INTRODUCTION

Osteosarcoma (OS) is an aggressive malignant neoplasm arising from primitive transformed cells of mesenchymal origin that exhibit osteoblastic differentiation and produce malignant osteoid. It is the most common histological form of primary bone cancer [(1)]. It is a relatively rare malignancy, with approximately 900 new cases reported in the United States per year [(2)].

It represents less than 1% of cancers reported within the United States, with a peak incidence of 4.4 cases per million per year in the adolescent and young adult population. Despite their rarity, osteosarcomas are the most common primary malignancy of bone, representing approximately 3.4% of all childhood cancers and 56% of malignant bone tumors in children[(3)].

Osteosarcoma classification into various subtypes is not only by the predominant histologic pattern, but also by its anatomic location and sometimes by its histological grade [(4)].

Genomic technologies are now being used to identify new molecular markers or signatures for both diagnostic and prognostic purposes. Recently, the molecular classification of pediatric osteosarcoma is reported [(5)].

The classification of nonconventional subtypes of primary OS is based not only on histological features but also on gross morphologic features, which are reflected at imaging. Each subtype exhibits distinct radiologic features that may be mimicked by various benign and malignant entities. For accurate diagnosis, it is important to be aware of radiographic and cross-sectional imaging features that allow differentiation of each nonconventional subtype of OS from its mimics [(6)].

The primary tumor must be evaluated by plain radiographs in two planes, which are mainly helpful to describe osseous changes, complemented by cross-sectional imaging, ideally magnetic resonance imaging (MRI), both of which should be performed before biopsy. MRI is considered the most useful tool to evaluate an osteosarcoma's intramedullary and soft tissue extension and its relation to vessels and nerves [(7)].

Complete radical surgical en bloc resection is the treatment of choice in osteosarcoma [(1)]. The use of adjuvant postoperative systemic chemotherapy is critical for the treatment of patients with OS [(8)].

The present understanding of outcome and prognosis for osteosarcoma is driven by certain serum markers, clinical staging and histologic response to chemotherapeutic agent.

AIM OF THE ESSAY

The aim of this essay is to highlight the literature on the Nonconventional Osteosarcoma by discussing the recent updated classifications, etiology, pathogenesis, diagnosis, different options of the treatment, prognosis and follow-up.

EPIDEMIOLOGY

Osteosarcoma follows a bimodal distribution, with an initial peak in the late adolescent and young adult period and a second peak during or after the 6th decade of life [(3)].

Adolescent and early adult osteosarcoma (ages 0–24 years) occurs at an age-adjusted incidence of 4.4 per million within the United States. Incidence is higher among males (male:female ratio, 1.43:1), but peaks earlier among females (age 12 vs 16 years). An association between rapid bone growth and osteosarcoma has been argued, given the tumor’s typical metaphyseal location and its peak incidence during adolescence and early adulthood [(9)].

Incidence is highest among Asian/Pacific Islanders (5.3 per million) followed by blacks (5.1 per million), Hispanics (4.9 per million), whites (4.4 per million), and American Indian/Alaskan natives (3.0 per million).

The second peak, between the ages of 60 and 85, demonstrates an incidence within the United States of 4.2 per million, and is overall more common among females (male:female ratio, 0.89:1), though Paget-associated osteosarcoma is more frequent among males (male:female ratio, 1.58:1).

The greatest incidence within this age group is among blacks (4.6 per million), followed by whites (3.7 per million), Hispanics (3.0 per million), American Indian/Alaskan natives (2.9 per million), and Asian/Pacific Islanders (1.9 per million) [(2)].

OS occurs most frequently in the lower long bones [(10)].

