

Bone Cancer, Version 2.2025

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Abstract

Ewing sarcoma and osteosarcoma constitute 36% of all primary bone cancers. However, these 2 subtypes represent the most commonly diagnosed bone cancer types in the pediatric and adolescent population. Although still largely unknown, certain genetic mutations, rearrangements, and/or predisposition syndromes likely play a role in the pathogenesis of bone cancer. Osteosarcoma may also develop as a direct result of the long-term side effects of radiation therapy. With the implementation of a multimodality approach to treatment, including multiagent neoadjuvant and adjuvant chemotherapy regimens, targeted therapy options, surgery, and radiation, individuals with Ewing sarcoma and osteosarcoma are showing higher cure rates and improved overall survival. The NCCN Guidelines for Bone Cancer provide a consensus and evidence-based framework for the workup, management, and surveillance of local and recurrent/metastatic disease.

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Overview

Primary bone cancers are extremely rare neoplasms accounting for ~0.2% of all cancers, although the true incidence is difficult to determine secondary to the rarity of these tumors.¹ In 2025 an estimated 3,770 people will be diagnosed in the United States and 2,190 people will die of these diseases.²

Primary bone cancers demonstrate wide clinical heterogeneity and may be curable with proper treatment. In adults, chondrosarcoma is the most common primary bone cancer, accounting for more than 40% of newly diagnosed bone cancers, followed by osteosarcoma (~25%), chordoma (10%), and Ewing sarcoma (8%).³ Other less common primary bone tumors include giant cell tumor of bone (GCTB) and undifferentiated pleomorphic sarcoma. In children and adolescents, osteosarcoma and Ewing sarcoma are far more common than chondrosarcoma and chordoma.^{3,4} High-grade undifferentiated pleomorphic sarcoma of bone and GCTB are relatively rare tumors, with each constituting <5% of primary bone tumors.⁵ GCTB has both benign and exceptionally rare malignant forms. Various types of bone cancers are named based on their

histologic line of differentiation. Chondrosarcomas differentiate toward cartilage, osteosarcomas toward bone, angiosarcoma and epithelioid hemangioendothelioma show endothelial (vascular) differentiation, and chordoma shows notochordal differentiation. Several primary bone cancers, including Ewing sarcoma, are of unknown lineage. Chondrosarcoma is more prevalent in individuals >50 years of age.⁶ Osteosarcoma and Ewing sarcoma develop mainly in children and young adults. Chordoma is more common in males, with the peak incidence in the fifth to sixth decade of life.⁷⁻⁹

The pathogenesis and etiology of most bone cancers remain unclear. Gene rearrangements between the FET (usually *EWSR1*) and ETS (usually *FLI1*) family of genes have been implicated in the pathogenesis of Ewing sarcoma.¹⁰⁻¹⁴ Specific germline mutations have been linked to the development of osteosarcoma.¹⁵ Li-Fraumeni syndrome, characterized by a germline mutation in the *TP53* gene, is associated with a high risk of developing cancer, including osteosarcoma.¹⁶⁻¹⁸ Osteosarcoma is the most common second primary malignancy in patients with a history of retinoblastoma, characterized by a germline mutation in the

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To view disclosures of external relationships for the NCCN Guidelines panel, go to <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels>

The full NCCN Guidelines for Bone Cancer are not printed in this issue of JNCCN. The complete and most recent version of these guidelines is available free of charge at [NCCN.org](https://www.nccn.org).

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 indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

retinoblastoma gene *RBI*.^{19–21} Increased incidences of osteosarcoma have also been associated with other genetic mutations and inherited genetic predisposition syndromes.²¹ Osteosarcoma is also the most common radiation-induced bone sarcoma.^{22,23}

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has markedly improved the prognosis for patients with osteosarcoma and Ewing sarcoma.^{24,25} With current multimodality treatment, approximately 60%–70% of patients diagnosed with osteosarcoma (without clinically evident metastases) are cured, and ~90% of patients diagnosed with osteosarcoma can be treated with limb-sparing approaches.^{26–28} Five-year relative survival rates have improved to 82% in patients with localized Ewing sarcoma.²⁹ In patients with Ewing sarcoma and osteosarcoma, a cure is still achievable in selected patients diagnosed with metastatic disease at presentation.^{30,31} The 5-year survival across all types of primary bone cancers is 68%.¹

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bone Cancer focus on chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma. The guidelines also provide recommendations for treating GCTB. Although typically benign, GCTB is locally aggressive and can lead to significant bone destruction. Malignant transformation is also possible.

Staging

The eighth edition of the AJCC staging classification (2018) is based on the assessment of histologic grade (G), tumor size (T), and presence of regional (N) and/or distant metastases (M).³²

The NCCN Bone Cancer Panel would like to clarify that although some studies interpret imaging before chemotherapy treatment based on the extent of tumor invasion relative to the periosteum (eg, extraperiosteal, intraperiosteal) for prognostic purposes, these terms do not specifically occur in any validated staging systems and the significance is unknown.

Principles of Bone Cancer Management
Multidisciplinary Team Involvement

Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team of physicians with demonstrated expertise in the management of these tumors. The core team should include, at minimum, the following: orthopedic oncologist, bone pathologist, medical/pediatric

oncologist, radiation oncologist, and musculoskeletal radiologist. Other specialists who may be critical in certain cases include the following: thoracic surgeon, plastic surgeon, interventional radiologist, physiatrist, vascular/general surgeon, neurosurgeon/orthopedic spine surgeon, and palliative care physician. Additional surgical subspecialties may be included as clinically indicated.

Long-term surveillance and follow-up are necessary when considering the risk of recurrence and comorbidities associated with systemic therapy and radiation therapy (RT). Life-long follow-up is recommended for surveillance and treatment of late effects of surgery, RT, and systemic therapy in long-term survivors. Patients should be given a survivorship prescription to schedule follow-up with a multidisciplinary team. Fertility issues should be discussed with appropriate patients.³³ For information on disease- and survivorship-related issues for adolescent and young adult (AYA) patients, please refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at NCCN.org) as clinically appropriate. Finally, select patients with a family history of genetic predisposition to bone sarcomas may benefit from genetic consultation and testing.

Diagnostic Workup

Suspicion of a malignant bone tumor in a patient with a symptomatic lesion often begins when a poorly marginated lesion is seen on a plain radiograph.

In patients <40 years, an aggressive, symptomatic bone lesion has a significant risk of being a malignant primary bone tumor. Referral to an orthopedic oncologist should be considered before further workup.

In patients ≥40 years of age, workup for potential bone metastasis is recommended as indicated. This would include history and physical, bone scan, chest x-ray, and CT of the chest/abdomen/pelvis with intravenous contrast. Additional testing, such as serum protein electrophoresis, complete blood count (CBC), comprehensive metabolic panel, prostate-specific antigen test, or mammogram may also be included.³⁴ Other imaging studies such as FDG-PET/CT (category 2B) may be performed as clinically indicated.^{34–36}

Prior to biopsy, all patients with suspected bone sarcoma should undergo complete staging and consultation with an oncologist regarding prebiopsy imaging.

Depending on the suspected type of primary bone cancer, the standard staging workup can include history and physical, x-ray, cross-sectional imaging of the primary site (eg, contrast-enhanced MRI of the entire bone, and/or CT scan if MRI contraindicated), screening MRI of spinal axis, and CT chest/abdomen/pelvis with contrast.³⁷ FDG-PET/CT and/or bone scan can be considered if clinically indicated. Fertility consultation should be offered to individuals of child-bearing potential if cytotoxic chemotherapy will be given.

Laboratory studies, such as CBC, comprehensive metabolic panel with calcium to assess for hypercalcemia, lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) should be done before definitive treatment and periodically during treatment and surveillance. Molecular studies can be considered to delineate potential therapeutic options.

Biopsy

Percutaneous (core needle) or incisional (open) biopsy are the 2 techniques historically used in the diagnosis of musculoskeletal lesions.^{38,39}

Open biopsy is the most accurate method because of larger sample size, which is useful for performing additional studies such as immunohistochemistry or cytogenetics.⁴⁰ However, open biopsy requires general or regional anesthesia and operating room facilities; moreover, it can lead to contamination of surrounding tissues. Core biopsy can be performed under moderate sedation. Core needle biopsy is also highly diagnostic, with accuracy rates ranging from 88% to 96% when adequate samples are obtained.^{41–44} Core biopsy is associated with a low complication rate, and cost savings may be realized when needle biopsy is employed in selected patients.^{41,44,45} Advances in imaging techniques have contributed to the increasing use of image-guided percutaneous biopsy for the diagnosis of primary and secondary bone tumors.⁴⁶ Furthermore, rates of complications, particularly altered treatment and outcomes, are considerably higher with open biopsy.^{39,47} Although no randomized controlled trials have compared core needle biopsy with open biopsy, the higher complication rate and cost of open biopsy have resulted in a shift to the use of primarily core biopsy for diagnosis.

The guidelines recommend core-needle or open biopsy to confirm the diagnosis of primary bone tumor before any surgical procedure or fixation of primary site. Biopsy should be performed at a center that will provide definitive treatment for patients with a suspected primary malignant bone tumor. At the time of biopsy, careful consideration should be given to appropriate measures to protect against impending pathologic fracture. The placement of biopsy is critical to the planning of limb-sparing surgery. A multidisciplinary approach including the radiologist and orthopedic oncologic surgeon, should be taken to follow appropriate biopsy procedures and decrease risk of adverse patient outcomes.^{48,49} In a multicenter review of 597 patients with musculoskeletal tumors, alteration of the treatment plan (complex resection or the use of adjunctive treatment) was encountered in 19% of patients and unnecessary amputation was performed in 18 patients.⁴⁷

Both core needle and open biopsy techniques are associated with risk of local tumor recurrence, either by tumor spillage or tumor seeding along the biopsy tract, if the scar is not removed en bloc during the tumor resection. The risk of tumor seeding is less with core needle biopsy.^{50–52} Nevertheless, the same principles should be applied for core needle and open biopsy.

Appropriate communication between the surgeon, musculoskeletal or interventional radiologist, and bone pathologist is critical in planning the biopsy route. In the case of children, consultation with a pediatric oncologist is recommended. It is essential to select the biopsy route in collaboration with the surgeon to ensure that the biopsy tract lies within the planned resection bed so that it can be resected with the same wide margins as the primary tumor during surgery. Although the risk of tumor seeding is not significant with FNA biopsy, it is not suitable for the diagnosis of primary lesions since the diagnostic accuracy of FNA is less than that of core needle biopsy.⁵³

Surgery

Surgical margins should be negative for most sarcomas, wide enough to minimize potential local recurrence, and narrow enough to maximize function. Wide excision implies histologically negative surgical margins which is necessary to optimize local control. Local control may be achieved either by limb-sparing surgery or amputation. In selected cases, amputation may be the most appropriate option to achieve this goal. However, limb-sparing surgery is preferred if reasonable functional outcomes can be achieved. Final pathologic evaluation should include assessment of surgical margins and size/dimensions of tumor. Fresh tissue may be needed for molecular studies and tissue banking. The response to preoperative therapy should be evaluated utilizing pathologic mapping. Consultation with a physiatrist may assist with mobility training and prescribing an appropriate rehabilitation program.

