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Contemporary Management of Metastatic Bone Disease: Tips and Tools of the Trade for General Practitioners

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Metastatic bone disease has a substantial impact on mortality and health-related quality of life. The aging of the population in the United States and the improved survival rate of patients with cancer have led to an increase in the prevalence of osseous metastatic lesions that are symptomatic and may require orthopaedic care. Skeletal related events in neoplastic disease include pain, pathologic fracture, hypercalcemia, and neural compression including spinal cord compression. Approximately 400,000 patients develop metastatic bone disease in the United States annually, and bone is the fourth most common metastatic site, after the lymphatic system, lung, and liver¹⁻³. Seventy percent of patients with metastatic breast or prostate cancer compared with 20% to 30% of patients with metastatic lung or gastrointestinal cancers develop bone metastases². Breast cancer patients experience a mean of 2.2 to 4.0 skeletal events annually, while prostate cancer patients experience a mean of 1.5 skeletal

events³. The general orthopaedic practitioner is the primary evaluator and treating physician for an increasing population of patients with skeletal events. The purpose of this paper is to review contemporary strategies for the management of metastatic bone disease.

Prognosis in metastatic bone disease is determined by the primary tumor and cell type. Table I illustrates some of these differences as well as current survival estimates^{4,5}. Figures 1-A and 1-B show a pathologic fracture related to metastatic breast carcinoma that healed following internal fixation and radiation. An accurate diagnosis and staging of metastatic bone disease are fundamental to guiding an evidence-based approach to management.

Diagnosis

The clinical evaluation and diagnostic studies of the patient who presents with a skeletal lesion of unknown etiology should be approached carefully and thoughtfully. Although the approach

should be individualized, a general workup might include any of the tests shown in Table II in addition to a complete history and physical examination. This workup identifies 85% of primary lesions⁶. Another 10% are identified by biopsy. The remaining 5% generally remain undiagnosed despite extensive workup and biopsy. It is important to recognize primary bone tumors, or solitary or oligometastatic tumors, because the goals of treatment may include complete local resection to improve survival. Even patients with a known primary and/or known metastatic disease may warrant a biopsy of the new lesion for confirmation, especially if the patient has been disease-free for a prolonged period of time, and if the lesion is not characteristic of the known primary tumor.

Indications for Treatment

Treatment of metastatic bone disease is guided by the nature of the skeletal related event, the responsiveness of the

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TABLE I Tumor Characteristics

Primary Tumor	Common Type of Bone Destruction	Fracture-Healing* (%)	5-Year Relative Survival Rates with Distant Metastases† (%)	Radiosensitivity‡
Breast	Mixed	37	23.8	+++
Lung	Lytic	0	3.7	++
Thyroid	Lytic	NA	53.9	++
Kidney	Lytic	44	11.6	-
Prostate	Blastic	42	27.8	+++
Melanoma	Lytic	NA	15.1	++

*Data are from the study by Gainor and Buchert⁴. NA = not available. †Data are from the American Cancer Society⁵. ‡Radiosensitivity was rated as high (+++), intermediate (++), low (+), or none (-).

lesion to adjuvant care, and the overall condition and survival expectation of the patient. Pathologic fractures are an important cause of morbidity and mortality in patients with metastatic bone disease. Pathologic fractures have a diminished ability to heal spontaneously. Fracture stabilization with internal fixation or arthroplasty may

substantially improve patient mobility and quality of life. In the lower extremity and spine, internal fixation should be performed in most patients expected to survive another six to twelve weeks. Although morbidity and even mortality (8% for total hip replacement) can be high, intervention substantially improves the remaining quality of life⁷. In

the upper extremity, conservative measures are more likely to be successful, particularly in patients with limited life expectancy.

