

Clinical factors affecting prognosis of limb osteosarcoma in China: a multicenter retrospective analysis

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Abstract

Objective: This study was performed to explore the relationship between various clinical factors and the prognosis of limb osteosarcoma.

Methods: We retrospectively analyzed the clinical data of 336 patients with limb osteosarcoma treated from June 2000 to August 2016 at 7 Chinese cancer centers. Data on the patients' clinical condition, treatment method, complications, recurrences, metastasis, and prognosis were collected and analyzed. Kaplan–Meier analysis and Cox regression models were used to analyze the data.

Results: The patients comprised 204 males and 132 females ranging in age from 6 to 74 years (average, 21.1 years). The overall 3- and 5-year survival rates were 65.0% and 55.0%, respectively. The 5-year overall survival rate was 64.0% with standard chemotherapy and 45.6% with

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non-standard chemotherapy. Cox regression analysis demonstrated that standard chemotherapy, surgery, recurrence, and metastasis were independent factors associated with the prognosis of limb osteosarcoma.

Conclusion: The survival of patients with limb osteosarcoma can be significantly improved by combining standard chemotherapy and surgery. The overall survival rate can also be improved by adding methotrexate to doxorubicin–cisplatin–ifosfamide triple chemotherapy.

Keywords

Osteosarcoma, multicenter analysis, prognosis, chemotherapy, recurrence, metastasis

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Introduction

Osteosarcoma is the most common primary malignant tumor of the bone. Two to three people of every 1 million are diagnosed every year, accounting for 0.2% of malignant tumors and 11.7% of primary bone tumors.^{1–3} Osteosarcoma has a bimodal age distribution, with the first peak occurring during adolescence (about 15 years of age) and the second peak occurring in later adulthood (about 75 years of age).^{4–5} Osteosarcoma commonly occurs in the long bones of the extremities near the metaphyseal growth plates. The most common sites are the femur and tibia.⁶ Prior to the 1970s, amputation was the standard treatment for osteosarcoma, but the long-term survival rate was low. Since the application of standard chemotherapy and extensive tumor resection, the 5-year overall survival rate has increased from <20% to >60%, and the limb salvage rate among those with osteosarcoma has increased from 10%–20% to 80%–90%.⁷ However, the 5-year survival rate of patients with bone cancer in China is 17.1%,⁸ which is lower than that in the United States (66.0%).⁹ We retrospectively collected patient data from seven cancer centers in China to explore the association of several clinical factors with the prognosis of limb osteosarcoma.

Materials and methods

All patients with osteosarcoma in the present study were treated at seven institutions from June 2000 to February 2016. The inclusion criteria for this study were histologically proven osteosarcoma, localization of the primary tumor to the limbs, surgical treatment for the tumor, and a follow-up time of ≥ 3 years [the endpoint of follow-up was loss to follow-up or death during the observation period or reaching the end of the study period (June 2019)]. Enneking surgical staging¹⁰ was applied to determine the clinical stage of the tumor.

From June 2000 to December 2003, various chemotherapy regimens were used to treat the patients with osteosarcoma. The chemotherapy treatments used from January 2004 to February 2016 consisted of preoperative and postoperative adriamycin–cisplatin–ifosfamide (ADM-CDP-IFO) triple chemotherapy (hereafter referred to as DIA) with or without methotrexate (MTX). Second-line chemotherapy mainly included paclitaxel, vincristine, pemetrexed, and docetaxel. We divided the patients into a standard chemotherapy group and non-standard chemotherapy group according to the chemotherapy cycles and doses. In the standard chemotherapy group, the patients received (1) DIA or DIA combined

with second-line chemotherapy (DIA + MTX or DIA + MTX combined with second-line chemotherapy), and the dosages of CDP, IFO, ADM, and MTX were 120 to 140 mg/m², 15 g/m², 90 mg/m², and 8 to 10 g/m², respectively; (2) two or more chemotherapy cycles preoperatively and four or more cycles postoperatively; and (3) administration of chemotherapy 2 weeks after surgery. If the regimen did not meet any of the above descriptions, the patients were assigned to the non-standard chemotherapy group.