Radiation Therapy

RT is used either as an adjuvant to surgery for patients with resectable tumors or as definitive therapy in patients with tumors not amenable to surgery. Specialized techniques such as intensity-modulated RT; particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery/stereotactic RT should be considered as clinically indicated to deliver high radiation doses while maximizing normal tissue sparing.^{54,55} RT should be administered at the same specialized center that is providing surgical and systemic interventions. See “Principles of Radiation Therapy” in these guidelines at NCCN.org for treatment volumes and radiation doses specific to each subtype.

Ewing Sarcoma

Ewing sarcoma is characterized by the fusion of the *EWS* gene (*EWSR1*) on chromosome 22q12 with various members of the ETS gene family (*FLI1*, *ERG*, *ETV1*, *ETV4*, and *FEV*).^{11,12} The *EWSR1::FLI1* fusion transcript resulting from the fusion of *EWSR1* and *FLI1* on chromosome 11 and the corresponding chromosomal translocation, t(11;22)(q24;q12), is identified in about 85% of patients with Ewing sarcoma.^{11,14} In 5% to 10% of cases, *EWSR1* is fused with other members of the ETS gene family. In rare cases, *FUS* can substitute for *EWSR1*, resulting in fusion transcripts with no *EWSR1* rearrangement [*FUS::ERG* fusion transcript resulting from the translocation t(16;21)(p11;q24) or *FUS::FEV* fusion transcript resulting from the translocation t(2;16)(q35;p11)].^{56,57} Overall, 90% of Ewing sarcomas will have 1 of 4 cytogenetic translocations. Ewing sarcoma is also characterized by the strong expression of cell surface glycoprotein MIC2 (CD99).^{58,59} The expression of CD99 may be useful in the differential

diagnosis of Ewing sarcoma from other small round-cell neoplasms, although it is not exclusively specific to these tumors.⁶⁰ Similar in morphology with various molecular signatures, other primary round cell sarcoma of bone, previously referred to as Ewing-like sarcomas, are a heterogeneous group of tumors that primarily affect the pediatric and adolescent population.⁶¹ These tumors include CIC-rearranged sarcomas (eg, *CIC::DUX4*), *BCOR*-rearranged sarcomas, and round cell sarcomas with *EWSR1* fusions with non-ETS genes.⁶²

Typically, Ewing sarcoma occurs in AYAs, with an incidence of 1 case per 1.5 million.⁶³ The most common primary sites are the pelvic bones, femur, and the bones of the chest wall, although any bone may be affected.²⁴ However, in approximately 20% of cases, these tumors emerge from extraosseous tissue.⁶³ When arising in a long bone, the diaphysis is the most frequently affected site.²⁴ On imaging, the bone appears mottled. Periosteal reaction is classic, and it is referred to as “onion skin” by radiologists.

Patients with Ewing 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.

Prognostic Factors

The important indicators of favorable prognosis 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.^{64–71} Ewing sarcoma in the spine and sacrum is associated with significantly worse outcome and prognosis than primary Ewing sarcoma in other sites.⁷² In a systematic review, Bosma et al also reported tumor size (diameter >8 cm) and histologic response to initial systemic treatment (≥90% necrosis) to be important prognostic variables.⁷³ Nevertheless, metastatic disease at presentation is the most significant adverse prognostic factor observed in those with Ewing sarcoma, as it is for other bone sarcomas.^{30,68,74} The lungs, bone, and bone marrow are the most common sites of metastasis. In a retrospective analysis of 975 patients from the EICESS Study Group, 5-year relapse-free survival (RFS) was 22% for patients with metastatic disease at diagnosis compared with 55% for patients without metastases at diagnosis.³⁰ Among patients with metastases, there was a trend for better survival for those with lung metastases compared with those with bone metastases or a combination of lung and bone metastases.^{30,75} Metastases to uncommon sites (ie, brain, liver, spleen) were associated with a worse prognosis in a retrospective study of 30 patients.⁷⁶ Poor histologic/radiologic response to chemotherapy has also been identified as an adverse prognostic factor in patients with localized nonmetastatic disease,^{67,71,77,78} even when chemotherapy was followed by complete (R0) resection.⁷⁹

The results of the Intergroup Ewing's Sarcoma Study (IESS) analyzing the clinicopathologic features of 303 cases of Ewing sarcoma showed that patients with primary tumors in pelvic bones have lower survival rates compared with patients with lesions in distal bones of the extremities.⁸⁰ In an analysis of 53 patients (24 adult and 29 pediatric) with Ewing sarcoma treated with chemotherapy, Gupta et al identified pelvic disease and time to local therapy as significant prognostic factors associated

with event-free survival (EFS) in a multivariate analysis.⁸¹ In another retrospective analysis of patients with Ewing sarcoma from a large population-based cancer registry, Lee et al determined that adult age, Hispanic ancestry, metastatic disease, large tumor size, and low socioeconomic status are poor prognostic factors for overall survival (OS).⁸²

Workup

If Ewing sarcoma is suspected as a diagnosis, the patient should undergo complete staging before biopsy (Figure 1). This should include CT of the chest with or without contrast as clinically indicated (noncontrast CT is recommended for restaging); contrast-enhanced; MRI with or without CT of the primary site; whole body FDG-PET/CT (preferred) and/or bone scan; and possibly bone marrow biopsy and/or screening MRI with or without contrast of the spine and pelvis. In a systematic review and meta-analysis, Treglia et al reported that the combination of FDG-PET/CT with conventional imaging is a valuable tool for the staging and restaging of Ewing sarcoma, with 96% sensitivity and 92% specificity.⁸³ Another systematic review indicated that FDG-PET without bone marrow biopsy may be considered for staging in newly diagnosed Ewing sarcoma patients, as FDG-PET demonstrated 100% sensitivity and 96% specificity based on pooled patient data from four studies.⁸⁴ Results from ACRIN 6660, a multicenter prospective cohort study conducted by the American College of Radiology Imaging Network comparing whole-body MRI and conventional imaging in pediatric patients with common malignant tumors (including Ewing sarcoma), found that the noninferior accuracy for diagnosis of distant metastasis was not established for the use of whole-body MRI compared with conventional imaging.⁸⁵ However, the accuracy of whole-body MRI was higher for patients with solid tumors compared with those with lymphomas ($P=.006$).

Cytogenetic and/or molecular studies of the biopsy specimen should be performed to evaluate t(11;22), or other less common translocations (Figure 1). Comprehensive genomic profiling has also been used to identify potentially actionable translocations in patients with sarcoma.^{86,87} In the case that pathologic workup of targeted PCR, fluorescence in situ hybridization, or cytogenetics is negative, comprehensive genomic profiling or other fusion panels for Ewing sarcoma should be considered to identify translocations, including atypical translocations.

Preliminary reports suggest that *EWSR1::FLI1* translocation is associated with a better prognosis than other variants.^{88–90} However, reports from the EURO-EWING 99 study and the Children's Oncology Group study suggest that with currently available effective therapies, patients with Ewing sarcoma have similar outcomes, regardless of fusion subtype in contrast to previous reports.^{91,92} In addition to *EWSR1*, *FUS* should be considered as a fusion gene partner in the molecular diagnosis to identify the rare cases of Ewing sarcoma with *FUS::ERG* or *FUS::FEV* fusion transcripts.^{56,57} Because serum LDH has been shown to have prognostic value as a tumor marker, the guidelines have included this test as part of initial evaluation (Figure 1).

Fertility consultation should also be considered as appropriate. The American Society for Reproductive Medicine recommends that conversations concerning fertility be undertaken by

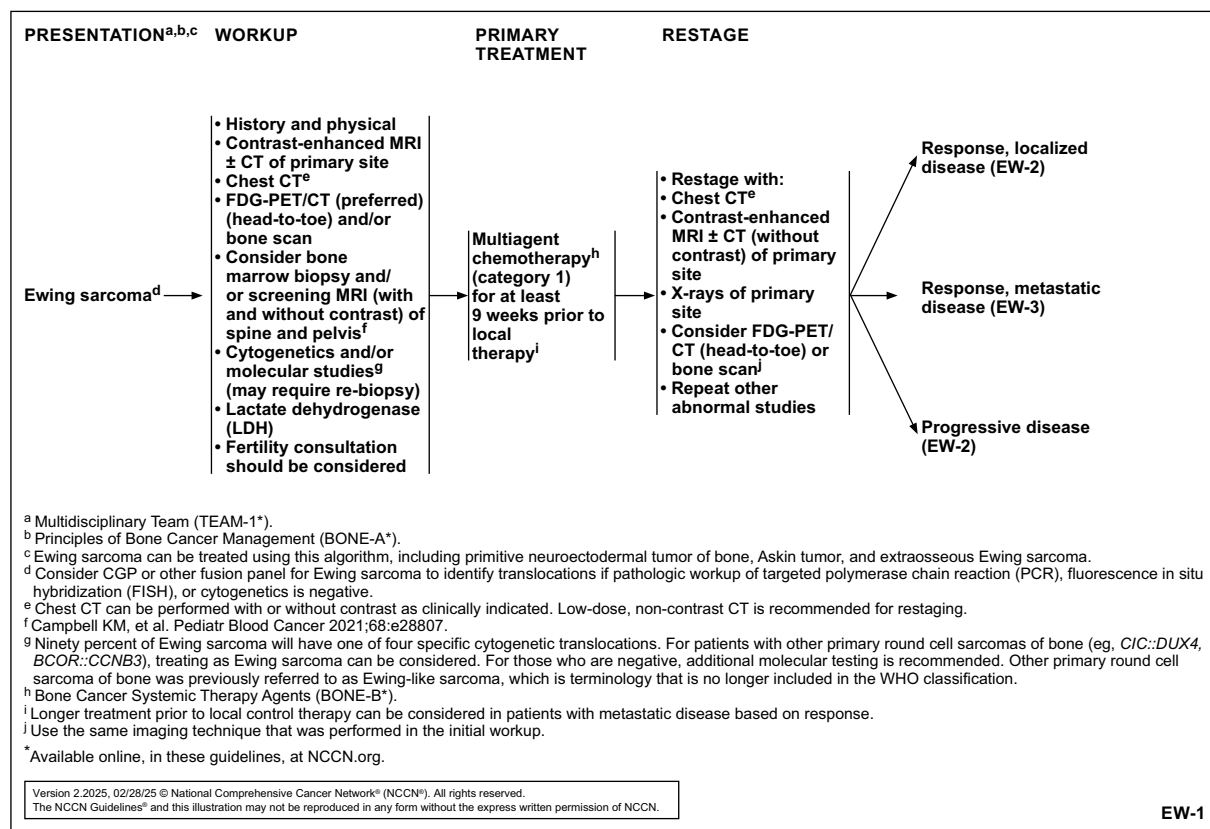


Figure 1. EW-1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

an interdisciplinary medical team comprised of oncologists, reproductive endocrinologists and urologists, and reproductive surgeons trained in fertility preservation methods and that fertility preservation programs be affiliated with an experienced assisted reproductive technology program.^{93,94} For further details and recommendations, refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at NCCN.org).

