Am J Cancer Res 2025;15(6):2618-2630
www.ajcr.us /ISSN:2156-6976/ajcr0164674

Original Article

Effects of cisplatin, paclitaxel combined with high-dose methotrexate as adjuvant therapy on survival rates in osteosarcoma patients, and analysis of influencing factors

Yixin Wang[1*], Lang Jin[1*], Chuanjie Zong[1], Xidong Zhang[2]

[1]Department of Pharmacy, Cangzhou People's Hospital, Cangzhou 061000, Hebei, China; [2]Department of Pharmacy, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei, China. [*]Equal contributors and co-first authors.

Received March 21, 2025; Accepted May 28, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Osteosarcoma is a prevalent primary malignant bone tumor in young adults and adolescents, characterized by a high recurrence rate despite advancements in chemotherapy and surgical methods. This study investigated the effects of integrating high-dose methotrexate with cisplatin and paclitaxel on survival outcomes in osteosarcoma patients, and to identify prognostic factors influencing these outcomes. A retrospective analysis was conducted on 208 osteosarcoma patients treated between January 2013 and December 2018. Patients were divided into two groups: standard chemotherapy group (SC, n = 104) and cisplatin + paclitaxel + high-dose methotrexate (CPM, n = 104). The primary endpoints were progression-free survival (PFS) and overall survival (OS), while secondary endpoints included efficacy assessments. Kaplan-Meier survival curves were used to assess survival distributions, and statistical analyses were performed using SPSS 29.0. The CPM group demonstrated significantly longer PFS (16.85 ± 3.40 months vs. 15.72 ± 3.21 months, $P = 0.015$) and higher 5-year OS rates (54.81% vs. 40.38%, $P = 0.037$) compared to the SC group. Completion of chemotherapy and a response rate greater than 90% were identified as strong positive prognostic indicators. In contrast, pathologic fractures at diagnosis, lung metastases, and elevated lactate dehydrogenase levels were associated with poorer outcomes. Multivariate analysis underscored chemotherapy response and treatment adherence as independent survival predictors. The combination of cisplatin and paclitaxel with high-dose methotrexate significantly improves PFS and OS compared to standard chemotherapy. Moreover, treatment completion and achieving a chemotherapy response greater than 90% are critical factors for favorable prognosis.

Keywords: Osteosarcoma, chemotherapy, survival rates, prognostic factors

Introduction

Osteosarcoma is the most prevalent primary malignant bone tumor, predominantly affecting adolescents and young adults. Despite advances in surgical and chemotherapeutic strategies, its prognosis remains poor, particularly in the recurrent and metastatic cases [1, 2]. Standard chemotherapy regimens, including doxorubicin, cisplatin, and high-dose methotrexate, often combined with ifosfamide, have long served as backbone of osteosarcoma treatment, offering survival benefits compared to surgery alone. Nonetheless, these regimens are associated with significant treatment-related morbidity and face challenges such as drug resistance and limited efficacy in preventing recurrence and metastasis [3-5].

Cisplatin, a key agent in such regimens, induces cytotoxicity through DNA crosslinking, thereby inhibiting cellular replication. Methotrexate, at high doses, interferes with folate metabolism, impairing DNA synthesis and cell proliferation. Despite their therapeutic roles, resistance to these agents remains a major hurdle in achieving optimal therapeutic outcomes. Consequently, ongoing research seeks to explore synergistic drug combinations that can enhance efficacy while potentially reducing the

https://doi.org/10.62347/RLWT8295

adverse effects associated with high-dose monotherapies [6-8].

Paclitaxel, a microtubule-stabilizing agent, has garnered attention in recent decades for its distinct mechanism of action that impairs microtubule dynamics essential for cell division. Its application in various solid tumors has demonstrated potential beyond conventional chemotherapeutics. In osteosarcoma, paclitaxel may offer a novel avenue for inhibiting cancer cell proliferation and inducing apoptosis, possibly overcoming drug resistance associated with traditional agents [9-11].

Identifying the factors influencing survival in osteosarcoma patients remains a complex but essential endeavor. Existing literature has established several key prognostic indicators, including tumor size, location, histologic response to chemotherapy, and the presence of metastases (particularly pulmonary involvement), which play pivotal roles in risk stratification and individualized treatment planning [12, 13]. However, there remains a gap in understanding how these prognostic indicators interact with novel treatment regimens.

The present study seeks to address this gap by evaluating the therapeutic efficacy of a cisplatin-paclitaxel-methotrexate (CPM) regimen compared to standard chemotherapy. In addition to assessing survival outcomes, we aimed to provide a comprehensive analysis of the prognostic variables that influence treatment response and long-term prognosis in patients receiving the CPM regimen.

Materials and methods

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and adhered to the Good Clinical Practice guidelines developed by the International Conference of Harmonisation. Ethical approval was obtained from the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University.

Study design

A retrospective analysis was conducted on 208 osteosarcoma patients treated at the Fourth Hospital of Hebei Medical University from January 2013 to December 2018. Clinical data were obtained from medical record system and routine follow-up documentation. Before propensity score matching (PSM), patients were categorized into two groups based on their treatment regimen: the standard chemotherapy group (SC) (n = 157), which received doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate; and the cisplatin + paclitaxel + high-dose methotrexate (CPM) group (n = 122).

To minimize baseline heterogeneity, PSM was implemented using a 1:1 nearest-neighbor protocol with a caliper width of 0.2 standard deviation. Matching variables included clinically relevant prognostic factors: age at diagnosis, presence of pathological fractures, lung metastasis, and histological subtype based on the 2020 WHO classification of osteosarcoma. The final matched cohort comprised 208 patients (104 pairs), with balanced intergroup comparability as verified by standardized mean differences < 0.1 and nonsignificant chi-square metrics ($P > 0.05$) for all covariates. In the CPM group, patients were further stratified by survival duration: those with survival periods exceeding three years were classified into the long survival group (L group, 62 patients), and those with shorter survival periods were assigned to the short survival group (S group, 42 patients).

Eligibility criteria

Inclusion criteria: 1) age between 2 and 39 years; 2) diagnosis of relapsed or refractory osteosarcoma, or measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) [14]; 3) adequate bone marrow function, evidenced by neutrophils ≥ 0.5×10^9/L or WBC ≥ 3×10^9/L, and a platelet count > 100×10^9/L; 4) a glomerular filtration rate ≥ 70 ml/min/1.73 m^2 (renal function), bilirubin levels ≤ 1.5 times the upper limit of normal (liver function), and a shortening fraction ≥ 28% or an ejection fraction ≥ 50% (cardiac function); 5) a Karnofsky score ≥ 60 [15], a WHO performance status ≤ 2 [16], or a Lansky score ≥ 60% [17]; 6) complete medical records.

