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Review Article

An Update on Osteosarcoma

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Abstract

Following lymphomas and brain malignancies, osteosarcomas are the most prevalent primary bone tumours in children and adolescents. The development of osteoid, or immature bone, by malignant mesenchymal cells serves as its defining characteristic. However the cause of the OS is still unknown, however in children, the disease appears to be sporadic. Genetics also plays major role in OS, thus This article examines the origin, clinical manifestation, diagnostic procedures, and treatment of osteosarcoma. Adjuvant chemotherapy was introduced in the 1970s, increasing patient 10-year survival from 30% to around 50% as a result of tumour excision. The first step to enhancing these figures is a greater comprehension of this illness.

Keywords: Osteosarcomas; Pagets Disease; Malignant Mesenchymal Cells; Tumour; Osteoid; Limb Salvage; Osteoblast, Plain Radiograph; Computed Tomography; MRI; MFH (Malignant Fibrous Histiocytoma)

Introduction

Osteosarcoma is most common primary malignancy of bone that represent 50-70% of skeletal tumour also known as osteogenic sarcomas it is highly destructive and it is second most common type of primary malignant tumour of bone after multiple myeloma. This tumour mostly affects children, adolescents and adults between 10-25 years of age. With 3.4 incidences per million individuals worldwide each year, it is a very uncommon bone tumour. The histology findings of osteoid development in conjunction with malignant mesenchymal cells are characteristic of the uncommon sarcoma known as osteosarcoma. They are aggressive neoplasm, with local bone destruction, they Invade to nearby soft tissues, and have highly metastatic potential most Often to lungs. This disease is very rare before the age of five. Formation of pseudo capsule around the penetrating tumour and pleomorphic spindle shaped cells capable of producing osteoid matrix is the peculiar feature of this tumour. Person suffering from Pagets disease have high risk of having this tumour, about 56% of all osteosarcomas present around knee and this disease is more common in male as compared to female, Patients suffering from OS are commonly taller in comparison to population of same age group. The actual cell origin of osteosarcoma is unknown, but it is believed that osteosarcoma most likely is derived from mesenchymal stem cells or progenitor cells in the osteoblast lineage as a result of disruption in the Osteoblast differentiation pathway. OS mostly arises from the medullary Cavity of the metaphysis of the growing long bones or they may also arise on the surface of long bones or confined only to cortex or they may arise at extracellular site. OS arises from medullary cavity is mostly high grade osteosarcoma whereas OS arising from surface of bone is of lower grade. Distal femur (30%) followed by proximal tibia (15%) and proximal humerous (15%) are most affected bones due to presence of proliferative

growth plates. The tumour is primary when the underlying bone is normal and secondary when it is altered by condition such as prior irradiation, infarction or other disorders. For diagnosis, evaluation, the degree of tumour involvement, and the division of the kind of operation and, if necessary, the type of reconstruction, plain radiographs, computed tomography, MRI, angiography, and bone scintigraphy are utilised. Years ago all patients of OS were treated with amputation but the cure rate was only 10% and all patients died within year of diagnosis. The percentage of patients who are cured now for localised OS at onset cases treated in specialised bone tumour centres with pre and post-operative chemotherapy followed by surgery varies from 60 to 70%. For more than 90% of patients, surgery is conservative (limb salvage). However, an open biopsy or a fine needle biopsy is used to confirm the diagnosis of OS in order to examine the tumor's histology. Currently, limb-sparing surgery is followed by a four-drug neoadjuvant therapy comprising of large doses of methotrexate, doxorubicin, cisplatin, and ifosfamide [1].

Bone

Your body's structural framework is made of bone. Bones are typically hollow. According to the American Cancer Society and other researchers (2016), calcium salts are deposited onto a network of fibrous tissue called matrix that makes up the outside of bones. Compact (cortical) bone makes up the dense exterior layer of bones, which covers the softer, more porous trabecular bone inside. The periosteum, a layer of fibrous tissue, covers the exterior of the bone. The soft tissue known as bone marrow is found in the medullary cavity of some hollow bones [3]. Bone has two different types of cells and is extremely strong and durable. The cells that form new bone are called osteoblasts, while the cells that break down existing bone are called osteoclasts. New bone is constantly developing and old bone is constantly disintegrating throughout our bodies. Our bones benefit from two primary cell types that maintain them strong and in the right shape.

- By creating the bone matrix, osteoblasts contribute to bone formation (the connective tissue and minerals that give bone its strength).
- Osteoclasts assist bones maintain their appropriate structure by breaking down bone matrix to stop too much from growing up.

Osteoblasts and osteoclasts contribute to maintaining the balance of these elements in the blood by adding or removing minerals from the bones. In some bones the marrow is only fatty tissue. The marrow in other bones is a mixture of fat cells and blood forming cells. The blood-forming cells produce red blood cells, white blood cells, and blood platelets. Other cells in the marrow include plasma cells, fibroblasts, and reticuloendothelial cells.

Bone cancer

Bone cancer starts in the bone. When the body's cells start to proliferate out of control, cancer develops. Cancerous cells can develop in almost any portion of the body and spread to other organs. A neoplastic development of bone tissue is referred to as a bone cancer.

