Osteosarcoma: Complete Image

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ABSTRACT

Osteosarcoma, also known as Osteogenic sarcoma is a type of cancer developed in connective tissues of the body. Studies show that 20% of total cancer patients may suffer from OS, especially kids and teens below 25 years of age. This type of cancer affects bone and its formation, leading to brittling or enlargement of compromised bone. The complete cure remains a question, yet there are many treatments that contribute to lower the effect, such as Radiotherapy, Chemotherapy, Gene Therapy etc. while some number of malignant tumours can be removed by surgery, prosthetics and limb salvage can pose problems to the oncologists regarding the age range of patients which are mostly paediatrics.

KEY WORDS: Osteosarcoma, bone, breast cancer, therapy.

INTRODUCTION

Osteosarcoma (OS) is a primary malignant tumour of the bone, occurring globally at a rate of 3.4 cases per million individuals annually [1]. The main pathway for osteosarcoma to spread is via direct entry into the bloodstream or lymphatic system [5]. Osteosarcoma (OS) is a high-grade malignancy of mesenchymal origin characterized by the production of osteoid. It represents the most prevalent primary bone cancer and frequently proves fatal in both paediatric and adult populations [2]. Before the 1970s, amputation was seen as the only way to stop the spread of cancerous cells, post 1970s adjuvant chemotherapy upscaled to 50% [1]. Osteosarcomas arise from primitive mesenchymal cells and typically develop in bone, with soft tissue involvement being rare. If left untreated, the disease tends to progress aggressively, both locally and through metastasis. Prior to the advent of combination chemotherapy, over 90% of individuals with osteosarcoma died of lung metastases [3].

Epidemiology

Osteosarcoma (OS) is an uncommon type of sarcoma characterized histologically by the presence of malignant mesenchymal cells producing osteoid [1]. Characterized by the presence of malignant mesenchymal cells responsible for producing osteoid and/or immature bone tissue [3]. Osteosarcoma ranks as the third most prevalent cancer among adolescents, surpassed only by lymphomas and brain tumours. Its annual incidence among children under 15 years of age is approximately 5.6 cases per million. The highest occurrence is observed during the second decade of life, while cases before the age of five are rare. Osteosarcoma typically arises sporadically, with limited associations to inherited defects in cell cycle regulation. However, approximately 70% of tumour samples exhibit chromosomal abnormalities [1]. Osteosarcoma occurs at a rate of 2–3 cases per million annually in the general population, with a significantly higher incidence during adolescence. The peak annual occurrence reaches 8–11 cases per million among individuals aged 15 to 19 years. In this age group, osteosarcomas constitute approximately 15% of all solid extracranial malignancies, with males being affected 1.4 times more often than females [3].

Etiology

Several environmental factors have been linked to a heightened risk of developing osteosarcoma in the future, such as radiation exposure, use of teriparatide, and childhood consumption of fluoridated drinking water. However, more recent research has challenged the associations with the latter two.

Secondary osteosarcoma is most frequently linked to Paget's disease of bone and prior radiation exposure. Experimental studies have demonstrated osteosarcoma induction in animals exposed to beryllium, alkylating agents, the Finkel-Biskis-Jinkins (FBJ) virus, and the Rous sarcoma virus. Additionally, case reports have documented associations between osteosarcoma and a history of electrical burns, physical trauma, and joint replacement procedures.

Types

There are majorly two types of OS, primary osteosarcoma and secondary osteosarcoma.

Primary Osteosarcoma

A. Central

Central, or intramedullary osteosarcoma (OS), is the most common subtype of this malignancy, typically originating within the bone marrow. It frequently affects the metaphyseal regions near the ends of long bones, including those in the arms and legs. On a cellular level, central OS develops due to abnormal behaviour in osteoblasts—specialized cells essential for bone growth and formation.[5]

Conventional OS

Conventional osteosarcoma (COS) most often presents as a central or intramedullary high-grade malignancy arising in the metaphyseal regions of long bones, and accounts for approximately 75–80% of all osteosarcoma cases. Microscopically, it consists of spindle to polyhedral-shaped cells with pleomorphic nuclei and frequent mitosis. The defining histological feature is the production of osteoid by tumour cells, which must be detectable—even in minimal amounts—within the lesion. Based on the dominant extracellular matrix, COS is traditionally classified into osteoblastic, chondroblastic, or fibroblastic subtypes.[4]

Telangiectatic OS

Telangiectatic osteosarcoma is characterized by abundant vascularity and minimal osteoid formation, which can pose challenges for both tissue biopsy and radiographic detection. This subtype tends to localize in the epiphyseal regions of bones. Given its classification as a high-grade malignancy, all such cases are presumed micro metastatic at the time of diagnosis and require treatment through surgical intervention combined with systemic chemotherapy.[2]

