



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology™

Bone Cancer

V.1.2007

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

See [NCCN Categories of Consensus](#)

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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

Summary of the Guidelines updates

Summary of major changes in the 1.2007 version of the Bone Cancer guidelines from the 1.2006 version include:

Chondrosarcoma:

(CHON-1):

- Under Relapse (Local relapse/Local recurrence), the recommendations for “Excision” now includes pathways for “Negative/Postive margins” .
- After Local Relapse, the recommendation for “Amputation” was deleted and RT was clarified to “RT for unresectable disease”

Ewing’s Sarcoma:

(EW-1):

- Workup: “Consider screening MRI of spine and pelvis” and “Fertility consultation as appropriate” were added .
- Under Primary Treatment: Recommendation changed to read “Multiagent chemotherapy at least 12-24 weeks prior to local therapy”.
- Footnote “d”: Now specifies that chemotherapy should include “a combination of at least 3 of the following...” and moved “treat for 12-24 weeks” to the algorithm under “Primary Treatment”.

(EW-2):

- Primary RT pathway was changed to “Definitive RT and chemotherapy”.
- Surveillance: “MRI” recommendation was deleted and the phrase “long term surveillance” was removed from the “Consider bone scan recommendation”.
- New footnote “f” added about considering RT use for close margins.
- Removed 12-24 weeks under all chemotherapy regimens and replaced with new footnote “g” that states “There is category 1 evidence for a total of 36 weeks of chemotherapy including that received prior to local therapy”.
- Lower branch: Now reads “*Unresponsive or progressive disease.....*” and for Progressive disease/relapse recommends “*Chemotherapy or Best supportive care*”.

Osteosarcoma:

(OSTEO-1):

- Workup: “Fertility consultation as appropriate” was added.
- Footnote about the percentage of surface tumors that will be high grade osteosarcomas was deleted.
- Footnote “c”: Removed “2-6 cycles” and “growth factors” now includes a link to the ([NCCN Myeloid Growth Factors Guideline](#)).

(OSTEO-2):

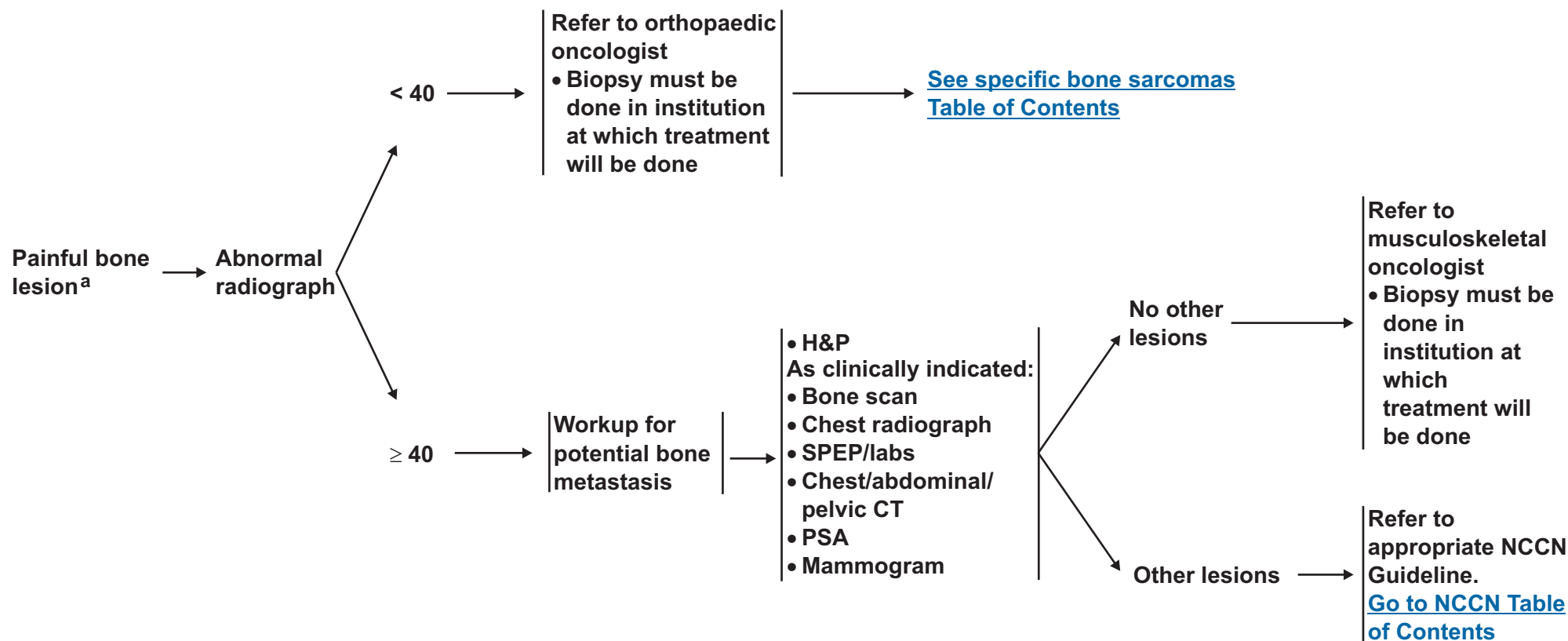
- Included recommendations for Restaging; added footnote “c” to all chemotherapy recommendations; and deleted recommendation for “physical therapy” under Negative margins/Good response .

