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ORIGINAL ARTICLE

# Retrospective analysis of the effect of treatment of osteosarcoma complicated by pathological fracture by neoadjuvant chemotherapy combined with limb salvage surgery

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## Summary

***Purpose:*** *To explore the efficacy of neoadjuvant chemotherapy combined with limb salvage surgery for the treatment of osteosarcoma complicated by pathological fracture.*

***Methods:*** *215 osteosarcoma patients who were admitted in our hospital from 2001 and 2012 were followed up for 5 years and were retrospectively analyzed among them. The patients were divided into 4 groups based on their condition and treatment method to observe the 5-year overall survival and tumor-free survival (TFS) in each group. Adverse reactions caused by chemotherapy were recorded and analyzed. In addition, the quality of life was compared in these 4 groups.*

***Results:*** *No significant differences were observed in postoperative overall survival and TFS between patients who were subjected to limb salvage surgery (Group A) and amputation (Group B). Similarly, there was no difference between patients who underwent surgery for pathological fracture and those without fracture (Group D). However, the survival of non-preoperative chemotherapy group (group C) was significantly different from that of preoperative chemotherapy group (group C vs group A/B/D, p=0.008, p=0.042, p=0.010, respectively). Besides, the TFS of non-preoperative chemotherapy group was significantly lower than that of preoperative chemotherapy group (group C vs. group A/B/D, p=0.012, p=0.002, p=0.008, respectively). Vomiting was the main adverse effect in our research. In the comparison of quality of life, social function and physical limitations in the limb-salvage group were superior to the amputation group.*

***Conclusions*** *Neoadjuvant chemotherapy combined with limb salvage surgery is effective for the patients with osteosarcoma complicated by pathological fractures.*

***Key words:*** *limb salvage surgery, neoadjuvant chemotherapy, osteosarcoma, pathological fracture*

## Introduction

Osteosarcoma is a malignant tumor originating from mesenchymal tissue and is characterized by spindle-shaped stromal cells which can produce osteoid tissue. It is the most common malignancy in the skeletal system which mainly affects adolescents. Its predilection site is the metaphysis of long tubular bones, with 42% of the femur, 19% of the tibia, 10% of the humerous, 8% of the skull and jaw, and 8% of the pelvis [1].

Treating osteosarcoma complicated by pathological fractures is difficult. Previous experience has shown that the prognosis of this disease is usually poor [2,3]. In addition, most clinicians are willing to conduct limb salvage surgery for local high-grade malignant osteosarcoma, however, if it is complicated by pathological fractures, the surgical decision will be difficult to perform. On the one hand, some clinicians believe that immediate and

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aggressive removal of the tumor could stop the progression of disease caused by the fracture. Besides, early amputation has always been a surgical treatment for osteosarcoma complicated by pathological fractures [4-7]. However, others believe that limb salvage surgery has become an irreplaceable treatment for local high-grade malignant osteosarcoma with pathological fractures due to its acceptable clinical outcome [1,8-10].

Neoadjuvant chemotherapy in osteosarcoma was first performed by Rosen et al. [11] to change the traditional mode of adjuvant chemotherapy. Different from the traditional adjuvant chemotherapy which is administered after osteosarcoma surgery, neoadjuvant chemotherapy is performed immediately after pathological confirmation of osteosarcoma. After continuous revisions and improvements, it has now been widely used in osteosarcoma patients. Kraybill et al. [12] performed neoadjuvant chemotherapy and preoperative radiotherapy on 64 patients with high-grade malignant soft tissue sarcoma. The results showed that 97% of patients could receive 3 or more cycles of chemotherapy despite its toxic side effects, for the duration was short. The median of survival was 7.7 years, and the 5-year predicted survival was 56%. Moreover, Scully et al. [13] have shown that osteosarcoma patients with pathological fractures have a high rate of local recurrence and a low survival rate. It is believed that a simple limb salvage treatment could not improve the prognosis of patients. Therefore, we aimed to explore the efficacy of neoadjuvant chemotherapy combined with limb salvage surgery for the treatment of osteosarcoma complicated by pathological fracture.



