CLINICAL ARTICLE

Neoadjuvant Chemotherapy and Expandable Prosthesis Reconstruction to Treat Osteosarcoma around the Knee in Children

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Objective: Survival and reconstruction in osteosarcoma is quite challenging. The study aimed to investigate the prognosis in patients treated with neoadjuvant chemotherapy and determine the clinical outcomes of expandable endoprosthesis reconstruction in children.

Methods: From January 2009 to December 2014, we retrospectively analyzed 29 skeletally immature children (mean age, 10.5 years; range, 6–15 years) with osteosarcoma around the knee. Of the 29 patients who underwent neoadjuvant chemotherapy and limb salvage surgery, an expandable prosthesis was implanted for reconstruction. No patients were missed during follow-up. The evaluation index involved follow-up time, complication, functional results, and lengthening procedures. The survivorship and recurrence were assessed by GraphPad Software, and the function was evaluated by the Musculoskeletal Tumor Society (MSTS) scoring system.

Results: A mean follow-up time was 8.9 years (range, 6–12 years), and the overall 5-year survival was 89.1% based on Kaplan–Meier analysis. Three patients suffered a relapse and one underwent amputation. Lung metastasis developed in one patient. At 6 months after the operation, patients had a mean MSTS score of 27 points (range, 24–29). Two patients underwent revision surgery, one for implant infection and one for aseptic loosening. Prognosis is correlated with alkaline phosphatase change after treatment.

Conclusions: Chemotherapy scheme and limb salvage can achieve high survival rates. This expandable prosthesis was associated with good function and low complication rates. The character of expandability could be a method to overcome discrepancies in the growth period.

Key words: Child; Expandable prosthesis; Knee; Neoadjuvant chemotherapy; Osteosarcoma

Introduction

Osteosarcoma is the most common primary bone malignant disease, which occurs in seven per one million children a year.[1] The current protocols to treat osteosarcoma include neoadjuvant chemotherapy, postoperative adjuvant chemotherapy, and surgery.[2,3] Although standard chemotherapeutic regimens for treating osteosarcoma are associated with significant toxicity and long-term complications, 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. Chemotherapy is necessary to manage the micrometastatic disease, which is present but not detectable in most patients at diagnosis. Chemotherapy protocols vary in institutions as no standardized method shows a superior prognosis. Meanwhile, limb salvage after tumor resection, particularly in immature patients, is a challenge.[4] The growth of the lower extremity is attributed to 35% and 30% to the epiphyses of

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the distal femur and proximal tibia, respectively.[5] Surgical resection completely removes the lesion with adequate margins. Reduced epiphysis in surgery results in a potential discrepancy.[6] Small anatomic size, high functionality, and mechanical demands of activity in immature patients are also problems.

With the recent availability of multimodal treatment combining imaging, chemotherapy, and surgical techniques, 70%–85% of malignant tumors are efficiently treated with limb salvage. Limb reconstruction after tumor resection includes arthrodeses, megaprosthesis, allografts, and allograft-prosthetic devices.[7–9] The main limitation of arthrodeses is poor activity and appearance. Megaprosthesis and allograft-prosthetic devices are confined to affect the physis.[7] Allografts are hard to match the small anatomic size in immature patients[8] and increase the risk for osteolysis and degenerative arthritis. A rejection reaction is also common.

Prosthetic implantation has been proposed to result in physical improvement. However, unlike other sites, resection of osteosarcoma around the knee causes the loss of bone growth. Expandable prostheses have been designed to overcome these problems.[10] There are positive results reported about the device;[11] although, some studies demonstrate that the expandable prosthesis has high complication and revision rates.[12,13] The complications are aseptic loosening, infection, disable prolong device, and implant fracture. In addition, the failure of the gear mechanism is often reported in the noninvasive expandable prosthesis.

Therefore, we analyzed our experience with neoadjuvant chemotherapy and expandable prosthesis reconstruction. In addition, we investigated: (i) the prognosis in patients treated with this chemotherapy scheme; and (ii) limb salvage and the clinical outcomes of expandable endoprosthesis reconstruction in children.

Patients and Methods

Study Design

We reviewed 29 immature participants (younger than 15 years) with high-grade osteosarcoma around the knee between January 2009 and December 2013 at a single institution. This research has been approved by the Institutional Review Board (IRB) of our institutions (No. P2020026). Principles of all research were followed and all procedures were conducted according to the guidelines established by the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all subjects or, if subjects were under 18, from a parent and/or legal guardian.

