Primary bone cancers are extremely rare neoplasms, likely accounting for fewer than 0.2% of all cancers, although its true incidence is difficult to determine secondary to the rarity of these tumors. In 2009, an estimated 2570 new cases will be diagnosed in the United States and 1470 people will die of the disease. Primary bone cancers show wide clinical heterogeneity and are often curable with proper treatment. Osteosarcoma (35%), chondrosarcoma (30%), and Ewing’s sarcoma (16%) are the 3 most common forms of bone cancer. Malignant fibrous histiocytoma (MFH) and fibrosarcoma of the bone constitute fewer than 1% of all primary bone tumors. Chondrosarcoma is usually found in middle-aged and older adults; osteosarcoma and Ewing’s sarcoma are more common in younger individuals. The NCCN Bone Cancer Guidelines provide evidence-based recommendations for the management of primary bone cancers.
Bone Cancer

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Text continues on p. 699

develop mainly in children and young adults. Various 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 hemangiendothelioma and hemangiopericytoma. Notochordal tissue gives rise to chordoma. Several primary bone cancers, including Ewing’s sarcoma family of tumors (ESFT), are of unknown histologic origin.

The pathogenesis and etiology of most bone cancers remain unclear. Gene rearrangements in the EWS and ETS family of genes have been implicated in the pathogenesis of Ewing’s sarcoma.4–7 Specific genetic alterations also play a role in osteosarcoma pathogenesis.8,9 Although trauma is frequently implicated in sarcomas, a cause-and-effect relationship between a traumatic event and the development of bone cancer has not been identified. A quantifiable risk exists for developing bone sarcomas after therapeutic radiation.10,11 Osteosarcoma is the most common radiation-induced sarcoma, and is the most common second primary malignancy in patients with a history of retinoblastoma.12,13 Li-Fraumeni syndrome is a hereditary cancer syndrome in which there is a germ-line mutation of the p53 gene resulting in sarcomas such as osteosarcoma, early onset of bilateral breast cancer, and several other neoplasms.14–17

In the past, a diagnosis of osteosarcoma and Ewing’s sarcoma was associated with a poor prognosis. A generation ago, Marcove et al. described the survival pattern of newly diagnosed patients with osteosarcoma.
WORKUP

Painful bone lesion

Abnormal radiograph

Age < 40 y

Refer to orthopaedic oncologist
• Biopsy should be performed at treating institution

See specific bone sarcomas
• Chondrosarcoma (facing page)
• Ewing’s sarcoma (page 692)
• Osteosarcoma (page 694)

Age ≥ 40 y

Workup for potential bone metastasis

• H&P
As clinically indicated:
• Bone scan
• Chest radiograph
• SPEP/labs
• Chest/abdominal/pelvic CT
• PSA
• Mammogram

No other lesions (possible bone primary)

Refer to orthopaedic oncologist
• Biopsy should be performed at treating institution

Other lesions (non-bone primary suspected)

Refer to appropriate NCCN Guideline.
See the NCCN Table of Contents online at www.NCCN.org

Painless bone lesions require evaluation by a musculoskeletal radiologist and referral to multidisciplinary teams. See Multidisciplinary Team (page 696).

See Principles of Bone Cancer Management (page 696):

There is considerable controversy regarding the grading of chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should be considered when deciding local treatment. Wide excision should provide negative surgical margins for tumor. This may be achieved by either limb-sparing resection or limb amputation.
### Bone Cancer Version 3:2010

#### CHONDROSARCOMA

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Primary Treatment</th>
<th>Surveillance</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade and intracompartmental</td>
<td>Intralesional excision ± surgical adjuvant or Wide excision, if resectable or Consider RT, if unresectable</td>
<td>Physical exam and chest and lesion radiograph every 6-12 mo for 2 y, then yearly as appropriate</td>
<td>Local recurrence</td>
</tr>
<tr>
<td>High grade (grade II or III) or Clear cell or Extracompartmental</td>
<td>Wide excision, if resectable or Consider RT, if unresectable</td>
<td>Physical exam</td>
<td>Local recurrence</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>Treat as osteosarcoma (category 2B) See NCCN Osteosarcoma Guidelines (page 694)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Treat as Ewing’s Sarcoma (category 2B) See NCCN Ewing’s Sarcoma Guidelines (page 692)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Positive margins → Consider RT
- Negative margins → Observe
- Wide excision, if resectable or RT, if unresectable
- Local recurrence
- Systemic relapse
- Clinical trial or Surgical excision

---

**a** See Multidisciplinary Team (page 696).
**b** See Principles of Bone Cancer Management (page 696).
**c** There is considerable controversy regarding the grading of chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should be considered when deciding local treatment.
**d** Wide excision should provide negative surgical margins for tumor. This may be achieved by either limb-sparing resection or limb amputation.
**PRESENTATION**

**WORKUP**

- MRI ± CT of primary site
- Chest CT
- PET and/or bone scan
- Consider bone marrow biopsy or screening MRI of spine and pelvis
- Cytogenetics and/or molecular studies (may require re-biopsy)
- LDH
- Fertility consultation as appropriate

**PRIMARY TREATMENT**

- Multiagent chemotherapy (category 1) for at least 12-24 wk before local therapy

**RESTAGE**

- For patients with localized disease
  - Restage with:
    - Chest imaging
    - Local imaging
    - Consider PET or bone scan
  - Repeat other abnormal studies

- For patients with metastatic disease
  - Restage with:
    - Chest imaging
    - Local imaging
    - Consider PET or bone scan
    - Repeat other abnormal studies

- Stable disease after response to primary treatment

- Progressive disease after primary treatment

---

**Bone Cancer Version 3:2010**

**EWING’S SARCOMA**

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See Multidisciplinary Team (page 696).

