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Original Article

Neoadjuvant chemotherapy, wide resection and custom prosthetic replacement for tumors of the proximal femur

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Abstract: Endoprosthetic reconstruction after bone tumor resection is accepted treatment for femoral tumors. The objective of this study is to evaluate the effectiveness and functional outcomes of custom prosthetic replacement of the proximal femur in patients undergoing oncologic resection. Data of 28 consecutive patients with proximal femur tumors receiving wide resection and prosthetic replacement (16 total hip replacements [THR], 12 bipolar half-hip replacements [HHR]) from January 2005-June 2014 were analyzed retrospectively. Postoperative lower limb function was evaluated using American Musculoskeletal Tumor Society 1993 function scores (MSTS 93). Mean follow-up was 28.6 months (range: 6-138 months). No patients had prosthesis-related complications or revision surgery, 3 had local recurrence of malignancy (8.3%), and 2 had venous thromboembolism resolved with medication. Mean MSTS 93 score was 84.8% (THR 85% vs. HHR 81%, P=0.044). Two patients (10.7%) suffered relapse and 9 (32.1%) died from lung metastasis. Survival rates were 91.7% at 1 year in both groups; 64.8% and 59.4% in THR and HHR groups after 30 months. In conclusions, Neoadjuvant chemotherapy, extended tumorectomy and special prosthetic replacement of proximal femur effectively treated femoral tumors, with minimal local recurrence and satisfactory functional outcomes.

Keywords: Femoral tumor, prosthesis, neoadjuvant chemotherapy, function reconstruction, half-hip replacement (HHR), total hip replacement (THR)

Introduction

The proximal femur is one of the most common locations for primary malignant bone tumors and metastatic bone tumors [1]. Approximately 16% of Ewing's sarcomas, 13% of chondrosarcomas and 10% of osteosarcomas develop at this location [2]. Amputation has generally been performed for patients with malignant tumors of the proximal femur, which may arrest the tumor but leads to patients' physical disability [3]. However, as a result of the growing awareness of bone tumors, along with improvements in chemotherapy, advances in surgical techniques, application of new reconstruction materials and improved imaging techniques, more and more patients with malignant tumors of the proximal femur can receive limb salvage surgery as a more acceptable alternative to amputation [3, 4].

Currently, the most widely applied method for limb salvage is endoprosthetic reconstruction after resection of the bone malignancy [4]. At one time, patients with malignant bone tumors had low survival rates after such surgeries [5], but today's patients have greater long-term survival with better functional recovery [6]. Nevertheless, although endoprosthetic replacement of the proximal femor is a prominent method of addressing femoral tumors, complications after this procedure are reported frequently, and objective assessments of long-term functional outcomes are lacking [7]. Among the other options that are available for reconstructive surgery, including autografts [8], allografts [9], modular endoprosthesis and custom prosthesis [10], surgeons and investigators still do not agree on the best method for reconstructing the hip after proximal femur resection. For example, while custom endoprosthesis is

noted for resulting in fewer complications than modular endoprosthesis, it is considered to be the most expensive option for replacement of the proximal femur [10]. On the other hand, modular endoprosthesis offers procedural and cost advantages for limb salvage surgeries, but may not produce functional outcomes equal to those of custom prosthesis. A recent study reported 99% limb salvage with no mechanical failure or periprosthetic fractures, concluding that modular endoprosthetic replacement was an exceptionally durable reconstructive option after resecting proximal femoral tumors [3]. Bernthal et al. [11] reported long-term survival of cemented bipolar proximal femoral replacement in 86 patients, concluding that endoprosthetic reconstruction represented a durable technique. In that study, survival was similar between modular prostheses and custom-designed prostheses.

We hypothesized that combined treatment of proximal tumors with effective pre- and postoperative chemotherapy and custom-designed prosthesis would not only provide a better surgical outcome in terms of function, but would also reduce patients' recurrence rate and increase their survival rate. Based on our prior experience with 104 cases of osteosarcoma near the knee, [12] preoperative MRI examination would accurately determine the optimum tumor resection range and prosthesis size, helping to facilitate effective tumorectomy and preserve limb function. Therefore, the present study aimed to explore the effectiveness, key factors and functional outcomes of custom-designed prosthetic replacement of the proximal femur in patients undergoing oncologic resection of femoral tumors and soft-tissue sarcomas.

