

# Technique and Results after Immediate Orthotopic Replantation of Extracorporeally Irradiated Tumor Bone Autografts with and without Fibular Augmentation in Extremity Tumors

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## Research article

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# Abstract

**Background:** the reconstruction of the bone defects after the resection of bone tumors remains a considerable challenge and one of the possibilities is the orthotopic replantation of the irradiated bone autograft. One technical option with this technique is the addition of an autologous fibular graft, with or without microvascular anastomosis. The aim of our study was to evaluate the clinical results of the treatment of our patient cohort with a specific view to the role of fibular augmentation.

**Methods and patients:** we were able to include 21 patients with 22 reconstructions. In all cases, the bone tumor was resected with wide margins and irradiated with 300 Gy. The autograft was orthotopically replanted and stabilized by means of osteosynthesis implants. 15 patients underwent an additional fibular augmentation, 8 of which received microvascular anastomoses or, alternatively, a local pedicled fibular interposition.

**Results:** the most common diagnosis was a Ewing-sarcoma (8 cases) and the most common location was the femur (12 cases). The mean follow-up time was 70 months. During follow-up, 59% of patients underwent an average of 2.54 revision surgeries, with the most common reason being pseudarthrosis (6 cases). Complete bony integration of the irradiated autografts was achieved in 81.8% of cases after 13.6 months on average. In case of successful reintegration the autograft was shorter (n.s.). Fibular augmentation with or without microvascular anastomosis/pedicled blood supply did not correlate with the pseudarthrosis rate.

**Conclusions:** the replantation of extracorporeally irradiated bone autografts is an established method for the reconstruction of bone defects after tumor resection. Our rate of complications is comparable to those of other studies and with other methods of bone reconstruction (e.g. prosthesis). In our opinion, this method is especially well suited for younger patients with extraarticular bone tumors maintainable joints. However, these patients should be ready to accept longer treatment periods.

## Background

Most primary malignant bone tumors are localized in the long bones with the majority occurring in the meta-/epiphyses. About 10% of primary malignant tumors affect the diaphyseal part of the long bones[1]. The resection of these tumors causes large defects in these load-bearing bones and their reconstruction represents a challenge. Biological as well as endoprosthetic methods for the reconstruction of long bone continuity have been developed. Biological reconstruction methods include the use of allografts, segmental transport or the reimplantation of sterilized resected bone segments [2] with each of these methods entailing specific advantages and disadvantages. The long term problems are infection, transplant necrosis, loosening or pseudarthrosis. The reimplantation of a sterilized autograft offers the advantages of a perfect anatomical match and immediate availability. The available methods for the devitalization of the bone autograft are sterilization by irradiation, by fluid nitrogen and pasteurization [2]. Our center has a longstanding experience with the sterilization of tumor-bearing bone autografts by irradiation. This technique was first described by Spira et al in 1968 [3] and has since become established in the treatment of malignant bone tumors. This method allows an anatomic reconstruction and later bone remodeling especially in young patients[4]. However, there are only few reports with series including more than 15 patients.

There are two major problems with this strategy: One is the creeping resorption of the allograft, the other is the reported high rate of pseudarthroses. In order to combat these issues, the augmentation of the allograft with a vascularized or a non-vascularized fibula segment is an option. Until now, the role of fibular augmentation of an irradiated autograft has not been fully established.

## Patients Und Methods

The aim of our study was to evaluate the outcomes of the treatment of malignant bone tumors by replantation of the extracorporeally irradiated bone segments, to establish the rate of successful bone healing and to evaluate the role of (non-) vascularized fibular augmentation of the reconstruction. Additional factors, which might influence the result were also analyzed.

This retrospective analysis was performed based on our tumor database and current follow-up data. We identified 21 consecutive patients with resection, irradiation and replantation of the tumor bone segment, operated between 1999 and 2015. The same surgeon treated all patients. The indications for this procedure were the following:

- Indication for wide resection of the tumor
  
- Localization of the tumor in the metaphysis or diaphysis of a long bone
  
- Sufficient residual bone stability

The diagnosis of the tumor was ascertained by an incision or core-needle biopsy based on radiological imaging (MRI, CT- and/or PET-CT scan). Primary bone tumors as well as metastases of other tumor entities were included. Systemic therapy was applied in some patients depending on the requirements of the underlying tumor condition.

