SCOPING REVIEW

Osteosarcoma Management in the Precision Medicine Era: Bibliometric Analysis and Clinical Progress (2015–2024)

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Abstract

Objectives: Osteosarcoma, the most common high-grade malignant bone tumor, has experienced only limited progress in therapeutic options, highlighting the urgent need for more effective treatments. This review examines bibliometric trends and clinical developments in osteosarcoma research from 2015 to 2024, with a particular focus on precision medicine and personalized therapy.

Methods: A search in the Web of Science Core Collection identified 17,476 osteosarcoma-related publications for bibliometric analysis. Key metrics, including publication trends, international collaborations, and emerging research topics, were evaluated using the Bibliometrix R package. Additionally, a clinical review examined recent innovations in diagnostic imaging, prognostic biomarkers, chemotherapy resistance, targeted therapies, immunotherapies, and surgical techniques.

Results: Research publications on osteosarcoma steadily increased, peaking at 2,009 in 2021, with significant contributions from China, the United States, Japan, India, and Italy. Key research themes encompassed apoptosis, metastasis, chemotherapy resistance, and immunotherapy. Advances in imaging techniques, such as dynamic MRI and PET/CT, have significantly enhanced tumor staging and prediction of treatment response. Emerging biomarkers, including genetic alterations (TP53, RB1, MYC) and inflammatory markers, have become important prognostic tools. Surgical innovations, including patient-specific instrumentation and limb-sparing techniques, have improved patient outcomes. Furthermore, targeted therapies (kinase inhibitors, antibody-drug conjugates) and immunotherapies (CAR T-cell therapy, immune checkpoint inhibitors) have demonstrated promising results in clinical trials.

Conclusion: Integrating bibliometric insights with clinical advancements underscores the importance of personalized approaches in osteosarcoma management. Predictive imaging biomarkers and precision-targeted therapies play a crucial role, and future research should focus on their clinical validation to enhance patient outcomes.

Level of evidence: V

Keywords: Bibliometric review, Biomarkers, Immunotherapy, Osteosarcoma, Therapeutic innovations

Introduction

Osteosarcoma is the most common high-grade primary malignant bone tumor, histologically characterized by the direct production of osteoid or immature bone matrix by malignant mesenchymal cells.[1]

Despite significant advances in oncology, the standard therapeutic approach for osteosarcoma—comprising neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy—has undergone limited evolution

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since its establishment in the 1980s.[2,3] As a result, patient outcomes have plateaued, with 5-year survival rates stagnating at approximately 60–70% for localized disease and only 20–30% for metastatic cases.[4] This underscores the urgent need for novel therapeutic strategies to improve prognosis, particularly for advanced and recurrent osteosarcoma.[5]

Over the past decade (2015–2024), research on osteosarcoma has experienced significant growth, with notable advancements in molecular profiling, biomarker discovery, targeted therapeutics, immunological strategies, and surgical technologies.[6] At the same time, innovations in diagnostic imaging and the rise of precision medicine have created new opportunities for personalized treatment approaches.[7,8] This comprehensive bibliometric and narrative review aims to systematically assess recent research trends and clinical advancements in the management of osteosarcoma. Specifically, it combines quantitative bibliometric insights with critical clinical evaluations, offering an updated synthesis of current knowledge and highlighting future directions that may address ongoing treatment challenges.

Materials and Methods

Bibliometric Analysis

Literature Search Strategy

A comprehensive literature search was performed using the Web of Science Core Collection (WoSCC) database. The search terms 'osteosarcoma' OR 'osteogenic sarcoma' were applied in the Topic field. Only original articles and reviews published in English between January 1, 2015, and December 31, 2024, were included. Non-research documents, such as editorials, conference abstracts, letters, and other non-original works, were excluded from the analysis. Initially, 20,099 records were retrieved. After removing duplicates (22 records) and irrelevant document types, 17,476 unique publications were retained for detailed analysis.