Bone abnormal growths can either be benign or cancerous [4].

Types of bone cancer

On the basis of previous studies the bone cancer may be classified into two groups.

Figure 1: Diagrammatic representation for types of bone cancer.

Primary bone cancer

A primary bone cancer begins in the bone itself or in tissues and cells that are derived from bones. Sarcomas are real (or primary) cases of bone cancer. The distal femur and proximal tibia (around the knee joint) are frequent sites for primary (benign and malignant) bone cancer [6]. Two more categories for bone cancer may be used [7].

Primary benign bone cancer

The primary benign bone cancers are mostly neoplastic, developmental, traumatic, infectious or inflammatory in etiology. Examples of primary benign bone cancers are: Enchondroma, Osteoidosteoma, Osteochondroma, Osteoblatoma, Chondromyxoid Fibroma and Giant cell tumor of bone (It is initially benign and then after converts into malignant).

Primary malignant bone cancer

The original malignant bone tumours are etiologically fast-spreading and highly metastatic. Osteosarcoma, Chondrosarcoma, Ewing's Sarcoma, Fibrosarcoma, MFH (Malignant Fibrous Histiocytoma)/PUS (Pleomorphic Undifferentiated Sarcoma), and Giant Cell Tumor of Bone are examples of primary malignant bone tumours (It is initially benign and then after converts into malignant).

Secondary bone cancer

When cancer cells from a primary tumour in another part of the body travel to the bone, it results in secondary cancer. Sometimes only a single bone region is impacted. However, the disease will typically spread to several locations in most patients. The terms "bone secondaries" and "bone metastases" can both refer to secondary tumours in the bone. Always, a primary cancer in another part of the body is the root cause of secondary cancer in the bone.

[https://www.macmillan.org.uk/information-and-support/bone-cancersecondary/understanding-cancer/what-is-secondary-bone cancer.html]

Figure 2: The diagram shows cells breaking away from a tumor and spreading into the blood stream.

Osteosarcoma

The most prevalent primary malignant bone tumours are osteosarcomas. Clinical and surgical approaches to treating OS have undergone significant change. Despite these advancements, OS treatment has not yet used a specific targeted therapy.

OS is the second cause of cancer-related death and the third most prevalent malignant disease in adolescents worldwide. OS is the most typical malignant bone tumour in children. According to histology, it is a primary mesenchymal tumour that affects kids and young adults by causing malignant cells to create osteoid [8,9].

Osteosarcoma is a spindle cell tumour of the bone that forms osteoid. A malignant tumour that produces osteoid called an osteosarcoma arises from primitive mesenchymal bone-forming cells. The simplest way to recognise OS is by its anatomical position.

Conventional OS indicates that intramedullary cancers are more frequent than surface (periosteal) lesions. According to Nguyen., *et al*. [10], osteosarcoma tumours differ depending on the line of differentiation, histologic grade, tumour site, and previous treatments. Osteosarcomas are derived from primitive mesenchymal cells.

They originate from bone and only rarely from soft tissue. Untreated, they run a dismal course with local and often metastatic disease progression. Before the introduction of polychemotherapy >90% of patients with osteosarcoma died from pulmonary metastases [11]. The primary malignant bone tumour that most frequently affects kids, teenagers, and young adults is osteosarcoma. Long bones have a tendency to develop osteosarcoma, which most frequently affects the distal femur (43%), proximal tibia (23%), or humerus (10%) [12].

The damaged bone will typically start to hurt and swell, and the discomfort will typically be so severe that it will cause the patient to become awake. A pathologic fracture can occasionally cause a patient to present dramatically, with the onset of significant pain or other symptoms. At presentation, 15%-20% of individuals will have clinically discernible metastases. The most frequent site of metastasis for disease, the lung, accounts for more than 85% of all cases, while the second most frequent site is the bone [12].

A thorough history, physical examination, and plain radiographs are the first steps in the evaluation of a patient with probable osteosarcoma [13]. Few cases of OS are known to be caused by hereditary disorders in cell cycle regulation, while approximately 70% of tumour tissues show a chromosomal aberration. These frequently entail changes to DNA helicases or tumor-suppressor genes [14]. In terms of anatomical location, radiographic appearance, histological subgroups, sites of metastases, progression, and response to therapy, osteosarcomas are diverse tumours [15].

Osteosarcoma is currently thought to be the second causative agent of cancer-related deaths among children and young adults. Although osteosarcomas often develop from the metaphysis of a developing long bone's medullary cavity, they could even develop on a bone's surface or be restricted to the cortex may occur in a soft tissue (extra-skeletal) location [16].

S. No.	Risk Factors	Reason
1	Age	Most osteosarcomas occur during the teen growth spurt
2	Height	Children with this cancer usually are tall for their age.
3	Gender	This cancer is more common in boys than girls.
4	Radiation Treatment	People treated with radiation therapy have a slightly higher risk.
5.	Bone Diseases	People with some non-cancerous bone diseases such as Paget disease or multiple hereditary osteochondromas (benign bone tumors) have a slightly higher risk
6.	Genetic Factor	Children with some inherited cancer syndromes may be at higher risk of osteosarcoma. Those include retinoblastoma, a rare eye cancer; Li-Fraumeni syndrome; Rothmund-Thompson syndrome; Diamond-Blackfan anemia; Bloom syndrome; and Werner syndrome

Table 1: Possible risk factors for Osteosarcoma. [https://www.ummchealth.com/Health_Care_Services/Cancer/Children/Cancer_Types/Bone_Cancer/Osteosarcoma/Risk_Factors_and_Symptoms/Risk_Factors___Symptoms.aspx].

