This update presents selected publications in the area of musculoskeletal tumors including metastatic bone disease between June 2017 and May 2018. The publications cited represent primarily Level-III and Level-IV studies. The rarity and variability of musculoskeletal tumors make well-powered higher-level studies challenging to complete. Articles from *The Journal of Bone & Joint Surgery* and *Clinical Orthopaedics and Related Research* were the main focus, with additional studies of interest from other selected journals.

**Bone**

**Primary Bone Malignancies**

In 1,792 patients with primary bone sarcomas, duration of symptoms of <4 months or >4 months was found to have no correlation with survival. Parosteal osteosarcoma, chordoma, and low-grade chondrosarcoma were excluded from consideration. Location in the axial skeleton had the strongest negative impact on survival, and a chondrosarcoma diagnosis had the most positive impact on survival. The trend of decreased duration of symptoms with increased tumor size did not reach significance. There was a significant relationship between duration of symptoms and age, as every 1 year of increased age corresponded with a 1.3-week increase in the reported duration of symptoms. Even though the duration of symptoms has recall bias, this study raises the point that other factors such as biology seem to have a more dominant impact on prognosis than duration of symptoms.

Primary bone malignancies of the distal part of the tibia are commonly treated with amputation. In 1 study, Han et al. compared 27 distal tibial malignancies treated with amputation with 52 distal tibial malignancies treated with intraoperative microwave-induced hyperthermia followed by curettage and internal fixation. The authors found that the rate of survival, complications, and local recurrence were not significantly different. However, they did note that 6 patients treated with microwave-induced hyperthermia had local recurrences and no patient treated with amputation had a local recurrence at follow-up times of 12 to 158 months. The Musculoskeletal Tumor Society (MSTS) scores were higher in the patients undergoing limb salvage at 85% compared with the patients undergoing amputations at 66%.

In another study, high-grade osteosarcomas close to the knee and receiving neoadjuvant chemotherapy were treated with limb salvage and were compared on the basis of the presence (28 cases) or absence (13 cases) of epiphyseal extension of the tumor. The MSTS scores did not differ significantly between the groups, but knee range of motion was better in patients without tumor involvement of the epiphysis. Two patients in the epiphyseal extension group and 1 patient in the metaphyseal group had soft-tissue recurrences, but no recurrences were noted at osteotomy sites.

**Sarcoma Basic Science**

Indocyanine green fluorescence angiography was used to quantify primary and metastatic osteosarcoma in a mouse model. Fourman et al. noted that the fluorescence of the primary tumor was linearly related to the burden of metastatic disease, but that fluorescence and tumor size were not related. With demonstrated efficacy in detecting osteosarcoma, indocyanine green angiography is envisioned to help to confirm interoperative margins.

**Cartilage**

The reported outcomes of a group of 162 pelvic primary central chondrosarcomas from 5 centers with a mean follow-up of 12.6
years included notable risks of recurrence and disease-related sequelae even in low-grade tumors. The recurrence rates were 30% for grade-I tumors, 33% for grade-II tumors, and 56% for grade-III tumors. Disease-related death was 3% for grade-I tumors, 33% for grade-II tumors, and 54% for grade-III tumors. High grade, large size, and marginal or intralesional margins negatively impacted disease-specific survival. Infection was the most common complication (19%)\(^6\).

Given these guarded outcomes with some chondrosarcomas, Song et al. developed nomograms to predict 3 and 5-year overall and cancer-specific survival for patients with these tumors\(^5\). The nomograms cover grade-II and III chondrosarcomas and use data on age, histologic subtype, grade, surgical procedure (but not margins), size, and metastasis to produce their predictions. They do not factor in anatomic location. This information may be helpful in counseling patients, planning interventions, and identifying patients for new treatments.

