International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 13; Issue: 8; August 2026
Website: www.ijrrjournal.com
Review Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Osteosarcoma: A Comprehensive Literature Review on Epidemiology, Pathogenesis, Diagnosis, and Evolving Therapeutic Strategies

Dominicus Dimitri[1], Komang Septian Sandiwidayat[2]

[1]Resident, Dept. Orthopaedic & Traumatology, Faculty of Medicine, Udayana University, Bali, Indonesia
[2]Orthopaedic Surgeon, Dept. Orthopaedic & Traumatology, Faculty of Medicine, Udayana University, Bali, Indonesia

Corresponding Author: Dominicus Dimitri

DOI: https://doi.org/10.52403/ijrr.20260801

ABSTRACT

Osteosarcoma is the most common primary malignant bone tumor, predominantly affecting adolescents and young adults. Advances in therapeutic strategies, including neoadjuvant chemotherapy, surgery, and limb reconstruction, have significantly improved the 5-year survival rate for non-metastatic cases to 60–70%, compared to historical rates of only 10–20%. Key prognostic factors include histological response to preoperative chemotherapy, alkaline phosphatase levels, and lactate dehydrogenase. However, prognosis remains poor for patients with metastases, particularly pulmonary metastases, or tumors located in the pelvis and axial skeleton. Data from Indonesia reveal relatively low survival rates, with a mean survival of only 28 months, indicating limited access to optimal treatment. Recent research developments, such as gene therapy, immunotherapy, and advanced reconstructive techniques, hold promises for improving therapeutic outcomes and patient quality of life in the future.

Keywords: Osteosarcoma, neoadjuvant chemotherapy, prognosis, limb reconstruction, gene therapy.

INTRODUCTION

Osteosarcoma is a highly aggressive malignant tumor originating from mesenchymal cells, characterized by spindle-shaped stromal cells that produce osteoid or bone-like tissue.[1] It is the most common form of primary malignant bone tumor, accounting for approximately 20% of all cases, and predominantly affects young patients.[2] The mortality rate of osteosarcoma remains high, particularly in developing countries. In contrast, developed countries benefit from a wide range of treatment options, greater public awareness of early medical consultation, and stronger trust in modern medical interventions.

In developing countries such as Indonesia, the challenges in osteosarcoma management are multifaceted. These include limited access to advanced treatment modalities, high costs associated with medical care and surgical procedures, and socioeconomic factors that often delay diagnosis and treatment. Moreover, many patients tend to seek alternative or traditional therapies as the first line of treatment, resulting in late presentation and advanced disease at the time of medical evaluation.

Bones, particularly long bones, play a critical role in human biomechanics as the structural framework that bears mechanical loads and functions as levers for skeletal

muscle locomotion. Malignancy in the bone often leads to significant disability, severe morbidity, and, in many cases, mortality. The unclear etiology and poor prognosis of osteosarcoma emphasize the urgent need for ongoing research in pathology, genetics, molecular biology, and surgical techniques to improve patient outcomes by reducing disability, morbidity, and mortality.[1,2]

A comprehensive understanding of osteosarcoma, including its pathophysiology, clinical manifestations, diagnostic approaches, and treatment strategies—is essential for optimizing patient management, from early diagnosis and non-pharmacological interventions to surgical treatment.

This paper aims to provide a detailed overview of osteosarcoma, including the latest advancements in its management. It is hoped that this work will enhance both the author's and readers understanding, contributing to further education and knowledge development in this field.

METHODS

Study Design

This study is designed as a narrative literature review aimed at summarizing current knowledge and recent advancements in the understanding and management of osteosarcoma. The review focuses on epidemiology, pathophysiology, diagnostic approaches, treatment modalities, and clinical outcomes, with a particular emphasis on challenges faced in developing countries, such as Indonesia.

Search Strategy

A comprehensive literature search was conducted using electronic databases, including PubMed, ScienceDirect, Scopus, and Google Scholar, covering publications from 2000 to 2025. Search terms included: "osteosarcoma," "pathophysiology of osteosarcoma," "diagnosis of osteosarcoma," "osteosarcoma treatment,", "limb salvage surgery in osteosarcoma," and "osteosarcoma in developing countries." Boolean operators (AND/OR) were used to refine search queries (e.g., *"osteosarcoma AND chemotherapy," "osteosarcoma AND surgical management"*).

Eligibility Criteria

The review included:

- Peer-reviewed original articles, systematic reviews, meta-analyses, and clinical guidelines.
- Studies published in English or Indonesian.
- Research involving human subjects focusing on clinical aspects of osteosarcoma.
- Studies were excluded if they were case reports with insufficient data, preclinical studies with animal models only, or non-peer-reviewed sources such as conference abstracts or editorials.

Data Extraction and Analysis

Relevant data were extracted and organized into thematic categories, including epidemiology, clinical presentation, imaging, histopathology, treatment strategies (chemotherapy, surgical options, and reconstruction techniques), and survival outcomes. Key findings were synthesized and compared across studies to highlight consensus, differences, and emerging trends. No statistical meta-analysis was performed, as the aim of this review was qualitative synthesis.

Quality Assessment

The quality of included studies was assessed using adapted checklists from the Joanna Briggs Institute (JBI) and the PRISMA guidelines for literature reviews. Only studies with moderate to high methodological quality were included in the final synthesis.

RESULTS AND DISCUSSION

Definition of Osteosarcoma

Osteosarcoma, often referred to as osteogenic sarcoma, is a primary malignant bone tumor characterized by the direct formation of immature bone or osteoid tissue by tumor cells. As its name suggests,

being a sarcoma, this tumor originates from mesenchymal cells.[3,5] Histologically, the WHO classifies osteosarcoma into several types; however, the term osteosarcoma most commonly refers to the high-grade, central type, which is the most frequently found variant.[6] According to Campanacci and Enneking, osteosarcoma must be distinguished from several other tumors due to its highly variable pathological features, such as:[3]

- **Fibrosarcoma** – spindle cell and collagenogenic appearance
- **Malignant fibrous histiocytoma** – histio-fibroblastic areas with a storiform pattern
- **Chondrosarcoma** – produces cartilaginous matrix
- **Aneurysmal Bone Cyst** – telangiectatic appearance with giant cells
- **Ewing's Sarcoma** – small round cell appearance

Epidemiology of Osteosarcoma

In an epidemiological study by Campanacci, osteosarcoma accounted for 15% of all biopsied primary bone tumors. Among primary malignant bone tumors, it ranks second in frequency after multiple myeloma. The incidence of classical osteosarcoma is 3 cases per million population per year, representing 0.2% of all malignant tumors. Approximately 75% of osteosarcoma cases occur in patients aged between 15 and 25 years. Males are more frequently affected than females, with a ratio of 1.5:1. Osteosarcoma is rare in patients under 6 years of age or over 60 years. Bone tumors in older individuals are usually secondary bone tumors, such as Paget's disease or undifferentiated chondrosarcomas caused by radiation.[3]

Overall, 80% to 90% of osteosarcomas occur in long tubular bones. The axial skeleton (skull, facial bones, spine, ribs, and sternum) is rarely affected, and when present, it is more frequently found in adults. The femur, tibia, and humerus account for approximately 85% of extremity tumors, while less than 1% are found in the bones of the hands and feet. In long bones, osteosarcoma usually arises from the metaphysis. Tumors originating from the diaphysis are rare, and those from the epiphysis are extremely rare. Epidemiological studies on osteosarcoma are highly useful for diagnosis, as classifications based on factors such as age groups and predilection sites assist clinicians in establishing a diagnosis of malignant bone tumors.[3]

A recent cohort-based study covering data from 1975–2017 and 2000–2017, with a wide racial scope, found that 86% were primary osteosarcoma cases, while 14% were secondary osteosarcomas. Among age groups, primary osteosarcoma peaked in the 10–24 years age group, whereas secondary osteosarcoma peaked in the 80–84 years age group. Interestingly, in this study, male osteosarcoma cases peaked twice—during youth and again in older age—while this second peak was not observed in females.[7]

Most cases across all age groups involved long bones of the lower extremities, followed by long bones of the upper extremities, while the least frequent predilection site was short bones of the upper extremities in all age groups. Table 1 shows that the frequency of osteosarcoma in axial bones increases with age, with the pelvis being the most common site in individuals over 60 years. This information helps clinicians prevent diagnostic errors when osteosarcoma is found at non-extremity long bone locations in patients over 25 years of age. Histological findings of primary and secondary osteosarcoma remain unclassified. The study also reported that osteosarcoma was most prevalent among Black individuals, followed by Hispanic individuals.[7]

The incidence trends of osteosarcoma over the past five decades are also noteworthy. Osteosarcoma in young patients (0–9 years) has doubled over the past four decades. However, the 5-year survival rate after osteosarcoma diagnosis has significantly improved, particularly in younger patients,

reflecting advancements in osteosarcoma management that have benefited patients.[7]

Table 1. Frequency of primary osteosarcoma by age and location (SEER cohort data, 2000–2018)