Data Extraction and Duplicate Removal

Data were exported from the WoSCC in plain text format, including complete bibliographic records and cited references. Bibliometric data were then imported into the R-based bibliometric analysis tool, Bibliometrix. Duplicate records were removed based on exact title matching within Bibliometrix, ensuring the integrity and accuracy of the data for subsequent analyses.

Analytical Methods and Tools

Bibliometric analysis was conducted using the Bibliometrix package in R (version 4.x). Descriptive bibliometric indicators were calculated to assess publication trends, identify the top contributing countries, institutions, authors, and the most productive journals, as well as influential articles. Specifically, the annual number of publications was calculated explicitly to determine the publication trend over the decade (2015–2024). International collaboration networks among countries were generated and visualized clearly to highlight global research partnerships. Identification of the most productive authors and most cited publications was performed explicitly to recognize influential contributors and seminal research papers. Author-defined keywords and Keywords-Plus provided by WoS were extracted and analyzed to identify the most prominent research themes and topics.

Visualization of Results

Bibliometrix, along with its visualization functions and the ggplot2 package, was used to generate clear graphical representations of the bibliometric results, including annual publication trends, keyword co-occurrence, country collaboration networks, top-cited articles, and the most productive journals. All visualizations were exported as high-resolution images for inclusion in the manuscript.

Clinical and Scientific Review

Scope and Purpose

Along with the bibliometric analysis, a narrative clinical review was conducted to summarize recent advancements in osteosarcoma therapy. This review focused on targeted therapies, immunotherapy, surgical innovations, and key translational insights, including studies of the tumor microenvironment, autophagy, and mechanisms of drug resistance. The primary goal was to integrate the latest clinical advances with the quantitative bibliometric trends, offering a cohesive summary of the current therapeutic landscape and outlining promising directions for future research.

Inclusion and Exclusion Criteria

Studies included in the narrative review were identified using the Population-Intervention-Study Design framework. Eligible populations consisted of patients with histologically confirmed osteosarcoma, regardless of stage, age, or anatomical location. Relevant interventions encompassed standard chemotherapy regimens, surgical approaches (such as limb-salvage surgery or amputation), novel systemic therapies (e.g., kinase inhibitors, immune checkpoint inhibitors, CAR T-cell therapy), adjunctive treatments like Mifamurtide or radiotherapy, and innovative drug delivery and reconstructive techniques, including 3D-printed implants. Study designs eligible for inclusion included randomized controlled trials, prospective and retrospective cohort studies, large case series with significant clinical findings, and translational research studies with direct clinical implications. Editorials, letters, meeting abstracts, and isolated case reports lacking generalizable insights were excluded from the review.

Supplemental Literature Search

To ensure comprehensive coverage of recent developments, targeted supplementary searches were conducted in the PubMed and Scopus databases, focusing on publications from 2020 to 2024. These additional searches specifically targeted emerging therapies and technologies, including targeted therapies, immunotherapy, CAR-T cell strategies, and 3D printing applications in osteosarcoma. Findings from these supplementary searches were cross-checked against the primary bibliometric dataset, and relevant high-impact studies published up to December 31, 2024, were included for detailed full-text review.

Study Selection and Data Extraction

Titles and abstracts retrieved from the clinical literature were independently screened by two reviewers for relevance based on predefined inclusion criteria. Eligible studies underwent detailed full-text evaluation, during which key data were extracted, including patient population characteristics, intervention details, primary clinical outcomes (overall survival, event-free survival, response rates, functional outcomes), and notable translational findings, such as molecular targets and mechanisms of drug resistance. Any discrepancies encountered during study selection or data extraction were resolved through consensus discussions between the reviewers or by consulting a third investigator, ensuring the consistency and accuracy of data collection.

