Long term results of using frozen bone autograft for reconstruction after resection of osteosarcoma around the knee in children

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Abstract

Introduction: Limb salvage has become the standard practice in the management of osteosarcoma. Limb salvage surgery represents a challenge in skeletally immature patients in whom further growth is anticipated. Several options are available for limb reconstruction in children, we report the long term results of using the freezing technique by liquid nitrogen for treatment of lower limb osteosarcoma in children using different reconstruction techniques.

Method: This study includes **24** children with lower limb osteosarcoma, average age was**13±3.2 y (6-18 y),** ten boys. The mean follow-up period was **87.3±44.7 m (28-224 m).** In 14 cases the lesion was in the femur, in ten patients it was in the tibia. Joint sparing and intercalary freezing was carried in out in **15** cases, while in five cases, osteoarticular freezing was performed, and a composite technique with a tumor prosthesis was performed in four cases.

Results: Ten patients remained disease-free, eleven patients lived with no evidence of disease, one was alive with the disease, and two patients died of the disease. Five- and ten -year rates of survival were **91.76%.** Graft five and ten years survival rates were **91.48% and 83.3 %** respectively. Function on the Enneking scale was excellent in **19** patients **(79.1%),** and good in three patient **(12.5%),** fair in one **(4.1%),** and poor in two patients **(8.3%),** mean MSTS score was **25±5.4 (6-30).** Mean union time was **8.7 m±2.1m (6-12m). Mean MSTS** score was higher among children who receive a joint sparing rather than a joint sacrificing resection; **27.2 versus 21.3.** Complications were recurrence in three cases **(12.5%),** all recurrences were from soft tissue, collapse of the osteoarticular graft occurred in two cases **(8.3%).** Fracture of the graft occurred in two cases **(8.3%),** nonunion occurred in three cases **(12.5%).** Leg length discrepancy occurred in seven cases, mean difference was **21**.8mm±8.3mm **(7-31mm),** lengthening was carried out in four cases and finally got had equal leg length, in three cases, shoe lefts were enough.

Conclusion: Reconstruction by frozen bone autograft for osteosarcoma around knee in children is easy, effective, biological, low-cost, immediate mobilization of joints, possible cryo-immune effects, with excellent long term functional outcome and with less complication.

Introduction

Limb salvage has changed from being an exception to a standard practice in the management of primary malignant bone tumors. **[1]** The majority of patients can be cured by the virtue of multidisciplinary team including oncologists, radiation oncologists, surgeons, pathologists, radiologists and involvement of patients in clinical trials**. [2]** Limb salvage surgery represents a challenge in skeletally immature patients in whom further growth is anticipated. **[3]** The selected treatment method should

deal with the current bone defect and the expected leg length discrepancy **(LLD)** at maturity. Surgeons have several choices for the reconstruction of large bone defects after tumor resection, e.g., endoprostheses, allografts, vascularized fibular grafts, composite arthroplasty, distraction osteogenesis, or biological reconstruction. **[4]** Biological reconstruction by reusing the resected tumor-bearing bone is steadily increasing, through using the extracorporeal irradiation, **[1]** autoclaving, **[5]** pasteurization**, [6]** or freezing **[7].** The common advantage of these techniques is the coincidence of configuration of the bone defects and the reconstructive material, so that the reconstructive procedure can be performed relatively easily. **[8]** Tsuchiya et al described the use of hypothermia to treat the bone containing the tumor using the liquid nitrogen at **−196°C** which was used as a cryogenic agent to destroy tumor cells. **[7]** Freezing devitalizes tumor cells by inducing ice crystal formation and cell dehydration. Only one cycle of **-196°C for 20** minutes is sufficient to kill all tumor cells. **[7]** Another possible cause of cell death during cryosurgery is ischaemic infarction due to thrombosis of the microcirculation. **[9]**

Epiphyseal sparing tumor resection surgery has been attempted in recent years. This is likely attributable to better imaging technologies and more experience with limb-preservation techniques. The advantages of this technique are preservation of a normal joint in a young patient, the possibility of avoiding joint complications seen with osteoarticular grafts **(need for conversion to TKA at some point, joint instability)** and endoprostheses **(loosening, revisions). [10]**

In this work we evaluate the long term results frozen bone autograft for reconstruction after resection of osteosarcoma around the knee in children.

