National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Bone Cancer

Version 1.2011

NCCN.org

Continue

NCCN Guidelines™ Version 1.2011 Panel Members
Bone Cancer

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion

* J. Sybil Biermann, MD/Chair ¶
University of Michigan
Comprehensive Cancer Center

Douglas R. Adkins, MD †
Siteman Cancer Center at
Barnes-Jewish Hospital and Washington
University School of Medicine

Robert S. Benjamin, MD †
The University of Texas
M. D. Anderson Cancer Center

Brian Brigman, MD ¶
Duke Comprehensive Cancer Center

James E. Butrynski, MD
Dana-Farber/Brigham and Women's
Cancer Center

David Cheong, MD
H. Lee Moffitt Cancer Center
& Research Institute

Warren Chow, MD † ‡
City of Hope Comprehensive
Cancer Center

Deborah A. Frassica, MD §
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Frank J. Frassica, MD ¶
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Kenneth R. Hande, MD †
Vanderbilt-Ingram Cancer Center

Francis J. Hornicek, MD, PhD ‡ τ
Massachusetts General Hospital
Cancer Center

Robin L. Jones, MD, BSc, MRCP
University of Washington/Fred
Hutchinson Cancer Research Center

Joel Mayerson, MD τ ¶
The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and Solove
Research Institute

Sean V. McGarry, MD τ
UNMC Eppley Cancer Center at
The Nebraska Medical Center

Brian McGrath, MD τ
Roswell Park Cancer Institute

Carol D. Morris, MD ¶ τ
Memorial Sloan-Kettering Cancer Center

Richard J. O'Donnell, MD ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

R. Lor Randall, MD ¶
Huntsman Cancer Institute
at the University of Utah

Victor M. Santana, MD €
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

Robert L. Satcher, MD, PhD ¶
The University of Texas
M. D. Anderson Cancer Center

Herrick J. Siegel, MD ¶
University of Alabama at Birmingham
Comprehensive Cancer Center

Neeta Somaiah, MD †
Fox Chase Cancer Center

NCCN
Nicole McMillian, MS
Hema Sundar, PhD

¶ Surgery/Surgical oncology
† Medical oncology
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology
τ Orthopedics
€ Pediatric oncology

*Writing committee member

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Table of Contents
Bone Cancer

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

NCCN Guidelines™ Version 1.2011 Updates Bone Cancer

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion

Updates in Version 1.2011 of the NCCN Bone Cancer Guidelines from Version 3.2010 include:

Ewing's Sarcoma:

EW-2

- **Under Surveillance for Stable disease following primary treatment:**
  - **The recommendation for CBC changed from every 2-3 mo to "CBC and other laboratory studies as indicated".**
  - **The recommendation "Increase intervals for physical exam, chest and local imaging after 24 mo. Annually after 5 y (indefinitely)" changed from category 2A to category 2B.**

Osteosarcoma:

OSTEO-2

- **High grade osteosarcoma; Unresectable disease pathway: Samarium was removed as an option.**

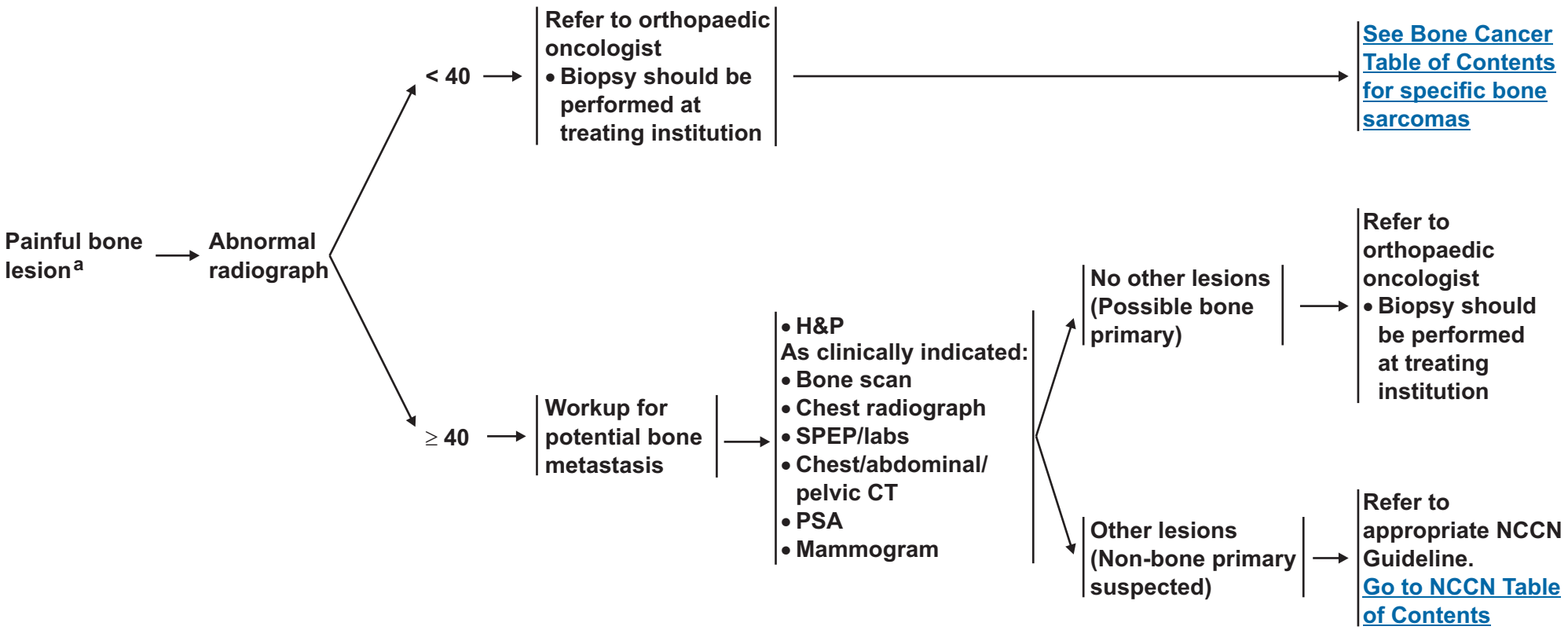
OSTEO-3

- **Surveillance: CBC changed to "CBC and other laboratory studies as indicated".**

(BONE-C): Principles of Bone Cancer Systemic Therapy

- **Under First line therapy (Primary/Neoadjuvant/Adjuvant): For VAC/IE, a new footnote was added that states, "In patients under 18y, evidence supports 2 week compressed treatment (category 1)".**

WORKUP[b]

