

Histopathological Response to Neoadjuvant Chemotherapy Assessed Using the Huvos Grading System and its Correlation with Pretreatment Clinicopathological Variables in Osteosarcoma: A Cohort Study from North East India

SOUMI BHATTACHARYYA¹, LOPA MUDRA KAKOTI², ANUPAM SARMA³, GAURAV DAS⁴,
PARTHA SARATHI ROY⁵, JYOTIMAN NATH⁶, SUKANYA GOGOI⁷



ABSTRACT

Introduction: Osteosarcoma is the most common primary bone malignancy affecting children and young adults. Neoadjuvant Chemotherapy (NACT) followed by surgery is the current modality of treatment for osteosarcoma. Histological evaluation of extent of tumour necrosis on resection is a well-established prognostic indicator in osteosarcoma correlating with survival in most cases. Identification of pretreatment clinicopathological factors associated with histological response may facilitate early risk stratification and individualised treatment planning.

Aim: To evaluate the histopathological response to NACT using the Huvos grading system and to determine its association with pretreatment clinicopathological variables in patients with osteosarcoma.

Material and Methods: A cohort study was conducted in the Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India, including biopsy-proven osteosarcoma patients treated with NACT followed by definitive surgery between September 2022 and August 2025 (data were collected from this time period). Study period was September 2025 to April 2026. Clinical, biochemical, radiological and pathological data were retrieved from the Institutional electronic medical records. Histopathological response was assessed on resection specimens according to the Huvos grading system. Patients with Huvos grades III-IV were classified as good responders, whereas those with grades I-II were considered poor responders. Associations between clinicopathological variables and histological response were

analysed using Fisher's-exact test. Overall Survival (OS) was estimated using the Kaplan-Meier method. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA).

Results: A total of 27 patients fulfilled the study inclusion criteria. The mean age was 23.2 years, with a male predominance (77.8%). The lower extremity was the most common site of involvement. A total of 4 patients (14.8%) were classified as good responders, while 23 patients (85.2%) were poor responders. No statistically significant association was observed between Huvos response and age, sex, tumour size, anatomical site, histological subtype, or serum alkaline phosphatase level ($p > 0.05$). The median follow-up duration was 18 months (range: 8-45 months). Kaplan-Meier survival analysis demonstrated a trend towards improved OS among good responders; however, the difference between the survival curves was not statistically significant (log-rank $p = 0.321$). Cox proportional hazards regression demonstrated a hazard ratio of 3.17 (95% CI: 0.29-34.99; $p = 0.347$) for good responders compared with poor responders.

Conclusion: Histopathological assessment using the Huvos grading system remains a practical and reliable method for evaluating response to NACT in osteosarcoma. In the present study, pretreatment clinicopathological variables were not significantly associated with histological response. Larger multicentric prospective studies incorporating molecular and radiological biomarkers are required to improve prediction of chemotherapy response before treatment initiation.

Keywords: Biomarkers, Bone neoplasms, Prognosis, Treatment outcome, Tumour necrosis

INTRODUCTION

Primary malignant bone tumours are uncommon, accounting for less than 0.2% of all malignancies worldwide [1]. Among these, osteosarcoma is the most frequently encountered primary malignant bone tumour in children, adolescents and young adults. Incidence is 4-5/1,000,000 per year [2]. It is characterised by the production of malignant osteoid by neoplastic mesenchymal cells and demonstrates a bimodal age distribution, with the first incidence peak occurring during adolescence and a second, smaller peak in older adults (more than 65 years of age) particularly in association with Paget disease or previous irradiation [3]. The metaphyseal region of long bones, especially around the knee joint, is the most common site of involvement (distal femur followed by proximal tibia

and proximal humerus) [4]. In addition to cancerous formation at the affected bone, osteosarcoma also carries a significant risk of metastasis (mostly lung) [5,6].

Before the introduction of multi-agent chemotherapy, the prognosis of osteosarcoma was poor because of the high incidence of occult pulmonary micrometastases at diagnosis [7]. The incorporation of NACT followed by complete surgical excision and adjuvant chemotherapy has markedly improved long-term survival. The National Comprehensive Cancer Network (NCCN) and European Society For Medical Oncology (ESMO) guidelines also follow multimodality treatment approach [8,9]. NACT is an integral component of multimodal treatment for osteosarcoma, providing early treatment of occult micrometastatic disease, reducing primary

tumour burden to facilitate limb-salvage surgery, and allowing assessment of tumour chemosensitivity through histopathological response before definitive surgery [10].