Patients & Method

This study includes **18** children with osteosarcoma around the knee, average age **was13±3 y (6-18 y),** ten girls and eight boys. The mean follow-up period was **75±32.7 m (25-191 m).** Inclusion criteria were age below **18** years, good response to chemotherapy, primary malignant bone tumor and non-osteolytic lesion. Length of the planned bone recycling is only limited by the ability to perform secure rigid fixation. Exclusion criteria were osteolytic lesion, previous freezing and recurrent cases. **In 12** cases the lesion was in the femur, while in six patients it was in the tibia. Joint sparing and intercalary freezing was carried in out **in 12** cases, while in five cases, osteoarticular freezing was performed, and a composite technique using a tumor prosthesis and frozen bone was performed in one case. Different freezing technique are showed in figure **1.**

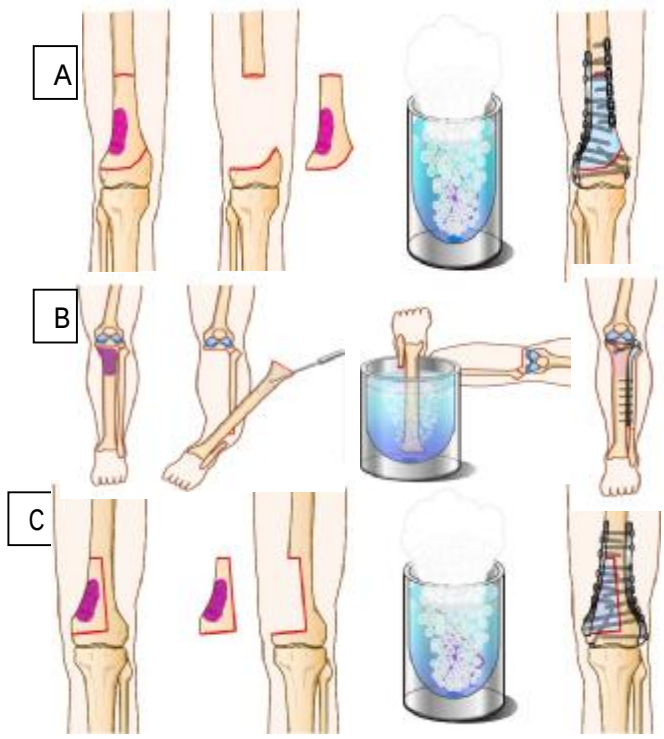

Figure 1

A: Free freezing

B: Pedicle freezing

C: Hemicortical freezing

Results

Nine patients remained disease-free, eight patients lived with no evidence of disease, and one patient died of the disease. Five- and ten -year rates of survival were **94.4%. (Fig.2a).** Graft five and ten years survival rates were **94.4% and 88.8 %** respectively**. (Fig. 2b).** Function on the Enneking scale was excellent **in 15** patients **(83.3%),** and good in three patient **(16.6%),** mean **MSTS** score was **26±2.88 (22-29).** Mean **MSTS** score was higher among children who receive a joint sparing rather than a joint sacrificing resection, **26.8 versus 24.4.** Complication was recurrence in one case**(5.5%),** from soft tissue, this case was treated by surgical excision, collapse of the graft occurred in one case from those who had osteoarticular freezing **(5.5 %),** and was managed by replacement by tumor prosthesis. Fracture of the graft was encountered in one case **(5.5%)** and treated by osteosynthesis. No deep infection had occurred in our series. Leg length discrepancy occurred in six cases, mean difference **was 20.8mm±8.6mm (7-31mm),** lengthening was carried out in four cases and finally got had equal leg length, in two cases, shoe lefts were used. Representative caase is presented in Figure **3.**

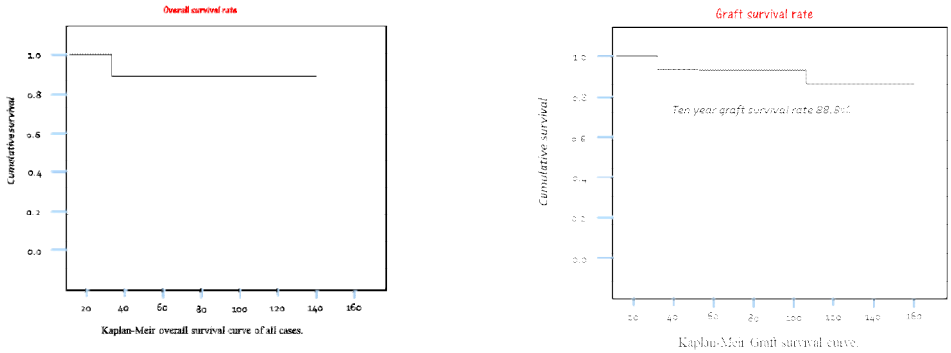

Figure 2. A: Kaplan Meyer overall survival rate, B: Kaplan Meyer graft survival rate