Exclusion criteria: 1) patients who had undergone radiotherapy for bone metastasis within two weeks prior to the start of study treatment,

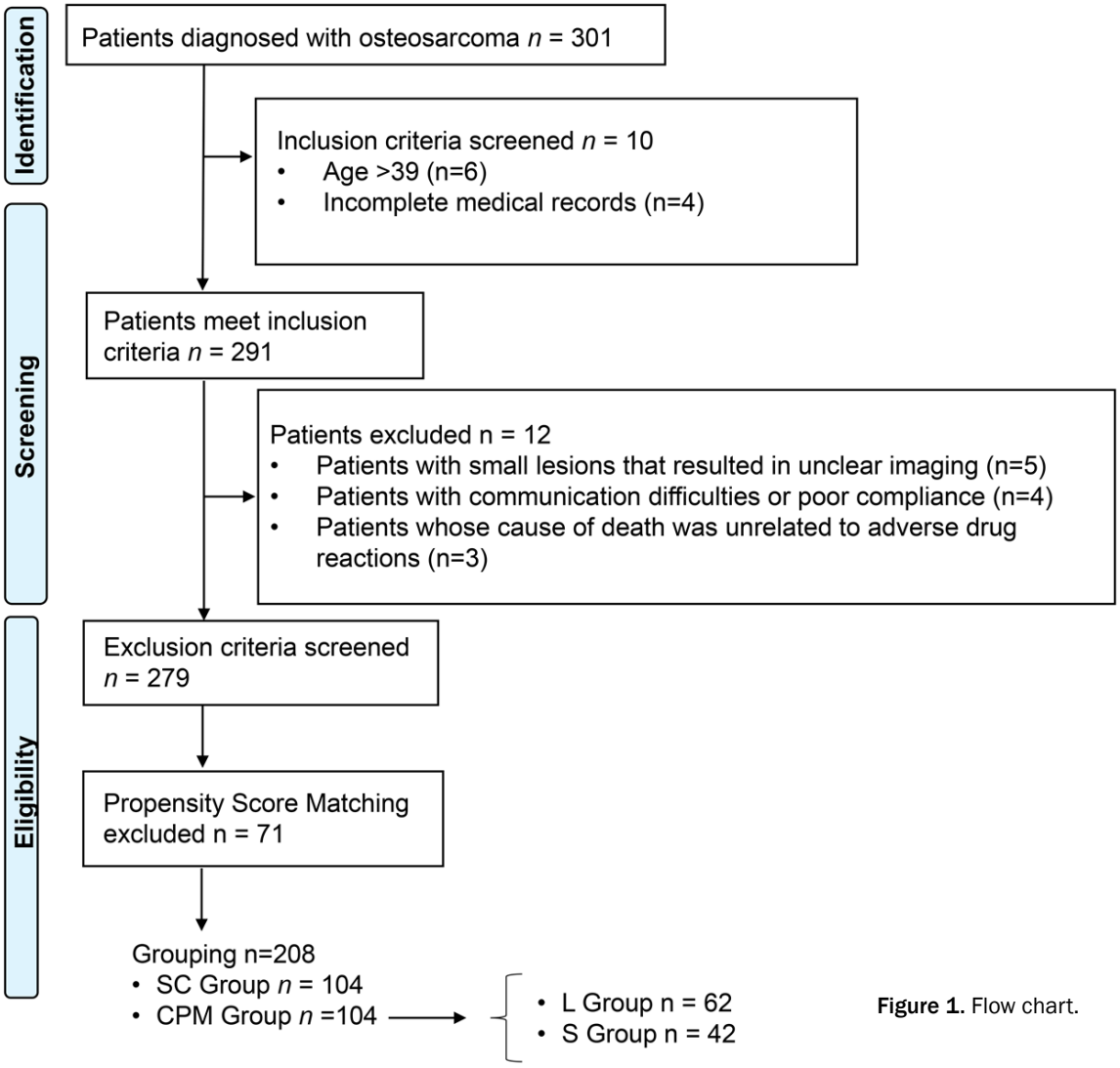

Figure 1. Flow chart.

any other form of external radiotherapy within four weeks prior, or who had received any small molecule kinase inhibitor within two weeks before the first dose of the study treatment; 2) patients with small lesions that resulted in unclear imaging, severe dysfunction of the liver, kidneys, coagulation system, immune system, circulatory system, or respiratory system; 3) patients with communication difficulties or poor compliance; 4) patients in pregnancy; 5) presence with serious nonmalignant illnesses, significant conduction abnormalities, or cardiac arrhythmias requiring antiarrhythmic medications; 5) patients whose cause of death was unrelated to adverse drug reactions or treatment-associated complications. The flowchart of the inclusion and exclusion criteria was shown in **Figure 1**.

Treatment approach

The chemotherapy regimen consisted of eight cycles, including four cycles of preoperative (neoadjuvant) chemotherapy followed by four cycles of postoperative (adjuvant) chemotherapy. Each cycle was administered every 21 days or upon recovery from toxicities related to the prior cycle.

In the SC group, each cycle included methotrexate (8 g/m^2, lot no. 0954-100MG, AMRESCO, US), ifosfamide (15 g/m^2, lot no. I123381, Aladdin Holdings Group Co., Ltd., Shanghai, China), doxorubicin (90 mg/m^2, lot no. 23214-92-8, Magic Biotechnology Co., Ltd., Wuhan, China), and cisplatin (120-140 mg/m^2, lot no. S31072, Yuanye Biotechnology Co., Ltd.,

Shanghai, China). In the CPM group, each cycle comprised methotrexate (8 g/m^2, lot no. 0954-100MG, AMRESCO, US), cisplatin (75 mg/m^2, lot no. S31072, Yuanye Biotechnology Co., Ltd., Shanghai, China), and paclitaxel (175 mg/m^2, lot no. BP0306, Bio-Lab Technology Co., Ltd., Beijing, China). Treatment continued until disease progression, intolerable toxicity, or patient withdrawal. The term "chemotherapy response > 90%" specifically refers to patients achieving a reduction in tumor size by over 90% from baseline measurements.

Patients who experienced clinical benefit with minimal adverse events could continue treatment beyond progression at the investigator's discretion. In cases of disease progression, patients received multidisciplinary interventions and best supportive care. Post-treatment, all patients were monitored biannually for tumor status until December 2023.

Prognostic variables analyzed included sex, age, tumor size, degree of necrosis, histological subtype, and primary tumor location. Survival time was measured from the date of diagnosis to the last follow-up. Radiological examinations, including chest X-rays, were routinely performed to monitor for lung metastases.

Data collection

Before treatment initiation, comprehensive baseline data were collected for all patients. Serum alkaline phosphatase and lactate dehydrogenase (LDH) levels were measured using a BECKMAN Synchron CX20 fully automated biochemistry analyzer (BECKMAN Coulter, Inc., Brea, CA, USA). LDH levels were categorized based on the upper limit of normal provided by our laboratory, which is 248 U/L. Normal LDH levels were defined as ≤ 248 U/L, and high levels were > 248 U/L. Following chemotherapy, tissue samples were collected via biopsy and examined histologically to evaluate the patient's histological response to the initial chemotherapy. A good histological response is defined as more than 90% tumor necrosis, while a poor response indicates less than 90% necrosis.

