The Results of Transplantation of Intercalary Allografts after Resection of Tumors

A LONG-TERM FOLLOW-UP STUDY*

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ABSTRACT: We reviewed the results of 104 intercalary allograft procedures that had been performed, between April 1974 and August 1992, in 100 patients, usually after resection of a segment of bone because of an osseous neoplasm. The median duration of follow-up was 5.6 years. Retention of the graft and return to essentially normal function were the measures of success and, on that basis, eighty-seven (84 per cent) of the 104 reconstructions were successful. Of the fifteen limbs in which the reconstruction failed, four were salvaged with insertion of a second allograft and three, with use of some other technique.

Of the 104 allograft procedures, eight (including two in patients who had a recurrent tumor) were followed by an amputation; thus, the ultimate rate of salvage was 92 per cent for the entire series. Thirty-one grafts failed to unite at one junction with the host or both, within one year after the operation, and this necessitated eighty-one additional operative procedures to achieve a good result.

Life-table regression analysis showed that age, gender, anatomical site, and length of the graft were not associated with significant differences in the over-all outcome. Infection (p = 0.0001); fracture (p = 0.002); stage of the lesion (p = 0.007); and use of adjuvant chemotherapy or radiation, or both (p = 0.008), all had an adverse effect on the survival of the allograft.

Despite the relatively high rate of non-union that necessitated additional operations, these data indicate that transplantation of allografts for the treatment of intercalary defects has a high rate of success and usually results in a functional limb.

Transplantation of massive allografts has become more frequent over the years as a treatment for a number of orthopaedic problems[42-44]. Although initially ad-

vocated for the treatment of bone tumors[9,13,23-25,34,36-41] and joint disease[11,19], the allograft procedure is now most often used to add bone stock to the defective femoral shaft and acetabulum or knee after failed total joint replacements[1,6,52,53]. Refinements in bone-banking, detection of viruses, cryopreservation of cartilage, and techniques of joint reconstruction have increased the safety and efficacy of the allograft procedure[5,14,21,48,50], and its popularity seems to be at an all-time high.

Of considerable importance to orthopaedists using allografts are the associated difficulties and complications, particularly when the grafts are inserted after resection of a tumor into a systemically compromised host or when the operative site is depleted of muscle and soft tissues or has been subjected to radiation[13,24,36,39]. Such complications include allograft-related infection[39], fracture[2,39,45,49], and non-union[23-25,39,41,45], all of which materially compromise the results. However, these complications usually occur within the first three to four years, and after that the graft appears to become a relatively competent, stable system[39]. In contrast, for metal implants, the early years are the good ones, and the devices begin to fail at an increasing rate in the later time-periods[3,4,7,8,15,29,35,46].

One concern of those who work with allografts is that the outcome is unpredictable. It is evident that not all grafts behave the same, and it has become important to attempt to define the factors that affect the results. Many factors have been implicated. One that has occasionally been mentioned but not emphasized is the type of graft that is used — that is, whether it is osteoarticular, intercalary, used in combination with a prosthesis, or employed as part of an arthrodesis. As has been shown in several reports from our group and other institutions, the intercalary allografts seem to have the best record, but there is only speculation as to why this is so[24,25,34,39,41].

The purpose of the current study was to analyze the results in a series of patients in whom intercalary allografts were inserted at the Massachusetts General Hospital between April 1974 and August 1992. We attempted to establish the rate of success with use of these grafts and to ascertain what factors contributed to their success.

TABLE I

DIAGNOSES FOR THE ONE HUNDRED PATIENTS
WHO WERE MANAGED WITH INTERCALARY ALLOGRAFTS

Diagnosis	No. of Patients
Ewing sarcoma	21
Chondrosarcoma	16
Adamantinoma	15
Central osteosarcoma	15
Parosteal osteosarcoma	7
Malignant fibrous histiocytoma	5
Metastatic carcinoma	5
Osteoblastoma	5
Soft-tissue sarcoma	3
Giant-cell tumor of bone, desmoplastic fibroma, angiosarcoma, fibrous dysplasia	4 (1 each)

Materials and Methods

Since November 1971, we have transplanted a total of 803 massive fresh-frozen allografts from the extremities (excluding the hemipelvis) of cadavera, mostly for reconstruction after the resection of malignant neoplasms. Of these allografts, 190 were intercalary (inserted between two segments of the same bone, without inclusion of a second bone for an arthrodesis), and 153 of the 190 were followed for at least two years. We excluded forty hemicylindrical grafts (those including only a portion of the circumference of the cortex), three grafts inserted in patients who had severe fibrous dysplasia, and one graft used as an internal strut in a patient who had an aneurysmal bone cyst; an additional five grafts were lost to follow-up. Thus, the study group comprised 104 grafts in 100 patients. Four grafts were second grafts, inserted after an earlier graft had failed; for the purpose of this study, these four grafts were counted separately and were classified as failures.

