THE FINAL DIAGNOSIS OSTEOGENIC SARCOMA

Edited by: Dr.R.G.W.Pinto(Goa)

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Collaboration between EFCS (European Federation of Cytology Society) and Asian Society of Cytopathology

Dr.K.K.Unni

by Dr Nirmala Jambhekar Professor & Head (retd) Department of Pathology , Tata Memorial Hospital , Mumbai

Dr Unni is the best known name in the world for the final diagnosis of bone tumours. He hails from the southern state of Kerala and he did his medical graduation in 1962 from the All India Institute of Medical Sciences.He subsequently completed his residency from the Mayo Graduate School in 1970 and later did a fellowship from Mayo Clinic Rochester in 1974 .He worked briefly on the Mayo Lung Project before joining as a staff , Mayo Clinic, in the Division of Anatomic and Surgical Pathology, Department of Laboratory Medicine in 1974 . He rose to become the section head in 1982, and later a consultant in Department of Orthopedic Surgery in 1991 and a consultant, Division of Orthopedic Oncology in 1991. He remained as a faculty at the Mayo clinic for 32 years contributing immensely to the subject of Bone tumours .

The senior and very famous Bone tumour pathologist Dr David Dahlin was his mentor and Dr Unni's services were soon recruited by Dr Dahlin as a coauthor for the very popular book on Bone tumours . Apart from this Dr Unni has been the core authors of the WHO Blue book and the

AFIP fascicle on Bone tumours and he has written several original articles on the subject. He is credited with describing newer entities such as Clear cell chondrrosarcoma, small cell and some other tumours , and also for establishing treatment guidelines for bone tumours.

After retiring from the Mayo clinic in 2007 Dr Unni joined the department of pathology at the Medical College Wisconsin and continued to be the Emeritus Professor of Pathology & Orthopedics at the Mayo Clinic

Dr Unni is recognized as the worlds greatest bone pathologist and he received innumerable consultation cases daily from all over the world

But he always emphasized that bone tumors are uncommon , and hence a pathologist cannot make a living by signing out merely bone

tumours. His routine sign outs at the Mayo Clinic encompassed all anatomic sites including significant non-gynaec cytology . In fact his

expertise was seeked by his Mayo colleagues on all difficult cases and The particularly in the frozen section scenario , a place which he professed

to like very much . He valued intradepartmental consults with colleagues and often stated that the more you see the better you get .

Several pathologists from all over the world came to the Mayo Clinic to learn bone tumours from Dr Unni and this was in addition to the

numerous generations of Mayo residents whom he trained . His contribution in musculoskeletal oncology helped soar the reputation of the orthopaedic department nationally and internationally . As has been rightly said by William Osler “As is your pathology , so is your medicine”

Mayo Clinic Board of Trustees established the Mayo Clinic Distinguished Alumni Award in 1981 for those who reached leadership in his or her field and this was conferred on Dr Unni in 2014

I was fortunate to work with Dr Unni on an UICC ICRETT fellowship in 1990.There were certain remarkable qualities about him which I was privileged to notice during my interactions .He took great pride in making fast and confident decisions while reporting ; this was something which he most certainly imbibed from his mentor, Dr David Dahlin, who believed that a pathologist needs to make a quick and firm decisive diagnosis so as to alleivate the patient's anxiety , and help the clinician take a treatment decision .Dr Unni strongly believed that surgical pathology diagnosis is based on visual memory and a diagnosis is made intituitively and should be done within 24 hours of receiving the slides and not by overthinking and staring at a slide for a long time.

This despite the fact that his personal consultation cases accrued from all over the world were unusual and the most difficult .Also making mistakes is unavoidable but one should admit it when it does happen. The most difficult bone tumor according to Dr Unni is an Osteoblastoma and he would admit that he has either over diagnosed or under diagnosed this tumour at times .He also emphasized that looking at the gross specimen was very important and often helps to make a diagnosis

Dr Unni disliked two things: abbreviations such as ABC when one could easily say Aneurysmal Bone Cyst , and emails in lieu of a simple phone call. He believed that it is so very easy to sometimes simply

walk up and talk to the concerned person if in the same office rather than sending emails .

Dr Dahlin used to reside just across the Mayo Clinic and often came

down to the department before lunch time to have a look at some of Dr Unni's difficult and interesting cases .It was amazing and so very

wonderful to see the respect and affection Dr Unni showed to his mentor during these visits . The lunch time interactions of these two doyens

with the junior colleagues were full of infectious humour and bonhomie. The residents regarded Dr Unni as one of the kindest teachers they

have ever had . Dr Unnis contribution to the subject was aptly and jovially given its due by Dr David Dahlin when he once mentioned to

me that he would have never asked Dr Unni to do bone tumours if he had realized that Dr Unni would upstage him so fast ! I was indeed

extremely fortunate to have done a fellowship with Dr Krishnan Unni whose stature was that of an icon in his own lifetime


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distinguished service in the development of the
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The Distinguished Pathologist Award was established by the Council of the USCAP for recognition of contributions to pathology over the years.

Award Presentation at Business Meeting

Tuesday, March 5, 2013 - 3:30-5:00 PM
CC Ballroom 1-4

Dr. Krishnan Unni was born and raised in Kerala, India. He received his medical degree at the All India Institute of Medical Sciences in 1962. He then came to the United States and continued his training at Memorial Hospital in Worcester, MA, after which he did a f ellowship in pathology at Mayo Graduate School in Rochester, MN. Following his training in 1970, he returned to India. By 1973, he had returned to Rochester, MN and joined the staff at Mayo Clinic. He trained extensively under Dr. David Dahlin and after DrDahlin's retirement, continued to build on the collection of bone tumors started by his mentor. He became a Professor of both Pathology and Orthopedics. After more than 30 years, he retired from Mayo Clinic at the end of 2006. He is currently working at the Medical College of Wisconsin in Milwaukee, WI.

- Mayo Graduate School/University of Minnesota: Pathology – Examining Membe
- New Delhi, India: House Job – Surgery 1964 -1965
- Memorial Hospital, Massachusetts 1965 -1967
- Mayo Clinic – Consultantin Pathology 1974 -2006
- Mayo Medical School – Instructor in Pathology 1974 -1978
- Mayo Medical School – Assistant Professor of Pathology 1978 -1981
- Mayo Medical School – Associate Professor of Pathology 1981 -1987
- Mayo Medical School – Professor ofPathology 1987 -2006
- Mayo Clinic – Consultant in Orthopedics 1991 -2006
- Mayo Medical School – Professor of Orthopedics 1992 -2006
- Mayo Medical School – Professor Emeritus of Pathology 2007 – Present

- Mayo Medical School – Professor Emeritus of Orthopedics 2007– Present
- Medical College of Wisconsin – Consultant in Pathology 2007– Present

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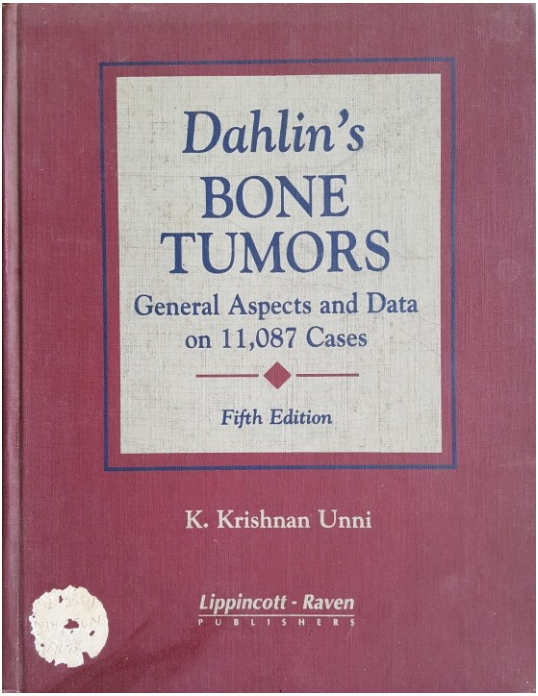
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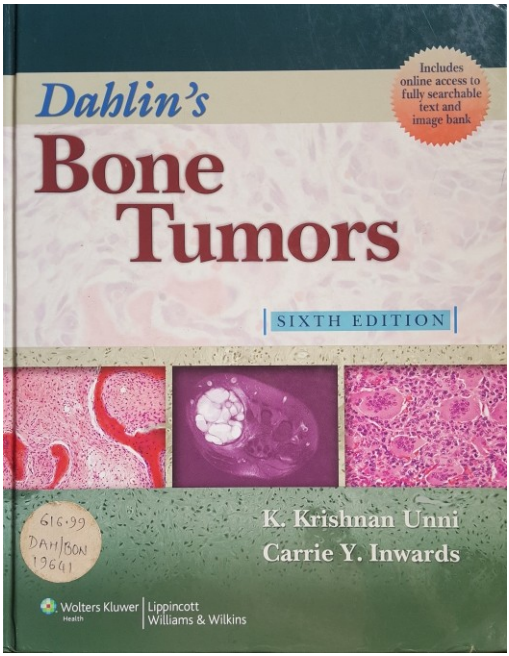
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Krishnan Unni, M.D., is a professor of pathology at the Medical College of Wisconsin, and a professor of pathology and orthopedics in the Mayo Clinic College of Medicine in Rochester.

He is an icon in the pathology of benign and malignant bone and soft tissue tumors. He has recognized new entities, including clear cell chondrosarcoma and small cell osteosarcoma, and has helped to establish current treatment guidelines.


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Osteosarcoma

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INTRODUCTION AND DEFINITION

Osteosarcoma is a high-grade primary malignant tumor characterized by bone or osteoid production by tumor cells. Usually osteosarcomas arise from bones, but in rare instances, osteosarcoma may originate from extraskeletal connective tissues (1-3).

CLINICAL PRESENTATION AND RADIOLOGY

Clinically osteosarcoma appears as a progressively enlarging bone mass. Conventional osteosarcoma arise usually from metaphysis of the long bones. Osteosarcomas are present in various groups of age going from 5 to 50 years, knowing that there is a clear male predominance in adolescents and young adults. Osteosarcomas arising from plat bones are usually associated with prior irradiation.

Radiological examination including standard radiology, CT and MRI is a reference diagnostic technique and allows the initial diagnosis to be made. Progress in imaging techniques used through its richness of morphological parameters, is capable of performing an accurate diagnosis. Areas of bone destruction, periosteum abnormalities, Codman's triangle, infiltration of soft tissues, bone formation, cartilaginous formation and parameters of ossifying myositis are well visible and constitute the basis of the radiological diagnosis. The malignant nature and bone origin of the tumor may also be confirmed.

PATHOLOGY SAMPLES

The pathological diagnostic technique is a subject of discussion in the literature. In the past, pathological diagnosis has been based on surgical biopsy analysis. The tissue material, being of large volume, allowed detailed analysis in great comfort. The disadvantage of surgical biopsy was its morbidity and a delay in treatment until complete healing. The use of coreneedle biopsy is preferred more recently. This technique is minimally invasive, well tolerated by patients and does not require special post-biopsy care. Interestingly, this technique has not been accepted by all pathologists. Some of them argue that the paucity of tumor cells and the analysis of the stroma (osteoid, cartilage) is not optimal on samples of limitedvolume.

Finally, fine-needle aspiration (FNA) being not-invasive and repetitive, has achieved real success as a diagnostic method and was introduced in the diagnosis of osteosarcoma. The diagnosis of osteosarcoma is relatively easy, because they are high-grade and polymorphous malignancies occurring in the specific radiological and clinical setting. In other hand it was reported that in some cases FNA could not be performed due to the firmness of the tumor

HISTOPATHOLOGY

Conventional bone-forming sarcomas arising within bone variant are divided into osteoblastic, chondroblastic and fibroblastic subtypes. Osteosarcomas are high-grade malignancies showing cellular pleomorphic and bone or bone-matrix formation. In osteoblastic subtype, mononucleated osteoblasts tend to be isolated within abundant bone-matrix and less or more unmineralized bone structures. In chondroblastic osteosarcomas predominant cartilaginous component in different stages of maturity is present. Cellular anaplasia and pericytoid pattern may be particularly present. In fibroblastic subtype, numerous spindle-shapes cells are present, while production of bone or cartilage may be scant.

Round cell variant is composed of roundish cells with areas of bone formation, which should be differentiated from Ewing's sarcoma.

Parosteal osteosarcoma and **periosteal** osteosarcoma are tumors, usually well differentiated that occur on the surface of the bone. Finally **high-grade surface** osteosarcoma present as

high-grade conventional sarcoma localized on the bone surface. All these last three variants are rather clinical and radiological modifications of conventional osteosarcoma. Immunohistochemistry plays a little role in the diagnosis. SATB2 immunoreactivity may be used to reinforce osteoblastic differentiation.Additionally, no specific diagnostic molecular pathology tests are available.

