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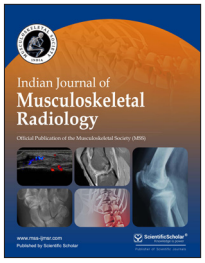

Review Article

World health organization classification of bone tumors (fifth edition): What a radiologist needs to know?

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ABSTRACT

Since 1967, the World Health Organization (WHO) classification of tumors is regarded as a reference standard and practical guide and provides a precious resource not only for the histopathologists and oncosurgeons but also for the radiologists involved in cancer care. Primary bone tumors are a rare and heterogeneous group of neoplasms that have a broad spectrum of morphological, biological, genetic, and radiological features. Appropriate imaging workup and accurate histopathological diagnosis are crucial for appropriate management and prognostication. The fourth edition of the WHO classification of tumors of soft tissue and bone was introduced in 2013. In the past 7 years, there have been considerable advances in the understanding of this large and diverse group of tumors. With technological advances and the introduction of new molecular and genetic data about some bone tumors, there has been reorganization in the classification and introduction of a few new entities. The new WHO classification of soft tissue and bone tumors introduced in 2020 (fifth edition) has made essential refinements in the classification and has also introduced many new entities. Newly identified genetic alterations and corresponding immunohistochemical markers are included in the new classification, and this has helped in the reclassification of the existing tumor entities. These novel genetic alterations not only help in prognostication but are a target for potential therapeutic options which can bring a paradigm shift in the chemotherapeutic regimen for these entities in the future. The sole basis for the classification of bone tumors is histopathological. Although radiologists are not expected to know about the exquisite pathological details of bone tumors, a broad knowledge of the recent updates, including the reclassification of a few entities or the introduction of some, is vital for narrowing the differentials in imaging. A multidisciplinary approach including an orthopedic oncologist, radiologist, pathologist, surgical, and medical oncologist is required for accurate diagnosis and management of primary bone tumors. We hereby present a simplified review for the radiologists comprising the relevant details of the updates in bone tumors along with a simplified diagnostic algorithm to characterize these lesions.

Keywords: World Health Organization classification of bone tumors, radiology, imaging

INTRODUCTION

Primary bone tumors are a rare and heterogeneous group of neoplasms that account for 0.2% of all human neoplasms, and these neoplasms have a broad spectrum of morphological, biological, genetic, and radiological features.[1] Primary bone tumors frequently affect younger age groups, and often the etiology is unknown. Benign tumors often present as incidental findings, whereas malignant tumors are often diagnosed at a late stage.[2] Appropriate imaging workup and accurate histopathological diagnosis are crucial for appropriate management and prognostication. The fourth edition of the World Health Organization (WHO) classification of tumors of soft tissue and bone was introduced in 2013.[3] In the past 7 years, there have been considerable advances in the understanding of this large and diverse group of tumors. The new WHO classification of soft

tissue and bone tumors introduced in 2020 (fifth edition) has made essential refinements in the classification and has also introduced many new entities [Table 1].[4]

Since 1967, the WHO classification of tumors is regarded as a reference standard and practical guide and provides a precious resource not only for histopathologists and

Table 1: 2020 WHO classification of bone tumors.

S. No.	Category	Sub-category	Nature
1.	Chondrogenic tumors	Subungual exostosis	Benign
		Bizarre parosteal osteochondromatous proliferation.	
		Periosteal chondroma	
		Enchondroma	
		Osteochondroma	
		Chondroblastoma NOS	
		Chondromyxoid fibroma	
		Osteochondromyxoma	
		Chondromatosis NOS	Intermediate
		Atypical cartilaginous tumor	
		Chondrosarcoma, grades 1	Malignant
		Chondrosarcoma, grades 2	
		Chondrosarcoma, grades 3	
		Periosteal chondrosarcoma	
		Clear cell chondrosarcoma	
		Mesenchymal chondrosarcoma	
		Dedifferentiated chondrosarcoma	
2.	Osteogenic tumors	Osteoma NOS	Benign
		Osteoid osteoma NOS	
		Osteoblastoma NOS	Intermediate
		Low-grade central osteosarcoma	Malignant
		Osteosarcoma NOS	
		Parosteal osteosarcoma	
		Periosteal osteosarcoma	
		High-grade surface osteosarcoma	
		Secondary osteosarcoma	
3.	Fibrogenic tumors	Desmoplastic fibroma	Intermediate
		Fibrosarcoma NOS	Malignant
4.	Vascular tumors of bone	Hemangioma NOS	Benign
		Epithelioid hemangioma	Intermediate
		Epithelioid hemangioendothelioma NOS	Malignant
		Angiosarcoma	
5.	Osteoclastic giant cell-rich tumors	Aneurysmal bone cyst	Benign
		Non-ossifying fibroma	
		Giant cell tumor of bone NOS	Intermediate
		Giant cell tumor of bone, malignant	Malignant
6.	Notochordal	Benign notochordal cell tumor	Benign
		Chordoma NOS (Chondroid chordoma)	Malignant
		Dedifferentiated chordoma	
		Poorly differentiated chordoma	
7.	Other mesenchymal tumors of bone	Chondromesenchymal hamartoma of the chest wall	Benign
		Simple bone cyst	
		Fibrous dysplasia	
		Osteofibrous dysplasia	
		Lipoma NOS	
		Hibernoma	
		Osteofibrous dysplasia-like adamantinoma	Intermediate
		Mesenchymoma NOS	

(Contd...)

Table 1: *(Continued)*

S. No.	Category	Sub-category	Nature
		Adamantinoma of long bones (Dedifferentiated adamantinoma)	Malignant
		Leiomyosarcoma NOS	
		Pleomorphic sarcoma, undifferentiated	
		Bone metastases	
8.	Hematopoietic neoplasms of bone	Plasmacytoma of bone	
		Hodgkin disease NOS	
		Malignant lymphoma, non-Hodgkin, NOS; Diffuse large B-cell lymphoma NOS; Follicular lymphoma NOS; Marginal zone B-cell lymphoma NOS; T-cell lymphoma NOS; Anaplastic large cell lymphoma NOS; Malignant lymphoma, lymphoblastic, NOS: Burkitt lymphoma NOS	
		Langerhans cell histiocytosis NOS	
		Langerhans cell histiocytosis, disseminated	
		Erdheim-Chester disease	
		Rosai-Dorfman disease	
9.	Undifferentiated small round cell sarcomas of bone and soft tissue	Ewing sarcoma	
		Round cell sarcoma with EWSR1–nonETS fusions	
		CIC-rearranged sarcoma	
		Sarcoma with BCOR genetic alterations	

Newly added entities are highlighted in bold and italics. NOS: Not otherwise specified

oncosurgeons but also for the radiologists involved in cancer care. The sole basis for the classification of bone tumors is histopathological. Although radiologists are not expected to know about the exquisite pathological details of bone tumors, a broad knowledge of the recent updates, including the reclassification of a few entities or the introduction of some, is vital for narrowing the differentials in imaging. A multidisciplinary approach including an orthopedic oncologist, radiologist, pathologist, surgical, and medical oncologist is required for accurate diagnosis and management of primary bone tumors.

