EDITORIAL

Diagnosis and Management of Bone Sarcomas; Rizzoli`s Approach

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Sarcomas of bone are primary, mesenchymal tumors originating from bone cells. Most occur in children and young adults and develop in the extremities, especially the distal femur. The most common symptoms are pain and an enlarging mass. The likely diagnosis of a suspected bone tumor is related to age. Above the age of 5 years, a destructive bone lesion is most commonly a primary bone sarcoma; after the age of 40 years, it tends to be metastasis or myeloma (1).

A bone sarcoma will almost always be obvious in radiographs; failure to obtain a radiograph is associated with a significant delay in the diagnosis of a bone sarcoma. The next imaging step is magnetic resonance imaging of the involved compartment and adjacent joints. Computed tomography should be used in case of diagnostic problems or doubt, to visualize more clearly calcification, periosteal bone formation, cortical destruction, or soft tissue involvement.1 Radiography or computed tomography of the chest is required to accurately assess the lungs for metastasis. A technetium bone scan can be obtained to look for other similar bone lesions (metachronous lesions) or metastatic bony disease. Laboratory tests and tumor markers are not helpful in the staging of bone sarcomas. General staging using bone scintigraphy, chest radiographs and computed tomography scan should be carried out to assess the extent of distant disease.

The objectives of staging for patients with bone sarcomas are (1) to aid in planning treatment, (2) to provide insight into the prognosis, (3) to evaluate the results of treatment, (4) to facilitate effective inter-institutional communication, and (5) to contribute to continuing investigation of human malignancies (1-5). In 1980, a system for surgical staging of musculoskeletal sarcomas was proposed, studied and adopted by the Musculoskeletal Tumor Society and subsequently by the American Joint Committee of Cancer. This system was established initially at the University of Florida in 1977 based on data collected from 1968 through 1976 by Dr. William Enneking. This system considers the grade (G, G1, G2), local extent (T, T1, T2), and presence of metastasis (M0, M1). The American Joint Committee of Cancer staging system follows a TGNM system, in which "T" (tumor) refers to the size of the primary tumor, "G" (grade) refers to the histopathological grade, "N" (nodes) refers to the presence of lymph node involvement, and "M" (metastasis) refers to the distant spread (2).

Biopsy is the last step of staging; it can be closed (percutaneous) or open, if a closed biopsy was not diagnostic. It should be carried out at the reference center, ideally by the surgeon who is to perform the definitive tumor resection or a radiologist member of the team. The principles of the biopsy are minimal contamination of normal tissues; core needle biopsy, preferably imaging guided; longitudinal incision for an open biopsy; meticulous hemostasis; if a tourniquet is used, the limb should be elevated before inflation for 5 - 10 minutes; if a suction drain is placed, it should be in proximity to the incision site itself so that the drain site will be resected with the specimen at the time of definitive resection; and adequate sampling of representative areas for histology and cultures (1-5).

Surgery is the primary therapeutic approach for bone sarcoma patients. Before the 1970s, amputation was the standard treatment for bone sarcoma patients. Over the last decades, the evolution of axial imaging techniques, chemotherapy and radiation therapy, and the advances in surgical techniques, metallurgy, implants' design and allograft availability led to a significant advance in the treatment of bone sarcomas, and greatly improved surgeons' ability for limb salvage resection and reconstruction. The goal of bone sarcoma resection is complete tumor removal with microscopically negative margins. The tumor with the biopsy scar surrounded by a cuff of healthy tissue must be removed en bloc. Intralesional surgery should be avoided because it will lead to a high risk of local recurrence regardless of whether the patient receives perioperative radiation therapy or chemotherapy. If neurovascular structures are not encased (ie, not more than 50% surrounded in the case of arteries or motor nerves) they can be spared. If arteries are encased, arterial resection with reverse interpositional vein graft, synthetic graft, or vein allograft should be necessary to bypass the vessel and leave the encased

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structure with the resection specimen for en bloc resection. Pathological fractures in patients with bone sarcomas should not be considered an absolute indication for amputation. Limb-salvage surgery of selected patients with a pathological fracture, particularly one that unites after chemotherapy, does not appear to increase the risk of local recurrence or death. Patients should be treated by neoadjuvant chemotherapy, and their tumors should then be resected with safe surgical margins. In contrast, pathological fractures in chemo-resistant primary bone sarcomas are a relative contraindication for limb salvage surgery (3).

