Metastatic Tumors

Management of upper extremity bone metastases

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ABSTRACT

Metastatic bone disease represents a significant burden of disease. Metastatic disease can seed in any bone of the body, but one of the most common long bones affected is the humerus. Although painful and often disabling, metastatic bone disease of the upper extremity often can be treated more conservatively than the lower extremity because of lower weight-bearing demands. However, the surgical management of upper extremity metastatic bone disease is an evolving field, and recent clinical studies have demonstrated several key principles. Intramedullary nailing and whole bone irradiation may be an optimal combination for prophylactic fixation. The addition of polymethyl methacrylate cement adds immediate stabilization to internal fixation and decreases postoperative pain. Plate and screw fixation can be used in lesions that cannot be treated with intramedullary nailing, but caution is necessary to avoid complications related to surgical technique. Finally, periarticular and intraarticular lesions may be managed with a hemi- or total-joint prosthesis for both the shoulder and elbow to provide the maximal functional outcome. Surgical intervention together with appropriate adjunctive therapies can decrease patient-important pain and skeletal-related events while improving quality of life in patients living with metastatic bone disease of the upper extremity.

Key Words
metastatic bone, upper extremity, surgical management

INTRODUCTION

Metastatic bone disease represents a significant burden on the healthcare system. In 2008 more than 280,000 adults in the United States were living with metastatic bone disease. Metastatic bone disease most commonly originates from solid organ tumors of the breast, lung, kidney, prostate, and thyroid. In the United States cancer death rates overall have declined from a peak of 215.1 per 100,000 in 1991, to 173.1 per 100,000 in 2009, and therefore the number of people living with metastatic bone disease is on the rise.

The local cellular environment of bone metastases includes carcinoma cells, osteoblasts, osteoclasts, and mineralized bone matrix and associated embedded growth factors. Bone metastases can be classified as being either osteolytic when bone destruction is predominant, osteoblastic when bone deposition is most predominant, or mixed osteoclastic, and osteolytic. Osteolytic lesions are characterized by increased bone resorption by osteoclasts, and weak and brittle bone similar to osteoporosis. Patients who develop metastatic bone disease may be diagnosed through routine surveillance or after a skeletal related event (SRE). SREs are variably defined in the literature as pathologic fractures, spinal cord compression, or requirement for radiotherapy to treat bone pain or impending fracture. SREs often are difficult to treat and severely diminish patients’ quality of life, and they are also associated with substantial socioeconomic costs.

Metastatic bone disease can seed in any bone of the body, but one of the most common long bones affected is the humerus. Although painful and often disabling, metastatic bone disease of the upper extremity often can be treated more conservatively than the lower extremity because the upper extremity has lower weight-bearing demands. Nonetheless, many complete or displaced pathologic fractures of the humerus may require surgical intervention. Plates and screws, intramedullary (IM) nails, and endoprosthetic replacements are options for surgical management in upper extremity metastatic bone disease.

Patient evaluation is critical when considering indications for operative treatment. The overall health of the patient must be evaluated before surgery. Although there are no absolute criteria for predicting survival, poor prognostic factors include hypercalcemia, cytopenia from bone marrow failure, cachexia and poor performance status.

In a recent review of the surgical management of metastatic bone disease of the humerus, Scolaro et al. suggested that intraarticular and unconstrained lesions of the humeral head or metaphysis should be fixed with an endoprosthetic replacement, and that metadiaphyseal or diaphyseal lesions that are well contained can be stabilized with a proximal humeral locking plate or an IM nail. Polymethyl methacrylate (PMMA) bone cement may be a useful augment to enhance immediate stabilization. Distal lesions that are extraarticular within 5 cm of the olecranon fossa often can be treated with single- or dual-plate fixation with PMMA cement, or a replacement with a total elbow prosthesis. Finally, lesions that are intraarticular or...
uncontained within the elbow joint should undergo total elbow arthroplasty.

The objective of this review is to summarize recent innovations in the surgical management of upper extremity metastatic bone disease. We present a brief summary of the key findings from the most recent clinical research studies.