After the introduction of the fifth edition of the WHO classification of tumors of soft tissue and bone, a few articles are published outlining the recent updates and comparison with the previous edition, but these articles are difficult to understand by the radiologists as these articles mainly focus on the histopathological details, genetic alteration, and new markers.[5] We hereby present a simplified review for the radiologists comprising the relevant details of the updates in bone tumors along with a simplified diagnostic algorithm to characterize these lesions.

HOW TO APPROACH A BONE TUMOR?

Many factors come into play when we encounter and try to diagnose a case of bone tumor. These factors include the age of the patient, location in the skeleton system (axial or appendicular) and multiplicity. Whenever a patient complains of bone pain and swelling pointing toward a neoplastic pathology affecting bone, conventional radiography (CR) is the first imaging modality used to evaluate the lesion because it is widely available and affordable. Despite the advances in the imaging field in the form of multiplanar and functional imaging, the role of CR cannot be neglected, and it is still the most relevant first investigation. A radiograph gives us much information about the bone tumor, including location within the long bone (epiphyseal, diaphyseal, or metaphyseal), the pattern of bone destruction (geographic, moth-eaten, or permeative), zone of transition, type of periosteal reaction, matrix mineralization, and adjacent soft-tissue involvement. Most bone tumors can be diagnosed, or at least we can narrow down our differentials on plain radiographs. By seeing above mentioned criteria, bone tumors can be classified into benign, intermediate, and malignant entities on radiography.[6,7] However, there are some limitations of CR. Lesions located in the region of complex anatomies such as the pelvis, scapula, and spine are challenging to evaluate on CR. The extent of marrow and soft-tissue involvement, including neurovascular bundles, joint involvement, presence of skip lesions, and distant metastasis, is challenging to assess on CR. These factors are essential for staging the disease, and ultimately deciding the treatment and outcome. Computed tomography (CT) and magnetic resonance imaging (MRI) help to cover all these aspects.[8] An algorithm for the radiological diagnosis of bone tumors is presented in [Figure 1].

The role of radiologists does not end with the imaging diagnosis and staging of the bone tumor, but he has a significant role to play in planning and performing image-guided biopsies (ultrasound or CT guided), which helps to

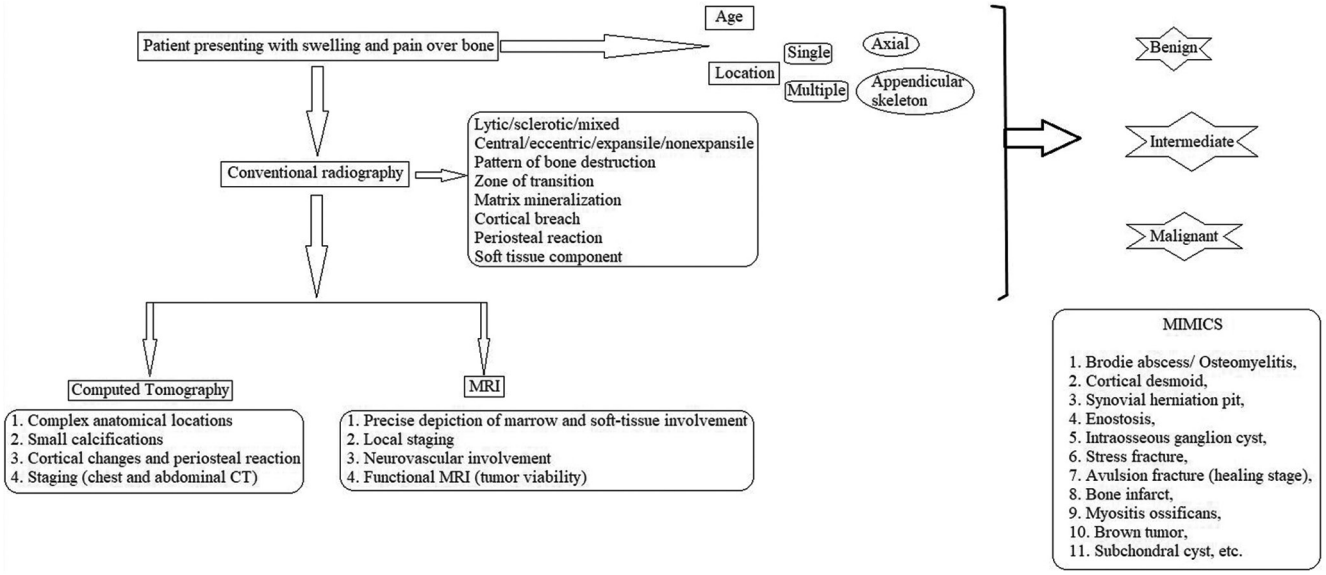

Figure 1: An algorithm for the radiological diagnosis of bone tumors.

draw the specimen from the most viable part of the tumor. Histopathological evaluation of samples obtained under image guidance is the final step in diagnosing and grading bone tumors. The biopsy track should always be planned after discussing with the surgeon so that the biopsy track is excised with the tumor to avoid recurrence.[9]

WHAT'S NEW IN 2020 WHO CLASSIFICATION OF BONE TUMORS?

With technological advances and the introduction of new molecular and genetic data about some bone tumors, there has been reorganization in the classification and introduction of a few new entities. Newly identified genetic alterations and corresponding immunohistochemical markers are included in the new classification, and this has helped in the reclassification of the existing tumor entities.[4] These novel genetic alterations not only help in prognostication but are a target for potential therapeutic options which can bring a paradigm shift in the chemotherapeutic regimen for these entities in the future. Radiologists play an essential role in the multidisciplinary team involved in the care of bone tumor patients, and therefore they need to be aware of important new development in the latest WHO classification. Major changes in the categories of the tumor, their biological potential and summary of newly added and recategorized entities in the 2020 WHO Classification of Bone Tumors with their Clinical and Imaging characteristics are summarized in [Tables 2 and 3]. In the upcoming sections, we will be discussing various categories of bone tumors and the updates in the new classification with an emphasis on their imaging appearance.

Chondrogenic tumors

The latest classification has recategorized chondroblastoma and chondromyxoid fibroma from the intermediate to benign category. Previously, enchondroma and periosteal chondroma [Figure 2] were listed together under the term chondroma, but now they are reclassified as separate benign entities. Synovial chondromatosis (SC), which has a high recurrence after excision, is recategorized from benign to intermediate category. The SC has recurrence rates varying from 10% to 15%. It can undergo malignant transformation into synovial chondrosarcoma in 1–5% of cases in the long run. There is a significant overlap between SC and synovial chondrosarcoma in terms of clinical behavior and radiological appearance, however cortical destruction and marrow invasion in the setting of multiple recurrences raise the suspicion of malignant transformation.[4]

The previous classification used the terms "atypical cartilaginous tumor (ACT)" and "Chondrosarcoma Grade 1 (CS1)" interchangeably and classified them in the intermediate category.[3] In the appendicular skeleton, these lesions behave in a locally aggressive fashion and do not metastasize. Therefore, in the current classification, the term ACT is used when the lesion is located in the appendicular skeleton, whereas CS1 is used when the lesion is located in the axial skeleton even though both lesions are identical in histomorphology. Reclassifying CS1 in the malignant category benefits understanding that these lesions need more extensive surgery than the benign lesion. The radiologist needs to understand another critical difference in the terminology, that is, between

Table 2: Major changes in the categories of tumor and their biological potential in the latest classification of bone tumors.

