NCCN

Bone Cancer

Clinical Practice Guidelines in Oncology

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Abstract

Primary bone cancers are extremely rare neoplasms, accounting for fewer than 0.2% of all cancers. The evaluation and treatment of patients with bone cancers requires a multidisciplinary team of physicians, including musculoskeletal, medical, and radiation oncologists, and surgeons and radiologists with demonstrated expertise in the management of these tumors. Long-term surveillance and follow-up are necessary for the management of treatment late effects related to surgery, radiation therapy, and chemotherapy. These guidelines discuss the management of chordoma, giant cell tumor of the bone, and osteosarcoma. (*JNCCN* 2013;11:688–723)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Primary bone cancers are extremely rare neoplasms accounting for fewer than 0.2% of all cancers, although the true incidence is difficult to determine because of the rarity of these tumors.^{1,2} In 2013, an estimated 3010 new cases will be diagnosed in the United States and 1440 people will die of the disease.³ Primary bone cancers demonstrate wide clinical heterogeneity and are often curable with proper treatment. Osteosarcoma (35%), chondrosarcoma (30%), and Ewing sarcoma (16%) are the most common forms of bone cancer. Malignant fibrous histiocytoma, fibrosarcoma, chordoma, and giant cell tumor of the bone (GCTB) are rare tumors, constituting up to 1% to 5% of all primary malignant bone tumors.⁴ GCTB has both benign

Please Note

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Disclosures for the NCCN Bone Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Bone Cancer Panel members can be found on page 723. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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and malignant forms, with the benign form the most common subtype.

Various types of bone cancers are named based on their histologic origin: chondrosarcomas arise from cartilage, osteosarcomas arise from bone, and fibrogenic tissue is the origin of fibrosarcoma of bone, whereas vascular tissue gives rise to hemangiopericytoma and hemangiopericytoma. Notochordal tissue gives rise to chordoma. Several primary bone cancers, including Ewing sarcoma family of tumors (ESFT), are of unknown histologic origin. Chondrosarcoma is usually found in middle-aged and older adults. Osteosarcoma and Ewing sarcoma develop mainly in children and young adults. Chordoma is more common in men, with peak incidence in the fifth to sixth decades of life.^{5,6}

The pathogenesis and origin of most bone cancers remains unclear. Gene rearrangements between the *EWS* and *ETS* family of genes have been implicated in the pathogenesis of ESFT.^{7–10} Specific germ-line mutations have also been implicated in the pathogenesis of osteosarcoma.^{11,12} The Li-Fraumeni syndrome characterized by a germ-line mutation in the *TP53* gene is associated with a high risk of developing osteosarcoma.^{13–15} Osteosarcoma is the most common second primary malignancy in patients with a history of retinoblastoma, characterized by a mutation in the retinoblastoma gene *RBI*.^{11,16,17} Increased incidences of osteosarcoma have also been associated with other inherited genetic predisposition syndromes characterized by mutations in the DNA helicase genes.^{11,12} Osteosar-

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WORKUP^{a,b}

HISTOLOGIC SUBTYPE

- All patients should be evaluated and treated by a multidisciplinary team with expertise in the management of chordoma^a
- History and physical
- Adequate imaging (eg, x-ray, CT ± MRI) of primary site and screening MRI of spinal axis
- CT scan of chest, abdomen, and pelvis
- Consider PET scan
- Consider bone scan if PET is negative
- Biopsy to confirm histologic subtype^{b,c}

Conventional
or
Chondroid

See Presentation and
Primary Treatment
(facing page)

Dedifferentiated

See NCCN Guidelines for
Soft Tissue Sarcoma (to
view the most recent
version of these
guidelines, visit NCCN.org)

^aSee Multidisciplinary Team (page 700).
^bSee Principles of Bone Cancer Management (page 701).
^cBiopsy should be done after imaging studies are completed; biopsy type may vary depending on anatomic location. Optimally, biopsy should be performed at a center of excellence where definitive management is given. Cord compression may limit surgical procedures.

CHOR-1

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CHORDOMA

PRESENTATION

PRIMARY TREATMENT

ADJUVANT TREATMENT

Sacrococcygeal
and
Mobile spine

Wide resection^b
± RT,^{d,e}
if resectable

OR

Consider RT^e
if unresectable

Consider RT^{d,e}
for positive surgical
margins or for large
extracompartmental
tumors

See Surveillance
(page 692)

Skull base/Clival

Intralesional excision^f
± RT,^{d,e}
if resectable

OR

Consider RT^e
if unresectable

Follow-up
MRI to
assess
adequacy of
resection

- Consider RT^{d,e}
for positive surgical
margins or for large
extracompartmental
tumors
- Consider re-resection
if necessary

^bSee Principles of Bone Cancer Management (page 701).

^dRadiation therapy may be given preoperatively, intraoperatively, and/or postoperatively.

^eSee Principles of Radiation Therapy (pages 704-705).

^fMaximal safe resection. Maximal tumor removal is recommended when appropriate.

CHOR-2

CHORDOMA

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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GIANT CELL TUMOR OF THE BONE

WORKUP

PRESENTATION

- History and physical examination
- Imaging (eg, x-ray, MRI ± CT) of primary site
- Chest imaging
- Bone scan (optional)
- Biopsy to confirm diagnosis^{a,b}
- If there is malignant transformation, treat as described for osteosarcoma (See page 696)

Localized disease

Metastatic disease
at presentation

See page 694

^aBrown tumor of hyperparathyroidism should be considered as a differential diagnosis.^bSee Principles of Bone Cancer Management (page 701).

GCTB-1

^cIntralesional excision, with an effective adjuvant is adequate.
^dDenosumab should be continued until disease progression in responding patients.
^eSee Bone Cancer Systemic Therapy Agents (pages 702-703).
^fRT has been associated with increased risk of malignant transformation.
^gTreatment of primary tumor is as described for localized disease.
^hSee Principles of Radiation Therapy (pages 704-705).

GCTB-2

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GIANT CELL TUMOR OF THE BONE

SURVEILLANCE

RECURRENCE

- Physical exam
- Imaging (x-ray, MRI ± CT) of surgical site as clinically indicated
- Chest imaging every 6 mo for 2 years then annually thereafter

Local recurrence

Resectable

Consider chest
imagingConsider
denosumab prior
to surgery
(see previous
page)Resectable
with unacceptable
morbidity
or
unresectable
axial lesions

See previous page

Metastatic
recurrence

GCTB-3

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OSTEOSARCOMA

^bSee Principles of Bone Cancer Management (page 701).^dSee Bone Cancer Systemic Therapy Agents (pages 702-703).^fSelected elderly patients may benefit from immediate surgery.^gResponse is defined by pathologic mapping per institutional guidelines; the amount of viable tumor is reported as <10% of the tumor area in cases showing a good response and 10% in cases showing a poor response.^hSee Principles of Radiation Therapy (pages 704-705).

PRIMARY TREATMENT

^dSee Bone Cancer Systemic Therapy Agents (pages 702-703).
^hSee Principles of Radiation Therapy (pages 704-705).

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OSTEOSARCOMA

SURVEILLANCE

RELAPSE

- Chest imaging
- CBC and other laboratory studies as indicated
- Imaging of primary siteⁱ
- Consider PET scan and/or bone scan (category 2B)
- Reassess function every visit
- Follow-up schedule: (Orthopedic and Oncologic)
 - Every 3 mo for year 1 and 2
 - Every 4 mo for year 3
 - Every 6 mo for year 4 and 5 and yearly thereafter

^dSee Bone Cancer Systemic Therapy Agents (pages 702-703).

ⁱUse the same imaging technique that was performed in the initial workup.

OSTEO-4

MULTIDISCIPLINARY TEAM

Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team with expertise in the management of these tumors. The team should meet on a regular basis and should include:

Core Group

- Musculoskeletal oncologist
- Bone pathologist
- Medical/pediatric oncologist
- Radiation oncologist
- Musculoskeletal radiologist

Specialists Critical in Certain Cases

- Thoracic surgeon
- Plastic surgeon
- Interventional radiologist
- Physiatrist
- Vascular/general surgeon
- Neurosurgeon
- Additional surgical subspecialties as clinically indicated

BONE-A

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PRINCIPLES OF BONE CANCER MANAGEMENT

Biopsy

- Biopsy diagnosis is necessary before any surgical procedure or fixation of primary site.
- Biopsy is optimally performed at a center that will do definitive management.
- Placement of biopsy is critical.
- Biopsy should be core needle or surgical biopsy.
- Technique: apply same principles for core needle or open biopsy. Needle biopsy is not recommended for skull base tumors.
- Appropriate communication between the surgeon, musculoskeletal radiologist, and bone pathologist is critical.
- Fresh tissue may be needed for molecular studies and tissue banking.
- In general, failure to follow appropriate biopsy procedures may lead to adverse patient outcomes.
- Final pathological evaluation should include assessment of surgical margins and size/dimensions of tumor.

Surgery

- Wide excision should achieve histologically negative surgical margins.
- Negative surgical margins optimize local tumor control.
- Local tumor control may be achieved by either limb-sparing resection or limb amputation (individualized for a given patient).
- Limb-sparing resection is preferred to optimize function if reasonable functional expectations can be achieved.

Laboratory Studies

- Laboratory studies such as CBC, LDH, and ALP may have relevance in the diagnosis, prognosis, and management of patients with bone sarcoma and should be performed before definitive treatment and periodically during treatment and surveillance.

Treatment

- Fertility issues should be addressed with patients prior to commencing chemotherapy.
- Care for bone cancer patients should be delivered directly by physicians on the multidisciplinary team (category 1).
(See previous page)

Long-Term Follow-up and Surveillance/Survivorship

- Patients should have a survivorship prescription to schedule follow-up with a multidisciplinary team.
- Lifelong follow-up is recommended for surveillance and treatment of late effects of surgery, radiation, and chemotherapy in long-term survivors.

BONE-B

BONE CANCER SYSTEMIC THERAPY AGENTSChordoma

- Imatinib^{1,2}
- Imatinib with cisplatin³ or sirolimus⁴
- Erlotinib⁵
- Erlotinib + cetuximab⁶
- Sunitinib⁷

Giant Cell Tumor of Bone

- Denosumab⁸⁻¹⁰
- Interferon alfa¹¹⁻¹³
- Peginterferon¹³

Osteosarcoma[†]

- First-line therapy (primary/neoadjuvant/adjuvant therapy or metastatic disease)
 - Cisplatin and doxorubicin¹⁴⁻¹⁶
 - MAP (High-dose methotrexate, cisplatin, and doxorubicin)^{17,18}
 - Doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate¹⁹
 - Ifosfamide, cisplatin, and epirubicin²⁰
- Second-line therapy (relapsed/refractory or metastatic disease)
 - Docetaxel and gemcitabine²¹
 - Cyclophosphamide and etoposide²²
 - Cyclophosphamide and topotecan²³
 - Gemcitabine²⁴
 - Ifosfamide and etoposide²⁵
 - Ifosfamide, carboplatin, and etoposide²⁶
 - High-dose methotrexate, etoposide, and ifosfamide²⁷
 - ¹⁵³Sm-EDTMP for relapsed or refractory disease beyond second-line therapy²⁸
 - Sorafenib²⁹

BONE CANCER SYSTEMIC THERAPY AGENTS
 (References)

- ¹Geoerger B, Morland B, Ndiaye A, et al. Target-driven exploratory study of imatinib mesylate in children with solid malignancies by the Innovative Therapies for Children with Cancer (ITCC) European Consortium. *Eur J Cancer* 2009;45:2342-2351.
- ²Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. *Cancer* 2004;101:2086-2097.
- ³Casali PG, Stacchiotti S, Grosso F, et al. Adding cisplatin (CDDP) to imatinib (IM) re-establishes tumor response following secondary resistance to IM in advanced chordoma [abstract]. *J Clin Oncol* 2007;25(18 Suppl):Abstract 10038.
- ⁴Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. *Ann Oncol* 2009;20:1886-1894.
- ⁵Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. *Anticancer Drugs* 2009;20:953-955.
- ⁶Linden O, Ehinger M, Kinhult S, et al. Cetuximab and EGFR inhibitors in patients with neurological symptoms due to chordoma [abstract]. *J Clin Oncol* 2012;30(Suppl):Abstract 10024.
- ⁷George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol* 2009;27:3154-3160.
- ⁸Blay J, Chawla SP, Martin Broto J, et al. Denosumab safety and efficacy in giant cell tumor of bone (GCTB): Interim results from a phase II study [abstract]. *J Clin Oncol* 2011;29(Suppl):Abstract 10034.
- ⁹Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res* 2012;18:4415-4424.
- ¹⁰Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010;11:275-280.

