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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Bone Cancer guidelines from the 1.2009 version include:

**(BONE-1)**
- ≥ 40 pathway: After workup, branch points changed to “No other lesions (possible bone primary)” and “Other lesions (non-bone primary suspected)”.

**Chondrosarcoma:**
**(CHON-1):**
- Footnote “c” that states, “There is considerable controversy regarding the grading of Chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should also be considered in deciding local treatment.” is new to the page.

**Ewing's Sarcoma:**
**(EW-1):**
- Primary Treatment: “Multiagent chemotherapy” changed from category 2A to category 1.
- Footnote “c” was revised as follows, “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.

**(EW-2):**
- First column:
  - Top pathway: Changed to “Stable disease following response to primary treatment”.
  - Bottom pathway: The phrase “Unresponsive” was removed from “Unresponsive or progressive disease...”
- Surveillance: “CBC” changed from annually to every 2-3 months as part of the “Physical exam, chest...”
- Progressive Disease/Relapse column: Recommendations for “Early relapse and Late relapse” were combined and are now listed as “Clinical trial or Chemotherapy ± RT” with corresponding footnote “j” that states, “Chemotherapy regimens can include irinotecan/temozolomide or cyclophosphamide/topotecan” is new to the page.
- Footnote “h”: “There is category 1 evidence for a total of 36 weeks of chemotherapy including that received prior to local therapy.” changed to “There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.”
- Footnote “i” is new to the page.

**Osteosarcoma:**
- No changes to the Guidelines.

**(BONE-B):** Principles of Bone Cancer Management
- Biopsy; Bullet #7: “Fresh tissue is needed...” changed to “Fresh tissue may be needed...”

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WORKUP\textsuperscript{b}

\textbf{Painful bone lesion\textsuperscript{a}} \rightarrow \textbf{Abnormal radiograph} \\

\textbf{< 40} \rightarrow \textbf{Refer to orthopaedic oncologist}  \\
- Biopsy should be performed at treating institution

\textbf{≥ 40} \rightarrow \textbf{Workup for potential bone metastasis}  \\
- H&P
- As clinically indicated:  
  - Bone scan
  - Chest radiograph
  - SPEP/labs
  - Chest/abdominal/pelvic CT
  - PSA
  - Mammogram

\textbf{No other lesions} (Possible bone primary)  \\
- Refer to orthopaedic oncologist  \\
- Biopsy should be performed at treating institution

\textbf{Other lesions} (Non-bone primary suspected)  \\
- Refer to appropriate NCCN Guideline.  
  Go to NCCN Table of Contents

\textbf{See specific bone sarcomas Table of Contents}

\textsuperscript{a}Painless bone lesions require evaluation by a musculoskeletal radiologist and referral to multidisciplinary teams.  See Multidisciplinary Team (BONE-A).

\textsuperscript{b}See Principles of Bone Cancer Management (BONE-B).

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## Chondrosarcoma

<table>
<thead>
<tr>
<th>PRESENTATIONa,b,c</th>
<th>PRIMARY TREATMENT</th>
<th>SURVEILLANCE</th>
<th>RELAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade and Intracompartmental</td>
<td><strong>Intralesional excision ± surgical adjuvant or</strong> Wide excision, d if resectable or Consider RT, if unresectable</td>
<td>Physical exam, chest and lesion x-ray every 6-12 mo for 2 y then yearly as appropriate</td>
<td>Local recurrence</td>
</tr>
</tbody>
</table>

| High grade (grade II, grade III) or Clear cell or Extracompartmental | **Wide excision, d if resectable or** Consider RT, if unresectable | • Physical exam  
• Primary site radiographs and/or cross-sectional imaging as indicated  
• Chest imaging every 3-6 mo for 5 y, then yearly for a minimum of 10 y  
• Reassess function at every follow-up visit | Local relapse  
Wide excision, d if resectable or RT, if unresectable  
Systemic relapse  
Clinical trial or Surgical excision |

| Dedifferentiated | Treat as osteosarcoma (category 2B)  
See NCCN Osteosarcoma Guidelines (OSTEO-1) |

| Mesenchymal | Treat as Ewing’s Sarcoma (category 2B)  
See NCCN Ewing’s Sarcoma Guidelines (EW-1) |