See Principles of Bone Cancer Management (page 696).

Any member of the Ewing’s family of tumors can be treated using this algorithm, including primitive neuroectodermal tumor, Askin’s tumor, PNET of bone, and extraosseous Ewing’s sarcoma.

90% of Ewing’s family tumors will have 1 of 4 specific cytogenetic translocations.

See Bone Cancer Systemic Therapy Agents (pages 697 and 698).

*Use the same imaging technique that was performed in the initial workup.*
EWING’S SARCOMA

**LOCAL CONTROL THERAPY**

- Wide excision
  - Positive margins
  - Negative margins
- Definitive RT and chemotherapy
- Preoperative RT
- Amputation in selected cases (such as tumors of the foot)

**ADJUVANT TREATMENT/ADDITIONAL THERAPY**

- Continue chemotherapy (category 1) followed by RT or RT and chemotherapy (category 1, for chemotherapy)
- Chemotherapy (category 1)
- Chemotherapy ± additional RT
- Postoperative chemotherapy, consider RT depending on margin status

**SURVEILLANCE**

- Physical exam, CBC, and chest and local imaging every 2-3 mo
- Increase intervals for physical exam and chest and local imaging after 24 mo; annually after 5 y (indefinitely)
- Consider PET or bone scan

**PROGRESSIVE DISEASE/RELAPSE**

- Early relapse
  - Clinical trial or Chemotherapy ± RT
- Late relapse
  - RT
  - Chemotherapy or Best supportive care

**Notes:**

- See Bone Cancer Systemic Therapy Agents (pages 697 and 698).
- Use the same imaging technique performed in the initial workup.
- RT may be considered for close margins.
- There is category 1 evidence for between 28 and 49 weeks of chemotherapy, depending on the chemotherapy and dosing schedule used.
- For late relapse, consider retreatment with previously effective regimen.

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WORKUP\textsuperscript{a,b}

- Plain films
- MRI ± CT of primary site
- Chest imaging including chest CT
- PET and/or bone scan
- LDH
- Alkaline phosphatase
- Fertility consultation as appropriate

Low grade osteosarcoma:\textsuperscript{c}
- Intramedullary + surface

Periosteal osteosarcoma

Consider chemotherapy\textsuperscript{d,e}

Wide excision

High grade

Low grade

Preoperative chemotherapy\textsuperscript{d,e,f}
- (category 1)

Reassess tumor as appropriate
- Restage with pretreatment imaging modalities:
  - Chest imaging
  - Local imaging
  - Consider PET scan
  - Consider bone scan

Unresectable

- RT ± sensitizers
- Samarrium

Good response\textsuperscript{g}

Positive margins

- Wide excision, if resectable

Poor response\textsuperscript{g}

Good response\textsuperscript{g}

Negative margins

Low grade osteosarcoma: intramedullary + surface

\textsuperscript{a} See Multidisciplinary Team (page 696).
\textsuperscript{b} See Principles of Bone Cancer Management (page 696).
\textsuperscript{c} Dedifferentiated parosteal osteosarcomas are not considered to be low-grade tumors.
\textsuperscript{d} Chemotherapy may be intravenous or intra-arterial.
\textsuperscript{e} See Bone Cancer Systemic Therapy Agents (pages 697 and 698).
\textsuperscript{f} Selected elderly patients may benefit from immediate surgery.
\textsuperscript{g} Response defined by pathologic mapping.


## Adjuvant Treatment

<table>
<thead>
<tr>
<th>Chemotherapy&lt;sup&gt;d,e&lt;/sup&gt;</th>
<th><strong>Surveillance</strong></th>
<th><strong>Relapse</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>* Physical exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Chest imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* CBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Local imaging: see note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Reassess function every visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up schedule:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Every 3 mo for y 1 and 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Every 4 mo for y 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Every 6 mo for y 4 and 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and yearly thereafter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chemotherapy<sup>d,e</sup>

- Consider additional local therapy
- Consider changing chemotherapy

### Chemotherapy<sup>d,e</sup>

- Consider changing chemotherapy

### Response

- Surveillance

### Relapse

- Chemotherapy<sup>e</sup> and/or resection if possible

### Surveillance Relapse

- Physical exam
- Chest imaging
- CBC
- Local imaging: consider bone scan (category 2B)
- Reassess function every visit

**Follow-up schedule:**

- Every 3 mo for y 1 and 2
- Every 4 mo for y 3
- Every 6 mo for y 4 and 5, and yearly thereafter

### Relapse

- Chemotherapy<sup>e</sup> and/or resection if possible

### Response

- Surveillance

### Relapse

- Resect or Best supportive care or Clinical trial or Samarium or Palliative RT

---

<sup>d</sup>Chemotherapy may be intravenous or intra-arterial.

<sup>e</sup>See Bone Cancer Systemic Therapy Agents (pages 697 and 698).

