

Osteosarcoma: Epidemiology, genetic mutations, and therapeutic strategies

ZiYang Wang*

Walnut High School, California, 91789, USA

*Corresponding author: 1811000323@mail.sit.edu.cn

Abstract. Osteosarcoma accounts for about 3% of all childhood cancers and is the most common primary malignant bone tumor. It primarily peaks in adolescence, around the age of 15 - 19. However, it is still possible for adults to be affected by osteosarcoma. Current treatment for osteosarcoma includes a combination of surgical resection and chemotherapy. However, the increasing resistance to chemotherapy drugs has led to an increase in disease mortality. In addition, its complex genetic underpinnings contribute to its aggressive behavior and resistance to current therapies. This review explores osteosarcoma's epidemiology, potential risk factors, molecular mechanisms, and current diagnostic and treatment strategies. The disease exhibits a bimodal age distribution, with variations across racial and ethnic groups. Distinct genetic mutations, including TP53 and RB1, disrupt cell cycle regulation and drive uncontrolled proliferation. Despite advances in treatment, challenges such as resistance to chemotherapy persist. Emerging targeted therapies, including MDM2 and CDK4/6 inhibitors, offer promise, but further research is essential. The multifaceted nature of osteosarcoma necessitates collaborative efforts to enhance understanding, refine diagnostics, and develop innovative therapies.

Keywords: osteosarcoma; epidemiology; genetic mutations; therapeutic strategies.

1. Introduction

Osteosarcoma is an uncommon yet violent form of bone cancer, presenting a formidable challenge within the realm of oncology. This malignancy predominantly afflicts the skeletal system, primarily manifesting within the long bones, and is notable for its predilection towards striking adolescents and young adults. It is often characterized by the uncontrolled growth of unusual cells within the bone tissue, causing the formation of a tumor. This tumor can weaken the bone, making it more susceptible to bone injuries, such as fractures. It is classified as a form of cancer originating within the bones, most commonly in regions characterized by rapid bone growth during adolescence. Comprising roughly 3% of all childhood cancers, osteosarcoma emerges as the most prevalent primary malignant bone tumor, but a much smaller percentage of the cancer in adults. Statistics reveal a distinct predilection for affecting individuals aged 10 to 30, with a slightly higher occurrence rate observed in male. However, that does not mean that the older population is not affected by osteosarcoma. In fact, around 10% of the cancer is detected in people over 60 [1]. Additionally, the incidence of this malignancy displays variations across racial groups, with elevated rates noted among individuals of African and Asian descent [2]. These trends emphasize the necessity of probing potential genetic and environmental factors that might contribute to the development of osteosarcoma.

The current treatment landscape for osteosarcoma involves a multimodal approach that combines surgical resection and chemotherapy. However, one of the major challenges in osteosarcoma treatment is the development of resistance to chemotherapy. Over time, tumor cells can become resistant to the drugs, rendering the treatment less effective and leading to disease progression. Furthermore, the aggressive nature of osteosarcoma necessitates effective therapeutic strategies, yet standard approaches often face limitations in cases of metastatic or relapsed disease [3]. Genetically, the disease's complexity and heterogeneity hinder the identification of consistent driver mutations and their functional implications. Limited comprehensive genomic data and a dearth of reliable preclinical models impede understanding of its genetic basis, while the rarity of osteosarcoma poses difficulties in gathering adequate samples for analysis. Bridging the gap between genetics and

treatment requires collaborative efforts to elucidate key genetic drivers and develop tailored therapeutic approaches that address the diverse genetic landscape of osteosarcoma. Nevertheless, recent strides in molecular biology have illuminated potential genetic and molecular anomalies that could potentially play a pivotal role in its initiation and progression. Mutations within tumor suppressor genes, such as TP53 and RB1, have emerged as prime candidates in the pathogenesis of osteosarcoma, disrupting the regulation of cell cycles and fostering unbridled cell proliferation.