There were 9 female and 12 male patients. The range of the age at the time of operative treatment was between 10 and 83 years (median age 36.4 years), 3 of them younger than 18 years. These 21 patients underwent 22 primary operations. One patient had a simultaneous partial femur and tibia resection. No patient was lost to follow-up. The details to the patients are displayed in Table 1.

Table 1  
Patient characteristics (sex: m = male, f = female)

Pat ID	Age	Sex	Tumor Entity	Location	Fibula-augmentation	Type of complication	Number of revisions	Bony union achieved
1	10	m	Ewing Sarcoma	tibia	yes	infection	5	yes
2	11	m	Osteosarcoma	femur	yes		0	yes
3	66	f	Osteosarcoma	femur	no	pseudarthrosis	2	yes
4	57	m	Leiomyosarcoma	tibia	yes		0	yes
5	26	f	Ewing Sarcoma	femur	yes		0	yes
6	13	m	Osteosarcoma	femur	yes	pseudarthrosis	4	Prosthesis
7	58	m	HCC-Metastasis	femur	no	infection	2	yes
8	27	m	Ewing Sarcoma	femur	yes		0	yes
9	37	f	Osteosarcoma	femur	yes	pseudarthrosis	8	yes
10	79	f	RCC-Metastasis	tibia	no	hematoma	1	yes
11	32	m	Ewing Sarcoma	calcaneus	yes	hematoma	1	pseudarthrosis
12	29	m	Ewing Sarcoma	calcaneus	no		0	not possible (total bone)
13	20	f	Ewing Sarcoma	tibia	yes	wound healing	2	yes
14	73	f	RCC-Metastasis	femur	yes		0	yes
			RCC-Metastasis	tibia	yes	infection	3	yes
15	31	m	Chondrosarcoma	tibia	no		0	yes
16	36	f	Ewing Sarcoma	calcaneus	no	wound healing	2	yes
17	49	m	RCC-Metastasis	femur	yes		0	yes
18	68	m	Myxofibrosarcoma	femur	yes	pseudarthrosis	1	yes
19	83	m	RCC-Metastasis	femur	no	pseudarthrosis	1	yes
20	62	m	Osteosarcoma	tibia	yes		0	yes

Pat ID	Age	Sex	Tumor Entity	Location	Fibula-augmentation	Type of complication	Number of revisions	Bony union achieved
21	12	f	Ewing Sarcoma	femur	yes	pseudarthrosis	1	pseudarthrosis

For sterilization we used high-dose irradiation in all but the first patient, where thermal sterilization in an autoclave was used.

In the case of fibular augmentation, harvesting the graft was the first step of surgery. A wide resection of the tumor was subsequently performed. The explanted tumor-bearing bone segment was packed into a double sterile bag and transported to the radiation oncology department. To minimize any build-up effect and to keep radiation time short, the bag was wrapped with flab material and placed beneath the linear accelerator with the lowest possible distance to the accelerator head, usually on a tray in the accessory slot. A dose of 300 Gy using an opposing field technique was applied in a single fraction. After radiation, the bone (fragment) was immediately returned to the operation room.

In the next step, the irradiated bone was prepared for replantation, the soft tissue parts were resected as necessary (Fig. 1) followed by replantation and osteosynthesis. In 15 patients, an augmentation with a fibular graft was used. In 8 of these 15 cases, we used a vascularized fibula or performed a pedicled fibular interposition. The decision which method (vascularized/non-vascularized) fibula was used, depended primarily on the location. If a fibular transposition into a tibial defect was possible, we used a pediculated vascularized graft. In the first cases of femoral defects, we used free vascularized fibula grafts. Later, due to good reported experiences with non-vascularized fibula graft in literature [5], we changed our strategy and used non-vascularized grafts. The conventional radiographic controls were performed 6 weeks, 3, 6, 9 and 12 months after the surgery and then as required. The local tumor follow-up was done preferably by means of additional MRI. The definition of bony union was assessed by an experienced musculoskeletal radiologist based on the conventional radiographs obtained at follow-up (Fig. 2).

Significance analysis was performed using the Log-Rank test or the Chi-Square test, defining a 95% confidence interval. The univariate analysis (Cox proportional-hazards regression) was used for the evaluation of the influence of the distance of bone resection and of the reconnection of fibular vessels on the pseudarthrosis rate. The level of significance was set at less than 0.05. The data analysis software used was IBM® SPSS® Statistics 25. The institutional ethics committee approved this study.