Tumor Location	0–9 years (n/%)	10–24 years (n/%)	25–59 years (n/%)	>60 years (n/%)	All Ages (n/%)
Long bones of upper extremities	59 (16.7%)	267 (12.3%)	117 (10.7%)	37 (9.7%)	480 (12.0%)
Short bones of upper extremities	2 (0.6%)	13 (0.6%)	9 (0.8%)	4 (1.0%)	28 (0.7%)
Long bones of lower extremities	267 (75.6%)	1591 (73.5%)	538 (49.2%)	138 (36.0%)	2534 (63.4%)
Short bones of lower extremities	7 (2.0%)	37 (1.7%)	26 (2.4%)	10 (2.6%)	80 (2.0%)
Vertebral column	1 (0.3%)	26 (1.2%)	41 (3.7%)	31 (8.1%)	99 (2.5%)
Chest area	1 (0.3%)	28 (1.3%)	42 (3.8%)	21 (5.5%)	93 (2.3%)
Pelvis	3 (0.8%)	121 (5.6%)	121 (11.1%)	68 (17.9%)	313 (7.8%)
Mandible	2 (0.6%)	43 (2.0%)	96 (8.8%)	36 (9.4%)	177 (4.4%)
Face or skull	11 (3.1%)	39 (1.8%)	104 (9.5%)	38 (9.9%)	193 (4.8%)
Total	353	2165	1094	383	3997

Epidemiological studies indicate that metastases are more common in the elderly population (>60 years). In younger patients, metastatic cases are found in 18–22% of cases, whereas in older patients, this figure rises to 33.3%. Metastatic cases are most commonly found in tumors located in axial bones, particularly the pelvis.[7,8]

Etiology of Osteosarcoma

To date, the exact cause of osteosarcoma remains unknown. Numerous studies have attempted to identify the precise cause, but no definitive conclusions have been made. Factors considered to contribute to osteosarcoma include viral infections, radiation exposure, and genetics.[5]

Genetic factors are believed to play a role in the development of osteosarcoma due to the high incidence of osteosarcoma in patients with hereditary retinoblastoma. Furthermore, children with osteosarcoma often have mutations in the p53 gene.9 Osteosarcoma is more commonly observed in Black patients (of African descent), which has been linked to genetic factors, as TP53 gene mutations are frequently found in individuals of African ancestry.[7]

Pathogenesis of Osteosarcoma

Normal Bone Biology

Bone consists of four main cell types: osteoblasts, osteoclasts, osteocytes, and bone lining cells. The bone microenvironment also includes cartilage surrounding the bone, composed of chondrocytes, endothelial cells, and fibroblasts forming the bone stroma, as well as hematopoietic and mesenchymal stem cells derived from bone marrow. Mesenchymal stem cells are precursors of osteoblasts, osteocytes, fibroblasts, and chondrocytes.[9,10]

Stem cells differentiate in response to the presence or absence of various transcription factors. Peroxisome proliferator-activated receptor gamma (PPARγ) promotes differentiation of mesenchymal stem cells into adipocytes, while Runt-related transcription factor 2 (Runx2) and sex determining region Y-box transcription factor 9 (SOX9) promote differentiation into osteochondroprogenitor cells. These cells regulate osteoblast and bone matrix formation and recruit hematopoietic cells for vascularization. Altering transforming growth factor-beta (TGFβ) expression can further promote differentiation into chondrocytes, while also stimulating alkaline phosphatase (ALP) activity and calcium deposition.[9,10]

Runx2 is a transcription factor that induces the expression of a series of osteogenesis-

related genes. Runx2 upregulates osterix (Sp7), which is necessary for osteochondroprogenitor cells to differentiate into osteoblasts; as well as osteocalcin, Type I collagen, and ALP to stimulate osteoblast formation. Finally, Runx2 induces expression of CDK2 inhibitor p27KIP1, coordinating cell cycle arrest of osteoblasts at G1, which is essential for normal bone development. Importantly, Runx2 and ALP expression decreases as cells differentiate into osteoblasts, and low Runx2 expression is required for normal osteoblast function.[10]

Bone morphogenetic proteins (BMPs) are a group of over 30 proteins, some of which belong to the TGFβ family, that regulate mesenchymal stem cell differentiation into osteoblasts by activating and inhibiting several genes that influence Runx2 and Sp7 expression. Wnt signaling proteins and fibroblast growth factors (FGFs) further contribute to this regulation.[10]

Once differentiated, osteoblasts coordinate with osteoclasts to model and remodel bone, maintaining bone homeostasis. Osteoblasts are bone-forming cells that create cartilage, which is later mineralized into bone using calcium. Osteoclasts, derived from hematopoietic stem cells, are bone-resorbing cells that break down bone using electrolytes and bone-degrading enzymes. During development, the body models bone by removing bone in some areas while synthesizing bone in others. After development, this process is called remodelling, as the bone retains its structure but is continuously regenerated.[9]

The receptor activator of nuclear factor kappa-B ligand (RANKL) determines when stored bone must be resorbed. RANKL, present on the surface of osteoblasts and stromal cells, binds to RANK on osteoclast surfaces. Through varying RANKL expression, osteoblasts can control osteoclast differentiation and bone resorption. Elevated calcium levels can also stimulate osteoclast activity, contributing to bone resorption. Osteoclasts work in a negative feedback loop with osteoblasts, secreting factors that inhibit osteoclast activity and provide substrates for osteoblast activity.[9]

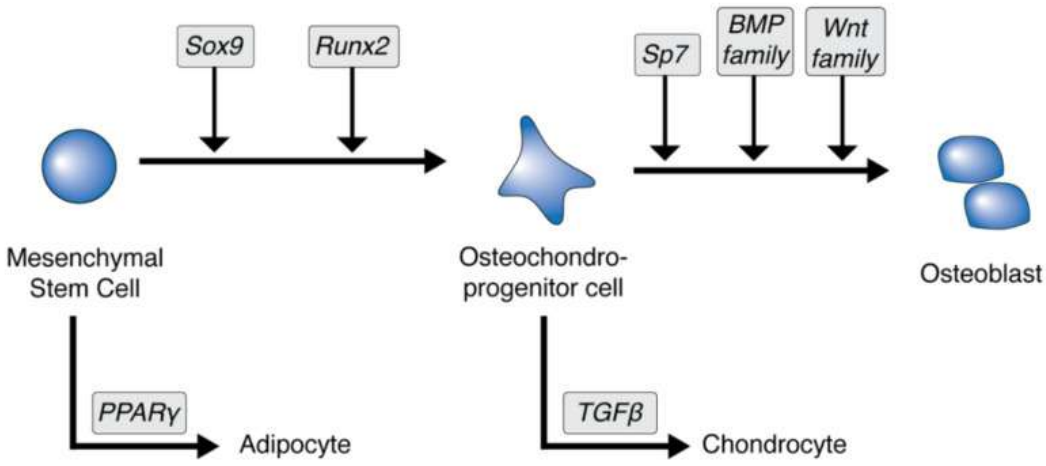

Figure 1. Differentiation of stem cells into osteoblasts triggered by various factors.

Cellular Origin of Osteosarcoma

Osteosarcomagenesis was initially thought to arise solely from mesenchymal stem cells; however, current data suggest that osteosarcoma can originate from various stages of bone development, including mesenchymal stem cells, osteoblasts, and osteoclasts. Most sarcomas are caused by genetic translocations, but osteosarcoma is characterized by a complex karyotype and is not driven by a single factor.[9,10]

To date, mutations in the tumor suppressor genes TP53 and RB1 are believed to play a major role in the development of

osteosarcoma. Laboratory studies have shown that when p53 and RB1 genes are disrupted in stem cells, these cells can transform into tumor cells resembling osteosarcoma.[9,10]

Genes involved in osteoblast development, particularly the Wnt protein family, are also implicated in osteosarcoma. Excessive activation of Wnt proteins and their subtypes can induce osteoblast transformation into osteosarcoma. This has been supported by findings that β-catenin, a key mediator of the Wnt pathway, is highly overexpressed in osteosarcoma tumors.

The bone morphogenetic protein (BMP) group and transforming growth factor-beta (TGFβ), which are involved in osteoblast differentiation, also contribute to osteosarcomagenesis. TGFβ1 and TGFβ3 are proportionally expressed during osteosarcoma development. TGFβ is known to activate SMAD4 (mothers against decapentaplegic homolog 4), a protein group linked to the formation of certain malignancies such as pancreatic and ovarian cancers, and is now recognized as having a connection to osteosarcoma.[9,10]

The Runx2 gene plays a central role in triggering osteoblast formation from osteochondroprogenitor cells by activating osteocalcin, type I collagen, and ALP—all of which are also involved in osteosarcomagenesis. Runx2 is closely linked with the proto-oncogenes Rb and Myc, being directly regulated by both, creating a complex interplay in the dysregulation of normal cells into osteosarcoma. Furthermore, Runx2 interacts with other genes, such as p27KIP1 and ALP. Due to its significant role in osteosarcoma development, the level of Runx2 expression is strongly correlated with poor prognosis in osteosarcoma patients.[9,10]

Another gene involved in osteoblast differentiation from stem cells is Gli1, which activates the sonic hedgehog (Shh) signaling pathway. Several other pathways are associated with cell migration, invasion, and pulmonary metastasis in osteosarcoma. Extracellular signal-regulated kinase 1/2 (ERK 1/2) has been identified as crucial for osteosarcoma migration and invasion. Matrix metalloproteinases (MMPs) are a group of proteins essential for extracellular matrix degradation, which plays a critical role in malignant tumor migration and invasion. Studies have demonstrated overexpression of MMP-2 and MMP-9, as well as significant upregulation of their regulators, in osteosarcoma patients with pulmonary metastasis.[9,10]

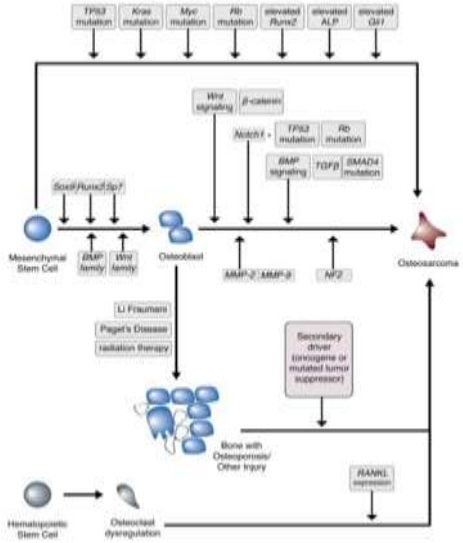

Figure 2. Overexpression of several transcription factors and oncogenes, along with dysregulation of tumor suppressor genes, contributing to osteosarcoma development.

