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...
and malignant forms, with the benign form being 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 hemangioblastoma 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 RB.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 Osteosarcoma is the most common second primary malignancy in patients with a history of retinoblastoma, characterized by a mutation in the retinoblastoma gene RB.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 Osteosarcoma is the most common second primary malignancy in patients with a history of retinoblastoma, characterized by a mutation in the retinoblastoma gene RB.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
Bone Cancer, Version 2.2013

WORKUP\textsuperscript{a,b}

- All patients should be evaluated and treated by a multidisciplinary team with expertise in the management of chordoma\textsuperscript{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\textsuperscript{b,c}

HISTOLOGIC SUBTYPE

- Conventional or Chondroid
- Dedifferentiated

See Presentation and Primary Treatment (facing page)

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

\textsuperscript{a}See Multidisciplinary Team (page 700).
\textsuperscript{b}See Principles of Bone Cancer Management (page 701).
\textsuperscript{c}Biopsy 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.

CHORDOMA
Bone Cancer, Version 2.2013

CHORDOMA

PRESENTATION

WIDE RESSECTION

± RT, if resectable

OR

Sacrococcygeal and Mobile spine

Consider RT if unresectable

OR

Skull base/Clival

INTRALESIONAL EXCISION

± RT, if resectable

Follow-up MRI to assess adequacy of resection

Consider RT for positive surgical margins or for large extracompartmental tumors

Consider re-resection if necessary

PRIMARY TREATMENT

ADJUVANT TREATMENT

Consider RT for positive surgical margins or for large extracompartmental tumors

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

See Surveillance (page 692)

See Principles of Bone Cancer Management (page 701).

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

See Principles of Radiation Therapy (pages 704-705).

See Principles of Bone Cancer Management (page 701).

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

See Principles of Radiation Therapy (pages 704-705).

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See Principles of Radiation Therapy (pages 704-705).

See Principles of Bone Cancer Management (page 701).

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

See Principles of Radiation Therapy (pages 704-705).

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

CHOR-1

CHOR-2
SURVEILLANCE

- Physical exam
- Imaging (eg, x-ray, CT ± MRI) of surgical site as clinically indicated
- Chest imaging every 6 mo for 5 y, then annually thereafter
- Cross-sectional abdominal imaging annually

RECURRENT

Local recurrence → Surgical excision\(^{b}\) and/or RT\(^{e}\) and/or Systemic therapy\(^{g}\)

Metastatic recurrence → Systemic therapy\(^{g}\) and/or Surgical excision\(^{b}\) and/or RT\(^{e}\) Best supportive care

TREATMENT

\(^{a}\)See Principles of Bone Cancer Management (page 701).
\(^{b}\)See Principles of Radiation Therapy (pages 704-705).
\(^{g}\)See Bone Cancer Systemic Therapy Agents (pages 702-703).
WORKUP

- 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)

PRESENTATION

- Localized disease
- Metastatic disease at presentation

See page 694

\(^a\)Brown tumor of hyperparathyroidism should be considered as a differential diagnosis.
\(^b\)See Principles of Bone Cancer Management (page 701).
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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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**SURVEILLANCE**

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

**RECURRENCE**

- Local recurrence
  - Resectable
    - Consider chest imaging
  - Unresectable
    - Metastatic recurrence
      - Consider denosumab prior to surgery (see previous page)
  - Resectable with unacceptable morbidity or unresectable axial lesions
    - See previous page

**GCTB-3**
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WORKUP

- History and physical
- MRI ± CT of primary site
- Chest imaging including chest CT or PET scan and/or bone scan
- MRI or CT of skeletal metastatic sites
- LDH
- ALP
- Fertility consultation as appropriate

PRIMARY TREATMENT

Low-grade osteosarcoma:
- Intramedullary + surface
- Wide excision

High-grade osteosarcoma:
- Intramedullary + surface
- Chemotherapy (category 2B)

Metastatic disease at presentation
- See facing page

ADJUVANT TREATMENT

- Consider chemotherapy
- Wide excision

- See Surveillance (page 699)