Synthesis of Findings

Data extracted from clinical and translational studies were synthesized into a structured narrative, organized into thematic categories that mirrored prominent bibliometric trends. These themes included targeted therapies, immunotherapy approaches, surgical innovations, and advancements in diagnostic and therapeutic delivery strategies. Particular emphasis was placed on linking novel clinical developments to the research trends identified through bibliometric analysis, creating an integrated narrative that highlights the translation of basic scientific discoveries into clinical practice.

Ethical and Reporting Considerations

This study did not involve human subjects or confidential patient data, as all analyses were based solely on published literature. Therefore, formal Institutional Review Board (IRB) approval was not required. This review followed the PRISMA guidelines for narrative literature reviews and established standards for reporting bibliometric analyses, ensuring transparency, reproducibility, and scientific rigor throughout the reporting process.[9] All sources cited in this review have been properly referenced, ensuring adherence to the highest standards of academic integrity.

Results

Bibliometric Trends in Osteosarcoma Research (2015–2024)

A comprehensive bibliometric analysis of osteosarcoma-related publications from the Web of Science Core Collection database revealed substantial research activity over the decade from 2015 to 2024. The initial search retrieved 20,099 records. After filtering for English-language original articles and reviews and removing duplicates, 17,476 unique records were retained for analysis.

The annual publication trend steadily increased from 1,316 articles in 2015, peaking at 2,009 in 2021, before experiencing a slight decline and stabilizing around 1,788 articles in 2024. Despite this fluctuation, the consistently high annual output reflects sustained global interest and continued investment in osteosarcoma research [Figure 1].

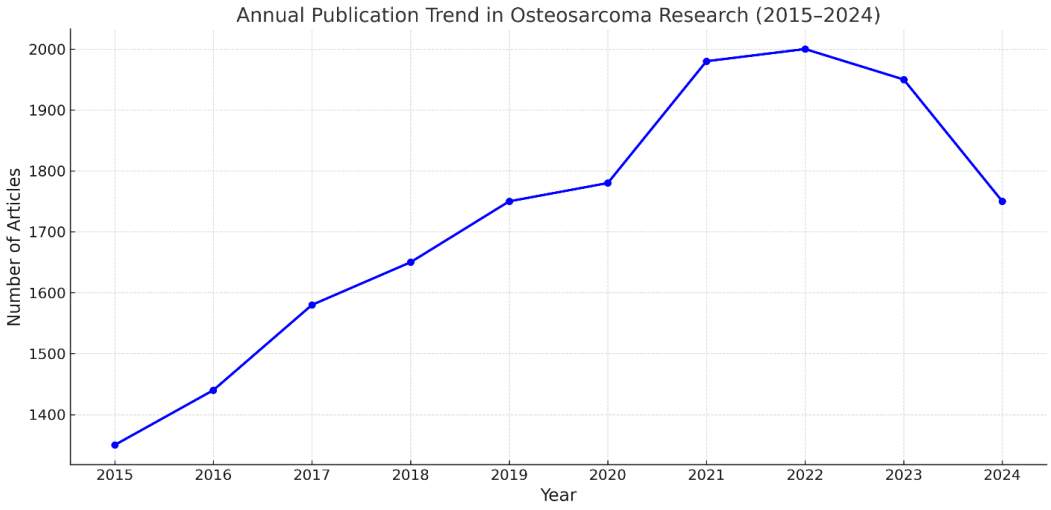

Figure 1. Annual trend of osteosarcoma-related publications from 2015 to 2024, demonstrating peak research output in 2021

Global Contributions and Collaborative Networks

The bibliometric data highlighted significant international contributions, with 54,849 distinct authors across 2,518 sources. China emerged as the leading contributor with 8,299 publications, followed by the United States (2,386 publications), Japan (710 publications), India (699 publications), and Italy (658 publications). China also led in total citations (155,085 citations). However, the United Kingdom (with an average of 23.5 citations per article) and the United States (with an average of 22 citations per article) exhibited higher average article impact.

Analysis of international collaboration revealed that 17.22% of the articles resulted from international co-authorship, highlighting significant global partnerships. The

United Kingdom, Italy, and France exhibited the highest multiple-country publication ratios (approximately 50%, 25.8%, and 30.6%, respectively), indicating strong participation in international research networks [Figure 2].

