

How to Overcome Complications of Allograft Transplantation?

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Purpose: We evaluated the complications of allograft reconstruction after a bone tumor resection, and reviewed literatures to overcome such complications.

Materials and Methods: We retrospectively reviewed clinical records and radiographs of fifteen patients in whom reconstruction with allograft after bone tumor resection.

Results: Eight patients were men and seven were women with a mean age of 27.1 years (1-56 years) and a mean follow-up period of 89.5 months (33-165 months). All postoperative complications related to the allograft were recorded. Twenty patients (80.0%) obtained a radiologic bony union at a mean of 8.35 months (4-12 months). The mean Musculoskeletal Tumor Society score was 73.5% (46.6-93.0%). Nine patients (60.0%) experienced one event and 3 (20.0%) patients experienced multiple events during the follow-up period. Recorded events were infection (3), fracture (2), nonunion (2), limb length discrepancy (2) and varus deformity (2). The mean event free survival period was 60.8 months (6-144 months). The mean allograft survival period was 80.2 months and the 5 year survival rate of the allografts was 83.0%.

Conclusion: In order to overcome complications, the combination of an allograft and vascularized fibular graft is highly recommended. In the near future, the tissue engineering technique, the application of the stem cell and PRP, could reduce the complication of allograft such as resorption and nonunion.

Key words: bone tumor, allograft transplantation, complication

Introduction

Allograft reconstruction is one of the functional reconstructive options, as a biologic reconstructive alternative to the bone defect in limb salvage surgery.¹⁻³⁾ However, allograft transplantation after malignant bone tumor and aggressive benign bone tumor have shown a high rate of complications.²⁾ Mankin et al reported the complications of allograft in 870 massive frozen cadaveric allografts over a long term.²⁾ During the first 3 years complications including fracture (19%), nonunion (17%) and infection (11%) before achieving stability with their grafts.²⁾ Many other authors reported similar results concerning complication after allograft reconstruction.³⁻⁹⁾

The most common causes of graft failure are limited incorpora-

tion of the allograft into host tissue, infections, fractures, or unopposed resorption.¹⁰⁾ Early vascular invasion is a critical factor in bone allograft incorporation and consequent success of the surgery. Bone formation is correlated with better vascular invasion and remodeling of the graft. However, it has been proven that only slow and incomplete bone integration is possible by using frozen allografts in the treatment of bone defects.^{11,12)} Therefore, accelerating and increasing the revascularization may be critical to allow bone healing and integration.¹¹⁾ In this context, vascularized autografts retain their biologic and mechanical properties, heal by primary union, and can result in hypertrophy in response to load.^{13,14)} Moreover, there is hypothesis that the use of autologous bone marrow mononuclear cell has a role in the re-building of large segmental defects.¹¹⁾

The purpose of this study was to evaluate the complications of reconstruction after a bone tumor resection for the period of event-free survival, and allograft survival as well as to elucidate how to prevent and overcome these complications based on our experiences and the literatures that have been reviewed.

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Materials and Methods

We retrospectively reviewed the records of consecutive patients who underwent allograft reconstruction between 1990 and 2008. Inclusion criteria included (1) implantation of an allograft for treatment of aggressive benign bone tumor and malignant bone tumor; (2) absence of prior surgical treatments for the bone tumor; (3) complete clinical, radiographic, and pathologic records; and (4) minimum follow-up period of 2 years since allograft reconstruction. We calculated the postoperative follow-up period from the date of the primary allograft surgery to the most recent patient encounter or death.

We observed twenty-six patients who had allograft reconstruction performed by one surgeon. We excluded eleven patients who had less than two years of follow-up period, and nine of eleven who died within two years of the initial allograft implantation. Two of eleven patients were excluded because of insufficient clinical information due to follow-up loss. The remaining fifteen patients were the subjects of this study.