Patients and methods

Study design and ethical considerations

Between January 2005 and June 2014, our surgical team performed extended tumorectomy and special prosthetic replacement for 28 consecutive patients with tumors of the proximal femur. All baseline, perioperative and postoperative data of these consecutive patients (19 males, 9 females) were analyzed retrospectively. The Internal Review Board of PLA General Hospital, Beijing, China, reviewed and approved the study protocol. All patients provided signed informed consent for their data to be reviewed in this study.

Patient data

All lymphoma patients who underwent resection of tumors of the proximal femur and received prosthetic replacement were required to meet the following conditions: have a solitary lesion; and have a pathological fracture or a high risk of pathological fracture (Mirels score > 9 points) [13]. All patients were diagnosed according to the results of preoperative biopsy and were staged according to Enneking bone tumor classification [14]. Based on hospital's general rule, patients were provided for total hip replacement (THR). However, if surgeon decides and advises patients to receive half-hip replacement (HHR), patients will respect surgeon' final decision. The economic burden among all patients was similar and it will not contribute any bias of current study. Current retrospective study included 2 groups: a total hip replacement group (THR group) with 16 patients, including 7 patients with osteosarcoma, 4 with Ewing's sarcoma, 4 with mesenchymal chondrosarcoma and 1 with fibrosarcoma who all underwent total hip arthroplasty; and a half-hip replacement group (HHR group), with 12 patients, including 3 patients with osteosarcoma, 3 with malignant fibrous histiocytoma, 3 with chondrosarcoma, 2 with lymphoma and 1 with alveolar soft tissue sarcomas who all underwent hemiarthroplasty. All patients underwent bipolar prosthetic replacement.

Pre- and postoperative chemotherapy

Chemotherapy was given to all patients pre- and post-operatively, including 3 cycles preop and 6-9 cycles postop. Chemotherapy drugs included ifosfamide, doxorubicin, methotrexate, cisplatin and vindesine for osteosarcoma; ifosfamide, vindesine and doxorubicin for Ewing's sarcoma; ifosfamide, doxorubicin and dacarbazine for malignant fibrous histiocytoma and alveolar soft tissue sarcoma. Lymphoma patients were treated according to a preoperative chemotherapy regimen recommended by the Department of Hematology in our institution. A list of chemotherapy regimens for each diagnosis is shown as **Appendix A**.

Anaesthesia and intra- and postoperative medications

Intramuscular injection of atropine 0.5 mg was applied 30 min before anesthesia. Patients were monitored routinely for ECG, BP, SPO2, and BIS. After induction of anesthesia using intravenous infusion of midazolam 0.05 mg/kg, etomidate 0.2 mg/kg, sufentanil 0.3 ug/kg, and rocuronium 0.6 mg/kg, patients received endotracheal intubation; mechanical ventilation VT 8 ml/kg, respiratory rate 10 to 14 beats/min, respiratory ratio of 1:2, to maintain the ETCO2 at 35~45 mmHg. Anesthesia was maintained with 1% sevoflurane, 3 mg·kg^{-1}·h-1 propofol, 0.1~0.2 μg/(kg·min) remifentanil. Propofol and opioid administration were applied as needed based on BIS values, and rocuronium muscle relaxant was administered intraoperatively if necessay. Antibiotics were administered from day of surgery using ceftriaxone (Roche Pharmaceuticals Ltd., Shanghai) 2 g intravenous infusion per day for 7 days.