Attachment Pages:

(BONE-B):

- Biopsy: Noted that Core needle or open biopsy are preferred over FNA.
- Surgery: Included bullet about extending palliative care.
- Added new section about “Long Term Follow-up and Surveillance.”

WORKUP^b



^aPainless bone lesions require evaluation by a musculoskeletal radiologist and referral to multidisciplinary teams. [See Multidisciplinary Team \(BONE-A\)](#).

^b[See Principles of Bone Cancer Management \(BONE-B\)](#).

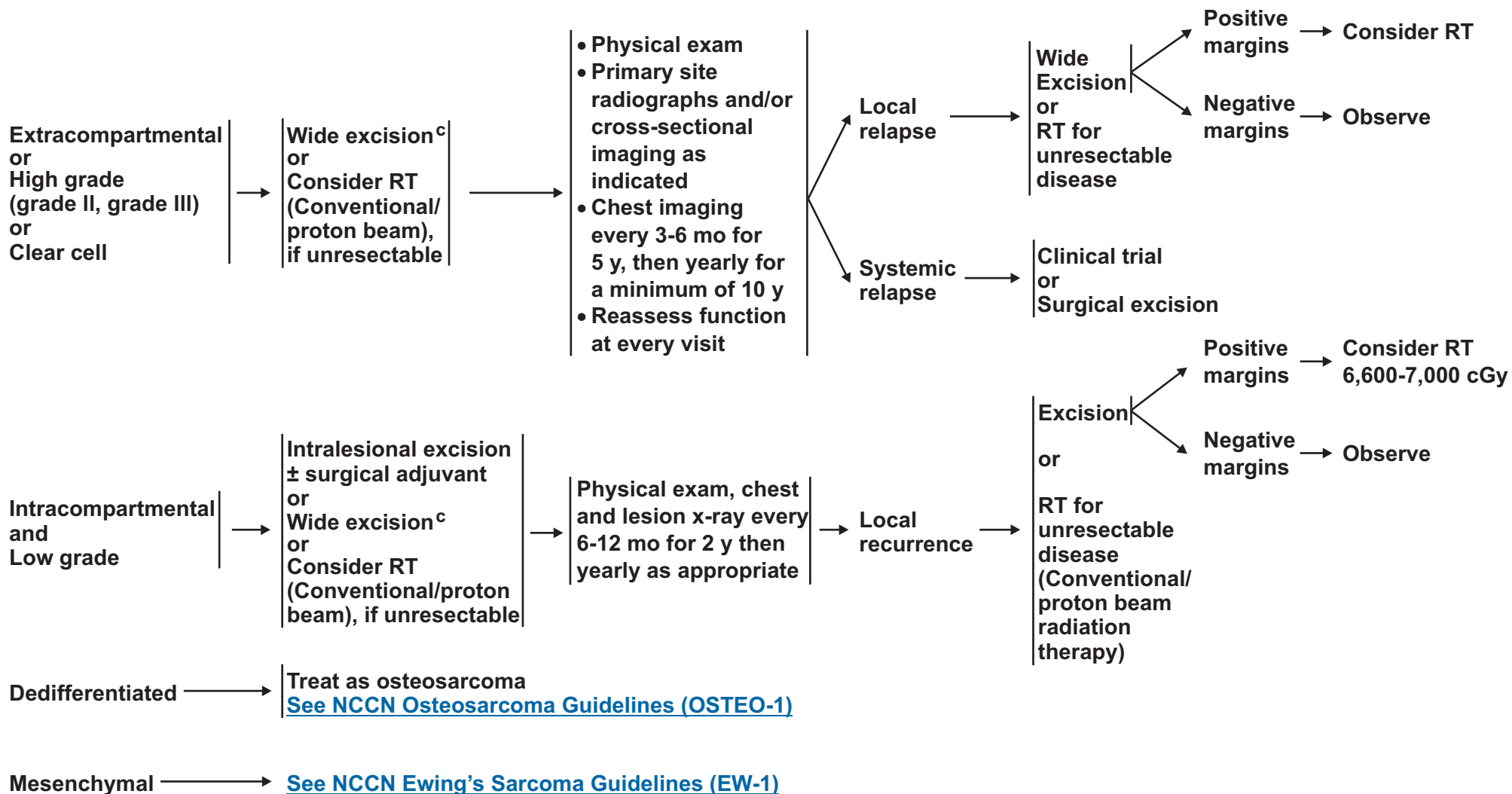
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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRESENTATION ^{a,b}