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BONE CANCER SYSTEMIC THERAPY AGENTS
(References Cont.)

- ¹¹Kaiser U, Neumann K, Havemann K. Generalised giant-cell tumour of bone: successful treatment of pulmonary metastases with interferon alpha, a case report. *J Cancer Res Clin Oncol* 1993;119:301-303.
- ¹²Kaban LB, Troulis MJ, Ebb D, et al. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. *J Oral Maxillofac Surg* 2002;60:1103-1111.
- ¹³Yasko AW. Interferon therapy for giant cell tumor of bone. *Curr Opin Orthop* 2006;17:568-572.
- ¹⁴Bramwell V, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992;10:1579-1591.
- ¹⁵Lewis IJ, Nooij 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.
- ¹⁶Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997;350:911-917.
- ¹⁷Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol* 2000;18:4016-4027.
- ¹⁸Winkler 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* 1988;6:329-337.
- ¹⁹Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. *Ann Oncol* 2003;14:1126-1134.
- ²⁰Basaran M, Baybek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. *Oncology* 2007;72:255-260.
- ²¹Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer* 2008;113:419-425.
- ²²Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer* 2009;115:2980-2987.
- ²³Saylors RL 3rd, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol* 2001;19:3463-3469.
- ²⁴Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol* 2007;25:2755-2763.
- ²⁵Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol* 1987;5:1191-1198.
- ²⁶Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer* 2005;44:338-347.
- ²⁷Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. *Eur J Cancer* 2007;43:752-761.
- ²⁸Anderson 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;20:189-196.
- ²⁹Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol* 2012;23:508-516.

BONE-C (2 OF 2)

PRINCIPLES OF RADIATION THERAPY

- Patients should be strongly encouraged to have radiation therapy at the same specialized center that is providing surgical and systemic interventions.
- Specialized techniques such as intensity-modulated radiation therapy; particle-beam RT with protons, carbon ions, or other heavy ions; stereotactic radiosurgery; or fractionated stereotactic radiotherapy should be considered as indicated to allow high-dose therapy while maximizing normal tissue-sparing.

CHORDOMA

- Base of Skull
 - Postoperative RT (R1 and R2 resection)¹ or RT for unresectable disease - >70 Gy
 - Consider postoperative RT for R0 resections
- Mobile Spine
 - Consider preoperative RT (19.8-50.4 Gy) and postoperative RT to total dose of 70 Gy (depending on normal tissue tolerances)

GIANT CELL TUMOR OF BONETreatment of Metastatic Disease

- Consider RT (50-60 Gy) for unresectable/progressive/recurrent disease that has not responded to serial embolizations, denosumab, IFN, or pegylated IFN.
- An increased risk of malignant transformation following RT has been noted in some studies.

OSTEOSARCOMATreatment of Primary Tumor

- RT should be considered for patients with positive margins of resection, subtotal resections, or unresectable disease
 - Postoperative RT (R1 and R2 resections):¹ ≥55 Gy (64-68 Gy to area of highest risk)
 - Unresectable disease: 60 - >70 Gy depending on normal tissue tolerance

Treatment of Metastatic Disease

- Consider use of ¹⁵³Sm-EDTMP
- Consider use of Stereotactic radiosurgery, especially for oligometastases

¹R0 = No microscopic residual disease, R1 = Microscopic residual disease, R2 = Gross residual disease

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PRINCIPLES OF RADIATION THERAPY
(References)

Chordoma

Amichetti M, Cianchetti M, Amelio D, et al. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev* 2009;32:403.

Park L, Delaney TF, Liebsch NJ, et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. *Int J Radiat Oncol Biol Phys* 2006;65:1514-1521.

Giant Cell Tumor of Bone

Caudell JJ, Ballo MT, Zagars GK, et al. Radiotherapy in the management of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 2003;57:158.

Hug EB, Muentner MW, Adams JA, et al. 3-D-conformal radiation therapy for pediatric giant cell tumors of the skull base. *Strahlenther Onkol* 2002;178:239.

Malone S, O'Sullivan B, Catton C, et al. Long-term follow-up of efficacy and safety of megavoltage radiotherapy in high-risk giant cell tumors of bone. *Int J Radiat Oncol Biol Phys* 1995;33:689.

Ruka W, Rutkowski P, Morysiński T, et al. The megavoltage radiation therapy in treatment of patients with advanced or difficult giant cell tumors of bone. *Int J Radiat Oncol Biol Phys* 2010;78:494.

Mixed Histology Reports

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;74:732-739.

Kamada T, Tsujii H, Yanagi T, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. Working Group for the Bone and Soft Tissue Sarcomas. *J Clin Oncol* 2002;20:4466.

Wagner TD, Kobayashi W, Dean S, et al. Combination short-course preoperative irradiation, surgical resection, and reduced-field high-dose postoperative irradiation in the treatment of tumors involving the bone. *Int J Radiat Oncol Biol Phys* 2009;73:259-266.

BONE-D (2 OF 2)

Bone Cancer

Text continued from p. 689

coma is also the most common radiation-induced bone sarcoma.^{18,19}

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and ESFT.^{20,21} With current multimodality treatment, approximately three-quarters of all patients diagnosed with osteosarcoma are cured and 90% to 95% of adult patients diagnosed with osteosarcoma can be successfully treated with limb-sparing approaches rather than amputation.²² Survival rates have improved to almost 70% in patients with localized ESFT.²¹ A cure is still achievable in selected patients diagnosed with metastatic ESFT and osteosarcoma at presentation.^{23,24}

These guidelines focus on chordoma, chondrosarcoma, ESFT, GCTB, and osteosarcoma. This manuscript highlights only a portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer. Please refer to NCCN.org for the complete version of these guidelines.

Staging

The 2010 AJCC staging classification is shown in Table 1 (available online, in these guidelines, at NCCN.org [ST-1]). This system is based on the assessment of histologic grade (G), tumor size (T), and presence of regional (N) and/or distant metastases (M). The Surgical Staging System (SSS) is another staging system for bone and soft tissue sarcomas developed by the Musculoskeletal Tumor Society (Table 2, available at NCCN.org [ST-1]).²⁵ (available at NCCN.org [ST-1]).²⁵ This system stratifies both bone and soft tissue sarcomas by the assessment of the surgical grade (G), local extent (T), and presence or absence of regional or distant metastases. It may be used in addition to the AJCC staging system.

Principles of Bone Cancer Management

Multidisciplinary Team Involvement

Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team of physicians with demonstrated expertise in the management of these tumors. Long-term surveillance and follow-up are necessary when considering the risk of recurrence and comorbidities

associated with chemotherapy and radiation therapy (RT). Life-long follow-up is recommended for surveillance and treatment of late effects of surgery, RT, and chemotherapy in long-term survivors. Patients should be given a survivorship prescription to schedule follow-up with a multidisciplinary team. Fertility issues should be discussed with appropriate patients before initiation of treatment.²⁶

Diagnostic Workup

Suspicion of a malignant bone tumor in a patient with a painful lesion often begins when a poorly marginated lesion is seen on a plain radiograph. In patients younger than 40 years, an aggressive, painful bone lesion has a significant risk of being a malignant primary bone tumor, and referral to an orthopedic oncologist should be considered before further workup. In patients 40 years of age and older, CT scan of the chest, abdomen, and pelvis; bone scan; mammogram; and other imaging studies as clinically indicated should be performed if plain radiographs do not suggest a specific diagnosis.²⁷

All patients with suspected bone sarcoma should undergo complete staging before biopsy. The standard staging workup for a suspected primary bone cancer should include chest imaging (chest radiograph or chest CT to detect pulmonary metastases), appropriate imaging of the primary site (plain radiographs, MRI for local staging, and/or CT scan), and bone scan.²⁸ Whole-body MRI is a sensitive imaging technique for detecting skeletal metastases in patients with small cell neoplasms, ESFT, and osteosarcoma.^{29,30} Imaging of painless bone lesions should be evaluated by a musculoskeletal radiologist followed by appropriate referral to a multidisciplinary treatment team if necessary. Laboratory studies, such as CBC, lactate dehydrogenase (LDH), and alkaline phosphatase (ALP), should be performed before initiation of treatment.

PET or PET/CT is an alternative imaging technique that has been used in the pretreatment staging of soft tissue and bone sarcomas.^{31,32} Recent reports in the literature have shown the utility of PET scans in the evaluation of response to chemotherapy in patients with osteosarcoma, ESFT, and advanced chordoma.^{33–36} PET or PET/CT with the investigational radioactive substance ¹⁸F-fluoromisonidazole (FMISO) has been shown to identify the hypoxic component in residual chordomas before RT.³⁷ This

approach is being evaluated in clinical trials and would be helpful in identifying tumors with low oxygen levels that are more resistant to RT.

Biopsy

Incisional (open) and percutaneous biopsy (core needle or fine-needle aspiration) are the techniques used historically in the diagnosis of musculoskeletal lesions.^{38,39} Open biopsy is the most accurate method because of the larger sample size, which is useful for performing additional studies such as immunohistochemistry or cytogenetics.⁴⁰ However, open biopsy requires general or regional anesthesia and an operating room, whereas core biopsy can be performed under local anesthesia, with or without sedation. Core needle biopsy has also been used as an alternative to open biopsy for diagnosing musculoskeletal lesions, with accuracy rates ranging from 88% to 96% when adequate samples are obtained.^{41–44} Cost savings may be realized when needle biopsy is used in selected patients.⁴¹ Recent advances in imaging techniques have contributed to the increasing use of image-guided percutaneous biopsy for the diagnosis of primary and secondary bone tumors.⁴⁵ The preferred method for biopsy remains controversial because no randomized controlled trials have compared core needle biopsy with open biopsy.

The guidelines recommend core needle or open biopsy to confirm the diagnosis of primary bone tumor before any surgical procedure or fixation of primary site. Biopsy should be performed at the center that will provide definitive treatment for patients with a suspected primary malignant bone tumor. At biopsy, careful consideration should be given to appropriate stabilization of the bone and/or to measures to protect against impending pathologic fracture. The placement of biopsy is critical to the planning of limb-sparing surgery, and failure to follow appropriate biopsy procedures may lead to adverse patient outcomes.^{38,39} In a multicenter review of 597 patients with musculoskeletal tumors, alteration of the treatment plan (complex resection or the use of adjunctive treatment) was encountered in 19%, and unnecessary amputation was performed in 18 patients.⁴⁶

Both open and core needle biopsy techniques are associated with risk of local tumor recurrence, either through spillage of tumor or tumor seeding along the biopsy tract if the scar is not removed en bloc during tumor resection. The risk of tumor seeding is less with core needle biopsy.^{47,48} Nevertheless, the

same principles should be applied for core needle and open biopsy. Appropriate communication between the surgeon, musculoskeletal oncologist, and bone pathologist is critical in planning the biopsy route. It is essential to select the biopsy route in collaboration with the surgeon to ensure that the biopsy tract lies within the planned resection bed so that it can be resected with the same wide margins as the primary tumor during surgery. Although fine-needle aspiration is not associated with a significant risk of tumor seeding, it is not suitable for the diagnosis of primary lesions, because its diagnostic accuracy is less than that of core needle biopsy.⁴⁹

Surgery

Surgical margins should be negative, wide enough to minimize potential local recurrence, and narrow enough to maximize function. Wide excision implies histologically negative surgical margins, and is necessary to optimize local control. Local tumor control may be achieved either through limb-sparing resection or limb amputation. In selected cases, amputation may be the most appropriate option to achieve this goal. However, limb-sparing resection is preferred if reasonable functional outcomes can be achieved. Final pathologic evaluation should include assessment of surgical margins and size/dimensions of tumor. The response to the preoperative regimen should be evaluated using pathologic mapping. Consultation with a physiatrist is recommended to evaluate for mobility training and to prescribe an appropriate rehabilitation program.

