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

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Chapter 8

Factors Affecting Nonunion of Allograft-host Junctions in Intercalary Reconstructions of the Femur and Tibia

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Abstract

Purpose: To assess risk factors for nonunion after intercalary allograft reconstruction, and to evaluate if cortical contact at the allograft-host junction results in a decreased likelihood of nonunion.

Methods: We retrospectively evaluated 96 osteotomies in 57 patients (34 males, 60%) with an intercalary allograft reconstruction of the femur or tibia for a primary bone tumor. Median follow-up was 8.6 years (95% CI 6.1-11.2). Only one-plane transverse osteotomies with plate fixation were included. The degree of cortical contact was radiographically classified into grades 1 (full contact over the entire length of the osteotomy), 2A (≥50% contact), 2B (<50% contact), and 3 (lack of cortical contact).

Results: There were a total of 15 non-uniting osteotomies (15/96, 16%). Nonunion was the cause for revision surgery in none of the 23 (0%) grade 1, two of 29 (7%) grade 2A, five of 28 (18%) grade 2B, and 8 of 16 (50%) grade 3 junctions. With grade 3 as the reference, the odds ratio for nonunion was 0.22 for grade 2B lesions ($p=0.03$) and 0.01 ($p=0.003$) for grade 2A lesions. Reconstruction site, patient age >16 years, localization within the bone or chemotherapy use did not significantly influence nonunion risk.

Conclusion: Our results suggest that the degree of cortical contact at the allograft-host junction is the most important factor for the risk of developing nonunion. Care should be taken to obtain rigid fixation with firm contact at the junction site.

Introduction

Primary malignant bone tumors of the metadiaphyseal or diaphyseal region of the long bones may be treated with joint-preserving intercalary resections[1, 2]. Many techniques have been described for reconstruction after such resections, of which allografts have been most commonly used. Nevertheless, intercalary allografts have been associated with substantial rates of complications. Nonunion is among the major complications (15-55%)[1, 3-10] and failure mechanisms (5-7%) of these reconstructions[1, 6].

Nonunion is assumed to result from a complex interplay between biological and mechanical factors, and its treatment is often problematic because one side of the junction is comprised of nonvascular bone[11]. Factors that have been associated with the risk of nonunion include the site of transplantation, use of chemotherapy, radiotherapy, patient age, localization of the osteotomy, and the use of intramedullary nails instead of plates[1, 3, 6, 8, 11]. In addition, it has been reported that failure to achieve stable fixation or bone contact at the junction may result in nonunion[12]. However, most studies included small patient groups with heterogeneous reconstructions, and conflicting results have been reported. Therefore, there is little solid evidence on risk factors for nonunion.

With this study, we aimed to evaluate the incidence of, and risk factors for, nonunion in intercalary allograft reconstructions of weight-bearing bones. Moreover, we aimed to evaluate if cortical contact at the allograft-host junction results in a decreased likelihood of nonunion.

Patients and Methods

Patient selection

We present a retrospective case series of all patients with an intercalary (whole-circumference) allograft reconstruction for a primary bone tumor of the femur or tibia, from two tertiary referral centers of orthopaedic oncology. From center one, patients who had their operations between 1989 and 2012 were included. From center two, we only included patients who had their operations between 2008 and 2012 because before that time, digital radiographs were not available, and contact at the allograft-host junction could therefore not be determined in a uniform matter. Our primary end-point was union of the allograft-host junction.

Minimum follow-up was 12 months. We excluded patients in whom the allograft was removed or revised within 12 months for reasons other than nonunion.