Impending pathologic fractures are often more easily treated, with less morbidity and easier recovery, than completed fractures. The rating system described by Mirels (Table III)⁸ is the

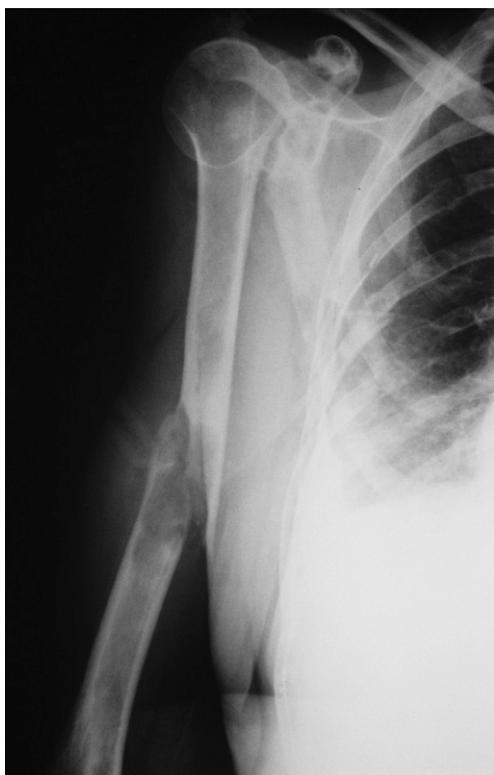


Fig. 1-A



Fig. 1-B

Figs. 1-A and 1-B A patient with metastatic breast carcinoma who developed a pathologic fracture of the humerus. **Fig. 1-A** Preoperative anteroposterior radiograph of the humerus demonstrating the pathologic fracture. **Fig. 1-B** Radiograph made after internal fixation and radiation therapy showing healing of the fracture.

TABLE II Testing Considerations for Workup of a New Skeletal Lesion

Laboratory Studies
Complete blood-cell count with differential
Electrolytes, blood urea nitrogen, and/or creatinine
Erythrocyte sedimentation rate
Liver function tests
Urinalysis
Calcium
Prostate-specific antigen
Carcinoembryonic antigen
Serum protein electrophoresis and immunoelectrophoresis
Radiographic Studies*
CT of chest, abdomen, and pelvis
Whole-body bone scan
Whole-body PET and/or CT scan

*CT = computed tomography, and PET = positron emission tomography.

most widely used predictor of pathologic fracture, and its use has demonstrated 91% sensitivity and 35% specificity⁹. Prophylactic fixation is recommended with a score of ≥ 9 , and should be considered with a score of 8. Those with a score of < 8 should be considered for local irradiation. The final decision to perform surgery should also consider individual patient-related factors such as his or her size and activity level.

The Spine Instability Neoplastic Score (SINS) classification system was developed by an expert panel to estimate the stability of tumors affecting the spinal column (see Appendix)¹⁰. The SINS classification is based on tumor behavior and the radiographic and clinical presentation of the patient with a tumor affecting the spine. Patients with a score of < 8 points have a stable spinal column and are at low risk for spontaneous vertebral fracture. Patients with a score of 8 to 12 points are at intermediate risk of spinal column fracture, or deformity, and patients with a score of > 12 points are at high risk.

General Considerations of Surgical Treatment

Occasionally, the patient with a solitary or oligometastatic disease should have a resection of the disease. Although cure likely occurs quite rarely, evidence has suggested that aggressive management of an isolated metastasis can pro-

long patient survival and improve palliation^{11,12}. These benefits are most likely to become manifest in patients with an isolated metastasis occurring after a prolonged disease-free interval following treatment of a localized primary tumor. Aggressive surgical management of a solitary thyroid metastasis much more often results in cure or at least substantial prolongation of survival.

Improved quality of life is the goal. When operative intervention is indicated, the surgical approach, choice of fixation, and use of adjuvant (polymethylmethacrylate [PMMA] or bone graft alternatives) should allow immediate and unrestricted weight-bearing without splint, cast, brace, or assistive device. Operative fixation should be durable for the life expectancy of the patient. PMMA is often used to provide immediate strength to the fixation¹³⁻¹⁸. PMMA is most beneficial in noncontained metaphyseal or acetabular defects when combined with internal fixation, and it

can improve screw fixation in pathologic bone. The exothermic polymerization reaction may kill tumor cells and minimize blood loss¹⁹. Biologic agents not only require time for incorporation (during which activity must often be restricted) but also may be limited by treatment and host factors. The surgical construct should be expected to last for the lifetime of the patient and, depending on the primary tumor and its susceptibility to adjuvants, may need to incorporate the possibility of local tumor progression.