<sup>h</sup>Use the same imaging technique performed in the initial workup.
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
- Orthopaedic oncologist
- Bone pathologist
- Medical/pediatric oncologist
- Radiation oncologist
- Musculoskeletal radiologist

Specialists Critical in Certain Cases
- Thoracic surgeon
- Plastic surgeon
- Interventional radiologist
- Physiatrist
- Vascular surgeon
- Additional surgical subspecialties

**Biopsy**
- Biopsy diagnosis is necessary before any surgical procedure or fixation of primary site.
- Optimally performed at a center that will perform 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.
- Appropriate communication between surgeon, musculoskeletal radiologist, and bone pathologist is critical.
- Fresh tissue may be needed for molecular studies.
- In general, failure to follow appropriate biopsy procedures may lead to adverse patient outcomes.

**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.

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

**Treatment**
- Fertility issues should be addressed with patients before commencing chemotherapy.
- Preferably, care for bone cancer patients should be delivered directly by physicians on the multidisciplinary team (category 1; see page 696).

**Long-Term Follow-up and Surveillance/Survivorship**
- Patients should have a survivorship prescription to schedule follow-up with a multidisciplinary team.
- Extended therapy and surveillance may be necessary to address potential late effects of surgery, radiation, and chemotherapy in long-term survivors.
**Bone Cancer Version 3:2010**

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**BONE CANCER SYSTEMIC THERAPY AGENTS**

**Chondrosarcoma**
- Conventional chondrosarcoma (grades 1-3) has no known standard chemotherapy options
- Mesenchymal chondrosarcoma: follow Ewing’s regimens
- Dedifferentiated chondrosarcoma: follow osteosarcoma regimens

**Ewing’s Sarcoma**
- First-line therapy (primary/neoadjuvant/adjuvant)\(^1\)
  - VAC/E (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide)\(^1\)
  - VAI (vincristine, doxorubicin, and ifosfamide)\(^2,3\)
  - VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)\(^4\)

**Osteosarcoma**
- Primary therapy for metastatic disease at initial presentation
  - CVD (cyclophosphamide, vincristine, and doxorubicin)\(^5\)
  - VAC/E (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide)\(^1\)
  - VAI (vincristine, doxorubicin, and ifosfamide)\(^2,3\)
  - VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)\(^4\)

**Second-line therapy (relapsed or refractory disease)\(^1\)**
- Cyclophosphamide and topotecan\(^8,9\)
- Temozolomide and irinotecan\(^10-12\)
- Ifosfamide and etoposide\(^13\)
- Ifosfamide, carboplatin, and etoposide\(^14\)
- Docetaxel and gemcitabine\(^15\)

**Osteosarcoma**
- First-line therapy (primary/neoadjuvant/adjuvant or primary therapy for metastatic disease)
  - Cisplatin and doxorubicin\(^16-18\)
  - MAP (high-dose methotrexate, cisplatin, and doxorubicin)\(^19,20\)
  - Doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate\(^21\)
  - Ifosfamide and etoposide\(^22\)
  - Ifosfamide, cisplatin, and epirubicin\(^23\)

**Second-line therapy (relapsed or refractory disease)**
- Docetaxel and gemcitabine\(^15\)
- Cyclophosphamide and etoposide\(^24\)
- Cyclophosphamide and topotecan\(^9\)
- Gemcitabine\(^25\)
- Ifosfamide and etoposide\(^26\)
- Ifosfamide, carboplatin, and etoposide\(^14\)
- High-dose methotrexate, etoposide, and ifosfamide\(^27\)
- Samarium-153 ethylene diamine tetramethylene phosphonate (\(^{153}\)Sm-EDTMP) for relapsed or refractory disease beyond second-line therapy\(^28\)

**MFH of Bone**
- Follow osteosarcoma regimens

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*Chemotherapy should include growth factor support (see NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).*

†Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.

\(^1\)Vincristine may be added to any of the regimens below.

References on page 698
coma presenting to Memorial Sloan-Kettering Cancer Center (MSKCC), reporting that nearly 80% of patients would develop metastatic disease and ultimately die of the disease. All patients with extremity osteosarcomas were treated with amputation. The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis of these patients. With current multimodality treatment, approximately three quarters of all patients diagnosed with osteosarcoma are cured. Nearly 90% of adult patients diagnosed with osteosarcoma are successfully treated with limb-sparing approaches rather than amputation; progression-free survival (PFS) has been observed in 60% to 75% of patients with localized Ewing’s sarcoma. In osteosarcoma and Ewing’s sarcoma, a cure is still achievable, even in patients diagnosed with metastatic disease at presentation.18–20

The NCCN Clinical Practice Guidelines in Oncology: Bone Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) focus on chondrosarcoma, Ewing’s sarcoma, and osteosarcoma.

Staging
The 2010 American Joint Committee on Cancer (AJCC) staging classification is shown in the staging table (available online, in these guidelines, at www.NCCN.org [ST-1]). This system is based on the assessment of histologic grade (G), tumor size (T), 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 (available online, in these guidelines, at www.NCCN.org [ST-1]).21 This system stratifies bone and soft tissue sarcomas according to 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 with demonstrated expertise in the management of these tumors. Appropriate team members are listed on page 696. Long-term surveillance and follow-up are necessary when considering the risk for recurrence and comorbidities associated with chemotherapy and radiation therapy (RT). Extended therapy and surveillance may be necessary for long-term survivors to address the potential side effects of surgery, RT, and chemotherapy. Patients should be given a survivorship prescription to schedule follow-ups with a multidisciplinary team. Fertility issues should be discussed with appropriate patients before they start treatment.22