Determining the extent of resection

During limb salvage surgery, the important goals are to prevent local recurrence, reduce the mortality rate and preserve the function of the affected limb. Preoperative MRI examination was performed for all patients to evaluate the outcomes of neoadjuvant chemotherapy, and to accurately define the extent of resection required. Then the surgical procedure was determined based on that assessment. The tumor margins and the post-chemotherapy formation of the peritumoral fat boundary were detected according to the T1-weighted MRI images in combination with T2-weighted MRI images. Normal tissues at 3 cm beyond the tumor margins were excised. Pathological examination was performed for all patients after surgery and no tumor cells were observed in excised tissue outside the tumor margin. The pathway of preoperative biopsy was also completely removed to help prevent tumor recurrence. Overall, we found that precise preoperative design for each individual case improved the accuracy of resection and anatomic reconstruction. In our surgeries, the key to good postoperative functional outcomes was firm reconstruction of the gluteus medius muscle and focused and correct rehabilitation of femoral neck anteversion.

Surgical procedure

The patient was placed in the lateral recumbent position after receiving general anesthesia. A curved posterolateral incision about 18-25 cm in length was made along the line connecting the tip of the greater trochanter and the posterior superior iliac spine. The skin, subcutaneous tissue, fascia, muscle and tumor at the biopsy site were removed vertically via this incision. The skin, subcutaneous tissue and tensor fascia lata were cut open layer by layer. The gluteus maximus was dissected bluntly to expose the greater trochanter, external rotators and vastus lateralis muscle. According to the osteotomy plane designed before surgery based on the imaging data, a maker was made on the femur using an osteotome. The superficial layer of the vastus lateralis muscle was sharply cut off at the muscle origin and raised distally to the primarily marked place and suspended after being ligated with a silk suture. The thickness of the vastus lateralis muscle at the attachment site of the femur was maintained at more than 1 cm. If the greater trochanter had not been invaded by tumor, vertical trochanteric osteotomy parallel to the femoral shaft was performed with an oscillating saw from a site 3 cm distal to the greater trochanter. Bone wax was used to control bleeding from the bone surface. If the greater trochanter had been invaded, the gluteus medius and gluteus minimus were resected at the insertion points in the upper part of the greater trochanter and suspended after being ligated. The external rotators were resected and retracted backwards to expose the joint capsule. A T-capsulotomy was then performed. The acetabulum was exposed, the ligamentum teres femoris was resected and the hip joint was dislocated. Femoral osteotomy was performed along the marked osteotomy plane and the segment containing the tumor lesion was completely removed. (Acetabular retractors were used to expose the acetabulum sufficiently, and the soft tissue around the joint capsule and inside the acetabulum was removed completely. A 45° eversion and 20° anteversion of the acetabulum were maintained and reaming of the acetabulum was carried out using varying sizes of acetabular reamers. A metal acetabular shell was inserted and a ceramic cup was installed). The proximal femoral prosthesis was inserted into 15°-20° of anteversion. The

Table 1. Characteristics of 28 patients

	THR (n=16)	HHR (n=12)	*P*
Characteristics			
Age (years)	32.3 (15.9)	48.3 (21.3)	0.031
Male gender	10 (62.5)	9 (75)	0.687
Enneking bone tumor staging[a]			0.190
2	6 (37.5)	1 (10)	
3	10 (62.5)	9 (90)	
Length of femoral resection, cm	21.3 (13.5, 24.5)	16.5 (12.0, 19.0)	0.121
Chemotherapy	11 (68.8)	9 (75)	0.999
Outcomes			
MSTS 93, %	85.0 (3.4)	81.0 (6.4)	0.044
Relapse	2 (12.5)	1 (8.3)	0.999
Death	5 (31.3)	4 (33.3)	0.999
Duration of follow-up (months)	23.5 (11.5, 40.5)	29.0 (17.5, 40.0)	0.599

Data on age and MSTS 93 are shown as mean ± standard deviation, other continuous data are presented as median (interquartile range), and categorical data are shown as count (%). THR: total hip replacement; HHR: half-hip replacement; MSTS 96: Musculoskeletal Tumor Society 1993. [a]Two missing data were found.

hip joint tension was detected and the hip joint stability was tested by 90° of hip flexion, 45° of internal flexion, overextension and external rotation. The leg length discrepancy was evaluated. The soft tissues around the acetabulum, such as the joint capsule, iliopsoas, etc., were tightened and sutured around the neck of the femur to build strength in the hip joint and prevent postoperative dislocation. The bone segment preserved from osteotomy of the greater trochanter or the gluteus medius and minimus muscles were sutured to a ring-shaped structure of the "greater trochanter" in the specially designed prosthesis to reconstruct the hip abductor muscles. The wound was closed after placing a drainage tube.

