Metastatic Lesions of the Proximal Femur

Yee-Cheen Doung, M.D., Samuel Kenan, M.D., and Timothy Rapp, M.D.

Abstract
Skeletal metastases are common in the adult population. The proximal femur is a frequently affected bone in the appendicular skeleton. The orthopaedic surgeon may be the first to find a pathologic lesion of the proximal femur and appropriate diagnosis and nonoperative management is essential prior to surgical treatment. Bisphosphonates and radiation therapy are used in conjunction with surgical management to minimize pain and prevent further destruction. Surgical management may consist of internal fixation, with or without polymethylmethacrylate, or endoprosthetic replacement. The goal of treatment is to relieve pain and allow for function while minimizing systemic complications.

Cancer is the second leading cause of mortality in adults, leading to 565,650 deaths in 2008. In 2008, there were approximately 1,400,000 new diagnoses of cancer, over half of which were from lung, breast, prostate, kidney, and thyroid carcinomas. In breast cancer patients, it has been reported that 70% have skeletal metastases at the time of death. Recent reviews have demonstrated that 68% of prostate cancer patients, 35% of lung cancer patients, and 42% of thyroid cancer patients develop metastases to the skeleton. As treatments improve for solid tumors and patient survival times increase, metastases to the long bones will continue to be a problem encountered by orthopaedic surgeons.

The most common site of skeletal metastases is in the spine, followed by the femur and the humerus. Within the proximal femur, half of metastatic lesions are located in the femoral neck, 20% in the pertrochanteric region, and 30% in the subtrochanteric region. Pathologic fractures that occur secondary to the development of skeletal metastases have been reported to have a nonunion rate of up to 65%.

With improvements in the medical management of these malignancies, patients with metastatic disease are living longer and leading more active lives. However, with the high reported nonunion rate, pathologic fractures pose challenges with regard to fixation, which ultimately impacts quality of life and further care. The treatment of patients with bony metastases, therefore, benefits greatly from a team approach, with the goals of managing pain and improving function.

Diagnosis
Evaluation of a pathologic fracture or lesion in the femur requires a systematic approach. Although there have been no published series documenting the presence of sarcoma or other primary bone lesion for solitary lesions presenting in adults, it has been estimated that 10% are not secondary to metastatic disease. Therefore, prior to any treatment of a presumed pathologic fracture or metastatic lesion, it is essential a confirmed diagnosis is made. For example, whereas the treatment of many pathologic fractures of breast metastases is internal fixation, the treatment of primary chondrosarcoma of bone is wide resection. If an intramedullary nail were to be placed in the presence of chondrosarcoma, the entire femur and the insertion sites of the nail and the locking bolts would be contaminated.

Yee-Cheen Doung, M.D., was an Administrative Chief Resident, Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, and is currently an Assistant Professor, Department of Orthopaedics and Rehabilitation, Oregon Health and Science University, Portland, Oregon. Samuel Kenan, M.D., is Professor, Orthopaedic Surgery, and Timothy Rapp, M.D., Associate Professor, Orthopaedic Surgery, and Chief, Division of Division of Orthopaedic Oncology, Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, NYU Langone Medical Center, New York, New York.

Correspondence: Timothy Rapp, M.D., 160 East 34th Street New York, New York 10016; timothy.rapp@nyumc.org.
Subsequent resections would then include the femur and its tracts and potentially require a hip disarticulation or hemipelvectomy.

When there are multiple bony lesions present, coupled with a documented primary source, the diagnosis is simpler. However, when a solitary lesion is present, even with a history of known carcinoma, it cannot be assumed that the lesion is from that carcinoma. Rougraff and colleagues described a work-up sequence that diagnosed solitary lesions in 85% of their 40 patients. Their approach started with a thorough history and physical examination, followed by plain radiographs. Next, a chest radiograph was performed. In their series, 50% of patients had an identifiable primary source by this time. A bone scan was then performed, followed by computed tomography (CT) of the chest, abdomen, and pelvis. After the CT scans, an additional 25% of the patients had a diagnosis. Finally, a biopsy of the skeletal lesion was performed. This protocol provided a diagnosis for an additional 10% of patients and confirmed 25% of the initial diagnoses. The remaining 15% unknown cases were ultimately confirmed to be carcinoma of unknown primary origin.