Megaprosthetic or allograft reconstruction can be performed after bone sarcoma limb salvage resection. Allograft prosthesis composites are valuable options is certain tumor locations such as the proximal humerus and the proximal tibia for optimal soft-tissue reattachment to the allograft. In the femur, modular megaprostheses are used preferably. Biological reconstruction techniques include implantation of allografts or autografts such as vascularized fibula, particularly for intercalary bridging of diaphyseal defects. In growing children, allograft reconstruction is general performed, unless the resection involves the joint. In that case, an expandable prosthesis, or rotationplasty should be considered. In selected cases, preservation of the epiphyseal portion of the bone and the joint surface may be achieved by physeal distraction.4 Studies showed that limb salvage surgery can achieve as low risk of recurrence and the same disease-free survival as amputation. However, more studies are necessary to extinguish whether the reconstructive techniques are so satisfactory as to provide significantly better quality of life in those patients undergoing limb salvage procedures. Because of the extensive bone and soft tissue defects, the technically challenging and lengthy surgical procedures, the complex biomechanical reconstruction and the size of the implants, early and late implant-related complications including mechanical failure, aseptic loosening, infection, and dislocation are common; failure rates with various reconstruction methods range from 17-33% at 5 years, and 33-52% at 10 years (4).

Computer-assisted navigation surgery in musculoskeletal oncology allows surgical teams to merge computer technology, newly developed software, modern imaging techniques, and surgical instrumentation in a more precise and coordinated fashion. The goals are improved tumor resections and superior implant positioning, resulting in better patient outcomes and satisfaction, and longer implant survival.

The role of chemotherapy and radiation therapy for bone sarcomas is individualized. For osteosarcoma and Ewing's sarcoma there is a preference to treat the patient with chemotherapy at the beginning of the course, prior to surgical treatment, aiming to treat the potential micrometastatic disease, reduce the soft tissue mass about the bone tumor and/or mature the mass, allowing for easier resection. In patients with high grade tumors, those with metastases or local recurrence, and poor responders to first line treatment combining therapies that focus on different molecules in different transduction pathways, or different targets in the same pathway, or a single target by different mechanisms is required. Studies combining bisphosphonates (zoledronic acid) with chemotherapy have shown that zoledronic acid induces osteoclast apoptosis and also inhibits osteosarcoma, Ewing's sarcoma and chondrosarcoma cell proliferation (5). Novel therapeutic approaches target RANKL; these include osteoprotegerin, denosumab, and RANK-Fc. Gene therapy, cell and immune therapies are promising to down-regulate tumor genes or to overexpress genes of therapeutic interest in the microenvironment, and as immunotherapy.

Many different metric systems have been developed to address the quality of life of patients after bone sarcoma treatments; related studies have conclusively shown that limb salvage is superior to amputation with regards to function, but report no difference in quality of life; patients who had an amputation were as satisfied, competent and emotionally stable as patients who had limb salvage surgery.4 Therefore, amputation should be considered when curative surgery is possible and limb-salvaging resection is unlikely to obtain a negative margin or a functionally viable extremity.

Follow-up of the patients with bone sarcomas is critical; routine follow-up should include clinical and imaging examination for local recurrence and imaging of the chest for lung metastasis. For high-grade bone sarcomas, patients are followed at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and at yearly intervals thereafter. For low-grade bone sarcomas, intervals may be increased to 6 months for the first 2 years and then annually (4).

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