

The Osteosarcoma Odyssey: Tracking the Evolution of Systemic Treatment Strategies

Swarnava Chanda *, Dhairya Gupta and Abdul Quadir Rahmani

Department of Surgical Oncology, AIIMS Raipur, Chhattisgarh, India.

World Journal of Advanced Research and Reviews, 2026, 30(02), 224-236

Publication history: Received on 17 March 2026; revised on 02 May 2026; accepted on 05 May 2026

Article DOI: <https://doi.org/10.30574/wjarr.2026.30.2.1110>

Abstract

Osteosarcoma is an aggressive primary bone malignancy primarily affecting children and adolescents during peak growth periods. Historically, management was limited to surgical resection or amputation, which resulted in a dismal 20% long-term survival rate because of the presence of subclinical micrometastases. The introduction of systemic chemotherapy in the 1970s, particularly doxorubicin, cisplatin, and high-dose methotrexate, revolutionized outcomes by significantly increasing survival rates. The landmark “Multi-Institutional Osteosarcoma Study” definitively established combination chemotherapy as a necessity alongside surgery. Currently, the standard of care is a multimodal strategy comprising neoadjuvant chemotherapy, definitive surgery, and adjuvant chemotherapy. The MAP regimen remains the therapeutic backbone, achieving 60-70% survival for localised disease, though prognosis for metastatic or relapsed cases remains poor. While neoadjuvant chemotherapy does not offer a proven survival advantage over immediate surgery, it facilitates limb-salvage procedures and provides critical prognostic data through histological response assessment. Despite these historical successes, survival rates have plateaued over the last thirty years, and conventional agents cause severe permanent toxicities. Future directions focus on precision medicine to overcome chemoresistance and toxicity. Emerging strategies include targeted molecular therapies such as tyrosine kinase and IGF-1R inhibitors, alongside immunotherapy involving checkpoint inhibitors and CAR T-cells. Other innovations under investigation include antibody-drug conjugates, epigenetic modification therapy, and oncolytic viral therapy.

Keywords: Osteosarcoma; Chemotherapy; Targeted Therapies; Immunotherapy; Multimodal Treatment

1. Introduction

Osteosarcoma is the most common primary malignant bone tumour, predominantly affecting children and adolescents during the pubertal growth spurt [1,2]. Characterised by malignant mesenchymal cells producing immature bone or osteoid, it typically arises in the metaphyseal region of long bones such as the femur, tibia, and humerus [3,4]. While rare, with an incidence of 0.2-3 per 100,000 yearly, its aggressive nature and high likelihood of early metastasis make it a significant clinical challenge [5-7]. Historically, the management of osteosarcoma was exclusively surgical, typically involving the amputation of the affected limb. Prior to the 1970s, surgery alone achieved local control, but nearly 90% of patients developed pulmonary metastases and died within months, resulting in a dismal 5-year survival rate of approximately 20% [8-10]. This clinical failure led to the understanding that the vast majority of patients have subclinical micrometastases disseminated at the time of diagnosis.

The "revolutionary era" began in the 1970s and 80s with the discovery of effective systemic agents, including doxorubicin, cisplatin, and high-dose methotrexate. Landmark trials, such as the “Multi-Institutional Osteosarcoma Study” (MIOS), definitively proved that combination chemotherapy following surgery increased survival rates from roughly 11% to over 60% [11]. Today, the standard of care is a multimodal approach combining neoadjuvant

* Corresponding author: Swarnava Chanda

chemotherapy (NACT), definitive surgery, and adjuvant chemotherapy [12,13]. The mainstay treatment is the MAP regimen, consisting of high-dose methotrexate (HD-MTX), adriamycin (doxorubicin), and cisplatin [14]. For certain histological variants, such as the intermediate-grade periosteal osteosarcoma, the role of systemic therapy remains debatable, though it is often suggested for high-risk features like medullary involvement [15,16].

NACT has become the preferred standard because it facilitates limb-salvage surgery (LSS) over amputation by shrinking the primary tumour and provides crucial prognostic data through the assessment of histological response [13,17]. A response of $\geq 90\%$ tumour necrosis in the resected specimen is a robust indicator of improved event-free survival (EFS) and overall survival (OS) [18-20]. However, despite these advancements, survival rates for localised disease have stagnated at 60-70% for the last three decades [2,12]. Outcomes for patients with metastatic or relapsed disease remain poor, with survival dropping below 20-30% [21]. Furthermore, standard chemotherapeutic agents carry a high burden of severe toxicities, including cardiotoxicity, nephrotoxicity, and hearing loss [22,23].

To break this survival plateau and reduce treatment morbidity, research is shifting toward precision medicine. Emerging research investigates targeted molecular therapies, such as insulin-like growth factor-1 receptor (*IGF-1R*) and tyrosine kinase inhibitors (TKIs), and immunotherapy approaches like immune checkpoint inhibitors and CAR T-cell therapy [24-26]. Other innovative strategies under development include antibody-drug conjugates (ADCs), epigenetic modification therapy, and oncolytic viral therapy [27,28]. This review provides an extensive analysis of the role of systemic therapy, moving from the surgical past to the multidisciplinary present, and explores the biological innovations poised to define the future of osteosarcoma management.

2. Historical Perspective: The Revolutionary Shift from Surgery Alone

Prior to the 1970s, the management of osteosarcoma was a clinical exercise in futility, characterized by a nearly uniform mortality rate that transformed the diagnosis into a virtual death sentence for children and adolescents. In this "surgical era", the standard of care was radical local intervention, typically involving the amputation of the affected limb [12,29]. However, despite achieving excellent local control, the long-term survival rate remained a dismal 20%. This failure was eventually understood to be the result of subclinical micrometastases, which were disseminated through the bloodstream and already present in the lungs at the time of initial diagnosis in roughly 80-90% of patients [30,31]. The revolutionary shift began in the early 1970s when phase II trials identified systemic agents with significant activity against these disseminated cells, most notably doxorubicin (adriamycin), which showed a 43% response rate, and HD-MTX with leucovorin rescue to mitigate its life-threatening toxicity [32,33]. The subsequent introduction of cisplatin and ifosfamide further expanded the therapeutic arsenal, leading to the development of the multi-agent MAP regimen [10,26,34]. The necessity and efficacy of these drugs were definitively proven by the landmark MIOS trial in the early 1980s, which demonstrated that combination chemotherapy following surgery increased the 6-year EFS from a mere 11% in the observation group to 61% in the treated group [11]. This breakthrough not only improved OS to the current 60-70% range but also facilitated a profound shift in surgical philosophy. The use of NACT allowed for the shrinkage and encapsulation of primary tumours, making LSS a safe and viable alternative to amputation. Consequently, the limb preservation rate in specialised centres skyrocketed from approximately 10% in the 1970s to over 80-90% in the modern era [35,36]. This transition from an exclusively surgical approach to a multimodal standard of care represents one of the greatest triumphs in paediatric oncology, even as survival rates for localised disease have largely stagnated for the last three decades, underscoring the urgent need for the next generation of systemic innovations.