Typically, OS appears in growing bones, such as those near the ends of long bones, in children and young adults. Most cancers grow in the proximal tibia or distal femur, the bottom portion of the thigh bone, which surrounds the knee (the upper part of the shinbone). The next most frequent location is the proximal humerus, which is the portion of the upper arm bone closest to the shoulder. But any bone, including those in the jaw, shoulder, and pelvic (hips), can develop OS. Older folks are most affected by this. OS typically appears in children.; however it may develop exceptionally any age in any bone.

Figure 3: Prevalence of bone tumors with occurrence of Osteosarcoma in bony regions.

Adjuvant chemotherapy was first used to treat OS in the 1970s, raising survival rates to 50% [17], Amputation was the standard course of treatment for high-grade OS until to the mid-1970s. By 1990, chemotherapy and limb salvage began to receive more attention in the management of high-grade OS. The survival rate as of right now is around 65% [18].

Subtypes of osteosarcoma

The OS can be divided into three grades: high grade, intermediate grade, and low grade depending on how they appear under a microscope. The tumor's grade informs medical professionals of the likelihood that the cancer may progress and spread to other bodily parts.

High grade osteosarcoma

These osteosarcomas grow at the fastest rate. They mimic aberrant bone when observed under a microscope, and they even

include many of cells that are going through cell division. High grade OS primarily affects children, and the three most common types are osteoblastic, chondroblastic, and fibroblastic high grade OS.

Intermediate grade osteosarcoma

Between high-grade and low-grade osteosarcomas are these infrequent tumours.

Periosteal (juxtacortical intermediate grade) tumours frequently form between the cambium and cortex layers of the periosteum. These tumours are visible under the microscope as regions of calcified cartilagenous material. These operating systems grow at the slowest rate. Under a microscope, they frequently look like ordinary bone and have few dividing cells. the typically seen Low Grade OS.

Figure 4: Diagrammatic representation for types of Intermediate Grade Osteosarcoma.

Low grade osteosarcoma

These OS have the slowest rate of growth. They often have few dividing cells and resemble regular bone under the microscope. The Low grade OS, which is frequently seen.

Parosteal Juxtacortical low grade OS, which makes up 4-6% of all OS cases, develops from the periosteum and primarily affects the distal femur's posterior parts. Low grade OS that is well differentiated and intramedullary or intraosseous.

Prevalence

Cancers are prevalent, but osteosarcoma is not. In the US, between 800 and 900 new cases of osteosarcoma are identified every year. About half of these are in children and teens. Between the ages of 10 and 30 is when children and young adults are most

Figure 5: Diagrammatic representation for types of Low Grade Osteosarcoma.

likely to develop osteosarcoma. Although teenagers are the age group most frequently affected, osteosarcoma can strike anyone at any time. Over 60-year-old patients account for 10% of all osteosarcoma cases. Osteosarcomas make up about 2% of children malignancies but a significantly lesser portion of adult cancers. Geographic Pattern is mostly responsible for irregular incidence of OS. Selected populations from Latin America and Asia (Indian, Japanese, and Chinese) have low OS prevalence rates [19]. As discussed above Prevalance rate of OS is higher in male Population in comparison to females in most of the countries, male to female ratio of 1.28:1is common in age groups between 25-59 and even higher (1.43:1) in the group aged 0-24. While there is variance in the ratio across populations, for example, in Western Europe, the OS incidence is higher in females aged 60+ than in males of the same age, and in Australia and Canada, the incidence is even higher in males aged 75+ [20]. One meta-analysis showed that people who are "extremely tall" and "taller than normal" are at an elevated risk of developing osteosarcoma, and people who have frequent pregnancies are also at an elevated risk of OS [21]. According to a study by Longhi., *et al*. [22], there is a substantial link between height and the diagnosis of osteosarcoma in growing persons. This finding suggests that growth hormones and/or rapid bone growth during puberty and in utero may be involved in the pathogenesis of cancer. In the US, Asian/Pacific Islander children and adolescents are most commonly diagnosed with OS, followed by African Americans (25-59 years) and Caucasians (60+ years) [23]. According to data published for the years 1975-1995, In African American populations, Prevalance rate of OS is higher in children and young adolescents, while lower prevalence rate

were present among Caucasian Americans [23]. One of the recent study by Bleyer A., *et al*. [24], also observed that incidence of OS is very high in African American including Hispanics, compared to Caucasian American populations [24]. Similarly in older groups also OS is diagnosed with a higher rate in African Americans as compared to Caucasians [25]. This was supported by rates of 4.6 cases per million people in Black people compared to 3.7 for non-Hispanic White, 3.0 for Hispanic people, 2.9 in American Indian/Alaska Native and 1.9 for Asian/Pacific Islanders aged 60+ years old [21].