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### References:
- See Multidisciplinary Team (BONE-A).
- See Principles of Bone Cancer Management (BONE-B).
- There is considerable controversy regarding the grading of Chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should also be considered in deciding local treatment.
- Wide excision should provide negative surgical margins for tumor. This may be achieved by either limb-sparing resection or limb amputation.
Ewing's sarcoma

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

**WORKUP**

**PRIMARY TREATMENT**
- Multiagent chemotherapy (category 1) for at least 12-24 weeks prior to local therapy

**RESTAGE**
- For patients with localized disease
  - Restage with:
    - Chest imaging
    - Local imaging
    - Consider PET scan or bone scan

**Response**
- See Stable disease following response to Primary Treatment (EW-2)
- See Progressive disease following Primary Treatment (EW-2)

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

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**Bone Cancer**

**Ewing’s Sarcoma**

**LOCAL CONTROL THERAPY**

- Stable disease following response to primary treatment
  - Wide excision
  - Definitive RT and chemotherapy
    - Positive margins
    - Negative margins
  - Preoperative RT
    - Wide excision
  - 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)
- Post-operative chemotherapy, consider RT depending on margin status

**SURVEILLANCE**

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

**PROGRESSIVE DISEASE/RELAPSE**

**Early relapse**
- Clinical trial or Chemotherapy ± RT

**Late relapse**
- Chemotherapy or Best supportive care

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1. Use the same imaging technique that was performed in the initial workup.
2. RT may be considered for close margins.
3. There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.
4. For late relapse, consider re-treatment with previously effective regimen.
5. Chemotherapy regimens can include irinotecan/temozolomide or cyclophosphamide/topotecan.
WORKUP\textsuperscript{a,b}

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

Low grade osteosarcoma\textsuperscript{c}:

- Intramedullary + surface

High grade osteosarcoma:

- Intramedullary + surface

Primary Treatment

- Wide excision

Low grade

- Chemotherapy\textsuperscript{d}

High grade

- Consider chemotherapy\textsuperscript{d}

- Wide excision

See Primary Treatment (OSTEO-2)

ADJUVANT TREATMENT

See Surveillance (OSTEO-3)

\textsuperscript{a} See Multidisciplinary Team (BONE-A).
\textsuperscript{b} See Principles of Bone Cancer Management (BONE-B).
\textsuperscript{c} Dedifferentiated parosteal osteosarcomas are not considered to be low grade tumors.
\textsuperscript{d} Chemotherapy may be intravenous or intra-arterial and should include a combination of at least two of the following agents: (doxorubicin, cisplatin, ifosfamide, high-dose methotrexate) and growth factors (See NCCN Myeloid Growth Factors Guideline).

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**Bone Cancer**

**Osteosarcoma**

**Primary Treatment**

**Preoperative Chemotherapy (category 1)**

- Wide excision, if resectable

- Consider additional local therapy

- Consider changing chemotherapy

**Resectable tumor as appropriate:**

- Restage with pretreatment imaging modalities:
  - Chest imaging
  - Local imaging
  - Consider PET scan
  - Consider bone scan

**Unresectable**

- RT ± sensitizers
- Samarium

- Chemotherapy

**Positive margins**

- Good response
  - Consider additional local therapy
  - Consider changing chemotherapy

- Poor response
  - Consider changing chemotherapy

**Negative margins**

- Good response
  - Chemotherapy

- Poor response
  - Consider changing chemotherapy

**High grade osteosarcoma:** Intramedullary + surface

- Preoperative chemotherapy (category 1)

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*d* Chemotherapy may be intravenous or intra-arterial and should include a combination of at least two of the following agents: (doxorubicin, cisplatin, ifosfamide, high-dose methotrexate) and growth factors (See NCCN Myeloid Growth Factors Guideline).

*e* Selected elderly patients may benefit from immediate surgery.

*f* Response defined by pathologic mapping.

