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Bone Cancer

The Multidisciplinary Management of Osteosarcoma

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Opinion statement

Patients with suspected or confirmed osteosarcoma should be evaluated and treated at a comprehensive cancer center within a multidisciplinary sarcoma program that includes pediatric, medical and radiation oncologists, orthopedic and surgical oncologists, musculoskeletal pathologists, and radiologists. Successful treatment involves proper diagnosis, neoadjuvant and adjuvant multi-agent chemotherapy, and aggressive surgery with an emphasis toward limb-preserving procedures. Treatment of osteosarcoma should be undertaken within the framework of large cooperative group clinical trials for children, adolescents, and adults. Patients treated with osteosarcoma should be followed closely both for recurrence of disease and for development of late effects of the treatment of their cancer. The treatment of metastatic, recurrent and/or refractory disease is more controversial. Despite advances in systemic treatment, surgical technique, and supportive care, the overall outcome is still poor.

Introduction

Osteosarcoma is the most common primary malignant neoplasm of bone in children and adolescents. It is characterized by the proliferation of malignant mesenchymal cells that are capable of producing osteoid or immature bone [1]. Although rare, with only 400 new cases diagnosed per year in the United States, osteosarcoma represents the sixth most common malignancy in adolescents and young adults [2]. Prior to 1970, the overall prognosis for patients with osteosarcoma was dismal with a 10%–20% overall survival rate for patients with localized disease treated with aggressive surgery. Over the past 30–40 years with the introduction of neoadjuvant and adjuvant systemic chemotherapy, the survival has increased dramatically to about 65%–75% for patients without clinically evident metastatic disease at presentation [3]. The improvements in chemotherapy have been paralleled by improvements in surgical techniques that achieve local control with limb-sparing procedures, and improvements in diagnostic and imaging techniques.

This chapter will review the current multidisciplinary treatment of osteosarcoma and recent developments in the management of this aggressive neoplasm, as well as stress the importance of treating and evaluating patients with osteosarcoma within a multidisciplinary sarcoma program or cancer center

that offers comprehensive care through the input and contributions of pediatric, medical, and radiation oncologists, orthopedic and surgical oncologists, and musculoskeletal pathologists and radiologists.

Clinical presentation, diagnostic evaluation, and biopsy

- The vast majority of patients with osteosarcoma present with localized pain at the primary tumor site. The most commonly affected bones are the metaphyseal region of long bones such as the distal femur, proximal tibia, and proximal humerus although osteosarcoma can arise in any bone in the body [4]. A detailed history with a complete physical exam should be performed prior to any evaluation. Physical examination may reveal the presence of a tender and firm soft tissue mass at the primary site. If a diagnosis of osteosarcoma or another malignant bone or soft tissue tumor is suspected, the patient should be transferred to a comprehensive cancer center with a multidisciplinary sarcoma program for further evaluation and treatment. Laboratory evaluation is generally normal. However, serum alkaline phosphatase and lactate dehydrogenase levels have been reported elevated in 30%–40% of patients and have been associated with a poorer prognosis [5,6].
- Plain radiographic films are usually the first diagnostic imaging study undertaken and should include the entire affected bone. The classical appearance of osteosarcoma on plain films shows destruction of the normal trabecular bone with presence of a Codman's Triangle formed by new periosteal formation and elevation of the cortex [7]. CT and MRI scanning are used to delineate the extent of the primary tumor and planning of definitive surgery. MRI is particularly useful to determine the intra and extraosseous extent, soft tissue, and contiguous structure involvement of the tumor. Care again must be taken to image the entire involved bone. Metastatic evaluation at diagnosis should include a Chest CT scan to detect pulmonary metastasis. Nuclear medicine imaging techniques are being used increasingly to aid in the initial staging/metastatic evaluation and response to therapy. Technetium–99-m bone scans are a standard part of the metastatic evaluation as they are very sensitive in detecting bony metastases, present in 10% of patients with osteosarcoma [8]. 18-Fluorodeoxyglucose Positron emission tomography(18FDG-PET) with or without the combination of a whole body CT is also being increasingly used in the initial staging and treatment monitoring although a clear benefit has not been demonstrated [9,10]. A consensus on the imaging guidelines for children, adolescents and young adults with osteosarcoma has been put forward by the Children's Oncology Group (COG) [11•].
- Tissue biopsy of osteosarcoma must be obtained to confirm the diagnosis even though radiographic imaging is highly suggestive. The biopsy should be carefully planned with multidisciplinary input from the musculoskeletal radiologist, pathologist, and orthopedic and surgical oncologists so as to ensure the feasibility of procedure, the adequacy of specimen, and above all to maintain the viability of a definitive surgery with possibility of limb salvage. At our institution, we find that CT-guided core biopsies performed by a skilled interventional musculoskeletal radiologist will yield the diagnosis the majority of the time. The advantage of CT-guided core biopsy is that this can often be done more rapidly and require only local anesthesia versus an open biopsy. Multiple large core needle biopsies are often necessary to yield enough tissue to make the diagnosis and consider