3. Current Standards: The Multimodal Approach

The contemporary management of osteosarcoma, the most common primary bone malignancy in children and adolescents, is defined by a multidisciplinary, multimodal approach [37,38]. This strategy, which combines radical surgery with intensive systemic chemotherapy and occasionally radiotherapy, has transformed the disease from a nearly uniform death sentence to a curable condition for approximately 60-70% of patients with localised disease [26,33].

The successful treatment of osteosarcoma requires a highly coordinated effort among pediatric or medical oncologists, orthopedic surgeons, pathologists, and radiologists [39,40]. Given the rarity and complexity of these tumours, it is strongly recommended that therapy be performed in specialised centres capable of providing the full spectrum of care [41]. In most countries, standard practice involves treating patients within the framework of prospective multi-institutional clinical trials, which aim to optimise outcomes and identify new prognostic factors [2,33].

4. Systemic Polychemotherapy: The MAP Regimen

Systemic therapy is the primary tool for eradicating subclinical micrometastases, which are present in the majority of patients at the time of diagnosis. Without chemotherapy, roughly 80-90% of patients develop pulmonary metastases and die, highlighting the insufficiency of surgery alone [30,31].

The current standard backbone for systemic treatment is the MAP regimen, which includes three essential drugs - HD-MTX, doxorubicin (adriamycin) and cisplatin [14]. HD-MTX is administered with leucovorin rescue to mitigate life-threatening toxicity, it inhibits DNA synthesis and cell replication [42]. Doxorubicin is an anthracycline antibiotic that prevents DNA replication, though its use is limited by potential permanent cardiotoxicity [43]. Cisplatin is a platinum compound that induces cancer cell death through DNA crosslinking [44]. The total duration of these multi-agent regimens typically spans 6 to 12 months [45].

While some protocols add ifosfamide (MAPI regimen), particularly for high-risk or metastatic cases, clinical trials like INT-0133 have shown that the routine addition of ifosfamide to standard MAP does not always provide a survival advantage for all patients [46].

Table 1 Evidence for Core Chemotherapeutic Agents (MAP Regimen)

Category / Study	Regimen / Intervention	Key Findings / Outcomes	Significance
Standardization of Therapy (MIOS, 1991) [11]	MAP + BCD (Bleomycin, Cyclophosphamide, and Dactinomycin) vs. Surgery Alone	6-year EFS increased from 11% to 61%. OS increased from 51% to 71%.	Definitively proved the necessity of adjuvant chemotherapy for high-grade localized disease.
Addition of Ifosfamide (INT-0133, 2007) [46]	MAP vs. MAP + Ifosfamide (MAPI)	The addition of Ifosfamide to standard MAP did not enhance EFS or OS for all patients.	Suggested that a 4th drug (Ifosfamide) is not routinely necessary for all localized cases.
Regimen Optimization (Meta-analysis by Anninga et al., 2011) [47]	2-drug vs. 3-drug vs. 4-drug combinations	Better progression-free survival (PFS) and OS were seen with 3-drug combinations (MAP) than 2-drug combinations.	Confirmed MAP as the optimal baseline regimen over simpler pairings.
Good Responders (EURAMOS-1, 2015) [48]	MAP vs. MAP + Interferon-alpha	No survival benefit was found from adding Interferon-alpha to the MAP regimen.	Validated that MAP alone is sufficient for patients achieving $\geq 90\%$ tumour necrosis.
Histological Response (EURAMOS-1, 2016) [49]	MAP (Adjuvant) vs. MAP + IE (for poor responders)	Adding Ifosfamide and Etoposide (IE) to MAP for poor responders failed to improve EFS or OS.	Reinforced that MAP remains the standard even for those with a poor histological response to induction.

5. Neoadjuvant vs. Adjuvant Therapy

The choice between NACT and adjuvant chemotherapy has been extensively studied. While NACT has become the clinical standard of care, multiple prospective and retrospective trials have demonstrated that it does not offer a statistically significant survival advantage over immediate surgery followed by adjuvant chemotherapy.

Table 2 Comparison of Evidence: Neoadjuvant vs. Adjuvant Therapy

Study	Study Design	Neoadjuvant Outcomes	Adjuvant Outcomes	Key Findings / Significance
MSKCC (1992) [50]	Retrospective (279 pts)	No survival difference detected.	No survival difference detected.	Reinforced that immediate vs. delayed definitive surgery does not compromise outcomes.
COSS Group (1999) [51]	Retrospective (1608 pts)	No survival difference detected.	No survival difference detected.	Large-scale analysis confirmed that survival is equivalent regardless of timing.
POG-8651 (2003) [52]	Randomised Trial	5-y PFS: 61%. OS: 76%. Limb Salvage: 50%.	5-y PFS: 69%. OS: 79%. Limb Salvage: 55%.	Found no significant difference in survival or limb-salvage rates between the two arms.
Bacci et al. (2005) [53]	Retrospective (1148 pts)	5-y EFS: 61%.	5-y EFS: 43%.	No significant difference in 5-y EFS; relapses in the NACT group generally occurred later.

Despite the lack of survival superiority, NACT is the preferred standard for several crucial reasons. It allows time for the manufacture of complex custom megaprotheses or biological reconstruction planning. Chemotherapy helps demarcate the tumour from surrounding tissue by inducing an avascular capsule, facilitating LSS over amputation. It also provides immediate treatment for subclinical micrometastases disseminated at diagnosis. NACT allows for the assessment of histological response (tumour necrosis) in the resected specimen, which remains the most robust prognostic indicator available to clinicians.

6. Surgical Standards: Margins and Reconstruction

Complete surgical removal of all detectable tumour sites is mandatory for a cure. The primary goal of surgery is to safely remove the tumour while preserving as much extremity function as possible. Modern surgical techniques have shifted the standard from amputation to LSS, which is now achievable in 80-90% of cases [17,29].

Surgical success is heavily dependent on achieving adequate margins. According to Enneking's criteria, margins must be at least "wide," meaning the lesion is removed as a single block surrounded by an unviolated cuff of healthy tissue [54]. Inadequate margins significantly increase the risk of local failure, which is a major factor in reduced overall survival. Options for reconstruction include endoprosthetic devices, biological reconstruction, or complex procedures like rotationplasty [55].

7. The Role of Histological Response

The evaluation of tumour necrosis in the resected specimen is one of the most reliable prognostic indicators in osteosarcoma. Response is typically graded using the Huvos or Salzer-Kuntschik systems - good and poor responders [56,57]. Good responders are defined as patients with $\geq 90\%$ tumour necrosis. These patients have a significantly better 5-year event-free survival (roughly 70-80%) compared to poor responders [18-20]. Poor responders are patients with $< 90\%$ necrosis have a much lower survival rate, often between 35-45% [58].

Attempts to modify postoperative chemotherapy for poor responders (salvage therapy) have been a major focus of research. However, large trials like EURAMOS-1 failed to prove that adding ifosfamide and etoposide to postoperative regimens improved survival for those with a poor histological response [48].