Postoperative management

The affected limb was placed in the position of abduction to neutral for 4-6 weeks after surgery. The drainage tube was removed 3-5 days after surgery. Intravenous injection of antibiotics was administered for about 7 days to prevent infection. Isometric exercise of quadriceps and calf muscles was started on the second postoperative day to enhance postoperative functional recovery and prevent thrombosis formation. The timing of postoperative ambulation was determined based on the status of soft tissue recovery. Weight-bearing was started 4-6 weeks after surgery (crutch walking).

Postoperative follow-up

Patients were evaluated at post-operative follow-up visits every three months within 2 years after surgery, every six months between 3 and 5 years after surgery, and every one year following 5 years after surgery. The follow-up included patient's oncology situation and lower-extremity function. At 6 months after surgery, patients' lower-extremity function was evaluated using the Musculoskeletal Tumor Society 1993 (MSTS' 93) scoring system.

Statistical analysis

Data on age and MSTS 93 are presented as mean ± SD (standard deviation). Other continuous data are presented as median (interquartile range) and categorical data are shown as count (%). To compare differences between two groups, the independent t-test and Mann-Whitney U test were implemented for continuous parameters and Fisher's exact test was implemented for categorical variables. A Kaplan-Meier curve was generated to measure survival status of the study population and Gehan-Breslow-Wilcoxon test was implemented to examine the differences between two groups. A two-sided $P < 0.05$ was defined as statistical significance. Data analyses were performed using IBM SPSS Statistics for Windows (Version 22.0, IBM Corp., Armonk, NY, USA).

Results

Table 1 summarizes the demographic and clinical characteristics and long-term outcomes of 28 patients. Patients in the HHR group were older than those in the THR group (48.3 years vs. 32.3 years, P=0.031). No statistically significant differences were found between the two groups in gender distribution, Enneking bone tumor staging, proportion of patients receiving chemotherapy and length of femoral resection. The mean length of femoral resection for all 28 patients was 19.3 cm (SD=9.6,

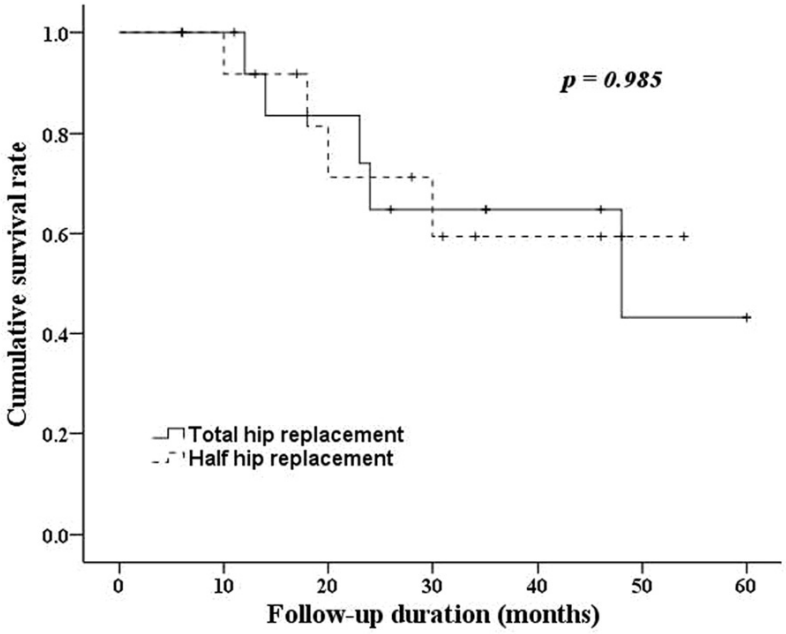

Figure 1. Kaplan-Meier curve of 5-year overall survival in 28 patients. Data were tested by Gehan-Breslow-Wilcoxon test.