Intercalary allografts were the preferred method of reconstruction for any patient with a primary bone tumor in whom we considered it possible to resect the tumor with adequate margins while preserving joints. Alternative treatments included vascularized fibular autografts, hybrid reconstructions, or intercalary (custom-made) implants. Osteoarticular allografts[13, 14] or modular endoprostheses[15] were used when (part of) a joint had to be sacrificed. To minimize bias with regard to the influence of contact at the allograft-host junction, we chose to only include transverse one-plane osteotomies in reconstructions with plate fixation (either plates alone, or in combination with an intramedullary nail); whenever technically feasible, this was the preferred method for cutting and fixation of allografts in both centers. A prerequisite for inclusion was the availability of digital radiographs in the anteroposterior and lateral direction taken in the first 30 days after surgery, because these radiographs were used to assess the degree of contact at the allograft-host junction.

During the periods under study, a total of 208 osteotomies were performed in 104 patients for an intercalary allograft reconstruction of the femur or tibia. We excluded 112 osteotomies (54%): 29 (26%) because the osteotomy could not be assessed on postoperative imaging, 26 (23%) because imaging from the first postoperative month was not available, 21 (19%) because it was a step-cut or oblique osteotomy, 16 (14%) because other types of osteosynthesis were used, eight (7%) because the reconstruction failed due to other reasons within 12 months after the index procedure, six (5%) because the patient died within 12 months after the index procedure, and four (4%) because the patient was lost to follow-up. This left 96 osteotomies in 57 patients (34 males, 60%) available for analysis. Thirty-seven patients (65%) were operated on in center one, 20 (35%) in center two. Median follow-up was calculated using the reverse Kaplan-Meier method, and was equal to 8.6 years (95% confidence interval [CI], 6.1-11.2).

Surgical technique

Allografts were harvested and processed according to techniques that have been described previously[1, 8, 16, 17]. The diagnoses were based on preoperative biopsy, and the biopsy tracts were excised in continuity with the tumor. Resections were planned on an array of conventional radiographs, magnetic resonance imaging (MRI), and computed tomography (CT). All patients received prophylactic cephalosporin antibiotics. During tumor resections, the allografts were thawed in saline solution. Allografts were cut freehanded[1] or with use of computer navigated techniques[18]. Intraoperatively, the surgeon checked that cortical contact could be obtained. In a subset of our patients, a virtual bone bank system was used to select the allograft that best matched the planned resection[19]. Additional cancellous bone grafting was performed in 11 osteotomies (11%), indications included dissatisfying compression at the osteotomy and suboptimal bone quality at the docking site.

Antibiotics were continued for one to seven days after surgery. Postoperatively, patients were mobilized under supervision of a physical therapist. Routine follow-up included conventional radiographs in two directions. MRI and/or CT scans were obtained in case of (suspected) complications. We recorded patient sex, age at surgery, diagnosis, tumor localization, date of surgery, localization within bone level (diaphyseal or meta-epiphyseal), type of neoadjuvant or adjuvant therapy, total resection length, the use of additional (intramedullary) bone grafts, and muscle flaps.

Radiographic classification

We introduce a novel classification system, in which we classify the degree of contact into grades 1, 2A, 2B, and 3. Grade 1 was defined as full contact over the entire length of the osteotomy in both directions; no radiolucent line was visible. Grade 2 was defined as partial contact and was further divided into grades 2A (≥50% contact) and 2B (<50% contact). Grade 3 was defined as a lack of cortical contact; a radiolucent line was visible over the entire length of the osteotomy (figures 1-4).

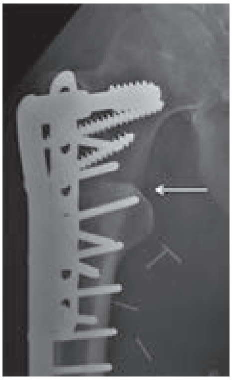

Figure 1. Anteroposterior X-ray of a proximal femoral allograft. A radiolucent line cannot be identified; there is full contact (white arrow): grade 1.