Treatment

Chemotherapy

Multiagent chemotherapy regimens including VDC (vincristine, doxorubicin, and cyclophosphamide) alternating with ifosfamide and etoposide (IE) have been shown to be effective in patients with localized Ewing sarcoma in single- as well as multi-institution collaborative trials in the United States and Europe. Multiagent chemotherapy for at least 9 weeks is recommended prior to surgery to downstage the tumor and increase the probability of achieving a complete resection with microscopically negative margins (R0) (Figure 1). Data supports the use of adjuvant chemotherapy following surgical resection, resulting in improved RFS and OS.^{95–99} Surgical resection with or without RT is used for local control following chemotherapy (Figure 2).

The addition of ifosfamide, alone or in combination with etoposide to standard chemotherapy, was evaluated in patients with newly diagnosed, nonmetastatic Ewing sarcoma.^{97,100–104} In the Pediatric Oncology Group-Children's Cancer Group study (INT-0091), 398 patients with nonmetastatic Ewing sarcoma were randomized to receive chemotherapy with VACD (vincristine, dactinomycin, cyclophosphamide, and doxorubicin) alone

or VACD alternating with ifosfamide and etoposide (VACD-IE) for a total of 17 cycles.⁹⁷ The 5-year EFS rate was significantly higher in the VACD-IE group than in the VACD alone group (69% and 54%, respectively; $P=.005$). The 5-year OS rate was also significantly better among patients in the VACD-IE group (72% and 61%, respectively; $P=.01$). VACD-IE also was associated with lower incidences of local failure (11%) compared with VACD (30%) irrespective of the type of local control therapy; 5-year cumulative incidences of local failure were 30% in the VACD arm compared with 11% in the VACD-IE arm.¹⁰⁵

While dose escalation of alkylating agents in the VDC-IE regimen did not improve the outcome for patients with localized disease,¹⁰⁶ chemotherapy intensification through interval compression improved outcome in patients with localized disease.¹⁰⁷ In a randomized trial for patients <50 years with localized Ewing sarcoma (n=568), Womer et al reported that VDC-IE given on an every-2-week schedule was found to be more effective than VDC-IE given on an every-3-week schedule, with no increase in toxicity; median 5-year EFS was 73% and 65%, respectively.¹⁰⁷

The EURO EWING 2012 was a randomized analysis conducted to compare the induction and consolidation regimens for newly diagnosed Ewing sarcoma in both the United States and Europe.¹⁰⁸ Six hundred forty patients between the ages of 2 and 49 years were randomized to 2 treatment arms. Treatment arm A received the European regimen: VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) induction therapy followed by vincristine, actinomycin D, with ifosfamide or cyclophosphamide, or busulfan and melphalan consolidation. Treatment arm B received the United States regimen: compressed VDC/IE induction

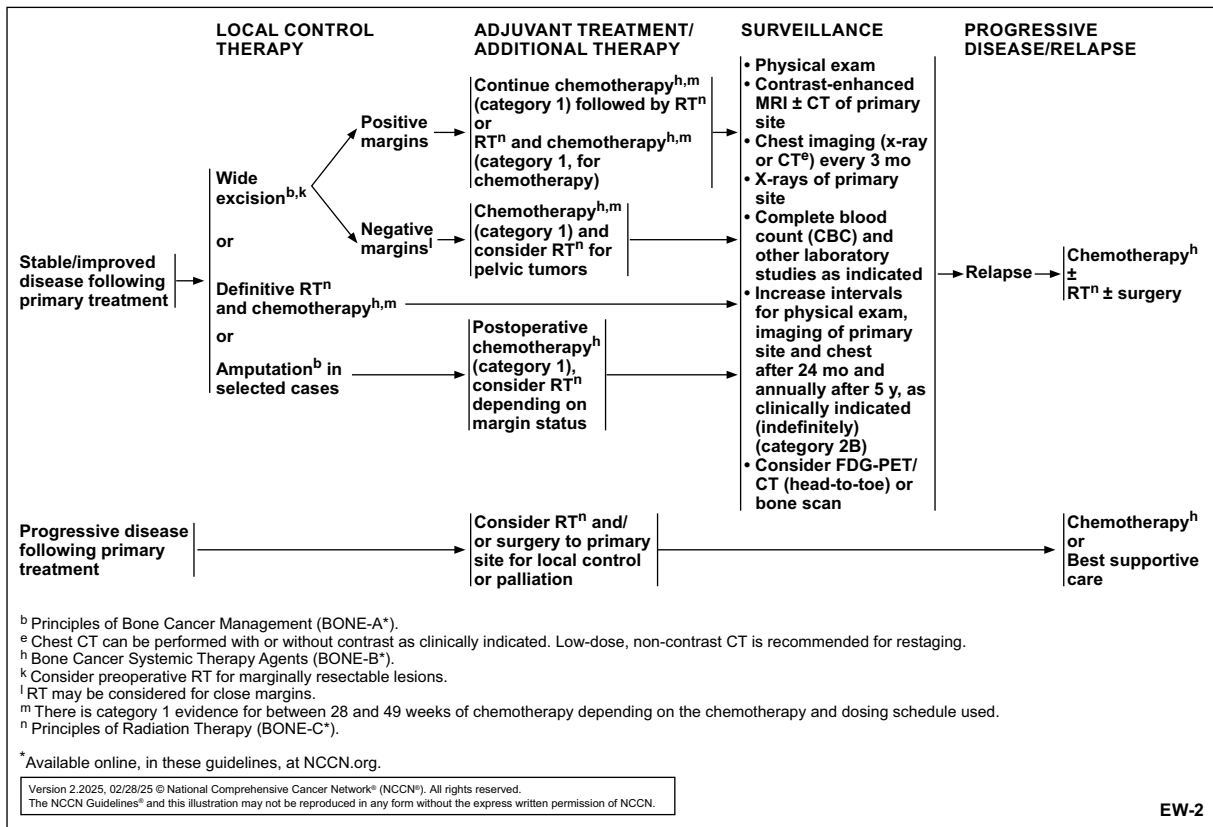


Figure 2. EW-2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

followed by vincristine and cyclophosphamide (VC), or vincristine, actinomycin D, and ifosfamide, with busulfan and melphalan consolidation. The primary endpoint of the study was EFS and the secondary endpoints were OS and toxicity. EFS at 3 years was 61% and 67% for treatment arm A and B, respectively (adjusted hazard ratio [HR], 0.71 [95% credible interval, 0.55–0.92 in favor of treatment arm A). Grade 3–5 febrile neutropenia occurred in 74% of participants in treatment arm A and in 58% of participants in treatment arm B. More participants in treatment arm A required at least one platelet transfusion; however, more participants in treatment arm B required more blood transfusions. The VDC/IE regimen proved superior to the European regimen in terms of EFS and OS with similar toxicity profiles.

IESS-I and IESS-II showed that RT plus adjuvant chemotherapy with VACD was superior to VAC in patients with localized nonmetastatic disease.⁹⁶ The 5-year RFS rates were 60% and 24% for VACD and VAC, respectively ($P < .001$). The corresponding OS rates were 65% and 28% ($P < .001$).

In the INT-0091 study, which included 120 patients with metastatic disease, there was no significant difference in the EFS and OS rates between the VACD-IE and VACD regimens.⁹⁷ The 5-year EFS rate was 22% for both regimens and the 5-year OS rate was 34% and 35% for the VACD-IE and VACD groups, respectively. In a study of 68 patients (44 patients with locoregional disease and 24 patients with distant metastases), Kolb et al reported 4-year EFS and OS rates of 82% and 89%, respectively, for patients with locoregional disease treated with intensive chemotherapy (doxorubicin and vincristine with or without high-dose cyclophosphamide) followed by ifosfamide and etoposide.¹⁰² In

patients with distant metastases, the corresponding survival rates were 12% and 18%, respectively. Miser et al also reported similar findings in patients with Ewing sarcoma with metastases at diagnosis.¹⁰⁹

The EICES-92 study investigated whether cyclophosphamide has efficacy similar to ifosfamide in patients with standard-risk Ewing sarcoma (small localized tumors) and whether the addition of etoposide to a regimen already containing ifosfamide improves survival in patients with high-risk disease (large tumors or metastatic disease at diagnosis).¹¹⁰ Patients with standard-risk disease were randomly assigned to VAID (vincristine, dactinomycin, ifosfamide, and doxorubicin; $n = 76$) followed by either VAID or VACD ($n = 79$).¹¹⁰ The 3-year EFS rates were 73% and 74%, respectively, for VACD and VAID, suggesting that cyclophosphamide has the same efficacy as ifosfamide in this group of patients. Patients with high-risk disease were randomly assigned to VAID or VAID plus etoposide (EVAID). The 3-year EFS rate was not significantly different between the 2 treatment groups (52% and 47%, respectively, for EVAID and VAID).¹¹⁰

As a follow-up to the EICES-92 study, the Euro-EWING99-R1 trial evaluated cyclophosphamide as a replacement for ifosfamide as part of consolidation therapy that also included vincristine and dactinomycin (VAC vs VAI) after VIDE induction chemotherapy in 856 patients with standard-risk Ewing sarcoma. VAC was statistically not inferior to VAI but was associated with a slight increase in events (–2.8% decrease in 3-year EFS). The proportion of patients experiencing severe hematologic toxicity was slightly higher in the VAC arm, but renal tubular function impairment was more significant for patients receiving VAI.¹¹¹

High-Dose Therapy Followed by Hematopoietic Cell Transplant
High-dose therapy followed by hematopoietic cell transplant (HDT/HCT) has been evaluated in patients with localized as well as metastatic disease. HDT/HCT has been associated with potential survival benefit in patients with nonmetastatic disease.^{112,113} However, studies that have evaluated HDT/HCT in patients with primary metastatic disease have shown conflicting results.^{114–120}

The EURO-EWING 99 study was the first large randomized trial designed to evaluate the efficacy and safety of multiagent induction chemotherapy with 6 courses of VIDE, local treatment (surgery and/or RT), and HDT/HCT in 281 patients with Ewing sarcoma with primary disseminated disease.¹¹⁵ After a median follow-up of 3.8 years, the EFS and OS rates at 3 years for the entire study cohort were 27% and 34%, respectively.¹¹⁹ The EFS rates were 57% and 25%, respectively, for patients with complete and partial response after HDT/HCT. Patients' age, tumor volume, and extent of metastatic spread were identified as relevant risk factors. The outcome of patients with and without HDT/HCT was not performed because of the bias introduced early in the nontransplant group (82% of patients without HDT/HCT died after a median time of 1 year).