Bone Microenvironment

Signaling components of the bone microenvironment play a crucial role in osteosarcoma development. BMP2 and TGFβ circulate within the bone microenvironment, contributing to osteoblast formation but also participating in osteosarcomagenesis and malignancy. Growth-related factors may also contribute to sarcomagenesis because they are essential for osteoblast-driven bone formation. Chondrocytes secrete high-mobility group box 1 protein (HMGB1), which stimulates osteoblast proliferation and may induce osteosarcoma cell proliferation.[9]

Factors secreted throughout the bone microenvironment also contribute to abnormal osteoclast activity, which can lead to osteosarcoma. As previously mentioned, osteoclast activity is regulated by RANK signaling, mediated by RANKL expression on osteoblasts. Dysregulation of RANKL expression and ligand binding by osteoblasts and other cells in the bone microenvironment can impair bone resorption by osteoclasts and allow uncontrolled bone formation. Cancer cells secrete factors such as interleukins (IL-6, IL-11**)** and TGFβ, which can modulate RANK expression on osteoclast surfaces, further reducing bone resorption and contributing to tumor progression.[9]

In addition to being precursors for osteoblasts, chondrocytes, and osteosarcoma cells, mesenchymal stem cells (MSCs) themselves play a role in tumor development. Cytokines secreted by MSCs in the bone microenvironment, including TGFβ and tumor necrosis factor-α (TNFα)**,** can inhibit lymphocyte proliferation and block immune responses, allowing tumors to evade inflammatory responses. MSCs can also stimulate angiogenesis by differentiating into fibroblasts and producing growth factors, thus increasing blood supply to the tumor.[9]

Finally, various factors secreted by MSCs, including TGFβ**,** E-cadherin**,** and microRNAs, have been shown to regulate epithelial-to-mesenchymal transition (EMT)**,** resulting in a more invasive tumor phenotype.[10]

Primary bone cancers are not the only cancers that develop within the bone microenvironment. Many cancers metastasize to bone due to its nutrient-rich environment, including breast cancer, prostate cancer, and other carcinomas. Compared to osteosarcoma, which is predominantly bone-forming (osteoblastic), bone metastases are usually bone-destructive (osteolytic). This nutrient-rich environment, which facilitates tumor metastasis, aligns with the "seed and soil" theory, wherein seeds (cancer cells) thrive in fertile soil (the bone microenvironment).[11]

Clinical Features of Osteosarcoma

Clinical Symptoms of Osteosarcoma

The most common clinical symptom of osteosarcoma is persistent, continuous pain that can last for weeks or months. The pain progressively worsens and is often accompanied by swelling or a palpable mass.[9] The pain is typically aggravated by activity, does not improve with rest, and often intensifies at night, especially when the patient is about to sleep.[12]

Swelling or mass in patients with osteosarcoma is often accompanied by movement impairment. When the pain is located near a joint, joint effusion may also be present. Swelling and masses can be difficult to detect in axial bones and the pelvis, which often leads to a delayed diagnosis in such cases. In some instances, osteosarcoma may be an incidental finding after trauma.[9] Systemic symptoms that may arise include hypermetabolic signs such as weight loss, which are associated with metastasis and advanced disease.[12]

Pain in Osteosarcoma

The exact mechanism of osteosarcoma-related pain is still being studied, but several theories explain its pathophysiology. The first involves high osteoclast activity, in which osteoclasts acidify the extracellular microenvironment (pH 4.0–5.0).

Nociceptors in bone marrow, bone, and periosteum are highly sensitive to protons, and the presence of free hydrogen ions in this acidic environment stimulates these nociceptors. This theory is supported by findings that treatments inhibiting osteoclast activity, such as bisphosphonates or denosumab, can reduce pain intensity in osteosarcoma patients.[13]

Another theory suggests that pain is caused by products released by the tumor or the host's response to the tumor. Substances implicated include prostaglandins, bradykinin, tumor necrosis factor-alpha, endothelins, interleukins-1 and -6, epidermal growth factor, transforming growth factor-alpha, platelet-derived growth factor, and nerve growth factor (NGF). NGF is particularly notable in tumor-associated bone pain because it actively activates sensory neurons expressing tropomyosin receptor kinase A (TrkA) receptors or modulates the expression of TrkA or p75 receptors.[13]

Osteosarcoma pain also has a neuropathic component, as patients with uncontrolled pain often respond to gabapentin. This is likely due to tumor invasion of sensory nerve endings in the bone, bone marrow, and periosteum).[13]

Physical Examination of Osteosarcoma

Physical examination in bone tumors is crucial, as it helps differentiate between benign and malignant lesions. On inspection, a mass is often observed, particularly in the metaphyseal area of long bones, along with skin changes such as telangiectasia, lymphedema characterized by shiny skin appearance, and, in advanced cases, ulcers with or without tissue liquefaction. On palpation, the mass is typically firm, with regular or irregular margins, fixed to the bone, sometimes with palpable bruit or pulsation. The mass may feel warm and is usually tender to touch. On movement assessment, there may be a limited range of motion in the adjacent joint due to joint structure damage or mass effect.[13]

Figure 3. Osteosarcoma of the shoulder showing shiny skin appearance and telangiectasia.

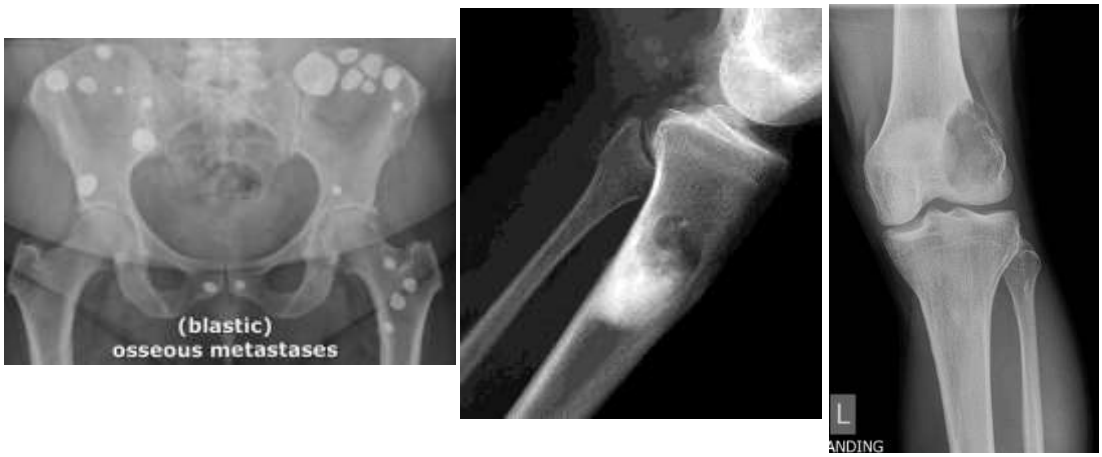

Figure 4. Radiographic bone lesion patterns; Left: blastic lesion; Middle: lytic lesion; Right: mixed lesion.

