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ORIGINAL ARTICLE

Long-term Results for Limb Salvage with Osteoarticular Allograft Reconstruction

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Abstract Osteoarticular allograft reconstruction after extremity tumor resection has been shown to have a high rate of complications. Although good functional results have been seen, long-term outcomes have not been well studied. We performed a retrospective review of 20 patients who underwent primary osteoarticular allograft reconstruction after extremity sarcoma resection. All postoperative complications related to the allograft reconstruction were recorded. Musculoskeletal Tumor Society 1993 and Toronto Extremity Salvage Score scores were used for functional evaluation at last followup. Minimum followup was 10 years (mean, 16 years; range, 10–21 years). Seventy percent of patients experienced an event during the followup period. Recorded events were fracture (nine patients), progressive arthritis (five), nonunion (four), and infection (two). Sixty percent of allografts were removed at a mean of 5.2 years. Progressive arthritis led to total joint arthroplasty in five patients (25%). Mean Musculoskeletal Tumor Society and Toronto Extremity Salvage Score functional scores were 25 of 30 and 95% for patients who retained their original allograft. Osteoarticular allograft reconstruction for extremity sarcomas had a high rate of adverse events (70%) and allograft removal (60%) at long-term followup. Functional outcomes of patients with intact grafts were comparable to outcomes with segmental replacement prostheses reported in the literature.
Level of Evidence: Level IV, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

With the evolution of surgical techniques, adjuvant therapies, and imaging modalities, limb-sparing surgery has become a reasonable alternative to amputation for malignant tumors of the extremities [6, 22]. Its role was confirmed by evidence that limb-sparing surgery does not compromise survival compared with amputation [30, 33]. The prospect of maintaining a highly functional limb thus has led to dedicated investigations regarding how to best reconstruct the bone defect left by tumor resection.

Allografts have been used commonly since the 1970s for reconstruction of the remaining bone after limb-sparing tumor resection. Numerous studies have reported high rates of major complications, including fracture, nonunion, and infection, which often require removal or revision of the allograft [5, 12, 15, 22, 26]. The largest long-term series [22] concluded most failures occurred in the first 1 to 3 years and allografts that survived this period achieved relative stability and afforded good function for the patient. These findings have since been supported by others [15, 22, 26]. However, patient outcomes beyond 10 years have not

been well studied. The durability of allograft reconstruction is becoming even more important as survival rates for patients with sarcoma continue to improve [5, 10, 27].

The purpose of this study was to provide long-term results on the incidence of early and delayed adverse events for patients with sarcoma treated with resection and osteoarticular allograft reconstruction. The secondary aims were to determine allograft survival, freedom from degenerative joint disease, and long-term functional scores.

Materials and Methods

After Institutional Review Board approval, we retrospectively reviewed the records of consecutive patients who were treated with allograft reconstruction by the senior surgeon (RDL) between 1986 and 2002. Inclusion criteria were defined as (1) implantation of an osteoarticular allograft for treatment of a primary sarcoma of bone; (2) absence of prior surgical treatments for the sarcoma; (3) complete clinical, radiographic, and pathologic records; and (4) minimum followup of 10 years from allograft reconstruction. We calculated postoperative followup from the date of the primary allograft surgery to the most recent patient encounter or death.

We identified 60 patients who had osteoarticular allograft reconstruction performed by the senior author (RDL). Fifteen patients were excluded from this study because of a diagnosis other than sarcoma. We excluded 18 patients who had less than 10 years followup, nine of whom died within 2 years of the initial allograft implantation. Seven patients were excluded because of insufficient clinical information. The remaining 20 patients are the subjects of this study.

The 10 females and 10 males had a mean age of 20 years (range, 11–45 years) at the time of surgery and a minimum followup of 10 years (mean, 16 years; range, 10–21 years). The histologic diagnoses leading to segmental resection included 17 osteosarcomas, two chondrosarcomas, and one Ewing's sarcoma. The tumors were located in the distal femur (eight patients), proximal tibia (six), proximal humerus (four), distal radius (one), and proximal ulna (one). Eighteen patients received chemotherapy, and two patients (chondrosarcoma) did not receive chemotherapy for treatment of the tumor.