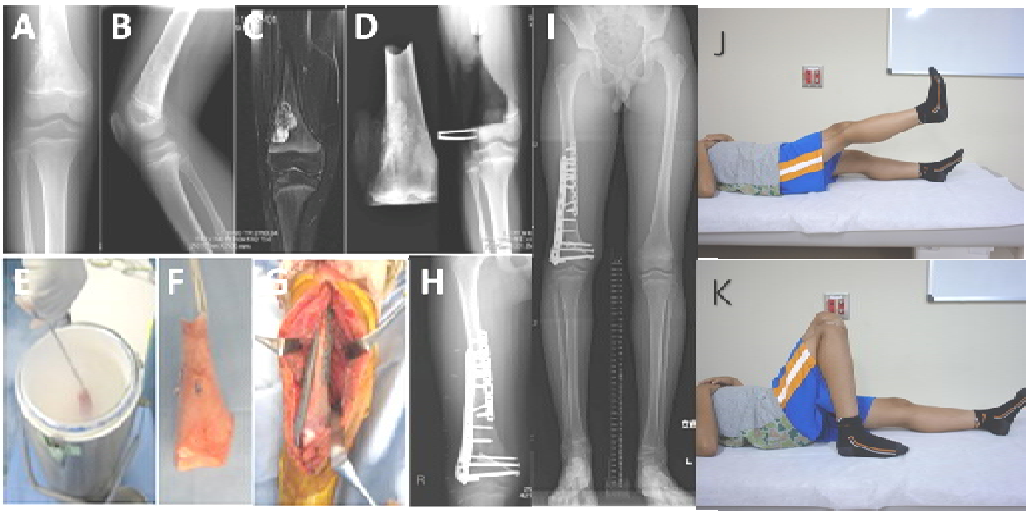

Figure 3: ***Case presentation representing a ten years old boy at time of surgery with osteosarcoma distal right femur.*** **A,B: Anteroposterior and lateral view of distal femur XP showing the tumor mass. C: T2 weighed MRI image of the distal femur showing the tumor mass with high signal intensity. D: Intraoperative XP showing the freely resected segment to be frozen, and the host bone. E: Introperative photo of free freezing. F: The tumor bearing bone after freezing. G: The frozen segment after repositioning and fixation. H: Post-operative XP of the distal femur after freezing and fixation. I: Long leg film showing the LLD of 3 cm. J,K: Clinical photo of the knee in full flexion and full extension.**

Discussion

Cryosurgery was first used in the management of bone tumors at the Memorial Sloan-Kettering Cancer Center in the United States **in 1964** as a palliative procedure on a patient with a metastasis to the humerus from the lung. **[15, 16]** Marcove et al. **[17]** reported the use of liquid nitrogen for the treatment of osteosarcoma **in 1984**, they used repetitive freezing and thawing to destroy tumor cells present at the margin of the curettage, no evidence of residual tumor though en bloc excision of the tumor was not performed at that time. Many authors have described the use of cryosurgery for the management of benign and malignant bone tumors. **[18]**Yamamoto et al **[7]** documented the efficacy of treatment with liquid nitrogen on osteosarcoma cells, in vitro and in vivo, in addition, they found that frozen autografts had adequate biomechanical properties. Takata et al **[19]** reported that bone morphogenetic activity was better preserved in frozen autografts treated by liquid nitrogen than in those treated with autoclaving and pasteurisation. Among the different surgical modalities which are available for limb reconstruction in children, the use of intraoperative freezing by liquid nitrogen has multiple advantages; it is a simple technique, lower cost, preserves osteoinduction and osteoconduction**,[19]** relatively short time, with perfect anatomical fit, no graft rejection, no transmitted diseases, sufficient biomechanical strength**[7]** easy attachment of tendons and ligaments to bone, no harmful denatured substances, early revitalization and possible cryo-immunological effects. It necessitates less demanding equipments and requirements compared to other heat or radiation treated bone grafts. **[20]** Overall survival rate in our cases was 94.4% at five and ten years. This survival rate is higher compared with other studies. Tinao et al **[10]** reported survival rate of 86% in a study included **35** patients treated by epiphyseal preservation and allograft reconstruction, Campannacci L.et al **[21]** reported a survival rate of **72.2%at** five years in a study included **19** children treated by allograft-prosthetic composite for proximal tibial reconstruction. N. E. Picard et al **[3]** reported a survival rate of **80 %** in their series of **55** children treated by non-invasive extendible endoprosthesis.

