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Original Article

Neoadjuvant chemotherapy followed by limb-sparing surgery for osteosarcoma: a retrospective cohort study on efficacy, safety, and prognostic factors

Min Yi[1,2], Kai Zheng[3], Hui Ma[3], Yajie Chen[1], Yunfeng Tang[4]

[1]Department of Orthopedic Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [2]Trauma Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [3]Department of Operating Room, West China Hospital, Sichuan University/West China School of Nursing, Sichuan University, Chengdu 610041, Sichuan, China; [4]Head and Neck Oncology Ward, Cancer Center, West China Hospital, Sichuan University/West China School of Nursing, Sichuan University, Chengdu 610041, Sichuan, China

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Abstract: This retrospective study evaluated the outcomes of neoadjuvant chemotherapy (NACT) combined with limb-sparing surgery (LSS) for osteosarcoma (OS). A total of 204 OS patients treated at West China Hospital, Sichuan University between February 2020 and February 2023 were enrolled. Based on treatment modalities, patients were assigned to a control group (n=100; undergoing LSS) and an observation group (n=104; receiving NACT+LSS). Comparative analyses were performed to assess clinical outcomes, safety, inflammatory markers (C-reactive protein [CRP], tumor necrosis factor [TNF]-α), tumor-associated biomarkers (carcinoembryonic antigen [CEA], serum alkaline phosphatase [ALP], lactate dehydrogenase [LDH]), humoral immunity indicators (immunoglobulin [Ig] A/M/G), and 3-year prognosis (including metastasis and survival). Univariate and multivariate binary logistic regression analyses were conducted to identify independent determinants of therapeutic responses. Compared with the control group, the observation group demonstrated notably superior overall response and 3-year survival rates, while the overall incidence of adverse events was comparable, with no significant increase in severe adverse reactions. After intervention, both groups exhibited significant reductions in CRP, TNF-α, CEA, ALP, LDH, and IgA/M/G levels, with the observation group showing lower CRP, TNF-α, CEA, ALP, and LDH and higher IgA/M/G than the control group. Additionally, the 3-year incidence of lung metastasis was significantly lower in the observation group. Multivariate regression analysis identified maximum tumor diameter ≥7.8 cm, LSS alone, and elevated CEA as independent risk factors for poor treatment response, while increased IgA levels emerged as an independent protective factor. These results support the clinical benefit of NACT combined with LSS in OS, without increasing the risk of adverse events or severe specific adverse reactions.

Keywords: Limb sparing surgery, neoadjuvant chemotherapy, osteosarcoma, clinical efficacy, factors influencing therapeutic outcome

Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor, with an incidence peak in adolescence, predominantly affecting adolescents and young individuals [1]. A key pathological feature is the production of immature bone or osteoid by malignant cells, with the long bones, including the femur, tibia, and humerus, being the most frequently involved sites [2]. Risk factors associated with OS development include increased stature, higher birth weight, history of therapeutic irradiation, and hereditary retinoblastoma [1]. Globally, the annual incidence of OS is approximately 3.4 cases per million population. Localized disease carries a recurrence risk of 40%, which rises to 80% following metastasis [3]. Correspondingly, overall survival rate drops sharply from over 70% in non-metastatic cases to approximately 20% in metastatic patients [4].

Limb sparing surgery (LSS) remains the cornerstone of OS treatment; however, long-term therapeutic outcomes are often suboptimal [5]. The introduction of neoadjuvant chemotherapy

