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
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, 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.

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

| 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-054 [33]            | 1993–1995       | 133        | DOXO, MTX, CDDP, IFOS        | 71%/56%                 |
| INT-0133, CCG-7921,     | 1993–1997       | 662        | DOXO, MTX, CDDP, ±IFOS, ±MTP | 78%/67% for MTP arm.    |
| POG-9351 [31••]         |                 |            |                               |                         |
| 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.
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 (osteoarticual 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 endoprosthesis (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 metastases 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-

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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                          |
|                       | CT non-contrast                              | Every 3 months × 2 years, Every 6 months × 3 years, Every 12 months × 5 years |
| Chest                 | 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
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 EURA-MOSI 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.
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

** Of major importance

1. Huvos A.: Bone Tumors: Diagnosis, Treatment Prognosis (2nd ed.). Philadelphia: WB Saunders, 1991.

2. Gurney JG, Swenson AR, Bulterys M: Malignant bone tumors. In Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995. SEER program, National Cancer Institute, Bethesda, MD: 1999–2010.

3. Link MP, Gebhardt MC, Meyers PA: Osteosarcoma. In Principles and Practice of Pediatric Oncology. Edited by Pizzo A, Poplack D: Philadelphia: Lippincott Williams and Wilkins: 2002:1051–1089.

4. Meyers PA, Gorlick R: Osteosarcoma. Pediatr Clin North Am 1997, 44:973. doi:10.1016/S0031-3955(05)70540-X.

5. Ferrari S, Bacci G, Picci P, et al.: Long-term follow-up and post relapse survival in patients with non-metastatic osteosarcoma of the extremity treated with neoadjuvant chemotherapy. Ann Oncol 1997, 8:765. doi:10.1023/A:1008221713505.

6. Thorpe WP, Reilly JJ, Rosenberg SA: Prognostic significance of alkaline phosphatase measurements in patients with osteogenic sarcoma receiving chemotherapy. Cancer 1979, 43:2178–2181. doi:10.1002/1097-0142(197906)43:6<2178::AID-CNCR2820430603>3.0.CO;2-9.

7. Kesselring FO, Penn W: Radiological aspects of "classic" primary osteosarcoma: value of some radiological investigations: a review. Diag Imaging 1982, 51:78–92.

8. McKillop JH, Etcubanas E, Goris ML: The indications for and limitations of bone scintigraphy in osteogenic sarcoma: a review of 55 patients. Cancer 1981, 46:2603–2606.

9. McCarrville MB, Christie R, Dau NC, Spunt SL, Kaste SC: PET/CT in the evaluation of childhood sarcomas. AJR Am J Roentgenol 2005, 184:1293–1304.

10. Volker T, Denecke T, Steffen I, Misch D, Schonberger S, et al.: Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. J Clin Oncol 2007, 25:5435–5441. doi:10.1200/JCO.2007.12.2473.

11. Meyer JS, Nadal IR, Marina N, Womer RB, Brown KL, et al.: Imaging guidelines for children with ewing sarcoma and osteosarcoma: a report from the Children’s Oncology Group Bone Tumor Committee. Pediatr Blood Cancer 2008, 51:163–170.

Consensus guidelines from the Children’s Oncology Group Bone Tumor Committee for imaging children, adolescents and young adults with osteosarcoma and ewing sarcoma.

12. Hau A, Kim I, Kattapuram S, Hornick JF, et al.: Accuracy of CT-guided biopsies in 359 patients with musculoskeletal lesions. Skeletal Radiol 2002, 31:349–353.

13. Peabody TD, Simon MA: Making the diagnosis: keys to a successful biopsy in children with bone and soft-tissue tumors. Orthop Clin North Am 1996, 27:453–459.

14. Friedman MA, Carter SK: The therapy of osteogenic sarcoma: current status and thoughts for the future. J Surg Oncol 1972, 4:482–510.

15. Meyers P: Osteosarcoma. In Pediatric Bone and Soft Tissue Sarcomas. Edited by Pappo A. Berlin: Springer-Verlag: 2006; 219–233.

16. Jaffe N, Frei E, Traggis D, et al.: Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma. N Engl J Med 1974, 291:994–997.