The mean age and standard deviation for the 100 patients was 28.3 ± 18 years (range, four to sixty-nine years; median [and standard error], 21.5 ± 1.4 years). The mean duration of follow-up was seventy-three months (range, twenty-four to 220 months; median [and standard error], 67.2 ± 6.0 months). Forty-seven patients were male and fifty-three were female.

Of the 104 grafts, forty-seven were used after resection of a high-grade tumor; forty-two, a low-grade tumor; and seven, a benign tumor. The remaining eight were used for treatment of a non-tumorous condition (Table I). Thirty-nine allografts were inserted in the femur; thirty-eight, in the tibia; nineteen, in the humerus; three each, in the radius and the fibula; and two, in the ulna.

The allografts were obtained from the Massachusetts General Hospital Bone Bank. All allografts were obtained, processed, and studied for bacterial or viral
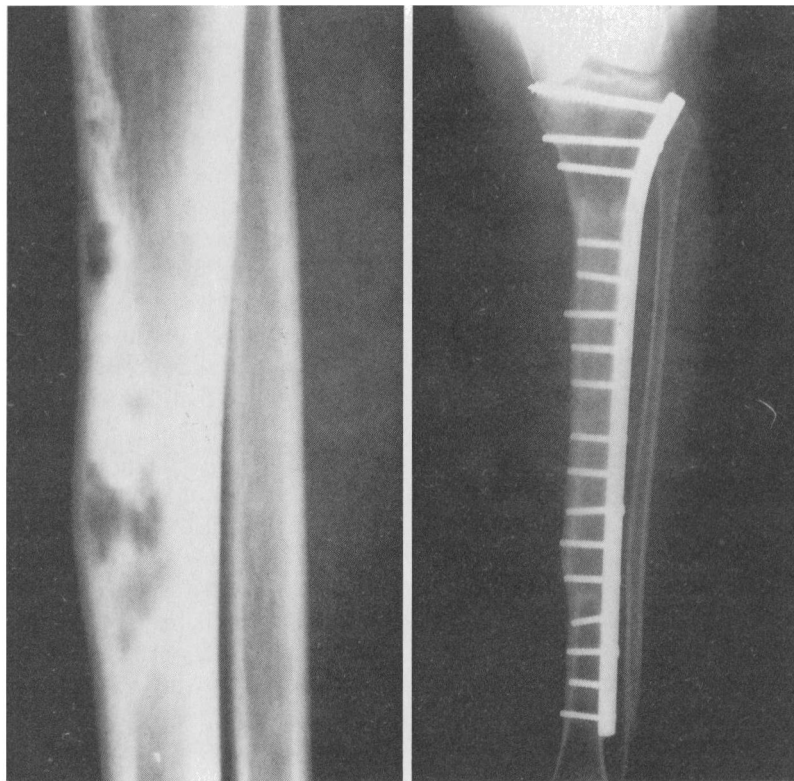

FIG. 1-A   FIG. 1-B

Figs. 1-A and 1-B: Radiographs of an eighteen-year-old woman who was managed with an intercalary allograft because of an adamantinoma of the tibia.
Fig. 1-A: Radiograph showing the adamantinoma.
Fig. 1-B: Eight years after the operation, the host-allograft junctions have healed completely. The patient had full function.

TABLE II

COMPLICATIONS ASSOCIATED WITH THE
ONE HUNDRED AND FOUR INTERCALARY ALLOGRAFTS*

Complication	No. of Grafts
High-grade tumors (n = 47)	
Death	8 (17%)
Metastasis	11 (23%)
Local recurrence	4 (9%)
All allografts (n = 104)	
Infection	12 (12%)
Fracture	18 (17%)
Non-union	31 (30%)

*Some allografts were associated with more than one complication, so the data are not additive.

infection, or both, in accordance with the recommendations of the American Association of Tissue Banks[14,21,50] and the tests available at the time. In the early part of the study (1974 through 1982), there seemed to be little reason for concern with regard to transmission of viruses. That circumstance changed, and the Massachusetts General Hospital Bone Bank currently takes elaborate precautions to avoid such transmission, including subjecting blood from the donor heart to testing for antibodies to human immunodeficiency viruses 1 and 2 and human immunodeficiency virus antigen as well as polymerase chain reaction assay in order to detect acquired immunodeficiency syndrome, testing for s and c antigens for hepatitis B, and testing with hepatitis-C-virus antibody assay (HCV 2.0) in order to detect hepatitis C[5,21,48].