Synovial chondromatosis of the knee may lead to arthritis severe enough to warrant total knee arthroplasty. Houdek et al. found that, for total knee arthroplasty in 20 patients with synovial chondromatosis, knee function was improved but complications were common\(^7\). Five patients had disease recurrence and 7 patients needed additional procedures, including 2 revision total knee arthroplasties for recurrence. Two patients had amputations, 1 because of the development of a chondrosarcoma.

**Ewing Sarcoma**

In their analysis of treatment in 388 patients with nonmetastatic Ewing sarcoma, Albergo et al. found that adjuvant radiation significantly decreased local recurrence in marginally resected tumors (5-year local recurrence-free survival of 96% compared with 81%)\(^8\). This difference is seen more clearly in the limb tumor subgroup than in the central tumor subgroup. Radiation did not impact local recurrence in patients with wide resections. This study reinforces the value of a wide resection and shows the benefit of radiation when this margin is not achieved.

Thévenin-Lemoine et al. compared magnetic resonance imaging (MRI) scans of 20 long bone Ewing sarcomas, performed before and after chemotherapy, and pathology specimens to judge their accuracy in delineating the extent of the tumor\(^9\). The post-chemotherapy MRI was most accurate, with a median difference from the pathologic specimen of 5.0 mm (interquartile range [IQR], 2.0 to 13.0 mm). The pre-chemotherapy MRI had a median difference from the pathologic specimen of 19.0 mm (IQR, 4.3 to 38.2 mm). T1 weighting was the most accurate MRI sequence and gadolinium contrast did not improve accuracy. The authors concluded that resection of a tumor using a 20-mm margin based on the post-chemotherapy T1 MRI sequence will result in negative margins.

**Giant Cell Tumor**

Denosumab has become popular in the treatment of giant cell tumor, especially when a joint is at risk. In their study, Errani et al. reported higher rates of local recurrence in a group of 25 patients treated with denosumab (60%) compared with 222 patients treated without denosumab (16%)\(^9\). Denosumab use was the only significant difference in multivariate analysis. However, the authors noted that the groups were not identical, with the denosumab group having more distal radial tumors, a higher percentage of stage-III tumors, and less phenol use than their historic controls. Although this study does not establish denosumab as a cause of recurrence, it reminds us that denosumab is not expected to eradicate all tumor cells in giant cell tumors and raises the possibility that it may be more difficult to maintain local control in denosumab-treated giant cell tumors.

A novel cryogenic local adjuvant of ethanol and liquid nitrogen mixed 1:3 demonstrated similar efficacy to liquid nitrogen in killing giant cell tumor cells in a model. Seven patients in which this treatment was used had no recurrence or fracture after a follow-up of 19 to 30 months. This semisolid material is readily produced and has some handling advantages compared with liquid nitrogen. Longer follow-up may establish it as an attractive tool in the treatment of giant cell tumor\(^11\).

Giant cell tumors were discovered to limit immune surveillance through mechanisms found in various cancers. Low CD8+ T cell infiltration was a characteristic of more aggressive giant cell tumors. One mechanism that may inhibit immune cell infiltration, human leukocyte antigen (HLA) class-I antigen defects, was found in 50% of giant cell tumor mononuclear stromal cells but did not correlate with tumor aggressiveness. Another mechanism, high expression of cell surface antigen B7-H3, was found in 37% of giant cell tumors and did correspond with increased local tumor invasiveness. Understanding the giant cell tumor’s pathways to limit immune cell infiltration holds promise for future medical treatment as agents are developed to inhibit these pathways\(^12\).

**Spine**

Shah et al.\(^13\) described a technique of en bloc spondylectomy using threadwire saws to cut the vertebral bodies in 33 patients. The saws are passed between the vertebral bodies and the thecal sac during the posterior stage of the surgical procedure and then are utilized to cut the vertebral bodies during the anterior stage. Dural tears were noted in 27% of cases, but only in 1 case was a tear secondary to use of the saw. Negative margins were achieved in 94% of patients, with the 2 positive margins involving the dura.

