NCCN Guidelines® Insights
Bone Cancer, Version 2.2017
Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Bone Cancer provide interdisciplinary recommendations for treating chordoma, chondrosarcoma, giant cell tumor of bone, Ewing sarcoma, and osteosarcoma. These NCCN Guidelines Insights summarize the NCCN Bone Cancer Panel's guideline recommendations for treating Ewing sarcoma. The data underlying these treatment recommendations are also discussed.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Bone Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Bone Cancer

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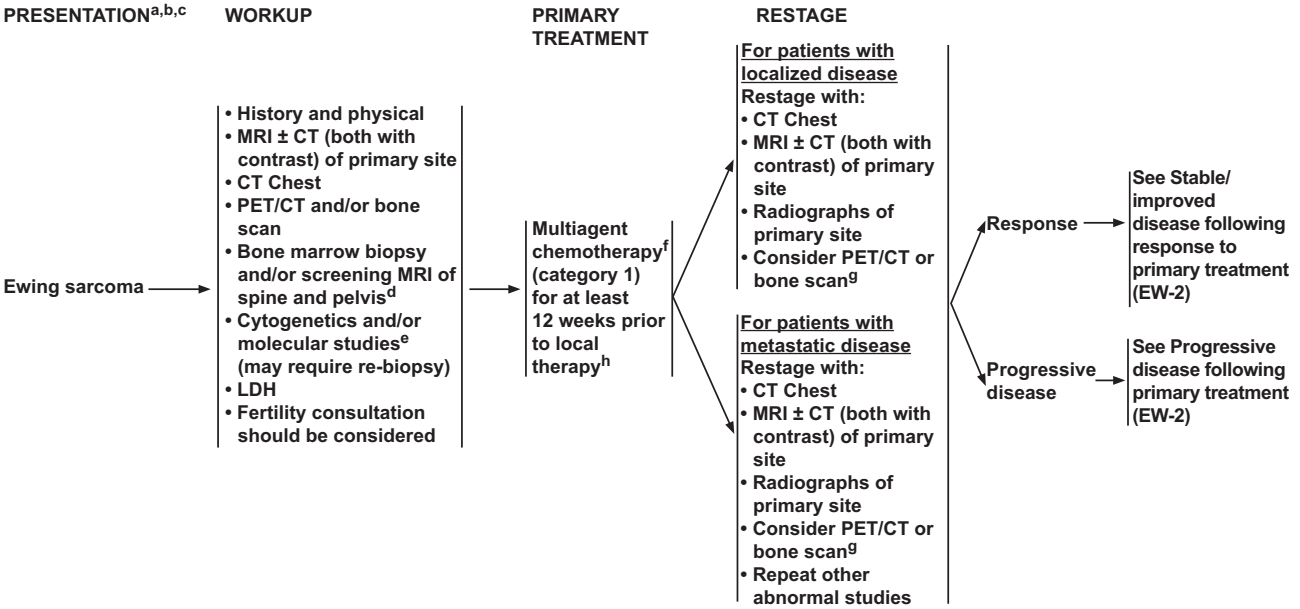


[a]See Multidisciplinary Team (TEAM-1).
[b]See Principles of Bone Cancer Management (BONE-A).
[c]Ewing sarcoma can be treated using this algorithm, including primitive neuroectodermal tumor of bone, Askin's tumor, and extraosseous Ewing sarcoma.
[d]Kumar J, Seith A, Kumar A, et al. Whole-body MR imaging 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 sarcoma will have one of four specific cytogenetic translocations.
[f]See Bone Cancer Systemic Therapy Agents (BONE-B).
[g]Use the same imaging technique that was performed in the initial workup.
[h]Longer primary treatment duration can be considered in patients with metastatic disease based on response.