17. Cortes EP, Holland JF, Wang JI, et al.: Amputation and adriamycin in primary osteosarcoma. N Engl J Med 1974, 291:998–1000.

18. Gasparini M, Rouesse J, van Oosterom A, et al.: Phase II study of cisplatin in advanced osteogenic sarcoma. European Organization for Research on Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer Treat Rep 1985, 69:115–117.

19. Marti C, Kroner T, Remagen W, et al.: High-dose ifosfamide in advanced osteosarcoma. Cancer Treat Rep 1985, 69:115–117.

20. Goorin AM, Harris MB, Bernstein M, et al.: Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol 2002, 20:426–433.

A Pediatric Oncology Group study of etoposide and high-dose ifosfamide therapy in patients with metastatic osteosarcoma at diagnosis. Response rates and projected progression free survival was favorable compared to previous trials. However, long term data has not been reported.

21. Rosen G, Tan C, Sannaneechai A, et al.: The rationale for multiple drug chemotherapy in the treatment of osteogenic sarcoma. Cancer 1975, 35:936–945.

22. Rosen G, Marcove RC, Caparros B, et al.: Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. Cancer 1979, 43:2163–2177.

23. Goorin AM, Schwartzentruber DJ, Devidas M, et al.: Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. J Clin Oncol 2003, 21:1574–1580.

24. Bielack SS, Kempf-Bielack B, Delling G, et al.: Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma group protocols. J Clin Oncol 2002, 20:776.
Very large series of patients from a multicenter database reviewing prognostic factors in high grade osteosarcoma.

25. Winkler K, Beron G, Delling G, et al.: Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol 1986, 6:329–337.

26. Hudson M, Jaffe MR, Jaffe N, et al.: Pediatric osteosarcoma: therapeutic strategies, results and prognostic factors derived from a 10 year experience. J Clin Oncol 1990, 8:1988–1997.

27. Rosen G, Caparrós B, Huvos AG, et al.: Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982, 49:1221–1230.

28. Bacci G, Picci P, Ferrari S, et al.: Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 164 patients preoperatively treated with high doses of methotrexate followed by cisplatin and doxorubicin. Cancer 1993, 72:3227–3238.

29. Saeter G, Alvegard TA, Elomaa I, et al.: Treatment of osteosarcoma of the extremities with the T–10 protocol, with emphasis on the effects of pre-operative chemotherapy with single-agent high-dose methotrexate: a Scandinavian Sarcoma Group Study. J Clin Oncol 1999, 17:666–677.

30. Provisor AJ, Ettinger DJ, Nachman JB, et al.: Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. J Clin Oncol 1997, 15:76–84.

31. Meyers PA, Schwartz CL, Krailo MD, et al.: Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival—A report from the Children's Oncology Group. J Clin Oncol 2008, 26: 633–638.

Large randomized trial of patients with localized osteosarcoma. Although a significant survival advantage was conferred with addition of MTP-PE, the study has been criticized for its analysis and interpretation of event free survival and overall survival.

32. Fuchs N, Bielack SS, Epler D, et al.: Long-term results of the co-operative German-Austrian-Swiss osteosarcoma group's protocol COSS–86 of the intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. Ann Oncol 1998, 9:893–899.

33. Bacci G, Briccoli A, Ferrari A, et al.: Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. Eur J Cancer 2001, 37:2030–2039.

34. Lewis II, Noolj MA, Whelan J, et al.: Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 2007, 99: 112–128.

A large randomized trial comparing dose intensification with doxorubicin and cisplatin. Dose intensification significantly increased favorable histologic response though had no increase in event free survival or overall survival questioning histologic response as an outcome measure.

35. Ferrari S, Smeland S, Mercuri M, et al. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma groups. J Clin Oncol 2005, 23: 8845–8852.

A joint study by the Italian and Scandinavian Sarcoma Groups exploring the effect of the addition of high-dose ifosfamide to standard therapy. There was no benefit of high-dose ifosfamide over standard dose ifosfamide.