Diagnostic Workup
Suspicion of a malignant bone tumor often begins when a poorly marginated lesion is seen on a plain radiograph in a patient with a painful lesion. In patients younger than 40 years, an aggressive, painful bone lesion has a significant risk for being a malignant primary bone tumor, and referral to an orthopedic oncologist should be considered before further workup. Patients 40 years and older whose plain films and history do not suggest a specific diagnosis should undergo evaluation for metastatic carcinoma, including chest radiograph; chest, abdominal, and pelvic CT; bone scan; mammogram; and other imaging studies as clinically indicated (see page 690).23

All patients with suspected bone sarcomas should undergo complete staging before biopsy. Standard staging workup for a suspected primary bone sarcoma should include chest imaging (chest radiograph or CT to detect pulmonary metastases), appropriate imaging of the primary site (plain radiographs, MRI for local staging, and/or CT scan), and bone scan.24 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 a CBC, lactate dehydrogenase (LDH), or alkaline phosphatase, should be performed before treatment is initiated.

PET is an alternative imaging technique used in the pretreatment staging of soft tissue and bone sarcomas.25 Recent reports have shown the efficacy of PET scans in evaluating chemotherapy response in osteosarcoma and ESFT.26,27

Biopsy
Biopsy should be performed using either core needle or surgical biopsy techniques. At biopsy, careful consideration should be given to appropriate stabiliza-
tion of the affected bone and/or measures to protect against impending pathologic fracture. Because location of the biopsy is critical to limb-salvage techniques, it should be performed at the facility that will provide definitive management of the suspected primary malignant bone tumor.

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, although in selected cases, amputation may be the most appropriate option. However, limb-sparing resection is preferred if reasonable functional outcomes can be achieved. Response to the preoperative regimen should be evaluated with pathologic mapping. Consultation with a physical therapist is recommended to evaluate for mobility training and to determine an appropriate rehabilitation program.

Chondrosarcoma
Chondrosarcomas characteristically produce cartilage matrix from neoplastic tissue devoid of osteoid and may occur at any age, but are more common in older adults. Conventional chondrosarcomas of the bone constitute approximately 85% of all chondrosarcomas and are divided as either primary or central lesions arising from previously normal-appearing bone preformed from cartilage; secondary or peripheral tumors that arise or develop from preexisting benign cartilage lesions, such as enchondromas; or from the cartilaginous portion of an osteochondroma.

Malignant transformation has been reported in lesions found in patients with Ollier’s disease (enchondromatosis). The anatomic location, histologic grade, and size are essential prognostic features of the lesion, despite whether it is primary or secondary, or central or peripheral. Peripheral or secondary tumors are usually low grade with infrequent metastasis. Other rare subtypes that constitute approximately 10% to 15% of all chondrosarcomas include clear cell, dedifferentiated, myxoid, and mesenchymal forms.

Symptoms of chondrosarcoma are usually mild and depend on tumor size and location. Patients with pelvic or axial lesions typically present later in the disease course, because the associated pain has a more insidious onset and often occurs when the tumor has reached a significant size. Central chondrosarcomas show cortical destruction and loss of medullary bone trabeculations on radiographs, as well as calcification and destruction.

MRI will show the intramedullary involvement and extraosseous extension of the tumor. Secondary lesions arise from preexisting lesions. Serial radiographs will show a slow increase in size of the osteochondroma or enchondroma. A cartilage “cap” measuring greater than 2 cm on a preexisting lesion or documented growth after skeletal maturity should suggest sarcomatous transformation.

Treatment
Histologic grade and tumor locations are the most important variables used to determine primary treatment. Resectable low-grade and intracompartmental lesions are treated with intralesional excision with or without adjuvant therapy. Wide excision with negative margins is the preferred treatment for some low-grade lesions because of their larger size and intraarticular or pelvic localization. High-grade (grade II, III, or clear cell) or extracompartmental lesions are treated with wide excision, if resectable, obtaining negative surgical margins.

Unresectable high- and low-grade lesions are treated with RT (see page 691). Proton-beam RT has been associated with excellent local tumor control and long-term survival in patients with low-grade skull base chondrosarcomas.

Chemotherapy is not very effective in chondrosarcomas, especially in conventional and dedifferentiated chondrosarcomas. Although Mitchell et al. reported that adjuvant chemotherapy with cisplatin and doxorubicin was associated with improved survival in patients with dedifferentiated chondrosarcoma, this finding could not be confirmed in other studies. Recently, Cesari et al. reported that the addition of chemotherapy improved survival rates in patients with mesenchymal chondrosarcoma. Another report from the German study group also confirmed that the outcome was better in younger patients. However, no prospective randomized trials have been performed, and therefore the role of chemotherapy in the treatment of chondrosarcomas remains undefined.
No chemotherapy regimens have been established for conventional chondrosarcoma (grades 1–3). The NCCN Bone Cancer Guidelines suggest that dedifferentiated chondrosarcomas could be treated as osteosarcoma, and mesenchymal chondrosarcomas treated as Ewing's sarcoma, best approached as a function of their grade. Both of these options have a category 2B recommendation.

**Surveillance**

Surveillance for low-grade lesions consists of a physical examination, imaging of the lesion, and a chest radiograph every 6 to 12 months for 2 years, then yearly as appropriate. Surveillance for high-grade lesions consists of a physical examination, imaging of the primary site, and/or cross-sectional imaging as indicated. Chest imaging is also indicated every 3 to 6 months for the first 5 years, and yearly thereafter for a minimum of 10 years, because late metastases and recurrences after 5 years are more common with chondrosarcoma than with other sarcomas.\(^\text{35}\) Functional assessment should be performed at every visit (see page 691).