Preoperative workup consisted of history and clinical examination, routine laboratory tests, plain radiography of the affected limb, and, in cases that required further characterization of the lesion for operative planning, MRI or CT scan of the affected limb. A technetium−99m bone scan or CT scan was performed to assess for metastatic lesions. The use of preoperative and/or postoperative chemotherapy was based on sarcoma type and size and individual patient characteristics, such as functional status, tolerance of side effects, tumor response, and wishes of the patient.

Surgical technique followed standard oncologic principles of segmental resection previously described [9, 32]. We used fresh-frozen cadaveric allografts. Ligaments and tendons were reattached whenever feasible, but this varied on a case-by-case basis. Immediate postoperative immobilization was used in all cases with either casts or splints for a minimum of 6 weeks.

We recorded all postoperative complications related to the allograft reconstruction. Allografts fail in various ways. Because of our focus on allograft outcome, we defined various failure modes as events. An event constituted revision of any part of the allograft, surgical addition of hardware for additional structural support, removal of the allograft, or amputation. We characterized specific events as follows. Nonunion was defined as no evidence of radiographic bridging of the approximated ends between the allograft and host bone on two consecutive radiographs taken at least 2 months apart at a minimum of 6 months from the index procedure. Degenerative joint disease (DJD) was defined as progressive degenerative changes on postoperative radiographs compared with preoperative radiographs. Degenerative changes included joint space narrowing, osteophytes, subchondral cysts, and subchondral sclerosis. We measured functional outcomes using the Musculoskeletal Tumor Society 1993 rating scale (MSTS) [8] and the Toronto Extremity Salvage Score (TESS) [3].

Survival function values and curves were calculated with a Kaplan-Meier product limit estimator [16]. Time zero was defined as the date of the primary allograft reconstruction. The end point for event-free survival was the first event or, for patients who did not have an event, the last followup. The end point for allograft survival was the date of allograft removal or amputation or the date of last followup for patients who retained their allograft. The end point for DJD-free survival was date of joint resurfacing of the allograft or the date of allograft removal with subsequent endoprosthetic reconstruction resulting from DJD. The end point for patient survival was the date of death or last date the patient was known to be alive. We compared mean MSTS and TESS scores using the Mann-Whitney-Wilcoxon test.

Results

Seventy percent (14 of 20) of patients experienced an event during the followup period, and 11 patients experienced multiple events. The initial events were fracture in 45% (nine patients at a mean of 3.2 years) and DJD in 25% (five patients at a mean of 6.6 years) (Fig. 1). Four patients

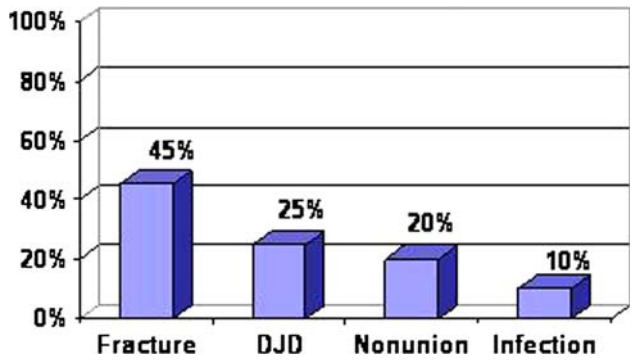

Fig. 1 This graph shows the allograft-related complications that occurred in our patients. All infections occurred after secondary procedures performed to treat complications. The infection rate after the initial allograft reconstruction was 0%.

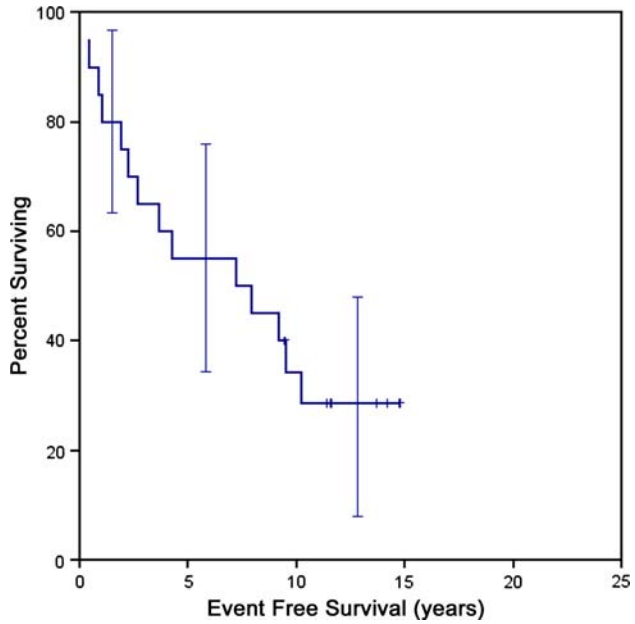

Fig. 2 The Kaplan-Meier curve represents event-free survival for all patients.

