Imaging Recommendations for Diagnosis, Staging, and Management of Bone Tumors

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Ind J Med Paediatr Oncol 2023;44:257–260.

Abstract

Primary bone sarcomas account for less than 1% of diagnosed cancers each year. In this era of multiplanar and functional imaging, the approach to the radiographic diagnosis of bone cancers goes much beyond traditional radiography. Radiographs are still the most pertinent part of the initial diagnosis of bone tumors. Multimodal imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), can help with issues such as complex anatomy, marrow assessment, soft assessment, and better local staging. The emerging imaging modality such as positron emission tomography (PET)-CT/PET-MRI has further transformed the imaging of bone malignancies. Radiologist plays an important role in the workup, staging, and management of bone tumors. The purpose of this article is to review imaging recommendations for better diagnosis, staging, and management of bone tumors.

Keywords
- bone tumor
- imaging
- management
- MRI
- radiograph
- radiology
- staging

Introduction

The diagnosis, staging, and management of bone tumors involve a holistic approach including meticulous history taking and clinical examination by experienced orthopaedic onco-surgeon and imaging interpretation. Teamwork in multidisciplinary meetings between expert radiologists, orthopaedic onco-surgeon, and pathologists help in deciding a road map for diagnosing and treatment of bone tumors. Radiographs remain the most pertinent part of initial evaluation of bone tumors. Next best modality is magnetic resonance imaging (MRI) which is usually indicated for confirmation, better characterization of the lesion, and local staging. Computed tomography (CT) scan is usually advised to asses bone erosion, to see nidus in osteoid osteoma and matrix evaluation. Positron emission tomography (PET)-CT provides critical information regarding occult metastasis to lung and distant bone. PET-CT and MRI have additional use in assessment of response to therapy. We provide an overview of the multidisciplinary approach to the imaging, diagnosis, treatment, and surveillance of bone tumors from the perspective of an onco-radiologist.

The article is not under consideration for publication elsewhere. Each author participated sufficiently for the work to be submitted. The publication is approved by all authors.

Risk Factors and Etiopathogenesis

Bone cancers are not linked with known risk factors. But there are few factors that can raise the risk of bone cancers.[1]

DOI https://doi.org/10.1055/s-0042-1760313.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Risk of osteosarcoma and Ewing sarcoma is highest for those between the ages of 10 and 30 years, whereas risk for chondrosarcoma increases in older age group above 40 years. Osteosarcoma, Ewing sarcoma, and chondrosarcoma show slightly male predominance over females.[2] Prior radiotherapy and Paget's disease are known risk factors for secondary osteosarcoma.[3] Multiple enchondromatosis can show degeneration into chondrosarcoma. Hereditary retinoblastoma and Li–Fraumeni syndrome have increased risk of osteosarcoma. EWS and ETS family of genes rearrangements have been implicated in the pathogenesis of Ewing sarcoma.[4]

Epidemiology, Clinical Presentation in India and Global

Primary bone sarcomas account for less than 1% of diagnosed cancers each year. Global incidence ranges from 3 to 7 per 100,000 individuals affected yearly. Osteosarcoma (35%) and Ewing sarcoma (16%) have high incidence in children and young adults in the second decade of life, while chondrosarcoma (30%) is most common in older age groups.[5] In Indian data, bone tumors from approximating 0.2% of all cancers, with osteosarcoma, chondrosarcoma, and Ewing sarcoma being the most common cancers in this subset.[6] Pain is the most common presenting symptom of primary bone cancers and is usually associated with local swelling.[7] These symptoms may mimic common musculoskeletal injuries, and pain often begins after minor physical trauma. Pathologic fracture may be the first presentation of a primary bone tumor. Systemic symptoms are rare but are more common in Ewing sarcoma and include unexplained relapsing fever.

Imaging Referral Guidelines

The National Comprehensive Cancer Network (NCCN) provides interdisciplinary evidence-based recommendations for the assessment and management of primary bone cancers. They focus on chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma. The guidelines also provide recommendations for treating giant cell tumors of bone which is benign, but locally aggressive and can lead to significant bone destruction. NCCN suggests that workup of an abnormal radiograph is decided by the age of the patient. If the patient is more than 40 years of age, metastatic workup should be performed with chest/abdomen/pelvis CT, chest radiograph, bone scan, mammogram, and prostate-specific antigen. If no other lesions are detected elsewhere, the patient should be referred to orthopaedic oncologists for evaluation of possible bone primary. If the patient's age is less than 40 years, the patient should be directly referred to an orthopaedic oncologist for biopsy.

