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Metastatic Bone Disease

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With improved medical treatments of cancer, cancer patients are living longer and many will go on to develop metastatic disease. Bone is the third most common site of metastasis. Bony metastasis is an important contributing factor to the deterioration of patient's lives due to pain, fracture, and loss of function. Bony metastasis is a problem that will be affecting increasing numbers of patients and most practicing orthopaedic surgeons will provide care to this group of patients. A biopsy and staging workup are essential in the initial treatment of patients with bony lesions. Treatment for patients with metastatic disease is primarily palliative, with the goals of limiting pain and rapidly returning patients to function. Surgical indications include pathological fractures, impending pathological fractures, and intractable pain that have failed non-operative management. Treatment of pathological fractures differs from treatment of conventional fractures due to effects of tumor biology on host bone and effects of cancer on patients' general medical condition. Through an understanding of these factors, the orthopaedic surgeon can use techniques that maximize the likelihood of creating a lasting, stable construct, resulting in elimination pain and rapid return of patients to function.

With improved medical treatment of cancer, cancer patients are living longer and many will go on to develop metastatic disease[1, 2]. After lung and liver, bone is the third most common site of metastatic disease. Sixty to eighty-four percent of patients with metastatic disease have bony involvement with 70% of these patients suffering from bony pain as a result of their disease[3]. Metastatic bone disease is a major contributor to the deterioration of the quality of life of patients with cancer as it causes pain, impending and actual pathological fractures, and loss of function[4]. The majority of bony metastatic lesions will be treated non-operatively with modalities such as radiation, chemotherapy, radio-frequency ablation, immunotherapy, hormonal therapy, bone-seeking isotopes, and bisphosphonates[5-8]. Some patients, however, will require orthopaedic intervention. The purpose of orthopaedic intervention is primarily palliative, with the objective of improving the quality of the patient's remaining life. Although many cancer patients will ultimately be treated by orthopaedic oncologists, most orthopaedic surgeons will be faced with the task of providing care to patients with metastatic disease.

The appropriate initial work-up for patients presenting with an aggressive bone lesion is of paramount importance, and failure in this regard may compromise the intended outcome. The initial imaging test of choice is plain radiography with orthogonal views. Aggressive lesions are typically larger than 5 cm, have a wide margin of transition between lesion and normal medullary bone, display cortical interruption, periosteal reaction, and may include pathological fracture. In patients older than 40, the likelihood that an isolated aggressive bony lesion is metastatic is 500 times greater than it being a primary sarcoma; nonetheless, it is imprudent to proceed to treatment without a staging workup or a biopsy[9]. Prior to definitive treatment, a tissue diagnosis should be obtained in all cases other than when there is a known, histological diagnosis of bony metastatic disease. Even in cases in which patients are known to carry a diagnosis of cancer, a staging workup may be indicated before proceeding to treatment of a bony lesion. In patients presenting with a significant pathologic fracture, it may not be feasible to perform multiple scans for staging. In this case, the surgeon can proceed with biopsy but should not proceed with definitive treatment unless it can be established via the biopsy that the lesion is not a sarcoma. Some of the reasons to establish a diagnosis and provide staging include[10]:

1. The possibility that the lesion could be a sarcoma; thus, a biopsy would prevent inappropriate treatment such as inadvertent passage of a reamer though the lesion.
2. Other lesions may be identified which are more amenable to biopsy than the index lesion.
3. Additional lesions may be identified that alter local treatment or require separate treatment.
4. Preoperative embolization may be required to prevent excessive bleeding (i.e. renal cell carcinoma).
5. A biopsy may be avoided if a diagnosis can be made through a noninvasive diagnostic test such as serum or urine protein electrophoresis for multiple myeloma.
6. A full staging workup will aid the pathologist in making the correct tissue diagnosis.
7. Non-surgical treatment by be equally efficacious as surgical treatment in some cases.

Elements of the staging work-up include:

1. History: This may identify additional areas of pain that need to be imaged. History may also point towards a source of the primary lesion if it is unknown. The patient's overall functional level, level of mobility, social supports, ongoing oncologic treatments, and medical co-morbidities may impact the orthopaedic treatment plan.
2. Physical exam: This may also identify additional areas of abnormality that need to be imaged.