Post-treatment data collection included clinical status, treatment details, and pathological findings. Overall survival (OS) was calculated from the date of study enrollment until death from any cause, with survival distributions analyzed using the Kaplan-Meier method. Serial chest computed tomography (CT) scans and whole-body Technetium-99m-MDP bone scintigraphy were conducted every six months for the first three years and annually thereafter to monitor for recurrence or metastasis. These scans were used to assess tumor necrosis, detect metastatic lesions and recurrence. Additional localized imaging evaluations were performed based on clinical symptoms. Patients with operable lung metastases underwent open thoracotomy and wedge resection of the pulmonary nodule.

The primary endpoints of this study were progression-free survival (PFS) and overall survival, comparing outcomes between the SC group and the CPM group. Secondary endpoints included descriptive assessments of therapeutic efficacy between these two groups.

Statistical analysis

To minimize confounding bias inherent to retrospective analyses, PSM was conducted using SPSS v29.0 (SPSS Inc., Chicago, IL, USA). Clinically relevant covariates that may influence laryngeal/hypopharyngeal cancer prognosis, including age, pathological fracture at diagnosis, lung metastases, and histological subtypes defined by the 2020 WHO osteosarcoma classification criteria, were included in a multivariable logistic regression model to generate propensity scores. A non-replacement 1:1 nearest-neighbor matching protocol was implemented, with a caliper threshold set at 0.2 standard deviations of the logit-transformed propensity scores. Matching quality was systematically validated using a dual verification framework: all covariates achieved standardized mean differences [SMD] < 0.1, and χ^2 tests showed no significant differences between groups (P > 0.05). Post-matching visual assessment confirmed overlap and comparability of propensity score distributions.

The data were analyzed with SPSS v29.0 statistical software. Continuous variables were initially assessed for normal distribution using the Shapiro-Wilk test. For normally distributed continuous data, an independent samples t-test was conducted between groups, and the results were presented as mean ± standard deviation (X ± s). Categorical data are presented as [n (%)] and were analyzed using the chi-square test. A *p*-value of less than 0.05 was

Table 1. Baseline characteristics of included cases before PSM

Parameters	SC Group (n = 157)	CPM Group (n = 122)	t/χ^2	P
Male/Female	96 (61.15%)/61 (38.85%)	64 (52.46%)/58 (47.54%)	2.118	0.146
Age (years)	21.63 ± 4.13	22.85 ± 4.72	2.291	0.023
Location of tumor			6.734	0.081
Proximal	66 (42.04%)	60 (49.18%)		
Diaphysis	6 (3.82%)	6 (4.92%)		
Distal	84 (53.5%)	51 (41.8%)		
NA	1 (0.64%)	5 (4.1%)		
Pathologic fracture at diagnosis (Yes/No)	14 (8.92%)/143 (91.08%)	21 (17.21%)/101 (82.79%)	4.307	0.038
Lung metastases (Yes/Possible/No)	19 (12.1%)/8 (5.1%)/130 (82.8%)	5 (4.1%)/16 (13.11%)/101 (82.79%)	10.245	0.006
Other metastases (Yes/Possible/No)	5 (3.18%)/2 (1.27%)/150 (95.54%)	4 (3.28%)/2 (1.64%)/116 (95.08%)	0.067	0.967
2020 WHO classification of osteosarcoma			10.956	0.027
Conventional	135 (85.99%)	104 (85.25%)		
Low-grade Central	14 (8.92%)	4 (3.28%)		
Parosteal	3 (1.91%)	1 (0.82%)		
High-grade surface	3 (1.91%)	4 (3.28%)		
Other	2 (1.27%)	9 (7.38%)		

PSM: Propensity score matching; SC: Standard chemotherapy group; CPM: Cisplatin, paclitaxel, and high-dose methotrexate; NA: Not long bone; WHO: World Health Organization.

considered statistically significant. Correlation analyses were conducted using Pearson correlation for continuous variables and Spearman correlation for categorical variables. Toxicity rates across subgroups were compared using chi-square tests and logistic regression models. Time-to-event outcomes, including PFS and OS were analyzed using Kaplan-Meier survival curves, log-rank tests, and Cox regression analysis.

Results

Propensity score matching

Prior to PSM, 279 patients were included in the analysis (SC group, n = 157, CPM group, n = 122) (**Table 1**). Prior to matching, significant differences were observed in several baseline parameters: age (P = 0.023), pathologic fracture at diagnosis (P = 0.038), lung metastases (P = 0.006) and the 2020 WHO osteosarcoma classification (P = 0.027). These findings highlighted the necessity for statistical matching to ensure comparability in subsequent analyses. Other variables, including gender distribution, tumor location, and presence of other metastases did not show significant differences between the two groups (P > 0.05).

Demographic and basic data

After 1:1 propensity score matching, 208 patients were included in the final analysis (n = 104 per group). Post-matching analysis confirmed balanced baseline characteristics between the SC and CPM groups (**Table 2**). Gender distribution showed no significant difference ($P = 0.887$). The mean age was comparable between the two groups ($P = 0.092$). Tumor location showed slight variations, without statistical significance ($P = 0.932$). Similarly, there were no significant differences in the pathologic fracture at diagnosis ($P = 0.385$, $P = 0.968$), or other metastatic sites ($P = 0.427$). The 2020 WHO classification revealed a predominance of conventional osteosarcoma in both groups ($P = 0.701$). These findings indicate that baseline characteristics were comparable between the two groups, ensuring a reliable comparison of treatment outcomes.

The survival rate

To evaluate the effect of the CPM regimen on survival rates in osteosarcoma patients, PFS and OS were compared between the CPM and SC groups. The CPM group exhibited significantly prolonged PFS ($P = 0.015$) (**Table 3**). The 3-year PFS rate was notably higher in the CPM group compared to the SC group ($P = 0.037$), whereas the 5-year PFS rates did not differ significantly ($P = 0.260$). For OS, the 5-year OS was significantly higher in the CPM group compared to the SC group ($P = 0.037$), while the 3-year OS rates did not differ significantly between groups ($P = 0.328$). These results sug-

Table 2. Comparison of baseline characteristics between the SC group and CPM group after PSM

Parameters	SC Group (n = 104)	CPM Group (n = 104)	t/χ^2	P
Male/Female	62 (59.62%)/42 (40.38%)	63 (60.58%)/41 (39.42%)	0.020	0.887
Age (years)	21.95 ± 2.38	22.54 ± 2.65	1.694	0.092
Location of tumor			0.438	0.932
Proximal	45 (43.27%)	44 (42.31%)		
Diaphysis	4 (3.85%)	3 (2.88%)		
Distal	52 (50%)	55 (52.88%)		
NA	3 (2.88%)	2 (1.92%)		
Pathologic fracture at diagnosis (Yes/No)	10 (9.62%)/94 (90.38%)	14 (13.46%)	0.754	0.385
Lung metastases (Yes/Possible/No)	10 (9.62%)/8 (7.69%)/86 (82.69%)	10 (9.62%)/9 (8.65%)/85 (81.73%)	0.065	0.968
Other metastases (Yes/Possible/No)	5 (4.81%)/2 (1.92%)/97 (93.27%)	2 (1.92%)/1 (0.96%)/101 (97.12%)	1.700	0.427
2020 WHO classification of osteosarcoma			2.191	0.701
Conventional	91 (87.5%)	97 (93.27%)	0.754	0.385
Low-grade Central	8 (7.69%)	4 (3.85%)		
Parosteal	2 (1.92%)	1 (0.96%)		
High-grade surface	2 (1.92%)	1 (0.96%)		
Other	1 (0.96%)	1 (0.96%)		

PSM: Propensity score matching; SC: Standard chemotherapy; CPM: Cisplatin, paclitaxel, and high-dose methotrexate; NA: Not long bone; WHO: World Health Organization.

