What's New in Musculoskeletal Oncology

Valerae O. Lewis


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This update will focus on the material published or presented over the past year in the field of musculoskeletal oncology.

Osteosarcoma
Osteosarcoma is the most common primary malignant bone tumor. The current treatment regimen, developed in the 1980s, significantly improved survival as compared with historic controls. However, relapse and metastasis still represent major obstacles to the successful treatment of the disease. Most patients with metastasis of osteosarcoma do not survive. There is a need to identify which patients are at highest risk for relapse so that novel therapies can be initiated as early as possible. Several investigators have worked to identify prognostic factors that not only have the ability to stratify patient outcomes but also may serve as novel targets for the treatment of osteosarcoma. Huang et al., using immunohistochemistry, analyzed the levels of αV integrins and vascular endothelial growth factor (VEGF) in paraffin sections from twenty patients with untreated osteosarcoma and thirty-one patients with doxorubicin/cisplatin/ifosfamide-treated osteosarcoma. They found that the expression of αV integrins and VEGF was much higher in osteosarcoma as compared with normal bone tissue and that expression was significantly reduced after chemotherapy (doxorubicin/cisplatin/ifosfamide) treatment. While the expression of αV integrins in the specimens from patients who had been managed with chemotherapy was positively correlated with osteosarcoma relapse and Enneking stage, only the expression of VEGF was associated with the development of metastases. No correlation was found between the expression of these factors and patient age, sex, tumor subtype, percent necrosis, or location. Additional statistical analysis revealed that the expression of αV integrins was an independent risk factor for osteosarcoma relapse. These data demonstrate that the expression of αV integrins and the expression of VEGF in osteosarcoma may be helpful predictors of outcome.

Macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine, is implicated in many aspects of tumor progression, including cell proliferation, invasion, and angiogenesis. Han et al. examined whether MIF expression was related to survival in a study of patients with high-grade osteosarcoma. Immunohistochemistry studies and microvessel density measurements were performed on pre-chemotherapy biopsy specimens from fifty-eight patients with osteosarcoma. MIF expression correlated with microvessel density and independently predicted both overall survival and metastasis-free survival. In vitro studies involving the use of two osteosarcoma cell lines revealed that treatment of the osteosarcoma cells with MIF induced a dose-dependent increase in VEGF, a potent pro-angiogenic factor, and knockout of MIF in these cell lines resulted in decreased cell invasion. The authors concluded that MIF not only could serve as a prognostic marker but also may serve as a putative target in the development of novel strategies for the treatment of osteosarcoma.

Although several clinicopathological prognostic factors have been identified, the importance of these prognostic factors over time has not been examined. Kim et al. examined whether the clinical characteristics of patients with osteosarcoma in whom metastases developed after two years differed from those of patients in whom metastases developed earlier. The authors retrospectively reviewed 420 patients with stage-IIB osteosarcoma that had been treated with surgery and chemotherapy. Metastases occurred in 167 of the 420 patients. Among these 167 patients, 73.7% had metastases within two years after diagnosis and 26.3% had metastases more than two years after diagnosis. The authors assessed twelve prognostic factors and found that an age of more than thirty years, large tumor volume, location of the tumor in the proximal part of the humerus, no neoadjuvant chemotherapy, non-methotrexate-
patterns predict oncologic outcome, Kim et al. examined tumor growth variables over time may explain the varied results reported change that they identified in the prognostic value of some patients with osteosarcoma were performed for different after two years. Many of the studies on examining the outcome gradual decline in prognostic value and lost its importance factor after two years. Poor histological response showed a canceration were the major poor prognostic factors. However, only time-related changes regarding their prognostic value. Chondroblastic subtype, which had no prognostic relevance during the first two years, emerged as an independent poor prognostic factor after two years. Poor histological response showed a decline in tumor necrosis and therefore diminished value. It is hypothesized that the change in necrosis rate is an independent poor prognostic factor. However, only time-related changes regarding their prognostic value. Chondroblastic subtype, which had no prognostic relevance during the first two years, emerged as an independent poor prognostic factor after two years. Poor histological response showed a gradual decline in tumor necrosis and lost its importance factor after two years. Many of the studies on examining the outcome of patients with osteosarcoma were performed for different durations of follow-up. The authors hypothesized that the change in the proportion of necrosis over time may explain the varied results reported with regard to the prognostic value of these different factors.

In another attempt to identify prognostic factors and to predict oncologic outcome, Kim et al. examined tumor growth patterns. The authors retrospectively reviewed 347 patients with Enneking stage-IIB and American Joint Committee on Cancer (AJCC) stage-II osteosarcoma who were managed with surgery and neoadjuvant chemotherapy. The patients were divided into three groups on the basis of tumor growth pattern: concentric (64.8%), eccentric (20.3%), and longitudinal (14.7%). Among patients with AJCC stage-IIA osteosarcoma, no survival difference was found according to growth pattern; however, in those with AJCC stage-IIB osteosarcoma, longitudinal tumors were associated with significantly better survival than concentric tumors were.

In another report, the same authors also examined whether a parameter that considers both the change in tumor volume and the rate of tumor necrosis could predict metastasis-free survival of patients with localized osteosarcoma. The authors retrospectively reviewed 151 patients with stage-II osteosarcoma who had been managed with surgery and neoadjuvant chemotherapy. The change in tumor volume was measured and calculated on the basis of magnetic resonance images made before and after chemotherapy. A poor tumor necrosis rate independently correlated with a metastasis-free survival period, and tumor volume change independently correlated with a necrosis rate (relative risk, 2.02; 95% confidence interval, 1.05 to 3.89; p = 0.035). Decreased tumor volume was associated with a good response (sensitivity, 80.2%; specificity, 68.6%; positive predictive value, 74.7%) and increased stable tumor volume predicted a poor response (sensitivity, 68.6%; specificity, 80.2%; positive predictive value, 75.0%). Thus, the authors concluded that the necrosis rate, adjusted by the tumor volume change, is an independent prognostic factor in cases of osteosarcoma and may serve, in combination with other prognostic factors, as a basis for risk-adapted therapy.