Operative treatment consisted of resection of the tumor (when present) with use of a wide soft-tissue margin or, less often, a marginal margin[17] and insertion of an allograft segment tailored to fit the bone defect. Seven grafts were fixed with intramedullary rods and the remaining ninety-seven, with an array of plate-and-screw combinations. Of these ninety-seven grafts, fifty-six were fixed with one long plate held with cortical and, occasionally, cancellous-bone screws (Figs. 1-A and 1-B); fourteen, a long plate and one or two separate smaller plates at the sites of osteosynthesis (Figs. 2-A and 2-B); twenty-one (inserted early in the series), two shorter plates at each junction (with an unsupported segment sometimes left in between) (Figs. 3-A and 3-B); and six, a variety of special systems involving cancellous-bone screws, buttress plates, staples, and so on, designed to hold the new segment to a very short host metaphyseal region. Sixteen segments had a length of less than ten centimeters; fifty-nine, a length of between ten and eighteen centimeters; and the remaining twenty-nine, a length of more than eighteen centimeters.

All patients received antibiotics intravenously both intraoperatively and postoperatively, usually for one week, and then orally for a variable period after discharge from the hospital. The extremity was immobilized in a cast, usually for six to eight weeks; this was most often followed by use of a brace until radiographic

union was achieved. Partial weight-bearing was started after operations on the lower extremities and was continued until the graft had united and the limb was considered stable. All patients who had had an operation on a lower extremity received anticoagulation with warfarin for one to three months.

Postoperatively, the patients were evaluated with regard to function, with use of a system that was reported previously by one of us and colleagues[38]. This system is quite comparable with that proposed by Enneking et al.[18]. A grade of excellent meant that the patient had no evidence of disease, was pain-free, and had essentially normal function with no limitations (except with regard to high-performance sports activities); a grade of good, that there was some degree of impairment of function that did not necessitate bracing or use of supports (such as crutches or a cane) or interfere with the patient's occupation or lifestyle (except with regard to sports activities); and a grade of fair, that a brace or support was needed for walking or prehension and that the patient had sufficient pain to impair function. The graft was considered to have failed if it was removed or if the limb was amputated. Death as a result of a local recurrence was also an indication of failure, but only six patients had a local recurrence and none of them died as a result.
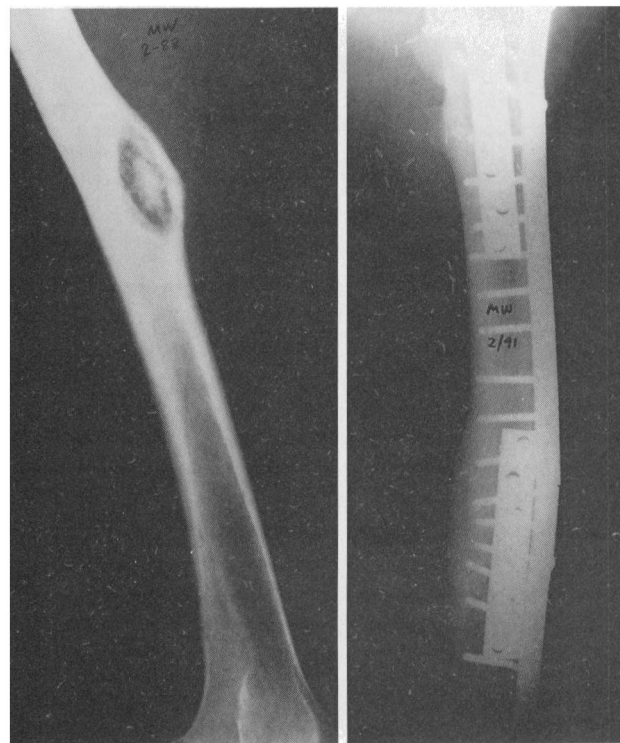

