Osteosarcoma Around the Knee Treated With Neoadjuvant Chemotherapy and a Custom-designed Prosthesis

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abstract
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This article describes a novel approach using high-dose neoadjuvant chemotherapy with wide tissue resection and a specially designed artificial joint in 104 patients with stage IIB osteosarcoma near the knee. Sixty-four lesions were located at the distal femur, 39 at the proximal tibia, and 1 invaded the proximal tibia from the distal femur. Pathological fracture was present in 9 patients. Three courses of high-dose methotrexate, doxorubicin, and ifosfamide were administered preoperatively, and 6 courses were administered postoperatively. Preoperative radiographs and magnetic resonance images were obtained to determine the required tumor resection range and prosthesis size. Osteotomy of 3 cm of normal bone outside the tumor and wide resection of normal peripheral soft tissue were performed. Reconstruction with a rotary hinge or simple hinge prosthesis, as appropriate, was then performed. The Musculoskeletal Tumor Society 93 scoring system was used to evaluate limb function 6 months postoperatively. At final follow-up, recurrence, complication, survival, and amputation rates were 4%, 18%, 85%, and 4%, respectively. No recurrences were observed at the ends of amputated bones. Complications included infection (6%), nerve injury (3%), and prosthesis-related events (2% dislocation, 3% breakage, and 1% dislocation-related). Mean Musculoskeletal Tumor Society 93 score was 28 points, which indicated an excellent functional outcome. The low recurrence rate is attributed to the efficacy of the chemotherapy and the accuracy of the margin of resection.

Effective chemotherapy reduces the risk of tumor metastasis and clarifies the tumor margin. Accurate identification of the resection margin reduces the risk of local recurrence.

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Figure: Preoperative anteroposterior (A) and lateral (B) radiographs. Anteroposterior radiograph 7 years postoperatively showing fusion of the femur with the prosthesis with the allograft. Function of the right knee was excellent (C).
Osteosarcoma, a primary malignant tumor of the skeleton characterized by formation of immature osteoid tissue, is the most common bone cancer in children and adolescents but is also observed in older patients. Most tumors that occur in children are high-grade. The most frequently used surgical techniques for the treatment of osteosarcoma near the knee include resection, resection followed by reconstruction, and, in indicated cases, amputation of the extremity. Chemotherapy is also necessary to manage micrometastatic disease, which is present but not detectable in most patients at diagnosis. Due to technical advances in diagnostic imaging, neoadjuvant chemotherapy and improved surgical methods, limb-salvage therapy is widely regarded as an acceptable alternative to amputation for most patients.

Following primary tumor resection, reconstruction techniques currently include the use of allografts, modular or custom prostheses, composite allograft prostheses, rotationplasty, and arthrodesis. Custom prosthetic reconstruction has been helpful for the treatment of tumors located at the proximal tibia. Although associated with greater functional and physiological benefits compared with limb amputation, limb-salvage therapies involving prosthetic reconstruction also result in massive bone and soft tissue loss. Consequently, patients receiving such therapies may sustain significant degrees of impairment and disability. Furthermore, survival rates are predicted to be lower due to possible tumor recurrence. A need exists for more effective, limb-sparing treatment approaches for patients with osteosarcoma near the knee joint.

This article describes the use of a novel approach for the treatment of osteosarcoma near the knee joint. The approach comprises high-dose neoadjuvant chemotherapy, wide tissue resection, limb-salvaging reconstructive surgery, and the use of a specially designed artificial joint.

**Materials and Methods**

**Patients**

This retrospective cohort study included 104 patients with osteosarcoma near the knee joint who underwent surgical resection of the tumor followed by reconstruction with a specially designed prosthesis between April 2003 and June 2010 at the authors’ institution. Of these patients, 70 were males and 34 were females. Mean age was 20 years (range, 8-61 years). Informed consent was obtained from all patients, and the study was approved by the ethics committee. Mean follow-up was 40.3±20.1 months (range, 12-94 months). Sixty-four lesions were located at the distal femur, 39 were located at the proximal tibia, and 1 invaded the proximal tibia from the distal femur. Pathological fracture occurred in 9 patients.