Surgical treatment was divided into limb salvage and amputation. Limb salvage included tumor resection and prosthesis replacement, tumor inactivation with replantation, and other procedures. The surgical method employed depended on the size and location of the tumor, neurovascular involvement, skeletal maturity, patient age, presence of pathological fracture, biopsy results, clinical stage, special patient requirements, economic capacity, and other factors.

Follow-up consisted of outpatient visits or telephone interviews once every 3 months for the first 2 years postoperatively, then once every 4 months during the 3rd year, once every 6 months during the 4th and 5th years, and once a year from the 6th to 10th years. Osteosarcoma presents both a local problem and a concern for distant metastasis. The workup included imaging of the primary site (usually X-ray) and chest imaging [computed tomography (CT)]. More detailed imaging (CT or magnetic resonance imaging) of abnormalities identified on primary imaging was required for suspected metastatic disease. (For some patients with local swelling and pain, we found definite osteosarcoma-related changes in the imaging examination, and patients confirmed to have osteosarcoma by local puncture biopsy and immunohistochemistry were diagnosed with postoperative recurrence of

osteosarcoma. For some patients with cough and other lung symptoms, the imaging examination showed nodules or lesions in their lungs. With the cooperation of respiratory physicians, local fine-needle aspiration biopsy and immunohistochemistry were applied to confirm the presence of pulmonary metastasis of osteosarcoma; such patients were diagnosed with pulmonary metastasis of osteosarcoma. For patients with multiple metastases, we applied an emission CT bone scan or positron emission tomography–CT for confirmation.)

The Kaplan–Meier method was applied to create survival curves. The multivariate Cox proportional hazards method was applied for multivariate analysis, and meaningful single factors were incorporated into a Cox regression analysis with the forward Wald approach. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients and survival

In total, 336 patients with an initial diagnosis of osteosarcoma were included in the present study (204 males and 132 females; mean age, 21.1 years; range, 6–74 years). Patients aged <14 years accounted for 29.47% (*n* = 99), those aged 15 to 39 years accounted for 61.01% (*n* = 205), and those aged >40 years accounted for 9.52% (*n* = 32). The median follow-up time was 45 months (range, 12–201 months), and the mean follow-up time was 53.38 months. The primary tumor locations were mainly around the knee, including the distal femur (*n* = 176), proximal tibia (*n* = 89), proximal humerus (*n* = 26), proximal femur (*n* = 15), proximal fibula (*n* = 13), distal tibia (*n* = 13), distal humerus (*n* = 3), and radius (*n* = 1) (Table 1). The 3- and 5-year overall survival rates for all

patients were 65.0% (n=222) and 55.0% (n=111), respectively, and the 3- and 5-year disease-free survival rates were 52.0% (n=176) and 45.0% (n=96), respectively (Figures 1 and 2; survival curve of all 336 patients). The 5-year overall survival rate of male patients (n=204) and female patients (n=132) was 54.9% and 55.9%, respectively, and the 5-year overall survival rate of patients aged <14 years (n=99), 15 to

39 years (n=205), and >40 years (n=32) was 47.7%, 59.0%, and 53.7%, respectively. There were no significant differences in sex or age among these groups of patients ($\chi^2=0.061$ and $\chi^2=3.510$, respectively).

Preoperative biopsy and surgical staging

In total, 215 patients underwent core needle biopsy preoperatively, while the remaining patients did not. The 5-year overall survival rates were 55.3% and 55.1%, respectively, with no significant difference ($\chi^2=0.082$). In terms of surgical staging, 319 patients had Enneking stage II cancer while 17 patients had Enneking stage III. The 5-year overall survival rates were 57.0% and 22.1%, respectively, with statistical significance ($\chi^2=18.301$, $P=0.000$) (Table 2).

Chemotherapy

The 5-year overall survival rate in the standard chemotherapy group (n=176)

Table 1. Primary tumor locations of 336 patients with osteosarcoma.