The degree of tumour necrosis observed in the post-chemotherapy resection specimen remains the most widely accepted pathological indicator of response to NACT. The Huvos grading system, introduced by Huvos and Rosen, categorises histological response into four grades according to the percentage of chemotherapy-induced tumour necrosis [11]. Patients with Huvos grades III and IV ($\geq 90\%$ tumour necrosis) are regarded as good responders and generally demonstrate superior event-free and OS compared with those showing Huvos grades I and II. Consequently, histopathological response serves as an important prognostic marker and has been incorporated into routine pathological reporting of osteosarcoma.

Despite its established prognostic significance, Huvos grading can only be assessed after surgical resection, limiting its utility in predicting chemotherapy response before treatment. Identification of pretreatment clinical, biochemical, radiological and pathological variables associated with histological response would therefore be valuable in optimising treatment strategies and identifying patients who may benefit from alternative therapeutic approaches. However, published evidence regarding such predictors remains inconsistent, particularly in resource-limited settings.

The present study was undertaken to evaluate the histopathological response to NACT using the Huvos grading system in osteosarcoma and to investigate its association with pretreatment clinicopathological variables in patients treated at a tertiary cancer centre in Northeast India.

MATERIALS AND METHODS

The present cohort study was conducted in the Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India. The study included consecutive patients diagnosed between September 2022 and August 2025 who fulfilled the eligibility criteria. Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study (IEC NO-13000552). Study period was eight months from September 2025 to April 2026. All biopsy-proven cases of osteosarcoma that received NACT followed by definitive surgical resection at the institute during the study period were screened for inclusion.

Inclusion criteria:

- Histologically confirmed osteosarcoma (on pretreatment biopsy) who have completed Institutional NACT and subsequently underwent definitive surgical resection;
- Availability of complete clinicopathological records and histopathological slides for review.

Exclusion criteria:

- Age less than 10 years (because of the limited number of eligible cases during the study period and to maintain a relatively homogeneous study population with comparable treatment protocols and clinicopathological characteristics);
- Patients who did not have slides available for further evaluation
- de novo metastatic disease.

Study Procedure

Clinical, biochemical, radiological and pathological information was retrieved from the Institutional electronic medical record system. Data collected included patient age, sex, tumour location, tumour size, duration of symptoms, history of pathological fracture, pre NACT serum alkaline phosphatase level, histological subtype, lymphovascular invasion, perineural invasion, pathological stage and follow-up information (from EMR and postoperative histopathology report).

Neoadjuvant Chemotherapy (NACT) protocol: Patients were treated according to the Institutional Osteosarcoma Group Study 12 (OGS-12) protocol, which was the standard treatment regimen adopted by the multidisciplinary sarcoma team at the present study centre. As this was a retrospective study, treatment allocation was not influenced by the investigators, thereby ensuring a uniform treatment approach across the study population. The regimen consisted of doxorubicin (75 mg/m^2) and cisplatin (75 mg/m^2) two cycles followed by Doxorubicin (75 mg/m^2) and Ifosfamide (2.2 g/m^2) two cycle before definitive surgical resection. Details of chemotherapy cycles and cumulative drug doses were obtained from the medical oncology records. After surgery, four cycles of Ifosfamide (2.2 g/m^2) and Cisplatin (75 mg/m^2) were given as adjuvant therapy. All patients completed the planned NACT before surgery. Minor scheduling delays occurred in some patients because of clinical considerations but did not result in discontinuation of treatment.

Histopathological assessment: Archived haematoxylin and eosin-stained slides from resection specimens were independently reviewed by two experienced pathologists who were blinded to patient outcomes. Very few cases showed discrepancy and resolved by joint review to achieve consensus. Formal interobserver agreement statistics were not performed. Resection specimens were grossed according to Institutional protocol. A full-face longitudinal section demonstrating the maximum tumour dimension was obtained and extensive sampling was performed using a grid-based approach, with at least one tissue block submitted per centimetre of tumour to ensure representative assessment of chemotherapy-induced changes. Fibrosis, haemorrhage, cystic degeneration and calcification were excluded from necrosis during the time of calculation. Acellular osteoid was also not included. The percentage of viable tumour and chemotherapy-induced necrosis was assessed microscopically. For classification of bone neoplasm, World Health Organisation (WHO) Classification of Tumours, 5th edition of bone and soft tissue tumour was followed [4]. Histological response was graded according to the Huvos grading system:

Grade I: $<50\%$ tumour necrosis

Grade II: $50\text{--}89\%$ tumour necrosis

Grade III: $90\text{--}99\%$ tumour necrosis

Grade IV: 100% tumour necrosis

Patients with Huvos grades III and IV were classified as good responders, whereas patients with grades I and II were considered poor responders.