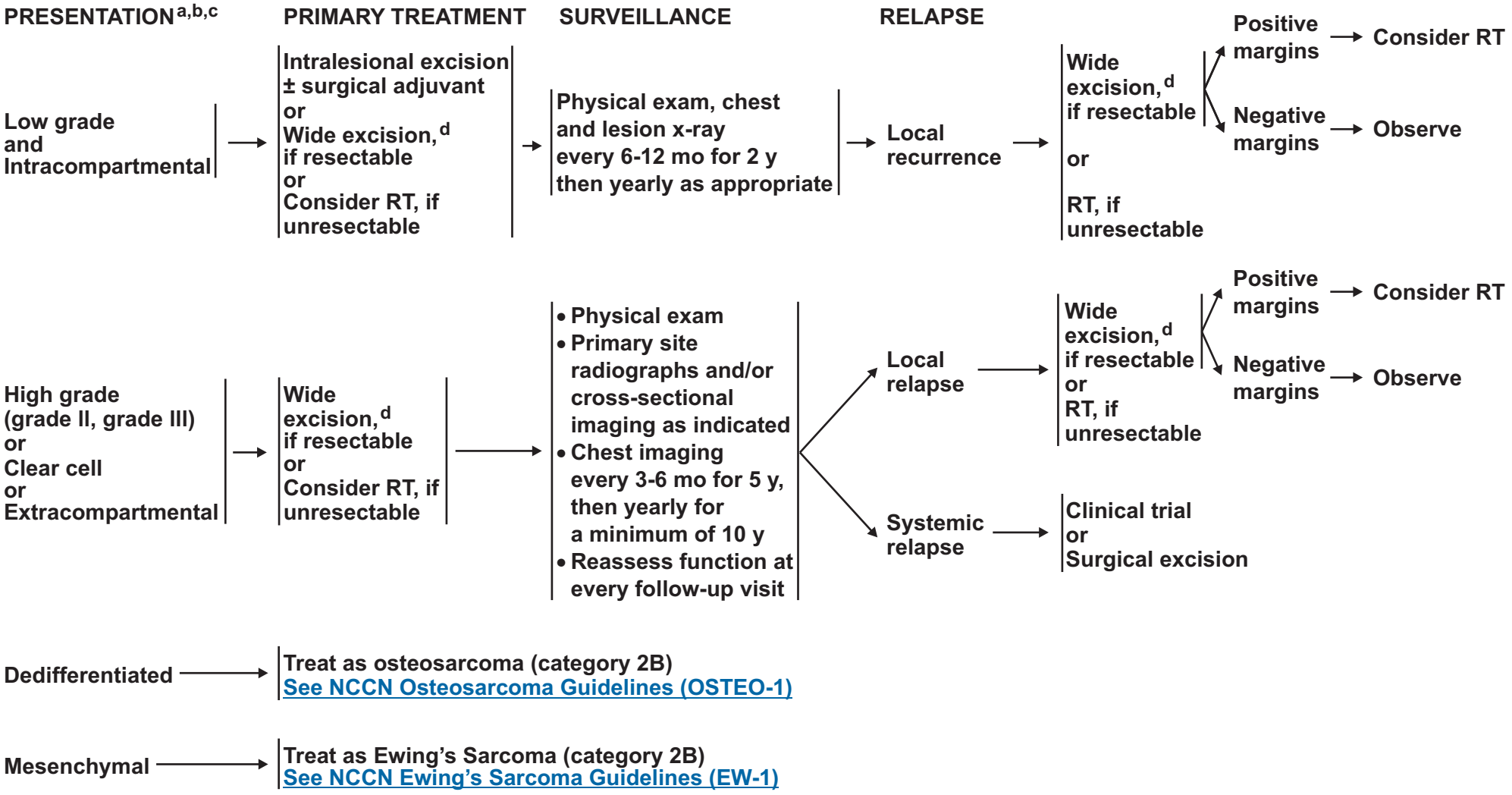


[a]Painless bone lesions require evaluation by a musculoskeletal radiologist and referral to multidisciplinary teams. See Multidisciplinary Team (BONE-A).
[b]See Principles of Bone Cancer Management (BONE-B).

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.

NCCN Guidelines™ Version 1.2011
Chondrosarcoma

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion



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

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

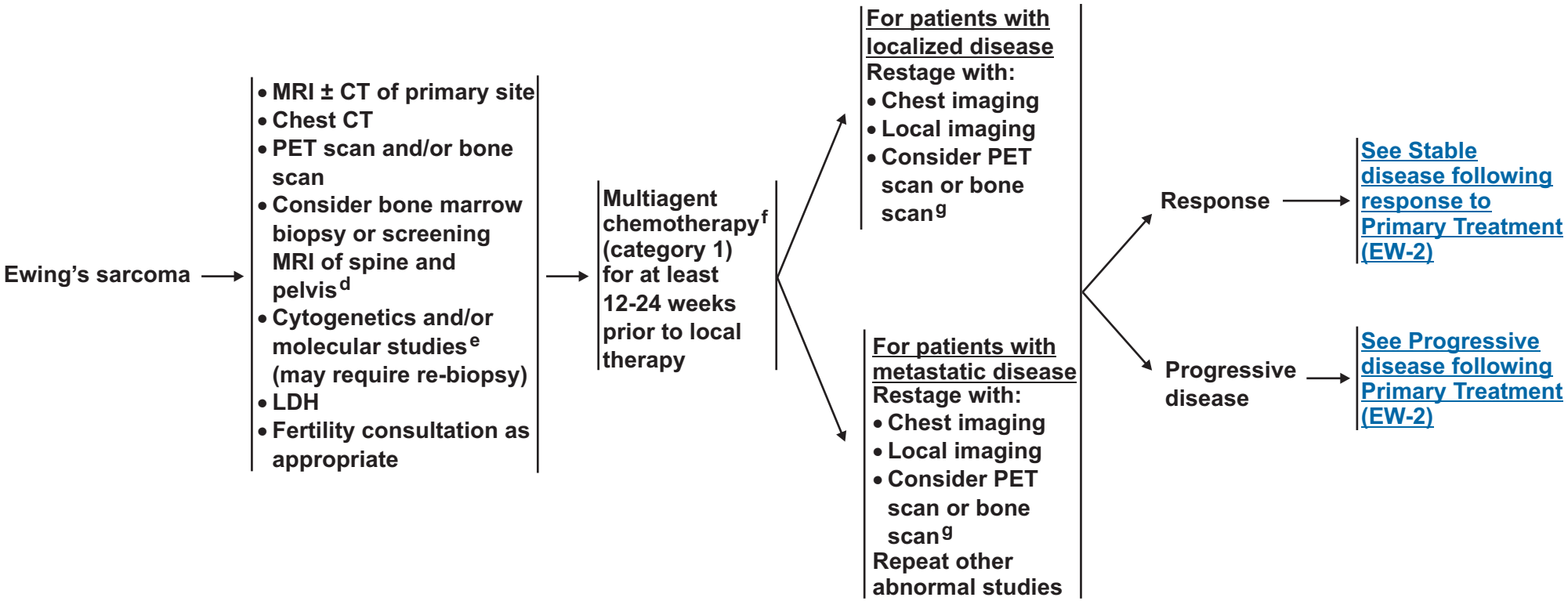
[c] There is considerable controversy regarding the grading of Chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should also be considered in deciding local treatment.

[d] Wide excision should provide negative surgical margins for tumor. This may be achieved by either limb-sparing resection or limb amputation.

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.

NCCN Guidelines™ Version 1.2011
Ewing's Sarcoma

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion



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

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

[c] 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.

[d] Kumar J, Seith A, Kumar A, et al. Whole-body MR imaging with the use of parallel imaging for detection of skeletal metastases in pediatric patients with small cell neoplasms: comparison with skeletal scintigraphy and FDG PET/CT. Pediatr Radiol 2008;38:953-962. Epub 2008 Jul 18.

[e] 90% of Ewing's family tumors will have one of four specific cytogenetic translocations.

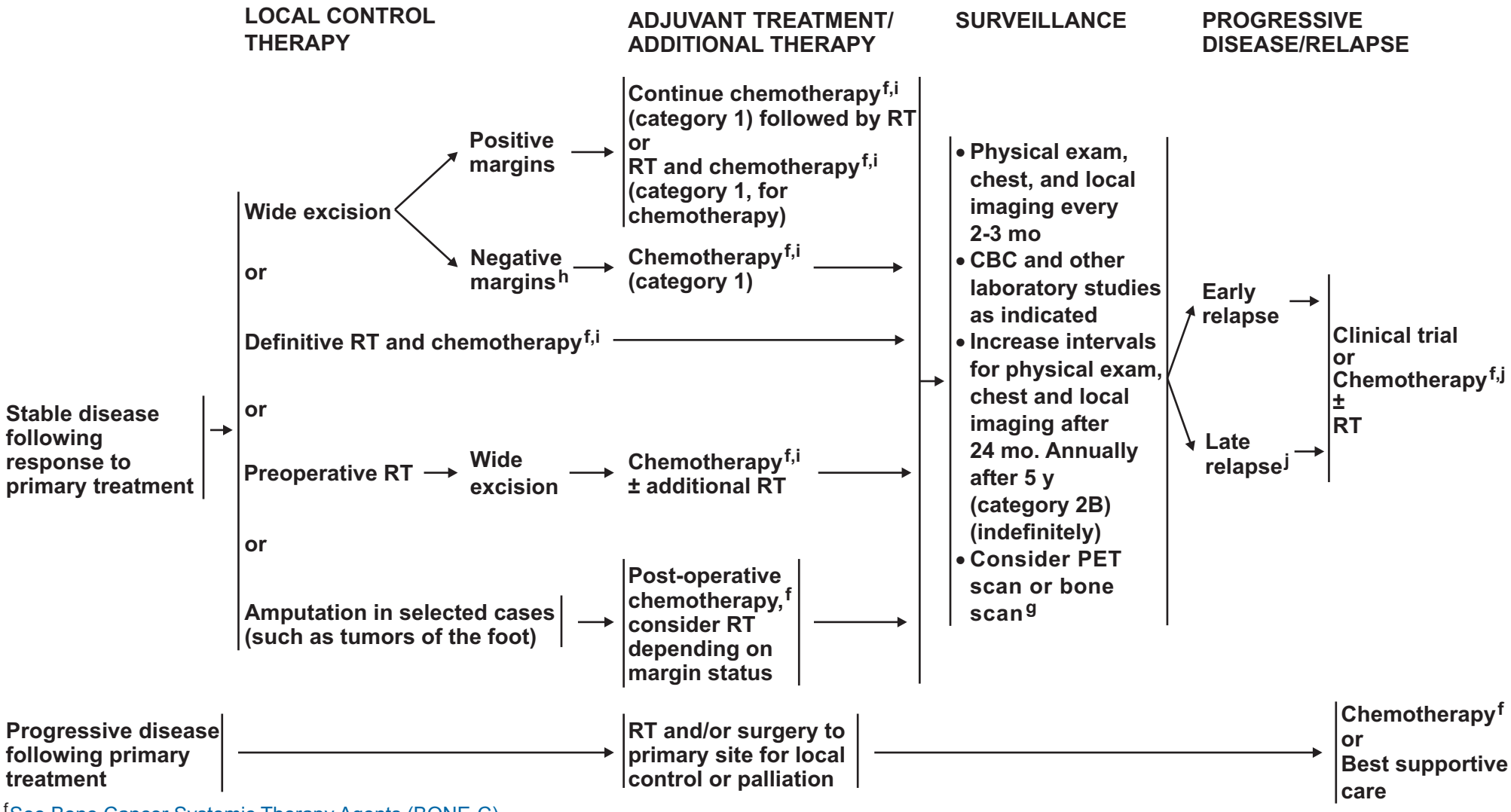
[f] See Bone Cancer Systemic Therapy Agents (BONE-C).