Small-cell OS

Small-cell osteosarcoma (SOS) accounts for approximately 1–2% of all osteosarcoma cases. Histologically, it is marked by small cells featuring round, hypo chromatic nuclei and minimal nuclear polymorphism, resembling the morphology seen in Ewing's sarcoma. However, the presence of osteoid produced by tumour cells confirms the diagnosis of osteosarcoma and distinguishes it from Ewing's sarcoma. Radiographic imaging typically reveals a destructive lesion characterized by both lytic areas and sclerosis.[1]

Low grade OS

Low-grade osteosarcoma (LOS) comprises approximately 1–2% of all osteosarcoma cases and typically presents in individuals in their third or fourth decade of life. Due to its subtle histological features, LOS can be challenging to diagnose, as it may mimic other lesions such as parosteal osteosarcoma, fibrous dysplasia, or desmoplastic fibroma. Although there is a potential risk of progression to conventional high-grade osteosarcoma if treated solely with curettage, LOS is generally associated with a markedly more favourable prognosis.[1] This tumour primarily arises in the metaphyseal regions of long bones in young adults and is distinguished by a low rate of mitotic activity.[4]

B. Surface

Surface osteosarcoma, also called peripheral OS, ranks as the second most prevalent subtype of the disease. Unlike central OS, it usually develops along the external surface of bones, presenting as a hardened, ossified growth. It most commonly affects the lower portion of the femoral shaft and is generally regarded as less aggressive compared to other osteosarcoma variants.[5]

Parosteal OS

Parosteal osteosarcoma (PAOS) is a low-grade variant of osteosarcoma that arises from the periosteal layer of bone. Accounting for 4–6% of all osteosarcoma cases, it most commonly affects the posterior surface of the distal femur, though it can also involve regions such as the proximal humerus and proximal tibia. Radiographic imaging typically reveals a densely ossified, lobulated mass with preservation of the medullary cavity. Histologically, PAOS is characterized by parallel-oriented bone trabeculae, resembling the pattern seen in periosteal reactive bone formation.[1]

Periosteal OS

Representing less than 1% of all osteosarcoma cases, this subtype originates in the space between the cortical bone and the inner layer of the periosteum. Histologically, periosteal osteosarcoma is characterized by parallel-arranged osseous trabeculae embedded predominantly in a chondroid matrix, with limited osteoid content. It is classified as intermediate-grade based on histological assessment.[4] Histologically, periosteal osteosarcoma exhibits chondroblastic characteristics and is the sole subtype classified as intermediate-grade. Based on the degree of tumour invasion, management typically involves systemic chemotherapy.[2]

High grade OS

High-grade osteosarcomas, including the classic osteoblastic variant, represent the most rapidly proliferating and aggressive category of osteosarcomas. Most subtypes fall within this group, encompassing

osteoblastic, chondroblastic, fibroblastic, small cell, telangiectatic, high-grade surface, and extra-skeletal forms.[2]

Secondary Osteosarcoma

Secondary osteosarcomas develop in structurally abnormal bone, most often affecting individuals over the age of 50, particularly near the knee or hip joints. These cases comprise approximately 4% of all osteosarcoma diagnoses. According to the 2020 WHO classification, secondary osteosarcomas are categorized into six distinct subtypes: those associated with Paget's disease of bone, radiation exposure, bone infarction, chronic osteomyelitis, orthopaedic implants, and underlying conditions such as fibrous dysplasia. Although histological features vary across subtypes, hallmark characteristics include osteoid formation by tumour cells, nuclear pleomorphism, and a high rate of mitotic activity.[4]

Staging

Cancer staging assesses how far a tumour has progressed or is likely to spread within the body, and serves as a critical tool in forecasting prognosis.[6] Tumour staging is conducted using either the Enneking/Musculoskeletal Tumour Society classification or the American Joint Commission on Cancer (AJCC) system. In the AJCC framework, staging is determined by four key components, each denoted by a letter: T for the size of the primary tumour, N for involvement of regional lymph nodes, M for the presence of metastasis, and G for histological grade.[2]

Table1. AJCC type of staging.[6]

Class	Grade(G)	Lymph node(N)	Metastasis(M)	Size(T)
IA	Low	None	None	TI < 8cm
IB	Low	None	None	T2＞8cm
IIA	High	None	None	TI < 8cm
IIB	High	None	None	T2＞8cm
III	Any	Skip metastasis	Skip metastasis	Any
IVA	Any	None	Lung metastasis	Any
IVB	Any	Lymph node metastasis/None	Non-lung metastasis	Any