PRIMARY TREATMENT

SURVEILLANCE

RELAPSE



^a See [Multidisciplinary Team \(BONE-A\)](#).

^b See [Principles of Bone Cancer Management \(BONE-B\)](#).

^c Negative margins in surgery should be obtained. Wide excision may include radical resection and/or amputation; and may be required to achieve negative margins.

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PRESENTATION^{a,b,c}

WORKUP

PRIMARY
TREATMENT

RESTAGE

Ewing's sarcoma
(primitive
neuroectodermal
tumor, Askin's
tumor)

- PET scan as clinically indicated
- MRI ± CT
- Chest CT
- Bone scan
- Bone marrow biopsy (optional)
- Cytogenetics and/or molecular studies^d (may require re-biopsy)
- LDH
- Fertility consultation as appropriate
- Consider screening MRI of spine and pelvis

Multiagent chemotherapy^e
for at least
12-24 weeks
prior to local
therapy

For patients with localized disease
Restage with:
• Chest imaging
• Local imaging
• Bone scan (optional)

For patients with metastatic disease
Restage with:
• Chest imaging
• Local imaging
• Bone scan (optional)
And repeat other abnormal studies

Response

[See Adjuvant Treatment \(EW-2\)](#)

Progressive disease

[See Progressive Disease/Relapse \(EW-2\)](#)

^aSee [Multidisciplinary Team \(BONE-A\)](#).

^bSee [Principles of Bone Cancer Management \(BONE-B\)](#).

^cAny member of the Ewing's family of tumors can be treated using this algorithm.

