SCOPING REVIEW

Multifocal Osteosarcoma: Practical Insights for Orthopedic Surgeons

Khodamorad Jamshidi, MD; Alireza Mirzaei, PhD; Shahabaldin Beheshti Fard, MD; Edward Y. Cheng, MD

Research performed at Bone and Joint Reconstruction Research Center, Shafa Orthopedic Hospital, Iran University of Medical Sciences, Tehran, Iran, and Department of Orthopedic Surgery, University of Minnesota, Minneapolis, Minnesota, USA.

Received: 19 December 2025 *Accepted: 13 May 2026*

Abstract

Objectives: Multifocal osteosarcoma (MFOS) is an aggressive presentation of osteosarcoma characterized by multiple skeletal lesions without visceral metastasis. Despite decades of clinical recognition, its biological basis, classification, and optimal management remain poorly defined, particularly regarding distinctions between synchronous and metachronous disease. Synchronous and metachronous MFOS differ in pathogenesis, imaging characteristics, clinical behavior, treatment feasibility, and prognosis.

Methods: A narrative review of the literature was conducted using PubMed, Scopus, and Google Scholar. Studies addressing the definition, classification systems, pathogenesis, imaging characteristics, treatment approaches, and outcomes of MFOS were identified and synthesized, with particular emphasis on differences between synchronous and metachronous forms.

Results: MFOS accounts for approximately 1.5% of osteosarcoma cases. Synchronous MFOS typically presents with widespread sclerotic lesions, limited surgical options, and poor survival. In contrast, metachronous MFOS more closely resembles conventional osteosarcoma, is more often amenable to surgical resection, and demonstrates comparatively improved outcomes. Genetic predisposition syndromes and microenvironmental factors appear to play contributory roles in selected cases. However, no definitive molecular markers currently exist to distinguish true multicentric disease from early skeletal metastasis.

Conclusion: MFOS remains a diagnostically and therapeutically challenging condition with distinct clinical and prognostic differences between synchronous and metachronous forms. Improved molecular characterization and collaborative research efforts are needed to refine classification, guide treatment strategies, and improve outcomes in this rare and aggressive disease.

Level of evidence: V

Keywords: Metachronous, Multifocal osteosarcoma, Synchronous

Introduction

Conventional osteosarcoma (OS) is the most common subtype of OS [1] and typically arises in the metaphyseal region of long bones, particularly around the knee. [2,3] It generally presents as a solitary, aggressive bone lesion.[1,4,5] Hematogenous dissemination is common, with the lungs representing the primary site of metastasis.[6] Secondary spread to other sites often involves other skeletal sites.[6]

A small subset of OS manifests as multifocal osteosarcoma (MFOS) without visceral involvement, and it is unclear whether this represents a new primary lesion or metastatic disease.[7] MFOS accounts for approximately 1.5% of all OS[5] and includes two types: either synchronous or metachronous lesions, based on the temporal relationship between lesions, as defined in prior clinicopathologic series and classification systems.[7] Lesions that are identified at

Corresponding Author: Alireza Mirzaei, Bone and Joint Reconstruction Research Center, Department of Orthopedics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; 2. Department of Orthopedic Surgery, University of Minnesota, Minneapolis, Minnesota, USA

Email: mirzaeialireza26@gmail.com, mirza093@umn.edu

THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

diagnosis or within six months of each other are considered synchronous, accounting for approximately 40% of MFOS cases.[7] Metachronous lesions appear more than six months after the initial lesion is detected and represent about 60% of MFOS lesions.[7] Some authors argue that metachronous MFOS is a separate primary tumor in susceptible mesenchymal tissue, whereas synchronous multifocal OS is metastasis from the primary lesion.[8] However, there is currently no consensus, and the underlying pathogenesis of MFOS remains uncertain.

This review aims to compile and evaluate the current evidence on the two types of MFOS, focusing on key aspects such as definition, classification, molecular mechanisms, radiographic patterns, treatment approaches, and overall prognosis.

Materials and Methods

The literature reviewed in this article was identified through searches of medical databases, primarily PubMed, Scopus, and Google Scholar, using combinations of the terms 'multifocal osteosarcoma,' 'synchronous,' and 'metachronous,' with emphasis on studies reporting clinical presentation, imaging features, treatment strategies, prognosis, and outcomes.

