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Intercalary Femur Allografts Are an Acceptable Alternative After Tumor Resection

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Abstract

Background With the improved survival for patients with malignant bone tumors, there is a trend to reconstruct defects using biologic techniques. While the use of an intercalary allograft is an option, the procedures are technically demanding and it is unclear whether the complication rates and survival are similar to other approaches.

Questions/purposes We evaluated survivorship, complications, and functional scores of patients after receiving intercalary femur segmental allografts.

Patients and Methods We retrospectively reviewed 83 patients who underwent an intercalary femur segmental allograft reconstruction. We determined allograft survival using the Kaplan-Meier method. We evaluated patient function with the Musculoskeletal Tumor Society scoring system. Minimum followup was 24 months (median, 61 months; range, 24–182 months).

Results Survivorship was 85% (95% confidence interval: 93%–77%) at 5 years and 76% (95% confidence interval: 89%–63%) at 10 years. Allografts were removed in 15 of the 83 patients: one with infection, one with local recurrence, and 13 with fractures. Of the 166 host-donor junctions, 22 (13%) did not initially heal. Nonunion rate was 19% for diaphyseal junctions and 3% for metaphyseal junctions. We observed an increase in the diaphysis nonunion rate in patients fixed with nails (28%) compared to those fixed with plates (15%). Fracture rate was 17% and related to areas of the allograft not adequately protected with internal fixation. All patients without complications had mainly good or excellent Musculoskeletal Tumor Society functional results.

Conclusions Diaphyseal junctions have higher nonunion rates than metaphyseal junctions. The internal fixation should span the entire allograft to avoid the risk of fracture. Our observations suggest segmental allograft of the femur provides an acceptable alternative in reconstructing tumor resections.

Level of Evidence Level IV, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

Due to early diagnosis, advanced chemotherapy, and accurate preoperative imaging techniques, many tumors involving the metadiaphyseal region of long bones currently can be treated with epiphyseal preservation [19]. The tumor en bloc resections originate in segmental bone defects that represent a challenging reconstructive problem. Surgical options for reconstructing metadiaphyseal defects include biologic reconstructions (ie, not using megaprostheses), such as autogenous vascularized fibular grafts [7, 14, 24], autogenous extracorporeally irradiated bone [3, 8, 16], segmental bone transportation or distraction osteogenesis [5, 22], massive allograft [17, 19, 20], and the combination of massive allograft with autogenous vascularized fibular grafts [6]. Nonbiologic reconstructions, on the other hand, use intercalary endoprostheses [1, 2, 4, 12].

Reconstructions of the femoral diaphysis after resection of bone tumors are surgically demanding. Although all previous surgical options had been advocated to reconstruct these defects, few articles describe specifically the results in these particular bones. Krieg et al. [16] described 16 patients treated for a primary bone sarcoma of the femur by wide local excision of the tumor, extracorporeal irradiation, and reimplantation; an additional vascularized fibular graft was used in 13 patients. These authors reported a complications rate of 44% without failure of the graft. Hanna et al. [12] reviewed 23 patients who underwent limb salvage by endoprosthetic replacement of the femoral diaphysis for a primary bone tumor with a reconstruction survival of 85% at 5 years and 68% at 10 years. For several decades, we have treated patients with metadiaphyseal defects of the femur after a tumor resection with intercalary massive allograft for reconstruction. Whether these have similar complication rates and survival compared to other techniques is unclear.

We therefore determined (1) the mid- and long-term allograft survival, (2) local recurrences, (3) complications, (4) risk factors for allograft failures, and (5) function in patients treated with this reconstruction.

Patients and Materials

Between February 1987 and May 2008, we performed 198 femoral intercalary allografts for metadiaphyseal defects for tumors or other indications. The indications for surgery were (1) bone tumors growing in the metadiaphyseal area with no or partial compromise of both epiphysis, (2) a residual epiphysis of 1 cm or more to allow fixation of the osteotomy junction and safe oncologic margins, and (3) tumors with no evidence of progression clinically or on MRI studies during chemotherapy. The contraindications for surgery were (1) patients in whom preoperative imaging studies demonstrated evidence of epiphyseal compromise of the tumor and (2) tumor progression while on chemotherapy. For this study, we excluded patients treated with intercalary allografts that included joint arthrodesis (61 patients) and hemicylindrical grafts (52 patients) and patients who died of disease before 2 years of followup (two patients). This left 83 patients who underwent a whole cylindrical intercalary femur segmental allograft reconstruction (Table 1). Mean age was 26 years (range, 2–80 years); 35 patients were female and 48 were male. The original diagnoses included osteosarcoma (n = 41), Ewing's sarcoma (n = 15), chondrosarcoma (n = 7), bone metastasis (n = 5), giant cell tumors (n = 4), malignant fibrohistiocytoma (n = 4), liposarcoma (n = 1), fibrosarcoma (n = 1), and intercalary reconstruction (n = 5). Minimum followup was 24 months (median, 61 months; range, 24–182 months). No patients were recalled specifically for this study; all data were obtained from medical records and radiographs.

