Pedicle frozen autograft-prosthesis composite reconstructions for malignant bone tumors of the proximal femur

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Abstract

Background Limb salvage surgery is becoming increasingly popular after tumor resection in the lower extremity. Biological reconstruction and use of megaprosthesis are main methods for malignant bone tumors of the proximal femur, which remain controversial due to short- and long-term complication in the proximal femur. Tumor-bearing bone treated by liquid nitrogen is one of biological reconstruction. This study aimed to evaluate the mid- and long-term functional outcomes and complications in patients treated with frozen autograft-prosthesis composite (FAPC) reconstructions in the proximal femur. Methods This retrospective study included 19 patients (10 women, 9 men) with malignant tumors of the proximal femur who underwent tumor-wide resection and FAPC reconstruction (mean age, 46 years; range, 9-77 years). The mean follow-up period of 66 months (range, 9-179 months). Functional outcomes, oncological outcome and complications were evaluated by Musculoskeletal Tumor Society score, clinical and radiological examinations. Results The overall survival rate was 68.4%, and the mean Musculoskeletal Tumor Society functional score was 26.4 points (88%). FAPC survival rates were 100% and 50% at 5 and 10 years, respectively. Five of the 19 patients (26%) had complications: 2 required prosthesis removal and 2 developed a deep infection around acetabular. Wear of the acetabulum occurred in 2 cases, while disease recurrence was occurred in 1 case. There were no cases of greater trochanter avulsion, obvious absorption around frozen bone, prosthesis loosening or leg length discrepancy. Conclusions Due to without femoral osteotomy, ease of soft-tissue attachment and preservation of bone matrix, FAPC reconstruction provide early limb stability and satisfactory functional outcome after malignant bone tumor resection in the proximal femur.

Background
The proximal femur is a common site of malignant bone tumors, however, the options for reconstruction after tumor resection are limited because hip-joint need to be reconstructed. In the recent years, due to great advances in chemotherapy, radiotherapy, radiological examination and surgical techniques, which remarkably improves patient quality of life. The 5-year survival rate has increased to close to 70% in non-metastatic osteosarcoma, while the lower-extremity functional outcomes were 71–87% on the Musculoskeletal Tumor Society (MSTS) system[1, 2]. Meanwhile, no significant difference was reported in overall survival rate or functional outcome between amputation and limb-sparing surgery[3]. Therefore, limb salvage surgery is becoming increasingly popular after tumor resection in the lower extremity[2-4].

Megaprosthesis and allograft–prosthesis composite (APC) reconstructions are the most widely used in the proximal femur reconstruction [4, 5]. Megaprosthesis and APC reportedly have various advantages in short- and long-term functional outcomes, respectively[4, 6, 7]. However, the biological and nonbiological reconstructions after malignant tumor resection remain controversial in the proximal femur. In principle, the ideal proximal femur reconstruction method includes local tumor control, optimal limb function stability, and restoration of the maximal hip abductor function. Since 1999, we developed a tumor-bearing autograft using liquid nitrogen and published its use for reconstruction in patients with malignant bone tumor[8]. Pedicle freezing is a method of creating a tumor-bearing autograft using liquid nitrogen[9].

Here, we focused on the radiological and functional outcomes for frozen autograft–prosthesis composite (FAPC) reconstruction by pedicle freezing in the proximal femur. This study attempted to answer following questions: (1) investigate the mid- and long-term functional outcomes and complications in patients treated with FAPC reconstruction and
(2) compare the functional outcomes and survival rates of various reconstruction methods.

Methods

Patients

This retrospective study included a total of 23 consecutive patients with malignant tumors of the proximal femur who underwent tumor-wide resection and FAPC reconstruction between 2003 and 2015 at Kanazawa University Hospital. The follow-up period for each patient was >6 months. Four patients were excluded from this study: 1 for whom data were incomplete; 1 for whom underwent a freezing operation of the total femur; and 2 patients for whom the follow-up period was < 6 months. Finally, 19 patients (10 women, 9 men) were included in this study (Table 1). The mean patient age was 46 years (range, 9–77 years), while the mean follow-up period was 66 months (range, 9–179 months).