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In addition, neurological deficits, vascular insufficiency, areas of skin compromise, and overall strength and level of fitness can be determined.

3. Lab studies, to identify anemia, thrombocytopenia, and electrolyte abnormalities such as hypercalcemia that are occasionally seen with metastatic bone disease.
4. Specialized tests, such as serum and urine protein electrophoresis, or prostate specific antigen, may be helpful when history and physical exam point towards specific diagnoses.
5. Advanced local imaging, such as CT or MRI may be helpful when primary disease is considered a possibility, or when further elaboration of the anatomy of the lesion is needed.
6. Whole body bone scintigraphy and orthogonal plain radiographs of entire long bones of any lesions that are identified and may require treatment.
7. Computed tomography of the chest, abdomen and pelvis, in cases when the primary lesion is unknown.
8. PET scanning, which has high sensitivity for identifying tumors, infections, and other physiological processes throughout the bone and soft tissues of the body, is an emerging technology which may become a part of the staging work-up.
9. The last step in staging is biopsy, either percutaneous or incisional.

Operative indications for skeletal lesions include most pathological fractures, impending pathological fractures, and intractable pain that has not responded to non-operative treatments[11-13]. Operative intervention for metastatic disease is generally a palliative procedure. The goals of surgery are to achieve local tumor control and restore structural stability of the affected bone in order to restore function as quickly as possible. Patients with metastatic disease have a shortened life-span, therefore surgical intervention should have the aim of allowing immediate use of the affected part via creation at surgery of a stable mechanical construct

Most pathological fractures benefit from surgical intervention. It has been suggested that non-operative treatment may be a reasonable option in patients that have a pathological fracture in a non-weight bearing bone or one where fixation is not indicated, such as the proximal fibula, clavicle, or scapula or in some tumors about the acetabulum[4]. Thus, most pathological fractures in other weight-bearing bones should be treated operatively when the patient has an acceptable life span and their general medical condition is such that the risks of surgery are not excessive.

Most surgeons approach the decision regarding projected-life span and a decision for surgery on a case by case basis. However, a minimum life span of 6 weeks has been suggested for relatively simple procedures such as intramedullary nailing, while a minimum life span of 6 months has been suggested for complex procedures such as acetabular or endoprosthetic reconstruction[4]. Risk factors associated with an increased rate of early post-operative death include hemoglobin < 7, increasing numbers of bony metastases, visceral metastases, and lung cancer[14, 15]. Consultation with medical and/or radiation oncologists is critical to aid the orthopaedic surgeon in estimating the patient's remaining life span, to provide pre-operative risk stratification, and to properly time the planned surgery in terms of chemotherapeutic issues. With this information, the patient and surgeon may have an informed discussion regarding the risks and benefits of surgery.

The decision to operate on an impending pathological fracture also requires careful consideration. The advantages of prophylactic fixation of an impending fracture include avoiding the pain and loss of function that result when a pathological fracture occurs. In addition, internal fixation of a bone prior to fracture is generally a safer, easier, faster operation than fixation after a fracture has occurred. However, if there is only a low likelihood that a pathological fracture will occur, it may be in the patient's best interest to avoid the risks and recovery from an operation when non-operative treatments of the lesion may be appropriate. Therefore, an important determination is whether a lesion has a high or low likelihood of pathological fracture.

Harrington's classic definition of an impending pathological fracture of a long bone included cortical destruction of 50% or greater, a lesion 2.5cm or larger in the proximal femur, pathological avulsion fracture of the lesser trochanter, and pain with stressing the bone despite radiation therapy[12]. This was an inadequate classification. A scoring system based on 4 parameters has been developed by Mirel to predict the risk of fracture and recommend treatment (Tables I and II)[16]. Mirel's system is based on plain radiographs and clinical exam. It has been shown to be reproducible and more sensitive and valid than clinical judgment[17, 18]. The components of the scoring system are the location (upper extremity, lower extremity, or peritrochanteric region), radiographic appearance of the lesion (blastic, mixed, or lytic), width of the lesion within the involved bone (less than one third, one third to two thirds, or greater than two thirds), and pain (mild, moderate, or aggravated by function). A score of 1 to 3 points is given for each component of the scoring system and the aggregate score predicts the likelihood of fracture and serves as a guide for recommending for surgery. In the authors' opinion, any lesion that causes significant mechanical pain requires surgical intervention.