Supporting Examinations for Osteosarcoma

Laboratory Tests

Several laboratory findings may be associated with osteosarcoma. Routine blood tests may reveal leukocytosis, thrombocytosis or thrombocytopenia, elevated C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR). These markers indicate an inflammatory process in patients with osteosarcoma.[1]

Osteosarcoma induces excessive bone turnover, involving both bone destruction and formation. Elevated alkaline phosphatase (ALP) levels are common due to increased osteoblast activity as they attempt to repair tumor-induced defects. This ALP elevation occurs due to high phosphatase activity during mineralization.[14]

Lactate dehydrogenase (LDH) is also routinely measured, as its level correlates with the prognosis of several tumors, including osteosarcoma. Higher LDH levels are associated with more severe malignancy. The increase in LDH results from cancer cells' high energy synthesis demands for metabolism, as well as bone tissue destruction.[15]

Radiological Examination of Osteosarcoma

1. X-Ray

Plain radiography is crucial for the initial evaluation of bone lesions, as it can provide diagnostic clues and guide further appropriate imaging. X-rays should be taken in two projections and include the entire affected bone and adjacent joints to assist in determining proper surgical management.[17]

Radiographic features of osteosarcoma vary. Most lesions show a mixed lytic and sclerotic pattern in the metaphyseal region. Purely lytic or sclerotic lesions are rare. Lesions often appear aggressive, with a "moth-eaten" pattern and indistinct or permeative margins, sometimes with multiple small cortical holes. In cases responding well to chemotherapy, the surrounding bone may appear more defined, making the tumor look more geographic. Among the various features, the most commonly observed is the Codman's triangle, representing new bone formation with concurrent bone destruction.[17]

Soft tissue involvement is common in osteosarcoma; on plain films, this appears as a soft tissue mass. Near joints, this extension can be difficult to differentiate from effusion. Cloud-like sclerosis due to malignant osteoid production and calcification can be seen within the mass. Periosteal reactions are typically visible after the tumor breaches the cortex. Various periosteal patterns, including Codman's triangle, multilaminar ("onion-skin"),

spiculated, and sunburst appearances, all indicate aggressive pathology.[17]

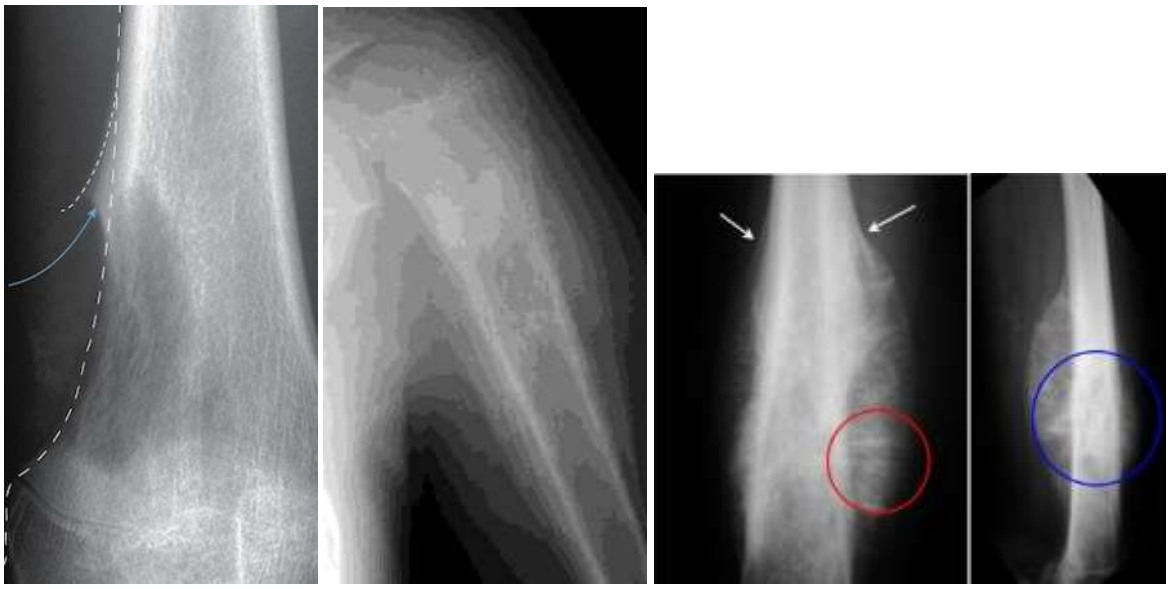

Figure 5. Periosteal reactions; Left: Codman's triangle; Middle: onion-skin appearance; Below: sunburst appearance.

2. CT Scan

CT scanning can be locally useful when radiographs are inconclusive, particularly in anatomically complex areas. Axial slices provide better visualization of bone destruction and the extent of soft tissue masses compared to radiography. CT can also detect minimal mineralized bone matrix not visible on X-rays. This modality is especially useful in evaluating flat bones, where periosteal reactions may be less apparent.[16]

Although CT scans are rarely required for evaluating long tubular bone tumors, they are the most accurate modality for detecting metastases, especially in the lungs. However, MRI is superior for assessing soft tissue extension and medullary involvement due to its better soft tissue contrast.[2]

3. MRI

MRI is the imaging modality of choice for evaluating the local extent of osteosarcoma due to its excellent bone marrow and soft tissue contrast, as well as multiplanar visualization capabilities. MRI is considered the most important imaging technique for accurately staging local osteosarcoma and planning surgical management. Staging requires assessment of the tumor's relationship to its anatomic compartment of origin and to adjacent compartments. Compartments include bone, joints, and well-defined fascial soft tissue spaces. Disease confined to its original compartment has a better prognosis than disease spreading to other compartments.[18]

The most accurate sequence for determining the longitudinal extent of disease is T1-weighted spin-echo. Short-tau inversion recovery (STIR) sequences may overestimate tumor size due to bone marrow edema or hyperplasia, which can mimic tumor signal intensity. The maximum longitudinal tumor extent should be measured, along with the distance from the closest articular surface. Longitudinal extension usually occurs in the medullary bone but may sometimes be more extensive intracortically.[18]

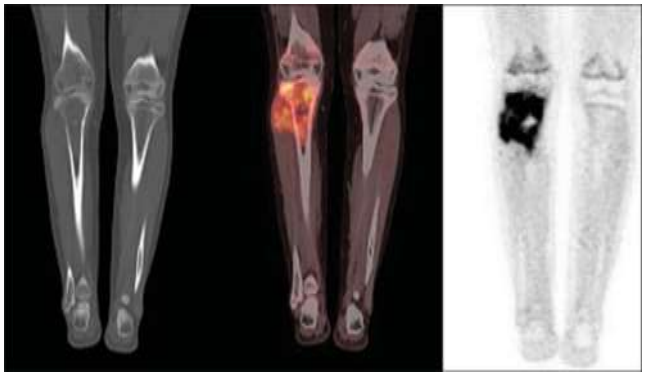

Figure 6. PET/CT scan findings in osteosarcoma.

The extraosseous tumor's relationship to neurovascular structures is well depicted on STIR, fat-suppressed T2-weighted, or proton density-weighted sequences. Neurovascular structures are classified as free of tumor (clearly surrounded by muscle or fat), abutting tumor (tumor adheres to vascular tissue), or fully involved (infiltrated or encased by tumor). Joint involvement can be diagnosed when tumor tissue extends directly into the joint through subarticular bone and cartilage. In knee joint tumors, extension along cruciate ligaments is also a diagnostic clue.[18]

4. Nuclear Imaging

Osteosarcoma almost always shows increased tracer uptake, particularly with technetium-99m (99mTc) methylene diphosphonate. However, increased uptake is not specific to osteosarcoma, making bone scanning a sensitive but nonspecific modality. Bone scans are advantageous for early detection of multifocal lesions or metastases.[19]

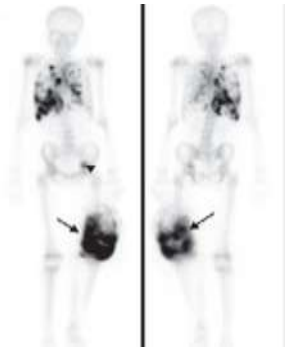

Figure 7. Bone scan of osteosarcoma with metastasis.

PET/CT has proven to have excellent sensitivity and specificity, although it is costly. A meta-analysis of 26 studies reported PET/CT sensitivity and specificity of 93% and 97% for bone metastases, and 90% and 96% for other organ metastases, respectively. This makes PET/CT a valuable tool for diagnosing and monitoring osteosarcoma progression.[19]

Classification of Osteosarcoma

1. Osteosarcoma Grading

The severity of osteosarcoma can be classified using two methods: Enneking and the American Joint Commission on Cancer (AJCC). The purpose of grading is to determine prognosis and guide appropriate treatment, whether pharmacological or surgical.[17]

Table 2. Enneking Classification for Malignant Bone Tumor Grades[6]

Grade	Pathological Features	Location	Metastasis
I A	Low differentiation (G1)	Intracompartmental (T1)	None (M0)
I B	Low differentiation (G1)	Extracompartmental (T2)	None (M0)
II A	High differentiation (G2)	Intracompartmental (T1)	None (M0)
II B	High differentiation (G2)	Extracompartmental (T2)	None (M0)
III A	Low differentiation (G1)	Intracompartmental (T1)	Present (M1)
III B	High differentiation (G2)	Extracompartmental (T2)	Present (M1)

Table 3. AJCC Classification for Osteosarcoma Grades[6]

Grade	Tumor Size	Metastasis	Pathological Grade
I A	Tumor ≤ 8 cm	None	Low
I B	Tumor > 8 cm	None	Low
II A	Tumor ≤ 8 cm	None	High
II B	Tumor > 8 cm	None	High
III	"Skip" lesion within the same bone	High	
IV A	Any size	Lung only	Low/High
IV B	Any size	Other sites	Low/High

2. Histopathological Classification of Osteosarcoma

The **WHO** classifies osteosarcoma into several types under the group of osteogenic tumors. This classification is periodically updated to assist clinicians and pathologists in categorizing osteosarcoma. The subtypes include:[6]

- Low-grade central osteosarcoma
- Conventional osteosarcoma
- Parosteal osteosarcoma
- Periosteal osteosarcoma
- High-grade surface osteosarcoma
- Secondary osteosarcoma

Low-Grade Central Osteosarcoma (LGCOS)

Low-grade central osteosarcoma (LGCOS) is a low-grade malignant neoplasm producing bone tissue within the intramedullary cavity, consisting of fibroblastic tumor cells. Radiologically, it usually appears as a lesion in the metaphysis or meta-diaphysis, showing lytic or sclerotic expansile patterns with incomplete trabeculation.