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

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.

NCCN Guidelines™ Version 1.2011
Ewing's Sarcoma

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion

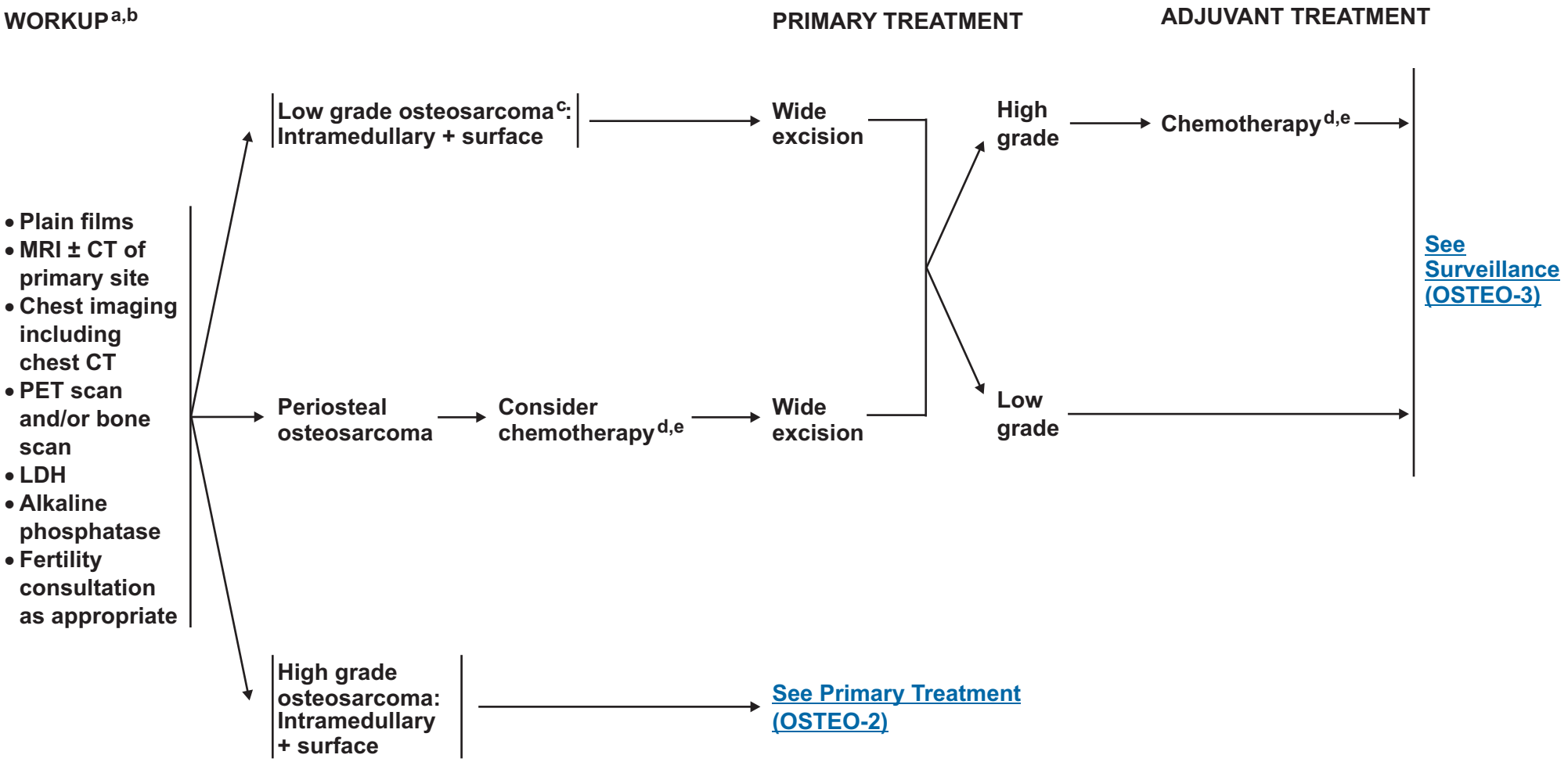


[f] See Bone Cancer Systemic Therapy Agents (BONE-C).
[g] Use the same imaging technique that was performed in the initial workup.
[h] RT may be considered for close margins.
[i] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.
[j] For late relapse, consider re-treatment with previously effective regimen.

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.

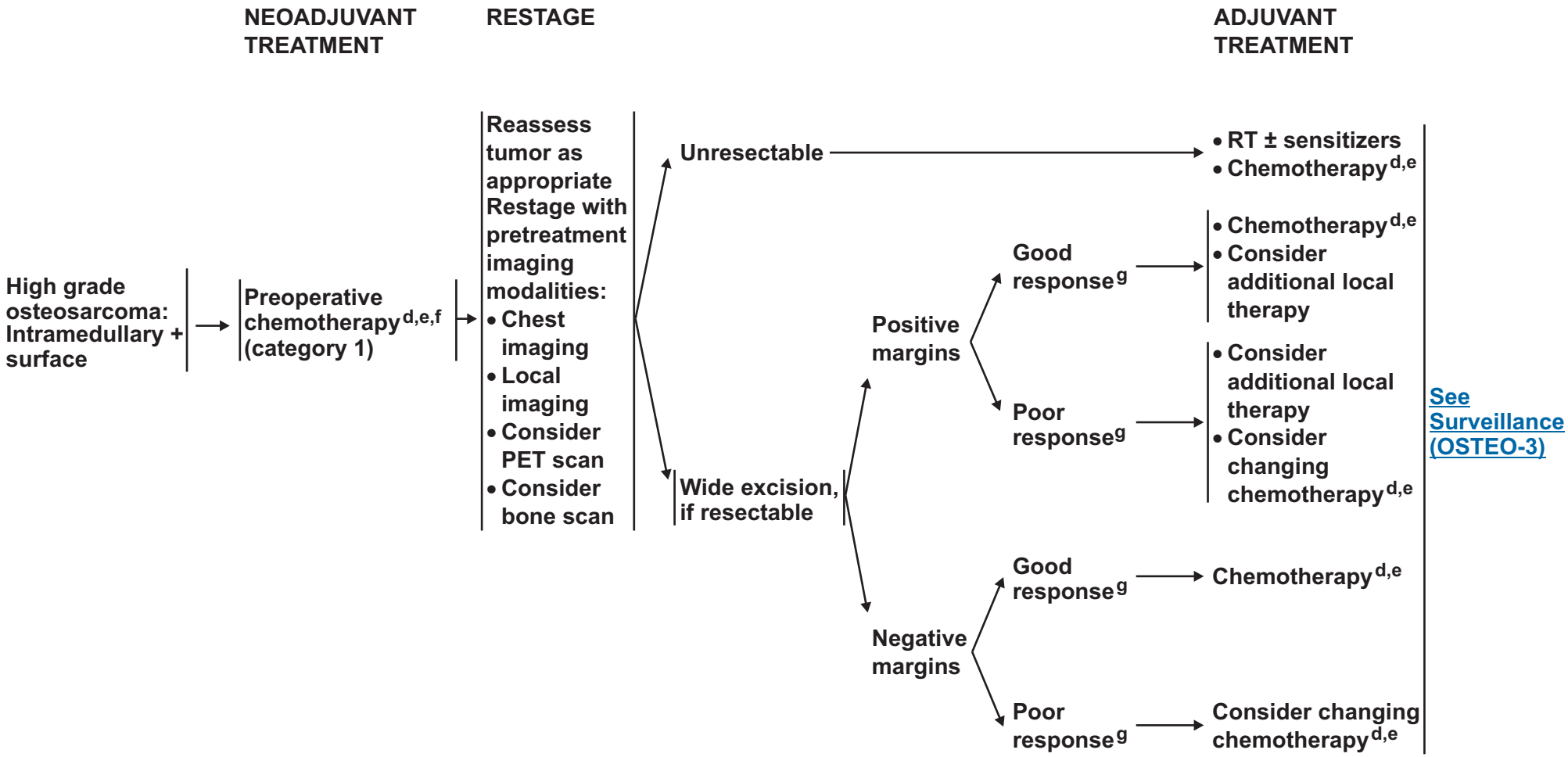
NCCN Guidelines™ Version 1.2011
Osteosarcoma

