephrotoxic, providing a valid treatment alternative in patients with kidney failure. Similarly to bisphosphonates, denosumab is generally well tolerated, with hypocalcemia and osteonecrosis of the jaw being the most common complications.

26.7.4 Embolization

Embolization is the selective occlusion of blood vessels that feed a tumor. Most metastatic lesions are hypervascular; some lesions such as renal and thyroid metastases are highly hypervascular. Embolization is a useful adjunctive procedure for the treatment of bone metastasis. Indication for embolization is control of hemorrhage, facilitation of subsequent surgery, inhibition of tumor growth, and relief of pain. Embolization can be single session or serial; repeat embolization is indicated when there is pain or imaging evidence of progressive disease. Pre-embolization, diagnostic

digital subtraction angiography must be performed in order to identify the feeding vessels. Embolization is technically successful when intravascular contrast material stops, or tumor's hypervascularity is completely eliminated, or when >80% of the tumor's vascularity is decreased in comparison with the initial angiography. It has been shown that embolization of a hypervascular bone metastasis reduces the intraoperative blood loss and the surgical time and that preoperative embolization has greater effectiveness in reducing intraoperative blood loss when surgery is performed at the same day of embolization. The post-embolization syndrome manifested with fever, pain, and malaise has been described in 18–86% of embolization cases. Embolization can also cause normal tissue loss and may be associated with nerve palsy, skin breakdown, subcutaneous or muscle necrosis, and infection.

26.7.5 Thermal Ablation

Ablative techniques allow for both tumor destruction and palliation of pain from bone metastasis. Thermal ablation was introduced as a palliative treatment of painful bone metastasis in the early 2000s. The aim of thermal ablation techniques is to induce coagulative necrosis with heat, ideally around 70 °C for bone lesions. Radiofrequency, cryotherapy, laser, and microwave thermal ablation are the mostly used techniques.

Radiofrequency ablation (RFA): Radiofrequency ablation (RFA) is the most frequently used thermal ablation technique, with high success rates for bone and soft tissue tumors for skeletal events and local tumor control. Radiofrequency ablation works by conducting an alternating current of high-frequency radio waves, which passes through a probe placed within the lesion.

Cryotherapy: Cryotherapy works by argon gas that is delivered through a partially insulated probe positioned at the center of the lesion. The low temperature causes loss of the cell membrane integrity and cell death. Cryotherapy has shown a greater reduction in analgesic doses and shorter hospitalization time after the procedure compared to radiofrequency ablation. Moreover, cryotherapy can be used for osteoblastic lesions since ice can penetrate bone.

26.7.6 Electrochemotherapy

Mir et al. first described electrochemotherapy (ECT) for the treatment of cutaneous nodules of head and neck malignant tumors, as the combination of permeabilizing electric pulses with intravenous infusion of a chemotherapeutic drug to which the cellular membranes are usually poor or non-permeant. The electric current pulses to the tumor tissue induce the opening of the transmembrane channels, therefore allowing the chemotherapeutic drugs to enter the cell, increasing a localized cytotoxic effect. Electrochemotherapy has proven effectiveness in the treatment of metastasis from solid tumors such as breast cancer and melanoma located in the skin or subcutaneous tissue.

26.7.7 High-Intensity Focused Ultrasound (HIFU)

High-intensity focused ultrasound is considered a safe and the only completely noninvasive and extracorporeal procedure to treat primary solid tumors and bone metastasis. High-intensity focused ultrasound causes a temperature rise in tissues inside the targeted area, resulting in coagulative necrosis at a thermal threshold of 65–85 °C, depending on the tissue absorption coefficient. Ultrasound beam focus results in high intensities only at a specific location within a small volume that minimizes the potential for thermal damage to tissue outside the focal region. Several lesions can be treated per session, and treatment may be repeated as many times as needed because there is no dose limit and no ionizing radiation from MRI and diagnostic ultrasound as opposed to

other systems that are guided by radiographs, and maintenance of the system is low. Other advantages are the low cost of the procedure as compared with traditional surgery, no remaining scars, and faster recovery, and if any hemorrhage occurs, ultrasound has the potential to stop it. The main limitation is that high-intensity focused ultrasound cannot be used to treat vertebral metastases.