The EURO-EWING 99 and Ewing-2008 randomized trial asked whether consolidation high-dose chemotherapy improved survival in patients with localized Ewing sarcoma.¹²⁰ Two hundred forty patients at high risk were randomly assigned to receive 7 VAI courses (n=118) or one course of busulfan and melphalan (BuMel) HDT with autologous HCT (n=122), after a VIDE 6-course induction plus one VAI consolidation course. Patients were followed up for 15 years; median follow-up time was 7.8 years. Patients treated with BuMel had greater improvement in 3-year EFS (69.0% vs 56.7%) and 8-year EFS (60.7% vs 47.1%) compared with VAI-treated patients. Three treatment-related deaths occurred: two due to BuMel toxicity and one due to VAI toxicity. More patients experienced severe acute toxicities related to the BuMel versus the VAI course.

Local Control Therapy

Surgery and RT are the local control treatment modalities used for patients with localized disease, but no randomized trials have compared these approaches head-to-head (Figure 2).

In patients with localized Ewing sarcoma treated in cooperative intergroup studies, no significant effect of local control modality (surgery, RT, or surgery plus RT) was seen on OS or EFS rates.^{105,121} In the CESS 86 trial, although radical surgery and resection plus RT resulted in better local control rates (100% and 95%, respectively) than definitive RT (86%), no improvement was seen in RFS or OS because of higher frequency of metastases after surgery.¹²¹ In the INT-0091 study, the incidences of local failure were similar for patients treated with surgery or RT alone (25%), but surgery plus RT resulted in lower incidences of local failure (10.5%).¹⁰⁵ The 5-year EFS rate was also not significantly different between the groups (42%, 52%, and 47% for patients treated with surgery, RT, and surgery plus RT, respectively).

Data from other retrospective analyses suggest that surgery (with or without postoperative RT) affords better local control than RT alone in patients with localized disease.^{122,123} 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 (with or without postoperative RT) than after definitive RT (7.5% vs 26.3%, respectively; $P=.001$), whereas the local control rate with preoperative RT was comparable to that of the surgery group (5.3%).¹²² A retrospective analysis of sequential studies (INT-0091, INT-0154, or AEWS0031) performed by the Children's Oncology Group also demonstrated that definitive RT was associated with a higher risk of local failure than surgery plus RT at 25.0% and 6.3%, respectively, but there was no effect on distant failure.¹²⁴

Definitive RT could be an effective treatment option for patients with tumors in anatomic locations not amenable to achieve surgery with wider resection margins.^{125,126} In a retrospective analysis of patients with Ewing sarcoma of vertebrae treated in the CESS 81/86 and EICESS 92 studies, definitive RT resulted in a local control rate of 22.6%, which was comparable to those of other tumor sites treated with definitive RT; EFS and OS at 5 years were 47% and 58%, respectively.¹²⁵ 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.^{127,128} Local control therapy has also been associated with improved outcomes in patients with primary metastatic disease.^{129–131} In the EURO-EWING 99 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.¹²⁹ Retrospective analysis of 198 patients from EURO-EWING 99 showed no improvement of 5-year EFS associated with adjuvant RT in the setting of completely resected disease of the chest wall.¹³²

NCCN Recommendations

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 9 weeks (category 1) (Figure 1). Longer duration could be considered for patients with metastatic disease based on response. VDC/IE is the preferred regimen for patients with localized disease and is a category 1 recommendation. See "Bone Cancer Systemic Therapy Agents" in the full NCCN Guidelines (available at NCCN.org) for a list of other chemotherapy regimens that are recommended for patients with localized and metastatic disease. Of note, patients with other primary round cell sarcoma of bone can be treated like Ewing sarcoma.

Disease should be restaged with imaging following primary treatment (Figure 1). Chest imaging (specifically noncontrast CT) is recommended for restaging. Additionally, primary site imaging should include contrast-enhanced MRI with or without CT and plain radiography. Head-to-toe FDG-PET/CT or bone scan can be used for restaging depending on the imaging technique that was used in the initial workup.

Patients with stable or improved disease after primary treatment should be treated with local control therapy (Figure 2). Local control options include wide excision, definitive RT with chemotherapy, or amputation in selected cases.^{122,125,127,129} The choice of local control therapy should be individualized and depends on tumor location, size, response to chemotherapy, patient age, anticipated morbidity, and patient preference.¹⁰⁵

Adjuvant chemotherapy following wide excision or amputation is recommended for all patients regardless of surgical margins. (EW-2) The panel strongly recommends that the duration of chemotherapy after wide excision or amputation should be between 28 and 49 weeks depending on the type of regimen and the dosing schedule (category 1).^{95–97} The addition of postoperative RT to chemotherapy is recommended for patients with positive or very close surgical margins.¹²² Denbo et al reported that in patients with smaller tumor size (<8 cm) and negative margins, postoperative RT can be omitted without any decrement in OS.¹³³ 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.

In the setting of widely metastatic disease, palliative therapies may be considered (Figure 3). For metastatic disease that may be amenable to local therapy, local control modalities, in the form of wide excision or definitive RT with adjuvant chemotherapy, are recommended. Regardless of postoperative margin status, chemotherapy for at least 28 to 49 weeks is to be administered (category 1). RT, in addition to chemotherapy, may be considered for positive surgical margins. After adjuvant treatment, metastases may be managed according to the location. In the case of oligometastatic disease, excision or RT is recommended. Stereotactic radiosurgery/stereotactic body RT (SBRT) can be considered, especially for oligometastases.^{134–136} For pulmonary metastases, dependent on the response, resection and/or whole lung irradiation (WLI) may be considered.¹³⁷

Based on the EORTC-SIOP phase III study published in 1988, which concluded there to be no survival benefit of WLI over adjuvant chemotherapy for patients with osteosarcoma, a systematic review of both prophylactic as well as curative WLI in patients with osteosarcoma and Ewing sarcoma was conducted.^{138,139} Only 2 studies compared the results of chemotherapy alone and chemotherapy and curative WLI in patients with metastatic Ewing sarcoma. In both trials, patients experienced some benefit with WLI and chemotherapy when compared with chemotherapy alone. For instance, in the EICESS-92 trial, patients who also received WLI showed a 12% improvement in 5-year OS.^{139,140} Ultimately, it was concluded that the decision to use WLI should be based on the patient's risk of pulmonary metastases and any coexisting respiratory diseases.¹³⁹ Progressive disease after primary treatment is best managed with RT and/or surgery to primary site followed by chemotherapy or best supportive care.

Surveillance

Surveillance of patients with Ewing sarcoma should include a physical examination, CBC and other laboratory studies (as indicated), contrast-enhanced MRI with or without CT, and plain radiographs of the primary site (Figure 2). Chest imaging (x-ray or CT) is recommended every 3 months. Head-to-toe FDG-PET/CT or bone scan can be considered as appropriate. Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years, and as clinically indicated (indefinitely) (category 2B).¹⁴¹

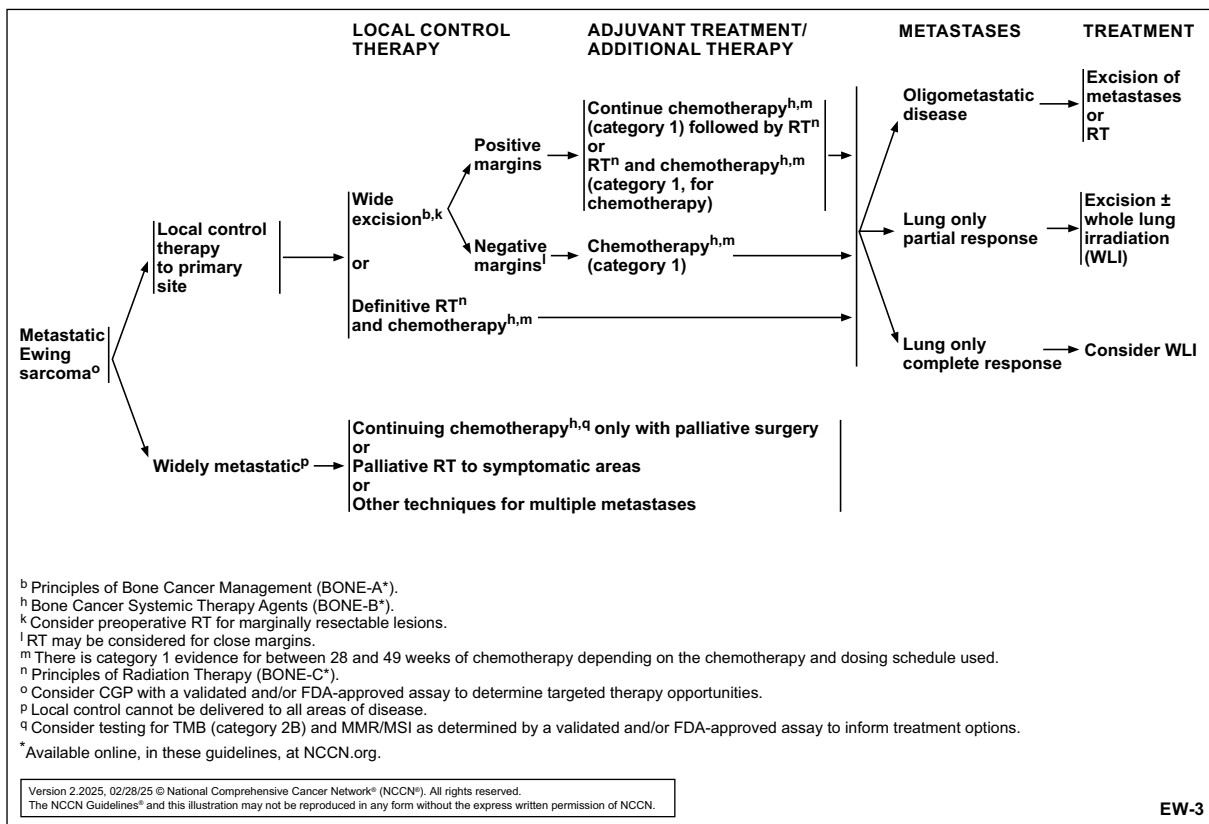


Figure 3. EW-3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

Relapsed or Refractory Disease

Approximately 30%–40% of patients with localized Ewing sarcoma at presentation and 60%–80% with metastatic disease at presentation experience recurrence (local and/or distant) and have a very poor prognosis.¹⁴² 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 at initial diagnosis, and initial recurrence are considered adverse prognostic factors.^{143–146} In a retrospective analysis, site of first relapse and time to first relapse were significant prognostic factors for adult patients with localized Ewing sarcoma.¹⁴⁷ The probability of 5-year postrelapse survival was 55% and 22%, respectively, for patients with local and distant relapse. The probability of 5-year postrelapse survival was also significantly higher for patients with late relapse than for those with early relapse.^{30,142,147} Overall, it is reported that close to 70% of relapses are early relapses, of which two-thirds occur at distant sites (in the lungs and/or bones). Patients who initially presented with widespread disease are more likely to relapse at distant sites, whereas those individuals who presented with localized disease are more likely to develop local relapse.¹⁴⁸

Topoisomerase I inhibitors (topotecan and irinotecan) in combination with cyclophosphamide and temozolomide have been associated with favorable response rates in patients with relapsed or refractory bone sarcomas.^{149–155} In a series of 54 patients with relapsed or refractory Ewing sarcoma, cyclophosphamide and topotecan induced responses in 44% of patients (35% of patients had a complete response and 9% had a partial response).¹⁵⁰ After a median follow-up of 23 months, 26% of patients were in continuous remission. In a retrospective analysis of patients with recurrent or progressive Ewing sarcoma, irinotecan and temozolomide resulted in an overall objective response rate of 63%. The median time to progression (TTP) for all the evaluable patients ($n=20$) was 8.3 months (16.2 months for the subset of patients with recurrent disease).¹⁵³ Patients who were in a 2-year first remission and those with primary localized disease had better median TTP compared with those who relapsed within 2 years from diagnosis and patients with metastatic disease at diagnosis.