The value of adjuvant therapy for the treatment of osteosarcoma is well established. The Children's Oncology Group recently reported the results of a study that was performed to determine the efficacy of adding muramyl tripeptide to the chemotherapy regimen for patients with newly diagnosed osteosarcoma. Six hundred and sixty-two patients with osteosarcoma without clinically detectable metastatic disease in whom the tumor was considered to be resectable were randomized to four treatment groups. All patients received identical cumulative doses of cisplatin, doxorubicin, and methotrexate and underwent definitive surgical resection of the primary tumor. Patients were then randomly assigned to receive or not to receive ifosfamide and/or muramyl tripeptide. The primary end points for analysis were event-free survival and overall survival. The authors reported that the addition of ifosfamide to cisplatin, doxorubicin, and methotrexate did not enhance event-free survival or overall survival for patients with osteosarcoma; however, the addition of muramyl tripeptide to chemotherapy resulted in a significant improvement in overall survival and a trend toward a better event-free survival. This study is very promising as it represents one of the first clinical advancements in the treatment and outcome of osteosarcoma in the last twenty years.

While the above results presented by Meyers et al. are encouraging, several authors have voiced some words of caution before muramyl tripeptide is adopted as the standard of care. Bielack et al. pointed out that, while these results are promising, treatment decisions should not be based on a single trial. In addition, they noted that the data failed to show that muramyl tripeptide improved event-free survival in cases of osteosarcoma and that the event-free survival for the three-drug arm was identical regardless of whether or not muramyl tripeptide was added. Such an observation, they asserted, argued against any substantial efficacy of muramyl tripeptide, at least in this combination. Also, as it has been found that event-free survival and overall survival are closely linked in patients with osteosarcoma, Bielack et al. further questioned why this was not the case in the study by Meyers et al. Thus, they concluded that while the updated results of the study strongly suggest that muramyl tripeptide may be a good option, substantial uncertainties remain regarding its true role in the treatment of osteosarcoma and thus confirmatory trials are recommended before the agent is to be considered for routine use.

Recurrent or relapsed osteosarcoma remains a treatment dilemma. Bielack et al. evaluated patient and tumor characteristics, treatment, and outcomes in a study of 249 consecutive patients with multiply recurrent osteosarcoma. The patients had received combined-modality therapy on neoadjuvant Cooperative Osteosarcoma Study Group protocols and had had development of second and subsequent osteosarcoma recurrences. The prognostic factors and outcomes were analyzed. The five-year overall and event-free survival rates declined for each recurrence, with rates of 16% and 9% for the second recurrence, 14% and 0% for the third recurrence, 13% and 6% for the fourth recurrence, and 18% and 0% for the fifth recurrence, respectively. The duration of relapse-free intervals and the number of lesions at the time of recurrence.
correlated with outcomes. Only one of 205 patients with recurrence survived for more than five years without surgical resection of the recurrence. When the recurrence was resected, the five-year overall and event-free survival rates were 32% and 18% for the second recurrence, 26% and 0% for the third recurrence, 28% and 13% for the fourth recurrence, and 53% and 0% for the fifth recurrence, respectively. Little information on the potential efficacy of chemotherapy for subsequent recurrences was presented. However, in this study, the use of chemotherapy did correlate with longer survival in patients without surgical remissions. The authors confirmed the importance of surgical treatment of the recurrent disease; however, the exact role of additional treatment with chemotherapy in the face of recurrent disease, particularly in the adjuvant situation, remains to be defined.

Postoperative deep infection is an unfortunate and dire complication for patients with osteosarcoma who have undergone resection and reconstruction. Recently, several studies have investigated the effect of postoperative infection in patients with osteosarcoma who have been managed with limb salvage. Jeys et al. examined patients who had development of a deep infection within one year after surgery. Forty-one patients who underwent resection and reconstruction with an endoprosthetic implantation from 1981 to 2000 were identified. Patients who had development of an infection within one year after endoprosthetic implantation had a significantly better survival rate (p = 0.017). The ten-year survival rate was 84.5% for patients with osteosarcoma with infection, compared with 62.3% for those without infection. No significant difference in the percent necrosis was identified between these two groups. Infection was identified as an independent prognostic factor. The authors concluded that there was evidence for increased survival after deep postoperative infection in patients with osteosarcoma.

Lee et al. also examined the impact of postoperative deep infection on the survival of patients with osteosarcoma. The authors identified thirty-one patients with osteosarcoma who had development of a deep infection within one year after an operation. They compared the clinicopathological characteristics of these thirty-one patients with those of 316 patients who did not have an infection. The authors also identified sixty-two patients without infection who were matched for prognostic factors such as histological response, tumor size, and location. No local recurrence developed in patients with infection. The five-year overall and metastasis-free survival rates for the thirty-one patients with infection were as high as 89% and 73%, respectively. However, unlike Jeys et al., Lee et al. found that after matching for clinical factors, no difference in survival was noted between patients with and without infection. Lee et al. suggested that the positive effect on survival as reported in other series may have been related to the clinical characteristics of the patients with infection rather than to an antitumor effect due to the infection. Deep infection can have a devastating effect on patients with endoprosthetic limb salvage, and additional investigations are needed to clarify the precise effects of infection on long-term survival.