## Methods

*Subjects*

This study consisted of 215 osteosarcoma patients who were treated in our hospital between 2001 and 2012, including 137 males and 78 females. The patients were aged 15-56 years, with an average age of 26.8±7.6 years. This study was approved by the ethics committee of the First People's Hospital of Changzhou. Signed informed consents were obtained from all participants before the study entry. Inclusion criteria of the subjects were as follows: First, they must be histologically diagnosed with osteosarcoma; second, they have received neoadjuvant chemotherapy for at least one cycle. Based on the patient's physical condition and treatment methods, they were divided into 4 groups. Group A included 73 cases of osteosarcoma patients with pathological fractures who underwent neoadjuvant chemotherapy and limb salvage surgery; Group B consisted of 48 cases of osteosarcoma patients with pathological fractures who were treated with neoadjuvant chemotherapy and amputation; Group C included 36 cases of patients with pathological fractures who were directly operated; Group D included 58 cases of patients without pathological fractures who received neoadjuvant chemotherapy and limb salvage surgery.

The chemotherapy regimens in this study involved doxorubicin, methotrexate, ifosfamide and cisplatin. The patients received doxorubicin in the first week (90 mg/m$^2$). In the 3rd week, methotrexate was first intravenously infused (8-12 mg/m$^2$) followed by 12 intramuscular injections of folinin (6-15 mg) each time. Then, the same drug in the 3$^{rd}$ week was used in the 4$^{th}$ week. On the first 2 days of the 5$^{th}$ week, ifosfamide was intravenously infused (3 g/m$^2$), and cisplatin (120 mg/m$^2$) was administered on the 3$^{rd}$ day. Then, the same drugs in the 5rd week were used in the 8$^{th}$ week. Patients received one cycle of preoperative chemotherapy and 4 cycles of postoperative chemotherapy.

The follow up of patients in the 4 groups began after surgery. The follow-up time varied from 6 to 60 months, with an average of 53.6 months. During the postoperative period of chemotherapy, X-ray examination of limbs and bilateral lungs were performed monthly. Then, X-ray examination of limbs and bilateral lungs were conducted every 3 months while lung CT and bone scans were performed every 6 months. Patients with abnormalities such as pain, cough, hemoptysis, etc. were reexamined at any time.

*Observation indexes*

The 5-year overall survival and TFS were compared in each group of patients. The related adverse reactions during chemotherapy were evaluated according to the common adverse reaction grading standards established by WHO [14]. The Quality of Life Survey was conducted using the Health Measurement Scale (SF-36) [15] which involves 8 aspects including physical limitations, physical function, somatic pain, social function, general health, emotional function, vitality and mental health. The SF-36 was completed by the patient him/herself on a scale of 0-100 points. Each item's score was recognized as the original point, which was then converted into standard score. Standard score = (original points - the lowest score of this entry) × 100% / (the highest score - the lowest score). The survey was conducted on the 6$^{th}$ and 12$^{th}$ month respectively after the treatment.

*Statistics*

SPSS21.0 statistical software (Armonk, NY, USA) was used for statistical analyses. All quantitative statistical software data in this paper were presented as mean ± standard deviation. Chi square test was used for comparing data of different groups. Kaplan-Meier method was used to generate the overall survival curves and TFS curves. $P<0.05$ showed statistical significance.

## Results

*General data*

A total of 215 osteosarcoma patients admitted to our hospital between January 2001 and Janu-

ary 2012 were included in this study. According to the status of fracture, chemotherapy and surgical methods, these patients were divided into 4 groups, namely group A (73 cases), group B (48 cases), group C (36 cases) and group D (58 cases). The age, gender, ECOG performance status (ECOG PS) score, tumor site, tumor stage, metastatic site, and tumor necrosis rate (Huvos) of the 4 groups are shown in Table 1.

*Overall survival analysis*

Follow up lasted for 60 months and the results showed that the mean overall survival in groups A, B, C and D were 51.6±3.2 months, 52.2±2.6 months, 37.6±4.3 months and 53.1±4.1 months, respectively. Log-rank analysis displayed that there was no significant difference in survival between group A and B or group A and D (p>0.05) (Figure 1A and 1B). Only the survival of group C was significantly different from that of groups A, B and D, with the p value of 0.008, 0.042, 0.010, respectively (Figure 1C, 1D and 1E).