Table2. MSTS/Enneking type of staging.[4]

Class	Location	Grade	Metastasis
IA	Intra compartmental	Low	No metastasis
IBI	Extra compartmental	Low	No metastasis
IIA	Intra compartmental	High	No metastasis
IIB	Extra compartmental	High	No metastasis
III	Any location	Any	Metastasis present

PATHOPHYSIOLOGY

The pathogenesis of osteosarcoma is closely tied to rapid skeletal development, frequently presenting during the pubertal growth phase in the metaphyseal regions of long bones. The high-grade intramedullary subtype represents approximately 80% of all diagnoses. The appendicular skeleton is the predominant site, with the distal femur, proximal tibia, and proximal humerus collectively accounting for 75–90% of cases. Specific

bone involvement includes the femur (42%), tibia (19%), and humerus (10%), though extra-appendicular sites such as the skull, jaw, and ilium (in the pelvis) are also documented.[4] In adults, osteosarcoma frequently develops as a secondary cancer, often in bones previously affected by other conditions. This includes bones with Paget disease, where approximately 1% of patients eventually develop osteosarcoma (a rate potentially decreasing due to bisphosphonate treatment). Additionally, ionizing radiation exposure is linked to about 3% of adult cases, with the cancer appearing anywhere from 4 to 40 years after the exposure.[4] From a tissue perspective, the defining feature of osteosarcoma is the presence of cancerous tumour cells that directly create abnormal bone-like material, called malignant osteoid. These cancer cells often resemble normal bone-forming cells (osteoblasts) because of their dense, pink-staining interior (eosinophilic cytoplasm), but they are much larger and have highly abnormal nuclei (marked nuclear atypia). The malignant osteoid they produce varies widely, appearing either as fine, delicate, web-like strands or as thick, haphazard pieces of bone.[8]

RADIOTHERAPIES

- **CHEMOTHERAPY**

Chemotherapy is administered prior to surgery to shrink the tumour and optimize conditions for limb-salvage surgery, as well as following surgery to eliminate any remaining lesions and metastases. The typical duration for chemotherapy ranges from 6 to 12 months and involves a combination of several highly effective agents, such as doxorubicin (Adriamycin, ADM), cisplatin (DDP), ifosfamide (IFO), etoposide (to a lesser degree), or high-dose methotrexate (HDMTX), which are used in various combinations. In fact, adjuvant MAP (Methotrexate, Adriamycin, and Cisplatin) chemotherapy is the standard treatment for patients with tumours that can be surgically removed, usually involving two to six cycles of preoperative chemotherapy, followed by additional cycles of adjuvant chemotherapy after surgery. Preoperative chemotherapy is administered 8 to 10 weeks before surgery. Postoperative chemotherapy is given within 21 days after surgery and can last between 12 to 29 weeks. Because of the potential adverse effects associated with multidrug therapy, such as cardiac and atrial dysfunction, as well as renal and liver toxicity, follow-up assessments should be conducted during and post-treatment, including echocardiograms, audiograms, and toxicity tests. Additional treatments may help to mitigate the side effects of chemotherapy, such as the use of antiemetics or opioids.[9]

The standard MAP chemotherapy (methotrexate, doxorubicin, cisplatin) remains the mainstay for metastatic osteosarcoma, but multiple drug trials have failed to improve survival. Pirarubicin showed limited benefit (median survival 10 months) in recurrent cases. Pemetrexed produced only one partial response and a 5.5-month median survival. Carboplatin, though less toxic, was less effective than cisplatin. Inhaled lipid cisplatin avoided typical toxicities and gave a few complete/partial responses in patients with small lung lesions, but phase II results are still unpublished.

Adding or escalating ifosfamide offered no survival advantage (5-year survival ~18–25%). Etoposide with MAP + ifosfamide showed a 52% two-year survival but severe toxicities and no clear benefit in later trials. Other agents—topotecan, high-dose thiotepa with autologous transplant, gemcitabine, and L-alanosine—also produced minimal or no clinical benefit.

Overall, despite extensive phase II and early-phase studies, no alternative or additional agents have significantly improved outcomes beyond standard MAP therapy for metastatic osteosarcoma.[10]

Before the 1970s, the primary treatment for osteosarcoma involved limb amputation, resulting in a 5-year survival rate of only 10%. However, the introduction of surgical intervention combined with modern, intensive multi-agent chemotherapy led to a significant increase in 5-year survival rates, now around 60–70%. Current treatment regimens for osteosarcoma generally consist of neoadjuvant (preoperative) therapy followed by adjuvant (postoperative) therapy if necessary. The most frequently used chemotherapy agents include cisplatin, doxorubicin, ifosfamide, and high-dose methotrexate with leucovorin calcium rescue.