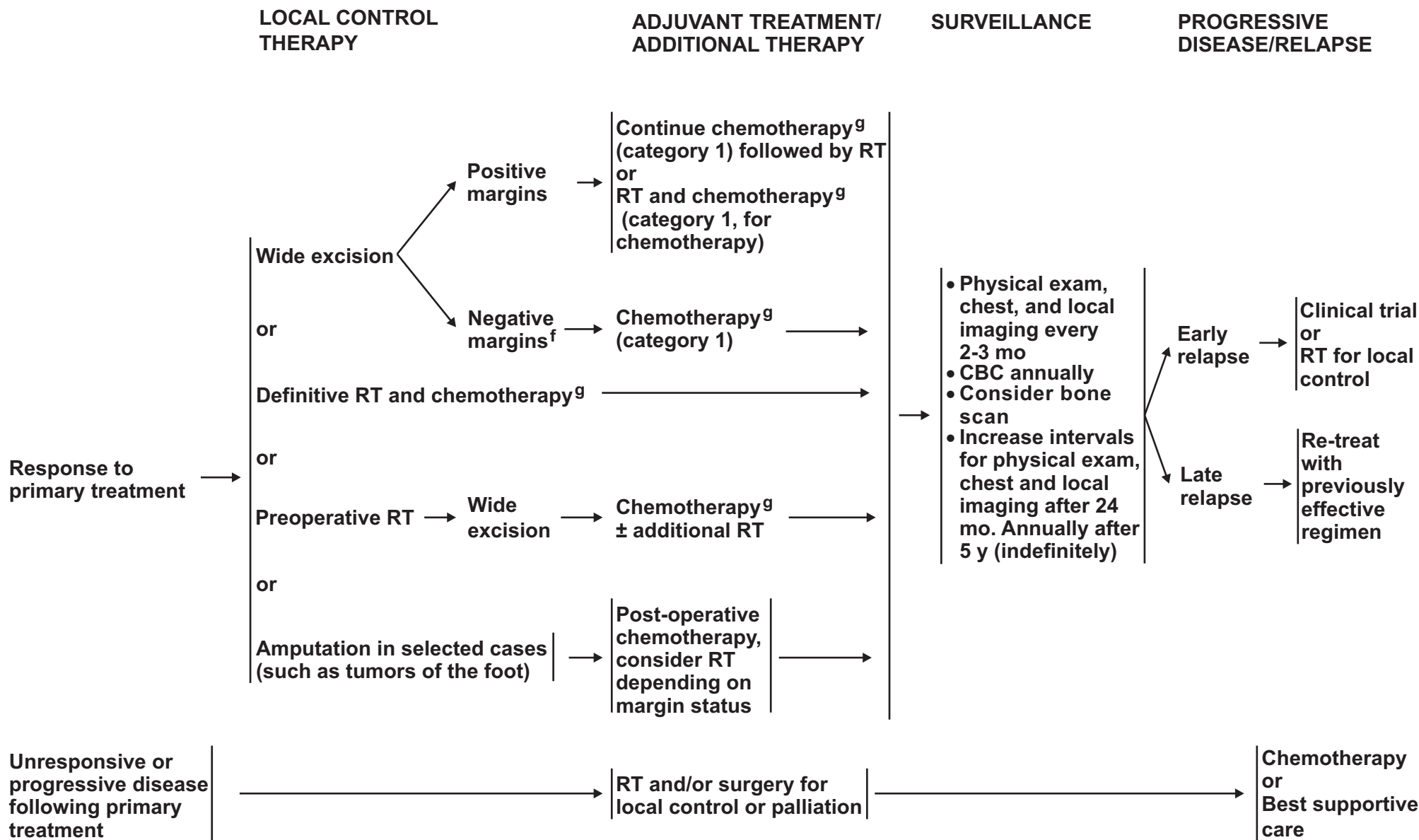
^d90% of Ewing's family tumors will have one of four specific cytogenetic translocations.

^eChemotherapy should include a combination of at least three of the following:

- Ifosfamide and/or cyclophosphamide
- Etoposide
- Doxorubicin
- Vincristine
- Growth factor support ([See NCCN Myeloid Growth Factors Guidelines](#))

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^fRT may be considered for close margins.

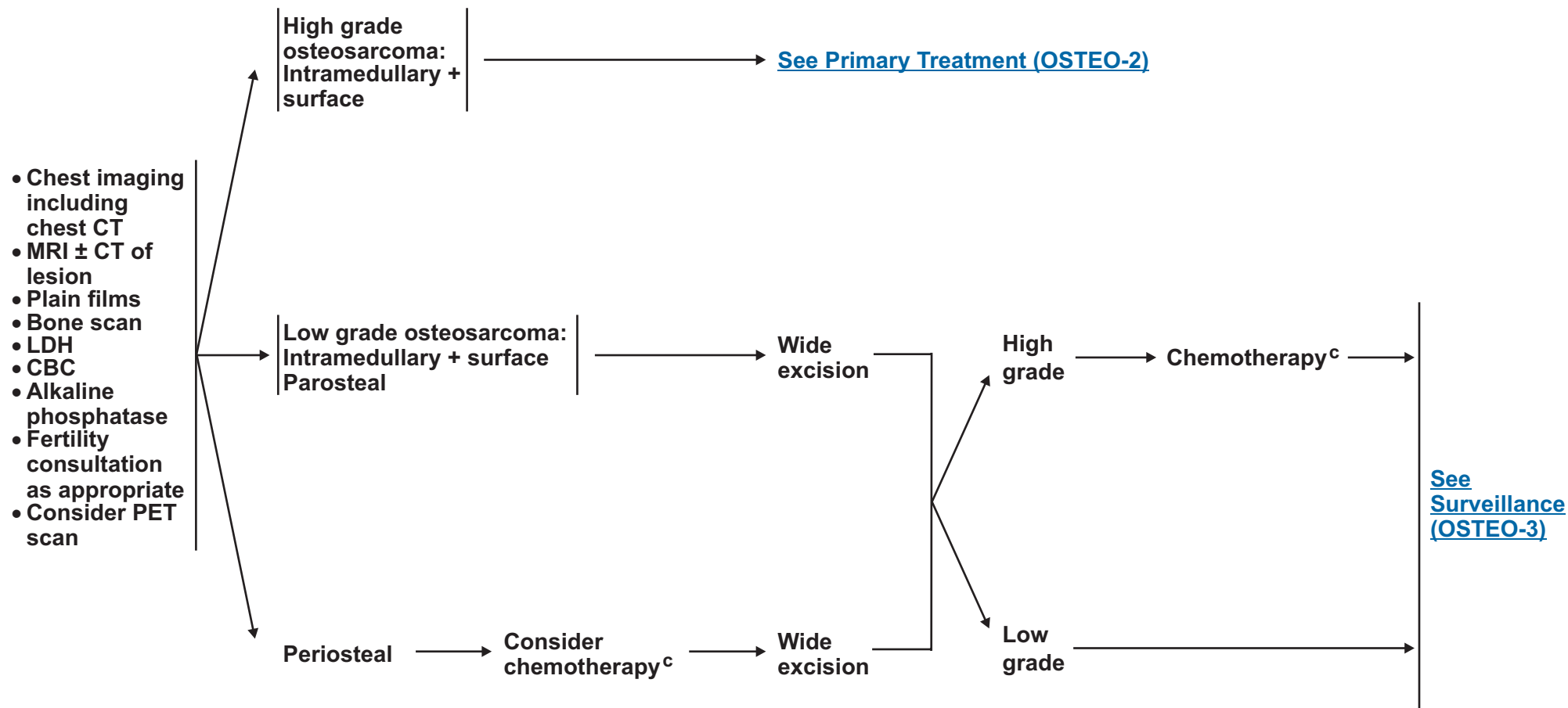
⁹There is category 1 evidence for a total of 36 weeks of chemotherapy including that received prior to local therapy.

