Reconstructive techniques in musculoskeletal tumor surgery : management of pelvic and extremity bone tumors

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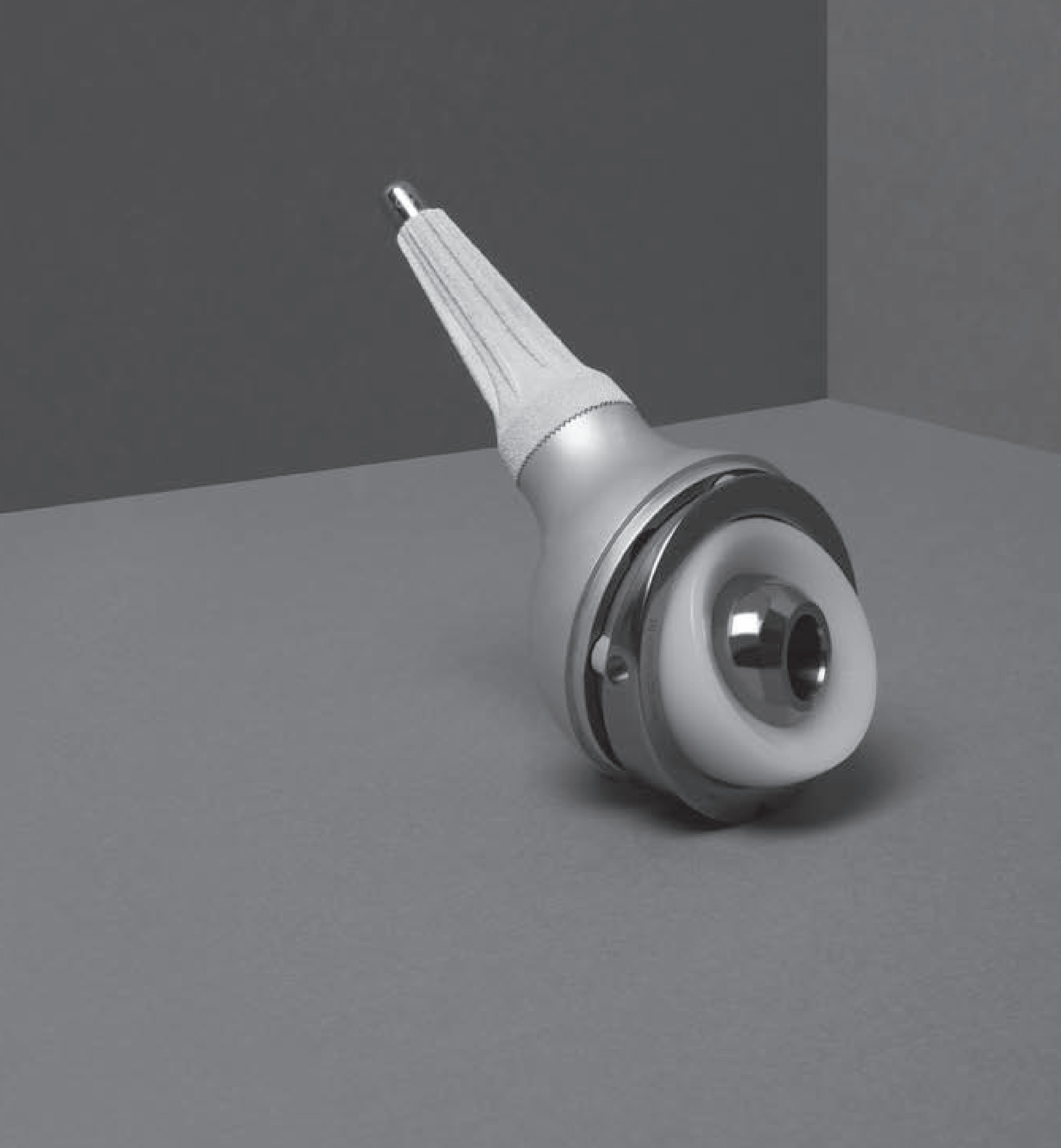
Part II

Management of Extremity Bone Tumors



Chapter 5

Intercalary Allograft Reconstructions Following Resection of Primary Bone Tumors

A Nationwide Multicenter Study

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Abstract

Background: Favorable reports on the use of massive allografts to reconstruct intercalary defects underline their place in limb-salvage surgery. However, little is known about optimal indications as reports on failure and complication rates in larger populations remain scarce. We evaluated the incidence of and risk factors for failure and complications, time to full weight-bearing, and optimal fixation methods for intercalary allografts after tumor resection.

Methods: A retrospective study was performed in all four centers of orthopaedic oncology in the Netherlands. All consecutive patients reconstructed with intercalary (whole-circumference) allografts after tumor resection in the long bones during 1989 to 2009 were evaluated. The minimum follow-up was 24 months. Eighty-seven patients with a median age of 17 years (1.5 to 77.5) matched inclusion criteria. The most common diagnoses were osteosarcoma, Ewing sarcoma, adamantinoma, and chondrosarcoma. The median follow-up period was 84 months (25 to 262). Ninety percent of tumors were localized in the femur or the tibia.

Results: Fifteen percent of our patients experienced a graft-related failure. The major complications were nonunion (40%), fracture (29%), and infection (14%). Complications occurred in 76% of patients and reoperations were necessary in 70% of patients. The median time to the latest complication was 32 months (0 to 200). The median time to full weight-bearing was nine months (1 to 80). Fifteen grafts failed, 12 of which failed in the first four years. None of the 34 tibial reconstructions failed. Reconstruction site, patient age, allograft length, nail-only fixation, and non-bridging osteosynthesis were the most important risk factors for complications. Adjuvant chemotherapy and irradiation had no effects on complication rates.

