ORIGINAL ARTICLE

Marginal resection for osteosarcoma with effective preoperative chemotherapy

Xiu-chun Yu MD, Ming Xu MD, Ruo-xian Song MD, Song-feng Xu MD

Department of Orthopaedics, The General Hospital of Jinan Military Region, Jinan, China

Objective: To present the clinical results of marginal resection with effective preoperative chemotherapy for treatment of osteosarcoma.

Methods: Thirty-eight patients (20 male and 18 female, average age 17 years), underwent marginal resection after confirmation of effective preoperative chemotherapy between 1999 and 2008 and the results were analyzed retrospectively. The distal femur was involved in 22 cases, proximal tibia in 11, proximal humerus in 4, and proximal fibula in 1. Thirty-seven patients were stage IIB and one IIIB. Twenty-nine patients were treated with the DIA, and 9 with the MMIA protocol. Twenty-one patients underwent tumor resection and bone allograft transplantation. The epiphysis was preserved in 9 patients, and not in the other 12. Eleven patients underwent tumor resection and prosthetic replacement, and 4 tumor resection with autograft implantation. One patient underwent tumor resection and allograft with preservation of the epiphysis; another underwent marginal tumor resection only.

Results: All patients received effective preoperative chemotherapy. At a median follow-up of 52 months, local recurrence had developed in one patient (2.6% local recurrence rate). Pulmonary metastases developed in 9 patients (23.7%). Five patients died of metastases, one died of intracranial hemorrhage due to thrombocytopenia caused by postoperative chemotherapy. The overall 2-year survival rate was 87.3%, and event-free survival rate 75.5%. The overall 5-year survival rate was 74.7%, and event-free survival rate 60.8%. Excellent to good function of affected limbs was achieved in 60.5%.

Conclusions: With careful preoperative evaluation and effective preoperative chemotherapy marginal resection of osteosarcoma can produce good results. Marginal resection of osteosarcoma should be performed by an experienced surgeon who is familiar with the limb salvage rules for osteosarcoma.

Key words: Osteosarcoma; Chemotherapy, adjuvant; Limb salvage

Introduction

Osteosarcoma occurs mainly in children and adolescents and the 5-year survival rate of patients treated with neoadjuvant chemotherapy and appropriate surgery can be more than 70%¹. Currently, common surgical techniques for treating osteosarcoma include wide resection of tumor and reconstruction with prosthesis, osteoarticular allograft, autoclaved autograft, or a combination of these techniques. Even with effective preoperative chemotherapy, most surgeons would not consider marginal resection of osteosarcoma because of the risk of recurrence. However some surgeons have reported the possibility of treating osteosarcoma with marginal resection and effective chemotherapy^{2–5}. Since January 1999 we have treated

osteosarcoma with marginal resection in patients in whom preoperative chemotherapy was assessed to be effective. The purpose of this study was to evaluate the clinical outcomes of marginal resection for limb osteosarcoma.

Materials and methods

Between January 1999 and February 2008, 38 patients with osteosarcoma, (20 male and 18 female with an average age of 17 years), underwent marginal resections with effective preoperative chemotherapy. The distal femur was involved in 22 patients, proximal tibia in 11, proximal humerus in 4, and proximal fibula in 1. Thirty-seven patients had stage IIB, and one had stage IIIB, osteosarcoma. Neoadjuvant chemotherapy and limb salvage surgery with marginal resection of osteosarcoma was adopted in these patients. Chemotherapy drugs included high-dose methotrexate (HD-MTX, 10 g/m²), adriamycin (ADR, 30 mg/m² × 3), ifosfamide (IFO, 2.0 g/m² × 5) and cisplatin (DDP, 120 mg/m²). Two

Address for correspondence Xiu-chun Yu, MD, Department of Orthopaedics, The General Hospital of Jinan Military Region, Jinan, China 250031 Tel: 0086-531-51666644; Fax: 0086-531-51666644; Email: yxch36@yahoo.com.cn

Received 8 January 2009; accepted 8 March 2009.