**Relapse**

Local recurrence or relapse should be treated with wide excision, if the lesions are resectable. RT should be considered after wide excision with positive surgical margins (see page 691). Negative surgical margins should be observed. Unresectable recurrences are treated with RT.

Surgical excision is an option for systemic relapse of a high-grade lesion or patients should be encouraged to participate in a clinical trial.

**ESFT**

ESFT are a group of small, round-cell neoplasms that include Ewing's sarcoma, primitive neuroectodermal tumor (PNET), Askin's tumor, PNET of bone, and extraosseous Ewing's sarcoma. Ewing's sarcoma is characterized by the fusion of the EWS gene on chromosome 22q12 with various members of the ETS gene family (FLI1, ERG, ETV1, ETV4, and FEV).\(^\text{5,6}\) The EWS-FLI1 fusion transcript resulting from the chromosomal translocation t(11;22) (q24;q12) is identified in approximately 85% of Ewing's sarcomas, such as Ewing's sarcoma, PNET, and Askin's tumor.

Ewing's sarcoma is poorly differentiated and is also characterized by the strong expression of cell-surface glycoprotein MIC2 (CD99).\(^\text{53,54}\) The expression of MIC2 may be useful in the differential diagnosis of Ewing's sarcoma and PNET from other small round-cell neoplasms, although it is not exclusively specific to these tumors.\(^\text{55}\)

Ewing's sarcoma typically occurs in adolescents and young adults; the most common primary sites are the femur, pelvic bones, and bones of chest wall, although any bone may be affected. When arising in a long bone, the diaphysis is the most frequently affected site and appears mottled on imaging. Periosteal reaction is classic and is referred to as “onion skin” by radiologists.

Patients with Ewing's sarcoma, similar to those with bone sarcomas, present with localized pain or swelling. Unlike with other bone sarcomas, constitutional symptoms, such as fever, weight loss, and fatigue, are occasionally noted at presentation. Abnormal laboratory studies may include elevated serum LDH and leukocytosis.

Important indicators of favorable prognosis include a distal site of primary disease, normal serum LDH level at presentation, and absence of metastatic disease at presentation.\(^\text{56–58}\) Nearly one quarter will present with metastatic disease, which is the most significant adverse prognostic factor in Ewing's sarcoma as it is for other bone sarcomas.\(^\text{59,60}\) Lungs, bones, and bone marrow are the most common sites of metastasis. In a retrospective analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS) Group, 5-year relapse-free survival was 22% for patients with metastatic disease at diagnosis compared with 55% for those without.\(^\text{60}\) The results of the Intergroup Ewing's Sarcoma Study, analyzing the clinicopathologic features of 303 cases of Ewing's sarcoma, showed that patients with primary tumors in pelvic bones have the lowest survival rates compared with those with lesions in distal bones of the extremities.\(^\text{61}\)

**Workup**

When ESFT is suspected, patients should undergo complete staging before biopsy. This should include CT of the chest, plain radiographs of the primary site, CT or MRI of the entire bone or area involved, PET scan, and/or bone scan. An MRI of the spine and pelvis should also be considered. An ongoing diagnostic study is comparing whole-body MRI and conventional imaging for detecting distant metastases in

Cytogenetic analysis of the biopsy specimen should be obtained to evaluate the t(11;22) translocation. Although preliminary reports suggest that EWS-FLI1 translocation is associated with a better prognosis than other variants, this must be evaluated in large clinical trials. Bone marrow biopsy should be considered to complete the workup. Because serum LDH has been shown to have prognostic value as a tumor marker, the NCCN Bone Cancer Guidelines have included this test as part of the initial evaluation (see page 692). Fertility consultation should be considered for women of child-bearing age and men.

**Primary Treatment**

Multiagent chemotherapy regimens, including ifosfamide and/or cyclophosphamide; etoposide; doxorubicin and/or dactinomycin; and vincristine have been shown to be effective in patients with localized Ewing’s sarcoma in single- and multi-institutional collaborative trials in the United States and Europe.65,66 The Intergroup Ewing’s Sarcoma Studies (IESS-I and IESS-II) showed that the 4-drug regimen VACD (vincristine, dactinomycin, cyclophosphamide, and doxorubicin) was superior to the 3-drug regimen VAC (vincristine, dactinomycin, and cyclophosphamide) in terms of relapse-free (60% vs. 24%) and overall survival.67,68

In the Pediatric Oncology Group-Children’s Cancer Group (POG-CCG) study (INT-0091), patients with Ewing’s sarcoma or PNET of the bone were randomized to undergo chemotherapy with VACD alone or alternating with ifosfamide and etoposide (VACD-IE) for 17 cycles.69 In patients with nonmetastatic disease, the 5-year event-free survival rate was 69% in the VACD-IE group compared with 54% in the VACD alone group. Overall survival was also significantly higher among patients in the VACD-IE group (72% vs. 61%). However, the addition of ifosfamide and etoposide to VACD did not improve outcomes of patients with Ewing’s sarcoma or PNET of bone with metastases at diagnosis.70 Kolb et al.71 from MSKCC also reported similar findings. The 4-year event-free and overall survival rates were 82% and 89%, respectively, for patients with locoregional disease, and 12% and 17.8%, respectively, for those with distant metastases.