Radiation Therapy

RT is used either as an adjuvant to surgery for patients with resectable tumors or as definitive therapy in patients with tumors not amenable to surgery. Specialized techniques such as intensity-modulated radiation therapy (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; stereotactic radiosurgery (SRS); or fractionated stereotactic radiotherapy (FSRT) should be considered as clinically indicated to deliver high radiation doses while maximizing normal tissue-sparing. RT should be administered at the same specialized center that is providing surgical and systemic interventions. See “Principles of Radiation Therapy” in the full version of these guidelines for treatment volumes and radiation doses specific to each subtype (to view the most recent version of these guidelines, visit NCCN.org).

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Chordoma

Chordomas arise from the embryonic remnants of the notochord and are more common in older adults. Chordomas predominantly arise in the axial skeleton, with the sacrum (50%–60%), skull base (25%–35%), and spine (15%) the most common primary sites.^{6,50} Chordomas are classified into 3 histologic variants: conventional, chondroid, and dedifferentiated. Conventional chordomas are the most common histologic subtype, characterized by the absence of cartilaginous or mesenchymal components. Chondroid chordomas present with histologic features of chordoma and cartilage elements, accounting for 5% to 15% of all chordomas. Dedifferentiated chordomas constitute approximately 2% to 8% of all chordomas and have features of high-grade spindle cell sarcoma and an aggressive clinical course.⁵⁰

Chordomas of the spine and sacrum present with localized deep pain or radiculopathies, whereas cervical chordomas can cause airway obstruction or dysphagia and might present as an oropharyngeal mass. Neurologic deficit is more often associated with chordomas of the skull base and mobile spine than with chordomas of the sacrococcygeal region.⁶

Workup

Initial workup should include a history and physical examination with adequate imaging (radiograph, CT, and MRI) of the primary site, screening MRI of spinal axis, and CT scan of the chest, abdomen, and pelvis. PET scan or bone scan (if PET scan is negative) can be considered for unusual cases. Benign notochordal cell tumors (BNCTs) are considered precursors to chordomas and do not require surgical management.^{51,52} CT scan and MRI may be useful in distinguishing BNCTs from chordomas.^{53,54}

For skull base chordomas, CT is useful to delineate bone destruction and the presence of calcifications, whereas MRI is the preferred modality for defining the tumor margin from brain, characterizing the position and extension of tumors into the adjacent soft tissue structures, and visualizing blood vessels.^{55,56} For sacrococcygeal chordomas, CT and MRI are useful for assessing soft tissue involvement, calcifications, and epidural extension.^{57–59} MRI provides more precise and superior contrast with surrounding soft tissues compared with CT, and is helpful to assess recurrent or metastatic lesions.^{57,58}

CT is also of particular importance to assess bony involvement, calcifications, and soft tissue and epidural extension of spinal chordomas, whereas MRI is the best imaging modality to detect tumor extension, cord compression, local recurrence, and residual tumor in the surgical scar tissue after surgical resection.^{60,61} CT scan is also useful in planning the reconstruction of the resistant osseous defect in tumors of the proximal sacrum.

Biopsy to confirm histologic subtype should be performed after imaging studies and may vary depending on the anatomic location of the tumor. Needle biopsy is not recommended for skull base tumors. Suspected sacral chordomas should be biopsied dorsally rather than transrectally.

Treatment

Surgery: Wide excision with adequate margins is the preferred primary treatment for patients with chordoma.^{62,63} A recent retrospective analysis of 962 patients with chordoma identified in the SEER database demonstrated that surgery significantly improves the overall survival (OS).⁶³ Several other reports have confirmed the prognostic significance of wide surgical margins, in terms of relapse-free survival and OS, in patients with chordomas of the sacrum,^{64–66} skull base^{67–71} and spine.^{66,72}

Among patients with chordoma of the mobile spine, Boriani et al⁷² reported that only margin-free en bloc resection was associated with continuous disease-free survival (DFS) with a follow-up of longer than 5 years; 12 of 18 patients were continuously disease-free at an average of 8 years after en bloc resection, whereas all patients who were treated with intralesional excision experienced recurrences in less than 2 years. In patients with chordomas of the sacrum and spine, Ruggieri et al⁶⁵ reported a local recurrence rate of only 17% after wide surgical margins compared with 81% after intralesional excision or marginal surgery. Tzortzidis et al⁶⁸ reported that aggressive microsurgical resection is associated with long-term, tumor-free survival with good functional outcome in patients with cranial base chordomas; gross total removal was achieved in 72% of patients, resulting in local control rates of 50%. In a recent 10-year meta-analysis that included 802 patients with skull base chordomas, Di Maio et al⁷¹ reported that those with incomplete resection were 3.83 times more likely to experience a recurrence at 5 years than those with complete resection.

Radiation Therapy: RT (preoperative, postoperative, or intraoperative) is used in combination with surgery to improve local control and DFS for patients with resectable sacral and skull base chordomas.^{67,73–78} In a retrospective series involving 24 patients with sacral and spine chordomas, combination of short-course preoperative RT, resection, and reduced-field high-dose postoperative RT resulted in 5-year DFS and local control rates of 54% and 72%, respectively.⁷⁵ In a more recent retrospective series of 15 patients with sacrococcygeal chordoma who underwent surgical treatment, intralesional resection with postoperative RT was associated with lower local recurrence rates (20%) than extralesional resection without RT (100%, with a mean time to recurrence of 2 years); the time to recurrence was also significantly longer in patients who received RT after surgery.⁷⁷ RT in combination with surgery is also associated with improved local recurrence rates in patients with conventional or chondroid chordomas of the skull base.^{74,76}

Particle beam RT (either alone or in combination with photon beam RT) with high-energy protons^{79–87} or carbon ions^{88–92} has resulted in local control rates ranging from 62% to 81% in patients with skull base and extracranial chordomas involving the spine and sacrum. In patients with sacral chordomas tumors treated with a combination of high-energy proton and photon beam RT, local control rates were higher in patients with primary tumors compared with those with recurrent tumors.⁸⁵ Carbon ion RT also resulted in preservation of urinary and anorectal function compared with surgery in patients with sacral chordomas.⁹²

Specialized techniques such as IMRT, SRS, and FSRT have also been associated with good local control rates in cranial and extracranial chordomas.^{93–97}

Systemic Therapy: Chordomas are not sensitive to chemotherapy except for the potentially dedifferentiated portion of high-grade dedifferentiated chordomas.⁹⁸ Several signal transduction pathways, including platelet-derived growth factor receptor, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR), have been implicated in the pathogenesis of chordomas, leading to the development of targeted therapies.^{99,100}

In a phase II trial of 56 patients with advanced chordoma treated with imatinib, 70% of patients had stable disease. The clinical benefit rate as deter-

mined based on RECIST criteria (complete response + partial response and stable disease ≥ 6 months) was 64%, and the median progression-free survival (PFS) in the intention-to-treat population was 9 months.³⁶ Imatinib in combination with cisplatin or sirolimus has also been effective in small series of patients with advanced chordoma resistant to prior imatinib therapy.^{101,102} The efficacy of EGFR inhibitors such as gefitinib, erlotinib, and cetuximab in patients with advanced chordoma resistant to imatinib has also been demonstrated in case reports.^{103–105}

NCCN Recommendations: Tumor location is the most important variable determining the choice of primary treatment for patients with conventional or chondroid chordomas. Dedifferentiated chordomas are usually managed as described in the NCCN Guidelines for Soft Tissue Sarcoma (to view the most recent version of these guidelines, visit NCCN.org).

Wide excision, with or without RT, is the primary treatment option for patients with resectable conventional or chondroid chordomas of the sacrum and mobile spine.^{62,63} Intralesional excision with or without RT (followed by MRI to assess the adequacy of resection) is the preferred treatment for patients with resectable skull base tumors of conventional or chondroid histology. Maximal safe resection is recommended when appropriate.⁷⁰ Adjuvant treatment with RT can be considered for large extracompartmental tumors or for positive surgical margins after resection. Postoperative RT has been associated with improved local control and DFS after surgery with macroscopic surgical margins or intralesional excision.^{73,76,77,106,107} Re-resection, if necessary, can be considered for skull base tumors with positive surgical margins.

RT is the primary treatment option for patients with unresectable chordomas, irrespective of the tumor location.

Surveillance

Surveillance consists of a physical examination, imaging (radiograph, MRI with or without CT) of the surgical site as clinically indicated, chest imaging (every 6 months for 5 years and annually thereafter), and annual cross-sectional abdominal imaging.

Relapsed Disease

Chordomas are characterized by a high rate of local recurrence, and distant metastases to lungs, bone, soft tissue, lymph nodes, liver, and skin have been reported in up to 40% of patients with local recur-

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rence.^{64,79,108,109} Among patients with recurrent chordomas of skull base and spine, Fagundes et al⁷⁹ reported a higher 2-year actuarial OS rate for patients treated with subtotal resection than those who received supportive care only (63% and 21%, respectively; $P=.001$). However, some studies have reported that surgery and RT are associated with lower local control rates for recurrent tumors compared with primary tumors in patients with sacral chordomas.^{85,95}

Patients with recurrent disease can be managed with surgery and/or RT and/or systemic therapy. The guidelines have included imatinib with or without cisplatin or sirolimus and erlotinib with or without cetuximab as systemic therapy options for patients with recurrent tumors.

Giant Cell Tumor of the Bone

GCTB is a rare benign primary tumor of the bone, accounting for approximately 3% to 5% of all primary bone tumors, with a strong tendency for local recurrence, which may metastasize to the lungs.^{110,111} GCTB usually occurs between 20 and 40 years of age. The distal femur and proximal tibia are the most common primary sites. Malignant transformation to high-grade osteosarcoma has been observed in rare cases and is associated with a poor prognosis.^{112,113}

Workup

Initial workup should include a history and physical examination with adequate imaging (radiograph, CT, and MRI) of the primary site. CT is useful to define the extent of cortical destruction, whereas MRI is the preferred imaging modality to assess the extension of tumors into the adjacent soft tissue and neurovascular structures.^{114,115} Chest imaging is essential to identify the presence of metastatic disease. Bone scan can be considered for unusual cases. Biopsy is essential to confirm the diagnosis. Brown tumor of hyperparathyroidism should be considered as a differential diagnosis, although routine evolution of serum calcium, phosphate, and parathyroid hormone levels can help exclude this diagnosis.¹¹⁶

Treatment

Surgery: Wide excision and intralesional curettage are the 2 surgical treatment options for patients with resectable tumors.^{117–123} Wide excision is associated with a lower risk of local recurrence than intralesional curettage, with the local recurrence rates ranging

from 0% to 12% for wide excision and 12% to 65% for intralesional curettage. In some studies, the extent of intralesional excision and the tumor stage have been identified as prognostic indicators for risk of recurrence.^{124–126} Blackley et al¹²⁵ reported a local recurrence rate of 12% in 59 patients who were treated with curettage with high-speed burr and bone grafting, which was similar to that observed with the use of adjuvants; most of the patients had grade II or III tumors. In another retrospective analysis of 137 patients, Prosser et al¹²⁶ reported local recurrences in 19% patients after curettage as a primary treatment; the local recurrence rate was only 7% for patients with grade I and II tumors confined to the bone, compared with 29% for those with grade III tumors with extraosseous extension.