Eight patients were men and seven were women with a mean age of 27.1 (range, 1–56 years) at the time of surgery and a minimum follow-up period of 33 months (mean, 89.5 months; range 33–166 months). The diagnoses were osteosarcoma in nine patients, chon-

drosarcoma in three patients, giant cell tumor in two patients and metastatic bone tumor in one patient. The types of reconstruction were the intercalary reconstructions in five patients, allograft-prosthesis composites in four patients, osteoarticular reconstructions in three patients, and arthrodesis in two patients. Ten patients received chemotherapy, and five patients with chondrosarcoma or giant cell tumor did not receive chemotherapy (Table 1).

The operative procedures conformed to principles of the management of malignant and aggressive bone tumors.¹⁵⁾ No surgical margins of resection were positive according to the operation records and the pathologic reports. We used fresh-frozen cadaveric allografts for reconstruction. Reconstruction of the ligaments, tendons, and joint capsule were handled as meticulously and carefully as possible. Immobilization was performed in all cases with either casts or splints for a minimum of 6 weeks, on a case-by-case basis.

All postoperative complications related to the allograft transplantation were recorded. We also focused on the treatment that was given for each complication (Table 1). The events consisted of surgical addition of allograft for structural support, revision of any part of the allograft, and removal of the allograft. We recorded specific events as following way. Nonunion was defined as no evidence of radiographic bridging of the approximated ends between allograft

Table 1. Patients' Characteristics

No	Age	Sex	Location	Diagnosis	Type of reconstruction	Union (months)	Functional score (%)	Oncologic result	Follow-up (months)	Event number	Event-free survival (months)	Allograft survival (months)
1	12	M	PT	Osa	Arthrodesis	12	60	NED	127	2	69	74
2	24	M	Pelvis	Chondrosa	Arthrodesis	4	50	CDF	113	1	101	113
3	1	M	PT	Osa	Intercalary	8	76	CDF	165	1	21	165
4	6	F	DF	Osa	Intercalary	9	76	CDF	58	1	37	58
5	37	F	ST	Osa	Intercalary		83	CDF	76	1	6	76
6	56	F	PF	MBT	APC	9	60	CDF	166	1	98	98
7	13	M	PH	Osa	Osteoarticular		46.6	CDF	47	2	9	29
8	44	M	PT	Chondrosa	Intercalary	12	77	CDF	40	2	21	40
9	14	F	DF	Osa	APC	5	83	CDF	128	0	128	128
10	11	F	PT	Osa	Intercalary	11	93	CDF	110	0	110	110
11	31	F	PH	Osa	Osteoarticular	12	90	CDF	144	0	144	144
12	53	F	Patella	Osa	Osteoarticular		83	CDF	33	0	33	33
13	22	M	DF	GCT	Intercalary	4	83	CDF	46	0	46	46
14	46	M	DF	GCT	APC	9	83	CDF	38	0	38	38
15	37	M	Pelvis	Chondrosa	APC	5	60	CDF	52	0	52	52
Average	27.1					8.3	73.6		89.5	0.8	60.8	80.2

PT, proximal tibia; Osa, osteosarcoma; NED, no evidence of disease; Chondrosa, chondrosarcoma; CDF, continuous disease free; DF, distal femur; ST, shaft tibia; PF, proximal femur; MBT, metastatic bone tumor; APC, allograft-prosthesis composite; PH, proximal humerus; GCT, giant cell tumor.

and host bone on two consecutive radiographs taken, at least two months apart in a minimum of 6 months from the index procedure.⁴⁾ Limb leg discrepancy was observed in an immature skeletal patient after allograft transplantation. Implant/prosthesis infection involved various extents, from simple wound problems such as marginal necrosis to deep infections due to allograft. The evaluation criteria of Musculoskeletal Tumor Society 1993 was used for functional evaluation and radiologic bony union was evaluated at the last follow-up.¹⁶⁾