Histopathologically, LGCOS is characterized by fascicles of mild to moderate spindle cells with nuclear atypia within a fibrosclerotic stroma. Mitotic activity is low, but there is still a risk of progression to a high-grade sarcoma (dedifferentiation). Prognosis is generally favorable with local excision, provided dedifferentiation has not occurred.[6,9]

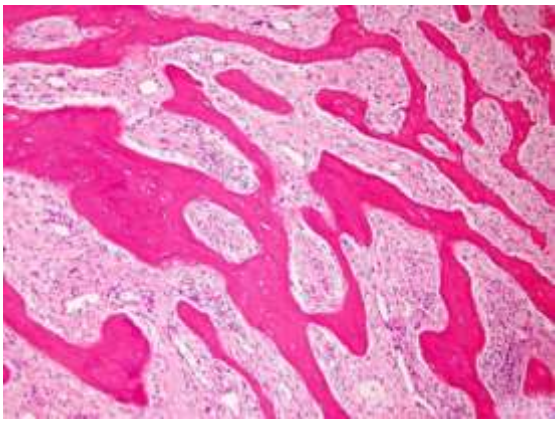

Figure 8. Histopathological features of low-grade central osteosarcoma.

Conventional Osteosarcoma (COS)

According to WHO, osteosarcoma is a high-grade intramedullary sarcoma that produces bone tissue. WHO divides osteosarcoma into conventional**,** telangiectatic**,** and small cell subtypes. COS typically arises in the distal femur, proximal tibia, and proximal humerus. Clinical findings of COS align with previously described symptoms such as pain, mass, and movement restriction.[6,9]

Radiologically, COS shows permeative bone destruction with mineralization, creating a mixed lytic and sclerotic lesion with poorly defined, immature margins. Periosteal reactions such as onion-skin, sunburst, and Codman's triangle appearances are commonly observed.[6,9]

Histopathologically, COS has a broad spectrum. The tumor exhibits a permeative growth pattern, with bone marrow replaced by tumor tissue and trabecular erosion. Tumor cells may spread through Haversian systems, causing skip lesions. Neoplastic cells appear markedly anaplastic with pleomorphism and may be fusiform, plasmacytoid, or epithelioid. Mitoses are numerous, often atypical. The bone matrix produced is typically primitive woven bone with irregular arrangement. Non-mineralized matrix appears eosinophilic, while mineralized matrix is basophilic. Based on matrix histology, COS is classified as osteoblastic (76–80%), chondroblastic (10–13%), and fibroblastic (10%). Osteoblastic type shows trabeculae or dense bone formation; chondroblastic type shows hyaline cartilage with marked cytologic atypia; fibroblastic type exhibits spindle or epithelial-like.[6,9]

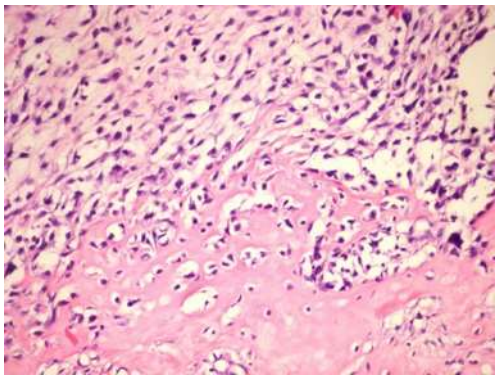

Figure 9. Histopathological features of conventional osteosarcoma.

Immunohistochemically, many markers are not highly diagnostic. Frequently observed antigens include SATB2, osteocalcin (BGLAP), osteonectin (SPARC), osteoprotegerin (TNFRSF11B), RUNX2, S100, actin, and CD99. Osteosarcoma typically does not express CD31, CD45, or FPS. SATB2 is highly sensitive for osteoblastic differentiation but not specific. Although nonspecific, SATB2 helps differentiate SCOS from Ewing sarcoma, as SATB2 is generally absent in the latter. [6,9]

Telangiectatic Osteosarcoma (TAEOS)

Telangiectatic osteosarcoma (TAEOS), as its name suggests, has prominent vascular features and may resemble an aneurysmal bone cyst. TAEOS is typically located around the knee and proximal humerus, originating in the metaphysis with extension to epiphysis or diaphysis. Radiologically, it presents with aggressive bone destruction, expansile remodeling, extraosseous extension, and frequent pathological fractures. TAEOS comprises cystic cavities filled with blood or empty spaces, with septa of variable thickness containing pleomorphic cells with nuclear hyperchromasia. Osteoid formation is usually focal and confluent but may be absent on biopsy. [6,9]

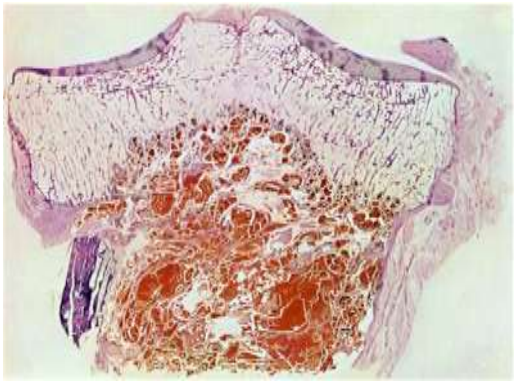

Figure 10. Histopathological features of telangiectatic osteosarcoma of the proximal tibia.

Small Cell Osteosarcoma (SCOS)

Small cell osteosarcoma (SCOS) has a similar distribution but is also frequently found in diaphyseal regions of long bones. SCOS is predominantly lytic with non-mineralized radiological features, resembling other tumors. It consists of small cells with sparse cytoplasm and osteoid production. The nuclei are round to oval with fine-to-coarse chromatin. In spindle cell variants, chromatin appears granular with indistinct nucleoli. [6,9]

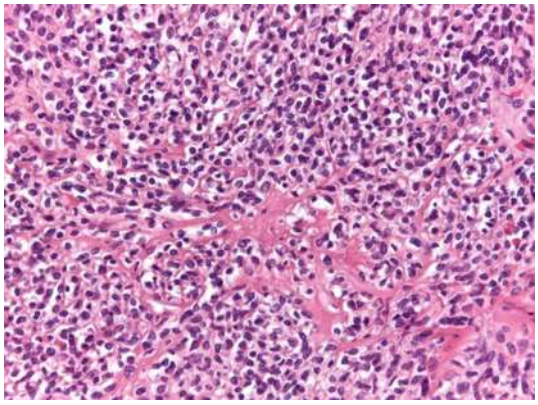

Figure 11. Histopathological features of small cell osteosarcoma.

Parosteal Osteosarcoma

Parosteal osteosarcoma is a low-grade neoplasm that produces bone tissue, arising from the cortical bone surface. Most parosteal osteosarcomas occur on the posterior aspect of the distal femur (70%), with other common sites including the proximal tibia and proximal humerus. Clinically, it presents as a mass with pain, and when near joints, it causes restricted motion. Radiologically, it appears as a lobulated mineralized mass on the bone surface, with denser mineralization in the central area compared to the periphery. The attachment to bone may be narrow or broad; in narrow-based lesions, a cleavage plane (lucent line) may be seen on radiographs. The underlying cortex may appear normal, thickened, or destructed. [6,9]

Histopathologically, parosteal osteosarcoma exhibits well-formed bone trabeculae with spindle cell fascicles. The tumor is hypocellular with minimal atypia and low mitotic activity. At the periphery, spindle cells may invade adjacent skeletal muscle. If bone tissue is absent in biopsy specimens, it may be misdiagnosed as desmoplastic fibroma. Parosteal osteosarcoma carries a 15–40% risk of dedifferentiation. Immunohistochemistry may involve MDM2 and CDK4 markers. [6,9]

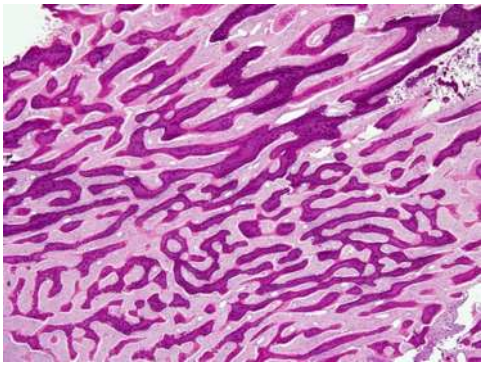

Figure 12. Histopathological features of parosteal osteosarcoma.

Periosteal Osteosarcoma

Periosteal osteosarcoma is an intermediate-grade chondroblastic sarcoma arising from the bone surface, typically beneath the periosteum. It is most commonly found in the diaphysis of the femur and tibia. Radiologically, it appears as a fusiform, lucent surface mass with variable mineralization, showing striated ossification or “hair-on-end” patterns. The cortex may be thickened with solid or laminated periosteal reactions, and Codman’s triangle may also be present. A challenge in understanding periosteal osteosarcoma is the absence of consistent genetic anomalies. Some cases show TP53 mutations, but these are not specific. The tumor consists of atypical cartilage arranged in irregular lobules with interspersed atypical sarcomatous cells producing bone matrix. Perpendicular periosteal reactions are visible as hair-on-end patterns on X-rays. [6,9]

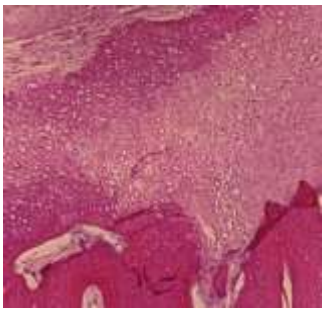

Figure 13. Histopathological features of periosteal osteosarcoma.