FIG. 2-A   FIG. 2-B

Figs. 2-A and 2-B: Radiographs of a forty-five-year-old man who had resection of a low-grade osteosarcoma of the femur and insertion of an intercalary allograft.
Fig. 2-A: Radiograph showing the osteosarcoma.
Fig. 2-B: Almost four years postoperatively, the host-donor sites have healed completely. The patient had no restrictions of activity.
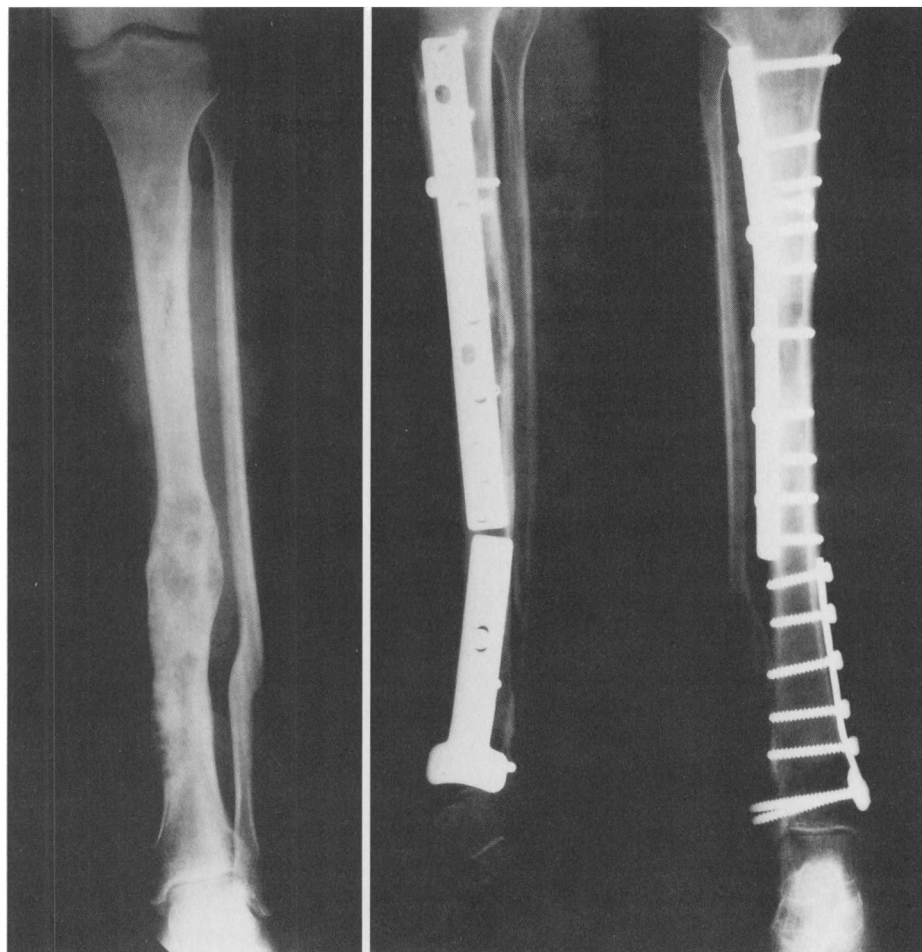
FIG. 3-A   FIG. 3-B

Figs. 3-A and 3-B: Radiographs of a twenty-five-year-old woman who had resection of an adamantinoma of the tibia with fixation with two plates.
Fig. 3-A: Radiograph showing the adamantinoma.
Fig. 3-B: Eight years postoperatively, union had occurred. The patient had full function.

Union was assessed entirely on the basis of radiographs and was defined as the absence of a radiolucent line at the host-donor junction and the presence of a smooth external continuity of cortical bone on all sides at the junction[31]. Non-union was arbitrarily defined as an absence of union at one year after the operation. The time to union varied rather widely, occurring at a mean of 9.4 months (range, three to twenty months) at the proximal site and at a mean of 9.1 months (range, five to twelve months) at the distal site.

Results

Of the 104 grafting procedures, fifty-one (49 per cent) led to an over-all result that was excellent; thirty-six (35 per cent), good; two (2 per cent), fair; and fifteen (14 per cent), a failure. Thus, the composite rate of satisfactory results (good and excellent combined) was 84 per cent. A Kaplan-Meier[30] life-table analysis, with the duration of follow-up ranging from two to twelve years, revealed that most of the failures occurred in the first three to four years (Fig. 4). Although some failures occurred after that point, the pattern in sub-

sequent years was generally one of stability.

Of the fifteen limbs in which the procedure failed, four were salvaged with use of a second allograft and three, with some other technique. For eight of the 100 patients, the most appropriate procedure was deemed to be an amputation. Thus, ninety-two patients, including those who had had removal of the graft, retained the limb.

Both the Kaplan-Meier[30] life-table analysis and the Cox regression technique[10] revealed that age, gender, anatomical site, and length of the graft were not associated with significant differences in the over-all outcome ($p < 0.05$). The stage of the lesion ($p = 0.007$); infection ($p = 0.0001$); fracture ($p = 0.002$); and the use of adjuvant chemotherapy or radiation, or both ($p = 0.008$), all had an adverse effect on the survival of the graft.