Pathological diagnoses included osteosarcoma in 8 patients, chondrosarcoma in 3 patients, undifferentiated pleomorphic sarcoma in 1 patient, and metastatic tumor in 7 patients (breast cancer in 3, lung cancer in 1, renal cell carcinoma in 2, and hepatocellular carcinoma in 1). New-adjuvant and adjuvant chemotherapy were administrated to 12 patients. This retrospective study was approved by the ethics committee of Kanazawa University.

Surgical procedure and postoperative management

The indications for FAPC include osteoblastic tumor or destruction of less than 1/3 of the cortical bone on a radiological examination. The lateral approach with a wide excision was used in all patients and biopsy tracts were excised with the surgical margin. The gluteus medius and iliopsoas muscles were cut and the proximal femur was exposed with the surrounding soft tissues. The pedicle freezing was performed as follows (Fig 1): 1. Protection of the surrounding normal soft tissue using surgical sheets; 2. Rotation of the proximal femur; 3. Freezing in liquid nitrogen for 20 minutes; and 4. Thawing at room
temperature for 15 minutes and in distilled water for 15 minutes\cite{9}. An intertrochanteric osteotomy was performed and the greater trochanter was preserved, and the bipolar hemiarthroplasty, cemented (antibiotic and anti-tumor drugs were included), long-stemmed prosthesis (span the frozen area) were used in reconstruction. Finally, the gluteus medius and iliopsoas muscles were re-attached to their original anatomical sites using braided polyblend polyethylene sutures. Postoperatively, functional exercises were performed immediately from day 1. Full weight-bearing was permitted at 6 weeks postoperative.

**Outcome measurement**

All patients underwent clinical and radiological examinations at follow-up. Prosthetic failure was defined as removal of the original prosthesis for any cause. Bone absorption was defined as a lucent shadow around the autograft bone by radiological examination. The follow-up period was every 6 weeks to 3 months in years 1 and 2 after surgery, every 6 months in years 2–5 years, and every 6-12 months thereafter. (Routine examinations included anteroposterior and lateral radiography, chest CT, and a bone scan or MRI as necessary.)

**Statistical analyses**

Patients function was evaluated using the MSTS functional score. The survival analysis was performed using the Kaplan-Meier method. The analyses were performed using SPSS ver. 24.0(IBM®).

**Results**

The average prosthetic length of the femoral component was 224 mm (range, 100–335 mm), while mean length of freezing area was 138 mm (range, 50–270 mm). The overall survival rate was 68.4%, and the disease-free survival were 50% and 50% at 5 and 10
years respectively (Fig. 2A, B). Five-year and 10-year recurrence were 100% and 80%, respectively (Fig. 2C). At the last follow-up, 6 of 19 patients were continuous disease free, 3 were alive with disease, 4 had no evidence disease after treatment for metastasis or recurrence, and 2 patients had lung metastasis for which they underwent thoracoscopic excision. 1 patient had bone metastasis of lung cancer that was treated by wide resection. One other patient had local recurrence of disease from residual soft tissue around the femur and underwent re-resection. Five patients died of the disease. The mean MSTS functional score of the patients was 26.4 points (rang, 19-30 points)

Among the 4 patients with the follow-up period >10 years, the FAPC survival rates were 100% and 50% at 5 and 10 years respectively (Fig. 2D). Five of the 19 (26%) patients had complications, including 1 (no.2) who developed a fracture at 12 months postoperative that was managed with conservative treatment; at 112 months postoperative, the prosthesis broke and the patient was subjected to conversion to megaprosthesi. Another patient (no.12) developed local recurrence of the disease from residual soft tissue around the proximal femur for which hip disarticulation was performed at 107 months postoperative (Table 1).

Two cases of deep infection around the acetabulum were managed with debridement, antibiotic bone cement implantation, and acetabular component revision. Wear of the acetabulum occurred in 2 cases, both of which were treated by conversion to an acetabular component at 97 and 106 months postoperatively. One patient had a dislocation that was managed using closed reductions. At the last follow-up, no patients had greater trochanter avulsion, obvious absorption around the frozen bone, prosthetic loosening, or leg length discrepancy.