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

- Physical exam
- Chest imaging
- CBC
- Local imaging: Consider PET scan and/or 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 and/or resection if possible → Response → Surveillance

Relapse → Resect or Best supportive care or Clinical trial or Samarium or Palliative RT
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**
- 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

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PRINCIPLES OF BONE CANCER MANAGEMENT

Biopsy
- Biopsy diagnosis is necessary prior to any surgical procedure or fixation of primary site.
- Optimally performed at center which 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.
- 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, ALP, may have relevance in the diagnosis, prognosis, and management of bone sarcoma patients and should be done prior to definitive treatment and periodically during treatment and surveillance.

Treatment
- Fertility issues should be addressed with patients prior to commencing chemotherapy.
- Preferably, care for bone cancer patients should be delivered directly by physicians on the multidisciplinary team (category 1).
  See (BONE-A)

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 for long-term survivors.

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### Staging

#### Table 1

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for Bone Sarcomas**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
<th>Histopathologic Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>MX</td>
<td>GX</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
<td>G0</td>
</tr>
<tr>
<td>T1</td>
<td>N1</td>
<td>M1</td>
<td>G1</td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
<td>M1a</td>
<td>G1</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M1b</td>
<td>G1</td>
</tr>
</tbody>
</table>

- **Primary Tumor (T)**
  - **TX**: Primary tumor cannot be assessed
  - **T0**: No evidence of primary tumor
  - **T1**: Tumor 8 cm or less in greatest dimension
  - **T2**: Tumor more than 8 cm in greatest dimension
  - **T3**: Discontinuous tumors in the primary bone site

- **Regional Lymph Nodes (N)**
  - **NX**: Regional lymph nodes cannot be assessed
  - **N0**: No regional lymph node metastasis
  - **N1**: Regional lymph node metastasis

- **Distant Metastasis (M)**
  - **MX**: Distant metastasis cannot be assessed
  - **M0**: No distant metastasis
  - **M1**: Distant metastasis
    - **M1a**: Lung
    - **M1b**: Other distant sites

- **Histopathologic Grade (G)**
  - **GX**: Grade cannot be assessed
  - **G1**: Well differentiated — Low Grade
  - **G2**: Moderately differentiated — Low Grade
  - **G3**: Poorly differentiated — High Grade
  - **G4**: Undifferentiated — High Grade

**Note**: Ewing's sarcoma is classified as G4.

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Low (G1)</td>
<td>Intracompartmental (T1)</td>
</tr>
<tr>
<td>IB</td>
<td>Low (G1)</td>
<td>Extraparlemental (T2)</td>
</tr>
<tr>
<td>IIA</td>
<td>High (G2)</td>
<td>Intracompartmental (T1)</td>
</tr>
<tr>
<td>IIB</td>
<td>High (G2)</td>
<td>Extraparlemental (T2)</td>
</tr>
<tr>
<td>III</td>
<td>Any (G) + Regional or distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

**Surgical Staging System (SSS)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Low (G1)</td>
<td>Intracompartmental (T1)</td>
</tr>
<tr>
<td>IB</td>
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<td>High (G2)</td>
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<td>III</td>
<td>Any (G) + Regional or distant metastasis</td>
<td></td>
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</table>

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Primary Bone cancers are extremely rare neoplasms, accounting for less than 0.2% of all cancers. \(^1\) An estimated 2,380, new cases will be diagnosed in 2008 in the US and 1470 people will die from the disease. \(^5\) Primary bone cancers demonstrate wide clinical heterogeneity, and, perhaps most importantly, are often curable with proper treatment. Various types of bone cancers are named based on their histologic origin: chondrosarcomas arise from cartilage, osteosarcomas arise from bone, and fibrogenic tissue is the origin of fibrosarcoma of bone, whereas vascular tissue gives rise to hemangiopericytoma and hemangiopericytoma. Notochordal tissue gives rise to chordoma. Several primary bone cancers, including Ewing’s family of tumors, are of unknown histologic origin.

Osteosarcoma (35%), chondrosarcoma (30%), and the Ewing’s sarcoma (16%) are the three most common forms of bone cancer. Osteosarcoma and Ewing’s sarcoma develop mainly in children and young adults. Chondrosarcoma is usually found in middle-aged and older adults. Malignant fibrous histiocytoma (MFH) and fibrosarcoma of the bone constitute less than 1% of all primary bone tumors. The NCCN Bone cancer guidelines focus on chondrosarcoma, Ewing’s sarcoma and osteosarcoma.

