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Fifty Years of Bone Tumors

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Abstract

There have been enormous advances in the treatment of bone tumors over the past half century. The most notable of these has been the transition from amputation as the standard of care to limb salvage surgery. This transition is the result of advances in imaging techniques, accurate diagnosis, systemic therapies (including chemotherapy), and prosthetic design for reconstruction of musculoskeletal defects. Advances have also been made in the management of benign and metastatic bone tumors.

Keywords

Bone; Metastasis; Sarcoma; Limb salvage

INTRODUCTION

Orthopaedic oncology has changed more dramatically in the past half century than in any period in its history. During this time, major discoveries in a diverse array of disciplines coalesced into the diagnostic and therapeutic advances that continue to benefit patients today.

In this article, we will trace progress resulting from clinical discoveries, advances in imaging and prosthesis design, and findings from pathology and clinical trials. We will also discuss the impact of new local and systemic adjuvant therapies in the surgical management of benign and malignant bone tumors, and summarize the major advance of the past half-century: the transition from amputation to limb salvage surgery. We will emphasize developments at our own institution, Memorial Sloan Kettering Cancer Center (MSKCC), whose orthopaedic oncology service is the oldest in the world and played a pivotal role in several advances in orthopaedic oncology during the last century.

Bone tumors are categorized as benign, primary malignant, or metastatic. Benign tumors are frequently asymptomatic and discovered incidentally, so their true incidence is unknown. Estimates suggest that they are at least 100 times more common than primary malignant neoplasms.[1,2] Primary malignant bone tumors account for 0.2% of all cancers (5,000 new cases per year) in the United States.[1,3] This relatively low figure should not discount these

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tumors' importance to the treating clinician; despite the medical advances of the past 50 years, the mortality rate of these tumors remains significant (up to 50%) and many of the patients are young.

Osteosarcoma is the most common primary malignant bone tumor and has a bimodal age distribution: an initial peak in incidence in the second decade of life, and another in patients older than 60, usually secondary to other factors such as radiation therapy and Paget's disease. Chondrosarcoma is the second most common malignant bone neoplasm in adults, whereas Ewing sarcoma which is the second most common in childhood. Bone is the third most common site for metastatic disease. Roughly 400,000 new cases are diagnosed annually in the United States.[4]

CLASSIFICATION OF BONE TUMORS

The World Health Organization continues to provide a periodically updated classification system based on the tumor's presumed tissue of origin and staging determined by histology, the tumor's size, and the presence or absence of metastases.[1]

DIAGNOSIS

Diagnosis begins with a history, which requires a thorough knowledge of the incidence and natural history of bone tumors and of the predisposing and genetic factors associated with tumor development. For instance, familial genetic mutations, such as those in *TP53* in Li-Fraumeni Syndrome and *RB1* in hereditary retinoblastoma, predispose affected individuals to osteosarcoma.

Many benign tumors are latent and asymptomatic, but most patients with active bone tumors present with pain. The characteristics of the symptoms often help the physician make a diagnosis, such as in osteoid osteoma, which frequently presents with severe pain in young patients and is reliably relieved by nonsteroidal anti-inflammatory medication. A sudden increase in local pain in a patient with a proven low-grade cartilage tumor may indicate a transition to a high-grade or dedifferentiated chondrosarcoma.

IMAGING

Despite advances in three-dimensional imaging, plain radiographs remain the mainstay of diagnosis for bone tumors. Location of a lesion in a bone, matrix characteristics, presence of cortical destruction, presence and type of periosteal reaction, and soft tissue extension are invaluable in suggesting a diagnosis. The imaging modalities that have been developed in the past half century—notably computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scans—complement plain radiograph findings and are essential for staging and planning management.[5,6] Accurate identification of tumor margins using these imaging modalities has greatly enhanced surgeons' ability to perform accurate resections.

The diagnosis and treatment of bone tumors is truly multidisciplinary, as pathologists frequently rely on interpretation of imaging studies before proffering a definitive diagnosis.

Advances in interventional radiology have simplified biopsy techniques[7] and facilitated an increasing number of minimally invasive therapeutic procedures, such as cryoablation[8] and radiofrequency ablation,[9,10] allowing some tumors to be successfully treated without open surgery. In the operating room, imaging advances have facilitated accurate bony resections through computer navigation technology. Computer-assisted tumor surgery has been shown to decrease the frequency of positive margins and complications.[11,12]

PATHOLOGY

Most bone tumors can be diagnosed on the basis of a simple microscopic examination with clinical and radiographic assistance. In recent decades helpful techniques have been introduced. For instance, immunohistochemistry is routinely used in the diagnosis of Ewing sarcoma. Molecular studies, such as fluorescence in-situ hybridization, are used to detect genetic mutations in tumors and are often employed distinguish between conditions that closely resemble each other histologically. For instance, these techniques have proved useful in the diagnosis of giant cell tumor, chondroblastoma, and aneurysmal bone cyst.[13]

At MSKCC, genetic sequencing is frequently preformed using the Integrated Mutation Profiling for Actionable Targeting (MSK-IMPACT) platform. Developed in 2017, MSK-IMPACT is frequently used to identify targetable mutations in bone tumors as well as to assist in diagnosing challenging cases.[14] Similar next-generation sequencing platforms are now used widely around the world.