Our relatively high survival rate may be partially attributed to the strict selection criteria of this procedure, performing this procedure in only good responders to neoadjuvant chemotherapy. Local recurrence rate in our series is comparable to other methods of reconstruction; Hong et al. **[1]** reported markedly low local recurrence rates after limb preservation surgery with extracorporeal irradiation in a large series of **101** patients. They reported local recurrence rates of **2.9%, 0%,** and **20%**for patients with Ewing sarcoma, osteosarcoma, and chondrosarcoma, respectively. They however reported relatively higher distant recurrence rates of **22.9%, 16.6%, and 30%** for the same tumors. Picardo et al. **[3]** reported no local recurrences in their series. It is noteworthy that no recurrence occurred in cases that had marginal resection, while the only case of recurrence had occurred in the group of cases that had a wide marginal resection. This is consistent with Jeon et al. **[24]** who reported **35** local recurrences in **445** osteosarcomas and could not find relationship between adequacy of soft tissue margin and local recurrence in the corresponding area. Fracture of the graft in our series was less than other

techniques. Aponte-Tinao et al**. [10]** reported fracture of the allograft in **11** of **35** patients **(31%).** Campanacci et al**. [21]** reported six fractures in nineteen allografts **(32%).** Yu et al. **[25]** reported three fractures in five patients **(66%)** treated with preservation of the epiphysis after resection of high-grade osteosarcomas and reconstruction using inactivated bone.

Although there was no significant difference in the union time between pedicle and free frozen cases, the occurrence of nonunions was greater in the free frozen group compare to the pedicle frozen group **(22.2% versus 0%);** Shimozaki et al. **[26]** previously reported a lower complication rate in the pedicle frozen as compared to free frozen cases in a comparative study. In our series, overall complication rate was **33.3%.** However, our small sample size means that even one or two complications might have resulted in a much higher percentage of complications. Particular attention should be paid to **LLD** as a late sequel in pediatric tumor surgery; it is an inevitable outcome when the physis is affected by the tumor or surgical resection. The level of activity and functional outcome is largely dependent upon how the **LLD** is managed in addition to other factors **[20].** Lengthening is performed when the **LLD** is **>20**mm and is performed in the "virgin" bone; that is, if the frozen bone is the femur, we lengthen the tibia, and vice versa. This is because full revitalization of the frozen bone takes up to six years **[27],** and the goal is to attain a biomechanically stable regenerate. Additionally, we do not prefer to interfere with the fixation procedure and we prefer to avoid masking of any local recurrence. Lengthening was performed by distraction osteogenesis using the Taylor spatial frame **(TSF),** and distraction is started at the standard time point after the osteotomy; the distraction process was uneventful.

Functional outcomes in this series are encouraging with excellent results achieved in **94.4%** of cases comparable to the results of minimally invasive and noninvasive extendible prosthesis, intercalary resection and allograft reconstruction, and resurfaced allograft prosthesis composite reconstruction **[3, 10, 20, 21].**

Tumor response to preoperative neoadjuvant chemotherapy is an important prognostic facto, especially if the patient is to enroll into the recent **EURAMOS** protocol where postoperative chemotherapy is dependent on the tumor response to neoadjuvant chemotherapy **[29].** The drawbacks of this technique include the inability to perform histological analysis of the entire specimen; however, partial histopathological examination is always done to assess the response to neoadjuvant chemotherapy according to the Rosen and Huvos grading system, **[15].** And the development of modified radiological score by Miwa et al greatly assists the decision to define the good and poor responder preoperatively. **[30].**

Conclusion

Reconstruction by frozen bone autograft method is easy, effective, biological, low-cost, immediate mobilization of joints, possible cryo-immune effects, with excellent long term functional outcome and with less complication. Reconstruction by frozen bone autograft for treatment of osteosarcoma around the knee is a good reconstructive choice in a child with osteosarcoma, with good response to chemotherapy, with non osteolytic lesion, best result could be obtained when the joint preservation is possible and intercalary freezing could be carried out.

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