Treatment decision in patients with bone metastases requires complete staging, biopsy, and oncological principles. Useful algorithms for decision-making and treatment have been proposed; pain should be first treated with analgesics, bisphosphonates, and denosumab, and secondly with radiotherapy, electrochemotherapy, radiofrequency ablation, embolization, high-intensity focused ultrasound, and chemotherapy, and finally, if there is no pain relief radiation, electrochemotherapy, radiofrequency ablation, embolization, and high-intensity focused ultrasound can be repeated.

26.7.8 Interventional Oncology Procedures and Bone Augmentation (IO)

Many of the above-described techniques can be now performed percutaneously, with minimal trauma, as they can be image-guided procedures (Figs. 26.1 and 26.2). Imaging techniques

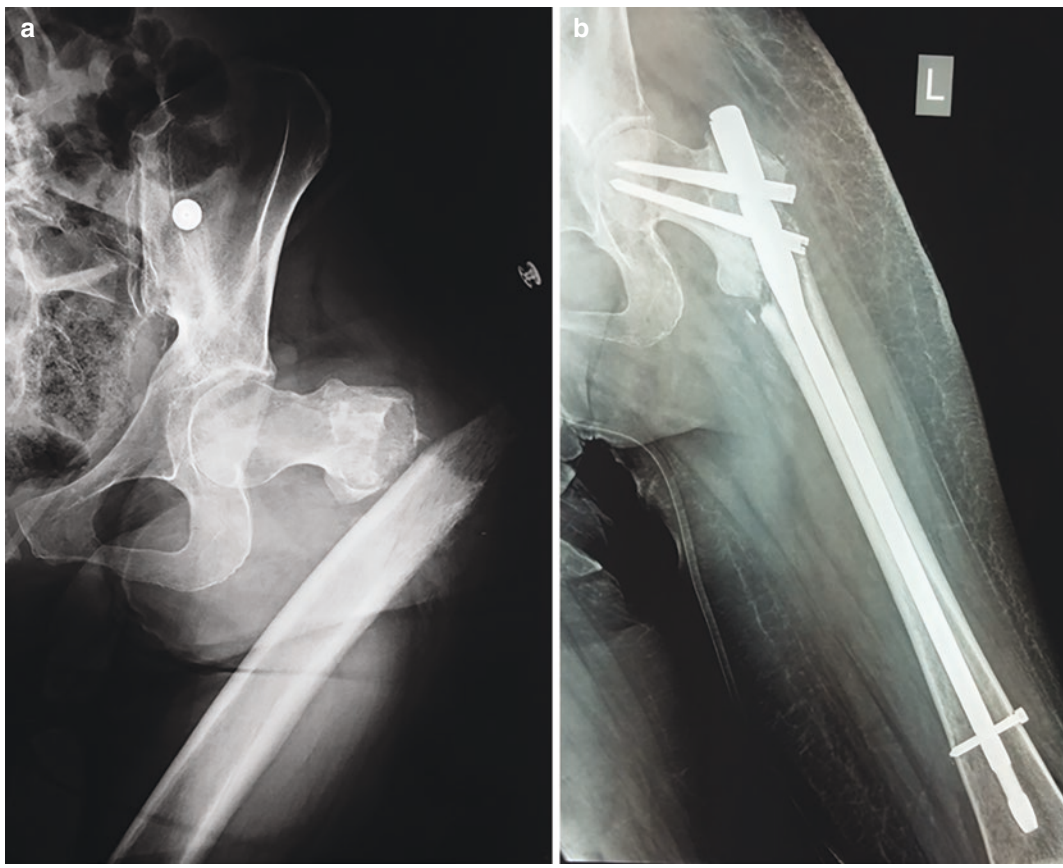

Fig. 26.1 (**a**) A female patient with a pathological subtrochanteric left-hip fracture; biopsy showed breast cancer. (**b**) Closed reduction and reconstruction-type intramedullary nail osteosynthesis were done