Results

Definition

MFOS represents a rare presentation of OS, characterized by the presence of two or more osteosarcomatous lesions within the skeleton in the absence of visceral, particularly pulmonary, metastasis.[9] Historically, MFOS was considered a distinct pathological entity, believed to represent multiple independent primary osteosarcomas developing within the same individual.[9] This concept arose from clinical observations of patients, often children or adolescents, who presented with several bone lesions but no detectable lung metastases.[9] The lesions were frequently distributed symmetrically and involved the metaphyseal regions of long bones, leading to the term "multifocal" or "multicentric" osteosarcoma.[9] Subsequently, MFOS was classified into synchronous and metachronous forms based on the temporal pattern of lesion development. In the synchronous type, multiple skeletal lesions are evident at the time of diagnosis or within a short interval thereafter, whereas in the metachronous form, new osseous lesions appear after an initial disease-free period following treatment of the primary tumor.[9] Contemporary molecular and pathological evidence, however, suggests that most cases of MFOS likely represent skeletal metastases rather than independent primaries.[10-12] Clonal analyses have shown striking similarities between primary and subsequent lesions, supporting the view that these tumors share a common origin and disseminate hematogenously within the skeleton before or without visceral involvement.[10-12] True MFOS, arising as separate primary tumors, is exceptionally rare and is generally associated with hereditary cancer syndromes such as Li-Fraumeni, hereditary retinoblastoma, or Rothmund–Thomson syndrome, which predispose to multiple de novo malignancies.[9]

In current clinical practice, the diagnosis of MFOS remains based on clinical and radiologic findings, since definitive molecular proof distinguishing the two metastases from a new primary tumor remains lacking. As a result, the term "multifocal osteosarcoma" primarily denotes a pattern of skeletal-only dissemination rather than a proven biological subtype. Nevertheless, differentiating MFOS from conventional metastatic OS may be challenging in some scenarios.

In most patients with metastatic OS, bone metastases appear after or together with lung involvement.[9] Only a small subset of cases develop skeletal metastases without pulmonary disease,[9] and it is precisely this limited group that blurs the boundary between metastatic OS and MOFS. In routine clinical settings, however, the practical convention is to designate any OS presenting with multiple skeletal lesions but without lung involvement as "multifocal osteosarcoma," regardless of whether the underlying mechanism represents true multicentricity or early skeletal metastasis.

MFOS must also be differentiated from skip metastases, which represent secondary tumor foci located in the same bone, in proximity to the primary lesion, or across the adjacent joint within a continuous limb segment synchronously.[13] Skip metastases share the same medullary canal and vascular drainage as the primary tumor and are therefore considered part of the same local disease process rather than multifocal dissemination.[14] In contrast, MFOS involves lesions in non-contiguous bones, often in anatomically distant sites, and reflects a systemic skeletal process rather than localized spread.[14] The recognition of this distinction is clinically important because skip metastases are managed as locally advanced disease, whereas MFOS signifies a systemic pattern with markedly poorer prognosis.

Altogether, the term MFOS should be reserved for cases with two or more non-contiguous skeletal lesions in the absence of visceral metastasis, acknowledging that, based on current evidence, this pattern most often represents a form of skeletal-only metastatic dissemination rather than true MFOS.

Classification

Historically, several classification systems have been proposed for MFOS. In 1969, Amstutz[15] introduced a three-type classification based on patient age, histological grade, and the timing of lesion presentation. In this framework, Types 1 and 2 correspond to synchronous MFOS (simultaneous or nearly simultaneous): Type 1 typically occurs in children and adolescents and is characterized by high-grade OS involving multiple skeletal sites, whereas Type 2 arises in adults and is associated with low-grade OS. Type 3 was designated as metachronous MFOS, with lesions appearing months/years apart. Approximately a decade later, Mahoney et al.[16] refined this scheme by incorporating specific time-based criteria. In their four-type classification, Types A and B corresponded to Types I and II of the Amstutz classification, respectively, whereas Type III in the Amstutz system was subdivided into two categories: lesions developing between 5 and 24 months (Type C) and those arising after 24 months (Type D). Despite their historical relevance, both the Amstutz and Mahoney classifications are now considered limited, as they included cases with

concomitant pulmonary metastases and relied on detection methods that are less accurate than those available today.

In contemporary practice, MFOS is generally divided into two categories: synchronous MFOS, where additional lesions are found within six months, and metachronous MFOS, characterized by the appearance of new lesions after six months without visceral involvement.[7] In both categories, the absence of simultaneous pulmonary metastases distinguishes MFOS from conventional OS with skeletal metastasis.[7]

A thorough understanding of the evolution of these classification systems and the application of the current, simplified criteria enables more accurate interpretation of radiographic and clinical findings, thereby facilitating prognostic evaluation and guiding surgical management.