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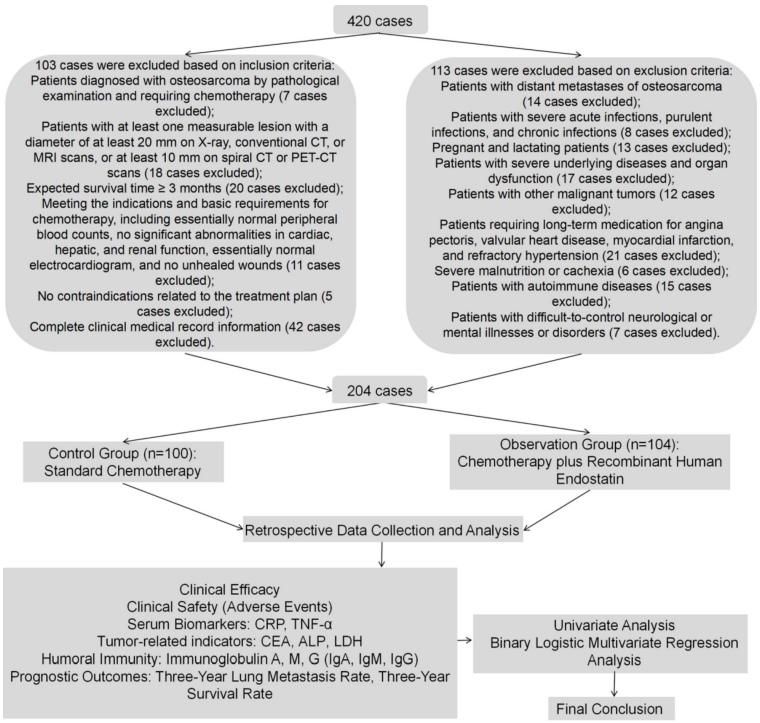

Figure 1. Patient selection flowchart.

(NACT) has been shown to improve survival in patients with stage III-IV OS [6]. Despite the use of surgery combined with NACT and postoperative adjuvant chemotherapy, the 5-year survival rate of OS patients remains unsatisfactorily [7]. This limitation is partly attributed to the incomplete eradication of OS cells due to nonspecific drug delivery, which may lead to tumor recurrence and progression [8].

First-line neoadjuvant and adjuvant chemotherapy regimen for OS typically involves a combination of high-dose methotrexate (HD-MTX), cisplatin (DDP), ifosfamide (IFO), and Adriamycin (ADM). While this protocol improves surgical outcomes, challenges such as chemoresistance and treatment-related toxicity persist [9]. Papakonstantinou et al. [10] reported that combining NACT with LSS could achieve higher 5-year overall survival rate in OS patients.

However, clinical data on evaluating NACT combined with LSS for OS are limited, and the influencing factors affecting therapeutic effectiveness remain underexplored. Therefore, this study was conducted to systematically assess the clinical outcomes of NACT+LSS and to identify key determinants of treatment response, thereby providing guidance for optimizing therapeutic strategies and patient management.

Materials and methodology

Case selection

This retrospective study reviewed 204 cases of OS treated between February 2020 and February 2023. Patients were divided into a control group (n=100; receiving LSS alone) and an observation group (n=104; receiving NACT+LSS). The study protocol was approved by the Ethics Committee of West China Hospital, Sichuan University. All procedures were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. **Figure 1** presents the process of patient selection.

Inclusion criteria: (1) Histopathological confirmation of OS and a clinical decision for chemotherapy [11]; (2) The presence of ≥1 bidimensionally measurable lesion based on imaging modality (X-ray/standard computed tomography [CT]/magnetic resonance imaging [MRI]: ≥20 mm; spiral CT/positron emission tomography [PET]-CT: ≥10 mm); (3) An anticipated survival of ≥3 months; (4) Meeting the indications and basic requirements for NACT or LSS, defined by essentially normal hematologic, hepatic, renal, and cardiac (per electrocardiograph) function, and no unhealed trauma; (5) Absence of therapy-specific contraindications; (6) Complete medical records.

Expected survival of ≥3 months [12] was determined by the following objective criteria assessed at pre-treatment evaluation: good physical condition: Eastern Cooperative Oncology Group (ECOG) score ≤2 points; no immediate life-threatening complications (e.g., uncontrolled septic shock, acute intracranial hemorrhage); tolerability of main organ functions to planned treatment (e.g., left ventricular ejection fraction >40%, total bilirubin level <2 times the upper limit of the normal value); no untreated, rapidly progressing second primary tumor. Assessment was made by the attending physician team through comprehensive evaluation.

Exclusion criteria: (1) Distant metastases from OS or any other concurrent malignancies; (2) Serious acute, suppurative, or chronic infectious diseases; (3) Autoimmune disorders; (4) Severe dysfunction of major organs or severe comorbidities; (5) Conditions requiring long-term pharmacotherapy (e.g., angina, valvular disease, post-myocardial infarction status, refractory hypertension); (6) Severe malnutrition or cachexia; (7) Poorly controlled neurological or psychiatric disorders; (8) Pregnancy or breastfeeding. Refractory hypertension was defined as blood pressure persistently above 140/90 mmHg, despite use of three or more different types of antihypertensive drugs (including one diuretic) at appropriate dosages [13].