differential diagnoses with sufficient tissue for immunostains and cytogenetic studies. Core biopsy at our institution approaches 95% accuracy in establishing a diagnosis, and is our diagnostic method of choice. However, the decision to utilize CT-guided biopsy versus open biopsy should be made on a case by case basis as a 25% non-diagnostic rate has been reported by other institutions [12]. When a core biopsy is either non-diagnostic or not technically possible, an open biopsy can be performed. The principles of open biopsy for osteosarcoma and other malignant bone tumors is to obtain adequate tissue without jeopardizing opportunity for limb salvage by contaminating tissue with malignant cells, and should be performed by a skilled orthopedic or surgical oncologist. The biopsy should be performed with a longitudinal incision so that the entire biopsy tract can be excised during later surgery, and careful hemostatic control should be attained to minimize the development of a hematoma contaminated with malignant cells [13].

Systemic therapy

- Prior to the introduction of adjuvant systemic chemotherapy the overall survival of osteosarcoma was less than 20% with the majority of patients developing metastatic disease presumably from the presence of microscopic subclinical metastatic disease present at the time of diagnosis[14]. With modern multimodality therapy combining systemic chemotherapy and complete surgery, the cure rate now approaches over 70% for patients with non-metastatic osteosarcoma [15].
- Many trials investigating adjuvant chemotherapy in osteosarcoma patients have been performed in the past 30 years. Some of the notable trials over the past 10 years are summarized in Table 1. Initial efforts defined active agents as high-dose methotrexate with leucovorin rescue, doxorubicin, cisplatin, and ifosfamide with or without etoposide [16–20•]. The development of combination chemotherapy with administration of the aforementioned active agents has been mostly empiric though is now the cornerstone of chemotherapy.
- The initial rationale for administering neoadjuvant chemotherapy was based on the development of limb-salvage procedures. Originally, limb-salvage endoprostheses were custom made taking several weeks to months to manufacture. Neoadjuvant therapy was employed as a means of bridging the gap from biopsy to resection [21,22]. However, it had been suggested that neoadjuvant therapy might improve survival as well as improve limb-salvage rates. A randomized study (POG–8651) conducted by the Pediatric Oncology Group from 1986 to 1993 compared immediate surgery followed by post-operative chemotherapy versus presurgical chemotherapy followed by surgery. The event-free survival (EFS) was similar in both groups: 65% for immediate surgery and 61% for neoadjuvant therapy with similar incidence of limb salvage (50%–55%) in both [23••]. Another rationale for using neoadjuvant chemotherapy is the capability of individualizing therapy based on tumor response. It has been reported from numerous trials that histologic response with tumor necrosis greater than 90% confers a better prognosis [22–26••]. The strategy of intensifying or altering post-operative therapy based on poor tumor necrosis has been used successfully in the 1980s by investigators at the Memorial Sloan Kettering Cancer Center on the T10 trial and later confirmed by the Rizzoli Institute [27,28]. However, the impressive

Table 1. Selected recent large studies of chemotherapy for localized osteosarcoma

Study Protocol	Years conducted	Patients, n	Chemotherapy	OS/EFS
COSS-86 [32]	1986–1988	171	DOXO, MTX, CDDP, ±IFOS	72%/66%
POG-8651 [23••]	1986–1993	100	DOXO, BCD, CDDP	78%/65%
IOR-OS4 [33]	1993–1995	133	DOXO, MTX, CDDP, IFOS	71%/56%
INT–0133, CCG-7921, POG-9351 [31••]	1993–1997	662	DOXO, MTX, CDDP, ±IFOS, ±MTP	78%/67% for MTP arm.
EOI-3 [34••]	1993–2002	497	DOXO, CDDP, ±GCSF	56%/40%
ISG/SSG-1 [35•]	1997–2000	182	DOXO, MTX, CDDP, IFOS	77%/64%