Pathogenesis

The underlying pathogenesis of MFOS remains incompletely understood. However, several hypotheses have been proposed. The clonal evolution hypothesis suggests that synchronous lesions may share a common clonal origin, consistent with early metastatic seeding.[17,18] Conversely, metachronous lesions may exhibit distinct histological or molecular profiles, supporting the theory of independent tumorigenesis rather than a metastatic event. However, the inherent genomic instability and heterogeneity of OS introduce uncertainty regarding this hypothesis.[19]

A second major hypothesis for the pathogenesis of MFOS highlights the role of genetic predisposition.[20] The strongest associations are seen with hereditary cancer syndromes such as Li-Fraumeni syndrome (TP53 mutations) and hereditary retinoblastoma (RB1 mutations).[21] In Li-Fraumeni syndrome, several reports describe both synchronous and metachronous MFOS, supporting the concept that intrinsic genomic instability can give rise to multiple independent tumors. Similarly, OS is a well-recognized secondary malignancy among retinoblastoma survivors, and in some cases, this takes a multifocal form, likely reflecting systemic genetic vulnerability.[21] Other syndromes, such as Rothmund–Thomson syndrome (associated with RECQL4 mutations), have also been implicated in rare instances [Table 1], further emphasizing the role of genetic and microenvironmental susceptibility in the development of MFOS.[22-33]

Table 1. MFOS-associated syndromes

Syndrome	Reported/reference	Synchronous	Metachronous
Li-Fraumeni	Saucier et al. [22]		11
	Brandal et al. [23]		3
	Zils K et al. [24]		1
	Huby et al. [25]		1
Retinoblastoma	Pratt et al. [26]	3	
	Potepan et al. [27]	1	
	Bielack et al. [28]	4	
Rothmund–Thomson syndrome	Zils et al. [29]		
	Anbari et al. [30]	2	1
Paget's disease	Deyrup et al. [31]	1	1
	Andrew et al. [32]	5	
Bone infarct	Sivrioglu et al. [33]	1	

A third hypothesis proposes that abnormalities in the bone microenvironment may trigger the development of MFOS. Conditions such as Paget's disease of bone and chronic bone infarction alter normal bone remodeling and repair processes, potentially increasing susceptibility to malignant transformation. In these contexts, MFOS may arise on the background of pre-existing pathology, supporting the idea that local microenvironmental disturbances contribute to the multifocal presentation of the disease.

Despite these insights, no reliable pathogenesis-based marker currently exists to distinguish MFOS from conventional OS, as well as synchronous from metachronous MFOS; however, future research integrating multiregion genomic sequencing, clonal evolution analysis, and longitudinal molecular profiling of primary and secondary lesions may clarify whether these entities represent distinct biological processes or variations along a metastatic continuum.

According to the data summarized in [Table 1], Li-Fraumeni–associated MFOS tends to present more often as metachronous disease, whereas retinoblastoma-associated MFOS more commonly manifests in the synchronous form.

Imaging characteristics

Radiographically, synchronous MFOS is characterized by multiple, sclerotic lesions that often extend into adjacent soft tissue.[34] In a series of 62 radiographs investigated by Corradi et al., the majority of cases demonstrated at least one dominant lesion with features typical of primary OS, most commonly located in the metaphyseal region, although

extension into the epiphysis and diaphysis was also observed.[7] Similar features have been corroborated in other case series.[35] These findings frequently mimic skeletal metastases.[7] [Figure 1]

Cross-sectional imaging, particularly magnetic resonance imaging (MRI) and computed tomography (CT), is recommended for detailed local assessment.[36] In addition, whole-body bone scintigraphy using 99m technetium-MDP offers high sensitivity for detecting metastatic lesions, assessing the metabolic activity of bone lesions, and accurately staging the disease.[36]