Treatment protocols

Patients in the control group received LSS alone. First, the tumor-bearing bone segment was identified by bone scanning and surgically excised. Complete resection included the tumor and adjacent blood vessels and nerves located 3-5 cm from the tumor edge. Following the procedure, a marginal pathological assessment was performed intraoperatively; if the surgical resection margin was inadequate, further resection of the osteoepiphysis was performed. Then, bone segment transplantation was performed. The corresponding autologous bone segments were prepared 30 minutes before implantation, rinsed, and soft tissue removed. A fixation device was installed inside the medullary canal, and the cavity was irrigated with 3% hydrogen peroxide. Cancellous lag screws were applied perpendicularly to the epiphyseal ends and the broken bone surface. Finally, bone reconstruction was achieved by connecting the osteoepiphysis to the host bone through vertically fixed cancellous lag screws, with particulate autogenous cancellous bone implanted at the junction. Postoperatively, patients underwent plaster immobilization for 6 weeks, followed by gradual functional rehabilitation exercises.

Patients in the observation group received additional routine NACT (HD-MTX+DDP+IFO+ADM regimen; Shanghai Yuanye Bio-Technology Co., Ltd., B25455-50mg, W21161-250 mg, T92743-1 ml, T92569-1 ml), on the basis of the treatment applied in the control group. One cycle of NACT was administered preoperatively, followed by three cycles postoperatively, with each cycle consisting of a seven-week four-drug regimen. The specific medication plan was as follows:

Day 1 of the first week: High-dose MTX (8 g/m^2) was administered for 4-6 hours, with continuous monitoring of blood drug concentration; calcium folinate rescue was initiated for 6 hours post-administration and continued until the blood methotrexate concentration dropped to a safety range.

Days 1-2 of the third week: DDP (100-120 mg/m^2) and ADM (60 mg/m^2) were administered as intravenous bolus injections.

Days 1-6 of the fifth week: IFO (2 g/d) was continuously pumped intravenously on a daily basis.

LSS was performed in Week 8, following the same surgical procedure as in the control group. Beginning two weeks postoperatively, patients continued with three additional cycles of the chemotherapy regimen described above.

Information extraction

Clinical efficacy. The post-treatment lesion response assessment was conducted for both groups in accordance with the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) [14]. Outcomes were classified as: complete response (CR), disappearance of all lesions; partial response (PR), ≥30% decrease in the sum of the longest diameters or the sum of the single greatest diameters of target lesions; stable disease (SD), <30% shrinkage or <20% growth in the sum of target lesion diameters; progressive disease (PD), >20% increase in the sum of target lesion diameters or emergence of new lesions. Overall response was defined as CR+PR+SD, while PD is considered non-response. Complete remission was defined exclusively as CR, excluding PR or SD. Based on these definitions, patients were grouped for subsequent subgroup analysis.

Incidence of adverse events. Post-surgical adverse events were monitored, specifically including leukopenia, renal injury, liver impairment, gastrointestinal reactions, and thrombocytopenia [15]. In the observation group, elec-

tronic medical records were systematically reviewed for potential specific adverse reactions, including cardiac toxicity (electrocardiographic abnormalities, elevated myocardial enzyme levels), bleeding tendencies (epistaxis, gingival bleeding, subcutaneous ecchymosis), and allergic reactions. All adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Serum indices. Peripheral venous blood samples (5 mL) were collected after an overnight fast at baseline and following completion of the second intervention course. Samples were centrifuged to obtain serum, and concentrations of C-reactive protein (CRP) and tumor necrosis factor (TNF)-α were detected using enzyme-linked immunosorbent assay (ELISA).

Tumor-associated biomarkers. Pre- and post-intervention serum levels of carcinoembryonic antigen (CEA), serum alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) were determined employing an automatic biochemical analyzer (rate method).