High-Grade Surface Osteosarcoma

High-grade surface osteosarcoma is a high-grade malignant neoplasm producing bone tissue, originating from the bone surface

(cortex). It most commonly affects the femur, tibia, and humerus, particularly in diaphyseal or diametaphyseal regions. Radiographs show a radiopaque mass extending into soft tissue from the cortical surface, with a fluffy, ill-defined immature ossification. Dense ossification and spiculated periosteal reactions, similar to periosteal osteosarcoma, may also be observed. Radiologically, it resembles periosteal osteosarcoma, but medullary involvement and cortical erosion are less common in periosteal types. Histologically, it is almost identical to conventional osteosarcoma, except for its cortical origin.[6,9]

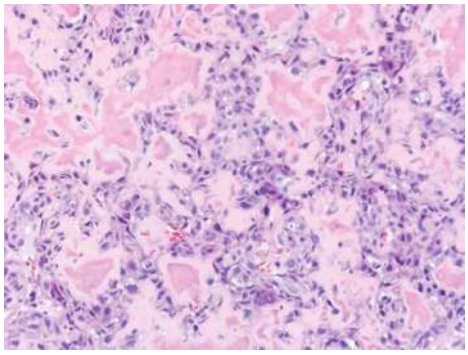

Figure 14. Histopathological features of high-grade surface osteosarcoma

Secondary Osteosarcoma

Secondary osteosarcoma arises from abnormal bone, which has pre-existing conditions such as Paget's disease, radiation-induced sarcoma, infarct-associated osteosarcoma, chronic osteomyelitis, implant-associated osteosarcoma, or fibrous dysplasia. Locations of secondary osteosarcoma follow the distribution of Paget's disease, with the femur (34%), pelvis (24%), and humerus (24%) being the most common sites. Secondary osteosarcoma usually arises in long bones with prior lesions. Clinical findings resemble other osteosarcomas but often include pathological fractures and a history of prior bone lesions. Radiographs show lytic bone destruction with large extraosseous masses. Pathogenesis is linked to continuous bone destruction and formation, causing mutations, or exposure to external factors like radiation. Histopathologically, secondary osteosarcoma is indistinguishable from conventional osteosarcoma, so clinical history is essential for diagnosis.[6,9]

Management of Osteosarcoma

Conventional treatment for osteosarcoma consists of a combination of neoadjuvant and adjuvant chemotherapy, radiotherapy, and surgery. Before the use of chemotherapy, the survival probability of osteosarcoma patients was only about 20%, even with surgical amputation, indicating the presence of micrometastases (usually in the lungs) before surgery. Low-grade osteosarcoma can often be treated with excision alone, and chemotherapy is avoided if the final pathology shows a low grade. The management of osteosarcoma cannot be carried out by orthopedic surgeons alone; the team consists of radiologists, pathologists, oncologists, radiation oncologists, and orthopedic surgeons. The first step in treating osteosarcoma is establishing an accurate diagnosis, in which the roles of orthopedic surgeons, oncologists, radiologists, and pathologists are crucial. Diagnosing a patient with malignant bone cancer drastically changes the patient's life trajectory, as well as that of the child patient's parents. Moreover, optimal osteosarcoma management, which includes chemotherapy, radiotherapy, and surgery, requires teamwork.[9]

Chemotherapy

Studies on the effects of chemotherapy on osteosarcoma began in the 1970s. At that time, chemotherapy was used as adjuvant treatment after surgery to eliminate residual lesions and metastases that could not be completely removed with surgery alone. By the late 1970s, to eliminate subclinical tumor components before surgery, reduce the surrounding reactive zone, and create favorable conditions for limb-salvage surgery, preoperative chemotherapy was boldly and successfully introduced into

clinical practice. This approach later became known as neoadjuvant chemotherapy.[9]

The importance of neoadjuvant chemotherapy lies in its ability to provide early systemic treatment to eradicate micrometastases, allow evaluation of preoperative chemotherapy based on tumor necrosis rates (which guide postoperative chemotherapy management), reduce tumor edema, increase limb-salvage rates, and reduce recurrence rates. This concept was widely accepted and became widely applied in clinical practice, gradually forming a comprehensive limb-salvage treatment strategy that complements neoadjuvant chemotherapy, making limb-salvage surgery the primary choice for osteosarcoma and significantly improving 5-year survival rates. The concept of neoadjuvant chemotherapy is a milestone in the history of osteosarcoma treatment and continues to be used today.[9]

Chemotherapy agents for osteosarcoma have evolved since the 1970s. Currently, the most commonly used and highly effective agents are adriamycin (ADM), high-dose methotrexate (HDMTX), cisplatin (DDP), and ifosfamide (IFO). Several chemotherapy regimens may combine these drugs in various dosages and sequences. MAP adjuvant chemotherapy, consisting of HDMTX, ADM, and DDP, remains the cornerstone of therapy. Most hospitals worldwide administer 2–6 cycles of preoperative chemotherapy, spanning a total of 6–18 weeks.[9]

The toxic and adverse effects of chemotherapy cannot be ignored, including liver and kidney dysfunction, bone marrow suppression, neurotoxicity, and gastrointestinal reactions. Unfortunately, ADM-induced cardiomyopathy may be permanent. Additionally, cisplatin can cause high-frequency hearing loss in up to 11% of patients. Ongoing research and basic clinical trials focus on optimizing drug combinations, dosing, and minimizing toxic side effects, with the goal of improving treatment efficacy and survival rates while reducing harm to the human body.[9]

Vascular interventional therapy, involving intra-arterial infusion of chemotherapy drugs and microsphere embolization, has been employed to treat osteosarcoma, providing the advantage of low systemic doses with high local drug concentrations. The limitations of anticancer drugs have been improved by the use of nanocarriers. Various nano-platforms capable of delivering chemotherapy drugs precisely to the tumor site have been developed to enhance therapeutic effects and minimize side effects, although most are still in the experimental stage. This approach represents a promising direction for the future development of chemotherapy in clinical applications.[9]

Post-Chemotherapy Evaluation

Clinical and radiographic data, along with postoperative microscopic examination, show that current combination chemotherapy regimens result in substantial tumor mass reduction in at least 50% of osteosarcoma patients. Moreover, in some of these patients, complete or near-complete tumor necrosis (90%) can be achieved, which is associated with a significantly better prognosis, including longer relapse-free intervals and higher survival rates, compared to tumors that respond poorly to chemotherapy. These observations form the basis for pathological assessment of treatment effects in postoperative specimens.[9]

Pathological assessment of chemotherapy effects is now universally accepted as an integral element of the multimodal approach. Additionally, the response rate (necrosis) is used as a factor in modifying subsequent (postoperative) treatment protocols. The effectiveness of chemotherapy is evaluated using the Huvos grading system.[9]

Table 4. Histologic grading of chemotherapy effects on osteosarcoma	
Grade	**Tumor Response**
1	None or minimal
2	Extensive necrosis, with >10% viable tumor
3	Extensive necrosis, with <10% viable tumor
4	Complete necrosis

Spontaneous necrosis is a common phenomenon in various malignant neoplasms, including osteosarcoma. Therefore, the presence of necrosis may not always reflect treatment effects. It is estimated that up to 60% of necrosis can occur spontaneously and may not reflect treatment, but subtotal (90%) or complete necrosis almost never occurs spontaneously in osteosarcoma and is typically attributed to treatment.[9]

Tumor necrosis is characterized by the death of sarcomatous cells with pyknosis and nuclear fragmentation or by the complete loss of tumor tissue. Pre-necrotic changes associated with therapy include the development of bizarre nuclei, chromatin homogenization, and cytoplasmic vacuolization. Complete removal of sarcomatous cells within the tumor osteoid or residual host bone is often observed. In such areas, sarcomatous tissue is replaced by hyalinized vascular stroma. Cystic cavities filled with mucinous material remain as remnants of previously denser sarcomatous areas with minimal or no tumor bone formation.[9]

MRI, and when possible combined with PET, has the potential to provide estimates of viable residual tumor before surgery, although its actual clinical value is still under investigation. The most accurate assessment of therapeutic effects remains based on pathological mapping of resected specimens.[9]

Radiotherapy

For patients who are not surgical candidates or in whom the tumor remains at the resection margins, as well as for patients with osteosarcoma showing poor response to chemotherapy, local radiotherapy has been found to assist in management. Initial results confirm that external beam irradiation combined with systemic therapy can serve as a fairly effective modality for local control and symptom relief. After effective induction chemotherapy for non-metastatic limb osteosarcoma, Machak et al. suggested that radiotherapy is a reliable method for controlling local disease and preserving limb function.[9]