Conclusions: We report high complication rates and considerable failure rates for the use of intercalary allografts; complications primarily occurred in the first years after surgery, but some occurred much later after surgery. To reduce the number of failures, we recommend reconsidering the use of allografts for reconstructions of defects that are ≥15 cm, especially in older patients, and applying bridging osteosynthesis with use of plate fixation.

Introduction

Until the 1970s, the treatment of high-grade extremity sarcoma routinely consisted of the amputation of affected limbs. Despite aggressive surgery, the five-year survival rate was ≤20%[1-3]. Because of the introduction of chemotherapy and advances in imaging and surgical techniques, limb salvage became feasible in an increasing number of patients and five-year survival rates increased to 55% to 70%[4-11].

Most primary malignant bone tumors are localized in the epiphysis and/or metaphysis of the long bones, often necessitating resection of joints. Still, numerous tumors are located in the metaphysis or diaphysis[10,12], in which case it is desirable to save adjacent joints. Reconstruction with intercalary allografts is a well-accepted surgical technique to reconstruct the osseous defect after such resections. Intercalary allografts have been recommended as a reliable solution with long-term success rates and good functional outcome in 82% to 84% of patients[13,14]. As intercalary allografts have relatively good stability compared with autografts, the main advantage of using intercalary allografts is the opportunity to biologically reconstruct a large long-bone deficit without donor site morbidity. Nevertheless, allografts are associated with high rates of infection (0% to 18%), fracture (0% to 30%), and delayed union or nonunion (15% to 55%)[13-20]. Finally, widespread use might be restricted by limited availability in some countries and by the minor possibility of transmission of infectious diseases.

In this multicenter study, we retrospectively evaluated (1) incidence of and risk factors for failure, (2) incidence of and risk factors for complications (with special emphasis on infection, fracture, and nonunion), (3) time to full weight-bearing, and (4) optimal fixation methods for intercalary allograft reconstructions after bone tumor surgery.

Materials and Methods

In the Netherlands, primary bone tumors are treated in four appointed centers for orthopaedic oncology. To identify eligible patients, we assessed all massive allografts that were delivered to these centers by our national bone bank between 1989 and 2009. All consecutive whole-circumference resections of primary tumors in the long bones that were reconstructed with an intercalary allograft were included and retrospectively reviewed. The minimum follow-up was 24 months (figure 1).

Eighty-seven patients (46 male patients and 41 female patients) with a median age of 17 years (1.5 to 77.5) matched our inclusion criteria. Twenty-eight patients (32%) were younger than 14 years of age and 44 patients (51%) were younger than 18 years of age. The most common diagnoses were osteosarcoma (34 patients [39%]), Ewing sarcoma (17 patients [20%]), adamantinoma (15 patients [17%]), and chondrosarcoma (11 patients [13%]). Fifty-two patients (60%) received chemotherapy (34 for conventional osteosarcoma, 17 for Ewing sarcoma, and one for juxta-cortical osteosarcoma, according to EURAMOS [European and American Osteosarcoma Study Group] or Euro-EWING protocol), and nine patients (10%) underwent radiation therapy. The median follow-up was 84 months (25 to 262). Fifty-seven patients (66%) had follow-up for more than five years and 29 patients (33%) had follow-up for more than ten years (figure 2).

Tumor localizations included the femur (44 patients [51%]), the tibia (34 patients [39%]), the humerus (seven patients [8%]), and the radius (two patients [2%]). Twenty reconstructions (23%) were located in the proximal third of the bone and 24 reconstructions (28%) were located in the distal third of the bone. The remaining 43 reconstructions (49%) were diaphyseal. Thirty-five reconstructions (40%) spanned diaphysis to metaphysis, and nine reconstructions (10%) also affected the epiphysis. The median allograft reconstruction length (and standard deviation) was 14.0 ± 4.8 cm (5.0 to 30.0) and did not differ significantly among reconstructions of femur (16.0 cm), tibia (14.0 cm), humerus (14.0 cm), and radius (13.0 cm).

Allografts were harvested under sterile conditions during postmortem tissue donation and were stored at -80°C by our national bone bank. Processing was performed by either Osteotech (Eatontown, New Jersey) or the Musculoskeletal Transplant Foundation (Edison, New Jersey). Allografts were thawed in saline solution and antibiotics in the operating room during tumor resection. All patients received perioperative antibiotics according to protocol.

Allografts were attached to host bones with an array of plate-and-screw combinations in 62 patients (71%) (examples in figures 3A and 3B), a combination of intramedullary nails and plate(s) in 12 patients (14%), intramedullary nails only (in all cases locked at both ends) in eight patients (9%) (examples in figures 4A, 4B, and 4C), and screws with or without cerclage wires in five patients (6%). In the latter group, patients were 1.5 to 12 years of age. Primary hybrid reconstructions, combining intercalary allografts with vascularized fibular autografts, were performed in six patients (7%).