Humoral immunity. Serum immunoglobulins (IgA, IgM, IgG) concentrations were assessed using Flow cytometry with fluorescent-labeled monoclonal antibodies.

Prognosis. Patients were followed quarterly for three years via telephone calls, outpatient visits, and pathological record review to monitor lung metastasis and overall survival.

Primary and secondary outcome measures

In this study, the primary endpoints were clinical efficacy, incidence of adverse events, and prognosis. Secondary endpoints included serum indices, tumor-associated biomarkers, and humoral immunity-related indicators.

Statistical analysis

All statistical analyses were performed using SPSS 21.0. Measurement data were first assessed for normality using the Shapiro-Wilk test and for homogeneity of variance. Variables conforming to normal distribution and homogeneity of variance were expressed as mean ± standard deviation (SD). Inter-group comparisons were conducted using independent-samples t-test, and pre- versus post-treatment changes were examined using paired t-test.

Qualitative data were reported as frequencies (percentages), and inter-group differences were assessed using chi-square tests. For ordinal categorical data (e.g., efficacy grading), the Mann-Whitney U test was used.

Survival analysis was performed using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. All patients were followed up until the occurrence of the endpoint event, with no censored data. To identify predictors of treatment outcomes, univariate and multivariate binary logistic regression analyses were performed. A *P*-values <0.05 was deemed statistically significant.

Results

Baseline characteristics

As shown in **Table 1**, baseline characteristics, including sex, age, body mass index (BMI), Enneking stage, tumor location, and maximum tumor diameter (MTD), were comparable between the observation and control groups (all P>0.05).

Treatment efficacy

As summarized in **Table 2**, clinical efficacy differed significantly between the two groups. The observation group had 94 responsive cases, compared to 65 in the control group, revealing a statistically higher overall response rate in the observation group (P<0.001).

Clinical safety outcomes

Clinical safety assessment revealed comparable overall adverse event rates between the two groups (**Table 3**). Adverse events observed in the observation group, including leukopenia, renal injury, liver impairment, gastrointestinal reactions, and thrombocytopenia, were all grades 1-2 (mild to moderate) according to CTCAE, with no significant differences compared to controls (P>0.05). No severe adverse events (CTCAE grade 3 or above) were reported in either group. In addition, there were no documented cases of severe cardiac toxicity, major bleeding events, or allergic reactions in the observation group. Three patients experienced transient and mild electrocardiographic abnormalities (e.g., sinus tachycardia, CTCAE grade 1), which were resolved spon-

Table 1. Comparison of baseline characteristics between the two groups

	Control group (n=100)	Observation group (n=104)	χ^2/t	P
Sex			0.889	0.346
Male	66 (66.00)	62 (59.62)		
Female	34 (34.00)	42 (40.38)		
Age (years)	21.00±4.82	19.96±4.03	1.674	0.096
Body mass index (kg/m^2)	22.05±2.13	22.28±2.13	0.771	0.442
Enneking staging			0.978	0.323
IIA	45 (45.00)	54 (51.92)		
IIB	55 (55.00)	50 (48.08)		
Tumor location			0.963	0.810
Femur	58 (58.00)	55 (52.88)		
Tibia	28 (28.00)	30 (28.85)		
Fibula	9 (9.00)	11 (10.58)		
Humerus	5 (5.00)	8 (7.69)		
Maximum tumor diameter (cm)	7.60±2.23	8.09±2.42	1.502	0.135

Table 2. Comparison of treatment responses between the two groups

Response	Control group (n=100)	Observation group (n=104)	χ^2	P
CR	0 (0.00)	0 (0.00)		
PR	18 (18.00)	49 (47.12)		
SD	47 (47.00)	45 (43.27)		
PD	35 (35.00)	10 (9.62)		
Overall response (CR+PR+SD)	65 (65.00)	94 (90.38)	19.107	<0.001

Note: CR, complete response; PR, partial response; SD, Stable disease; PD, Progressive disease.