CYTOPATHOLOGY

Cytological smears vary depending tumor histological subtype. Usually, the exact cytological diagnosis of osteosarcoma is based on the simultaneous presence of malignant polymorphic cells and bone or cartilage elaboration. At the same time, the cytological diagnosis of osteosarcoma subtype may be not easy because not all components may be present. Approximately in half of tumors osteoid is missing suggesting cytologically other type of pleomorphic sarcoma (leiomyosarcoma, synovial sarcoma, MFH, etc). In such cases the diagnosis requires comparing cytology information with radiology information (5,6).

Conventional variant of osteosarcoma, whatever the histological subtype, appear relatively constantly on cytological slides. Smears are usually hypercellular and show in various proportions of osteoblasts, osteoclasts and bone-forming matrix. Osteoblasts present as roundish, epithelioid or spindle-shaped atypical cells with eccentric nuclei. Osteoclasts present as benign- or malignant-looking multinucleated giant cells. Non-specific spindleshaped or oval non-specific cell are also found. Bone-forming matrix may be osseous or chondroid. When May-Grunwald-Giemsa or Diff-Quik stains are used, osteoid stains eosinophilic or orange. Cartilaginous matrix stains intensively magenta or pinkish. Welldifferentiated cartilage stains dark-blue. Finally, bone-producing myxoid matrix and vascular structures may also be found (2,5-11) (Fig. 1-6).

Round cell variant of osteosarcoma is composed of roundish cells. Frequently double cell population with larger – clearer cells and smaller – darker cells is present suggesting Ewing's sarcoma. In some cases osteoid is present making the diagnosis more comfortable.

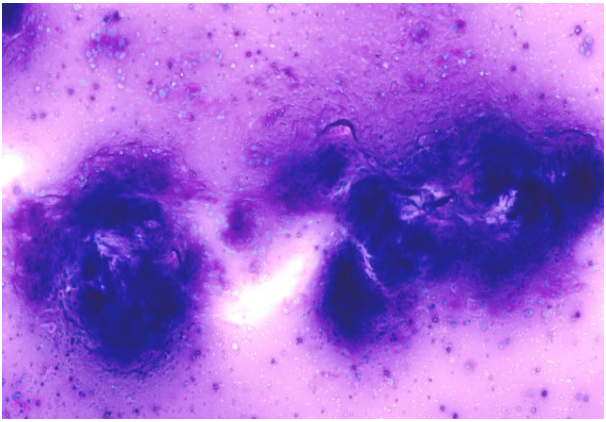
CYTOLOGY PERFORMANCES AND DIFFERENTIAL DIAGNOSIS

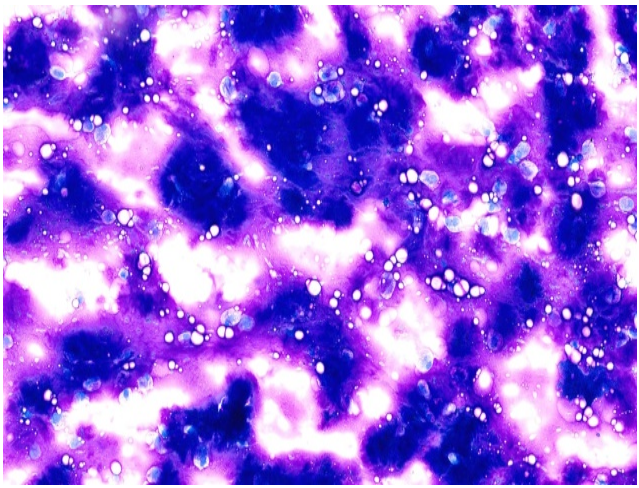
Conventiona osteosarcoma is a subtype which shows high percentage of accurate and

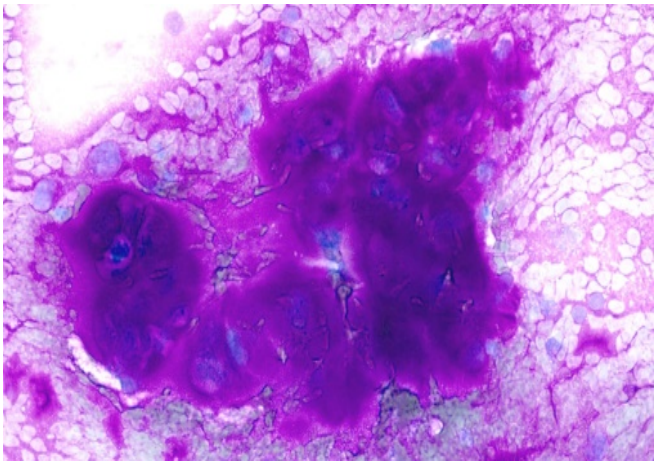
"malignant" diagnoses. An accurate cytologic diagnosis relies upon the presence of the characteristic osteoblasts and osteoid or bone-producing matrix. Many authors (5,7,9, 10) proved that FNA accuracy may significantly vary depending high-grade versus low-grade osteosarcoma and conventional versus superficial osteosarcoma. Small cell sarcoma may a challenging diagnosis, since it morphologically resembles to Ewing sarcoma (7, 12, 13, 14). Parosteal osteosarcoma shows moderately cellular, spindle to polygonal cells with minimal pleomorphism. Osteoclast-like giant cells and abundant chondro-osseous matrix are present(5).

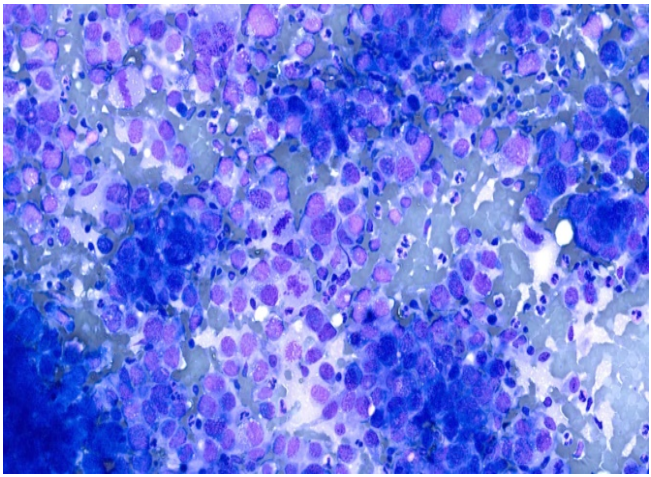
While the false-negative rate is very low, accurate diagnosis of osteosarcoma is not easy when osteoid or cartilage is absent on the smear (5-8). However, in these cases, the diagnosis of malignancy is obvious. The errors reported are false diagnoses of sarcoma NOS or carcinoma (7,9). Among false-negative diagnoses, giant cell tumor and aneurysmal bone cyst are the most poorly diagnostic errors (6). Imaging in this context is of special value, since radiology may help in the diagnosis with a typical pattern of irregular peripheral calcification.

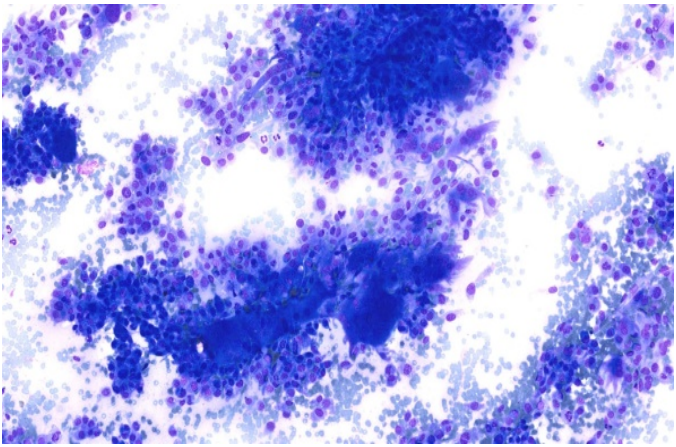
Collective analysis of the most important cytology reports from the literature (5, 6, 7, 8, 9,10) shows that among 334 primary osteosarcomas diagnosed by FNA, 82.3% cases were diagnosed accurately or as malignancy, 0.2% were suspicious and 4.3% were false-negative.The not significant rate was 13.2%.These data are presented in Table 1.