Ciernik et al. demonstrated that proton therapy provides high-dose radiation therapy for local treatment of unresectable or incompletely resected osteosarcomas. However, osteosarcoma is generally considered radioresistant. Recently, radiosensitizers have become a new research focus. Radiosensitizers can enhance tumor cell sensitivity to radiotherapy without damaging normal tissues, thereby improving radiation efficacy with high safety. Recent studies confirmed that combining ginseng polysaccharides with radiotherapy can improve osteosarcoma cell radiosensitivity. Although sensitizers may represent a new breakthrough in radiotherapy, advances in radiotherapy techniques and equipment have already improved long-term survival rates in tumor patients.[9]

In the future, osteosarcoma radiotherapy will likely be based on radiosensitization research, combined with advanced techniques such as stereotactic radiotherapy, proton radiotherapy, and heavy-ion radiotherapy, alongside integrated surgical and chemotherapeutic management, to achieve better therapeutic outcomes with low doses and high precision. Its role in comprehensive limb-salvage adjuvant treatment cannot be overlooked.[20]

Immunotherapy

Immunotherapy aims to regulate immune system functions to kill tumor cells, maintain immune regulation and balance,

and inhibit tumor cell growth and differentiation. Immunotherapeutic approaches in cancer treatment have gained importance as adjuvant tumor therapies due to their specific and effective results, particularly by providing new and effective treatments for advanced, metastatic, and recurrent osteosarcoma.[10]

As a fundamental element of immunotherapy, cytokines regulate immune cell activation, proliferation, and functional activity. Osteosarcoma immunotherapy includes non-specific immunotherapy, specific immunotherapy, adoptive immunotherapy, and immuno-guided therapy. Tumor immune responses have been reported for over 100 years. Currently, interleukin-2 (IL-2) has been used in postoperative osteosarcoma treatment to achieve clinical effects by activating effector T cells and enhancing natural killer (NK) cell functions.[10]

Additionally, T-cell–mediated cellular immunity largely contributes to the body's anti-tumor immune response, while NK cell–mediated innate immunity serves as the first line of defense. Checkpoint inhibitors are also an exciting research area. However, it is now understood that tumor cells have low immunogenicity and therefore are not strongly recognized by the immune system. Consequently, if immunogenic molecules are delivered and expressed in tumor cells, tumor immunogenicity can be increased, generating strong immune stimulation against the immune system. This idea has given rise to new areas of tumor immunotherapy.[10]

At present, the development of immunotherapy in osteosarcoma management is still in its early stages, leaving much room for exploration to improve osteosarcoma cure rates.[10]

Gene Therapy

Given that the fundamental cause of osteosarcoma is genetic mutations, genetic research is crucial in prevention and treatment strategies. Gene therapy is a biomedical method that introduces normal or therapeutic genes into human target cells via vectors to repair genetic damage, counteract mutation effects, or exert therapeutic benefits. [10]

Gene therapy in osteosarcoma focuses on tumor suppressor genes, suicide genes, combined gene therapy, antisense genes, immune genes, and anti-angiogenic genes. Currently, tumor suppressor genes such as p53, p16, p21, and Rb have been tested for treatment. Research results suggest that p53 protein expression can serve as a prognostic biomarker to predict osteosarcoma patient survival, making p53 gene a potential target for osteosarcoma gene therapy.[10]

Ye et al. reported that overexpression of wild-type p53 increases chemotherapy sensitivity in multidrug-resistant (MDR) osteosarcoma cells, potentially providing new insights for overcoming chemotherapy resistance. The thymidine kinase (TK)/ganciclovir (GCV) system is preferred for treating mutations in suicide genes. [10]

Furthermore, combined gene therapy with other treatment methods has shown more significant effects, not only producing synergistic benefits but also reducing side effects caused by high-dose single-drug therapy. Combining gene therapy with other treatments for osteosarcoma patients represents a promising and significant future approach, particularly genetically modified T-cell therapy. [10]

Currently, although gene therapy has made great breakthroughs in osteosarcoma treatment and offers promising prospects, it is still in the experimental stage and far from actual clinical application. [10]

Surgery

Tumor surgery aims to remove the tumor extensively, with the goal of achieving complete resection of cancerous tissue. In this context, surgery can be divided into two types: limb salvage and amputation. [10]

Amputation

Amputation is an important treatment approach for early osteosarcoma cases. After ineffective adjuvant therapy,

amputation is considered a necessary and effective treatment alternative for malignant bone tumors that can cause extensive cell damage. Amputation is performed with a tumor-free margin of at least 5 cm. Most clinicians believe that 5 cm beyond the tumor margin is considered tumor-free. However, there is a need for reliable reference standards for measurement based on plain radiographs, CT scans, and MRIs, as macroscopic findings of tumor-free margins can be misleading. [10]

In a study by Evans et al., it was found that some amputated patients were those with lower incomes, lacking insurance, and with larger, more advanced tumors. This finding hypothesized that patients undergoing amputation tend to be in a more advanced stage, with suspected neglect that requires lower-cost management. [24]

Currently, the management of osteosarcoma is directed as much as possible to avoid amputation due to the significant functional and psychological impacts, favoring limb salvage therapy whenever possible. However, surgical modality selection for osteosarcoma patients should be individualized and differentiated from one case to another to achieve optimal outcomes in terms of disease control, function, and patient quality of life.[10,20,21]

Limb Salvage Surgery

The goal of surgical treatment for osteosarcoma has evolved from merely saving lives to maximizing the function of the affected limb. Limb salvage surgery refers to surgical procedures that restore bone and joint function after extensive resection of malignant bone tumors in the limbs. The key to successful surgery lies in choosing appropriate margins. With the increasing adoption of comprehensive limb salvage therapy combined with neoadjuvant chemotherapy, limb salvage surgery has been more widely applied in clinical practice. In fact, 80–95% of all patients with malignant bone and soft tissue sarcomas can undergo limb salvage surgery. Although the local recurrence rates of amputation and limb salvage are similar, limb salvage patients have a higher 5-year survival rate. Limb salvage surgery preserves the patient's integrity not only functionally but also cosmetically. Osteosarcoma surgery must ensure complete removal of the lesion to avoid local recurrence and distant metastasis. If the lesion is not entirely removed during surgery, the local recurrence rate can reach as high as 25%.[24]

In recent years, ablation has been gradually applied to limb salvage surgery for OS (osteosarcoma) and has achieved good clinical results. Tumor ablation refers to the use of physical or chemical methods to destroy tumor cells. There are two ablation methods: thermal ablation and chemical ablation. After tumor removal, significant bone and soft tissue defects may form. With advancements in bone tissue engineering and materials science, it is now highly feasible to reconstruct bone and soft tissue defects formed after tumor resection through tumor bone inactivation replantation, allograft bone transplantation, autologous bone transplantation, or prosthetic or megaprosthesis replacement. Each reconstruction method has its own advantages and disadvantages. Prosthetic replacement allows for rapid limb function recovery; however, there is a long-term risk of device loosening and wear. A major advantage of allografts is that tendons and ligaments remain attached to the grafted bone for soft tissue attachment. However, the disadvantages of allograft transplantation include risks of fracture, nonunion, joint instability, and osteoarthritis of the reconstructed joint. Autologous bone transplantation also carries risks of fracture and nonunion. The advantage of tumor bone inactivation replantation is that it is a simple operation, does not require bone matching, and conserves bone substitute materials. The drawback is that pathological fractures tend to occur during the bone repair and reconstruction process due to the inactivation procedure. [10]

Computer-assisted tumor surgery is becoming increasingly attractive in

osteosarcoma management. Currently, no commercially available tools meet all the software and hardware requirements for osteosarcoma surgery. This will be a direction for future research and innovation.[10]

Reconstructive Surgery

Reconstructive surgery following musculoskeletal tumor excision has advanced significantly due to improved chemotherapy protocols and imaging techniques, allowing for more effective tumor removal while preserving limb function. Various reconstruction techniques are available, including metallic implants such as prostheses and biological reconstructions using bone. Biological reconstructions may involve autografts (from the patient) or allografts (from donors), with autografts considered the superior option due to lower complication rates. Advances in microvascular techniques have popularized vascularized bone transfers, which overcome limitations of non-vascularized grafts. In countries without bone banks, sterilized tumor-affected bone can be reimplanted, although this approach is structurally weaker.[22]

Allograft integration is a slow and complex process involving osteoinduction, osteoconduction, and creeping substitution, where grafted bone is gradually resorbed and replaced by new host bone. This process is influenced by factors such as chemotherapy, radiotherapy, and patient age. Proper soft tissue coverage and stable fixation are crucial for successful outcomes. Complications commonly associated with allografts include infection, non-union, resorption, and fracture, with the highest risk occurring within the first two years post-surgery. Managing these complications often requires additional surgeries, and infections are particularly challenging due to the limited vascularization of the graft.[22]

Functional outcomes are generally best with intercalary grafts (auto- or allograft), especially when tumor size and location allow joint preservation. For pelvic tumors, autografts yield better functional results than allografts due to their use in smaller tumors. However, autograft availability is limited, making allografts necessary for large resections. Alternative techniques, such as vascularized fibular grafts or combining vascularized autografts with allografts, have shown promise, particularly in upper limb reconstruction, though they are technically demanding and time-consuming.[22]