NCCN Guidelines Index
Bone Cancer Table of Contents
Discussion



[a] See Multidisciplinary Team (BONE-A).
[b] See Principles of Bone Cancer Management (BONE-B).
[c] Dedifferentiated parosteal osteosarcomas are not considered to be low grade tumors.
[d] Chemotherapy may be intravenous or intra-arterial.
[e] See Bone Cancer Systemic Therapy Agents (BONE-C).

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.



[d] Chemotherapy may be intravenous or intra-arterial.
[e] See Bone Cancer Systemic Therapy Agents (BONE-C).
[f] Selected elderly patients may benefit from immediate surgery.
[g] Response defined by pathologic mapping.

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.

SURVEILLANCE

- Physical exam
- Chest imaging
- CBC and other laboratory studies as indicated
- Local imaging[h]: 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** →

RELAPSE

Chemotherapy[e] and/or resection if possible

→ **Response** → **Surveillance**

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

[e] See Bone Cancer Systemic Therapy Agents (BONE-C).

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

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.

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
- 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.

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.

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)††
  - VAC/IE (Vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide)[1, †††]
  - VAI (vincristine, doxorubicin and ifosfamide)[2,3]
  - VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)[4]

- Primary therapy for metastatic disease at initial presentation
  - CVD (Cyclophosphamide, vincristine, and doxorubicin)[5]
  - VAC/IE (Cyclophosphamide, vincristine, and doxorubicin 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)††††
  - Cyclophosphamide and topotecan[6-9]
  - 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

†Chemotherapy should include growth factor support (See NCCN Myeloid Growth Factors Guidelines)
††Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.
†††In patients under 18y, evidence supports 2 week compressed treatment (category 1) (Womer RB, West DC, Krailo MD, Dickman PS, Pawel B, for the Children's Oncology Group AEWS0031 Committee. Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT). J Clin Oncol (Meeting Abstracts) 2008;26:10504.)
††††Vincristine may be added to any of the regimens below.

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.

References on next page

BONE CANCER SYSTEMIC THERAPY AGENTS
(References)

[1]Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003;348:694-701.
[2]Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. J Clin Oncol. 2001;19:1818-1829.
[3]Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment--cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol. 2008;26:4385-4393.
[4]Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer. 2006;47:22-29.
[5]Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol. 2004;22:2873-2876.
[6]Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group. J Clin Oncol. 2006;24:152-159.
[7]Hunold A, Weddeling N, Paulussen M, Ranft A, Liebscher C, Jurgens H. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer. 2006;47:795-800.
[8]Kushner BH, Kramer K, Meyers PA, Wollner N, Cheung NK. Pilot study of topotecan and high-dose cyclophosphamide for resistant pediatric solid tumors. Med Pediatr Oncol. 2000;35:468-474.
[9]Saylors RL, 3rd, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol. 2001;19:3463-3469.
[10]Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. Pediatr Blood Cancer. 2009;53:1029-1034.
[11]Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. Clin Cancer Res. 2004;10:840-848.
[12]Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer. 2007;48: 132-139.
[13]Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol. 1987;5:1191-1198.
[14]Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer. 2005;44:338-347.
[15]Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer. 2008;113:419-425.
[16]Bramwell V, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol. 1992;10:1579-1591.
[17]Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst. 2007;99:112-128.
[18]Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet. 1997;350:911-917.

Continue

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.

BONE CANCER SYSTEMIC THERAPY AGENTS
(References)

[19]Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol. 2000;18:4016-4027.
[20]Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol. 1988;6:329-337.
[21]Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. Ann Oncol. 2003;14:1126-1134.
[22]Goorin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol. 2002;20:426-433.
[23]Basaran M, Bavbek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. Oncology. 2007;72:255-260.
[24]Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. Cancer. 2009;115:2980-2987.
[25]Merimsky O, Meller I, Flusser G, et al. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. Cancer Chemother Pharmacol. 2000;45:177-181.
[26]Gentet JC, Brunat-Mentigny M, Demaille MC, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. Eur J Cancer. 1997;33:232-237.
[27]Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. Eur J Cancer. 2007;43:752-761.
[28]Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol. 2002;20:189-196.

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.

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone *(Primary malignant lymphoma and multiple myeloma are not included)*

(7th ed., 2010)

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 bone sarcomas, the designation **NX** may not be appropriate and cases should be considered **N0** unless clinical node involvement is clearly evident.

Distant Metastasis (M)

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
G4	Undifferentiated

Note: Ewing's sarcoma is classified as G4.

Stage Grouping

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated on 03/19/10

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Primary Bone cancers are extremely rare neoplasms, likely accounting for less than 0.2% of all cancers, although the true incidence is difficult to determine secondary to the rarity of these tumors.[1, 2] In 2009, an estimated 2,570 new cases will be diagnosed in the US and 1,470 people will die from the disease.[3] Primary bone cancers demonstrate wide clinical heterogeneity, and, perhaps most importantly, are often curable with proper treatment. Osteosarcoma (35%), chondrosarcoma (30%), and the Ewing's sarcoma (16%) are the three most common forms of bone cancer. Malignant fibrous histiocytoma (MFH) and fibrosarcoma of the bone constitute less than 1% of all primary bone tumors. Chondrosarcoma is usually found in middle-aged and older adults. Osteosarcoma and Ewing's sarcoma develop mainly in children and young adults. 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 sarcoma family of tumors (ESFT), are of unknown histologic origin.

The pathogenesis and etiology of most bone cancers remains unclear. Gene rearrangements between *EWS* and *ETS* family of genes have been implicated in the pathogenesis of Ewing's sarcomas.[4-7] Specific genetic alterations also play a role in osteosarcoma pathogenesis.[8, 9] 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.[10, 11] Osteosarcoma is the most common radiation-induced sarcoma. It is also the most common second primary malignancy in patients with a history of retinoblastoma.[12, 13] 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.[14-17]

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 Cancer Center (MSKCC). 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 progression-free survival (PFS) has been observed in 60-75% of patients with localized Ewing's sarcoma. In both osteosarcoma and Ewing's, a cure is still achievable, even in patients diagnosed with metastatic disease at presentation.[18-20]

The NCCN Bone cancer guidelines focus on chondrosarcoma, Ewing's sarcoma and osteosarcoma.

Staging

The 2010 American Joint Committee on Cancer (AJCC) staging classification is shown in Table 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 (Table 2).[21] This system stratifies both bone and soft-tissue sarcomas by the assessment of the surgical grade (G), 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 when 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 follow-up with a multidisciplinary team. Fertility issues should be discussed with appropriate patients prior to commencing 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 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.[23]

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.[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 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.[25] Recent reports in literature have demonstrated the utility of PET scans in the evaluation of chemotherapy response in osteosarcoma and ESFT.[26, 27]

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.[28-30] Conventional chondrosarcoma of the bone constitutes approximately 85% of all chondrosarcomas and 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.[29, 31, 32] 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.[33-36] The peripheral or secondary tumors are usually low grade with infrequent metastasis.[37] In addition to conventional chondrosarcoma, there are several other rare subtypes constituting about 10-15% of all chondrosarcomas.[29] These 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.[33,38, 39] Central chondrosarcomas demonstrate cortical destruction and loss of medullary bone trabeculations on radiographs, as well as calcification and destruction.[38]

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.[40]

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.[41-44] Wide excision with negative margins is the preferred treatment option for some low-grade lesions because of their larger size and intra-articular 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.[34]

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.[45, 46]

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.[47] However, this finding could not be confirmed in other studies.[48-50] Recently, Cesari and colleagues reported that the addition of chemotherapy improved survival rates in patients with mesenchymal chondrosarcoma.[51] Another report from the German study group also confirmed that the outcome was better in younger patients with mesenchymal chondrosarcoma who received chemotherapy.[52] Since there have not been any prospective randomized trials, the role of chemotherapy in the treatment of chondrosarcomas remains undefined.