Table 1. Demographic data

Variable	Value
Number of patients	83
Diagnosis (number of patients)	
Osteosarcoma	41
Ewing's sarcoma	15
Chondrosarcoma	7
Bone metastasis	5
Giant cell tumor	4
Malignant fibrohistiocytoma	4
Liposarcoma	1
Fibrosarcoma	1
Failure of an intercalary reconstruction	5
Median followup (months)	61 (24–182)
Mean age (years)	26 (2–80)
Gender (female:male)	35:48
Chemotherapy (number of patients)	
Yes	53
No	30

The surgery began with resection of the lesion, including biopsy scars, with appropriate bone and soft tissue margins, and insertion of a fresh deep-frozen allograft segment, sized to fit the bone defect (Video 1) (supplemental materials are available with the online version of CORR). We harvested and stored these nonirradiated allografts according to a previously described technique [18]. To achieve the closest anatomic match, we selected allografts based on a comparison of radiographs and CT scans of the patient and donor (Video 2, 3) (supplemental materials are available with the online version of CORR). After being thawed in a warm solution, the donor bone was cut to the proper length. All allograft-host junctions were made using a transverse osteotomy (Video 4) (supplemental materials are available with the online version of CORR). From a total of 166 host-donor junctions, 95 were located in the diaphyseal bone and 71 in the metaphyseal bone. We used plates and screws for internal fixation in 70 junctions located at the diaphysis and in 38 for the metaphysis (Fig. 1). We used intramedullary locked nails in 25 diaphyseal and six metaphyseal

Fig. 1A–B (**A**) An AP radiograph shows a patient with a diaphyseal osteosarcoma. (**B**) An AP radiograph shows a 4-year followup control with an intercalary allograft stabilized with two-plate fixation in the proximal and distal metaphyseal osteotomies. The entire length of the allograft is protected with lateral plate fixation.

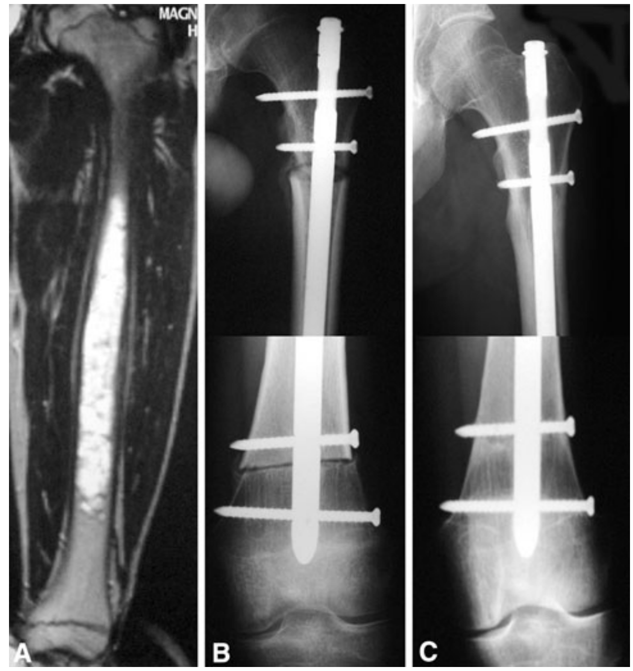

Fig. 2A–C (**A**) A MR image shows a 36-year-old patient with a diaphyseal chondrosarcoma. (**B**) An AP radiograph shows a 6-month followup control with an intercalary allograft stabilized with a locked intramedullary nail. (**C**) An AP radiograph shows a 7-year control of the intercalary allograft with incorporation of the graft and healing of both osteotomies.

osteotomies (Fig. 2). In 27 host-donor junctions, where a thin epiphyseal segment was saved, only cancellous screws were used for fixation. We gave 1 g cefazolin intravenously for the first postoperative week unless there was a history of penicillin or cephalosporin allergy, in which case the patient received 600 mg clindamycin. No routine anticoagulation therapy was used.