Schoenfeld et al. reviewed spine surgery for metastases in 3,135 patients and found that surgeons performing ≥49 spine surgical procedures of any type per year had fewer complications in their surgical procedures for spine metastases than did lower-volume surgeons\(^14\). Hospitals with lower volumes of spine surgery also had higher rates of complications in spine metastasis surgery. The authors also found that African Americans and Hispanics were more likely to be treated in lower-volume hospitals and by lower-volume surgeons.
A prospective analysis of spine metastases from cancer of unknown origins in 287 patients demonstrated better patient-reported quality-of-life scores in patients treated with surgery and radiation compared with those treated with radiation only. Quality-of-life superiority in the surgery group was noted at the first postoperative survey and persisted through the 6-month postoperative follow-up of the study. Within the surgery group, the circumferential decompression subgroup had better functional and physical well-being scores than the laminectomy group.

Navigation
Intraoperative surgical navigation continues to develop as a tool to resect bone precisely, especially in challenging locations such as the pelvis. In a report of 23 pelvic and sacral bone sarcomas, Abraham et al. used a navigated drill, saw, or osteotome to make or guide the osteotomies. All bone margins were negative, but 2 soft-tissue margins were positive for tumor. Two transient femoral nerve palsies were noted, possibly because of the placement of the reference frame on the superior pubic ramus.

Another study extended navigation techniques to benign aggressive tumors because of their risk of local recurrence. Farfalli et al. treated 26 tumors that were at least 5 mm from the nearest joint with navigated en bloc resection. At a follow-up of 24 to 56 months, no local recurrences were noted. A group of 43 patients with the same type of tumors was treated with curettage and was followed from 24 to 61 months, with 2 local recurrences. This provides another example of how extending bone margins may decrease local recurrence. The initial resection and reconstruction costs as well as the complexity of this approach need to be weighed against the consequences of the recurrences that it may prevent.

An interoperative, cone-beam, computed tomography (CT)-guided navigation system was found to improve accuracy of bone cuts for all users in a Sawbones model (Pacific Research Laboratories). Sternheim et al. first demonstrated that, for orthopaedic tumor surgeons, navigated bone cuts were significantly more accurate than non-navigated cuts. Second, the authors found that, when using navigation, there was no significant difference in accuracy between levels of surgeon experience (resident, fellow, staff orthopaedic surgeon, tumor surgeon).

Reconstruction
Femoral-head autograft was used as the primary acetabular foundation in reconstructing 5 type-I+II pelvic defects and 8 type-II+III defects in 13 patients. Constrained liners were used in the total hip arthroplasties, and patients were allowed partial weight-bearing at 6 weeks with full weight-bearing upon graft union. Two patients had benign aggressive tumors and 11 patients had primary malignancies. The median follow-up was 36 months (range, 8 to 99 months). The only 2 recurrences had inadequate margins and were in the subgroup of 5 chondrosarcomas. All autografts healed and there was 1 dislocation.

Hipfl et al. reported on treating pelvic defects with a stemmed cup in 21 primary tumors and 27 metastatic tumors at a median follow-up of 6.6 years. Although local control was achieved in all cases, complications were common. A revision surgical procedure was needed in 18 cases (37.5%), 4 of which had multiple revisions. Seven patients had dislocations (15%), and 2 of those were ultimately treated with revision. Two patients had hindquarter amputations for nononcologic reasons. The mean MSTS score for 24 surviving and available patients was 21 points (range, 8 to 28 points) of 30 points.

Another approach to treating primary bone tumors is to eradicate the tumor within the bone intraoperatively. The tumor-free native bone can then be used as part of an immediate reconstruction. Killing of the tumor was compared between treatment by freezing (85 patients) and by extracorporeal irradiation (79 patients). This study found no difference in rates of union, complication, or fracture.