Survival data were collected from hospital record. OS was calculated from the date of histopathological diagnosis to the date of death or the date of the last documented follow-up. Patients who were alive at the end of the study period or lost to follow-up were censored on the date of their last recorded clinical contact. Date of censoring was 30.04.2026. The interval between completion of NACT and definitive surgery was recorded for all patients. It was 21 days. Median duration of NACT was three months. Surgery was limb salvage only. All patients included in the study received identical chemotherapy.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistics version 29.0. Continuous variables were summarised using mean or median, as appropriate, while categorical variables were expressed as frequencies and percentages. Associations between clinicopathological variables and histological response were analysed using Fisher's-exact test because of the relatively small sample size. OS was defined as the interval from the date of histopathological diagnosis to the date of death from any cause or the date of the last documented follow-up. Death from any cause was considered the event for survival analysis. Patients who were alive at the end of the study period were right-censored on the administrative censoring date (30th April 2026) or on the date of their last documented follow-up, whichever occurred

first. Patients who were lost to follow-up were censored on the date of their last documented clinical contact. Survival probabilities were estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Clinicodemographic analysis: A total of 27 patients with biopsy-proven osteosarcoma fulfilled the inclusion criteria during the study period. The mean age at diagnosis was 23.2 years (range: 10-52 years), with a marked male predominance (21 males, 77.8%; 6 females, 22.2%). The lower extremity was the most frequently involved site (19/27, 70.4%), comprising 14 distal femoral, four proximal tibial, and 1 fibular lesion. Five tumours arose in the humerus, while two involved the ilium and one occurred in the maxilla. The median tumour size was 9.5 cm. Pathological fracture was documented in three patients. Conventional osteosarcoma was identified in all resection specimens. Histological subtyping revealed 19 osteoblastic and eight chondroblastic variants. Most patients (17 of 27) received four cycles of NACT according to the Institutional OGS-12 protocol.

Histopathological response to Neoadjuvant Chemotherapy (NACT): Tumour response was evaluated using the Huvos grading system, based on the percentage of chemotherapy-induced tumour necrosis. Patients were classified as follows: 1) Huvos Grade I (<50% necrosis): 17 patients; 2) Huvos Grade II (50-89% necrosis): six patients; 3) Huvos Grade III (90-99% necrosis): four patients; 4) Huvos Grade IV (100% necrosis): no patients.

For statistical analysis, patients with Huvos Grades III and IV were classified as good responders, whereas those with Grades I and II were considered poor responders. Overall, good responders: 4 patients (14.8%) poor responders: 23 patients (85.2%) The predominance of poor responders indicates limited histological response to NACT in the present cohort.