Table 3. Comparison of safety profiles between the two groups

Indicators	Control group (n=100)	Observation group (n=104)	χ^2	P
Leukopenia (grades 1-2)	0 (0.00)	3 (2.89)		
Renal injury (grades 1-2)	0 (0.00)	3 (2.89)		
Liver impairment (grades 1-2)	0 (0.00)	3 (2.89)		
Gastrointestinal reactions (grades 1-2)	5 (5.00)	2 (1.92)		
Thrombocytopenia (grades 1-2)	3 (3.00)	5 (4.81)		
Total	8 (8.00)	16 (15.38)	2.678	0.102

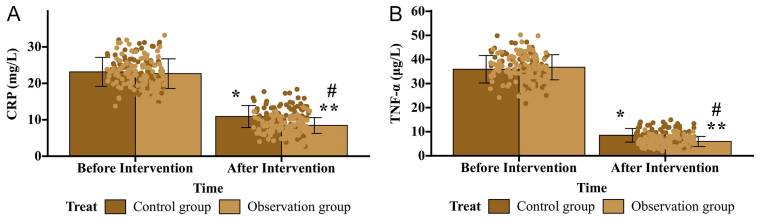

Figure 2. Comparison of serum levels of inflammatory markers between the two groups before and after treatment. A. C-reactive protein (CRP). B. Tumor necrosis factor (TNF)-α. Note: *P<0.05, **P<0.01 vs. pre-intervention in the same group; #P<0.05 vs. control at the same timepoint.

taneously without special treatment; Two patients had mild epistaxis or gingival bleeding (CTCAE grade 1), which were controlled after symptomatic treatment.

Evaluation of serum indices

The dynamics of serum inflammatory markers are illustrated in **Figure 2**. Baseline CRP and TNF-α levels were comparable between groups (P>0.05). Both cohorts exhibited significant decreases in CRP and TNF-α after treatment (P<0.05), with the observation group demonstrating greater

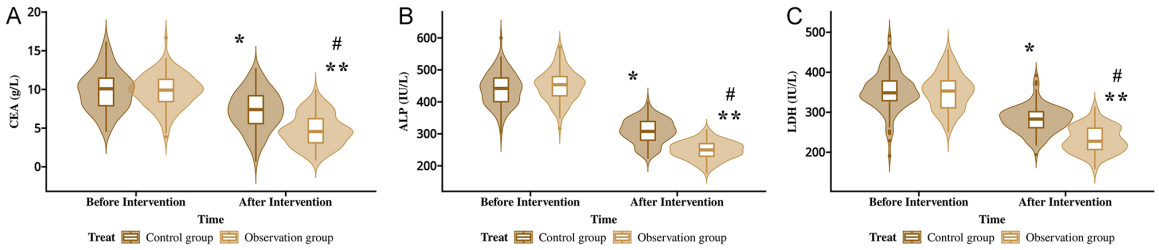

Figure 3. Comparison of serum levels of tumor-associated biomarkers between the two groups before and after treatment. A. Carcinoembryonic antigen (CEA). B. Alkaline phosphatase (ALP). C. Lactate dehydrogenase (LDH). Note: *P<0.05, **P<0.01 vs. pre-intervention values in the same group; #P<0.05 vs. control group at the same timepoint.

Table 4. Comparison of humoral immune function parameters between the two groups

Indicators	Control group (n=100)	Observation group (n=104)	t	P
IgA (mg/L)				
Before intervention	2.62±0.68	2.48±0.79	1.354	0.177
After intervention	1.17±0.51**	1.76±0.67*	7.057	<0.001
IgM (mg/L)				
Before intervention	1.25±0.46	1.26±0.36	0.173	0.863
After intervention	0.81±0.29**	0.96±0.23*	4.101	<0.001
IgG (mg/L)				
Before intervention	11.56±2.29	11.68±3.07	0.315	0.753
After intervention	7.86±1.85**	9.81±2.89*	5.715	<0.001

Note: Ig, immunoglobulin; *P<0.05, **P<0.01 (intra-group comparison to baseline).

Table 5. Comparison of prognostic outcomes between the two groups

Indicators	Control group (n=100)	Observation group (n=104)	χ^2	P
Lung metastasis rate	65 (65.00)	33 (31.73)	22.606	<0.001
Survival rate	50 (50.00)	78 (75.00)	13.631	<0.001

reductions compared with the control group (P<0.05).