Complications

Tumor-Related

Of the forty-seven patients who had a high-grade (stage-IIB or III[17]) lesion (no patient had a stage-IIA lesion), eight (17 per cent) died, eleven (23 per cent) had
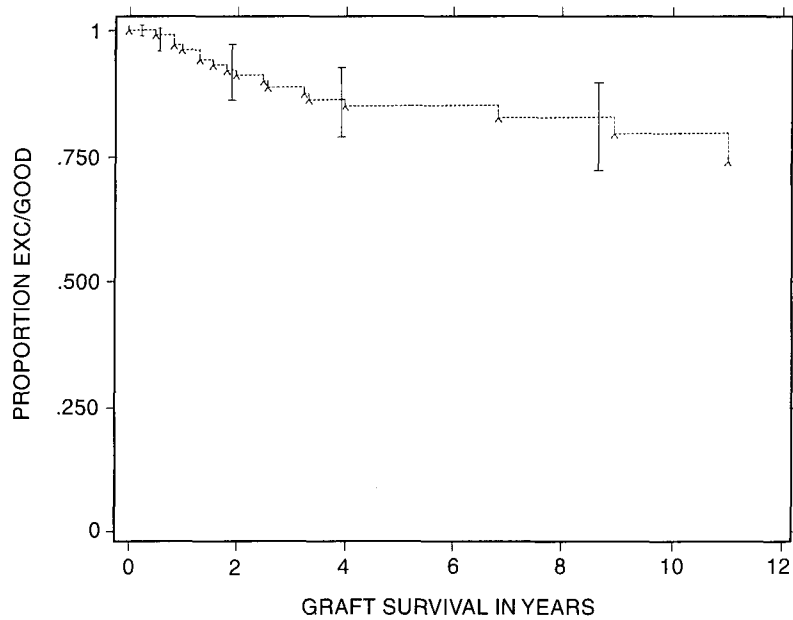
FIG. 4

Life-table showing the over-all survival of the 104 intercalary allografts, as calculated with the Kaplan-Meier[30] method. Eighty-four per cent of the graft procedures had a good or excellent end result. The I-bars indicate the 95 per cent confidence levels.

metastases, and four (9 per cent) had a local recurrence. Of the latter four patients, two had an amputation, and none of the four died of the disease. These data are consistent with the results that have been reported in association with the treatment of high-grade sarcoma by most authors[13,24,27,32].

Allograft-Related

Non-union: Thirty-one allografts did not unite; the non-unions were classified as proximal (ten), distal (ten), or both proximal and distal (eleven). Nine non-unions were associated with other complications, including fracture (five), infection (three), and both fracture and infection (one). No non-union that was not associated with other complications was associated with failure of the allograft; in fact, the effect of a non-union on the outcome was barely significant ($p = 0.02$) (Fig. 5). An attempt to assess whether non-union occurred with greater frequency when the junction was diaphyseal-diaphyseal, metaphyseal-diaphyseal, or metaphyseal-
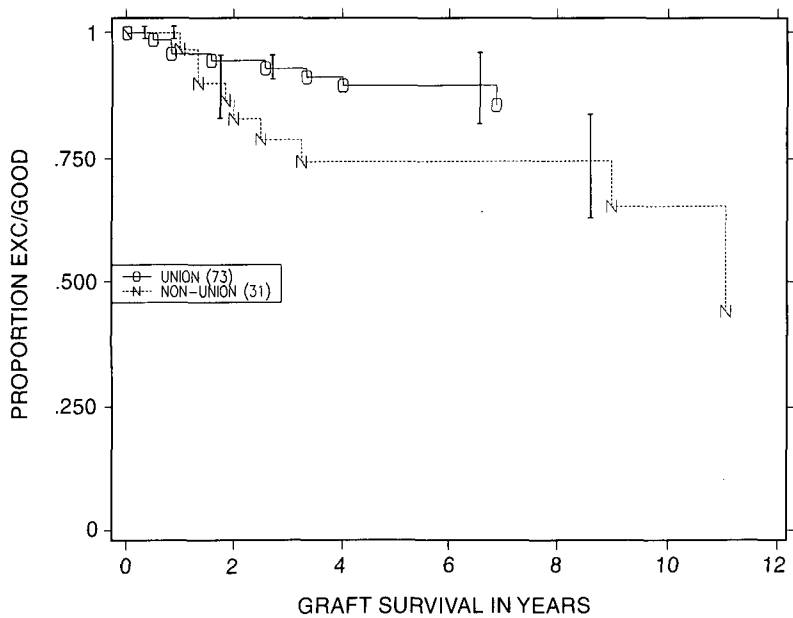