In the past, the diagnosis of osteosarcoma and Ewing’s sarcoma was associated with a poor prognosis. A generation ago, Marcove and colleagues described the survival pattern of newly diagnosed patients with osteosarcoma presenting to Memorial Sloan-Kettering Hospital. Nearly 80% of osteosarcoma patients would develop metastatic disease and ultimately succumb to the disease. All patients with extremity osteosarcomas were treated with amputation. The development of multi-agent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and Ewing’s sarcoma. With current multi-modality treatment, approximately three quarters of all patients diagnosed with osteosarcoma are cured. Nearly 90% of adult patients diagnosed with osteosarcoma can be treated successfully with limb-sparing approaches rather than amputation, and 60-75% progression-free survival has been observed in patients with localized Ewing’s sarcoma. In both osteosarcoma and Ewing’s, cure is still achievable, even in patients diagnosed with metastatic disease at presentation. \(^6^\) \(^8^\)

The pathogenesis and etiology of most bone cancers remains unclear. While 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. There is a quantifiable risk of developing bone sarcomas after therapeutic radiation. \(^9^\) \(^10^\)
Osteosarcoma is the most common radiation-induced sarcoma. It is also the most common second primary malignancy in patients with a history of retinoblastoma.\(^{11,12}\) Li-Fraumeni syndrome is a family cancer syndrome in which there is a germ line mutation of the p53 gene that results in familial sarcomas, including osteosarcoma as well as other sarcomas, early onset of bilateral breast cancer, and several other neoplasms.\(^{13-16}\) Molecular translocations have been established with Ewing’s sarcoma, myxoid chondrosarcoma and other tumors.\(^{17-21}\) Specific genetic alterations also play a role in osteosarcoma pathogenesis.\(^{22,23}\)

### Staging

The 2002 American Joint Committee on Cancer (AJCC) TNM staging classification is shown in Table 1. This system is based on 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 (Table 2).\(^{24}\) This system stratifies both bone and soft-tissue lesions by assessment of the surgical grade (G), the local extent (T), and the 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. Long-term surveillance and follow-up is necessary considering the risk of recurrence and comorbidities associated with chemotherapy and radiation therapy (RT). Extended therapy and surveillance may be necessary for long term survivors to address potential side effects of surgery, RT and chemotherapy. Patients should be given a survivorship prescription to schedule a follow-up with a multidisciplinary team. Fertility issues should be discussed with appropriate patients prior to commencing treatment.\(^{25}\)

#### 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 under 40, 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 prior to further work-up. In patients 40 and over, if plain films and history do not suggest a specific diagnosis, evaluation for a metastatic carcinoma, including chest radiograph, computed tomography (CT) of the chest, abdominal and pelvic, bone scan, mammogram, and other imaging studies as clinically indicated, should be performed.\(^{26}\)

All patients with suspected bone sarcoma should undergo complete staging prior to biopsy. The standard staging work-up for a suspected primary bone sarcoma should include imaging of the chest (chest radiograph or chest CT to detect pulmonary metastases), appropriate imaging of the primary site [plain radiographs, magnetic resonance imaging (MRI) for local staging and/or CT scan] and bone scan.\(^{27}\) 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), alkaline phosphatase (ALP) should be done prior to initiation of treatment.

Positron emission tomography (PET) is an alternative imaging technique that has been utilized in the pretreatment staging of soft-tissue and bone sarcomas.\(^{28}\) Recent reports in literature have demonstrated the utility of PET scans in the evaluation of chemotherapy response in osteosarcoma and Ewing’s Sarcoma family of tumors.\(^{29,30}\)
Biopsy