Tumor entities	2013 WHO Classification	2020 WHO Classification
Chondroblastoma	Intermediate (rarely metastasizing)	Benign
Chondromyxoid fibroma	Intermediate (locally aggressive)	Benign
Synovial chondromatosis	Benign	Intermediate (locally aggressive)
Chondrosarcoma grade 1	Intermediate (locally aggressive)	Malignant
Epithelioid hemangioma	Intermediate (locally aggressive and rarely metastasizing) tumor	Intermediate (locally aggressive) tumor
Aneurysmal bone cyst	Tumor of undefined neoplastic nature; Intermediate (locally aggressive)	Osteoclastic giant cell-rich tumor; Benign
Non-ossifying fibroma	Fibrohistiocytic tumor	Osteoclastic giant cell-rich tumor
Chondromesenchymal hamartoma of the chest wall	Tumor of undefined neoplastic nature	Other mesenchymal tumor of bone
Simple bone cyst	Tumor of undefined neoplastic nature	Other mesenchymal tumor of bone
Fibrous dysplasia	Tumor of undefined neoplastic nature	Other mesenchymal tumor of bone
Osteofibrous dysplasia	Tumor of undefined neoplastic nature	Other mesenchymal tumor of bone
Osteofibrous dysplasia like	Tumor of undefined neoplastic nature;	Other mesenchymal tumor of bone;
Adamantinoma	Malignant tumor	Intermediate (locally aggressive)
Adamantinoma	Miscellaneous tumor	Other mesenchymal tumor of bone
Pleomorphic undifferentiated sarcoma	Miscellaneous tumor	Other mesenchymal tumor of bone
Langerhans cell histiocytosis	Tumor of undefined neoplastic nature	Hematopoietic neoplasm of bone
Erdheim-Chester disease	Tumor of undefined neoplastic nature; Intermediate (locally aggressive)	Hematopoietic neoplasm of bone; Malignant
Rosai-Dorfman disease	Tumor of undefined neoplastic nature	Hematopoietic neoplasm of bone
Ewing sarcoma	Miscellaneous tumor	Undifferentiated small round cell sarcoma
Leiomyosarcoma	Myogenic tumor	Other mesenchymal tumor of bone
Leiomyoma	Myogenic tumor	Removed
Lipoma	Lipogenic tumor	Other mesenchymal tumor of bone
Liposarcoma	Lipogenic tumor	Removed
Benign fibrous histiocytoma	Fibrohistiocytic tumor	Removed
Giant cell lesions of the small bones	Osteoclastic giant cell rich tumor	Removed

WHO: World Health Organization

central and peripheral ACT/CS1. The term "central ACT/CS1" is used when the tumor is located in the medulla of the bone, whereas the term "peripheral ACT/CS1" is used when the tumor arises from the cartilaginous cap of a pre-existing osteochondroma. Central ACT/CS1 can further be classified into primary (*de novo*) and secondary (arising from preexisting enchondroma) categories. About 50% of high-grade chondrosarcoma share IHD1 or IHD2 mutations with enchondroma/ACT/CS1 suggesting the genetic connection between these entities. The location of high-grade chondrosarcoma is similar to that of ACT/CS1.[4] It is challenging to differentiate between enchondroma and ACT/CS1 radiologically. Some imaging features which can help to differentiate enchondroma from ACT/CS1 are listed in [Table 4].

Osteochondromas are benign bony outgrowths covered by a cartilaginous cap with clear continuity of cortex and medulla. The lesions can be sessile or pedunculated, and these lesions generally point away from the joint. The growth of osteochondroma ceases after the fusion of physis. Some clinical and radiological criteria predict the development of malignancy in the cartilaginous cap. Clinical features include syndromic association, an increase in the size of mass, pain, and the development of symptoms due to compression of the adjacent neurovascular bundle [Figure 3]. Radiological criteria are very objective and include the thickness of the cap of more than 20 mm, altered appearance on sequential studies, and development of soft-tissue mass. MRI has a clear advantage over any other modality for visualization of the cartilaginous cap. MRI sequences such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) also help distinguish between benign cartilaginous cap and malignancy developing within it. Imaging helps to obtain a biopsy sample from the most viable (enhancing and with restricted diffusion) part of the cap to increase diagnostic yield. Progression to malignancy occurs in 1% of cases of solitary osteochondroma and 20% of cases of hereditary multiple exostoses. ACT/CS1 constitutes more than 90% of cases of malignancies in osteochondroma, and CS 2–3 constitutes the rest of the cases.[10]

Table 3: Summary of newly added and recategorized entities in 2020 WHO classification of bone tumors with their clinical and imaging characteristics.

Category	Sub-category	Common locations in the skeleton system; Most common age group affected; Radiographic features
Chondrogenic tumors	Periosteal chondroma	Proximal humerus and distal femur; 3rd–5th decade; Arise from the periosteum of long bones and shows saucerisation of the adjacent bony cortex with a sclerotic periosteal reaction and ring and arc pattern of calcification.
	Enchondroma	Small tubular bones of hand/feet and long bones; 1st–3rd decade; small osteolytic lesions with no/mild endosteal scalloping and ring and arc pattern of calcification. No cortical destruction and periosteal reaction. Multiple lesions can be seen in Ollier disease and Maffucci syndrome
	Chondroblastoma NOS	Epiphysis or apophysis of a long bone; 1st–3rd decade; well-defined lytic lesion (<5 cm) with geographical bone destruction and thin sclerotic margins. Rings and arcs calcification can be seen. Intense adjacent marrow edema is often seen on MRI. Might be associated with joint effusion.
	Chondromyxoid fibroma	Metaphyseal region of long bones; 2nd and 3rd decade; well-defined lytic lesion with geographical bone destruction and sclerotic margins. No cortical destruction and periosteal reaction. Pseudotrabeculation can be seen.
	Chondromatosis NOS	Knee and hip; 4th–5th decade; soft-tissue mass surrounding the joint with numerous uniform-sized calcified loose bodies demonstrating rings and arcs calcification.
	Atypical cartilaginous tumor	Appendicular skeleton (femur, humerus, tibia, ribs); 3rd–6th decades; osteolytic lesions with no/mild endosteal scalloping and ring and arc pattern of calcification. No cortical destruction and periosteal reaction.
	Chondrosarcoma, grades 1	Axial skeleton (pelvis, scapula, skull base); 3rd–6th decades; osteolytic lesions with no/mild endosteal scalloping and ring and arc pattern of calcification. No cortical destruction and periosteal reaction.
Vascular tumors of bone	Epithelioid hemangioma	Multifocal regional distribution (long and flat bones); all age groups; expansile radiolucent, lytic or cystic-appearing lesions with narrow transition zone and endosteal scalloping.
Osteoclastic giant cell-rich tumors	Aneurysmal bone cyst	Metaphysis of long bones, posterior elements of the spine; 1st and 2nd decade; a sharply defined, eccentric expansile multicystic lucent bone lesion, with fluid-fluid levels on MRI
	Non-ossifying fibroma	Metaphysis of a long bone; 1st and 2nd decade; multiloculated, lucent lesion eccentrically located in the metaphysis near the physis of a long bone with a thin sclerotic rim.
Notochordal	Poorly differentiated chordoma	Clivus, skull base, and cervical spine; children and young adults; destructive lytic lesion with expansile soft-tissue mass. Calcification is uncommon.
Other mesenchymal tumors of bone	Chondromesenchymal hamartoma of the chest wall	Ribs; neonate; or infants; well-defined, expansile, partly calcified mass involving one or more ribs with fluid-fluid levels on MRI.
	Simple bone cyst	Metaphysis of long bones (humerus>femur); 1st and 2nd decades; centrally located well defined geographic lytic lesion with a narrow zone of transition, thin sclerotic margin with no periosteal reaction or soft-tissue component. Sometimes they are associated with a pathologic fracture. Fallen fragment sign and trap door sign can be seen.
	Fibrous dysplasia	Long bones, craniofacial bones, and ribs (monostotic or polyostotic); 1st–3rd decade; expansile or non-expansile lytic lesion with usually smooth and homogenous appearance, with endosteal scalloping and cortical thinning. Ground glass matrix is generally seen. No periosteal reaction. Rind sign at the margins is seen.
	Osteofibrous dysplasia	Mid-diaphysis of tibia; 1st decade; a bubbly lytic lesion centered in the tibial cortex, sclerotic margins, no periosteal reaction, pseudo trabeculation, and anterior bowing can be seen.
	Lipoma NOS	Calcaneum, femur; 4th–5th decade; benign-appearing osteolytic bone lesion with well-defined margins and occasional central calcification giving cockade sign.
	Hibernoma	Spine and pelvis; 5th–7th decade; sclerotic (most commonly) or osteolytic with peripheral sclerosis.
	Osteofibrous dysplasia-like adamantinoma	Mid-diaphysis of tibia; 3rd decade; a bubbly lytic lesion centered in the tibial cortex, with sclerotic margins, cortical destruction with soft tissue extension, no periosteal reaction, intramedullary extension common.