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WORKUP^{a,b}

PRIMARY TREATMENT



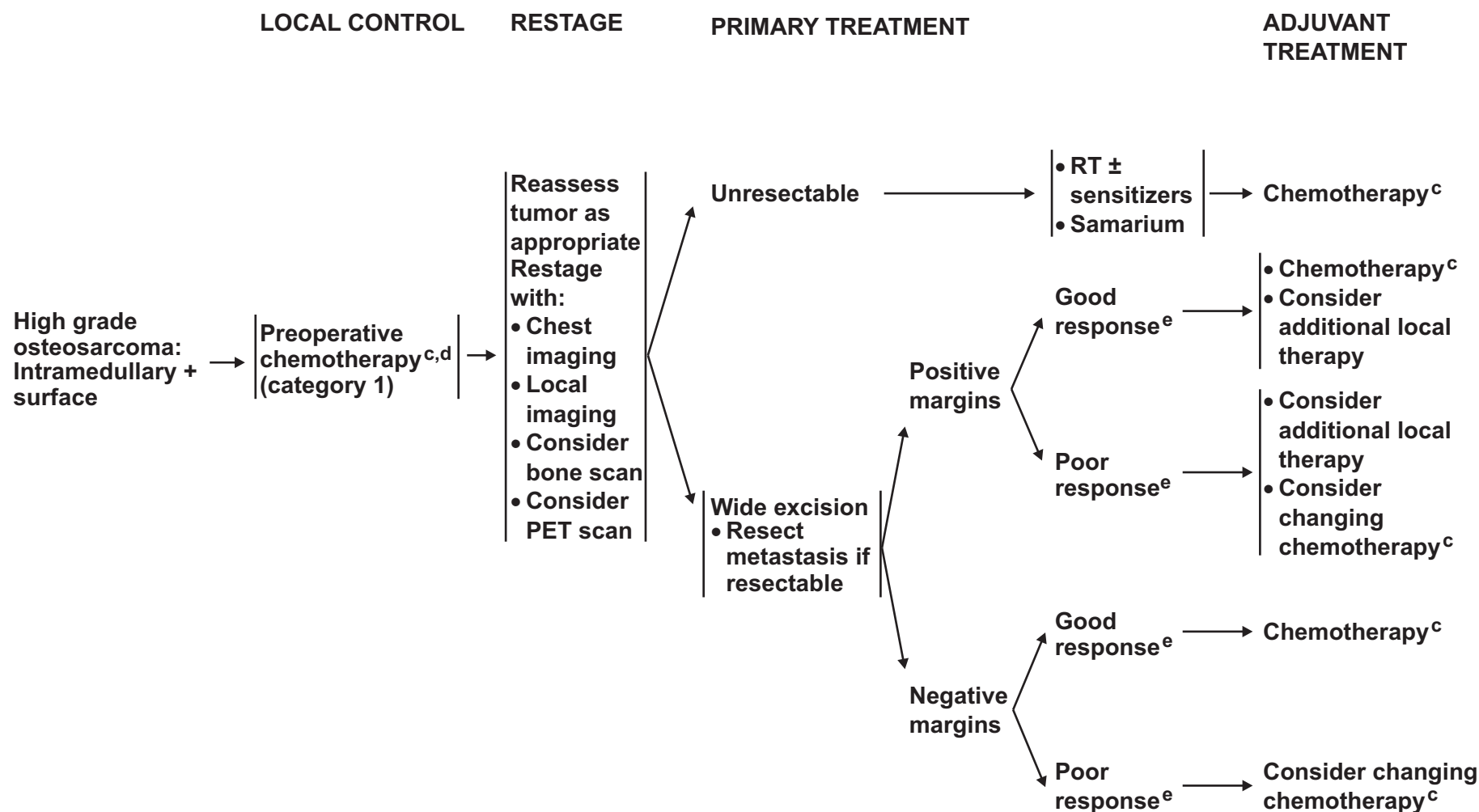
^aSee Multidisciplinary Team (BONE-A).