Surgical adjuvants have been used in conjunction with intralesional curettage to improve local control rates. However, the findings from studies that have evaluated intralesional curettage with and without adjuvant in the same cohort of patients with primary or recurrent GCTB are inconsistent, with some reporting decreased local recurrence rates with the use of adjuvants.^{121,123,127–129} Others, however, have reported no significant difference in local recurrence rates with and without adjuvants.^{130–132}

Wide excision is also associated with poor functional outcome and more surgical complications.^{133–137} Therefore, intralesional curettage is considered the preferred treatment in most patients with stage I or II tumors. Wide excision is usually reserved for more aggressive stage III tumors with extraosseous extension or for otherwise unresectable tumors.^{126,138–141}

Radiation Therapy: RT has been used either as a primary treatment or in combination with surgery to improve local control and DFS for patients with marginally resected, unresectable, progressive, or recurrent disease.^{142–152} In a recent retrospective analysis of 58 patients with GCTB (45 with primary tumor and 13 with recurrent tumor) treated with RT, the 5-year local control and OS rates were 85% and 94%, respectively.¹⁵¹ Median follow-up was 8 years. In this analysis, patient age was the only prognostic factor associated with rates of local control (96% for younger patients vs 73% for the older group), OS (100% vs 87%), and DFS (96% vs 65%). Other studies have identified tumor size greater than 4 cm, recurrent tumors, and RT doses of 40 Gy or less as negative prognostic factors for local control.^{147–149}

Specialized techniques such as 3-dimensional conformal RT and IMRT have also been associated with good local control rates in patients with GCTB in locations that are not amenable to complete surgical resection.^{153,154}

NCCN Recommendations *Localized Disease:* Intralesional excision with or without an effective adjuvant is an adequate primary treatment for resectable tumors.^{130–132}

Serial arterial embolizations have been shown to be effective in the management of patients with giant cell tumors of the extremities, especially for tumors with large cortical defects or joint involvement, and those with large giant cell tumors of the sacrum.^{155–158} A few case reports have reported the efficacy of interferon and pegylated interferon in the management of GCTB.^{159–162} More recently, results of a phase II study of denosumab (a fully humanized monoclonal antibody against the RANK ligand) showed significant activity in patients with unresectable or recurrent GCTB, resulting in tumor response (defined as the elimination of at least 90% of giant cells or no radiologic progression of the target lesion for up to 25 weeks) in 86% (30 of 35) of evaluable patients.^{163,164}

For patients with lesions that are resectable with unacceptable morbidity or unresectable axial lesions, the guidelines have included serial embolizations, denosumab, interferon, or pegylated interferon as primary treatment options. RT has been associated with an increased risk of malignant transformation and should be used in patients with tumors that are not amenable to embolization, denosumab, or interferons.

After primary treatment, patients with stable/improved disease can be observed. For patients with stable/improved disease with incomplete healing after primary treatment, intralesional excision is recommended if the lesion has become resectable. Patients with unresectable disease should be treated with denosumab. The guidelines recommend continuation of denosumab until disease progression in patients experiencing response.

Metastatic Disease: For patients presenting with resectable metastases, the guidelines recommend that the primary tumor be managed as described for localized disease.^{110,111,165,166} Intralesional excision is recommended for resectable metastatic sites. Denosumab, interferon, or pegylated interferon; observa-

tion; or RT are included as options for patients with unresectable metastases.

Surveillance

Surveillance should include a physical examination, imaging (radiograph, MRI with or without CT) of the surgical site as clinically indicated, and chest imaging every 6 months for 2 years and then annually thereafter.

Recurrent disease (local or metastatic) should be managed as per primary treatment for localized disease or metastatic disease at presentation.

Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor in children and young adults.² The median age for all patients with osteosarcoma is 20 years. In adults older than 65 years, osteosarcoma develops as a secondary malignancy related to Paget disease of the bone.¹⁶

Osteosarcoma constitutes a family of lesions with a variety of histologic features and natural histories. Osteosarcomas are broadly classified into intramedullary, surface, and extraskeletal.¹⁶⁷ High-grade intramedullary osteosarcoma is the classic or conventional form, constituting nearly 80% of osteosarcomas.¹⁶⁷ It is a spindle cell tumor that produces osteoid or immature bone. The most frequent sites are the metaphyseal areas of the distal femur or proximal tibia, which are the sites of maximum growth. Low-grade intramedullary osteosarcoma constitutes fewer than 2% of all osteosarcomas, and the most common sites are similar to those of conventional osteosarcoma.¹⁶⁸

Parosteal and periosteal osteosarcomas are juxtacortical or surface variants. Parosteal osteosarcomas are low-grade lesions accounting for up to 5% of all osteosarcomas.¹⁶⁸ The most common site is the posterior distal femur. This variant tends to metastasize later than the conventional form. Transformation of low-grade parosteal osteosarcoma into high-grade sarcoma has been documented in 24% to 43% of cases.^{169,170} Periosteal osteosarcomas are intermediate-grade lesions most often involving the femur followed by the tibia.¹⁶⁸ High-grade surface osteosarcomas are rare, accounting for 10% of all juxtacortical osteosarcomas.^{171,172} Pain and swelling are the most frequent early symptoms. Pain is often intermittent in the beginning and a thorough work-up sometimes is delayed because symptoms may be

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confused with growing pains. Osteosarcoma spreads hematogenously, with the lung being the most common metastatic site.

Prognostic Factors

Tumor site and size; patient age; presence and location of metastases; histologic response to chemotherapy; type of surgery; and surgical margins are significant prognostic factors for patients with osteosarcoma of the extremities and trunk.^{173–178} In an analysis of 1702 patients with osteosarcoma of the trunk or extremities treated in the Cooperative Osteosarcoma Study Group (COSS) protocols, patient age at diagnosis, tumor site, and primary metastases were identified as predictors of survival.¹⁷⁵ In patients with extremity osteosarcomas, size and location of the tumor within the limb at diagnosis also had a significant influence on outcome.¹⁷⁵ All factors except age were significant in multivariate testing, with surgical remission and histologic response to chemotherapy emerging as the key prognostic factors. In a recent report of the combined analysis of 3 European Osteosarcoma Intergroup randomized controlled trials, Whelan et al¹⁷⁸ reported that good histologic response to preoperative chemotherapy, distal location (other than proximal humerus/femur), and female sex were associated with improved survival.

In patients with proven primary metastatic osteosarcoma, the number of metastases at diagnosis and the completeness of surgical resection of all clinically detected tumor sites are of independent prognostic value.²⁴ Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients with no metastatic disease.^{179,180}

Elevated serum ALP and LDH levels have also been identified as prognostic indicators in patients with osteosarcoma.^{174,176,177} In a cohort of 1421 patients with osteosarcoma of the extremity, Bacci et al¹⁷⁶ reported significantly higher serum LDH levels in patients with metastatic disease at presentation than in those with localized disease (36.6% vs 18.8%; $P < .0001$). The 5-year DFS correlated with serum LDH level (39.5% for patients with high LDH levels and 60% for those with normal values). In another retrospective analysis of 789 patients with osteosarcoma of the extremity, Bacci et al¹⁷⁷ reported that the serum ALP level was a significant prognostic factor of event-free survival (EFS) in patients with osteosarcoma of extremity; the 5-year EFS rate was 24% for patients with a serum ALP value more than

4 times higher than the normal value, and 46% for patients with high values below this limit ($P < .001$). However, in multivariate analysis, these markers did not retain their prognostic significance when compared with tumor volume, age, and histologic response to chemotherapy.^{174,176}

Workup

Osteosarcomas present both a local problem and a concern for distant metastasis. Initial workup should include imaging of the primary site (MRI, with or without CT), chest imaging, PET scan, and/or bone scan. More detailed imaging (CT or MRI) of abnormalities identified on primary imaging is required for suspected metastatic disease.

Plain radiographs of osteosarcomas show cortical destruction and irregular reactive bone formation. Bone scan, although uniformly abnormal at the lesion, may be useful to identify additional synchronous lesions. MRI provides excellent soft tissue contrast and may be essential for operative planning. MRI is the best imaging modality to define the extent of the lesion within the bone and soft tissues, detect “skip” metastases, and evaluate anatomic relationships with the surrounding structures. In addition, ALP and LDH are frequently elevated in patients with osteosarcoma. Serum LDH was significantly higher in patients with metastatic disease at presentation than in patients with localized disease.¹⁷⁶

Treatment

Surgery: Surgery (limb-sparing surgery or amputation) remains an essential part of management of patients with osteosarcoma.¹⁸¹ Studies that have compared limb-sparing surgery and amputation in patients with high-grade nonmetastatic osteosarcoma have not shown any significant difference in survival and local recurrence rates.^{182–184} However, limb-sparing surgery is associated with better functional outcomes.¹⁸⁵ In patients with high-grade osteosarcomas with good histologic response to neoadjuvant chemotherapy, limb-sparing surgery is considered the preferred surgical modality if wide surgical margins could be achieved.^{182,186} Amputation is generally reserved for patients with tumors in unfavorable anatomic locations not amenable to limb-sparing surgery with adequate surgical margins.^{181,186}

Chemotherapy: The addition of adjuvant and neoadjuvant chemotherapy regimens to surgery has improved outcomes in patients with localized osteo-

sarcoma. Early trials used chemotherapy regimens including at least 3 or more of the following drugs: doxorubicin, cisplatin, bleomycin, cyclophosphamide or ifosfamide, dactinomycin, and high-dose methotrexate.^{187–192} Subsequent clinical trials have demonstrated that short intensive chemotherapy regimens including cisplatin and doxorubicin with or without high-methotrexate and ifosfamide produce excellent long-term results, similar to those that have been achieved with multiagent chemotherapy.^{193–200}

In a randomized trial conducted by the European Osteosarcoma Group, the combination of doxorubicin and cisplatin was better tolerated compared with a multidrug regimen, with no difference in survival between the groups in patients with operable, non-metastatic osteosarcoma.¹⁹⁴ In both groups, the 3- and 5-year OS rates were 65% and 55%, respectively, and the 5-year PFS rate was 44%. In the INT-0133 study, which compared the 3-drug regimen (cisplatin, doxorubicin, and methotrexate) with the 4-drug regimen (cisplatin, doxorubicin, methotrexate, and ifosfamide) for the treatment of patients with non-metastatic resectable osteosarcoma, no difference was seen in 6-year EFS rates (63% and 64%, respectively) and OS rates (74% and 70%, respectively) between the groups.²⁰⁰

Chemotherapy regimens without doxorubicin or cisplatin have also been evaluated in patients with localized osteosarcoma with the goal of minimizing long-term cardiotoxicity and ototoxicity.^{201,202} In a phase II study, the combination of cisplatin, ifosfamide, and epirubicin was active and reasonably well tolerated in patients with nonmetastatic osteosarcoma of the extremity.²⁰¹ With a median follow-up of 64 months, the 5-year DFS and OS rates were 41.9% and 48.2%, respectively. In another randomized multicenter trial (SFOP-OS94), the combination of ifosfamide and etoposide resulted in a higher histologic response rate than the regimen containing high-dose methotrexate and doxorubicin (56% and 39%, respectively). However, the 5-year OS was similar in both arms and no significant difference was seen in 5-year EFS rates.²⁰² Good histopathologic response (>90% necrosis) to neoadjuvant chemotherapy has been shown to be predictive of survival regardless of the type of chemotherapy administered after surgery.^{176,203} In an analysis of 881 patients with nonmetastatic osteosarcoma of the extremities treat-

ed with neoadjuvant chemotherapy and surgery at the Rizzoli Institute, Bacci et al²⁰⁴ showed that the 5-year DFS and OS correlated significantly with histologic response to chemotherapy. The 5-year DFS and OS rates in good and poor responders were 67.9% versus 51.3% ($P<.0001$) and 78.4% versus 63.7% ($P<.0001$), respectively. A report from the Children's Oncology Group also confirmed these findings; the 8-year postoperative EFS and OS rates were 81% and 87%, respectively, in good responders.²⁰³ The corresponding survival rates were 46% and 52%, respectively, in poor responders.