range: 10-60 cm). Most patients were males (67.9%) and 71.4% received chemotherapy. The THR group had higher MSTS 93 scores than the HHR group (85% vs. 81%, *P*=0.044). Local tumor recurrence was noted in 3 patients (10.7%). All 28 cases were not diagnosed as pulmonary metastasis in the beginning. However, there are 9 cases with late pulmonary metastasis and 4 of them got resection of lung tumor. All 9 cases (32.1%) were dead before end of study period. Mean follow-up of all patients was 30.5 months (SD=23.6, range: 6-108 months). The percentages of death and relapse were similar in both groups (**Table 1**).

Figure 1 shows that the two groups of patients shared similar survival status. The survival rates for 1-year, 3-year and last visit were 91.7%, 64.8%, and 43.2%, respectively, in the THR group. In the HHR group, the survival rate was 91.7% at 1 year, which then dropped to and was maintained at 59.4% after 30 months (**Figure 1**).

Tumor recurrence was observed in 3 patients, including 2 patients with osteosarcomas and 1 with chondrosarcoma. Amputation was performed for these three patients. Prosthesis-related complications, including fracture, dislocation, implant breakage, modular failure, acetabular erosion in hemiarthroplasty, and migration, were not observed in any patient and no revision surgery was performed. Deep vein thrombosis was observed in 2 patients, which resolved within two weeks after administering medication.

Pre- and post-operative conditions of the current special prosthetic replacement are demonstrated in **Figure 2**, which depicts a 24-year-old male patient with Ewing's sarcoma in the right proximal femur (**Figure 2**).

Discussion

In the present study, 36 consecutive patients with tumors of the proximal femur were treated using preoperative neoadjuvant chemotherapy, extended tumorectomy and custom prosthetic replacement. Results of this study revealed that local recurrence of femoral malignancies occurred in only 3 of the 36 patients receiving oncologic resection and customized bipolar prosthesis. The recurrence rate among the 36 patients was 8.3%. We believe that this low recurrence rate is related to the application of neoadjuvant chemotherapy and the performance of extended tumorectomy. In addition, evaluation of postoperative lower limb function using the American Musculoskeletal Tumor Society 1993 version (MSTS 93) demonstrated a mean functional score of 84.8%, representing satisfactory functional outcomes of the lower extremities in the majority of patients. The percentages of death and relapse were similar between patients receiving THR and HHR, with 91.7% survival in both groups at one year, leveling off to 64.8% for the THR group and 59.4% for the HHR group after 30 months.

Preoperative chemotherapy

Although the chemotherapy regimens for tumors of the proximal femur may be associated with significant toxicity and long-term side effects [15], in our experience, administering

Figure 2. Case presentation: A 24-year-old male patient with Ewing's sarcoma in right proximal femur. A. Preoperative radiograph; B. MRI T2 image obtained before chemotherapy; C. MRI T2 image obtained after 3 cycles of chemotherapy; D. Radiograph obtained 5 days after surgery; E. Radiograph obtained 3 months after surgery; F. Radiograph obtained 1 year after surgery.

effective chemotherapy is still the key to successful limb preserving surgery. We individualize the chemotherapy regimens, because it serves the Chinese population better. We consider tumor type and patient's age. The appropriate chemotherapy can improve the patient's survival and produce a favorable local condition for special prosthetic replacement. We carried out 3-4 cycles of standardized chemotherapy for all malignant tumors before surgery. We combined three chemotherapy drugs during a 5-7-day cycle to control disease better. Application of neoadjuvant chemotherapy has helped to increase patients' survival rates up to 80% [16]. Some investigators have noted that functional results and survival after proximal femur replacement were increased more for primary tumors than for metastatic disease [17], which also speaks to the value of chemotherapy. Among our cases, we credit pre- and postoperative chemotherapy regimens, which differed depending on the tumor type, for the success of the replacement surgeries and the low recurrence rate.