^bSee Principles of Bone Cancer Management (BONE-B).

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

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[See Surveillance \(OSTEO-3\)](#)

^cChemotherapy may be intravenous or intra-arterial and should include at least two of the following: doxorubicin, cisplatin, ifosfamide, high-dose methotrexate, and growth factors ([See NCCN Myeloid Growth Factors Guideline](#)).

^dSelected elderly patients may benefit from immediate surgery.

^eResponse defined by pathologic mapping.

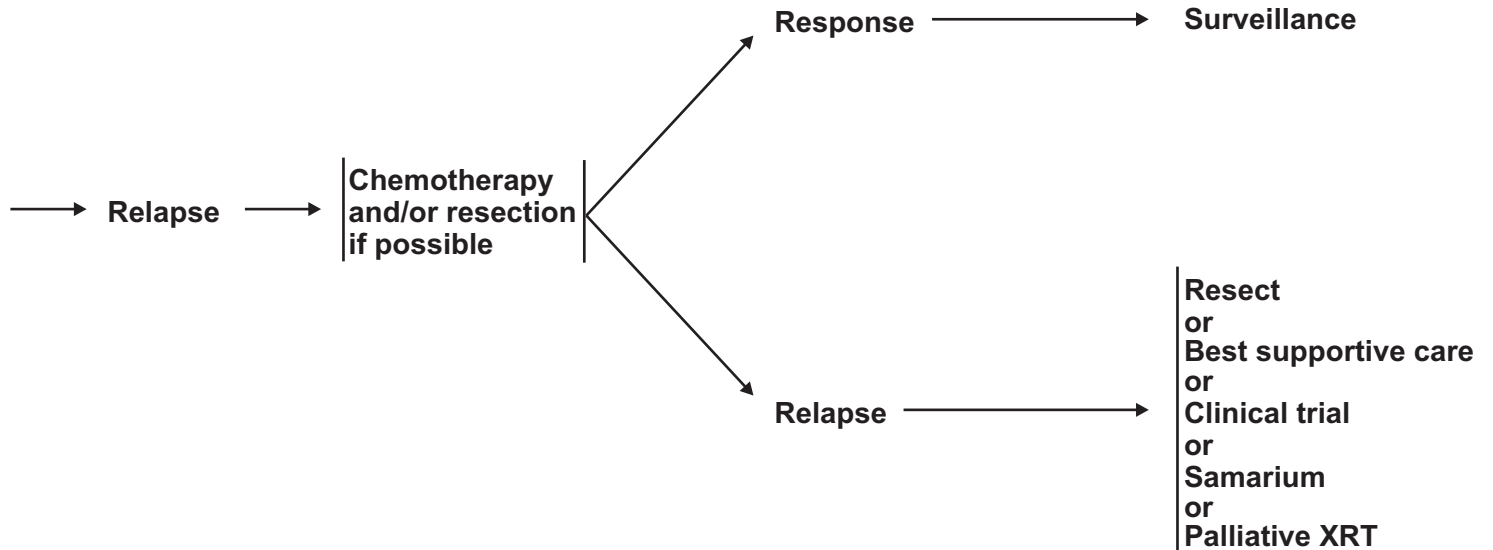
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SURVEILLANCE

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



Note: All recommendations are category 2A unless otherwise indicated.
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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

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.