Exclusion criteria were: (1) encircling of important vessels and nerves by the tumor such that en bloc tumor resection was difficult; (2) insufficient soft tissue to cover the replaced joint after tumor resection; (3) inability of the patient to tolerate chemotherapy or a poor response to chemotherapy, such that the prognosis was considered unsatisfactory; (4) myelosuppression in response to chemotherapy; and (5) active infection.

**Preoperative Imaging and Diagnosis**

In all patients, the initial diagnosis of osteosarcoma was obtained from preoperative radiograph and magnetic resonance imaging (MRI) findings, and the diagnosis was confirmed by aspiration biopsy and pathological test findings. Pretreatment osteosarcoma staging was then performed; all patients were diagnosed with osteosarcoma stage IIIB. Radiographs or computed tomography scans determined the absence or presence of metastasis. Magnetic resonance imaging was used to assess chemotherapy effectiveness and determine readiness for surgical resection. T1-weighted MRIs were used to assess whether the tumor size was reduced in the medullary cavity and whether fat clearance existed between the bone cortex, periosteal reaction boundary, and the surrounding soft tissue. T2-weighted MRIs were used to assess whether edema in the medullary cavity and the surrounding soft tissue had resolved. If these chemotherapy effectiveness signs were observed, surgical resection was scheduled. If not, patients received an additional 1 to 2 courses of chemotherapy. Magnetic resonance imaging was also used to measure the scope of resection and to facilitate prosthesis design.

**Neoadjuvant Chemotherapy**

The current chemotherapeutic approach involved the administration of 3 agents at dosages higher than those used in traditional T-series regimens over a 5-day period. This approach was efficacious in Chinese patients with osteosarcoma in the current study. Each course of chemotherapy comprised 2 g/m² of ifosfamide (days 1-5), 8 g/m² of methotrexate (day 3), and 40 mg/m² of doxorubicin (5 day 5) administered intravenously every 3 weeks. Three courses were administered prior to salvage surgery unless imaging indicated no response to the chemotherapy, and 6 courses were administered post-operatively.

**Prosthesis Design**

The scope of resection was not determined until the effectiveness of preoperative chemotherapy was confirmed. Preoperative radiographs and MRIs of the femur or tibia were used to determine the necessary prosthesis size, and the growth potential of the patient was considered. Factors such as the size of the knee joint and the patient’s age were considered when selecting the type of prosthesis and when determining the stem length and diameter of the tibial component. An appropriately sized stem diameter was essential to reduce the possibility of stem breakage.

A rotary hinge prosthesis (for adults) or simple hinge prosthesis (for adoles-
cens) was selected on the basis of the knee joint perimeter. Thirty-four artificial joints were provided by Link Orthopedics, Ltd, (Beijing, China) a subsidiary of the artificial joint maker Waldemar Link (Hamburg, Germany), and 70 artificial joints were provided by the Beijing Lidakang Technology Co, Ltd (Beijing, China).

An extendible open trauma prosthesis was used for 13 patients younger than 14 years and with tumors of the distal femur. Mean length of extension was 3 cm.

SURGICAL TECHNIQUE
Salvage surgery was not performed until the effectiveness of preoperative chemotherapy was confirmed. Wide tumor resection, performed along the shaft, included 3 cm of normal bone outside the tumor. Wide soft tissue resection was also performed. For tumors located in the distal femur, artificial joint replacement was performed after wide tumor resection. For tumors located in the proximal tibia, artificial joint replacement and patellar tendon reconstruction were performed after wide tumor resection. Tumor resection was carefully performed to reduce the risk of malignant cell dissemination and tumor seeding. If the soft tissue encircling the prosthesis was in poor condition, the medial head of the gastrocnemius muscle was shifted and repaired. After applying a compressive dressing, the affected limb was placed in a neutral abduction position with the knee slightly flexed. The drainage tube was removed if the amount of fluid drained was less than 50 mL. Anticoagulation therapy with low-molecular-weight heparin sodium was routinely administered for the first 7 postoperative days. Isometric contraction exercises were initiated during the early postoperative stage, and knee flexion exercises were initiated 3 weeks postoperatively.