Overall, reconstructive strategies must balance tumor control, functional preservation, and complication risks. Thorough preoperative planning, stable fixation, effective infection control, and long-term follow-up are key to achieving successful outcomes in patients undergoing limb reconstruction after tumor excision.[22]

Osteosarcoma Prognosis

Currently, the prognosis of osteosarcoma is relatively good compared to previous decades, with the 5-year survival rate after diagnosis increasing dramatically to around 40%, whereas previously it was only 10–20%. At present, the use of neoadjuvant chemotherapy combined with surgery for non-metastatic osteosarcoma of the extremities provides a cure rate of approximately 60–70%. Several predictors can determine patient recovery, including histological response to preoperative chemotherapy, alkaline phosphatase levels, and lactate dehydrogenase).[7,8]

Older age is thought to affect osteosarcoma prognosis, as aggressive therapy is often avoided in older patients due to the high risks associated with the tumor, especially when the tumor location is inoperable. Treating osteosarcoma in older patients is a double-edged sword, as their condition can also deteriorate due to the treatment itself. Male gender is also associated with a higher mortality rate compared to females. The mechanism is not yet known, but differences in sex hormone levels, pharmacokinetics, and treatment response are suspected to be plausible mechanisms.[7,8]

Tumor location, particularly in the pelvis and axial bones, is linked to higher mortality, which is associated with a higher likelihood of metastasis and the difficulty of achieving adequate surgical management in those areas. Metastasis, particularly to the lungs, is one of the worst prognostic factors, with 5-year survival rates after diagnosis being very low (<10%).[7]

Studies conducted in Indonesia have shown relatively low survival rates. This is reflected in an average overall survival of only about 28 months and a disease-free period of only around 10 months. Combination therapy has also demonstrated longer survival durations. Chemotherapy alone can provide a survival of 9 months, which increases to 18 months when combined with surgery, and up to 21 months when combined with surgery and radiotherapy.[23]

CONCLUSION

Osteosarcoma remains a challenging malignancy with complex management strategies that require a multidisciplinary approach involving chemotherapy, surgery, and in certain cases, radiotherapy and emerging therapies such as gene therapy. Advances in neoadjuvant chemotherapy, combined with limb salvage surgery, have significantly improved survival rates for non-metastatic cases, achieving 5-year survival rates of 60–70%, compared to the historically low rates of 10–20%. Prognostic factors, including histological response to preoperative chemotherapy, alkaline phosphatase, and lactate dehydrogenase levels, play crucial roles in predicting outcomes.

Despite these advances, prognosis remains poor for patients with metastatic disease, particularly pulmonary metastases, and for tumors located in challenging anatomical regions such as the pelvis and axial skeleton. Older age, male gender, and limited access to optimal healthcare are associated with poorer outcomes. In Indonesia, survival rates remain lower compared to global data, with an average survival of 28 months, underscoring the need for improved diagnostic and therapeutic strategies.

Future directions in osteosarcoma treatment involve the development of more effective systemic therapies, exploration of gene therapy, immune-based approaches, and advanced reconstructive techniques to optimize both survival and functional outcomes. Continued research and early detection are key to further improving prognosis and quality of life for osteosarcoma patients.

Declaration by Authors

Ethical Approval: Not applicable

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Messerschmitt PJ, Garcia RM, Abdul-Karim FW, Greenfield EM, Getty PJ. Osteosarcoma. Journal of the American Academy of Orthopaedic Surgeons. 2009;17(8):515–527. doi:10.5435/00124635-200908000-00005. https://doi.org/10.5435/00124635-200908000-00005
2. Arndt CAS, Rose PS, Folpe AL, Laack NN. Common musculoskeletal tumors of childhood and adolescence. Mayo Clinic Proceedings. 2012;87(5):475–487. doi:10.1016/j.mayocp.2012.01.015. https://doi.org/10.1016/j.mayocp.2012.01.015
3. Campanacci M. Bone and Soft Tissue Tumors: Clinical Features, Imaging, Pathology and Treatment. 2nd ed. Vienna: Springer-Verlag; 1999. doi:10.1007/978-3-7091-3846-5. https://doi.org/10.1007/978-3-7091-3846-5
4. Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed. Philadelphia: Elsevier Saunders; 2013. ISBN: 978-1-4377-1781-5.
5. Picci P. Osteosarcoma (osteogenic sarcoma). Orphanet Journal of Rare Diseases. 2007; 2:6. doi:10.1186/1750-1172-2-6. https://doi.org/10.1186/1750-1172-2-6
6. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. WHO Classification of Tumours, 5th ed, Vol 3. Lyon: International Agency for Research on Cancer; 2020. https://publications.iarc.fr/588
7. Cole S, Gianferante DM, Zhu B, Mirabello L. Osteosarcoma: a Surveillance, Epidemiology, and End Results program-based analysis from

1975 to 2017. Cancer. 2022;128(11):2107–2118. doi:10.1002/cncr.34163. https://doi.org/10.1002/cncr.34163
8. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn PCW, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 cohort. European Journal of Cancer. 2019; 109:36–50. doi: 10.1016/j.ejca.2018.11.027. https://doi.org/10.1016/j.ejca.2018.11.027
9. Czerniak B. Dorfman and Czerniak's Bone Tumors. 2nd ed. Philadelphia: Elsevier; 2016. ISBN: 978-0-323-02396-2.
10. Rathore R, Van Tine BA. Pathogenesis and current treatment of osteosarcoma: perspectives for future therapies. Journal of Clinical Medicine. 2021;10(6):1182. doi:10.3390/jcm10061182. https://doi.org/10.3390/jcm10061182
11. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, et al. Bone metastases: an overview. Oncology Reviews. 2017;11(1):321. doi:10.4081/oncol.2017.321. https://doi.org/10.4081/oncol.2017.321
12. Peabody TD, Attar S, editors. Orthopaedic Oncology: Primary and Metastatic Tumors of the Skeletal System. Cham: Springer; 2014. doi:10.1007/978-3-319-07323-1. https://doi.org/10.1007/978-3-319-07323-1
13. Jimenez-Andrade JM, Mantyh WG, Bloom AP, Ferng AS, Geffre CP, Mantyh PW. Bone cancer pain. Annals of the New York Academy of Sciences. 2010; 1198:173–181. doi:10.1111/j.1749-6632.2009.05429. x. https://doi.org/10.1111/j.1749-6632.2009.05429.x
14. Yeniyol S, Ricci JL. Alkaline phosphatase levels of murine pre-osteoblastic cells on anodized and annealed titanium surfaces. European Oral Research. 2018;52(1):12–19. doi:10.26650/eor.2018.78387. https://doi.org/10.26650/eor.2018.78387
15. Fu Y, Lan T, Cai H, Lu A, Yu W. Meta-analysis of serum lactate dehydrogenase and prognosis for osteosarcoma. Medicine (Baltimore). 2018;97(19):e0741. doi:10.1097/MD.0000000000010741. https://doi.org/10.1097/MD.0000000000010741
16. Prater S, McKeon B. Osteosarcoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Archived May 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK563177/
17. Kundu ZS. Classification, imaging, biopsy and staging of osteosarcoma. Indian Journal of Orthopaedics. 2014;48(3):238–246. doi:10.4103/0019-5413.132491. https://doi.org/10.4103/0019-5413.132491
18. Inarejos Clemente EJ, Navarro OM, Navallas M, Ladera E, Torner F, Sunol M, et al. Multiparametric MRI evaluation of bone sarcomas in children. Insights into Imaging. 2022;13(1):33. doi:10.1186/s13244-022-01177-9. https://doi.org/10.1186/s13244-022-01177-9
19. Liu F, Zhang Q, Zhou D, Dong J. Effectiveness of 18F-FDG PET/CT in the diagnosis and staging of osteosarcoma: a meta-analysis of 26 studies. BMC Cancer. 2019;19(1):323. doi:10.1186/s12885-019-5488-5. https://doi.org/10.1186/s12885-019-5488-5
20. Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2021;32(12):1520–1536. doi: 10.1016/j.annonc.2021.08.1995. https://doi.org/10.1016/j.annonc.2021.08.1995
21. Evans DR, Lazarides AL, Visgauss JD, Somarelli JA, Blazer DG 3rd, Eward WC. Limb salvage versus amputation in patients with osteosarcoma of the extremities: an update in the modern era using the National Cancer Database. BMC Cancer. 2020; 20:995. doi:10.1186/s12885-020-07502-z. https://doi.org/10.1186/s12885-020-07502-z
22. San-Julian M, Vazquez-Garcia B. Biological reconstruction in bone sarcomas: lessons from three decades of experience. Orthopaedic Surgery. 2016;8(2):111–121. doi:10.1111/os.12243. https://doi.org/10.1111/os.12243
23. Sjakti HA, Putri IA, Windiastuti E. Survival rate of pediatric osteosarcoma in Indonesia: a single-center study. Paediatrica Indonesiana. 2022;62(1):27–31. doi:10.14238/pi62.1.2022.27-31. https://doi.org/10.14238/pi62.1.2022.27-31

How to cite this article: Dominicus Dimitri, Komang Septian Sandiwidayat. Osteosarcoma: a comprehensive literature review on epidemiology, pathogenesis, diagnosis, and evolving therapeutic strategies. *International Journal of Research and Review*. 2026; 13(8): 1-22. DOI: *10.52403/ijrr.20260801*

******