8. Management of Metastatic Disease and Variants

The prognosis for primary metastatic osteosarcoma, found in roughly 15% of patients at presentation, remains poor, with survival dropping to 20-30% [21,59]. The current standard for these patients is identical to localised disease but requires the mandatory surgical removal of all metastatic foci, usually via video-assisted thoracoscopic surgery (VATS) or bilateral exploratory thoracotomy for pulmonary lesions [60].

Table 3 Management Options for Osteosarcoma Variants

Variant	Grade	Management Options
High-Grade Central (Conventional)	High-grade	Multimodal approach: NACT (typically the MAP regimen), followed by definitive surgery (ideally LSS) and adjuvant chemotherapy.
Periosteal Osteosarcoma	Intermediate grade	Complete surgical excision with clear margins is the mainstay. The role of systemic chemotherapy is debatable; it is generally suggested only for high-risk features like medullary involvement, high-grade histopathology, or for preoperative tumour downsizing.
Parosteal Osteosarcoma	Low-grade	Wide surgical excision alone is the standard. Chemotherapy is restricted to cases that transform into high-grade malignancies or present with metastatic spread.
Low-Grade Central Osteosarcoma	Low-grade	Managed identically to parosteal osteosarcoma: wide surgical excision alone.
High-Grade Surface Osteosarcoma	High-grade	Behave like and are treated similarly to high-grade central tumours: a combination of surgery and intensive multi-agent chemotherapy.
Small Cell Osteosarcoma	High-grade	Resembles Ewing's sarcoma but produces osteoid; managed using standard high-grade osteosarcoma protocols.
Secondary Osteosarcoma	High-grade (usually)	Often arises from radiation or Paget's disease; managed with aggressive surgery and polychemotherapy that accounts for any previous treatment exposures.
Extraskeletal Osteosarcoma	High-grade	Originates in soft tissues; management follows a multidisciplinary approach analogous to conventional high-grade bone-based disease (surgery plus polychemotherapy).
Craniofacial Osteosarcoma	Variable	Complete surgical resection is the primary treatment; the benefit of adjuvant chemotherapy is discussed in the literature but remains under debate due to lower metastatic rates in non-skull sites.
Telangiectatic Osteosarcoma	High-grade	Classified as a high-malignancy tumour; generally, follows the standard multimodal protocols for high-grade central disease.

The management of osteosarcoma variants and special populations requires a nuanced deviation from standard high-grade protocols to balance oncological efficacy with specific histological behaviors and patient comorbidities. Periosteal osteosarcoma (PO), an intermediate grade chondroblastic variant representing roughly 1% of cases, is primarily managed through complete surgical resection. While the role of systemic therapy for PO remains controversial and is not routinely recommended by ESMO, experts often suggest its use for high-risk features such as medullary involvement, high-grade histopathology, or to facilitate tumour downsizing before surgery [16]. In contrast, parosteal osteosarcoma and its medullary counterpart, low-grade central osteosarcoma, are typically treated with wide surgical excision alone. Systemic chemotherapy for these low-grade variants is generally reserved only for rare cases that transform into high-grade malignancies or present with distant metastatic spread [61].

Rarer variants like small cell osteosarcoma, which histologically resembles Ewing's sarcoma but produces an osteoid matrix, are generally managed using standard high-grade osteosarcoma protocols [62]. Secondary osteosarcoma, which often arises from prior radiation exposure or Paget's disease, presents a significant clinical challenge due to its frequent occurrence in unfavorable axial sites and its historically grave prognosis. Treatment for these patients involves aggressive surgery and polychemotherapy that must carefully account for any previous cytotoxic exposures [63]. Similarly, extraskeletal osteosarcoma, a high-grade malignancy originating in soft tissues - is managed with a multidisciplinary approach analogous to conventional bone-based disease [64]. For craniofacial osteosarcoma, complete surgical resection remains the mainstay of treatment, although the use of adjuvant chemotherapy is discussed as a potentially beneficial supplement despite the lower metastatic rate for non-skull sites [65].

Among special populations, older patients (typically aged 41 to 65) represent a distinct group that often presents with more unfavorable axial lesions and faces a higher risk of treatment-related morbidity [66,67]. Conversely, while osteosarcoma is the most common bone malignancy in adolescents, it remains extremely rare in children under the age

of five. Ultimately, because these variants and populations are rare, the medical community emphasizes the necessity of treatment within specialised centres and participation in international collaborative trials to optimize survival outcomes while minimizing the high burden of permanent toxicities.

9. Challenges and Complications

Table 4 Complications of Chemotherapy

Complication	Causative Agent(s)	Related Supportive Management
Cardiotoxicity / Cardiomyopathy	Doxorubicin (Adriamycin), Anthracyclines	Use of continuous-infusion doxorubicin; administration of cardioprotective agents; baseline and regular echocardiography and electrocardiograms.
Nephrotoxicity / Renal Dysfunction	Cisplatin, Ifosfamide, High- dose Methotrexate	Rigorous hydration protocols and alkalinisation; meticulous monitoring of serum creatinine and clearance; use of Carboxypeptidase G2 (glucarpidase) for extreme MTX levels; high-flux renal dialysis.
Hemorrhagic Cystitis	Ifosfamide	Mandatory administration of Mesna (uroprotection) and aggressive hydration protocols.
Myelosuppression / Hematologic Toxicity	Most standard agents (e.g., Ifosfamide, Cisplatin, Methotrexate)	Administration of hematopoietic growth factors (e.g., G-CSF) to reduce the duration of severe granulocytopenia; blood and platelet transfusions as required.
Ototoxicity / Hearing Loss	Cisplatin	Baseline and serial audiograms to monitor high-frequency hearing loss.
Nausea and Vomiting (Emesis)	Highly emetogenic agents (especially Cisplatin)	Standard use of serotonin antagonists (e.g., ondansetron) either alone or in combination with dexamethasone.
Methotrexate Toxicity (Mucositis, Hepatorenal Failure)	High-dose Methotrexate	Leucovorin (Cytovorum factor) rescue; close pharmacokinetic monitoring of plasma MTX levels until they fall below safe thresholds (typically <0.1–0.3 µmol/L).
Neurotoxicity / Encephalopathy	Ifosfamide	Close clinical monitoring; temporary or permanent interruption of the causative agent if symptoms occur.
Infections / Septic Shock	Resulting from myelosuppression and persistent leukopenia	Use of G-CSF; early intervention with broad-spectrum antibiotics; hospitalization for management of febrile neutropenia.
Gonadal Dysfunction / Infertility	Intensive polychemotherapy	Fertility testing (e.g., seminal analysis) and offering cryopreservation (sperm banking) prior to starting therapy.
Secondary Malignancies (e.g., Leukemia, CNS tumours)	Late effect of various agents (e.g., alkylating agents)	Lifelong follow-up including regular history, physical examinations, and investigations to detect late sequelae as early as possible.
Electrolyte Abnormalities (e.g., Hypomagnesaemia)	Cisplatin, Ifosfamide	Frequent laboratory monitoring and appropriate intravenous or oral supplementation.