EW-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

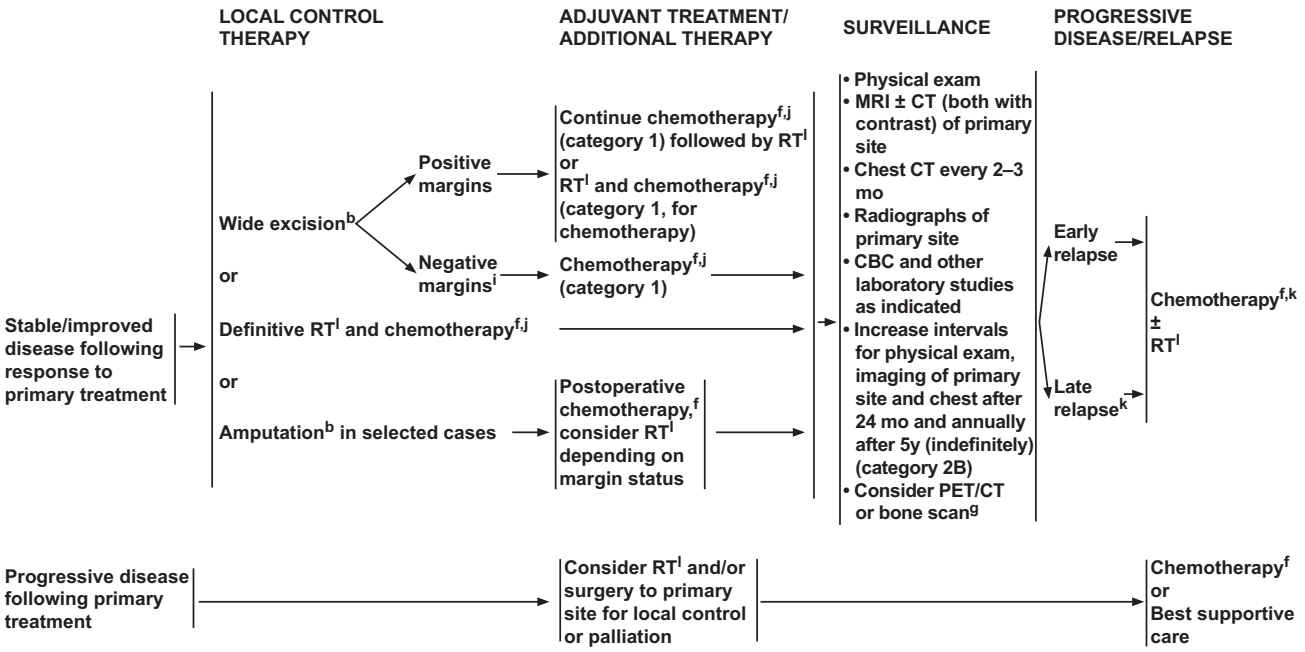
Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

The NCCN Bone Cancer Panel is an interdisciplinary group of representatives from NCCN Member Institutions consisting of specialists in orthopedics/orthopedic oncology, surgical oncology, medical oncology, radiation oncology, pathology, and pediatric oncology. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer include evidence-based recommendations for the assessment and management of primary bone cancers. The panel updates the guidelines on an annual basis with additional interim updates as appropriate. The recommendations for treating Ewing sarcoma are summarized in this article, along with the relevant panel discussion. The latest full version of these guidelines is available at NCCN.org.

Bone Cancer Background

Primary bone cancers are extremely rare neoplasms accounting for less than 0.2% of all cancers, although



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

EW-2

the true incidence is difficult to determine secondary to the rarity of these tumors.[1] In 2016, an estimated 3,300 people were diagnosed in the United States and 1,490 people died of the disease.[2] Primary bone cancers demonstrate wide clinical heterogeneity and are often curable with proper treatment. Osteosarcoma (35%), chondrosarcoma (30%), and Ewing sarcoma (16%) are the 3 most common forms of bone cancer. 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 sarcoma, are of unknown histologic origin.