COSS—Cooperative Osteosarcoma Study Group, POG—Pediatric Oncology Group, IOR—Istituto Ortopedico Rizzoli, CCG—Children's Cancer Group, EOI—European Osteosarcoma Intergroup, ISG/SSG—Italian Sarcoma Group/Scandinavian Sarcoma Group, DOXO—Doxorubicin, MTX—Methotrexate, CDDP—Cisplatin, IFOS—ifosfamide, BCD—bleomycin, cytoxan, actinomycin D, GCSF—granulocyte colony-stimulating factor.

results on these trials improving the overall outcome of "poor responders" by tailoring post-operative therapy were not duplicated in other large cooperative group studies [25,29,30]. The question of intensification and individualization of therapy based on tumor necrosis is currently being investigated in the current large cooperative trial through the European and American Osteosarcoma Group (EURAMOS1, AOST0331, ClinicalTrials.gov/NCT00134030) a multinational collaboration of the COG, Cooperative Osteosarcoma Group (COSS), the Scandinavian Sarcoma Group (SSG), and the European Osteosarcoma Intergroup (EOI). Patients with poor necrosis are randomized to receive high-dose methotrexate, doxorubicin, cisplatin, with or without the addition of ifosfamide and etoposide. On the other hand, patients with a good response will continue high-dose methotrexate, cisplatin, and doxorubicin are then randomized to a maintenance arm with pegylated interferon alpha. Currently, over 1000 patients have been enrolled on this trial as of January 2009.

- The addition of ifosfamide with or without etoposide to 3 drug regimens of high-dose methotrexate, cisplatin, and doxorubicin in the treatment of primary localized osteosarcoma is controversial. Several groups have obtained favorable results with ifosfamide containing regimens. However, in a recent large randomized controlled American collaborative trial (INT–0133) the addition of ifosfamide to standard therapy was investigated as well as the addition of the immunomodulator muramyl-tripeptide-ethanolamine (MTP-PE). The addition of ifosfamide did not affect overall survival or EFS. Although the addition of MTP-PE did result in a statistically significant improvement in overall survival (78% vs 70%) [31••]. The standard use of MTP-PE will likely be the subject of future confirmatory trials.

Surgical management

- Over the last 30 years, advances in chemotherapy, imaging, surgical technique, and biomaterial engineering have ushered in a new era of surgical management for osteosarcoma. The basic tenet for the treatment of osteosarcoma is that complete resection is a prerequisite for cure [24]. Whereas radical resection by amputation was the mainstay of therapy into the 1970s, currently more than 85% of patients undergo wide resection with limb-sparing surgery [36]. Although no randomized studies have been done, large retrospective studies have

shown no survival advantage to amputation over limb-salvage procedures [37,38]. Negative surgical margins (defined as at least 1 cm in bone with 2–5 cm recommended) and tumor responsiveness are directly associated with local recurrence. In patients with marginal resections and with tumor necrosis less than 90% after preoperative chemotherapy, local recurrence has been reported as high as 30% [39]. Therefore, limb salvage is recommended when adequate surgical margins can be achieved. Only surgeons with adequate experience should perform limb-preserving procedures [40].

- Reconstructive options for limb-salvage surgery include autogenous bone grafts (vascularized or devascularized), structural bone grafts (osteoarticular and intercalary), and metallic endoprosthetics. The technique selected is a function of the location of the tumor, age of the patient, and types of adjuvant therapies that will be employed, as well as the surgeon's comfort level with a particular procedure. Our institution primarily utilizes endoprosthetic reconstruction. We have reported low rates of infection, mechanical failure, revision, and local recurrence with this technique [41,42]. Significant improvements in biomaterial engineering over the past 20 years including circumferential porous coating, modular components, and hydroxyapatite-coating have led to excellent outcomes [43]. Most recently, exciting data is emerging on the Compress implant, an endoprosthesis designed to mitigate complications of aseptic loosening by preventing stress shielding and particle-induced osteolysis through compressive forces at the bone-implant interface [44].
- A unique challenge in reconstruction after osteosarcoma resection in the pediatric population is the issue of limb growth. Prior to the advent of extendable prostheses, a complex surgical procedure was required to replace one modular component with a longer one [45]. More sophisticated lengthening systems have entered the market including the redesigned Phenix prosthesis (Phenix Medical, Paris, France), which uses an electromagnet outside the body to heat a tube of plastic inside the prosthesis, thus expanding an internal spring [46]. A British endoprothesis (Stanmore Implants Worldwide, United Kingdom) uses an external rotating magnetic field to induce a magnet embedded in the prosthesis to rotate and power a small motor that elongates the prosthesis [36]. While these technologies are still in development and are expensive, they hold great promise for the future of endoprosthetic reconstruction as they eliminate the need for subsequent surgeries in skeletally immature patients.