The management of osteosarcoma is fraught with significant challenges, primarily characterized by a persistent stagnation in survival rates, which have remained fixed at approximately 60-70% for localized disease for over three decades [2,12]. A major contributing factor to this therapeutic plateau is the extreme genetic heterogeneity of these tumours and the complex tumour microenvironment, which frequently lead to the development of multi-drug chemoresistance. Current standard-of-care regimens, such as the MAP protocol, rely on intensive systemic agents that carry a high burden of acute and permanent toxicities. For instance, doxorubicin is associated with dose-limiting, irreversible cardiotoxicity and cardiomyopathy, while cisplatin often results in permanent high-frequency hearing loss

and renal impairment. Furthermore, ifosfamide can induce life-threatening neurotoxicity, encephalopathy, and hemorrhagic cystitis, and HD-MTX requires meticulous pharmacokinetic monitoring to prevent hepatorenal failure and severe mucosal damage [22,23].

The clinical dilemma of poor histological responders, patients achieving <90% tumour necrosis after induction therapy, remains an unsolved challenge, as attempts to improve their prognosis through "salvage" chemotherapy have not yet yielded convincingly better survival outcomes [48,49]. For those presenting with metastatic or recurrent disease, the outlook is even more dismal, with survival rates often dropping below 20-30% [21,59]. Diagnostic limitations further complicate care. For example, standard CT imaging frequently underestimates the total burden of pulmonary metastases, potentially missing contralateral lesions and necessitating bilateral open thoracotomy for comprehensive control [68]. Additionally, while NACT is widely practiced facilitating LSS, there is a noted lack of scientific evidence proving its survival superiority over immediate surgery followed by adjuvant chemotherapy.

Long-term survivors face a spectrum of late complications, including secondary malignancies like acute leukemia, permanent reproductive dysfunction such as azoospermia or amenorrhea, and chronic orthopedic issues related to megaprosthesis reconstructions [22,23]. Finally, because osteosarcoma is a rare malignancy, the medical community faces extreme difficulty in conducting the large-scale, randomized controlled trials necessary to validate new therapies. The logistical and financial hurdles of international collaborative research mean that innovation often moves slowly, reinforcing the urgent need for translational breakthroughs in targeted and biological strategies to move beyond the limitations of conventional chemotherapy.

10. Future Directions: The Era of Precision and Biological Therapy

Table 5 Biological Options

Category	Mechanism	Specific Agents
Targeted Molecular Therapies	<i>IGF-1R</i> Inhibitors	Figitumumab, Cixutumumab, Linsitinib
	Tyrosine Kinase Inhibitors	Regorafenib, Sorafenib, Apatinib, Pazopanib, Cabozantinib
	Signaling Pathways (<i>mTOR</i> , <i>JAK/STAT</i> , <i>Wnt/β-catenin</i>)	Temsirolimus, Everolimus, Ruxolitinib, Tofacitinib, Niclosamide
Immunotherapy	Immune Checkpoint Inhibitors	Pembrolizumab, Nivolumab
	Adoptive Cell Transfer	CAR T-cells (targeting <i>GD2</i> , <i>B7-H3</i> , <i>FOLR1</i>); TCR-engineered T-cells
	Immunomodulators	Mifamurtide, Interferon-α
Biological Innovations	Antibody-Drug Conjugates	ABBV-085 (targets <i>LRRC15</i>), Ifinatamab deruxtecan (targets <i>B7-H3</i>)
	Oncolytic Viral Therapy	<i>Delta-24-ACT</i> , <i>OBP-702</i> , <i>HSV1716</i>
	Epigenetic Therapy	DNMT inhibitors (Decitabine, MC3343), HDAC inhibitors (Vorinostat, Romidepsin)
Advanced Delivery and Radiation	Targeted Radiation	Radium-223, Samarium-153, Actinium-225
	Novel Delivery Systems	Nanoparticles (Rexin-G), Inhalation Chemotherapy (Liposomal cisplatin)

The future of osteosarcoma management lies in breaking the three-decade stagnation in survival rates through the integration of precision medicine and biological innovations. Central to this shift is the development of targeted molecular therapies that exploit specific pathways like the *IGF-1R*, which is mutated or amplified in a subset of cases. While monoclonal antibodies such as figitumumab and cixutumumab have shown modest results as monotherapies, research is pivoting toward co-targeting strategies, such as combining *IGF-1R* inhibitors with *mTOR* inhibitors to overcome compensatory signaling and resistance [24-26]. TKIs, including regorafenib, sorafenib, and apatinib, have demonstrated significant clinical promise, particularly in relapsed or metastatic settings where regorafenib has been shown to significantly improve progression-free survival [69]. Immunotherapy represents another critical frontier,

utilising agents like mifamurtide to activate pulmonary macrophages or immune checkpoint inhibitors targeting the *PD-1/PD-L1* pathway to restore the immune system's ability to attack tumour cells. Although PD-1 inhibitors like pembrolizumab and nivolumab have yielded mixed results as single agents, their potential in combination with chemotherapy or TKIs is being actively explored in early-phase trials [27]. Furthermore, adoptive T-cell therapies, such as CAR T-cells targeting antigens like *GD2*, *B7-H3*, or *FOLR1*, offer a way to engineer the patient's own immune system to attack malignant cells, though hurdles like poor T-cell infiltration and an immunosuppressive tumour microenvironment (TME) must still be overcome [26]. ADCs are emerging as "guided missiles" to deliver cytotoxic payloads directly to tumour surface proteins like *LRRC15* or *B7-H3*, potentially increasing efficacy while reducing systemic toxicity [70]. Innovative research is also focusing on epigenetic modification therapy, where combinations of DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors (e.g., vorinostat) aim to reactivate silenced tumour suppressor genes and promote the differentiation of malignant cells back into mature osteoblasts [71]. Additionally, oncolytic viral therapy using engineered adenoviruses like *Delta-24-ACT* is being investigated for its ability to selectively lyse cancer cells while stimulating a robust systemic immune response [72]. The delivery of these novel therapies is being further refined through the use of nanoparticles and inhalation chemotherapy specifically designed to target resistant pulmonary metastases [73]. The identification of predictive biomarkers, such as *VEGF* expression or specific PET-CT parameters, is also a priority to allow clinicians to tailor systemic therapy to the unique biological profile of each patient [74]. Ultimately, given the rarity of this malignancy, the successful translation of these biological breakthroughs into standard clinical practice will necessitate continued, robust international collaborative trials.