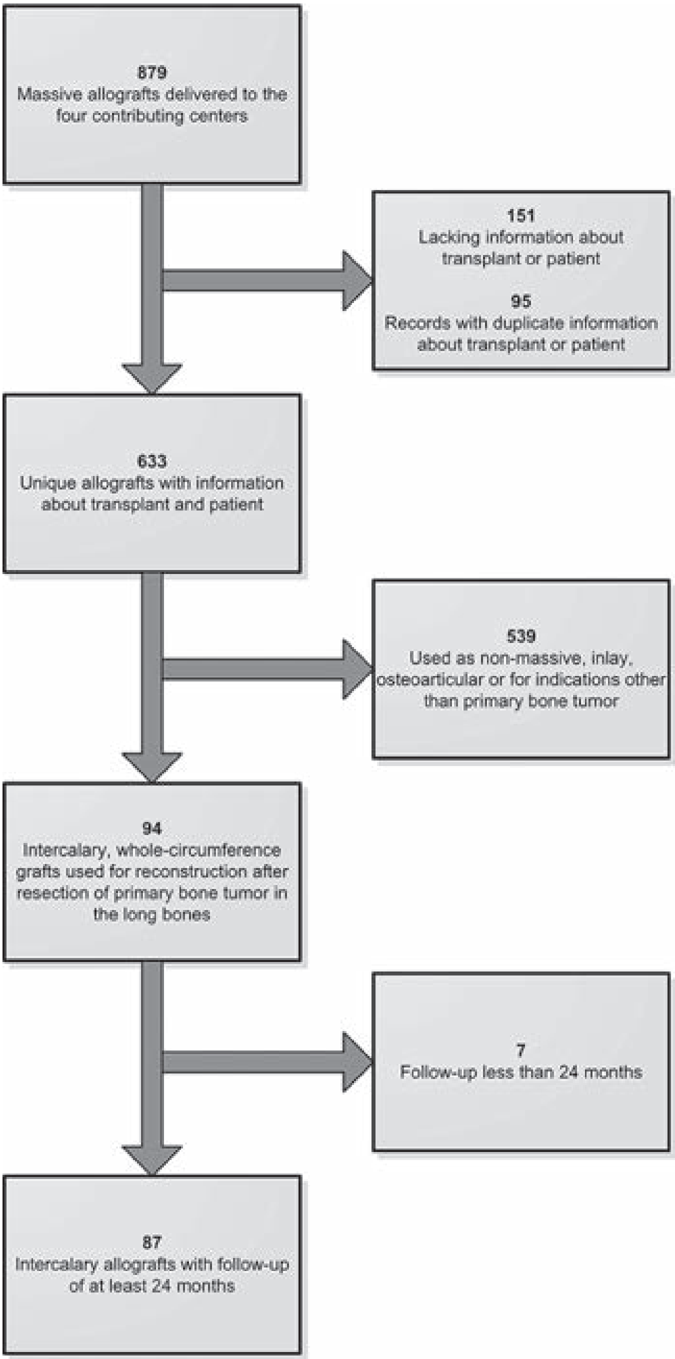


Figure 1. A flowchart showing an inclusion diagram.

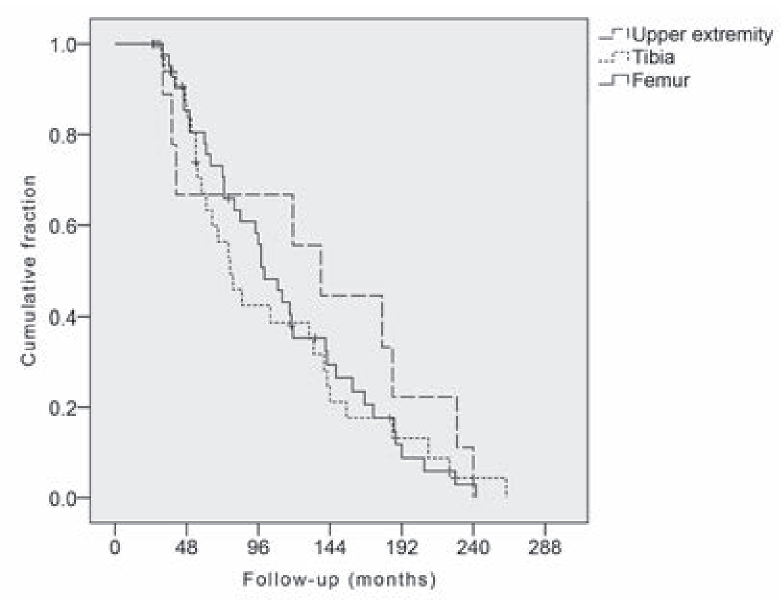
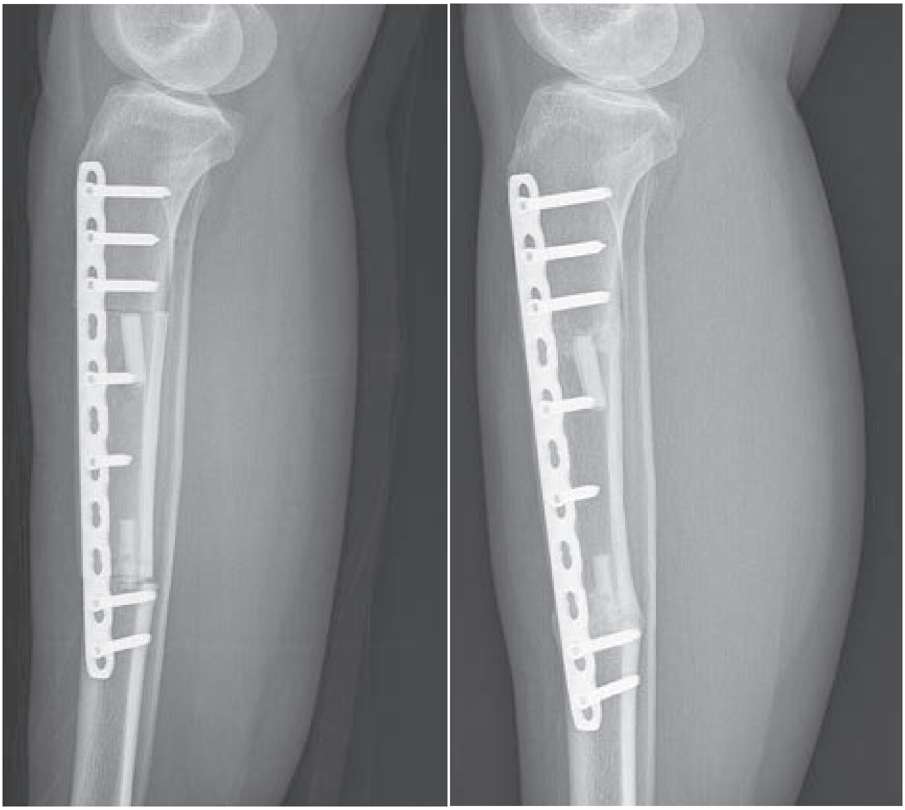