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has considerably improved the prognosis for patients with osteosarcoma and Ewing sarcoma.[3,4] With current multimodality treatment, approximately three-quarters of all patients diagnosed with osteosarcoma are cured, and 90% to 95% of patients diagnosed with osteosarcoma can be successfully treated with limb-sparing approaches rather than amputation.[5] Survival rates have improved to almost 70% in patients with localized Ewing sarcoma.[4] In patients with Ewing sarcoma and osteosarcoma, a cure is still achievable in selected patients diagnosed with metastatic disease at presentation.[6,7] The 5-year survival across all types of primary bone cancers is 66.6%.[1]

The NCCN Guidelines for Bone Cancer focus on chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma. The guidelines also provide recommendations for treating giant cell tumor of bone (GCTB). Although typically benign, GCTB is locally aggressive and can lead to significant bone destruction.

These NCCN Guidelines Insights summarize the existing data on Ewing sarcoma and describe the recommendations included in version 2.2017 of the guidelines.

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BONE CANCER SYSTEMIC THERAPY AGENTS

Ewing Sarcoma†

- **First-line therapy (primary/neoadjuvant/adjuvant therapy)††**
  - **VAC/IE (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide)[11,12,†††]**
  - **VAI (vincristine, doxorubicin, and ifosfamide)[13,14]**
  - **VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)[15]**
- **Primary therapy for metastatic disease at initial presentation††**
  - **VAdriaC (vincristine, doxorubicin, and cyclophosphamide)[16]**
  - **VAC/IE[11]**
  - **VAI[13,14]**
  - **VIDE[15]**
- **Second-line therapy (relapsed/refractory or metastatic disease)††††**
  - **Cyclophosphamide and topotecan[17-20]**
  - **Irinotecan ± temozolomide[21-27]**
  - **Ifosfamide (high dose) ± etoposide[28, 29]**
  - **Ifosfamide, carboplatin, and etoposide[30]**
  - **Docetaxel and gemcitabine[31]**

†Chemotherapy should include growth factor support (See NCCN Guidelines for Myeloid Growth Factors).
††Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.
†††In patients younger than 18 y, evidence supports 2-week compressed treatment.
††††Vincristine could be added to any of the regimens.

References on next page

Ewing Sarcoma

Gene rearrangements between the *EWS* and *ETS* family of genes have been implicated in the pathogenesis of Ewing sarcoma,[8–11] which typically occurs in adolescents and young adults. The most common primary tumor sites are the pelvic bones, femur, and bones of the chest wall, although any bone may be affected.[3] 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 is referred to as "onion skin" by radiologists. Patients with Ewing sarcoma, as with most patients with bone sarcomas, often 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 lactate dehydrogenase (LDH) and leukocytosis.

Prognostic Factors

Important indicators of favorable prognosis in Ewing sarcoma include a distal/peripheral site of primary disease, tumor volume <100 mL, normal LDH level at presentation, and the absence of metastatic disease at presentation.[12–18] Metastatic disease at presentation is the most significant adverse prognostic factor in Ewing sarcoma, as it is for other bone sarcomas, with the lungs, bone, and bone marrow being the most common metastatic sites.[6,16,19] Among patients with metastases, there was a trend for better survival among those with lung metastases compared with those with bone metastases or a combination of lung and bone metastases.[6]

Additional adverse prognostic factors have been identified in a retrospective analysis of patients with Ewing sarcoma from a large population-based registry. Adult age, Hispanic race, metastatic disease, large tumor size, and low socioeconomic status have been shown to be poor prognostic factors for overall survival (OS).[20] Several studies have identified

BONE CANCER SYSTEMIC THERAPY AGENTS
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primary tumor site as a significant prognostic factor, revealing significantly worse outcomes and prognosis for tumors of the pelvis, spine, and sacrum.[21–23] Poor histologic/radiologic response to chemotherapy has also been identified as an adverse prognostic factor in patients with localized nonmetastatic disease,[15,24,25] even when followed by R0 resection.[26]

Chemotherapy

Systemic therapy is an important component of treatment of Ewing sarcoma, with chemotherapy used prior to local control therapy (ie, surgery or radiation therapy [RT]), as well as in the adjuvant setting. 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 sarcoma in single- and multi-institution collaborative trials in the United States and Europe. Chemotherapy before surgery is often used to downstage the tumor and increase the probability of achieving a complete resection with negative margins. Adjuvant chemotherapy after surgical resection improves relapse-free survival (RFS) and OS in most patients.[27–31]