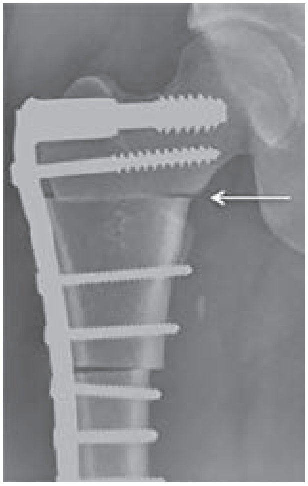

Figure 2: Anteroposterior X-ray of a proximal femoral allograft. There is ≥50% cortical contact at the proximal osteotomy (white arrow): grade 2A.

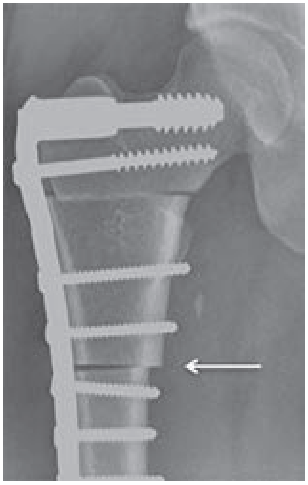

Figure 3: Anteroposterior X-ray of a proximal femoral allograft. There is <50% cortical contact at the distal osteotomy (white arrow): grade 2B.

All osteotomies were independently assessed and graded by two reviewers (MPAB, JIA) who had not been involved in the care of the patients. In case of disagreement, the reviewers met to reach consensus. The occurrence and time to complications were determined. Nonunion was defined as the lack of consolidation in at least two of the four cortices (anteroposterior and lateral radiographs) at 12 months[1, 6, 11]. Moreover, the junction was considered to be a

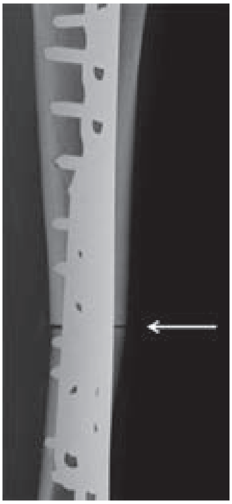

Figure 4: Lateral X-ray of a tibial allograft. A radiolucent line is visible over the entire length of the osteotomy (white arrow): grade 3.

nonunion if any additional operation had been performed to achieve union or because of problems with the fixation within 12 months after the index procedure – regardless of the eventual outcome[12].

Table 1. Study data

Variable	Number	Percent
Sex		
Male	34	60
Female	23	40
Age		
≤16 years	26	46
>16 years	31	54
Diagnosis		
Osteosarcoma	26	46
Adamantinoma	9	16
Ewing sarcoma	9	16
Chondrosarcoma	7	12
Pleomorphic undifferentiated sarcoma	2	4
Low-grade osteosarcoma	2	4
Sarcoma not otherwise specified	1	2
Synovial sarcoma	1	2
Diffuse-type giant cell tumor	1	2

Table 1. continued

Variable	Number	Percent
Reconstruction site		
Femur	39	68
Tibia	18	32
Adjuvant therapies		
Chemotherapy	34	60
None	19	33
Radiotherapy	2	4
Chemo- and radiotherapy	2	4
Osteosynthesis type		
Single plate	31	54
Double plate	23	40
Intramedullary nail + plate	3	5
Status at final follow-up		
No evidence of disease	46	81
Alive with disease	1	2
Died of disease	10	18

Study data

Median age at surgery was 17 years (range, 2-71 years). Predominant diagnoses were osteosarcoma (n=26, 46%), adamantinoma, and Ewing sarcoma (both; n=9, 16%) (table 1). At follow-up, 46 patients (81%) had no evidence of disease, one patient (2%) was alive with disease, and ten (18%) had died due to disease. Sixty-one osteotomies (64%) were located in the femur, 35 (37%) in the tibia. Sixty-five osteotomies (68%) were diaphyseal, 31 (32%) were meta-epiphyseal. Fifty-six osteotomies (58%) were subjected to (neo)adjuvant chemotherapy, two (2%) to radiotherapy, and two (2%) to both. Osteosynthesis was performed with a single long plate held with cortical screws in 53 osteotomies (55%), with a long plate combined with a separate smaller plate in 39 (41%), and with a plate combined with a nail in four (4%).