In summation, osteosarcoma stands as a complex and demanding disease entity that necessitates concerted research efforts to untangle its intricate mechanisms and bolster patient outcomes. Its intricate etiology, enigmatic origins, and limited array of treatment options underscore the pressing need for comprehensive research to enhance understanding of the disease, refine diagnostic techniques, and develop innovative therapeutic strategies. This paper embarks on an exploration of the multifaceted landscape of osteosarcoma, delving into its epidemiology, potential risk factors, underlying molecular mechanisms, and prevailing diagnostic and treatment paradigms. Striving to furnish a comprehensive introduction to the intricate realm of osteosarcoma research, this article offers valuable insights into the genetic underpinnings of osteosarcoma, meticulously delineating the molecular anomalies that might underlie osteosarcoma's aggressive behavior.

2. The epidemiology of Osteosarcoma

Osteosarcoma constitutes a small fraction of all cancers, accounting for approximately 2% of childhood malignancies. While it is relatively rare, osteosarcoma remains the most common primary malignant bone tumor. Its incidence is highest in adolescents and young adults, particularly during periods of rapid bone growth. Osteosarcoma's prevalence peaks at around 15-19 years of age, making it a critical concern for the adolescent population [1]. The incidence subsequently declines but experiences a secondary peak later in adulthood, demonstrating its unique age distribution patterns. Adolescents experiencing growth spurts are particularly vulnerable to this malignancy. The most common developed area of osteosarcoma is around the distal femur, proximal tibia, and proximal humerus [4]. However, osteosarcoma can still develop in any bone. Although it can occur at any age, osteosarcoma is less common in children under 10 and adults over 30 [1]. This bimodal age distribution highlights the disease's unique biological behavior, often linked to periods of rapid bone growth and remodeling. Gender differences also influence the epidemiology of osteosarcoma. It displays a slightly higher incidence in males than females, although the gender disparity is not as pronounced as in some other cancers. This gender distribution may reflect underlying biological and hormonal factors that contribute to the initiation and progression of the disease. Hormonal fluctuations during puberty could potentially play a role in shaping gender-specific osteosarcoma risk.

Osteosarcoma incidence varies across racial and ethnic groups, suggesting potential genetic and environmental influences. Some studies have reported elevated rates of osteosarcoma in individuals of African and Asian descent compared to those of European descent [2]. Genetic variations, environmental exposures, and lifestyle factors may contribute to these disparities, necessitating further investigation to elucidate the mechanisms underlying these differences. These disparities may be linked to genetic susceptibility, socio-economic factors, or distinct environmental exposures among different populations. Osteosarcoma incidence exhibits geographic variability, with differing rates observed across regions and countries. While the disease occurs worldwide, specific geographic factors, environmental exposures, and genetic predispositions may contribute to regional differences in incidence. Comprehensive studies examining the impact of environmental risk factors, such as radiation exposure, pollution, and lifestyle, could shed light on these geographical disparities. These disparities could be influenced by factors ranging from access to healthcare to environmental carcinogens [5].

3. Types of Osteosarcoma

There are two major categories of osteosarcoma, the central and surface. In the central osteosarcoma, this category includes those that arise in the central portion of the bone, such as the medullary cavity. Central osteosarcomas are the most common type and often occur in long bones like the femur, tibia, and humerus. In the surface osteosarcoma, these tumors develop on the surface of bones, typically near the periosteum (the outer covering of bones). Surface osteosarcomas are less common and may have distinct clinical and pathological characteristics, it arises from the periosteum of the bone [1].