Primary tumor site	Number of patients	Percent (%)
Distal femur	176	52.38
Proximal tibia	89	26.49
Proximal humerus	26	7.74
Proximal femur	15	4.46
Proximal fibula	13	3.87
Distal tibia	13	3.87
Distal humerus	3	0.89
Radius	1	0.30

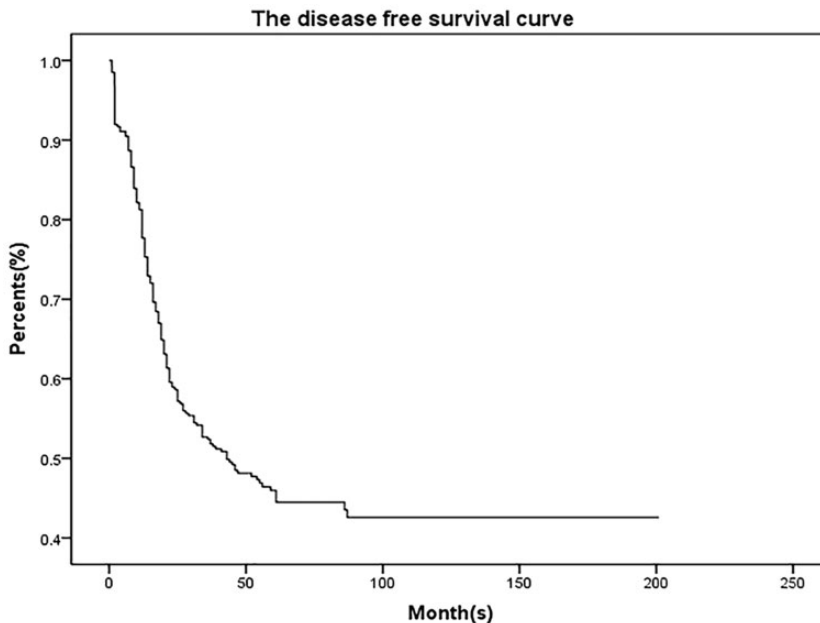


Figure 1. Disease-free survival curve of all 336 patients.

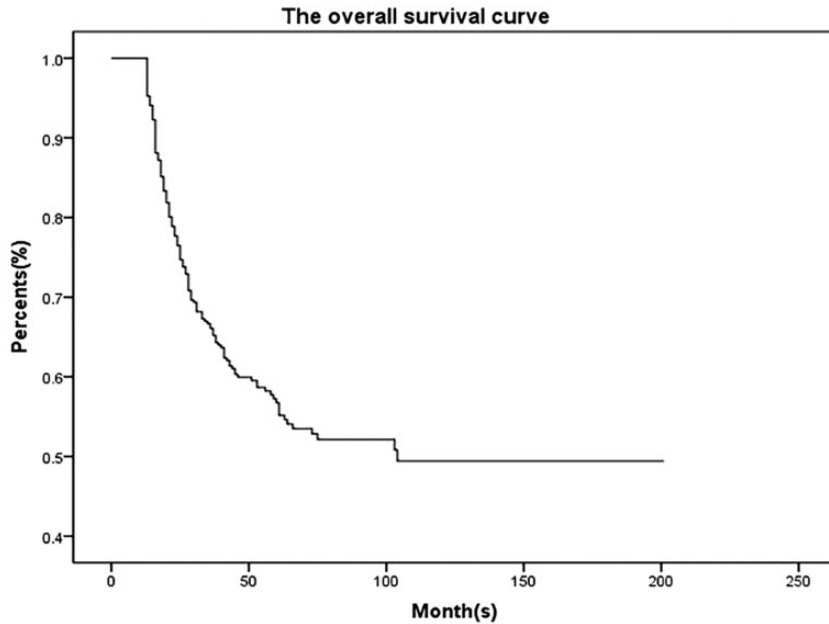


Figure 2. Overall survival curve of all 336 patients.

and non-standard chemotherapy group ($n = 160$) was 64.0% and 45.6%, respectively, and the 5-year disease-free survival rate in the standard and non-standard chemotherapy groups was 52.8% and 35.5%, respectively; this difference was statistically significant ($\chi^2 = 14.928$, $P = 0.000$) (Figures 3 and 4; survival curve of chemotherapy). Before surgery, the difference between the DIA group and DIA + MTX group was statistically significant ($\chi^2 = 4.451$, $P = 0.035$); after surgery, however no significant difference was found ($\chi^2 = 1.783$). The difference between the groups regardless of whether the preoperative and postoperative chemotherapy regimens were consistent was not statistically significant ($\chi^2 = 0.004$). Additionally, the 5-year overall survival rate with a tumor cell necrosis rate of $\geq 90\%$ ($n = 19$) and $< 90\%$ ($n = 48$) was 89.5% and 33.6%, respectively. The difference between these two rates was statistically significant ($\chi^2 = 11.652$, $P = 0.001$).