All areas of weakened bone present at the time of the operation as well as all areas likely to be weakened subsequently should be addressed in any planned reconstruction. Perioperative planning should include imaging of the entire bone and whole-body bone scan. Computed tomography (CT) and three-dimensional reconstructions are recommended for metastatic lesions in the periacetabular region and the spine in order to estimate the extent of osteolysis and compromise of cortical boundaries. Magnetic resonance imaging (MRI) is useful to assess epidural extension of the tumor and neural compromise in patients with metastatic disease affecting the spine. In the peripheral skeleton, MRI may overestimate the extent of tumor involvement to the bone and soft tissues, and offers poor assessment of the integrity of bone cortices and internal architecture. Other advanced imaging may include preoperative arteriography for assessment of the vascularity of metastatic lesions. Highly vascular lesions including renal cell cancer may benefit from preoperative embolization before resection or instrumentation to limit intraoperative bleeding²⁰.

TABLE III Mirels Rating System for the Prediction of Pathologic Fracture Risk⁸

Score	Site	Nature	Size*	Pain
1	Upper extremity	Blastic	$< 1/3$	Mild
2	Lower extremity†	Mixed	$1/3$ to $2/3$	Moderate
3	Peritrochanteric	Lytic	$> 2/3$	Functional

*Relative proportion of bone width involved by tumor. †Nonperitrochanteric lower extremity.

In the extremity long bones, both intramedullary and plate fixation are viable options, and current evidence, beyond biomechanical theory, does not support one intervention over the other. Intramedullary fixation provides the option of including the majority of the long bone in the reconstruction so that local extension of disease will have a limited effect on the stability of the fracture; however, the need to do so remains controversial. At least one study has demonstrated that prophylactic treatment of uninvolved areas of the bone has a much higher chance of causing complications related to the extended fixation than generating a benefit from the prophylaxis, as substantial disease progression in uninvolved areas turns out to be a rare event²¹. In more limited areas of bone involvement, plate fixation allows better segmental defect reconstruction and realignment. Plate fixation is generally superior for addressing meta-epiphyseal lesions, except in the proximal aspect of the femur. Although specific recommendations regarding choice of implant and extent of fixation are not well supported by evidence, the general principle is that the chosen reconstruction should allow immediate and unrestricted weight-bearing, should not require osseous healing for success, and should allow for some degree of disease progression. It would follow, therefore, that intramedullary devices should be statically locked, locking plates should be considered where appropriate, and the extent of fixation proximal and distal to the lesion should be sufficient to best ensure a solid construct and allow for some local tumor progression. Endoprosthetic reconstruction is generally the procedure of choice for tumors with extensive epiphyseal involvement and periarticular fractures not amenable to stable fixation. Specific strategies for surgical management of metastatic disease to skeletal regions are detailed in the following section.

Upper Extremity

The management of metastatic disease to the bones of the upper extremity is

more elective than treatment of metastatic disease to the lower extremity because the patient can usually be comfortable and active with nonoperative treatment although operative fixation often improves function.

The authors recommend curettage and reconstruction with plate, screws, and PMMA for lesions in the proximal part of the humerus if there is sufficient bone; otherwise, a cemented hemiarthroplasty is recommended if the tuberosities are preserved or proximal humeral endoprosthetic replacement if they are not. Diaphyseal lesions without segmental bone loss may be treated with plate fixation and PMMA or intramedullary rod with or without PMMA. When there is a large segmental loss, an intercalary replacement (endoprosthesis or allograft) is often necessary. Distal humeral lesions should be treated with column reconstruction utilizing plate fixation and PMMA. Olecranon osteotomy should be avoided if possible, as healing may be impaired by radiation. Total elbow replacement should be considered with substantial epiphyseal destruction.

Metastatic involvement distal to the elbow is rare. Lesions of the forearm are generally best treated with plate fixation and PMMA.

Lower Extremity

Pelvis and/or Acetabulum

Patients with painful metastases involving the non-weight-bearing areas of the ilium, ischium, pubis, and sacroiliac joints are treated effectively with radiation therapy.

Tumors involving the periacetabular pelvis are challenging²²⁻²⁴. The Appendix shows a contemporary adaptation of the classic Harrington system for classifying and managing acetabular deficiencies. We recommend nonoperative management initially as many respond favorably to radiation. Protrusion of the femoral head into the pelvis is not an emergency, is not associated with intrapelvic complications, and does not dramatically alter the reconstruction; therefore, prophylactic surgery done solely in an effort to prevent protrusion is not

warranted. Figures 2-A and 2-B show an example of an acetabular metastasis with protrusion before and after reconstruction.