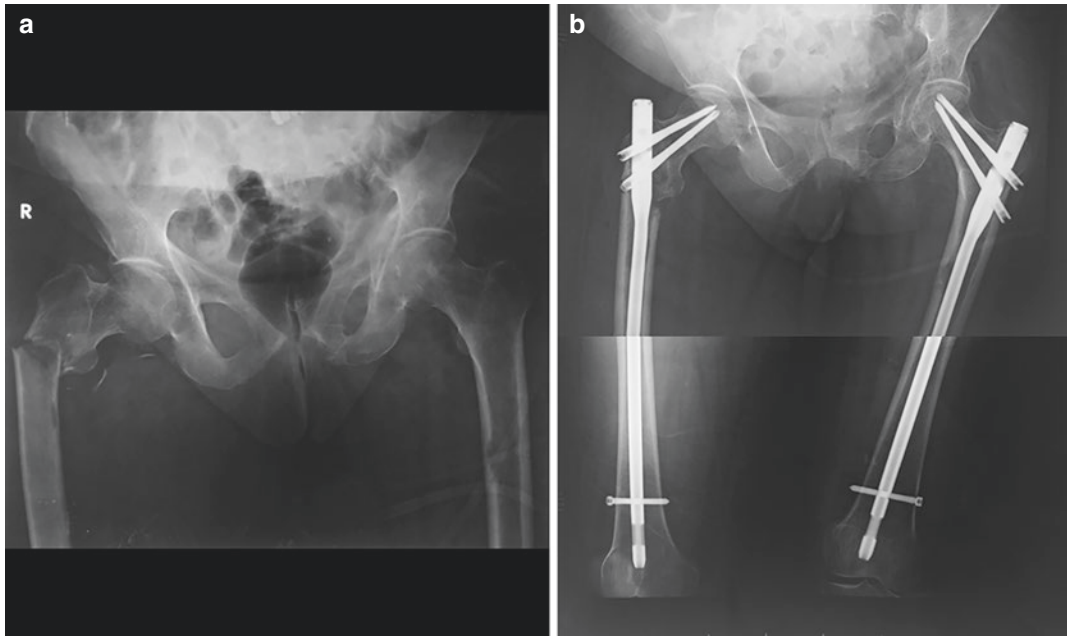

Fig. 26.2 (**a**) A female patient with a pathological subtrochanteric right-hip fracture and impending left-hip fracture; biopsy showed breast cancer. (**b**) Closed reduction of the right hip fracture and reconstruction-type intramedullary nail osteosynthesis of both femurs were done

vary from simple ultrasound guidance for soft tissue lesions to CT, MRI, and cone beam CT reconstructions with the use of C-arm or angiographic suites. Developments in this field include fusion imaging and needle guidance systems, which superimpose the needle track to the MPR reconstruction. The ablation techniques should usually be accompanied by stabilization procedures, especially in weight-bearing areas (Fig. 26.3), where the ablation affects the structural integrity of the bone. If the ablation occurs in non-weight-bearing areas, it can be a stand-alone procedure (Fig. 26.4). Otherwise, there is an increased risk of a secondary fracture and thus it should be accompanied by augmentation with intraosseous polymer injection (Fig. 26.5). This type of polymers could be percutaneously injected, independently, as a palliative procedure.

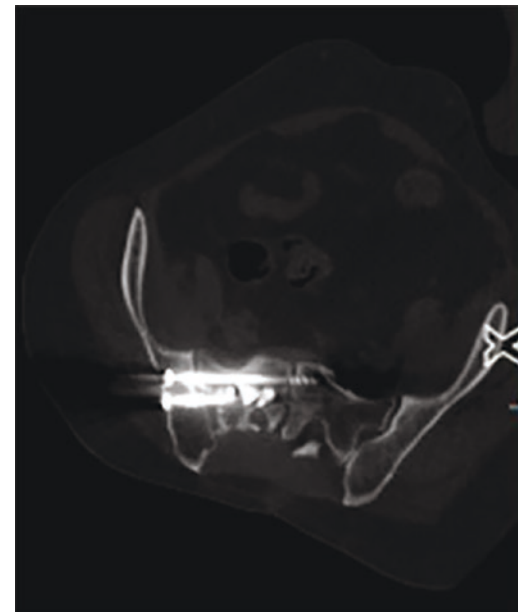

Fig. 26.3 A sarcoma male patient with residual tumor and a pathological fracture post-surgery and radiotherapy. The patient was treated with percutaneous microwave ablation combined to augment sacroplasty with cement injection and placement of two cannulated screws. Computed tomography axial reconstruction shows the cement and the cannulated screws in position