The outcome for patients with osteosarcoma varies not only with subtype but also with location. The overall survival of patients with an osteosarcoma of the pelvis is worse than that of patients with an osteosarcoma of an extremity. However, the risk factors associated with the poorer survival of these patients are poorly understood. Fuchs et al. attempted to identify the factors affecting survival and the development of local recurrence and metastasis in patients with osteosarcoma of the pelvis. The authors retrospectively reviewed forty-three patients who had high-grade pelvic osteosarcoma. The lesions included twenty chondroblastic osteosarcomas, ten fibroblastic osteosarcomas, eleven osteoblastic osteosarcomas, one giant-cell-rich osteosarcoma, and one small-cell osteosarcoma. Patients were managed with chemotherapy and surgical resection. Surgery type (internal or external hemipelvectomy) did not affect survival; however, surgical margin did. Fifteen patients (35%) had a local recurrence. At a median of 3.5 years, only 30% of the patients were alive with no evidence of disease. The overall and disease-free five-year survival rates were 38% and 29%, respectively. Location of the tumor in the ilium and a tumor size of >10 cm were found to be major risk factors for the development of local recurrence. None of the patients with a local recurrence were alive at the time of follow-up. The cumulative rate of recurrence with death as a competing risk factor was 34% (95% confidence interval, 19% to 46%) at five years. A tumor size of >10 cm and inadequate surgical margins were found to be major risk factors for the development of metastases. As expected, metastasis at the time of presentation carried a poor prognosis.

Low-grade juxtacortical and low-grade intramedullary osteogenic sarcomas, although histologically indistinguishable, have been studied and classified as separate entities. Schwab et al. retrospectively reviewed fifty-nine patients with these two entities to compare the rates of local recurrence, grade progression, and survival. Forty-five patients had a low-grade juxtacortical osteogenic sarcoma, and fourteen had a low-grade intramedullary osteogenic sarcoma. The authors found that the rates of local recurrence, dedifferentiation, distant metastases, and survival were similar for both groups. Although limited by the small numbers, their data suggest that low-grade intramedullary and juxtacortical osteogenic sarcomas are clinically distinguishable only by their location relative to the cortex but not by their behavior or oncologic outcome.

**Chondrosarcoma**

The grading of cartilage lesions remains controversial and difficult. It has been emphasized that the diagnosis of chondrosarcoma cannot be made in a vacuum and that clinical and radiographic correlation are necessary. The Skeletal Lesions Interobserver Correlation among Expert Diagnosticians (SLICED) Study Group attempted to quantify the interobserver reliability of the determination of the grade for cartilaginous...
Lesions among a group of experienced musculoskeletal pathologists and radiologists. All physicians received a brief history and preoperative radiographs. The pathologists reviewed the hematoxylin and eosin-stained slides for each case. The radiologists reviewed any additional imaging that was available. A total of forty-six cases were reviewed. The lesions were classified as benign, low-grade malignant, or high-grade malignant. As a measure of reliability, kappa coefficients were used to measure the percentage of agreement among raters. The kappa coefficient for inter-rater reliability was only 0.345 for the radiologists and 0.443 for the pathologists, indicating only fair and moderate agreement. The kappa coefficients for the subgroup of cases that were thought to be high-risk were even worse. Interestingly, an improved kappa coefficient was noted for the radiologists when magnetic resonance images were available for the lesions in question. Taken together, these data reveal that, even among specialists, the reliability of grading cartilage lesions is low. These findings may explain the different outcomes that have been reported for patients with chondrosarcoma. In addition, they suggest that the use of biopsy for the diagnosis of borderline lesions is questionable.

Dedifferentiated chondrosarcomas that arise in osteochondromas are extremely rare. In order to evaluate the oncologic outcome and to describe the specific clinical, radiographic, and histological features of such lesions, Staals et al. reviewed the files of the Rizzoli Institute for the years 1970-1997. They identified eight patients with a dedifferentiated chondrosarcoma. These cases accounted for 5.5% of all cases of chondrosarcomas arising from exostoses. The eighteen patients included twelve men and six women with an average age of forty-six years. These patients were noted to be slightly older than patients with conventional chondrosarcoma in preexisting exostoses. Eight lesions occurred in patients with multiple osteochondromas, and ten occurred in patients with solitary lesions. The most common locations were the pelvis (six) and the femur (five). Symptoms included pain, swelling, and a growing mass. The average duration of symptoms was eighteen months. Histological evaluation of the resected lesions revealed that the cartilage component was generally grade 1 or 2. The dedifferentiated components were osteosarcoma (nine), malignant fibrous histiocytoma (eight), or fibrosarcoma (one). The dedifferentiated component represented an average of 59% (range, 20% to 100%) of the lesion. The overall prognosis was found to be poor. However, patients who were managed with a combination of surgery and chemotherapy had a better overall survival rate than did those who were managed with surgery alone. Although the series was small, which was due in part to the rarity of the disease, the authors concluded that these lesions should be treated in a multimodality fashion consisting of wide resection and chemotherapy.

The surgical treatment of low-grade chondrosarcoma remains controversial. Streitbürger et al. reviewed their experience with the surgical treatment of eighty patients with a grade-I chondrosarcoma; 86.25% of the patients had a primary chondrosarcoma of bone, and 13.75% had a secondary chondrosarcoma of bone. The surgical procedures were defined as intralesional (eighteen), marginal (sixteen), and wide (forty-six). The overall rate of local recurrence was 17.5%. However, all pelvic chondrosarcomas that were treated with intralesional curettage recurred, and 4.9% of the patients had development of metastatic disease. Although intralesional procedures were associated with a significantly higher rate of local recurrence, intralesional curettage did not influence the overall rate of survival or the rate of metastasis. A significantly higher rate of recurrence was noted when intralesional curettage was compared with wide resection. The authors concluded that intralesional curettage is a viable option for the treatment of a grade-I chondrosarcoma in the extremity. A higher overall risk of local recurrence can be expected, but the procedure does not compromise survival. However, the authors recommended that this treatment option should be avoided in the pelvis as the rate of recurrence was found to be 100%.

