Management of Metastatic Bone Disease Algorithms for Diagnostics and Treatment

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Abstract. Background: Bone is a frequent site of metastases in advanced cancer and is associated with significant skeletal morbidity. Current treatment options are aimed at preserving and improving functional independence and quality of life. Materials and Methods: A review of current literature focusing on diagnostic tools and treatment approaches of bone metastasis in advanced cancer was performed and conclusions were incorporated into diagnostic and treatment algorithms. Results: Radiologic imaging has added valuable tools for screening and diagnostics of bone metastasis. Clinical management of skeletal metastasis includes improved pain management, introduction of bone modifying agents and advancements in surgical and radiation therapy. We propose three algorithms enhancing the sensitivity of diagnostics and improving multidisciplinary management of vertebral and non-vertebral bone metastasis. Conclusion: Bone metastases are an expression of a systemic disease. Treatment options include highly specialized modalities yet need to be tailored to individual needs. Algorithms help standardize treatment procedures and can improve treatment outcome in a multidisciplinary setting.

Structural integrity of the bone is meticulously regulated through the actions of osteoclasts and osteoblasts. The dynamics of bone resorption and formation in this context are determined by the stress and force bone is subjected to and orchestrated by cytokines and other factors. The healthy skeletal structure is lost if this balance is disturbed by either bone metastasis or cancer treatment (1). In cancer patients, the skeletal morbidity is conferred upon by the burden of bone metastasis and by cancer treatment-induced bone loss (CTIBL). Cessation of hormonal support, necessary for maintenance of healthy bone structure, is a common problem for aging men and women. In this context of treatment, adjuvant use of aromatase inhibitors (AI) in breast cancer and androgen deprivation therapy (ADT) in prostate cancer are associated with an additional significant bone loss and an increased fracture rate (2-4). In fact, the Fracture Intervention Trial (FIT) showed a significant increase in mortality risk in postmenopausal women with osteoporosis-induced fractures (5). The lifetime risk of fracturing either the hip or spine averages almost 40% in women and 12% in men over 50, reflecting the need for early detection and treatment of these endocrine disturbances and the resulting osteoporosis (6, 7).

This increase in fracture rate and its consequences associated with use of an AI or ADT has not been adequately addressed in the oncology setting in the past. Increased awareness and approval of the osteoprotective agent denosumab, in this non-metastatic setting, has led to a significant reduction in bone fractures in postmenopausal breast cancer patients treated in the adjuvant setting with an AI and non-metastatic prostate cancer patients treated with ADT (8, 9). In addition to anti-hormonal treatment, prolonged chemotherapy can also affect the endocrine output of
reproductive hormones critically necessary for maintaining healthy bone metabolism (10, 11).

Metastasis to the bone occurs in 70% of advanced breast, lung, kidney, thyroid and prostate cancer, whereas patients with gastrointestinal cancers suffer from this form of metastasis in only 20% of cases. Metastasis to the bone can present itself as either lytic, blastic or as mixed lesions (12). In osteolytic bone lesions, bone resorption exceeds the rate of bone formation, whereas in osteoblastic lesions the opposite is true. In both cases, a fragile bone structure is produced. Bone metastases form breast cancer have been described as prototypic osteolytic lesions, whereas bone metastases from prostate cancer as osteoblastic metastases. Histologically, however, accelerated osteolytic and osteoblastic pathological processes can coexist in the same lesion, irrespective of the radiological appearance (13).

Various biological factors endorse the bone as a common site of cancer metastasis. Besides a favorable high blood flow to the red bone marrow, adhesive factors in the bone marrow stroma and the special environment within the hematopoetic stem cell niche allow tumor cells to take up residency and dormancy, thereby evading possible effects of systemic therapy (14).

About half the patients with these lesions suffer skeletal complications like pathological fractions, spinal cord compression and eminent pain requiring radiation therapy or surgery. These four complications are referred to as skeletal-related events (SRE) and confer morbidity and major loss of quality of life upon patients with metastasis of the bone. Several studies have even shown a reduction in overall survival (15-17). Pathological fractures and the necessity of radiation therapy are the most common SREs, emphasizing the extent of bone damage and pain associated with metastasis to the bone. Such pain-inducing complications further lead to immobility and loss of functional independence (18). Under-treatment of bone pain occurs in up to 60% of patients with advanced cancer and constitutes a major cause of psychological distress, manifesting itself in depression and anxiety (19, 20).

Current management of bone metastases entails a multidisciplinary approach since cancer is an expression of a systemic disease. Therefore, integrating various disciplines like orthopedic surgery, radiation oncology and medical oncology into the big picture of an individual case can cause some friction. The best course of action is not always straight forward since each specialty might look at the problem at hand from a different angle. The best way to unite these different angles and views is often through guidelines and algorithms, which can yield a foundation for decision making but can also be tailored to individual needs, often the case in advanced cancer.

Through implementing evidence-based diagnostics and interventions the striving for improvement in survival and prevention of SREs has the best chance to succeed. We, therefore, propose a clinical algorithm for diagnostics and treatment of bone metastasis and integrate the current management and research into it.