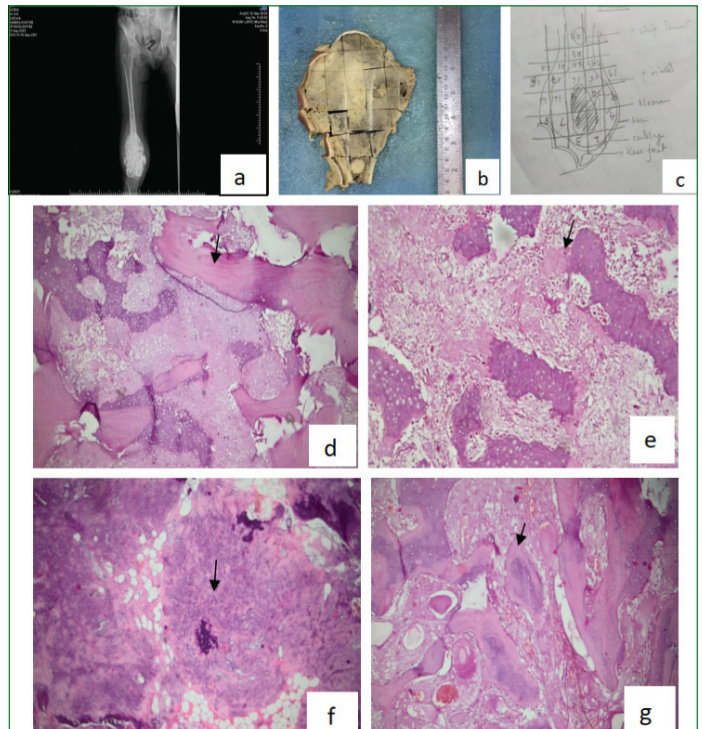
Correlation between pretreatment clinicopathological variables and huvos response: Clinicopathological variables were compared between good and poor responders using Fisher's-exact test. No statistically significant association was observed between histological response and the following parameters (age, sex, tumour size, tumour location, serum alkaline phosphatase level, pathological fracture, histological subtype) (all $p > 0.05$). Although patients with normal pretreatment ALP appeared to have a more favourable histopathological response, the association was not statistically significant, and no conclusions regarding tumour burden can be drawn from the present study. The correlation of pre NACT clinicopathological variables with post NACT Huvos response is shown in [Table/Fig-1].

Variables	Subcategory	Good responders	Poor responders	n (%)	p-value
Age	Upto 20 years	2	12	14 (51.8)	0.613
	>20 years	2	11	13 (48.2)	
Gender	Male	3	18	21 (77.7)	1.00
	Female	1	5	6 (22.3)	
Duration	Upto 12 weeks	3	11	14 (51.8)	0.481
	>12 weeks	1	12	13 (48.2)	
Site	Lower extremity	3	16	19 (70.4)	1.00
	Upper extremity	1	4	5 (18.5)	
	Flat bone	0	3	3 (11.1)	
H/O fracture	Present	0	4	4 (14.8)	1.00
	Absent	4	19	23 (85.2)	
Size	Upto 8 cm	1	10	11 (40.7)	0.294
	>8 cm	3	13	16 (59.3)	

ALP level (Pre NACT)	Increased	3	20	23 (85.1)	1.00
	Normal	1	3	4 (14.9)	
Type of OGS	Chondroblastic	1	7	8 (29.6)	1.00
	Osteoblastic	3	16	19 (70.4)	
Interval of last chemo and surgery	<4 Weeks	1	4	5 (18.5)	0.402
	4 and more than 4 weeks	3	19	22 (81.5)	

[Table/Fig-1]: Association of pre NACT clinicopathological variables with post NACT Huvos response.

The radiological, gross, and histopathological features of the post-NACT osteosarcoma specimen are shown in [Table/Fig-2a-f].



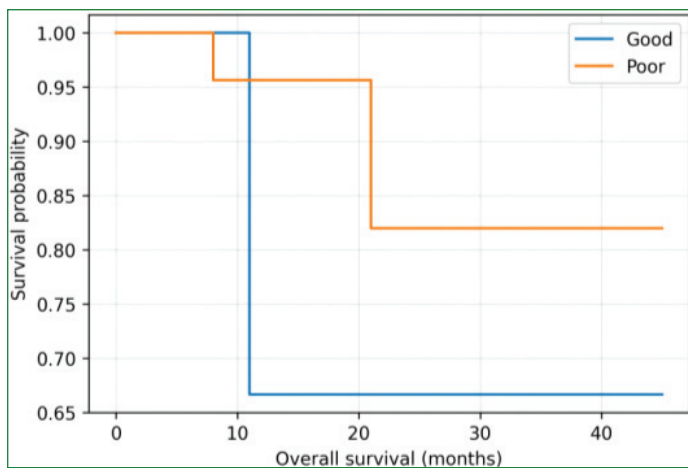
[Table/Fig-2]: a) X-ray shows a large mass with sunburst appearance present on lower end of femur; b,c) Showing gross photo of post NACT osteosarcoma specimen and entire tumour taken as grid fashion (arrow shows viable tumour); d,e) Showing viable osteoblastic and chondroblastic elements (H&E, 10x); f,g) Showing chemotherapy induced changes (sclerosis and necrosis); (H&E, 10x).