Clinical/Diagnostic Workup

Persistent bone pain lasting more than a few weeks should raise concern and lead to further immediate evaluation. Swelling will be present only when the tumor has breached the cortex and periosteum.[7] Before 5 years of age, a destructive bone lesion is most commonly metastatic neuroblastoma or eosinophilic granuloma; above 5 years, it is often a primary bone sarcoma; after 40 years of age, it tends to be metastasis, myeloma or lymphoma.[8]

Patients with suspected bone tumors should be referred immediately to a cancer center with an experienced orthopaedic oncologist for further workup. The clinical history should focus on symptoms such as duration, intensity, and timing of complaints, family history, and previous radiotherapy. A recent injury must not prevent appropriate diagnostic procedures. Physical examination should focus on the size, consistency of the swelling, tenderness, location and mobility, relation of swelling to the underlying bone, and the presence of local lymph nodes.

There is not much role of laboratory investigations in the workup of bone tumors. However, some tests are of prognostic value in the follow-up in Ewing sarcoma and osteosarcoma, such as alkaline phosphatase and lactate dehydrogenase.[9] Blood workup such has serum electrophoresis with immunofixation helps in diagnosing multiple myeloma.[10] For suspected Ewing sarcoma, cytogenetic and/or molecular studies of the biopsy specimen can be performed to evaluate the t (11;22) translocation, and a bone marrow biopsy should be considered to complete the workup.[11] Histopathology is the gold standard for diagnosis of bone tumors but should be ordered after imaging is performed.

Imaging Guidelines—Diagnosis

Radiography remains the mainstay for initial diagnosis. CT, MRI, an PET CT are useful in evaluating the extent of lesion and its local and distant staging for the appropriate treatment and in assessing therapeutic response.[12] Biopsy should be performed after imaging to confirm the diagnosis and decide further management. Imaging is also crucial to decide the need and target site for biopsy. All cases of suspected bone tumors should be discussed by orthopaedic oncologist at a multidisciplinary meeting that includes the expert radiologist who has interpreted the imaging and the pathologist who has reviewed the biopsy material and the surgeon and oncologist undertaking treatment. This will minimize the risk of errors in diagnosis, avoid unnecessary biopsies, staging, risk assessment, and treatment.

As per the European Society for Medical Oncology (ESMO) guidelines, whenever a bone tumor is suspected, a conventional radiograph is ordered first to confirm the bone origin of the pathology. It is the most indispensable, inexpensive, and readily available investigation. It should be ordered in two orthogonal planes and should include the proximal and distal joints as well. Not only it helps in primary assessment of benign or aggressive nature of the tumor, it provides important diagnostic information that can be correlated with MRI later. The most important determinators in the analysis of a potential bone tumor are morphology and location of the lesion and age of the patient. The morphology

indicators are lytic/sclerotic, matrix mineralization (osseus, calcified, fibrous), zone of transition, cortical erosion, periosteal reaction, soft tissue component, location (epi/meta/diaphysis or eccentric/central/ juxtacortical), and multiplicity.[13] The age of the patient is crucial to note before deciding the possible differentials. For example, benign tumors and primary bone sarcomas are more common in early decades of life, while the top differentials for a bone lesion in patients older than 50 years are lymphoma, myeloma, and metastasis.

Following radiographs, further evaluation requires MRI of the entire compartment with adjacent joints. MRI is the best modality for local staging and surgical planning, that is, assessment of proximity of mass to neurovascular structures, intertumoral extension, and skip lesions, which are important for planning the length of surgical resection and deciding limb salvage surgery.[14]

CT should be performed only in case of diagnostic problems or doubt or to provide additional information, such as better visualization of calcifications, periosteal bone formation, and cortical breach. All imaging should be completed before biopsy to avoid confounding of intrinsic tumor characteristics by post-biopsy inflammation or altered tissue planes.