Surgery

Among all patients, 308 patients underwent limb salvage (including tumor resection and prosthesis replacement in 228 patients, inactivation of the tumor and replantation in 39 patients, and other procedures in 41 patients) and 28 patients underwent amputation (Table 3). The 5-year overall survival rate in the limb salvage group and amputation group was 57.4% and 32.1%, respectively; this difference was statistically significant ($\chi^2 = 10.690$, $P = 0.001$). The proportion of patients who underwent standard chemotherapy with limb salvage surgery was much higher than that of patients who underwent amputation. Among 308 patients who underwent limb salvage procedures, 159 (51.62%) received standardized chemotherapy while only 10 of 28 (35.71%) who underwent amputation received such therapy. Among the total study population, 39 patients developed various complications. The complication with the highest incidence was infection, accounting for 43.59% (Table 4).

Table 2. Univariate analysis of 336 patients with osteosarcoma.

	Number of patients	Overall survival rate (%)				Disease-free survival rate (%)			
		3-year	5-year	χ^2	P value	3-year	5-year	χ^2	P value
All	336	65.0	55.0	–	–	52.0	45.0	–	–
Sex									
Male	204	65.2	54.9	0.061	0.805	52.0	45.1	0.025	0.875
Female	132	65.2	55.9			51.5	43.7		
Age in years									
≤ 14	99	58.6	47.7	3.510	0.173	46.5	38.6	0.963	0.618
15–39	205	67.3	59.0			53.2	48.6		
≥ 40	32	71.9	53.7			59.4	36.8		
Tumor site									
Around the knee	265	62.2	51.8	4.504	0.034	48.7	40.8	6.570	0.010
Outside of the knee	71	74.6	68.8			63.4	59.2		
Preoperative puncture									
Yes	215	65.1	55.3	0.082	0.775	53.0	45.2	0.114	0.736
No	121	65.3	55.1			49.6	43.5		
Surgical staging									
Enneking stage II	319	67.1	57.0	18.301	0.000	54.5	47.0	–	–
Enneking stage III	17	29.4	22.1			–	–		
Chemotherapy									
Standard	176	72.3	64.0	14.928	0.000	59.9	52.8	9.898	0.002
Non-standard	160	57.2	45.6			42.8	35.5		
Preoperative chemotherapy									
DIA	84	54.8	42.4	4.451	0.035	46.4	38.8	0.684	0.408
DIA + MTX	79	67.1	61.4			55.7	47.5		
Postoperative chemotherapy									
DIA	84	57.1	48.0	1.783	0.182	44.0	36.8	1.096	0.295
DIA + MTX	116	67.2	59.1			51.7	47.9		
Uniformity									
Yes	131	58.8	52.3	0.004	0.949	51.1	43.9	1.211	0.271
No	143	63.6	49.6			45.5	39.4		
Surgery									
Limb salvage	308	67.9	57.4	10.690	0.001	53.9	46.0	9.033	0.003
Amputation	28	35.7	32.1			28.6	28.6		
Tumor cell necrosis rate									
$\geq 90\%$	19	89.5	89.5	11.652	0.001	84.2	78.2	13.400	0.000
$< 90\%$	48	54.2	33.6			29.2	21.2		
Recurrence and metastasis									
None	162	95.7	92.7	239.047	0.000	95.7	92.7	374.240	0.000
Only recurrence	32	59.4	40.7			15.6	0		
Only lung metastasis	96	38.5	17.8			11.5	1.3		
Multiple metastases	46	17.4	8.7			6.5	2.2		

Chemotherapy, standard: (1) DIA or DIA combined with second-line chemotherapy preoperatively, DIA + MTX or DIA + MTX combined with second-line chemotherapy postoperatively, (2) more than two chemotherapy cycles preoperatively and more than four cycles postoperatively; (3) chemotherapy was applied 2 weeks after surgery. Non-standard: If the regimen did not meet the above descriptions, it fit into the non-standard chemotherapy group. *DIA*, doxorubicin-cisplatin-ifosfamide. *MTX*, methotrexate. *Uniformity*: yes, chemotherapy is uniform preoperatively or postoperatively; no, chemotherapy is diverse preoperatively or postoperatively. *Multiple metastases*, pulmonary metastasis and recurrence were simultaneous; χ^2 , chi-square goodness-of-fit test).