Figure 6: Prevalence of Osteosarcoma in different countries using analysis based on Human Development Index (HDI).

Signs and symptoms of osteosarcoma

Osteosarcoma are usually found because of the symptoms they cause, listed below:

- **Pain and swelling:** The most typical symptom of OS is pain in the affected bone, which is typically located in the upper arm or around the knee. At first, the pain might not be constant and may be worse at night. The pain often increases with activity and may result in a limp if the tumor is in a leg bone.

- **Swelling:** Localized swelling is another common symptom, but it could not become apparent for a few weeks after the pain first manifests. Depending on where the tumour is, you might be able to feel a lump or mass. In young children and teenagers who are healthy and active, limb swelling and discomfort are extremely common. They may not immediately necessitate a visit to the doctor because they are much more likely to be caused by common bumps and bruises. This can delay a diagnosis. If your child exhibits these symptoms and they don't go away within a few weeks (or if they get worse), you should see a doctor so that the cause may be identified and, if required, treated.

Bone fractures (breaks) Because osteosarcoma weakens the bone in which it forms, bones frequently do not break. Osteosarcomas are uncommon, weaken bones more than other bone tumours, and increase the risk of fracture at the site of the tumour. Although osteosarcoma may weaken the bone it develops in, fractures (breaks) are uncommon. People with fractures near to or through an OS frequently recall a leg that was achy for a few months before suddenly becoming extremely painful when the fracture occurred. Rare telangiectatic osteosarcomas are an exception, as they tend to weaken bones more than other types and are more likely to result in breaks at the tumour site. Individuals who have suffered a fracture next to or through an osteosarcoma frequently describe a limb that was painful for weeks or months. The most common symptoms of osteosarcoma include:

- Bone pain or tenderness.
- A mass (tumor) that can be felt through the skin.
- Swelling and redness at the site of the tumor.
- Increased pain with lifting (if it affects an arm).
- Limping (if it affects a leg).
- Limited movement (if it affects a joint

Pathophysiology of OS

- **Environmental Factors:** According to some theories, osteosarcoma-causing physical, chemical, and biological factors exist. The roles of ionising radiation and ultraviolet light are the most understood of these. In women who put radium to watch faces to make them luminous [26], the first pathogenic association between radiation exposure and osteosarcoma was discovered. However, only 2% of cases of osteosarcoma are related to radiation exposure [27], Chemicals such as methylcholanthrene, chromium salts, beryllium oxide, zinc beryllium silicate, asbestos, and aniline dyes have all been related to osteosarcoma development [28-31].
- **Chromosomal Abnormalities**: The most frequent genomic abnormalities in osteosarcoma are amplifications of chromosomes 6p21, 8q24, and 12q14, as well as loss of heterozygosity of 10q21.1, according to a recent study of pretherapeutic biopsy samples. Additionally, it was determined

that patients with these alleles had worse prognoses [32], Osteosarcoma is associated with a number of chromosomal anomalies, including the deletion of chromosomes 9, 10, 13, and 17, as well as the gain of chromosome 1 [33].

Tumour suppressor gene dysfunction

Two well-known tumor-suppressor genes are p53 and retinoblastoma (Rb). Tumor suppressor genes, however, may experience their own mutations and lose their protective ability. As a result, more somatic mutations could develop, leading to a cell line that replicates uncontrollably. Pathogenesis of osteosarcoma has been linked to mutations in the p53 and Rb genes [34], In 50% of all malignancies and 22% of osteosarcomas, the p53 gene is mutated [33]. The osteosarcoma tumorigenesis has also been linked to the Rb tumour suppressor. The Rb gene is essential for controlling the cell cycle, and an inherited mutation of the Rb gene results in retinoblastoma syndrome, which predisposes a person to a variety of cancers, including osteosarcoma. Through its interaction to the transcription factor E2F, the Rb protein controls the cell cycle. Rb inhibits E2F until it is phosphorylated by the CDK4/cyclin D complex. The constant cycling of cells is made possible by Rb mutations [35], and both germ-line and somatic Rb mutations enhance the risk of osteosarcoma. Even the familial risk of osteosarcoma may be explained by the loss of the Rb gene [36].

Transcription factors

From double-stranded DNA, messenger RNA (mRNA) sequences are created during transcription. In order to start the process, transcription factors make it easier for promoter sequences for particular genes to bind. While transcription is typically tightly regulated, osteosarcoma, like other malignancies, may experience deregulation. Gene rearrangement may lead to the overproduction of transcription factors or the creation of a brand-new, hyperactive transcription factor. The activator protein 1 complex (AP-1) regulates transcription and affects the differentiation, proliferation, and bone metabolism of cells.

The Foes and Jun proteins, which come from the c-foes and c-jun proto-oncogenes, respectively, make up AP-1. When compared to benign Osteoblastic lesions and low-grade osteosarcomas, high-grade osteosarcomas had much higher levels of Foes and Jun, which are linked to the likelihood of metastases [37,38]. Myc is a transcription factor that promotes cell division and proliferation in the nucleus. Myc amplification has been connected to the development of osteosarcoma and its chemotherapy resistance. Osteosarcoma growth and adiposity loss are caused by the overexpression of Myc in bone marrow stromal cells [39].