Radiation therapy

- Osteosarcoma is a relatively radioresistant malignancy. For this reason, adjuvant chemotherapy and surgery have been the mainstays of therapy. Prophylactic whole lung irradiation was used in the late 1970s as a means of reducing lung metastases post-operatively [47,48]. However, the addition of prophylactic lung irradiation has not demonstrated a clear advantage over adjuvant chemotherapy [49].
- Radiation therapy in the primary local control setting should be reserved on a case-by-case basis for patients with unresectable tumors and/or where margins of resection are positive [50,51]. Typically these tumors involve the head and neck or spinal region. For definitive radiation therapy, doses of 55–60 Gy are given with conventional daily fractionation of 1.8 Gy.

- The use of radiation therapy in the treatment of osteosarcoma may need to be re-investigated with modern radiation delivery techniques such as intensity modulated radiation therapy and proton beam therapy where the delivery of radiation to a target volume is improved while scatter to surrounding organs can be minimized [52]. At our institution, we have used stereotactic radiosurgery to treat small unresectable primary tumors and unresectable metastases usually to the brain and spinal cord.
- Radiation therapy can be used as an effective palliative measure particularly for painful bony metastases. Samarium–153 ethylene diamine tetramethylene phosphonate (153Sm-EDTMP) is a bone-seeking radiopharmaceutical that was approved by the United States Food and Drug Administration in 1998 for palliation of bone metastases [53]. Standard dose (1 mCi/kg) and high-dose 153Sm-EDTMP (30 mCi/kg) have been used with palliative benefit for patients with osteosarcoma and skeletal metastases [54,55]. However, autologous stem cell rescue is necessary due to myeloablation with high doses of 153Sm-EDTMP.

Management of recurrent and/or metastatic osteosarcoma

- In contrast to the 60%–70% long-term survival of patients who present with localized osteosarcoma, patients with clinically evident metastatic disease at diagnosis have a poor prognosis. About 20% of patients will present with metastatic osteosarcoma, and the overall survival is reported from 10% to 50% [56••,57•]. There is no standard approach for treatment of patients with metastatic disease at diagnosis despite multiple clinical trials. Combination chemotherapy with doxorubicin, ifosfamide, etoposide, cisplatin, and high-dose methotrexate are currently used at our institution for treatment. A Pediatric Oncology Group Trial with high-dose ifosfamide and etoposide induction therapy followed by adjuvant high-dose methotrexate, doxorubicin, and cisplatin chemotherapy with lower dose ifosfamide and etoposide had a 59% overall response rate with a 2 year projected survival of 39% for lung only and 58% for bone only involvement [20]. Although these results appear to be superior, the long-term survival data have not been reported. In most studies, however, patients with bony metatases fared poorly versus those with pulmonary metastases, and survival appears to inversely correlate with the number of metastases [56,58]. Notwithstanding that there is no standard for treatment of metastatic disease at diagnosis, we recommend aggressive multi-agent chemotherapy, primary local control, and metastasectomy if possible.
- A total of 30%–40% of patients with localized osteosarcoma will develop a recurrence in spite of incredibly aggressive chemotherapy and surgery. In several large series, the 5-year survival has been reported between 23% and 29% [59,60•], and complete surgery was required to achieve cure. In both studies, survival also correlated with the number of metastases at the time of recurrence as well as the recurrence-free interval. Patients with pulmonary metastases should have resection of disease by a skilled thoracic surgeon. Bilateral pulmonary disease is not a contraindication to resection and these patients should have staged thoracotomies. The use of chemotherapy in the adjuvant setting for metastatic osteosarcoma continues to be studied. Although controversial, many centers including ours advocate use of adjuvant chemotherapy when there is a solitary lung recurrence

occurring less than 24 months from initial diagnosis, and a period of close observation for greater than 24 months from initial diagnosis [61,62]. Ifosfamide with or without etoposide is the favored salvage regimen. As there is no standard other than complete surgical metastasectomy, the decision of adjuvant chemotherapy is made on an individual basis. Hence, it is of paramount importance that a skilled thoracic oncologic surgeon be involved in the management of these patients.