Schwab et al. also examined the incidence of local recurrence of grade-I chondrosarcoma of the long bones and its influence on survival. The authors retrospectively reviewed one hundred sixty-four patients who had undergone surgical treatment of a grade-1 chondrosarcoma of the long bones. The method of surgical resection of the lesions varied extensively (amputation, wide resection, marginal resection, and intralralional resection), and the authors acknowledged that the treatment of these lesions evolved over the time of the study. Local recurrence occurred in twenty-one patients (13%). Four tumors recurred at a higher grade, and six patients had more than one local recurrence. Seven of the twenty-one patients with local recurrence had metastasis, and six of these twenty-one patients died of the disease. Local recurrence, progression of grade at the time of recurrence, and distant metastases were all associated with a decrease in overall survival; however, the difference in survival was not apparent until after five years, and it was more pronounced after ten years. It was hypothesized that local recurrence may be a declaration of a more aggressive phenotype despite the appearance of the primary lesion, and thus the authors noted that they have adopted a practice of treating local recurrences more aggressively.

Ewing Sarcoma

The prognosis for patients with recurrent Ewing sarcoma is very poor. The Children’s Oncology Group attempted to identify the prognostic factors for these patients. Two hundred and sixty-two patients with recurrent Ewing sarcoma were identified. All patients were managed as part of a single prospective multi-institutional randomized study (INT0091) over a six-year period. The median time to the first recurrence was 1.3 years (1.4 years for patients who presented with localized disease and one year for patients who presented with metastatic disease). Like previous investigators, the authors found that the time to the
first recurrence was the most significant predictor of post-recurrence survival. The estimated five-year survival rate was 30% (95% confidence interval, 17% to 43%) for those in whom the disease recurred at least two years after the initial diagnosis, compared with 7% (95% confidence interval, 3.7% to 11%) for those in whom the disease recurred earlier. No difference was detected between patients in whom the disease recurred less than one year after the initial diagnosis and those in whom it recurred one to two years after the initial diagnosis. Patients with metastatic disease at the time of the initial diagnosis, patients with an elevated serum lactic dehydrogenase level (LDH) at the time of diagnosis, and female patients were found to have a significantly worse rate of survival after recurrence. In addition, patients who had recurrence both locally and at a distant site were found to have a worse prognosis. Age at the time of diagnosis, age at the time of recurrence, initial tumor size, and isolated pulmonary recurrence were not found to be predictive of survival after recurrence. The authors did, however, define a subset of patients with recurrent disease who were more likely to survive, including those with a longer time to first recurrence, initially localized disease, and a normal LDH level at the time of diagnosis. Unfortunately, no detailed data on post-recurrence therapy were collected, so the authors were unable to comment on the impact of post-recurrence therapy on outcome. However, all patients with a recurrent Ewing sarcoma would benefit from collaborative trials to improve post-recurrence survival.

A search of the Surveillance, Epidemiology and End Results (SEER) database allows one to evaluate the incidence of and survival rates associated with cancer within the United States. Using the SEER database, Esiashvili et al. evaluated the incidence of and survival rates associated with Ewing sarcoma for the past three decades.19 The authors presumed that this query would generate different data than those reported in the published clinical trials. Actuarial survival rates were examined for three ten-year intervals: 1973 to 1982, 1983 to 1992, and 1993 to 2004. The overall incidence of Ewing sarcoma has not changed significantly in the last thirty years, averaging 2.93 cases per 1,000,000 people annually. Although the percentage of localized cases of Ewing sarcoma increased slightly from 57% in the period from 1973 to 1982 to 67% in the period from 1993 to 2004, the proportion of patients with unstaged disease decreased (from 17% to 5%). The authors hypothesized that the decrease in unstaged cases may be reflective of improvements in diagnostic imaging. The five-year survival rates for patients with localized disease and patients with metastatic disease had increased in the period after 1993 (from 44% to 68% and from 16% to 39%, respectively). In addition, the ten-year survival rates for patients with localized and metastatic Ewing sarcoma both increased during this period as well (from 39% to 63% and from 16% to 32%, respectively). This analysis indicates that there has been a clear improvement in the survival rates associated with both localized and metastatic disease; however, additional investigation is warranted to provide additional treatment options, especially for patients with metastatic disease.

**Soft-Tissue Sarcomas**

Soft-tissue sarcomas are a rare and heterogeneous group of neoplasms that are often difficult to classify definitively. An accurate diagnosis is critical for proper treatment. Although the gold standard is open biopsy, many centers are steering away from that method; however, the role of fine-needle aspiration in this setting is still evolving. There have been few studies demonstrating the reliability of fine-needle aspiration biopsy in cases of high-grade sarcoma. Fleshman et al. reviewed their cytopathology database and identified all fine-needle aspiration specimens designated as high-grade sarcomas20. They reported a sensitivity of 94%, a positive predictive value of 97%, and an overall accuracy of 91%. Approximately 75% of the aspiration specimens were obtained from primary, previously undiagnosed, malignant lesions. The authors attributed some of the accuracy to a close collaboration between the pathologists and the orthopaedic oncologists, who were skilled in radiographic interpretation. Despite the high success rate reported in that study, the authors did include a note of caution. They stated that cytological evaluation is a specialized skill set and that cytologists who are unfamiliar with soft-tissue sarcomas may wish to pursue other techniques in order to make an accurate diagnosis.

Retrospective data have suggested that some patients with small soft-tissue sarcomas can be safely managed with surgery alone. Pisters et al. conducted a prospective trial to attempt to determine the local recurrence rates and oncologic outcomes for such patients21. Eighty-eight patients with a T1 primary soft-tissue sarcoma were entered in the protocol between March 1996 and April 2002. Fifty-one of these patients were managed with function-preserving surgery. Postoperative external-beam radiation was only given to patients with histologically positive margins (16%). The median duration of follow-up was seventy-five months. Local recurrence was seen in 13% of the patients. The cumulative rates of local recurrence at five and ten years were 7.9% and 10.6%, respectively, and the sarcoma-specific death rates at five and ten years were 3.2% and 3.2%, respectively. The results of that trial indicate that carefully selected patients with T1 lesions can undergo resection without adjuvant radiation and expect acceptable local control and excellent long-term survival.