The most doxorubicin-resistant U2OS osteosarcoma cell-line variations have increased Myc, and SaOS-2 methotrexate-resistant variants have gained Myc [40]. Numerous growth factors are produced by osteosarcoma cells, and they have both autocrine and paracrine effects. Cell proliferation is enhanced when growth factors like connective tissue growth factor (CTGF), transforming growth factor (TGF), and insulin-like growth factor (IGF) are expressed in a dysregulated manner. Growth factor receptors may be constitutively active and overexpressed. These receptors' related signal transduction may also be overactivated. Growth factors including IGF (insulin-like growth factor)-I and IGF-II are frequently overexpressed in osteosarcomas. When these ligands bind to the appropriate receptors, like the IGF-1R, the PI3K and MAPK transduction pathways are activated. Thus, this encourages cell division [41].

Anoikis, a type of apoptosis, is brought on when cells are detached from a matrix or basement membrane. Given the propensity of osteosarcoma cells to separate from matrix components and to metastasize, this is particularly relevant to the disease. Despite abnormal cell-cell and cell-matrix interactions, osteosarcoma cells are resistant to anoikare and continue to grow. Anchorage-independent growth is the word for this resistance to Anoikis (AIG).

Diagnosis

Osteosarcoma is usually found when a person goes to the doctor because of signs or symptoms they are having. If a bone tumor is suspected, tests will be needed to find out for sure.

Medical history and physical exam

A doctor will want to take a thorough medical history to learn more about the symptoms if a patient exhibits signs or symptoms that point to a tumour in or near a bone. A physical examination might reveal information about potential tumours and other health issues. An aberrant lump, for instance, can be visible or palpable to the doctor.

Plain radiography

Simple radiography is useful for describing osseous changes because osteosarcomas can appear osteoblastic, osteolytic, or mixed. They frequently include soft tissue, where patchy calcifications from newly formed bone or spiculae may be seen. The Codman triangle, which is thought to be typical for osteosarcomas, is a triangular area of periosteal calcification at the boundary between the tumour and healthy tissue.

Imaging tests Imaging tests provide images of the interior of the body using x-rays, magnetic fields, or radioactive materials. There are several reasons to perform imaging exams, including:

- To assist in determining whether a suspicious region has cancer
- To assist in figuring out whether a cancer may have originated in another area of the body.

To establish whether the treatment is effective

- **Bone x-ray:** Bone images can be captured using a bone X-ray. Another name for it is bone radiography. In this test, the body is exposed to a small amount of radiation, which results in digital images of the bones or images on film. When a doctor suspects a bone tumor, this is frequently the first test performed. On the basis of straightforward bone x-rays, doctors can frequently identify a bone tumour like OS. However, additional imaging tests might also be required.

Computed tomography (CT) scan the definition of cortical abnormalities, fracture sites, mineralization, and neurovascular involvement can be accomplished with the help of computed tomography (CT) scans. The CT scan creates fine cross-sectional images of various body parts using x-rays. When a bone x-ray reveals a malignancy, CT scans are occasionally used to determine whether the tumour has spread to adjacent muscle, fat, or tendons, though MRI is frequently preferable in this situation. A CT scanner rotates around a person laying on a table, taking multiple images as it goes, unlike a standard x-ray, which only captures one.

Magnetic resonance imaging (MRI) scan for a safe definitive surgery, magnetic resonance imaging (MRI) is the ideal modality to evaluate the soft tissue component, its interaction to adjacent tissues, arteries, and nerves, and its intramedullary extension. To ensure that lesions, such as intramedullary tumour foci that do not directly touch the primary lesion, are not missed, an MRI must capture the entire affected bone as well as any nearby joints. Instead of using x-rays, these scans create detailed images using strong magnets and radio waves, which emit no radiation. Before the scan, a contrast agent called gadolinium may be injected into a vein to enhance visibility of features.

Chest x-ray

This examination is occasionally carried out to check for lung cancer spread. Although it can detect larger tumours, a CT scan is preferable for detecting smaller ones. A chest x-ray usually won't be necessary if a CT scan of the chest is performed instead.

Radionuclide bone scans

If a malignancy has migrated to other bones, bone scans might reveal this. Compared to standard x-rays, it can detect smaller metastatic areas. Scans of the bones can also reveal the extent of the bone damage brought on by the cancer. On the bone scan, portions of diseased bone will appear as thick, grey to black patches that have been given the name "hot spots." Although arthritis, an infection, or other bone illnesses can also create hot patches, they are signs of malignancy. To determine what is causing the change, Other imaging tests or a bone biopsy may be needed.

Positron emission tomography (PET) scan PET scans make use of glucose, a type of sugar bound to a radioactive atom. The radioactivity can be found with a specialised camera. A large amount of the radioactive sugar is absorbed by cancer cells due to their rapid metabolism. PET scans are excellent for scanning the complete body for cancer. Sometimes it can be used to determine if a tumour is cancerous or not (benign). To more precisely locate various types of cancer, it is frequently paired with CT scans.