Face or skull		
Age	5-yrRS	% of AS
0–25	64.9%	3.2%
60+	32.5%	5.3%

Mandible		
Age	5-yrRS	% of AS
0–25	64.5%	1.9%
60+	36%	5.8%

Vertebral column		
Age	5-yrRS	% of AS
0–25	58.9%	1.2%
60+	5.7%	4.9%

Pelvic region		
Age	5-yrRS	% of AS
0–25	25.4%	3.6%
60+	4.4%	18.8%

Lower long bones		
Age	5-yrRS	% of AS
0–25	64.1%	74.5%
60+	29.8%	26.7%

Chest region		
Age	5-yrRS	% of AS
0–25	51.9%	1.8%
60+	19.7%	4.1%

Upper long bones		
Age	5-yrRS	% of AS
0–25	56.6%	11.2%
60+	7.3%	7.5%

Upper short bones		
Age	5-yrRS	% of AS
0–25	75%	0.3%
60+	78%	0.7%

Lower long bones		
Age	5-yrRS	% of AS
0–25	86.8%	1.1%
60+	27.6%	1.4%

Figure (1): Five-year relative survival rates (RS) by anatomic site (AS) for individuals with osteosarcoma age 0–25 years and 60+ years.The percent (%) of AS is the % of patients in that age group with osteosarcoma at that location [10].

RISK FACTORS AND PATHOGENESIS

1. Bone Growth and Tumorigenesis

OS has a predilection for developing in rapidly growing bone. A number of studies have established a correlation between the rapid bone growth experienced during puberty and osteosarcoma development [11].

2. Environmental Factors

Physical, chemical, and biological agents have been suggested as carcinogens for osteosarcoma. Among these, the role of ultraviolet and ionising radiation is the best established. However, radiation exposure is implicated in only 2% of cases of osteosarcoma and is not thought to play a major role in paediatric disease [12].

The chemical agents linked to osteosarcoma formation include methylcholanthrene and chromium salts, beryllium oxide, zinc beryllium silicate, asbestos, and aniline dyes [13].

3. Chromosomal Abnormalities

A number of chromosomal and genetic syndromes have been linked to osteosarcoma. Osteosarcoma has been reported in patients with Bloom syndrome, Rothmund-Thompson syndrome, Werner syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma [14].

4. Growth Factors

Dysregulated expression of growth factors such as transforming growth factor (TGF), insulin-like growth factor (IGF) and connective tissue growth factor (CTGF) leads to the accelerated proliferation of cells [15].

Parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), and the receptor (PTHR1) have been implicated in the progression and metastasis of osteosarcoma [15].

5. Tumour Angiogenesis

Tumour angiogenesis is essential for sustained osteosarcoma growth and metastasis. Without a supporting vasculature, osteosarcoma cells would be unable to obtain the nutrients and oxygen necessary for proliferation.

Metastasis to the lungs and bone, the most common sites for osteosarcoma spread, also relies on the formation and maintenance of blood vessels. Radiation therapies, while compromising tumour cells, also destroy the vascular component of tumours and block the supply of nutrients. So, radio- and chemotherapies act by these dual actions [15].

6. Tumor Invasion

Invasion of the surrounding tissues by osteosarcoma also involves degradation of the extracellular matrix. Matrix metalloproteinases (MMPs) are principally involved in the breakdown of the extracellular matrix and are regulated by natural inhibitors such as tissue inhibitors of MMPs (TIMPs), RECK, and $\alpha 2$ macroglobulin**.**In the setting of osteosarcoma, MMPs break down extracellular collagens, facilitating both tumour and endothelial cell invasion [16].

7. Osteoclast Function

Osteosarcoma invasion of bone relies on interactions between the bone matrix, osteosarcoma cells, osteoblasts, and osteoclasts. Osteoclasts are the principle bone-resorbing cells, and the substantial osteolysis exhibited by some osteosarcomas is the direct result of increased osteoclastic activity.

During the initial stages of osteosarcoma invasion, growth factors such as TGF-β are released from the degraded bone matrix and act on osteosarcoma cells, stimulating the release of PTHrP, interleukin-6 (IL-6) and interleukin-11 (IL-11). These cytokines then stimulate osteoclasts, facilitating further invasion and release of proresorptive cytokines [17].