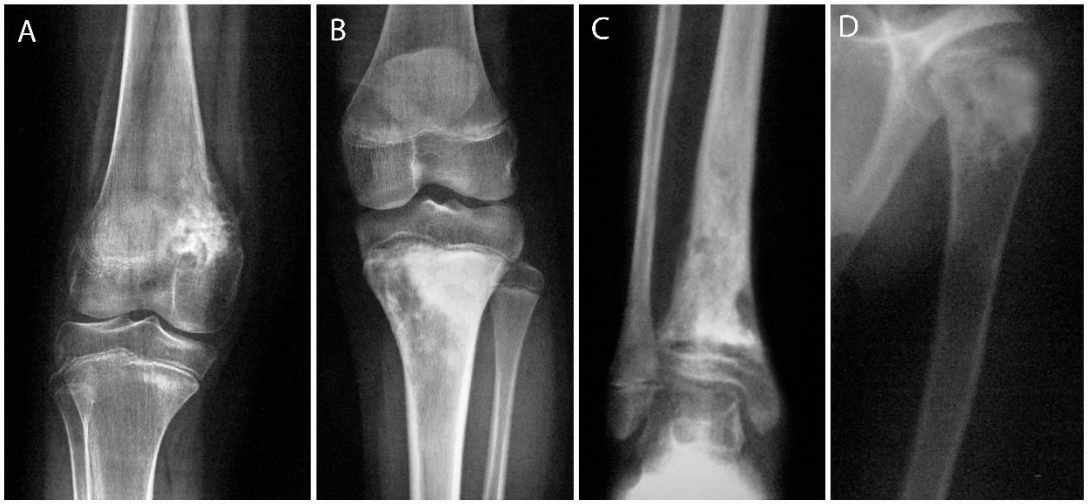

Figure 1. Radiographic images illustrating synchronous multifocal osteosarcoma involving five distinct sites in a 10-year-old boy.(A) Anteroposterior radiograph of the right distal femur and proximal tibia showing synchronous lesions in both areas.(B) Anteroposterior radiograph of the left distal femur and proximal tibia displaying a synchronous lesion in the proximal tibia.(C) Anteroposterior radiograph of the right distal tibia and ankle demonstrating a synchronous lesion in the distal tibia.(D) Anteroposterior radiograph of the left shoulder revealing a synchronous lesion in the proximal humerus.

In contrast, metachronous MFOS more frequently exhibits mixed blastic, lytic lesions with a wide zone of transition.[7] In a cohort of 50 radiographs studied by Corradi *et al*., the lesions typically displayed a wide zone of transition and showed signs of soft-tissue extension, along with a periosteal reaction that closely resembled the conventional findings associated with conventional OS.[7] Subsequent studies have reported similar findings,[8,37] reinforcing that metachronous lesions, while temporally distinct, radiographically mirror the classic presentation of solitary OS [Figure 2].

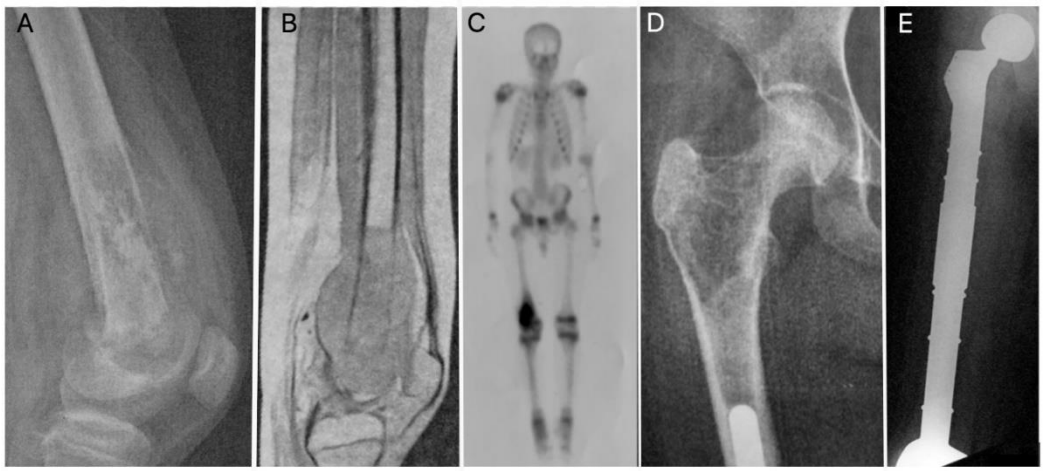

Figure 2. (A) Preoperative lateral radiograph of the distal femur showing a lytic, blastic, ill-defined lesion in a 14-year-old female; (B) Preoperative T1-weighted sagittal MRI illustrating the size of the soft-tissue component and medullary involvement; (C) Tc 99 bone scan at presentation showing only distal femoral involvement; (D) Anteroposterior radiograph of the proximal femur after 6 years of the initial surgery, demonstrating a lytic lesion in the proximal part of the same femur; (E) Anteroposterior radiograph of the femur showing total femur replacement 3 years after the second surgery