(20%) had nonunions, all of which occurred after surgical treatment for a complication. Two patients (10%) had deep infections, both of which occurred after surgical treatment for a complication. One patient had a concurrent fracture and was treated with resection of the allograft and replacement with a total hinged knee. The other case eventually resulted in amputation. The mean event-free survival was 6.9 years (range, 0.5–14.8 years). The 2-, 5-, and 10-year event-free survival rates were 75% (15 patients), 55% (11 patients), and 34% (six patients), respectively (Fig. 2).

The mean allograft survival was 8.8 years for all allografts and 5.2 years for the 60% of allografts that were removed and replaced by either another allograft or an endoprosthesis. The 2-, 5-, and 10-year allograft survival rates were 80% (16 patients), 60% (12 patients), and 45% (nine patients), respectively (Fig. 3).

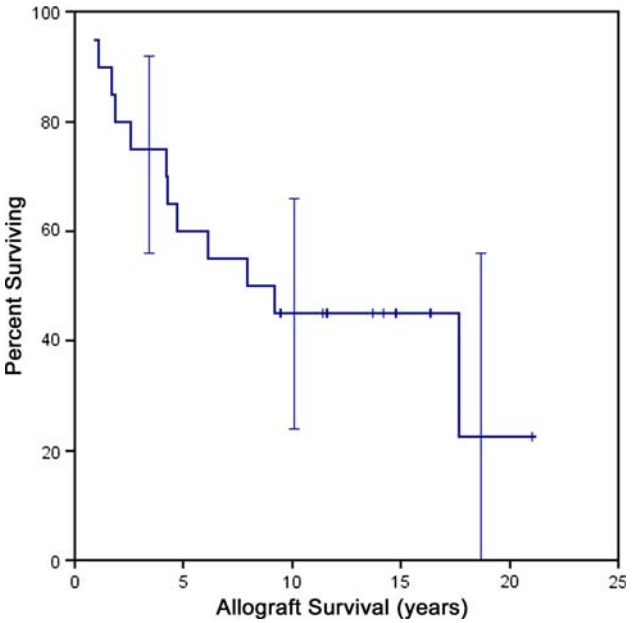

Fig. 3 This Kaplan-Meier curve represents allograft survival for all patients.

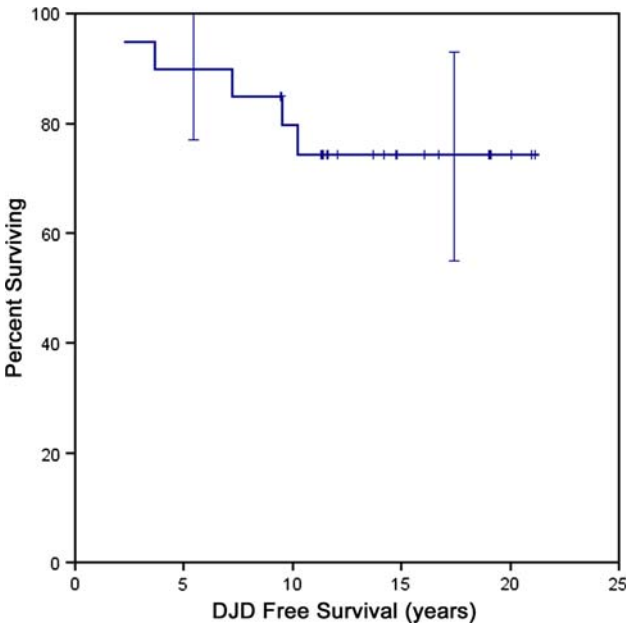

Fig. 4 The Kaplan-Meier curve represents DJD-free survival for all patients.

Five patients (25%) required surgical intervention for DJD at a mean of 6.6 years after the initial allograft reconstruction (range, 2.3–10.3 years). The 5- and 10-year DJD-free survival rates were 90% (18 patients) and 80% (16 patients), respectively (Fig. 4).