Event-free survival, allograft survival and patient survival were assessed with Kaplan-Meier survival analysis. The end point for event-free survival was the time of occurrence of first event, and for patients who did not experience an event, the date of the last follow-up. The end point for allograft survival was the date of allograft removal or amputation or the date of last follow up for patients who retained their allograft. The end point for patient survival was the date of death or last date the patient was known to be alive.⁴⁾

Results

Twelve of fifteen patients (80.0%) obtained a radiologic bony union at mean of 8.35 months (range, 4-12 months). Two patients with nonunion were treated by plate fixation and autogenous iliac bone

graft. Bony union was not observed in one patient (case 12) because reconstruction in this patient was performed mostly between soft tissues (Table 2).

Nine of fifteen patients (60.0%) experienced an event during the follow-up period, and three patients (case 1, 7, 8) experienced multiple events (Fig. 1). Three patients (20.0%) had infections, and the infected allograft was removed in two patient (case 6, 7). Two patients (13.3%) had allograft fractures, and one patient (case 1) was treated by multiple plating and bone graft, and the other (case 8) was treated by long leg cast. Two patients (13.3%) had varus deformities (13.3%), and one of these patients (case 9) was treated by corrective osteotomy, and the other (case 3) was treated by ipsilateral fibular transposition. Varus deformities seemed to be resulted from allograft resorption similar to allograft fracture. Two patients (13.3%) had limb leg discrepancies, which is treated by gradual lengthening, vascularized fibular bone graft and secure internal fixation after lengthening. In the follow-up radiograph, we observed resorption of allograft which was later remodeled by transposed fibula or vascularized fibula bone graft (case 3, 4, 10). The mean event-free survival was 60.6 months (range, 6-144 months). The 2-, 5-, and 10-year event-free survival rates were 61.1%, 55.0% and 13.7% respectively (Fig. 2).

Allograft was removed three of fifteen patients (20%). The causes

Table 2. Events, Overcome of Events, Fibular Use and Cause of Allograft Removal

No	Events	Overcome of events	Fibular use	Cause of allograft removal
1	Fracture at 69 months Limb leg discrepancy at 81 months	Plating & bone graft Internal bone transport	None	Local recurrence
2	Infection at 101 months	Surgical debridement	None	Intact
3	Varus deformity at 21 months	Ipsilateral fibular transposition	Used	Intact
4	Limb leg discrepancy at 37 months	Lengthening of allograft & VFBG	Used	Intact
5	Nonunion at 6 months	Plating & bone graft	None	Intact
6	Infection at 98 months	Allograft removal	None	Infection
7	Nonunion at 9 months Infection at 29 months	Iliac bone graft Allograft removal & VFBG	Used	Infection
8	Varus deformity at 21 months Fracture at 36 months	Corrective osteotomy & bone graft Long leg cast	None	Intact
9	None	Not applicable	None	Intact
10	None	Not applicable	Used	Intact
11	None	Not applicable	None	Intact
12	None	Not applicable	None	Intact
13	None	Not applicable	None	Intact
14	None	Not applicable	None	Intact
15	None	Not applicable	None	Intact

VFBG, vascularized fibular bone graft.

of removal were infection in two patients (case 6, 7) and local recurrence in one patient (case 1). Infection was effectively controlled by vascularized fibular bone graft (VFBG) in one patient (case 7). A patient with local recurrence was treated by insertion of tracer after allograft removal.

The mean allograft survival period was 80.2 months and the 2-, 5-, and 10-year allograft survival rates were 88.9%, 83.0% and 60.5% respectively (Fig. 3). The mean MSTS scores were 73.5% (range, 46.6–90.0%) at the final point of the follow-up period.

Discussion

Allograft transplantation after malignant bone tumor and aggressive benign bone tumor have been reported to have a high rate of complications.² Especially during the first 3 years the allograft resulted in fracture (19%), nonunion (17%) and infection (11%) before achieving

stability with their grafts.² Therefore most complications of allograft transplantation occurred within the first 3–5 years postoperatively.^{2,17} The events occurred at a mean of 53.1 months in our series.