External splinting with a brace with the knee in full extension was used until the wound had healed. After 2 days, the drains were removed and the wound was inspected. Ice or a cryotherapy device was used to help minimize postoperative swelling and discomfort. Postoperatively, a physical therapist instructed patients on brace use, crutched walking, and quadriceps contractions. Passive ROM exercises were begun 2 weeks after the operation and were supervised by a physiotherapist. The patient was allowed partial weightbearing at 8 to 12 weeks. Full weightbearing was allowed when there was evidence of osteotomy healing.

Postoperatively, we saw most patients at 1 week, 2 weeks, 1 month, 2 months, 3 months, and then every 3 months thereafter until 2 years, after which we met annually. Beginning 1 month after the operation, we obtained plain radiographs at every visit. We performed functional evaluation using the revised 30-point functional classification system established by the Musculoskeletal Tumor Society (MSTS) [10], which assessed pain, functional limitation, walking distance, use of a support, emotional acceptance, and gait. Each variable was assessed on a 5-point scale. From the medical records, we obtained the following information: method of fixation, use of adjuvant chemotherapy, and complications. Surgical complications were defined according to the Clavien-Dindo classification [9] that separates complications in five grades: Grade I, any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiographic interventions, with acceptable therapeutic regimens including drugs, such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes, and physiotherapy; Grade II, complication requiring pharmacologic treatment with drugs other than those allowed for Grade I complications; Grade III, complication requiring surgical, endoscopic, or radiographic intervention; Grade IV, life-threatening complication; and Grade V, death of a patient. We analyzed only Grades III, IV, and V complications in this series. There were no missing data in this series.

Three of us (LAT, GLF, LER) reviewed all postoperative radiographs and followup radiographs for each patient and chose comparable AP and lateral radiographs for analysis. We recorded the radiographic appearance of the junction. We considered the allograft-host junction to be radiographically healed when the junction line no longer was visible or the junction was bridged with periosteal bone on four cortices on AP and lateral radiographs.

The method of Kaplan-Meier [15] was used to estimate the allograft survival rate. We considered the procedure a failure if the allograft was removed due to a revision procedure or amputation. Cox regression was used to analyze which factors (location of osteotomy, use of chemotherapy, and type of osteosynthesis) negatively influenced the results. SPSS® 17.0 for Windows® (SPSS Inc, Chicago, IL) was used for statistical analyses.

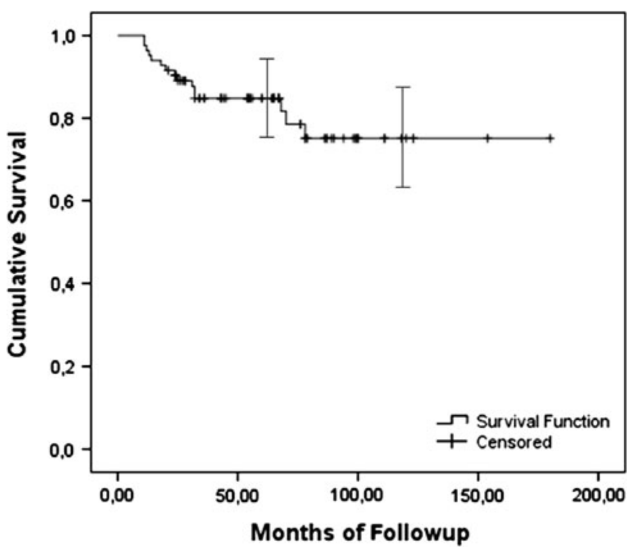

Fig. 3 A graph shows a Kaplan-Meier curve for survival of the intercalary allografts. The overall survival rate of the 83 intercalary allografts was 85% at 5 years (95% CI: 93%–77%) and 76% at 10 years (95% CI: 89%–63%).

Results

The overall survival rate of the 83 intercalary allografts was 85% at 5 years (95% confidence interval [CI]: 93%–77%) and 76% at 10 years (95% CI: 89%–63%) (Fig. 3). Thirteen patients died of pulmonary metastases after 24 months without failure of the reconstruction. Three patients had local recurrences. Two were in the soft tissue and were resected with wide margins so the allograft was not affected. The remaining patient had an amputation.