The addition of muramyl tripeptide phosphatidyl-ethanolamine (MTP-PE) to chemotherapy has also been evaluated in patients with osteosarcoma.^{200,205} The addition of MTP-PE to chemotherapy was associated with a statistically significant improvement in 6-year OS (from 70% to 78%) and a trend toward better EFS in patients with nonmetastatic resectable osteosarcoma.²⁰⁰ However, the improvement was not statistically different in patients with metastatic disease.²⁰⁵ MTP-PE is not approved by the FDA for the treatment of patients with osteosarcoma.

Localized Disease

The guidelines recommend wide excision as the primary treatment for patients with low-grade (intramedullary and surface) osteosarcomas and periosteal lesions. Chemotherapy before wide excision could be considered for patients with periosteal lesions. Although chemotherapy (neoadjuvant or adjuvant) has been used in the treatment of patients with periosteal osteosarcoma, no data support that the addition of chemotherapy to wide excision improves outcome in patients with periosteal osteosarcoma.^{206,207} In a review of 119 patients with periosteal sarcoma published by the European Musculoskeletal Oncology Society, the use of neoadjuvant chemotherapy was not a prognostic factor, although it was used in most of the patients.²⁰⁷ More recently, Cesari et al²⁰⁶ also reported similar findings; the 10-year OS rate was 86% and 83% for patients who received adjuvant chemotherapy with surgery and those who underwent surgery alone, respectively ($P=.73$). After wide excision (of resectable lesions), the guidelines have included postoperative chemotherapy with a category 2B recommendation for patients with low-grade (intramedullary and surface) or periosteal sarcomas with pathologic findings of high-grade disease.

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Preoperative chemotherapy before wide excision is preferred for patients with high-grade osteosarcoma (category 1).^{193–202} Selected elderly patients may benefit from immediate surgery. After wide excision, patients with a good histologic response (amount of viable tumor <10% of the tumor area) should continue to receive several more cycles of the same chemotherapy. Patients with a poor response (viable tumor ≥10% of the tumor area) could be considered for chemotherapy with a different regimen. However, attempts to improve the outcome of poor responders through modifying the adjuvant chemotherapy remain unsuccessful.^{208–211} Surgical re-resection with or without RT can be considered for positive surgical margins. An ongoing randomized trial of the European and American Osteosarcoma Study Group is evaluating treatment strategies for resectable osteosarcoma based on histologic response to preoperative chemotherapy.

RT or adjuvant chemotherapy is recommended if the sarcoma remains unresectable after preoperative chemotherapy. Proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.²¹²

Chemotherapy should include appropriate growth factor support (see the NCCN Guidelines for Myeloid Growth Factors for growth factor support; to view the most recent version of these guidelines, visit NCCN.org). A list of specific chemotherapy regimens is available in “Bone Cancer Systemic Therapy Agents” on pages 702–703.

Metastatic Disease at Presentation

Approximately 10% to 20% of patients present with metastatic disease at diagnosis.^{24,213} The number of metastases at diagnosis and complete surgical resection of all clinically detected tumor sites are of independent prognostic value in patients with primary metastatic disease at presentation.²⁴ Unilateral metastases and lower number of lung nodules were associated with improved outcomes with chemotherapy in patients with synchronous lung metastases.^{179,180} The 2-year DFS rate was significantly higher for patients with only 1 or 2 metastatic lesions than for those with 3 or more lesions (78% and 28%, respectively).¹⁷⁹

Although chemotherapy is associated with improved outcomes in those with nonmetastatic high-grade localized osteosarcoma, the results were significantly poorer in those with metastatic disease

at presentation.^{213–215} In a study of 57 patients with metastatic disease at presentation treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide, the 2-year EFS and OS rates were 21% and 55%, respectively, compared with 75% and 94% in patients with nonmetastatic disease at presentation, treated with the same chemotherapy protocol.²¹⁵

Among patients with primary metastases treated in cooperative osteosarcoma trials, long-term survival rates were higher for those whose metastases were excised after chemotherapy and surgery of the primary tumor compared with those whose metastases could not be removed (48% and 5%, respectively).²¹⁶ The combination of aggressive chemotherapy with simultaneous resection of primary and metastatic lesions has also resulted in improved outcomes in patients with osteosarcoma of the extremity with lung metastases at presentation.²¹⁷

For patients with resectable metastases (pulmonary, visceral, or skeletal) at presentation, the guidelines recommend preoperative chemotherapy followed by wide excision of the primary tumor. Chemotherapy and metastasectomy are included as options for the management of metastatic disease. Unresectable metastatic disease should be managed with chemotherapy and/or RT followed by reassessment of the primary site for local control.

Surveillance

Once treatment is completed, surveillance should occur every 3 months for 2 years, then every 4 months for year 3, every 6 months for years 4 and 5, and annually thereafter. Surveillance should include a complete physical, chest imaging, and imaging of the primary site. PET scan and/or bone scan (category 2B) may also be considered. Functional reassessment should be performed at every visit.

Relapsed or Refractory Disease

Approximately 30% of patients with localized disease and 80% of patients presenting with metastatic disease will experience relapse. The presence of solitary metastases, longer time to first relapse, and complete resectability of the disease at first recurrence have been reported to be the most important prognostic indicators for improved survival, whereas patients not amenable to surgery and those with a second or a third recurrence have a poor prognosis.^{218–222} In patients with primary nonmetastatic

osteosarcoma, a longer relapse-free interval to pulmonary metastases was significantly associated with better survival.²²¹ The prognostic significance of surgical clearance among patients with second and subsequent recurrences was also confirmed in a recent report of survival estimates derived from large cohorts of unselected patients treated in the COSS group trials.²²³

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials.^{224,225} In a phase II trial of French Society of Pediatric Oncology, ifosfamide and etoposide resulted in a response rate of 48% in patients with relapsed or refractory osteosarcoma.²²⁵ In another phase II trial, cyclophosphamide and etoposide resulted in a 19% response rate and a 35% rate of stable disease in patients with relapsed high-risk osteosarcoma.²²⁴ PFS at 4 months was 42%. Single-agent gemcitabine and combination regimens such as docetaxel and gemcitabine; cyclophosphamide and topotecan; and ifosfamide, carboplatin, and etoposide have also been effective in the treatment of patients with relapsed or refractory bone sarcomas.^{226–229}

Samarium-153 ethylene diamine tetramethylene phosphonate (¹⁵³Sm-EDTMP), a bone seeking radiopharmaceutical, has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases.^{230,231} Anderson et al²³⁰ reported that ¹⁵³Sm-EDTMP with peripheral blood progenitor cell support had low nonhematologic toxicity and provided pain palliation for patients with osteosarcoma local recurrences or osteoblastic bone metastases.²³⁰ Results of a recent dose-finding study also showed that ¹⁵³Sm-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.²³¹

Targeted inhibition of a variety of molecular pathways, such as insulin-like growth factor 1 receptor (IGF-1R), mTOR, SRC family of kinases, and vascular endothelial growth factor receptors (VEGFRs), is being evaluated in clinical trials to improve outcomes in patients with relapsed or refractory osteosarcoma. In a recent phase II trial from the Italian Sarcoma Group (n=30), sorafenib (a VEGFR inhibitor) showed activity in patients with relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy.²³² The PFS at 4 months (primary end point) was 46%. Median PFS and OS were 4 and 7 months, respectively. The clinical benefit rate (defined as no progression at 6

months) was 29%. Partial response and stable disease were seen in 8% and 34% of patients, respectively, and were durable for 6 months or more in 17% of patients.

The safety and efficacy of high-dose chemotherapy/autologous stem cell transplantation has also been evaluated in patients with locally advanced, metastatic, or relapsed sarcoma.^{233,234} In the Italian Sarcoma Group study, treatment with carboplatin and etoposide followed by stem cell rescue, combined with surgery, induced complete response in chemosensitive patients.²³⁴ Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12%, respectively. The efficacy of this approach in high-risk patients has yet to be determined in prospective randomized studies.

The optimal treatment strategy for patients with relapsed or refractory disease has not been defined. If relapse occurs, patients should undergo second-line chemotherapy and/or surgical resection. Based on the results of the recent phase II trial, the guidelines have included sorafenib as a systemic therapy option for patients with relapsed disease.²³² A list of other second-line chemotherapy regimens is provided in “Bone Cancer Systemic Therapy Agents” on pages 702–703. Surveillance is recommended for patients responding to second-line therapy.

Patients experiencing disease progression or relapse after second-line therapy could be managed with resection, palliative RT, or best supportive care. The guidelines have also included ¹⁵³Sm-EDTMP as an option. Participation in a clinical trial should be strongly encouraged.

References

1. Unni KK. Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1996.
2. Chow W, Haglund K, Randall RL. Bone sarcomas. In: Haller DG, Wagman LD, Camphausen C, Hoskins WJ, eds. Cancer Management: A Multidisciplinary Approach Medical, Surgical, & Radiation Oncology. 14th ed. Norwalk, CT: UBM Medical LLC; 2011.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
4. Fletcher D, Unni K, Mertens F. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002.
5. McMaster ML, Goldstein AM, Bromley CM, et al. Chordoma: incidence and survival patterns in the United States, 1973–1995. Cancer Causes Control 2001;12:1–11.

