

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.