Ethics and statistical analysis

All study procedures were in accordance with the ethical standards of Dutch law (Medical Research involving Human Subjects Act) and with the 1964 Helsinki declaration and its later amendments. For this type of study formal consent is not required.

All data were complete. Logistic regression analyses were used to assess the influence of potential risk factors of the occurrence of nonunion. Outcomes are expressed in odds ratios (OR), 95% confidence intervals (95% CI) and p-values. SPSS 21.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, with the level of significance at $p < 0.05$.

Results

There were a total of 15 non-uniting osteotomies (15/96, 16%). Revision operations for nonunion were performed after a median of 17.5 months (range, 4 months to 9 years) after the index procedure. Twenty-three osteotomies (24%) were classified as grade 1, 29 (30%) as grade 2A, 28 (29%) as grade 2B and 16 (17%) as grade 3, respectfully. The kappa value between the two observers was 0.734 (substantial[20]). The classification of the two observers was identical for 79 osteotomies (82%); further discussion to achieve consensus was needed for 17 osteotomies (18%). Nonunion was the cause for revision surgery in none of the 23 osteotomies that were classified as grade 1, in two of 29 (7%) that were classified as grade 2A, in five of 28 (18%) that were classified as grade 2B, and in 8 of 16 (50%) osteotomies that were classified as grade 3 (Table 2).

Table 2. Table showing the number of osteotomies included in each category, the number of osteotomies that were revised for nonunion, and the corresponding odds ratios, 95% confidence intervals and p-values. Because there were zero events in the grade 1 osteotomies, we chose to use grade 3 osteotomies as the reference category. For the same reason, the odds ratio, 95% confidence interval and p-value could not be calculated for grade 1 osteotomies

Classification, category	Total number of osteotomies	Number revised for nonunion	% Non-Union	95% confidence interval		P-value
				Lower	Upper	
Grade 1	23	0	0%	-	-	-
Grade 2A	29	2	7%	0.01	0.42	0.003
Grade 2B	28	5	18%	0.05	0.86	0.03
Grade 3	16	8	50%	Ref.	Ref.	-

Twelve of 61 femoral osteotomies (20%) and three of 35 tibial osteotomies (9%) did not initially heal (p=0.149). The risk of nonunion was not significantly associated with patient age, although the risk was slightly lower in patients of 16 years or younger (7/52, 13%) than in patients aged over 16 years (13/60, 22%) (p = 0.258). Also, epimetaphyseal junctions appeared to have a slightly lower risk of nonunion (5/40, 13%) than diaphyseal osteotomies (15/72, 21%) (p = 0.270).

The risk of nonunion did not differ significantly between patients who received chemotherapy (14/70, 20%) and those who did not (6/42, 14%) ($p = 0.445$).

Discussion

Nonunion is among the leading causes for failure of intercalary allografts. In this retrospective case series, we evaluated risk factors for nonunion and assessed whether cortical contact at the allograft-host junction results in a decreased likelihood of nonunion.

Our study had a number of limitations. First, we recognize the retrospective design of this study and the selection bias for the patients who were treated in two different countries by two different groups. We were not able to obtain the presence of other potential risk factors, such as smoking status. Second, because digital radiographs were not available before 2008 in one of our centers, we included patients who were treated at different periods in time. However, over the years, little has changed in our perioperative protocols. Third, the number of events was limited and therefore, we could not perform a multivariable analysis. Fourth, the group has some inherent heterogeneity, which could affect the incidence of nonunion. To minimize the risk of bias, we chose to only include one-plane transverse osteotomies that were fixed using one or more plate(s).