11. Conclusion

The management of osteosarcoma has undergone a radical transformation, evolving from a purely surgical discipline into a sophisticated multimodal standard that has increased long-term survival to approximately 60-70% for patients with localised disease. The revolutionary introduction of combination chemotherapy, particularly the MAP regimen consisting of HD-MTX, doxorubicin, and cisplatin, remains the fundamental pillar of current systemic treatment. NACT has become the established standard of care, facilitating LSS and providing invaluable prognostic data through the evaluation of histological tumour necrosis. Despite these significant historical achievements, survival rates have largely stagnated over the past three decades, and the prognosis for patients with metastatic or recurrent disease remains persistently poor. Furthermore, the severe and often permanent toxicities associated with conventional agents, such as cardiotoxicity and nephrotoxicity, highlight an urgent need for more refined therapeutic options. The future of osteosarcoma management is increasingly focused on precision medicine and the development of biologically driven strategies. Promising research into targeted molecular therapies (such as TKIs and IGF-1R inhibitors), immunotherapy (including GD2-targeted CAR T-cells and immune checkpoint inhibitors), and ADCs offers hope for improved specificity and reduced morbidity. Additionally, novel approaches like epigenetic modification therapy and oncolytic viral therapy are being investigated to counteract chemoresistance. Ultimately, achieving the next major breakthrough in survival will depend on robust international collaborative trials and the successful translation of these biological innovations into routine clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest associated with this study.

Consent for publication

There is consent for the publication of this paper.

Funding

No funding sources.

Artificial Intelligence

During the preparation of this work, the authors used Google NotebookLM to summarize the available data. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

References

- [1] Taran SJ, Taran R, Malipatil NB. Pediatric Osteosarcoma: An Updated Review. *Indian J Med Paediatr Oncol.* 2017 Jan-Mar;38(1):33-43. doi: 10.4103/0971-5851.203513. PMID: 28469335; PMCID: PMC5398104.
- [2] Durfee, R.A., Mohammed, M. and Luu, H.H. Review of Osteosarcoma and Current Management. *Rheumatol Ther* 3, 221–243 (2016). <https://doi.org/10.1007/s40744-016-0046-y>
- [3] Evola, Francesco and Cucuzza, Maria and Evola, Giuseppe. (2026). OSTEOSARCOMA IN THE PEDIATRIC AGE. *EuroMediterranean Biomedical Journal.* 13. 127-131. 10.3269/1970-5492.2018.13.29.
- [4] Ivan A, Cojocaru E, Sirbu PD, Al Namat DR, Tîrnovanu ŞD, Butnariu LI, Bernic J, Bernic V, Țarcă E. Clinical and Pathological Profile of Children and Adolescents with Osteosarcoma. *Diagnostics.* 2025; 15(3):266. <https://doi.org/10.3390/diagnostics15030266>
- [5] Moukengue B, Lallier M, Marchandet L, Baud'huin M, Verrecchia F, Ory B, Lamoureux F. Origin and Therapies of Osteosarcoma. *Cancers (Basel).* 2022 Jul 19;14(14):3503. doi: 10.3390/cancers14143503. PMID: 35884563; PMCID: PMC9322921.
- [6] Picci P. Osteosarcoma (osteogenic sarcoma). *Orphanet J Rare Dis.* 2007 Jan 23;2:6. doi: 10.1186/1750-1172-2-6. PMID: 17244349; PMCID: PMC1794406.
- [7] Rogers KM, Conran RM. Educational Case: Pediatric Osteosarcoma. *Acad Pathol.* 2019 Mar 5;6:2374289519833902. doi: 10.1177/2374289519833902. PMID: 30859126; PMCID: PMC6402068.
- [8] Misaghi A, Goldin A, Awad M, Kulidjian AA. Osteosarcoma: a comprehensive review. *SICOT J.* 2018;4:12. doi: 10.1051/sicotj/2017028. Epub 2018 Apr 9. PMID: 29629690; PMCID: PMC5890448.
- [9] Ibrahim T, Mercatali L, Amadori D. Bone and cancer: the osteoncology. *Clin Cases Miner Bone Metab.* 2013 May;10(2):121-3. PMID: 24133529; PMCID: PMC3796999.
- [10] Jaffe N, Puri A, Gelderblom H. Osteosarcoma: evolution of treatment paradigms. *Sarcoma.* 2013;2013:203531. doi: 10.1155/2013/203531. Epub 2013 May 27. PMID: 23781130; PMCID: PMC3678494.
- [11] Link MP, Goorin AM, Horowitz M, Meyer WH, Belasco J, Baker A, Ayala A, Shuster J. Adjuvant chemotherapy of high-grade osteosarcoma of the extremity. Updated results of the Multi-Institutional Osteosarcoma Study. *Clin Orthop Relat Res.* 1991 Sep;(270):8-14. PMID: 1884563.
- [12] Pilavaki P, Gahanbani Ardakani A, Gikas P, Constantinidou A. Osteosarcoma: Current Concepts and Evolutions in Management Principles. *J Clin Med.* 2023 Apr 9;12(8):2785. doi: 10.3390/jcm12082785. PMID: 37109122; PMCID: PMC10143544.
- [13] Alaseem A, Alanezi M, Almhrij F, Alanezi K, Alrasheed K, Alrefaei N, Alshaygy I, Albishi W, AlHashem H. Comparative outcomes of neoadjuvant chemotherapy versus upfront surgical resection in osteosarcoma: a systematic review and meta-analysis. *World J Surg Oncol.* 2025 Nov 22;23(1):446. doi: 10.1186/s12957-025-04115-3. PMID: 41275279; PMCID: PMC12659466.
- [14] Yu D, Zhang S, Feng A, Xu D, Zhu Q, Mao Y, Zhao Y, Lv Y, Han C, Liu R, Tian Y. Methotrexate, doxorubicin, and cisplatin regimen is still the preferred option for osteosarcoma chemotherapy: A meta-analysis and clinical observation. *Medicine (Baltimore).* 2019 May;98(19):e15582. doi: 10.1097/MD.00000000000015582. PMID: 31083238; PMCID: PMC6531127.
- [15] Liu XW, Zi Y, Xiang LB, Han TY. Periosteal osteosarcoma: a review of clinical evidence. *Int J Clin Exp Med.* 2015 Jan 15;8(1):37-44. PMID: 25784972; PMCID: PMC4358427.
- [16] Assi T, Kattan J, Nasserredine H, Rassy E, Briand S, Court C, Verret B, Le Cesne A, Mir O. Chemotherapy in the management of periosteal osteosarcoma: A narrative review. *J Bone Oncol.* 2021 Sep 10;30:100389. doi: 10.1016/j.jbo.2021.100389. PMID: 34567961; PMCID: PMC8449265.
- [17] Papakonstantinou E, Stamatopoulos A, I Athanasiadis D, Kenanidis E, Potoupnis M, Haidich AB, Tsiridis E. Limb-salvage surgery offers better five-year survival rate than amputation in patients with limb osteosarcoma treated with neoadjuvant chemotherapy. A systematic review and meta-analysis. *J Bone Oncol.* 2020 Sep 15;25:100319. doi: 10.1016/j.jbo.2020.100319. PMID: 33088699; PMCID: PMC7567946.
- [18] Richardson SM, Wurtz LD, Collier CD. Ninety Percent or Greater Tumor Necrosis Is Associated With Survival and Social Determinants of Health in Patients With Osteosarcoma in the National Cancer Database. *Clin Orthop Relat*

Res. 2023 Mar 1;481(3):512-522. doi: 10.1097/CORR.0000000000002380. Epub 2022 Sep 13. PMID: 36099400; PMCID: PMC9928876.