Follow-up and Evaluation
All patients visited the outpatient department. The Musculoskeletal Tumor Society (MSTS) 93 scoring system was used to evaluate limb function 6 months postoperatively. This scoring system assigns numerical values of 0 to 5 in the following categories: pain in the reserved limb, limb activity, grade of patient satisfaction, need for external support, walking ability, and gait.

RESULTS
Clinicopathological findings for the 104 patients with stage IIB osteosarcoma near the knee are summarized in Table 1. Complications, osteosarcoma recurrence, and survival and amputation rates for these patients are presented in Table 2. Prosthesis-related complications occurred in 14 patients. Tumor recurrence at the local soft tissue was observed in 4 patients, and amputation was performed for these patients after the administration of chemotherapy. No tumor recurrence was observed at the ends of amputated bones. Pathological fractures healed after the administration of chemotherapy, and patients with pathological fractures survived. Seven patients with pulmonary metastases survived. Sixteen patients died due to a metastasized osteosarcoma tumor. The total survival rate was 84.6%. A case of successful limb-salvage surgery for osteosarcoma of the distal right femur is shown in Figure 1.

Infection Management
Postoperatively, early-stage prosthetic joint infection occurred in 3 patients, and delayed infection occurred in 3 other patients. All infections were deep. Limb amputation was performed in 1 patient with early infection because he could not afford the cost associated with additional limb preservation procedures. In all other patients, the prosthesis was removed after identifying the infection, and bone cement containing vancomycin was placed intraoperatively. When routine blood test findings (erythrocyte sedimentation rates, and C-reactive protein values) had normalized (range, 3–6 months postoperatively), revision surgery was performed. Intraoperative quick-frozen section biopsy was performed for soft tissue surrounding the prosthesis to evaluate the extent of inflammatory cell infiltration. The bone cement
was then removed, and a new prosthesis was implanted. Revision surgery was performed successfully in all 6 patients. A case illustrating the successful management of an infection is shown in Figure 2.

Prosthesis Breakage

Breakage of the root of the stem was observed 18 months postoperatively in 1 patient, 20 months postoperatively in a second patient, and 72 months postoperatively in a third patient. One-stage prosthesis removal and revision surgery were performed successfully in all 3 cases. Successful revision surgery for a prosthesis breakage is shown in Figure 3.

Prosthesis Dislocation Due to Mechanical Wearing and Loosening

Prosthesis dislocation caused by mechanical wearing occurred in 2 patients. In each of these patients, dislocation was observed more than 12 months postoperatively. One-stage liner change and reduction was performed in each patient. No loosening of the prosthesis was observed in a patient who received limb-salvage therapy.

Nerve Injury

Common peroneal nerve injury was found in 2 patients in whom the dorsal flexion of the toes and ankle joint was limited. Numbness occurred on the lateral side of the leg in 1 other patient. In all 3 patients, recovery from nerve injury was complete within 3 months postoperatively.

Functional Scoring

All patients were scored by the MSTS 93 system. Mean score was 28 points (range, 19-30 points).

DISCUSSION

The current approach includes a novel high-dose neoadjuvant chemotherapeutic regimen, wide resection of the bone and soft tissue, and a specially designed artificial joint. This study included 104 patients. The recurrence rate was low (4%) compared with other studies involving similar patients. This low recurrence rate is most likely attributable to the design of the neoadjuvant chemotherapy and to the use of extensive tissue resection. Also notable were the low rates of complication (18%) and amputation (4%) and the high survival (85%) rate. Furthermore, few prosthesis-related events, such as dislocation (2%), breakage (3%), or dislocation-related incidents (1%), were observed. Further studies of this approach to limb-salvage therapy are needed.