Surgical options and functional recovery

In order to achieve satisfactory outcomes for patients with tumors of the proximal femur who undergo prosthetic replacement, we consider that surgeons should pay close attention especially to the following two aspects. First, 15°-20°of femoral neck anteversion should be maintained when placing the proximal femoral prosthesis. Second, the hip abduction should be reconstructed. For patients without tumor invasion to the greater trochanter, the superficial bone block of the greater trochanter should be maintained. The bone block together with the gluteus medius and minimus should be fixed to the ring-shaped structure in the upper part of the prosthesis. For patients with tumor invasion to the greater trochanter, the gluteus medius and minimus should be detached from the greater trochanter and sutured to the ring-shaped structure of the prosthesis after osteotomy. Reconstruction of the hip abduction can prevent hip dislocation. In the present study, the mean MSTS93 scores of the THR and HHR groups at the last follow-up were 85% and 81% respectively. Ogilvie et al. [7] reported a mean postoperative MSTS score of 67.7% for 34 patients who underwent prosthetic replacement of the proximal femur. Similarly, Finstein et al. [18] reported a postoperative MSTS score of 71% for 13 patients who underwent prosthetic replacement of the proximal femur, and Zhang et al. [19] reported a mean MSTS score of 79% for 96 patients who underwent bipolar prosthetic replacement for proximal femoral tumors. In the present study, the THR group had higher MSTS scores than previous reports, while the mean score for HHR patients was similar to previous scores. This clearly suggests that the functional recovery of patients who undergo total hip arthroplasty is better than that of patients who undergo bipolar hip replacement. For patients with primary benign tumors and chemotherapy-sensitive malignant tumors of the proximal femur, we recommend total hip arthroplasty because the expected survival of patients with benign tumors or chemotherapy-sensitive malignant tumors is satisfactory after appropriate preoperative treatment, and the acceptable postoperative function can satisfy the physical and mental needs of patients. In the present study, although our overall recurrence rate was low (8.3%), we found no significant difference between the THR and HHR groups in recurrence. Other previous reports also found no difference in the recurrence rate between patients receiving total hip arthroplasty and those receiving hemiarthroplasty [20].

Postoperative complications and functional recovery

No prosthesis-related complications occurred in any patient in the current study. However, deep vein thrombosis occurred in two patients, one patient with chondrosarcoma and one with osteosarcoma. According to previous reports, the incidence of deep vein thrombosis following hip joint replacement is 3%-4% [21]. In the present study, the incidence was 5.5%, which is slightly higher than that of the ordinary hip replacement. This is related to the inactivity of tumor patients during the perioperative period and the potential hypercoagulable state [20]. Isometric exercises of quadriceps and calf muscles should be carried out in the early postoperative period to prevent deep vein thrombosis. All patients receive just isometric exercises and no pharmacologic deep venous thrombosis prophylaxis. For patients with deep vein thrombosis, early diagnosis is critical so that early and active medical treatment can be carried out to achieve satisfactory functional results. Recent studies have reported novel surgical applications and good functional results. Jawad et al. [22] reported the outcomes of proximal femoral reconstruction using a constrained hip system approved for oncologic reconstruction. Among a diverse group of 33 patients with massive bone loss associated with tumors of the proximal femur with deficient hip abductors, all achieved good to excellent function with the application of a tripolar acetabulum liner following proximal femoral resection. The authors noted that this option provides a painless gait and exceptional stability. Chandrasekar et al. [23] also reported experience with 100 cases receiving modular endoprosthesis as proximal femur replacement, with a 5-year implant survival of 90.7% and low complication rate. Risk of amputation after the replacement surgery was 4%, which was related to the rate of local recurrence. Ruggieri et al. [24] performed total femur resection, which achieved good local control in a small series. However, although survival was low among patients with extensive sarcomas, the femoral prosthetic

reconstruction achieved good functional outcomes in patients who survived longer. We prefer to perform total hip arthroplasty for patients with primary benign tumors and chemotherapy-sensitive malignant tumors because it can give patients better function. During surgery, it is important for the femoral neck anteversion to be maintained and the hip abduction should be reconstructed to enhance postoperative functional recovery. After surgery, the patient's status should be observed closely to prevent complications such as deep vein thrombosis.