The use of adjuvant chemotherapy for the treatment of localized resectable soft-tissue sarcoma in adults remains controversial. Pervaiz et al. performed a systematic review of randomized controlled trials to reassess the efficacy of doxorubicin-based chemotherapy with respect to recurrence and survival22. The intent of that review was to update a 1997 meta-analysis to assess the efficacy of doxorubicin-based chemotherapy with respect to recurrence and survival. The authors performed a comprehensive literature review to identify randomized clinical trials of adjuvant chemotherapy for adult
patients diagnosed with a localized resectable soft-tissue sarcoma. Since their review in 1997, four new eligible trials were identified, resulting in a total of eighteen trials representing 1953 patients. The outcome measures, calculated through the fixed-effect or random-effect model, were local, distant, and overall recurrence and survival. The odds ratio for local recurrence was 0.73 (95% confidence interval, 0.56 to 0.94) in favor of chemotherapy. For distant and overall recurrence, the odds ratio was 0.67 (95% confidence interval, 0.56 to 0.82) in favor of chemotherapy. In terms of survival, doxorubicin alone did not have a significant odds ratio (0.84; 95% confidence interval, 0.68 to 1.03), but the odds ratio for doxorubicin combined with ifosfamide was 0.56 (95% confidence interval, 0.36 to 0.85) in favor of chemotherapy. The authors concluded that this meta-analysis confirms the marginal efficacy of chemotherapy for the treatment of localized resectable soft-tissue sarcoma with respect to local recurrence, distant recurrence, overall recurrence, and overall survival; however, chemotherapy is not without substantial morbidity, and its application must be weighed against its associated toxicities.

Although the frontline use of chemotherapy for the treatment of solitary soft-tissue sarcomas remains controversial, most clinicians support the use of chemotherapy in the advanced/palliative setting. The efficacy of palliative chemotherapy was investigated by Karavasilis et al.22, who identified 488 patients with a soft-tissue sarcoma who had first-line chemotherapy for the treatment of metastatic disease between 1991 and 2005. The most prevalent histological subtypes were leiomyosarcoma (35%), synovial sarcoma (13%), liposarcoma (10%), and malignant fibrous histiocytoma (10%). The median age was forty-nine years, and the majority of patients (83%) received chemotherapy for the treatment of metastatic disease. In all, 61% of the patients received single-agent chemotherapy, usually doxorubicin. The authors reported an objective response (defined as a complete or partial response) in 33% of the patients (including 53% of those with synovial sarcoma), stable disease in 22%, and disease progression in 45%. The median duration of response was nine months, and the median duration of overall survival after treatment was twelve months. In multivariate analysis, an age of less than forty years, liposarcoma, and synovial histology were found to be positive independent prognostic factors. Bone involvement was found to be a negative prognostic factor. In addition, patients who were managed with combination chemotherapy were found to have longer overall survival in comparison with patients who were managed with a single agent. The authors concluded that although palliative chemotherapy may be beneficial for some patients with advanced soft-tissue sarcoma, especially those with synovial sarcoma and liposarcoma subtypes, the overall outcome is poor and new treatment options are needed.

The histological response to chemotherapy is generally regarded as a prognostic variable for patients with bone sarcomas; however, this is not the case for those with soft-tissue sarcomas. Lucas et al. reported on the clinicopathological findings for thirty-one patients with soft-tissue sarcomas of an extremity that were treated with the same neoadjuvant chemotherapy followed by resection.24 The authors used a non-validated histological grading system, but they noted that the criteria that they used to assess the histological response to therapy were simple and took into account the major histological patterns seen after therapy. The chemotherapy was found to induce substantial alterations in the soft-tissue sarcomas. On the basis of the percentage of post-treatment viable tumor, tumors were categorized similarly to the Huvos score as showing an excellent response (≤5% viability), a moderate response (6% to 49% viability), or a poor response (≥50% viability). Nineteen percent of the tumors had an excellent response, 10% had a moderate response, and 71% had a poor response. When compared with clinical outcome, neither the presence of these histological parameters nor the histological response groups correlated with overall or event-free survival. Thus, chemotherapy can induce substantial alterations in soft-tissue sarcomas; however, the authors showed that neither these alterations nor the extent of tumor necrosis carries prognostic value.

In order to assess the prognosis for patients at the time of surgery, Bifulco et al. investigated whether the assessment of cell invasiveness would be of some prognostic value.25 The authors derived cell cultures from resected sarcomas and subjected them to in vitro cell-invasion assays. For each primary cell culture, the sarcoma cell invasion index was determined by comparing the extent of invasion to the human fibrosarcoma HT1080 cell invasion extent. The cell invasion index was then evaluated with respect to the outcome of the disease (range of follow-up, fourteen to forty-eight months). A low cell invasion index (39.7% ± 8.9%) was seen in cell cultures derived from the sarcomas of patients with no progression of the disease and with a longer interval of disease-free survival (21 ± 0.8 months), whereas a higher cell invasion index (61% ± 5%) was seen in tumor cells derived from the sarcomas of patients with progression of the disease and with a shorter disease-free survival (9 ± 3 months). Although only seven cases were analyzed, a significant correlation was found between disease-free survival and the cell invasion index. This finding supports the premise that cell invasion assays performed in vitro on cells derived from human sarcomas may be predictive of disease outcome and may give clinicians additional information regarding patients who may warrant closer observation or additional treatment.