The overall complication rate was high (60%) in our study. Similar studies reported the complication rates between 39% and 70%.^{2–4,9,18,19} Even though the complications occurred in 60% of the patients, only 20% of the patients with complication experienced allograft removal. These results corroborate even if most allograft transplantation experience such events, the removal of allograft can usually be avoided, case by case. However, other authors reported opposite results.^{4,20}

In four cases in our series, fibula bone was utilized by various methods such as fibula bone transposition and VFBG. Fibula transposition was performed in cases where proximal tibia had immature skeletal ages (case 3, 10). After mean follow up period of 137.5 months (165+110 months), allograft resorption and hypertrophy of fibula were observed. In the late 1980s, Capanna et al. introduced the concept of hybrid reconstruction by combining allograft shell with free vascularized fibula.²¹ Many authors reported that combined graft (VFBG + allograft) provided good results in reconstruction of proximal tibia.^{22,23} Fibular transposition is a simpler surgical method compared to VFBG, so fibular transposition can be option of biologic augmentation in proximal tibia reconstruction as the reason of anatomic neighboring districts.

VFBG was performed to reconstruct a segmental defect after gradual lengthening of allograft due to limb leg discrepancy (case 4) and to reconstruct a defect after removal of allograft due to infection (case 7). VFBG is the ideal material for reconstruction especially in the childhood.^{22,23} In a case of allograft removal, VFBG reconstruction was performed for infection control. VFBG was favorable when

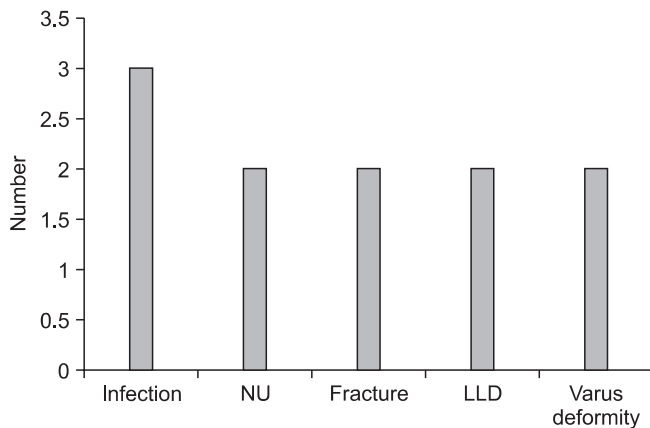


Figure 1. This graph shows the allograft-related complications that occurred in patients (NU, nonunion; LLD, limb length discrepancy).

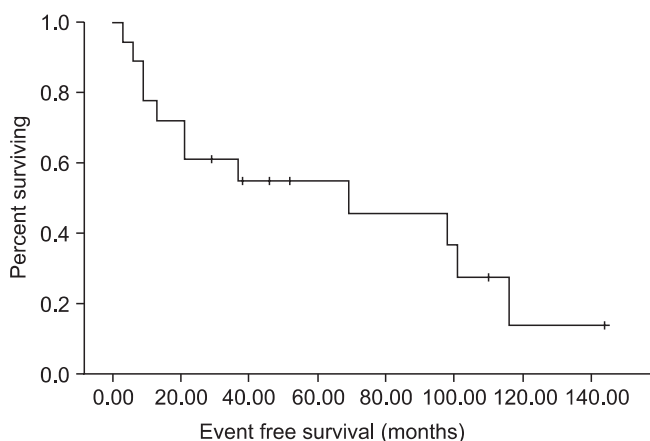


Figure 2. The Kaplan-Meier survival curve represents event free survival for all patients.