DOI: 10.1111/j.1757-7861.2009.00037.x

protocols were adopted in our patients, one was the MMIA protocol which includes HD-MTX, ADR and IFO, the other was the DIA protocol which includes DDP, ADR and IFO. Twenty-nine patients were treated with the DIA, and nine with the MMIA, protocol. Postoperatively, chemotherapy with the same drugs and doses as preoperatively was repeated for 6–10 courses.

Documentation of a good chemotherapeutic response

Evidence of a good chemotherapeutic response consisted of alleviation of pain, shrinkage and hardening of any local mass, an improved range of motion in the affected limb, reduction in serum alkaline phosphatase (AKP) and lactate dehydrogenase (LDH) concentrations to within the normal range; sclerotic changes and clearly defined margins of the lesion as observed on plain radiographs, marked shrinkage of tumor, diminishment of marrow edema and remarkable shrinkage of any extension of the tumor into soft tissue on magnetic resonance imaging (MRI). Without these changes, a poor chemotherapeutic response was determined.

Calculation of tumor cell necrosis rate (TCNR)

The TCNR was calculated according to our domestic methods⁶, and graded according to the Huvos criteria²: Grade I, little if any identifiable effect; Grade II, areas of acellular tumor osteoid, necrotic, and/or fibrotic material attributable to the effect of chemotherapy, with other areas of histologically viable tumor; Grade III, predominant areas with acellular tumor osteoid, as well as necrotic and/or fibrotic material attributable to the effect of chemotherapy, with only scattered foci of histologically viable tumor cells; Grade IV, no histologic evidence of viable tumor within the specimen.

Timing and techniques of surgery

After two cycles of preoperative chemotherapy, limb salvage operations were performed. Limb-salvaging surgery was conducted by means of intentional marginal resection, which preserves important structures such as the major neurovascular bundles, tendons, ligaments, muscles and the epiphysis. Twenty-one patients underwent tumor resection and bone allograft implantation. Among these patients, the epiphysis was preserved in nine and not in the other twelve. Eleven patients underwent tumor resection and prosthetic replacement, and four tumor resection with autograft implantation. One patient underwent tumor resection and allograft transplantation with preservation of the epiphysis; another underwent marginal tumor resection only.

Observation and follow-up

All patients were followed up regularly as outpatients. The patients were informed that data from them would be submitted for publication, and gave their consent for this. Limb function and presence of local recurrence and metastasis were recorded at each visit. The functions of the affected limb was evaluated using the revised 30-point functional classification system established by the International Society of Limb Salvage and the Musculoskeletal Tumor Society⁷. This functional score includes six parameters: pain, function, emotional acceptance, use of walking supports, walking ability, and gait. Each parameter is given a value ranging from 0 to 5 according to specific criteria. The individual scores are added together to obtain an overall functional score, with a maximum of 30 points. Event-free survival was defined as the time from a patient's entry into this study to his or her death with the disease in remission, local recurrence of disease after definitive surgery, development of distant metastases, or last contact. Survival was defined as the time from entering study until death or last contact.

The Kaplan-Meier method was used for survival analysis. All statistics were performed with SPSS 11.0 software (Chicago, USA) and $P < 0.05$ was regarded as significant.

Results

All patients completed preoperative chemotherapy. The histological response to preoperative chemotherapy was classified as grade II (6), grade III (13) and grade IV (19). All patients underwent postoperative chemotherapy. One died from intracranial hemorrhage due to thrombocytopenia caused by postoperative chemotherapy.

With a follow-up ranging from 14 to 117 months (mean, 52 months), nine patients were followed up for over 5 years, eleven for 3–5 years, nine for 2–3 years and nine for 1–2 years. One patient had a local recurrence at 24 months after surgery; the local recurrence rate for this group is 2.6%. Pulmonary metastases developed in nine patients (23.6%) during follow-up, five died and four are alive with tumor, one patient died from a complication of postoperative chemotherapy. The overall 2-year survival rate was 87.3%, and event-free survival rate 75.5%. The overall 5-year survival rate was 74.7%, and event-free survival rate 60.8% (Figs. 1, 2).