Combination therapy with vincristine, irinotecan, and temozolomide also appears to be active and well-tolerated in patients with relapsed or refractory Ewing sarcoma, with an overall response rate (ORR) of 68%.¹⁵⁶ 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 and carboplatin may be warranted.¹⁵⁷ HDT/HCT has been associated with improved long-term survival in patients with relapsed or progressive Ewing sarcoma in small, single-institution studies.^{158–160} The role of this approach is yet to be determined in prospective randomized studies.

The CABONE trial, a multicenter, single-arm phase II trial, evaluated the activity of cabozantinib in patients with advanced Ewing sarcoma and osteosarcoma.¹⁶¹ Currently approved for renal carcinoma, hepatocellular carcinoma, and medullary thyroid

cancer, cabozantinib is a vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase inhibitor with inhibitory activity against the MET receptor. For Ewing sarcoma, the primary endpoint in this study was a 6-month objective response, while the secondary endpoints included safety, 6-month nonprogression, best overall response, 1-year and 2-year PFS and OS, and metabolic response (evaluated by FDG-PET/CT 28 days after the first dose). The primary endpoint was achieved with a 6-month objective response of 26% (95% CI, 13–42) among 39 patients with Ewing sarcoma. Additionally, the median OS was reported to be 10.2 months with a median PFS of 4.4 months. OS was noted to be 84% at 6 months, 48% at 12 months, and finally 14% at 24 months. Forty-two percent (95% CI, 25–61) of patients exhibited a metabolic tumor response. Cabozantinib was well-tolerated among patients with the most common grade 3 or 4 adverse effects being hypophosphatemia, elevated aspartate aminotransferase, palmar-plantar syndrome, pneumothorax, and neutropenia.¹⁶¹

The efficacy of regorafenib has been evaluated in the phase II SARC024 trial in 30 patients with metastatic Ewing sarcoma whose disease progressed following at least 1 line of therapy. The 8-week progression-free rate was 63% and the median OS was 53 weeks.¹⁶²

The phase III rEECur trial compared the efficacy of high-dose ifosfamide (IFOS) ($n=73$) against topotecan and cyclophosphamide (TC) ($n=73$) in patients with relapsed or refractory Ewing sarcoma.¹⁶³ The median EFS was 3.7 months and 5.7 months for TC and IFOS, respectively, and the median OS was 10.4 months and 16.8 months for TC and IFOS, respectively. Greater survival for EFS and OS was also seen in individuals aged < 14 years.

A retrospective study evaluated docetaxel in combination with gemcitabine in 22 children and young adults with refractory bone sarcomas.¹⁶⁴ The median duration of response was 4.8 months and the objective response rate was 29%.

The combination of ifosfamide, carboplatin, and etoposide has also been evaluated in three Children's Cancer Group phase I/II trials in 97 patients with relapsed or refractory bone sarcomas.¹⁶⁵ The ORR was 51%.

A single-arm phase II study evaluated the efficacy and safety of lurbinectedin in a cohort of 28 adult patients with relapsed Ewing sarcoma.¹⁶⁶ Treatment with lurbinectedin resulted in an ORR of 14.3% and a median duration of response of 4.2 months.

In a study evaluating 26 patients treated for local recurrence of Ewing sarcoma, surgical treatment was associated with better survival ($P<.001$).¹⁶⁷ In addition to chemotherapy, surgery may be a treatment option for some patients who experience relapsed disease.

NCCN Recommendations

Treatment options for patients with relapsed or refractory disease include participation in a clinical trial and chemotherapy (with or without RT or with or without surgery) (Figure 2). See “Bone Cancer Systemic Therapy Agents” in these guidelines (available at NCCN.org) for a list of other systemic therapy regimens recommended for patients with relapsed or refractory Ewing sarcoma.

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. With bimodal age distribution, incidences first peak among patients aged 10 to 14 years, and again in patients >65 years.¹⁶⁸ In adults >65 years, osteosarcoma may develop as a secondary malignancy related to Paget disease of the bone.¹⁹ Osteosarcoma is broadly classified into 3 histologic subtypes (intramedullary, surface, and extraskeletal).¹⁶⁹

High-grade intramedullary osteosarcoma is the classic or conventional form, comprising nearly 80% of osteosarcomas.¹⁶⁹ It is a spindle cell or pleomorphic tumor that produces osteoid or immature bone. The most frequent sites include the metaphysis of the distal femur or proximal tibia, which correspond to the physes of maximum growth in normal skeletal development. Low-grade intramedullary osteosarcoma comprise <2% of all osteosarcomas; the most common sites are similar to that of conventional osteosarcoma.¹⁷⁰

Parosteal and periosteal osteosarcomas are juxtacortical or surface variants. Parosteal osteosarcomas are low-grade lesions accounting for up to 5% of all osteosarcomas.¹⁷⁰ The most common site is the posterior distal femur. This variant is associated with very low metastatic potential. Transformation of low-grade parosteal osteosarcoma into high-grade osteosarcoma has been documented in 24%–43% of cases.^{171,172} Periosteal osteosarcomas are intermediate-grade lesions, showing partial cartilaginous differentiation, and most often involve the femur, followed by the tibia.¹⁷⁰ High-grade surface osteosarcomas are very rare, accounting for 10% of all juxtacortical osteosarcomas.^{173,174}

Pain and swelling are the most frequent early symptoms. Pain is often intermittent in the beginning, and a thorough workup sometimes is delayed because symptoms may be confused with growing pains or confounded by musculoskeletal injury. Osteosarcoma spreads hematogenously, with the lung being the most common metastatic site, though “skip lesions” in the same bone can also occur.

For treating extraskeletal osteosarcomas, please see the NCCN Guidelines for Soft Tissue Sarcoma (available at NCCN.org).

Prognostic Factors

Tumor site and size, patient age, presence and location of metastases, histologic response to chemotherapy, and type of surgery and surgical margins are significant prognostic factors for patients with osteosarcoma of the extremities and trunk.^{175–183} A meta-analysis and systematic review of 18,126 participants showed that patient sex, tumor site (extremity versus nonextremity), tumor size, response to chemotherapy, and surgery (amputation versus salvage) were identified as prognostic factors in osteosarcoma.¹⁸⁴ In patients with extremity osteosarcomas, in addition to these variables, size and location within the limb at diagnosis also had significant influence on outcome.¹⁸⁴ All factors except age were significant in multivariate testing, with surgical remission and histologic response to chemotherapy emerging as the key prognostic factors. In a meta-analysis of data from prospective neoadjuvant chemotherapy trials in 4,838 patients with osteosarcoma, female sex was associated with increased chemotherapy-induced tumor necrosis and greater OS, and children had better outcomes than adolescents and adults.¹⁸⁵ In a report of the combined analysis of 3 European Osteosarcoma Intergroup randomized controlled trials, Whelan et al reported that good histologic response to preoperative

chemotherapy, distal location (other than proximal humerus/femur), and female gender were associated with improved survival.¹⁸⁰ However, high body mass index in patients with osteosarcoma was associated with lower OS compared with patients with normal body mass index.¹⁸⁶

In patients with proven primary metastatic osteosarcoma, the number of metastases at diagnosis and the completeness of surgical resection of all clinically detected tumor sites are of independent prognostic value.³¹ Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients without metastatic disease.^{187,188}

Elevated serum ALP and LDH levels have also been identified as prognostic indicators in patients with osteosarcoma.^{176,178,179,189,190} In a cohort of 1,421 patients with osteosarcoma of the extremity, Bacci et al reported significantly higher serum LDH levels in patients with metastatic disease at presentation than in patients with localized disease (36.6% vs 18.8%; $P<.0001$).¹⁷⁸ The 5-year disease-free survival (DFS) correlated with serum LDH levels (39.5% for patients with high LDH levels and 60% for those with normal values). In another retrospective analysis of 789 patients with osteosarcoma of the extremity, it was reported that serum ALP level was a significant prognostic factor of EFS in patients with osteosarcoma of the extremity; the 5-year EFS rate was 24% for patients with a serum ALP value of more than four times higher than the normal value and 46% for patients with high values below this limit ($P<.001$).¹⁷⁹ However, in multivariate analyses, these markers did not retain their prognostic significance when compared with tumor volume, age, and histologic response to chemotherapy.^{176,178}

Workup

Osteosarcomas present both a local control problem and a concern for distant metastasis. Initial workup should include imaging of the primary site (contrast-enhanced MRI with or without CT), chest imaging including chest CT, and head-to-toe FDG-PET/CT and/or bone scan (Figure 4). More detailed imaging (MRI with and without contrast or CT) of skeletal metastatic sites to identify abnormalities identified on primary imaging is required for suspected metastatic disease.

Plain x-rays 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. Serum LDH was significantly higher in patients with metastatic disease at presentation than in patients with localized disease.¹⁷⁸

Given that osteosarcoma is most common among children and AYAs, the effect of cancer and its treatment on fertility must be discussed with patients (Figure 4). Fertility preservation methods and alternatives should be discussed with patients as appropriate. For further details and recommendations, refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at NCCN.org).