The most productive authors during this period were primarily based in China, with Zhang Y (269 articles), Wang Y (266 articles), and Liu Y (214 articles) leading the field. This indicates that prominent research groups based in specific Chinese institutions actively collaborate both nationally and internationally [Figure 3].

The leading journals publishing osteosarcoma research included Oncology Letters (339 articles), Frontiers in Oncology (283 articles), and the International Journal of Molecular Sciences (253 articles), highlighting the multidisciplinary nature of research dissemination across the fields of oncology and molecular biology.

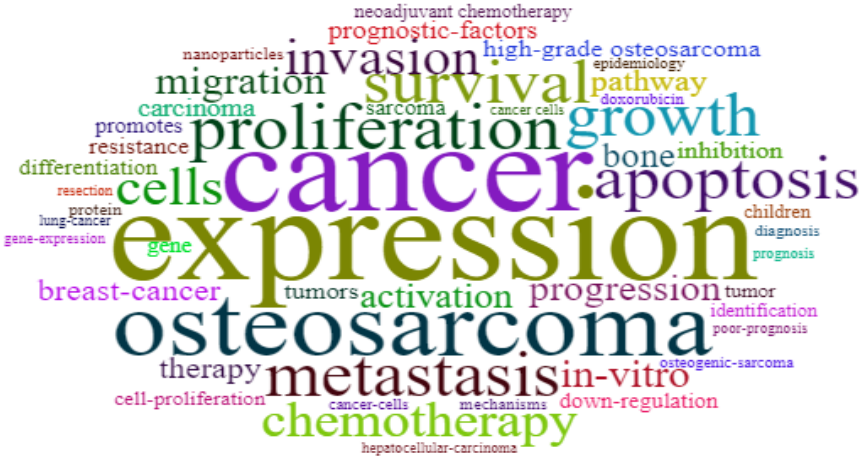

Figure 2. Word cloud

Figure 3. International collaboration network illustrating countries contributing prominently to osteosarcoma research publications (2015–2024)

Most Influential Research Topics and Themes

A keyword analysis was performed to identify the most influential and frequently studied research topics. Excluding the core term 'osteosarcoma,' the most prominent author-defined keywords were 'apoptosis,' 'proliferation,' 'prognosis,' 'metastasis,' and 'cancer.' These terms highlight key biological processes, clinical outcomes, and therapeutic challenges central to osteosarcoma research.

Keywords-Plus analysis further highlighted 'expression,' 'proliferation,' 'metastasis,' 'survival,' and 'apoptosis' as frequently occurring themes. These topics highlight the research community's strong focus on understanding tumor biology, the mechanisms underlying tumor progression and metastasis, as well as the factors that influence patient prognosis and survival outcomes.

Highly cited articles published during this period also

reflected these research emphases, with influential studies focusing on advanced therapeutic approaches and fundamental tumor biology. The most cited article was by Isakoff et al. (2015), published in The Journal of Clinical Oncology (1,190 citations),[10] followed by Tawbi et al. (2017) in Lancet Oncology (944 citations)[11] and Ahmed et al. (2015), also in The Journal of Clinical Oncology (761 citations).[12] These seminal publications underscore the sustained clinical and research focus on innovative treatments and therapeutic resistance mechanisms.

Overall, this bibliometric analysis outlines the dynamic landscape of osteosarcoma research, highlighting significant international collaboration, concentrated research efforts on critical biological and clinical challenges, and ongoing efforts toward therapeutic innovations.