Discussion

Wide excision of the lesion is the standard treatment in the treatment of malignant bone
tumors. Various reconstruction methods after bone tumors excision have been developed, including megaprosthesis, allografting, and tumor-bearing bone grafts (irradiated bone, pasteurized bone, and frozen bone). With the collaboration of multidisciplinary team, the life expectancy has been increased significantly in the malignant tumor patients. Due to biological reconstructions can achieve acceptable long-term functional outcome, biological reconstructions have received increasing attention.

Tumor-bearing bone graft is one of biological reconstructions. In the past 20 years, tumor-bearing autografts frozen with liquid nitrogen have been reported as safe and effective for treating osteoblast tumors of various types and locations in basic experimental studies and clinical practices [8, 10-14]. The benefits include a shorter union period, restoration of bone stock, lower cost, osteoinduction, osteoconduction, perfect fit, ease of soft-tissue attachment, activation of antitumor immune response and decreased disease transmission [8, 11]. In fact, FAPC by pedicle method has the significant advantage in proximal femoral tumors. First, it is unnecessary to perform a femoral osteotomy and wait for the junction healing. Second, the ligaments and soft tissue around the proximal femur were easy to reattach original anatomic site and increased hip joint stability. Third, it can potentially preserve maximal bone matrix to avoid limiting retreatment options due to insufficient bone mass. This technique achieves early limb stability while recovery time and immediately promoting activity. In theory, all biological reconstructions have similar advantages and disadvantage. However, due to the loss of osteoinductive and osteogenic properties after thermal or radiation treatment, the allograft might have potential risk factors that lead to further surgery, such as nonunion with the host bone, graft fracture, bone resorption, hip abductor avulsion, and immunological reactions [5-7]. Takata et al. also reported that tumor-bearing frozen bones maintains their microstructure and
osteoinductive ability compared to pasteurization, autoclaving and allograft [10].
Biomechanical stability is of great concern to biological reconstructions. Lee et al. reported that the pasteurization decreases the biologic and mechanical properties and reduces strength to less than that of an allograft[15]. Interestingly, Yamamoto et al. had reported that the frozen bone has sufficient biomechanical strength for limb reconstruction that is comparable to pasteurized autografts and allografts[12].

Previous studies reported that an APC 5-year survival and satisfactory MSTS score rates of 72–90% and 77–90%, respectively. APC is a better reconstruction option if easily available. Remarkably, graft-host junction union is a major problem, and the nonunion rate is reportedly 5%–19%[5, 6, 16-18]. On the other hand, Eid et al.[19] reported on using the pasteurized APC in 18 patients and had outcomes of MSTS functional score was 80%, 5-and 10-year graft survival rates of 86%, mean graft-host junction union time of 13 months, and 1 case of non-union. Chen et al.[20] also reported use of extracorporeal irradiated APC with an MSTS score of 72%, mean graft-host junction union time of 20 months, and 5-year graft survival rate of 85%. It seems that all biological reconstruction methods feature acceptable functional outcomes and implant survival rates. A few cases of nonunion or delayed union have been reported, although many studies reported that using the step-cut osteotomy, autogenous or allogenous bone graft into host bone, and non-cemented prostheses increased graft-host junction healing and stability in all biological reconstructions[5, 18, 21] (Table 2).

Greater trochanter stability in biological reconstruction is also a concern. Abductors reconstruction methods are controversial, including tendon to soft tissue, tendon to tendon, tendon to bone and bone to bone. However, complications include greater trochanter nonunion, trochanteric fracture, hip abductors avulsion, and resorption, which
lead to poor function and a protracted postoperative rehabilitation period\cite{18, 19}.