Patients

The patients in this study underwent neoadjuvant chemotherapy and expandable prosthesis reconstruction after tumor resection. The persistent epiphysis was confirmed by X-ray. The eligible participants met the following criteria: (i) confirmed by aspiration biopsy and pathological test; (ii) complete neoadjuvant chemotherapy; (iii) no invasion of tibial artery and vein on imaging (MRI); (iv) no invasion of tibial (peroneal) nerve on imaging (MRI); and (v) no preoperative metastasis. Exclusion criteria were as follows: (i) previous nonstandard treatment; (ii) intolerant to chemotherapy; and (iii) active infection. The series included 19 male, ten female patients, with a mean age of 10.5 years (range 6 to 15 years). Twenty-six lesions were located at the distal femur and three at the proximal tibia (Table 1). All patients' initial diagnosis of osteosarcoma was obtained through a preoperative radiograph and magnetic resonance imaging (MRI). All patients had Stage IIB tumors according to the Ennecking staging system[14] and received neoadjuvant chemotherapy.

Chemotherapy

The chemotherapy protocol consisted of ifosfamide, methotrexate and doxorubicin. Ifosfamide was given at 2 g/m^2/day on days 1 to 5 while methotrexate at 8 g/m^2/day was given on day 3. Doxorubicin was administrated at 40 mg/m^2/day on day 5. After three cycles, nine individuals were added to one course because of the broad invasion of the lesion. Considering the preoperative reaction and tolerance, 6–9 courses of chemotherapy were finished postoperatively.

Initial Surgery

Age and tumor extension were the main factors for expandable implant reconstruction. MRI was mandatory to exclude any joint contamination and for surgical planning. Wide resection margins were attained in patients. The initial length of the expandable prosthesis was 2 cm longer than resected specimens. The average length of prosthesis gained was 18 cm, the average prosthesis diameter was 1.14 cm, the stem length was 14.8 cm. The patellar tendon was reattached to the prosthesis groove in three patients with proximal tibia osteosarcoma. A medial gastrocnemius muscle flap was used to rebuild soft-tissue coverage of the device in two patients with insufficient normal soft-tissue.

Extended Surgery

The discrepancy was defined as the difference in length from the anterior superior spine to the malleolus medialis, and pelvic incline. Patients were considered for external limb lengthening with a difference of over 3 cm by radiography. Minimal invasive surgery was conducted to lengthen the implant. The expandable prosthesis had a lengthening mechanism composed of two titanium alloy tubes connected with a screw (Fig. 1). The titanium alloy tube was rotated and expanded, lengthening the prosthesis. It took a 360° rotation to obtain 1 mm of expansion. It is locked by the variable size of the prolonged loop embedded in the gap between two alloy tubes (Fig. 2). The length of expansion was shorter than 2 cm every time to avoid a nerve strain injury.

TABLE 1 General information of patients

Case	Age (years)	Gender	Lesion position	Ennecking grade	Prognosis	Complications
1	10	Female	Distal femur	Stage IIB	Survival	
2	13	Male	Distal femur	Stage IIB	Survival	
3	13	Male	Distal femur	Stage IIB	Survival	
4	7	Male	Distal femur	Stage IIB	Survival	
5	13	Male	Distal femur	Stage IIB	Survival	
6	13	Male	Distal femur	Stage IIB	Survival	
7	15	Female	Distal femur	Stage IIB	Survival	
8	10	Male	Distal femur	Stage IIB	Survival	Prosthesis infection
9	9	Male	Distal femur	Stage IIB	Survival	
10	12	Male	Distal femur	Stage IIB	Relapse	
11	10	Male	Distal femur	Stage IIB	Survival	
12	14	Male	Distal femur	Stage IIB	Survival	Aseptic loosening
13	14	Male	Distal femur	Stage IIB	Survival	
14	11	Female	Distal femur	Stage IIB	Survival	
15	8	Male	Distal femur	Stage IIB	Survival	
16	10	Female	Distal femur	Stage IIB	Survival	
17	6	Female	Distal femur	Stage IIB	Survival	
18	6	Female	Distal femur	Stage IIB	Survival	
19	6	Male	Distal femur	Stage IIB	Survival	
20	9	Female	Proximal tibia	Stage IIB	Metastasis	
21	9	Female	Distal femur	Stage IIB	Survival	
22	12	Male	Distal femur	Stage IIB	Survival	
23	13	Female	Distal femur	Stage IIB	Survival	
24	9	Female	Distal femur	Stage IIB	Relapse	
25	8	Male	Distal femur	Stage IIB	Survival	
26	14	Male	Proximal tibia	Stage IIB	Survival	Nervous symptoms
27	10	Male	Distal femur	Stage IIB	Relapse	
28	11	Male	Proximal tibia	Stage IIB	Survival	
29	9	Male	Distal femur	Stage IIB	Survival	