Conventional chondrosarcoma (grades 1-3) has no established chemotherapy regimens. The 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.[35] Functional assessment 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 (ESFT)

ESFT are a group of small round-cell neoplasms which 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 *EWS* gene on chromosome 22q12 with various members of the *ETS* gene family (*FLI1*, *ERG*, *ETV1*, *ETV4* and *FEV*).[5, 6] The *EWS-FLI1* fusion transcript resulting from the chromosomal translocation, t(11;22)(q24;q12) is identified in about 85% of Ewing's sarcomas. This translocation is identified in Ewing's sarcoma, primitive neuroectodermal tumor (PNET) and Askin's tumor. Ewing's sarcoma is poorly differentiated and is also characterized by strong expression of cell-surface glycoprotein MIC2 (CD99).[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 for these tumors.[55]

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.

The important indicators of favorable prognosis include a distal site of primary disease, normal serum lactic acid dehydrogenase (LDH) level at presentation, and the absence of metastatic disease at the time of presentation.[56-58] Nearly one quarter of these patients present with metastatic disease, which is the most significant adverse prognostic factor in Ewing's sarcoma, as it is for other bone sarcomas.[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 RFS was 22% for patients with metastatic at diagnosis compared with 55% for patients without metastases at diagnosis.[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 compared to those with lesions in distal bones of the extremities.[61]

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. An ongoing diagnostic study is comparing whole-body MRI and conventional imaging for detecting distant metastases in pediatric patients with ESFT, Hodgkin's lymphoma, non-Hodgkin's 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. Preliminary reports suggest that *EWS-FLI1* translocation is associated with a better prognosis than other variants.[62-64] However, this has to be evaluated in large clinical trials. Bone marrow biopsy should be considered to complete the workup. Since 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 (EW-1). 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-institution as well as multi-institutional collaborative trials in the US and Europe.[65, 66]

The Intergroup Ewing's Sarcoma Studies (IESS-I and IESS-II) showed that the four-drug regimen VACD (vincristine, dactinomycin, cyclophosphamide and doxorubicin) was superior to the three-drug regimen VAC (vincristine, dactinomycin and cyclophosphamide) in terms of relapse-free survival (RFS) (60% vs. 24%) and overall survival (OS).[67, 68]

In the Pediatric Oncology Group-Children's Cancer Group (POG-CCG) study (INT-0091), patients with Ewing's sarcoma or PNET of bone were randomized to receive chemotherapy with either VACD alone or alternating with ifosfamide and etoposide (VACD-IE) for a total of 17 cycles.[69] In patients with nonmetastatic disease, the five-year event-free survival (EFS) rate was 69% in the VACD-IE group as compared with 54% in the VACD alone group. OS was also significantly better among patients in the VACD-IE group (72% vs. 61% in the VACD group). 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. from MSKCC also reported similar findings.[71] The 4-year EFS and OS rates for patients with local-regional disease were 82% and 89% respectively. In patients with distant metastases the corresponding survival rates were 12% and 17.8% respectively.

The EICESS-92 study investigated whether cyclophosphamide has a similar efficacy as 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). In the SR patients the 3-year EFS rates for VACA and VAIA were 73% and 74% respectively. In the high-risk patients the 3-year EFS rates were 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. The EFS rates in the high-risk group, though not statistically significant, indicate there is a suggestive benefit of adding 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. In this study, six courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) is administered as an intensive induction chemotherapy for patients with ESFT.[73]

NCCN Recommendations

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. See NCCN Guidelines for Myeloid Growth Factors in Cancer Treatment for growth factor support. For localized Ewing's sarcoma, VAC/IE given on an every 2 week schedule was found to be more effective than VAC/IE given on an every 3 week schedule. Median 3-year EFS was 76% and 65% respectively.[74]

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

- VAC/IE (vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide)[69]
- VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)[72]
- VIA (vincristine, ifosfamide and doxorubicin)[72]

The guidelines recommend the combination of cyclophosphamide, vincristine and doxorubicin (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.

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,[75, 76] 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 the duration of chemotherapy should be between 28 and 49 weeks depending on the type of regimen and the dosing schedule (category 1).

Progressive disease following 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 exam, chest and local imaging every 2-3 months.[77, 78] Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years.

Treatment for Relapsed or Refractory Disease

About 30%-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. Patients with longer time to first recurrence have a better chance of survival following recurrence. Late relapse (2 years or more after diagnosis), lung only metastases, local recurrence that can be treated with radical surgery and intensive chemotherapy are the most favorable prognostic factors, whereas early relapses (less than 2 years after diagnosis) with metastases in lungs and/or other sites, recurrence at local and distant sites, elevated LDH at initial diagnosis and initial recurrence are considered as 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 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/II studies conducted by the Children's Cancer Group, the overall response rate in patients with recurrent or refractory sarcoma was 51%; OS at 1 and 2 years was 49% and 28%, respectively. OS appeared significantly improved in patients who had CR or PR.[83]

Docetaxel in combination with gemcitabine was found to be well tolerated and demonstrated 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 topotecan produced 44% response rate (35% of patients had complete response and 9% had 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 retrospective analysis of patients with recurrent or progressive Ewing's sarcoma treated with irinotecan and temozolomide at the MSKCC, the median time-to-progression (TTP) was 8.3 months.[89] In the subset of patients with recurrent disease, it was 16.2 months. Median TTP was better for patients who were in a 2-year first remission and for those with primary localized disease than for those who relapsed within 2 years from diagnosis and for patients with metastatic disease at diagnosis.

Inhibition of insulin-like growth factor-1 receptor (IGF1R) may be an interesting approach in the treatment of some subtypes of sarcomas. Monoclonal antibodies such as figitumumab and R1507 have demonstrated safety and suggested possible efficacy in early phase trials in 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.[92-98] The role of this approach in high-risk patients is 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, chemotherapy with or without RT. If a relapse is delayed, as sometimes occurs with this sarcoma, re-treating with previously effective regimen may be useful. The NCCN guidelines have included the following regimens as options for patients with relapsed or refractory disease:

- 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.[1] 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.[99] 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 and complete resection with negative margins are significant prognostic factors for patients with osteosarcoma of the extremities and trunk.[100, 101] Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients with no metastatic disease.

In an analysis of 1,702 patients with osteosarcoma treated with neoadjuvant chemotherapy in cooperative study group protocols, axial tumor site, male sex, and a long history of symptoms were associated with poor response to chemotherapy. Patient age and location within the limb had significant influence on outcome at the time of diagnosis.[100] All factors except age were significant in multivariate testing, with surgical remission and histologic response to chemotherapy emerging as the key prognostic factors. Elevated serum LDH level is also associated with a worse prognosis. Bacci et al. reported on 1421 patients with osteosarcoma of the extremity treated over a 30 year period. In this cohort, serum level of LDH was significantly higher in patients with metastatic disease at presentation than in patients with localized disease and the 5-year disease-free survival (DFS) rate was 39.5% and 60% respectively.[102] The 5-year DFS correlated with serum level of LDH at univariate and multivariate analysis (39.5% for patients with high LDH levels and 60% for those with normal values), although it lost its significance when histologic response to chemotherapy was also considered in the multivariate analysis.

Workup

Osteosarcomas present both 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 imaging modality 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, ALP and LDH are frequently elevated in patients with osteosarcoma.