Localized Disease: Results from the Intergroup Ewing Sarcoma Study trials (IESS-I and IESS-II) first showed that RT plus adjuvant chemotherapy with VACD (vincristine, dactinomycin, cyclophosphamide, and doxorubicin) was superior to VAC (vincristine, dactinomycin, and cyclophosphamide) in patients with localized nonmetastatic disease.[28] Additional studies evaluated the addition of ifosfamide alone or in combination with etoposide to standard chemotherapy for patients with newly diagnosed, nonmetastatic disease.[29,32–36] In the Pediatric Oncology Group-Children's Cancer Group study INT-0091, patients with nonmetastatic Ewing sarcoma were randomized to receive chemotherapy with either VACD alone or alternating with ifosfamide and etoposide (VACD-IE).[29] The 5-year event-free sur-

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PRINCIPLES OF RADIATION THERAPY

EWING SARCOMA

Treatment of Primary Tumor

- Definitive RT
  - Should start by week 12 of VAC/IE chemotherapy or week 18 of VIDE chemotherapy
  - Treatment volumes and doses:
    - 45 Gy to initial gross tumor volume (GTV1) + 1–1.5 cm for clinical target volume 1 (CTV1) + 0.5–1 cm for planning target volume 1 (PTV1)
      - GTV1 defined as: pre-treatment extent of bone and soft tissue disease. If the tumor has responded to chemotherapy and normal tissues have returned to their natural position, GTV1 should exclude pre-chemotherapy soft tissue volume that extended into a cavity (eg, tumors indenting lung, intestine, or bladder resume normal position following chemotherapy).
    - Cone-down (CD) to cover original bony extent + a total of 55.8 Gy to postchemotherapy soft tissue volume (GTV2) + 1–1.5 cm for CTV2 + 0.5–1 cm for PTV2
    - Consider increasing boost dose to a total of 59.4 Gy for chemotherapy response <50%
- Preoperative RT
  - May be considered for marginally resectable tumors and is given concurrently with consolidation chemotherapy
  - Treatment volumes and doses:
    - 36–45 Gy for initial GTV + 2 cm
- Postoperative RT
  - Should begin within 60 days of surgery and is given concurrently with consolidation chemotherapy
  - Treatment volumes and doses:
    - R0 resection:[1] Consider treatment for poor histologic response even if margins are adequate (45 Gy to GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1)
    - R1 resection:[1] 45 Gy GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1
    - R2 resection:[1] 45 Gy to GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1 followed by CD to residual disease plus a total of 55.8 Gy to GTV2 + 1–1.5 cm for CTV2 + 0.5–1 cm for PTV2

Hemithorax Irradiation

- Should be considered for chest wall primaries with extensive ipsilateral pleural involvement
- 15–20 Gy (1.5 Gy/fx) followed by CD to primary site (final dose based on resection margins)

Treatment of Metastatic Disease

- Whole-lung irradiation following completion of chemotherapy/metastasectomy (category 3)
  - 15 Gy (1.5 Gy/fx) for patients <14 years
  - 18 Gy for patients >14 years
- Current Children's Oncology Group (COG) study stratifies age before or after 6 years (12 vs. 15 Gy)

[1]R0 = No microscopic residual disease, R1 = Microscopic residual disease, R2 = Gross residual disease

vival (EFS) and OS rates were significantly higher in the VACD-IE group than the VACD alone group, and VACD-IE also was associated with lower incidences of local failure compared with VACD, irrespective of the type of local control therapy.[37]