We were able to obtain functional scores for 14 of the 19 living patients, the other patients being lost to followup during the long study period. The mean MSTS and TESS scores for the 14 evaluated patients were 23 (range, 12–28) and 90% (range, 74%–98%), with 30 and 100% representing normal function, respectively. The mean MSTS and TESS scores were lower for the nine patients who had their allograft removed (22 and 87%, respectively) compared with the five patients who retained their original allograft (25 and 95%, respectively), although these results were not statistically significant ($p = 0.298$ and $p = 0.083$, respectively).

Discussion

Osteoarticular allograft reconstruction after extremity tumor resection has been shown to have a high rate of complications. Although good functional results have been seen, long-term outcomes have not been well studied. We performed a retrospective review of 20 patients who underwent primary osteoarticular allograft reconstruction after extremity sarcoma resection to determine long-term ($\geq$10 years) results.

Limitations to our study include small sample size, retrospective study design, and variety among patients in diagnoses, tumor locations, and use of chemotherapy. Allografts have been well studied, but reports with long-term data are lacking. In seeking to characterize the long-term outcomes of a procedure that rarely is done in the United States any more, we were left with a small group of patients to examine retrospectively. The group had some inherent heterogeneity in terms of chemotherapy, diagnosis, and tumor location, which could have affected the incidence of complications. Surgical techniques did evolve during the study period because many of these cases occurred during a time when limb salvage procedures were very new and tumor surgeons were performing the procedures without having standardized training. We attempted to limit the range of techniques by drawing all cases from one surgeon (RDL).

The overall rate of events was high (70%) as is typical for allograft reconstruction in patients with tumors. Similar studies with shorter followups report complication rates between 39% and 59% [5, 10, 15, 21, 27]; however, most of these studies include benign and low-grade malignant tumors, which are known to have better outcomes [22, 28]. Furthermore, our overall event rate includes DJD as a complication, which is not reported in most studies. With a mean followup of 16 years (range, 10–21 years), well beyond the typical followup for previous allograft studies, it became clear DJD is a major event that can affect long-term function and graft survival.

Although studies have shown articular cartilage viability after cryopreservation [20, 29], it is clear radiographically and histologically that the cartilage on osteoarticular allografts degenerates with time and eventually leads to DJD [7, 13]. Twenty-five percent of our patients underwent total joint arthroplasty for DJD at a mean of 6.6 years. Fox et al. [10] cited an average of 6 years to the development of arthritis in their study. Enneking and Campanacci [7] examined the articular cartilage of osteoarticular allografts for histopathologic changes in the first 5 years and found 86% had no viable chondrocytes. They also noted the onset and severity of articular cartilage degeneration seemed to be related to the degree of anatomic incongruity and instability at the allograft-host joint [7]. Remarkably, however, the necrotic cartilage still functioned well and appeared radiographically normal for up to 2 years [7]. This agrees with the points made by Fox et al. [10] that the joint may look worse than it feels and that patients often can be followed with observation only.

The most common complication in our study patients was allograft fracture, occurring in 45% of them. Factors that have been associated with an increased risk of fracture include nonunion, prior irradiation, and the combination of chemotherapy and plate fixation (as opposed to intramedullary fixation) [6]. One study that reviewed 185 allograft fractures found functional outcomes after fracture were worse in patients who had long allografts, femoral location, prior chemotherapy, or associated infection or nonunion [31]. To reduce fracture rate, some authors recommend minimizing the number of screws or using intramedullary methods of allograft fixation because screw holes create stress risers where fractures can occur [1, 6, 15, 31, 34]. However, fracture seems to be a consequence of the allograft at least as much as a problem with fixation technique [1]. Allografts incorporate into host bone by a process of creeping substitution, which involves partial reabsorption of the allograft and formation of new, vascularized bone, leaving the allograft in a weakened state during the process [10, 28, 34]. Similar to Berrey et al. [1], we found no allograft fractures occurred during the first 5 postoperative months, and most occurred from 5 months to 3 years after surgery.