We identified 38 patients with complications requiring a second surgery, including the three with local recurrences: one with deep infection, 14 with fractures, and 20 with nonunions. In 15 of these 38 patients, the allograft was removed. In the patient with an acute deep infection, we removed the allograft and implanted a temporary cement spacer with antibiotics. After 6 weeks of intravenous antibiotics and another 6 weeks of oral antibiotics, we reimplanted an intercalary allograft. The fracture rate was 17% (14 of 83); most occurred at the distal femur metaphysis (13 fractures) and were related to areas of the allograft not covered by the internal fixation (Fig. 4). We initially fixed 12 of these fractured allografts with plate and screws and two with an intramedullary nail. In 13 of these patients, the allografts were removed. In one pediatric patient, the fracture was at the diaphysis and was stabilized with a strut allograft and a new plate without removing the original allograft. Of the 13 patients with fracture, nine were reconstructed: eight had another intercalary graft, and one had conversion to an osteoarticular allograft. We salvaged the remaining four patients using a distal femur endoprostheses. Twenty patients developed a nonunion: two at both osteotomies and 18 at one osteotomy. Of these 20 patients, 15 received preoperative chemotherapy and three received adjuvant radiotherapy. Although all patients with a nonunion required a second surgery, such as replating, autograft addition, or nail dynamization, none were associated with failure of the allograft. Twenty-two of

Fig. 4A–C In a patient who was reconstructed after tumor resection with an intercalary femur allograft stabilized with an intramedullary nail and screws, a fracture occurred at the level where the allograft was not covered by the internal fixation. (**A**) AP and (**B**) lateral radiographs show the metaphyseal area is not protected with internal fixation. (**C**) A lateral radiograph shows the knee after a metaphyseal fracture in the area not protected with internal fixation.

166 (13%) host-donor junctions did not initially heal. For diaphyseal junctions, the nonunion rate (20%, 19 of 95) was higher ($p = 0.000$) than the rate for metaphyseal junctions (1%, three of 71). The nonunion rate was 28% (seven of 25) for diaphyseal junctions fixed with nails and 15% (11 of 70) for those fixed with plates and screws. We found no relationship between nonunion rates and the use of different fixation ($p = 0.1$) or between patients treated with chemotherapy and Grade III to V complications ($p = 0.14$).

In the 68 patients who retained the allograft, the mean MSTS functional score was 27 of 30 (range, 24–30) at a mean followup of 68 months (range, 26–182 months).

Discussion

The principal aim of limb salvage is to preserve function without compromising survival. Due to early diagnosis, more accurate imaging techniques, and advanced chemotherapy, many tumors compromising the metadiaphyseal region of long bones can be treated with epiphyseal preservation [18], permitting a better limb function because of the conservation of the proximal and distal joint. These tumor resections originate in segmental bone defects that can be reconstructed using diverse alternatives [1, 3, 6, 14, 17, 22]. Implantation of intercalary femoral allografts after tumor resection is one biologic option, especially in young and physically active patients who place high demands on the reconstructions. However, most studies analyze all types of intercalary reconstruction without focusing on this anatomic site. There is little literature showing the results of isolated femoral intercalary reconstructions (Table 2). We therefore determined (1) the mid- and long-term allograft survival, (2) local recurrences, (3) complications, (4) risk factors for allograft failures, and (5) function in patients treated with this reconstruction.

Our study has certain limitations. First, we have no control group with alternate approaches, since one always treats these patients the way one believes best and would not likely randomize them into groups with alternative methods. Second, the group has some inherent heterogeneity in terms of diagnosis, chemotherapy, the amount of soft tissue resection, extension of internal fixation, amount of compression at the host-donor junction, and anatomic allograft fitting, which could affect the incidence of complications. Although this is a large series for the type of reconstruction, the subgroups are too small and heterogeneous (with various confounding and uncontrolled variables) to have adequate power to identify whether and how these influence graft survival.