PROPHYLACTIC STABILIZATION

Propylactic stabilization may be considered in cases of painful upper extremity metastatic bone disease to prevent an impending fracture. Internal fixation or endoprosthetic joint replacement may be used depending on the location and size of the lesion in the bone, and the entire length of bone should be protected to prevent subsequent periprosthetic fractures. Alvi and Damron reviewed 96 humeral lesions, including 24 treated with IM nailing or cemented arthroplasty and two treated with plate and screw fixation. Embolic phenomena may result from increased vascularity in pathologic intramedullary canals allowing for increased potential of emboli to escape into the systemic circulation. In this series, 12 patients had complications potentially related to embolic causes, but all were minor, none were fatal, and none occurred in the stabilization of the humerus. The authors concluded that there was no significant increased risk of embolic phenomena from pathologic bone as a result of surgical intervention and that continued prophylactic stabilization of the entire bone should be offered as the standard of care.

Eleven of the 96 patients in this series experienced progression, only one of which was a humeral lesion treated with an IM nail. Disease progression at the distal end of a bone may be the direct consequence of seeding in the intramedullary canal when accessed surgically, and later editorial to this article suggested that any patient undergoing prophylactic stabilization should receive subsequent whole bone irradiation to prevent disease progression at the distal end of the prosthesis.

PMMA BONE CEMENT

PMMA bone cement has been used as a structural augment in the fixation of pathologic lesions for decades. PMMA increases immediate structural stability and helps provide rapid pain relief after surgery. Sun et al. recently conducted a retrospective analysis of 51 patients with 65 extremity lesions that were injected with PMMA cement under CT guidance for impending pathologic fractures, four of which were in the upper extremity. The authors found a significant decrease in overall pain and concluded that minimally invasive injection of PMMA cement into pathologic lesions may be a useful novel technique to rapidly decrease pain and improve function.

Two studies examined the addition of cytotoxic chemotherapy drugs to PMMA cement in metastatic bone disease. The aim of this specific technique is to prevent local recurrence and development of new metastatic lesions. These studies demonstrated that the addition of up to 2 g of methotrexate per 40 g of bone cement did not alter the biomechanical properties of the cement in an in vivo rabbit model. There was also a significant decrease in the number of metastases as well as longer survival in the rabbits in the methotrexate-loaded cement group when compared with only cement. Despite the success of this animal model, this technique has not yet been widely adapted into clinical practice.

OPEN REDUCTION AND INTERNAL FIXATION

The surgical goals for upper extremity metastatic bone disease are to provide a single procedure that will stabilize the bone, restore immediate function, and decrease pain for the remainder of the patient’s lifetime. Pathologic bone often is osteopenic with little to no healing potential, which increases the demands placed on fixation constructs. In comparison to the lower extremities, upper extremities have decreased load bearing demands.

Plate and Screw Fixation

Plate and screw fixation in the presence of pathologic bone has been used with variable success in upper extremity metastatic bone disease. Pathologic fracture sites often have insufficient bone stock that compromise screw fixation, and plate positioning to protect the entire bone may be technically demanding. Sukamp et al. prospectively followed 187 patients who received a locking plate for acute pathologic fracture of the proximal humerus. At 1-year follow-up, patients reported significant improvements in range of motion and Disabilities of Arm, Shoulder and Hand (DASH) scores. However, there were 52 immediate postoperative complications, 25 directly attributed to improper surgical technique. The most common error was intraoperative screw perforation of the humeral head. The authors concluded that locking plates for acute pathologic fractures of the proximal humerus can have good functional outcomes provided that meticulous surgical principles are followed.

Weiss et al. reviewed 63 humeral metastatic bone tumors stabilized with intrasional curettage and plate fixation. The authors reported 14 complications, seven of which required a second procedure. All 63 patients reported satisfactory pain relief, and 50 regained independence in their activities of daily living.

Intramedullary (IM) Nailing

IM nails provide an excellent method of fixation for fractures of the diaphysis and metaphysis of the humerus because they provide immediate stabilization and recreate anatomic length after tumor debulking. Pretell et al. retrospectively examined 22 pathologic fractures of the humerus treated with an anterograde locked IM nail and reported a mean hospital stay of 4.3 days with no operative complications. Nine of the patients were able to perform activities of daily living (ADLs) by the 6-week follow-up visit, and all patients reported minimal to no pain. Neither lesionsal curettage, nor bone irradiation, were used in any of the 22 patients, and none of the patients were followed for local disease progression.
suitable for upper extremity functional demands. This nails when subjected to bending or rotation. As such, they are opaque to x-ray beams and do not introduce artifact on the humerus. The patient experienced pain relief and carbon fiber IM nail for treatment of a pathologic fracture of the humerus. The authors concluded that nailing should be the method of choice for proximal humeral fractures, 24 patients received screw fixation technique may be used. In the subgroup distal lesions precluding intramedullary nailing, a plate and concluded that nailing should be the method of choice for diaphyseal fractures compared to early disassembly of an elbow prosthesis. Overall, there were only two failures: one failure was attributed to a shoulder prosthesis penetrating the skin and the second attributed to early disassembly of an elbow prosthesis. Overall, there was a 2% infection rate for all joints. The authors concluded that total joint prostheses for metastatic disease do not have poorer outcomes than other surgical treatment options for the management of metastatic bone disease.