Treatment Approaches

Management of synchronous MFOS remains highly challenging due to the multifocal and often symmetrical distribution of lesions, which limits the feasibility of complete surgical resection.[38] In the most extensive available series, Bacci et al.[39] reported that following neoadjuvant chemotherapy, resection of both primary and secondary lesions was only practical in 16 of 42 patients (38%). An additional 12 (29%) patients were eligible for isolated resection of the primary lesion, while the remaining 14 (33%) patients had neither the primary nor the secondary lesion amenable to surgical resection due to extensive skeletal involvement. Similarly, Corradi et al. [7] reported that out of 22 synchronous cases, only 4 (18%) patients were considered candidates for surgical intervention, radiotherapy, or both.[7] These findings highlight that surgery is often restricted to highly selected cases, and systemic therapy typically constitutes the cornerstone of management.

In contrast, metachronous MFOS more frequently allows for surgical intervention, reflecting its more focal presentation and greater similarity to conventional solitary OS. In the series by Corradi et al., 9 of 34 patients (26%) underwent surgical resection after neoadjuvant chemotherapy.[7] While the overall proportion of operable cases remains modest, the likelihood of surgical eligibility appears higher in metachronous disease compared with synchronous MFOS. This supports the notion that metachronous MFOS, often interpreted as new primary tumors rather than widespread metastatic dissemination, may be more amenable to localized control strategies.

Prognosis

The overall prognosis of MFOS is poor; however, outcomes differ between synchronous and metachronous forms. Synchronous MFOS is consistently associated with worse survival. In the study by Bacci et al., among 42 patients with synchronous MFOS, only 3 achieved long-term survival, with a mean interval of 23 months between surgery and death.[39] Similarly, Corradi et al. reported that among 21 synchronous patients, only one survived at a median follow-up of 15 months.[7]

By contrast, metachronous MFOS demonstrates comparatively more favorable, though still limited, outcomes. In Corradi's cohort of 34 metachronous cases, 7 patients survived at a median follow-up of 17 months.[7] These findings suggest that metachronous MFOS, often considered to represent new primary tumors, carries a slightly better prognosis and offers a greater chance of survival compared to synchronous MFOS. This observation could be attributed to several factors. First, in metachronous MFOS, patients typically receive systemic chemotherapy for their primary osteosarcoma, and the secondary lesions—often too small to be detected on imaging—respond to chemotherapy in a manner similar to the primary lesion. In other words, the initial chemotherapy can help eradicate microscopic disease and delay the emergence of new lesions. Second, lesions often appear sequentially and in fewer sites, which makes surgical excision more feasible. When new lesions appear later, they may be fewer in number and still surgically resectable. Finally, the time gap between primary and secondary tumors allows for treatment and recovery, improving the chance of prolonged survival.

Discussion

While the clinical and radiographic distinctions between synchronous and metachronous MFOS are increasingly recognized, the molecular pattern of these rare conditions remains largely unexplored. Such a molecular signature can provide critical insights into whether lesions arise through early metastatic dissemination from the same clone or represent independent primary tumors in genetically susceptible bone tissue. Future studies should leverage next-generation sequencing (NGS), DNA methylation profiling, and multi-omics analyses, such as transcriptomics or proteomics, to clarify the evolutionary origins of MFOS lesions.

Early evidence in conventional OS suggests that genomic instability, epigenetic dysregulation, and altered microRNA signatures may drive tumor metastasis.[40-42] Whether these features differ between synchronous and metachronous MFOS remains unknown. Similarly, mass Spectrometric-Based proteomic and metabolomic approaches hold promise for identifying biomarkers that can distinguish new primary tumors from early metastatic spread, potentially aiding in diagnosis and treatment stratification.[43]

Given the rarity of MFOS, collaborative multi-institutional efforts and the establishment of molecular registries will be essential to generate sufficiently powered datasets. Such investigations could not only refine our understanding of MFOS pathogenesis but also reveal novel therapeutic targets and prognostic biomarkers, ultimately bridging the gap between clinical observation and precision oncology.

Conclusion

MFOS represents a rare but clinically significant presentation of OS that continues to challenge conventional diagnostic, therapeutic, and biological paradigms. The distinction between synchronous and metachronous disease is not merely temporal but reflects meaningful differences in radiographic patterns, surgical feasibility, treatment response, and prognosis. Current evidence suggests that most cases represent skeletal-only metastatic dissemination rather than true multicentric tumorigenesis, although genetically predisposed subsets may follow distinct biological pathways. Despite advances in imaging and systemic therapy, outcomes—particularly for synchronous MFOS—remain poor, underscoring the need for improved risk stratification and treatment strategies. Future progress will depend on collaborative, multi-institutional efforts integrating comprehensive molecular profiling, longitudinal follow-up, and standardized classification criteria to refine disease definitions, guide individualized management, and ultimately improve survival in this aggressive and understudied condition.