- Other therapeutic approaches to the management of metastatic and/or recurrent disease are mentioned elsewhere in this review, and include radiation to sites of metastases, Samarium–153, bisphosphonates, and other new promising investigational agents currently in clinical trials (Table 3).

Surveillance

- Judicial surveillance for recurrence is required in all patients with osteosarcoma. At our institution we generally follow the recently published recommended guidelines from the Children's Oncology Group Bone Tumor Committee [11]. Patients are screened for recurrence for 10 years after therapy is completed. The guidelines for surveillance post-chemotherapy are summarized in Table 2. It is important that careful attention be paid to cumulative radiation doses and that the ALARA (as low as reasonably achievable) principle is utilized for imaging associated radiation in particular for PET/CT scans, which can confer a substantial amount of whole body radiation for pediatric patients [63].

Late effects

- Clearly, tumor recurrence is the most significant problem for patients with osteosarcoma. However, as the overall survival of patients with osteosarcoma has improved over the last several decades, the long-

Table 2. Recommended guidelines for tumor directed surveillance [11]

Site	Imaging	Frequency/Duration
Primary	AP and lateral radiographs	Every 3 months × 2 years, Every 6 months × 3 years, Every 12 months × 5 years
	MRI with gadolinium and/or CT with contrast	If abnormal imaging or symptoms
Chest	CT non-contrast	Every 3 months × 2 years, Every 6 months × 3 years, Every 12 months × 5 years
	AP and lateral radiographs	Every 12 months × 5 years after last CT
Bone metastases	AP and lateral radiographs	Every 3 months × 2 years, Every 6 months × 3 years, Every 12 months × 5 years
	MRI with gadolinium and/or CT with contrast	If abnormal imaging or symptoms
	Whole body (99 m)Tc-MDP Bone Scan	If abnormal imaging or symptoms
	Whole body FDG-PET	If abnormal imaging or symptoms and PET positive on prior scan

AP—anterior posterior; MRI—magnetic resonance imaging; CT—computerized tomography; 99 mTc-MDP—99 m technetium methylene disphosphonate; FDG-PET—fluorodeoxyglucose positron emission tomography.

term side effects of treatment have become more evident. Aside from the recurrence of primary cancer, another worrisome long-term consequence is the development of a secondary malignancy. The incidence of a second malignancy in several large retrospective cohorts has been reported between 2.2% and 3.4% [64–66]. Leukemia was most prevalent followed by breast, soft tissue, lung, kidney, central nervous system, and other cancers.

- The long-term effects of therapy for osteosarcoma are numerous, potentially life threatening and debilitating. Although relatively infrequent, anthracycline-induced cardiac toxicity can be fatal. Careful observation of cumulative anthracycline dosage, avoidance of rapid infusion [67], and surveillance of cardiac function with routine serial echocardiography or multi-gated acquisition (MUGA) scans should be part of routine practice. Evidence supporting the use of cardioprotective agents such as dexrazoxane is debatable [68] and we recommend using dexrazoxane on an individual basis for patients with high risk of developing cardiac effects.
- Other late sequelae include, but are not limited to, nephrotoxicity from ifosfamide and cisplatin, ototoxicity from cisplatin, and male infertility likely from ifosfamide [69, 70].
- We recommend life-long screening for late sequelae at a comprehensive cancer center with an established long-term follow up or cancer survivorship program.