In central osteosarcoma, there are also different types of cases. As of now, the four main types of cancer in osteosarcoma are conventional, telangiectatic, small-cell and low-grade osteosarcoma. Conventional osteosarcoma is the most common and well-known subtype of osteosarcoma. It typically occurs in the long bones of adolescents and young adults and is characterized by the production of osteoid, a bone-like material. Conventional osteosarcoma can be further classified into subtypes based on the appearance of the tumor cells and the extent of osteoid production. Telangiectatic Osteosarcoma is characterized by the presence of dilated blood vessels within the tumor, giving it a "spongy" or cavernous appearance on imaging. Telangiectatic osteosarcoma is often found in the long bones of adolescents and can be associated with aggressive behavior and a higher likelihood of metastasis. Small-cell osteosarcoma is a rare subtype characterized by small, uniform tumor cells. It tends to occur in the extremities and may have a higher chance of local recurrence. Despite its name, it is distinct from small cell carcinoma and has unique molecular and pathological features. Low-grade osteosarcoma is also a rare subtype that exhibits a less aggressive behavior compared to other types of osteosarcomas. It typically occurs in the bones of the extremities and has a lower potential for metastasis. However, it still requires appropriate treatment due to its potential for local recurrence [6].

There are three different types of surface osteosarcoma as of now. This includes the parosteal, periosteal and high-grade surface osteosarcoma. parosteal osteosarcoma, also known as juxtacortical osteosarcoma, is a rare subtype that arises adjacent to the bone surface, typically from the periosteum. It tends to occur in young adults and often involves the long bones, such as the distal femur and proximal tibia. Histologically, parosteal osteosarcoma exhibits a well-differentiated appearance, resembling mature bone tissue. These tumors usually grow slowly and are associated with a relatively favorable prognosis compared to other aggressive osteosarcoma subtypes. Periosteal osteosarcoma is characterized by a layered or "onion skin" appearance on histopathological examination, attributed to the gradual deposition of bone layers by tumor cells. Periosteal osteosarcoma is most commonly found in adolescents and young adults and is frequently located in the femur. Despite being low-grade, it can still be locally aggressive. High-grade surface osteosarcoma represents a more aggressive subtype that arises from the bone surface. Unlike its low-grade counterparts, high-grade surface osteosarcoma demonstrates greater cellular atypia and a higher proliferation rate. These tumors are often large and locally aggressive, with the potential for metastasis [6].

4. Gene Mutation and Potential Therapy

Osteosarcoma, a malignant bone tumor with a predilection for adolescents and young adults, is characterized by complex genetic alterations that contribute to its pathogenesis. Several genes have been implicated in the development of osteosarcoma, including TP53, RB1, and various components of the Wnt signaling pathway. The Cancer Genome Atlas (TCGA) provides comprehensive genomic data, revealing that TP53 and RB1 mutations are frequent in osteosarcoma, disrupting key cellular processes.

TP53 is a tumor suppressor gene. It provides the instructions to make the protein called p53, it is responsible for controlling cell divisions by stopping cells proliferating in an uncontrollable manner. It is a very crucial gene in humans since it prevents tumor formation, an indication of the presence of cancer in the body. However, this gene is commonly mutated in osteosarcoma, which often leads to

loss of function, resulting in impaired cell cycle control and reduced apoptosis [7]. Similarly, RB1 mutations can deregulate the cell cycle by relieving its inhibitory effects on cell division [8]. Moreover, the Wnt signaling pathway, vital for bone development, can be perturbed by mutations in genes like APC and CTNNB1 (beta - catenin).