The EICESS-92 study investigated whether cyclophosphamide has a similar efficacy to ifosfamide in standard-risk patients and whether the addition of etoposide improves survival in high-risk patients with Ewing’s sarcoma. Standard-risk patients (small tumors) were randomly assigned to VAIA (vincristine, dactinomycin, ifosfamide, and doxorubicin) followed by either VAIA or VACA (vincristine, dactinomycin, cyclophosphamide, and doxorubicin).72 High-risk patients (large tumors or metastatic disease at diagnosis) were randomly assigned to VAIA or VAIA plus etoposide (EVAIA). For the standard-risk patients, 3-year event-free survival rates for VACA and VAIA were 73% and 74%, respectively. In the high-risk patients, the 3-year event-free survival rates for EVAIA and VAIA were 52% and 47%, respectively. The results of this study suggest that cyclophosphamide has the same efficacy as ifosfamide in standard-risk patients. Furthermore, the event-free survival rates in the high-risk group, though not statistically significant, suggest a benefit with the addition of etoposide to ifosfamide.

The European Ewing Tumour Working Initiative of National Groups 1999 (EURO-EWING 99) study is designed to evaluate the efficacy and safety of combination chemotherapy with or without peripheral stem cell transplantation, RT, and/or surgery in patients with Ewing’s sarcoma. Six courses of VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) are administered as an intensive induction chemotherapy for patients with ESFT.73

**NCCN Recommendations:** All patients with Ewing’s sarcoma undergo primary treatment followed by local control therapy and adjuvant treatment (see page 693). Primary treatment consists of multiagent chemotherapy along with appropriate growth factor support for 12 to 24 weeks (see the NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors for growth factor support; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). For localized Ewing’s sarcoma, VAC alternating with ifosfamide and etoposide (VAC/IE) given on an every-2-week schedule was found to be more effective than on an every-3-week schedule, with median 3-year event-free survival rates of 76% and 65%, respectively.74

The NCCN guidelines have included the follow-
ing regimens for first-line therapy (primary/neoadjuvant/adjuvant) for patients with localized disease or metastatic disease at presentation (page 697):

- VAC/IE \(^{69}\)
- VIDE \(^{72}\)
- VIA (vincristine, ifosfamide, and doxorubicin) \(^{72}\)

The guidelines recommend VAC (without the alternating cycle of ifosfamide and etoposide) as the preferred option for the treatment for primary metastatic disease at presentation. \(^{70,71}\) VAC/IE, VIDE, and VIA regimens are included as alternative treatment options.

After primary treatment, patients should be restaged with an MRI of the lesion and chest imaging. PET or bone scan can be used for restaging depending on the imaging technique used during initial workup. Patients responding to primary treatment should be treated with local control therapy. Local control options include wide excision with or without preoperative RT, \(^{75,76}\) definitive RT with chemotherapy, or amputation in selected cases (see page 693). Adjuvant chemotherapy with or without RT is recommended (regardless of surgical margins) after local control treatment (surgery or RT). The panel strongly recommends that the duration of chemotherapy be 28 and 49 weeks, depending on the type of regimen and dosing schedule (category 1).

Progressive disease after primary treatment is best managed with RT with or without surgery, followed by chemotherapy or best supportive care.

**Surveillance**

Surveillance of patients with Ewing’s sarcoma consists of a physical examination, and chest and local imaging every 2 to 3 months. \(^{77,78}\) Surveillance intervals should be increased after 2 years, then annually after 5 years.

**Treatment of Relapsed or Refractory Disease**

Approximately 30% to 40% of patients with Ewing’s sarcoma experience recurrence (local and/or distant) and have a very poor prognosis. The timing and type of recurrence are the important prognostic factors; those with longer time to first recurrence have a better chance of survival. Late relapse (≥ 2 years after diagnosis), lung-only metastases, and local recurrence that can be treated with radical surgery and intensive chemotherapy are the most favorable prognostic factors, whereas early relapses (< 2 years after diagnosis) with metastases in the lungs and/or other sites, recurrence at local and distant sites, elevated LDH at initial diagnosis, and initial recurrence are considered adverse prognostic factors. \(^{79–81}\)

Ifosfamide in combination with etoposide with or without carboplatin has been evaluated in clinical trials for the treatment of patients with relapsed or refractory sarcoma. \(^{82,83}\) In a phase II study, the combination of ifosfamide with mesna and etoposide was highly active, with acceptable toxicity in the treatment of recurrent sarcomas in children and young adults. \(^{82}\) In phase I and II studies conducted by the CCG, the overall response rate in patients with recurrent or refractory sarcoma was 51%; the overall survival rates at 1 and 2 years were 49% and 28%, respectively. Overall survival appeared significantly improved in patients who experienced a complete or partial response. \(^{83}\)

Docetaxel in combination with gemcitabine was found to be well tolerated and showed antitumor activity in the treatment of children and young adults with refractory bone sarcoma. \(^{84}\) Topoisomerase I inhibitors, topotecan \(^{85–88}\) and irinotecan, \(^{89–91}\) in combination with cyclophosphamide and temozolomide, respectively, have shown promising response rates in patients with relapsed or refractory solid tumors. Cyclophosphamide and irinotecan produced a 44% response rate (35% of patients had a complete and 9% a partial response) in patients with recurrent or refractory Ewing’s sarcoma. \(^{86}\) After a median follow-up of 23.1 months, 25.9% of patients were in continuous remission. In a retrospective analysis of patients with recurrent or progressive Ewing’s sarcoma treated with irinotecan and temozolomide at MSKCC, the median time-to-progression (TTP) was 8.3 months. \(^{88}\) In those with recurrent disease, TTP was 16.2 months. Median TTP was better for patients experiencing a 2-year first remission and those with primary localized disease than for patients who experienced relapse within 2 years from diagnosis and for those with metastatic disease at diagnosis.