European Intergroup Cooperative Ewing's Sarcoma Study EICESS-92 investigated whether cyclophosphamide was similarly efficacious to ifosfamide in patients with small localized tumors. Patients were randomly assigned to VAIA (vincristine, dactinomycin, ifosfamide, and doxorubicin) followed by either VAIA or VACA (vincristine, dactinomycin, cyclophosphamide, and doxorubicin).[38] The 3-year EFS rates were 73% and 74% for VACA and VAIA, respectively, suggesting a similar efficacy of cyclophosphamide to ifosfamide in this cohort. As a follow-up to EICESS-92, the Euro-EWING99-R1 trial evaluated cyclophosphamide as a replacement for ifosfamide as a part of consolidation therapy that also included vincristine and dactinomycin (VAC vs VAI) after VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) induction chemotherapy in patients with standard-risk Ewing sarcoma. VAC was statistically not inferior to VAI; however, 3-year EFS was slightly higher for patients receiving VAI.[39]

Various dosage paradigms of VAC-IE (vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide) have been investigated. Although dose escalation of alkylating agents in VAC-IE did not improve outcomes for patients with localized disease,[40] chemotherapy intensification through interval compression has been shown to improve outcomes. The current standard of care for multiagent chemotherapy in the United States was established through Children's Oncology Group (COG) protocol AEWS0031 (ClinicalTrials.gov identifier: NCT00006734), which examined interval-compressed versus standard administration of VAC-IE for newly diagnosed, localized Ewing sarcoma. This trial showed that chemotherapy administered in 2-week intervals was more effective than 3-week intervals without increasing toxicity.[41]

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Metastatic Disease: The addition of ifosfamide and/or etoposide to standard chemotherapy has not been shown to improve outcomes for patients presenting with metastatic disease.[29,32,34,42] The INT-0091 study showed no significant difference in survival rates between the VACD-IE and VACD regimens.[29] In another study, treatment with high-intensity chemotherapy (doxorubicin and vincristine with or without high-dose cyclophosphamide, followed by ifosfamide and etoposide) led to 4-year EFS and OS rates of 82% and 89%, respectively, for patients with locoregional disease, but corresponding survival rates of 12% and 18%, respectively, for patients with distant metastases.[34] Miser et al[42] reported similar findings in patients presenting with metastatic Ewing sarcoma. Finally, EICESS-92 investigated whether the addition of etoposide to ifosfamide-containing regimens improved survival in patients with large tumors or metastatic disease.[38] Patients were randomly assigned to VAIA or VAIA plus etoposide (EVAIA), but no significant differences in 3-year EFS were observed between the treatment groups.

Local Control Therapy

Surgery and RT are the local control treatment modalities used for patients with localized disease. However, no randomized studies have compared these treatment modalities. In patients with localized Ewing sarcoma treated in cooperative intergroup studies, no significant effect of local control modality (surgery, RT, or surgery + RT) was observed for OS or EFS.[37,43]

In the CESS 86 trial, although radical surgery and resection plus RT resulted in better local control rates (100% and 95%, respectively) compared with definitive RT (86%), there was no improvement in RFS or OS because of a higher frequency of metastases after surgery.[43] In the INT-0091 study, incidence of local failure was similar for patients treated with surgery or RT alone (25%), but surgery plus RT resulted in lower incidence of local failure (10.5%).[37]

The 5-year EFS rate was also not significantly different between patients treated with surgery, RT, and surgery plus RT. Local control therapy has also been associated with improved outcomes in patients with primary metastatic disease.[44–46] In the Euro-EWING99 trial, the 3-year EFS was significantly lower in patients with primary metastatic disease who did not receive any local control therapy compared with those treated with local therapy for primary tumor.[44]

Data from other retrospective analyses suggest that surgery (± postoperative RT) affords better local control than RT alone in patients with localized disease.[47,48] The combined analysis of 1,058 patients treated in the CESS 81, CESS 86, and EICESS-92 trials showed that the rate of local failure was significantly lower after surgery (± postoperative RT) than after definitive RT, whereas the local control rate in the preoperative RT group was comparable to that of the surgery group.[47] The most recent retrospective analysis of sequential studies (INT-0091, INT-0154, or AEWS0031) performed by the COG also demonstrated that definitive RT was associated with a higher risk of local failure than surgery plus RT, but there was no effect on distant failure.[48]