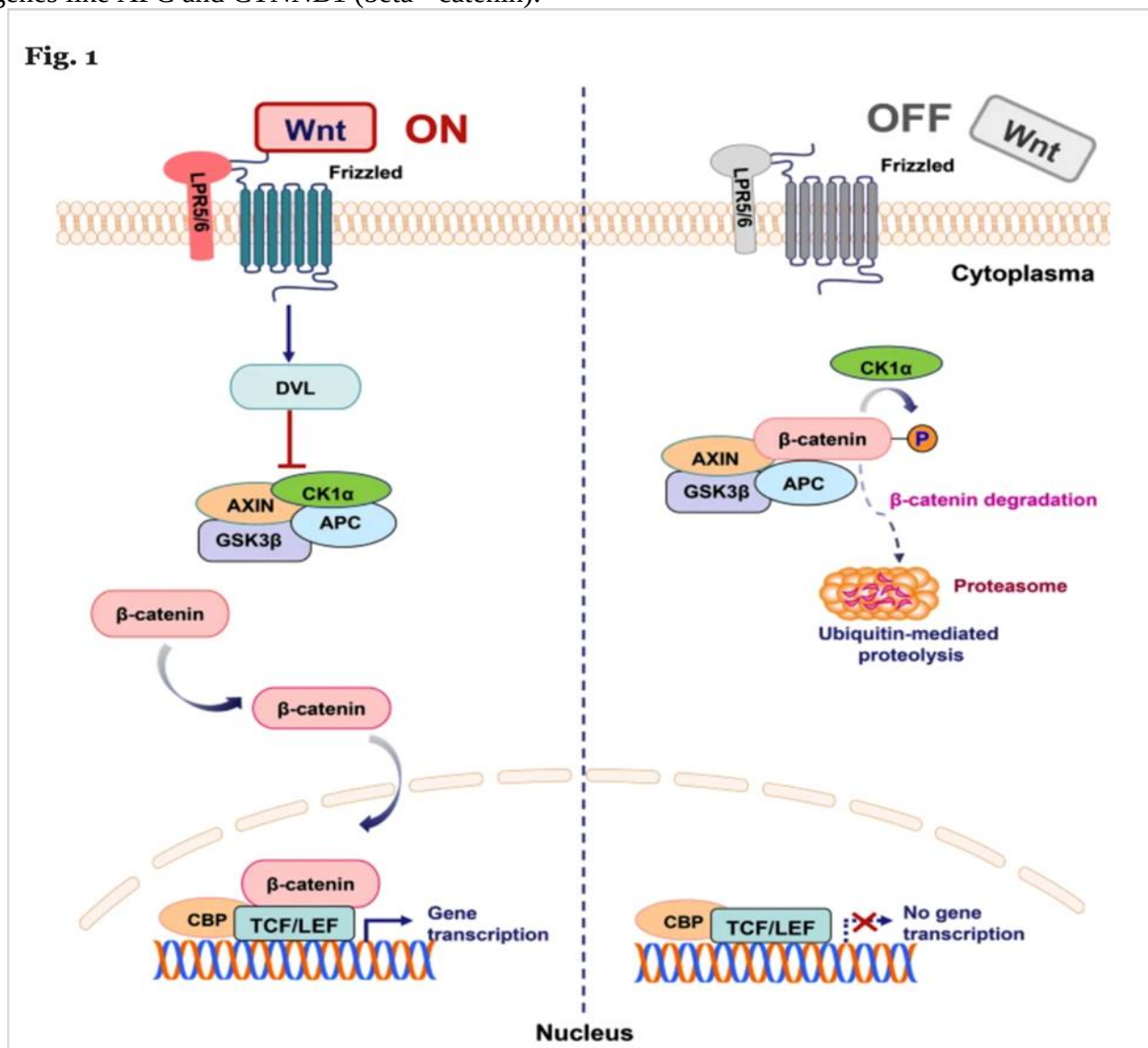


Fig. 1 the pathway of normal and mutated Wnt pathway (Cheng et. Al)

As shown in figure 1, The pathway is initiated when a Wnt protein, which is a secreted signaling molecule, binds to its cell surface receptor, called a Frizzled receptor, and sometimes a co-receptor called LRP5/6. When Wnt ligands bind to their receptors, a series of intracellular events are triggered that inhibit the destruction complex, which is a series of proteins shown here. This leads to decreased phosphorylation of β -catenin, preventing its degradation. As a result, β -catenin accumulates in the cytoplasm. The accumulated β -catenin translocate into the nucleus, where it associates with transcription factors of the TCF/LEF family (T-cell factor/lymphoid enhancer factor). This complex acts as a transcriptional coactivator, facilitating the expression of specific target genes. The β -catenin/TCF complex activates the transcription of target genes involved in various cellular processes, including cell proliferation, survival, and differentiation. These target genes can vary depending on the cell type and context. The activation of Wnt target genes influences cellular responses. In some cases, it promotes cell proliferation, survival, and stem cell maintenance. In other cases, it can induce cell differentiation and tissue-specific functions. In osteosarcoma, one of the key genetic alterations involving the Wnt pathway is the mutation in the CTNNB1 gene, which encodes for the β -catenin protein. β -catenin is a crucial component of the Wnt signaling pathway, where it acts as a