Survival analysis: The median duration of follow-up was 18 months (range: 8-45 months). At the final follow-up, 16 patients were alive without evidence of disease, three patients had died, four patients developed pulmonary metastasis, and four patients were lost to follow-up. Death was considered as the event for survival analysis. Patients with pulmonary metastasis does not constitute separate category, they are included among the alive patient during the survival analysis.

The OS was estimated using the Kaplan-Meier method. Kaplan-Meier analysis showed no statistically significant difference in OS between good and poor responders (log-rank $p = 0.321$). Given the small number of observed deaths, the survival analysis had limited statistical power. In Cox proportional hazards analysis, poor responders (Huvos Grades I-II) were used as the reference category (HR=1.00). Good responders (Huvos Grades III-IV) had an estimated HR of 3.17 (95% CI: 0.29-34.99; $p = 0.347$). This association was not statistically significant and should be interpreted cautiously because of the small sample size and limited number of observed deaths. Kaplan-Meier survival analysis curve shows comparison of OS among good and poor responders [Table/Fig-3].

DISCUSSION

The NACT followed by complete surgical resection remains the standard treatment for conventional high-grade osteosarcoma. It



[Table/Fig-3]: Kaplan-Meier survival analysis curve shows comparison of Overall Survival (OS) among good and poor responders.

has transformed the management of osteosarcoma by improving local control, facilitating limb-salvage surgery and increasing long-term survival [12]. Still considerable heterogeneity exists in individual tumour response to chemotherapy. Histopathological assessment by percentage of chemotherapy-induced tumour necrosis using Huvos grading system remains the most reliable predictor of treatment response and continues to represent the gold standard for evaluating the effectiveness of neoadjuvant therapy. The present study evaluated the association between pretreatment clinicopathological variables and histopathological response, as well as the prognostic significance of Huvos grading in patients treated according to the Institutional OGS-12 protocol.

Histopathological response: The Huvos grading system, first proposed by Huvos and colleagues, categorises tumour response according to the percentage of residual viable tumour following chemotherapy [11,13]. Patients demonstrating $\geq 90\%$ tumour necrosis (Grades III and IV) consistently exhibit superior disease-free and OS compared with those showing lesser degrees of necrosis. Consequently, Huvos grading has become an integral component of pathological reporting in osteosarcoma.

In the present study, only 14.8% of patients were classified as good responders, whereas 85.2% were poor responders. Notably, none of the patients achieved complete pathological response (Huvos Grade IV), indicating that complete tumour necrosis following NACT was not observed in the present cohort. Although complete pathological response is uncommon in osteosarcoma, its absence in the present study may reflect the aggressive biological behaviour of high-grade osteosarcoma, interpatient variability in chemotherapy sensitivity, the use of a single Institutional OGS-12 treatment protocol, or the relatively small sample size.

The present study findings are generally consistent with previous studies evaluating histopathological response following NACT. Prabowo Y et al., reported good histological response in approximately 23.4% of patients, whereas the remaining 76.6% were poor responders [14]. Similarly, the recent Vietnamese study by Do KH et al., observed a considerably higher proportion of good responders (51.4%) [15]. Lewis IL et al., in the year 2007 reported good histology response in 36% patients [16].

Survival analysis: Histopathological response following NACT has consistently been recognised as one of the strongest prognostic indicators in osteosarcoma. Large international studies have demonstrated significantly better survival among patients achieving $\geq 90\%$ tumour necrosis following preoperative chemotherapy. In 2019, Smeland S et al., {European and American Osteosarcoma Study (EURAMOS-1) study} involving more than 2,000 patients found that three year and five year OS from biopsy were 79% and 71% in [17]. Luetke A et al, in 2014 stated that modern, dose intensive chemotherapy in conjunction with surgery achieves a

five year event free survival of 60-70% in localised osteosarcoma [18]. In the present study, Kaplan-Meier survival analysis did not demonstrate a statistically significant difference in OS between good and poor responders. This finding should be interpreted cautiously because the survival analysis was based on only three death events during the follow-up period, substantially limiting statistical power and the precision of survival estimates. Therefore, the absence of statistical significance should not be interpreted as evidence that histopathological response lacks prognostic value, but rather as a consequence of the limited sample size, low event rate and retrospective study design.

Differences among studies may be attributed to variations in chemotherapy protocols, patient selection, tumour biology, stage at diagnosis and treatment compliance. Delayed presentation remains a common challenge in developing countries and may partly explain the relatively poor histological response observed in the present study.