Although treatment algorithms for soft-tissue sarcomas have been developed, disparities in care exist. Martinez et al. examined the SEER database to discern whether disparities exist in the treatment of and outcomes associated with soft-tissue sarcomas.26 The authors assessed racial/ethnic differences in patient and tumor-specific characteristics, treatment, and disease-specific survival among 6406 adult patients with soft-tissue sarcomas who were diagnosed and managed between 1988 and 2003. Patients were categorized into one of four
racial/ethnic groups: whites, African-Americans, Hispanics, and Asians. Comparisons of treatment and disease-specific survival were conducted with regression models that adjusted for patient age, sex, SEER geographic region, extent of disease, tumor grade, tumor size, and histological characteristics. Significant racial/ethnic differences in treatment and survival were identified. Hispanics tended to be diagnosed at a younger age than their white, African-American, or Asian counterparts. African-Americans, Asians, and Hispanics tended to have larger tumors at the time of presentation, and Hispanics and African-Americans were less likely to receive radiation therapy in addition to surgery. African-Americans had lower rates of adjuvant radiation with surgery (odds ratio, 0.77; 95% confidence interval, 0.66 to 0.90), and Hispanics had significantly lower rates of limb-sparing surgery (odds ratio, 0.76; 95% confidence interval, 0.59 to 0.97). African-Americans (hazard ratio, 1.39; 95% confidence interval, 1.13 to 1.70) demonstrated a disease-specific death rate that was 39% higher than that for their white counterparts, even when controlling for factors that influence sarcoma-specific survival (patient age, sex, SEER geographic region, extent of disease, tumor grade, tumor size, and histological characteristics). While the authors noted that identifying the causes for these disparities was beyond the scope of the study, it was thought that the cause for these disparities is multifactorial and may be attributable to poor access to health care, access barriers (such as the lack of cancer-specific physician expertise), the lack or poor quality of insurance, low socioeconomic status, language barriers, or the unavailability of reliable transportation. Nonetheless, the identification of these racial/ethnic disparities in terms of treatment and outcome among patients with soft-tissue sarcomas should alert clinicians and cause us to focus our efforts toward improving soft-tissue sarcoma treatment and outcomes for all patients, especially those most at risk.

**Benign Bone and Soft-Tissue Tumors**

The treatment of benign bone tumors is continually evolving. Radiofrequency ablation has been shown to be a very effective minimally invasive treatment option for the treatment of osteoid osteomas. Several investigators have extended the technique for the treatment of other benign lesions. Christie-Large et al. described the technique and clinical and imaging outcomes for four patients who were managed with radiofrequency ablation for the treatment of chondroblastoma. All patients had the typical symptoms and imaging findings consistent with a diagnosis of chondroblastoma. Two patients underwent an initial computed tomography-guided diagnostic biopsy that confirmed the diagnosis of chondroblastoma prior to radiofrequency ablation, and the remaining two patients had a biopsy during the procedure. The lesion size ranged from 1.5 to 2.5 cm (mean size, 1.8 cm). The mean duration of follow-up was one year. All patients reported resolution of symptoms at two to six weeks after ablation. At the time of the latest follow-up, three patients remained completely asymptomatic and one patient had minor pain that was not limiting activity. All patients had magnetic resonance images that demonstrated resolution of the edema pattern around the lesion and resolution of the internal lesional signal characteristics. That study, although limited by the short duration of follow-up, revealed that radiofrequency ablation is a viable option for the treatment of chondroblastoma; however, additional follow-up is warranted.

Many benign bone lesions can cause extensive bone destruction, and, even after surgical eradication, they have the propensity to recur. Aneurysmal bone cysts are associated with a high rate of recurrence. Large epiphysial lesions may be difficult to treat aggressively because of the fear of damaging the physis and cartilage. Several investigators have hypothesized that the location of an aneurysmal bone cyst at a periarticular or juxtaphysial site increases the risk of recurrence. In order to investigate this hypothesis, Lin et al. retrospectively reviewed fifty-three patients with an aneurysmal bone cyst that had been treated between 1989 and 2004. All patients underwent curettage of the lesion. Ten patients (18.9%) had a local recurrence. All of the recurrences developed in pediatric patients with aneurysmal bone cysts in either a juxtaphysial location (eight cases) or a periarticular position (two cases). There were no recurrences in pediatric patients in whom the tumor was separated from the physis or the articular surface. An age of twelve years or younger was significantly associated with recurrence. The data suggest that the risk of recurrence is highest for pediatric patients with juxtaphysial or periarticular aneurysmal bone cysts. The authors hypothesized that a surgeon may be justifiably cautious and less likely to be aggressive when curetting lesions in these areas and that this may lead to difficulty eradicating disease. However, the authors also hypothesized that recurrence of aneurysmal bone cysts may not be strictly a matter of surgical technique and incomplete excision but that there may be an inherent propensity toward recurrence for aneurysmal bone cysts in the juxtaphysial and perilarticular locations.

Although not as locally aggressive as aneurysmal bone cysts, unicameral bone cysts can be difficult to eradicate. The Simple Bone Cyst Trial Group (part of the Pediatric Orthopaedic Society of North America Clinical Trials Network) conducted a multicenter randomized clinical trial in which the rates of healing of simple bone cysts that were treated with intralesional injections of bone marrow were compared with the rates of healing of those that were treated with methylprednisolone acetate. Ninety patients were randomly allocated to treatment with either bone-marrow or steroid injection. Each patient received a maximum of three injections, with at least three months between injections. Two patients were lost to follow-up, and the remaining patients were followed for two years. The primary outcome, determined by a radiologist who was blinded to the type of treatment, was radiographic evidence of healing. Forty-two percent of the cysts that were treated with methylprednisolone acetate healed,
What’s New in Musculoskeletal Oncology

compared with 23% of cysts that were treated with bone marrow. The study demonstrated a lower healing ratio for these bone cysts than was found in previous studies; however, the authors attributed that finding to the elimination of the biases associated with many case studies. The blinded evaluation of the treatment outcomes allowed for an objective evaluation of cyst healing. In addition, the authors attributed the lower healing rates in the study to longer follow-up (more than two years) and limiting the number of injections to three. Nonetheless, that study confirmed that injections of methylprednisolone acetate are superior to injections of bone marrow for the treatment of bone cysts.