Efforts are currently underway to assess how patients may respond to preoperative chemotherapy based on their genetic makeup. One notable effort by Man et al. involved creating a multigene classifier capable of predicting osteosarcoma responses to preoperative chemotherapy at diagnosis. They identified forty-five genes associated with poor responders, who exhibited overexpression of these genes. Despite receiving aggressive chemotherapy treatments that include high doses of methotrexate, these patients frequently experience relapses and pulmonary metastases.

The therapeutic potential of bisphosphonates, including zoledronic acid, minodronate, risedronate, and alendronate, has gained significant attention recently due to their ability to inhibit the growth of human osteosarcoma cells. In addition, Horie et al. showcased the antitumor effects of zoledronic acid in combination with either paclitaxel (PAC) or gemcitabine (GEM) in mouse models of osteosarcoma.[11]

- **IMMUNOTHERAPY**

Immunotherapy has shown promise in the treatment of OS, particularly in cases that are advanced or resistant to conventional therapies. OS **has a** reputation for being able to elude the host immune system, mostly by expressing immunological checkpoint proteins such as PD-L1, which inhibit immune response and allow unrestrained cancer cell growth. Through stromal cell remodelling, cell signalling, soluble factor production, and immune cell differentiation, PD-L1 has been demonstrated to influence immunosuppression and tumour invasion in gastric cancer cells significantly. It might also have a comparable function in OS. By using the host's immune system to identify and eliminate tumour cells—with an emphasis on reactivating T cells—immunotherapy aims to combat this immune evasion. Immunosuppressive signalling cascades are disrupted by drugs like pembrolizumab and nivolumab, which target immunological checkpoints like PD-L1 and CTLA-4. This reactivates T cells to launch an anti-tumour response. Both pembrolizumab and nivolumab have been They were found to be more successful when used in combination with other medications than when used alone, and they are approved as second-line therapies for gastric cancer, while further research is required before they can be used for OS. A different trial indicated that pembrolizumab had a median overall survival of 5.6 months in gastric cancer, whereas nivolumab had a median overall survival of 5.3 months with a placebo 4.1.

There is also ongoing research into other immunotherapy approaches, like cancer vaccinations. The need for further improvement is highlighted by the inconsistent outcomes of many strategies, especially those requiring dendritic cell activation, in preclinical and clinical trials. Treatment-related toxicity continues to be a significant obstacle in immunotherapy. Serious adverse consequences, such as gastrointestinal, endocrine, and dermatological damage, can result from immune system overactivation. Neurotoxicity, cardiotoxicity, and pulmonary toxicity are more severe immune-related side effects. Therapy is usually stopped and corticosteroids or immunosuppressive drugs may be given if severe toxicity occurs. It is thought that these negative effects occur from autoimmune-like reactions caused by immunological attacks on healthy tissues that have molecular markers in common with tumour cells.[5]