FIG. 5

Life-table[30] showing the effect of non-union on success of the allografts. The rate of success (a good or excellent result) was 89 per cent for the seventy-three grafts that united, compared with 71 per cent for the thirty-one that had not united at one year ($p = 0.02$). The I-bars indicate the 95 per cent confidence levels.
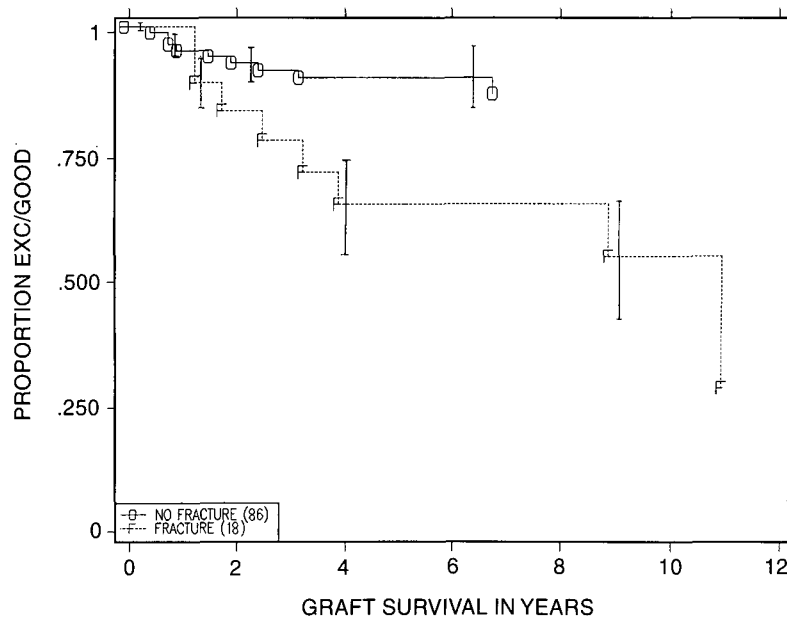
FIG. 6

Life-table[30] showing the effect of fracture on success of the allografts. The rate of success (a good or excellent result) was 56 per cent for the eighteen grafts that had a fracture (all but four fractures occurred before three years), compared with 90 per cent for the grafts that had not fractured as many as eighteen years after the initial operation (p < 0.002). The I-bars indicate the 95 per cent confidence levels.

metaphyseal failed to show a significant difference, although the rate of non-union for metaphyseal-metaphyseal junctions was half that for the other two sites. Furthermore, the type of fixation did not appear to play much of a role. Although four of the seven femoral allografts that were fixed with intramedullary rods went on to a non-union, this number is clearly too small to comment on. The values for the other types of plate-and-screw combinations did not differ signifi-

cantly from one another. A single operation, in which the internal fixation was replaced or adjusted and autogenous graft was added to the site, resulted in union of thirteen of the thirty-one allografts. Nine additional grafts necessitated two such operations and two grafts, three operations, before union was achieved. The seven remaining allografts were removed, and either another allograft was inserted or some other treatment was performed. Thus, seven (23 per cent) of thirty-one non-
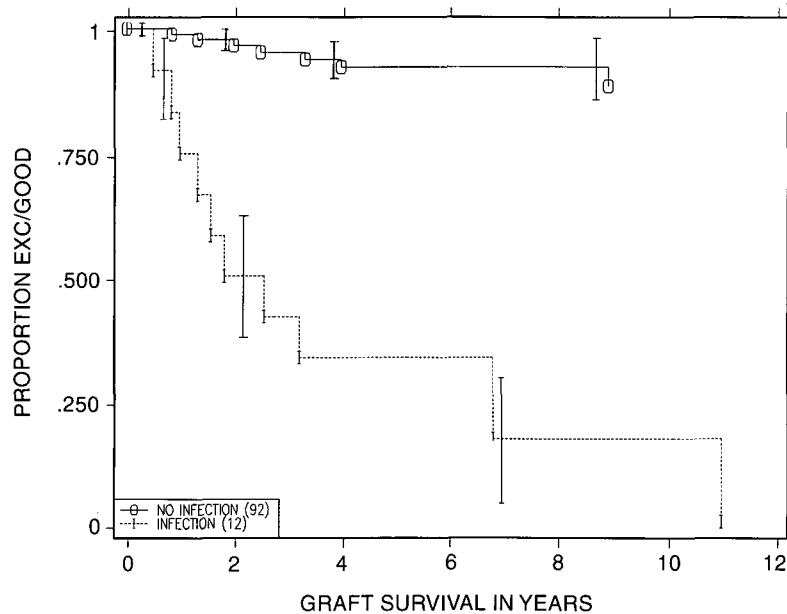