Functional evaluation of these patients was classified according to the criteria of the International Society of Limb Salvage and the Musculoskeletal Tumor Society⁷. There were fourteen patients with excellent limb function, nine with good, eleven with fair and four with poor. The combined excellent and good rate for affected limbs was 60.5%. Among the ten patients who underwent limb

Figure 1 Overall survival of patients with osteosarcoma treated in our hospital.

salvage operations which preserved the epiphysis, three could flex the affected knee joint $\geq 110^\circ$ (Figs. 3–6), two 90° – 110° , four 60° – 90° , and one $<60^\circ$. The length of the affected limb equaled that of the unaffected limb in four patients, was 2 cm shorter than the other limb in five, and 5 cm shorter in one.

Discussion

Treatment of osteosarcoma by surgery alone results in poor 5-year survival rates (20%)^{8,9}. With the introduction of neoadjuvant chemotherapy, the prognosis has improved dramatically, 49%–76% survival rates during 5-to 8-year follow-up periods having been reported^{8,9}.

Figure 2 Event-free survival of patients with osteosarcoma treated in our hospital.

Figure 3 Pre-chemotherapy radiograph of a patient with osteosarcoma of the distal femur.

This shows an osteolytic lesion accompanied by osteogenic destruction with periosteal reaction and a soft tissue mass.

Neoadjuvant chemotherapy has permitted surgeons to use less radical resection and thus to preserve limb function. Low recurrence rates (5.4%–15.5%) have been achieved by limb-sparing surgery with wide resection combined with chemotherapy⁸.

Figure 4 Post-chemotherapy radiograph of the distal femur of patient shown in figure 3.

This shows sclerotic changes and marked shrinkage of tumor with good margins and no soft tissue mass.

Figure 5 Radiograph at 96 months post-surgery.

This patient underwent tumor resection and inactivated bone implantation with preservation of the epiphysis. The radiograph shows that after an intramedullary nail and screws had been inserted into the residual epiphysis and the bone defect filled with bone cement (no barium) the implanted bone healed.

The current standard treatment for osteosarcoma includes neoadjuvant chemotherapy and limb-sparing surgery. Currently two methods of tumor resection exist: wide resection and marginal resection. Wide resection often requires excising more normal soft and bone tissue around the osteosarcoma, leading to more operative complications and poorer limb function. Marginal resection usually results in a poor outcome for patients with osteosarcoma when the chemotherapeutic effect has been difficult to evaluate. Marginal resection of osteosarcoma should be performed only if the preoperative chemotherapeutic effect has been documented as a good response. However, to reduce the risk of local recurrence, the tumor should be excised marginally only around structures that are important for limb function (e.g. major vessels and nerves). Muscles should be excised at least 1 cm from the tumor.

The aims of marginal resection of osteosarcoma are to reduce bone and soft-tissue defects, to reduce occurrence of limb-sparing complications and to improve limb

function without increasing the risk of local recurrence or jeopardizing the patient's life. Since 1987 Tsuchiya *et al.* have treated 21 patients with osteosarcoma with intentional marginal resection after good results from chemotherapy^{5,9,10}. Four patients with lesions in the proximal fibula were treated by marginal resection of the fibular head, which preserved the common peroneal nerve, lateral collateral ligament, and biceps femoris tendon. The epiphysis was preserved in eight patients, and the bone defect reconstructed by distraction osteogenesis. Joint resection (resection of one or both epiphyses) was performed in nine patients. As for reconstruction, liquid nitrogen-treated or autoclaved bone graft and prosthesis composites were used in two patients, liquid nitrogen-treated bone graft in one, osteochondral allograft in one, and megaprotheses in five patients. No local tumor recurrence was seen at mean follow-up of 97 months. Pulmonary metastases developed in four patients at a mean follow-up of 35.8 months. Three patients had no evidence of disease and 17 patients remained disease-free. One patient died of hepatitis. The overall cumulative survival rate was 100% and the event-free survival rate was 78%. The overall average function of the 21 patients was evaluated as 93% of normal. So they thought it was possible to treat osteosarcoma by marginal resection along with good preoperative chemotherapy.