- [19] Sever N, Şimşek F, Onur İD, Arvas H, Guliyev T, Şakalar T, Çiçek CM, Orman S, Çetin EB, Kayaş K, Akbaş S, Ağyol Y, Güren AK, Erel P, Kocaaslan E, Paçacı B, Tunç MA, Çelebi A, Majidova N, Durnalı A, Şimşek M, Şahbazlar M, Işık S, Arıkan R, Ercelep Ö, Sarı M, Köstek O, Bayoğu İV. Prognostic Factors in High Grade Osteosarcoma Patients Who Received Neoadjuvant Therapy and Subsequently Underwent Surgery: Data from the Turkish Oncology Group. *J Clin Med*. 2025 Mar 17;14(6):2024. doi: 10.3390/jcm14062024. PMID: 40142832; PMCID: PMC11943382.
- [20] Hanafy E, Al Jabri A, Gadelkarim G, Dasaq A, Nazim F, Al Pakrah M. Tumor histopathological response to neoadjuvant chemotherapy in childhood solid malignancies: is it still impressive? *J Investig Med*. 2018 Feb;66(2):289-297. doi: 10.1136/jim-2017-000531. Epub 2017 Sep 27. PMID: 28954845; PMCID: PMC5800352.
- [21] Harris MA, Hawkins CJ. Recent and Ongoing Research into Metastatic Osteosarcoma Treatments. *Int J Mol Sci*. 2022 Mar 30;23(7):3817. doi: 10.3390/ijms23073817. PMID: 35409176; PMCID: PMC8998815.
- [22] Hurkmans EGE, Brand ACAM, Verdonschot JAJ, Te Loo DMWM, Coenen MJH. Pharmacogenetics of chemotherapy treatment response and -toxicities in patients with osteosarcoma: a systematic review. *BMC Cancer*. 2022 Dec 19;22(1):1326. doi: 10.1186/s12885-022-10434-5. PMID: 36536332; PMCID: PMC9761983.
- [23] Janeway KA, Grier HE. Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects. *Lancet Oncol*. 2010 Jul;11(7):670-8. doi: 10.1016/S1470-2045(10)70062-0. Epub 2010 Mar 27. PMID: 20347613.
- [24] Tarone L, Iacoviello A, Di Lorenzo A, Verta R, Cossu C, Conti L, Cavallo F, Riccardo F. Exploring Emerging Therapeutic Targets in Osteosarcoma by Revisiting the Immune and Cancer-Intrinsic Hallmarks of Cancer. *Cancers (Basel)*. 2025 Nov 30;17(23):3846. doi: 10.3390/cancers17233846. PMID: 41375047; PMCID: PMC12691020.
- [25] Yu, S., Yao, X. Advances on immunotherapy for osteosarcoma. *Mol Cancer* 23, 192 (2024). <https://doi.org/10.1186/s12943-024-02105-9>
- [26] Morya VK, Magar AG, Park SH, Noh KC. Systemic strategies for osteosarcoma: advances and future directions. *Discov Oncol*. 2025 Jul 18;16(1):1367. doi: 10.1007/s12672-025-02208-9. PMID: 40679695; PMCID: PMC12274193.
- [27] Han Z, Chen G, Wang D. Emerging immunotherapies in osteosarcoma: from checkpoint blockade to cellular therapies. *Front Immunol*. 2025 Mar 18;16:1579822. doi: 10.3389/fimmu.2025.1579822. PMID: 40170852; PMCID: PMC11958959.
- [28] Spalato-Ceruso, M., Ghazzi, N.E. and Italiano, A. New strategies in soft tissue sarcoma treatment. *J Hematol Oncol* 17, 76 (2024). <https://doi.org/10.1186/s13045-024-01580-3>
- [29] Dhammi IK, Kumar S. Osteosarcoma: A journey from amputation to limb salvage. *Indian J Orthop*. 2014 May;48(3):233-4. doi: 10.4103/0019-5413.132486. PMID: 24932025; PMCID: PMC4052018.
- [30] Sheng G, Gao Y, Yang Y, Wu H. Osteosarcoma and Metastasis. *Front Oncol*. 2021 Dec 10;11:780264. doi: 10.3389/fonc.2021.780264. PMID: 34956899; PMCID: PMC8702962.
- [31] Fan TM, Roberts RD, Lizardo MM. Understanding and Modeling Metastasis Biology to Improve Therapeutic Strategies for Combating Osteosarcoma Progression. *Front Oncol*. 2020 Jan 31;10:13. doi: 10.3389/fonc.2020.00013. PMID: 32082995; PMCID: PMC7006476.
- [32] Wang J, Li M, Guo P, He D. Survival benefits and challenges of adjuvant chemotherapy for high-grade osteosarcoma: a population-based study. *J Orthop Surg Res*. 2023 Jun 27;18(1):465. doi: 10.1186/s13018-023-03922-2. Erratum in: *J Orthop Surg Res*. 2023 Nov 6;18(1):834. doi: 10.1186/s13018-023-04326-y. PMID: 37370182; PMCID: PMC10304229.
- [33] Carrle D, Bielack SS. Current strategies of chemotherapy in osteosarcoma. *Int Orthop*. 2006 Dec;30(6):445-51. doi: 10.1007/s00264-006-0192-x. Epub 2006 Aug 3. PMID: 16896870; PMCID: PMC3172747.
- [34] Voûte PA, Souhami RL, Nooij M, Somers R, Cortés-Funes H, van der Eijken JW, Pringle J, Hogendoorn PC, Kirkpatrick A, Uscinska BM, van Glabbeke M, Machin D, Weeden S. A phase II study of cisplatin, ifosfamide and doxorubicin in operable primary, axial skeletal and metastatic osteosarcoma. *European Osteosarcoma Intergroup (EOI). Ann Oncol*. 1999 Oct;10(10):1211-8. doi: 10.1023/a:1008361612767. PMID: 10586339.