Tumor-associated biomarker expression

Serum levels of tumor-associated biomarkers are presented in **Figure 3**. Initial levels of CEA, ALP, and LDH were similar between groups (P>0.05). After treatment, all these biomarkers showed significant reductions compared to their pre-interventional values (P<0.05). Furthermore, the observation group displayed more pronounced suppression in CEA, ALP, and LDH compared to the control group (P<0.05).

Humoral immunity assessment

Humoral immune parameters are detailed in **Table 4**. Baseline IgA, IgM, IgG levels showed no significant intergroup disparities (P>0.05). After intervention, both groups showed declines in these markers (P<0.05); however, the observation group maintained significantly higher IgA, IgM, and IgG concentrations compared to the control group (P<0.05).

Survival and prognostic analysis

The median follow-up duration was 36 months. Assessment of 3-year prognosis (**Table 5**) demonstrated a clear advantage for the observation group, with lower lung metastasis rates (31.73% vs. 65.00%) and higher survival rate (75.00% vs. 50.00%; P<0.05). Consistently, Kaplan-Meier survival curves (**Figure 4**) confirmed superior 3-year pulmonary metastasis-free survival and overall survival in the observation group compared to the control group (Log-rank test, both P<0.001).

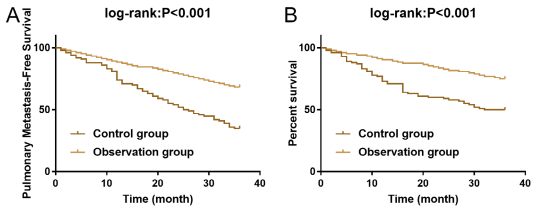

Figure 4. Survival analysis of OS patients in both treatment cohorts. A. Pulmonary metastasis-free survival curves. B. Overall survival curves.

Predictors of clinical response in OS

Univariate analysis (**Table 6**) showed no significant associations between treatment response and sex, age, BMI, Enneking staging, tumor location, TNF-α, ALP, LDH, IgM, or IgG ($P>0.05$). However, significant associations were observed for treatment modality, CPR, and IgA levels ($P<0.05$).

Multivariate binary logistic regression analysis (**Table 7**) was further conducted to identify predictors of treatment response. Variables with $P<0.05$ in univariate analysis (treatment approach, CRP, TNF-α, IgA) were included, along with clinically relevant factors such as age, Enneking staging, and MTD. Independent risk factors for poor treatment response included MTD ≥7.8 cm (OR=2.507, 95% CI: 1.145-5.488), LSS alone (OR=4.969, 95% CI: 2.181-11.322), and elevated CEA (OR=1.236, 95% CI: 1.051-1.452; all $P<0.05$), while elevated IgA levels (OR=0.470, 95% CI: 0.283-0.780, $P<0.001$) conferred an independent protective effect.

Discussion

The pathological hallmark of OS is its mesenchymal origin, featured by spindle-shaped cells that produce immature bone-like tissue. Epidemiological data indicate a higher susceptibility in male population [16, 17]. Treatment efficacy of NACT is frequently limited by chemoresistance, disease recurrence, and metastasis, highlighting the need for innovative strategies to improve therapeutic outcomes [18].

In this study, NACT combined with LSS significantly improved treatment responses in OS patients compared to LSS alone, while maintaining a favorable safety profile without increasing the incidence of severe specific adverse reactions. Although LSS surgically removes lesions while preserving limb function, complete removal is often challenging, resulting in tumor residue and limited curative effects. Its integration with NACT allows for the elimination of residual tumor cells, suppression of tumor cell proliferation, and enhancement of surgical sensitivity, thus improving overall therapeutic efficacy [19]. More specifically, MTX, as an antimetabolite, inhibits tumor cell proliferation and interferes with DNA synthesis and mitotic division [20]. DDP, a platinum-based chemotherapeutic, induces tumor cell apoptosis by disrupting tumor cell replication and transcription [21]. IFO, a nitrogen mustard alkylating agent, forms DNA cross-linking through its metabolites and inhibit the replication and transcription of tumor cells [22]. ADM, as an anthracycline antibiotic, directly induces tumor cell apoptosis and inhibits tumor angiogenesis [23]. The combination of these four agents exerts synergistic anti-OS effects, thus enhancing overall therapeutic efficacy.