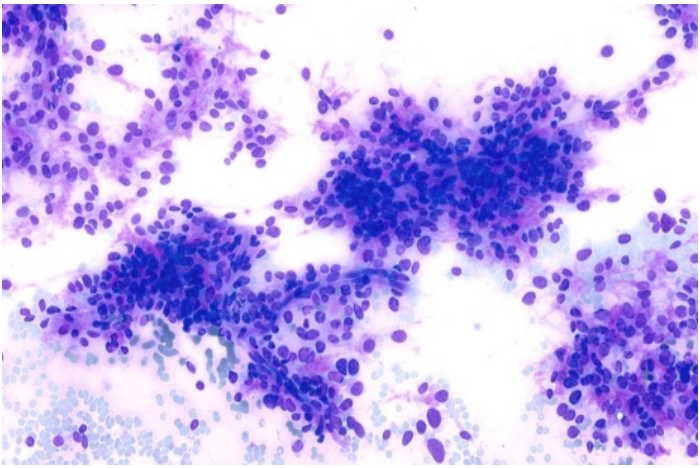


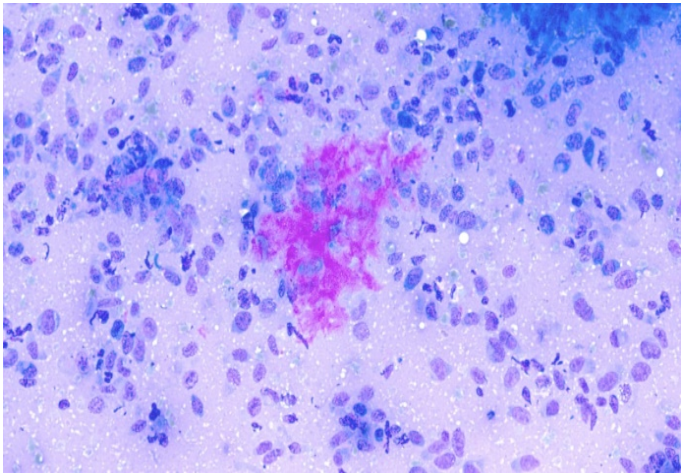


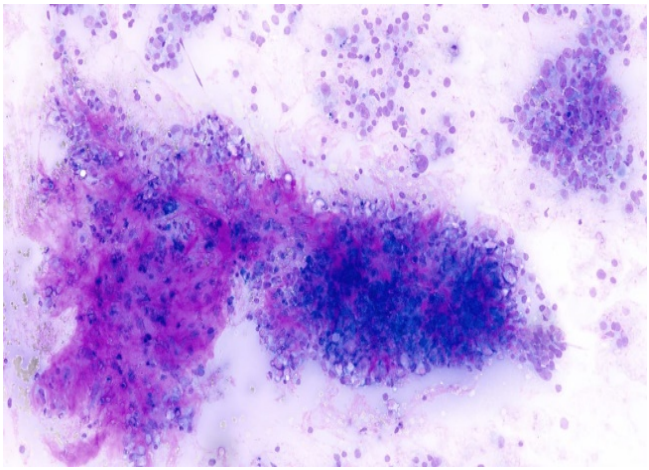


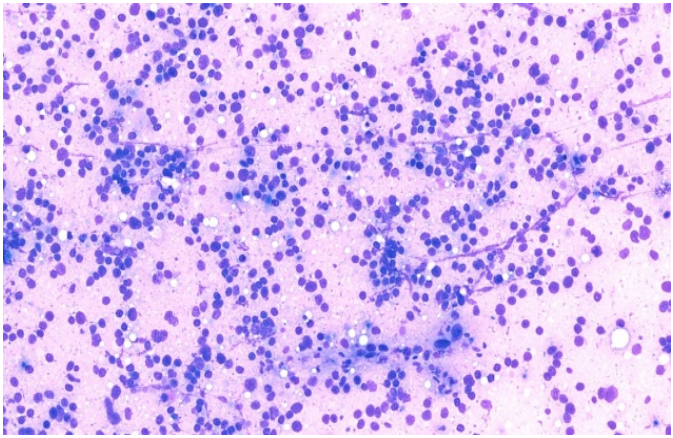


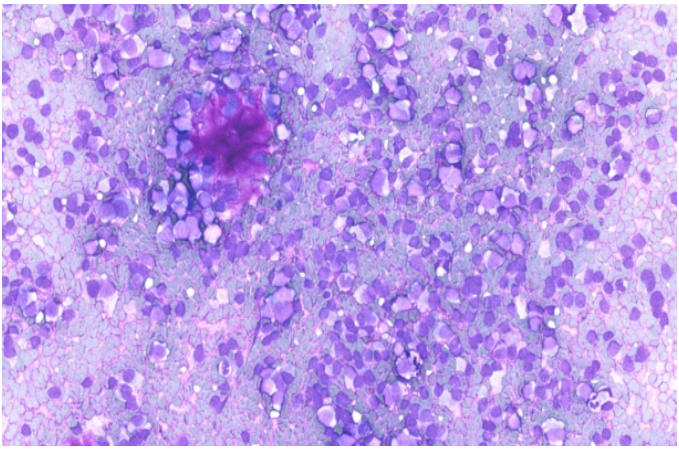


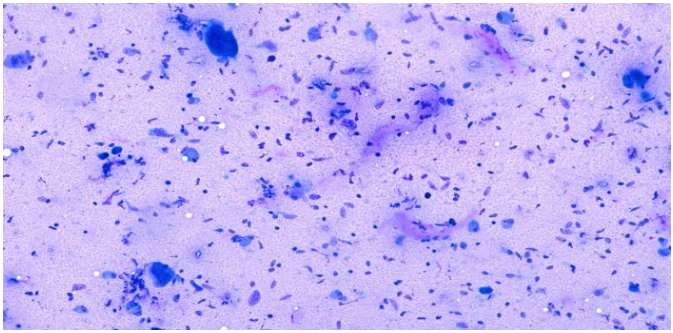


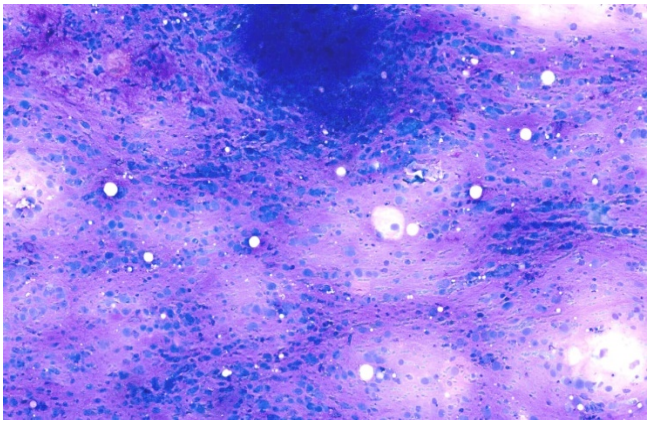


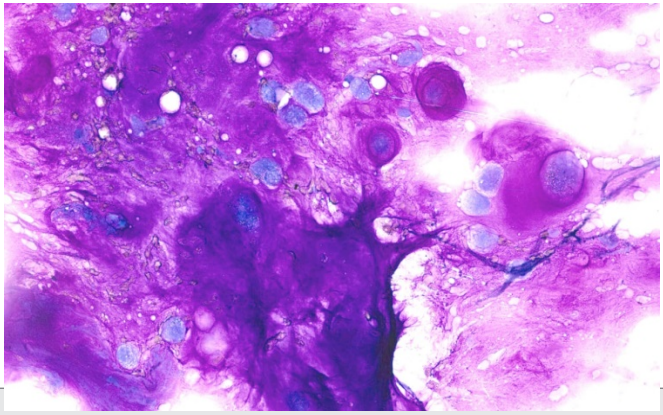












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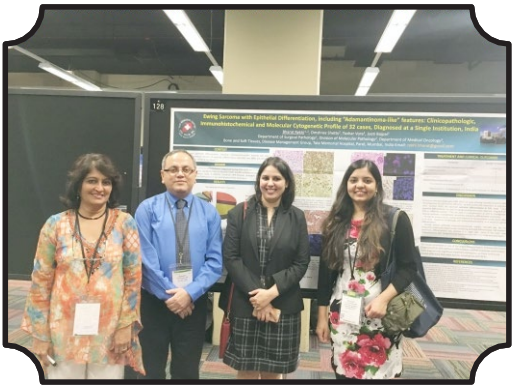

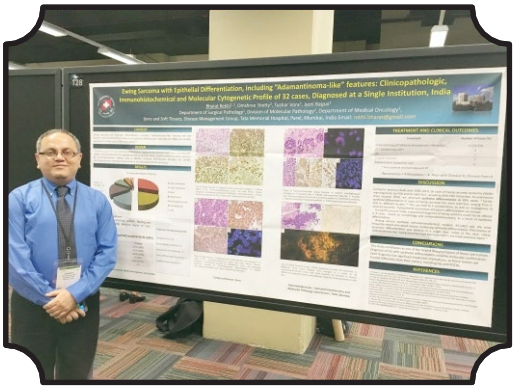
Ewing Sarcoma with Epithelial Differentiation, including "Adamantinoma-like" features: Clinicopathologic, Immunohistochemical and Molecular Cytogenetic Profile of 32 cases, Diagnosed at a Single Institution, India
TREATMENT AND CLINICAL OUTCOMES
DISCUSSION
CONCLUSION
REFERENCES


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OSTEOSARCOMA AND ITS CLINICOPATHOLOGICAL SPECTRUM

Authors: Aditi Rathi MD, Bharat Rekhi MD, DNB, MIAC, FICP, FRCPATH

Affiliation: Department of Pathology, Homi Bhabha National Institute (HBNI) University, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

INTRODUCTION:

Osteosarcoma (OS) is the most common primary malignant neoplasm of the bone, predominantly seen in the pediatric and adolescent patients. In terms of location, it is predominantly situated near the metaphysis of long bones such as the distal femur, proximal tibia, and proximal humerus, less common sites include the skull, jaw, and pelvis. Histopathologically, it is characterized by the formation of immature bone or osteoid by malignant osteoblasts. This locally aggressive tumor tends to present with early systemic metastasis, primarily into the lungs. The 5-year overall survival rate in such patients is 70%.

Classification of an osteosarcoma is based on various criteria, such as tumor location, histopathological features, and genetic characteristics. According to the World Health Organization (WHO) classification, osteosarcoma is sub classified into central (medullary) and surface (peripheral) subtypes, each with distinctive histopathological features. Central subtypes comprise conventional, telangiectatic, low-grade, and small cell types, while the surface osteosarcomas include parosteal, periosteal, and high-grade subtypes. This taxonomy serves to encapsulate the heterogeneity inherent in osteosarcoma, guiding tailored therapeutic strategies and prognostic assessments.

Treatment modalities typically involve a synergistic approach involving surgery, chemotherapy, and, in select cases, radiation therapy, targeting both the primary tumor and potential metastatic lesions.

EPIDEMIOLOGY AND ETIOLOGY:

OS is a relatively rare cancer, with an annual incidence rate of 4.7 per million individuals among children and adolescents aged 0 to 19 years, contributing to 8.9% of cancer-related deaths in this age group.

Despite improvements in the quality of life for OS patients over the recent decades, its etiology remains elusive. Various risk factors, such as Paget's disease, hereditary retinoblastoma, Li–Fraumeni syndrome, Rothmund–Thomson syndrome, Diamond–Blackfan anaemia, Bloom syndrome, Werner syndrome, ionizing radiation, exposure to beryllium, a **virus**-induced osteosarcoma named after its discoverers, Finkel, Biskis, and Jinkins (FBJ) virus, osteochondromatosis, enchondromatosis, fibrous dysplasia, orthopaedic prosthetics, alkylating agents,and exposure to ionizing radiation, are associated with disease progression. Chromosomal abnormalities, including amplifications of chromosomes 6p21, 8q24, and 12q14, and losses in chromosomes 9, 10, 13, and 17, have been identified. Elevated expression of insulin-like growth factors in OS tissues has been reported, and the tumor microenvironment plays a crucial role in OS development, involving osteolysis and a positive correlation between aggressiveness and osteolysis levels. This involves a complex interplayof factors, including RANK and RANKL regulation, resulting in a vicious cycle between OS cell proliferation and bone degradation, revealing the highly heterogeneous nature of the OS tumor microenvironment, comprising various cell types such as osteoclasts, osteoblasts, fibroblasts, endothelial cells, and immune cells.

This complexity poses challenges in diagnosis and treatment, with heterogeneous tumors displaying resistance to chemotherapy and an increased risk of relapse and metastasis.

SYMPTOMS AND DIAGNOSIS:

OS typically manifests with localized pain, swelling, tenderness, and inflammation near the affected bone.

The diagnosis and assessment of OS involve a comprehensive approach utilizing medical imaging modalities such as a plain radiograph/X-ray, magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT) scans.

Imaging characteristics of conventional osteosarcoma (COS) commonly reveal permeative bone destruction, mixed lytic/sclerotic appearance, and ill-defined, immature tumor ossifications. Periosteal responses, characterized by reactive new bone formation, are evident, often displaying unique patterns such as perpendicular orientation to the tumor, or sunburst-like divergence. Codman triangles may be observed peripherally, indicating interrupted central periosteal response. Isotope bone scans demonstrate increased activity within osteoblastic tumor areas, reflecting peritumoral hyperemia.

The confirmation of the clincoradiological impression required histopathological examination through microscopic scrutiny of excised tissue obtained by biopsy.

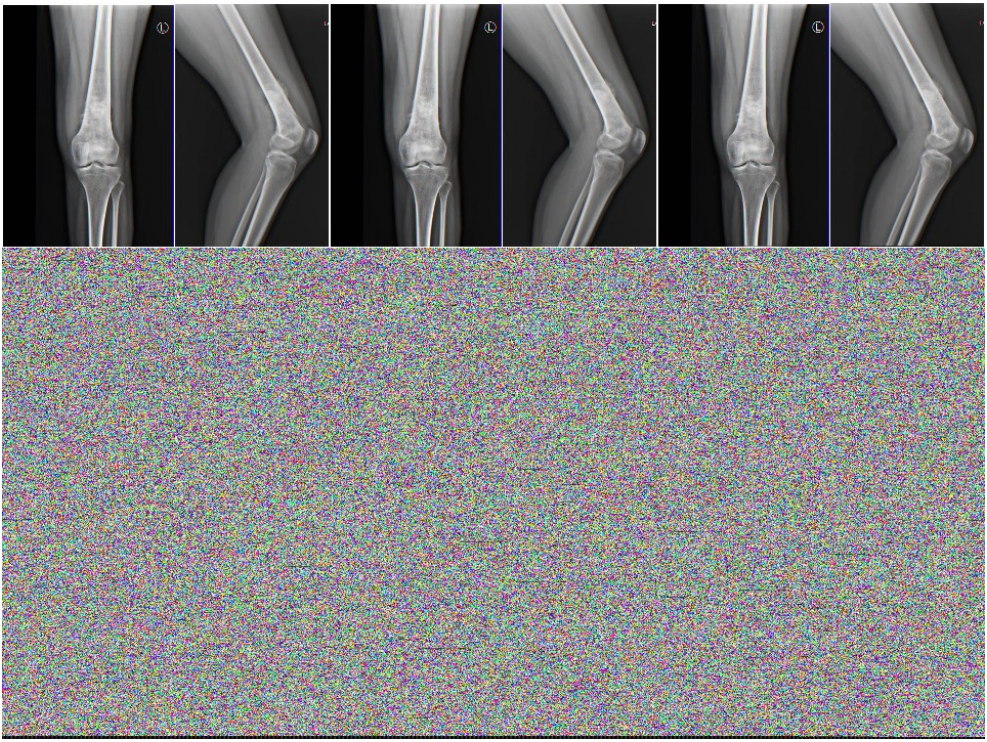


Fig. 1. Plain radiograph (AP and lateral views) showing a sclerotic, destructive lesion in the lower end of femur with abnormal periosteal reaction.

HISTOPATHOLOGICAL SUBTYPES:

1. **CONVENTIONAL OSTEOSARCOMA:** It encompasses three distinct forms: osteoblastic, chondroblastic, and fibroblastic. As the predominant pathological subtype of OS, it constitutes 80% of all cases. This subtype is characterized by a high-grade malignant bone-forming mesenchymal neoplasm that generates osteoid, exhibits high necrosis, and displays several mitotic figures, including atypical mitosis. A crucial diagnostic criterion for COS involves the presence of compelling evidence showcasing bone or osteoid production by the tumor cells within the neoplasm. Conventional osteosarcoma may manifest diverse histopathological patterns, including osteoblastic (76–80%), chondroblastic (10–13%), and fibroblastic (10%) types based on the predominant matrix. Currently, no correlation exists between histological patterns,with regards to treatment, and prognosis.