Femoral Head and Neck

Endoprosthetic reconstruction is the treatment of choice in this location because of the high risk of failure associated with internal fixation of existing or impending pathologic fractures^{25,26}.

Intertrochanteric Femoral Involvement

In the presence of limited bone loss, curettage of the tumor, packing of the defect with PMMA, and stabilization with a hip screw side plate or intramedullary hip screw are satisfactory options. Beyond biomechanical theory, there is a lack of evidence to support one technique over the other. PMMA strengthens the reconstruction particularly with a noncontained defect. There is no evidence to support curettage of the tumor per se beyond what is necessary to facilitate the reconstruction. With more extensive bone loss, endoprosthetic reconstruction should be considered with reconstruction of the calcar through implant selection or PMMA. In the presence of extensive involvement of the greater trochanter, a proximal femoral replacement prosthesis is indicated.

Subtrochanteric Femoral Involvement

Forces in this region may reach six times body weight, placing extreme demands on fixation devices²⁷. Second and third-generation intramedullary reconstruction nails are generally the treatment of choice in this area and allow for an array of fixation alternatives in both proximal and distal interlocking. Use of a proximal femoral replacement prosthesis should be considered when proximal bone is unlikely to provide stable fixation with nails despite the use of PMMA, if previous fixation has failed, or with extensive peritrochanteric tumor involvement. The disadvantages of routine use of these prostheses include cost, need for increased exposure, bleeding, neurovascular injury, and hip abductor muscle weakness^{28,29}.



Fig. 2-A

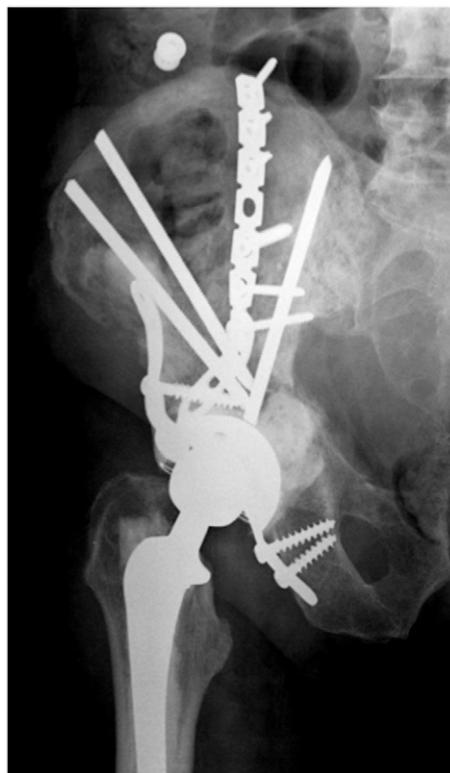


Fig. 2-B

Figs. 2-A and 2-B A patient who had an acetabular metastasis. **Fig. 2-A** Preoperative anteroposterior radiograph showing the pathologic fracture of the acetabulum with protrusion. **Fig. 2-B** Radiograph made after reconstruction showing internal fixation, PMMA, protrusion cage, constrained liner, and cemented femoral stem.

Femoral Shaft

Closed intramedullary nailing is appropriate for small tumors. Larger lesions with open section defects may require open curettage with PMMA in addition to internal fixation. Routine treatment of the “entire bone” with a reconstruction type of intramedullary nail remains controversial but should be considered in patients with prolonged life expectancy and with multiple myeloma. A few large diaphyseal lesions require a modular intercalary prosthesis. Rarely, a total femoral replacement is needed for the patient with extensive involvement of the femur.

Distal Part of the Femur and Proximal Part of the Tibia

Smaller lesions in this area may be treated with osteosynthesis and PMMA. Large destructive lesions in the distal aspect of the femur and proximal part of the tibia should be treated with plate fixation when the articular surface can

be maintained and the joint is otherwise normal. When the articular surface cannot be maintained, or the patient has advanced osteoarthritis, a total knee replacement is indicated. With extensive bone loss, proximal tibial replacement may be required. The extensor mechanism should be preserved when possible. When the patellar tendon attachment cannot be preserved, extensor mechanism reconstruction can be performed; however, the necessary use of muscle flaps and the complex rehabilitation required must be balanced with patient survival.