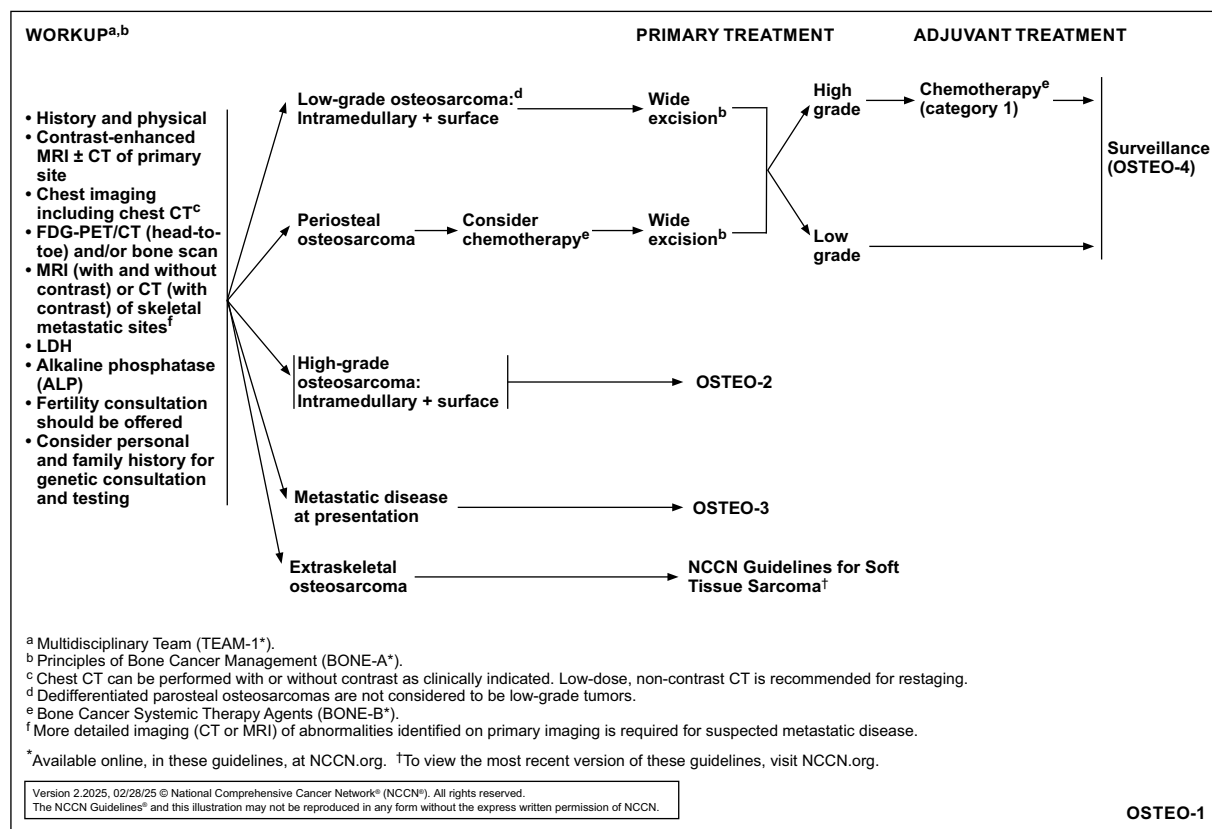


Figure 4. OSTEO-1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

Finally, a number of genetic aberrations may underlie osteosarcoma.¹⁹¹ For instance, it is reported that nearly 70% of patients with osteosarcoma may exhibit mutations in the tumor suppressor retinoblastoma gene, *RBI*.¹⁹¹ Genetic cancer syndromes that exhibit a predisposition for osteosarcoma include Li-Fraumeni syndrome, hereditary retinoblastoma, Rothmund-Thomson syndrome type 2, Bloom syndrome, Werner syndrome, RAPADILINO syndrome, and Diamond-Blackfan anemia. Thus, the panel recommends that genetic consultation and testing be considered for patients diagnosed with chondrosarcoma or osteosarcoma who possess a family or personal history of bone sarcomas (Figure 4).²¹

Treatment

Surgery

Surgery (limb-sparing surgery or amputation) remains an essential part of comprehensive care for patients with osteosarcoma (Figure 4, Figure 5, and Figure 6).¹⁹² Studies that have compared limb-sparing surgery and amputation in patients with high-grade, nonmetastatic osteosarcoma have not shown any significant difference in survival and local recurrence rates between these procedures.^{193–195} However, limb-sparing surgery is associated with better functional outcomes.¹⁹⁶ In patients with high-grade osteosarcomas with good histologic response to neoadjuvant chemotherapy, limb-sparing surgery is considered the preferred surgical modality if wide surgical margins can be achieved (Figure 5).^{193,197} Amputation is generally reserved for patients with tumors in unfavorable anatomic locations not amenable to limb-sparing surgery with adequate

surgical margins and for management of local relapse when limb-sparing procedures are not practical.^{192,197}

Chemotherapy

The addition of adjuvant and neoadjuvant chemotherapy regimens to surgery has revolutionized outcomes in patients with localized osteosarcoma (Figure 4, Figure 5).¹⁹⁸ Early trials used chemotherapy regimens including at least 3 or more of the following drugs: doxorubicin, cisplatin, bleomycin, cyclophosphamide or ifosfamide, dactinomycin, and high-dose methotrexate.^{199–204} Subsequent clinical trials have demonstrated that short, intensive chemotherapy regimens including cisplatin and doxorubicin with or without high-dose methotrexate and ifosfamide produce excellent long-term results, similar to those achieved with standard-dose multiagent chemotherapy.^{205–214} Cisplatin and doxorubicin and high-dose methotrexate, cisplatin, and doxorubicin (MAP) are included as category 1 recommended regimens for first-line therapy. MAP is preferred in patients <40 years with excellent performance status. In the event a patient receiving high-dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended.

In a randomized trial conducted by the European Osteosarcoma Group, the combination of doxorubicin and cisplatin was better tolerated compared with a multidrug regimen with no difference in survival between the groups in patients with operable, nonmetastatic osteosarcoma.²⁰⁶ The 3-year and 5-year OS rates were 65% and 55%, respectively, in both groups. The 5-year PFS rate was 44% in both groups. In the INT-0133 study, which

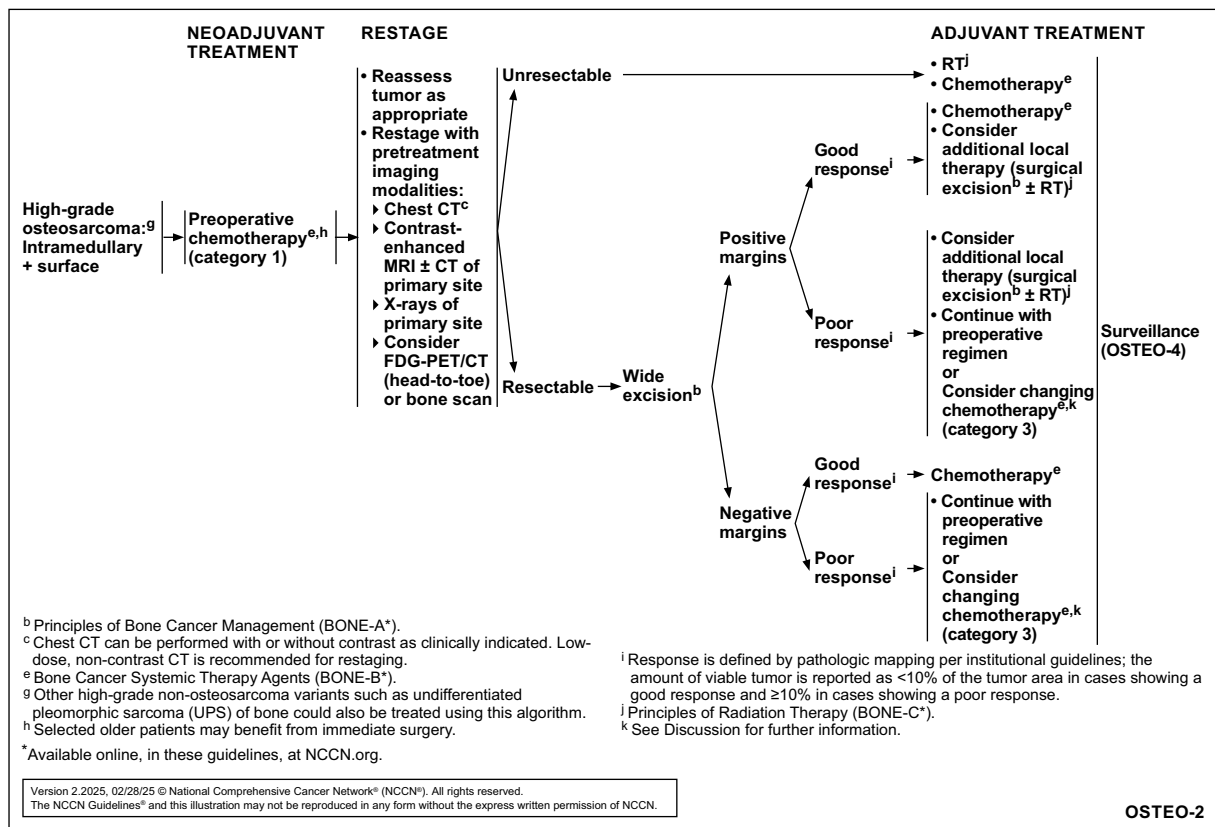


Figure 5. OSTEO-2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

compared the 3-drug regimen (cisplatin, doxorubicin, and methotrexate) with the 4-drug regimen (cisplatin, doxorubicin, methotrexate, and ifosfamide) for the treatment of patients with nonmetastatic resectable osteosarcoma, there was no difference in the 6-year EFS (63% and 64%, respectively) and OS (74% and 70%, respectively) between the two groups.²¹²

Chemotherapy regimens without doxorubicin or cisplatin have also been evaluated in patients with localized osteosarcoma with the aim of minimizing long-term cardiotoxicity and ototoxicity.^{215,216} In a randomized multicenter trial (SFOP-OS94), the combination of ifosfamide and etoposide resulted in a higher histologic response rate than the regimen containing high-dose methotrexate and doxorubicin (56% and 39%, respectively). However, the 5-year OS was similar in both arms and there was no significant difference in 5-year EFS rates.²¹⁶

Good histopathologic response (>90% necrosis) to neoadjuvant chemotherapy is associated with improved survival regardless of the type of chemotherapy administered after surgery.^{141,217,218} In an analysis of 881 patients with nonmetastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and surgery at the Rizzoli Orthopaedic Institute, Bacci et al showed that the 5-year DFS and OS correlated significantly with histologic response to chemotherapy.²¹⁹ The 5-year DFS and OS in patients with good and poor response to chemotherapy were 67.9% versus 51.3% ($P<.0001$) and 78.4% versus 63.7% ($P<.0001$), respectively. A report from the Children's Oncology Group also confirmed these findings; the 8-year postoperative EFS and OS rates were 81% and 87%, respectively, in patients with good response.²¹⁷ The corresponding survival

rates were 46% and 52%, respectively, in patients with poorly responding disease. For individuals with poorly responding disease, completion of chemotherapy is still warranted, as outcomes are still better than those who do not complete chemotherapy.