X-rays

Most bone cancers show up on x-rays of the bone. The bone at the site of the cancer may look "ragged" instead of solid. The cancer can also appear as a hole in the bone. Sometimes doctors can see a tumor around the defect in the bone that might extend into nearby tissues (such as muscle or fat).

Biopsy A biopsy removes a portion of a tumor's tissue so that it may be examined under a microscope and evaluated in a lab. Only by doing this can it be determined that the tumour is cancer and not

another bone condition. If cancer is found, the biopsy can determine whether it is a primary bone cancer or cancer that originated elsewhere and disseminated to the bone (metastasis). Bone cancer is diagnosed using a variety of tissue and cell samples. It's crucial that your biopsy is performed by a surgeon with knowledge of the diagnosis and management of bone cancers. X-rays, the patient's age, and the location of the tumour are used to determine the type of biopsy that should be performed based on whether the tumour appears benign (not cancer) or malignant (cancer).

Needle biopsy Both fine (aspiration) and core needle biopsies are available. To prepare the area for the biopsy in both cases, a medication is administered first. A tiny amount of fluid and a few tumour cells are removed from the tumour using a syringe and a very thin needle during fine needle aspiration (FNA). If the tumour is close to the body's surface, the doctor may occasionally be able to feel where to place the needle. The doctor can guide the needle while viewing a CT scan if the tumour is too deep to feel. The procedure is known as a CT guided needle biopsy, and it is frequently carried out by an x-ray specialist by the name of ay. In it, the doctor removes a small cylinder of tissue (approximately 1/16 inch in diameter and 1/2 inch long) with a bigger needle. For the diagnosis of primary bone cancer, many experts believe that a core needle biopsy is preferable to FNA.

Surgical bone biopsy: In order to remove a little portion of tissue during this operation, the surgeon must make a skin incision to access the tumour. Another name for this is an incisional biopsy. An excisional biopsy is one in which the entire tumour is removed, not just a small portion of it. These biopsies are frequently performed while the patient is sedated (drugs are used to put you into a deep asleep). A nerve block, which causes a sizable area to become numb, can also be used. If this kind of biopsy is required, it's crucial that the surgeon performing the cancer removal also does the biopsy.

Lab tests

Every sample taken during a biopsy is submitted to a pathologist to be examined under a microscope. The tumour cells may also be subjected to tests to check for chromosome or gene alterations. With the aid of these tests, it is possible to distinguish OS from malignancies that resemble it under the microscope and, on occasion, to determine whether the OS is likely to react to treatment. If osteosarcoma is discovered, the pathologist will grade it, which is a gauge of how quickly the cancer is most likely to advance and spread based on the appearance of its cells. Low grade cancers have an appearance similar to that of normal bone tissue, but high grade cancers have a very aberrant appearance.

Blood tests

Although blood tests are not required to diagnose OS, they might be beneficial once one has been established. Before surgery and other treatments, blood cell counts and blood chemistry tests are performed to get a sense of a person's general health. For instance, high levels of chemicals in the blood, such as alkaline phosphatase and lactate dehydrogenase (LDH), can suggest that the OS may be more advanced than it appears. Additionally, these tests are utilised to keep tabs on a patient's health while they are receiving chemotherapy.

Osteosarcoma stages

After an osteosarcoma diagnosis, medical professionals will attempt to determine whether it has spread and, if so, how far. The staging procedure is what it is. How much cancer is present in the body is determined by the cancer's stage. It helps evaluate the cancer's severity and the most effective course of treatment. When discussing survival rates, doctors also refer to the stage of the malignancy. The results of physical examinations, imaging tests, and any biopsies are used to determine the stage of an osteosarcoma and are covered under Tests for Osteosarcoma.

Staging System of the Musculoskeletal Tumor Society (MSTS): The MSTS system, often called the Enneking system, is one that is frequently used to stage osteosarcoma. It is founded on three important pieces of knowledge:

- The tumor's grade (G), which is based on how it appears under a microscope and indicates how likely it is to enlarge and spread.

Tumors can be high grade (HG) or low grade (G1) (G2). High-grade tumour cells appear more aberrant, whereas low-grade tumour cells resemble normal cells more and are less likely to grow and spread quickly.

- The size of the primary tumour (T), which can be extra compartmental (T2) if it has spread beyond the bone into other surrounding structures, or intracompartmental (T1) if

it has largely remained within the bone. If the tumour has migrated to neighbouring lymph nodes, which are bean-sized collections of immune system cells, or to other organs, it has metastasized (M). M0 tumours are ones that have not migrated to the lymph nodes or other organs, whereas M1 tumours have.

The TNM staging system

The American Joint Commission on Cancer (AJCC) TNM method is another technique occasionally used to stage bone malignancies, including osteosarcomas. This system is founded on 4 important bits of knowledge:

- T specifies the size of the primary tumour and if it affects various bone regions.

N indicates how far the infection has progressed to surrounding (local) lymph nodes. Rarely do bone cancers move to the lymph nodes.