Laitinen et al.\textsuperscript{22} retrospectively compared 21 patients who received IM nailing and PMMA cement augmentation with 19 patients who received IM nailing only. The authors detected no difference between the groups for complications or functional outcomes, with the exception that the PMMA cement group experienced overall less pain at 6 wk using the Musculoskeletal Tumor Society (MSTS) score assessing analgesia for musculoskeletal pain. The authors attributed this finding to the rapid stabilization of the fracture site as a result of PMMA.\textsuperscript{22}

Collis et al.\textsuperscript{23} reported a single patient who received a carbon fiber IM nail for treatment of a pathologic fracture of the humerus. The patient experienced pain relief and functional benefit comparable to that seen in the study by Laitinen et al.\textsuperscript{23} It was postulated that the carbon fiber nail may add benefit in patients who require repeated cross-sectional imaging postoperatively.\textsuperscript{23,24} Carbon fiber nails are not opaque to x-ray beams and do not introduce artifact on CT or MRI. Although carbon fiber nails are strong through axial loading, they are actually weaker than standard IM nails when subjected to bending or rotation. As such, they may not allow for use in lower limb constructs but may be suitable for upper extremity functional demands. This construct warrants further study and investigation in terms of its role in pathologic fracture fixation.\textsuperscript{23}

**ARThROPLASTY**

Wedin et al.\textsuperscript{25} prospectively followed 214 patients who underwent surgical intervention for pathologic fractures of the humerus. The authors found that 130 of the lesions were localized in the diaphysis followed by 69 in the proximal humerus and 15 in the distal region of the humerus. Median follow-up was 8 mo. The authors reported a 7% (8 of 117) failure rate with IM nailing of diaphyseal fractures compared with an 18% (2 of 11) failure rate with plate fixation and concluded that nailing should be the method of choice for fixation of diaphyseal fractures. However, in instances of distal lesions precluding intramedullary nailing, a plate and screw fixation technique may be used. In the subgroup analysis of proximal humeral fractures, 24 patients received a hemiarthroplasty or total arthroplasty, 29 received IM nail fixation, and 11 received a modular tumor prosthesis. There were no complications in the hemiarthroplasty or total arthroplasty group and two failures for each of the nail and modular tumor prostheses groups. The authors concluded that a cemented hemiprosthesis is the fixation strategy of choice for lesions of the proximal humerus.\textsuperscript{25}

Sorensen et al.\textsuperscript{26} performed a cross-sectional study of 140 upper and lower extremity joints replaced for metastatic disease or hematologic malignancy. Of the 140 joints reviewed, 16 were shoulders and five were elbows. Among the upper extremity arthroplasty patients, there were only two failures: one failure was attributed to a shoulder prosthesis penetrating the skin and the second attributed to early disassembly of an elbow prosthesis. Overall, there was a 2% infection rate for all joints. The authors concluded that total joint prostheses for metastatic disease do not have poorer outcomes than other surgical treatment options for the management of metastatic bone disease.\textsuperscript{26}

Rolf et al.\textsuperscript{27} reported four patients who received endoprosthetic elbow replacements for metastatic renal cell carcinoma. There were no perioperative complications and no local disease recurrences after resection. It was noted by the authors that although metastases from renal cell carcinoma are hypervascular, none of the four patients underwent preoperative angiography or embolization. Functional outcomes were recorded at follow-up (mean 36 mo), and all patients were able to resume ADLs with an average flexion and extension in the prosthetic elbow of of 113° to 20°, respectively. The outcomes of this case series are excellent; however, the authors acknowledge that a larger analysis of total elbow prosthesis must be completed to assure accurate and reliable outcome assessments.