MANAGEMENT

Benign Lesions

The majority of asymptomatic benign bone tumors are latent and managed with patient reassurance and observation. Symptomatic, active benign tumors are usually successfully treated with simple intralesional excision with or without filling the defect with bone graft or a substitute (e.g., methyl methacrylate). Aggressive benign tumors, such as giant cell tumors of bone (GCTB), can be very destructive and have a very high incidence of recurrence—up to 60% in some series.[15] Large periarticular lesions occasionally require wide resection and joint replacement or even amputation. However, with meticulous curettage and use of a high-speed burr combined with employment of physical adjuvants, recurrence rates have been reduced to less than 12%, with preservation of adjacent joints in most cases. At MSKCC, cryosurgery was introduced by Ralph Marcove in 1965.[16] The use of other physical adjuvants—including chemicals (e.g., phenols), thermal treatments (e.g., argon beam), and methyl methacrylate—has been reported to be successful.[17] Greenberg and Lee achieved favorable results in local control of GCTB by inserting bisphosphonate-impregnated methyl methacrylate into the surgical cavity following curettage.[18]

Radiation has been used to treat aggressive benign tumors, including GCTB, in inaccessible areas (e.g., the spine and pelvis) and recurrences recalcitrant to other nonradical surgical treatments. While success has been reported with this therapeutic modality, malignant transformation is a concern.[19]

Recently, the systemic use of the monoclonal antibody denosumab, which inhibits osteolysis by blocking RANK-ligand activities of osteoclasts, has been used as an adjuvant. Unfortunately, this does not destroy the true neoplastic stromal cells, so its use is reserved as an adjuvant to surgery.[20] The effectiveness of long-term use for the management of inoperable giant cell tumors is being examined in clinical trials.

Primary Malignant Bone Tumors

Advances in the treatment of malignant bone tumors are the culmination of not only the emergence of effective chemotherapy, but also advances in imaging modalities (which allowed for more accurate assessment of anatomic extent of tumors) and prosthetic design (which allowed for meaningful reconstruction), and the demonstration that in both soft tissue and bone sarcoma the combination of limb salvage and appropriate adjuvants resulted in equivalent survival.

•Limb salvage.—Although sporadically attempted prior to the 1970s, limb salvage was far from the standard of care.[21] The first report was by Sir Henry Morris in London in the late 19th century.[22] In the 1940s, Dallas B. Phemister and C. Howard Hatcher laid the foundation for limb salvage as it is practiced today; they used principles set forth by pathologist Jakob Erdheim, who recognized the importance of identifying the microscopic extent and margins of a tumor.[23] Phemister reported on cases of conservative bone surgery involving resection of the involved segment and reconstruction with autograft (which he called transplant). He contended that in carefully selected cases, a limited percentage of extremities can be saved.[21,24] It was not until 1977, however, that Ralph C. Marcove at Memorial Sloan Kettering Cancer Center performed the first total femur replacement using a metal endoprothesis. Marcove was also the first to demonstrate successful limb salvage rather than proximal amputation in cases of high-grade bone sarcomas.[25] He noted that the residual limbs were weak but useful and allowed for ambulation.

Marcove continued to lead the way in limb salvage along with his mentor, Kenneth C. Francis. Together, these surgeons pioneered techniques for distal femoral resections, total femur replacement, shoulder girdle resections, scapular resections, and pelvic resections, and showed them to be a realistic alternative to amputation.[26] These limb salvage surgeries were made possible by innovation in prosthetic design. The earliest modern era orthopaedic implants had been made for joint arthroplasty by Sir John Charnley and others in the 1960s, and these early principals of prosthetic design led to the creation of larger tumor prostheses. Dr. Francis’s proximity to the New Jersey headquarters of the orthopaedic device manufacturer Howmedica allowed for collaboration between surgeon and engineer in the design and development of prostheses.[27] Since that time, reconstruction of bone defects has evolved significantly, and now includes not only metal megaprostheses with a variety of options in shape, size, and attachment to native bone, but also biologic options, such as autograft, allograft, and bone transport.[28-30] Advances in plastic and reconstructive surgery, such as the use of free myocutaneous flaps and filet flaps, has improved outcomes following major resection of bone, muscle, and skin in limbs that might otherwise have significant healing challenges.[31,32]