Clinical Results

Temporal Evolution of Epidemiological Patterns in Osteosarcoma

Recent epidemiological analyses from 2000 to 2021 reveal notable demographic shifts in osteosarcoma distribution. Historically, osteosarcoma exhibited a single peak incidence during adolescence. However, recent studies, particularly among Japanese populations, now document a clear bimodal age distribution, with distinct incidence peaks during adolescence and late adulthood. This shift may reflect changing demographic patterns, environmental factors, or improved diagnostic accuracy in elderly patients.[4] Core epidemiological features remain stable, including a consistent male-to-female ratio of approximately 1.13:1 and predominant anatomical locations (lower extremities, 78%; upper extremities, 12%; axial sites, 10%).[13] However, the proportion of patients presenting with metastatic disease at diagnosis has increased from 12–19% historically to approximately 27% after 2012, underscoring the need for earlier diagnosis and improved detection strategies.[14] The rise in osteosarcoma diagnoses among elderly populations further highlights the necessity for tailored therapeutic approaches and optimal health resource allocation in aging populations.[6]

Advances and Standardization in Osteosarcoma Imaging

Magnetic resonance imaging (MRI) has established its crucial role in evaluating osteosarcoma, with recent advancements enhancing both diagnostic precision and prognostic accuracy. The introduction and validation of dynamic contrast-enhanced MRI (DCE-MRI) and standardized assessment systems such as Bone-RADS have significantly improved the evaluation of tumor margins, local invasiveness, and early therapeutic responses.[15,16] The relative wash-in rate (rWIR), a novel MRI biomarker, has emerged as a powerful prognostic tool. Patients with rWIR ≥2.3 exhibited significantly higher event-free survival rates at 2 and 5 years (85% and 75%, respectively) compared to those with lower rWIR (<2.3), whose corresponding rates were substantially lower (55% and 50%).[17]

Complementing MRI, 18F-FDG PET/CT provides invaluable metabolic insights, with baseline SUV_max values below six correlating with better clinical responses. Additionally, PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) help identify skip lesions and joint invasion, crucial factors influencing surgical planning.[18,19] Together, standardized multimodal imaging techniques provide a comprehensive and precise characterization of osteosarcoma, facilitating individualized clinical decision-making.[15,19]

Prognostic Biomarkers in Osteosarcoma: Current Perspectives

Recent genomic and molecular studies have identified key prognostic biomarkers in osteosarcoma, offering new opportunities for patient stratification and therapeutic planning. Approximately 90% of osteosarcomas show loss of TP53 through intron 1 rearrangements or deletions, while RB1 deletions occur in up to 30% of cases, highlighting their early roles in tumorigenesis.[20,21] Patients with osteosarcoma who exhibit MYC amplification or CDKN2A/B deletions should be considered high-risk. Clinicians managing these patients should prioritize early enrollment in targeted therapy clinical trials (e.g., those investigating MYC inhibitors) or adopt more intensive surveillance protocols, including earlier and more frequent imaging follow-ups.[7,22,23]

Inflammatory biomarkers such as CAR (>0.25) and NLR (>2.04) have significant prognostic value. Clinicians should routinely assess these markers before surgery. Patients with elevated CAR or NLR values should receive enhanced postoperative monitoring, early multidisciplinary evaluation for metastatic potential, and potentially tailored chemotherapy regimens in consultation with medical oncology. In an extensive multicenter study of 235 patients, elevated CAR and NLR independently predicted poor survival with high diagnostic accuracy (CAR AUC = 0.733, NLR AUC = 0.703), highlighting their clinical potential.[24] However, immune biomarkers, such as PD-L1 expression, have demonstrated limited predictive value in osteosarcoma, underscoring the complexity of the tumor's immune microenvironment.[25,26] Nevertheless, integrating multiple biomarkers into prognostic nomograms has improved predictive accuracy (concordance indices up to 0.781), reinforcing the need for comprehensive biomarker profiling in clinical practice.[24,27]