(Contd...)

Table 3: *(Continued)*

Category	Sub-category	Common locations in the skeleton system; Most common age group affected; Radiographic features
	Mesenchymoma NOS	Long bones (metaphysis), pelvic bones; 1st and 2nd decade; lytic expansile lesions with sclerotic rim, internal ring-like calcifications, and features of cortical thinning and/or destruction with soft tissue mass.
	Adamantinoma of long bones (Dedifferentiated adamantinoma)	Mid-diaphysis of tibia; 2nd–3rd decades; a bubbly lytic lesion centered in the tibial cortex, with sclerotic margins, cortical destruction with soft tissue extension, no periosteal reaction, intramedullary extension common. It has a propensity to metastasize to distant locations.
	Leiomyosarcoma NOS	Long bones and flat bones; 7th–8th decades; osteolytic lesion with an aggressive pattern of bone destruction.
	Pleomorphic sarcoma, undifferentiated	Femur, humerus and tibia; 3rd–5th decade; highly destructive with a wide zone of transition (occasionally expansile). Periosteal reaction is uncommon. The lesion usually has no matrix mineralization.
Hematopoietic neoplasms of bone	Langerhans cell histiocytosis NOS	Skull, pelvis and femur; 1st decade; solitary or multiple punched out lytic lesions without sclerotic rim. Hole within a hole sign, button sequestrum and geographic destruction is seen in the skull. A floating tooth is seen in the mandible and vertebra plana are seen in the spine.
	Langerhans cell histiocytosis, disseminated	Skull, pelvis and femur; 1st decade; multiple organ systems with multiple lesions are seen. Skeletal lesions are similar to Langerhans cell histiocytosis NOS.
	Erdheim-Chester disease	Femur and tibia (Multifocal involvement); middle age; bilaterally symmetrical cortical sclerosis obliterating the cortico-medullary differentiation. Cardiac involvement and retroperitoneal fibrosis can be seen leading to arrhythmias and hydronephrosis.
	Rosai-Dorfman disease	Femur, tibia, skull; 2nd decade; skeletal lesions are typically lytic and intramedullary, sometimes with surrounding sclerosis. Permeative destruction, Cortical thinning, and focal breakthrough can also be seen. It was previously termed "sinus histiocytosis with massive lymphadenopathy." Bone involvement is seen in 5–10% of cases.
Undifferentiated small round cell sarcomas of bone and soft tissue	Ewing sarcoma	The diaphysis of long bones, flat bones; 1st and 2nd decade; large osteolytic lesion with a permeative pattern of destruction and wide zone of transition extending into adjacent soft tissues. Lamellated (onion skin) periosteal reaction is common.
	Round cell sarcoma with EWSR1–nonETS fusions	Long bones and flat bone; broad age range; large osteolytic lesion with the permeative pattern of destruction and wide zone of transition extending into adjacent soft tissues.
	CIC-rearranged sarcoma	Predominantly involve soft tissue with rare involvement of bones; broad age range; lytic or mixed lytic-sclerotic lesion with an aggressive periosteal reaction.
	Sarcoma with BCOR genetic alterations	Pelvis and long bones; 1st and 2nd decade; lytic or mixed lytic-sclerotic lesion with an aggressive periosteal reaction.

WHO: World Health Organization, NOS: Not otherwise specified

Table 4: Imaging features that differentiate Enchondroma from ACT/CS1.

	Enchondroma	ACT/CS1
Appearance	Clustered cartilage deposits	Confluent mass
Tumor size	Less than 5 cm	More than 5 cm
Endosteal scalloping	Less than 2/3 of cortical thickness	More than 2/3 of cortical thickness
Expansile bony remodeling	Generally Absent	May be present
Soft tissue extension	Absent	May be present
Radiotracer uptake on bone scan	Less or no	More
Presence of marrow fat signal on MRI	Present	Present/absent

CS1: Chondrosarcoma grade 1, ACT: Atypical cartilaginous tumor

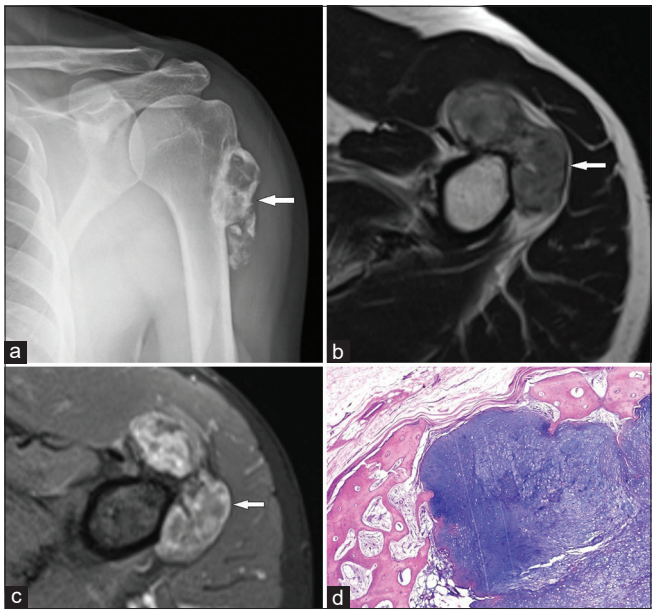

Figure 2: A 40-year-old male presented with swelling in the proximal left arm which on radiography (a) demonstrated well defined calcified mass lesion centered over the humeral cortex (solid arrow). Axial T2 W Magnetic resonance imaging (MRI) image (b) shows the lesion (solid arrow) is centered over the periosteum and appears hyperintense as compared to adjacent muscles with internal areas of hypointensities. Axial T1 W post-contrast MRI image (c) shows heterogeneous enhancement in the lesion (solid arrow), (d) hematoxylin and eosin section shows hyaline lobules of bland chondrocytes with periosteal rimming. The diagnosis of this case was periosteal chondroma.