Nonunion occurred in 20% of patients in our series, but all cases occurred after surgical treatment for a prior allograft complication. Reported rates of osteoarticular allograft nonunion range from 9% to 14% [14, 23, 34]. As with fracture, nonunion is related to problems with incorporation of the dead allograft bone into the living host bone. If the living host bone has poor osteoinductive capacity, correcting a nonunion is difficult. One study reported 30% of nonunions resulted in allograft failure, requiring replacement of the allograft or amputation of the limb [14]. In the same study, 17% of nonunions persisted

even after three or more surgical attempts to correct the nonunion [14]. Some factors associated with an increased risk of nonunion are infection, adjuvant chemotherapy, and the use of intercalary allografts, which have two osteotomy sites that need to heal [6, 14]. The risk may be reduced by achieving rigid and stable fixation and using cancellous autograft at junctions [6, 7, 34]. Nonunions that occur in the setting of infection, fracture, or chemotherapy typically require replacement of the allograft, whereas uncomplicated nonunions more often are salvageable [14].

Infection occurred in 10% of our patients; however, all infections followed secondary procedures performed for other events rather than the initial allograft reconstruction. The consequences nonetheless were noteworthy, with both cases resulting in allograft removal and one resulting in amputation. Infections are difficult to avoid in these operations for numerous reasons: multiple surgeries, resection of large amounts of tissue, skin sloughing, adjuvant treatments, and poor blood supply to the allograft [6, 10, 17, 24]. Superficial infections may resolve with oral or intravenous antibiotics, irrigation, and débridement. Infections that involve the allograft usually require allograft removal, maintenance of limb length with a spacer or external fixator, an extended course of intravenous antibiotics, and reconstruction with a new allograft or endoprosthesis once the infection has resolved [6, 17]. Dion and Sim [6] reported approximately ⅓ of patients who have an infected allograft eventually will need an amputation.

Although few patients escape complications, published results for allografts show success rates of 66% to 84% [5, 10, 15, 21, 22, 27, 28]. According to the criteria outlined by Mankin et al. [22], success is defined as having no evidence of disease and no major pain or functional limitations. We also found high functional scores of 23 of 30 and 90% using the MSTS and TESS scoring systems, respectively. These scores reflect the degree of function as perceived by the surgeon (MSTS) and the patient (TESS). Higher scores were found in patients who retained their original allograft, although the sample size is too small to draw definitive conclusions. Malo et al. [18] used MSTS and TESS scores to evaluate function after endoprosthetic replacement for bone sarcomas and found similar MSTS and TESS mean scores of 24 of 30 and 82%, respectively.

In our series, 60% of allografts failed and were replaced with another allograft or an endoprosthesis. All but one of our patients who experienced fracture as a first event required multiple surgeries for complications. These results corroborate the concern that even if most patients eventually achieve satisfactory results, the course can be extremely difficult for the patient and the surgeon [28].

Still, we acknowledge clinical success is the ultimate goal. In countries where the high cost of endoprostheses is a major consideration for determining treatment, patients may be willing to undergo multiple surgeries as long as they can retain a functional, tumor-free limb. Furthermore, endoprostheses are not readily available for reconstruction of the distal radius, which can be reconstructed with an allograft. In the United States, however, endoprostheses have largely replaced allografts as the preferred method for limb reconstruction after tumor resection. Although they have their own complications of loosening, wear, mechanical failure, and instability [35], complications occur later [22, 28] and seem to be easier to fix. Another option that has become more common is the combination of an intercalary allograft and a free vascularized fibula graft, which has been shown to have fewer problems with fracture, nonunion, and infection compared with either individual treatment [2, 19, 25]. The use of free vascularized fibula grafts also may have a role in osteoarticular allografts, either in the initial reconstruction or in treating the common complications of allografts [11].

To improve the outcomes of allograft reconstruction, we must identify techniques that limit the event rate. DeGroot et al. [4] described a reduced rate of fractures in cement-filled allografts of the proximal humerus. They also reported decreased severity of subchondral fractures and subsequent articular collapse in cement-filled allografts [4]. Therefore, cement may even improve the incidence of DJD in allograft reconstruction. Preventing fracture and nonunion also may limit the infection rate by avoiding additional surgeries.

We found allograft reconstruction for extremity sarcomas had a high rate of adverse events (70%) and allograft removal (60%) in patients followed for at least 10 years. Osteoarticular allografts are susceptible to DJD as a late complication that threatens function of the graft. Because most patients experienced one or more major complications that adversely affected function, excellent long-term outcomes were rare in our series. Nevertheless, allografts remain a viable option for limb-sparing tumor resections when the cost of endoprostheses is prohibitive and in the upper extremity where weightbearing stresses are minimized and endoprostheses are not always available.

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