    - Osteoblastic osteosarcoma contains neoplastic bone as the principal matrix,ranging from thin, "lace-like" trabeculae to compact bone.

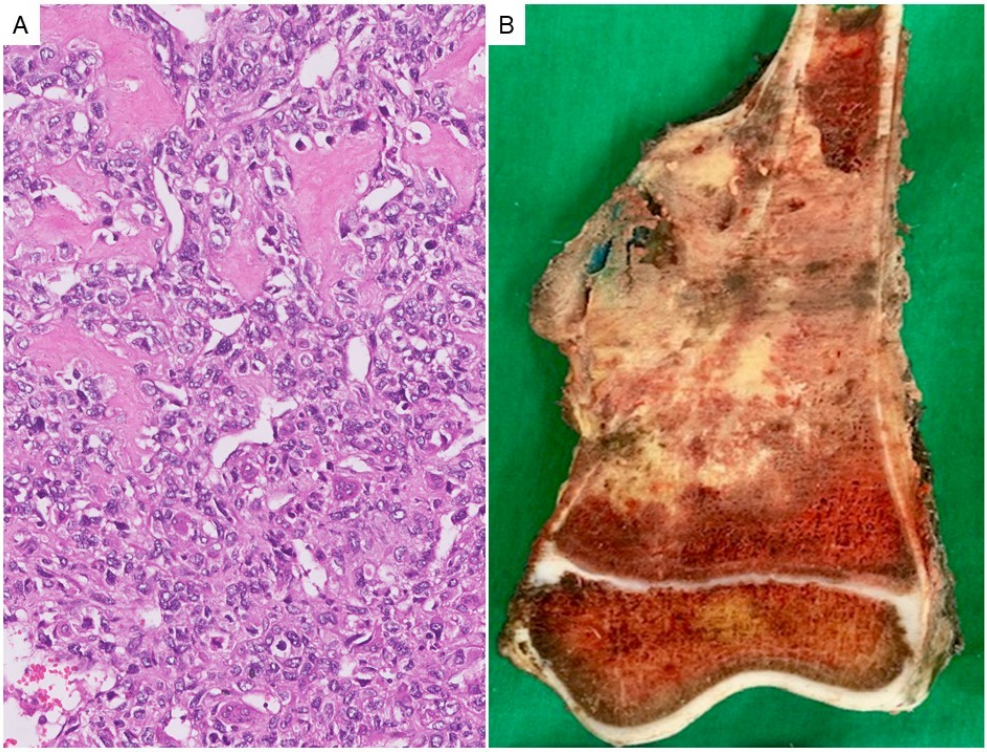


Fig.2. Conventional high-grade osteosarcoma. A. Microscopically, markedly pleomorphic, malignant cells forming "pink" osteoid" with scattered mitotic figures. B. Post-Neo-adjuvant chemotherapy (NACT) resection specimen showing largely residual viable tumor in the metadiaphyseal region with adjacent soft tissue component.

Chondroblastic osteosarcoma predominantly consists of hyaline cartilage with severe cytological atypia. The chondroid matrix may appear myxoid. While trying to differentiated a chondroblastic osteosarcoma from a chondrosarcoma, it is noteworthy that in case a malignant cartilaginous neoplasm is seen in a pediatric patient, it has more chances to be a chondoblastic osteosarcoma than a chondrosarcoma, which is mostly seen in older patients. Of course, radiological correlation is useful in such case scenarios.

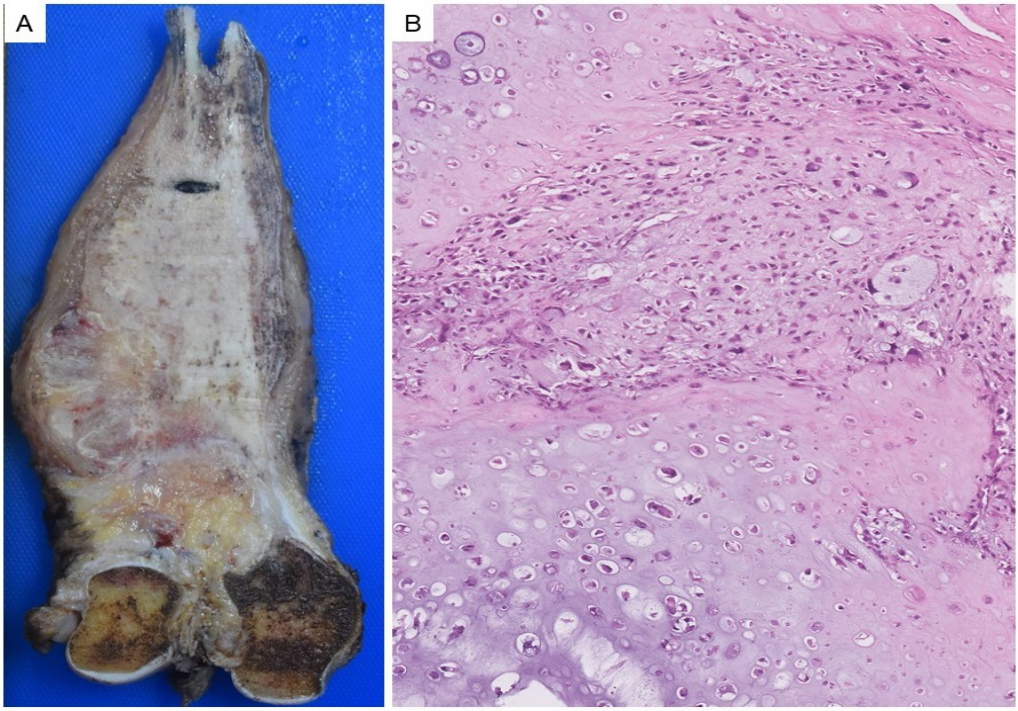


Fig.3. Post NACT resection specimen of an osteosarcoma, showing a glistening to grey-white cut surface. B. Microscopic appearance: Malignant cartilaginous areas, indicative of residual chondroblastic osteosarcoma.

1. **FIBROBLASTIC OSTEOSARCOMA** is characterized by spindle-shaped or epithelioid malignant cells associated with extensive extracellular collagen, often arranged ina fascicular and or storiform growth pattern. In such cases, a differential diagnosis of an intraosseous leiomyosarcoma may be considered. The two tumors can be differentiated by immunohistochemical satins. A leiomyosarcoma will display variable positivity for desmin, SMA and h-caldesmon (any two of these three immunostains need to be positive for the diagnosis).

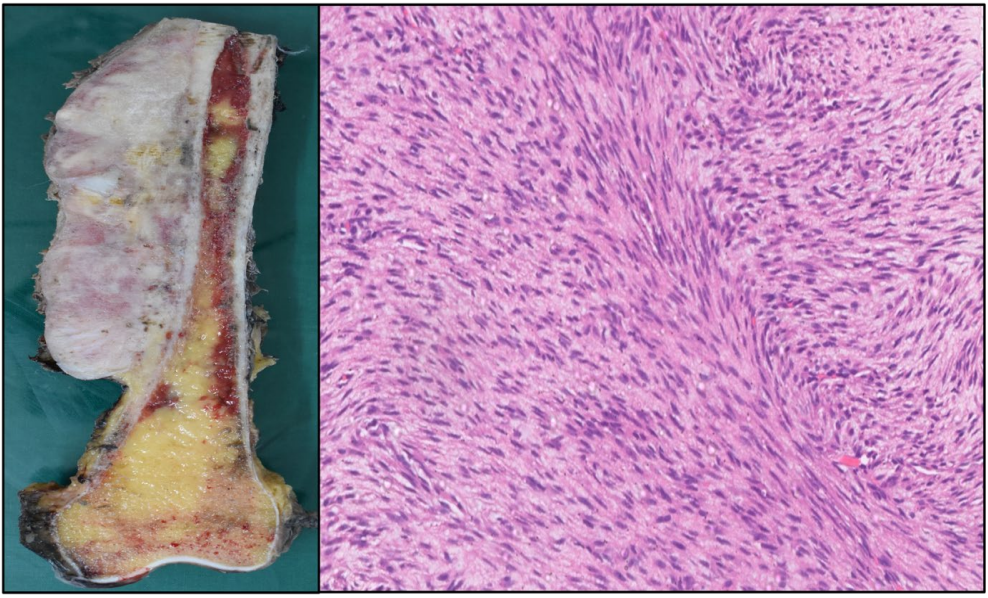


Fig. 4. Cut surface of a resected specimen of a fibrobalsti-type osteosarcoma. A gey-white, fleshy tumor involving the diaphysis with a prominent soft tissue component. Microscopically, malignant spindle cells arranged in a fascicular pattern, lacking osteoid.

2. TELANGIECTATIC OSTEOSARCOMA: It has radiographic and histological similarities to an aneurysmal bone cyst. Typically, this lesion induces radiolucent bone destruction with asymmetric bone expansion, lacking the periosteal neocortex shell commonly seen in aneurysmal bone cysts. An interrupted periosteal reaction may serve as a diagnostic clue. Histopathologically, telangiectatic osteosarcoma consists mainly of blood-filled sinusoids, resembling aneurysmal bone cysts at low power. However, higher magnification reveals nuclear pleomorphism and a high mitotic rate, distinguishing it from the bland sinusoidal lining cells found in aneurysmal bone cysts.Although the presence of bone or osteoid produced by tumor cells aids in diagnosis, the extracellular matrix is often histologically sparse in telangiectatic osteosarcoma.

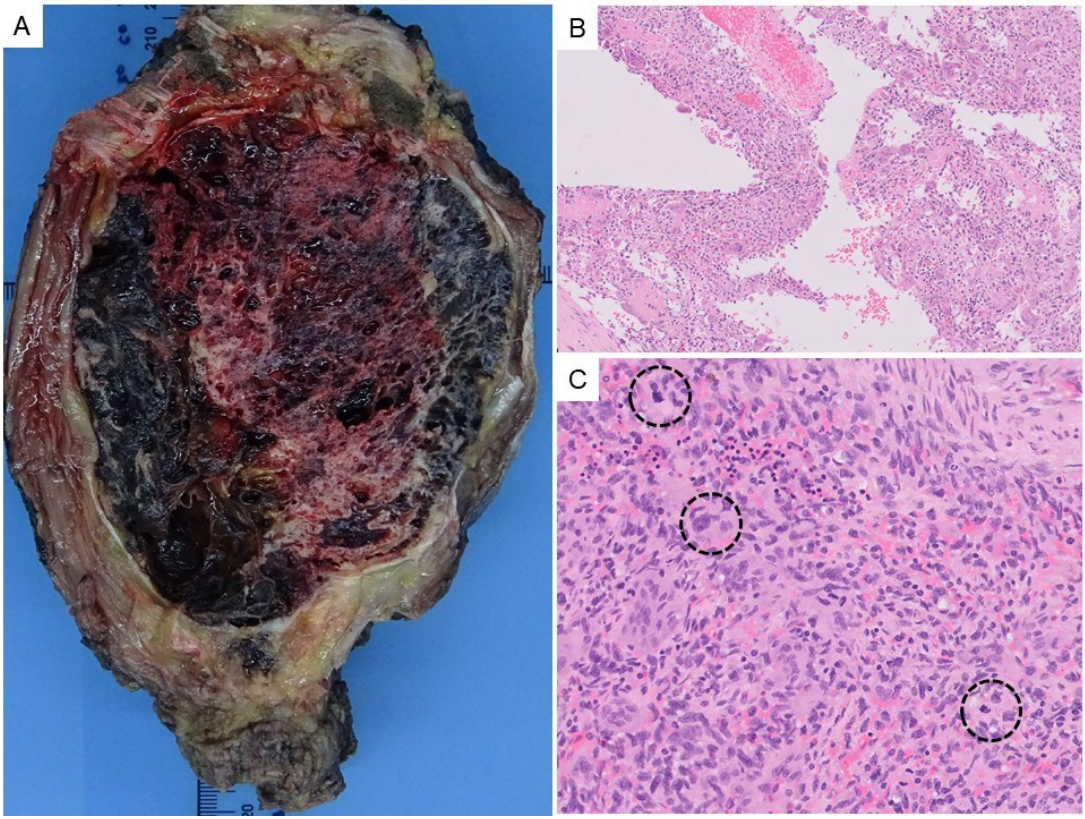


Fig. 5. Resected specimen of a telangiectatic osteosarcoma, showing a cystic cavity with hemorrhagic and necrotic contents. B. Wall-like pseudocystic areas, containing multinucleate osteoclast-like giant cells, reminiscent of an aneurysmal bone cyst-like areas. C. Tumor cells containing markedly pleomorphic cells with interspersed mitotic figures, including atypical forms (circles).