Emerging therapies

- Over the past several decades, new chemotherapeutic agents have been added to the armamentarium of anticancer drugs. However, few agents have shown activity or clinical benefit in osteosarcoma. Combination therapy with gemcitabine and docetaxel in refractory bone sarcomas was well tolerated and demonstrated antitumor activity [71].
- Immune approaches to osteosarcoma therapy continue to be investigated. Immunotherapy has been utilized in the therapy for osteosarcoma for several decades notably with the administration of interferon-alpha [72]. The effect of maintenance pegylated interferon alpha is currently being studied in the EURAMOS1 trial in patients with a good response to neoadjuvant chemotherapy. Another approach has been to use the immuno-stimulant muramyl-tripeptide phosphatidyl-ethanolamine (MTP-PE), which is derived from Bacille Calmette-Guerin and is a potent macrophage activator. Recently, addition of liposomal MTP-PE in combination with adjuvant chemotherapy resulted in a statistically significant increase in overall survival (78% OS) versus standard combination chemotherapy (70% OS) [31]. Other immune strategies have focused on generating T-cell responses by vaccination with the anti-idiotypic antibody mimicking CD55, a complement regulatory protein expressed by many solid tumors including osteosarcoma [73, 74]. The use of dendritic cell vaccines to enhance cytotoxic T-cell activation is being evaluated in xenograft models as well.
- Small molecule therapy with inhibition of the Src kinase pathway involved in osteoclast activity has been shown to have anti-proliferative and pro-apoptotic activity in osteosarcoma cell lines and xenograft models [75, 76]. The orally available Src tyrosine kinase inhibitor AZD0530 is currently being investigated in a phase II clinical trial in osteosarcoma with pulmonary recurrence post-metastasectomy conducted by the Sarcoma Alliance Research through Collaboration

Table 3. Select current trials for treatment of osteosarcoma

Trial name	Phase	ID, Status
Combination chemotherapy, PEG-interferon alfa-2b, and surgery in treating patients with osteosarcoma	III	COG-AOST0331, NCT00134030, MRC-EURAMOS1, Active
A study of R1507 in recurrent or refractory sarcomas	II	NCT00615680, SARC011, active
A placebo-controlled study of AZD0530 in patients with recurrent osteosarcoma localized to the lung	II	SARC012, NCT00752206 Approved, not yet active
Evaluation of zoledronic acid as a single agent or as an adjuvant to chemotherapy in high grade osteosarcoma	II/III	NCT00691236, Active
A study of bevacizumab in combination with chemotherapy for treatment of osteosarcoma	III	NCT00667342, Active
Inhalation SLIT cisplatin for the treatment of osteosarcoma metastatic to the lung	I/II	NCT00102531, Active
Deforolimus in treatment of sarcoma—SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Deforolimus)	III	NCT00538239, Active
Trial of dasatinib in advanced sarcomas	II	SARC009 NCT00464620, Active
A study to determine the activity of SCH 717454 in subjects with relapsed osteosarcoma or Ewing's sarcoma (Study P04720)	II	NCT00617890, Active
High dose methotrexate with leucovorin rescue with or without glucarpidase in osteosarcoma	II	NCT00634322, Active
Phase II trial of pemetrexed in second line advanced/metastatic osteosarcoma	II	NCT00523419, Active

(SARC) global cooperative network (SARC012, NCT00752206). Other recent trials using small molecule biologic therapy have focused on targeting the insulin like growth factor receptor (IGFR) with the monoclonal antibody R1507 (SARC011, NCT00615680) expressed in osteosarcoma and other sarcomas as well as targeting HER–2 with the monoclonal antibody trastuzumab overexpressed in 30%–40% of osteosarcoma tumors (COG-AOST0121, NCT00023998, study completed). A summary of selected current open trials for osteosarcoma is listed in Table 3.

Summary

- The prognosis of localized osteosarcoma has improved dramatically over the past 30 years with multi-modality treatment of aggressive surgery and combination chemotherapy. Despite these advances for localized disease and with the development of newer chemotherapeutic agents, the prognosis for metastatic, refractory and recurrent osteosarcoma is still dismal. Multidisciplinary management within a comprehensive cancer center is extremely important to the diagnosis, medical, surgical, and overall care of patients with osteosarcoma. A concerted effort should be made to treat osteosarcoma within the scope of a large international collaborative trial such as the EURAMOSI trial. For patients that have completed treatment, oncologists must be particularly attentive to long-term surveillance for recurrence and development of late-effects from chemotherapy. Finally, a continued emphasis should be placed on preclinical basic science and translational research aimed at furthering our understanding of osteosarcoma with the ultimate goal of providing patients new, molecularly targeted therapies.

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