However, definitive RT may be an effective treatment option for patients with tumors in anatomic locations not amenable to surgery with wider resection margins.[49,50] Tumor size and RT dose have been shown to be predictive of local control rates in patients with nonmetastatic Ewing sarcoma treated with chemotherapy and definitive RT.[51,52] In a retrospective analysis of patients with Ewing sarcoma of the spine treated in the CESS 81/86 and EICESS-92 studies, definitive RT resulted in a local control rate comparable to that of other tumor sites treated with definitive RT; EFS and OS rates at 5 years were 47% and 58%, respectively.[49]

Treating Relapsed/Refractory Disease

Approximately 30% to 40% of patients with Ewing sarcoma experience recurrence (local and/or distant) and have a very poor prognosis. Patients with a longer time to first recurrence have a better chance of survival after recurrence. Late relapse (≥2 years from the time of original diagnosis), lung-only metastases, local recurrence that can be treated with radical surgery, and intensive chemotherapy are the most favorable prognostic factors, whereas early relapse (<2 years from the time of original diagnosis) with metastases in lungs and/or other sites, recurrence at local and distant sites, elevated LDH level at initial diagnosis, and initial recurrence are considered adverse prognostic factors.[53–56] In a recent retrospective analysis, site of first relapse and time to first relapse were significant prognostic factors for adult patients with localized Ewing sarcoma.[57] The probability of 5-year postrelapse survival was 50% and 13% for patients with local and distant relapse, respectively. The probability of 5-year postrelapse survival was also significantly higher for patients with late versus early relapse.[6,57,58]

Ifosfamide in combination with etoposide with or without carboplatin has been shown to be active in clinical trials for the treatment of patients with relapsed or refractory sarcoma.[59,60] A recent review of 239 patients with Ewing sarcoma suggested a potential risk-reduction benefit of high-dose versus conventional chemotherapy for treating first relapse.[61] High-dose ifosfamide with or without etoposide appears to be an active second-line therapy for relapsed, refractory, or metastatic disease.[59,62] Non–ifosfamide-based chemotherapy regimens have also demonstrated activity and good tolerability in patients with relapsed or refractory bone sarcomas. Regimens that appear to be active in this patient group include docetaxel and gemcitabine[63]; topoisomerase I inhibitors (topotecan, irinotecan) with cyclophosphamide and temozolomide[64–70]; cyclophosphamide and topotecan[65]; irinotecan and temozolomide[68]; and vincristine, irinotecan, and temozolomide.[71] A review of 107 patients with relapsed or refractory Ewing sarcoma examined the combination of etoposide with a platinum agent (ie, cisplatin or carboplatin), suggesting that further study of etoposide/carboplatin may be warranted.[72]

NCCN Recommendations

Workup: Patients presenting with symptomatic bone lesions should be referred to an orthopedic oncologist and a biopsy should be performed at the treating institution. For additional workup of patients with Ewing sarcoma, the panel recommends a history and physical, and imaging of the primary site and potential metastatic sites. Cytogenetic and/or molecular studies of the biopsy specimen should be performed to evaluate the t(11;22) translocation, and a bone marrow biopsy should be considered to complete

the workup. Because serum LDH has been shown to have prognostic value as a tumor marker, the NCCN Guidelines have included this test as part of initial evaluation. Fertility consultation should also be considered. In the 2017 update, imaging of the primary site was clarified to include MRI with or without CT, both with contrast. Other imaging recommendations include chest CT and whole-body PET/CT and/or bone scan. Screening MRI of the spine/pelvis is also recommended in lieu of, or in addition to, bone marrow biopsy (see recommendations on EW-1, page 157).

Primary Treatment: All patients with Ewing sarcoma should be 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 at least 12 weeks (category 1; see EW-1, page 157). Longer duration could be considered for patients with metastatic disease based on response. VAC-IE is the preferred regimen for patients with localized disease, whereas VAdriaC (vincristine, doxorubicin, and cyclophosphamide) is the preferred regimen for patients with metastatic disease.[29,34,42] A list of other chemotherapy regimens recommended for patients with localized and metastatic disease is available on BONE-B (page 159).