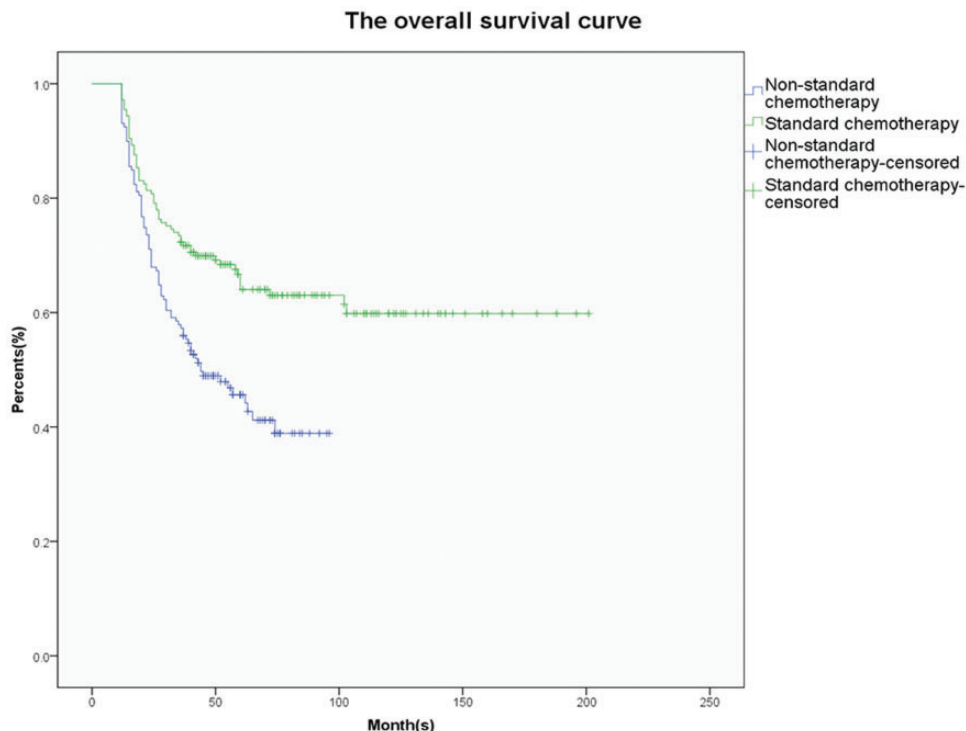


Figure 3. Overall survival curve of patients who underwent chemotherapy.

Recurrence and metastasis

Among all patients, recurrence alone occurred in 32 patients, lung metastasis alone occurred in 96, and multiple metastases occurred in 46 (pulmonary metastasis and recurrence occurred simultaneously). The total recurrence rate was 23.21%, and the lung metastasis rate was 42.26%. The 5-year overall survival rate with no recurrence and no metastasis, only recurrence, only metastasis, and multiple metastases was 92.7%, 40.7%, 17.8%, and 8.7%, respectively ($\chi^2 = 239.047$, $P = 0.000$) (Table 2). Among all patients, 78 developed recurrence after surgery, 54 were part of the reoperation group, 11 were in the chemotherapy group, and 13 were in the untreated group. Amputation was performed in 28 patients, accounting for 51.85% of all patients with recurrence who agreed to

undergo reoperation, confirming that amputation was the main treatment for postoperative recurrence. Additionally, 142 patients developed lung metastasis (including lung metastasis at the initial diagnosis and postoperative pulmonary metastasis), among whom 83 were in the chemotherapy group, 26 were in the surgery (lung operation) combined with chemotherapy group, 16 were in the radiotherapy combined with chemotherapy group, and 17 were in the untreated group. The differences in survival among the various treatments after lung metastasis were statistically significant ($\chi^2 = 15.401$, $P = 0.002$). The overall survival of patients who underwent pulmonary lobectomy combined with chemotherapy after lung metastasis was higher than that of patients who underwent other treatments and was far higher than that of untreated patients.