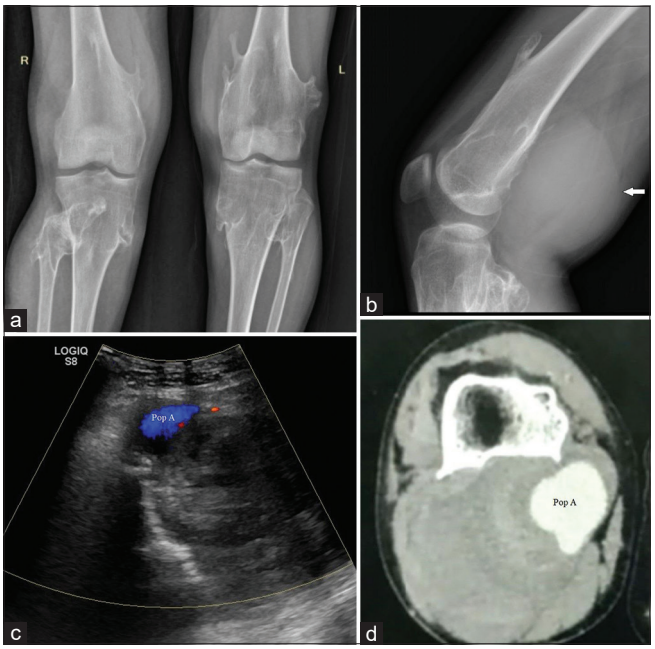

Figure 3: A 20-year-old male patient with diaphyseal aclasis presented with firm swelling in the left popliteal region, (a) Radiograph of the bilateral knee joint showing multiple sessile and pedunculated bony outgrowth arising from femur, tibia, and fibula pointing away from the joint suggesting multiple osteochondromas, (b) lateral radiograph of the left knee shows a soft-tissue density mass (solid arrow) in the popliteal region, (c) ultrasound with Doppler examination revealed popliteal artery (Pop A) in the periphery of the mass lesion with no color flow in the rest of the lesion, and (d) computed tomography angiography image shows large popliteal artery pseudoaneurysm with peripheral thrombosis. The cause of popliteal artery pseudoaneurysm could be irritation of the vessel wall by an underlying osteochondroma. Endovascular repair of the aneurysm was performed.

Osteogenic tumors

Osteoid osteoma (OO) and osteoblastoma are differentiated based on size and location in the skeleton system [Figure 4]. OOs are more predominantly seen in the diaphyseal or metadiaphyseal region of long bones, whereas osteoblastomas are more prevalent in posterior elements of the spine. Osteoblastoma can sometimes become aggressive and is classified in an intermediate category. Lesions <2 cm are classified as OO and lesions ≥2 cm osteoblastoma in the presence of classic clinical and radiological features. Nevertheless, both OO and osteoblastoma share the same molecular genetic alteration.[11,12]

The previous classification included secondary osteosarcoma in the conventional osteosarcoma (COS) subtype, but now, the recent classification has described it in a separate category. Now osteosarcoma not otherwise specified (NOS) includes only three subtypes: COS, telangiectatic osteosarcoma, and small cell osteosarcoma. COS accounts for the majority of osteosarcoma [Figure 5]. Osteosarcoma NOS can also be subdivided into different types based on the dominant matrix: Osteoblastic, chondroblastic, and fibroblastic; However, this subdivision has no role in predicting prognosis. COS and telangiectatic osteosarcoma are more commonly encountered in the metaphyseal region of long bones whereas small cell osteosarcoma is predominantly seen in the diaphysis. Recent classification has also removed Clear cell and chondroblastoma-like osteosarcoma subtypes from the osteogenic tumors.[4]

In the latest classification, secondary osteosarcoma is divided into six subtypes: [4]

a) Osteosarcoma in Paget's disease of bone,
b) Radiation-induced osteosarcoma
c) Infarct related osteosarcoma
d) Chronic osteomyelitis related
e) Implant-related osteosarcoma
f) Osteosarcoma secondary to fibrous dysplasia.

The prognosis of secondary osteosarcoma occurring as a result of Paget's disease of bone and radiation treatment is poorer than COS.

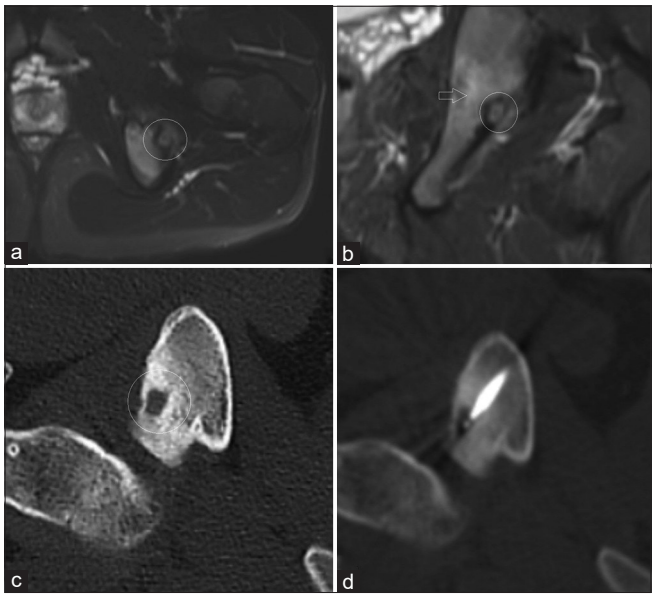

Figure 4: A 16-year-old male patient with osteoid osteoma presented with pain in the left hip joint which was more at night and relieved by aspirin, (a and b) magnetic resonance imaging of the patient revealed a well-defined osteolytic lesion (circle) measuring 6–7 mm in size, located in the left acetabulum with adjacent marrow edema (arrow), a hypointense nidus can also be visualized in the area, computed tomography (CT) in bone window setting shows a well-defined osteolytic lesion (circle) in the left acetabulum with adjacent reactive sclerosis, (d) CT-guided radiofrequency ablation of the lesion was performed.

Fibrogenic tumors

The 2020 WHO classification has not updated this category of bone tumors. It includes the desmoplastic fibroma of bone in the intermediate grade and fibrosarcoma in the malignant grade. These tumors are composed of spindle cells with variable collagen.[4]

Desmoplastic fibroma is an extremely rare tumor of bone (<0.1% of all bone tumors) that is locally aggressive but does not metastasize. It is considered the bony counterpart of desmoid tumors found in the soft tissues and is a diagnosis of exclusion. Both desmoplastic fibroma and desmoid tumors are histologically identical. Low-to-intermediate signal intensity is characteristic of MRI.[13] Transition to fibrosarcoma or osteosarcoma is extremely rare. The recurrence rate after curettage is generally more than 70%, so the preferred management is resection with wide margins.