Table 3. Comparison of survival outcomes between patients of SG and CPM groups

Variable	SC Group (n = 104)	CPM Group (n = 104)	t/χ^2	P
PFS (month)	15.72 ± 3.21	16.85 ± 3.40	2.450	0.015
3-year PFS rate (%)	46 (44.23%)	61 (58.65%)	4.331	0.037
5-year PFS rate (%)	39 (37.5%)	47 (45.19%)	1.269	0.260
3-year OS rate (%)	55 (52.88%)	62 (59.62%)	0.957	0.328
5-year OS rate (%)	42 (40.38%)	57 (54.81%)	4.337	0.037

SC: Standard chemotherapy group; CPM: Cisplatin, paclitaxel, and high-dose methotrexate; PFS: Progression-free survival; OS: Overall survival.

Table 4. Multivariate regression analysis of treatment regimens and therapeutic efficacy

Influencing factors	OR	P
Treatment regimen (SC/CPM)-PFS (month)	1.234	0.051
Treatment regimen (SC/CPM)-The rate of progressionfree survival at 3 years (%)	1.119	0.056
Treatment regimen (SC/CPM)-The overall survival rate at 5 years (%)	1.211	0.053

SC: Standard chemotherapy group; CPM: Cisplatin, paclitaxel, and high-dose methotrexate; PFS: Progression-Free Survival; OR: Odds Ratio.

gest that the addition of cisplatin and paclitaxel to high-dose methotrexate may extend progression-free intervals and improve long-term survival.

Multivariate regression analysis further explored associations between treatment regimen and survival outcomes (**Table 4**). The CPM regimen was associated with a trend toward improved PFS (odds ratio [OR] = 1.234, P = 0.051) and a higher likelihood of achieving 3-year PFS (OR = 1.119, P = 0.056), although these did not reach statistical significance. Additionally, the 5-year OS rate was marginally higher in the CPM group (OR = 1.211, P = 0.053), suggesting a potential long-term survival benefit.

Comparison of demographic and basic data between patients with long and short survival in the CPM cohort

Comparative analysis between patients in the long survival (L) and short survival (S) groups within the CPM cohort revealed several significant prognostic indicators (**Table 5**). The inci-

Table 5. Comparison of baseline characteristics between the short (S) and long (L) survival groups in CPM cohort

Parameters	S Group (n = 42)	L Group (n = 62)	χ^2	P
Male/Female	27 (64.29%)/15 (35.71%)	36 (58.06%)/26 (41.94%)	0.406	0.524
Age (years)			0.679	0.41
16 and below	11 (26.19%)	12 (19.35%)		
17-39	31 (73.81%)	50 (80.65%)		
Primary site (Axia/Extremity)	20 (47.62%)/22 (52.38%)	20 (32.26%)/42 (67.74%)	2.496	0.114
Pathologic fracture at diagnosis (Yes/No)	32 (76.19%)	30 (48.39%)	8.039	0.005
Lung metastases (Yes/No)	28 (66.67%)	27 (43.55%)	5.371	0.02
Other-site metastasis (Yes/No)	6 (14.29%)	2 (3.23%)	2.896	0.089
Local recurrence (Yes/No)	6 (14.29%)	3 (4.84%)	1.758	0.185
Completed treatment (Yes/No)	30 (71.43%)	58 (93.55%)	9.411	0.002
Chemotherapy response (Greater than 90%/Less than 90%)	3 (7.14%)/39 (92.86%)	21 (33.87%)/41 (66.13%)	10.076	0.002

S: Short survival; L: Long survival; CPM: Cisplatin, paclitaxel, and high-dose methotrexate.

Table 6. Comparison of clinical and treatment-related parameters between the L and S groups in CPM cohort

Variable	S Group (n = 42)	L Group (n = 62)	χ^2	P
Surgery type			1.024	0.599
Local excision	4 (9.52%)	8 (12.9%)		
Radical excision	25 (59.52%)	40 (64.52%)		
Amputation	13 (30.95%)	14 (22.58%)		
SAP level			3.675	0.055
Normal	15 (35.71%)	34 (54.84%)		
High	27 (64.29%)	28 (45.16%)		
LDH level			5.067	0.024
Normal	17 (40.48%)	39 (62.9%)		
High	25 (59.52%)	23 (37.1%)		
Radiation			4.148	0.042
Yes	7 (16.67%)	2 (3.23%)		
No	35 (83.33%)	60 (96.77%)		
Histology			5.58	0.134
Osteoblastic	34 (80.95%)	40 (64.52%)		
Chondroblastic	5 (11.9%)	7 (11.29%)		
Fibroblastic	2 (4.76%)	6 (9.68%)		
Teleangiectatic	1 (2.38%)	9 (14.52%)		

S: Short survival; L: Long survival; CPM: Cisplatin, paclitaxel, and high-dose methotrexate; PMS: SAP: Serum alkaline phosphatase; LDH level: Lactate Dehydrogenase.

dence of pathologic fractures at diagnosis was notably higher in the S group compared to the L group ($P = 0.005$). Lung metastases were also more frequent in the S group ($P = 0.02$). Furthermore, only 7.14% of patients in the S group achieved a chemotherapy response > 90%, compared to 33.87% in the L group (P = 0.002). There were no significant differences between the two groups in terms of gender distribution, age, primary tumor site, presence of other metastases, or local recurrence. These findings suggest that the presence of pathologic fractures, lung metastasis, treatment completion sessions, and suboptimal chemotherapy response are associated with short survival in osteosarcoma patients.