Custom-designed prostheses have several advantages over traditional modular prostheses. First, the tibia prosthesis stem (intramedullary part) would be matched perfectly with the cavity of the tibia because of accurate preoperative measurements. In the current study, preoperative imaging was obtained to determine the diameter of the medullary cavity of the tibia to design an appropriately sized prosthesis stem so that it perfectly matched the cavity diameter. In contrast, the diameter of the stem of the traditional modular prosthesis is not as well matched to the diameter of the medullary cavity of the tibia. Second, the custom-designed prosthesis allows a smoother transition from bone to prosthesis, which prevents the formation of stress concentration points and reduces...
the risk of loosening or abrasion. A third advantage relates to the risk of infection and the complications of anesthesia, both of which increase with operative time. The time required for reconstruction with a custom-designed prosthesis is significantly shorter than that for reconstruction with the traditional modular prosthesis. However, the custom-designed prosthesis requires careful preoperative measurements based on MRI findings. If these measurements are not accurate, the likelihood of successful surgery is poor. In such situations, the risk of a failed surgery is reduced by reconstruction with the modular prosthesis.

The primary goals of limb-sparing procedures are to avoid local recurrence, reduce mortality, and preserve limb function. Zhang et al\(^\text{16}\) reported that specially designed prostheses may achieve satisfactory postoperative limb function and good quality of life. However, the 4-year tumor-free survival rate reported by Zhang et al\(^\text{18}\) was 55%, and the rate of local recurrence was 10%. Mean follow-up in the current study was 40 months; 88 patients survived without tumor recurrence and 4 patients had local recurrence. Each patient in the current study underwent MRI examination preoperatively, and each prosthesis was designed according to the MRI image of the tumor. Osteotomy, including 3 cm of normal bone outside the tumor and wide resection of normal peripheral soft tissue, was performed to ensure a low local recurrence rate.

Although standard chemotherapeutic regimens for treating osteosarcoma are associated with significant toxicity and long-term complications,\(^\text{17}\) effective chemotherapy is essential to the success of limb-sparing surgeries. The chemotherapeutic regimen selected for the current study ensured a relatively high survival rate and created appropriate conditions for chemotherapy (ie, methotrexate, doxorubicin, and ifosfamide) are common components of T-series regimens used in the treatment of osteosarcoma. However, in the current study, combination chemotherapy involving 5-day courses of these agents was administered to enhance their synergistic pharmacologic actions. In addition, the dose of each agent was increased relative to those used in common T-series regimens. These doses were chosen based on their previously established efficacies for Chinese patients with osteosarcoma.\(^\text{18}\)

Limb-sparing surgery is performed to provide better functional outcomes. Kokavec et al\(^\text{19}\) evaluated the functional outcomes of 3 surgical procedures for the treatment of osteosarcoma around the knee joint: resection of the tibialis anterior with removal of a margin of the proximal fibula, wide resection of the distal femur or the proximal tibia with total knee arthroplasty, and amputation; the functional scores for these procedures were 100, 95, and 80.2, respectively. The difference in the score between patients who underwent wide tumor resection with total knee arthroplasty and those who underwent amputation was statistically significant. Hayashi et al\(^\text{20}\) reported that surgery involving marginal resection of malignant tumors after chemotherapy can achieve satisfactory postoperative function. Nonetheless, controversy remains regarding the relationship between the range of tumor resection and postoperative functional recovery. When the range of tumor resection is large, the rate of local recurrence is low, but loss of function becomes severe.\(^\text{20}\) The current authors performed wide tumor resection instead of marginal resection to decrease the possibility of local recurrence. Wide resection was performed after accurately identifying the tumor range. Pathological tests were performed for all tumor specimens, and no residual tumor tissue was observed at the ends of amputated bones. The 5-year survival rate was 71%. The current findings suggest that limb-sparing reconstructive surgery, including prosthesis replacement, helps facilitate maximal limb function recovery without affecting the survival rate.