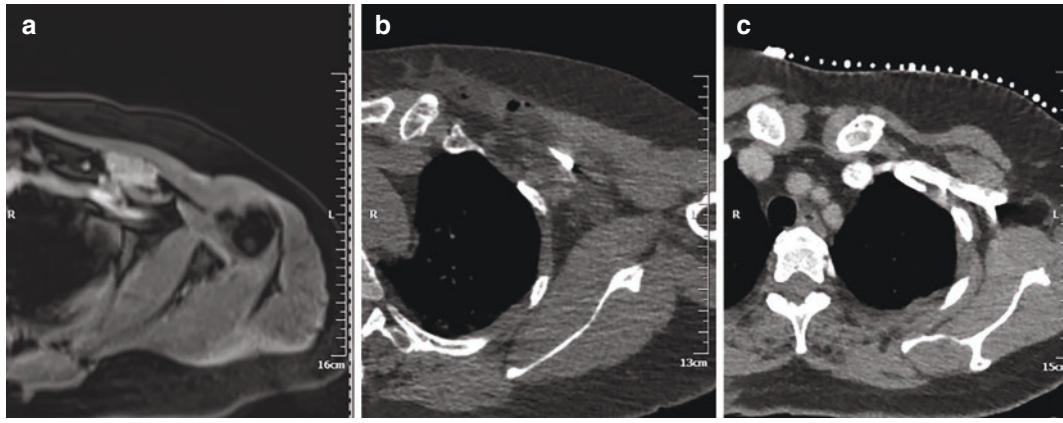

Fig. 26.4 A female breast cancer oligometastatic patient. (**a**) MRI post-contrast injection shows a solitary infraclavicular lymph node. The patient was treated with cryoablation under CT guidance. (**b**) Hypodense appearance of the ice around the needle. (**c**) Follow-up image at 6 months by contrast-enhanced CT shows disappearance of the lesion