Figure 2. Kaplan-Meier curve for patient follow-up plotted according to localization (n = 87).

Two separate definitions were applied to assess the union of allograft-host junctions. In the first definition, to compare the incidence of nonunion with that in prior series, unions of junctions were determined with use of conventional radiographs, and nonunion was defined as the lack of continuity in three cortices at the junction one year after surgery. If assessment of union was inconclusive on conventional radiographs, union was assessed with computed tomography (CT). In the second definition, to analyze risk factors for nonunion, surgical intervention to facilitate union of osseous junctions, at least six months after primary surgery, was defined as nonunion.

Allografts that were removed or were replaced were defined as failures. Graft-related failures were considered separately for statistical analysis. The type of osteosynthesis was defined as bridging if the intramedullary nail or plate osteosynthesis spanned the entire allograft and had a proximal and distal fixation zone in unaffected bone.



Figures 3A and 3B. Postoperative lateral radiographs showing a twenty-six-year-old woman who underwent osteosynthesis and received an 11-cm-long allograft that was implanted after radical resection of a low-grade osteosarcoma. (3A) Osteosynthesis was performed with use of a bridging plate. Two intramedullary fibular allografts were used to augment the reconstruction. (3B) Both proximal and distal osteotomy lines had excellent consolidation at thirteen months postoperatively.

We evaluated sex, age, diagnosis, affected bone, date of primary surgery, localization within bone level, and type of neo-adjuvant or adjuvant therapy. For reconstructions, we evaluated graft and fixation type, addition of autografts, and length of the reconstruction. Allograft length was measured on conventional radiographs and was corrected for magnification. We determined occurrence and time to complications. These determinations were performed separately for the lower extremity. Time to full weight-bearing was determined for lower-extremity reconstructions. Weight-bearing was allowed if the limb was considered stable, on the basis of imaging, physical examination, and duration since surgery. Study data were obtained from medical records, operation reports, and imaging, and were specified in terms of frequencies and percentages (table 1). All data were complete except for time to full weight-bearing, for which there were missing data in 29 (37%) of the 78 patients in the lower-extremity reconstruction group.

Figures 4A-C. Radiographs of a sixty-nine-year-old man who underwent resection of an adamantinoma in the tibia and implantation of an allograft. (4A) A lateral radiograph made one day after implantation of the allograft. An intramedullary nail was used to fixate this 15-cm-long allograft. Osteotomy lines can be easily identified. (4B) A radiograph made thirteen months after implantation of the allograft. There is persistent pseudarthrosis of the distal allograft-host junction. Cancellous bone grafting and plate osteosynthesis were performed at the distal junction. (4C) An anteroposterior radiograph made thirty-eight months after the initial operation. Satisfactory consolidation was still not seen at the distal osteotomy site. Four months later, the intramedullary nail was removed and a vascularized fibular transposition was performed.

Nominal variables were compared between groups with use of chi-square tests, and continuous variables were compared between groups with use of Mann-Whitney tests. Logistic regression analysis was performed for nominal or categorical values in case of (a trend toward) significance. Cox regression analysis was performed for influence on time to failure. Kaplan-Meier curves were used to analyze time to complications. Outcomes are expressed in odds ratios (ORs), hazard ratios (HRs), 95% confidence intervals (95% CI), and p-values (significance was set at $p < 0.05$).

Table 1. Study data

Variable	All localizations* (n = 87)	Lower extremity* (n = 78)
Sex		
Male	46 (53)	40 (51)
Female	41 (47)	38 (49)
Diagnosis		
Osteosarcoma (conventional type)	34 (39)	31 (40)
Ewing sarcoma	17 (20)	13 (17)
Adamantinoma	15 (17)	15 (19)
Chondrosarcoma	11 (13)	9 (12)
Pleomorphic undifferentiated sarcoma	3 (3)	3 (4)
Juxta-cortical osteosarcoma	3 (3)	3 (4)
Low-grade osteosarcoma	2 (2)	2 (3)
Leiomyosarcoma	1 (1)	1 (1)
Hemangioma	1 (1)	1 (1)
Patient age at the time of diagnosis		
Less than fourteen years	28 (32)	26 (33)
Less than eighteen years	44 (51)	41 (53)
Localization		
Femur	44 (51)	44 (56)
Tibia	34 (39)	34 (44)
Humerus	7 (8)	-
Radius	2 (2)	-
Localization within bone piece		
Diaphyseal	43 (49)	38 (49)
Metadiaphyseal	35 (40)	31 (40)
Epidiaphyseal	9 (10)	9 (12)
Neo-adjuvant and adjuvant therapy		
Neo-adjuvant chemotherapy	51 (59)	44 (56)
Adjuvant chemotherapy	52 (60)	45 (58)
Neo-adjuvant radiation therapy	2 (2)	2 (3)
Adjuvant radiation therapy	9 (10)	7 (9)
Osteosynthesis		
Bridging osteosynthesis	54 (62)	50 (64)
Plates†	62 (71)	55 (71)
Bridging plate(s)	35 (40)	33 (42)
Intramedullary nail and plate(s)	12 (14)	11 (14)
Intramedullary nail only	8 (9)	7 (9)
Screws and cerclage wires	5 (6)	5 (6)
Hybrid grafts (allograft and vascularized fibula)	6 (7)	6 (8)
Complications		
Number of complications		
None	21 (24)	21 (27)
One	26 (30)	23 (30)
Two	23 (26)	19 (24)