Biopsy should be done using either core needle or surgical biopsy techniques. At the time of biopsy, careful consideration should be given to appropriate stabilization of that bone and/or measures to protect against impending pathologic fracture. Since placement of the biopsy is critical to limb salvage techniques, biopsy should be performed at the center 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 it is necessary to optimize local control. Local tumor control may be achieved either by 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. Utilizing pathologic mapping, the response to the preoperative regimen should be evaluated. Consultation with a physical therapist is recommended to evaluate for mobility training and to prescribe 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 are divided as follows: (i) primary or central lesions arising from previously normal-appearing bone preformed from cartilage; (ii) 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 arising in patients with Ollier’s disease (enchondromatosis). Whether the lesion is primary or secondary, central or peripheral, the anatomic location, histologic grade and size of the lesion are essential prognostic features. The peripheral or secondary tumors are usually low grade with infrequent metastasis. In addition to the above mentioned types, there are other subtypes that include clear cell, dedifferentiated, myxoid and mesenchymal forms of chondrosarcoma.

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

MRI will show the intramedullary involvement as well as extraosseous extension of the tumor. Secondary lesions arise from preexisting lesions. Serial radiographs will demonstrate a slow increase in size of the osteochondroma or enchondroma. A cartilage “cap” measuring greater than two centimeters on a pre-existing lesion or documented growth after skeletal maturity should raise the suspicion of sarcomatous transformation.

Treatment

The histologic grade and tumor locations are the most important variables that determine the choice of the primary treatment. Resectable low-grade and intracompartmental lesions are treated with intralesional excision with or without adjuvant therapy or wide excision with negative margins. 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. Proton beam radiation therapy has been associated with excellent local tumor control and long-term survival in patients with low-grade base of skull chondrosarcomas.54,55

Chemotherapy is not very effective in chondrosarcomas especially in conventional and dedifferentiated chondrosarcomas. Mitchell and colleagues reported that adjuvant chemotherapy with cisplatin and doxorubicin was associated with improved survival in patients with dedifferentiated chondrosarcoma.56 However, this finding could not be confirmed in other studies.57,58,59 Recently, Cesari and colleagues reported that the addition of chemotherapy improved survival rates in patients with mesenchymal chondrosarcoma.60 Another report from the German study group also confirmed that the outcome was better in younger patients with mesenchymal chondrosarcoma who received chemotherapy.61 Since there have not been any prospective randomized trials, the role of chemotherapy in the treatment of chondrosarcomas remains undefined.

NCCN guidelines suggest that dedifferentiated chondrosarcomas could be treated as osteosarcoma and mesenchymal chondrosarcomas could be 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 exam; imaging of the lesion and chest radiograph every 6-12 months for 2 years and then yearly as appropriate.

Surveillance for high-grade lesions consists of a physical exam, imaging of the primary site and/or cross-sectional imaging as indicated as well as chest imaging every 3-6 months for the first 5 years and yearly thereafter for a minimum of 10 years, as late metastases and recurrences after 5 years are more common with chondrosarcoma than with other sarcomas.39 Functional reassessment should be performed at every visit.

Relapse
Local recurrence or relapse should be treated with wide excision, if the lesions are resectable. RT should be considered following wide excision with positive surgical margins. 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.

Ewing’s Sarcoma Family of Tumors
Ewing’s sarcoma family of tumors (ESFT) includes Ewing’s sarcoma, primitive neuroectodermal tumor (PNET), Askin’s tumor, PNET of bone, and extraosseous Ewing’s sarcoma. Ewing’s sarcoma and primitive neuroectodermal tumor (PNET) are small round cell neoplasms developing in bone and soft tissue, defined by a chromosomal translocation, t(11;22)(q24;q12) and closely related variants. Ewing’s sarcoma is poorly differentiated and is also characterized by strong expression of cell-surface glycoprotein CD99.62-70

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

Patients with Ewing’s sarcoma, as with most patients with bone sarcomas, seek attention because of localized pain or swelling. Unlike 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. Lungs, bones, and bone marrow are the most common sites of metastasis. Nearly one quarter of these patients present with metastatic disease, which is the most significant negative prognostic factor in Ewing’s sarcoma, as it is for other bone sarcomas.  