Bone Cancer

6. Walcott BP, Nahed BV, Mohyeldin A, et al. Chordoma: current concepts, management, and future directions. *Lancet Oncol* 2012;13:e69–76.
7. de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. *J Clin Oncol* 2000;18:204–213.
8. Delattre O, Zucman J, Melot T, et al. The Ewing family of tumors—a subgroup of small-round-cell tumors defined by specific chimeric transcripts. *N Engl J Med* 1994;331:294–299.
9. Denny CT. Gene rearrangements in Ewing's sarcoma. *Cancer Invest* 1996;14:83–88.
10. Burchill SA. Molecular abnormalities in Ewing's sarcoma. *Expert Rev Anticancer Ther* 2008;8:1675–1687.
11. Calvert GT, Randall RL, Jones KB, et al. At-risk populations for osteosarcoma: the syndromes and beyond. *Sarcoma* 2012;2012:152382.
12. Martin JW, Squire JA, Zielenska M. The genetics of osteosarcoma. *Sarcoma* 2012;2012:627254.
13. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990;250:1233–1238.
14. McIntyre JF, Smith-Sorensen B, Friend SH, et al. Germline mutations of the p53 tumor suppressor gene in children with osteosarcoma. *J Clin Oncol* 1994;12:925–930.
15. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. *Cancer* 2012;118:1387–1396.
16. Ottaviani G, Jaffe N. The etiology of osteosarcoma. *Cancer Treat Res* 2009;152:15–32.
17. MacCarthy A, Bayne AM, Draper GJ, et al. Non-ocular tumours following retinoblastoma in Great Britain 1951 to 2004. *Br J Ophthalmol* 2009;93:1159–1162.
18. Kalra S, Grimer RJ, Spooner D, et al. Radiation-induced sarcomas of bone: factors that affect outcome. *J Bone Joint Surg Br* 2007;89:808–813.
19. Mavrogenis AF, Pala E, Guerra G, Ruggieri P. Post-radiation sarcomas. Clinical outcome of 52 Patients. *J Surg Oncol* 2012;105:570–576.
20. Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. *Oncologist* 2006;11:503–519.
21. Subbiah V, Anderson P, Lazar AJ, et al. Ewing's sarcoma: standard and experimental treatment options. *Curr Treat Options Oncol* 2009;10:126–140.
22. Federman N, Bernthal N, Eilber FC, Tap WD. The multidisciplinary management of osteosarcoma. *Curr Treat Options Oncol* 2009;10:82–93.
23. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol* 2000;18:3108–3114.
24. 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.
25. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res* 1980;106–120.
26. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917–2931.
27. Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin. A prospective study of a diagnostic strategy. *J Bone Joint Surg Am* 1993;75:1276–1281.
28. Heck RK, Peabody TD, Simon MA. Staging of primary malignancies of bone. *CA Cancer J Clin* 2006;56:366–375.
29. Kumar J, Seith A, Kumar A, et al. Whole-body MR imaging with the use of parallel imaging for detection of skeletal metastases in pediatric patients with small-cell neoplasms: comparison with skeletal scintigraphy and FDG PET/CT. *Pediatr Radiol* 2008;38:953–962.
30. Daldrop-Link HE, Franzius C, Link TM, et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG PET. *AJR Am J Roentgenol* 2001;177:229–236.
31. Schuetze SM. Utility of positron emission tomography in sarcomas. *Curr Opin Oncol* 2006;18:369–373.
32. Volker T, Denecke T, Steffen I, et al. Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. *J Clin Oncol* 2007;25:5435–5441.
33. Hawkins DS, Rajendran JG, Conrad EU, et al. Evaluation of chemotherapy response in pediatric bone sarcomas by [F-18]-fluorodeoxy-D-glucose positron emission tomography. *Cancer* 2002;94:3277–3284.
34. Hawkins DS, Schuetze SM, Butrynski JE, et al. [18F] Fluorodeoxyglucose positron emission tomography predicts outcome for Ewing sarcoma family of tumors. *J Clin Oncol* 2005;23:8828–8834.
35. Hawkins DS, Conrad EU 3rd, Butrynski JE, et al. [F-18]-fluorodeoxy-D-glucose-positron emission tomography response is associated with outcome for extremity osteosarcoma in children and young adults. *Cancer* 2009;115:3519–3525.
36. Stacchiotti S, Longhi A, Ferraesi V, et al. Phase II study of imatinib in advanced chordoma. *J Clin Oncol* 2012;30:914–920.
37. Mammar H, Kerrou K, Nataf V, et al. Positron emission tomography/computed tomography imaging of residual skull base chordoma before radiotherapy using fluoromisonidazole and fluorodeoxyglucose: potential consequences for dose painting. *Int J Radiat Oncol Biol Phys* 2012;84:681–687.
38. Liu PT, Valadez SD, Chivers FS, et al. Anatomically based guidelines for core needle biopsy of bone tumors: implications for limb-sparing surgery. *Radiographics* 2007;27:189–205; discussion 206.
39. Huang AJ, Kattapuram SV. Musculoskeletal neoplasms: biopsy and intervention. *Radiol Clin North Am* 2011;49:1287–1305.
40. Ashford RU, McCarthy SW, Scolyer RA, et al. Surgical biopsy with intra-operative frozen section. An accurate and cost-effective method for diagnosis of musculoskeletal sarcomas. *J Bone Joint Surg Br* 2006;88:1207–1211.
41. Skrzynski MC, Biermann JS, Montag A, Simon MA. Diagnostic accuracy and charge-savings of outpatient core needle biopsy compared with open biopsy of musculoskeletal tumors. *J Bone Joint Surg Am* 1996;78:644–649.
42. Welker JA, Henshaw RM, Jelinek J, et al. The percutaneous needle biopsy is safe and recommended in the diagnosis of musculoskeletal masses. *Cancer* 2000;89:2677–2686.
43. Mitsuyoshi G, Naito N, Kawai A, et al. Accurate diagnosis of musculoskeletal lesions by core needle biopsy. *J Surg Oncol* 2006;94:21–27.
44. Adams SC, Potter BK, Pitcher DJ, Temple HT. Office-based core needle biopsy of bone and soft tissue malignancies: an accurate

Bone Cancer

- alternative to open biopsy with infrequent complications. *Clin Orthop Relat Res* 2010;468:2774–2780.
45. Gogna A, Peh WC, Munk PL. Image-guided musculoskeletal biopsy. *Radiol Clin North Am* 2008;46:455–473, v.
 46. Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. *J Bone Joint Surg Am* 1996;78:656–663.
 47. Davies NM, Livesley PJ, Cannon SR. Recurrence of an osteosarcoma in a needle biopsy track. *J Bone Joint Surg Br* 1993;75:977–978.
 48. Saghieh S, Masrouha KZ, Musallam KM, et al. The risk of local recurrence along the core-needle biopsy tract in patients with bone sarcomas. *Iowa Orthop J* 2010;30:80–83.
 49. Yang YJ, Damron TA. Comparison of needle core biopsy and fine-needle aspiration for diagnostic accuracy in musculoskeletal lesions. *Arch Pathol Lab Med* 2004;128:759–764.
 50. Chugh R, Tawbi H, Lucas DR, et al. Chordoma: the nonsarcoma primary bone tumor. *Oncologist* 2007;12:1344–1350.
 51. Yamaguchi T, Suzuki S, Ishiwa H, Ueda Y. Intraosseous benign notochordal cell tumours: overlooked precursors of classic chordomas? *Histopathology* 2004;44:597–602.
 52. Deshpande V, Nielsen GP, Rosenthal DI, Rosenberg AE. Intraosseous benign notochord cell tumors (BNCT): further evidence supporting a relationship to chordoma. *Am J Surg Pathol* 2007;31:1573–1577.
 53. Yamaguchi T, Iwata J, Sugihara S, et al. Distinguishing benign notochordal cell tumors from vertebral chordoma. *Skeletal Radiol* 2008;37:291–299.
 54. Nishiguchi T, Mochizuki K, Ohsawa M, et al. Differentiating benign notochordal cell tumors from chordomas: radiographic features on MRI, CT, and tomography. *AJR Am J Roentgenol* 2011;196:644–650.
 55. Meyers SP, Hirsch WL Jr, Curtin HD, et al. Chordomas of the skull base: MR features. *AJNR Am J Neuroradiol* 1992;13:1627–1636.
 56. Weber AL, Liebsch NJ, Sanchez R, Sweriduk ST Jr. Chordomas of the skull base. Radiologic and clinical evaluation. *Neuroimaging Clin N Am* 1994;4:515–527.
 57. Rosenthal DI, Scott JA, Mankin HJ, et al. Sacrococcygeal chordoma: magnetic resonance imaging and computed tomography. *AJR Am J Roentgenol* 1985;145:143–147.
 58. Plathow C, Weber MA, Debus J, Kauczor HU. [Imaging of sacral chordoma: comparison between MRI and CT]. *Radiologe* 2005;45:63–68.
 59. Sung MS, Lee GK, Kang HS, et al. Sacrococcygeal chordoma: MR imaging in 30 patients. *Skeletal Radiol* 2005;34:87–94.
 60. Meyer JE, Lepke RA, Lindfors KK, et al. Chordomas: their CT appearance in the cervical, thoracic and lumbar spine. *Radiology* 1984;153:693–696.
 61. Ducou le Pointe H, Brugieres P, Chevalier X, et al. Imaging of chordomas of the mobile spine. *J Neuroradiol* 1991;18:267–276.
 62. Ferraresi V, Nuzzo C, Zoccali C, et al. Chordoma: clinical characteristics, management and prognosis of a case series of 25 patients. *BMC Cancer* 2010;10:22.
 63. Jawad MU, Scully SP. Surgery significantly improves survival in patients with chordoma. *Spine (Phila Pa 1976)* 2010;35:117–123.
 64. Fuchs B, Dickey ID, Yaszemski MJ, et al. Operative management of sacral chordoma. *J Bone Joint Surg Am* 2005;87:2211–2216.
 65. Ruggieri P, Angelini A, Ussia G, et al. Surgical margins and local control in resection of sacral chordomas. *Clin Orthop Relat Res* 2010;468:2939–2947.
 66. Stacchiotti S, Casali PG, Lo Vullo S, et al. Chordoma of the mobile spine and sacrum: a retrospective analysis of a series of patients surgically treated at two referral centers. *Ann Surg Oncol* 2010;17:211–219.
 67. Forsyth PA, Cascino TL, Shaw EG, et al. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. *J Neurosurg* 1993;78:741–747.
 68. Tzortzidis F, Elahi F, Wright D, et al. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. *Neurosurgery* 2006;59:230–237.
 69. Sen C, Triana AI, Berglind N, et al. Clival chordomas: clinical management, results, and complications in 71 patients. *J Neurosurg* 2010;113:1059–1071.
 70. Wu Z, Zhang J, Zhang L, et al. Prognostic factors for long-term outcome of patients with surgical resection of skull base chordomas-106 cases review in one institution. *Neurosurg Rev* 2010;33:451–456.
 71. Di Maio S, Temkin N, Ramanathan D, Sekhar LN. Current comprehensive management of cranial base chordomas: 10-year meta-analysis of observational studies. *J Neurosurg* 2011;115:1094–1105.
 72. Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: fifty years of experience. *Spine (Phila Pa 1976)* 2006;31:493–503.
 73. Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol* 1996;41:67–72.
 74. Foweraker KL, Burton KE, Maynard SE, et al. High-dose radiotherapy in the management of chordoma and chondrosarcoma of the skull base and cervical spine: Part 1—clinical outcomes. *Clin Oncol (R Coll Radiol)* 2007;19:509–516.
 75. Wagner TD, Kobayashi W, Dean S, et al. Combination short-course preoperative irradiation, surgical resection, and reduced-field high-dose postoperative irradiation in the treatment of tumors involving the bone. *Int J Radiat Oncol Biol Phys* 2009;73:259–266.
 76. Jian BJ, Bloch OG, Yang I, et al. Adjuvant radiation therapy and chondroid chordoma subtype are associated with a lower tumor recurrence rate of cranial chordoma. *J Neurooncol* 2010;98:101–108.
 77. Moojen WA, Vleggeert-Lankamp CL, Krol AD, Dijkstra SP. Long-term results: adjuvant radiotherapy in en bloc resection of sacrococcygeal chordoma is advisable. *Spine (Phila Pa 1976)* 2011;36:E656–661.
 78. Potluri S, Jefferies SJ, Jena R, et al. Residual postoperative tumour volume predicts outcome after high-dose radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol (R Coll Radiol)* 2011;23:199–208.
 79. Fagundes MA, Hug EB, Liebsch NJ, et al. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys* 1995;33:579–584.
 80. Hug EB, Lored LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999;91:432–439.
 81. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999;175(Suppl 2):57–63.