Among 64 patients with osteosarcoma treated with neoadjuvant chemotherapy and surgery in our hospital since January 1999, 38 patients underwent marginal resection and were followed up for a mean time of 52 months (12–99 months). One patient recurred locally at 24 months after surgery (Figs. 7–10, local recurrence rate

Figure 6 Photograph of patient in knee flexion.

Photo taken 96 months post-surgery shows the knee function is normal.

Figure 7 Pre-chemotherapy radiographs of a patient with osteosarcoma of the distal femur.

These show an osteogenic lesion accompanying by periosteal reaction and a soft tissue mass.

2.6%). Pulmonary metastases developed in nine patients (23.6%) during follow-up, five died and four remain alive with tumor, one patient died from chemotherapy complication. The 2-year overall survival rate was 87.3% and the 2-year event-free survival rate 75.5%. The 5-year overall survival rate was 74.7% and the 5-year event-free survival rate 60.8%. We think that marginal resection is an option for osteosarcoma with good respond to preoperative chemotherapy because our data is similar to that reported by others^{8,11–16} (Table 1).

Nowadays, most think that identifying the indications for marginal resection of osteosarcoma is a crucial issue; if not accurate, a lethal outcome can occur. The chemotherapeutic effect and surgical margin are the most important factors for osteosarcoma prognosis, but Tsuchiya *et al.* believe that the former is a more important justification than the latter for limb-salvaging procedures⁵. Efficient chemotherapy improves prognosis and minimizes the surgical margin. So it is most important to confirm the effectiveness of chemotherapy, and the accu-

racy of preoperative assessment of the extent of intramedullary tumor, when a smaller resection margin is being considered. When a good response is documented by at least two of four radiological methods, including plain radiography, MRI, angiography, and ²⁰¹Ti scintigram, more than 90% tumor necrosis can be expected and minimized resection can be performed¹⁰. We confirmed preoperative chemotherapeutic effects by not only plain radiography and MRI but also by changes in clinical appearance and serum LDH and AKP concentrations. We considered evidence of a good chemotherapeutic response to consist of disappearance of pain, shrinkage and rigidity of any local mass, normal range of movement of the affected limb, serum AKP and LDH reduced to within the normal range; sclerotic changes and clearly defined margins of the lesion visible on plain radiographs, marked shrinkage of tumor, diminishment of marrow edema and marked shrinkage of any extension of the tumor into soft tissue on MRI. If not, we determined that the chemotherapeutic response was poor.

Another factor which affects clinical outcome of osteosarcoma is tumor volume. The patient prognosis is likely to be satisfactory if the tumor volume is less than 150 ml¹⁷. So we should pay attention to tumor volume changes during chemotherapy while assessing the

Figure 8 Post-chemotherapy radiograph of the distal femur of patient shown in figure 7.

This shows sclerotic changes and marked shrinkage of tumor with good margins and no soft tissue mass.

Figure 9 Post-operative radiograph of patient shown in figures 7 and 8.

This shows the prosthesis location is normal.

Figure 10 Photo taken 24 months post-operatively of patient with osteosarcoma who underwent tumor resection and prosthesis replacement.

This shows tumor recurrence with a large soft tissue mass.

Table 1 Event-free survival in patients with osteosarcoma from the literature

Author	No. of patients	Follow-up time	5-year survival	5-year event-free-survival	Year of publication
Le Deley MC <i>et al.</i> ¹¹	234	77 months	76%	62%	2007
Basaran M <i>et al.</i> ¹²	45	64 months	48.2%	41.9%	2007
Bacci G <i>et al.</i> ¹³	1126	18.6 years	66%	55%	2007
Bacci G <i>et al.</i> ¹⁴	754	11 years	67%	60%	2007
Petrilli AS <i>et al.</i> ¹⁵	178	61 months	60.5%	45.5%	2006
Ferrari S <i>et al.</i> ¹⁶	182	55 months	77%	64%	2005
Bacci G <i>et al.</i> ⁸	1148	14.8 years	66%	57%	2005

chemotherapeutic effect if determining whether a marginal resection is to be performed. In our experience, marginal resection should be performed by an experienced surgeon who is familiar with handling limb salvage in cases of malignant bone tumor.