Hanna et al.\textsuperscript{28} presented outcomes with a total elbow prosthesis in patients after primary resections of both primary and secondary lesions of the distal humerus. The authors reported a high complication rate of 50% (9 of 18 patients) including aseptic loosening in three patients, local recurrence in two, infection in two, neurapraxia in one, and a periprosthetic fracture in one. Six of the 18 patients in the study had metastatic lesions secondary to a solid organ primary carcinoma. All patients reported decreased pain and increased ability to resume ADLs. Taken together with the results of Rolf et al.\textsuperscript{27} a total elbow prosthesis may be a viable option for distal humeral metastatic lesions.

**ADJUNCTS TO SURGERY**

**Radiotherapy**

Radiotherapy is an effective method of pain palliation in patients with metastatic bone disease.\textsuperscript{29,30} Chow et al.\textsuperscript{31} performed a meta-analysis of 25 randomized control trials, comparing single-fraction to multiple-fraction radiotherapy for the palliation of uncomplicated bone metastases. No difference was seen between the two treatment arms in overall response rates. In patients with bone metastases with shortened expected survival, single-fraction radiotherapy is recommended as the treatment of choice for palliation of painful bone metastases.

**Medical Therapy**

Systemic therapy in the treatment of metastatic bone disease attempts to target the osteoclast activating pathways to prevent excessive bone resorption and prevent SREs. Bisphosphonates have been regarded as the standard of care in delaying or preventing SREs in metastatic bone disease.\textsuperscript{32} In several clinical trials, it has been shown that zoledronic acid is effective in delaying SREs when compared with placebo groups.\textsuperscript{33,34} Denosumab is a monoclonal antibody that binds the receptor activator of nuclear kappa-β ligand (RANKL) to inhibit osteoclast differentiation and function.\textsuperscript{35} A review by Rofolo et al.\textsuperscript{36–40} summarized the results of three separate randomized controlled trials comparing the efficacy of denosumab to zoledronic acid in preventing SREs. The results showed that denosumab was superior to zoledronic acid in delaying the time to SRE (hazard ratio [HR] 0.82; 95% CI: 0.71-0.95; P<0.001 for noninferiority and P=0.01 for
superiority). As such, denosumab has emerged as a novel therapy in the control of SREs in the presence of metastatic bone disease.\textsuperscript{4,36–40}

CONCLUSION

The surgical management of upper extremity metastatic bone disease is an evolving field, and recent clinical studies have demonstrated several key principles. Intramedullary nailing and whole bone irradiation may be an optimal combination for prophylactic fixation. The addition of PMMA cement adds immediate stabilization to internal fixation and decreases postoperative pain. Plate and screw fixation can be used in lesions that cannot be treated with intramedullary nailing, but caution is necessary to avoid complications related to surgical technique. Finally, peri-articular and intraarticular lesions may be managed with a hemiarthroplasty or total joint arthroplasty for both the shoulder and elbow to provide the maximum functional outcome. Surgical intervention together with appropriate adjunctive therapies can decrease patient-important pain and SREs while improving quality of life in patients living with metastatic bone disease of the upper extremity.

REFERENCES AND RECOMMENDED READING

Papers of particular interest published within the annual period of review are highlighted as:
• of special interest
• of outstanding interest

22. A retrospective study including 21 patients with 22 pathologic humeral shaft fractures treated with an antegrade IM nail. No complications observed with any of the implants. Seventeen of 19 patients reported to be satisfied with the outcomes and return to ADLS following surgery. 23. Laitinen M, Niemenen J, Pakarinen TK. Treatment of pathological humerus shaft fractures with intramedullary nails with or without cement fixation. Arch Orthop Trauma Surg. 2011; 131:503–508.
27. Surgical treatment of 214 metastatic lesions of the humerus comparing outcomes of IM nails, plate and screw fixation finally ended embolization. The 214 lesions were divided into regions of the humerus. Results identified preferred treatment options based on location of the metastatic lesion within the humerus. Cemented hemiprosthesis was preferred construct for proximal lesions, IM nails for diaphyseal lesions, and finally plate and screw combinations for lesions of the distal humerus.
29. A study of 140 total joint replacements for metastatic disease of bone of which 21 were in the upper extremity. The study concluded...
that the rates for deep wound infection and postoperative complications were no higher than other methods such as plate and screw or intra medullary fixation of pathologic lesions.


A case series of four patients who had primary resection of metastatic lesions of the distal humerus from a primary renal cell carcinoma and preceded to be fitted with a custom made total elbow endoprosthesis. Between the four patients a good functional outcome was reported allowing patients to return to ADLs with little to no pain. This case series represents a rare scenario and more data is needed on the functional outcome of total elbow endoprosthesis in the setting of metastatic disease.