*Tumor-free survival analysis*

No significant difference was observed in overall survival between group A and B or group A and D (37.6±3.9 vs. 42.3±4.2months, p>0.05; 37.6±3.9 vs. 39.7±3.9months. p>0.05) (Figure 2A and 2B). TFS of group C (27.8±6.9 months) was markedly lower than that of group A, B, and D (p=0.012, p=0.002, p=0.008, respectively), and the difference was statistically significant (Figure 2C, 2D and 2E).

*Chemotherapy-related adverse reactions*

In this study, 4 drugs, including doxorubicin, methotrexate, ifosfamide and cisplatin were used for neoadjuvant chemotherapy. The main side effects were nausea and vomiting. In addition, diarrhea, stomatitis, neutropenia, thrombocytopenia, nephrotoxicity, anemia, hepatotoxicity, cerebral



**Table 1.** Demographic and clinical characteristics

| *Characteristics* | *Group A (n=73)* | *Group B (n=48)* | *Group C (n=36)* | *Group D (n=58)* |
|---|---|---|---|---|
| Age (years) | 29.3±6.5 | 27.6±4.8 | 24.7±7.8 | 25.9±6.3 |
| Female/Male | 53/20 | 31/17 | 22/14 | 31/27 |
| Primary site | | | | |
| Proximal tibia | 26 | 18 | 12 | 25 |
| Proximal humerus | 6 | 2 | 2 | 4 |
| Distal femur | 20 | 16 | 11 | 14 |
| Body and proximal femur | 5 | 3 | 2 | 3 |
| Other long bone | 6 | 3 | 2 | 4 |
| Other location | 10 | 6 | 7 | 8 |
| ECOG PS | | | | |
| 0 | 17 | 12 | 12 | 8 |
| 1 | 34 | 22 | 14 | 27 |
| 2 | 8 | 6 | 6 | 19 |
| 3 | 14 | 8 | 4 | 4 |
| Stage | | | | |
| IB | 5 | 3 | 3 | 4 |
| IIA | 8 | 4 | 3 | 19* |
| IIB | 57 | 39 | 29 | 34* |
| III | 3 | 2 | 1 | 1 |
| Sites of metastasis | | | | |
| Lung | 22 | 14 | 9 | 20 |
| No metastasis | 51 | 34 | 27 | 38 |
| Huvos | | | | |
| Grade 1 | 31 | 20 | - | 25 |
| Grade 2 | 20 | 10 | - | 12 |
| Grade 3 | 11 | 9 | - | 13 |
| Not applicable | 11 | 11 | - | 8 |