There are several options for reconstruction of defects in the femoral diaphysis after resection of the tumor. Autogenous fibular grafting is a biologic method with advantages, such as restoring bone stock and reported survival rates ranging from 70% to 89% [7, 14, 24], but may require a lengthy period of nonweightbearing to allow for union/graft hypertrophy (average time to full weightbearing, 28 weeks). Also, some reports show a high incidence of fractures (30%–50%) and nonunions (15%–25%) and substantial morbidity at the donor site, and the method may be limited for large defects [7, 14, 24]. Extracorporeally irradiated autogenous bone grafts are suitable for larger defects, with reported survival rates of 100% [14]. Irradiated bone is brittle and takes a long time to revascularize and incorporate into surrounding bone; therefore, the patient may require a lengthy period of nonweightbearing to allow for union incorporation. Fractures and nonunions are also common complications, and major complications are around 50% [3, 8, 16]. Limb salvage surgery using distraction osteogenesis with bone transport and application of an external fixator is a biologic reconstruction method with acceptable results [5, 22]. Nevertheless, Tsuchiya et al. [22] advises against using this method for segmental defects exceeding 15 cm in length, making the technique inappropriate for the larger femoral defects commonly seen in sarcomas located at the diaphysis. Endoprosthetic reconstruction of the femoral diaphysis, although resulting in a reasonable functional outcome, allows patients early weightbearing and function [1, 2, 4, 12], and some studies show reasonable survival rates [2, 12]. Complications with this reconstruction

Table 2. Comparison of results after intercalary femoral reconstructions from the literature

Study	Number of cases	Followup (years)	Reconstruction survival (%)	Complication rate	Infection rate	Local recurrence rate	Fracture rate	Nonunion rate	Function (MSTS)
Hanna et al. [12]	23	8	85% (5 year) 68% (10 year)	31%	4%	4%	13%	NA	87%
Krieg et al. [16]	16	4	100%	44%	0%	0%	6%	16%	85%
Aponte-Tinao et al.	83	5	85% (5 year) 76% (10 year)	46%	1%	4%	16%	24%	90%

MSTS = Musculoskeletal Tumor Society; NA = not available.

method include aseptic loosening, infection, mechanical failure, fracture of the prosthesis or adjacent bone, local recurrence, and metastatic spread. The problem with this technique is that a large segment of proximal and distal femoral bone is needed to fix the stem prosthesis, and in many situations, only a small segment of epiphysis remains after the tumor resections. This could limit the diaphyseal endoprosthesis indications.

The ultimate goal must always be to achieve adequate excision of the tumor. Three patients had local recurrences (4%); two were in the soft tissue and were resected with wide margins so the allograft was not affected. This rate of local recurrences is comparable to the series of Hanna et al. [12] reporting one local recurrence in 23 patients (4%).

In this series, fractures remained a major problem. The incidence of fracture in our series was 17%, and we found no association between fracture and the use of a plate. A higher incidence of allograft fracture is also reported in relation to screw holes, suggesting allografts are very sensitive to stress-concentrating defects [21, 23]. Vander Griend [23] reported plate fixation was associated with a higher rate of fracture of the allograft. In a previous report [19], we suggested the risk of fracture may be diminished by spanning the entire allograft with a long plate to provide extracortical support. In this study, most fractures were located at the distal femur metaphysis and were related to areas not covered by the internal fixation.

Nonunions were another common complication (24%). Hornicek et al. [13] suggested chemotherapy could negatively influence the allograft-host junction, considering the higher incidence of nonunion in patients receiving adjuvant therapy. We observed no association between allograft failure and adjuvant therapy: none of the patients with a nonunion had allograft failure. Another study analyzing the effect of internal fixation on healing of large allografts showed an association between achieving stable fixation and development of nonunion but no differences between the rate of union after fixation with a plate and after intramedullary fixation [23]. We found patients with plate fixation had lower numbers of nonunions. However, patients fixed with nails had a similar nonunion rate to those fixed with plates. We did observe a difference in nonunion rate comparing diaphyseal with metaphyseal osteotomies. This event is also described in a previous publication [19] and may be related to the better consolidation rate observed in metaphyseal bone. Only one of our patients developed deep infection, requiring a two-stage revision to a new allograft. Rates of infection in other studies of allograft reconstruction range from 6% to 30% [11, 17, 20], which is similar to or even higher than our rate.

The mean MSTS score for the patients retaining their allograft was 27 of 30 (range, 24–30). These are good results at nearly 10 years after surgery and compare favorably with similar studies [1, 12, 20]. These excellent functional benefits could be related to the possibility of preserving both the hip and the knee.

In conclusion, our observations suggest segmental allografts of the femur provide an acceptable alternative in reconstructing tumor resections.

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