Surgery may also be indicated for intractable pain that has responded poorly to non-operative management such as chemotherapy and radiation therapy[11, 13, 19]. Intralesional resection and internal fixation may be a good option in cases where conventional medical treatments have failed. There are also a number of options that may be considered as alternatives to surgery. Radiofrequency ablation has been shown to be an effective means of achieving pain control[20, 21] The technique involves passing a wire into the lesion under image guidance and using alternating electric current in the tip of the probe to heat the surrounding tissues resulting in cell death through coagulative necrosis[22]. Another method that has been described for the treatment of painful lesions is percutaneous cryoplasty. Using this technique, cryoprobes are inserted percutaneously into the lesion and cooled to -100° C within a few seconds, resulting in intracellular ice crystal formation and dehydration causing cell death[21]. Cementoplasty in which polymethylmethacrylate is percutaneously injected to

TABLE I. Mirel's Scoring System for Risk of Pathological Fracture.

Score (points)	Site	Radiographic Appearance	Bone Width Involved	Pain
1	Upper extremity	Blastic	Less than 1/3	Mild
2	Lower extremity (non-peritrochanteric)	Mixed (blastic-lytic)	1/3 to 2/3	Moderate
3	Peritrochanteric	Lytic	More than 2/3	Aggravated by function

TABLE II. Mirel's Scoring-Based Treatment Recommendations.

Total Score	Risk of Fracture	Recommended Treatment
9 or greater	Impending	Prophylactic fixation
8	Borderline	Consideration of fixation
7 or less	Not impending	Nonoperative treatment

metastatic spinal and pelvic lesions has also been described as an effective method of achieving local pain control, while at the same time providing structural support to the affected bone[21]. These alternative techniques may be particularly appealing in patients who are poor surgical candidates, who have a limited life span, or who wish to avoid surgical intervention.

There are a number of important considerations when surgical treatment of a metastatic pathological fracture is considered. Techniques that would be adequate for conventional fractures may not be sufficient for pathological fractures[10]. Due to the nature of the osteolytic lesion often present in metastatic disease, there may be substantial bone loss at the fracture site. Furthermore, the bone that remains has weakened mechanical properties and only limited ability to heal compared to normal bone, especially in light of the usual need for radiation and/or chemotherapy. Considering the altered biology at the fracture site and patient's shortened life span, specific approaches must be employed for the operative fixation of pathological fractures in order to obtain the best outcomes. The goals of treatment include pain relief, immediate mechanical stability, and the creation of a construct that will outlast the patient's life expectancy, thereby allowing the patient to return to function as quickly as possible[10]. Common errors include misunderstanding the degree of altered biology and quantity of pathologic bone, underestimating the patient's life expectancy, creating a construct that fails before the patient's death, and failing to plan for future disease. Reoperation is a particularly undesirable outcome in patients with terminal disease. The concept of performing the last operation first is preferred to the mistake of creating a construct with inadequate fixation and stability or creating a construct that does not account for future disease.

Knowledge of the specific tumor biology may also be helpful in guiding treatment. Average patient survival after bony metastasis is considerably shorter for lung cancer compared to breast or prostate cancer[10]. The effect of the tumor on host bone will also be influenced by the tumor type. For example, lung cancer is typically lytic, prostate cancer is typically blastic, and renal cell cancer can be very vascular resulting in a tendency to bleed. Rates of bony healing are influenced by tumor type and may vary widely with 0% healing for lung cancer, 37% healing for breast cancer, 44% healing for renal cell cancer, and 67% healing for myeloma. Response to adjuvant treatments such and radiation and chemotherapy will also differ based on tumor type.

Unlike conventional fracture surgery in which indirect fracture reduction is commonly employed, treatment of pathological fractures from metastatic disease often requires exposure of the fracture site so that the tumor can be excised or resected and adequacy of fixation assessed. Metastatic tumor excision is usually intralesional using a combination of curettes and high speed burrs, although occasionally the entire bone segment may be resected[4]. The combination of host bone destruction by the tumor and bone resection performed during the operation may result in significant bony defects. Although the bone healing response for different tumors is variable, it is generally limited; therefore, use of materials that require osteointegration such as allograft or autograft bone should be avoided[4, 11-13]. A better option for dealing with bone defects is polymethylmethacrylate bone cement which provides predictable, immediate, structural stability, and increased biomechanical rigidity when combined with metal implants[23-26]. Because bone cement is pliable, it is well suited to fill the irregular tumor cavities resulting from metastatic disease. In addition, the exothermic reaction that occurs then bone cement is used may result in additional local tumor necrosis at the lesion margins[23].