*p<0.05, compared with group A

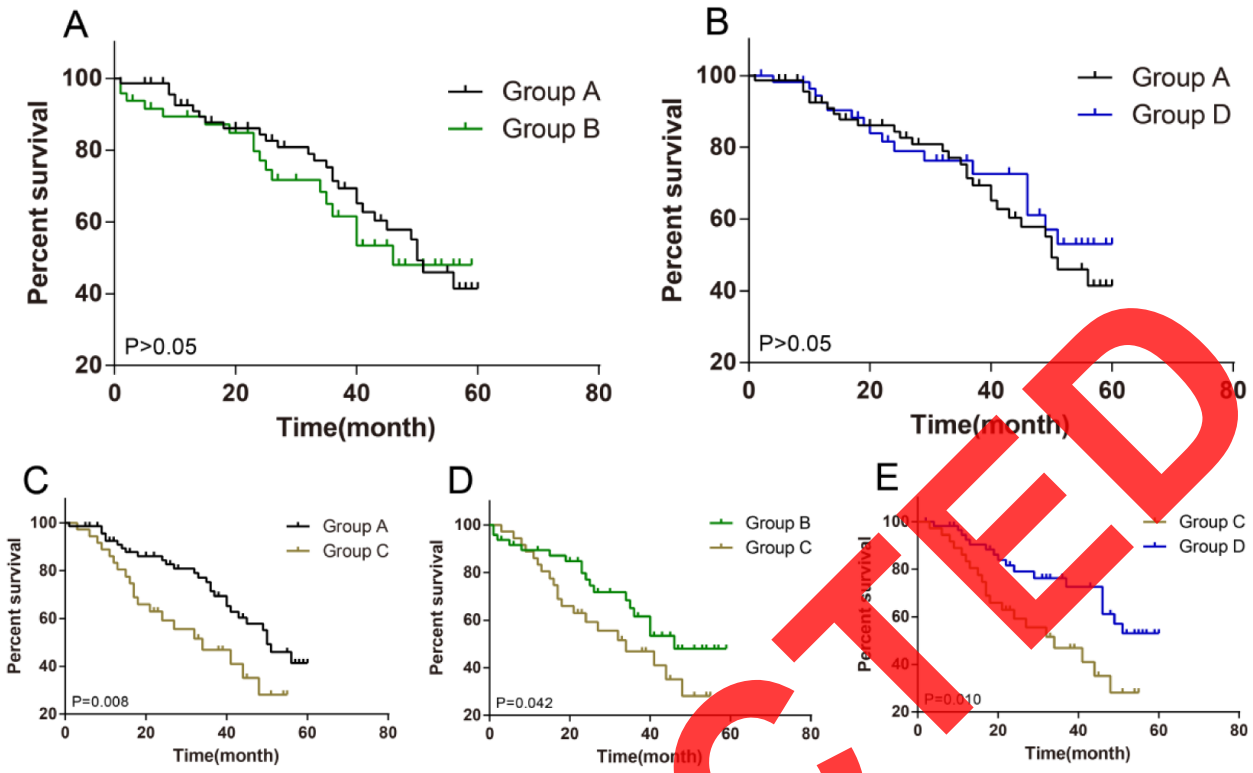


**Figure 1.** Analysis and comparison of overall survival. **A** and **B** show the comparison of survival between group A and B or between group A and D respectively. **C,D** and **E** show the comparison of survival between group C and group A, B and D, respectively. The survival of group C was significantly lower than the above three groups (p=0.008, p=0.042 and p=0.010, respectively).