Table 1. Study data

Variable	All localizations* (n = 87)	Lower extremity* (n = 78)
Three	9 (10)	8 (10)
Four	5 (6)	4 (5)
Five	2 (2)	2 (3)
Eight	1 (1)	1 (1)
Type of complication		
Infection	12 (14)	8 (10)
Fracture	25 (29)	23 (30)
Nonunion	35 (40)	29 (37)
Associated with osteosynthesis materials	23 (26)	22 (25)
Reoperation	61 (70)	53 (68)
Failure		
Total number of removed allografts	15 (17)	10 (13)
Allograft-related failures	13 (15)	9 (12)
Duration of follow-up		
Five years or more	57 (66)	51 (65)
Ten years or more	29 (33)	23 (29)

*The values are given as the number of patients, with the percentage in parentheses.
†The osteosynthesis with plates occurred with or without addition of fibular strut grafts and/or screws.

Results

Incidence of and Risk Factors for Failure

During follow-up, 15 patients (17%) had allografts removed, including 13 patients who had allografts removed because of graft-related complications (nine patients with complications in the femur and four patients with complications in the humerus) and two patients who had local recurrences and underwent ablative surgery (one patient underwent rotationplasty and one patient underwent amputation). The reasons for graft-related failures were fracture (n = 5), infection (n = 4), and nonunion (n = 4). Of the graft-related failures, 12 occurred in the first four years after the index surgery. Three patients had late failures due to nonunion after six years, fracture after 11 years, and infection after 15 years. None of the graft-related failures necessitated ablative surgery; limb salvage was achieved in 98% of patients.

There were no significant differences in allograft survival or complication rates for patients who underwent operations in the late 1980s and early 1990s (n = 31 [36%]), compared with those whose primary surgery took place after 1995.

Infection increased the risk of failure (n = 12; p = 0.02), and weak trends were seen for fracture (n = 25; p = 0.09) and nonunion (n = 35; p = 0.09). Failure rates were significantly higher in patients who were 18 years of age and older (n = 43; p < 0.01), in patients with reconstruction sites other than the tibia (n = 53; p < 0.01), and in patients undergoing diaphyseal reconstructions (n = 43; p = 0.04).

Failure rates for lower-extremity reconstructions were significantly higher in patients who were 18 years of age and older (n = 43; OR, 11.03; p = 0.03) and in patients undergoing reconstructions with an allograft of ≥15 cm in length (n = 39; OR, 10.40; p = 0.03) (table 2). In multivariable analyses, patients who were 18 years of age and older (n = 43) demonstrated higher failure rates, independent of diaphyseal localization (OR, 6.23) and reconstruction length ≥15 cm (OR, 6.15) (table 3). Because none of the tibial reconstructions failed, reconstruction site was excluded from regression analysis.

Table 2. Univariate logistic regression analysis for the risk of failure, infection, and nonunion.

	All localizations		Lower extremity	
Complications and covariates	Odds ratio*	p-value	Odds ratio*	p-value
Failure†				
Patient age of ≥18 years	7.22 (1.49 - 34.88)	0.01	11.03 (1.31 - 93.14)	0.03
Allograft length of ≥15.0 cm	3.30 (0.93 - 11.70)	0.07	10.40 (1.23 - 87.75)	0.03
Localization within bone piece: diaphyseal	-	-	4.29 (0.83 - 22.15)	0.08
Infection‡				
Localization: femur	0.28 (0.07 - 1.10)	0.07	-	-
Osteosynthesis: bridging plate(s)	0.26 (0.05 - 1.24)	0.09	-	-
Osteosynthesis: plates§	0.34 (0.09 - 1.18)	0.09	-	-
Nonunion#				
Localization: tibia	0.37 (0.15 - 0.95)	0.04	-	-
Osteosynthesis: intramedullary nail only	5.17 (0.98 - 27.32)	0.05	4.90 (0.88 - 27.12)	0.07
Patient age of ≥14 years	-	-	2.64 (0.91 - 7.66)	0.07
Allograft length of ≥10.0 cm	3.93 (0.81 - 19.17)	0.09	-	-

*The values are given as the odds ratio, with the 95% CI in parentheses. †There were thirteen patients who had failure in all locations and nine patients who had failure in the lower extremity. ‡There were twelve patients who had infection in all locations and eight patients who had infection in the lower extremity. §The osteosynthesis with plates occurred with or without addition of fibular strut grafts and/or screws. #There were thirty-five patients who had nonunion in all locations and twenty-nine patients who had nonunion in the lower extremity.