3. SMALL CELL OSTEOSARCOMA: Represents a rare histopathologic subtype of osteosarcoma, displaying a unique combination of histologic features from both osteosarcoma and Ewing sarcoma. Its radiologic features often deviate from the typical presentation of osteosarcoma due to minimal production of mineralized matrix. Histopathologically, it is composed of tumor cells with small-sized, round hyperchromatic nuclei, resembling Ewing sarcoma and lacking the characteristic several/many pleomorphic nuclei of a conventional high-grade osteosarcoma. Higher magnification may reveal spindle-shaped tumor cells, few pleomorphic cells alongwith areas of osteoid formation by the tumor cells, features that are not characteristic of Ewing sarcoma.

Controversies in diagnosing small cell osteosarcoma arise from shared immunohistochemical profiles with Ewing sarcoma, including positive membrane staining for CD99/MIC2. A reciprocal translocation between chromosomes 11 and 22 is commonly found in Ewing sarcoma unlike a small cell osteosarcoma. SATB2 would be diffusely positive in a small cell osteosarcoma, unlike Ewing sarcoma.

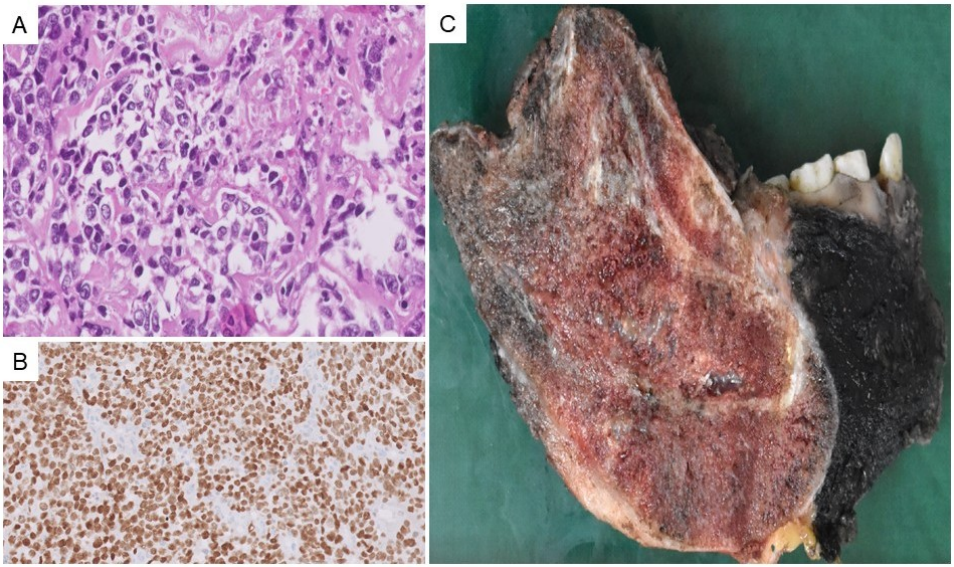


Fig.6. Small cell osteosarcoma. Malignant tumor composed of round to focally pleomorphic cells with intervening thin, branching eosinophilic material. B. Diffuse SATB2 immunostaining. C. Cut surface of the resected tumor showing largely residual, viable tumor.

4. **EPITHELIOID OSTEOSARCOMA:** It's a variant of OS wherein the tumor cells exhibit round or polyhedral rather than spindle-shaped morphology. Enlarged nuclei with one or more prominent nucleoli may be present, and the tumor cells may exhibit cohesive arrangements resembling poorly differentiated carcinomas making histological determination of whether the tumor is a sarcoma, or a carcinomabecomes challenging.

5. **OSTEOBLASTOMA-LIKE AND CHONDROBLASTOMA-LIKE OSTEOSARCOMA:** Osteoblastoma-like osteosarcoma histologically mimics

osteoblastoma by producing microtrabecular bone lined by osteoblasts. The radiographic appearance often suggests malignancy, posing a challenge as osteoblastoma itself may occasionally exhibit signs of malignancy. Complicating matters, some osteoblastomas may contain atypical-appearing osteoblasts, distinguishing this type of osteosarcoma fromosteoblastoma becomes particularly challenging in small biopsy samples. Key histopathologic parameters for malignancy include permeation of architecturally normal bone at the tumor interface and atypical mitotic activity, contrasting with benign osteoblastic tumors showing maturation and circumscription at their edges. Chondroblastoma-like osteosarcoma, is extremely rare, may appear histologically akin to chondroblastoma. The subtle histological differences involve osteoid or bone formation, atypical mitotic activity, and infiltration of adjacent intertrabecular spaces,distinguishing it from chondroblastoma.

6. LOW-GRADE CENTRAL OSTEOSARCOMA: This rare, atypical variant is characterized by a microtrabecular osseous matrix architecture set in a bland fibrous stroma. Its histological features often resemble low-grade parosteal osteosarcoma, and fibrous dysplasia or even be misdiagnosed initially as Paget disease. The accurate diagnosis relies on a thorough correlation with clinical imaging studies and meticulous evaluation of histopathologic findings. Notable imaging characteristics include indistinct circumscription, dense sclerosis, an interrupted periosteal reaction, or cortical infraction. Low-grade osteosarcomas are characterized by MDM2 and CDK4 immunoexpression and corresponding *MDM2* and CDK4 gene amplification.

7. SURFACE OSTEOSARCOMA: Surface osteosarcomas are osteosarcomas with epicentres outside the cortex of the underlying bone. These usually arise in

relation to the periosteum or the cortex of the bone with minimal or no involvement of the medullary cavity. Unlike conventional osteosarcomas, which are tumors of adolescents, these lesions usually arise in patients in the third and fourth decades.

- **Parosteal osteosarcoma**, presents as dense radio-opaque masses on the distal posterior femur, typically occurring a decade later than central osteosarcoma. Radiographically, it exhibits non-uniform density, lacks underlying periosteal reaction, and may have a cellular cartilage cap in 25-30% of cases. It represents low-grade osteosarcoma. Histopathologically, it features parallel bone trabeculae resembling periosteal new bone, with a sclerotic trabecular pattern. The bone formation is likened to "flowing steel wool," occasionally displaying immature osteoid between bone spicules, aiding in its diagnosis. There can be a challenge in differentiating fibrous dysplasia from a parosteal osteosarcoma.The infiltrative nature of the tumor cells constitutes a useful clue. Additionally, parosteal OS is associated with associated with genetic abnormalities, such as the amplification of *MDM2*and *CDK4* oncogenes. On the other hand fibrous dysplasia is associated with *GNAS* mutations.

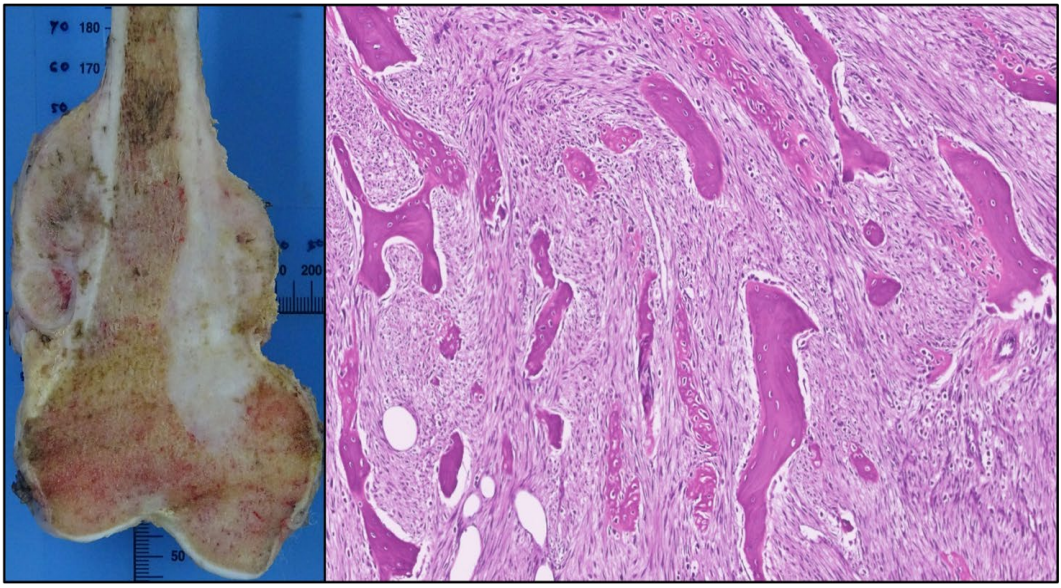


Fig. 7. Parosteal osteosarcoma. Cut surface showing a surface tumor (diaphyseal) with thick periosteal reaction. Microscopic appearance: Infiltrating spindle cells with intervening almost parallel bony trabeculae.

- **Periosteal osteosarcoma** is a rare primary slow growing, intermediate grade malignant bone tumor/sarcoma arising from the inner layer of the periosteum. It presents as a mass positioned between the cortex and the periosteum's cambium layer and often displays radiographically visible periosteal reaction, underlying cortical changes, and typically occurs along the femoral or tibial diaphysis. Histopathologically, the tumor contains osteoid-producing primitive mesenchymal cells between the cartilage lobules.

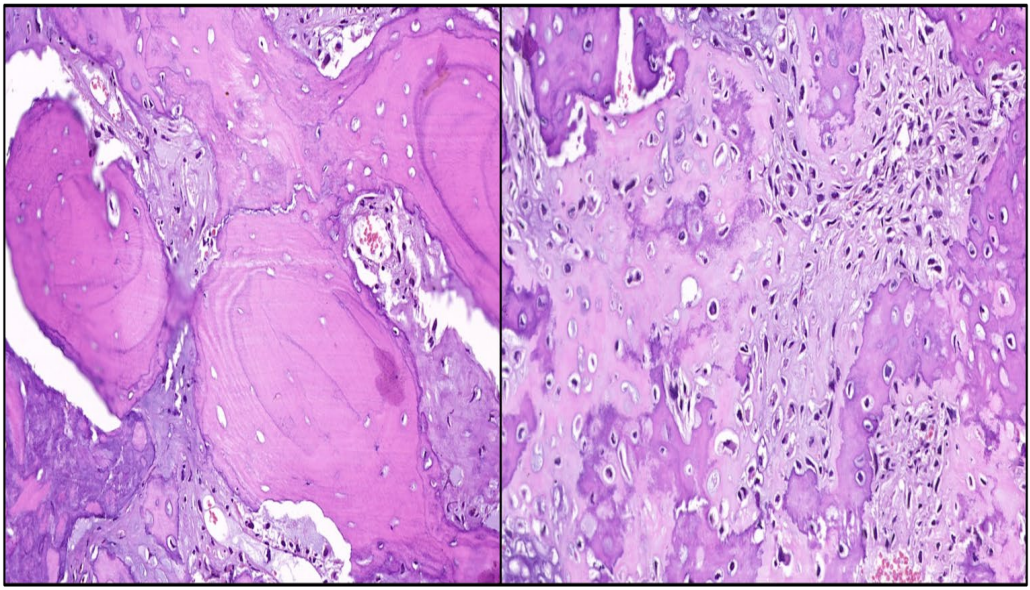


Fig. 8. Periosteal osteosarcoma (post NACT-treated specimen). Microscopic appearance. Maligantn cartilaginus neoplasm causing bone permeation, resembling a chondroblasti osteosarcoma.

- **High-grade surface osteosarcoma**, presents as surface bone lesion, exhibiting accelerated local growth and aggressiveness, leading to more pronounced symptoms compared to usual low-grade parosteal osteosarcomas. Radiographically, it may resemble low-grade parosteal osteosarcoma with dense sclerosis, mixed sclerosis, or occasionally as a soft tissue mass with limited radiodensity and no periosteal reaction suggesting its surface origin and malignant potential akin to conventional osteosarcoma. Microscopically, it is entirely high grade, possibly representing dedifferentiated parosteal osteosarcoma with the high-grade component replacing the low-grade one.

A diagnosis of an osteosarcoma, including its grade is crucial, given most high- grade osteosarcomas are treated with a neo-adjuvant chemotherapy followed by tumor resection. The resection specimen is evaluated for percentage of residual tumor versus treatment-related response.

Fig. 9. Post NACT-treated resection specimen of a high-grade, conventional osteosarcoma showing a dense white area (90% tumor response) in the proximal metadiaphysis of tibia.