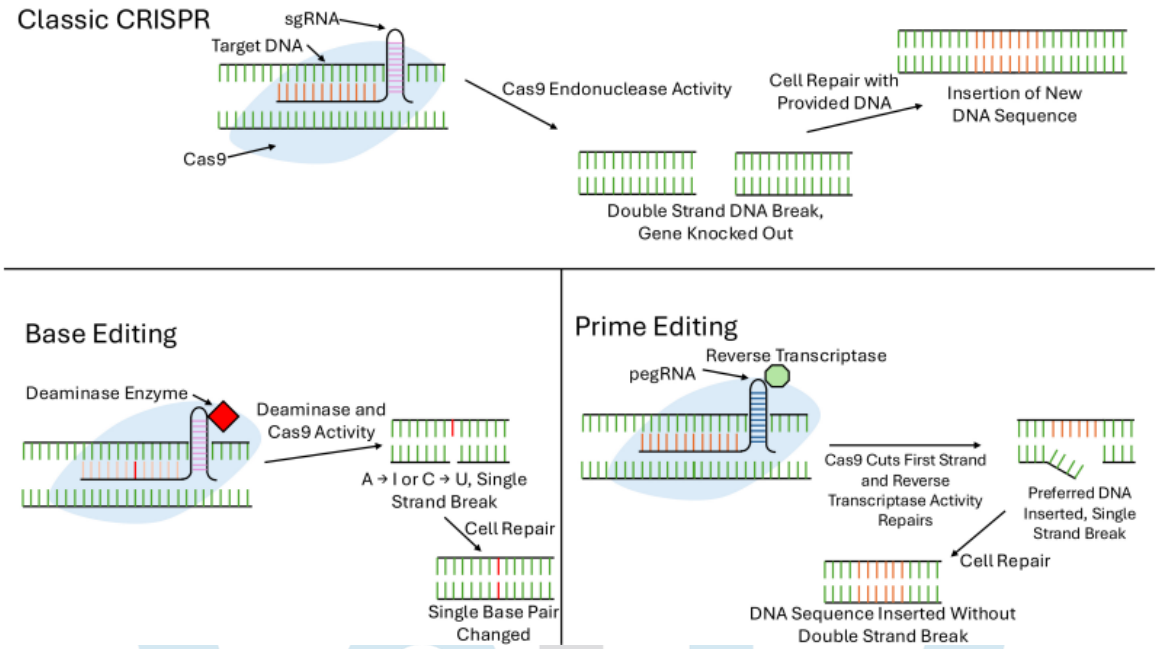
- **GENE THERAPY**

With ongoing advancements in medical science, emerging therapies for OS demonstrate significant potential. Gene therapy, which targets particular genetic and molecular elements that promote cancer growth and metastasis, is at the forefront of these innovative treatment approaches. Tumour suppressor genes, drug sensitization pathways, and gene-editing systems are examples of common targets.

CRISPR/Cas9 which helps repair damaged DNA segments to be repaired. By introducing functional gene copies into the host genome, gene therapy targeting tumour suppressor genes aids in the restoration of normal cell cycle regulation and physiological apoptosis. The G1 cell cycle checkpoint is disrupted by a mutation in the tumour suppressor gene TP53, which is frequently changed in OS. This raises the tumour's dependence on the G2 checkpoint to preserve DNA integrity in addition to encouraging tumour development. Given that many OS cells develop mutations or produce proteins that increase medication resistance, gene therapies targeted at altering drug-sensitizing pathways are also showing promise. The exosome, which is tiny extracellular vesicle typically engaged in cell-to-cell communication, is a significant contributor to this resistance and manipulation of the surroundings. Exosomes in cancer cells can transfer or upregulate drug efflux pumps like P-glycoprotein (P-gp), excrete chemotherapeutic drugs like doxorubicin, and transport multidrug-resistant mRNA from resistant to sensitive cells, all of which aid in the spread of resistance. It's interesting to note that exosomes are intriguing targets for gene therapy because of the same factors that make them efficient vectors for resistance. Exosomes have advantageous properties such as a long half-life, low toxicity, high solubility, and tiny size. The use of programmed exosomes as miRNA delivery vehicles has been investigated. new research demonstrating that they are frequently less lethal and more selective than existing techniques—perhaps as a result of interactions between the proteins in exosome membranes and the membranes of tumour cells. Exosomes infused with miR-665 were shown in a 2022 study to be able to prevent OS progression both in vivo and in vitro, all the while preserving favourable safety and effectiveness characteristics.

Exosomes have drawbacks despite their benefits, chief among them being the challenge of separating them in adequate amount and purity, as well as the dearth of information determining which particular exosomes work best for different cancer types. Furthermore, it is still unknown if alternative nanoparticle delivery methods, including hyper-cell-permeable micelles, would end up working better. Exosomes lack the selectivity of lab-engineered nanoparticles, although they share many advantageous characteristics. Researchers can also use CRISPR/Cas9 technology for precision genome editing and medication resistance gene identification through gene therapy. This enables the targeted alteration of genes involved in the development of OS and drug resistance, which may enhance the effectiveness of treatment. CRISPR fights cancer in several ways, with the traditional approach using a single-guide RNA (sgRNA) that is intended to bind a particular DNA sequence, as demonstrated by test repair mechanisms. CRISPR can directly cause double-strand breaks in the DNA of cancer

cells, interfere with immunological checkpoint genes, or deactivate oncogenes. According to a 2023 study, OS cell proliferation was suppressed both in vitro and in vivo when PLK1, a master regulator of the G2/M checkpoint, was successfully knocked out by CRISPR targeting.[5]



A schematic representation of the CRISPR/Cas9, base editing, and prime editing mechanisms, which compares the differences in components, progress, and outcomes for the three techniques.[5]

- **SURGERY**

The goal of cancer treatment is to improve disease-free survival. Complete tumour removal is the main goal of cancer surgery; limb preservation is always the secondary goal, and amputation is the last resort. It is also feasible to save (replace) limbs by carefully resecting.