In univariable Cox regression analysis for influence on time to failure, bridging plate fixation (HR, 0.11) and patient age of eighteen years or older (HR, 6.66) were the most important factors (see appendix). For lower-extremity reconstructions, patient age of 18 years or older (HR, 9.46) and allograft length of ≥15 cm (HR, 9.00) were related to a shorter time to failure (figure 5; see appendix). In multivariable analysis, patient age of 18 years or older was the most important factor influencing time to failure (see appendix). Its influence was also significant in multivariable analyses with infection (HR, 6.22 [95% CI, 1.37 to 28.20]; $p = 0.02$), fracture (HR, 8.27 [95% CI, 1.79 to 38.16]; $p < 0.01$), and nonunion (HR, 6.43 [95% CI, 1.42 to 29.18]; $p = 0.02$).

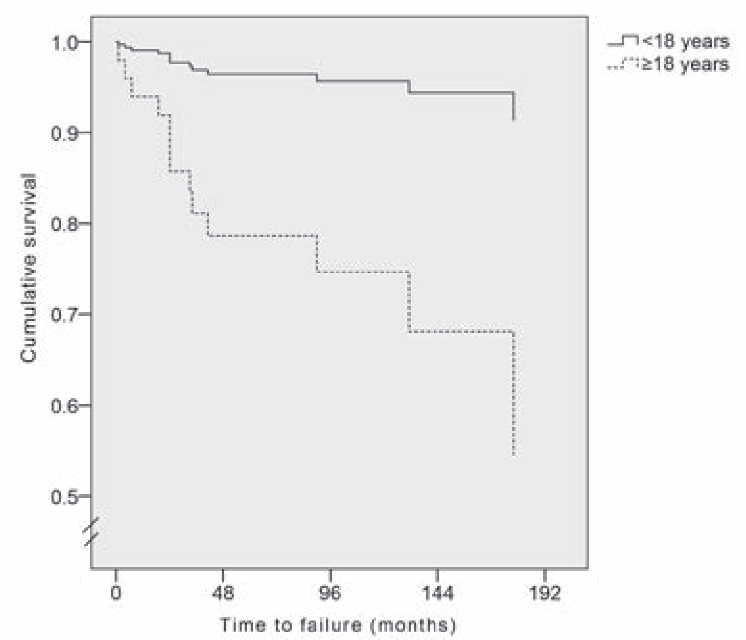


Figure 5. A line graph showing Cox regression analysis for the influence of patient age of eighteen years or more on the time to failure.

Complication Rates

During follow-up, 137 complications occurred in 66 patients (76%). Forty patients (46%) had two or more complications. With regard to major complications, 35 patients (40%) had nonunion, 25 patients (29%) had fracture, and 12 patients (14%) had infection. As for the time at which the different complications tended to occur, there were no significant differences. Twenty-three patients (26%) had a complication related to the osteosynthesis materials: broken implants (11 patients, eight of whom were under treatment for nonunion), aseptic loosening (five patients), pain (four patients), or malposition and instability of osteosynthesis materials (three patients).

Reoperations were performed in 61 patients (70%). Whereas reoperation rates were significantly lower in tibial reconstructions ($p < 0.01$), nail-only fixation increased reoperation rates ($p = 0.04$). Because none of the nail-only reconstructions were free from reoperations, regression analysis was not performed.

The median time to first complication was 14 months (0 to 66; 95% CI 9 to 19); 44% occurred in less than one year and 68% occurred in less than two years after the index procedure. The median time to the latest complication was 32 months (0 to 200; 95% CI 4 to 40); 24% occurred within one year after primary surgery and 70% occurred within four years.

Complication rates were significantly lower in tibial reconstructions ($n = 34$; $p = 0.01$). Nail-only fixation ($n = 8$) was weakly associated with a higher complication risk ($p = 0.09$). Because all nail-only reconstructions had at least one complication, multivariable analysis could not be performed.

Infection

Although not significant, the infection rate was lower for femoral reconstructions (OR, 0.28) (table 2). In eight (24%) of the 34 tibial reconstructions, muscle flaps were used. Of the six patients with a hybrid reconstruction, three developed infection ($p < 0.01$); all were adequately treated with antibiotics.

Fracture

None of the investigated factors significantly influenced fracture rates. In the lower extremity, fracture risk was higher after non-bridging fixation ($n = 28$; $p = 0.05$).

Nonunion

One year after primary surgery, there was lack of continuity of three cortices at the allograft-host junctions in 23 patients (26%). In two of the patients in whom the graft was considered to be incorporated on radiographs one year after primary surgery, cancellous bone grafting was performed at a later stage. In total, 35 patients (40%) with allografts required surgical intervention to facilitate the union of allograft-host junctions: ten patients underwent secondary surgery six to 12 months after the initial surgery, and the remaining 25 patients underwent secondary surgery more than a year after the initial surgery.

In univariable analysis, tibial localization (OR, 0.37) decreased the nonunion risk, but nail-only fixation (OR, 5.17) and allograft length of ≥10 cm (OR, 3.93) both showed trends toward higher nonunion rates (table 2). In multivariable analysis, nail-only fixation (OR, 7.30) and tibial localization (OR, 0.33) were of significance (table 3).

Time to Full Weight-Bearing

The median time to full weight-bearing was nine months (1 to 81, 95% CI 7.5 to 10.5). Because there were missing data in 37% of relevant patients, a comparison between groups was not performed.