Bone Cancer

82. Noel G, Habrand JL, Mammar H, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protontherapie D'Orsay experience. *Int J Radiat Oncol Biol Phys* 2001;51:392–398.
83. Noel G, Feuvret L, Ferrand R, et al. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. *Neurosurgery* 2004;55:1252–1260.
84. Noel G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol* 2005;44:700–708.
85. Park L, Delaney TF, Liebsch NJ, et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. *Int J Radiat Oncol Biol Phys* 2006;65:1514–1521.
86. Staab A, Rutz HP, Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys* 2011;81:489–496.
87. Yasuda M, Bresson D, Chibbaro S, et al. Chordomas of the skull base and cervical spine: clinical outcomes associated with a multimodal surgical resection combined with proton-beam radiation in 40 patients. *Neurosurg Rev* 2012;35:171–182.
88. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. *Int J Radiat Oncol Biol Phys* 2004;58:631–640.
89. Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. *Int J Radiat Oncol Biol Phys* 2007;68:449–457.
90. Takahashi S, Kawase T, Yoshida K, et al. Skull base chordomas: efficacy of surgery followed by carbon ion radiotherapy. *Acta Neurochir (Wien)* 2009;151:759–769.
91. Imai R, Kamada T, Sugahara S, et al. Carbon ion radiotherapy for sacral chordoma. *Br J Radiol* 2011;84 Spec No 1:48–54.
92. Nishida Y, Kamada T, Imai R, et al. Clinical outcome of sacral chordoma with carbon ion radiotherapy compared with surgery. *Int J Radiat Oncol Biol Phys* 2011;79:110–116.
93. Gabriele P, Macias V, Stasi M, et al. Feasibility of intensity-modulated radiation therapy in the treatment of advanced cervical chordoma. *Tumori* 2003;89:298–304.
94. Yoneoka Y, Tsumanuma I, Fukuda M, et al. Cranial base chordoma—long term outcome and review of the literature. *Acta Neurochir (Wien)* 2008;150:773–778.
95. Zabel-du Bois A, Nikoghosyan A, Schwahof A, et al. Intensity modulated radiotherapy in the management of sacral chordoma in primary versus recurrent disease. *Radiother Oncol* 2010;97:408–412.
96. Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium. *Neurosurgery* 2011;68:379–389.
97. Bugoci DM, Girvigian MR, Chen JCT, et al. Photon-based Fractionated Stereotactic Radiotherapy for Postoperative Treatment of Skull Base Chordomas. *Am J Clin Oncol* 2012.
98. Fleming GF, Heimann PS, Stephens JK, et al. Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. *Cancer* 1993;72:714–718.
99. Tamborini E, Miselli F, Negri T, et al. Molecular and biochemical analyses of platelet-derived growth factor receptor (PDGFR) B, PDGFRA, and KIT receptors in chordomas. *Clin Cancer Res* 2006;12:6920–6928.
100. Tamborini E, Viridis E, Negri T, et al. Analysis of receptor tyrosine kinases (RTKs) and downstream pathways in chordomas. *Neuro Oncol* 2010;12:776–789.
101. Casali PG, Stacchiotti S, Grosso F, et al. Adding cisplatin (CDDP) to imatinib (IM) re-establishes tumor response following secondary resistance to IM in advanced chordoma [abstract]. *J Clin Oncol* 2007;25:Abstract 10038.
102. Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. *Ann Oncol* 2009;20:1886–1894.
103. Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. *Anticancer Drugs* 2009;20:953–955.
104. Launay SG, Chetaille B, Medina F, et al. Efficacy of epidermal growth factor receptor targeting in advanced chordoma: case report and literature review. *BMC Cancer* 2011;11:423.
105. Linden O, Ehinger M, Kinshult S, et al. Cetuximab and EGFR inhibitors in patients with neurological symptoms due to chordoma (abstract). *J Clin Oncol* 2012;30(Suppl):Abstract 10024.
106. Thieblemont C, Biron P, Rocher F, et al. Prognostic factors in chordoma: role of postoperative radiotherapy. *Eur J Cancer* 1995;31A:2255–2259.
107. Boriani S, Saravanja D, Yamada Y, et al. Challenges of local recurrence and cure in low grade malignant tumors of the spine. *Spine (Phila Pa 1976)* 2009;34:S48–57.
108. Chambers PW, Schwinn CP. Chordoma. A clinicopathologic study of metastasis. *Am J Clin Pathol* 1979;72:765–776.
109. McPherson CM, Suki D, McCutcheon IE, et al. Metastatic disease from spinal chordoma: a 10-year experience. *J Neurosurg Spine* 2006;5:277–280.
110. Dominkus M, Ruggieri P, Bertoni F, et al. Histologically verified lung metastases in benign giant cell tumours—14 cases from a single institution. *Int Orthop* 2006;30:499–504.
111. Viswanathan S, Jambhekar NA. Metastatic giant cell tumor of bone: are there associated factors and best treatment modalities? *Clin Orthop Relat Res* 2010;468:827–833.
112. Anract P, De Pinieux G, Cottias P, et al. Malignant giant-cell tumours of bone. Clinico-pathological types and prognosis: a review of 29 cases. *Int Orthop* 1998;22:19–26.
113. Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. *Cancer* 2003;97:2520–2529.
114. Purohit S, Pardiwala DN. Imaging of giant cell tumor of bone. *Indian J Orthop* 2007;41:91–96.
115. Thomas DM, Skubitz KM. Giant cell tumour of bone. *Curr Opin Oncol* 2009;21:338–344.
116. Werner M. Giant cell tumour of bone: morphological, biological and histogenetical aspects. *Int Orthop* 2006;30:484–489.
117. McDonald DJ, Sim FH, McLeod RA, Dahlin DC. Giant-cell tumor of bone. *J Bone Joint Surg Am* 1986;68:235–242.
118. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. *J Bone Joint Surg Am* 1987;69:106–114.
119. Saiz P, Virkus W, Piasecki P, et al. Results of giant cell tumor of bone treated with intralesional excision. *Clin Orthop Relat Res* 2004;221–226.
120. Malek F, Krueger P, Hatmi ZN, et al. Local control of long bone giant cell tumour using curettage, burring and bone grafting without adjuvant therapy. *Int Orthop* 2006;30:495–498.
121. Kivioja AH, Blomqvist C, Hietaniemi K, et al. Cement is recommended in intralesional surgery of giant cell tumors: a

Bone Cancer

- Scandinavian Sarcoma Group study of 294 patients followed for a median time of 5 years. *Acta Orthop* 2008;79:86–93.
122. Errani C, Ruggieri P, Asenzio MA, et al. Giant cell tumor of the extremity: a review of 349 cases from a single institution. *Cancer Treat Rev* 2010;36:1–7.
 123. Klenke FM, Wenger DE, Inwards CY, et al. Giant cell tumor of bone: risk factors for recurrence. *Clin Orthop Relat Res* 2011;469:591–599.
 124. O'Donnell RJ, Springfield DS, Motwani HK, et al. Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. *J Bone Joint Surg Am* 1994;76:1827–1833.
 125. Blackley HR, Wunder JS, Davis AM, et al. Treatment of giant-cell tumors of long bones with curettage and bone-grafting. *J Bone Joint Surg Am* 1999;81:811–820.
 126. Prosser GH, Baloch KG, Tillman RM, et al. Does curettage without adjuvant therapy provide low recurrence rates in giant-cell tumors of bone? *Clin Orthop Relat Res* 2005:211–218.
 127. Becker WT, Dohle J, Bernd L, et al. Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. *J Bone Joint Surg Am* 2008;90:1060–1067.
 128. Balke M, Schremper L, Gebert C, et al. Giant cell tumor of bone: treatment and outcome of 214 cases. *J Cancer Res Clin Oncol* 2008;134:969–978.
 129. Pietschmann MF, Dietz RA, Utschneider S, et al. The influence of adjuvants on local recurrence rate in giant cell tumour of the bone. *Acta Chir Belg* 2010;110:584–589.
 130. Trieb K, Bitzan P, Lang S, et al. Recurrence of curetted and bone-grafted giant-cell tumours with and without adjuvant phenol therapy. *Eur J Surg Oncol* 2001;27:200–202.
 131. Turcotte RE, Wunder JS, Isler MH, et al. Giant cell tumor of long bone: a Canadian Sarcoma Group study. *Clin Orthop Relat Res* 2002:248–258.
 132. Ruggieri P, Mavrogenis AF, Ussia G, et al. Recurrence after and complications associated with adjuvant treatments for sacral giant cell tumor. *Clin Orthop Relat Res* 2010;468:2954–2961.
 133. Oda Y, Miura H, Tsuneyoshi M, Iwamoto Y. Giant cell tumor of bone: oncological and functional results of long-term follow-up. *Jpn J Clin Oncol* 1998;28:323–328.
 134. Boons HW, Keijser LC, Schreuder HW, et al. Oncologic and functional results after treatment of giant cell tumors of bone. *Arch Orthop Trauma Surg* 2002;122:17–23.
 135. Su YP, Chen WM, Chen TH. Giant-cell tumors of bone: an analysis of 87 cases. *Int Orthop* 2004;28:239–243.
 136. Rastogi S, Prashanth I, Khan SA, et al. Giant cell tumor of bone: is curettage the answer? *Indian J Orthop* 2007;41:109–114.
 137. Guo W, Sun X, Zang J, Qu H. Intralesional excision versus wide resection for giant cell tumor involving the acetabulum: which is better? *Clin Orthop Relat Res* 2012;470:1213–1220.
 138. Labs K, Perka C, Schmidt RG. Treatment of stages 2 and 3 giant-cell tumor. *Arch Orthop Trauma Surg* 2001;121:83–86.
 139. Mankin HJ, Hornicek FJ. Treatment of giant cell tumors with allograft transplants: a 30-year study. *Clin Orthop Relat Res* 2005;439:144–150.
 140. Mendenhall WM, Zlotecki RA, Scarborough MT, et al. Giant cell tumor of bone. *Am J Clin Oncol* 2006;29:96–99.
 141. Saini R, Bali K, Bachhal V, et al. En bloc excision and autogenous fibular reconstruction for aggressive giant cell tumor of distal radius: a report of 12 cases and review of literature. *J Orthop Surg Res* 2011;6:14.
 142. Dahlin DC. Caldwell Lecture. Giant cell tumor of bone: highlights of 407 cases. *AJR Am J Roentgenol* 1985;144:955–960.
 143. Schwartz LH, Okunieff PG, Rosenberg A, Suit HD. Radiation therapy in the treatment of difficult giant cell tumors. *Int J Radiat Oncol Biol Phys* 1989;17:1085–1088.
 144. Bennett CJ, Marcus RB, Million RR, Enneking WF. Radiation therapy for giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 1993;26:299–304.
 145. Chakravarti A, Spiro IJ, Hug EB, et al. Megavoltage radiation therapy for axial and inoperable giant-cell tumor of bone. *J Bone Joint Surg Am* 1999;81:1566–1573.
 146. Nair MK, Jyothirmayi R. Radiation therapy in the treatment of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 1999;43:1065–1069.
 147. Miszczek L, Wydmanski J, Spindel J. Efficacy of radiotherapy for giant cell tumor of bone: given either postoperatively or as sole treatment. *Int J Radiat Oncol Biol Phys* 2001;49:1239–1242.
 148. Caudell JJ, Ballo MT, Zagars GK, et al. Radiotherapy in the management of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 2003;57:158–165.
 149. Feigenberg SJ, Marcus RB Jr, Zlotecki RA, et al. Radiation therapy for giant cell tumors of bone. *Clin Orthop Relat Res* 2003:207–216.
 150. Ruka W, Rutkowski P, Morysinski T, et al. The megavoltage radiation therapy in treatment of patients with advanced or difficult giant cell tumors of bone. *Int J Radiat Oncol Biol Phys* 2010;78:494–498.
 151. Bhatia S, Miszczek L, Roelandts M, et al. Radiotherapy for marginally resected, unresectable or recurrent giant cell tumor of the bone: a rare cancer network study. *Rare Tumors* 2011;3.
 152. Kriz J, Eich HT, Mucke R, et al. Radiotherapy for giant cell tumors of the bone: a safe and effective treatment modality. *Anticancer Res* 2012;32:2069–2073.
 153. Hug EB, Muenster MW, Adams JA, et al. 3-D-conformal radiation therapy for pediatric giant cell tumors of the skull base. *Strahlenther Onkol* 2002;178:239–244.
 154. Roeder F, Timke C, Zwicker F, et al. Intensity modulated radiotherapy (IMRT) in benign giant cell tumors—a single institution case series and a short review of the literature. *Radiat Oncol* 2010;5:18.
 155. Lin PP, Guzel VB, Moura MF, et al. Long-term follow-up of patients with giant cell tumor of the sacrum treated with selective arterial embolization. *Cancer* 2002;95:1317–1325.
 156. Hosalkar HS, Jones KJ, King JJ, Lackman RD. Serial arterial embolization for large sacral giant-cell tumors: mid- to long-term results. *Spine (Phila Pa 1976)* 2007;32:1107–1115.
 157. Onishi H, Kaya M, Wada T, et al. Giant cell tumor of the sacrum treated with selective arterial embolization. *Int J Clin Oncol* 2010;15:416–419.
 158. Emori M, Kaya M, Sasaki M, et al. Pre-operative selective arterial embolization as a neoadjuvant therapy for proximal humerus giant cell tumor of bone: radiological and histological evaluation. *Jpn J Clin Oncol* 2012;42:851–855.
 159. Kaiser U, Neumann K, Havemann K. Generalised giant-cell tumour of bone: successful treatment of pulmonary metastases with interferon alpha, a case report. *J Cancer Res Clin Oncol* 1993;119:301–303.
 160. Kaban LB, Troulis MJ, Ebb D, et al. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. *J Oral Maxillofac Surg* 2002;60:1103–1111.