The patient's quality of life will improve after the tumour is removed and a viable, functional limb is rebuilt. However, the disease-free survival rate has significantly increased, and limb removal is rarely required due to the development of efficient surgical techniques and treatment regimens. More aggressive surgery and chemotherapy regimens should be used for metastatic cancers in order to increase the disease-free survival rate. As part of the treatment plan, radiotherapy and surgical resection are also advised. Lesions located in inaccessible locations are typically treated with it. To improve the success rates of limb-amputation procedures and lower the chance of tumour recurrence, preoperative irradiation could be administered before to the procedure.

They are found in places that are inaccessible, like the base of the cranium, the spinal column, and the pelvic bone. Patients who refuse surgery benefit from this radiation as well. Anacak et al. suggested an inventive method of performing intraoperative extracorporeal irradiation to the bone. After receiving 50 Gy of radiation, the damaged bone was reintroduced into the body. There were no signs of graft failure or local recurrence found in the exposed bone over the average 22-month follow-up period.[11]

CURRENT & FUTURE INSIGHTS

Nearly half of the clinical trials being carried out for metastatic osteosarcoma are assessing immunotherapies like PD-1, IL-2, or mifamurtide. Additionally, tyrosine kinase inhibitors have attracted a lot of attention, with numerous studies building on the data of potential drugs from this class that have been published, including Regorafenib.

Summary of ongoing metastatic osteosarcoma clinical trials

Clinical Trials.Gov Identifier	Therapy	Phase	Patients Enrolled	Completion Date
NCT01590069	Aerosolized Aldesleukin	I	70	December 2022
NCT01953900	iC9-GD2-CAR-VZV-CTLs	I	26	October 2034
NCT02517918	Metronomic chemotherapy (cyclophosphamide and methotrexate and zoledronic acid)	I	26	March 2022
NCT03612466	CycloSam® and external beam radiotherapy	I	20	September 2024
NCT04877587	Gemcitabine and ascorbate	I	20	May 2023
NCT00788125	Dasatinib, Ifosfamide, Carboplatin, and Etoposide	I/II	143	December 2021
NCT03811886	Natalizumab	I/II	20	October 2023
NCT02243605	Cabozantinib S-malate	II	90	June 2019
NCT02357810	Pazopanib Hydrochloride and Topotecan Hydrochloride	II	178	June 2022
NCT02389244	Regorafenib	II	132	March 2023
NCT02470091	Denosumab	II	56	September 2022
NCT02484443	Dinutuximab and Sargramostim	II	41	March 2020
NCT03063983	Metronomic chemotherapy (cyclophosphamide and methotrexate)	II	158	January 2022
NCT03643133	Mifamurtide and chemotherapy	II	126	October 2028
NCT03742193	Apatinib and Gemcitabine-docetaxel chemotherapy	II	43	September 2022
NCT04183062	BIO-11006 and Gemtax	II	10	November 2023
NCT04668300	Oleclumab and Durvalumab	II	75	June 2024
NCT04690231	Apatinib, etoposide and ifosfamide	II	79	June 2021
NCT04803877	Regorafenib and Nivolumab	II	48	June 2026
NCT05019703	Atezolizumab and Cabozantinib	II	40	December 2027
NCT03932071	Zoledronic Acid	IV	150	January 2023

The survival rate for individuals reported in clinical trials evaluating novel medicines has only slightly improved, at best, despite intense attempts to improve the outcome of patients with osteosarcoma, especially those with overt metastases. It appears that further fundamental research will be necessary to achieve the long-sought significant increases in patient survival.

Following well-planned animal investigations and phase II clinical trials, biology research and drug development involving pertinent molecular targets should identify viable candidate medicines for assessment in phase III trials. A well-designed clinical trial will accelerate the achievement of this objective.[10]

CASE STUDY

- **INTRODUCTION**

Extra-skeletal osteosarcoma is less common than osteosarcoma, which primarily occurs at the metaphysis of long bones. Less than 1% of all primary malignant breast tumours are primary breast osteosarcomas, making them extremely uncommon. Thus far, less than 200 cases have been reported.

The etiology and radiological features of primary breast osteosarcoma are not universally agreed upon. This study describes a case of primary breast osteosarcoma in which the patient underwent extensive imaging tests because of an unclear diagnosis prior to surgery. A literature review is also presented. In cases of breast osteosarcoma, the imaging database can be expanded using the findings of these tests.

A 44-year-old female patient came to our centre with a complaint of a painless lump in her right breast for the past two years. She discovered the lump in the upper right breast by chance two years ago. Initially, it was about the size of a soybean (approximately 1 cm × 0.5 cm) and slightly hard. There was no redness, swelling, warmth, pain, or discharge from the nipple in that area. Since the lump did not impact her daily life or work, the patient did not seek medical attention during the two years it gradually increased in size. By the time of the study, the lump had grown to approximately 7 cm in diameter and caused slight localized pain. The breasts appeared unequal in size and asymmetrical. The right breast was noticeably enlarged but showed no signs of redness, swelling, orange peel appearance, or dimpling. The nipple was neither inverted nor deviated, and no discharge was noted.