36. Grimer R: Surgical options for children with osteosarcoma. Lancet Oncol 2005, 6:85–92.

37. Simon MA, Aschliman MA, Thomas N, Mankin HJ: Limb salvage treatment versus amputation for osteosarcoma of the distal end of the femur. J Bone Joint Surg Am 1986, 68:1331–1337.

38. Ghellinzoni F, Picci P, Bacci G, et al.: Limb sparing versus amputation in osteosarcoma. Correlation between local control, surgical margins, and tumor necrosis: Istituto Rizzoli experience. Ann Oncol 1992; 3 (Suppl 2): S23–S27.

39. Picci P, Sangiorgi L, Bahamonde L, et al.: Risk factors for local recurrences after limb-salvage surgery for high-grade osteosarcoma of the extremities. Ann Oncol 1997, 8:899–903.

40. Bacci G, Forni C, Longhi A, et al.: Local recurrence and local control of non-metastatic osteosarcoma of the extremities: a 27 year experience in a single institution. J Surg Oncol 2007, 96:118–123.

41. Wiganowicz PZ, Eckardt JJ, Dorey FJ, et al.: Etiology and results of tumor endoprosthesis revision surgery in 64 patients. Clin Orthop Relat Res 1999, 358:64–74.

42. Torbert JT, Fox EJ, Hosalkar HS, et al.: Endoprosthetic reconstructions: results of long-term followup of 139 patients. Clin Orthop Relat Res 2005, 438:51–59.

43. Chao EY, Fuchs B, Rowland CM, et al.: Long-term results of segmental prosthesis fixation by extracorporal bone-bridging and ingrowth. J Bone Joint Surg Am 2004, 86:948–955.

44. Kramer MJ, Tanner BJ, Horvai AE, O’Donnell RJ: Compressive osseointegration promotes viable bone at the endoprosthetic interface: retrieval study of Compress implants. Int Orthop 2008, 32:567–571.

45. Eckardt JJ, Safran MR, Eilber FR, et al.: Expandable endoprosthetic reconstruction of the skeletally immature after malignant bone tumor resection. Clin Orthop Relat Res 1993, 297:188–202.

46. Neel MD, Wilkins RM, Rao BN, Kelly CM: Early multicenter experience with a non-invasive expandable prosthesis. Clin Orthop Relat Res 2003, 415:72–81.

47. Ram GB, Jinks JC, Childs DS Jr, et al.: Elective whole lung irradiation in the treatment of osteogenic sarcoma. Cancer 1976, 38:939–942.

48. Breur K, Cohen P, Schweisguth O, et al. Irradiation of the lungs as an adjuvant therapy in the treatment of osteosarcoma of the limbs. An E.O.R.T.C. randomized study. Eur J Cancer 1978, 14: 461–471.

49. Whelan JS, Burcombe RJ, Janinis J, et al.: A systematic review of pulmonary irradiation in the management of primary bone tumours. Ann Oncol 2002, 13:23–30.
50. Machak GN, Trachev SI, Soloyvov YN, et al.: Neoadjuvant chemotherapy and local radiotherapy for high-grade osteosarcoma of the extremities. Mayo Clinic Proc 2003, 78:147–155.

51. Delaney TF, Park L, Goldberg SI, et al.: Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 2005, 61:492–498.

52. Delaney TF, Liebsch NJ, Pedlow FX, et al.: Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Radiat Oncol Biol Phys 2009, 1–8 (in press).

53. Anderson PM, Wiseman GA, Dispenzieri A, et al.: High-dose samarium–153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002, 1:189–196.

54. Bruland OS, Skretting A, Solheim OP, et al.: Targeted radiotherapy of osteosarcoma using 153Sm-EDTMP. Acta Oncol 1996, 35:381–384.

55. Anderson PM, Nunez R: Samarium lexidronam (153Sm-EDTP): skeletal radiation for osteoblastic bone metastases and osteosarcoma. Expert Rev Anti-cancer Ther 2007, 7:1517–1527.

56. Harris MB, Giezer P, Goorin AM, et al.: Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group study. J Clin Oncol 1998, 16:3641–3648.