Inhibition of insulin-like growth factor-1 receptor (IGF-1R) may be an interesting approach in the treatment of some subtypes of sarcomas. Monoclonal antibodies, such as figitumumab and R1507, have shown safety and suggested possible efficacy in early-phase trials for patients with relapsed or refractory sarcomas, including Ewing’s sarcoma.

High-dose chemotherapy with stem cell rescue (HDT/SCR) has been evaluated in patients with...
relapsed or progressive Ewing’s sarcoma in several small studies.\textsuperscript{92–98} The role of this approach in high-risk patients has yet to be determined in prospective randomized studies.

**NCCN Recommendations:** Treatment options for patients with relapsed or refractory disease include participation in a clinical trial, or chemotherapy with or without RT (see page 693). If a relapse is delayed, as sometimes occurs with this sarcoma, retreatment with the previously effective regimen may be useful. The NCCN guidelines have included the following regimens as options for patients with relapsed or refractory disease (see page 697):

- Cyclophosphamide and topotecan
- Temozolomide and irinotecan
- Ifosfamide and etoposide
- Ifosfamide, carboplatin, and etoposide
- Docetaxel and gemcitabine

All patients with recurrent and metastatic disease should be considered for clinical trials investigating new treatment approaches.

**Osteosarcoma**

Osteosarcoma is the most common primary malignant bone tumor in children and young adults;\textsuperscript{1} the median age at diagnosis is 20 years. Osteosarcoma has 11 known variants with variable natural histories. Classic osteosarcoma constitutes nearly 80\% of osteosarcoma and is always a high-grade spindle cell tumor that produces osteoid or immature bone. The most frequent sites for this cancer are the metaphyseal areas of the distal femur or proximal tibia, which are the sites of maximum growth.

Although most osteosarcomas are medullary and high-grade, parosteal lesions are juxtacortical and occur most often in the posterior distal femur. This variant tends to metastasize later than the classic form and has low histologic grade. Another juxtacortical variant is periosteal osteosarcomas, which most often involves the femur followed by theibia and behaves with a severity that is intermediate between the parosteal and classic lesions.\textsuperscript{99} Other variants include osteosarcoma secondary to Paget’s disease or prior irradiation. Patients with retinoblastoma are also at an increased risk for developing a very aggressive variant of osteosarcoma.

Pain and swelling are the most frequent early symptoms. Pain in the beginning is often intermit-
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.

**Primary Treatment**

Although surgery remains an essential part of osteosarcoma management, the addition of adjuvant and neoadjuvant chemotherapy regimens has improved outcomes in patients with localized osteosarcoma. Early trials used multiagent chemotherapy regimens, including at least 3 or more of the following drugs: doxorubicin; cisplatin; bleomycin; cyclophosphamide or ifosfamide; dactinomycin; and high-dose methotrexate. The updated results of the randomized Multi-Institutional Osteosarcoma Study (MIOS) showed that 6-year event-free survival was significantly higher in patients randomized to adjuvant chemotherapy than in those who underwent observation only after surgery (61% and 11%, respectively).

Subsequent clinical trials have shown that short intensive chemotherapy regimens produce excellent long-term results, similar to those achieved with multiagent chemotherapy. In a randomized trial conducted by the European Osteosarcoma group, combination doxorubicin and cisplatin was better tolerated in patients with operable nonmetastatic osteosarcoma than a multidrug regimen, with no difference in survival between the groups. For both groups, the 3- and 5-year overall survival rates were 65% and 55%, respectively, and progression-free survival at 5 years was 44%. In a phase II/III trial, high-dose ifosfamide in combination with etoposide was effective as induction therapy in patients with newly diagnosed metastatic osteosarcoma despite significant myelosuppression, infection, and renal toxicity. The overall response rate was 59%, and projected 2-year progression-free survival rate for patients with metastases to lung was 39%. The survival rate for patients with bone metastases (with or without pulmonary metastases) was 58%. Combination cisplatin, ifosfamide, and epirubicin was also an active and reasonably well-tolerated regimen in patients with nonmetastatic extremity osteosarcoma, with a phase II study with a median follow-up of 64 months showing 5-year disease-free and overall survival rates of 41.9% and 48.2%, respectively.

Although neoadjuvant chemotherapy is associated with an improved prognosis in patients with high-grade localized osteosarcoma, the results were significantly poorer in those with metastatic disease at presentation. Two-year event-free and overall survival rates were 21% and 55%, respectively, versus 75% and 94% in patients with nonmetastatic disease at presentation, treated with the same chemotherapy protocol. 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. 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. showed that the 5-year disease-free and overall survival rates correlated significantly with histologic response to chemotherapy and were 67.9% versus 51.3% (P < .0001) in patients with good response and 78.4% versus 63.7% (P < .0001) in those with poor response, respectively. A report from the CCG also confirmed these findings; 8-year postoperative event-free and overall survival rates were 81% and 87%, respectively, in good responders to neoadjuvant therapy, and for poor survivors were 46% and 52%, respectively. Attempts to improve the outcome of poor responders through modifying the regimen remain unsuccessful.