•Chemotherapy.—The advent of modern limb salvage surgery coincided with the introduction of effective multiagent adjuvant chemotherapy in the treatment of osteosarcoma and Ewing sarcoma. The first favorable responses of bone sarcoma to chemotherapy were seen in the 1970s following treatment of osteosarcoma with doxorubicin by Engracio P. Cortes in Buffalo, NY.[33] Shortly thereafter, Sidney Farber and Norman Jaffe in Boston, Isaac Djurassi in Philadelphia, and Gerald Rosen at MSKCC demonstrated the effectiveness of high-dose methotrexate with leucovorin rescue.[34] Next, Wataru Sutow, working at MD Anderson in Houston, demonstrated that superior results were achieved by using a combination of agents.[35] Multicenter, randomized controlled trials conducted in the early 1980s firmly established the effectiveness of using multiagent adjuvant chemotherapy in the treatment of osteosarcoma.[34,36,37] Today, the standard chemotherapy for osteosarcoma includes doxorubicin, cisplatin, and high-dose methotrexate.[38,39]

Chemotherapy is given to treat micrometastases, which are present in over 80% of patients at the time of diagnosis. With the combination of chemotherapy and surgery for local control, survival has increased from less than 20% for osteosarcoma, and less than 10% in Ewing sarcoma, to approximately 70%.

Not only has the use of chemotherapy brought about vast improvements to systemic treatment of these diseases, but the timing of chemotherapy administration has evolved. One groundbreaking development was the introduction of preoperative chemotherapy, also known as neoadjuvant therapy, a term introduced at an American Society of Clinical Oncology meeting in the 1980s[40] during a discussion of Gerald Rosen's use of neoadjuvant chemotherapy to accommodate time needed to manufacture an implant for limb salvage surgery. The strategy proved to have other unexpected benefits in the treatment of chemotherapy-sensitive tumors, including reducing tumor size, thus making wide resection easier and allowing histological assessment of the amount of tumor necrosis caused by the treatment. This response was analyzed by Andrew Huvos, a bone pathologist at MSKCC, who found that necrosis in excess of 90% was a predictor of a good prognosis.[41] While rooted in necessity, this example demonstrated the concept of preoperative systemic therapy for bone sarcoma.

In an attempt to improve outcomes, Rosen included in his T10 treatment protocol the use of alternative drugs for patients with a poor histologic response to preoperative chemotherapy.[42] Unfortunately, follow-up studies failed to demonstrate an improvement in long-term survival.[43]

Since the introduction of chemotherapy for osteosarcoma, most new treatments that have been tested have failed to further improve survival. One exception is the inclusion of muramyl tripeptide, which in a clinical trial improved overall survival from 70% to 78%.[39] While approved for use outside the United States, it has not been approved in the United States and its use requires compassionate approval.

Chemotherapy for Ewing sarcoma saw a similar evolution.[44] Chemotherapy using cyclophosphamide was first shown to be useful for Ewing sarcoma in 1962,[45,46] and a decade later Rosen at MSKCC showed that multiagent chemotherapy was effective.[47]

Subsequent research has resulted in changes not only in the agents used to treat Ewing sarcoma, but also in the dose-intensity of those agents.[44,48] Work to identify the optimal regimen continues.[49,50]

Chemotherapeutic regimens for undifferentiated pleomorphic sarcoma of bone are similar to those for osteosarcoma.[51] Chondrosarcoma remains a chemoresistant disease, though investigations of systemic therapy continue, with new investigations focusing on the isocitrate dehydrogenase mutations that are seen in 50% of these tumors.[52] Nonetheless, surgery continues to be the primary means of treating chondrosarcoma.

In studies of chemotherapy-sensitive bone sarcomas, limb salvage procedures using wide resection and chemotherapy have shown equivalence—and even superiority—to amputation.[53-55] These reports resulted in a precipitous decline in the use of amputation in the management of all extremity sarcomas. Together, these developments in surgery, medicine, radiation therapy, and imaging modalities have allowed for limb salvage surgery to virtually replace amputation as the treatment of choice in most bone sarcomas.

•Amputation.—Despite the development of effective limb salvage, amputation remains the most appropriate intervention in some situations. These include cases in which resection's removal of neurovascular structures would leave the patient with a nonfunctional limb.[56] Additionally, modified amputations, such as rotationplasty, continue to have an important role, most notably for tumors around the knee in very young patients.[57,58]

In the approximately 15% of cases in which amputation is indicated, advances in surgical techniques and prosthetic fabrication have led to increased patient satisfaction and acceptance related to improved function and cosmetics. Recently, prosthetic fixation using osteointegration fixation of a metal stem inserted into the medullary cavity has been shown to be especially successful in patients with high femoral amputations.[59,60] Use of this technique obviates the need for using uncomfortable, ill-fitting sockets.