Fibrosarcoma is a sporadic malignant fibrogenic tumor of bone that occurs in the middle and old age groups.[14] Initially, malignant fibrous histiocytoma and fibrosarcoma of bone were considered as a single entity, but these lesions are distinct entities.[4]

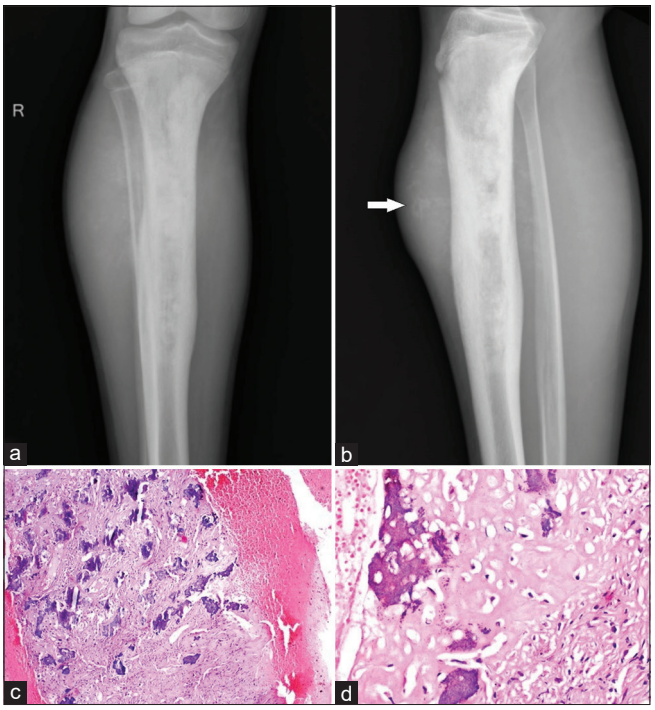

Figure 5: A 17-year-old female patient presented with a mass in the right upper leg for 2 months. The lesion was slowly increasing in size. Radiographic (a and b) evaluation revealed an ill-defined osteolytic and sclerotic mass lesion involving proximal tibial metaphysis and diaphysis with the permeative pattern of bone destruction, wide zone of transition, osseous matrix (arrow), and soft-tissue extension. A radiographic diagnosis of osteosarcoma was established and a biopsy of the lesion confirmed the same. Hematoxylin and eosin sections (c and d) show blood-filled spaces along with atypical spindle cells producing immature and neoplastic bone formation.

Vascular tumors

In 2020 WHO classification, epithelioid hemangioma of bone is moved from an intermediate locally aggressive and rarely metastasizing tumor to the intermediate locally aggressive tumor category.[4] Epithelioid hemangioma, epithelioid hemangioendothelioma, and angiosarcoma can be multifocal and involve multiple bones. Angiosarcoma accounts for <1% of malignant bone tumors. Angiosarcoma has the propensity to metastasize to other skeletal sites.[15]

Osteoclastic giant cell-rich tumors

It comprises a heterogeneous group of tumors and tumor-like lesions rich in osteoclast type multinucleate giant cells. There has been a recategorization of the aneurysmal bone cyst (ABC) and non-ossifying fibroma (NOF) into this group in the latest classification. In the present classification, the term "benign fibrous histiocytoma" is no longer in use.[4]

Giant cell tumors (GCT) can be categorized into benign or malignant [Figure 6]. Malignant GCTs represent 5–10% of GCT. Radiographs are not very helpful in differentiating benign from malignant GCTs. DWI and DCE MRI can help identify highly cellular components within the lesion, which can further be biopsied to obtain representable samples for histopathological evaluation.[16] Malignant GCTs can be categorized into primary (more favorable prognosis) and secondary (more common). Denosumab-treated GCT is now recognized as a distinct variant of GCT. Giant cell lesions of the small bones are now considered a true solid variant of ABC. Terminologies such as "giant cell lesion of small bones" and "giant cell reparative granuloma of small bone" are obsolete. ABC can be categorized into primary (*de novo*) and secondary (developing in preexistent tumors such as GCT, chondroblastoma, fibrous dysplasia, and NOF) [Figure 7]. Distinguishing primary from secondary ABC is important as the treatment for the two is completely different. [Table 5] summarizes features that help to distinguish primary from secondary ABC.[4]

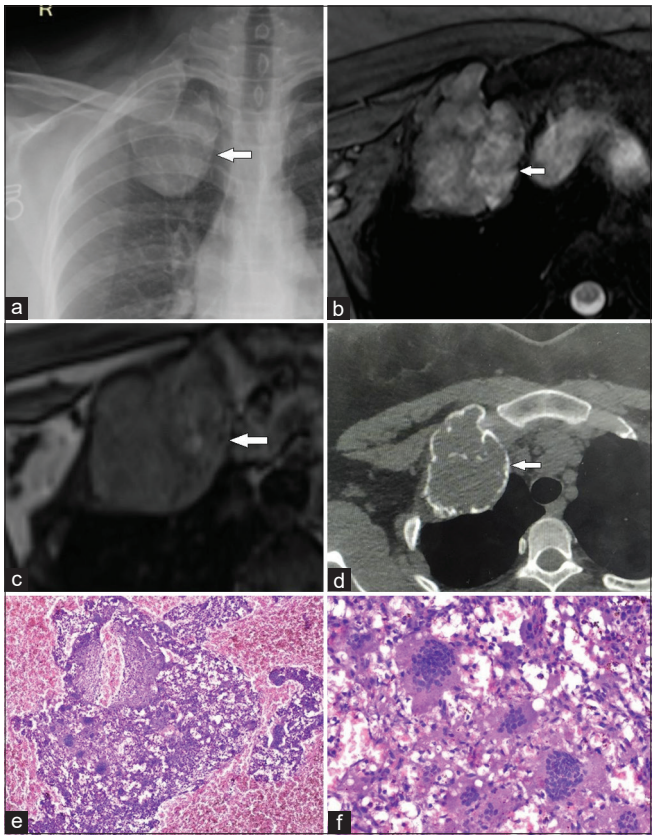

Figure 6: A 35-year-old female patient presented with swelling in the right anterior chest wall. Radiograph of the chest (a) revealed a well-defined lesion in the right upper thorax (arrow), and magnetic resonance imaging (b and c) revealed a well-defined expansile osteolytic lesion in the right second rib anteriorly with hyperintense signal intensity on T2 W images and hypointense signal intensity on T1 W images, Computed tomography (d) of the chest shows a well-defined expansile osteolytic lesion in the right 2nd rib anteriorly with cortical thinning and few internal bony septae, (e and f) hematoxylin and eosin sections show areas of hemorrhage with numerous osteoclasts like giant cells scattered in between the mononuclear round and spindle cells proliferation suggestive of giant cell tumor.

Notochordal tumors

Poorly differentiated chordoma (PDC) is a new entity that is added to the recent classification of bone tumors. Like conventional chordoma, PDC also has a predilection for the axial skeleton but it predominantly affects the clivus and skull base. It is generally seen in children, and young adults, with females affected slightly more than males. PDC is more aggressive than conventional chordoma. It generally demonstrates intermediate T2 signal intensity unlike conventional chordoma and shows avid contrast enhancement.[17]

Dedifferentiated chordoma is characterized by the presence of sarcomatous elements in addition to the chordoma (biphasic).[4] Biomorphic appearance can be visualized even on MRI.