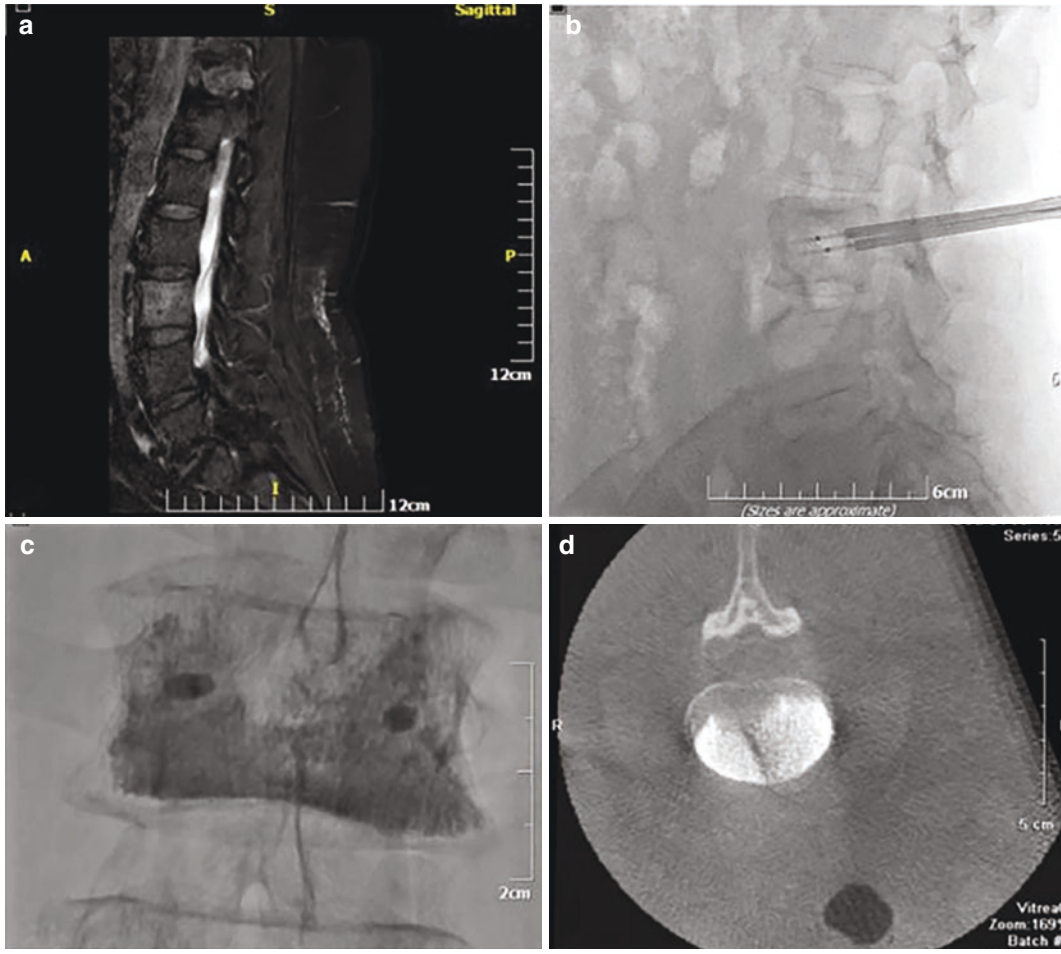

Fig. 26.5 A female breast cancer oligometastatic patient with a solitary L3 vertebral body metastasis. (**a**) T1-weighted sagittal fat suppression MRI shows lesion's uptake and enhancement. (**b**) Fluoroscopy lateral view shows two bipolar radiofrequency electrodes placed inside the lesion through percutaneous transpedicular approach. (**c**) Fluoroscopy posteroanterior view evaluates cement distribution following polymer injection. (**d**) Cone beam 3D CT reconstruction showing the filling of the vertebral body with the cement

Take-Home Message

- Bone metastasis occurs in most tumor types but is most prevalent in cancers of the breast, prostate, and lungs.
- Patients with bone metastasis may experience skeletal complications including bone pain, pathological fractures, spinal cord or nerve root compression, and hypercalcemia requiring orthopedic surgery and/or adjuvant treatments such as radiotherapy and chemotherapy.
- Acrometastasis is defined as bone metastasis distal to the elbow and the knee and accounts for approximately 0.1% of bone metastasis.
- Nonsurgical or minimally invasive palliative management is usually recommended for patients with very poor prognosis; radiotherapy, chemotherapy, vertebroplasty, and kyphoplasty have yielded satisfactory results for pain relief.

Summary

Bone is the third most common site for metastasis in cancer. Bone metastasis occurs in most tumor types but is most prevalent in cancers of the breast, prostate, and lungs. The incidence of bone metastasis in prostate cancer is 65–90%, in breast cancer 65–75%, and in lung cancer 17–64%, and it is less frequent in thyroid, renal, and colorectal (10%) cancers. Patients with bone metastasis may experience skeletal complications including bone pain, pathological fractures, spinal cord or nerve root compression, and hypercalcemia requiring orthopedic surgery and/or adjuvant treatments such as radiotherapy and chemotherapy. The main purpose of the treatment for bone metastasis is to improve symptoms and prevent symptomatic skeletal events. Paget's "seed and soil" hypothesis and Ewing's anatomical hypothesis have described the possible routes of migration and proliferation of cancer cells to bone. Pathological long-bone fractures in bone metastasis cause difficulties to the most experienced orthopedic oncology surgeons. Acrometastasis is defined as bone metastasis distal to the elbow and the knee and accounts for approximately 0.1% of bone metastasis. The prognosis of patients with acrometastasis is generally poor since it indicates a widespread disseminated disease in most cases. The spinal column is the third most common site for bone metastasis (after the lungs and the liver), and the most common site for bone metastasis; the thoracic spine is the most common spinal segment involved. Nonsurgical or minimally invasive palliative management is usually recommended for patients with very poor prognosis; radiotherapy, chemotherapy, vertebroplasty, and kyphoplasty have yielded satisfactory results for pain relief. The pelvis is the second most common site of bone metastasis after the spine. Clinical manifestations include pain, bone destruction causing mechanical instability, and pathological fractures. Palliative treatment of metastasis in any site of the skeleton includes radiotherapy, radiopharmaceuticals, chemotherapy, embolization, thermal ablation techniques, electrochemotherapy, and high-intensity focused ultrasound (HIFU).

Questions

Multiple correct answers are possible. Answers available in the book back matter.

1. The primary tumor that produces metastasis most frequently is:
   (a) Prostate cancer
   (b) Breast cancer
   (c) Lung cancer
   (d) Thyroid cancer
2. The seed and soil hypothesis stated that cancer cells metastasize:
   (a) Towards a favorable microenvironment or via the vessels
   (b) Per contiguity
   (c) At distance
   (d) Depending on the patient's characteristic
3. Acrometastasis accounts:
   (a) For 0.1% of bone metastasis
   (b) For 1% of bone metastasis

(c) For 10% of bone metastasis
(d) For 20% of bone metastasis

4. The most common site for bone metastasis is:
   (a) Spinal column
   (b) Femur
   (c) Distal radius
   (d) Knee
5. Bisphosphonates cause:
   (a) Osteoclast apoptosis
   (b) Osteoblastic generation
   (c) Osteoclast inhibition blocking RANK
   (d) Osteogenesis

Further Reading

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