Osteogenic Sarcoma

(Osteosarcoma)

Dr RG Wiseman Pinto
Prof and Head Dept of Pathology Goa
Ex Dean Goa University
President Asian Society of Cytopathology
Chairman International Affairs of IAC

Def WHO
Malignant Tumor in which the neoplastic cells produce bone

Age 10 to 25 years
Second peak after 40 y

Sex more in males

Location
De Novo
Long bones
Distal femur proximal tibia .proximal humerus

Site metaphysics

Multicentric
Synchronous or Metachronousv

Genetic
Molecular
Complex karyotype
Translocation
Gain .loss
Multiple chromosomes
TP 53 gene
RB gene

TP 53 pathway
Loss of function mutation in TP53

MDM2 amplification

Cell cycle alteration
CDK4
CDKN2A

Deletion . Amplification of chromosome 3 .6 .8

Risk factors
Pagets disease of bone
Radiations
Chemotherapy
Benign bone disease
Foreign body

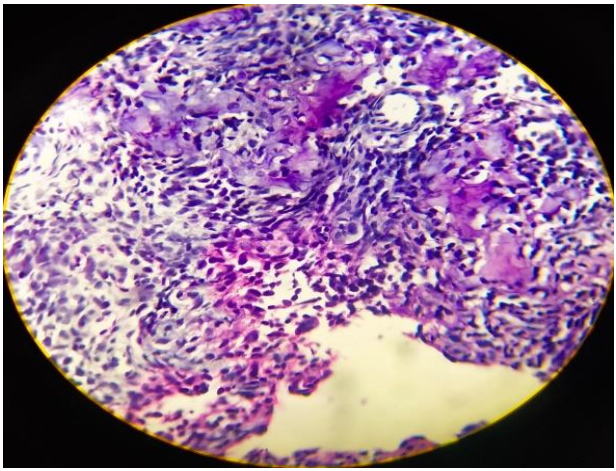
Genetic
Li Fraumeni Syndrome
TP 53 gene mutation
Hereditary Retinoblastoma RB

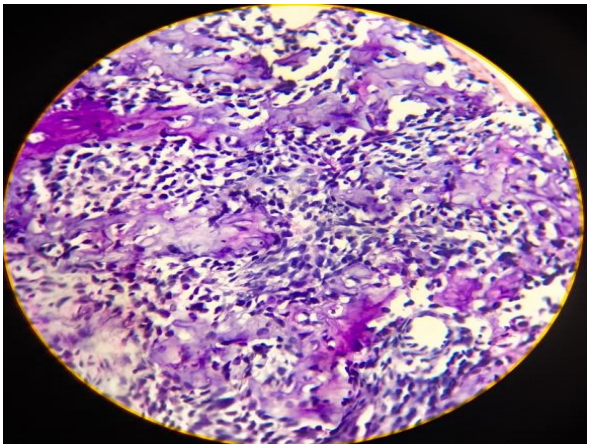
Microscopic types
Conventional
Osteoblastic
Chondroblastic
Fibroblastic
Giant cell rich
Epitheloid
Clear cell

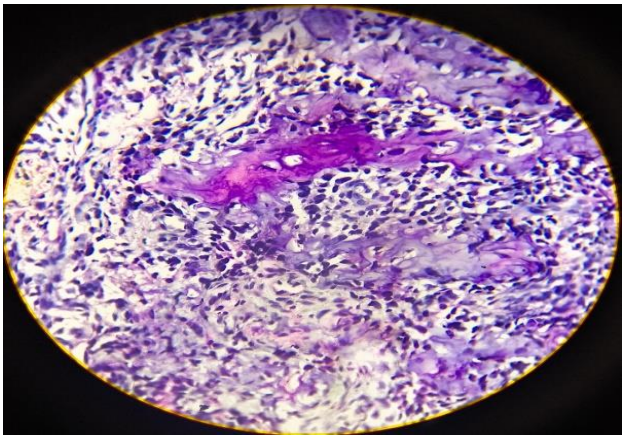
Others
Telangiectatic
Small cell
Low grade
Parosteal
Periosteal
OS of jaws
OS in Pagets

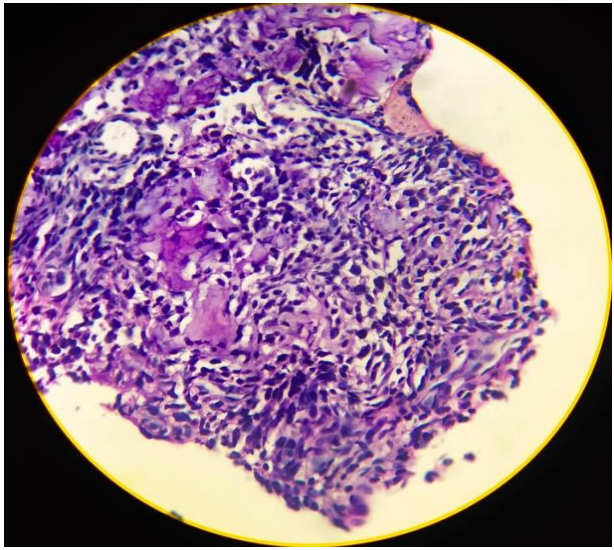
Histochemical
IHC
Alkaline Phosphatase
SATB2
Pitfall CK is expressed

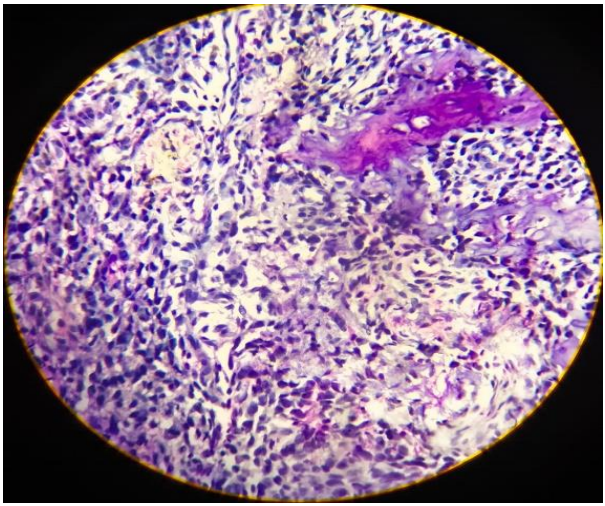
Osteoid formed by the tumor cells
Osteoid may be sparse or massive
Cells bizarre
Arranged in diffuse or nested
Blood vessels
Tumor giant cells
Pleomorhism
Osteoclast giant cells
Cartilage may be present

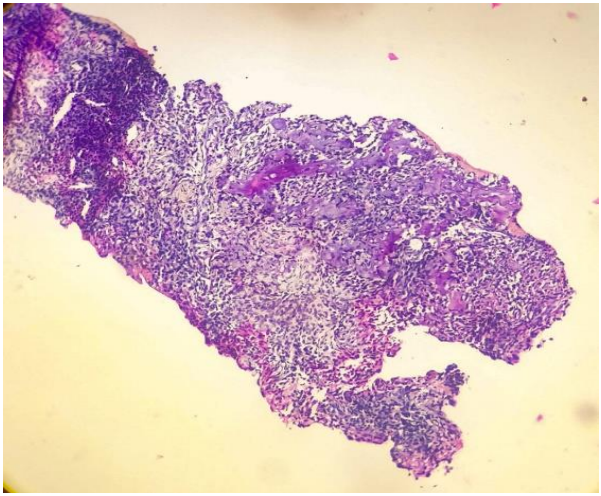


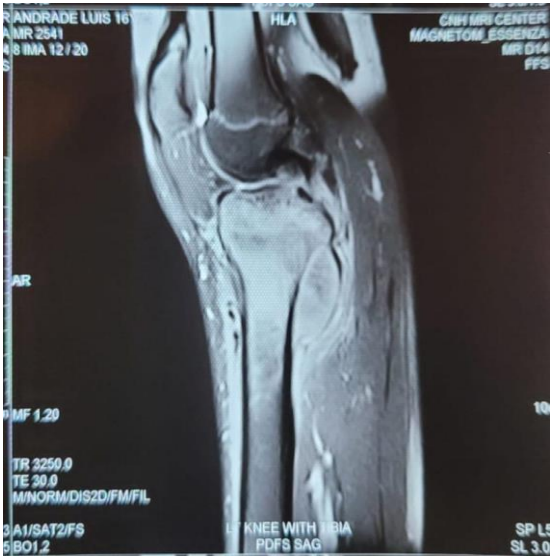








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CNH MRI CENTER
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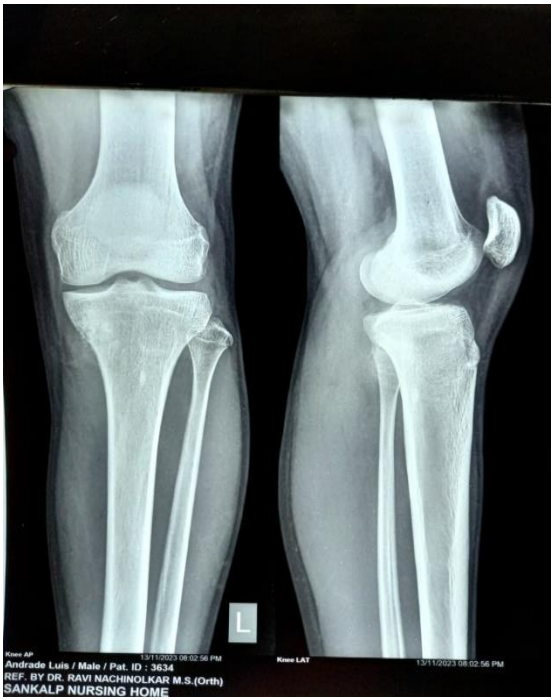
TR 2250.0
TE 30.0
M/NORM/DIS2D/FM/FIL
A1/SAT2/FS
BO1.2
KNEE WITH TIBIA
PDFS SAG
SP L5
SL 3.0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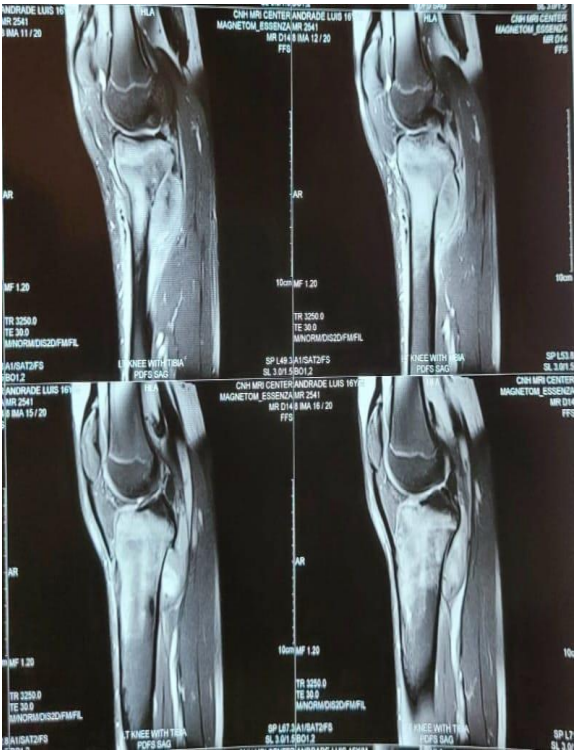
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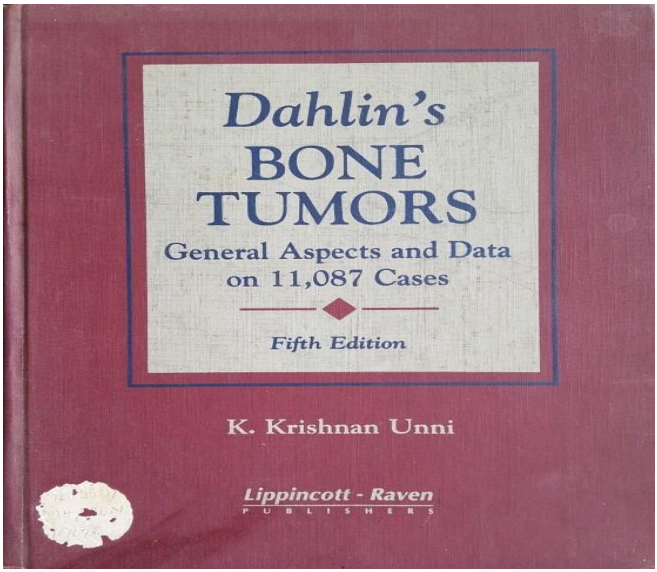
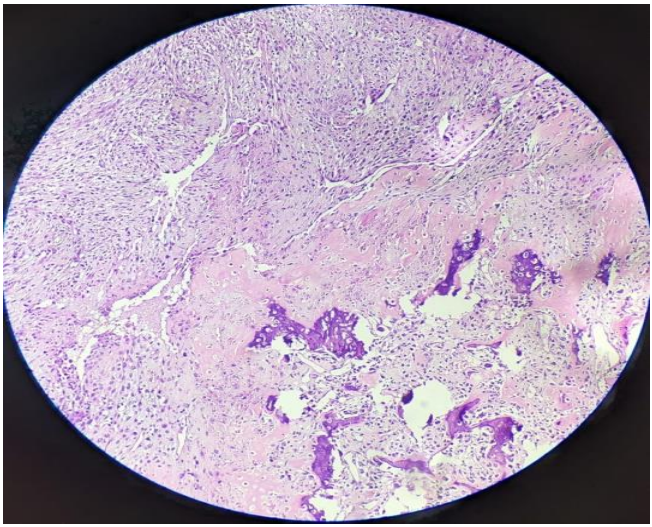