Restaging: Imaging to restage disease should follow primary treatment (see EW-1, page 157). Clarifications and additions were made to the recommendations for the 2017 update. The panel specified CT as the preferred modality for chest imaging and recommended MRI with or without CT for primary site imaging. Plain radiographs were added as a potential imaging tool for restaging. PET/CT and/or bone scan can be used for restaging depending on the imaging technique used in the initial workup. For patients with metastatic disease at presentation, studies that were abnormal at workup should be repeated.

Patients with stable or improved disease after primary treatment should receive local control therapy. For patients with progressive disease after primary treatment, the panel recommends consideration of RT and/or surgery of the primary site for local control or palliation. Further progressive or relapsed disease should be addressed with chemotherapy or best supportive care.

Local Control Therapy: Patients with stable or improved disease after primary treatment should receive local control therapy (see EW-2, page 158). Recommended options include wide excision, definitive RT with chemotherapy, or amputation in selected cases.[44,47,49,51] The choice of local control therapy should be individualized and is dependent on tumor location, size, response to chemotherapy, patient's age, anticipated morbidity, and patient preference.[37]

Adjuvant chemotherapy after wide excision is recommended for all patients regardless of surgical margins (category 1). The panel recommends that the duration of chemotherapy after wide excision should be between 28 and 49 weeks, depending on the type of regimen and the dosing schedule.[27–29] The addition of postoperative RT to chemotherapy is recommended for patients with positive or very close surgical margins (see BONE-C, page 161).[47] In patients with smaller tumor size (<8 cm) and negative margins, postoperative RT can be omitted without any decrement in OS.[73] The 15-year estimated OS for patients who received adjuvant RT was 80% compared with 100% for those who did not. The guidelines have included adjuvant chemotherapy alone for patients treated with wide excision and negative margins.

After amputation, the panel recommends postoperative chemotherapy with consideration of RT depending on margin status. Patients who received definitive RT and chemotherapy as part of initial local control therapy should proceed to surveillance.

Surveillance: Surveillance of patients with Ewing sarcoma should include a physical examination, CBC, and other laboratory studies as indicated. Chest CT without contrast should be performed every 3 months. Cross-sectional imaging of the primary site was specified to include MRI with or without CT, both with contrast, in addition to plain radiographs. PET/CT or bone scan can be considered in surveillance. Long-term surveillance should be performed annually after 5 years, indefinitely (category 2B).[74] For surveillance recommendations, see EW-2 (page 158).

Treating Relapsed/Refractory Disease: Treatment options for patients with relapsed or refractory disease include participation in a clinical trial and chemotherapy with or without RT. If a relapse is delayed, as sometimes occurs with this sarcoma, retreatment with a previously effective regimen may

be useful. See BONE-B (page 159) for a list of other chemotherapy regimens recommended for patients with relapsed or refractory disease. All patients with recurrent and metastatic disease should be considered for clinical trials investigating new treatment approaches and should receive best supportive care.

Conclusions

Treatment recommendations for Ewing sarcoma in the NCCN Guidelines for Bone Cancer are highlighted in these NCCN Guidelines Insights, along with a review of the relevant data. The NCCN Guidelines are updated at least annually, and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical trials where available combined with expert consensus of the NCCN panel. Independent medical judgment is required to apply these guidelines individually to provide optimal care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN panel strongly encourages participation in prospective clinical trials.

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Posttest Questions

1. Local control therapy is recommended for treating Ewing sarcoma that is improved following primary treatment with multiagent chemotherapy. Which options for local control therapy are recommended by the NCCN Guidelines?
   a. Chemotherapy alone
   b. Definitive RT plus chemotherapy
   c. Wide excision
   d. Amputation
   e. A, B, and C
   f. B, C, and D
2. True or False: Multimodality imaging should be used to restage disease following primary chemotherapy.
3. Which of the following is a recommended frontline chemotherapy regimen for metastatic disease at initial presentation?
   a. Vincristine/dactinomycin
   b. VAdriaC
   c. Docetaxel/gemcitabine
   d. MAP