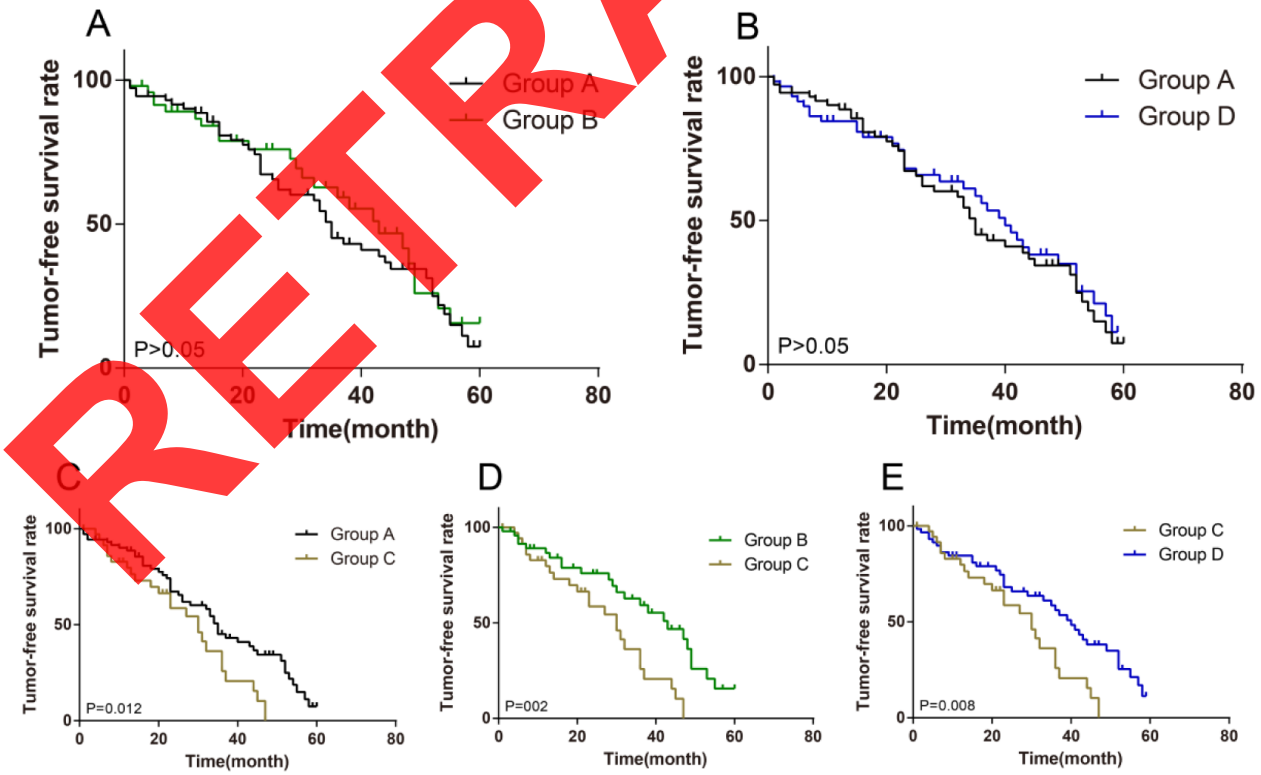


**Figure 2.** Analysis and comparison of tumor-free survival curves. **A** and **B** show the comparison of tumor-free survival between group A and B or between group A and D respectively. **C,D** and **E** show the comparison of tumor-free survival between group C and group A, B and D, respectively. The tumor-free survival of group C was significantly lower than the above three groups (p=0.012, p=0.002 and p=0.008, respectively).

**Table 2.** Adverse events during preoperative chemotherapy

| *Adverse events* | *Group A (n=73)* | *Group B (n=48)* | *Group D (n=58)* |
|---|---|---|---|
| Nausea/vomiting | 51 | 35 | 41 |
| Diarrhea | 11 | 8 | 9 |
| Stomatitis | 43 | 26 | 30 |
| Neutropenia | 36 | 23 | 24 |
| Thrombocytopenia | 33 | 26 | 27 |
| Nephrotoxicity | 12 | 9 | 10 |
| Anemia | 10 | 15* | 6 |
| Hepatotoxicity | 10 | 6 | 9 |
| CNS bleeding | 3 | 1 | 1 |

CNS: central nervous system, *p<0.05, compared with group A. As group C did not receive chemotherapy, no data was recorded for this group.

**Table 3.** Quality of life score

| | *Group A (n=73)* | *Group B (n=48)* | *Group C (n=36)* | *Group D (n=58)* |
|---|---|---|---|---|
| Emotional function | 86.3±10.2 | 75.8±5.2 | 82.1±7.3 | 88.6±11.5 |
| Social function | 82.4±8.5 | 44.8±6.7* | 77.1±8.2 | 83.2±9.9 |
| Mental health | 79.9±8.2 | 70.4±7.2 | 61.2±6.6 | 71.1±6.0 |
| Physical limitations | 74.2±8.9 | 48.3±5.3* | 50.4±7.7* | 78.2±8.9 |
| Body pain | 67.2±5.6 | 68.9±7.2 | 60.5±6.1 | 69.3±7.2 |
| Physical function | 67.6±7.0 | 58.8±6.2 | 57.4±6.8 | 67.2±7.9 |
| General health | 61.6±6.6 | 54.8±5.4 | 42.3±6.3* | 62.3±7.4 |
| Energy | 59.2±7.9 | 49.5±5.2 | 41.0±4.8* | 60.4±7.1 |

*p<0.05, compared with group A

hemorrhage and other adverse reactions were also observed. Among them, anemia was statistically different between the amputation group and limb salvage surgery group. Details are shown in Table 2.

*Comparison of quality of life*

The SF-36 questionnaire was completed by the patients themselves to assess and compare the quality of life through different aspects. The scores of social function and physical limitations in group A were higher than those in group B. The physical limitations, general health and vitality of group A were also higher than those of group C, and the difference was statistically significant. The rest of the items are shown in Table 3.