Moreover, the combination therapy for OS demonstrated enhanced suppression of CRP and TNF-α. CRP, a marker of systemic inflammatory response, is closely related to OS metastasis [24]. TNF-α, a pro-inflammatory cytokine, can accelerate OS progression by regulating interleukin (IL)-34 expression in OS cells, promoting angiogenesis, and enhancing recruitment of M2 macrophages [25]. Aberrant expression of both molecules is frequently observed in OS and may contribute to tumor initiation and progression [26]. Huang et al. [27] reported that ADM reduces serum TNF-α levels while increasing IL-10 concentrations in OS patients.

Significant reductions in OS-associated biomarkers, including CEA, ALP, and LDH, were also observed with the combination therapy. This may result from the synergistic action of NACT and LSS, which collectively enhance therapeutic efficacy and suppress these tumor-associated markers. Serum CEA has been indicated as a candidate predictor of NACT responsiveness in OS patients [28]. Elevated serum ALP and LDH levels, on the other hand, are closely related to poor survival outcomes, which can serve as OS patients' prognoses to some extent [29, 30]. Furthermore, the combination regimen effectively preserved humoral immune function in OS patients. Long-term follow-up over three years demonstrated significant protection against pulmonary metastasis,

Table 6. Univariate analysis of predictors for treatment response in osteosarcoma patients

Variable	No remission (n=45)	Total remission (n=159)	χ^2/t	P
Sex			0.380	0.538
Male (n=128)	30 (66.67)	98 (61.64)		
Female (n=76)	15 (33.33)	61 (38.36)		
Age (years)			0.843	0.359
<20 (n=92)	23 (51.11)	69 (43.40)		
≥20 (n=112)	22 (48.89)	90 (56.60)		
Body mass index (kg/m^2)			1.793	0.181
<22 (n=95)	17 (37.78)	78 (49.06)		
≥22 (n=109)	28 (62.22)	81 (50.94)		
Enneking staging			0.386	0.535
IIA (n=99)	20 (44.44)	79 (49.69)		
IIB (n=105)	25 (55.56)	80 (50.31)		
Tumor location			3.074	0.380
Femur (n=113)	21 (46.67)	92 (57.86)		
Tibia (n=58)	14 (31.11)	44 (27.67)		
Fibula (n=20)	5 (11.11)	15 (9.43)		
Humerus (n=13)	5 (11.11)	8 (5.03)		
Maximum tumor diameter (cm)			4.678	0.031
<7.8 (n=97)	15 (33.33)	82 (51.57)		
≥7.8 (n=107)	30 (66.67)	77 (48.43)		
Treatment approach			19.107	<0.001
Neoadjuvant chemotherapy+limb sparing surgery (n=104)	10 (22.22)	94 (59.12)		
Limb sparing surgery (n=100)	35 (77.78)	65 (40.88)		
CRP (mg/L)	23.93±4.17	22.58±3.95	1.999	0.047
TNF-α (μg/L)	35.91±5.58	36.48±5.45	0.616	0.539
CEA (g/L)	10.61±1.97	9.60±2.46	2.532	0.012
ALP (IU/L)	457.73±50.97	441.53±50.48	1.897	0.059
LDH (IU/L)	354.27±52.06	352.01±46.17	0.282	0.779
IgA (mg/L)	2.22±0.81	2.66±0.70	3.592	<0.001
IgM (mg/L)	1.21±0.43	1.28±0.40	1.019	0.309
IgG (mg/L)	11.00±2.82	11.79±2.90	1.623	0.106

Note: CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Ig, immunoglobulin.

Table 7. Multivariate analysis of independent predictors of treatment response

Variable	B	SE	Wald	P	OR	95% CI
Age (years)	-0.272	0.388	0.492	0.483	0.762	0.356-1.630
Enneking staging	0.130	0.388	0.112	0.738	1.139	0.532-2.436
Maximum tumor diameter (cm)	0.919	0.400	5.288	0.021	2.507	1.145-5.488
Treatment approach	1.603	0.420	14.558	<0.001	4.969	2.181-11.322
CRP (mg/L)	0.052	0.047	1.230	0.267	1.054	0.961-1.156
CEA (g/L)	0.212	0.082	6.585	0.010	1.236	1.051-1.452
IgA (mg/L)	-0.756	0.259	8.538	0.003	0.470	0.283-0.780

Note: CRP, C-reactive protein; CEA, carcinoembryonic antigen; IgA, immunoglobulin A.

accompanied by a corresponding improvement in overall survival.