To summarize, the surgical treatment of pathologic fractures relies on establishing a rigid mechanical construct rather than relying on the biology of bone to heal the fracture. As such, the operating surgeon should have a low threshold to open the fracture site and make certain that mechanical stability is achieved via the internal fixation performed. One good habit is to always ask oneself: "Where can I put the bone cement?" Adding bone cement once the internal fixation is in place will add stability to the fracture and ensure weight bearing continuity across the fracture site. This will prevent pain with subsequent mobilization and is an important last step in the surgical care of these fractures.

Fixation strategies used in the treatment of metastatic lesions and pathological fractures differ compared to those used in the treatment of a conventional fracture in the same location. In general, intramedullary fixation is preferred to plate fixation for pathological fractures in diaphyseal areas of weight-bearing long bones due to the increased strength of the intramedullary nail and lower likelihood that the implant will fail if osseous healing of the fracture does not occur[4, 27, 28].

Periarticular fractures or impending fractures due to juxta-articular lesions are often treated with endoprosthetic reconstruction since these approaches allow for immediate weight-bearing and do not require bone healing. In conventional arthroplasty used for the treatment of arthritis, non-cemented implants that are designed to promote bony in-growth are commonly employed. However, in arthroplasty performed for tumor, implants that rely on the cement rather than bony in-growth for stability are generally a better option because of impaired bone healing resulting from tumor biology and post-operative radiation or chemotherapy. The use of long stem prostheses also differs between conventional arthroplasty and arthroplasty performed for metastatic disease. In primary arthroplasty for degenerative disease, the use of long stems implants is generally not necessary. However, in arthroplasty for metastatic disease, long stems may be required to span segments of diseased bone, to provide greater implant stability, and to protect against the creation of a stress riser near an area of diseased bone. It is important for the surgeon to appreciate those conditions in which fixation of a pathologic lesion is not feasible and to move on to resection and replacement.

In conclusion, bony metastatic disease is a problem that will be affecting increasing numbers of patients. Most practicing orthopaedic surgeons will provide care to patients with metastatic disease. Treatment is palliative, with the goals of limiting pain and rapidly returning patients to function. A biopsy and possible staging workup are essential in the initial treatment of aggressive bony lesions. Surgical indications include pathological fractures, impending pathological fractures, and intractable pain that have failed non-operative treatments. Due to effects of tumor biology on patients' general medical condition and host bone, treatment of pathological fractures differs from the treatment of conventional fractures. By understanding these factors, the orthopaedic surgeon can maximize the likelihood successfully limiting pain and rapidly returning patients to function, thereby making an important contribution to improving the quality of their remaining lives.