Challenges and Advances in Managing Poor Responders

Histologic response to neoadjuvant chemotherapy is one of the strongest prognostic indicators in osteosarcoma management. Pathologists typically classify tumor necrosis induced by chemotherapy, with ≥90% necrosis indicating a good response and <90%, particularly <50%, indicating a poor response. Poor responders exhibit significantly worse clinical outcomes, characterized by higher risks of both local recurrence and metastatic disease.[28,29] Recent studies emphasize substantial differences in survival, with five-year survival rates ranging from approximately 37% to 66.5% in poor responders, compared to 84% to 88.8% in good responders.[30] Early and accurate identification of poor responders remains a critical clinical challenge.[23]

Surgical decision-making in patients who are poor responders presents unique challenges. Unlike good

responders, whose tumors often shrink significantly after chemotherapy, poor responders may experience minimal tumor regression or even progression.[29,31] This scenario complicates surgical planning, requiring orthopedic surgeons to carefully assess whether limb-salvage procedures remain feasible or if more radical interventions, such as amputation, might be necessary.[32] Consequently, limb salvage is the preferred approach when clear margins can be confidently achieved. However, surgeons must balance the goal of preserving limb function with the crucial need to prevent residual microscopic disease. Tumor location plays a significant role in these decisions; axial tumors (pelvis, sacrum, spine) may require more aggressive surgical margins due to anatomical constraints.

Advances in imaging techniques, such as MRI radiomics, diffusion-weighted imaging (DWI), and PET/CT, have significantly enhanced the early detection of chemoresistant osteosarcoma. Radiomics-based predictive models have demonstrated remarkable accuracy (AUC 0.95–0.97) in identifying patients who are poor responders to treatment.[33] Similarly, metabolic parameters from PET imaging, such as SUV_max reduction, strongly correlate with histologic response and prognosis.[34,35] The clinical application of these advanced imaging biomarkers can enable earlier identification of poor responders, facilitating timely adjustments in surgical planning, chemotherapy regimen modifications, or early intervention with novel therapeutic strategies.[36]

Systemic management strategies for poor responders remain challenging. Notably, the EURAMOS-1 trial, which evaluated intensified chemotherapy (MAPIE regimen), failed to show improved survival outcomes in poor responders compared to standard chemotherapy (MAP).[37] While guidelines, such as those from the NCCN,[38] suggest that alternative chemotherapy regimens could be considered, evidence supporting these changes remains limited. As a result, many oncologists continue to use standard chemotherapy regimens or encourage participation in clinical trials exploring targeted therapies or immunotherapies, including tumor-infiltrating lymphocyte (TIL) therapy and kinase inhibitors.[7,39]

Effective management of poor responders requires a highly coordinated, multidisciplinary approach involving orthopedic oncology, medical oncology, radiology, pathology, radiation oncology, and rehabilitation specialists. Regular multidisciplinary sarcoma tumor boards play a crucial role in facilitating personalized and informed treatment decisions, particularly in cases that are complex or borderline.[40,41] Furthermore, patients may benefit from seeking care at advanced centers, such as 'Specialist Sarcoma Centers,[42] where specialists with extensive expertise can provide unparalleled support. Additionally, early involvement in clinical trials exploring novel therapies is critical, given the limitations of intensified conventional chemotherapy.[43]

Surgical Innovations in Osteosarcoma Treatment

Recent advancements in surgical techniques have greatly enhanced limb-sparing approaches, improving patient outcomes and reducing complications. Techniques such as computer-assisted tumor surgery (CATS) and patient-specific instrumentation (PSI), supported by advanced 3D printing technology, have significantly increased surgical precision, reducing both operative complexity and duration.[44]

Three-dimensional printing has become a crucial tool in planning complex osteosarcoma surgeries. Patient-specific 3D models derived from CT and MRI data allow surgeons to visualize and rehearse osteotomies preoperatively, improving anatomical understanding and orientation during surgery, which in turn reduces operative times.[45,46] Patient-specific cutting guides fabricated through 3D printing significantly enhance the accuracy of planned bone resections, ensuring adequate oncologic margins while minimizing damage to healthy tissue.[47,48] Cadaveric and clinical studies have demonstrated that PSI achieves resection accuracy comparable to navigation systems, while also reducing operative time, minimizing intraoperative blood loss, and enhancing surgical efficiency.[49] For example, clinical evidence demonstrates significant reductions in operative time (272 to 209 minutes) and blood loss (2248 mL to 1390 mL) in pelvic osteosarcoma resections using 3D-printed guides compared to conventional techniques.[48,50] Similarly, randomized trials around the knee have confirmed significant decreases in intraoperative blood loss without increasing operative time.[51]