## Results

All patients with replantation of irradiated autografts could be included. One patient underwent synchronous dual tumor resection and replantation of irradiated bone in the distal femur and in the proximal tibia for bone metastases of a renal cell carcinoma.

The diagnoses were Ewing-sarcoma in 8 cases, metastatic disease in 6 cases (5 patients with renal cell carcinoma, one patient with hepatocellular carcinoma), osteosarcoma in 5 and one case each with high-grade chondrosarcoma, leiomyosarcoma and myxofibrosarcoma with bone involvement (Table 1). The most common site of the tumors was the femur in 12 cases, the tibia in 7 and the calcaneus in 2 cases. One patient had the tumor located in the scapula. The mean follow-up was 70 months (range between 16 and 154 months, median 58 months). In only 3 patients the follow-up was less than 2 years. In total, five patients deceased due to progressive disease during the observation period.

## Tumor control

We observed only one locoregional recurrence in 22 patients, resulting in a local control rate of 95.5%. This patient, a 13-year old boy, suffered from an osteosarcoma of the femoral diaphysis. He had been diagnosed with a pathologic fracture surrounded by a large hematoma and was initially treated by intramedullar nailing at another institution. We subsequently performed a resection with microscopically clear margins and retransplantation as described in the methods section. He developed a symptomatic pseudoarthrosis between the graft and the femur, which was salvaged by total femur reconstruction. 9 months after reconstruction, locoregional recurrence occurred (outside the initial graft area but inside the initial hematoma area), which was successfully salvaged by wide resection. We therefore attribute the locoregional recurrence to the (possibly tumor cell contaminated) initial fracture hematoma.

## Graft integration

Complete bony integration of the irradiated autograft was ultimately achieved in 18 of 20 lesions (90%) after a mean time of 13.6 months (range 4–35, median 10 months). In two patients with retransplantation of the whole bone, integration was formally not possible. Two patients developed pseudoarthroses that remained asymptomatic and did not require any further surgical treatment. Limb preservation was achieved in all patients.

## Complications

We observed complications that required surgical revision in 13 cases (59.1%). 6 of those were caused by symptomatic pseudoarthrosis with failure of the reconstruction and led to at least one surgical revision per patient. 4 Patients needed an additional operation because of wound hematoma or delayed wound healing and 3 because of a surgical site infection. In total, 33 revisions were necessary (average 2.54 revisions per case).

2 pseudoarthroses were observed after reconstruction without and 4 after reconstruction with fibular augmentation. There were no cases of autograft fracture (Table 1).

There were 11 tumors in the diaphyseal area of the bone. 7 lesions were located in the epi-/ metaphyseal part of the bone. Out of 18 cases of successful replantations in long bones, 15 osteotomies were located in the meta-diaphyseal zone, 18 in the diaphyseal area. 3 patients had a replantation of a meta-epiphyseal graft including the articular cartilage. When comparing the time required for the osteotomy to heal between diaphyseal and meta-epiphyseal sector, no significant difference was observed ( $p = 0.662$ ; 10.8 vs 11.4 months).

The length of the resected intercalary segment was not significantly correlated with the occurrence of pseudoarthrosis ( $p = 0.229$ ), but the cases with a pseudoarthrosis had longer resections lengths on average (16.9 cm vs 12.7 cm).

In 15 cases, we used a fibular augmentation, 7 of which were non-vascularized. There was one case of pseudoarthrosis in the group of vascularized and three in the group of non-vascularized augmentations. In our statistical analysis, however, there was no significant difference between these groups ( $p = 0.310$ ). With a microvascular anastomosis, the time to bony integration was 11 months on average (range 5–16 months) and 10 months in the non-vascularized group (range 5–12;  $p = 0.821$ ). The results of univariate analysis are shown in the Table 2.

Table 2  
results of univariate analysis regarding the risk of pseudarthrosis

	p-value
Location in bone (diaphyseal vs. meta-/epiphyseal)	0.662
Length of the resection	0.229
Vascularization of fibula graft	0.310

## Discussion

The reconstruction of bone defects is not a trivial task and several strategies are available: endoprotheses, allografts, autologous fibula grafts, allogeneic bone grafts and sterilized autologous grafts.