Biopsy is required for diagnosis confirmation and establishing tumor grade. It should be performed by a trained intervention radiologist or orthopaedic oncologist. The aim is to carefully plan the biopsy in the expected plane of surgery and avoid injury to neurovascular structures and development of hematoma. Image-guided needle biopsy should be preferred over open true cut biopsy because of lower complications and decreased risk of development of post-biopsy hematoma which has increased risk for local recurrence.[15] Image guidance can also help avoid targeting the necrotic/cystic/nonenhancing areas that may be nonavid on PET CT that can otherwise lead to a nondiagnostic yield. Improperly performed biopsies can also lead to misdiagnosis, local recurrence, amputation, and decreased survival. If there is a definite soft tissue component, ultrasound-guided biopsy is preferred while CT guidance is preferred in case of purely intraosseous lesions. While ordering biopsy, the referring orthopaedic oncologist should mention the potential site of surgical incision for limb salvage surgery so that the radiologist can insert the biopsy needle through the same site and avoid contaminating the surgical compartments requiring unnecessary amputation or additional soft tissue reconstructions. The pathologist reading the sample should receive information regarding the clinical/radiological context in which the tumor has arisen, relevant observations made at the time of biopsy, and whether the patient has received preoperative chemotherapy.

There are multiple staging systems for bone tumors in the literature. However, none of them are universally accepted. Malignant bone neoplasms are staged based on the size, regional lymph node involvement, and distant organ metastasis.[16] CT, bone scintigraphy, and fluorodeoxyglucose (FDG) PET-CT play a key role in staging. PET-CT is commonly performed to evaluate the distant metastatic disease spread and also treatment response. Noncontrast CT thorax is preferred over PET-CT to detect lung nodules that can deem a patient as metastatic.[17] Certain bone tumors have typical morphological features on CT such as calcified lung nodules in osteosarcoma metastasis. Counting the number of nodules and their location on CT also helps in metastasectomy planning.

Post chemotherapy treatment response is monitored primarily by MRI. Decrease in size of soft tissue component, decrease in marrow edema, decreased enhancement, and facilitated diffusion on diffusion-weighted imaging are indicators for positive response on MRI.[18] Increased sclerosis in bone metastasis following chemotherapy seen on CT also suggests response. PET-CT can also be used in tumor surveillance to assess tumor response to chemotherapy and radiation treatment, and for detection of recurrent tumors in follow up cases.

Principles of Management

Bone tumors are managed by a specialist group with experience in treating bone cancer, usually done through multidisciplinary team (MDT). MDT includes an orthopaedic onco-surgeon, a medical oncologist, and radiation oncologist.[19] Recommended treatment plan is usually a combination of surgery which includes wide local excision, limb-sparing surgery, amputation, and rehabilitation. Chemotherapy is usually provided in four ways, neoadjuvant chemotherapy prior to surgery, concurrent chemoradiotherapy, adjuvant chemotherapy, and palliative chemotherapy.[20] Radiotherapy is usually provided in radiosensitive tumors.

Follow-Up Imaging and Management of Recurrent Disease

Limited published evidence is available to support specific policies for surgically treated patient's follow-up. Lung relapses are the most common type of relapse. The ESMO guidelines (2021) for follow-up of high-grade bone sarcoma include physical examination, cross-sectional imaging, and plain radiograph of the primary site together with chest X-ray (CXR)/CT scan, at intervals of approximately every 3 months for the first 2 years; every 6 months for years 3 to 5; every 6 to 12 months for years 5 to 10; and thereafter every 6 months to 1 to 2 years. For low-grade bone sarcoma, the frequency of follow- up visits may be lower (e.g., 6 months for 2 years and then annually).[21] NCCN recommends separate regimes for the most common tumors. For osteosarcoma, MRI, contrast CT, local radiograph for local recurrence, and chest imaging (CT preferred over chest CXR) at following intervals—3 monthly $\times$ 2 years, 4 monthly $\times$ 3 years, 6 monthly $\times$ 4 to 5 years, and annually thereafter. PET-CT/bone scan can also be considered. For Ewing's sarcoma imaging recommendation is same as osteosarcoma at intervals 2 to 3 monthly for 2 years, followed by increasing intervals up to 5 years. In high-grade chondrosarcoma, MRI, local radiograph, and chest imaging (CT is preferred over CXR) at the following intervals: 3 to 6 monthly $\times$ 5 years and yearly after that till a minimum of 10 years.[22] Indian

randomized trial TOSS study showed an overall survival of patients who are treated for sarcoma of the limb is not inferior when followed up with a less intensive regimen than a more intensive protocol, in terms of frequency of visits and mode of imaging. CXR at 6-monthly intervals and patient education about the examination of the local site of the surgery will detect most recurrences without affecting the eventual outcome.[23]

Conflict of Interest
None declared.

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