Moreover, 3D printing technology enables the creation of custom implants tailored explicitly to individual anatomical defects resulting from tumor resection. Unlike traditional custom implants, modern 3D-printed prostheses—often fabricated from titanium alloys—can be produced rapidly, frequently within days, and are precisely designed to match the resected bone geometry.[52] Early clinical experiences with custom 3D-printed implants have been promising, with reports of minimal complications, excellent fit, no early loosening or deep infections, and improved initial stability due to their precise design and porous surfaces, which promote bony integration.[53] In particular, studies highlight successful outcomes with custom implants in complex anatomical reconstructions, including pelvic endoprostheses and glenoid components in proximal humeral tumors, demonstrating significant improvements in surgical outcomes and patient recovery.[46]

Beyond metal implants, biological reconstruction techniques, such as vascularized fibular grafts and the Capanna technique (which combines allograft and vascularized fibula), remain strong alternatives, showing union rates of approximately 93% and significantly reduced graft failure compared to traditional allografts (13% vs. 21.4%).[54,55]

Defining appropriate surgical margins remains crucial in osteosarcoma treatment, as it directly impacts local recurrence and survival rates. Traditionally, surgeons aim for wide anatomical margins, typically defined as ≥1–2 cm of normal soft tissue and ≥3 cm of bone beyond the tumor.[56] However, functional margins have gained prominence, emphasizing anatomical barriers (e.g., fascial septa, joint

capsule, vessel walls) that can prevent tumor spread, even with narrower physical clearance.[57,58] Modern high-resolution MRI aids surgeons in preoperative margin planning by accurately identifying whether tumors breach these anatomical barriers, thereby supporting the functional margin approach.[59] Nevertheless, studies reaffirm that achieving truly tumor-free margins remains essential, as inadequate margins significantly increase the risk of local recurrence and decrease survival rates.[60]

Emerging technologies, including intraoperative imaging, surgical navigation, tumor-targeted fluorescent dyes, and innovative imaging techniques, are designed to enhance the precision of margin determination during surgery.[61,62] These tools represent a precision surgery approach, optimizing functional preservation while maintaining oncologic outcomes.

Advances in Chemotherapy and Systemic Treatment Approaches

Chemotherapy remains a cornerstone in osteosarcoma treatment, but recent research has shifted toward targeted therapies, immunotherapies, and innovative drug-delivery systems to improve efficacy and reduce systemic toxicity. Agents such as Regorafenib and Apatinib have demonstrated promising efficacy in refractory disease, particularly when combined with immune checkpoint inhibitors.[7,63,64] Emerging targeted therapies, including MYC inhibitors and B7-H3–targeted antibody-drug conjugates, have produced meaningful clinical responses, highlighting a growing trend toward precision medicine.[65,66] Immunotherapeutic strategies, especially CAR T-cells targeting HER2, B7-H3, or GD2, have also shown preliminary safety and clinical activity, paving the way for future multimodal therapeutic approaches.[12,39,67]

Discussion

Clinical Practice Implications and Recommendations

Building on recent advancements, several practical recommendations can be outlined for orthopedic oncologists managing osteosarcoma. Orthopedic surgeons should increasingly integrate advanced surgical planning tools, including 3D imaging and printing technologies, into their routine clinical practice. The use of patient-specific 3D-printed cutting guides and anatomical models significantly enhances surgical precision, ensuring accurate margins and optimal functional preservation. Custom 3D-printed implants should also be considered, particularly in complex anatomical regions where standard implants may not suffice [Table 1].