Intramедullary cement-augmented intercalary allografts used in 46 cases for long bone segmental defects due to resection of primary bone tumors showed fewer complications than many previous studies. The rates of fracture (4.3%), nonunion (6.5%), and overall complications (33%) were less than those in most published reports. The mean time to graft union was 9 months (range, 3 to 36 months). The infection rate (8.7%) and allograft survival of 84.8% at a mean of 7.7 years are comparable with those in other reports.

Using free vascularized fibular grafts in 24 patients with spine and pelvic defects after the removal of malignant tumors resulted in disease-free survival of 72% at 5 years and 48% at 10 years, but there was a complication rate of 83%. Six patients had superficial or deep wound infections and another 5 patients had wound dehiscence. The free vascularized fibular graft union rate was 86%, with a mean union time of 7 months. The reoperation rate was 50%. The mean MSTS score was 53 points (range, 13 to 87 points). Fifteen patients were able to walk independently or with the use of an assistive device.

Using a rotated autologous distal clavicular graft to replace the proximal part of the humerus (clavicula pro humero) is an uncommon reconstruction technique usually reserved for pediatric primary bone tumors. Barbier et al. reported the outcomes of this technique in 7 patients with osteosarcoma (8 to 18 years of age). Two patients had no complications and 5 patients had 12 complications necessitating 6 surgical procedures. The median MSTS score was 23 points (range, 11 to 27 points) of 30 points, and the median Toronto Extremity Salvage Score (TESS) was 82% (range, 75% to 92%). The biggest challenge may be healing of the distal end of the clavicle, with a time to osseous union of about 2 years.

A constrained reverse shoulder prosthesis used in 8 patients showed 100% implant survival at a mean follow-up of 49 months (range, 36 to 90 months). Seven patients had primary or metastatic malignancies and 1 patient had osteomyelitis. Two cases were revisions of other implants. All patients had preservation of the axillary nerve and at least part of the...
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deltoid muscle. The only complication was 1 case of neuropathic pain. Sirveaux grade-1 scapular notching was noted in 2 cases. This seems to be a viable option for proximal humeral replacement even in cases with some deltoid muscle loss.

The revision of a tumor endoprosthesis in 21 patients with a current or projected leg-length discrepancy of >3 cm was performed with a noninvasive extendable prosthesis, which was subsequently lengthened in all but 1 patient. The mean lengthening was 51 mm, and the mean leg-length discrepancy improved from 44 mm at the start of this treatment to 15 mm at the time of the final follow-up. Eight patients underwent further revision, and 1 patient had an amputation. Five of these revisions were for implants that had reached maximum extension.

Follow-up
A randomized controlled trial of 500 nonmetastatic extremity sarcomas, examining CT or chest radiographic follow-up of the lungs at intervals of 3 or 6 months, showed that survival was not inferior with a less radiation-intensive mode and a less frequent follow-up interval. CT scans detected metastatic disease significantly earlier than chest radiographs, but this did not impact survival. The follow-up was 60 to 118 months. This is a heterogeneous group of tumors, but it highlights the challenges in treating metastatic sarcoma.

Metastatic Disease
A multicenter group created a prognostic model for survival in patients with symptomatic long bone metastases. Using clinical profiles, Karnofsky Performance Scores, and the presences of visceral and/or brain metastases, patients were placed in 1 of 4 categories. The median survival of each of these groups were 21.9 months, 10.5 months, 4.6 months, and 2.2 months.

Although the assessment of survival as described in the previous study generally helps with surgical decision-making and patient counseling, another study found that patients benefit very quickly from a surgical procedure. In that multicenter prospective study, Nooh et al. found that a surgical procedure for long bone metastatic disease improved function and pain within 2 weeks, but they did not note improvement in quality of life. Improvement in function and pain was observed at each time point over the entire 1-year postoperative study period. The presence of a fracture did not lower the functional results or make complications more likely. The study concluded that a patient with a life expectancy longer than 2 weeks could benefit from this type of surgical procedure, barring contraindications.