NCCN Recommendations

Localized Disease

The guidelines recommend wide excision as the primary treatment of patients with low-grade (intramedullary and surface) osteosarcomas and periosteal lesions (Figure 4). If pathologic high-grade disease is discovered after wide excision, adjuvant chemotherapy is a category 1 recommendation (Figure 4). Long-term results (>25 years of follow-up) from patients with high-grade, localized osteosarcoma reveal significant benefits of adjuvant chemotherapy on DFS and OS.²¹⁸ Chemotherapy prior to wide excision could be considered for patients with periosteal lesions (Figure 4). Although chemotherapy (neoadjuvant or adjuvant) has been used in the treatment of patients with periosteal osteosarcoma, there are no data to support that the addition of chemotherapy to wide excision improves outcome in patients with periosteal osteosarcoma.^{220–222} In a review of 119 patients with periosteal sarcoma published by the European Musculo-Skeletal Oncology Society, the use of neoadjuvant chemotherapy was not a prognostic factor, although it was used in the majority of the patients.²²¹ Cesari et al also reported similar findings; the 10-year OS rates were 86% and 83%, respectively, for patients who received adjuvant chemotherapy with surgery and for those who underwent surgery alone ($P=.73$).²²⁰ A systematic review of

13 studies, including 291 patients with periosteal osteosarcoma, found no statistically significant improvement in mortality rates among those who received surgery and (neo-) adjuvant chemotherapy and those who received surgery alone.²²²

Neoadjuvant chemotherapy prior to wide excision is preferred for those with high-grade osteosarcoma (category 1; Figure 5).^{187,205–207,210–212,215,216,223} Repeat imaging using pre-treatment imaging modalities should be used to reassess the tumor for resectability. Selected older patients may benefit from immediate surgery.

After wide excision, patients whose disease has a good histologic response (amount of viable tumor is <10% of the tumor area) should continue to receive several more cycles of the same chemotherapy. Surgical re-excision with or without RT can be considered in cases with positive surgical margins. In a study of 119 patients with osteosarcoma of the head and neck, combined modality treatment with surgery and RT (vs surgery alone) improved local control and OS for patients with positive or uncertain surgical margins.²²⁴ Combined photon/proton or proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.^{225,226}

Patients whose disease has a poor response (viable tumor is ≥10% of the tumor area) can continue with the preoperative regimen or be considered for chemotherapy with a different regimen (category 3; Figure 5). However, attempts to improve the outcome of those with poor response by modifying the adjuvant chemotherapy remain unsuccessful.^{213,227–230}

In individuals whose sarcoma remains unresectable after preoperative chemotherapy, RT or adjuvant chemotherapy is recommended (Figure 5). A randomized phase III trial of the European and American Osteosarcoma Study (EURAMOS) Group evaluated treatment strategies for resectable osteosarcoma based on histologic response to preoperative chemotherapy.^{227,231} The EURAMOS-1 trial included cohorts that received maintenance therapy with MAP; MAP with IFN- α -2b therapy; or MAP with ifosfamide and etoposide (MAPIE). The addition of maintenance IFN- α -2b therapy to MAP in the adjuvant setting did not improve outcomes for individuals whose disease had a good response to preoperative chemotherapy.²³¹ However, the authors note that a significant portion of patients assigned to the IFN arm (n=357) did not receive the intended dose of IFN- α -2b due to patient declination to initiate therapy (n=86; 24%) or premature termination of therapy (n=105; 39%). Additionally, adding ifosfamide and etoposide to MAP (ie, MAPIE) did not improve outcomes for individuals whose disease responded poorly to preoperative chemotherapy.²²⁷ Of the 307 EFS events reported, data showed restricted mean survival time was 43.3 months (95% CI, 40.1–46.4) for individuals who received MAP (n=153) and 44.1 months (41.1–47.1) in individuals assigned to the MAPIE (n=154) cohort. No difference in EFS between cohorts was reported.

Chemotherapy should include appropriate growth factor support. See the NCCN Guidelines for Hematopoietic Growth Factors (available at NCCN.org) for growth factor support. See “Bone Cancer Systemic Therapy Agents” in these guidelines (available at NCCN.org) for a list of specific chemotherapy regimens. Additional treatment options for patients whose disease has positive margins and poor response may include additional local therapy such as re-excision with or without RT (Figure 5).

Metastatic Disease at Presentation

Approximately 10%–20% of patients present with metastatic disease at diagnosis.^{31,232,233} The number of metastases at diagnosis and complete surgical resection of all clinically detected tumor sites are of independent prognostic value in patients with primary metastatic disease at presentation.³¹ Unilateral metastases and lower number of lung nodules were associated with improved outcomes with chemotherapy in patients with synchronous lung metastases.^{187,188} The 2-year DFS rate was significantly higher for patients with only 1 or 2 metastatic lesions than for patients with 3 or more lesions (78% and 28%, respectively).¹⁸⁷

Although chemotherapy is associated with improved outcomes in patients with nonmetastatic, high-grade, localized osteosarcoma, the results were significantly poorer in patients with metastatic disease at presentation.^{232,234–236} In a study of 57 patients with metastatic disease at presentation treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide, the 2-year EFS and OS rates were 21% and 55%, respectively, compared with 75% and 94% in patients with nonmetastatic disease at presentation, treated with the same chemotherapy protocol.²³⁵ High-dose ifosfamide plus etoposide was examined in a phase II/III trial of 43 patients with newly diagnosed metastatic osteosarcoma, revealing an ORR of 59% $\pm$ 8%, but considerable toxicity.²³⁷

Among patients with primary metastases treated in cooperative osteosarcoma trials, long-term survival rates were higher for patients whose metastases were excised following chemotherapy and surgery of the primary tumor compared with those patients whose metastases could not be removed (48% and 5%, respectively).²³⁸ The combination of aggressive chemotherapy with simultaneous resection of primary and metastatic lesions has also resulted in improved outcomes in patients with osteosarcoma of the extremity with lung metastases at presentation.²³⁹

NCCN Recommendations

For patients with resectable metastases (pulmonary, visceral, or skeletal) at presentation, the guidelines recommend preoperative chemotherapy followed by wide excision of the primary tumor (Figure 6). Chemotherapy, metastasectomy, and stereotactic RT are included as options for the management of resectable metastatic disease. In the event that pulmonary metastasectomy is not feasible, ablation procedures may be considered. A retrospective review of 83 patients with high-grade osteosarcoma and widespread metastases who underwent complete resection of the primary tumor and surgical removal of all detectable metastases followed by chemotherapy analyzed tumor characteristics, treatment regimens, and their impact on survival.²⁴⁰ Nine (10.8%) patients had an initial complete remission, of which one patient remained 12.7 years later. Sixty-three of the remaining 74 patients died secondary to their disease, and 2 died of other causes. Actuarial EFS and OS after 5 years was 1.4 $\pm$ 1.4%, and 8.7 $\pm$ 3.3%, respectively. Data showed that complete microscopic resection of the primary tumor and macroscopic complete resection of metastases (and local treatment), in addition to good response to first-line chemotherapy, resulted in better outcomes when compared with individuals whose disease progressed during first-line treatment. Patients who presented with pleural effusion and metastasis at distant bones also had poorer outcomes.

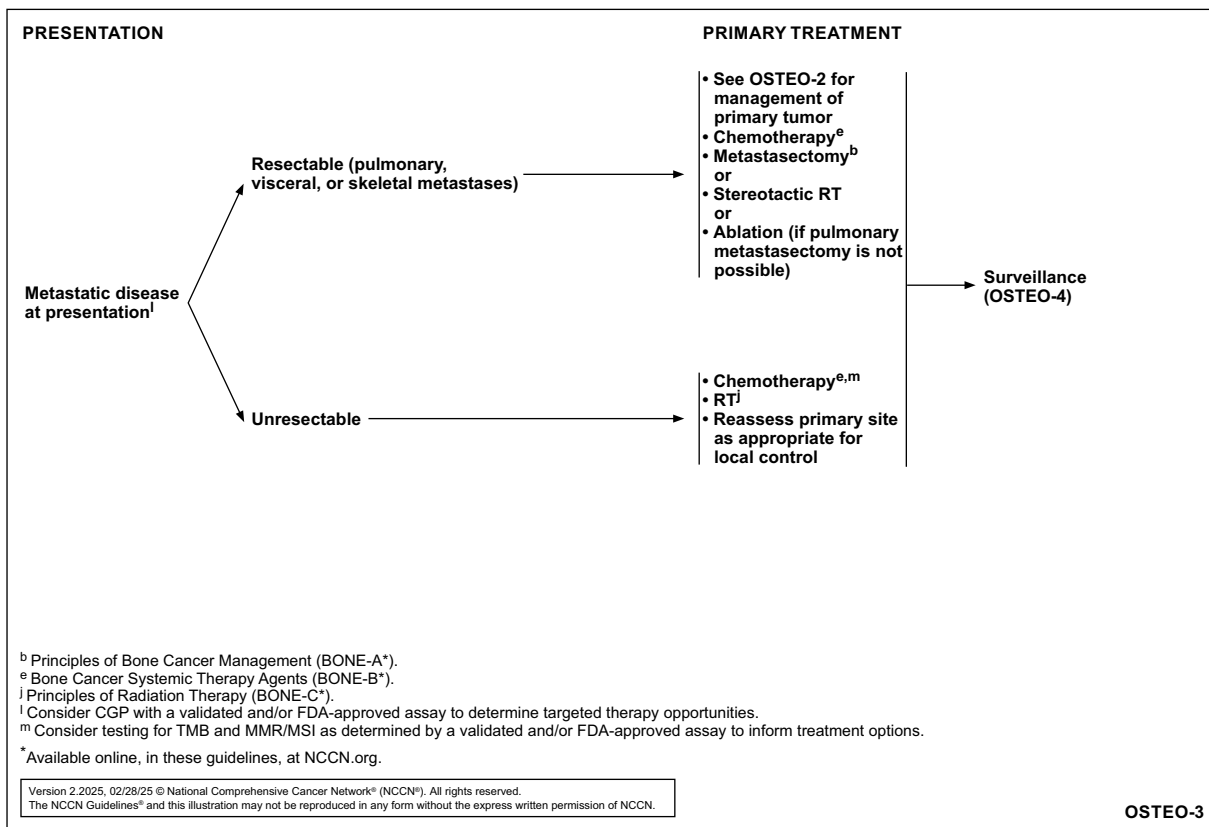


Figure 6. OSTEO-3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

In a study conducted by UCLA, 16 patients (who had received either prior chemotherapy or surgery) with lung metastases from high-grade sarcomas were treated with SBRT.¹³⁵ In total, 25 lesions were identified and treated with a median SBRT dose of 54 Gy (range 36–54 Gy) in 3 to 4 fractions.¹³⁵ Overall survival at 4 years was reported to be 78%.¹³⁵ In another study, 30 patients with sarcoma with pulmonary metastases received SBRT at a median dose of 50 Gy in 4 to 5 fractions.¹³⁴ Patients had received prior chemotherapy, surgery, or thoracic RT. Local control at 12 and 24 months was reported to be 94% and 86%, respectively, while OS was 76% and 43%.¹³⁴ These reports suggest that SBRT may prove to be a promising alternative to surgery for oligometastatic disease. Unresectable metastatic disease should be managed with chemotherapy and/or RT followed by reassessment of the primary site for local control (Figure 6).