Algorithm I: Presentation and Diagnostics

Metastases of the bone can be asymptomatic and detected incidentally during initial staging, at follow-up examination in the adjuvant setting or at treatment re-evaluation restaging. However, in 75% of patients, metastatic bone disease presents with pain, warranting further examination (21). We propose a diagnostic algorithm in Figure 1.

Bones, which must endure constant static force, such as the hips, femurs and vertebral column, become symptomatic early on, whereas other non-weight bearing bones, such as ribs or skull, may only become symptomatic late in disease due to pathologic fractures. Common sites of bone metastasis are the proximal femurs, pelvis, spine, ribs and skull. Rarely, acral metastasis to the hands and feet occur, mostly associated with lung cancer (22, 23).

Besides pain and pathological fractures, hypercalcaemia is a hallmark of advanced cancer, occurring in only about 10% of the patients with bone metastasis. However, hypercalcaemia is often of paraneoplastic origin through parathyroid hormone-related protein without signs of metastasis to the bone (24). Spinal cord compression, through infiltrating vertebral metastases or fractured osteolytic lesions, can cause debilitating pain and major neurological deficits.

Presentation of localized pain in the context of cancer usually warrants radiological imaging. Due to cost restraints, a plain radiograph is usually the initial diagnostic step to evaluate bone pain. However, for bone metastasis to be recognized by this method, osteolytic lesions must be at least 1 cm in diameter with a loss of bone mineral of 25-50% (25). Higher resolution and additional three-dimensional anatomic information is achieved through computed tomography (CT) scans and magnetic resonance imaging (MRI) imaging. CT shows its strength in visualizing the cortical integrity and helps evaluate the extent of structural destruction, outperforming MRI in this aspect. With its high contrast resolution, CT easily differentiates between osteolytic lesions, sclerotic lesions and soft tissue. This virtue is particularly useful, when localizing lesions for biopsy (26).

With MRI very small skeletal metastasis can be detected. MRI is favored for detection of vertebral metastasis and evaluating their association with the spinal cord. These advantages and the multi-planar imaging capability make MRI a helpful imaging tool in preparation for surgical and radiation procedures (27, 28).

For initial staging of cancer disease or in the context of follow-up examinations in disease-free patients, nuclear bone scintigraphic imaging with Technetium-99 (99mTc) is widely
accepted since it evaluates the whole skeletal system and is relatively inexpensive. 99mTc bone-scan cannot directly detect osteolytic metastasis since it is incorporated into sites with elevated bone turnover rates and is, hence, a marker of osteoblastic activity (29). Osteolytic metastasis with minimal osteoblastic bone formation can, thereby, produce false negative bone scans. If hotspots are detected, CT or MRI is needed to clarify further anatomic detail. In disease-free patients and in the absence of other metastasis in the follow-up examinations, a biopsy may be necessary to confirm metastatic disease. In addition, patients with oligo/singular bone metastasis and in the absence of other/visceral metastasis need to be identified with a high sensitivity since potential curative localized treatment options may be warranted. Novel imaging technologies with projected increased sensitivity and specificity have not been adequately tested in prospective trials if they offer additional value in terms of impact on skeletal morbidity and survival through earlier and more reliable detection of metastasis (30, 31).

Algorithm II: Treatment of Vertebral Bone Metastases

When cancer metastasizes to the bone, the axial skeleton is preferred. Within the axial skeleton, the vertebral column is most often affected. In more than 10% of cancer patients, these metastases are symptomatic (32).

When treating metastatic lesions to the bone, a multidisciplinary approach is necessary to gain local control over the lesions by means of radiation therapy or surgery. We propose, therefore, algorithm II for treatment of vertebral bone metastasis in Figure 2.

When tumor masses and pathological fractures of the vertebra cause compression of myeloradicular structures (i.e. nerve roots, spinal cord) with neurological deficits or uncontrollable pain, immediate surgical intervention is warranted. To provide temporary relief of symptoms related to pressure and edema secondary to tumor mass a therapy with corticosteroids should be concurrently initiated (33). Different factors must be considered when choosing the aggressiveness of the surgical intervention. Besides the preoperative neurological condition and the performance status, the aggressiveness of the primary tumor and the life expectancy of the patient are the determining factors (34). In advanced cancer diseases, a palliative decompression and stabilization, followed by radiation therapy, can improve the quality of life. However, if a prolonged overall survival is estimated, due to a very slow growing tumor or a relatively good prognosis, more aggressive interventions can be justified. Clearly, a sound interdisciplinary communication is necessary in order to select patients appropriately.

Pain inflicted by vertebral body fractures can also be treated by vertebroplasty or kyphoplasty. Kyphoplasty has been reported to cause less cement extravasation as the most common complication enabling a superior restoration of vertebral body height. Both techniques appear to have a comparable effectiveness in achieving pain relief; however, differences in functional outcome remain unclear (35).