Workup
If ESFT is suspected as a diagnosis, the patient should undergo complete staging prior to biopsy. This should include CT of the chest, plain radiographs of the primary site as well as a CT or MRI of the entire involved bone or area, PET scan and/or bone scan. MRI of spine and pelvis should be considered. A diagnostic study is underway to compare whole-body MRI and conventional imaging for detecting distant metastases in pediatric patients with Ewing’s family of tumors, lymphoma, rhabdomyosarcoma and neuroblastoma (www.cancer.gov/clinicaltrials/ACRIN-6660). Cytogenetic analysis of the biopsy specimen should be obtained to evaluate the t(11;22) translocation. Bone marrow biopsy should be considered to complete the workup. Serum LDH has been shown to have prognostic value as a tumor marker. NCCN Bone cancer guidelines have included this test as part of initial evaluation.

Treatment
All patients with Ewing’s sarcoma are treated with the following protocol: primary treatment followed by local control therapy and adjuvant treatment.

Primary treatment consists of multiagent chemotherapy along with appropriate growth factor support for 12-24 weeks. For localized Ewing’s sarcoma, chemotherapy given every 2 weeks was found to be more effective than chemotherapy given every 3 weeks. Median 3 year event-free survival was 76% and 65% respectively. Chemotherapy should include a combination of at least three of the following agents (ifosfamide and/or cyclophosphamide, etoposide, doxorubicin, and vincristine) and growth factor support. See NCCN Myeloid Growth Factors in Cancer Treatment Guidelines for growth factor support.

Recent reports from the Children’s Oncology group and Pediatric Oncology Group study shows that the addition of ifosfamide and etoposide to standard chemotherapy significantly improves the outcome for patients with non-metastatic Ewing’s sarcoma, PNET of bone or primitive sarcoma of the bone. However it does not improve the event free survival in patients with metastatic disease at diagnosis. Since this was not a prospective study, the authors acknowledge that the possibility of adding high dose cyclophosphamide could not be excluded and this might be equally effective when administered with etoposide. The results of an European Intergroup study (EICESS-92) confirmed that cyclophosphamide has similar efficacy as ifosfamide in standard risk patients and the addition of etoposide was beneficial for high risk patients.

Patients should be restaged following primary treatment with an MRI of the lesion and chest imaging. PET scan and/or bone scan can be used for restaging depending on the imaging technique that was used in the 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, definitive RT with chemotherapy or amputation in selected cases.

Adjuvant chemotherapy with or without RT is recommended (regardless of surgical margins) following local control treatment (surgery or RT). The panel strongly recommends that chemotherapy should be given for a total of 36 weeks including that received prior to local therapy (category 1).
Unresponsive or progressive disease 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 exam, chest and local imaging every 2-3 months. Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years.

**Relapse**

Recurrent Ewing’s sarcoma has a very poor prognosis with only 13% five-year survival rate. Patients with longer time to first recurrence have a better chance of survival following recurrence. High-dose chemotherapy (HDCT) with stem cell rescue has been shown to be effective in patients with relapsed or progressive Ewing’s sarcoma in several small studies. However, it is associated with severe toxicity. The role of this approach in high-risk patients is yet to be determined in prospective randomized studies.

If a relapse is delayed, as sometimes occurs with this sarcoma, re-treating with previously effective regimen may be useful, whereas RT for local control or participation in a clinical trial should be considered for an early relapse.

All patients with recurrent and metastatic disease should be considered for investigational approaches.

**Osteosarcoma**

Osteosarcoma is the most common primary malignant bone tumor in children and young adults. The median age for all osteosarcoma patients is 20 years. There are eleven known variants of osteosarcoma with quite variable natural histories. Classic osteosarcoma comprises 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. While 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 is low in histologic grade. Another juxtacortical variant is periosteal osteosarcomas, which most often involve the femur followed by the tibia and behave with a severity that is intermediate between that of the parosteal and classic lesions. Other variants include osteosarcoma secondary to Paget’s disease or prior irradiation. Patients with retinoblastoma are also at 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 intermittent and a thorough workup sometimes is delayed because symptoms may be confused with growing pains. Osteosarcoma spreads hematogenously, with the lung being the most common metastatic site.

Tumor site and size, presence and location of metastases, histologic response to chemotherapy are significant prognostic factors for patients with osteosarcoma of the extremities and trunk.