OSTEOSARCOMA

OSTEO-1

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.
WORKUP\textsuperscript{a,b}  PRIMARY TREATMENT  ADJUVANT TREATMENT

- Chest imaging including chest CT
- PET scan and/or bone scan
- MRI or CT of skeletal metastatic sites
- LDH
- ALP
- Fertility consultation as appropriate

\textbf{E} History and physical

MRI ± CT of primary site

- High-grade osteosarcoma:
  - Intramedullary + surface
  - Wide excision\textsuperscript{b}
  - High grade
  - Chemotherapy (category 2B)

- Low-grade osteosarcoma:
  - Intramedullary + surface
  - Wide excision\textsuperscript{b}
  - Low grade
  - See facing page

- Periosteal osteosarcoma
  - Consider chemotherapy\textsuperscript{d}
  - Wide excision\textsuperscript{b}

- Dedifferentiated parosteal osteosarcomas are not considered to be low-grade tumors.

- Metastatic disease at presentation See facing page

\textbf{NEOADJUVANT TREATMENT}

- Positive margins
  - Consider additional local therapy (surgical resection ± RT)\textsuperscript{h}

- Negative margins
  - Chemotherapy\textsuperscript{d}
  - Consider changing chemotherapy\textsuperscript{d}

\textbf{RESTAGE}

- Reassess tumor as appropriate
  - Restage with pretreatment imaging modalities:
    - Chest imaging
    - Imaging of primary site
    - Consider PET scan or bone scan

- Resectable
  - Wide excision\textsuperscript{b}

- Unresectable
  - Good response\textsuperscript{g}
    - Chemotherapy\textsuperscript{d}

  - Poor response\textsuperscript{g}
    - Consider changing chemotherapy\textsuperscript{d}

\textbf{ADJUVANT TREATMENT}

- RT\textsuperscript{h}
  - Chemotherapy\textsuperscript{d}

- Chemotherapy\textsuperscript{d}
  - Consider additional local therapy (surgical resection ± RT)\textsuperscript{h}

- Consider additional local therapy (surgical resection ± RT)\textsuperscript{h}
  - Chemotherapy\textsuperscript{d}
  - Consider changing chemotherapy\textsuperscript{d}

- See Surveillance (page 699)

\textsuperscript{a}See Principles of Bone Cancer Management (page 701).
\textsuperscript{b}See Bone Cancer Systemic Therapy Agents (pages 702-703).
\textsuperscript{c}Selected elderly patients may benefit from immediate surgery.
\textsuperscript{d}Response 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.
\textsuperscript{e}See Principles of Radiation Therapy (pages 704-705).
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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Metastatic disease

Resectable (pulmonary, visceral, or skeletal metastases)

Unresectable

• See page 697 for management of primary tumor

Chemotherapy

Medastectomy

• Chemotherapy

• RT

Reassess primary site as appropriate for local control

Surveillance

(See page 699)

SURVEILLANCE

RELAPSE

• Chest imaging
• CBC and other laboratory studies as indicated
• Imaging of primary site
• 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

Response

Surveillance

Relapse

Chemotherapy and/or resection if possible

Relapse/
Progression

Resection, if possible or Best supportive care or Clinical trial or Samarium-153 ethylene diamine tetramethylene phosphonate (153 Sm-EDTMP) or Palliative RT

OSTEOSARCOMA

\[d\] See Bone Cancer Systemic Therapy Agents (pages 702-703).

\[i\] Use the same imaging technique that was performed in the initial workup.
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

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. 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. 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 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. 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. 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. (See previous page)
Bone Cancer, Version 2.2013

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 CANCER SYSTEMIC THERAPY AGENTS

Chordoma

- Imatinib
- Imatinib with cisplatin or sirolimus
- Erlotinib
- Erlotinib + cetuximab
- Sunitinib