In conclusion, no adverse effects on survival or local recurrence having been found, our outcomes indicate that it is possible to perform marginal limb-sparing surgery in conjunction with effective chemotherapy for limb osteosarcoma. The long-term outcomes remain to be further proven.

References

1. Bacci G, Longhi A, Bertoni F, *et al.* Primary high-grade osteosarcoma: comparison between preadolescent and older patients. *J Pediatr Hematol Oncol*, 2005, 27: 129–134.
2. Huvos A. Pathologic assessment of preoperative (neoadjuvant) chemotherapy. In: Huvos, Andrew G., eds. *Bone Tumors: Diagnosis, Treatment and Prognosis*, 2nd edn. Philadelphia, PA: W.B.Saunders, 1991; 122–128.
3. Canadell J, Forriol F, Cara JA, *et al.* Removal of metaphyseal bone tumours with preservation of the

- epiphysis. Physeal distraction before excision. *J Bone Joint Surg Br*, 1994, 76: 127–132.
4. Amitani A, Yamazaki T, Sonoda J, *et al.* Preservation of the knee joint in limb salvage of osteosarcoma in the proximal tibia. A case report. *Int Orthop*, 1998, 22: 330–334.
 5. Tsuchiya H, Tomita K, Mori Y, *et al.* Marginal resection for osteosarcoma with caffeine assisted chemotherapy. *Clin Orthop Relat Res*, 1999, 358: 27–35.
 6. Yu XC, Liu XP, Zhou Y, *et al.* Feasibility of treatment for osteosarcoma with combined chemotherapy project: primary report (Chin). *Shiyong Yi Yao Za Zhi*, 2003, 20: 217–219.
 7. Enneking WF. Modification of the system for functional evaluation of surgical management of musculoskeletal tumors. In: Enneking WF, ed. *Limb Salvage in Musculoskeletal Oncology*. New York: Churchill Livingstone, 1987; 626–639.
 8. Bacci G, Longhi A, Fagioli F, *et al.* Adjuvant and neoadjuvant chemotherapy for osteosarcoma of the extremities: 27 year experience at Rizzoli Institute, Italy. *Eur J Cancer*, 2005, 41: 2836–2845.
 9. Kanazawa Y, Tsuchiya H, Nonomura A, *et al.* Intentional marginal excision of osteosarcoma of the proximal fibula to preserve limb function. *J Orthop Sci*, 2003, 8: 757–761.
 10. Hayashi K, Tsuchiya H, Yamamoto N, *et al.* Functional outcome in patients with osteosarcoma around the knee joint treated by minimised surgery. *Int Orthop*, 2008, 32: 63–68.
 11. Le Deley MC, Guinebreière JM, Gentet JC, *et al.* SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. *Eur J Cancer*, 2007, 43: 752–761.
 12. Basaran M, Bavbek ES, Saglam S, *et al.* A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. *Oncology*, 2007, 72: 255–260.
 13. Bacci G, Forni C, Longhi A, *et al.* Local recurrence and local control of non-metastatic osteosarcoma of the extremities: a 27-year experience in a single institution. *J Surg Oncol*, 2007, 96: 118–123.
 14. Bacci G, Longhi A, Forni C, *et al.* Neoadjuvant chemotherapy for radioinduced osteosarcoma of the extremity: the Rizzoli experience in 20 cases. *Int J Radiat Oncol Biol Phys*, 2007, 67: 505–511.
 15. Petrilli AS, de Camargo B, Filho VO, *et al.* Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: prognostic factors and impact on survival. *J Clin Oncol*, 2006, 24: 1161–1168.
 16. Ferrari S, Smeland S, Mercuri M, *et al.* Neoadjuvant chemotherapy with high-dose Ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. *J Clin Oncol*, 2005, 23: 8845–8852.
 17. Bieling P, Rehan N, Winkler P, *et al.* Tumor size and prognosis in aggressively treated osteosarcoma. *J Clin Oncol*, 1996, 14: 848–858.