PRINCIPLES OF BONE CANCER MANAGEMENT

Biopsy

- Optimally performed at center which will do definitive management.
- Placement of biopsy is critical.
- Core needle or open biopsy are preferred over FNA.
- Technique: Apply same principles for core needle or open biopsy.
- Appropriate communication between surgeon, musculoskeletal radiologist, and bone pathologist is critical.
- Fresh tissue is needed for molecular studies.
- In general, failure to follow appropriate biopsy procedures may lead to adverse patient outcomes.

Surgery

- Wide excision implies histologically negative margins and is necessary to optimize local control.
- Limb preservation is desirable, where possible, without compromising a satisfactory oncologic outcome.
- Surgical margins should be negative, wide enough to minimize potential local recurrence, and narrow enough to maximize function. In the individual case, amputation or limb sparing surgery may be the most appropriate options for achieving these goals.
- Extended palliative therapy may be necessary considering the comorbidities associated with chemotherapy and RT.

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.

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.

Staging

Table 1

**American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone Sarcomas**

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

Note: Because of the rarity of lymph node involvement in sarcomas, the designation **NX** may not be appropriate and could be considered **N0** if no clinical involvement is evident.

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

Stage IA	T1	N0	M0	G1, 2 Low grade
Stage IB	T2	N0	M0	G1, 2 Low grade
Stage IIA	T1	N0	M0	G3, 4 High grade
Stage IIB	T2	N0	M0	G3, 4 High grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

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Table 2

Surgical Staging System (SSS)

Stage	Grade	Site
IA	Low (G1)	Intracompartmental (T1)
IB	Low (G1)	Extracompartmental (T2)
IIA	High (G2)	Intracompartmental (T1)
IIB	High (G2)	Extracompartmental (T2)
III	Any (G) + Regional or distant metastasis	Any (T)

From Enneking WF, Spanier SS, Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106-120.

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Primary Bone cancers are extremely rare neoplasms, accounting for less than 0.2% of all cancers.^{1,2} An estimated 4,720 new cases will be diagnosed in 2007 in the US and 790 people will die from the disease.³⁻⁵ 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 hemangioendothelioma 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. 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. Appropriate team members are listed in [BONE-A](#). Long-term surveillance and follow-up is necessary considering the risk of recurrence and comorbidities associated with chemotherapy and RT. 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 any 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, chest, abdominal and pelvic CT, 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, 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.

FDG-PET (¹⁸F-fluorodeoxy-D-glucose positron emission tomography) 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 FDG-PET scans in the evaluation of chemotherapy response in osteosarcoma and Ewing's Sarcoma family of tumors.^{29,30}

Biopsy

Core needle or open biopsy techniques are preferred over fine needle aspiration (FNA). 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 is necessary to optimize local control. In selected cases, amputation may be the most appropriate option to achieve this goal but most patients will have limb-sparing surgical options. 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. Extended physiotherapy (above and beyond standard post-operative protocols) may be necessary considering the comorbidities of chemotherapy and radiation associated with limb salvage in the cancer patient.

Chondrosarcoma

Chondrosarcomas characteristically produce cartilage matrix from neoplastic tissue devoid of osteoid^{31,32} 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.^{33,34} 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.³⁵⁻⁴⁰ The peripheral or secondary tumors are usually low grade with infrequent metastasis.⁴¹ 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.^{35,42,43} Central chondrosarcomas demonstrate cortical destruction and loss of medullary bone trabeculations on radiographs.⁴² Evidence of calcification and destruction is seen. 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.⁴⁴

Workup and Treatment

The histologic grade and tumor locations are the most important variables that determine the choice of the primary treatment. Resectable low-grade lesions are treated with intralesional excision with or without adjuvant therapy or wide excision with negative margins. High-grade lesions (grade II, III, or clear cell) are surgically treated, obtaining a wide margin.⁴⁵⁻⁵² Unresectable high and low-grade lesions are treated with high-dose photons or proton beam radiation therapy ([CHON-1](#)). 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.^{53,54}

Dedifferentiated chondrosarcomas are high-grade lesions and should be treated as osteosarcoma. Similarly, mesenchymal chondrosarcomas are treated as Ewing's sarcoma, best approached as a function of their grade.