Surveillance

Once treatment is completed, surveillance should occur every 3 months for years 1 and 2, then every 4 months for year 3, then every 6 months for years 4 and 5, and annually thereafter, as clinically indicated. (OSTEO-4) Surveillance should include a complete physical exam and imaging of the primary site and chest as performed during initial disease workup. Head-to-toe FDG-PET/CT and/or bone scan (category 2B) may also be considered. Functional reassessment should be performed at every visit. CBC and other laboratory studies can be performed as clinically indicated.

Relapsed or Refractory Disease

Approximately 30%–40% of patients with localized disease and 80% of patients presenting with metastatic disease will relapse.^{241,242} The presence of solitary metastases, time to first relapse, and complete resectability of the disease at first recurrence have been reported to be the most important prognostic indicators for improved survival, whereas patients not amenable to surgery and those with a second or third recurrence have a poor prognosis.^{241–246} In patients with primary nonmetastatic osteosarcoma, a longer relapse-free interval to pulmonary metastases was significantly associated with better survival.²⁴⁵ The prognostic significance of surgical clearance among patients with second and subsequent recurrences was also confirmed in a report of survival estimates derived from large cohorts of unselected patients treated at the COSS group trials.²⁴⁷

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials.^{248–250} In a phase II trial of the French Society of Pediatric Oncology, high-dose ifosfamide and etoposide resulted in a response rate of 48% in patients with relapsed or refractory osteosarcoma.²⁴⁹ In another phase II trial, cyclophosphamide and etoposide resulted in a 19% response rate and 35% rate of stable disease in patients with relapsed high-risk osteosarcoma.²⁴⁸ PFS at 4 months was 42%.

In a noncomparative, double-blind, placebo-controlled, phase II trial (REGOBONE), the efficacy and safety of regorafenib, a multikinase inhibitor, was evaluated among patients with progressive metastatic osteosarcoma (who underwent 1–2 previous

lines of chemotherapy and had a performance status of ECOG 0–1).²⁵¹ It was found that 65% of patients in the regorafenib arm exhibited nonprogressive disease at 8 weeks compared with no patients in the placebo arm. In view of confirmed disease progression, 10 patients in the placebo arm were permitted to cross over to the regorafenib arm to receive treatment. The most commonly noted adverse effects associated with regorafenib included hypertension and hand-foot skin reaction. It was concluded that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. Similarly, in another randomized, double-blind phase II study (SARC024), the activity of regorafenib was again evaluated in patients with progressive metastatic osteosarcoma.²⁵² The study met its primary endpoint with a median PFS of 3.6 months in the regorafenib arm versus 1.7 months in the placebo arm (CI, 0.21–0.85; $P=.017$; HR, 0.42). The NCCN panel has included regorafenib under second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease) with a category 1 recommendation.

Similar to its activity in patients with advanced Ewing sarcoma, cabozantinib, as aforementioned, also exhibited activity in patients with advanced osteosarcoma. In the CABONE trial, the primary endpoint for patients with osteosarcoma included 6-month objective response as well as 6-month nonprogression.¹⁶¹ Secondary endpoints included safety, best overall response, 1-year and 2-year PFS and OS, and metabolic response (evaluated by FDG-PET/CT 28 days after the first dose). Similar to that of Ewing sarcoma, the primary endpoints for patients with osteosarcoma

were reached as 12% of patients showed an objective response and 33% were progression-free at 6 months. Seventeen percent of patients exhibited partial response and 62% of patients showed stable disease as their best overall response. Of those with stable disease, 33% of individuals displayed tumor shrinkage. Cabozantinib has thus been included in the guideline as a second-line treatment option for patients with relapsed, refractory, or metastatic osteosarcoma.

Single-agent gemcitabine and combination regimens such as docetaxel and gemcitabine; cyclophosphamide and topotecan; high-dose methotrexate with or without etoposide and ifosfamide; or ifosfamide, carboplatin, and etoposide have also been effective in the treatment of patients with relapsed or refractory bone sarcomas.^{152,164,165,216,253–257}

Radium 223 dichloride is an alpha-emitting, bone-targeting radiopharmaceutical and was studied in a phase I trial in 18 patients with recurrent or metastatic osteosarcoma.²⁵⁸ A metabolic response was observed in 1 patient, while mixed responses were observed in 4 patients. A response in brain metastases was observed in 1 patient. The median OS time was 25 weeks.

Samarium-153 ethylene diamine tetramethylene phosphonate (Sm-153-EDTMP) is a beta-particle-emitting, bone-seeking radiopharmaceutical that was previously recommended as a second-line treatment option in the guidelines based on data in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases.^{259,260} However, NCCN no longer recommends Sm-153-EDTMP in the guidelines as it is no longer available in the United States.

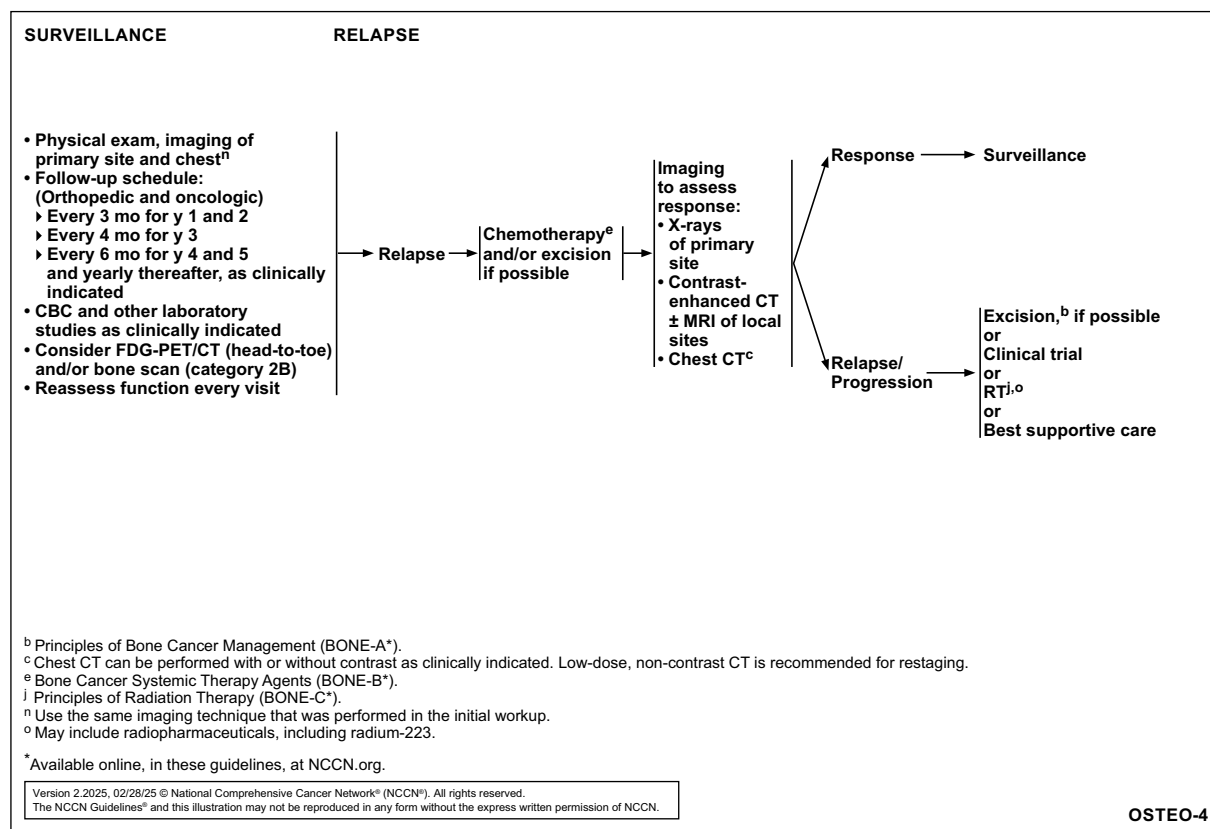


Figure 7. OSTEO-4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, Version 2.2025.

Targeted inhibition of a variety of molecular pathways such as mTOR, SRC family of kinases, and VEGFRs are being evaluated in clinical trials to improve outcomes in patients with relapsed or refractory osteosarcoma. In a phase II trial of the Italian Sarcoma Group (n=30), sorafenib (VEGFR inhibitor) demonstrated activity in patients with relapsed and unresectable high-grade osteosarcoma after progression of disease on standard multimodal therapy.²⁶¹ The PFS at 4 months (primary endpoint) was 46%. Median PFS and OS were 4 months and 7 months, respectively. The CBR (defined as no progression at 6 months) was 29%. Partial response and stable disease were seen in 8% and 34% of patients, respectively, and were durable for ≥6 months in 17% of patients. Sorafenib is a preferred second-line therapy option for osteosarcoma in the guidelines.

To extend the duration of activity, a study examined sorafenib combined with everolimus for patients with unresectable or relapsed high-grade osteosarcoma (n=38).²⁶² Data suggested that this regimen is active in the second-line setting, but toxicity required dose reductions and/or treatment interruptions in 66% of patients. Therefore, under second-line options for patients with osteosarcoma, sorafenib in combination with everolimus is categorized under “Other Recommended Regimens” (category 2B recommendation).

The safety and efficacy of HDT/HCT in patients with locally advanced, metastatic, or relapsed osteosarcoma have also been evaluated.^{263,264} In the Italian Sarcoma Group study, treatment with carboplatin and etoposide was followed by stem cell rescue, combined with surgery-induced complete response in chemosensitive disease.²⁶⁴ Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12%, respectively. The efficacy of this approach in patients with high-risk disease is yet to be determined in prospective randomized studies.

The optimal treatment strategy for patients with relapsed or refractory disease has yet to be defined. If relapse occurs, the patient should receive second-line chemotherapy and/or surgical resection when feasible, followed by imaging to assess treatment response (Figure 7). See “Bone Cancer Systemic Therapy Agents” in the complete guidelines (available at NCCN.org) for a complete list of second-line chemotherapy regimens. Surveillance is recommended for patients with disease that responds to second-line therapy.

Patients with disease progression or relapse after second-line therapy could be treated with resection, RT²⁶⁵ (that may include radiopharmaceuticals, including radium-223), or best supportive care (Figure 7). Participation in a clinical trial is strongly encouraged.

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