Limitations

This study has certain limitations, including primarily the small number of cases. Follow-up was also not long enough for about half of the patients. We did not report local control rates due to the effect of systemic therapy separating the influence of wide margin and systemic therapy is not possible in a heterogeneous population for sure. The MSTS 93 functional scores had shown statistically significant differences in current study. However, the significant clinical difference to explain why the THA patients did better cannot be fully explained only by MSTS 93 functional scores. We did not stratify the MSTS scores by degree of anteversion to show femoral anteversion and appropriate abductor repair/function improvements of patient outcome. We thought to maintain patients' original anteversion angle is important and we did not perform additional studies, including restoring appropriate anteversion, offset, and abduction strength to explain hip biomechanics and function. We make the case that surgical techniques are keys to good outcome; however, it cannot be satisfactorily proven with retrospective evaluation and the long term result of THR with mega tumor prosthesis is not clear. Additional prospective study of functional outcomes in a larger patient population with bone tumors who require prosthetic replacement of the proximal femur are warranted, with longer follow-up and detailed assessment of markers for recovery.

Conclusions

Neoadjuvant chemotherapy, extended tumorectomy and custom prosthetic replacement of the proximal femur were safe and effective in treating patients with femoral tumors. These measures resulted in minimal local recurrence (8.3%) and satisfactory functional outcomes. The low recurrence rate is attributed to the efficacy of neoadjuvant chemotherapy. Our operative results suggest that total hip arthroplasty should be applied for as many patients as possible with primary benign tumors and chemotherapy-sensitive malignant tumors because it produces better functional outcomes. The treatment protocol applied in this study may serve as a guide for making surgical decisions for patients requiring bone tumor resection.

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Disclosure of conflict of interest

None.

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Appendix A: Detail list of chemotherapy regimens for each diagnosis.

Table 1. Osteosarcoma and mesenchymal chondrosarcoma

Chemotherapy drugs	Dose	Administration	Time
Ifosfamide	2 g/m^2	Intravenous infusion	D1-D5
Methotrexate	8-10 g/m^2	Intravenous infusion	D3
Doxorubicin	30-40 mg/m^2	Intravenous infusion	D5
Cisplatin	120 mg/m^2	Intravenous infusion	D6

Notes: (a) in a course of treatment with methotrexate and cisplatin is not the same administration, for patients 30 years of age we use more Ifosfamide, methotrexate and doxorubicin this set of programs; for 30-year-old we use more than patients ifosfamide, doxorubicin and cisplatin this set of programs. (b) three cycles of preoperative chemotherapy, postoperative chemotherapy 6 cycles. (c) 3-4 weeks to repeat a course. (d) if found clear lung metastases, add vindesine 2 mg/m^2 (D1, D8).

Table 2. Ewing's sarcoma

Chemotherapy drugs	Dose	Administration	Time
Ifosfamide	2 g/m^2	Intravenous infusion	D1-D5
Vindesine	2 mg/m^2	Intravenous infusion	D1, D8
Doxorubicin	30-40 mg/m^2	Intravenous infusion	D5

Note: (a) per-op: three cycles of chemotherapy; post-op: six cycles of chemotherapy. (b) 3-4 weeks to repeat a course.

Table 3. Malignant fibrous histiocytoma and alveolar soft tissue sarcoma

Chemotherapy drugs	Dose	Administration	Time
Ifosfamide	2 g/m^2	Intravenous infusion	D1-D5
Dacarbazine	200-400 mg/m^2	Intravenous infusion	D1-D5
Doxorubicin	30-40 mg/m^2	Intravenous infusion	D5

Note: (a) per-op: three cycles of chemotherapy; post-op: three cycles of chemotherapy. (b) 3-4 weeks to repeat a course.