The safety and efficacy of HDT/SCR in patients with newly diagnosed metastatic osteosarcoma or relapsed osteosarcoma has also been evaluated. In the Italian sarcoma group study, treatment with carboplatin and etoposide followed by SCR, combined with surgery, induced complete response in chemosensitive patients. Transplant-related mortality was 3.1%. The 3-year overall and disease-free survival rates were 20% and 12%, respectively. The efficacy of this approach in high-risk patients remains to be determined in prospective randomized studies.

**NCCN Recommendations:** Wide excision is the primary treatment for patients with low-grade (intraduillary and surface) osteosarcomas, whereas preoperative chemotherapy is preferred for those with high-grade osteosarcoma (category 1) and periosteal lesions, before wide excision. Selected elderly patients may benefit from immediate surgery (see page 694).

After wide excision (for resectable lesions), postoperative chemotherapy is recommended for patients with low-grade or periosteal sarcomas with pathologic findings of high-grade disease. For high-grade os-
teosarcoma after wide excision, patients with a good histologic response should continue to undergo several more cycles of the same chemotherapy, whereas patients with a poor response should be considered for chemotherapy with a different regimen. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable after preoperative chemotherapy (see page 694).

Chemotherapy can be given intra-arterially or intravenously and should include appropriate growth factor support (see the NCCN Myeloid Growth Factors Guidelines for growth factor support [to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org]). The NCCN Bone Cancer Guidelines have included the following regimens for first-line therapy (primary/neoadjuvant/adjuvant) in patients with localized disease or primary therapy for metastatic disease (see page 697):

- Cisplatin and doxorubicin
- MAP (high-dose methotrexate, cisplatin, and doxorubicin)
- Doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate
- Ifosfamide and etoposide
- Ifosfamide, cisplatin, and epirubicin

**Surveillance**

Once treatment is completed, surveillance should occur every 3 months for 2 years, then every 4 months for year 3, and then every 6 months for years 4 and 5, and yearly thereafter. Examination should include a complete physical, chest imaging, and plain film of the extremity. Chest CT should be performed if the plain chest radiograph becomes abnormal. Bone scan (category 2B) may also be considered (see page 695). Functional reassessment should be performed at every visit.

**Treatment for Relapsed or Refractory Disease**

Approximately 30% of patients with localized disease and 80% presenting with metastatic disease will experience relapse. The presence of solitary metastases 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 third recurrence have a poor prognosis.

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials. In a phase II trial of the 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 stable disease in 35% of patients with relapsed high-risk osteosarcoma. Progression-free survival 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 been effective in the treatment of patients with relapsed or refractory bone sarcomas.

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. Andersen 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 show that 153Sm-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.

**NCCN Recommendations:** The optimal treatment strategy for patients with relapsed or metastatic disease has yet to be defined. If relapse occurs, patients should undergo second-line chemotherapy and/or surgical resection (see page 695). Surveillance is recommended for those who respond to second-line therapy. The NCCN Bone Cancer Guidelines include the following regimens as options for patients with relapsed or refractory disease (see page 697):

- Docetaxel and gemcitabine
- Cyclophosphamide and etoposide
- Cyclophosphamide and topotecan
- Gemcitabine
- Ifosfamide and etoposide
- Ifosfamide, carboplatin, and etoposide
- High-dose methotrexate, etoposide, and ifosfamide

Patients who experience progressive disease after second-line therapy should be treated with resection, RT for palliation, or best supportive care (see page 695). Participation in a clinical trial should be strongly encouraged. The guidelines also include 153Sm-EDTMP as a treatment option for relapsed disease after second-line therapy.
**Summary**

Primary bone cancers are rare neoplasms, with osteosarcoma, chondrosarcoma, and Ewing's sarcoma the 3 most common forms.

Chondrosarcoma is usually found in middle-aged and older adults. Wide excision is the preferred treatment for resectable low- and high-grade chondrosarcomas. Intralesional excision with or without adjuvant therapy is an alternative option for low-grade lesions. In small series of reports, the addition of chemotherapy improved outcomes in patients with mesenchymal chondrosarcomas. However, the role of chemotherapy in the treatment of chondrosarcomas is not yet defined.

Ewing's sarcoma is characterized by a chromosomal translocation t(11;22), resulting in the fusion of EWS gene with various members of the ETS family of genes, and develops mainly in children and young adults. Multiagent chemotherapy is the primary treatment for patients with Ewing's sarcoma. Patients who experience response to primary treatment are treated with local control therapy (surgery or radiation) followed by adjuvant chemotherapy. Progressive disease is best managed with RT with or without surgery followed by chemotherapy or best supportive care.

Osteosarcoma occurs mainly in children and young adults. Wide excision is the primary treatment for patients with low-grade osteosarcomas, whereas preoperative chemotherapy is preferred before wide excision for high-grade osteosarcoma and periosteal lesions. After wide excision (for resectable lesions), postoperative chemotherapy is recommended for patients with low-grade or periosteal sarcomas with pathologic findings of high-grade disease and those with high-grade sarcoma. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable after preoperative chemotherapy. Patients with relapsed or refractory disease should be treated with second-line therapy. Participation in a clinical trial should be strongly encouraged for patients experiencing progressive disease after second-line therapy.

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and Ewing's sarcoma. A small subset of patients diagnosed with metastatic disease at presentation can be cured with the proper treatment. Consistent with the NCCN philosophy, the panel encourages patients to participate in well-designed clinical trials to enable further advances.

**References**

Bone Cancer


### Individual Disclosures for the NCCN Bone Cancer Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
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The NCCN guidelines staff have no conflicts to disclose.