Sixteen percent of the osteotomies did not initially heal. Reported rates of nonunion in literature vary from 15 to 50%[1-5, 7, 9, 10, 21, 22]. However, as we noted previously, some studies assessed nonunion per patient, while others scored both osteotomies and therefore score more nonunions, but report a lower percentage of nonunion (table 3)[1]. In addition, previous authors used different definitions of nonunion. Most large studies determined union radiographically[3, 6, 9]. Although some defined nonunion as a lack of progressive healing at six months[23], most large studies defined nonunion as the lack of cortical continuity in three cortices after 12 months[6, 9]. Apart from that, previously reported incidences may have also included infected nonunions. To avoid bias, we chose to exclude patients with an infection from our study. Nevertheless, in clinical practice, the possibility of infection should always be excluded if a junction does not heal. Clinical workup should include physical examination, laboratory testing (including white blood cell count, C-reactive protein and sedimentation rate), a conventional radiograph or CT-scan and, in case of doubt, leukocyte scintigraphy.

A lack of cortical contact was the most important risk factor for nonunion in our study. None of the osteotomies that demonstrated full contact between the allograft and host bone developed a nonunion. A number of previous studies addressed the influence of gap size on healing of bone defects. Claes *et al* showed that primary bone deposition in the metatarsus of sheep occurs in osteotomy gaps of less than 1 mm and that inferior healing occurs in gaps greater than 2 mm[24]. They concluded that treatment of simple diaphyseal fractures is improved when interfragmentary gaps are prevented.

One option to maximize the contact surface between allogeneic and host bone is to use step cut osteotomies, which have been associated with a 74% increase in contact surface as compared with transverse osteotomies[23]. Although step-cut osteotomies may be preferable theoretically, transverse osteotomies are still the technique of choice in our centers, for a number of reasons. First, transverse osteotomies consist of a single cut and are the least technically demanding. Therefore, the chance of obtaining full contact is higher than with more complicated step-cut osteotomies. Second, a transverse osteotomy is the only type of osteotomy in which uniform pressure distribution between can be obtained[23]. Third, in contrast to step cut osteotomies, transverse osteotomies do not require further soft tissue exposure. The limited extent of soft tissue dissection has been described as a factor that contributes to the chance of initial healing of allografts[23, 25]. Fourth, transverse osteotomies are quick and therefore may be associated with a lower risk of infection as compared to more complicated step cut osteotomies.

Frisoni *et al* analyzed factors affecting outcomes of intercalary femoral allografts[6]. They radiographically reviewed osteotomies to assess contact at the allograft-host junctions, and defined "good contact" as at least two of the four cortices being separated by a radiolucent line of less than 2 mm. They reported that "good" versus "poor" contact did not influence the risk of delayed union. However, it may be questioned how one can reliably or reproducibly measure a gap of 1 to 2 mm on radiographs that have not been taken according to a predefined protocol. In future studies, CT scan images may be used to determine the exact gap size. Because CT images were only available for a small number of patients, we chose to classify the osteotomies in a limited number of categories that could easily and reproducibly be distinguished on conventional radiographs. Indeed, our classification system demonstrated good interrater reliability.

Our results suggest that cortical contact is an important factor for union of allograft-host junctions. The osteoconductive allograft acts as a scaffold for host bone growth; the more contact there is between host bone and the scaffold, and the closer the scaffold is, the quicker incorporation may be expected[26, 27]. Enneking and Campanacci performed a clinicopathological study in 73 retrieved massive allografts. They observed that 'accurate and intimate' contact appeared to promote healing, although they described that incorporation may occur when gaps up to 4 mm are present, as long as the construct is securely immobilized[28]. We concur with Cascio *et al*, stating that attention should be paid to produce rigid, precise contact at the junction[23]. We recommend the use of fluoroscopy in two directions to determine the degree of contact at the osteotomy level, and suggest that a revision of plate fixation or addition of a second plate should be performed in cases in which less than 50% of cortical contact is observed intraoperatively.