Megaprosthesis has satisfactory short- to medium-term outcome, early mobilization and weight-bearing, and short operative time; however, abductor muscles reattachment is a problem of great concern; many reports have shown that using an artificial ligament to affix the megaprosthesis can promote soft-tissue reconstruction and achieve better joint stability and functional outcomes\cite{22}. In fact, artificial ligament use is probably unable to reduce the occurrence of prosthetic complications such as aseptic loosening, prosthesis breakage, infection, and stress shielding\cite{23}. In addition, long-term prosthetic failure rates are 6–33\%, mean MSTS scores were 63–83\%, and the major complications were infection (5–13\%) and dislocation (0–20\%) \cite{4, 17, 23-25} (Table 2). Likewise, the studies reported that using silver- or iodine- coated implants can reduce overall infection rates\cite{26, 27}. As mentioned above, many useful products or methods can prevent further complications; however, a higher cost burden, unavailability in some countries and the limited bone mass complicate revision surgeries.

In the current study, the functional outcome was similar to those of other methods of reconstruction. The mean MSTS functional score was 88\%, and the 5- and 10-year graft survival rates were 100\% and 50\%, respectively. At the last follow-up, no prosthesis loosening or obvious lucent shadows around the autograft bone on radiological examination was seen, nor was hip abductors avulsion, abductor muscle weakness, or biomechanical changes caused by the freezing process. Only 1 patient had local recurrence around the residual soft tissue for which hip disarticulation was performed after 2 re-excisions. Wear of the acetabulum occurred in 2 patients despite the use of bipolar hemiarthroplasty, but this might be an inevitable long-term complication of joint replacement.
We prefer to use antibiotic-loaded cement and long-stem prostheses to reduce fracture and infection rates and provide immediate stability. More importantly than all of that, no femoral osteotomy accelerate rehabilitation by enabling full weight-bearing soon after the operation. This technique features desirable outcomes and provide biomechanical stability that is comparable to those of other methods of biological reconstruction or megaprosthesis.

The various reconstructive alternatives have acceptable oncological and functional outcomes. However, each method has its drawbacks, and choosing the method that maximizes the benefits for patients is a major concern. Surgeons must carefully consider the patient’s age, general condition, response to chemotherapy, and expectations when individualizing a treatment plan.

This study had several limitations. First, due to its retrospective design and single center, a relatively small number of patients were enrolled, a follow-up >10 years was available for only 4 of the 19 patients. Second, no control group was available for comparison of functional outcomes; thus, our results could be compared to only those of prior studies. Similarly, the accuracy of our results was lower than those of randomized study. Third, the patients had various diagnoses and were treated with various chemotherapy regimens, which might have affected survival rates and functional outcomes. Therefore, to assess the efficacy and safety of this procedure, a prospective study will compare the functional outcomes and survival rates of several reconstruction methods over a long-term follow-up period.

Conclusions

Our findings suggest that FAPC reconstruction is a good method of treatment for patients with malignant bone tumor in the proximal femur. Due to without femoral osteotomy, FAPC reconstruction can achieve early limb stability and immediate activity, which is
comparable to other methods of biological reconstruction or megaprosthesis.

List Of Abbreviations

APC: allograft-prosthesis composite
FAPC: frozen autograft-prosthesis composite
MSTS: Musculoskeletal Tumor Society

Declarations

**Ethics approval and consent to participate**

The study was approved by the ethics committee of Kanazawa University, and written informed consent was obtained from all patients before surgical treatment. The authors certify that they have obtained the written patient consent. The patients provided consent for their clinical information to be reported in the journal. However, consent was not applicable because the patients’ personal information and images are not reported in the article.

**Consent for publication**

We have consent for publication.

**Availability of data and materials**

The datasets will be available from the corresponding author if need to obtain the data and materials.

**Competing interests**

The author declare that they have no conflict of interest.

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**Authors' Contributions**

GX performed the study design, analysis of date and manuscript drafting. SM collected the
data and revised the manuscript. All operations were performed by HT, NY, KH, AT, KI, YT, YA, HY and SM analyzed the data. All authors approved the final manuscript.

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Tables

Due to technical limitations the tables are available as downloads in the Supplementary Files.

Figures
Figure 1

Frozen autograft-prothesis composite used for femoral reconstruction

Figure 2

Kaplan-Meier curve of overall survival (A) Kaplan-Meier curve of the disease-free survival (B) Kaplan-Meier curve of the recurrence-free survival (C) Kaplan-Meier curve of the graft 5- and 10-year survival rates (D)
Supplementary Files

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Table 1.jpg
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