transcriptional coactivator. Normally, in the absence of Wnt signals, β -catenin levels are tightly regulated through degradation of the destruction complex. This ensures that β -catenin does not accumulate in the nucleus and activate target genes. However, mutations in CTNNB1 can disrupt this regulatory mechanism, leading to the accumulation of β -catenin in the nucleus. This aberrant accumulation results in the activation of Wnt target genes even in the absence of proper signaling, promoting uncontrolled cell growth and proliferation – hallmarks of cancer development. This sustained activation of Wnt signaling can contribute to the transformation of normal bone cells into malignant osteosarcoma cells [9].

Activation and deactivation of these mutated genes drive pivotal changes in osteosarcoma development. When TP53 is inactivated, cells are less likely to undergo programmed cell death in response to DNA damage or other stressors. This paves the way for the survival and proliferation of damaged cells, fostering tumor growth [7]. In contrast, RB1 inactivation promotes cell cycle progression, enabling unchecked cellular division [8]. Activation of the Wnt pathway through CTNNB1 mutations, stimulates cell proliferation and inhibits differentiation, further fueling tumor growth. Deactivation of these pathways through targeted therapies is a promising avenue for treating osteosarcoma. Recent advancements in cancer research have led to the development of targeted therapies aimed at exploiting specific genetic alterations in tumors, including those present in osteosarcoma. One such approach involves utilizing small molecule inhibitors to target aberrant signaling pathways. For TP53-mutated osteosarcomas, strategies targeting downstream effectors to restore the tumor suppressor function. Such examples are MDM2 inhibitors, which will influence p53 localization, foster its degradation, and block its ability to transactivate [7]. Another treatment method is miRNA-based therapy. The miRNA family (miR-34a, miR-34b, miR-34c) manages tumor suppression and is controlled by the p53 gene. Synoradzki Et al reported that miRNA - 34a promotes cisplatin sensitivity in osteosarcoma cells, decreasing the oncogenic property of the tumor cells [7]. However, there are many side effects that come with the drugs such as ototoxicity, nephrotoxicity and gastrointestinal toxicity. Furthermore, OS cells can develop resistance to the drug's property after a period of time. For RB1-mutated osteosarcoma, CDK4/6 inhibitors are being explored to counteract the effects of RB1 mutations. The inhibitor is shown to deactivate or RB1, which slows cell cycle progression. However, Knudsen et al have shown that progression of cell cycle will continue even if CDK4/6 drugs are used [8]. In osteosarcomas with activated Wnt signaling, efforts are focused on disrupting the pathway. TTK inhibitors aim to block the aberrant activity of the CTNNB1 gene, curbing excessive cell growth [10]. Additionally, the identification of other dysregulated genes, such as those involved in angiogenesis or immune evasion, offers potential targets for novel therapies.

5. The prevailing diagnostic and treatment of Osteosarcoma

The current treatment paradigm for osteosarcoma involves a multimodal approach, typically combining surgery, chemotherapy, and occasionally radiation therapy. Surgical resection aims to remove the primary tumor while preserving limb function whenever possible. Limb salvage is a safe, surgical technique for treating 85-90% of patients with osteosarcoma. It has two steps: resection and reconstruction. Resection is a process to remove a certain organ or body parts. In this case, the surgeon would remove the osteosarcoma-infected tumor. The second step is reconstruction, where the surgeons would remove an area of the body to repair the target area. The reconstruction procedures have many different ways of completing it: It includes autograft, recycled autograft, allograft, and allograft prosthetic composite reconstructions. Autograft is graft tissue taken from a donor; autograft is a graft tissue taken from the patient's body. Amputation was once the standard treatment of OS, however, now it is only used when the affected area can no longer be salvaged. Chemotherapy, often utilizing drugs like high-dose methotrexate and cisplatin, targets rapidly dividing cancer cells before and after surgery, aiming to eradicate residual disease and prevent metastasis. However, the process not only targets the cancerous cells, but also the healthy ones: the patient's immune system will be severely impacted, side effects include fatigue, hair loss, anemia, etc. Radiation therapy is another