One important observation during histopathological assessment was that estimation of tumour necrosis alone may not fully represent the biological response to chemotherapy. Chemotherapy induces numerous additional morphological alterations, including fibrosis, hyalinisation, calcification, haemorrhage, osteoid maturation, inflammatory infiltrates and accumulation of foamy macrophages. Distinguishing therapy-induced necrosis from acellular fibrous or calcified areas may occasionally be challenging and may contribute to interobserver variability in Huvos grading. Future studies incorporating quantitative assessment of these chemotherapy-induced changes may provide a more comprehensive evaluation of pathological response. Recent advances in osteosarcoma research have highlighted the potential role of molecular biomarkers like single gene alterations and the use of high throughput array based technologies predicting chemotherapy response before surgery [19]. Biomarkers such as circulating tumour Deoxyribonucleic Acid (DNA), microRibonucleic Acid (RNA) expression profiles and advanced Magnetic Resonance Imaging (MRI) parameters are currently under investigation and may complement conventional histopathological assessment in future clinical practice. Integration of these emerging modalities with established pathological grading systems may facilitate individualised treatment strategies like gene therapy, immunotherapy or radiation innovations [20].

Clinical relevance: Although no clinicopathological parameter significantly predicted histopathological response in the present study, the findings remain clinically relevant. It contributes valuable real-world data from a tertiary oncology centre in Northeast India, where published evidence remains limited. The results suggest that conventional clinicopathological parameters alone may be insufficient to reliably predict chemotherapy response before surgery. Therefore, future studies should investigate molecular biomarkers, genetic alterations and advanced imaging techniques that may improve pretreatment prediction of chemotherapy response and facilitate personalised therapeutic strategies. The findings also emphasise the need for larger prospective multicentric studies with longer follow-up.

The strength of the study are: 1) All patients were managed using a uniform Institutional treatment protocol and underwent comprehensive histopathological reassessment by experienced pathologists; 2) Chemotherapy response was evaluated using the internationally accepted Huvos grading system. In addition, survival analysis was performed to assess the prognostic implications of histological response; 3) Inclusion of survival analysis; 4) The study also provides valuable real-world data from a tertiary referral cancer centre in Northeast India, where published literature remains limited.

Limitation(s)

The present study has many limitations: 1) Its retrospective single-centre study design and inclusion of only patients completing the surgery (selection bias); 2) Lack of multivariable analysis due to

limited sample size, potential under powering (Type II error), Lack of interobserver agreement statistics for Huvos grading; 3) The duration of follow-up was relatively short, with very small number of good responder; 4) Molecular biomarkers and advanced radiological parameters that may predict chemotherapy response were not evaluated.

CONCLUSION(S)

Histopathological assessment using the Huvos grading system remains a simple, reproducible and clinically relevant method for evaluating response to NACT in osteosarcoma. In the present study, no significant association was observed between pretreatment clinicopathological variables and histological response. Although patients with good histological response demonstrated a trend towards improved OS, statistical significance was not achieved, probably because of the limited sample size and short follow-up duration. Larger multicentric prospective studies incorporating molecular biomarkers, advanced imaging techniques and longer follow-up are required to improve pretreatment prediction of chemotherapy response and optimise risk-adapted management of osteosarcoma.

Acknowledgement

The authors sincerely thank Dr. Bhuvaneshwar Borooah Cancer Institute.

Author's contribution: Author contribution statement All authors made substantial contribution in conceptualisation, methodology, analysis and final reviewing of manuscript.