Tibial Shaft and Distal End of the Leg

Lesions in the tibia and foot are rare. Small radiosensitive lesions can be treated with plate fixation and PMMA. Intramedullary nailing is a favorable option in the tibial shaft. As in the femoral and humeral shafts, segmental defects may be addressed with a modular intercalary prosthesis if necessary

(Fig. 3). Occasionally, below-the-knee amputation is required for advanced refractory disease that is causing substantial impairment.

Spine

The spine represents the most common site for metastatic disease to the skeleton. Tumors affecting the spinal column have a substantial and measurable impact on health-related quality of life in affected patients. Specific domains affected include pain, physical function, neural function, mental health, and social function. Outcome instruments specific for patients with tumors affecting the spine may be more responsive to change than generic health outcomes measurement instruments³⁰.

Spinal stability measured by the SINS classification system and neural compromise are important considerations in choosing a strategy for the management of tumors affecting the spine. For patients with a stable spine



Fig. 3
Intercalary prosthesis used to reconstruct segmental defect of tibia.

and a radioresponsive tumor, radiation therapy is generally considered the treatment of choice. Confocal beam radiation may considerably improve the dose of radiation at the site of the tumor while protecting adjacent tissues. However, radiation therapy has limited utility in patients with an unstable spine, a fracture of a vertebra, or with neural impairment due to tumor or bone compressing the neural elements.

Effective surgical approaches to metastatic disease include vertebral augmentation or open decompression and realignment of the spinal column with internal fixation. Vertebral augmentation with kyphoplasty or vertebroplasty can be effective in stabilization of a pathologic vertebral fracture in most levels of the spine³¹. A percutaneous approach to vertebral augmentation permits stabilization of the spine with limited morbidity. Vertebral augmentation is especially effective for patients with myeloma of the spine, and patients with vertebral lesions without extension

to the epidural space and without neural compromise³². Vertebral augmentation may be followed within days by radiation therapy to limit local recurrence of disease.

Patients with metastatic disease affecting the spinal column and neural compromise due to epidural extension of tumor or fracture, or to spinal deformity, are candidates for open decompression of the neural elements and primary reconstruction of the spine with internal fixation with or without vertebral augmentation. Patchell et al. reported considerably better improvements with regard to pain and neural function in patients with metastatic tumor affecting the spine and spinal cord compression who were treated with open decompression and stabilization of the spine with instrumentation and radiation compared with those who had radiation therapy alone³³. Tokuhashi et al. developed a scoring system for tumors affecting the spine that is useful in guiding a surgical approach to patients with metastatic disease affecting the spine³⁴. This system considers the primary tumor type, stage of disease, overall patient condition, and neural status of the patient in recommending options including nonoperative and operative care.

En bloc resection may be indicated for solitary and oligometastatic disease with treatable metastases. An effective en bloc resection requires an excision of the affected segments of the spinal column including extraosseous extension of the tumor. Survival in selected patients treated with an en bloc resection is improved compared with intralesional approaches^{35,36}. The surgical staging system of Boriani et al. is useful in planning margins for resection³⁷. The en bloc resection is not appropriate for patients with tumor extending to the epidural space or patients with substantial comorbidities and limited life expectancy.

Adjuvant and Alternative Modalities **Radiation Therapy**

Radiation therapy is an important adjunctive modality in the treatment of metastatic bone disease. It may be used

prophylactically for lesions at risk for subsequent fracture. Perioperative external beam radiation therapy is associated with a decrease in the rates of secondary procedures and improved functional status of patients with previously unirradiated long bone, acetabular, and spinal lesions. Additionally, it minimizes disease progression and risk of implant failure³⁸. Postoperative irradiation does not appear to have a significant effect on callus formation and does not adversely affect PMMA strength³⁹. Hypofractionation (single dose) compared with standard course (approximately two-week) therapy is currently under investigation at some centers. Confocal beam radiation may be useful in targeting tumor specifically, and limiting damage to surrounding radiosensitive tissues, especially for metastatic bone lesions affecting the spine and epidural space. Confocal beam radiation therapy may also permit repeat treatment of regions that have been treated previously with a maximal tolerable dose of external beam therapy.