Comparison of clinical and treatment-related parameters between the L and S groups in the CPM cohort

Elevated LDH levels were significantly more prevalent in the S group ($P = 0.024$) (**Table 6**). In

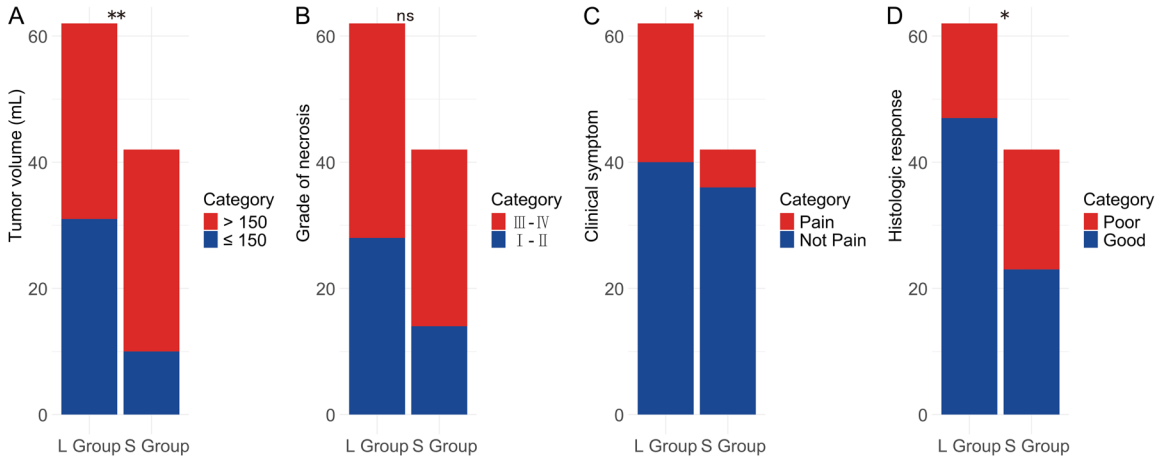

Figure 2. Comparison of pathologic condition between the L and S subgroups. A. Tumor volume (mL); B. Grade of necrosis; C. Clinical symptom; D. Histologic response. S: Short survival; L: Long survival. ns: No statistically significant difference; *: $P < 0.05$; **: $P < 0.01$.

contrast, radiation therapy was administered more frequently in the S group ($P = 0.042$). Although serum alkaline phosphatase (SAP) levels tended to be higher in the S group, the difference did not reach statistical significance ($P = 0.055$). No significant differences were observed between the groups regarding surgery type and histological subtype; most patients in both groups underwent radical excision, and osteoblastic osteosarcoma was the predominant subtype. These findings indicate that high LDH levels and radiation therapy were associated with shorter survival in osteosarcoma patients, while other factors such as surgery type and SAP levels were less conclusive.

Comparison of pathologic condition between the L and S groups in the CPM cohort

Tumor volume differed significantly between the two groups: 76.19% of patients in the S group had tumor volumes > 150 mL, compared to 50% in the L group (P = 0.007) (**Figure 2**). A higher proportion of patients in the L group reported the absence of pain symptoms ($P = 0.017$). Histological response to chemotherapy was significantly better in the L group ($P = 0.025$). However, the degree of necrosis did not differ significantly between groups, with comparable distributions across grades I-II and III-IV ($P = 0.228$).

These findings suggest that smaller tumor volume, absence of pain, and a good histologic response were correlated with improved survival outcomes in patients with osteosarcoma.

Correlation analysis between significant factors with patient survival rate

Correlation analysis identified several factors significantly associated with survival outcomes in osteosarcoma patients (**Figure 3**). Pathologic fracture at diagnosis was negatively correlated with survival (rho = -0.278, $P = 0.004$), as were lung metastases (rho = -0.227, $P = 0.020$) and high LDH levels (rho = -0.221, $P = 0.024$). In contrast, completion of treatment (rho = 0.301, $P = 0.002$) and a strong chemotherapy response (greater than 90%) (rho = 0.311, $P = 0.001$) were positively associated with survival. Tumor volume ≤ 150 mL was also positively correlated with better patient survival (rho = 0.263, $P = 0.007$). Clinical symptoms, specifically the presence of pain, were negatively correlated (rho = -0.234, $P = 0.017$) with survival. Histological response to chemotherapy also positively influenced survival, with a good response correlating to better outcomes (rho = 0.220, $P = 0.025$). Radiation therapy, however, was negatively correlated with survival (rho = -0.235, $P = 0.017$). These correlations underscore the multifactorial nature of survival outcomes in osteosarcoma, highlighting the prognostic value of treatment adherence, robust chemotherapy response, and limited tumor burden.

Univariate analysis

Univariate analysis identified clinical and treatment-related factors significantly associated

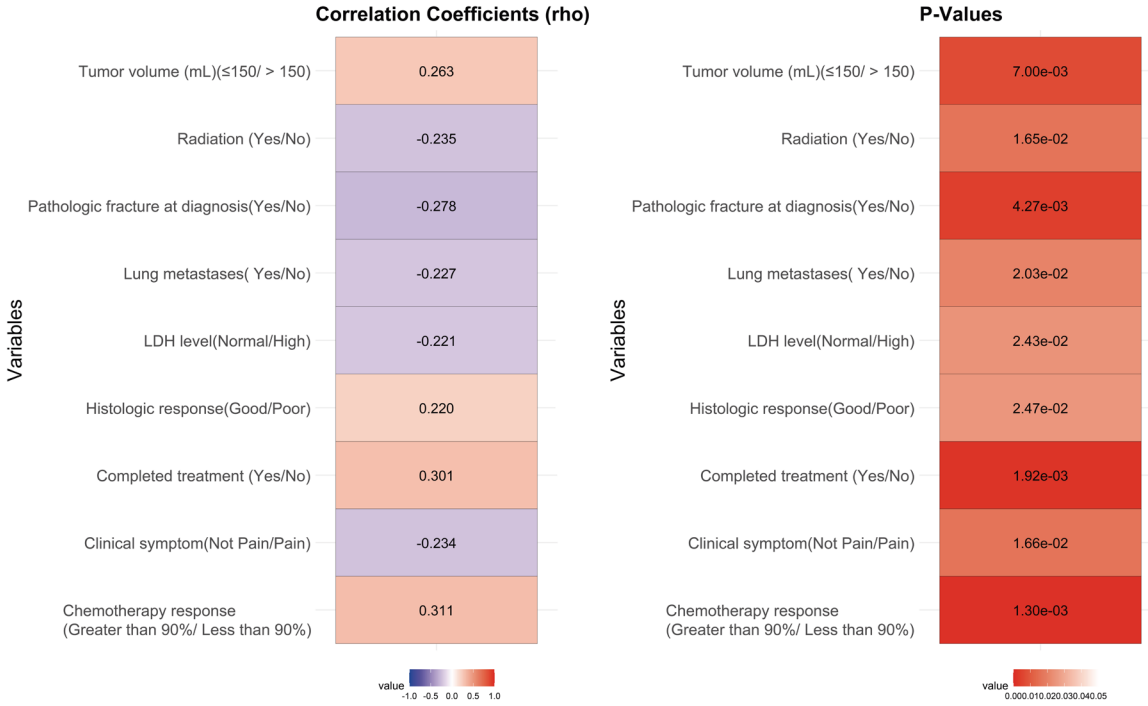

Figure 3. Correlation analysis of significant factors with survival rates in osteosarcoma patients. LDH level: Lactate Dehydrogenase.