In conclusion, the results of this study indicate that the degree of contact at the allograft-host junction is the most important factor for the risk of nonunion. Other factors that may contribute to the risk of nonunion are diaphyseal localization and patient age. Our novel classification system of grading allograft-host contact closely correlated with clinical outcome and demonstrated good interrater reliability. Although future, larger studies will have to confirm our findings, this study suggests that care should be taken to obtain firm cortical contact at the junction.

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Table 3. Overview of literature on allograft reconstructions and reported information on allograft-host nonunions

Data	Aponte-Tinao (2012)	Ortiz-Cruz (1997)	Bus (2014)	Frisoni (2012)	Muscolo (2004)	Current study
No. of patients	83	100	87	101	59	57
Type of reconstruction	ICA (100)	ICA (100)	ICA (93) HGR (7)	ICA (74) HGR (26)	ICA (100)	ICA (100)
Localizations (%)	FEM (100)	FEM (38), TIB (37), HUM (18), RAD (3), FIB (3), ULN (3)	FEM (51), TIB (39), HUM (8), RAD (2)	FEM (100)	FEM (68), TIB (32)	FEM (68), TIB (32)
Follow-up (range, unless otherwise specified)	Median 61 months (24-182)	Median 67 months (24-220)	Median 84 months (25-262)	Median 112 months (24-238)	Median 60 months (24-262)	Median 103 months (95% CI 73-134)
Fixation method (%)	PLT (65), IMN (19), SCR (16)	S-PLT (80), D-PLT (13), IMN (7)	PLT (71), IMN + PLT (14), IMN (9), SCR (6)	PLT (90), IMN (10)	PLT (52), IMN (33), SCR (16)	S-PLT (55), D-PLT (41), IMN + PLT (5)
Osteotomy type (%)	TRV (100)	N/R	TRV (100)	TRV (80), STC (20)	TRV (100)	TRV (100)
Reconstruction length (range)	N/R	<10 cm: 16%; 10-18 cm: 15% >18 cm: 28%	Median 14 (5-30)	N/R	N/R	Median 14 (5-30)
Definition of nonunion	N/R	Radiographically; presence of radiolucent line or absence of smooth external continuity of cortical bone at 12 months.	Radiographically; lack of continuity in three cortices after 12 months. Clinically; reoperation for nonunion.	Radiographic; lack of continuity in three cortices after 12 months.	N/R	Radiographically; lack of continuity in two or more cortices after 12 months. Clinically; reoperation for nonunion.
Nonunion - patients (%)	24	30	Radiographic; 26. Clinical; 40.	45	15	27
Nonunion -osteotomies (%)	13	15	N/R	N/R	9	18
Notes regarding nonunion	Higher risk for diaphyseal than for metaphyseal junctions. No influence of fixation type. All nonunions were salvaged with secondary surgery.	Only nonunions that were associated with other complications (infection, fracture) resulted in failure. No significant influence of junction localization or fixation type.	Lower risk in tibial reconstructions. Higher risk after fixation with an intramedullary nail.	Patient age >18 years, use of postoperative chemotherapy, and osteotomy line distance >5 cm from the joint line were individual risk factors for nonunion.	Higher risk for diaphyseal than for metaphyseal junctions. Slightly higher risk for diaphyseal junctions fixed with nails than for diaphyseal junctions fixed with plates.	The degree of contact at the junction was the most important factor.

Type of reconstruction: ICA, intercalary allograft; HGR, hybrid graft reconstruction (allograft + vascularized fibular graft). Localizations: FEM, femur; TIB, tibia; HUM, humerus; RAD, radius; FIB, fibula; ULN, ulna. Fixation method: S-PLT, single plate (one long plate); D-PLT, double plates (one long plate combined with a separate smaller plate). Osteotomy type: TRV, transverse; STC, step cut. N/R, not reported.

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