**Workup**

Osteosarcomas present a local problem and a concern for distant metastasis. Imaging of the primary lesions is accomplished with plain radiographs, MRI, and/or CT and bone scan. PET scan can also be considered. Plain radiographs of osteosarcomas show cortical destruction and irregular reactive bone formation. Bone scan, while 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 study to define...
the extent of the lesion within the bone as well as within the soft tissues, to detect “skip” metastases and to evaluate anatomic relationships with the surrounding structures. In addition, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) are frequently elevated in patients with osteosarcoma.

Treatment
Neoadjuvant and adjuvant chemotherapy are effective for localized disease at diagnosis.\textsuperscript{105-112} Chemotherapy can be given either intravenously or intra-arterially and should include at least two of the following agents (doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate with leucovorin rescue) and growth factor support.\textsuperscript{113-121} See NCCN Myeloid Growth Factors in Cancer Treatment Guidelines for growth factor support.

Wide excision is the primary treatment for patients with low-grade (intramedullary and surface) osteosarcomas, whereas preoperative chemotherapy is preferred for high-grade osteosarcoma (category 1) and periosteal lesions, prior to wide excision. Selected elderly patients may benefit from immediate surgery.

Following 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 osteosarcoma, following wide excision, patients with a good histologic response should continue to receive several more cycles of the same chemotherapy, whereas patients with a poor response should be considered for further chemotherapy with a second-line regimen. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable following preoperative chemotherapy.

Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients with no metastatic disease. The safety and efficacy of HDCT in patients with newly diagnosed metastatic osteosarcoma or relapsed osteosarcoma has been reported in two studies. In a phase II-III trial, high dose ifosfamide in combination with etoposide was effective as induction therapy in patients with metastatic osteosarcoma but was also associated with significant infection and renal toxicity.\textsuperscript{122} In the Italian sarcoma group study, HDCT with carboplatin and etoposide followed by stem cell rescue, combined with surgery induced complete response in chemosensitive patients.\textsuperscript{123}

Novel therapies could be considered for patients with unresectable pulmonary or any bone metastases, since prognosis is poor for this group of patients.\textsuperscript{124-128}

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 done if the plain chest radiograph becomes abnormal. Bone scan (category 2B) may also be considered in this case. Functional reassessment should be performed at every visit.

Relapse
If relapse occurs, the patient should again receive chemotherapy and/or surgical resection.\textsuperscript{129,130} Surveillance is recommended for patients who responded to treatment. Patients with progressive disease should be treated with resection, RT for palliation or best supportive care. Participation in a clinical trial should be strongly encouraged.
Summary

Primary bone cancers are extremely rare neoplasms. Osteosarcoma, chondrosarcoma, and Ewing’s sarcoma are the three most common forms of bone cancer.

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 has improved outcomes in patients with mesenchymal chondrosarcomas. However, the role of chemotherapy in the treatment of chondrosarcomas still is not defined.

Ewing’s sarcoma is characterized by a chromosomal translocation, t(11;22) and develops mainly in children and young adults. Multiagent chemotherapy is the primary treatment for patients with Ewing’s sarcoma. Patients responding to primary treatment are treated with local control therapy (surgery or radiation) followed by adjuvant chemotherapy. Unresponsive or 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 for high-grade osteosarcoma and periosseous lesions, prior to wide excision. Following wide excision (for resectable lesions), postoperative chemotherapy is recommended for patients with low-grade or periosseous sarcomas with pathologic findings of high grade disease and those with high-grade sarcoma with good histologic response to primary treatment. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable following preoperative chemotherapy.

The development of multi-agent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and Ewing’s sarcoma. Patients diagnosed with metastatic disease at presentation can be cured with the proper choice of treatment. High-dose chemotherapy with stem cell rescue has been shown to be effective in patients with relapsed or progressive Ewing’s sarcoma in several small studies. High-dose chemotherapy has also been effective in patients with newly diagnosed metastatic osteosarcoma or relapsed osteosarcoma.

Many novel therapies are being studied in clinical trials. Consistent with the NCCN philosophy, the panel encourages patients to participate in well-designed clinical trials to enable further advances.
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