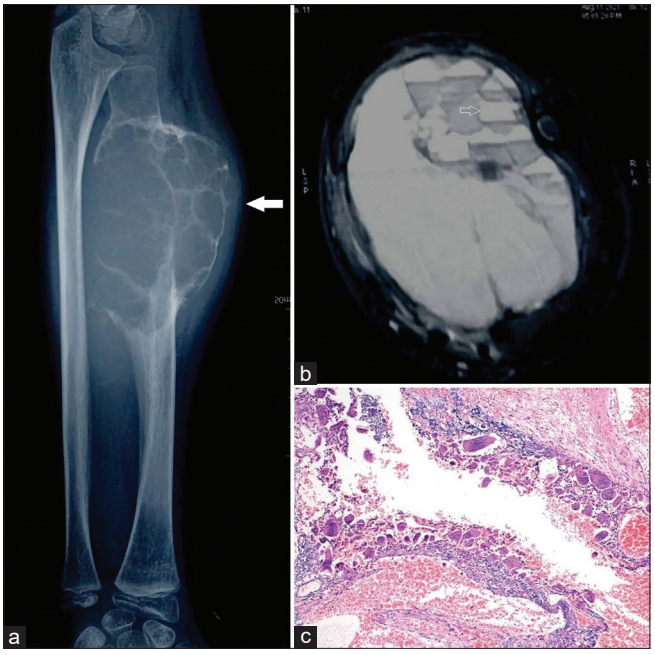

Figure 7: A 10-year-old male with an aneurysmal bone cyst of radius showing a well-defined expansile osteolytic lesion (solid arrow) with multiple thin internal bony septae giving soap bubble appearance on radiography (a), (b) axial T2 W Magnetic resonance imaging image showing multiple fluid-fluid levels within the lesion (arrow), (c) Hematoxylin and eosin sections show blood-filled cystic spaces separated by fibrous septa with osteoclast type giant cells, fibroblasts in their walls.

Table 5: Features that differentiate primary from secondary ABC.

	Primary ABC	Secondary ABC
Age	1st–2nd decade	3rd decade
Location	Metaphysis with or without epiphyseal extension	Epiphysis (preexistent GCT or chondroblastoma) Diaphysis (preexistent NOF and FD)
Cortex	Intact	Breached with a soft tissue mass
USP6 gene rearrangement	Present in 70% of cases	Absent

ABC: Aneurysmal bone cyst, GCT: Giant cell tumors, NOF: Non-ossifying fibroma

Other mesenchymal tumors

This is the new category of bone tumor introduced in the 2020 WHO classification. Tumors included in this category in the present classification were previously categorized as tumors of undefined neoplastic nature or Miscellaneous tumors. Hibernoma of bone, mesenchymoma, and dedifferentiated adamantinoma are newly recognized entities. PUS was previously termed as "undifferentiated high-grade pleomorphic sarcoma." PUS can be primary or secondary. Secondary PUS may arise in pre-existent bone infarcts, Paget's disease and radiation necrosis.[18]

Hibernoma (tumor of brown adipose tissue) is a very rare benign tumor seen in the spine or pelvis of elderly patients (female>male). Mesenchymoma, also known as Fibrocartilaginous mesenchymoma, is a very rare, locally aggressive neoplasm seen in children and affects the metaphyseal region of long bones, most commonly followed by pelvic bones, vertebrae, and ribs.[4]

Adamantinoma is divided into three types in the recent classification: Classic adamantinoma (malignant), OFD-like adamantinoma, and dedifferentiated adamantinoma (newly introduced). OFD-like adamantinoma was previously categorized as a malignant tumor, but in recent classification, it is placed in the Intermediate (locally aggressive) category. Dedifferentiated adamantinoma is the rarest subtype and has an aggressive clinical course with metastasis seen in 2/3rd of the patients. This subtype may be associated with sarcomatoid dedifferentiation. In contrast classic adamantinoma displays a low rate of metastasis and longer survival. OFD and OFD like adamantinoma are more commonly seen in the young age group with females affected more than males, whereas classic and dedifferentiated adamantinoma is more commonly seen in males of the middle age group. OFD and all types of adamantinoma are typically located in the tibial cortex. Anterior bowing is more common in OFD and OFD like adamantinoma whereas marrow involvement and extraosseous extension are more commonly seen in classic and dedifferentiated adamantinoma.[19]

Hematopoietic neoplasms of bone

Multiple myeloma is the most common malignant bone tumor in adults [Figure 8]. It can present in either disseminated form (more common and poor prognosis) or as solitary plasmacytoma. The disseminated form presents as multiple punched-out lytic lesions predominantly involving the axial skeleton. Sometimes disseminated form presents as mere diffuse osteopenia with no identifiable lytic lesion. Solitary plasmacytoma in the majority of patients has latent systemic involvement at the time of presentation. The term "Plasma cell myeloma" is no longer in use. Multiple myeloma is removed from the fifth edition of the WHO classification of bone tumors and is included in the fourth edition of the

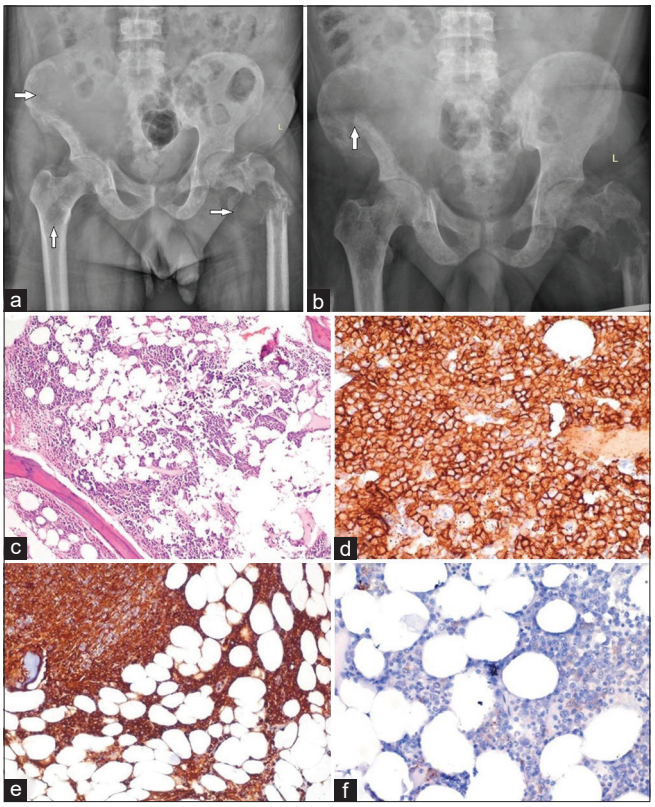

Figure 8: A 55-year-old female with multiple myeloma showing multiple osteolytic lesions in pelvic bones and bilateral femur (arrows) on the radiograph (a), follow-up radiograph after 2 weeks shows pathological fracture in the right iliac bone (arrow), hematoxylin and eosin sections from bone marrow show nodules/sheets of plasma cells (c), these plasma cells show diffuse immunopositivity for CD138 (d) and kappa (e), while Immunonegative for lambda (f).