Acknowledgement

N/A

Authors Contribution: Author(s) who conceived and designed the study: Khodamorad Jamshidi, Alireza Mirzaei/Author(s) who wrote the paper: Alireza Mirzaei, Edward Y.Cheng/Author(s) who collected data: Khodamorad Jamshidi, Shahabaldin Beheshti Fard, Alireza Mirzaei

Declaration of Conflict of Interest: Khodamorad Jamshidi: No conflicts of interest to disclose.Alireza Mirzaei: No conflicts of interest to disclose.Shahabaldin Beheshti Fard: No conflicts of interest to disclose.Edward Y. Cheng: No conflicts related to this article. However, for transparency, the following relationships that might be perceived as conflicts are disclosed:Edward Y. Cheng received royalties from Innomed, Inc. He is also the director of fellowship support from OMeGA and Smith & Nephew, Inc. Additionally, he serves as an editor for the Journal of Bone & Joint Surgery and also as a member of the Medical Board of Trustees for MTF Biologics.

Declaration of Funding: The Authors received NO financial support for this manuscript.

Declaration of Ethical Approval for Study: N/A

Declaration of Informed Consent: N/A

Khodamorad Jamshidi MD [1]
Alireza Mirzaei PhD [1, 2]
Shahabaldin Beheshti Fard MD [1]
Edward Y. Cheng MD [2]

1 Bone and Joint Reconstruction Research Center, Department of Orthopedics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

2 Department of Orthopedic Surgery, University of Minnesota, Minneapolis, Minnesota, USA

References

1. Rahmanian M, Khoropanah S, Hosseinzadeh Moghaddam S, et al. A Systematic Review and Meta-Analysis of Regorafenib's Effectiveness and Safety in the Treatment of Bone Sarcoma. Arch Bone Jt Surg. 2025;13(12):776-787. doi: 10.22038/ABJS.2025.87671.3969.
2. Jamshidi K, Bahrabadi M, Mirzaei A. Long-term Results of Osteoarticular Allograft Reconstruction in Children with Distal Femoral Bone Tumors. Arch Bone Jt Surg. 2017;5(5):296-301.
3. Jamshidi K, Hajialiloo Sami S, Naghizadeh H, Kargar Shooroki K, Ahmadi R, Seyyed Khabiri S. Osteosarcoma Management in the Precision Medicine Era: Bibliometric Analysis and Clinical Progress (2015-2024). Arch Bone Jt Surg. 2025;13(11):693-703. doi: 10.22038/ABJS.2025.87193.3953.
4. Jamshidi K, Haji Agha Bozorgi M, Mokhtari E, Bagherifard A, Mirzaei A. Scapular Osteosarcoma Treated by Scapulectomy with or Without Scapular Allograft: A Retrospective Case Series. Indian J Orthop. 2023;57(3):453-460. doi:10.1007/s43465-022-00813-2.
5. Jamshidi K, Zandrahimi F, Bagherifard A, Mohammadi F, Mirzaei A. An unusual presentation of osteosarcoma in the proximal femur with peculiar diagnostic characteristics: a retrospective series. Curr Orthop Pract. 2021;32(4).doi: 10.1097/BCO.0000000000001016.
6. Jenkin R, Allt W, Fitzpatrick P. Osteosarcoma. An assessment of management with particular reference to primary irradiation and selective delayed amputation. Cancer. 1972;30(2):393-400.
7. Corradi D, Wenger DE, Bertoni F, et al. Multicentric osteosarcoma: clinicopathologic and radiographic study of 56 cases. Am J Clin Pathol.2011;136(5):799-807. doi: 10.1309/AJCP0V0OATKCNAZP.
8. Lee HJ, Kim IO, Kim WS, Cheon JE, Kim KW, Yeon KM. Metachronous multifocal osteosarcoma: A case report and literature review. Clin Imag. 2002;26(1):63-68. doi: 10.1016/s0899-7071(01)00354-0.
9. Odri GA, Tchicaya-Bouanga J, Yoon DJY, Modrowski D. Metastatic Progression of Osteosarcomas: A Review of Current Knowledge of Environmental versus Oncogenic Drivers. Cancers (Basel). 2022;14(2):360.doi:10.3390/cancers14020360.
10. Gambera S, Abarrategi A, González-Camacho F, et al. Clonal dynamics in osteosarcoma defined by RGB marking. Nat Commun. 2018;9(1):3994. doi:10.1038/s41467-018-06401-z.
11. Wang D, Niu X, Wang Z, et al. Multiregion Sequencing Reveals the Genetic Heterogeneity and Evolutionary History of Osteosarcoma and Matched Pulmonary Metastases. Cancer Res. 2019;79(1):7-20. doi:10.1158/0008-5472.Can-18-1086.
12. Xu H, Zhu X, Bao H, et al. Genetic and clonal dissection of osteosarcoma progression and lung metastasis. Int J Cancer. 2018;143(5):1134-1142. doi:10.1002/ijc.31389.
13. Enneking WF, Kagan A. "Skip" metastases in osteosarcoma. Cancer. 1975;36(6):2192-205. doi:10.1002/cncr.2820360937.
14. Enneking WF, Kagan A. The implications of "skip" metastases in osteosarcoma. Clin Orthop Relat Res. 1975;(111):33-41. doi:10.1097/00003086-197509000-00005.
15. Amstutz HC. Multiple osteogenic sarcomata—metastatic or multicentric? Report of two cases and review of literature. Cancer. 1969;24(5):923-931. doi: 10.1002/1097-0142(196911)24:5<923::aid-cncr2820240509>3.0.co;2-e.
16. Mahoney JP, Spanier SS, Morris JL. Multifocal osteosarcoma. A case report with review of the literature. Cancer. 1979;44(5):1897-1907. doi: 10.1002/1097-0142(197911)44:5<1897::aid-cncr2820440552>3.0.co;2-2.
17. Gambera S, Abarrategi A, González-Camacho F, et al. Clonal dynamics in osteosarcoma defined by RGB marking. Nature Communications. 2018;9(1):3994. doi:10.1038/s41467-018-06401-z.
18. Brady SW, Ma X, Bahrami A, et al. The Clonal Evolution of Metastatic Osteosarcoma as Shaped by Cisplatin Treatment. Mol Cancer Res. 2019;17(4):895-906. doi:10.1158/1541-7786.Mcr-18-0620.