Postoperative Rehabilitation and Follow Up

The early weight bearing, active and passive motion was continued postoperatively. To ensure the tension union, activities were delayed for about 3 weeks in patients with patella ligament reattachment. All patients were examined with limb X-ray and lung computed tomography every 6 months during follow-up. In addition, PET scans were conducted every year. The purpose was to detect local control and distal metastases.

We collected clinical records (including sex, age, location of the lesion, pathological fracture, and resection length), the course of chemotherapy, the change of alkaline phosphatase between pre-and post-treatment,[15] and prosthesis characteristics (device length, stem diameter, stem length, time of

Fig. 1 (A) The image of the affected limb before surgery. (B) X-ray shows the lengthening device (arrow). (C) The titanium alloy tube was rotated to expand the prosthesis

Fig. 2 The different size of prolonged loop

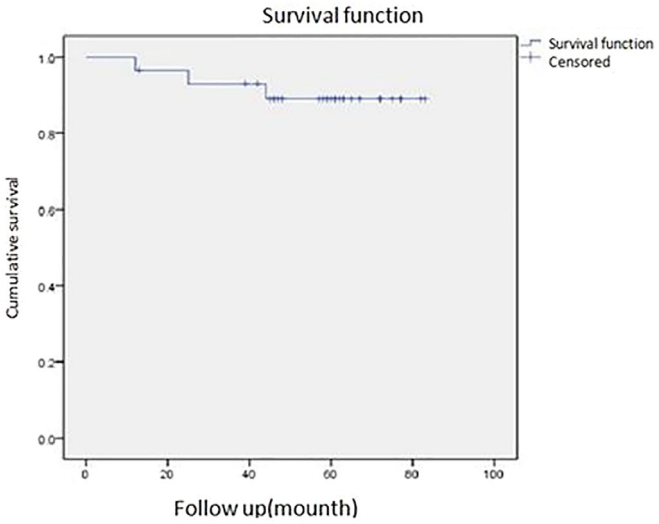

Fig. 3 Kaplan–Meier survival curve of 29 patients shows the overall survival is 89.1% at 5 years

lengthening, and complication). We analyzed the survival rate by the Kaplan–Meier method. The functional results were estimated by the Musculoskeletal Tumor Society (MSTS) at 6 months postoperatively. The six items were scored on a 0 (worst) to 5 (best) scale, including pain, function, emotional acceptance, supports (brace, cane, and crutches), walking ability and gait. Functional outcomes were ranked by score as follows: excellent (≥23 points), good (15–22 points), fair (8–14 points), and poor (<8 points).[16]

Statistics Analysis

As appropriate, data were presented as mean ± standard deviation (SD) or a percentage. In addition, correlation analyses were performed to determine the associations of various parameters with prognosis (survival, recurrence, and metastasis). All statistical analyses were conducted using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered significant.

Results

Prognosis and Survival

All patients had a mean follow-up time of 8.9 years (range from 6–12 years). The overall survival was 89.1% at 5 years (Fig. 3). One patient had died of lung metastasis after 8 months. Three patients had relapse during the follow-up time. Further chemotherapy and wide resection was conducted. Of those patients, two died of the disease, and one was alive without evidence of disease at the time of the latest follow-up. The mean value of alkaline phosphatase at admission and discharge were 234.81 and 133.64 U/L, respectively. The patients with recurrence or metastasis had higher serum alkaline phosphatase level than the normal range. A nonparametric correlations test revealed the connection between alkaline phosphatase change after treatment and prognosis ($P = 0.012$).

Limb Function

These twenty-nine patients had a mean MSTS 93 score of 27 points. Three patients with proximal tibia lesion presented lower function score than patients with distal femur lesion. The range of motion was 90°–120° and 100°–140° respectively. The correlations test demonstrated no dependence on the length of bone resection and MSTS score ($P > 0.05$).