Dahlin's
BONE
TUMORS
General Aspects and Data
on 11,087 Cases
Fifth Edition
K. Krishnan Unni
Lippincott - Raven
PUBLISHERS

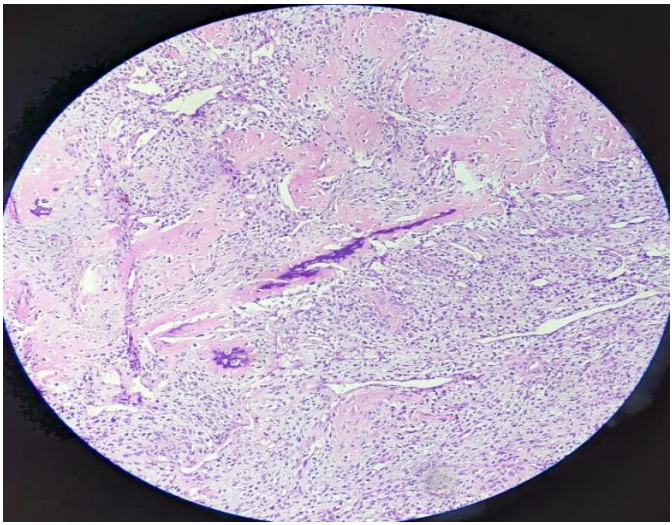
Histologic type	Total cases		Benign		Malignant	
	No.	Percentage (%)	Tumor	No.	Tumor	No.
Hematopoietic	4,443	40.07			Myeloma	3,749
					Lymphoma	694
Chondrogenic	2,420	21.83	Osteochondroma	872	Chondrosarcoma	775
			Chondroma	355	Secondary chondrosarcoma	120
			Chondroblastoma	119	Dedifferentiated chondrosarcoma	120
			Chondromyxoid fibroma	45	Mesenchymal chondrosarcoma	34
Osteogenic	2,136	19.27	Osteoid osteoma	331	**Osteosarcoma**	**1,694**
			Osteoblastoma	87	Parosteal osteosarcoma	69
Unknown	1,149	10.36	Giant cell tumor	568	Ewing's sarcoma	512
					Malignancy in giant cell tumor	35
					Adamantinoma	34
Histiocytic	92	0.83	Fibrous histiocytoma	9	Malignant fibrous histiocytoma	83
Fibrogenic	268	2.42	Hamartoma	1	Desmoplastic fibroma	12
					Fibrosarcoma	
Notochordal	356	3.21			Chordoma	356
Vascular	201	1.81	Hemangioma	108	Hemangioendothelioma	80
					Hemangiopericytoma	13
Lipogenic	8	0.07	Lipoma	7	Liposarcoma	1
Neurogenic	14	0.13	Neurilemoma	14		
Total	11,087	100.00		2,496		8,591

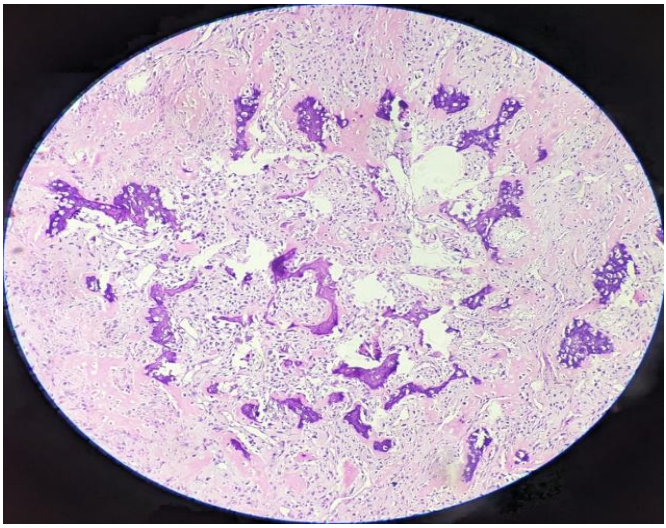
TABLE 11-1. *Types of osteosarcoma*

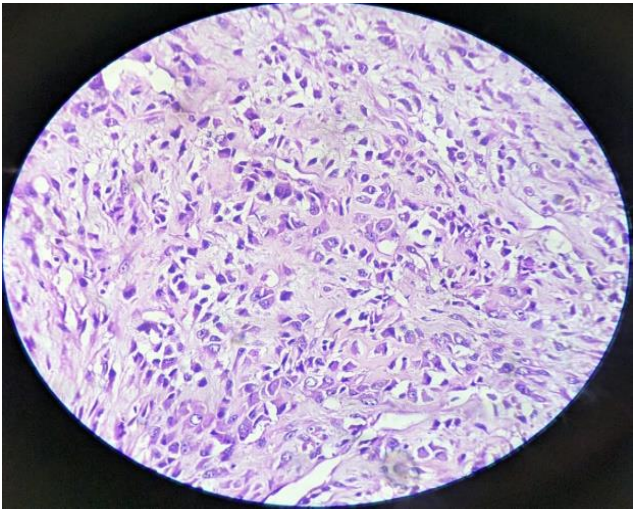
Type		Number of cases
Conventional osteosarcoma		1,240
Others		409
Osteosarcoma of jaw	109	
Osteosarcoma in Paget's disease	54	
Postradiation osteosarcoma	89	
Osteosarcoma in benign conditions	14	
Telangiectatic osteosarcoma	57	
Small cell osteosarcoma	22	
Low-grade osteosarcoma	20	
Multicentric osteosarcoma	6	
Periosteal osteosarcoma	26	
High-grade surface osteosarcoma	12	
Parosteal osteosarcoma		69
In dedifferentiated chondrosarcoma		68
Total		1,786

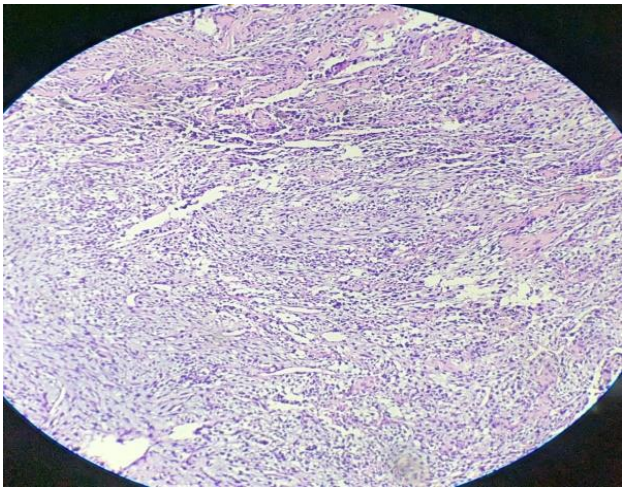
Slides referred from Dr.Nicette outside of Goa Medical College.

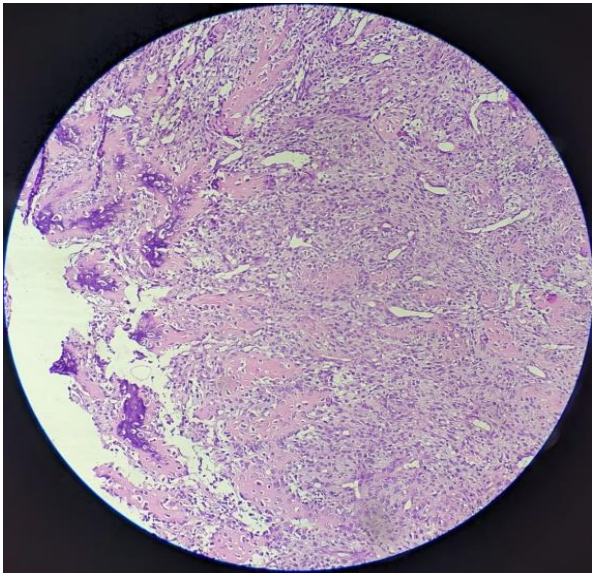


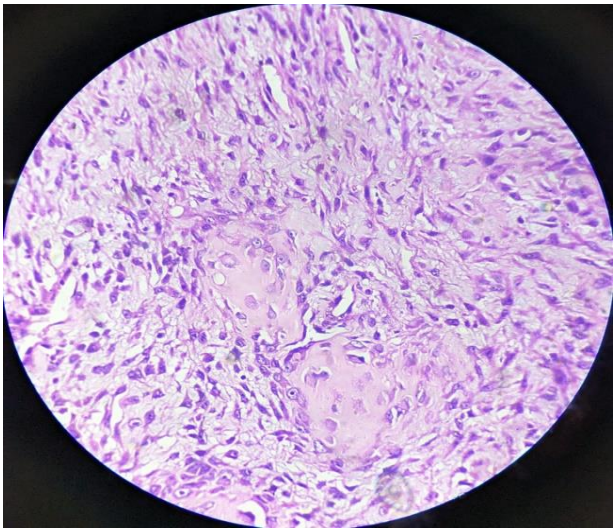


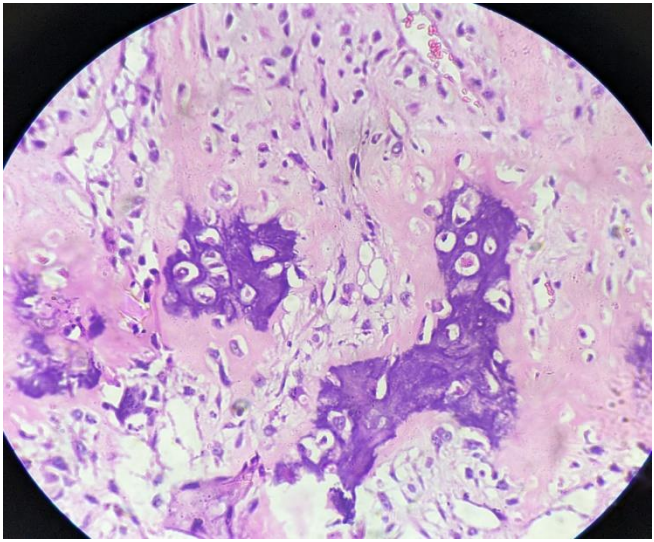












Osteosarcoma

By: Lon Furtado

Osteosarcoma is a malignant bone tumor characterized by the production of osteoid by malignant cells. It ranks as the second most common primary malignant bone tumor, constituting around 20% of primary bone cancers. Although it can affect individuals of any age, primary high-grade osteosarcoma is most prevalent in the second decade of life. The overall incidence is approximately 1:3 per 1 million per year.

Etiology and Risk Factors: The etiology of osteosarcoma remains unclear, and genetic factors rarely play a significant role. However, it may be more common in individuals with hereditary conditions like retinoblastoma, Rothmund-Thomson syndrome, and Li-Fraumeni syndrome. Secondary osteosarcomas can occur in association with Paget disease or following radiation therapy. Incidence is slightly higher in males, with exceptions for certain subtypes. All Skeletal locations may be affected, however, most primary osteosarcomas occur at sites of the most rapid bone growth, including the distal femur, the proximal tibia and the proximal humerus

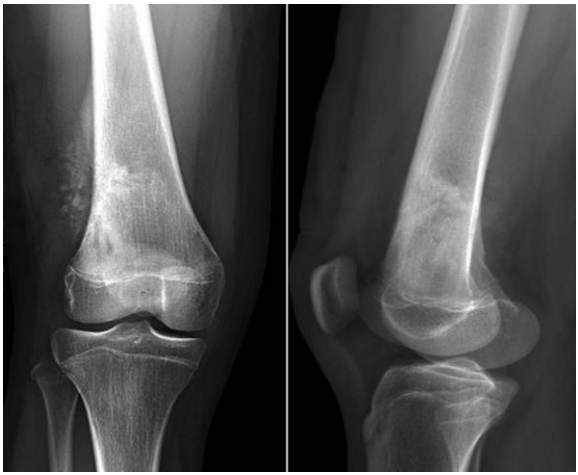
Presenting Features: Patients with high-grade osteosarcoma commonly experience progressive pain, often misdiagnosed initially as a musculoskeletal problem. Night pain can be a crucial indicator, though only a quarter of patients exhibit this symptom. Delayed diagnosis is common, with an average delay of approximately 15 weeks, attributed to factors such as failure to obtain early radiographs.