Besides surgery, radiation therapy is an efficacious treatment method for local tumor control and for palliation of painful bone metastasis. For pain control, high response rates of 85% have been reported with complete pain relief in about half of the patients. Most responders showed fast symptom relief within the first 2 weeks (36). Radiation therapy promotes ossification of osteolytic bone metastasis and can numb small nerve endings, thereby relieving pain and increasing stability of the bone (37). For patients already treated with external-beam irradiation (EBRT), a re-treatment approach with stereotactic body radiation therapy (SBRT) can be considered. SRBT minimizes radiation doses to the spinal cord by precise radiation delivery to vertebral metastases, thereby allowing effective retirement in terms of pain and local tumor control of previously radiated regions with EBRT (38).

If symptomatic metastasis to the bone is diffuse and of osteoblastic nature, therapeutic radioisotopes can be a treatment choice. 153Samarium and 89strontium deliver a therapeutic dose of beta radiation simultaneously to multiple bone sites. 223Radium has a strong affinity towards the bone and emits short-ranged high energy α-particles to cells (39). In a Phase III Trial (ALSYMPCA) with patients with castrate-resistant prostate cancer and bone metastasis only, it proved its efficacy, compared to best supportive care, by improving overall survival and the quality of life, in addition to reducing skeletal morbidity. However, the patient population was heterogeneous, including patients who had previously received docetaxel and patients deemed either unfit or unwilling to receive chemotherapy (40).

Algorithm III: Treatment of Non-vertebral Bone Metastasis

The treatment goals and caveats of non-vertebral bone metastasis are similar to the previous said, with palliation of pain and preservation and restoration of function being the primary focus. We, therefore, propose algorithm II for treatment of non-vertebral bone metastasis in Figure 3.

Pathological fractures are clearly an indication for surgical intervention with internal fixation even in advanced disease. An impending fracture of a long bone can warrant in selected patients with advanced disease a prophylactic fixation followed by postoperative radiation therapy (41). We recommend a prophylactic radiation of asymptomatic non-vertebral bone metastasis to increase local tumor control. If multiple symptomatic non-vertebral bone metastases are present, a treatment with therapeutic radioisotopes can be considered.
Besides effective systemic cancer treatments, bone-targeted agents like biphosphonates and the receptor activator of nuclear factor-kB ligand (RANKL) antibody denosumab have changed the course of metastatic cancer to the bone by reducing skeletal morbidity (42, 43).

Biphosphonates accumulate in the bone where they decrease bone resorption and increase mineralization by inhibiting the osteoclasts and inducing their apoptosis. Possible anti-tumor and anti-angiogenetic effects are still matter of current research (44). Pamidronate and zoledronic acid have been approved in the US and Europe for the treatment of cancer-related bone complications. Both biphosphonates have been shown to reduce skeletal morbidity by 30%, lower the incidence of SREs and delay time to first SRE in patients with metastatic bone disease significantly (45). Zoledronic acid has shown a greater risk reduction for development of skeletal complications than pamidronate in breast cancer by multiple event analysis (46). More than half of the patients reported moderate pain improvement, lasting almost 12 weeks. Besides being an additional treatment approach for pain relief, biphosphonates are part of the standard therapy for hypercalcaemia (47).

Denosumab is a monoclonal antibody that inhibits osteoclast-mediated bone destruction by binding to RANKL (48). Denosumab has shown superior efficacy compared to zoledronic acid in breast cancer and castration-resistant prostate cancer regarding such clinical end-points as time to first SRE, prevention of subsequent SREs and overall risk (49-51).

In order to delay time to first SRE and reduce skeletal morbidity in patients, it is recommended to initiate treatment with bone-targeted agents as soon as metastases of the bone are diagnosed, regardless if the metastases are symptomatic or not. This incremental gain in time before first SRE translates into additional quality of life since the consequences of a SRE can alter the course of the disease. The costs of consecutive treatments for early SREs are by far higher than the costs of bone-targeted agents preventing or delaying first SREs (52, 53).

**Conclusion**

There has been major progress in reducing skeletal morbidity in CTIBL and management of bone metastases in the last years. In the advanced cancer setting, treatment of bone metastases aims at palliating pain, maintaining function and preventing SREs. The development of new bone-targeted agents has significantly reduced skeletal morbidity and increased quality of life for patients with metastatic disease involving the bone. It is recommended to apply these drugs early on at diagnosis of bone metastases and not to wait until symptoms arise.
Specific local treatment modalities for bone metastasis have to be incorporated into comprehensive treatment approaches reflecting the systemic nature of metastatic disease. Treatment algorithms can promote such integration of various disciplines like orthopedic surgery, radiation oncology and medical oncology, in pursuit of tailoring optimal treatment strategies to individual patient need.

Conflicts of Interest

Dr. Jehn has received consulting and speaker fees from Amgen and Merck. Prof. Diel has received consulting and speaker fees from Amgen, Medtronic, Riemser and Teva. Dr. Overkamp has received consulting and speaker fees from Amgen. Dr. Schaefer has received consulting and speaker fees from Amgen. Prof. Kurth has received consulting and speaker fees from Amgen, Roche and Implantcast.
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