Table 7. Univariate analysis of factors affecting survival outcomes in osteosarcoma patients

Influencing factors	Coefficient	Std Error	Wald	P	OR	95% CI
Pathologic fracture at diagnosis (Yes/No)	-1.228	0.443	2.774	0.006	0.293	0.119-0.0681
Lung metastases (Yes/No)	-0.953	0.416	2.292	0.022	0.386	0.167-0.860
Completed treatment (Yes/No)	1.758	0.620	2.837	0.005	5.800	1.845-22.179
Chemotherapy response (Greater than 90%/Less than 90%)	1.896	0.656	2.888	0.004	6.659	2.087-29.785
LDH level (Normal/High)	-0.914	0.410	2.230	0.026	0.401	0.177-0.887
Radiation (Yes/No)	-1.792	0.830	2.160	0.031	0.167	0.024-0.734
Tumor volume (mL) (≤ 150/> 150)	1.163	0.442	2.629	0.009	3.200	1.377-7.897
Pain symptoms (No/Yes)	-1.194	0.515	2.320	0.020	0.303	0.102-0.791
Histological response (Good/Poor)	0.951	0.429	2.217	0.027	2.588	1.124-6.091

OR: Odds Ratio; CI: Confidence Interval; LDH level: Lactate Dehydrogenase.

with survival in osteosarcoma patients (**Table 7**). Pathologic fracture at diagnosis was significantly associated with reduced survival probability (coefficient = -1.228, *P* = 0.006), yielding an OR of 0.293 (95% CI, 0.119-0.681). Similarly, lung metastases were negatively associated with survival (coefficient = -0.953, *P* = 0.022), with an OR of 0.386 (95% CI, 0.167-0.860). Other variables negatively associated with survival included elevated LDH levels (coefficient = -0.914, P = 0.026; OR = 0.401, 95% CI: 0.177-0.887), receipt of radiation therapy (coefficient = -1.792, P = 0.031; OR = 0.167, 95% CI: 0.024-0.734), and the presence of pain (coefficient = -1.194, P = 0.020; OR = 0.303, 95% CI: 0.102-0.791).

In contrast, completion of treatment was a strong positive predictor of survival (coefficient = 1.758, *P* = 0.005), with an OR of 5.800 (95% CI, 1.845-22.179). A robust chemotherapy response (greater than 90%) also positively influenced survival outcomes (coefficient = 1.896, *P* = 0.004), with an OR of 6.659 (95% CI, 2.087-29.785). Furthermore, smaller tumor volume (≤ 150 mL) (coefficients = 1.163, *P* =

Table 8. Multivariate analysis of factors affecting survival outcomes in osteosarcoma patients

Influencing factors	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Pathologic fracture at diagnosis (Yes/No)	-1.433	0.622	-2.302	0.021	0.239	0.070	0.808
Lung metastases (Yes/No)	-1.674	0.646	-2.593	0.010	0.187	0.053	0.664
Completed treatment (Yes/No)	1.912	0.847	2.258	0.024	6.768	1.287	35.591
Chemotherapy response (Greater than 90%/Less than 90%)	2.597	0.887	2.927	0.003	13.421	2.358	76.393
LDH level (Normal/High)	-1.551	0.616	-2.520	0.012	0.212	0.063	0.709
Radiation (Yes/No)	-1.784	1.028	-1.735	0.083	0.168	0.022	1.260
Tumor volume (mL) (≤ 150/> 150)	1.131	0.623	1.817	0.069	3.100	0.915	10.507
Pain symptoms (No/Yes)	-1.894	0.724	-2.618	0.009	0.150	0.036	0.621
Histological response (Good/Poor)	1.485	0.650	2.284	0.022	4.416	1.235	15.793

OR: Odds Ratio; CI: Confidence Interval; LDH level: Lactate Dehydrogenase.

0.009, OR = 3.200, 95% CI: 1.377-7.897) and favorable histologic response (coefficients = 0.951, *P* = 0.027, OR = 2.588, 95% CI, 1.124-6.091) were also positively associated with survival outcomes. These findings highlight the prognostic significance of both baseline disease characteristics and treatment-related variables, particularly pathologic fracture, smaller tumor volume, treatment adherence, and chemotherapy response, in determining survival outcomes in osteosarcoma patients.

Multivariate analysis

Multivariate logistic regression identified several independent prognostic factors significantly associated with survival outcomes in osteosarcoma patients (**Table 8**). Pathologic fracture at diagnosis remained a significant negative predictor of survival (coefficient = -1.433, *P* = 0.021), with an OR of 0.239 (95% CI, 0.070-0.808). Similarly, the presence of lung metastases decreased survival probability (coefficient = -1.674, *P* = 0.010; OR = 0.187, 95% CI, 0.053-0.664). Completion of treatment was strongly predictive of improved survival outcomes (coefficient = 1.912, *P* = 0.024), with an OR of 6.768 (95% CI, 1.287-35.591). A superior chemotherapy response (greater than 90%) was the most robust factor associated with enhanced survival, with a coefficient of 2.597 (*P* = 0.003) and an OR of 13.421 (95% CI, 2.358-76.393). High LDH levels were linked to poorer survival (coefficient = -1.551, *P* = 0.012; OR = 0.212, 95% CI, 0.063-0.709), as were pain-related clinical symptoms (coefficient = -1.894, *P* = 0.009; OR = 0.150, 95% CI, 0.036-0.621). While radiation therapy and tumor volume (≤ 150 mL) displayed trends towards significance (*P* = 0.083 and *P* = 0.069, respectively), their effects were not statistically significant. A good histologic response also correlated with improved survival (coefficient = 1.485, *P* = 0.022; OR = 4.416, 95% CI, 1.235-15.793). This analysis underscores the prognostic values of metastasis status, treatment adherence, chemotherapeutic effectiveness, and clinical symptoms in predicting survival outcomes for patients with osteosarcoma.

Discussion

In this study, we evaluated the impact of adjuvant chemotherapy using a cisplatin-paclitaxel-methotrexate (CPM) regimen on survival outcomes in osteosarcoma patients and identified key clinical and pathological factors associated with outcomes.

The improved efficacy observed with CPM may be attributed to the synergistic pharmacological effects of its components. Cisplatin remains a cornerstone of osteosarcoma chemotherapy owing to its DNA crosslinking properties that disrupt cancer cell replication [18]. Paclitaxel, by stabilizing microtubules, inhibits mitotic progression and induces apoptosis [19], while high-dose methotrexate disrupts folate metabolism by inhibiting dihydrofolate reductase, effectively arresting DNA synthesis and cellular proliferation [20]. The combination of these agents may potentially produce a more comprehensive antitumor effect compared to the standard chemotherapy alone. Specifically, paclitaxel may provide a mechanistic advantage by addressing microtubule assembly, a mechanism less exploited by traditional osteosarcoma treatments. This hypothesis is supported by previous reports of paclitaxel en-

hancing chemotherapy sensitivity via its unique action on the cytoskeleton dynamics [21], potentially contributing to the improved survival outcomes observed in our study.