Pathogenesis

Metastatic lesions can present as lytic lesions, blastic lesions, or both. Osteolytic lesions are found far more commonly in metastatic disease and are more often associated with fracture and hypercalcemia. In 1889, Stephen Paget described a “seed to soil” hypothesis for breast metastases, which is the basis for the understanding of metastatic disease today: “When a plant goes to seed, its seeds are carried in all directions; but they can only form if they fall on congenial soil.” In other words, the skeleton provides for a microenvironment, or fertile soil, conducive to carcinogenic cells. The lytic lesion in metastatic disease has often been described as a cyclical pathway of destruction. Rougraff and colleagues described most metastatic lesions in 85% of their 40 patients. Their approach started with a thorough history and physical examination, followed by plain radiographs. Next, a chest radiograph was performed. In their series, 50% of patients had an identifiable primary source by this time. A bone scan was then performed, followed by computed tomography (CT) of the chest, abdomen, and pelvis. After the CT scans, an additional 25% of the patients had a diagnosis. Finally, a biopsy of the skeletal lesion was performed. This protocol provided a diagnosis for an additional 10% of patients and confirmed 25% of the initial diagnoses. The remaining 15% unknown cases were ultimately confirmed to be carcinoma of unknown primary origin.
been detected in prostate cancer cells. In vitro, cleavage of PTHrP to PTHrP-1-23 can stimulate bone formation, but these results have yet to be reproduced in vivo. Furthermore, BMP-7, a protein known for induction of bone formation, and PDGF have been found in breast and prostate oncogenic cells.

**Pharmacologic Treatment**

Based on these mechanisms, a host of pharmacologic treatments have been used to counteract the progression of osteolytic and osteoblastic lesions. Because osteolytic lesions are far more prevalent, the majority of current drug therapies are aimed at these lesions.

Although there are many source-specific medications, such as strontium for prostate cancer, hormonal therapy for breast cancer, and chemotherapeutic treatments specific to each primary solid tumor, a mainstay of treatment of osteolytic lesions is bisphosphonates. This class of drugs has risen to popularity in the treatment and management of osteoporosis, which is more common in the general population. Because oncogenic cells activate the same pathway implicated in osteoporosis – RANKL activation of osteoclasts – bisphosphonates have been found to be highly effective in slowing the progression of skeletal metastases. Molecularly, bisphosphonates block farnesyl diphosphate (FPP) synthase, an enzyme required in the production of cholesterol, farnesylation, and geranyl-geranylation. Geranyl-geranylation is essential in the survival and function of osteoclasts. As a result, bisphosphonates can induce osteoclast apoptosis.

In the evaluation of the effectiveness of current pharmacotherapy, a skeletal-related event (SRE) has been defined as an event involving fracture, orthopaedic intervention, radiation therapy, or spinal cord compression. The two most common bisphosphonates currently used in the treatment of osteolytic metastatic lesions are zoledronate and pamidronate. With the use of these bisphosphonates, there is a longer time to an SRE, and there is a decreased incidence of SREs per year. However, in patients with non-small cell lung carcinoma, the use of bisphosphonates does not improve survival.

**Radiation Therapy**

Another mainstay in the treatment of skeletal lesions is external beam radiation therapy. The goals of treatment are pain reduction, prevention of further bone destruction, and the maintenance of function. The molecular mechanisms of radiation therapy remain unknown. Current hypotheses include an anti-tumor effect of radiation secondary to disruption of the tumor cell’s DNA. Anti-osteoclast and anti-osteoblast function has also been documented in addition to inhibition of the release of chemical pain mediators following radiation therapy. There are a multitude of regimens ranging from 8 Gy for one session, to 24 Gy for six sessions, to 30 Gy for 10 sessions. All regimens show the same rates of pain relief and inhibition of osteolysis. However, there is an increased re-treatment rate with lower dose protocols. It is important to note that 30 Gy is the maximum allowable dose before radiation therapy adversely affects bone healing.

**Surgical Treatment**

There are many occasions where a patient presents with pain and is found to have a skeletal lesion prior to the development of a pathologic fracture. It is technically easier to treat an impending fracture than an existing fracture. These patients have less operative blood loss, a shorter hospital length of stay, a greater chance to be discharged to home versus a subacute nursing facility, and survive, on average, 6 months longer. Furthermore, the presence of a pathologic fracture is a marker for poor prognosis in patients with lung and breast carcinoma.

Because of the marked difference between the quality of life of the patients with impending fracture, as compared to existing fracture, it is often in the best interest of the patient to treat these lesions surgically before they precipitate a fracture event. The desire to fix these fractures is mitigated by the concerns of subjecting an oncologic patient to surgery, as the benefits may not outweigh the risks. Therefore,
it becomes imperative to determine which skeletal lesions should be prophylactically fixed. Initially, it was determined that if the lesion occupied more than 50% of the cortex, or if it was 2.5 cm in diameter, the lesion should be treated.16,17 However, there is no consistent relationship between the size of the lesion and fracture risk.18 Pain is also not a reliable sign. Mirels, in 1989, created a classification to attempt to predict which lesions would fracture19 (Table 1). The lesion was evaluated for site (upper extremity, lower extremity, peritrochanteric femur), pain (mild, moderate, functional), type of lesion (blastic, mixed, lytic), and size (under one-third bone diameter, one-third to two-thirds, more than two-thirds). There is a numerical value to each of these criteria from 1 to 3. In Mirels’ series, 65% of the lesions did not fracture, and their total calculated score ranged from 1 to 9, with a mean of 7. The remaining 35% of lesions developed a fracture, and their total score prior to fracture was 7 to 12, with a mean of 10. Therefore, if a total Mirels score of 9 or greater is identified, the lesion is more likely to fracture and therefore should be fixed. This classification was confirmed as having a sensitivity of 91% to 100% and specificity of 14% to 35%.20-21