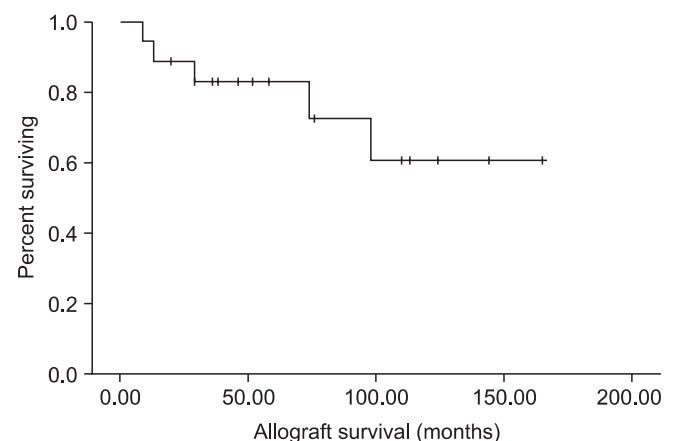


Figure 3. The Kaplan-Meier survival curve represents allograft survival for all patients.

compared with infection rates reported in allograft use (16–30%).^{2,9,13,17}

In our series, 3 patients (20%) experienced infections. Infection is only the reason for allograft removal except for local recurrence. Allograft was removed in two cases and surgical debridement and antibiotics treatment was done in the other case. Graft failure rates after infection is over 80% and approximately one third of patients who have infected allograft eventually will need an amputation.^{2,9,17,24} Infections are difficult to avoid in these operations for numerous reasons: multiple surgeries, resection of large amounts of tissue, skin sloughing, adjuvant treatment, and poor blood supply to the allograft.^{25–27}

Allograft fractures occurred in 13.3% of patients. In our series, there was no case of allograft removal after fracture. Many studies reported increased risk factors of allograft fracture, functional outcome after allograft fracture, strategies to reduce fracture rate, biomechanical behavior after allograft transplantation.^{3,18,20,24,28,29} In spite of these efforts, allograft fracture is still a common problem.

Nonunion occurred in 13.3%. In all cases, we achieved union after bone graft alone, or plating and bone graft. There was no case of allograft removal after nonunion. One study reported 30% of nonunions resulting in allograft failure, requiring replacement of the allograft or amputation of the limb.³⁰ And Hornicek et al. reported three or more surgical attempts to correct the nonunion.³⁰ Many studies reported increased risk factors of nonunion and reduced factors about surgical technique.^{25,29,30} As with fracture, nonunion was related to problems with incorporation of the dead allograft bone into the living host bone.⁴ If the living host bone has poor osteoinductive capacity, correcting a nonunion is expected to be difficult.⁴

Varus deformities (13.3%) occurred in proximal tibia. These deformities were corrected by corrective osteotomy (case 9) and ipsilateral fibula transposition (case 3). In the latter case, corrective osteotomy was performed at the proximal junction site due to progressive varus deformity. It may be the reason for allograft resorption and nonunion. In the follow-up radiograph, we observed varus deformities due to the result of allograft resorption similar to allograft fracture.

Limb leg discrepancies (13.3%) occurred in immature skeletal age. One case of LLD (case 1) was treated by internal bone transport and secure internal fixation. Another case of LLD (case 4) had internal bone transport of allograft and segmental defect was reconstructed by VFBB. Other two cases (case 3, 10) was augmented by ipsilateral fibular transposition in immature skeletal age before LLD was occurred. On last follow-up, the functional scores were acceptable (76%, 93%) and hypertrophied fibula seemed to have increasing bony mass

up to a remodelling level, which can be considered as the outcome of its reactive hypertrophy.^{13,31} Compared to other reconstructive options, the use of allograft and VFBB showed superior outcome especially in skeletal immaturity as in LLD.^{22,23}

Although rate of complication occurrence in allograft transplantation is high, published results for allografts show success rates of 66% to 84%.^{2,3,18,19,20} In our series, we also found high functional scores of 73.6% using MSTs scoring system. The lowest score was recorded in VFBB reconstruction after allograft infection (case 7, 46.6%) The highest score was recorded in a case that initially had ipsilateral fibula transposition with intercalary allograft reconstruction (case 10, 93%).