Relapse

Local recurrence or relapse should be treated with wide excision with or without radiation therapy depending on the margin status. Radiation therapy should be considered following excision with positive surgical margins. Negative surgical margins should be observed. Unresectable recurrences are treated with either conventional or proton beam radiation therapy ([CHON-1](#)). Surgical excision is an option for systemic relapse of a high grade lesion or patients should be encouraged to participate in a clinical trial.

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, 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 sarcomas⁵⁵. Functional reassessment should be performed at every visit ([CHON-1](#)).

Ewing's Sarcoma Family of Tumors (ESFT)

Ewing's sarcoma family of tumors 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 CD99.⁵⁶⁻⁶⁴

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.^{65,66}

Workup and Treatment

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, bone scan, and PET scan as clinically indicated.^{29,30} 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.^{67,68} NCCN Bone cancer guidelines have included this test as part of initial evaluation ([EW-1](#)).

All patients with Ewing's sarcoma are treated with the following protocol: (1) primary treatment with multiagent chemotherapy along with appropriate growth factor support for 12- 24 weeks (2) local control therapy (3) adjuvant chemotherapy with or without radiation therapy. See [NCCN Myeloid Growth Factors in Cancer Treatment Guidelines](#) for growth factor support. Patients should be restaged following primary treatment with an MRI of the lesion and chest imaging.

Local control options include wide excision with or without preoperative radiation therapy,^{69,70} definitive radiation therapy with chemotherapy or amputation in selected cases ([EW-2](#)). Chemotherapy should include a combination of at least three of the following agents: ifosfamide and/or cyclophosphamide, etoposide, doxorubicin, and vincristine.⁷¹⁻⁷⁹ 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, however it does not improve the event free survival in patients with metastatic disease at diagnosis.^{80,81}

Patients responding to primary treatment should always be treated further with adjuvant chemotherapy following local control treatment (surgery or radiation therapy), regardless of surgical margins. 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 radiation therapy with or without surgery followed by chemotherapy or best supportive care

Patients with recurrent and metastatic disease have a poor prognosis and should be considered for investigational approaches.^{82,83} High-dose chemotherapy with stem cell rescue is effective in this subset of patients, even though it is associated with severe toxicity.⁸⁴⁻⁸⁸

Relapse

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

Surveillance

Surveillance of patients with Ewing's sarcoma consists of a physical exam, chest and local imaging every 2-3 months.⁸⁹ Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years.

Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor in children and young adults.^{90,91} The median age for all osteosarcoma patients is 20 years. There are 11 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 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.

Workup and Treatment

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.^{29,30} 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. Magnetic resonance imaging (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.

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.^{92,93} Neoadjuvant and adjuvant chemotherapy are effective for localized disease at diagnosis.⁹⁴⁻⁹⁶ Chemotherapy can be given either intravenously or intra-arterially and should include at least two of the following drugs: doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate.⁹⁷⁻¹¹¹ Drug doses should be sufficiently high to mandate the use of myeloid

growth factors. See [NCCN Myeloid Growth Factors in Cancer Treatment Guidelines](#) for growth factor support.

Patients with periosteal and low-grade (intramedullary and surface) osteosarcomas, such as parosteal lesions, are treated with wide excision. Preoperative chemotherapy is preferred for high-grade osteosarcoma (category 1) and many of the variants as well, including periosteal lesions although selected elderly patients may benefit from immediate surgery ([OSTEO-1](#) and [OSTEO-2](#)). Patients with pathologic findings of high grade disease following wide excision for suspected low-grade or periosteal sarcomas should be given postoperative chemotherapy.

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. Radiation therapy followed by adjuvant chemotherapy is recommended for unresectable high-grade osteosarcoma ([OSTEO-2](#)).

Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients with no metastatic disease. Novel therapies could be considered for patients with unresectable pulmonary or any bone metastases, since prognosis is poor for this group of patients.¹¹²⁻¹¹⁶ In a phase II/III trial, high dose ifosfamide in combination with etoposide was found to be effective in patients with metastatic osteosarcoma but was associated with significant infection and renal toxicity.¹¹⁷

Relapse

If relapse occurs, the patient should again receive chemotherapy and/or surgical resection.^{118,119} Surveillance is recommended for patients who responded to treatment. Patients with progressive disease should be

treated with resection, radiation therapy for palliation or best supportive care. Participation in a clinical trial should be strongly encouraged.

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 may also be considered in this case (category 2B) ([OSTEO-3](#)). Functional reassessment should be performed at every visit.

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