Giant Cell Tumor of Bone

- Denosumab
- Interferon alfa
- Peginterferon

Osteosarcoma

- First-line therapy (primary/neoadjuvant/adjuvant therapy or metastatic disease)
  - Cisplatin and doxorubicin
  - MAP (High-dose methotrexate, cisplatin, and doxorubicin)
  - Doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate
  - Ifosfamide, cisplatin, and epirubicin
- Second-line therapy (relapsed/refractory or metastatic disease)
  - Docetaxel and gemcitabine
  - Cyclophosphamide and etoposide
  - Cyclophosphamide and topotecan
  - Gemcitabine
  - Ifosfamide and etoposide
  - Ifosfamide, carboplatin, and etoposide
  - High-dose methotrexate, etoposide, and ifosfamide
  - 113Sm-EDTMP for relapsed or refractory disease beyond second-line therapy
  - Sorafenib

BONE CANCER SYSTEMIC THERAPY AGENTS (References)

BONE CANCER SYSTEMIC THERAPY AGENTS

(References Cont.)


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 BONE

Treatment 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.

OSTEOSARCOMA

Treatment 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 \(^{153}\)Sm-EDTMP
- Consider use of Stereotactic radiosurgery, especially for oligometastases

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\(^1\)R0 = No microscopic residual disease, R1 = Microscopic residual disease, R2 = Gross residual disease

BONE-D (1 OF 2)
PRINCIPLES OF RADIATION THERAPY

(References)

Chordoma

Giant Cell Tumor of Bone

Mixed Histology Reports
coma is also the most common radiation-induced bone sarcoma.\textsuperscript{18,19}

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and ESFT.\textsuperscript{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.\textsuperscript{22} Survival rates have improved to almost 70\% in patients with localized ESFT.\textsuperscript{21} A cure is still achievable in selected patients diagnosed with metastatic ESFT and osteosarcoma at presentation.\textsuperscript{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]).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{28} Whole-body MRI is a sensitive imaging technique for detecting skeletal metastases in patients with small cell neoplasms, ESFT, and osteosarcoma.\textsuperscript{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.\textsuperscript{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.\textsuperscript{33–36} PET or PET/CT with the investigational radioactive substance \textsuperscript{18}F-fluoromisonidazole (FMISO) has been shown to identify the hypoxic component in residual chordomas before RT.\textsuperscript{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. 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. 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. Cost savings may be realized when needle biopsy is used in selected patients. 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. 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. 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.

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. However, 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.

**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).
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. Chordomas are classified into 3 histologic variants: conventional, chordoid, and dedifferentiated. Conventional chordomas are the most common histologic subtype, characterized by the absence of cartilaginous or mesenchymal components. Chordoid 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.

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.

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. CT scan and MRI may be useful in distinguishing BNCTs from chordomas.

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. For sacrococcygeal chordomas, CT and MRI are useful for assessing soft tissue involvement, calcifications, and epidural extension. MRI provides more precise and superior contrast with surrounding soft tissues compared with CT, and is helpful to assess recurrent or metastatic lesions. 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. 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. A recent retrospective analysis of 962 patients with chordoma identified in the SEER database demonstrated that surgery significantly improves the overall survival (OS). 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, skull base, and spine.

Among patients with chordoma of the mobile spine, Boriani et al 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 al reported a local recurrence rate of only 17% after wide surgical margins compared with 81% after intralesional excision or marginal surgery. Tzortzidis et al 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 al 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. 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. 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 extralobar 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. RT in combination with surgery is also associated with improved local recurrence rates in patients with conventional or chondroid chordomas of the skull base.

Particle beam RT (either alone or in combination with photon beam RT) with high-energy protons or carbon ions 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. Carbon ion RT also resulted in preservation of urinary and anorectal function compared with surgery in patients with sacral chordomas.

Specialized techniques such as IMRT, SRS, and FSRT have also been associated with good local control rates in cranial and extracranial chordomas.

**Systemic Therapy:** Chordomas are not sensitive to chemotherapy except for the potentially differentiated portion of high-grade dedifferentiated chordomas. 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.

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 determined 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. Imatinib in combination with cisplatin or sirolimus has also been effective in small series of patients with advanced chordoma resistant to prior imatinib therapy. 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.

**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. 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. Adjuvant treatment with RT can be considered for large extracompartamental 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.