Table 3. Multivariate logistic regression analysis for the risk of failure and nonunion

	All localizations		Lower extremity	
Complications and covariates	Odds ratio*	p-value	Odds ratio*	p-value
Failure†				
First analysis				
Patient age of ≥18 years	6.15 (1.25 - 30.34)	0.03	8.04 (0.92 - 70.53)	0.06
Allograft length of ≥15.0 cm	2.51 (0.67 - 9.36)	0.01	7.47 (0.85 - 65.75)	0.07
Second analysis				
Patient age of ≥18 years	6.23 (1.24 - 31.34)	0.03	8.57 (0.98 - 75.19)	0.05
Localization within bone piece: diaphyseal	1.68 (0.44 - 6.42)	0.45	2.66 (0.48 - 14.76)	0.26
Nonunion#				
Localization: tibia	0.33 (0.12 - 0.91)	0.03	0.38 (0.14 - 1.08)	0.07
Osteosynthesis: intramedullary nail only	7.30 (1.16 - 45.69)	0.03	6.66 (1.05 - 42.22)	0.04
Allograft length of ≥10.0 cm	3.81 (0.74 - 19.72)	0.11	2.97 (0.56 - 15.76)	0.20

*The values are given as the odds ratio, with the 95% CI in parentheses. †There were thirteen patients who had failure in all locations and nine patients who had failure in the lower extremity. ‡There were thirty-five patients who had nonunion in all locations and twenty-nine patients who had nonunion in the lower extremity.

Discussion

We evaluated (1) incidence of and risk factors for failure, (2) incidence of and risk factors for complications, (3) time to full weight-bearing, and (4) optimal fixation methods for intercalary allografts after tumor resection. Judging from the literature, intercalary allografts provide a reasonable solution in the reconstruction of large osseous defects, with the possibility of preserving native joints while avoiding donor site morbidity[13-18,21-26]. In our study, a considerable percentage of graft-related failures was observed (15%), and 76% of the patients had one or more complications. The major complications were nonunion (40%), fracture (29%), and infection (14%). In addition, 26% of patients had a complication related to the osteosynthesis implants.

Our 17% failure rate was comparable with prior studies, ranging from 10% to 39% (see appendix). Although it is conceivable that adverse events are influenced by techniques and implants used in the earlier period of our study compared with modern techniques, we found no differences in graft survival and complication rates between patients undergoing operations from 1989 to 1995 and those undergoing operations after 1995.

The most important risk factors for failure and complications in our study population were anatomical site other than tibia, patient age of eighteen years or older, allograft length of ≥15 cm, intramedullary nail-only fixation, and diaphyseal localization. Four of seven humeral reconstructions failed. Previous studies did not show significant differences in outcome between different anatomical sites[14,17,19].

Tibial reconstructions are often thought to be demanding because of limited possibilities of soft-tissue coverage and poor vascularity[22,27,28]. Nevertheless, we found lower complication and nonunion rates for tibial reconstructions. The fact that femoral allografts displayed lower infection rates might be explained by the better soft-tissue coverage of the femur as compared with the tibia.

In our population, adult age was associated with a higher risk of failure. Previous studies have also shown associations between increasing age and higher incidences of delayed union or nonunion[20,29].

Nail-only fixation was associated with a higher risk of nonunion and the reoperation rate was lower after plate fixation. Previous studies have shown that fixation providing rigid stability might improve allograft incorporation[13,30]. Vander Griend stated that there is an important association between achieving stable fixation, more easily done using plates, and decreasing nonunion[30].

Previously, allograft length has been described as a risk factor for fracture[20]. Although associated with a higher risk of both failure and nonunion, we were unable to identify an association between graft length and fracture rate.

Diaphyseal localization was adversely related to the time to failure. Previously, unfavorable results have been reported for diaphyseal junctions[13,15]. These unfavorable results might be explained by the smaller contact surface of these junctions, as compared with metaphyseal and epiphyseal junctions. However, other studies found no differences or even a higher rate of delayed union for osteotomy lines placed in metaphyseal cancellous bone[20,31].

Nonunion rates vary greatly throughout literature (15% to 55%)[13,14,16-19,32-34]. Whereas some studies assess nonunion per patient, others consider both osteotomy lines and thus score more nonunions. In a large prior study, nonunion was defined as the lack of continuity in three cortices at the junctional site one year after surgery[20]. Whereas 47% of patients in that study matched this definition, only 26% of patients in our study did. We chose to report on nonunion in a second way: if additional surgery was performed to facilitate union, taking place at least six months after implantation of the graft. Forty percent of our patients matched this definition. Previous large series have shown reoperation rates for nonunion ranging from 15% to 28%[13,15,20].

The overall complication rate in our study was high compared with those in previous series, which showed complication rates ranging from 42% to 46% (see appendix). However, this rate appears to be related to those complications that were tracked, rather than a difference in the incidence of major complications (infection, fracture, and nonunion).

Whereas adverse effects of adjuvant treatment have been described in the literature[20,29], we were not able to identify any unfavorable associations for adjuvant chemotherapy or irradiation.

Fracture and infection rates in our population were high, but comparable with previously reported rates[14,15,20,35,36]. Because of the retrospective character of this study, we were unable to retrieve all data on the time to full weight-bearing and, thus, conclusions must be made with caution. Nevertheless, partial and non-weight-bearing periods were considerable in our patients. Authors in previous studies have not reported time to full weight-bearing[13-15,20].

Our study had additional limitations. Although follow-up in our study is among the longest reported on intercalary allografts (see appendix), there is a possibility of underestimating real complication percentages, as there are considerable percentages of late complications. Also, we were unable to acquire functional outcome.