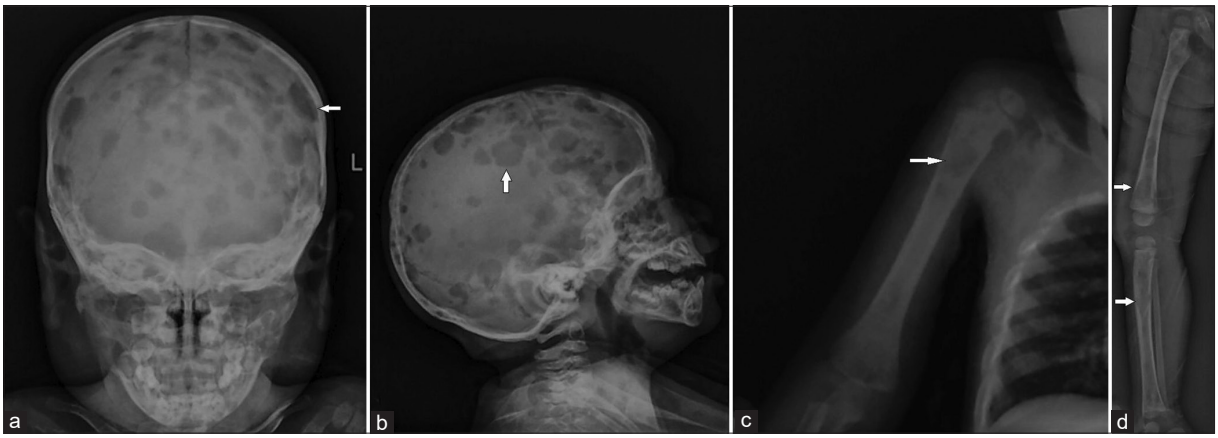

Figure 9: A 2-year-old child with disseminated Langerhans cell histiocytosis showing multiple well defined osteolytic lesions involving the skull with beveled edges (arrows in a and b), similar lesions can also be seen in the appendicular skeleton (arrows in c and d).

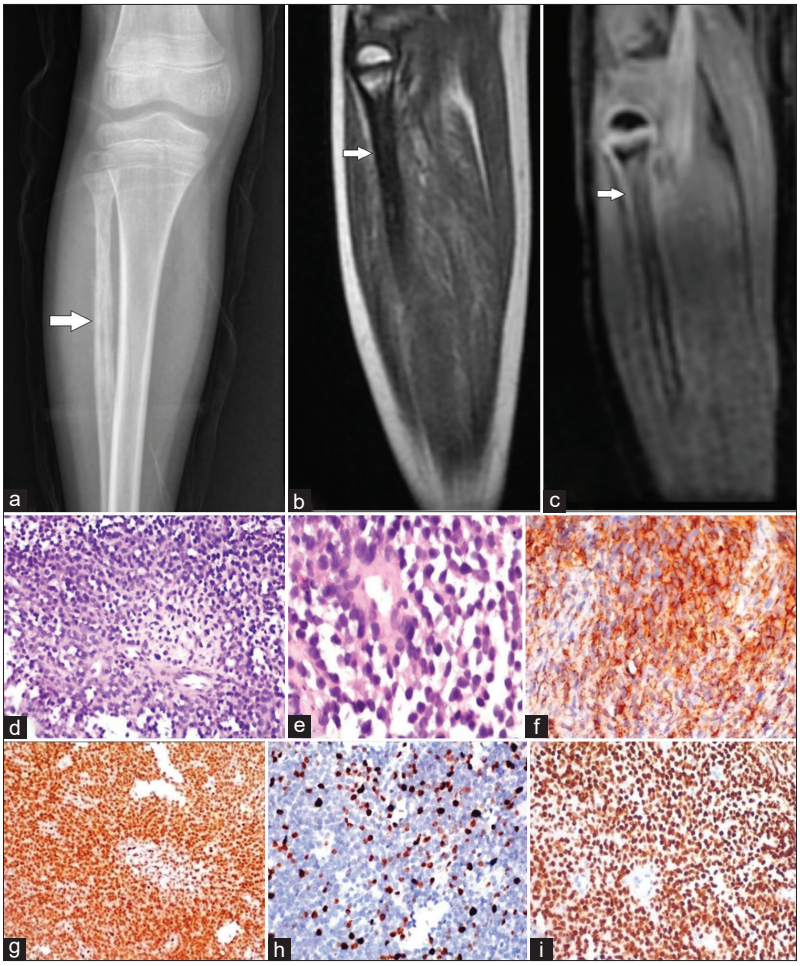

Figure 10: A 9-year-old male with Ewing sarcoma of right fibular diaphysis showing an ill-defined osteolytic lesion in the fibular diaphysis with the poor zone of demarcation, the permeative pattern of bone destruction and onion skin type of periosteal reaction (arrow in a), magnetic resonance imaging images show diffuse infiltration of marrow (b) with enhancement on the post-contrast image (c), hematoxylin and eosin sections show a malignant small round cell tumor (d), higher magnification demonstrating monomorphic round cells with fine granular chromatin with the absence of nucleoli (e), these tumor cells are diffusely immunopositive for CD99 (f), FLI-1 (g) and NKX2-2 (h) with increased Ki67 labeling index (i).

WHO classification of hematopoitic and lymphoid tissues published in 2017.[20]

Langerhans cell histiocytosis [Figure 9], Erdheim-Chester disease, and Rosai-Dorfman disease were classified previously in the category of tumors of undefined neoplastic nature, but in the recent classification, these tumors are classified in the category of hematopoietic neoplasms of bone.[4]

Primary bone lymphoma (PBL) can be unifocal or multifocal involvement of the skeletal system without evidence of systemic disease for 6 months. PBL is less common than secondary involvement from disseminated lymphoma. More than 80% of PBL are diffuse large B-cell lymphomas. Different types of bone lymphomas are indistinguishable from Imaging studies.[21]

Undifferentiated small round cell sarcomas of bone and soft tissue

A new chapter on undifferentiated small round cell sarcomas of bone and soft-tissue tumors is introduced in the 2020 WHO classification, which includes Ewing's sarcoma (EWS), round cell sarcoma with EWSR1–non-ETS fusions, CIC-rearranged sarcoma, and sarcoma with BCOR genetic alterations. These tumors are different from each other based on clinical features and molecular profiles. EWS is different from the other three because of the unique gene fusion involving the FET family of genes and a member of ETS transcription factors. EWS is the second most common malignant bone tumor after osteosarcoma in the pediatric and adolescent age group [Figure 10].[4]

CONCLUSION

In this review, we have summarized major changes in the 2020 WHO classification of bone tumors with relevant points for the information and knowledge of the radiologist. Radiologists play a crucial role in the team of physicians and surgeons involved in the care of bone tumor patients; Therefore, the radiologist needs to stay updated with the latest development and advances even if the basis of these developments is majorly molecular, genetic, and pathological. We have also summarized the imaging approach and parameters used for the evaluation of patients presenting with clinical features of bone tumors. Imaging features of many new entities are yet to be discovered, and with time, we may be able to understand these entities better with the help of further research and enhancement in the available literature.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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