REFERENCES

- [1] Heymann D, editor. Bone cancer: bone sarcomas and bone metastasis-from bench to bedside. 3rd ed. London: Academic Press; 2021.
- [2] Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current treatment and a collaborative pathway to success. *J Clin Oncol*. 2015;33(27):3029-35. doi: 10.1200/JCO.2014.59.4895.
- [3] Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. *Cancer Treat Res*. 2009;152:3-13. doi: 10.1007/978-1-4419-0284-9_1.
- [4] WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Soft Tissue and Bone Tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2020.
- [5] Jeffree GM, Price CH, Sissons HA. The metastatic patterns of osteosarcoma. *Br J Cancer*. 1975;32(1):87-107. doi: 10.1038/bjc.1975.136.
- [6] Mohseny AB, Szuhai K, Romeo S, Buddingh EP, Briaire-de Bruijn I, de Jong D, et al. Osteosarcoma originates from mesenchymal stem cells in consequence of aneuploidization and genomic loss of Cdkn2. *J Pathol*. 2009;219(3):294-305. doi: 10.1002/path.2603.
- [7] Anderson P. Liposomal muramyl tripeptide phosphatidyl ethanolamine: Ifosfamide-containing chemotherapy in osteosarcoma. *Future Oncol*. 2006;2(3):333-43. doi: 10.2217/14796694.2.3.333.
- [8] Biermann JS, Hirbe A, Ahlawat S, Bernthal NM, Binitie O, Boles S, et al. Bone cancer, version 2.2025, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2025;23(4):e250017. doi: 10.6004/jccn.2025.0017.
- [9] European Society for Medical Oncology. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(12):1520-36.
- [10] Alaseem A, Alanezi M, Almehrji F, Alanezi K, Alrasheed K, Alrefaei N, et al. Comparative outcomes of neoadjuvant chemotherapy versus upfront surgical resection in osteosarcoma: A systematic review and meta-analysis. *World J Surg Oncol*. 2025;23(1):446. doi: 10.1186/s12957-025-04115-3. PMID: 41275279; PMCID: PMC12659466.
- [11] 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;101(1):14-18.
- [12] Kim SY, Helman LJ. Strategies to explore new approaches in the investigation and treatment of osteosarcoma. *Cancer Treat Res*. 2009;152:517-28.
- [13] Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: Selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. *Cancer*. 1982;49(6):1221-30. doi: 10.1002/1097-0142(19820315)49:6<1221::AID-CNCR2820490625>3.0.CO;2-E.
- [14] Prabowo Y, Setiawan I, Kamal AF, Kodrat E, Labib Zulfar ML. Correlation between prognostic factors and the histopathological response to neoadjuvant chemotherapy in osteosarcoma: A retrospective study. *Int J Surg Oncol*. 2021;2021:8843325. doi: 10.1155/2021/8843325.
- [15] Do KH, Nguyen TV, Hoang TT, Do TC, Phan PD, Nguyen CV, et al. Histopathological response to neoadjuvant chemotherapy in patients with Enneking stage II conventional osteosarcoma of extremities: A retrospective single-institution study in Vietnam. *Cancer Control*. 2024;31:10732748241274188. doi: 10.1177/10732748241274188.
- [16] Lewis IJ, Nooij MA, Whelan J, Sydes MR, Grimer RJ, Hogendoorn PCW, et al. European Osteosarcoma Intergroup. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: A randomized phase III trial of the European Osteosarcoma Intergroup. *J Natl Cancer Inst*. 2007;99(2):112-28. doi: 10.1093/jnci/djk015.
- [17] Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn PCW, Krailo MD, et al. Survival and prognosis with osteosarcoma: Outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. *Eur J Cancer*. 2019;109:36-50. doi: 10.1016/j.ejca.2018.11.027.
- [18] Luetke A, Meyers PA, Lewis I, Juergens H. Osteosarcoma treatment- Where do we stand? A state-of-the-art review. *Cancer Treat Rev*. 2014;40(4):523-32. doi: 10.1016/j.ctrv.2013.11.006.
- [19] Kong C, Hansen MF. Biomarkers in osteosarcoma. *Expert Opin Med Diagn*. 2009;3(1):1-23.
- [20] Brar GS, Schmidt AA, Williams LR, Wakefield MR, Fang Y. Osteosarcoma: Current insights and advances. *Explor Target Antitumor Ther*. 2025;6:1002324. doi: 10.37349/etat.2025.1002324.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
2. Associate Professor, Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
3. Professor, Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
4. Professor, Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
5. Professor, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
6. Associate Professor, Department of Radiation Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
7. Assistant Professor, Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Soumi Bhattacharyya,
No. 3, Bhowani Thakur Lane, Rajbati North Gate, Burdwan-713104,
West Bengal, India.
E-mail: soumibmch@gmail.com

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: May 04, 2026
- Manual Googling: Aug 13, 2026
- iThenticate Software: Aug 17, 2026 (6%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

Date of Submission: May 02, 2026

Date of Peer Review: Jul 06, 2026

Date of Acceptance: Aug 18, 2026

Date of Publishing: Oct 01, 2026