All tumors are sensitive to radiation therapy; however, the doses required to achieve a response are widely variable by tumor type. So-called radiosensitive or radioresponsive tumors tend to respond to lower doses of irradiation and include myeloma, lymphoma, breast, and prostate carcinomas (Table I). So-called radioresistant tumors, such as renal cell carcinomas and sarcomas, require much higher doses. Lung and thyroid carcinomas and melanoma generally demonstrate intermediate responsiveness.

Medical Management

Medical management consists of symptom control, cytotoxic chemotherapy, and targeted therapy. Although a detailed discussion of these modalities is beyond the scope of this article, a concise review of targeted therapy is relevant.

Bisphosphonates, pyrophosphate analogs that bind calcium and concentrate in bone, are ingested by osteoclasts causing inhibition of pyrophosphate

and osteoclast cell death. Bisphosphonates also inhibit growth in tumor cell lines, decrease motility of tumor cells, demonstrate synergy with cytotoxic chemotherapy, decrease metastatic spread in mouse models, and may have immunomodulatory properties on T-cell activation.

In clinical trials of breast cancer patients, intravenous bisphosphonates have decreased skeletal related events, improved symptoms, and decreased locoregional and distant recurrence⁴⁰. Improvement with regard to symptoms and skeletal related events has also been shown with prostate and lung cancers and multiple myeloma. Oral forms have shown equivocal results. Risks of bisphosphonates include renal insufficiency, hypocalcemia, osteonecrosis of the jaw, and subtrochanteric stress fractures.

Angiogenesis inhibitors (thalidomide and bevacizumab) selectively target endothelial cells inhibiting tumor angiogenesis.

Osteoblastic metastases are mediated by osteoblasts. Breast and prostate cancer models implicate endothelin-1, which stimulates osteoblasts, in this process. Prostate-specific antigen affects PTHrP (parathyroid hormone-related protein) and may activate other growth factors. Calcitriol (vitamin D3) and endothelin-A receptor inhibitors (atrasentan and ZD4054) selectively target osteoblast activity.

Osteolytic metastases are mediated by osteoclast activity. In tumor models, interleukin-6 (IL-6) upregulation affects tumor cells and osteoclasts, RANKL (receptor activator of nuclear factor- κ B ligand) elaboration from tumor cells decreases production of osteoprotegerin, and PTHrP binding to stromal PTHrP (parathyroid hormone receptor 1) increases RANKL, which increases osteoclast activity. These factors, along with other complex factors within the bone-tumor milieu, precipitate bone demineralization, which releases bone morphogenetic protein (BMP), insulin-like growth factor-1 (IGF-1), and transforming growth factor- β (TGF- β), which in turn feed tumorigenesis resulting in a vicious

cycle. The drug denosumab directly binds RANKL, downregulating osteoclast activity, and may be beneficial.

Emerging Technologies

Radiofrequency Ablation

Radiofrequency ablation is a high-frequency alternating current used to destroy tumor cells. Radiofrequency ablation can be used to control local tumor growth, prevent recurrence, palliate symptoms, and extend survival duration for patients with certain tumors. It can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or CT. Radiofrequency ablation may be combined with conventional therapies or other percutaneous treatments such as cementoplasty.

Cementoplasty

Percutaneous injection of PMMA, with or without radiofrequency ablation, has demonstrated proven utility in the treatment of metastatic bone disease in both the spine and extremities. Although long-term results for the treatment of osteoporotic compression fractures have been equivocal^{41,42}, improved results have been demonstrated in the treatment of osseous spine metastases^{31,32}. Palliative improvements in the extremities⁴³⁻⁴⁶, acetabulum⁴⁷, and sacrum⁴⁸ have also been reported.

Although these procedures are often performed by physicians who are not orthopaedic surgeons, it is important to maintain a multidisciplinary approach with orthopaedic input in an effort to minimize complications⁴⁹. The ability to care for spinal metastasis with comprehensive approaches, ranging from percutaneous to open, empowers the orthopaedic surgeon to remain central to patient care through the spectrum of metastatic bone disease.

Overview

Metastatic bone disease remains a challenging orthopaedic problem. However, appropriate multidisciplinary interventions can decrease the prevalence of skeletal related events and have a profound impact on the quality of life of

affected patients. Interventions on the horizon show promise in improving our ability to address challenges and further improve patient care and outcomes.

Appendix

 Tables showing the systems for the Spine Instability Neoplastic Score and for the classification and management of acetabular defects are available with the online version of this article as a data supplement at jbjs.org.

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