Table 1. Summary of key innovative messages derived from recent advancements in osteosarcoma management, emphasizing clinical implications.

Section	Key Innovative Message
Epidemiological Patterns	Recent shift to bimodal age distribution highlights the necessity for tailored age-specific management strategies.
Diagnostic Imaging	Dynamic MRI biomarkers (e.g., rWIR ≥2.3) and PET metabolic parameters (SUVmax, MTV, TLG) significantly enhance early prognostication and response evaluation.
Prognostic Biomarkers	Integrated biomarker panels (genomic alterations and systemic inflammatory markers like CAR and NLR) provide superior predictive power over single biomarkers.
Chemotherapy Resistance	Radiomics and PET imaging allow precise early identification of chemotherapy resistance, potentially guiding timely therapeutic adjustments.
Surgical Innovations	3D-printed patient-specific instruments significantly reduce operative complexity and intraoperative blood loss and enhance surgical precision and efficiency.
Targeted Therapies	Emerging precision therapies (kinase inhibitors, antibody-drug conjugates, MYC inhibitors) show promise in refractory osteosarcoma, suggesting a future shift from conventional chemotherapy.
Immunotherapy	Early-phase CAR T-cell and checkpoint inhibitor trials indicate feasible safety and potential efficacy, necessitating further clinical validation.
Multidisciplinary Management	Specialist Sarcoma Centers and routine multidisciplinary tumor boards significantly improve complex decision-making and patient outcomes.

Genomic profiling of osteosarcoma samples—specifically evaluating TP53, RB1, MYC amplification, PTEN loss, CDKN2A/B deletions, and ATRX mutations—should be a standard component of routine pathological assessments, particularly for patients with poor chemotherapy responses or metastatic presentations. Identifying these genetic alterations can help guide personalized treatment strategies, including referral to targeted therapeutic clinical trials, adjustments to chemotherapy protocols, or the selection of more aggressive surgical margins. Regular multidisciplinary team meetings should explicitly address these biomarkers when developing individualized treatment plans for patients. Surgical planning must prioritize oncologic adequacy, clearly defining resection margins using advanced imaging, such as MRI, to delineate tumor boundaries and identify anatomical barriers. When appropriate, adopting functional margins based on these barriers can preserve critical structures without compromising cancer control. Surgeons should proactively engage multidisciplinary teams—comprising medical oncologists, radiologists, pathologists, plastic

surgeons, and rehabilitation specialists—to refine surgical strategies and guide perioperative management decisions, particularly in high-risk cases.

Managing poor chemotherapy responders requires a proactive, individualized approach. Clear margins should be aggressively pursued to minimize the risk of recurrence, although limb salvage should remain the primary goal when feasible. Close coordination with oncology colleagues is essential to explore alternative systemic therapies or clinical trial options. Rigorous postoperative surveillance, including frequent imaging assessments, is crucial for the early detection and management of relapses.

Conclusion

Despite substantial progress in osteosarcoma research over the past decade, improvements in clinical outcomes have been limited. This bibliographic and clinical review identifies key research trends and highlights significant advancements in diagnostic imaging, biomarker identification, surgical techniques, and targeted therapies. A critical new insight is the demonstrated clinical value of predictive imaging biomarkers, including advanced MRI radiomics, diffusion-weighted imaging, and PET-derived metabolic markers, which enable the early identification and tailored management of patients with poor responses to neoadjuvant chemotherapy. These imaging biomarkers, along with genomic and inflammatory biomarkers such as MYC amplification, TP53 mutations, and elevated CAR and NLR, offer promising tools for personalized therapeutic strategies. Future research should rigorously validate these biomarkers in prospective clinical studies and promote multidisciplinary collaboration to quickly translate these findings into clinical practice. This study provides valuable insight by demonstrating that integrating these predictive biomarkers can significantly improve osteosarcoma prognosis and therapeutic decision-making, ultimately leading to better patient outcomes.

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