Pigmented villonodular synovitis is a rare pathological entity affecting the synovium. Recently, a specific t(1;2) translocation involving the collagen 6A3 gene (on 2q35) and the macrophage colony-stimulating factor gene (on 1p13) was found to be present in some of the tumor cells in patients with pigmented villonodular synovitis. This fusion gene encodes for a protein that attracts non-neoplastic cells expressing macrophage colony-stimulating factor. Blay et al. evaluated the efficacy of imatinib treatment in a patient with recurrent and symptomatic pigmented villonodular synovitis. Treatment was initiated at a dose of 400 mg/day. A partial response was observed at two months, and complete remission was observed at five months. Treatment was discontinued at seven months. Two months after the cessation of imatinib treatment, a symptomatic painful relapse of the tumor was noted. Imatinib was reintroduced at the same dose, and a second complete remission was observed three months later. The authors hypothesized that imatinib may disrupt the paracrine loop found to be responsible for pigmented villonodular synovitis growth. Although additional investigation is warranted, this case report suggests that imatinib may have the ability to induce complete responses in patients with relapsing pigmented villonodular synovitis. This could provide a treatment option for patients in whom surgical eradication of pigmented villonodular synovitis is difficult or would result in substantial functional impairment.

Metastatic Bone Disease

The five most common carcinomas that metastasize to bone are breast, renal, lung, thyroid, and prostate. The detailed mechanism of organ-specific metastasis is poorly understood. Klein et al. searched for genes that are implicated in brain or bone metastasis of primary human breast cancer. The authors generated gene-expression profiles of brain and bone metastases derived from primary breast tumors and identified seventy-three genes differentially expressed between brain and bone metastases. In addition, they addressed the question of whether the identified gene set could accurately classify the location of metastases of primary relapsing breast tumors. Hierarchical cluster analysis showed that the bone metastases and breast tumors relapsing to bone lie in one cluster separate from brain metastases and primary tumors relapsing to the brain. Additional studies are needed; however, the genes identified may prove to be excellent markers to assess the site of recurrence in patients with breast cancer and may allow physicians to tailor their therapy.

Although bone metastasis from lung cancer is the cause of substantial morbidity, the prognosis for patients with this diagnosis has not been well documented. Some reports have suggested that the mean duration of survival in patients with stage-IV disease, including distant metastasis, is approximately six months. Sugíura et al. evaluated the prognostic factors and survival rates in a study of 118 patients with bone metastases secondary to lung cancer. The mean duration of survival was 9.7 months. The cumulative survival rates were 59.9% at six months, 31.6% at one year, and 11.3% at two years. Sugíura et al. identified eight prognostic factors: sex, performance status, histological type, number of bone metastases, site of bone metastases (bone metastasis to the appendicular bone), pathological fracture, systemic chemotherapy, and gefitinib therapy. The presence of adenocarcinoma, evidence of appendicular bone metastases, and the use of gefitinib independently predicted survival. The prognosis was worse for patients with metastasis to the appendicular skeleton. Among the patients with adenocarcinoma, the mean duration of survival was longer in the group treated with gefitinib. Gefitinib, an epithelial growth factor receptor (EGFR) inhibitor, is a new molecule-targeting treatment for lung cancer and is reported to have a considerable effect in female patients and non-smokers. These findings not only help to stratify the prognosis for the patient but also suggest that treatment with an EGFR inhibitor may improve survival in patients with metastatic lung cancer to bone.

Radiation therapy is often used for the palliative treatment of bone metastases. Chow et al. performed a systematic review of all published reports from fifteen randomized trials comparing single-fraction with multiple-fraction schedules for the palliative treatment of painful bone metastases. The quality of the clinical trials varied; however, the authors found no significant difference in response rates or acute toxicities. However, there was a trend toward an increased risk for patients receiving a single-fraction schedule in terms of pathological fractures and spinal cord compressions, but no significance was found. The likelihood of retreatment was 2.5-fold higher in association with the single-fraction schedule. The study revealed that there was substantial evidence that single-fraction therapy is as good as multiple-fraction therapy with regard to pain relief for patients with uncomplicated bone metastasis. However, single-fraction therapy is associated with a significantly higher retreatment rate. The authors proposed that single-fraction therapy may be most advantageous for patients with a short life expectancy, for whom the issue of retreatment may be irrelevant but the immediate improvement in terms of pain is desired.

Bisphosphonate therapy has significantly reduced the number and severity of skeletal complications secondary to...
osseous metastatic disease. As bisphosphonate therapy has been approved for the treatment of osteoporosis and is commonly used for the treatment of metastatic bone disease, there are now a considerable number of patients who have been undergoing bisphosphonate therapy for at least five years. Recently, several investigators have observed an apparent rise in the number of subtrochanteric insufficiency fractures and a unique low-energy femoral shaft fracture in association with long-term bisphosphonate therapy. Those authors identified a significant association of unique fracture geometry and patterns with prolonged therapy. Neviaser et al. found that alendronate use was a significant risk factor for the specific fracture pattern (odds ratio, 139.33; 95% confidence interval, 19.0 to 939.4), and this fracture pattern was 98% specific to alendronate users. Lenart et al., in a case-controlled study, found that bisphosphonate use for more than five years was associated with a similar fracture pattern. The fracture pattern that was identified was a simple transverse or oblique fracture with cortical thickening and beaking of the cortex in the subtrochanteric/shaft region. Goh et al. reported that a significantly greater proportion of patients with a minimally traumatic femoral subtrochanteric or shaft fracture undergo long-term bisphosphonate therapy as compared with those with an intertrochanteric or femoral neck fracture. The authors hypothesized that prolonged suppression of bone remodeling with alendronate may be associated with a new form of insufficiency fracture of the femur, and this fracture pattern may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair secondary to the prolonged bisphosphonate use. Although additional studies are warranted, the authors of those studies concluded that prolonged bisphosphonate therapy may place some patients at risk for this unique fracture pattern.