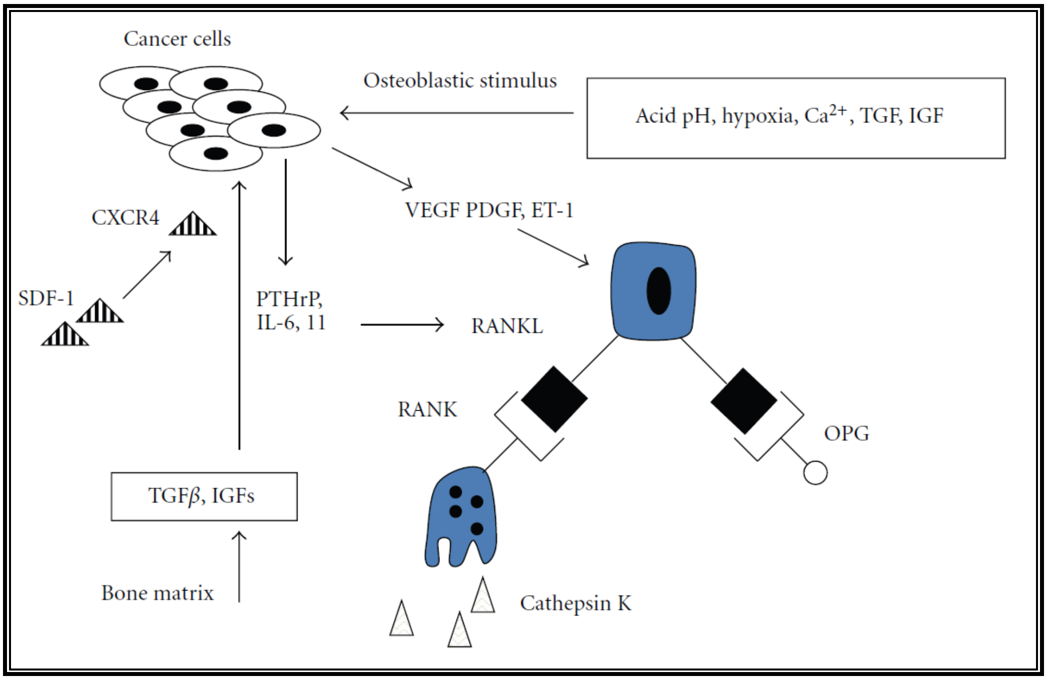

Figure (2): Vicious cycle of osteolysis by osteoclasts [15].

A. CLINICAL PRESENTATION

Patients typically present with localized pain and swelling of the affected area, with the most frequent sites of disease in descending order being the metaphyseal bone of the distal femur, the proximal tibia, and the proximal humerus. Although mild blunt trauma is often reported as an antecedent event, no convincing evidence to support an association between trauma and osteosarcoma currently exists. Pain may initially be described as activity- related, but over time it often progresses to pain at rest and night pain. Pain is typically reproducible with palpation [2].

According to European Society for Medical Oncology [18], the medical history should focus on symptoms such as duration, intensity and timing of complaints, for example night pain or fracture. Moreover, specific events for bone tumors include prior benign/malignant lesions, family history, and previous radiotherapy. A recent injury does not rule out a malignant tumor and must not prevent appropriate diagnostic procedures. All patients should have a full physical examination. Specific attention should be given to the size, consistency of the swelling, its location and mobility, the relation of swelling to the involved bone, and the presence of regional/local lymph nodes.

Clinical symptoms frequently last for weeks to months prior to presentation and are commonly attributed to “growing pains.” The median time from onset of symptoms to diagnosis is 4 months, though significant variability exists. Rarely, pathologic fracture is the presenting sign. Systemic complaints such as fever and weight loss are rare. Laboratory values are of little utility with the exception of alkaline phosphatase (ALP), which is elevated in approximately 40% of cases and lactate dehydrogenase (LDH), which is elevated in approximately 30% of cases [19].