- M signifies if the cancer has metastasized (spread) to other bodily organs. (The lungs and other bones are the most typical sites of spread.)
- The tumor's grade, denoted by the letter G, depicts how the cells appear under a microscope. High-grade tumour cells appear more abnormally than low-grade tumour cells, which are less likely to grow and spread quickly.

Prognosis and survival rates of osteosarcoma

Mainly cure rate depends on the type of cancer, location, size and other factors. In most of the cases the neoplastic benign cancers are more curable then the malignant metasteogenic cancers.

Localized tumors

The 5-year survival rate for those with localised OS is between 60% and 80% with current treatments. If all of the visible tumour can be surgically removed (resected), certain malignancies have a higher chance of being cured. (Chemotherapy is still a crucial component of treatment for high-grade OS that can be totally removed. Without it, the likelihood of the cancer returning is still very high.).

Metastatic tumors

If the OS has already spread when it is first discovered, the 5-year survival rate ranges from 15% to 30%. If the disease has just reached the lungs or if all tumours (including metastases) are amenable to surgical removal, the survival percentage is closer to 40%.

Osteosarcoma treatment

Treatment for OS can be accomplished in various ways based on the different factors and methods.

Surgery for OS

- Radiotherapy for OS
- Chemotherapy for OS
- Other new forms of treatment for OS

Surgery for osteosarcoma

Surgery is an important part of treatment for virtually all OS. It includes:

- The biopsy to diagnose the cancer.
- The surgical treatment to remove the tumor(s) the main goal of surgery is to remove all of the cancer. If even a small number of cancer cells are left behind, they might grow and multiply to make a new tumor. To lower the risk of this happening, surgeons remove the tumor plus some of the normal tissue that surrounds it. This is known as wide excision.

Radiotherapy for osteosarcoma

High-energy rays or particles are used in radiation treatment to eliminate cancer cells. Radiation therapy does not play a significant role in the treatment of osteosarcoma because radiation does not readily kill osteosarcoma cells. If surgery cannot entirely remove the tumour, radiation therapy may be helpful in some circumstances. For instance, osteosarcoma might begin in the hip or the face, particularly the jawbone. In these cases, it is frequently impossible to completely eliminate the cancer. After removing as much as feasible, radiation is administered in an effort to eradicate any leftover cancer cells. After the radiation, chemotherapy is frequently administered. If the cancer has returned or surgery is not an option, radiation can also be used to help reduce tumour development and control symptoms like pain and swelling.

Radioactive drugs (radiopharmaceuticals)

Advanced osteosarcoma patients may benefit from the use of bone-seeking radioactive medicines such samarium-153 or

radium-233 to decrease tumour growth and relieve symptoms like pain. These medications are administered through a vein and build up in the bones. The radiation they emit once there kills the cancer cells. Since external beam radiation would need to be directed at each afflicted bone, these medications are especially effective when cancer has spread too widely among the bones. These medications may occasionally be combined with external radiation therapy directed at the most agonising bone metastases. The main adverse effect of these medications is a reduction in blood cell counts, which may raise the risk of bleeding or infections, particularly if blood counts are already low.

Chemotherapy for osteosarcoma

Drugs are used in chemotherapy, also known as "chemo," to treat cancer. The medications can reach and eliminate cancer cells throughout the body and are often administered into a vein or artery. For the majority of persons with osteosarcoma, chemotherapy is a crucial component of treatment (although some patients with low-grade osteosarcoma might not need it). When first discovered, the majority of osteosarcomas don't seem to have spread past the primary tumour. Combining chemotherapy with surgery reduces the likelihood that these malignancies will recur.

Chemo drugs used to treat osteosarcoma The drugs used most often to treat osteosarcoma include:

- Methotrexate (given in high doses along with leucovorin to help prevent side effects)
- Doxorubicin (Adriamycin)
- Cisplatin or carboplatin
- Epirubicin
- Ifosfamide
- Cyclophosphamide
- Etoposide
- Gemcitabine
- Topotecan.

Usually, 2 or more drugs are given together. Some common combinations of drugs include:

- High-dose methotrexate, doxorubicin, and cisplatin (sometimes with ifosfamide)
- Doxorubicin and cisplatin.
- Ifosfamide and etoposide
- Isocyanide, cisplatin (or carboplatin), and epirubicin.

Other new forms of treatment for osteosarcoma

Medication

Chemotherapy is frequently successful in treating OS, but occasionally it fails or the tumour develops a resistance to it over time. Researchers are examining more recent medication classes that target OS cells in various ways [42]. As The goal of clinical trials is to find a strategy to assist the patient's own immune system in identifying and attacking the OS cells. Some patients benefit when chemotherapy is combined with the immune-modulating medication muramyl tripeptide, often known as MTP or mifamurtide [43].

Immune therapy

As a non-specific immune modulator, muramyl tripeptide (MTP), a synthetic analogue of a component of bacterial cell walls, has been created [T. Asano., *et al*. 1993]. Acrophages are targeted by and activated by MTP. According to Kleinerman, administration of liposome-encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) raised TNFS levels [Kleinerman., *et al*. 1992]. The MTP-PE liposomes can deliver the drug specifically to monocytes and macrophages. Monocytes and macrophages become stimulated and tumoricidal after receiving MTP-PE. E. G. MacEwen and others 1989 The European Medicines Agency has authorised MTP for the treatment of patients with osteosarcoma in light of the investigations. These findings imply that the use of bacterial components in the treatment of osteosarcoma patients reduces the likelihood of recurrence and metastasis.