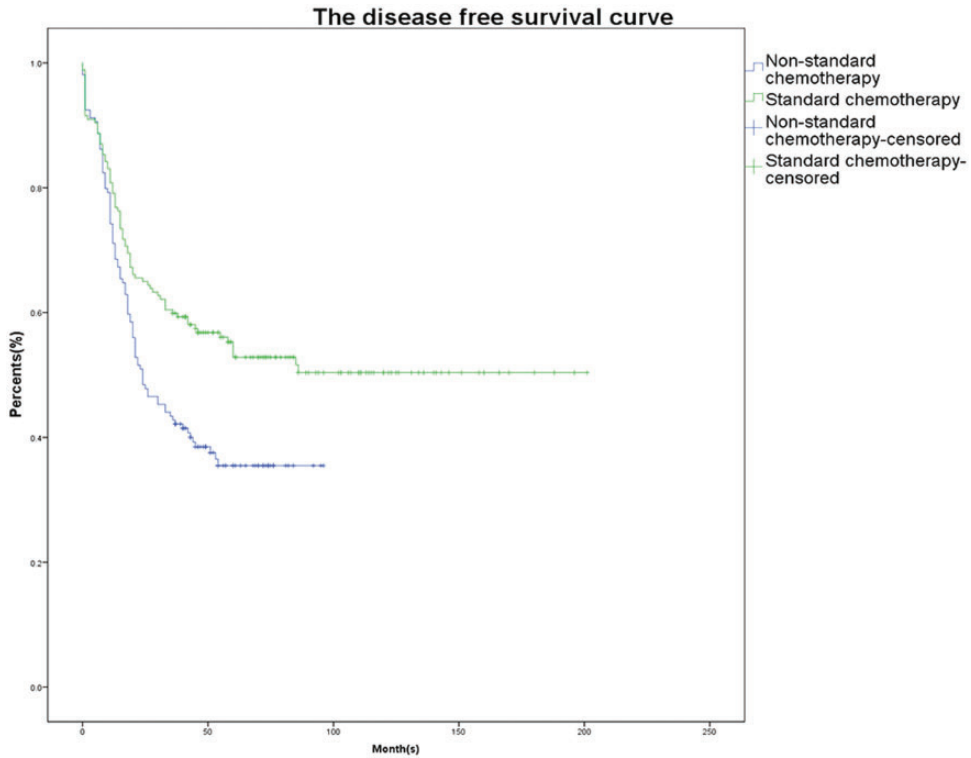


Figure 4. Disease-free survival curve of patients who underwent chemotherapy.

Table 3. Correlation between surgical approach and prognosis.

Surgery	Number of patients	Overall survival (%)		χ^2	P
		3-year	5-year		
Limb salvage	308	67.9	57.4	–	–
Tumor resection and prosthesis replacement	228	68.9	55.6	4.997	0.082
Tumor inactivation and replantation	39	56.4	49.6		
Other approaches	41	73.2	73.2		
Amputation	28	35.7	32.1	–	–

Multiple-factor analysis

The single-factor analysis showed that standard chemotherapy, the preoperative chemotherapy regimen, the tumor cell necrosis rate, surgery, the Enneking stage, recurrence, and metastasis were significantly correlated with the prognosis of

patients with limb osteosarcoma. Factors such as patient sex, patient age, tumor location, postoperative chemotherapy regimen, and preoperative puncture were not significantly correlated with the prognosis of limb osteosarcoma (Table 2). Additionally, after entering standard chemotherapy, the tumor

cell necrosis rate, surgery, the Enneking stage, recurrence, metastasis, and demographic factors (sex and age) into the multivariate Cox regression, the results showed that standard chemotherapy, surgery, recurrence, and metastasis were independent predictive factors for the prognosis of limb osteosarcoma (Table 5).

The results of the separate analyses of the seven centers involved in this study showed that standard chemotherapy, surgery, recurrence, and metastasis were statistically significant in the single-factor analysis and that recurrence and metastasis were the strongest independent predictive factors for the prognosis of limb osteosarcoma.