method to deal with OS. It is employed selectively, particularly for unresectable tumors or in cases where surgical margins are close. Nonetheless, this treatment is deemed controversial because of its low effectiveness and high risk of infection [11].

Unfortunately, there may seem to be numbers of treatment for OS; the outcomes of current methods are suboptimal, especially for patients with metastatic or relapsed disease. Novel therapies are urgently needed to improve survival rates and reduce treatment-related morbidity.

6. Conclusion

The future of osteosarcoma treatment hinges on unraveling the complexities of its genetics and microenvironment. With advancements in precision medicine, therapies tailored to individual genetic profiles hold great promise. Clinical trials evaluating targeted therapies are ongoing, and the incorporation of immunotherapeutic approaches, such as checkpoint inhibitors, could revolutionize treatment. However, challenges persist. The rarity of osteosarcoma poses hurdles in conducting large-scale trials, necessitating collaboration among research institutions and international networks. Resistance to targeted therapies and potential side effects also warrant careful consideration. Furthermore, understanding the interplay between genetic mutations and the tumor microenvironment is vital for designing effective therapeutic strategies.

References

- [1] Osteosarcoma - childhood and adolescence - statistics (2023) Cancer.Net. Available at: <https://www.cancer.net/cancer-types/osteosarcoma-childhood-and-adolescence/statistics>
- [2] Synoradzki, Kamil Jozef et al. "TP53 in Biology and Treatment of Osteosarcoma." *Cancers* vol. 13,17 4284. 25 Aug. 2021,
- [3] Chou, Alexander J., and Richard Gorlick. "Chemotherapy Resistance in Osteosarcoma: Current Challenges and Future Directions." *Expert Review of Anticancer Therapy*, vol. 6, no. 7, Informa, July 2006, pp. 1075-85
- [4] Surgery, Tumor. "Osteosarcoma (Conventional): Bone Tumor Cancer." Copyright 2014 by Tumorsurgery.org, tumorsurgery.org/tumor-education/bone-tumors/types-of-bone-tumors/osteosarcoma-conventional.aspx.
- [5] Mirabello, Lisa et al. "International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons." *International journal of cancer* vol. 125,1 (2009): 229-34.
- [6] Prater, Stephanie. "Osteosarcoma." *StatPearls - NCBI Bookshelf*, 23 May 2023, www.ncbi.nlm.nih.gov/books/NBK549868.
- [7] Synoradzki, Kamil Jozef et al. "TP53 in Biology and Treatment of Osteosarcoma." *Cancers* vol. 13,17 4284. 25 Aug. 2021
- [8] Knudsen, Erik S et al. "Cell Cycle and Beyond: Exploiting New RB1 Controlled Mechanisms for Cancer Therapy." *Trends in cancer* vol. 5,5 (2019): 308-324.
- [9] Zhang, Ya, and Xin Wang. "Targeting the Wnt/ β -catenin signaling pathway in cancer." *Journal of hematology & oncology* vol. 13,1 165. 4 Dec. 2020
- [10] Zaman, Guido J R et al. "TTK Inhibitors as a Targeted Therapy for CTNNB1 (β -catenin) Mutant Cancers." *Molecular cancer therapeutics* vol. 16,11 (2017): 2609-2617.
- [11] Zhao, Xin, et al. "Osteosarcoma: A Review of Current and Future Therapeutic Approaches." *Biomedical Engineering Online*, vol. 20, no. 1, BioMed Central, Mar. 2021.