After total knee arthroplasty with a specially designed prosthesis, functional recovery of the joint is related to reconstruction of the knee extensor mechanism and to the angle of knee flexion.\(^\text{21}\) Currently, no consensus exists regarding the best method of reconstruction of the extensor mechanism,\(^\text{21}\) which is difficult for patients with malignant tumors of the proximal tibia. repaired the knee extensor mechanism using autologous fascia and obtained satisfactory outcomes. However, the number of patients in the study by Yoshida et al\(^\text{22}\) was relatively small, and follow-up was short. The knee extensor mechanism can also be repaired using the gastrocnemius with the patellar tendon so that satisfactory outcomes are achieved.\(^\text{23}\) In the current study, all patients underwent knee extensor mechanism repair. At the femoral end, joint activity and muscle tone were increased by adjusting the quadriceps tension and changing the
valgus angle of the femoral condyle. At the tibial end, the knee extensor mechanism was restored by shifting the medial head of the gastrocnemius to reconstruct the patellar tendon and by binding the tibial tubercle to the prosthesis with wire. Transposition of the medial head of the gastrocnemius was performed during prosthesis replacement for 6 of 40 cases with osteosarcoma of the proximal tibia, and the outcome was satisfactory. Postoperative limb function was evaluated according to the MSTS 93 scoring system for all patients. Mean score 6 months postoperatively was 28 points, which is higher than the scores reported for other similar surgical procedures, but lower than those reported for unicompartimental replacement, rotational molding, and condylar retention. However, the last 3 procedures are associated with higher patient condition requirements (ie, early tumor detection and localization of the tumor) and a greater possibility of tumor recurrence and are, therefore, unsuitable for wide application.

The overall infection rate in the current study was 5.5%, which is similar to that reported in other investigations of the use of prosthetic devices in limb-sparing reconstruction surgeries for patients with osteosarcoma. Three patients, all of whom had tumors in the distal femur, experienced stem breakage. Several explanations exist for these complications. The first relates to the presence of a genu valgus angle in these patients. Because the junction between the prosthesis and the stem existed at the maximal position of the genu valgus angle, this position is likely to have become a stress concentration point, resulting in stem breakage. In patients who had no genu valgus angle, the prosthesis was not placed at an abnormal angle, so side stress was minimized, and no stem breakage was observed. A second consideration is that the prostheses of patients experiencing stem breakage were made in China (Beijing Lidakang Technology Co, Ltd). Casting technology is used in the manufacture of domestic prostheses, whereas forging technology is used in the manufacture of imported prostheses; this is important because the forged products are more stabilized than the casted products. Lastly, the stem diameter of the prosthesis placed in these 3 patients was 12 mm. In contrast, no stem breakage was observed in a patient whose prosthesis had a stem diameter greater than 12 mm. Although the stem diameter was designed to match the measured diameter of the tibial medullary cavity, it is possible that the risk of stem breakage increases as the root diameter decreases, particularly in patients with a genu valgus angle.

A limitation of the current study is that it did not address the capacity of the custom-designed prosthesis to restore mobility in patients who received an extendible prosthesis or those who underwent revision surgery following infection.

**CONCLUSION**

Using a novel approach involving high-dose neoadjuvant chemotherapy with wide tissue resection and a custom-designed prosthesis for limb salvage surgery in patients with osteosarcoma near the knee was effective and had favorable safety. Furthermore, comparison of the current findings with those reported in the literature suggests that outcomes may be better with the current approach. However, a need exists for head-to-head comparisons of different approaches to determine whether this is true.

**REFERENCES**