The goals of surgical treatment of the proximal femur are three-fold. The first is that the patient survives the operation. The second is that the patient can weightbear immediately through the affected extremity. The third is that the implant survival is greater than the patient survival. Surgical treatment falls into two general categories: internal fixation and endoprosthetic replacement (Figs. 3 and 4). Historically, both treatments were described between 1976 and 1980. Curettage of the lesion and subsequent placement of polymethylmethacrylate (PMMA) cement were first described, in 1976, by Harrington to allow for further mechanical stability.22 In his series, 85% of patients had good or excellent pain relief. The most common complication was deep infection. Cephalomedullary nails were described by Zickel and Mouradian,23 in 1976, to treat subtrochanteric and pertrochanteric pathologic fractures. The average time to union was 4.5 months. Complications included nail cut-out, wound complications, and pulmonary embolism. In 1980, Lane described the use of the Austin-Moore prosthesis to treat pathologic fractures about the proximal femur.24 Pain relief was good or excellent in all patients. There were no dislocations, but a 1.2% infection rate occurred.

Fractures of the proximal femur can be subdivided

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Figure 3 Treatment of pathologic lesion. A, preoperative photo; B, postoperative photo with internal fixation using cephalomedullary nail.
into intracapsular and extracapsular. Because of the high nonunion rate for intracapsular fractures or femoral neck fractures, the current recommendation to treat a femoral neck lesion is a cemented hemiarthroplasty.\(^2\) There is no consensus whether treatment should consist of a standard length stem or a long-stem prosthesis. If there is distal disease, then a long-stem prosthesis can mitigate potential future fractures of the femoral shaft. There is, though, a potential for cardiac complications with placement of a long-stem hemiarthroplasty.\(^2\). If there is acetabular involvement, a total hip arthroplasty is recommended. However, there is an increased dislocation rate with a total hip arthroplasty, as compared to a hemiarthroplasty.

For pertrochanteric and subtrochanteric fractures, the decision to fix the lesion or resect the lesion and replace it with an endoprosthesis is more complicated. Regarding internal fixation, the cephalomedullary nail is more successful than a sliding hip screw and side plate construct. Curettage of the tumor and liberal use of PMMA is recommended. However, plate and nail constructs have a high failure rate at 2 years after the index surgery. The union rate after internal fixation ranges from 75% to 90%.\(^4,25,27\) Most nonunions had subsequent radiation therapy, and patients with renal cell carcinoma had the highest reoperation rate.\(^2\)

Endoprosthetic reconstruction of the proximal femur in the pertrochanteric or subtrochanteric region requires extensive soft tissue dissection. Given the extent of the surgery, many patients will have residual weakness postoperatively. While nonunion is not a concern with endoprosthetic reconstruction, dislocation and infection occur more frequently.

There have been no prospective trials comparing the two procedures. There was a retrospective review of 146 lesions comparing internal fixation with cephalomedullary nail in 37 lesions to endoprosthesis in 109 lesions.\(^2\) Failure was described as need for reoperation. In this study, 16% of lesions undergoing osteosynthesis failed via nonunion or osteonecrosis, and 8.3% of endoprosthetic replacements failed via distal fracture or dislocation. The 2-year reoperation risk was increased in patients who underwent internal fixation.

As renal cell carcinomas are especially resistant to chemotherapy and radiation therapy, endoprosthetic reconstruction may be a more appropriate treatment method.\(^3\)

**Conclusions**

As treatments improve for solid tumors, metastases of long bones will continue to be a concern and problem. It is essential that an appropriate preoperative evaluation is

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**Figure 4** Treatment of pathologic lesion. **A**, preoperative photo; **B**, postoperative photo with internal fixation with cephalomedullary nail, cemented endoprosthesis.
performed and that prior to surgical intervention a diagnosis is made. Further nonsurgical treatments are important in the prevention of fracture or further destruction. The mainstays of nonsurgical treatment include the use of bisphosphonates and radiation therapy. The goals of surgical treatment are to decrease pain and allow for immediate weightbearing. Whether internal fixation or endoprosthesis is the appropriate treatment depends on the health and life expectancy of the patient as well as the location and amount of bone destruction present.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References