## Discussion

Osteosarcoma is the most common primary malignant bone tumor. It is invasively localized and prone to metastasis. Local hematoma is easily formed especially in cases complicated by pathological fractures, which is more conducive to tumor cell proliferation and metastasis. Amputation is the standard method for the treatment of osteosarcoma, but the patient's long-term survival rate is only 10-20%, while the amputation surgery also brings serious physical dysfunction to patients, seriously affecting their quality of life [16]. Before the 1970s, we could only perform simple amputation in the treatment of osteosarcoma because the size of the tumor could not be controlled. In recent years, there have been two major advances in the treatment of osteosarcoma: the application of comprehensive treatment based on high-dose chemotherapy and the development of limb salvage surgery which results in a significant reduction in limb amputation rate. However, approximately 90% of patients after limb salvage surgery develop complications, especially infections, prosthesis loosening, and local tumor recurrence, which may lead to the need for further surgery or amputation. In addition to the efficacy of amputation and limb salvage surgery, there are other factors affecting the prognosis of patients with osteosarcoma, including tumor size [17], poor response to chemotherapy [18], and serum lactate dehydrogenase levels [19,20], unhealed unstable fractures, anatomic location [6], age [21], and histological type.

Neoadjuvant chemotherapy was first performed by Rosen et al. [22] in 1976 and acted as an important aid in the treatment of osteosarcoma. Preoperative chemotherapy can provide sufficient time for limb salvage surgery and early elimination of small metastases, which could promote clear boundary of tumors and reduce the vitality of tumor cells, thus facilitating the successful limb salvage. Additionally, chemotherapy regimens can be revised according to the patient's response to postoperatively reduce the recurrence rate. Studies have shown that neoadjuvant chemotherapy can improve 60% of patients with osteosarcoma of the limbs and save most patients from amputation [23]. High-dose of methotrexate combined with cisplatin can delay surgery while ifosfamide can enhance the efficacy of preoperative chemotherapy.

In our study, no obvious difference was found in postoperative survival and TFS between patients with limb salvage surgery (group A) and patients with amputation (group B). This was consistent with a previous report by Abudu et al. [5] which included 40 cases of osteosarcoma patients with pathological fracture. However, Scully et al. [13] found that the rate of local recurrence of limb salvage surgery was markedly higher than that of patients with amputation. In another study of 46 patients with osteosarcoma and pathological fractures, 2 patients in the limb salvage group experienced recurrence while only one patient in the amputation group experienced recurrence [24]. In addition, no statistical difference was shown in the postoperative survival and TFS between fracture patients (group A) and those without fractures (group D).

It is worth mentioning that patients with neoadjuvant chemotherapy (group A, group B, and group D) had longer postoperative survival and TFS than those without chemotherapy. Based on the above results, we believe that with the application of neoadjuvant chemotherapy, osteosarcoma complicated by pathological fracture is no longer an absolute indication for amputation. Patients with high-grade malignant osteosarcoma complicated by fracture should be treated with limb salvage based on neoadjuvant chemotherapy. Our point of view is the same as that of Papagelopoulos et al. [25].

Nausea and vomiting are major chemotherapy-related adverse reactions. We found no statistical difference in adverse reactions between the amputation and limb salvage group except for anemia. At the same time, there was no significant difference in adverse reactions between patients with and without fracture. In the comparison of quality of life, social function and physical limitation in the limb salvage group were better than those in the amputation group. Meanwhile, physical limitation, general health and vitality in the chemotherapy group were better than those in the non-chemotherapy group. Ottaviani et al. have also demonstrated that no significant differences are observed in quality of life, mental health, social status, employment and marriage between patients with limb salvage and patients treated with amputation [26]. Therefore, we suggest that osteosarcoma patients complicated by pathological fractures should receive neoadjuvant chemotherapy combined with limb salvage surgery.

In summary, neoadjuvant chemotherapy provides good chances for limb salvage therapy in patients with osteosarcoma complicated by pathological fractures. Neoadjuvant chemotherapy combined with limb salvage preserves limbs on the premise of ensuring survival rate, and does not increase the local recurrence and metastasis rate. Meanwhile, it could improve the quality of life of patients.

## Conclusion

Neoadjuvant chemotherapy combined with limb salvage surgery is effective for patients with osteosarcoma complicated by pathological fractures, which is worth of recommendation.

## Conflict of interests

The authors declare no conflict of interests.



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