Discussion

Chemotherapy

In the 1960s, Jaffe¹¹ used multiagent chemotherapy comprising high-dose MTX, ADM, CDP, bleomycin, cyclophosphamide, and dactinomycin to treat patients

who had undergone postoperative amputation. The author concluded that postoperative chemotherapy increased survival. In the 1970s, Rosen et al.¹² designed a preoperative chemotherapy regimen called T5, which comprised methotrexate (200 mg/kg), vincristine (16 mg/m²), and ADM (45 mg/m²). The authors analyzed 31 patients who had been diagnosed with osteosarcoma and treated with the T5 regimen with a follow-up period of 30 to 52 months. During that time, 23 of 31 patients (75%) survived, with 21 of 23 showing no evidence of disease. This finding confirmed that preoperative chemotherapy had a more complete effect against primary tumors.

The survival rate of patients with osteosarcoma treated with amputation alone is only 10% to 20%, while that of patients treated with neoadjuvant chemotherapy combined with extensive tumor resection ranges from 60% to 80%.¹³ In our patient cohort, the survival rate with standard chemotherapy was much higher than that with non-standard chemotherapy, which is consistent with the data in the study by Jaffe.¹⁴ However, most patients did not receive standard chemotherapy, which had a serious negative impact on survival, resulting in a survival rate lower than that in other reports from other countries.¹⁵

We divided the patients into the DIA group, DIA + MTX group, and other group according to the chemotherapy regimen that they received. We found that the overall survival rate in the DIA + MTX

Table 4. Non-tumor postoperative complications.

	Number of patients	Percent (%)
All	39	100
Infection	17	43.59
Prosthesis-related	14	35.90
Wound nonunion	8	20.51

Prosthesis-related: mainly included prosthetic loosening and leg-length discrepancy.

Table 5. Cox multivariate analysis of 336 patients with osteosarcoma.

Cox regression analysis						
	B	SE	Wald	df	Sig.	Exp(B)
Standard chemotherapy	-0.412	0.177	5.412	1	0.020	0.662
Recurrence and metastasis	1.071	0.084	160.791	1	0.000	2.918
Surgery	1.122	0.263	18.299	1	0.000	3.070

B, regression coefficient; SE, standard error; Wald, test statistic; df, degrees of freedom; Sig, significance; Exp(B), index of B coefficient.

group was significantly higher than that in the DIA group both preoperatively and postoperatively, while there was a significant difference between the two groups only in preoperative chemotherapy ($\chi^2 = 4.451$, $P = 0.035$). Therefore, the overall survival rate was greatly increased by adding MTX to the DIA group. The Rizzoli Orthopaedic Institute in Italy¹⁶ and the Cooperative Osteosarcoma Study Group in Germany¹⁷ conformed that IFO combined with ADM, CDP, and MTX can definitely improve the effect of chemotherapy. Additionally, Lin et al.¹⁸ analyzed 185 patients with osteosarcoma treated with the four above-mentioned drugs, revealing that the optimization of MTX, CDP, ADM, and IFO based on Chinese patients' physiology increased the tolerance and efficacy of the treatment of osteosarcoma.

Surgery

Prior to the 1970s, amputation was the most common method for treatment of osteosarcoma. With the development of medical imaging, surgical technology, artificial joint material, and especially the emergence of neoadjuvant chemotherapy, the safety of limb salvage surgery has improved enough to become the mainstream treatment of choice. The limb function outcomes after limb salvage surgery have been confirmed to be superior to those after amputation (especially femoral amputation), and the benefits to patients' mental health and appearance are prominent.^{19,20}

In the present study, the limb salvage rate was 83.93%, which is accordance with the treatment rates of 80% to 90% reported in the literature.^{21,22} There were three main categories of limb salvage surgery in our study: tumor resection and prosthesis replacement, tumor inactivation and replantation, and others. Tumor resection and prosthesis replacement was the most common therapeutic approach. The 5-year

overall survival rate of patients who underwent limb salvage and amputation was 57.4% and 32.1%, respectively. Additionally, a significant difference was seen within the limb salvage surgery approach ($P < 0.05$); one possible reason is that patients who underwent limb salvage surgery had less severe clinical conditions. The cancer recurrence rate after limb salvage and amputation was 24.03% and 14.29%, respectively, and the lung metastasis rate after limb salvage and amputation was 40.58% and 60.71%, respectively. The reasons for such differences in clinical outcomes can be summarized as follows: (1) patients who underwent limb salvage had a small tumor load, no neurovascular involvement, and no metastasis; (2) the performance of standard chemotherapy with limb salvage surgery was more common than amputation; (3) patients who underwent limb salvage had a good response to chemotherapy; and (4) the range of tumor resection was larger in the amputation group and the resulting recurrence rate was lower.