57. Kager L, Zoubek A, Potschger U, et al.: Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol 2003, 21:2011–2018.

Large retrospective analysis of osteosarcoma patients presenting with metastasis treated on COSS group studies.

58. Thompson RC Jr, Cheng EY, Clohisy DR, et al.: Results of treatment for metastatic osteosarcoma with neoadjuvant chemotherapy and surgery. Clin Orthop Relat Res 2002, 397:240–247.

59. Ferrari S, Bricolli A, Mercuri M, et al.: Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol 2003, 21:710–715.

60. Kempf-Bielack B, Bielack SS, Jurgens H, et al.: Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Group (COSS). J Clin Oncol 2005, 20:559–568.

Retrospective analysis of a large cohort of relapsed osteosarcoma patients. Time to relapse and tumor burden at relapse were correlated with survival.

61. Chou AJ, Merola PR, Weder LH, et al.: Treatment of osteosarcoma at first recurrence after contemporary therapy. The Memorial Sloan Kettering Cancer Center Experience. Cancer 2005, 104:2214–2221.

62. Hawkins DS, Arndt CA: Pattern of disease recurrence and prognostic factors in patients with osteosarcoma treated with contemporary chemotherapy. Cancer 2003, 98:2447–2456.

63. Federman N, Feig SA: PET/CT in evaluating pediatric malignancies: a clinician’s perspective. J Nucl Med 2007, 48:1923–1931.

64. Bacci G, Ferrari C, Longhi A, et al.: Second malignant neoplasm in patients with osteosarcoma of the extremities treated with adjuvant and neoadjuvant chemotherapy. J Pediatr Hematol Oncol 2006, 28:774–780.

65. Aung L, Gorlick RG, Shi W, et al.: Second malignant neoplasms in long-term survivors of osteosarcoma: Memorial Sloan-Kettering Cancer Center experience. Cancer 2002, 95:1728–1734.

66. Goldsby R, Burke C, Nagarajan R, et al.: Second solid malignancies among children, adolescents, and young adults diagnosed with malignant bone tumors after 1976. Cancer 2008, 113:2597–2604.

67. Van Dalen EC, Van der Pal HI, Caron HN, Kremer LC: Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. Cochrane Database Syst Rev 2006, 4:1–22.

68. Van Dalen EC, Caron HN, Dickinson HO, Kremer LC: Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2008, 4:1–44.

69. Longhi A, Macchiagodena M, Vitali G, Bacci G: Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. J Pediatr Hematol Oncol 2003, 35:292–296.

70. Stohr W, Paulides M, Bielack SS, et al.: Nephrotoxicity of cisplatin and carboplatin in sarcoma patients: a report from the late effects surveillance system. Pediatr Blood Cancer 2007, 48:140–147.

71. Navid F, Willert JR, McCarville MB, et al.: Combination of gemcitabine and doetaxel in the treatment of children and young adults with bone sarcoma. Cancer 2008, 113:419–425.

72. Muller CR, Smeland S, Bauer HC, et al.: Interferon-alpha as the only adjuvant treatment in high-grade osteosarcoma: long term results of the Karolinska Hospital series. Acta Oncol 2005, 44:475–480.

73. Pritchard-Jones K, Spendlove I, Wilton C, et al.: Immune responses to the 105AD7 human anti-idiotypic vaccine after intensive chemotherapy, for osteosarcoma. Br J Cancer 2005, 92:1358–1365.

74. Ullenhag GJ, Spendlove I, Watson NG, et al.: T-cell responses in osteosarcoma patients vaccinated with an anti-idiotypic antibody, 105AD7, mimicking CD55. Clin Immunol 2008, 128:148–154.

75. Shor AC, Keshman EA, Lee FY, et al.: Dasatinib inhibits migration and invasion in diverse human sarcoma cell lines and induces apoptosis in bone sarcoma cells dependent on SRC kinase for survival. Cancer Res 2007, 67:2800–2808.

76. Manetti F, Santucci A, Locatelli GA, et al.: Identification of a novel pyrazolo[3, 4-d]pyrimidine able to inhibit cell proliferation of a human osteogenic sarcoma in vitro and in a xenograft model in mice. J Med Chem 2007, 50:5579–5588.