CYTOKINE: Numerous cytokines have been applied as immunotherapy in cancer patients. IFN- has been shown to be clinically effective in treating a number of cancers due to its capacity to induce differentiation and apoptosis as well as to inhibit proliferation and angiogenesis [J. Whelan., *et al*. 2010]. An worldwide randomised controlled trial examined the effectiveness of pegylated IFN—2b in individuals with osteosarcoma. Patients in the research received MAP therapy—methotrexate, doxorubicin, and cisplatin—with or without pegylated IFN-2b. Patients in the trial who had MAP or MAP + IFN—2b had 5-year overall survival

rates of 81% and 84%, respectively. Even though a research with a brief follow-up time reveals that adjuvant IFN-2b has little impact, the follow-up is still used to gauge long-term survival [S. S. Bielack., *et al*. 2015]. IL-2 stimulates the differentiation of lymphocytes into lymphokine-activated killer (LAK) cells, which can identify and eradicate a variety of tumour cells [J. B. Stern., *et al*. 1986]. Only a few clinical trials using IL-2 for sarcomas have been described [C. Meazza., *et al*. 2017]. Three-year event free and overall survival rates were 34% and 45%, respectively, in a clinical trial employing IL-2 with or without reinfusion of LAK for patients with metastatic osteosarcoma [C. Meazza., *et al*. 2017]. Two of the four patients with osteosarcoma showed a complete response in a study of high-dose IL-2 treatment for relapsed paediatric sarcoma, despite severe side effects that included increases in white blood cells (WBC), creatinine, glutamyltransferase, C-reactive protein, glucose, and body weight and decreases in red blood cells, platelets, protein, albumin, and cholinesterase [W. Schwinger., *et al*. 2005].

Peptide vaccine

In order to eradicate tumour cells, several vaccines targeting tumour lysates, proteins, and peptides have been employed in clinical trials in sarcoma patients [R. Takahashi., *et al*. 2013]. Tumor vaccines have also been used to activate patient immune systems. Antigen-presenting cells stimulate T cells that are specific for TAAs in the treatment of cancer because the tumour vaccines are shown on MHC molecules. Numerous vaccines have been looked into as potential vaccine therapies [R. Takahashi., *et al*. 2013], Tsukahara., *et al*. reported that high expression of papillomavirus binding factor was observed in osteosarcoma cell lines and tumor tissues.

Targeted therapy

Doctors are currently researching novel drugs that target particular chemicals on cancer cells. The term "targeted therapies" refers to them. Some of them are monoclonal antibodies, which are created versions of immune system proteins. These antibodies help to limit the growth of or kill cancer cells by attaching to certain proteins on the cancer cell. Antibodies against the protein insulin-like growth factor receptor 1 (IGF-1R), which may aid cancer cells in growing, are some examples that are currently being examined. [Weber., *et al*. 2015]. One such is dinutuximab (Unituxin), which binds to GD2, a protein crucial for the development of cancer cells. 1) Drugs that interfere with a tumor's capacity to form new blood vessels, such as Sorafenib (Nexavar) and Pazopanib, are among the other targeted treatments being investigated for use against osteosarcoma (Votrient). 2) Medicines like temsirolimus (Torisel) and everolimus that target the mTOR protein.

Conclusion

Osteosarcoma is highly occurred in adolescence and also in adults older than 65 years, it mostly occurs in subjects without germline mutations, hereditary syndromes associated with mutations in the TP53, RB, RECQ, WRN or BLM genes are also reported among osteosarcoma patients. Its a rare tumour, higher rate of incidence of the diagnosis of this deadly disease is mostly registered among young males of African origin, which was supported by the research findings conducted in Nigeria, Uganda, and Sudan. Whereas, high cancer rates are also detected among African Americans, suggesting genetic and racial predispositions to osteosarcoma. Most common site of OS occurrence is metaphysis of the long bones with femur (42%), tibia (19%) and humerus (10%) frequently found to be affected by the tumor, skull or jaw (8%) and pelvis (8%) are locations which are less frequently affected. The diagnostic and Prognostic marker for OS is serum alkaline phosphatase (ALP), with higher levels of ALP indicating higher disease burden. In case of adults this test is still a reliable marker for diagnosis in adults, whereas serum ALP levels vary in children and adolescents depending on age, sex, and puberty, rendering serum ALP unreliable as a diagnostic test for these patients, similarly serum acid phosphatase (ACP) varies along the same pattern as serum ALP in this age group, Study by Shimose and colleagues demonstrated that the ratio of ALP to ACP can be a better option to help diagnose osteosarcomas in children and adolescents. Increasing Patient survival rates in case of Osteosarcoma depends on clinicians being able to recognize the disease early and manage it appropriately, Still it needs to conduct more research to understand the cause, progression, genetic factors better testing options for earlier and more accurate diagnosis, and treatments that can reduce patient morbidity and mortality.

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