MRI-guided focused ultrasound demonstrated efficacy in pain relief as a first-line treatment for bone metastases. MRI-guided focused ultrasound had been shown to have some efficacy in pain relief after failure of conventional radiation therapy. In their study, Lee et al. found that first-line MRI-guided focused ultrasound was as effective as radiation therapy at relieving pain and was able to produce the relief more rapidly on average.

Another method of local control for bone metastases was described in 40 patients with renal cell carcinoma. Fifty bone metastases in these patients were treated using cryoablation with the intent of achieving local control. Patients with ≤5 metastases had better rates of local control (96%) than those with >5 metastases (53%). The control rate in patients with oligometastases compares favorably with any other form of local control. There were 2 bleeding complications necessitating additional treatment and 5 delayed fractures. Renal cell carcinoma is perhaps the most resistant to radiation among the carcinomas that commonly metastasize to bone, so it is encouraging to have another tool that seems effective on at least a subset of these patients.

In their study, Jernigan et al. found that patients treated with prophylactic femoral fixation for metastatic renal cell carcinoma with and without perioperative embolization had similar rates of blood transfusion. Of the 1,150 patients who underwent fixation without embolization, 31% had transfusions within 7 days of the surgical procedure, and of the 135 patients who underwent fixation with embolization, the rate was 30%. Additionally, none of the age groups demonstrated significant differences in transfusion rates. Jernigan et al. did not address the local recurrence risk without open tumor excision for renal cell carcinoma, but perhaps with improved minimally invasive means of local control, both embolization and tumor excision can be used selectively and not routinely for this challenging carcinoma.

In another study, Sevelda et al. reported on 11 patients with metastatic disease in whom total femoral replacement was attempted; most patients did not recover before succumbing to the disease. Despite avoiding patients who had disseminated cancer or who were expected to live <6 months, 8 patients died within 6 months, and 2 other patients had amputations at 8 and 17 months. The other patient lived for 31 months but had a dislocation. Sevelda et al. offered that palliative care may be preferable to a total femoral replacement for the patient with metastastic disease.

Soft Tissue
Surgical Procedures
Using data from 2 prospective trials, Ferrari et al. analyzed 60 patients who were <21 years of age and had either grade-3 synovial sarcomas of ≤5 cm (8 patients) or grade-2 synovial sarcomas of any size (52 patients); patients were treated with surgery only and had 100% survival at a median follow-up of 5.2 years. All patients had negative-margin surgical procedures, and in 68% this was a primary re-excision. Residual tumor was present in 54% of the re-excisions. Eight patients had local recurrences and were treated with a surgical procedure with or without adjuvant treatment. No metastases were noted in this lower-risk population.
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Diagnoses

In the workup of soft-tissue sarcomas, lymph node metastases are uncommon. A few histologic subtypes dominate the list of tumors at risk for lymph node spread. In a review of 15,525 patients with soft-tissue sarcoma in the U.S. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database, Jacobs et al. showed that 5.3% of patients had lymph node metastases at diagnosis.10 Rhabdomyosarcoma, clear cell sarcoma, epithelioid sarcoma, and round cell liposarcoma were noted to develop lymph node metastases most often. Synovial sarcoma has typically been included in this high-risk group. However, in this analysis, synovial sarcoma (885 patients) was not at a higher risk of lymph node involvement than the overall group of soft-tissue sarcomas.

Angiomatoid fibrous histiocytoma is a rare tumor with a low metastatic rate; however, Ulner et al. noted that many patients had lymph nodes labeled as suspicious in pretreatment imaging reports.11 Seven of 19 patients with available imaging had suspicious lymph nodes, and 1 of those 7 lymph nodes contained a metastasis. Standard uptake values from positron emission tomography scans were only available on 3 benign nodes and showed values of 3.0 to 10.9. Ulner et al. proposed that needle biopsy is a reasonable approach to evaluate adenopathy in angiomatoid fibrous histiocytoma given that abnormal nodes are not uncommon and nodal metastases are rare but possible.

References