Our study also highlights several prognostic factors critically associated with survival in osteosarcoma patients. Lung metastases, pathologic fractures at diagnosis, and elevated serum LDH levels emerged as independent risk factors for poor survival, underlying their critical roles in disease progression and treatment resistance. The association between lung metastasis and poor prognosis aligns with previous literature, given that the lungs are preferred metastatic sites in osteosarcoma, complicating treatment efforts and diminishing prognosis. Moreover, the ability of tumors to metastasize may reflect underlying biological aggressiveness that are difficult to overcome even with enhanced chemotherapy regimens [22, 23].

Interestingly, the analysis of prognostic factors underscored the critical role of pathologic features and treatment response in determining survival outcomes. Both pathologic fractures and lung metastasis were significantly correlated with poorer prognosis, highlighting the importance of early identification and aggressive management of these adverse features. Pathologic fractures might indicate advanced local disease or more aggressive tumor biology [24, 25], while lung metastases indicate systemic dissemination, both of which contribute to poor clinical outcomes [23, 26]. These findings highlight the necessity of timely detection and comprehensive management, including surgical intervention and targeted systemic therapies, especially for high-risk patients.

Completion of chemotherapy was identified as a strong positive prognostic factor, emphasizing the importance of treatment adherence in optimizing outcomes. The CPM regimen, with its potentially more manageable toxicity profile, may improve treatment compliance compared to standard regimens, thus enhancing therapeutic efficacy. This is further supported by the observation that a robust chemotherapeutic response (defined as > 90% in this study) was significantly correlated with improved survival. Such responses likely reflect substantial tumor reduction, which may enhance the success of subsequent treatments and reduce relapse risk [27, 28].

In terms of biochemical markers, elevated LDH levels were independently associated with poorer survival, affirming its role as a reliable indicator of tumor burden and cellular turnover in osteosarcoma. Elevated LDH levels may reflect increased tumor metabolic activity and hypoxic microenvironmental condition, both of which are commonly associated with aggressive tumor phenotypes and resistance to therapy. These findings suggest that LDH could serve not only as a therapeutic biomarker but also as a potential target for metabolic modulation in future therapeutic approaches [29-31].

Pain symptom also emerged as a negative prognostic marker, possibly reflecting extensive disease burden at diagnosis. Pain is often result from tumor invasion into adjacent tissues and bone destruction, suggesting significant local tumor aggression. Effective pain management, combined with strategies aimed at reducing tumor volume, may thus improve both patient quality of life and overall survival [32, 33].

The multivariate analysis in this study identified chemotherapy response and completion of treatment as independent protective factors for survival, suggesting that the therapeutic effectiveness of the CPM regimen played an essential role in determining clinical outcomes, irrespective of initial disease severity. This supports the hypothesis that effective systemic treatments, capable of significantly reducing tumor burden, can offset the negative impact of poor baseline prognostic indicators.

Despite the valuable insights provided, this study has several limitations. The retrospective nature and relatively small sample size may limit the generalizability of our findings and reduce the statistical power of subgroup analyses. The lack of randomization and a formal control group may introduce potential biases that may compromise the robustness of the comparisons between the CPM and SC groups. Additionally, inherent selection bias and uncontrolled confounding variables may have influenced treatment outcomes. Future studies should aim to address these limitations through larger, prospective, multi-center cohorts.

Incorporating comprehensive biomarker assessments could facilitate early prediction of treatment responses and toxicities, as well as enable personalized risk stratification based on molecular profiles. Moreover, investigation into adjunctive therapies, such as immunotherapy or bisphosphonates, may further enhance the therapeutic efficacy of existing regimens and improve outcomes in patients with high-risk osteosarcoma.

Conclusion

In conclusion, this study highlights the potential benefit of combining cisplatin and paclitaxel with high-dose methotrexate in improving survival outcomes for osteosarcoma patients, particularly in refractory cases. The findings emphasize the importance of personalized treatment strategies that consider both tumor biology and host response. Moving forward, future research should aim to elucidate the mechanism underlying chemotherapy synergy, identify biomarkers predictive of response, and optimize treatment protocols to maximize patient benefit.

Acknowledgements

This study was supported by the Mechanism study on the effect of long non coding RNA MIR22HG on apoptosis in osteosarcoma by regulating intracellular signaling pathways (No. 20220167).

Disclosure of conflict of interest

None.

Address correspondence to: Xidong Zhang, Department of Pharmacy, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Shijiazhuang 050000, Hebei, China. E-mail: 48801670@hebmu.edu.cn

References

[1] Yoshida A. Osteosarcoma: old and new challenges. Surg Pathol Clin 2021; 14: 567-583.
[2] Yang C, Tian Y, Zhao F, Chen Z, Su P, Li Y and Qian A. Bone microenvironment and osteosarcoma metastasis. Int J Mol Sci 2020; 21: 6985.
[3] Yu T, Cai Z, Chang X, Xing C, White S, Guo X and Jin J. Research progress of nanomaterials in chemotherapy of osteosarcoma. Orthop Surg 2023; 15: 2244-2259.
[4] Soares do Brito J, Santos R, Sarmento M, Fernandes P and Portela J. Chemotherapy regimens for non-metastatic conventional appendicular osteosarcoma: a literature review based on the outcomes. Curr Oncol 2023; 30: 6148-6165.
[5] He M, Wang Y, Xie J, Pu J, Shen Z, Wang A, Li T, Wang T, Li G, Liu Y, Mei Z, Ren Z, Wang W, Liu X, Hong J, Liu Q, Lei H, He X, Du W, Yuan Y and Yang L. M^7G modification of FTH1 and pri-miR-26a regulates ferroptosis and chemotherapy resistance in osteosarcoma. Oncogene 2024; 43: 341-353.
[6] Zhao Z, Wu Q, Xu Y, Qin Y, Pan R, Meng Q and Li S. Groenlandicine enhances cisplatin sensitivity in cisplatin-resistant osteosarcoma cells through the BAX/Bcl-2/Caspase-9/Caspase-3 pathway. J Bone Oncol 2024; 48: 100631.
[7] Tian Z, Qiao X, Wang Z, Li X, Pan Y, Wei X, Lv Z, Li P, Du Q, Wei W, Yan L, Chen S, Xu C, Feng Y and Zhou R. Cisplatin and doxorubicin chemotherapy alters gut microbiota in a murine osteosarcoma model. Aging (Albany NY) 2024; 16: 1336-1351.
[8] Niu J, Yan T, Guo W, Wang W, Ren T, Huang Y, Zhao Z, Yu Y, Chen C, Huang Q, Lou J and Guo L. The COPS3-FOXO3 positive feedback loop regulates autophagy to promote cisplatin resistance in osteosarcoma. Autophagy 2023; 19: 1693-1710.
[9] Tian N, Wang D, Li X, Xue M and Zheng B. Effect of paclitaxel combined with doxorubicin hydrochloride liposome injection in the treatment of osteosarcoma and MRI changes before and after treatment. Evid Based Complement Alternat Med 2022; 2022: 5651793.
[10] Qu Y, Kang M, Cheng X and Zhao J. Chitosan-coated titanium dioxide-embedded paclitaxel nanoparticles enhance anti-tumor efficacy against osteosarcoma. Front Oncol 2020; 10: 577280.
[11] Liu Y, Qiao Z, Gao J, Wu F, Sun B, Lian M, Qian J, Su Y, Zhu X and Zhu B. Hydroxyapatite-bovine serum albumin-paclitaxel nanoparticles for locoregional treatment of osteosarcoma. Adv Healthc Mater 2021; 10: e2000573.
[12] Lv Y, Wu L, Jian H, Zhang C, Lou Y, Kang Y, Hou M, Li Z, Li X, Sun B and Zhou H. Identification and characterization of aging/senescence-induced genes in osteosarcoma and predicting clinical prognosis. Front Immunol 2022; 13: 997765.
[13] Lei T, Qian H, Lei P and Hu Y. Ferroptosis-related gene signature associates with immunity and predicts prognosis accurately in patients with osteosarcoma. Cancer Sci 2021; 112: 4785-4798.
[14] Qu J, Zhang Y, Lu S, Xing W, Zheng Y, Sun H, Gao Q, Xia Q, Wang Z, Zhang H, Wang S, Qin J,