Normal pretreatment ALP levels have been associated with improved 5-year disease-free survival (67% vs 54%) and a longer time to disease recurrence (25 months vs 18 months). LDH also offers prognostic information, with an extreme elevation portending a poor outcome [20].

Despite these and other studies, the clinical utility of these markers is debatable. Approximately 10–20% of patients present with macroscopic evidence of metastatic disease and approximately 80% of patients present with microscopic metastatic disease, which is subclinical or undetectable using current diagnostic modalities. Metastatic disease typically develops hematogenously, with the most common sites of metastasis being the lungs followed by other bones. Skip metastases described as occurring hematogenously, may represent locoregional events and may occur in a manner distinct from distant hematogenous spread. They are generally thought of as local noncontinuous spread of disease within the same bone as the primary tumor. While it may represent metastatic bone disease, it is currently unclear whether this process is exactly the same as more distant hematogenous spread. Regardless, the presence of skip metastases portends dismal prognosis and may reflect an inherently different biology in this subset of tumors [2].

Metastatic lung disease has a better prognosis than does either metastatic bone disease or skip metastases. Patients with lung disease who have fewer than 3 nodules and unilateral disease may have a survival advantage, probably because surgery can render such individuals free of disease. This advantage remains somewhat controversial, however, and it has been suggested that increased 5-year survival is related to tumor necrosis greater than 98% and a disease-free interval of greater than 1 year rather than nodule number or location [21].

Patients with either progressive tumor growth while undergoing systemic treatment or with recurrent disease have a less than 20% rate of long-term survival. Other commonly referenced prognostic indicators include LDH elevation and Huvos tumor necrosis grade, following standard neoadjuvant chemotherapy administration and wide surgical resection. Interestingly, modifications of neoadjuvant treatment regimens to achieve better tumor necrosis thus far have not affected survival outcomes [22].

It has been speculated that Huvos grading simply describes inherent tumor responsiveness to chemotherapy and is not an indicator of systemic chemotherapy effectiveness, and furthermore, that manipulation of chemotherapy to improve local necrosis does not necessarily improve overall patient survival [2].

B. INVESTIGATIONS

I. Imaging studies

Conventional radiographs in two planes should always be the first investigation. When the diagnosis of malignancy cannot be excluded with certainty on radiographs, the next imaging step is magnetic resonance imaging (MRI) of the whole compartment with adjacent joints, which is the best modality for local staging of extremity and pelvic tumors [23]. Computed tomography (CT) should be used only in case of diagnostic problems or doubt, to visualize more clearly calcification, periosteal bone formation, cortical destruction, or soft tissue involvement [18].

Bone scans with technetium-99m show an increased uptake in primary tumour corresponding with bone formation and increased vascularity in the tumour area. Nuclear bone scanning is therefore very useful in evaluating skip metastases and metastases in other skeletal sites. Positron emission tomography (PET) is an important nuclear imaging modality [24].

II. Biopsy

The biopsy should be performed as the final step in the staging process, after imaging studies have been reviewed and considered by the multidisciplinary sarcoma team.

Biopsies may be performed in the operating room in an incisional open manner or as an outpatient procedure using a core needle technique.

An incisional biopsy yields a large amount of tissue and enjoys the highest rate of diagnostic success, approximately 96%. Careful hemostasis is critical to minimize hematoma formation. Incision and drain site location are vital, as they ultimately need to be resected with the tumor in an en bloc manner.

Core needle techniques are also acceptable, and in the setting of malignant bone tumors, yield reasonable, albeit reduced, diagnostic accuracy ranging from 74% to 88 % [25], with positive predictive value reported to be above 98% [26].

Fine needle aspiration, while useful for the identification of malignant cytologic features, provides too small a sample with no appreciable histologic architecture, and is not appropriate for the diagnosis of a primary sarcoma.

The histological features of the tumor should be described and the tumor type and subtype specified according to the 2002 WHO classification.