At the time of surgery, the height of patients ranges from 115 to 165 cm. The mean length of lower limbs was 76 cm (from 63 to 92 cm). The rate of lower limb/height in our cohort was 45% equally. Eighteen patients were performed lengthening surgery. An average lengthening of 4 cm per patient was obtained (Fig. 4).

Complications

One patient had prosthesis infection after 26 months postoperatively. It appeared swell and pain around joint. Leukocyte counts and erythrocyte sedimentation rate were higher than the normal level. Gram-negative bacilli was cultured from synovial fluid. Debridement and antibiotics were conducted in the early period. Leukocyte counts and erythrocyte sedimentation rate were normal. Bacterial cultures were negative. At the last follow-up, there was no evidence of infection or prosthesis loosening. One patient had clinical and radiographic signs of aseptic loosening. Complete revision of the primary prosthesis was undergone at the 4th year postoperative. Limb function score was 23 in this patient (MSTS 93 system). One patient suffered from numbness and

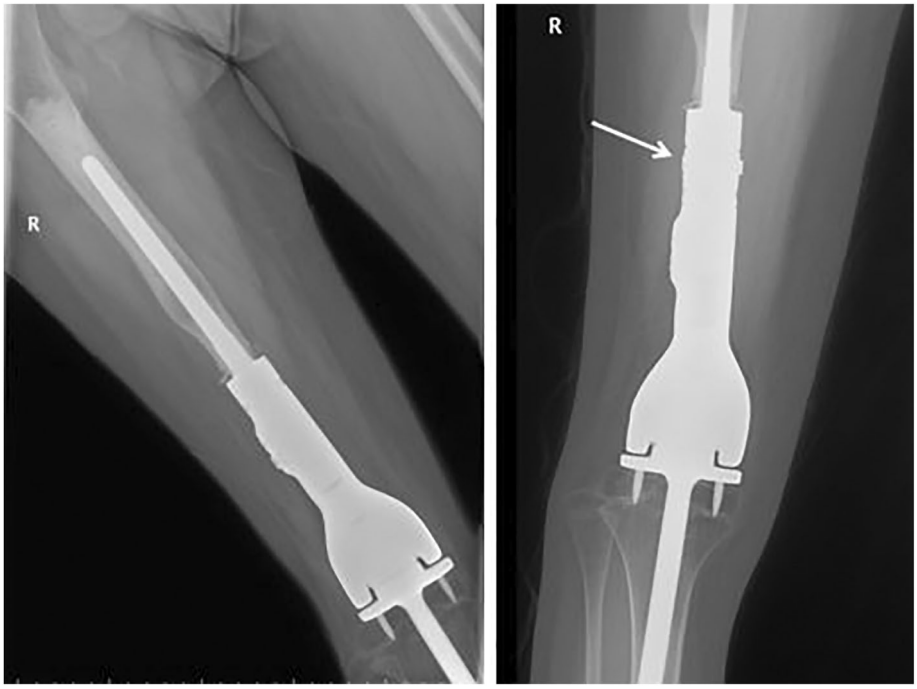

Fig. 4 The prosthesis was showed before and after extension. The arrow showed the prolonged loop

paresthesia. Neurotrophic medicine was used postoperatively to relieve the symptom within 6 months.

Discussion

This study aimed to evaluate the efficacy of wide resection and expandable prosthesis to treat osteosarcoma around the knee in children. When combined with neoadjuvant chemotherapy, this treatment results in an improved prognosis. The expandable prosthesis is an effective means to revise limb dependency.

Prognosis of Chemotherapy

Neoadjuvant chemotherapy is the necessary treatment for extremity osteosarcoma. This common conclusion was deduced by many studies.[17,18] Previously, this disease was only treated by amputation; however, effective neoadjuvant/preoperative and postoperative adjuvant chemotherapy regimens have allowed safe limb-sparing resections, improving survival rates. With the refinement of chemotherapy, most osteosarcoma patients currently receive doxorubicin, cisplatin and high-dose methotrexate as first-line therapy.[19] The addition of ifosfamide to the MAP regimen is an alternative to treat advanced osteosarcoma.[20] However, the best combination has not yet been confirmed.