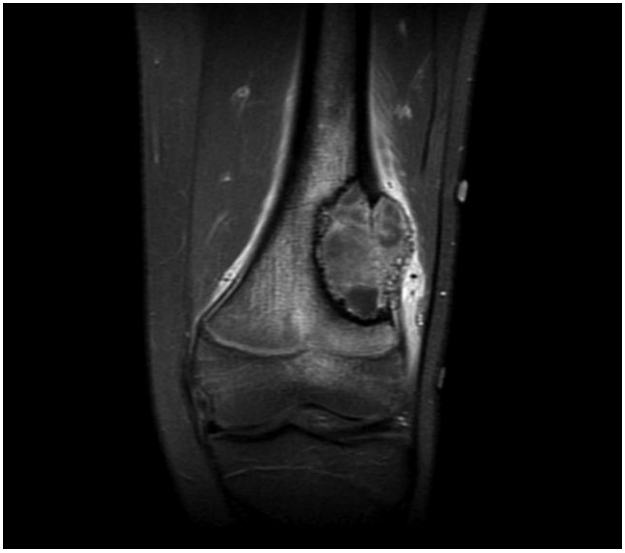
Diagnosis: Plain radiographs are crucial for diagnosing osteosarcoma, revealing an aggressive lesion in the metaphysis of long bones. The tumor may be predominantly blastic or lytic, with ill-defined permeative borders. If the tumor has broken through the cortex, a soft-tissue mass may be present at the time of diagnosis. Periosteal reaction may take the form of a "Codman triangle," or it may have a "sunburst" or "hair-on-end" appearance.Magnetic resonance imaging (MRI) is valuable for assessing tumor extent and to determine the relationship of the tumor to nearby anatomic structures., while bone scans and chest radiography/CT aid in identifying metastases. Biopsy is essential for categorization.

Classification: Osteosarcomas are classified as primary or secondary. Primary osteosarcomas include conventional, low-grade intramedullary, parosteal, periosteal, high-grade surface, telangiectatic, and small cell osteosarcomas. Secondary osteosarcomas arise in the context of other diseases, with Paget disease and previous radiation therapy being common factors.

Management: Historically, prognosis for osteosarcoma was poor, but modern treatment includes neoadjuvant chemotherapy, wide or radical surgery, and adjuvant chemotherapy. Pulmonary metastases are resected post-chemotherapy. The histologic response to neoadjuvant chemotherapy predicts long-term survival. Patients with relapse may require aggressive treatment, with factors like rapid relapse and unresectable pulmonary nodules indicating a poorer prognosis.

In summary, osteosarcoma, though rare, requires prompt diagnosis and comprehensive management involving a multidisciplinary approach for optimal outcomes.





Case Discussion

Osteosarcoma

By Dept Of Orthopaedics

Dr Zelio D'Mello

Dr Prabhav Dessai

Patient Details

- Name – Andrade Luis
- Age – 16 years
- Sex- Male

Chief Complaints

- H/o pain and swelling in left leg since 3 months
- Decreased movement in left knee since 1 month

History of Presenting Illness

- Patient was apparently alright 3 months ago after which he started developing pain in his left leg around the knee and then started noticing a swelling there after a few days
- Sudden in onset and progressive in nature
- Severe Intensity of pain
- Sharp stabbing type of pain localised to left leg without any radiation
- Patient started getting restriction of movement due to pain after 2 months of symptoms
- H/o weight loss present
- No h/o trauma, fever, lifting heavy weights

Other Common Features:

- Lymphadenopathy - unusual focal & regional lymph node involvement.
- Respiratory complaints and finding - late stage with lung metastasis.
- Fever & night sweats are rare.

Past History

- No h/o admissions in past or previous significant injury to affected leg previously

Family History

- No significant family history

Personal History

- Mixed diet
- Bowel and bladder habits regular

General Physical Examination

On admission –

- Pt was well nourished moderately built
- Capillary Refill Good
- Toe movements and sensations intact
- PICCLE – Absent

Vitals

- PR – 92
- Afebrile
- BP – 110/70
- RR – 14

Local Examination

Inspection

- Ill defined Swelling noted over proximal anterolateral aspect of tibia
- Knee kept in 70 degrees of flexion
- Skin over swelling appeared normal

Palpation

- Tenderness +
- 5x3cm
- Local rise in temperature +
- Distal pulsations palpable and sensations intact
- ROM of knee – Restricted Extension painful
- ROM of ankle – Full
- No limb length discrepancy noted

Skeletal Distribution

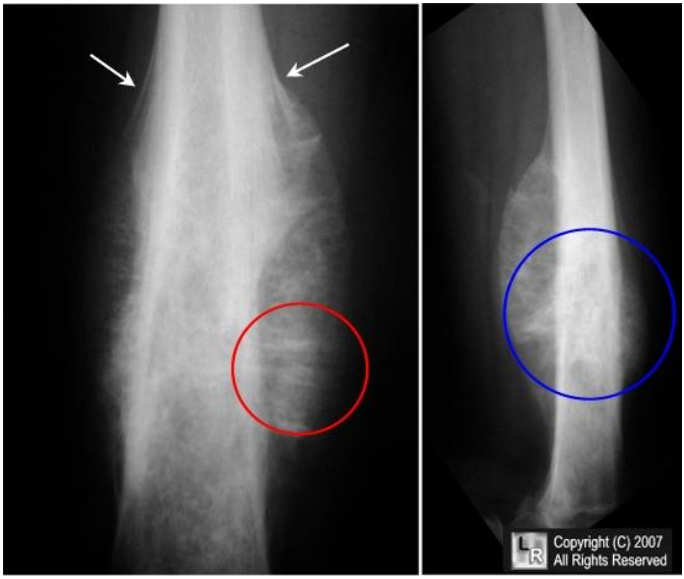
- Distal femur
- Proximal tibia
- Proximal humerus
- Others (sites of rapid bone growth)
- Metaphyseal(89%)>diaphyseal(10%)>epiphyseal(1%)

Etiology

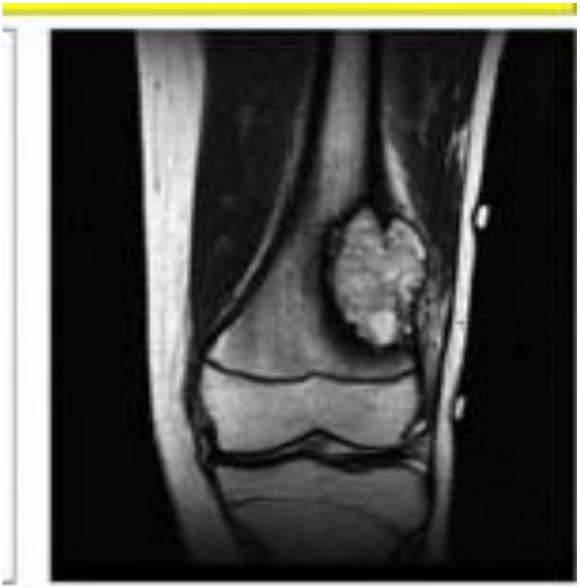
- Classified broadly into two types – Primary and Secomdary
- Rapid bone growth - adolescence growth spurt in the metaphyseal area near the growth plate.
- Genetic predisposition
    - hereditary form of retinoblastoma(RB gene mutation)
    - Li-Fraumeni syndrome (p53 gene mutation)
    - Rothmund - Thomson syndrome (autosomal recessive)
- Radiation exposure - mostly causes secondary forms.
- Other secondary forms most commonly associated with a pre-malignant condition
- Paget's disease of bone - mostly secondary forms.

Diagnostic Workup

- Biopsy of primary site for diagnosis and staging:
    - Core needle biopsy:
    - Open (surgical) biopsy:
- Lactate dehydrogenase (Higher levels of LDH indicate poor prognosis), alkaline phosphatase
- Plain x-ray of the affected bone
    - Demonstrates destruction of the normal trabecular bone with lytic and/or sclerotic lesions/Sometimes Mixed lesions, osteoid formation under the periosteum (Codman triangle)



MRI- know the extent of the lesion, evaluate any soft tissue component, and involvement of joint, nerves, and vasculature
The entire affected bone should be imaged to evaluate for the presence of skip lesions.
Metastatic work up
CT scan of the chest and bone scan to evaluate pulmonary and bone metastases
Positron emission tomography (PET) scan can be used as an alternative for systemic staging



Modes of Treatment

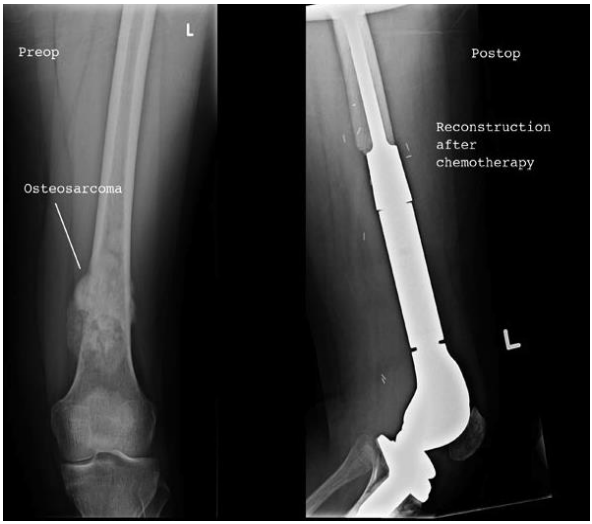
- Surgical
- Radiotherapy
- Chemotherapy
- Immunotherapy

Surgical Management

- Mainstay of surgical management is the complete en bloc resection of tumor
- Limb-sparing resections with maintenance of function preferred over amputation
- Limb salvage procedures now can provide rates of local control and long-term survival equal to amputation

Limb Salvage Surgery

- Removing the tumor with a wide margin of normal tissue surrounding it while preserving vascular and nerve supply to the extremity.
- Principle is to eradicate the bone tumor, retain integrity of skeletal system and preserve the limb with useful function.
- After resection, skeletal reconstruction done by bone grafting(auto or allograft) or by endoprosthesis (modular or custom made).
- Prosthetic reconstruction is more effective
- As compared to the radical amputation and external prosthetic fitting or limb sparing surgery with bone grafting this treatment is more effective in early mobilization.



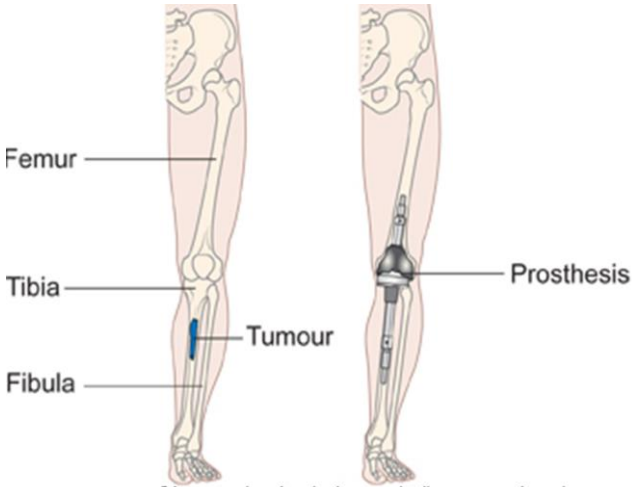


Diagram showing before and after surgery for a tumour in the tibia witha prosthesis replacing the bone

Chemotherapy

- Chemotherapy is indicated prior to wide local excision in high-grade osteosarcoma
- Adjuvant chemotherapy should be given after surgery
- Neoadjuvant therapy is given for two cycles followed by four cycles of adjuvant chemotherapy
- Cisplatin + doxorubicin are the mainstays of therapy:
- Cisplatin 100-120 mg/m2 IV + doxorubicin 60-75 mg/m2 IV over 48-hour continuous infusion every 3 weeks + G-CSF

Radiotherapy

- Historically, radiation has been used for the treatment of osteosarcoma
- Due to improved results with chemotherapy and surgery combined, RT is rarely used
- Indications for RT
    - Incompletely resected tumors with positive margins
    - Unresectable tumors
    - Palliation of symptoms

Immunotherapy

- Portion of the tumour is implanted in sarcoma survivor & is removed after 14 days.
- The sensitised lymphocytes from the survivor are infused into the patient.
  These cells selectively kill the cancer cells