A large lump, measuring about 8.0 cm × 6.0 cm, felt hard and slightly tender, was palpable beneath the right nipple. The lump had a smooth surface, indistinct borders, and was fixed in position with limited mobility. The tumour markers, including Carcinoembryonic Antigen (CA), CA 125, CA 19-9, and CA 15-3, were negative. The patient underwent thorough imaging examinations, including breast ultrasonography (Figures 1A, B), mammography (Figures 2A, B), chest Computed Tomography (CT) (Figures 3A, B), and whole-body bone Single Photon Emission Computed Tomography (SPECT) (Figures 5A–C). She then had a complete mastectomy followed by adjuvant chemotherapy. Currently, she has been living without any recurrence for two years.

Breast ultrasonography (Figures 1A, B) revealed multiple substantial lesions with strong echo masses, classified as BI-RADS 4c, in the right breast. This score strongly suggests cancer based on the case presentation above. The mammogram of the upper outer quadrant of the right breast showed a lobulated mass with irregular edges.

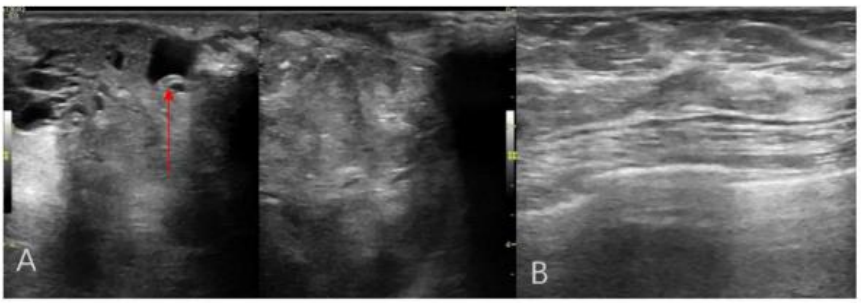


FIGURE 1
Breast ultrasonography radial scanning **(A, B)** An irregular hypoechoic mass in the right breast, with calcification (red arrow).

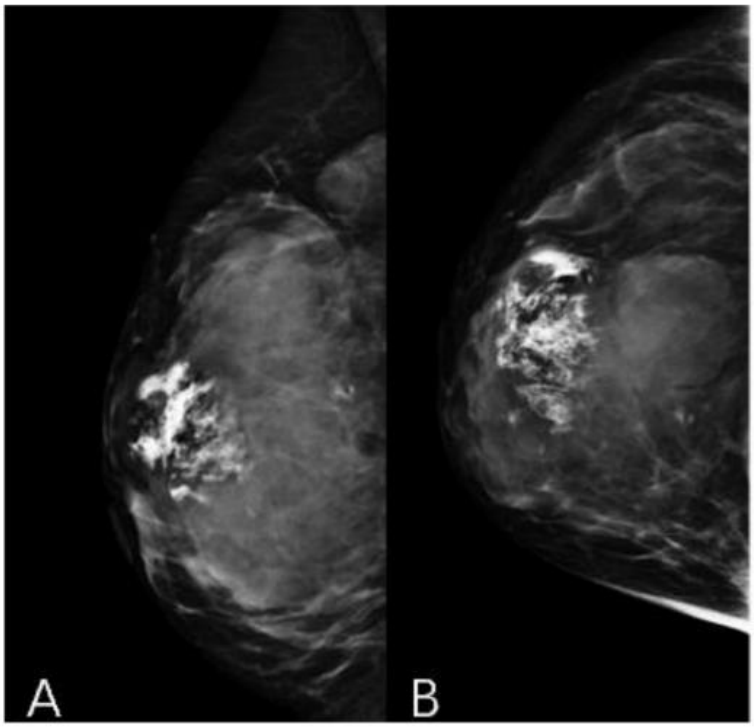


FIGURE 2
Mammography craniocaudal view **(A)** and mediolateral oblique view **(B)**. A large calcified mass is noted at the right breast.