FIG. 7

Life-table[30] showing the devastating effect of an infection of the allograft on the outcome. The rate of success (a good or excellent result) was 92 per cent for the ninety-two grafts that were not infected, compared with 17 per cent for those that were (p = 0.0001). All infections occurred by thirty-three months. The I-bars indicate the 95 per cent confidence levels.
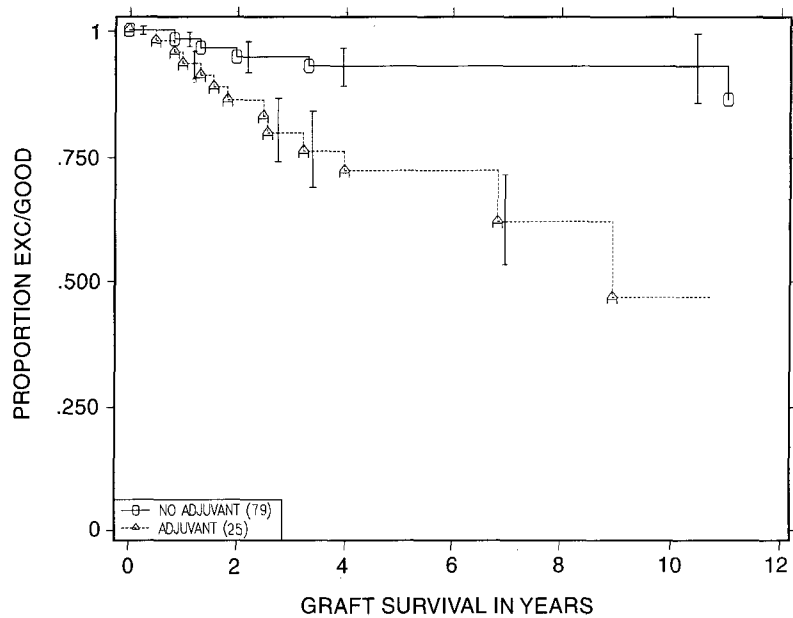
FIG. 8

Life-table[30] showing the effect of adjuvant chemotherapy or radiation, or both, on the success of the allografts. The rate of success (a good or excellent result) for the seventy-nine grafts in seventy-five patients who did not have adjuvant therapy was 91 per cent, compared with 60 per cent for the twenty-five grafts in twenty-five patients who did (p = 0.008). The I-bars indicate the 95 per cent confidence levels.

unions resulted in failure but the over-all prevalence of this type of failure was only 7 per cent for the 104 grafts.

Fracture: Eighteen allografts fractured: fourteen, before the third year, and the remaining four, at four, 6.5, eight, and twelve years (Fig. 6). The standard treatment was open reduction, replacement of the internal fixation device, and insertion of autogenous graft from the iliac crest; this treatment was successful for thirteen fractures. The remaining five of the eighteen allografts were considered to be failures, and either the graft was resected or (in one patient) an amputation was performed. All five failures were associated with another complication: infection (two), non-union (two), and non-union and infection (one). Excluding the limb that was amputated, the remainder were salvaged with use of another intercalary allograft, a metal implant, an osteoarticular allograft, or a vascularized fibular autogenous graft. Although the data are barely significant (p < 0.03), only
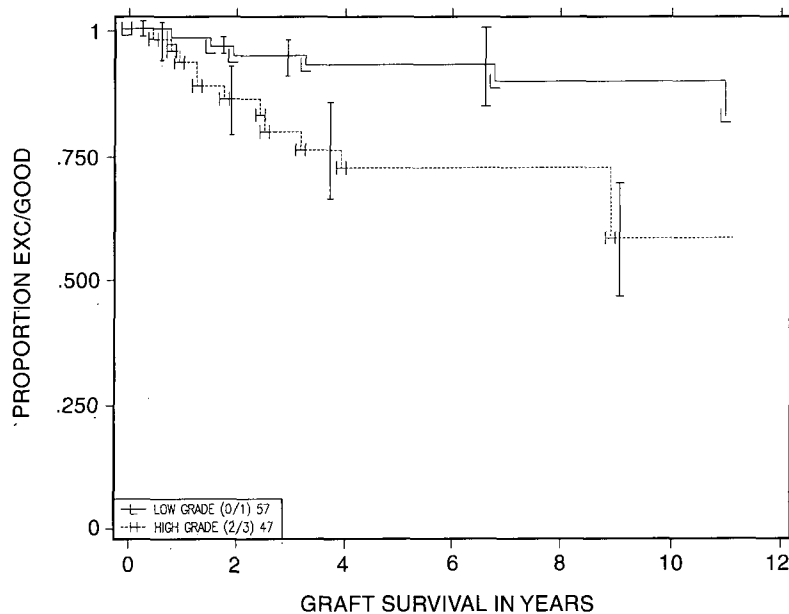

FIG. 9

Life-table[30] showing the effect of the stage of the disease[17] on the success of the allografts. The rate of success (a good or excellent result) for the forty-seven grafts in patients who had a high-grade tumor was significantly worse than that for the fifty-seven in patients who had a stage-0 or stage-I tumor (p < 0.007). The I-bars indicate the 95 per cent confidence levels.

seven of the fifty-six allografts that were fixed with a single long plate fractured, compared with seven of the twenty-one that were fixed with two plates.