Primary Treatment

While surgery remains an essential part of management of patients with osteosarcoma, 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 three or more of the following drugs: doxorubicin,

cisplatin, bleomycin, cyclophosphamide or ifosfamide, dactinomycin and high dose methotrexate.[103-106,107-110] The updated results of the randomized Multi-Institutional Osteosarcoma Study (MIOS) showed that 6-year EFS was significantly higher in patients randomized to adjuvant chemotherapy than those assigned to observation only following surgery (61% and 11% respectively).[109]

Subsequent clinical trials have demonstrated that short intensive chemotherapy regimens produce excellent long-term results, similar to those that have been achieved with multiagent chemotherapy.[111-113] In a randomized trial conducted by the European Osteosarcoma group, the combination of doxorubicin and cisplatin was better tolerated compared to a multi-drug regimen with no difference in survival between the groups in patients with operable, non-metastatic osteosarcoma.[113] The 3- year and 5-year OS rates were 65% and 55% respectively in both groups. PFS at 5 years was 44% in both groups. 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.[114] The overall response rate was 59%. The projected 2-year PFS rate for patients with metastases to lung was 39%. The corresponding survival rate for patients with bone metastases (with or without pulmonary metastases) was 58%. The combination of cisplatin, ifosfamide and epirubicin was also active and reasonably well-tolerated regimen in patients with nonmetastatic extremity osteosarcoma.[115] With a median follow-up of 64 months, the 5-year DFS and OS rates were 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 patients with metastatic disease at presentation.[103, 116, 117] Two-year EFS and OS rates were 21% and 55%, respectively compared to 75% and 94% in patients with non-metastatic disease at presentation, treated with the same chemotherapy protocol.[103] Good histopathological response (greater than 90% necrosis) to neoadjuvant chemotherapy has been shown to be predictive of survival regardless of the type of chemotherapy administered after surgery.[102,118] In an analysis of 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and surgery at the at the Rizzoli Institute, Bacci et al. showed that the 5-year DFS and OS correlated significantly with histological response to chemotherapy.[119] Five-year DFS and OS in good and poor responders were 67.9% vs. 51.3% ($P < 0.0001$) and 78.4% versus 63.7% ($P < 0.0001$) respectively. A report from the Children's Cancer Group also confirmed these findings. Eight-year postoperative EFS and OS rates were 81% and 87% respectively in good responders to neoadjuvant therapy.[118] The corresponding survival rates were 46% and 52% respectively in poor responders. However, attempts to improve the outcome of poor responders by modifying the adjuvant chemotherapy remain unsuccessful.[105]

The safety and efficacy of HDT/SCR in patients with newly diagnosed metastatic osteosarcoma or relapsed osteosarcoma has also been evaluated.[120, 121] In the Italian sarcoma group study, treatment with carboplatin and etoposide followed by stem cell rescue, combined with surgery induced complete response in chemosensitive patients.[121] Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12% respectively. The efficacy of this approach in high risk patients is yet to be determined in prospective randomized studies.

NCCN Recommendations

Wide excision is the primary treatment for patients with low-grade (intramedullary and surface) osteosarcomas, whereas preoperative chemotherapy is preferred for those with 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 chemotherapy with a different regimen. RT followed by adjuvant chemotherapy is recommended if the sarcoma remains unresectable following preoperative chemotherapy.

Chemotherapy can be given intra-arterially or intravenously[122, 123] and should include appropriate growth factor support. NCCN Guidelines for Myeloid Growth Factors in Cancer Treatment for growth factor support. The NCCN guidelines have included the following regimens for first-line therapy (primary/neoadjuvant/adjuvant) in patients with localized disease or primary therapy for metastatic disease:

- 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 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.

Treatment for Relapsed or Refractory Disease

About 30% of patients with localized disease and 80% of the patients presenting with metastatic disease will relapse. The presence of solitary metastases and complete resectability of the disease at first recurrence have been reported to the most important prognostic indicators for improved survival, whereas patients not amenable to surgery and those with a second or a third recurrence have a poor prognosis.[124, 125]

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials.[126, 127] In a phase II trial of French Society of Pediatric Oncology, ifosfamide and etoposide resulted in a response rate of 48% in patients with relapsed or refractory osteosarcoma.[127] In another phase II trial, cyclophosphamide and etoposide resulted in 19% response rate and 35% of stable disease in patients with relapsed high-risk osteosarcoma.[126] PFS at 4 months was 42%. Single agent gemcitabine and combination regimens such as docetaxel and gemcitabine, cyclophosphamide and topotecan, ifosfamide, carboplatin and etoposide have been effective in the treatment of patients with relapsed or refractory bone sarcomas.[83, 84, 88, 128]

Samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), a bone-seeking radiopharmaceutical has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases.[129, 130] Andersen et al. have reported that ^{153}Sm-EDTMP with peripheral-blood progenitor cell (PBPC) support had low non-hematologic toxicity and provided pain palliation for patients with osteosarcoma local recurrences or osteoblastic bone metastases.[129] Results of a recent dose-finding study also

demonstrated that ^{153}Sm-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.[130]

NCCN Recommendations

The optimal treatment strategy for patients with relapsed or metastatic disease has yet to be defined. If relapse occurs, the patient should receive second-line chemotherapy and/or surgical resection. Surveillance is recommended for patients who responded to second-line therapy. The NCCN guidelines have included the following regimens as options for patients with relapsed or refractory disease:

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

Patients with progressive disease following second-line therapy should be treated with resection, RT for palliation or best supportive care. Participation in a clinical trial should be strongly encouraged. The guidelines have also included ^{153}Sm-EDTMP as one of the treatment options for relapsed disease following second-line therapy.

Summary

Primary bone cancers are extremely rare neoplasms. Osteosarcoma, chondrosarcoma, and Ewing's sarcoma are the three most common forms of primary 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) resulting in the fusion of *EWS* gene with various members of the *ETS* family of genes. It 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. 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 periosteal lesions, prior to wide excision. 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 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 with progressive disease following second-line therapy.

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. A small subset of patients diagnosed with metastatic disease at presentation can be cured with the proper choice of treatment. Consistent with the NCCN philosophy, the panel encourages patients to participate in well-designed clinical trials to enable further advances.

References

1. Yasko AW, Chow W, Fressica D. Bone Sarcomas. In: Pazdur R, Wagman LD, Camphausen C, Hoskins WJ, eds. Cancer Management: A Multidisciplinary Approach (ed 11): CMPMedica LLC; 2008.

2. Unni KK. Dahlin's Bone Tumors: General Aspects and Data on 11,087 cases (ed 5). Philadelphia: Lippincott Williams & Wilkins; 1996.

3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474385.

4. de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. J Clin Oncol 2000;18:204-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10623711.

5. Delattre O, Zucman J, Melot T, et al. The Ewing family of tumors--a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N Engl J Med 1994;331:294-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8022439.

6. Denny CT. Gene rearrangements in Ewing's sarcoma. Cancer Invest 1996;14:83-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8597892.

7. Burchill SA. Molecular abnormalities in Ewing's sarcoma. Expert Rev Anticancer Ther 2008;8:1675-1687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18925858.

8. Kruzelock RP, Murphy EC, Strong LC, et al. Localization of a novel tumor suppressor locus on human chromosome 3q important in osteosarcoma tumorigenesis. Cancer Res 1997;57:106-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8988049.

9. Yamaguchi T, Toguchida J, Yamamuro T, et al. Allelotype analysis in osteosarcomas: frequent allele loss on 3q, 13q, 17p, and 18q. Cancer Res 1992;52:2419-2423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1568211.

10. Sagerman RH, Cassady JR, Tretter P, Ellsworth RM. Radiation induced neoplasia following external beam therapy for children with retinoblastoma. Am J Roentgenol Radium Ther Nucl Med 1969;105:529-535. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5775011.

11. Tucker MA, D'Angio GJ, Boice JD, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 1987;317:588-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3475572.

12. Araki N, Uchida A, Kimura T, et al. Involvement of the retinoblastoma gene in primary osteosarcomas and other bone and soft-tissue tumors. Clin Orthop Relat Res 1991:271-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1884549.

13. Schimke RN, Lowman JT, Cowan AB. Retinoblastoma and osteogenic sarcoma in siblings. Cancer 1974;34:2077-2079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4530747.

14. Li FP, Fraumeni JF. Prospective study of a family cancer syndrome. JAMA 1982;247:2692-2694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7077763.

15. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233-1238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1978757.

16. McIntyre JF, Smith-Sorensen B, Friend SH, et al. Germline mutations of the p53 tumor suppressor gene in children with osteosarcoma. J Clin Oncol 1994;12:925-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8164043.

17. Miller CW, Aslo A, Won A, et al. Alterations of the p53, Rb and MDM2 genes in osteosarcoma. J Cancer Res Clin Oncol 1996;122:559-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8781571.