In this retrospective study, patients were administered the three-drug regimens, and the overall survival was 89.1% at 5 years. We found it had lower toxicity and better tolerance. The relapse rate was not added, but the survival rate at 5 years was higher than that in multiple-discipline therapy studies.[21] The reason for the desirable prognosis might be that patients in our study were treated early and that the size of the lesion was limited. As an indirect detection method Alkaline phosphatase was measured pre- and post-treatment. The value of alkaline phosphatase decreased after treatment. When relapse or metastasis occurred, the value of alkaline phosphatase was abnormal. The correlation test confirmed that the changes of alkaline phosphatase pre- and post-treatment are involved in prognosis, although, other factors such as chemotherapy courses may also have an influence. Pathologic fracture may not be the contraindication of limb salvage.

Effect of Expandable Prosthesis

The special anatomy in children should be considered during reconstruction, and the risk of limb discrepancy after limb salvage surgery draws concern.[22] In addition, using a traditional prosthesis destroys the unaffected growth plate, causing additional crispation. Therefore, it should not be considered an option. Non-invasive expandable endoprostheses had been widely used in the field of osteosarcoma treatment.[10] Within the body of these implants are telescoped segments of prosthesis which slide relative to each other.[23] When placed at the center of a rotating electromagnetic field, implant was extended. The overall implant revision rate was 46.2%.[24]

We present an expandable prosthesis that restores defection of bone preserves the unaffected growth plate, and achieves adequate lengthening of the extremity. Small anatomic size is also the elementary factors in immature patients. In our series, the smallest device is 80 mm in length and 8mm in diameter. It was not necessary to expand the marrow. The prolonged loop would enhance the brace when

the prosthesis is prolonged. It is also different from the noninvasive expandable prosthesis. The screw's prolonged structure could avoid gear mechanism. The relationship between device complications like prosthesis breakage and the prosthesis size was not significant in our study. Previous reports suggested that infection and local recurrence are the main reasons for failure.[25,26] The more specific types of implant failure consisted of insufficient maximal prosthesis lengthening; premature extension failure; prosthesis fracture; bushing or articulation wear.[24] In our study, only one patient had an infection. Lower prosthesis complication rates reduced the risk of second intervention before replacement with a permanent prosthesis. This process saves medical expenses which plays an important role in developing countries. Functional assessment in the follow-up period indicated that the affected limb was competent for daily life.

Considering soft-tissue cover and nerve strain, the prosthesis was 2 cm longer than the initial bone loss initially. The lengthening operation time was based on whole length of limb measurement. The pelvic anteroposterior and full length of the lower limb radiographs had to be conducted to ensure the extent of limb discrepancy. The slight difference of limb length could be eliminated by a shoe lift. Patients were considered for external limb lengthening when the difference was over 3 cm. In our series, the prosthesis was prolonged by about 2 cm every 10 months postoperatively to avoid discrepancy. The average actual length reached was 4 cm with no observed nerve injury. This process needs compliance from the patient and the family who need to be conscious of the necessity of lengthening of implants and at least one revision. Also, further knee exercise is necessary on the part of the patient, and the patient's family.

An average functional score of 27 was obtained, and functional outcomes were ranked-excellent. Routine walking was achieved after muscle exercise. The bone loss affected muscle function slightly. The prosthesis could rebuild the defect and overcome dependency. Both factors were crucial in the reconstruction design.

Limitations and Strengths

The introduced chemotherapy with lower toxicity is suitable for Asians with the described dose and treatment courses. After limb surgery, the discrepancy that children face is a challenge in the long term. This study collected standard-met cases to show that the expandable prosthesis can be applied to immature patients in our hospital. The prosthesis is different from a noninvasive expandable prosthesis and megaprosthesis. This technique overcomes discrepancy and reduces the risk of invalid gears. The survival and function in patients confirmed the effectiveness.

This study had several limitations. First, this was a single-center study, with inherent selection bias. In addition to its small sample size, the patients were assessed retrospectively. Therefore, these findings should be confirmed in multicenter, prospective studies with larger sample size.

Conclusion

Expandable prosthesis combined with triplet neoadjuvant chemotherapy was associated with better prognosis and revised limb discrepancy with shorter incision. This method results in a good function in patients. According to study limitations, future larger series and multicenter cohort studies are imperative to determine its performance, results and complications.

Authors' Contributions

JQ Huang and WZ Bi conceived the study. JQ Huang, M Xu and WZ Bi performed the surgery. JP Jia, W Wang and G Hang collected the data. JJ Cheng performed statistical analyses. All authors read and approved the final manuscript.

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