Infection: As in most patients who have a limb-sparing operation and especially those who receive an allograft, infection was the most serious complication in the present series. There were twelve infections (12 per cent); this rate does not differ from that for the total group of allograft procedures performed during the study period or from that reported in association with other types of grafts[13,28,33,34,37,39]. All of the infections occurred within the first three years (range, one to thirty-three months) (Fig. 7), and four infections were complicated by other factors (operative treatment for a non-union in three and a skin slough in one). All but two infections necessitated resection of the graft, four limbs were successfully treated with use of another salvage technique, and six infections ultimately led to an amputation.

All complications and failures occurred with greater frequency in the twenty-five patients who had received either adjuvant chemotherapy or radiation, or both, to the host bed; the rate of success was 60 per cent for these patients. The seventy-nine grafts in the seventy-five patients who had not had adjuvant therapy had a 91 per cent rate of success (Fig. 8). Higher-grade lesions (those that were stage IIB[17] [forty-two] or stage III [five]) were associated with a significantly worse outcome than those classified as stage 0 (twelve), stage IA (eleven), or stage IB (thirty-four) (Fig. 9) (p < 0.007).

Discussion

Although the results are not always predictable, the use of allografts clearly has a place in the operative treatment of failed total joint replacements[1,6,45,46]; bone tumors[13,16,24,37,39]; and, less frequently (and perhaps less clearly), joint diseases such as osteonecrosis[11,19]. There is considerable controversy among surgeons as to whether metal implants or osteoarticular allografts are best suited for the treatment of lesions when a joint must be resected[4,15,16,29,35,46], but there is far less doubt about the use of intercalary segments, in which a joint plays no role. Intercalary allografts have a generally good reputation because they are easy to insert and fix, they are associated with a relatively low rate of complications, and they survive for a long duration[16,25,34,39,40], whereas metal implants and vascularized fibular grafts are both associated with problems. Metal devices are difficult to obtain and probably have a shorter life[7,8,46]; fibular transplants are associated with not inconsiderable donor-site morbidity and they may fail if the vascular repair is unsuccessful. The biomechanical properties of both of these systems fail to approximate those of the host tissue.

In the current study, the long-term rate of success for intercalary allografts was 84 per cent and the devices, after they had passed the critical first three-to-four-year period, seemed to hold up extraordinarily well for as long as fifteen years or more. Furthermore, even limbs in which the allograft has failed can be salvaged. Although fifteen grafts in the current study failed, only eight necessitated an amputation and two of these amputations were performed because of recurrence of the tumor. The remaining seven limbs in which the allograft failed were salvaged with insertion of another allograft, a metal part, a vascularized fibular transplant, or another such device. Thus, the over-all rate of retention of the limb with satisfactory function was 92 per cent, which is certainly acceptable.

Of concern, however, is that eighty-one additional operative procedures were needed to obtain the satisfactory results. Of the 100 patients, four had four additional operations; three, three; fourteen, two; and twenty-eight, one. These data suggest that, although the grafts were ultimately successful, success was not always easy to achieve, and the first or even the second procedure may not be sufficient to obtain union of a largely cortical-to-cortical surface.

In considering the factors that seem to affect the outcome, it is easy to list those related to immunity, which are cited so frequently as playing a major role. However, there are no clearly defined markers for transplantation in humans[20,26,47], except possibly sensitization in the DR locus, which some unpublished data have suggested augurs less successful results[22]. In the current series, the age of the patient, the length of the graft, and the involved bone did not play a role in the outcome. Furthermore, in contrast to the study of Vander Griend[54], our analysis of types of fixation revealed only that the use of two plates with unsupported bone between them did not appear to be as successful as the use of one long plate. Infection, fracture, and non-union had the most detrimental effects on the outcome. Non-union is the most frequent complication but, according to our data, is of least consequence. The use of adjuvant radiation and chemotherapy also decreased the likelihood of a primary union. Infection is clearly more frequent and probably is immunologically caused[20,28,33,51]. Fractures are caused by a slow or asymmetrical revascularization of the cortex, either of which may be associated with an immune response[2,12,45,49]. After the host-donor junctions have healed and vascular invasion has begun in the cortex, the bone seems to lose much of its susceptibility to fracture[25,37,39,42].

The results of the current study demonstrate that one long plate is the most satisfactory form of fixation. In fourteen procedures, we added autogenous graft to the host-donor junction sites but we did not recognize a difference in the outcome that justified this additional operative treatment. However, it is not possible to make a valid assessment of the value of such additional treatment on the basis of so few procedures.

In summary, intercalary allografts are an easily applied system for restoring function of the limb after resection of a tumor and are associated with a low rate

of ultimate failure. Although the rate of reoperation for non-union is high, the end result for many patients is that they can walk or use the upper extremity soon after the operation, and most regain their ability to live a relatively normal life. On the basis of these data, we believe that an allograft transplant is a safe, effective treatment for an intercalary defect in bone resulting from resection of a tumor.

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