•Radiation therapy.—Ewing sarcoma is unique among the primary bone sarcomas in that it is radiosensitive. Thus, local control may be achieved with radiation therapy, either alone or in combination with surgery. Surgery is often favored over radiation, except for tumors that are surgically inaccessible or that are expected to result in surgical margins that are very close or positive.[61] In these cases, neoadjuvant radiation therapy may be preferrable to adjuvant radiation therapy.[62] An exception is Ewing of the sacrum, for which good outcomes can be achieved with radiation therapy alone.[63]

Radiation therapy is not without risk. Postradiation sarcoma is a concern, especially in pediatric patients. Kuttesch Jr et al. reported that after treatment with radiation, patients with Ewing sarcoma had a 6.5% risk of secondary sarcoma during an average follow-up of 9.5 years.[64]

Radiation also has a role in the treatment of metastatic Ewing sarcoma. Whole-lung radiation therapy has been shown to provide survival benefit,[65,66] and radiation for metastatic sites to bone results in durable responses.[67]

Osteosarcoma and chondrosarcoma are not radiosensitive, and therefore radiation has a very limited role in their treatment and is reserved for cases of positive margins where re-resection is not feasible. In this setting, there is some benefit to radiation therapy.[68]

•**Metastatectomy.—**The most common site of metastases in primary bone sarcomas are the lungs, and survival is dramatically worse when metastatic disease exists.

The first known pulmonary metastasectomy was performed in 1940, but in the following decades the procedure was done only sporadically and in very select cases. It was not until 1971 that Nael Martini and colleagues at MSKCC provided the first formal report on the role of pulmonary metastasectomy in the treatment of patients with osteosarcoma.[69] In their patients with pulmonary metastases, 45% were alive and had minimal to no disability three years after local control with metastasectomy, compared to 5% of patients without pulmonary resection. The authors concluded that "aggressive surgical attack on the pulmonary metastases is justified and should be continued."[69]

Recent work has demonstrated that for sarcoma patients with lung metastases, pulmonary metastasectomy with complete resection of the tumor improves disease-free and overall survival compared with medical management alone.[70] Lin and colleagues identified several prognostic factors positively associated with survival after pulmonary metastasectomy, including having bone sarcoma (as opposed to soft tissue sarcoma).[71] Snyder et al. advocated for pulmonary metastasectomy in patients with isolated pulmonary metastases, local control, and adequate postoperative pulmonary reserve.[72] Additionally, they noted that bilateral, recurrent, and extensive pulmonary disease need not be contraindications to metastasectomy.

Metastatic Bone Cancer

As patients live longer with metastatic carcinoma, bone metastases are becoming a more common clinical entity and require durable fixation to maintain patients' mobility. In 1989, Hilton Mirels introduced criteria that, while imperfect, are still frequently used to classify the risk of pathologic fracture in patients with bone metastases.[73] These lesions are often treated with radiation if symptomatic and the risk of fracture is low, or with the combination of surgery and radiation in cases of mechanical instability and higher fracture risk. These treatments are considered palliative and stabilization was preferred over complete resection; however, recent work on oligometastatic disease in certain histologies has suggested that aggressive treatment with resection confers a survival advantages and is therefore may be indicated.[74] Treatment should be individualized for patients with metastatic disease to bone in order to avoid both undertreatment and overtreatment of disease. As such, predictive algorithms such as the PathFx tool (www.pathfx.org), developed at MSKCC, have been developed to assist physicians with estimating survival and therefore tailor treatment to each individual patient.[75,76]

CONCLUSION

Vast improvements have been made in the past 50 years in the identification and management of both benign and malignant bone tumors. These include advances in imaging,

diagnosis, and treatment. The use of adjuvants in benign diagnoses has helped to reduce recurrence rates. In malignant diseases, limb salvage and chemotherapy have led to a new treatment paradigm. However, improvement in the trajectory of patient survival has stalled: although overall survival rose from less than 10% in the prechemotherapy era (for chemotherapy-sensitive tumors) to roughly 75% following the initiation of modern chemotherapeutic regimens (e.g., doxorubicin, ifosfamide, and high-dose methotrexate for osteosarcoma), there has unfortunately been very little subsequent improvement in this outcome. Nonetheless, new avenues are being explored, including immunotherapy and targeted therapy. Moreover, advances in local control continue, including the use of distraction osteogenesis for limb salvage surgery as well as enhanced techniques for amputation, such as osteointegration and targeted muscle reinnervation. Although the role of radiation therapy remains limited outside of Ewing sarcoma, it does appear to be expanding, as use of intensity-modulated radiation therapy and proton- and carbon-based radiation are increasing.[77,78] Treatment using a multidisciplinary approach at a center with expertise in the complex care of primary bone sarcoma continues to be the gold standard of care for patients with these rare and complex tumors.

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