In conclusion, we found high rates of complications leading to reoperations. The majority of complications occurred in the first two years after implantation. Even though complication rates were high, the graft survival rate was 83% and limb salvage was achieved in 98% of patients. Reconstruction site, patient age, allograft length, nail-only fixation, and non-bridging osteosynthesis were the most important risk factors for complications. Nevertheless, in selected cases, intercalary allografts provide an acceptable surgical treatment of many bone tumors.

Appendices

Table A-1. Univariate Cox regression analysis for the time to failure (n = 15) and time to full weight-bearing (n = 49).

	All localizations		Lower extremity	
Covariates	Hazard ratio*	p-value	Hazard ratio*	p-value
Time to failure				
Infection	3.12 (0.95 - 10.20)	0.06	-	-
Fracture	2.81 (0.94 - 8.41)	0.06	4.67 (1.17 - 18.66)	0.02
Patient age of ≥18 years	6.66 (1.47 - 30.11)	0.01	9.46 (1.18 - 75.71)	0.03
Osteosynthesis: bridging plate(s)	0.11 (0.01 - 0.82)	0.03	0.15 (0.02 - 1.23)	0.08
Localization within bone piece: diaphyseal	2.83 (0.86 - 9.30)	0.08	4.08 (0.85 - 19.68)	0.08
Allograft length of ≥15.0 cm	2.80 (0.86 - 9.11)	0.09	9.00 (1.12 - 72.07)	0.04
Time to full weight-bearing				
Nonunion	-	-	0.36 (0.18 - 0.74)	<0.01
Osteosynthesis: intramedullary nail only	-	-	0.27 (0.09 - 0.77)	0.02
Adjuvant radiation therapy	-	-	0.42 (0.16 - 1.08)	0.07

*The values are given as the hazard ratio, with the 95% CI in parentheses.

Table A-2. Multivariate Cox regression analysis for the time to failure

	All localizations		Lower extremity	
Covariates	Hazard ratio*	p-value	Hazard ratio*	p-value
First analysis				
Patient age of ≥18 years	5.66 (1.25 - 25.68)	0.03	8.23 (1.03 - 66.03)	0.05
Osteosynthesis: bridging plate(s)	0.13 (0.02 - 0.98)	0.05	0.19 (0.02 - 1.48)	0.11
Second analysis				
Patient age of ≥18 years	5.57 (1.18 - 26.32)	0.03	7.45 (0.91 - 61.28)	0.06
Localization within bone piece: diaphyseal	1.78 (0.53 - 6.02)	0.36	2.72 (0.55 - 13.46)	0.22
Third analysis				
Patient age of ≥18 years	5.65 (1.21 - 26.27)	0.03	6.45 (0.79 - 52.67)	0.08
Allograft length of ≥15.0 cm	1.91 (0.58 - 6.37)	0.29	6.01 (0.74 - 49.04)	0.09
Fourth analysis				
Localization within bone piece: diaphyseal	2.85 (0.86 - 9.47)	0.09	3.70 (0.77 - 17.87)	0.10
Osteosynthesis: bridging plate(s)	0.11 (0.01 - 0.82)	0.03	3.70 (0.77 - 17.87)	0.09

*The values are given as the hazard ratio, with the 95% CI in parentheses.

Table A-3. Overview of literature on intercalary allografts.

Data	Ortiz-Cruz[14] (1997)	Frisoni[20] (2012)	Aponte-Tinao[13] (2012)	Muscolo[15] (2004)	Donati[16] (2000)	Zimel[18] (2009)	Cara[17] (1994)	Gerrand[19] (2003)	Current study (2013)
	Reference								
No. of patients	104	101	83	59	39	38	23	20	87
Localization									
Femur	38%	100%	100%	68%	72%	100%	61%	25%	51%
Tibia	37%	-	-	32%	28%	-	35%	30%	39%
Humerus	18%	-	-	-	-	-	4%	45%	8%
Radius	3%	-	-	-	-	-	-	-	2%
Fibula	3%	-	-	-	-	-	-	-	-
Ulna	3%	-	-	-	-	-	-	-	-
Follow-up*	67 (24 - 220)	112 (24 - 238)	61 (24 - 182)	60† (24 - 264)	-‡	84† (14 - 231)	35 (12 - 75)	54 (10 - 134)	84 (25 - 262)
Fixation type									
Plates	93%	90%	65%	-	59%	8%	78%	-	71%
Intramedullaray nail	7%	10%	19%	33%	15%	92%	4%	-	9%
Screws	-	-	16%	16%	-	-	-	-	6%
Plates and screws	-	-	-	52%	26%	-	-	-	-
Intramedullary nail and plate	-	-	-	-	-	-	17%	-	14%
Overall complications	-	-	46%	-	-	-	42%	-	76%
Specific complications									
Infection	12%	-	1%	5%	0%	18%	17%	10%	14%
Fracture	17%	27%	16%	7%	30%	3%	9%	0%	29%
Nonunion	30%	47%	24%	15%	55%	16%	15%	15%	40%
Failure	14%	24%	18%	15%	15%	39%	12%	10%	17%
Details	More complications with adjuvant therapy, no clear influence of osteosynthesis type.	26% hybrid grafts; age and allograft length adversely related to outcome.	More nonunions after intramedullary nail fixation and in diaphyseal junctions.	More nonunions in diaphyseal junctions.	29% of femoral and 73% of tibial reconstructions were hybrid grafts.	Allograft-prosthesis comparison; total population: 85 patients, 47 endoprostheses.	Deceased patients excluded.	All reconstructions reinforced with pressurized intramedullary cement.	-

*The values are given as the median, with the range in parentheses, in months. †The values are given as the mean, with the range in parentheses, in months. ‡This value was not reported for intercalary allografts specifically.

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