The physical outcome was also included in the follow-up of the present study. The patients who survived for 5 years after their operation reported having adjusted well to their physical limitations. Our conclusion confirms that reported by Ottaviani et al.²³

Recurrence and metastasis

In our dataset, recurrence and metastasis were the main causes of death and were independent factors affecting the prognosis of osteosarcoma. Our data also demonstrated a significant difference in survival between patients with recurrence and metastasis ($\chi^2 = 239.047$, $P = 0.000$). According to our study, among 78 patients with recurrence, the main treatment was reoperation combined with chemotherapy. Surgical eradication of recurrence with wide margins may be critical to maximizing the

chances for survival, although chemotherapy does not have a significant effect on survival.²⁴ Several novel methods have been introduced for the treatment of osteosarcoma recurrence. For example, Yu et al.²⁵ applied high-intensity focused ultrasound to 27 patients with local unresectable recurrence of osteosarcoma, and the 1-, 2-, and 3-year local disease control rates were 59.2%, 40.7%, and 33.1%, respectively. The authors conformed that high-intensity focused ultrasound is a safe and noninvasive treatment for local unresectable recurrence of osteosarcoma, with good local control and without severe complications.

A patient with osteosarcoma presenting with lung metastases is recommended to undergo the following chemotherapy regimen: (1) first-line chemotherapy: high-dose IFO, ADM, CDP, MTX; (2) second-line chemotherapy: vincristine, etoposide phosphate, bleomycin, cyclophosphamide, and arsenic trioxide. Many methods of osteosarcoma treatment have been reported to date, including targeted therapy (apatinib), radiotherapy, immunotherapy, and gene therapy. Kimura et al.²⁶ treated pulmonary metastases of osteosarcoma using caffeine combined with chemotherapy, which achieved a satisfactory outcome. In the present study, the overall survival rate of patients who underwent pulmonary lobectomy combined with chemotherapy after lung metastasis was higher than that of patients treated with other methods. Harting et al.²⁷ reported that 93 patients with osteosarcoma had a mean 33.6-month survival time after pulmonary lobectomy for lung metastasis, while 38 patients who did not undergo pulmonary lobectomy had a mean survival time of only 10.1 months. Further studies have confirmed that the time of lung metastasis and time to treatment after metastasis are important prognostic factors. Once a lung metastasis is found and if clinical conditions permit,

the tumor should be surgically treated quickly thereafter.²⁸

A significant difference was found between independent risk factors for the prognosis of osteosarcoma.^{29,30} The response to chemotherapy, alkaline phosphatase concentration, patient age, tumor size, recurrence, and metastasis each had a direct impact on prognosis.³¹

This study was retrospective in nature and thus has certain limitations. First, the clinical data were limited. The follow-up time was ≥ 3 years; therefore, the 5-year survival rate in this study was an estimated survival rate, and the follow-up time was not uniform; this resulted in a large gap between the overall survival and disease-free survival rates. Additionally, no questionnaires were conducted because the patients chose non-standard chemotherapy with provision of detailed rational reasons. However, the findings of this study far outweigh its shortcomings. Multicenter studies provide strong evidence of the future clinical diagnosis and treatment standards, and some new findings (e.g., adding MTX to DIA can improve the overall survival rate) might also inspire doctors to perform further research.

Conclusion

The survival of patients with limb osteosarcoma can be significantly improved by combining standard chemotherapy and surgery. Additionally, the overall survival rate can be improved by adding MTX to DIA.

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Authors' contributions

All authors drafted and critically revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Data are available upon request to the authors.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.


Ethics

This study was approved by the Ethics Committee of PLA 960th Hospital (because this study was initiated by PLA 960th Hospital, the ethics committees of all seven centers reached an agreement on the decision made by the Ethics Committee of PLA 960th Hospital). Written informed consent was obtained from every patient. We de-identified the patients' details such that their identity cannot be ascertained in any way.

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