- [35] Yuan G, Chen J, Wu D, Gao C. Neoadjuvant chemotherapy combined with limb salvage surgery in patients with limb osteosarcoma of Enneking stage II: a retrospective study. *Onco Targets Ther.* 2017 May 26;10:2745-2750. doi: 10.2147/OTT.S136621. PMID: 28603424; PMCID: PMC5457035.
- [36] Jing S, Ding F, Yuan Y, An J, He Q. Efficacy of Neoadjuvant Chemotherapy plus Limb-Sparing Surgery for Osteosarcoma and Its Impact on Long-Term Quality of Life. *Evid Based Complement Alternat Med.* 2022 Aug 8;2022:1693824. doi: 10.1155/2022/1693824. Retraction in: *Evid Based Complement Alternat Med.* 2023 Dec 6;2023:9850186. doi: 10.1155/2023/9850186. PMID: 35978993; PMCID: PMC9377866.
- [37] Tan JZ, Schlicht SM, Powell GJ, Thomas D, Slavin JL, Smith PJ, Choong PF. Multidisciplinary approach to diagnosis and management of osteosarcoma - a review of the St Vincent's Hospital experience. *Int Semin Surg Oncol.* 2006 Nov 3;3:38. doi: 10.1186/1477-7800-3-38. PMID: 17081310; PMCID: PMC1636057.
- [38] Federman N, Bernthal N, Eilber FC, Tap WD. The multidisciplinary management of osteosarcoma. *Curr Treat Options Oncol.* 2009 Apr;10(1-2):82-93. doi: 10.1007/s11864-009-0087-3. Epub 2009 Feb 24. PMID: 19238553.
- [39] Ritter J, Bielack SS. Osteosarcoma. *Ann Oncol.* 2010 Oct;21 Suppl 7:vii320-5. doi: 10.1093/annonc/mdq276. PMID: 20943636.
- [40] Rathore R, Van Tine BA. Pathogenesis and Current Treatment of Osteosarcoma: Perspectives for Future Therapies. *J Clin Med.* 2021 Mar 12;10(6):1182. doi: 10.3390/jcm10061182. PMID: 33809018; PMCID: PMC8000603.
- [41] Wittig JC, Bickels J, Priebat D, Jelinek J, Kellar-Graney K, Shmookler B, Malawer MM. Osteosarcoma: a multidisciplinary approach to diagnosis and treatment. *Am Fam Physician.* 2002 Mar 15;65(6):1123-32. PMID: 11925089.
- [42] Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist.* 2016 Dec;21(12):1471-1482. doi: 10.1634/theoncologist.2015-0164. Epub 2016 Aug 5. PMID: 27496039; PMCID: PMC5153332.
- [43] Belger C, Abrahams C, Imamdin A, Lecour S. Doxorubicin-induced cardiotoxicity and risk factors. *Int J Cardiol Heart Vasc.* 2023 Dec 27;50:101332. doi: 10.1016/j.ijcha.2023.101332. PMID: 38222069; PMCID: PMC10784684.
- [44] Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. *Eur J Pharmacol.* 2014 Oct 5;740:364-78. doi: 10.1016/j.ejphar.2014.07.025. Epub 2014 Jul 21. PMID: 25058905; PMCID: PMC4146684.
- [45] Moukengue B, Lallier M, Marchandet L, Baud'huin M, Verrecchia F, Ory B, Lamoureux F. Origin and Therapies of Osteosarcoma. *Cancers (Basel).* 2022 Jul 19;14(14):3503. doi: 10.3390/cancers14143503. PMID: 35884563; PMCID: PMC9322921.
- [46] Schwartz CL, Gorlick R, Teot L, Krailo M, Chen Z, Goorin A, Grier HE, Bernstein ML, Meyers P; Children's Oncology Group. Multiple drug resistance in osteogenic sarcoma: INT0133 from the Children's Oncology Group. *J Clin Oncol.* 2007 May 20;25(15):2057-62. doi: 10.1200/JCO.2006.07.7776. PMID: 17513810.
- [47] Anninga JK, Gelderblom H, Fiocco M, Kroep JR, Taminiu AH, Hogendoorn PC, Egeler RM. Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? *Eur J Cancer.* 2011 Nov;47(16):2431-45. doi: 10.1016/j.ejca.2011.05.030. Epub 2011 Jun 22. PMID: 21703851.
- [48] Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, Krailo MD, Gebhardt M, Pápai Z, Meyer J, Nadel H, Randall RL, Deffenbaugh C, Nagarajan R, Brennan B, Letson GD, Teot LA, Goorin A, Baumhoer D, Kager L, Werner M, Lau CC, Sundby Hall K, Gelderblom H, Meyers P, Gorlick R, Windhager R, Helmke K, Eriksson M, Hoogerbrugge PM, Schomberg P, Tunn PU, Kühne T, Jürgens H, van den Berg H, Böhling T, Picton S, Renard M, Reichardt P, Gerss J, Butterfass-Bahloul T, Morris C, Hogendoorn PC, Seddon B, Calaminus G, Michelagnoli M, Dhooge C, Sydes MR, Bernstein M; EURAMOS-1 investigators. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. *J Clin Oncol.* 2015 Jul 10;33(20):2279-87. doi: 10.1200/JCO.2014.60.0734. Epub 2015 Jun 1. Erratum in: *J Clin Oncol.* 2016 Nov 20;34(33):4059. doi: 10.1200/JCO.2016.70.9923. PMID: 26033801; PMCID: PMC4486345.
- [49] Marina NM, Smeland S, Bielack SS, Bernstein M, Jovic G, Krailo MD, Hook JM, Arndt C, van den Berg H, Brennan B, Brichard B, Brown KLB, Butterfass-Bahloul T, Calaminus G, Daldrup-Link HE, Eriksson M, Gebhardt MC, Gelderblom H, Gerss J, Goldsby R, Goorin A, Gorlick R, Grier HE, Hale JP, Hall KS, Harges J, Hawkins DS, Helmke K, Hogendoorn PCW, Isakoff MS, Janeway KA, Jürgens H, Kager L, Kühne T, Lau CC, Leavey PJ, Lessnick SL,