18. Grier. The Ewing Family of Tumors. The Pediatric Clinics of North America 1997;44:991-1004. Available at: http://linkinghub.elsevier.com/retrieve/pii/s0031395505705411.

19. Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric osteosarcoma. Oncologist 2004;9:422-441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15266096.

20. Wittig JC, Bickels J, Priebat D, et al. Osteosarcoma: a multidisciplinary approach to diagnosis and treatment. Am Fam Physician 2002;65:1123-1132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11925089.

21. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980:106-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7449206.

22. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24:2917-2931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16651642.

23. Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin. A prospective study of a diagnostic strategy. J Bone Joint Surg Am 1993;75:1276-1281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8408149.

24. Heck RK, Peabody TD, Simon MA. Staging of primary malignancies of bone. CA Cancer J Clin 2006;56:366-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17135693.

25. Schuetze SM. Utility of positron emission tomography in sarcomas. Curr Opin Oncol 2006;18:369-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721133.

26. Hawkins DS, Rajendran JG, Conrad EU, et al. Evaluation of chemotherapy response in pediatric bone sarcomas by [F-18]-fluorodeoxy-D-glucose positron emission tomography. Cancer 2002;94:3277-3284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12115361.

27. Hawkins DS, Schuetze SM, Butrynski JE, et al. [18F]Fluorodeoxyglucose positron emission tomography predicts outcome for Ewing sarcoma family of tumors. J Clin Oncol 2005;23:8828-8834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314643.

28. Bovee JVMG, Cleton-Jansen A-M, Taminiau AHM, Hogendoorn PCW. Emerging pathways in the development of chondrosarcoma of bone and implications for targeted treatment. Lancet Oncol 2005;6:599-607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16054571.

29. Gelderblom H, Hogendoorn PCW, Dijkstra SD, et al. The clinical approach towards chondrosarcoma. Oncologist 2008;13:320-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18378543.

30. Terek RM. Recent advances in the basic science of chondrosarcoma. Orthop Clin North Am 2006;37:9-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16311107.

31. Mankin HJ, Cantley KP, Schiller AL, Lippiello L. The biology of human chondrosarcoma. II. Variation in chemical composition among types and subtypes of benign and malignant cartilage tumors. J Bone Joint Surg Am 1980;62:176-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7358749.

32. Mankin HJ, Cantley KP, Lippiello L, et al. The biology of human chondrosarcoma. I. Description of the cases, grading, and biochemical

analyses. J Bone Joint Surg Am 1980;62:160-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7358748.

33. Bruns J, Elbracht M, Niggemeyer O. Chondrosarcoma of bone: an oncological and functional follow-up study. Ann Oncol 2001;12:859-864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11484965.

34. Fiorenza F, Abudu A, Grimer RJ, et al. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg Br 2002;84:93-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11837841.

35. Lee FY, Mankin HJ, Fondren G, et al. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am 1999;81:326-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10199270.

36. Sanerkin NG. The diagnosis and grading of chondrosarcoma of bone: a combined cytologic and histologic approach. Cancer 1980;45:582-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6928110.

37. Ahmed AR, Tan T-S, Unni KK, et al. Secondary chondrosarcoma in osteochondroma: report of 107 patients. Clin Orthop Relat Res 2003:193-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12782876.

38. Bergh P, Gunterberg B, Meis-Kindblom JM, Kindblom LG. Prognostic factors and outcome of pelvic, sacral, and spinal chondrosarcomas: a center-based study of 69 cases. Cancer 2001;91:1201-1212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11283918.

39. Enneking WF, Dunham WK. Resection and reconstruction for primary neoplasms involving the innominate bone. J Bone Joint Surg Am 1978;60:731-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/701308.

40. Norman A, Sissons HA. Radiographic hallmarks of peripheral chondrosarcoma. Radiology 1984;151:589-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6718712.

41. Leerapun T, Hugate RR, Inwards CY, et al. Surgical management of conventional grade I chondrosarcoma of long bones. Clin Orthop Relat Res 2007;463:166-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17632422.

42. Marcove RC. A 17-year review of cryosurgery in the treatment of bone tumors. Clin Orthop Relat Res 1982:231-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6950821.

43. Marcove RC, Stovell PB, Huvos AG, Bullough PG. The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. A preliminary report. Clin Orthop Relat Res 1977:147-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/837601.

44. Veth R, Schreuder B, van Beem H, et al. Cryosurgery in aggressive, benign, and low-grade malignant bone tumours. Lancet Oncol 2005;6:25-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15629273.

45. Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. Neurosurg Clin N Am 2000;11:627-638. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11082173.

46. Noel G, Feuvret L, Ferrand R, et al. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. Neurosurgery 2004;55:1252-1260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15574207.

47. Mitchell AD, Ayoub K, Mangham DC, et al. Experience in the treatment of dedifferentiated chondrosarcoma. J Bone Joint Surg Br 2000;82:55-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10697315.

48. Dickey ID, Rose PS, Fuchs B, et al. Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. J Bone Joint Surg Am 2004;86-A:2412-2418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15523011.

49. Grimer RJ, Gosheger G, Taminiau A, et al. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. Eur J Cancer 2007;43:2060-2065. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17720491.

50. Staals EL, Bacchini P, Bertoni F. Dedifferentiated central chondrosarcoma. Cancer 2006;106:2682-2691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16691621.

51. Cesari M, Bertoni F, Bacchini P, et al. Mesenchymal chondrosarcoma. An analysis of patients treated at a single institution. Tumori 2007;93:423-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18038872.

52. Dantonello TM, Int-Veen C, Leuschner I, et al. Mesenchymal chondrosarcoma of soft tissues and bone in children, adolescents, and young adults: experiences of the CWS and COSS study groups. Cancer 2008;112:2424-2431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18438777.

53. Ambros IM, Ambros PF, Strehl S, et al. MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumors. Evidence for a common histogenesis of Ewing's sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration. Cancer 1991;67:1886-1893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1848471.

54. Perlman EJ, Dickman PS, Askin FB, et al. Ewing's sarcoma--routine diagnostic utilization of MIC2 analysis: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. Hum Pathol 1994;25:304-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8150461.

55. Olsen SH, Thomas DG, Lucas DR. Cluster analysis of immunohistochemical profiles in synovial sarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma. Mod Pathol 2006;19:659-668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16528378.

56. Glaubiger DL, Makuch R, Schwarz J, et al. Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. Cancer 1980;45:2213-2219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7370962.

57. Gobel V, Jurgens H, Etspuler G, et al. Prognostic significance of tumor volume in localized Ewing's sarcoma of bone in children and adolescents. J Cancer Res Clin Oncol 1987;113:187-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3558454.

58. Mendenhall CM, Marcus RB, Enneking WF, et al. The prognostic significance of soft tissue extension in Ewing's sarcoma. Cancer 1983;51:913-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6821856.

59. Cangir A, Vietti TJ, Gehan EA, et al. Ewing's sarcoma metastatic at diagnosis. Results and comparisons of two intergroup Ewing's sarcoma studies. Cancer 1990;66:887-893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2201433.

60. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 2000;18:3108-3114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10963639.

61. Kissane JM, Askin FB, Foulkes M, et al. Ewing's sarcoma of bone: clinicopathologic aspects of 303 cases from the Intergroup Ewing's Sarcoma Study. Hum Pathol 1983;14:773-779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6885037.

62. Avigad S, Cohen IJ, Zilberstein J, et al. The predictive potential of molecular detection in the nonmetastatic Ewing family of tumors. Cancer 2004;100:1053-1058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14983502.

63. de Alava E, Kawai A, Healey JH, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. J Clin Oncol 1998;16:1248-1255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9552022.

64. Zoubek A, Dockhorn-Dworniczak B, Delattre O, et al. Does expression of different EWS chimeric transcripts define clinically distinct risk groups of Ewing tumor patients? J Clin Oncol 1996;14:1245-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed8648380.

65. Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. Oncologist 2006;11:503-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16720851.

66. Subbiah V, Anderson P, Lazar AJ, et al. Ewing's sarcoma: standard and experimental treatment options. Curr Treat Options Oncol 2009;10:126-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19533369.

67. Burgert EO, Nesbit ME, Garnsey LA, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. J Clin Oncol 1990;8:1514-1524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2099751.

68. Nesbit ME, Gehan EA, Burgert EO, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol 1990;8:1664-1674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2213103.

69. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348:694-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12594313.

70. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol 2004;22:2873-2876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15254055.