Univariate and multivariate analyses consistently identified that treatment failure in OS patients was associated with MTD ≥7.8 cm, chemotherapy-only regimens, elevated CEA, and low IgA levels. Accordingly, it is crucial to closely monitor patients with these risk profiles and modify their therapeutic regimens when necessary. Age, Enneking staging, and CRP did not emerge as independent predictors in the multivariate analysis, possibly due to sample distribution clustering, the mitigating effect of chemotherapy on stage differences, and the relatively low specificity of CRP. An MTD of ≥7.8 cm typically indicates a large tumor burden, which may limit drug penetration, ultimately challenging treatment efficacy. Chemotherapy alone, hindered by the bone-blood barrier, may inadequately control local tumor load, resulting in suboptimal outcomes. Elevated CEA levels suggest increased tumor invasiveness and metastatic potentials, as well as activation of drug-resistance pathways and immunosuppressive mechanisms, thereby complicating therapy. Reduced IgA may reflect impaired humoral immunity, malnutrition, or diminished tolerance to chemotherapy, further compromising treatment response.

Based on multivariate analysis results, several strategies can be considered to improve outcomes in high-risk OS patients: extending NACT cycle, pursuing wider intraoperative surgical margins, and increasing the frequency of postoperative lung metastasis surveillance for OS patients with MTD ≥7.8 cm, potentially in combination with anti-angiogenetic therapies. Patients with high baseline CEA levels may benefit from intensified NACT (e.g., extending from 3 cycles to 4-6 cycles) and shorter postoperative follow-up intervals. For patients with low IgA levels, immunomodulators, such as thymalfasin, can be administered during chemotherapy intervals to enhance host anti-tumor immunity.

In cases with both high CEA and low IgA alongside an MTD of ≥7.8 cm, clinicians should maintain vigilance for chemotherapy resistance; in such circumstances, prompt surgical intervention and consideration of targeted or immunotherapeutic approaches may be warranted. Beyond guiding risk stratification and therapeutic decision-making, CEA and IgA may serve as dynamic biomarkers for monitoring treatment efficacy. A decrease in CEA or an increase in IgA during therapy may suggest effective treatment, whereas persistent elevation of CEA or reduction in IgA may signal disease progression or drug resistance. Furthermore, these molecules could also serve as potential therapeutic targets, shedding light for the development of novel combined immunotherapy and targeted therapy strategies based on CEA- and IgA-related drug-resistance signaling pathways and immunosuppressive tumor microenvironment [31, 32].

This study also has several limitations. First, the impact of subsequent treatments (e.g., surgery, targeted therapy) on the survival of OS patients with lung metastases was not analyzed. Future studies are needed to guide subsequent treatment strategies and to more accurately evaluate prognoses in this patient population. Second, as an inherent limitation of retrospective studies, minor adverse reactions may have been underestimated due to variations in documentation standards; future multicenter, large-sample prospective analyses are needed to further evaluate the safety of the combined therapy. Third, the evaluation of multiple serological and immune markers in this study may increase the risk of type 1 errors (false positives). Subsequent studies employing independent validation cohorts should be carried out to control the false-positive rate and confirm the reliability of these findings.

Conclusion

NACT combined with LSS demonstrates superior outcomes compared to LSS alone in the management of OS. This approach improves clinical efficacy without increasing adverse event rates or severe specific adverse reactions. Additionally, it contributes to stronger suppression of CRP, TNF-α, CEA, ALP, and LDH, preserves humoral immune function, reduces the three-year incidence of lung metastasis, and improves three-year overall survival. OS patients with MTD ≥7.8 cm, individuals managed solely with LSS, or those presenting with high CEA or low IgA should be closely monitored, and their therapeutic regimens may require modification to optimize outcomes.

Disclosure of conflict of interest

None.

Address correspondence to: Min Yi, Trauma Center, West China Hospital, Sichuan University, No. 37, Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan, China. Tel: +86-028-85422426; E-mail: yeemean@163.com

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