Bone Cancer

161. Yasko AW. Interferon therapy for giant cell tumor of bone. *Current Opinion in Orthopaedics* 2006;17:568–572.
162. Wei F, Liu X, Liu Z, et al. Interferon alfa-2b for recurrent and metastatic giant cell tumor of the spine: report of two cases. *Spine (Phila Pa 1976)* 2010;35:E1418–1422.
163. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010;11:275–280.
164. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res* 2012;18:4415–4424.
165. Cheng JC, Johnston JO. Giant cell tumor of bone. Prognosis and treatment of pulmonary metastases. *Clin Orthop Relat Res* 1997;205–214.
166. Siebenrock KA, Unni KK, Rock MG. Giant-cell tumour of bone metastasising to the lungs. A long-term follow-up. *J Bone Joint Surg Br* 1998;80:43–47.
167. Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. *Am J Clin Pathol* 2006;125:555–581.
168. Antonescu CR, Huvos AG. Low-grade osteogenic sarcoma arising in medullary and surface osseous locations. *Am J Clin Pathol* 2000;114 Suppl:S90–103.
169. Sheth DS, Yasko AW, Raymond AK, et al. Conventional and dedifferentiated parosteal osteosarcoma. Diagnosis, treatment, and outcome. *Cancer* 1996;78:2136–2145.
170. Bertoni F, Bacchini P, Staals EL, Davidovitz P. Dedifferentiated parosteal osteosarcoma: the experience of the Rizzoli Institute. *Cancer* 2005;103:2373–2382.
171. Okada K, Unni KK, Sweet RG, Sim FH. High grade surface osteosarcoma: a clinicopathologic study of 46 cases. *Cancer* 1999;85:1044–1054.
172. Staals EL, Bacchini P, Bertoni F. High-grade surface osteosarcoma: a review of 25 cases from the Rizzoli Institute. *Cancer* 2008;112:1592–1599.
173. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *J Clin Oncol* 1994;12:423–431.
174. Ferrari S, Bertoni F, Mercuri M, et al. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: an analysis of 300 patients treated at the Rizzoli Institute. *Ann Oncol* 2001;12:1145–1150.
175. 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 Study Group protocols. *J Clin Oncol* 2002;20:776–790.
176. Bacci G, Longhi A, Ferrari S, et al. Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years. *Tumori* 2004;90:478–484.
177. Bacci G, Longhi A, Versari M, et al. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. *Cancer* 2006;106:1154–1161.
178. Whelan JS, Jinks RC, McTiernan A, et al. Survival from high-grade localised extremity osteosarcoma: combined results and prognostic factors from three European Osteosarcoma Intergroup randomised controlled trials. *Ann Oncol* 2012;23:1607–1616.
179. Bacci G, Briccoli A, Ferrari S, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with synchronous lung metastases: treatment with cisplatin, adriamycin and high dose of methotrexate and ifosfamide. *Oncol Rep* 2000;7:339–346.
180. Daw NC, Billups CA, Rodriguez-Galindo C, et al. Metastatic osteosarcoma. *Cancer* 2006;106:403–412.
181. Marulanda GA, Henderson ER, Johnson DA, et al. Orthopedic surgery options for the treatment of primary osteosarcoma. *Cancer Control* 2008;15:13–20.
182. Bacci G, Ferrari S, Lari S, et al. Osteosarcoma of the limb. Amputation or limb salvage in patients treated by neoadjuvant chemotherapy. *J Bone Joint Surg Br* 2002;84:88–92.
183. Mavrogenis AF, Abati CN, Romagnoli C, Ruggieri P. Similar survival but better function for patients after limb salvage versus amputation for distal tibia osteosarcoma. *Clin Orthop Relat Res* 2012;470:1735–1748.
184. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. 1986. *J Bone Joint Surg Am* 2005;87:2822.
185. Aksnes LH, Bauer HC, Jebsen NL, et al. Limb-sparing surgery preserves more function than amputation: a Scandinavian sarcoma group study of 118 patients. *J Bone Joint Surg Br* 2008;90:786–794.
186. Nagarajan R, Neglia JP, Clohisey DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? *J Clin Oncol* 2002;20:4493–4501.
187. Winkler K, Beron G, Kotz R, et al. Neoadjuvant chemotherapy for osteogenic sarcoma: results of a Cooperative German/Austrian study. *J Clin Oncol* 1984;2:617–624.
188. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med* 1986;314:1600–1606.
189. Eilber F, Giuliano A, Eckardt J, et al. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. *J Clin Oncol* 1987;5:21–26.
190. Link MP, Goorin AM, Horowitz M, et al. Adjuvant chemotherapy of high-grade osteosarcoma of the extremity. Updated results of the Multi-Institutional Osteosarcoma Study. *Clin Orthop Relat Res* 1991;8–14.
191. Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol* 1992;10:5–15.
192. 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.
193. Bramwell V, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992;10:1579–1591.
194. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997;350:911–917.
195. Fuchs N, Bielack SS, Epler D, et al. Long-term results of the cooperative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. *Ann Oncol* 1998;9:893–899.

Bone Cancer

196. Bacci G, Ferrari S, Berton F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol* 2000;18:4016–4027.
197. Bacci G, Briccoli A, Ferrari S, 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.
198. 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.
199. Lewis IJ, Nooij 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.
200. 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.
201. Basaran M, Bavbek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. *Oncology* 2007;72:255–260.
202. Le Deley MC, Guinebreteiere JM, Gentet JC, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. *Eur J Cancer* 2007;43:752–761.
203. Provisor AJ, Ettinger LJ, 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.
204. Bacci G, Mercuri M, Longhi A, et al. Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. *Eur J Cancer* 2005;41:2079–2085.
205. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. *Cancer* 2009;115:5339–5348.
206. Cesari M, Alberghini M, Vanel D, et al. Periosteal osteosarcoma: a single-institution experience. *Cancer* 2011;117:1731–1735.
207. Grimer RJ, Bielack S, Flege S, et al. Periosteal osteosarcoma—a European review of outcome. *Eur J Cancer* 2005;41:2806–2811.
208. Winkler K, Beron G, Dellling 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* 1988;6:329–337.
209. Smeland S, Muller C, Alvegard TA, et al. Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders. *Eur J Cancer* 2003;39:488–494.
210. Smeland S, Bruland OS, Hjorth L, et al. Results of the Scandinavian Sarcoma Group XIV protocol for classical osteosarcoma: 63 patients with a minimum follow-up of 4 years. *Acta Orthop* 2011;82:211–216.
211. Ferrari S, Ruggieri P, Cefalo G, et al. Neoadjuvant chemotherapy with methotrexate, cisplatin, and doxorubicin with or without ifosfamide in nonmetastatic osteosarcoma of the extremity: An Italian Sarcoma Group trial ISG/OS-1. *J Clin Oncol* 2012;30:2112–2118.
212. Ciernik IF, Niemierko A, Harmon DC, et al. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. *Cancer* 2011;117:4522–4530.
213. Meyers PA, Heller G, Healey JH, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. *J Clin Oncol* 1993;11:449–453.
214. Bacci G, Briccoli A, Mercuri M, et al. Osteosarcoma of the extremities with synchronous lung metastases: long-term results in 44 patients treated with neoadjuvant chemotherapy. *J Chemother* 1998;10:69–76.
215. Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. *Ann Oncol* 2003;14:1126–1134.
216. Winkler K, Torggler S, Beron G, et al. [Results of treatment in primary disseminated osteosarcoma. Analysis of the follow-up of patients in the cooperative osteosarcoma studies COSS-80 and COSS-82]. *Onkologie* 1989;12:92–96.
217. Bacci G, Mercuri M, Briccoli A, et al. Osteogenic sarcoma of the extremity with detectable lung metastases at presentation. Results of treatment of 23 patients with chemotherapy followed by simultaneous resection of primary and metastatic lesions. *Cancer* 1997;79:245–254.
218. Tabone MD, Kalifa C, Rodary C, et al. Osteosarcoma recurrences in pediatric patients previously treated with intensive chemotherapy. *J Clin Oncol* 1994;12:2614–2620.
219. Saeter G, Hoie J, Stenwig AE, et al. Systemic relapse of patients with osteogenic sarcoma. Prognostic factors for long term survival. *Cancer* 1995;75:1084–1093.
220. Ferrari S, Briccoli 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.
221. Buddingh EP, Anninga JK, Versteegh MI, et al. Prognostic factors in pulmonary metastasized high-grade osteosarcoma. *Pediatr Blood Cancer* 2010;54:216–221.
222. Briccoli A, Rocca M, Salone M, et al. High grade osteosarcoma of the extremities metastatic to the lung: long-term results in 323 patients treated combining surgery and chemotherapy, 1985–2005. *Surg Oncol* 2010;19:193–199.
223. Bielack SS, Kempf-Bielack B, Branscheid D, et al. Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. *J Clin Oncol* 2009;27:557–565.
224. Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer* 2009;115:2980–2987.
225. Gentet JC, Brunat-Mentigny M, Demaille MC, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. *Eur J Cancer* 1997;33:232–237.
226. Merimsky O, Meller I, Flusser G, et al. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. *Cancer Chemother Pharmacol* 2000;45:177–181.

Bone Cancer

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- 227.** Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer* 2008;113:419–425.
- 228.** Saylor RL, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol* 2001;19:3463–3469.
- 229.** Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer* 2005;44:338–347.
- 230.** 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;20:189–196.
- 231.** Loeb DM, Garrett-Mayer E, Hobbs RF, et al. Dose-finding study of ¹⁵³Sm-EDTMP in patients with poor-prognosis osteosarcoma. *Cancer* 2009;115:2514–2522.
- 232.** Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol* 2012;23:508–516.
- 233.** Lashkari A, Chow WA, Valdes F, et al. Tandem high-dose chemotherapy followed by autologous transplantation in patients with locally advanced or metastatic sarcoma. *Anticancer Res* 2009;29:3281–3288.
- 234.** Fagioli F, Aglietta M, Tienghi A, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian Sarcoma Group study. *J Clin Oncol* 2002;20:2150–2156.

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Individual Disclosures for the NCCN Bone Cancer Panel					
Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Douglas R. Adkins, MD	Amgen Inc.; Eisai Inc.; and Threshold Pharmaceuticals	None	None	None	3/28/13
Mark Agulnik, MD	None	None	None	None	4/6/12
Robert S. Benjamin, MD	Amgen Inc.	Amgen Inc.	Johnson & Johnson; Merck & Co., Inc.; Pfizer Inc.	None	3/28/12
J. Sybil Biermann, MD	None	None	None	None	12/9/12
Brian Brigman, MD, PhD	Lumicell Diagnostics; and Musculoskeletal Transplant Foundation	Musculoskeletal Transplant Foundation	None	None	7/18/12
James E. Butrynski, MD	None	None	None	None	12/9/12
David Cheong, MD	None	None	None	None	2/26/13
Warren Chow, MD	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Hoffman-LaRoche; and NCCN	Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	8/7/12
William T. Curry, MD	None	None	None	None	3/29/12
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