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 recurred.
Bone Cancer

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.117–121 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.121,122,127–129 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.\textsuperscript{153,154}

**NCCN Recommendations**

Localized Disease: Intralesional excision with or without an effective adjuvant is an adequate primary treatment for resectable tumors.\textsuperscript{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.\textsuperscript{155–158} A few case reports have reported the efficacy of interferon and pegylated interferon in the management of GCTB.\textsuperscript{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.\textsuperscript{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.\textsuperscript{110,111,165,166} Intralesional excision is recommended for resectable metastatic sites. Denosumab, interferon, or pegylated interferon; observa-

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{167} High-grade intramedullary osteosarcoma is the classic or conventional form, constituting nearly 80% of osteosarcomas.\textsuperscript{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.\textsuperscript{168}

Parosteal and periosseous osteosarcomas are juxtacortical or surface variants. Parosteal osteosarcomas are low-grade lesions accounting for up to 5% of all osteosarcomas.\textsuperscript{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.\textsuperscript{169,170} Periosteal osteosarcomas are intermediate-grade lesions most often involving the femur followed by the tibia.\textsuperscript{168} High-grade surface osteosarcomas are rare, accounting for 10% of all juxtacortical osteosarcomas.\textsuperscript{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
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.\(^\text{173–178}\) 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.\(^\text{175}\) In patients with extremity osteosarcomas, size and location of the tumor within the limb at diagnosis also had a significant influence on outcome.\(^\text{175}\) 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 al\(^\text{178}\) 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.\(^\text{24}\) Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients with no metastatic disease.\(^\text{179,180}\)

Elevated serum ALP and LDH levels have also been identified as prognostic indicators in patients with osteosarcoma.\(^\text{174,176,177}\) In a cohort of 1421 patients with osteosarcoma of the extremity, Bacci et al\(^\text{176}\) 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 al\(^\text{177}\) 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.\(^\text{174,176}\)

**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 high-grade nonmetastatic osteosarcoma than in patients with osteosarcoma with extremity involvement.

**Treatment**

**Surgery:** Surgery (limb-sparing surgery or amputation) remains an essential part of management of patients with osteosarcoma.\(^\text{181}\) 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.\(^\text{182–184}\) However, limb-sparing surgery is associated with better functional outcomes.\(^\text{185}\) 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.\(^\text{182,186}\) Amputation is generally reserved for patients with tumors in unfavorable anatomic locations not amenable to limb-sparing surgery with adequate surgical margins.\(^\text{181,186}\)

**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.\textsuperscript{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.\textsuperscript{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, nonmetastatic osteosarcoma.\textsuperscript{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 nonmetastatic 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{176,201} In an analysis of 881 patients with nonmetastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and surgery at the Rizzoli Institute, Bacci et al\textsuperscript{204} 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% (\textit{P}<.0001) and 78.4% versus 63.7% (\textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{200} However, the improvement was not statistically different in patients with metastatic disease.\textsuperscript{205} MTP-PE is not approved by the FDA for the treatment of patients with osteosarcoma.

Localize\textsuperscript{ed} 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.\textsuperscript{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.\textsuperscript{207} More recently, Cesari et al\textsuperscript{206} 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 (\textit{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.
Preoperative chemotherapy before wide excision is preferred for patients with high-grade osteosarcoma (category 1).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{24} Unilateral metastases and lower number of lung nodules were associated with improved outcomes with chemotherapy in patients with synchronous lung metastases.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{218–222} In patients with primary nonmetastatic...
osteosarcoma, a longer relapse-free interval to pulmonary metastases was significantly associated with better survival. 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.

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials. 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. 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. 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.

Samarium-153 ethylene diamine tetracetic acid (153Sm-EDTMP), a bone-seeking radiopharmaceutical, has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases. Anderson et al 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. Results of a recent dose-finding study also showed that 153Sm-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.

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 or unresectable high-grade osteosarcoma after failure of standard multimodal therapy. 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. 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. 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. 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

Bone Cancer


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Bone Cancer


Bone Cancer


The NCCN guidelines staff have no conflicts to disclose.