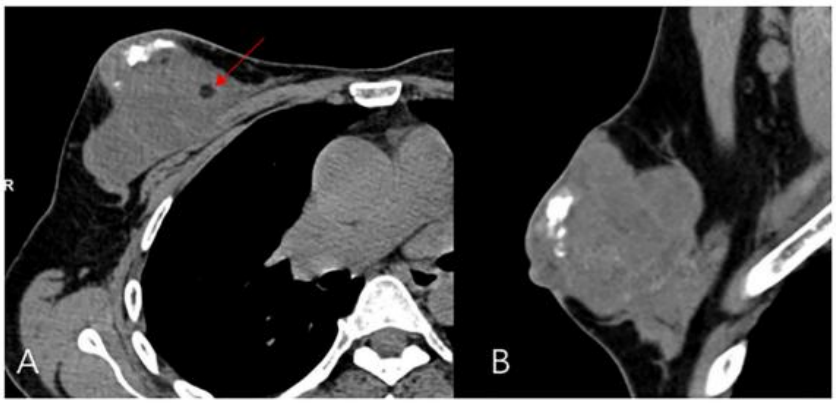


FIGURE 3
CT Transverse dislocation **(A)** and sagittal **(B)** view, a large calcified mass and round foci of fat (red arrow) is noted at the right breast.

Calcification on the craniocaudal view (Figure 2A) and mediolateral oblique view (Figure 2B). The CT scan showed that the edges of the mass were relatively clear, with uneven density and visible septal changes. Small round areas of fat density were visible on the inner side (Figures 3A, B). The whole-body bone SPECT showed intense uptake in the right breast, unlike the low or absent uptake seen in breast cancer (Figures 5A, B).

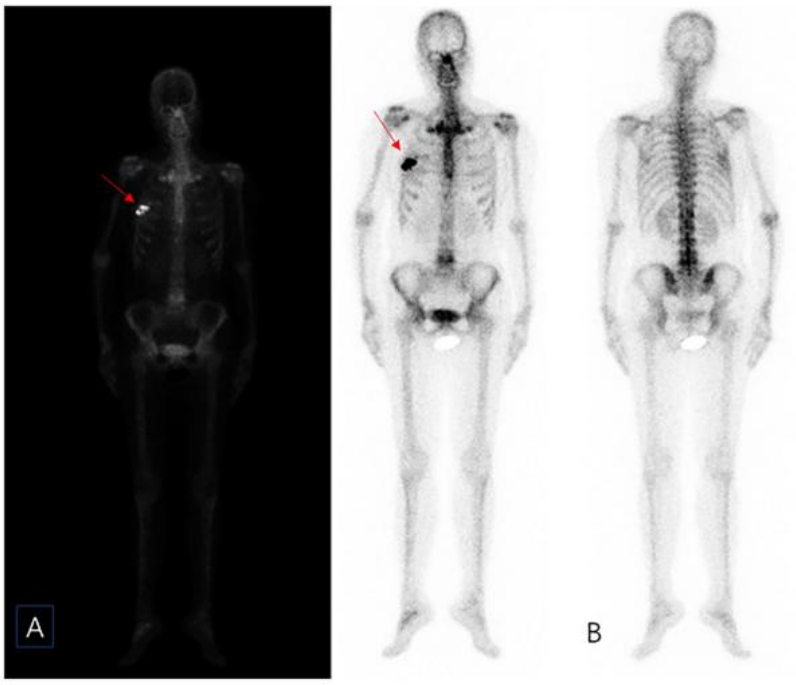


FIGURE 5
Whole-body bone imaging **(A, B)**. It showed that there was a mass-like abnormal radioactive concentration of outside the bone of the right chest (red arrow), without other abnormal concentrations.

- **Summary**

Primary breast osteosarcoma appears differently in imaging studies compared to breast cancer. DR, B-ultrasound, and CT show distinct patterns of calcifications. CT and MRI reveal differences in margins, density, and signal intensity. Whole body SPECT can help in distinguishing based on tracer uptake. Pathology can identify two types. Therefore, for breast tumours, we should stress the importance of preoperative puncture biopsy even more.[7]

CONCLUSION

Osteosarcoma (OS) represents a significant oncologic concern, particularly among paediatric and adolescent populations. Its aggressive nature and predilection for bone-forming tissues pose substantial diagnostic and therapeutic challenges. Although current treatment modalities—including radiotherapy, chemotherapy, gene therapy, and surgical resection—have contributed to improved management and survival rates, the absence of a definitive cure underscores the need for continued innovation. Age-specific factors further complicate surgical decisions, especially in limb salvage and prosthetic integration for growing children. Future research must focus on molecular characterization, targeted therapies, and personalized treatment approaches to enhance outcomes and reduce long-term morbidity in affected individuals.

ACKNOWLEDGEMENT

I would like to thank all the authors who came together for the fulfilment of this project. All my capable fellows have dedicated their hard work, knowledge and skillset for this result.

I would also like to thank our mentor, who guided, encouraged and led us throughout this review paper.

Lastly, I would like to thank all the authors, and publications using whose knowledge we came up with this project.

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