19. Muff R, Rath P, Ram Kumar RM, et al. Genomic instability of osteosarcoma cell lines in culture: impact on the prediction of metastasis relevant genes. PLoS One. 2015;10(5):e0125611. doi:10.1371/journal.pone.0125611.
20. Connolly EA, Boye K, Bonvalot S, et al. Genetic predisposition in sarcomas: clinical implications and management. eClin Med. 2025;83doi:10.1016/j.eclinm.2025.103203.
21. Hameed M, Mandelker D. Tumor Syndromes Predisposing to Osteosarcoma. Adv Anat Pathol. 2018;25(4):217-222. doi:10.1097/pap.0000000000000190.
22. Saucier E, Bougeard G, Gomez-Mascard A, et al. Li–Fraumeni-associated osteosarcomas: The French experience. Pediatr Blood Cancer. 2024;71(12):e31362. doi: 10.1002/pbc.31362.
23. Brandal P, Bjerkehagen B, Bruland ØS, Skjeldal S, Bogsrud TV, Hall KS. Synchronous and metachronous skeletal osteosarcomas: the Norwegian Radium Hospital experience. Acta Oncol. 2009;48(8):1165-1172. doi: 10.3109/02841860903032809.
24. Zils K, Wirth T, Loff S, Biskup S, von Kalle T, Bielack S. Multiple metachronous osteosarcomas in a patient with Li-Fraumeni syndrome. Pediatr Hematol Oncol. 2014;31(4):359-361. doi:10.3109/08880018.2013.848388.
25. Huby M, Brugières L, Mascard E, Gaspar N, Pannier S, Aurégan J-C. Difficulties of Management of Multiple Synchronous Bone Tumors in Li-Fraumeni Syndrome. Case Rep Orthop. 2019;2019(1):8732089. doi:10.1155/2019/8732089.
26. Pratt CB, Michalkiewicz E, Rao BN, Lipson M, Cain A, Kaste S. Multifocal osteosarcoma following retinoblastoma. Ophthal Gen. 1999;20(1):23-29. doi:10.1076/opge.20.1.23.2296.
27. Potepan P, Luksch R, Sozzi G, et al. Multifocal osteosarcoma as second tumor after childhood retinoblastoma. Skelet Radiol. 1999;28(7):415-421. doi: 10.1007/s002560050540.
28. Bielack SS, Baumhoer D, Hecker-Nolting S, et al. Osteosarcomas in retinoblastoma-survivors. A report of 28 affected patients from the cooperative osteosarcoma study group (COSS). EJC Paediatr Oncol. 2024;3.
29. Zils K, Klingebiel T, Behnisch W, et al. Osteosarcoma in patients with Rothmund–Thomson syndrome. Pediatr Hematol Oncol.2015;32(1):32-40. doi: 10.3109/08880018.2014.987939.
30. Anbari KK, Ierardi-Curto LA, Silber JS, et al. Two primary osteosarcomas in a patient with Rothmund-Thomson syndrome. Clin Orthop Relat Res (1976-2007). 2000;378:213-223. doi:10.1097/00003086-200009000-00032.
31. Deyrup AT, Montag AG, Inwards CY, Xu Z, Swee RG, Krishnan Unni K. Sarcomas arising in Paget disease of bone: a clinicopathologic analysis of 70 cases. Arch Pathol Lab Med. 2007;131(6):942-946. doi:10.5858/2007-131-942-SAIPDO.