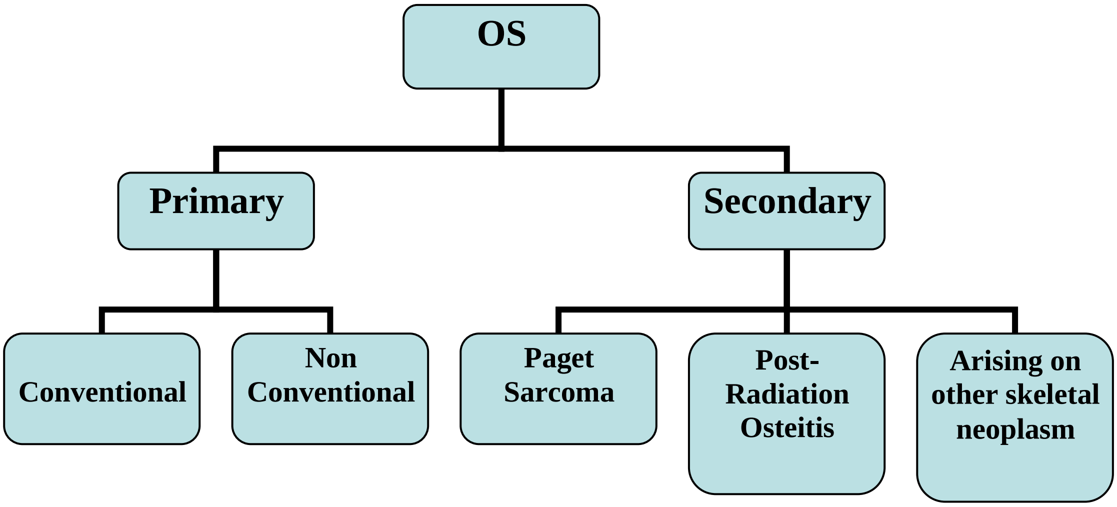

Figure (3): Osteosarcoma classification.

Staging system

Ideally, all cases of suspected bone tumors should be discussed at a multidisciplinary team meeting that includes the radiologist who has interpreted the imaging and the pathologist who has reviewed the biopsy material and the surgeon and oncologist undertaking treatment. This will minimize the risk of errors in diagnosis, staging, risk assessment, and treatment. Several staging systems for bone tumors are in use [27].

There are basically two systems used for staging OS. Enneking's classification was published in 1980 and contributed significantly to the research of OS. His system is simple to use and considers the histological grade of tumour, the local extent and the presence of metastases [24].

Stage	Site	Grade	Metastasis
IA	Intracompartmental	Low	No
IB	Extracompartmental	Low	No
IIA	Intracompartmental	High	No
IIB	Extracompartmental	High	No
III	Any	Any	Regional or distant

Table (1): Enneking's classification of osteosarcoma [28].

The other classification system is the American Joint Committee on Cancer staging system for musculoskeletal tumours. The AJCC staging score includes tumour size which is now rated as an important prognosticator [24].

Table (2): The New American Joint Committee on Cancer Staging System [29].

Stage	Local extent	Grade	Metastasis
IA	≤8cm	Low	None
IB	>8cm	Low	None
IIA	≤8cm	High	None
IIB	> 8cm	High	None
III	Any	Any	Skip metastases
IV-A	Any	Any	Pulmonary metastases
IV-B	Any	Any	Other metastases

The purpose of staging is three-fold:

1- First, a tissue diagnosis should be established.

2- Second, the extent of the local tumour should be defined in terms of medullary extension, soft tissue and neurovascular penetration, joint involvement and skip lesions in the same bone.

3- Finally, it is pivotal to identify and quantify metastatic disease.

General staging should be carried out to assess the extent of distant disease, including bone scintigraphy, chest radiographs, and CT [30].

Whole-body MRI and positron emission tomography (PET)/CT or PET/MRI are under evaluation both for staging and treatment response evaluation[31].