The option of endoprosthetic reconstruction by means of megaprotheses allows for the rapid stabilization of the affected bone or joint. Full weight bearing and predictable good function of the extremity can be achieved rapidly after bony integration of the stems within 4–8 weeks. However, there are only few reports on long term results with these megaprotheses, but for intercalary reconstruction, they have a loosening rate of 25% within a rather short follow-up time of 14 months. The most critical location was the femur[6]. In endoprosthetic joint replacements, Grimer et al. presented their results with a mean follow-up of 29 years. Every patient required on average 2.7 further operations during the follow-up period with the risk of infection being 1% per year of life and every further operation increasing the infection risk by 2.7%. The risk of secondary amputation was 16% [7]. Our revision rate (2.54 per case) is comparable with that reported for endoprosthetic reconstruction. Because of the long term results observed by Grimer et al. and an increasing risk of complications over time, the option of biological reconstruction becomes more important especially for young patients.

One of the latest published studies presents the results of 64 patients with allograft reconstruction of a resection defect in the lower extremity. The overall survival of the reconstructions was 90% after 15 years. 6% of patients underwent secondary amputation of the limb. At least one surgical revision was needed in 40.6% of patients [8]. Especially the diaphyseal reconstructions seemed to be difficult: 70% of these patients needed an operative revision and in 40% of them, non-union was the reason for the reoperation [9].

The portion of patients with surgical revision in our study was 59%. Pseudarthrosis also was the primary reason for revision in 27% of patients (46% of all reoperations). Despite this, the osteotomy healing time was comparable between diaphyseal and other locations. The diaphyseal location appears to have a higher failure rate of the mechanical reconstruction in the early phase of healing because of the high mechanical load on a small bone diameter. One possible explanation is the differences in bone biology and in mechanical behavior between these bone parts [10].

Because of the most common complication being pseudarthrosis, we analyzed the factors that could have influenced the outcome. In our patient cohort, we were unable to identify any predictive factors for a successful osteointegration. The length of the reimplanted bone segment within the group with failed reconstructions was longer, but at the same time, this is a factor, which is determined by the tumor extent. The literature contains more work on the role of fibular autograft interposition with or without vascular supply. The role of vascular supply is not yet finally clarified. Manfrini et al. could not show a positive influence of pedicled fibula autograft on the surgical revision rate (incl. pseudarthrosis)[11]. Other publications showed an advantage of the vascularized fibula in the case of an irradiated tumor bed or of perioperative chemotherapy [12]. The extensive review by Allsopp et al. in 2016 found no advantages with vascular

reconnection of fibular grafts. On the other hand, their work provides evidence of an even higher complication rate with vascularized autografts [13].

The type of sterilization of the bone graft also appears to have an influence on the healing capacity of the so treated bone. One experimental series demonstrated the lowest rate of pseudarthrosis after the replantation of irradiated bone in comparison to pasteurized or autoclaved bone [14]. We used the technique of autograft sterilization by irradiation. The dosage for a safe necrosis of tumor tissue with extracorporeal irradiation was calculated to be 250 Gy [15]. In the published literature, an application of radiation dosages between 50 to 300 Gy are described. We used 300 Gy to be on the safe side with respect to tumor necrosis. The negative effects of irradiation on bone biology is well established [16, 17]. We did not observe any cases of autograft fracture in our cohort [18]. For irradiated grafts, the cadaver study by Hernandez et al. did not show any influence on the biomechanical properties of the irradiated bone [19]. These findings might explain to a large extent the reconstruction failures and minimally longer time of osteotomy healing in our cohort, compared to other studies [20, 21]. Further studies would be required to further evaluate the influence of the irradiation dose on the clinical result after the bone reconstruction by irradiated autograft.

## Conclusion

One established method to reconstruct bone defects after tumor resection is the replantation of the irradiated autograft. The rate of complications with this method in our hands is comparable to previously published studies and to alternative methods of bone reconstruction (e.g. prostheses). In our opinion, this method is best suited for young patients with extraarticular bone tumors. However, these patients should be ready to accept longer treatment periods.

## Declarations

### Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee of LMU University Munich (03.07.2020, No. 20-463).

### Consent for publication:

Not applicable.

### Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

AK, FR and HRD designed the study. AK and YB performed the formal analysis and data investigation. AK wrote the original draft. FR, CB and HRD reviewed and edited the article. All authors read and approved the final manuscript. Every Author agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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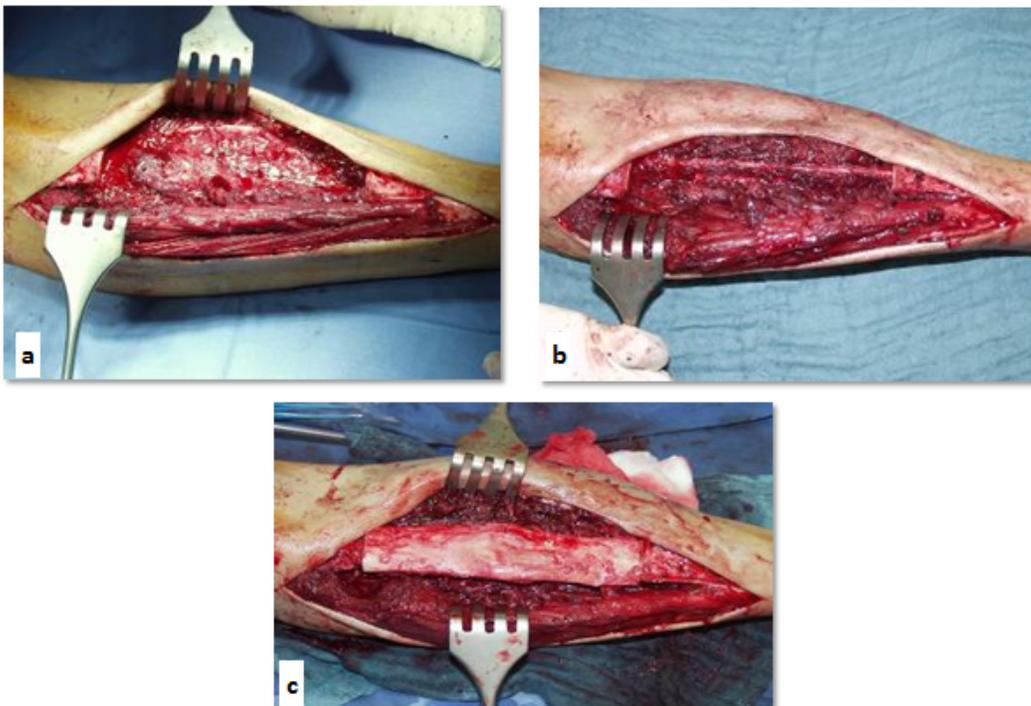
Not applicable.