32. Huvos AG, Butler A, Bretsky SS. Osteogenic sarcoma associated with Paget's disease of bone. A clinicopathologic study of 65 patients. Cancer. 1983;52(8):1489-1495. doi: 10.1002/1097-0142(19831015)52:8<1489::aid-cncr2820520826>3.0.co;2-x.
33. Sivrioglu AK, Aribal S, Onder H. Secondary multifocal osteosarcoma developing on the background of bone infarct. Case Rep. 2017;bcr-2017-220293. doi:10.1136/bcr-2017-220293.
34. Daffner RH, Kennedy SL, Fox KR, Crowley JJ, Sauser DD, Cooperstein LA. Synchronous multicentric osteosarcoma: the case for metastases. Skeletal Radiol. 1997;26(10):569-78. doi:10.1007/s002560050289.
35. Parham DM, Pratt CB, Parvey LS, Webber BL, Champion J. Childhood multifocal osteosarcoma. Clinicopathologic and radiologic correlates. Cancer. 1985;55(11):2653-2658. doi: 10.1002/1097-0142(19850601)55:11<2653::aid-cncr2820551121>3.0.co;2-a.
36. Setiawati R, Lay ES, Testini V, et al. Advance MR evaluation of synchronous multifocal osteosarcoma with pathologic fracture. BJR case Rep. 2021;7(4):20210015.doi:10.1259/bjrcr.20210015.
37. Jaffe N, Pearson P, Yasko AW, Lin P, Herzog C, Raymond K. Single and multiple metachronous osteosarcoma tumors after therapy. Cancer.2003;98(11):2457-2466. doi: 10.1002/cncr.11800.
38. Mettmann VL, Blattmann C, Friedel G, et al. Primary Multi-Systemic Metastases in Osteosarcoma: Presentation, Treatment, and Survival of 83 Patients of the Cooperative Osteosarcoma Study Group. Cancers (Basel). 2024;16(2):275.doi:10.3390/cancers16020275.
39. Bacci G, Fabbri N, Balladelli A, Forni C, Palmerini E, Picci P. Treatment and prognosis for synchronous multifocal osteosarcoma in 42 patients. J Bone Joint Surg Br. 2006;88(8):1071-1075. doi: 10.1302/0301-620X.88B8.17809.
40. Singh I, Rainusso N, Kurenbekova L, et al. Intrinsic Epigenetic State of Primary Osteosarcoma Drives Metastasis. Mol Cancer Res. 2024;22(9):864-878. doi:10.1158/1541-7786.Mcr-23-0055.
41. Morrow JJ, Khanna C. Osteosarcoma Genetics and Epigenetics: Emerging Biology and Candidate Therapies. Crit Rev Oncog. 2015;20(3-4):173-97.doi:10.1615/critrevoncog.2015013713.
42. Moriarity BS, Otto GM, Rahrmann EP, et al. A Sleeping Beauty forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis. Nat Genet. 2015;47(6):615-624. doi:10.1038/ng.3293.
43. Sirikaew N, Pruksakorn D, Chaiyawat P, Chutipongtanate S. Mass Spectrometric-Based Proteomics for Biomarker Discovery in Osteosarcoma: Current Status and Future Direction. Int J Mol Sci. 2022;23(17):9741.doi:10.3390/ijms23179741.