71. Kolb EA, Kushner BH, Gorlick R, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003;21:3423-3430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12972518.

72. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment--cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol 2008;26:4385-4393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18802150.

73. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 2006;47:22-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16572419.

74. Womer RB, West DC, Krailo MD, et al. Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT). J Clin Oncol (Meeting Abstracts) 2008;26:10504. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/10504.

75. Brown AP, Fixsen JA, Plowman PN. Local control of Ewing's sarcoma: an analysis of 67 patients. Br J Radiol 1987;60:261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3567471.

76. Scully SP, Temple HT, O'Keefe RJ, et al. Role of surgical resection in pelvic Ewing's sarcoma. J Clin Oncol 1995;13:2336-2341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7666092.

77. Bacci G, Forni C, Longhi A, et al. Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. Eur J Cancer 2004;40:73-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14687792.

78. Pritchard DJ, Dahlin DC, Dauphine RT, et al. Ewing's sarcoma. A clinicopathological and statistical analysis of patients surviving five years or longer. J Bone Joint Surg Am 1975;57:10-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1123355.

79. Bacci G, Ferrari S, Longhi A, et al. Therapy and survival after recurrence of Ewing's tumors: the Rizzoli experience in 195 patients treated with adjuvant and neoadjuvant chemotherapy from 1979 to 1997. Ann Oncol 2003;14:1654-1659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581274.

80. Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multi-modality therapy: A report from the Children's Oncology Group. Pediatr Blood Cancer 2008;51:334-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed18506764.

81. Rodriguez-Galindo C, Billups CA, Kun LE, et al. Survival after recurrence of Ewing tumors: the St Jude Children's Research Hospital experience, 1979-1999. Cancer 2002;94:561-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11900241.

82. Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol 1987;5:1191-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3114435.

83. Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer 2005;44:338-347. Available at:

84. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer 2008;113:419-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed18484657.

85. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group. J Clin Oncol 2006;24:152-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16382125.

86. Hunold A, Weddeling N, Paulussen M, et al. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer 2006;47:795-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16411206.

87. Kushner BH, Kramer K, Meyers PA, et al. Pilot study of topotecan and high-dose cyclophosphamide for resistant pediatric solid tumors. Med Pediatr Oncol 2000;35:468-474. Available at: http://www.ncbi.nlm.nih.gov/pubmed11070479.

88. Saylors RL, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol 2001;19:3463-3469. Available at: http://www.ncbi.nlm.nih.gov/pubmed11481351.

89. Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. Pediatr Blood Cancer 2009;53:1029-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19637327.

90. Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. Clin Cancer Res 2004;10:840-848. Available at: http://www.ncbi.nlm.nih.gov/pubmed14871959.

91. Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer 2007;48:132-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed16317751.

92. Barker LM, Pendergrass TW, Sanders JE, Hawkins DS. Survival after recurrence of Ewing's sarcoma family of tumors. J Clin Oncol 2005;23:4354-4362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15781881.

93. Burdach S, Jurgens H, Peters C, et al. Myeloablative radiochemotherapy and hematopoietic stem-cell rescue in poor-prognosis Ewing's sarcoma. J Clin Oncol 1993;11:1482-1488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8101562.

94. Engelhardt M, Zeiser R, Ihorst G, et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation in adult patients with high-risk or advanced Ewing and soft tissue sarcoma. J Cancer Res Clin Oncol 2007;133:1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16835746.

95. Horowitz ME, Kinsella TJ, Wexler LH, et al. Total-body irradiation and autologous bone marrow transplant in the treatment of high-risk Ewing's sarcoma and rhabdomyosarcoma. J Clin Oncol 1993;11:1911-1918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8410118.

96. Kushner BH, Meyers PA. How effective is dose-intensive/myeloablative therapy against Ewing's sarcoma/primitive neuroectodermal tumor metastatic to bone or bone marrow? The Memorial Sloan-Kettering experience and a literature review. J Clin Oncol 2001;19:870-880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157041.

97. McTiernan A, Driver D, Michelagnoli MP, et al. High dose chemotherapy with bone marrow or peripheral stem cell rescue is an effective treatment option for patients with relapsed or progressive Ewing's sarcoma family of tumours. Ann Oncol 2006;17:1301-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16782749.

98. Oberlin O, Rey A, Desfachelles AS, et al. Impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors: a study by the Societe Francaise des Cancers de l'Enfant. J Clin Oncol 2006;24:3997-4002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921053.

99. Grimer RJ, Bielack S, Flege S, et al. Periosteal osteosarcoma--a European review of outcome. Eur J Cancer 2005;41:2806-2811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16290134.

100. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol 2002;20:776-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11821461.

101. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. J Clin Oncol 1994;12:423-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8113851.

102. Bacci G, Longhi A, Ferrari S, et al. Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years. Tumori 2004;90:478-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15656333.

103. Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. Ann Oncol 2003;14:1126-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12853357.

104. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000;18:4016-4027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11118462.

105. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol 1988;6:329-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed2448428.

106. Ferrari S, Smeland S, Mercuri M, et al. Neoadjuvant chemotherapy with high-dose Ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. J Clin Oncol 2005;23:8845-8852. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16246977.

107. Eilber F, Giuliano A, Eckardt J, et al. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol 1987;5:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3543236.

108. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986;314:1600-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3520317.

109. Link MP, Goorin AM, Horowitz M, et al. Adjuvant chemotherapy of high-grade osteosarcoma of the extremity. Updated results of the Multi-Institutional Osteosarcoma Study. Clin Orthop Relat Res 1991:8-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1884563.

110. Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol 1992;10:5-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1370176.

111. Bramwell V, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol 1992;10:1579-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1403038.

112. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 2007;99:112-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed17227995.

113. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet 1997;350:911-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed9314869.

114. Goorin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol 2002;20:426-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11786570.

115. Basaran M, Bavbek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. Oncology 2007;72:255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18185020.

116. Bacci G, Briccoli A, Mercuri M, et al. Osteosarcoma of the extremities with synchronous lung metastases: long-term results in 44 patients treated with neoadjuvant chemotherapy. J Chemother 1998;10:69-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9531078.

117. Meyers PA, Heller G, Healey JH, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol

1993;11:449-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8445419.

118. Provisor AJ, Ettinger LJ, Nachman JB, et al. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. J Clin Oncol 1997;15:76-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8996127.

119. Bacci G, Mercuri M, Longhi A, et al. Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. Eur J Cancer 2005;41:2079-2085. Available at: http://www.ncbi.nlm.nih.gov/pubmed16115755.

120. Lashkari A, Chow WA, Valdes F, et al. Tandem high-dose chemotherapy followed by autologous transplantation in patients with locally advanced or metastatic sarcoma. Anticancer Res 2009;29:3281-3288. Available at: http://www.ncbi.nlm.nih.gov/pubmed19661346.

121. Fagioli F, Aglietta M, Tienghi A, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. J Clin Oncol 2002;20:2150-2156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11956277.

122. Bacci G, Ferrari S, Tienghi A, et al. A comparison of methods of loco-regional chemotherapy combined with systemic chemotherapy as neo-adjuvant treatment of osteosarcoma of the extremity. Eur J Surg Oncol 2001;27:98-9104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11237499.

123. Winkler K, Bielack S, Delling G, et al. Effect of intraarterial versus intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate, and ifosfamide on histologic tumor response in osteosarcoma (study COSS-86). Cancer 1990;66:1703-1710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2208024.

124. Saeter G, Hoie J, Stenwig AE, et al. Systemic relapse of patients with osteogenic sarcoma. Prognostic factors for long term survival. Cancer 1995;75:1084-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7850705.

125. Tabone MD, Kalifa C, Rodary C, et al. Osteosarcoma recurrences in pediatric patients previously treated with intensive chemotherapy. J Clin Oncol 1994;12:2614-2620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7989936.

126. Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. Cancer 2009;115:2980-2987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19452540.

127. Gentet JC, Brunat-Mentigny M, Demaille MC, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. Eur J Cancer 1997;33:232-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9135494.

128. Merimsky O, Meller I, Flusser G, et al. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. Cancer Chemother Pharmacol 2000;45:177-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10663634.

129. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002;20:189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773169.

130. Loeb DM, Garrett-Mayer E, Hobbs RF, et al. Dose-finding study of 153Sm-EDTMP in patients with poor-prognosis osteosarcoma. Cancer 2009;115:2514-2522. Available at: http://www.ncbi.nlm.nih.gov/pubmed19338063.