## References

1. Picci P, Manfrini M, Fabbri N, Gambarotti M, Vanel D. Atlas of musculoskeletal tumors and tumorlike lesions. Switzerland: Springer; 2014.
2. Panagopoulos GN, Mavrogenis AF, Mauffrey C, Lesensky J, Angelini A, Megaloikonomos PD, Igoumenou VG, Papanastassiou J, Savvidou O, Ruggieri P, et al. Intercalary reconstructions after bone tumor resections: a review of treatments. *European journal of orthopaedic surgery traumatology: orthopedie traumatologie*. 2017;27(6):737–46.
3. Spira E, Lubin E. Extracorporeal irradiation of bone tumors. A preliminary report. *Isr J Med Sci*. 1968;4(5):1015–9.
4. Gur E, Kollender Y, Meller I, Amir A, Zaretski A, Bickels J: **The use of free vascularized fibular grafts for reconstruction of segmental bone defects**. In: *Operative techniques in orthopaedic surgical oncology*. edn. Edited by Malawer M: Lippincott Williams & Wilkins, Philadelphia; 2012.
5. Krieg AH, Hefti F. Reconstruction with non-vascularised fibular grafts after resection of bone tumours. *The Journal of bone joint surgery British volume*. 2007;89(2):215–21.
6. Benevenia J, Kirchner R, Patterson F, Beebe K, Wirtz DC, Rivero S, Palma M, Friedrich MJ. Outcomes of a Modular Intercalary Endoprosthesis as Treatment for Segmental Defects of the Femur, Tibia, and Humerus. *Clin Orthop Relat Res*. 2016;474(2):539–48.
7. Grimer RJ, Aydin BK, Wafa H, Carter SR, Jeys L, Abudu A, Parry M: **Very long-term outcomes after endoprosthetic replacement for malignant tumours of bone**. *The bone & joint journal* 2016, **98-b**(6):857–864.
8. Muratori F, Totti F, D'Arienzo A, Scorianz M, Scoccianti G, Beltrami G, Campo FR, Citarelli C, Capanna R, Campanacci DA: **Biological Intercalary Reconstruction with Bone Grafts After Joint-Sparing Resection of the Lower Limb: Is this an Effective and Durable Solution for Joint Preservation?** *Surgical technology international* 2018, **32**:346 – 345.
9. Bus MP, Dijkstra PD, van de Sande MA, Taminiau AH, Schreuder HW, Jutte PC, van der Geest IC, Schaap GR, Bramer JA. Intercalary allograft reconstructions following resection of primary bone tumors: a nationwide multicenter study. *The Journal of bone joint surgery American*. volume 2014;96(4):e26.
10. Blokhuis TJ. Management of traumatic bone defects: Metaphyseal versus diaphyseal defects. *Injury*. 2017;48(Suppl 1):91-s93.
11. Manfrini M, Bindiganavile S, Say F, Colangeli M, Campanacci L, Depaolis M, Ceruso M, Donati D. Is There Benefit to Free Over Pedicled Vascularized Grafts in Augmenting Tibial Intercalary Allograft Constructs? *Clin Orthop Relat Res*. 2017;475(5):1322–37.
12. Malizos KN, Nunley JA, Goldner RD, Urbaniak JR, Harrelson JM. Free vascularized fibula in traumatic long bone defects and in limb salvaging following tumor resection: comparative study. *Microsurgery*. 1993;14(6):368–74.
13. Allsopp BJ, Hunter-Smith DJ, Rozen WM: **Vascularized versus Nonvascularized Bone Grafts: What Is the Evidence?** *Clinical orthopaedics and related research* 2016, **474**(5):1319–1327.

14. Yasin NF, Ajit Singh V, Saad M, Omar E. Which is the best method of sterilization for recycled bone autograft in limb salvage surgery: a radiological, biomechanical and histopathological study in rabbit. *BMC Cancer*. 2015;15:289.
15. Weichselbaum RR, Rotmensch J, Ahmed-Swan S, Beckett MA. Radiobiological characterization of 53 human tumor cell lines. *Int J Radiat Biol*. 1989;56(5):553–60.
16. Nguyen H, Morgan DA, Forwood MR. Sterilization of allograft bone: effects of gamma irradiation on allograft biology and biomechanics. *Cell tissue banking*. 2007;8(2):93–105.
17. Sabo D, Brocai DR, Eble M, Wannemacher M, Ewerbeck V. Influence of extracorporeal irradiation on the reintegration of autologous grafts of bone and joint. Study in a canine model. *The Journal of bone joint surgery British volume*. 2000;82(2):276–82.
18. Rahman N, Khan R, Badshah S. Effect of x-rays and gamma radiations on the bone mechanical properties: literature review. *Cell tissue banking*. 2018;19(4):457–72.
19. Hernandez CJ, Ramsey DS, Dux SJ, Chu EH, Rimnac CM. Irradiation does not modify mechanical properties of cancellous bone under compression. *Clin Orthop Relat Res*. 2012;470(9):2488–95.
20. Friedrich JB, Moran SL, Bishop AT, Wood CM, Shin AY. Free vascularized fibular graft salvage of complications of long-bone allograft after tumor reconstruction. *The Journal of bone joint surgery American volume*. 2008;90(1):93–100.
21. Li J, Wang Z, Guo Z, Chen GJ, Fu J, Pei GX. The use of allograft shell with intramedullary vascularized fibula graft for intercalary reconstruction after diaphyseal resection for lower extremity bony malignancy. *Journal of surgical oncology*. 2010;102(5):368–74.

## Figures



**Figure 1**

Technique of replantation a: resection of the tumor in the tibial diaphysis; b: transposition of the ipsilateral fibula into the tibial defect; c: interposition of the irradiated segment around the transplant prior to osteosynthesis.



**Figure 2**

Osteosarcoma of the distal femur in a 12-year-old boy; a + b: preoperative a.p. and lateral view; c + d: complete bony integration 4 years after operation