- Mascarenhas L, Meyers PA, Mottl H, Nathrath M, Papai Z, Randall RL, Reichardt P, Renard M, Safwat AA, Schwartz CL, Stevens MCG, Strauss SJ, Teot L, Werner M, Sydes MR, Whelan JS. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol.* 2016 Oct;17(10):1396-1408. doi: 10.1016/S1470-2045(16)30214-5. Epub 2016 Aug 25. PMID: 27569442; PMCID: PMC5052459.
- [50] Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, Applewhite A, Vlamis V, Rosen G. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol.* 1992 Jan;10(1):5-15. doi: 10.1200/JCO.1992.10.1.5. PMID: 1370176.
- [51] Bielack SS, Kempf-Bielack B, Heise U, Schwenzler D, Winkler K. Combined modality treatment for osteosarcoma occurring as a second malignant disease. Cooperative German-Austrian-Swiss Osteosarcoma Study Group. *J Clin Oncol.* 1999 Apr;17(4):1164. doi: 10.1200/JCO.1999.17.4.1164. PMID: 10561175.
- [52] Goorin AM, Schwartzentruber DJ, Devidas M, Gebhardt MC, Ayala AG, Harris MB, Helman LJ, Grier HE, Link MP; Pediatric Oncology Group. Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. *J Clin Oncol.* 2003 Apr 15;21(8):1574-80. doi: 10.1200/JCO.2003.08.165. PMID: 12697883.
- [53] Bacci G, Longhi A, Fagioli F, Briccoli A, Versari M, Picci P. Adjuvant and neoadjuvant chemotherapy for osteosarcoma of the extremities: 27 year experience at Rizzoli Institute, Italy. *Eur J Cancer.* 2005 Dec;41(18):2836-45. doi: 10.1016/j.ejca.2005.08.026. Epub 2005 Nov 17. PMID: 16298125.
- [54] Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res.* 1980 Nov-Dec;(153):106-20. PMID: 7449206.
- [55] Liu Z, Cai H, Li Y, Wang Z. Current Strategies for Limb Salvage and Reconstruction in Pediatric Lower Extremity Malignant Bone Tumors: Focus on Growth Preservation and Functional Outcomes. *Children (Basel).* 2025 Dec 16;12(12):1700. doi: 10.3390/children12121700. PMID: 41462839; PMCID: PMC12731801.
- [56] Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. *Arch Pathol Lab Med.* 1977 Jan;101(1):14-8. PMID: 299812.
- [57] Salzer-Kuntschik M, Brand G, Dellling G. Bestimmung des morphologischen Regressionsgrades nach Chemotherapie bei malignen Knochentumoren [Determination of the degree of morphological regression following chemotherapy in malignant bone tumors]. *Pathologe.* 1983 May;4(3):135-41. German. PMID: 6576329.
- [58] Prabowo Y, Setiawan I, Kamal AF, Kodrat E, Labib Zufar ML. Correlation between Prognostic Factors and the Histopathological Response to Neoadjuvant Chemotherapy in Osteosarcoma: A Retrospective Study. *Int J Surg Oncol.* 2021 Apr 26;2021:8843325. doi: 10.1155/2021/8843325. PMID: 33996154; PMCID: PMC8096583.
- [59] Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current Treatment and a Collaborative Pathway to Success. *J Clin Oncol.* 2015 Sep 20;33(27):3029-35. doi: 10.1200/JCO.2014.59.4895. Epub 2015 Aug 24. PMID: 26304877; PMCID: PMC4979196.
- [60] Salah S, Ahmad R, Sultan I, Yaser S, Shehadeh A. Osteosarcoma with metastasis at initial diagnosis: Current outcomes and prognostic factors in the context of a comprehensive cancer center. *Mol Clin Oncol.* 2014 Sep;2(5):811-816. doi: 10.3892/mco.2014.325. Epub 2014 Jun 23. PMID: 25054050; PMCID: PMC4106734.
- [61] Pacheco M, Guzmán R, Bonilla P. Dedifferentiated Low-Grade Osteosarcoma, Outcome with or Without Chemotherapy: A Systematic Review. *Orthop Res Rev.* 2023 Apr 28;15:79-89. doi: 10.2147/ORR.S404146. PMID: 37143718; PMCID: PMC10153403.
- [62] Martin SE, Dwyer A, Kissane JM, Costa J. Small-cell osteosarcoma. *Cancer.* 1982 Sep 1;50(5):990-6. doi: 10.1002/1097-0142(19820901)50:5<990::aid-cncr2820500529>3.0.co;2-r. PMID: 6953993.
- [63] Dray MS, Miller MV. Paget's osteosarcoma and post-radiation osteosarcoma: secondary osteosarcoma at Middlemore Hospital, New Zealand. *Pathology.* 2008 Oct;40(6):604-10. doi: 10.1080/00313020802320663. PMID: 18752128.
- [64] Puranik AD, Purandare NC, Bal MM, Shah S, Agrawal A, Rangarajan V. Extraskelletal osteosarcoma: An uncommon variant with rare metastatic sites detected with FDG PET/CT. *Indian J Med Paediatr Oncol.* 2014 Jan;35(1):96-8. doi: 10.4103/0971-5851.133732. PMID: 25006295; PMCID: PMC4080674.

- [65] Weber V, Stigler R, Lutz R, Kesting M, Weber M. Systematic review of craniofacial osteosarcoma regarding different clinical, therapeutic and prognostic parameters. *Front Oncol.* 2023 Mar 24;13:1006622. doi: 10.3389/fonc.2023.1006622. PMID: 37035145; PMCID: PMC10080080.
- [66] Longhi A, Errani C, Gonzales-Arabisio D, Ferrari C, Mercuri M. Osteosarcoma in patients older than 65 years. *J Clin Oncol.* 2008 Nov 20;26(33):5368-73. doi: 10.1200/JCO.2007.14.9104. Epub 2008 Sep 22. PMID: 18809616.
- [67] Jeon DG, Lee SY, Cho WH, Song WS, Park JH. Primary osteosarcoma in patients older than 40 years of age. *J Korean Med Sci.* 2006 Aug;21(4):715-8. doi: 10.3346/jkms.2006.21.4.715. PMID: 16891818; PMCID: PMC2729896.
- [68] Kayton ML, Huvos AG, Casher J, Abramson SJ, Rosen NS, Wexler LH, Meyers P, LaQuaglia MP. Computed tomographic scan of the chest underestimates the number of metastatic lesions in osteosarcoma. *J Pediatr Surg.* 2006 Jan;41(1):200-6; discussion 200-6. doi: 10.1016/j.jpedsurg.2005.10.024. PMID: 16410133.
- [69] Assi A, Farhat M, Hachem MCR, Zalaquett Z, Aoun M, Daher M, Sebaaly A, Kourie HR. Tyrosine kinase inhibitors in osteosarcoma: Adapting treatment strategies. *J Bone Oncol.* 2023 Nov 3;43:100511. doi: 10.1016/j.jbo.2023.100511. PMID: 38058514; PMCID: PMC10696463.
- [70] Chen B, Zheng X, Wu J, Chen G, Yu J, Xu Y, Wu WKK, Tse GMK, To KF, Kang W. Antibody-drug conjugates in cancer therapy: current landscape, challenges, and future directions. *Mol Cancer.* 2025 Nov 3;24(1):279. doi: 10.1186/s12943-025-02489-2. PMID: 41184856; PMCID: PMC12581584.
- [71] Katsianou MA, Andreou D, Korkolopoulou P, Vetsika EK, Piperi C. Epigenetic Modifications in Osteosarcoma: Mechanisms and Therapeutic Strategies. *Life (Basel).* 2025 Jul 28;15(8):1202. doi: 10.3390/life15081202. PMID: 40868849; PMCID: PMC12387225.
- [72] Karadimas T, Huynh TH, Chose C, Zervoudakis G, Clampitt B, Lapp S, Joyce D, Letson GD, Metts J, Binitie O, Mullinax JE, Lazarides A. Oncolytic Viral Therapy in Osteosarcoma. *Viruses.* 2024 Jul 16;16(7):1139. doi: 10.3390/v16071139. PMID: 39066301; PMCID: PMC11281467.
- [73] Sakkal M, Abdelmoteleb RWA, Al Ali A, Jordan YAB, Löbenberg R, Sarfraz M. Inhalable nanoparticle-based drug delivery system for non-small cell lung cancer therapy: promises and challenges. *Saudi Pharm J.* 2025 Dec 15;33(6):50. doi: 10.1007/s44446-025-00046-y. PMID: 41396464; PMCID: PMC12705525.
- [74] Zamborsky R, Kokavec M, Harsanyi S, Danisovic L. Identification of Prognostic and Predictive Osteosarcoma Biomarkers. *Med Sci (Basel).* 2019 Feb 11;7(2):28. doi: 10.3390/medsci7020028. PMID: 30754703; PMCID: PMC6410182