**Limb-Salvage Surgery**

Tumors in the pelvis not only carry a worse prognosis but their resection and reconstruction are a challenge, even to the most experienced orthopaedic oncologist. Delloye et al. evaluated twenty-four consecutive patients who underwent excision of a malignant pelvic bone tumor and allograft reconstruction. The living patients were followed for a minimum of twenty-four months. There were nineteen primary malignant bone tumors, sixteen of which were high-grade sarcomas, and there were five isolated metastases. Patients were examined clinically and radiographically and were assessed functionally with the Musculoskeletal Tumor Society score. Eighteen of the twenty-four resections involved the periacetabular area and were followed by reconstruction either with an alloprosthetic composite (thirteen) or with an osteochondral allograft alone (five). The other six resections involved the iliac bone. At the time of the latest follow-up (at a mean of forty-three months), eight patients were alive and free of disease, thirteen patients had died of disease, and seven patients had had a local recur-

rence. The morbidity rate was high. Complications included neurological deficits, prosthesis failure, infection, nonunion of the allograft, skin/wound necrosis, and arterial thrombosis. Eleven patients underwent surgical revision, with nine of these revisions related to the reconstruction. The average Musculoskeletal Tumor Society score at the time of the latest follow-up was 73% of the maximum possible score. The average score was 82% for the eleven patients with an age of less than twenty years at the time of the index procedure, and it was 65% for the thirteen older patients. Luna et al. presented their experience with pelvic allografts at the 2008 annual meeting of the Musculoskeletal Tumor Society. Age, sex, chemotherapy, blood loss, operative time, local recurrence, and performance of a multiple-stage procedure did not significantly affect allograft retention. However, there was a trend toward a better functional outcome in younger patients. Patients who retained the allograft had fair to good functional outcomes. Both studies confirmed that pelvic reconstruction after a limb-sparing resection is associated with a high risk of surgical complications, and although a pelvic allograft can restore the anatomy and provide good functional results, especially in young patients, proper patient selection is vital.

The architecture of the pelvis challenges the surgeon’s ability to perform a precise and accurate resection. Cartiaux et al. examined the surgical accuracy of an experienced surgeon in performing a tumor resection with a 1-cm surgical margin. The authors also attempted to evaluate the geometry of the host-graft reconstruction. Using a plastic pelvis, they designed an experimental model to simulate tumor resection and reconstruction. Four experienced surgeons were asked to resect and then reconstruct three different pelvic tumors. Twenty-four resection planes and twenty-four host-graft junctions were evaluated. The resection margins and osteosynthesis sites (gaps) were measured. The maximum gap, the gap volume (measured by filling the gap with an epoxy high-density paste and then evaluating images made with the computed tomography scanner), and the mean gap between host and graft were found to be 3.3 ± 1.9 mm, 2.7 ± 2.1 cm³, and 3.2 ± 2.1 mm, respectively. The correlation between the measured reconstructive parameters as described above and the degree of contact at the host-graft junction was poor. The authors concluded that, with the parameters used, they were unable to assess good host-graft geometry and that additional study in this regards is needed. With regard to the assessment of surgical resection, they determined that the four experienced surgeons were not able to abide by the 1-cm margin. The probability of a surgeon obtaining a 1-cm surgical margin (±5 mm) was 52% (95% confidence interval, 37% to 67%). This inaccuracy was explained by the anatomy of the pelvis and its complex geometry. The authors proposed that the use of computer-assisted navigation systems may improve the accuracy of pelvic tumor resection, especially when close margins are anticipated.

Several other investigators have evaluated the results of limb salvage in the young/skeletally immature patient. Van
Kampen et al. reviewed the results of forty proximal femoral endoprosthetic reconstructions that had been performed in children between the ages of two and fifteen years for the treatment of a malignant tumor in the proximal part of the femur. Their aim was to assess the durability of the implant and the reconstruction. There were twenty-one disease-free survivors. Nineteen patients died of tumor-related causes, and two were lost to follow-up. The mean duration of follow-up was 12.6 years for patients who survived and 2.9 years for those who died. Initially, cemented acetabular components were used, but, in the more recent procedures, unipolar replacements and uncemented implants were used. The failure rate (defined as revision of the acetabular component) was 75% for children ten years of age or less and 25% for those more than ten years of age. The unipolar replacements failed within ten years, because of either pain or subluxation, in children of all ages. Once the first hip replacement failed, the authors pointed out that additional procedures had varying degrees of success. The authors concluded that, overall, the success of proximal femoral endoprosthetic reconstruction in children is poor. Unfortunately, they did not report functional outcomes or limb-length discrepancies in this group of patients, which would be an important factor when deciding whether proximal femoral replacement is a viable option for reconstruction in the skeletally immature patient.

Rotationplasty is an excellent alternative to amputation for the treatment of distal femoral sarcomas in skeletally immature patients. A rotationplasty allows the patient to avoid many of the complications associated with amputation and limb-salvage surgery. However, because the procedure is uncommon, the surgical complications or risk factors for failure of the procedure have not been well described. Sawamura et al. reviewed twenty-five patients who had undergone rotationplasty and focused on the risk factors for failure and postoperative complications. Twenty-four patients underwent Van Nes rotationplasty for the treatment of a tumor of the distal part of the femur, and one had a Winkelmann type-B1 rotationplasty for the treatment of a proximal femoral osteosarcoma. The procedure was successfully accomplished in twenty-two of the twenty-five patients. Twenty patients in the study underwent resection of the femoral vessels. The high rate of vascular resection in the series was attributed to the early bias of the authors that it was better to resect and anastomose the vessels rather than to preserve and coil them. The most common complication (noted in three patients) was vascular compromise resulting in amputation. The late complications cited included tibial fracture (one), wound complications (two), nonunion (one), and slipped capital femoral epiphysis (one). The authors believed that the reason for vascular compromise was not due to a failure of the vascular anastomosis but rather to an initially successful anastomosis that was compromised by poor venous drainage or bleeding and hematoma formation. In that series, rotationplasty was successful in 88% of the patients, good function was achieved, and phantom pain was avoided.

Two methods are available for the management of the vascular structures during a rotationplasty: (1) resection and reanastomosis of the vessels or (2) retaining and rotating the vessels with the leg. It is not clear whether one method results in superior outcomes and a lower complication rate. Mahoney et al. examined the ankle brachial indices and complication rates in two groups of patients managed with each technique and concluded that both vascular management options are safe and that the complication rates are equal.

References


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