Kamel IR and Li H. Quantitative RECIST derived from multiparametric MRI in evaluating response of esophageal squamous cell carcinoma to neoadjuvant therapy. Eur Radiol 2022; 32: 7295-7306.
[15] McNair KM, Zeitlin D, Slivka AM, Lequerica AH and Stubblefield MD. Translation of Karnofsky Performance Status (KPS) for use in inpatient cancer rehabilitation. PM R 2023; 15: 65-68.
[16] Mol L, Ottevanger PB, Koopman M and Punt CJ. The prognostic value of WHO performance status in relation to quality of life in advanced colorectal cancer patients. Eur J Cancer 2016; 66: 138-143.
[17] Cerón-Rodríguez M, Barajas-Colón E, Ramírez-Devars L, Gutiérrez-Camacho C and Salgado-Loza JL. Improvement of life quality measured by Lansky Score after enzymatic replacement therapy in children with Gaucher disease type 1. Mol Genet Genomic Med 2018; 6: 27-34.
[18] Pan B, Li Y, Han H, Zhang L, Hu X, Pan Y and Peng Z. FoxG1/BNIP3 axis promotes mitophagy and blunts cisplatin resistance in osteosarcoma. Cancer Sci 2024; 115: 2565-2577.
[19] Lu L, Wang Y, Chen J, Li Y, Liang Q, Li F, Zhen C and Xie K. Targeting Mps1 in combination with paclitaxel inhibits osteosarcoma progression by modulating spindle assembly checkpoint and Akt/mTOR signaling. Oncol Lett 2021; 22: 797.
[20] Rajeswari B, Guruprasad CS, Nair M, Prasanth VR, Sugath BS and Thankamony P. High dose methotrexate containing regimen in pediatric non-metastatic extremity osteosarcoma patients: experience from a tertiary cancer center in India. Pediatr Hematol Oncol 2022; 39: 225-232.
[21] Smith ER, Leal J, Amaya C, Li B and Xu XX. Nuclear lamin A/C expression is a key determinant of paclitaxel sensitivity. Mol Cell Biol 2021; 41: e0064820.
[22] Mandava A, Kandem S, Juluri R, Reddy AK and Koppula V. Primary osteosarcoma of the sternum with lung metastases. Radiol imaging cancer 2024; 6: e230199.
[23] Liu F, Pang X, Yu Z and Wang K. Differential gene expression analysis for osteosarcoma lung metastases. Cancer Biomark 2022; 33: 379-387.
[24] Gonzalez MR, Bedi A, Karczewski D and Lozano-Calderon SA. Are pathologic fractures in patients with osteosarcoma associated with worse survival outcomes? A Systematic review and meta-analysis. Clin Orthop Relat Res 2023; 481: 2433-2443.
[25] Altwal J, Martin TW, Thamm DH and Séguin B. Configuration of pathologic fractures in dogs with osteosarcoma following stereotactic body radiation therapy: a retrospective analysis. Vet Comp Oncol 2023; 21: 131-137.
[26] Spinnato P. Calcified osteosarcoma lung metastases. Radiology 2024; 312: e240703.
[27] Tsukamoto S, Errani C, Angelini A and Mavrogenis AF. Current treatment considerations for osteosarcoma metastatic at presentation. Orthopedics 2020; 43: e345-e358.
[28] Travis WD, Dacic S, Wistuba I, Sholl L, Adusumilli P, Bubendorf L, Bunn P, Cascone T, Chaft J, Chen G, Chou TY, Cooper W, Erasmus JJ, Ferreira CG, Goo JM, Heymach J, Hirsch FR, Horinouchi H, Kerr K, Kris M, Jain D, Kim YT, Lopez-Rios F, Lu S, Mitsudomi T, Moreira A, Motoi N, Nicholson AG, Oliveira R, Papotti M, Pastorino U, Paz-Ares L, Pelosi G, Poleri C, Provencio M, Roden AC, Scagliotti G, Swisher SG, Thunnissen E, Tsao MS, Vansteenkiste J, Weder W and Yatabe Y. IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. J Thorac Oncol 2020; 15: 709-740.
[29] Xu Y, Yang L, Li M, Shu H, Jia N, Gao Y, Shi R, Yang X, Zhang Z and Zhang L. Anti-osteosarcoma trimodal synergistic therapy using NiFe-LDH and MXene nanocomposite for enhanced biocompatibility and efficacy. Acta Pharm Sin B 2024; 14: 1329-1344.
[30] Sun T, Ma J, Zhu S and Wang K. Diagnostic value of combined detection of AKP, TSGF, and LDH for pediatric osteosarcoma: a case-control study. Am J Transl Res 2024; 16: 3667-3677.
[31] Bian Y, Zhao K, Hu T, Tan C, Liang R and Weng X. A Se Nanoparticle/MgFe-LDH composite nanosheet as a multifunctional platform for osteosarcoma eradication, antibacterial and bone reconstruction. Adv Sci (Weinh) 2024; 11: e2403791.
[32] Liu H, Gao X and Hou Y. Effects of mindfulness-based stress reduction combined with music therapy on pain, anxiety, and sleep quality in patients with osteosarcoma. Braz J Psychiatry 2019; 41: 540-545.
[33] Kuo WJ, Shirvani BS, Guthmiller K, Varrassi G, Viswanath O and Koushik S. Tunneled fascia iliaca catheter placement for chronic pain from advanced osteosarcoma. Cureus 2023; 15: e36475.