References

1. **Bagi CM.** Targeting of therapeutic agents to bone to treat metastatic cancer. *Adv Drug Deliv Rev.* 2005 May 25;57(7):995-1010.
2. **Oien KA, Evans TR.** Raising the profile of cancer of unknown primary. *J Clin Oncol.* 2008 Sep 20;26(27):4373-5.
3. **Varadhachary GR, Abbruzzese JL, Lenzi R.** Diagnostic strategies for unknown primary cancer. *Cancer.* 2004 May 1;100(9):1776-85.
4. **Bickels J, Dadia S, Lidar Z.** Surgical management of metastatic bone disease. *J Bone Joint Surg Am.* 2009 Jun;91(6):1503-16.
5. **Franzius C, Schuck A, Bielack SS.** High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol.* 2002 Apr 1;20(7):1953-4.
6. **Houston SJ, Rubens RD.** The systemic treatment of bone metastases. *Clin Orthop Relat Res.* 1995 Mar(312):95-104.
7. **Janjan NA.** Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer.* 1997 Oct 15;80(8 Suppl):1628-45.
8. **Thurman SA, Ramakrishna NR, DeWeese TL.** Radiation therapy for the treatment of locally advanced and metastatic prostate cancer. *Hematol Oncol Clin North Am.* 2001 Jun;15(3):423-43.
9. **Simon MA, Finn HA.** Diagnostic strategy for bone and soft-tissue tumors. *J Bone Joint Surg Am.* 1993 Apr;75(4):622-31.
10. **Biermann JS, Holt GE, Lewis VO, Schwartz HS, Yaszemski MJ.** Metastatic bone disease: diagnosis, evaluation, and treatment. *J Bone Joint Surg Am.* 2009 Jun;91(6):1518-30.
11. **Bickels J, Kollender Y, Wittig JC, Meller I, Malawer MM.** Function after resection of humeral metastases: analysis of 59 consecutive patients. *Clin Orthop Relat Res.* 2005 Aug(437):201-8.
12. **Harrington KD.** Impending pathologic fractures from metastatic malignancy: evaluation and management. *Instr Course Lect.* 1986;35:357-81.
13. **Kollender Y, Bickels J, Price WM, Kellar KL, Chen J, Merimsky O, et al.** Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. *J Urol.* 2000 Nov;164(5):1505-8.
14. **Hansen BH, Keller J, Laitinen M, Berg P, Skjeldal S, Trovik C, et al.** The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. *Acta Orthop Scand Suppl.* 2004 Apr;75(311):11-5.
15. **Nathan SS, Healey JH, Mellano D, Hoang B, Lewis I, Morris CD, et al.** Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care. *J Clin Oncol.* 2005 Sep 1;23(25):6072-82.
16. **Mirels H.** Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res.* 1989 Dec(249):256-64.
17. **Damron TA, Ward WG.** Risk of pathologic fracture: assessment. *Clin Orthop Relat Res.* 2003 Oct(415 Suppl):S208-11.
18. **Damron TA, Morgan H, Prakash D, Grant W, Aronowitz J, Heiner J.** Critical evaluation of Mirels' rating system for impending pathologic fractures. *Clin Orthop Relat Res.* 2003 Oct(415 Suppl):S201-7.
19. **Vena VE, Hsu J, Rosier RN, O'Keefe RJ.** Pelvic reconstruction for severe periacetabular metastatic disease. *Clin Orthop Relat Res.* 1999 May(362):171-80.
20. **Goetz MP, Callstrom MR, Charboneau JW, Farrell MA, Maus TP, Welch TJ, et al.** Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol.* 2004 Jan 15;22(2):300-6.
21. **Callstrom MR, Charboneau JW, Goetz MP, Rubin J, Atwell TD, Farrell MA, et al.** Image-guided ablation of painful metastatic bone tumors: a new and effective approach to a difficult problem. *Skeletal Radiol.* 2006 Jan;35(1):1-15.
22. **Simon CJ, Dupuy DE, Iannitti DA, Lu DS, Yu NC, Aswad BI, et al.** Intraoperative triple antenna hepatic microwave ablation. *AJR Am J Roentgenol.* 2006 Oct;187(4):W333-40.
23. **Sim FH, Daugherty TW, Ivins JC.** The adjunctive use of methylmethacrylate in fixation of pathological fractures. *J Bone Joint Surg Am.* 1974 Jan;56(1):40-8.
24. **Frassica FJ, Frassica DA.** Evaluation and treatment of metastases to the humerus. *Clin Orthop Relat Res.* 2003 Oct(415 Suppl):S212-8.
25. **Kay PR.** Cement augmentation of pathological fracture fixation. *J Bone Joint Surg Br.* 1989 Aug;71(4):702.
26. **Kunec JR, Lewis RJ.** Closed intramedullary rodding of pathologic fractures with supplemental cement. *Clin Orthop Relat Res.* 1984 Sep(188):183-6.
27. **Brumback RJ, Toal TR, Jr., Murphy-Zane MS, Novak VP, Belkoff SM.** Immediate weight-bearing after treatment of a comminuted fracture of the femoral shaft with a statically locked intramedullary nail. *J Bone Joint Surg Am.* 1999 Nov;81(11):1538-44.
28. **Hardy DC, Descamps PY, Krallis P, Fabeck L, Smets P, Bertens CL, et al.** Use of an intramedullary hip-screw compared with a compression hip-screw with a plate for intertrochanteric femoral fractures. A prospective, randomized study of one hundred patients. *J Bone Joint Surg Am.* 1998 May;80(5):618-30.