Until now VFBB is the most attractive option to prevent and overcome complications after allograft transplantation. Many authors described the advantages of combined grafts (vascularized fibular bone graft + massive bone allograft) in reconstruction following segmental skeletal resection for bone sarcoma.^{22,23,31} The use of the free vascularized fibular graft as a salvage method for complications of allograft reconstruction of the long bones has been reported.^{32,33} The rationale for a combined graft is to combine the advantages provided by the mechanical endurance of a massive allograft to the biological properties of the vascularized fibula graft. The allograft provides adequate bone stock and early stability, while the VFBB facilitates the host-allograft union and can hypertrophy.^{31,34,35}

However VFBB is technically difficult and takes prolonged operative time. Moreover, long-learning curve is needed. Recently the repair of large defects by using prosthesis or hydroxyapatite bone substitutes combined with mesenchymal stem cells have become increasingly popular; moreover, allograft or autograft bones are also an attractive alternative to restore large segmental defects when combined with osteogenic proteins (like OP-1 or BMPs).^{11,36} Also there is hypothesis that the use of autologous bone marrow mononuclear cell has a role in the re-building of large segmental defects.¹¹ Also, Lucarelli et al. reported that stromal stem cells and platelet-rich plasma could be a key role in bone repair.³⁶

This study has the limitations of retrospective chart reviews without a control group, and standardization of surgical techniques. Other limitations include small sample size, variety among patients in diagnoses and location of tumor. Some patients in this study had a relatively short follow-up period.

Allograft reconstruction after bone tumor resection had a high rate of adverse events (60.0%) and allograft was removed in 20.0% during the follow-up period. Until now to overcome allograft related complications, the combination of an allograft and vascularized

fibular graft is highly recommended. In the near future, advance in tissue engineering technique and application of the stem cell and PRP to the allograft are expected to reduce the complication of allograft such as resorption and nonunion.

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골종양 절제 후 동종골을 이용한 재건술의 합병증 및 해결방법

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목적: 골종양을 절제한 후 동종골을 이용한 재건술 후 발생한 합병증을 평가하고 그 합병증에 대한 문헌고찰을 하고자 한다.

대상 및 방법: 골종양 절제 후 동종골을 이용한 재건술을 시행한 15예에 대하여 임상적 및 방사선학적 자료를 통해 후향적으로 연구를 시행하였다.

결과: 남자가 8예, 여자가 7예이었으며 평균 나이는 27.1세(1-56세), 평균 추시 기간은 89.5개월(33-146개월)였다. 21예(80.0%)에서 평균 8.35개월(4-12개월)에 방사선학적 골유합 소견을 보였다. Musculoskeletal Tumor Society 점수 평균은 73.5%(46.6-93.0%)였다. 동종골 이식과 관련된 술 후 합병증을 모두 기록하였다. 추시 기간 동안 9예(60.6%)에서 한 가지의 합병증이 발생하였고 3예(20.0%)에서 두 가지 이상의 합병증이 발생하였다. 합병증으로는 감염 3예, 골절 2예, 불유합 2예, 하지 부동 2예, 내반 변형이 2예였다. 합병증이 발생하지 않은 평균 기간은 60.8개월(6-144개월)이었다. 동종골의 평균 생존기간은 80.2개월이었고 5년 생존률은 83.0%였다.

결론: 동종골의 합병증을 줄이기 위하여 동종골을 이용한 재건술시 자가비골을 추가하는 것이 추천된다. 더 나아가 조직 공학 기술과 줄기 세포 및 혈소판 풍부 혈장의 적용이 동종골의 재흡수나 불유합 등의 합병증을 줄일 수 있을 것으로 생각된다.

색인단어: 골종양, 동종골 재건술, 합병증

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