Massive allografts in tumour surgery

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Abstract We offer our personal experience of the use of massive bone allografts after tumour resection. We demonstrate the long-term results from 71 patients (72 allografts) operated on between 1961 and 1990. The long-term survival rate in osteoarticular and intercalary grafts is around 60%. Fractures of the graft can be salvaged in most cases. Infection leads to the removal of the graft in almost all cases. Factors influencing the survival, remodelling and complications of the grafts are discussed. The regime of cryopreservation, fixation and loading of the graft influence these factors, as do the use of autologous bone chips around the allograft–host junction and the application of chemotherapy or radiation. Fracture of the graft can be salvaged in most cases, as opposed to infection which remains the most severe complication and can occur at any time. Even with the improvement of tumour endoprostheses, the use of allografts remains an option, especially in young patients.

Résumé Les auteurs rapportent leur expérience de l'utilisation des allogreffes massives après résection tumorale.

Les résultats à long terme de 71 patients (73 allogreffes) opérés entre 1961 et 1990 sont rapportés avec un taux de survie dans les greffes articulaires et intercalaires voisin de 60%. Les fractures de greffes peuvent être rattrapées dans de nombreux cas, mais l'infection conduit à retirer la greffe dans la plupart des cas. Les facteurs influençant le remodelage et les complications des allogreffes sont discutés. Le régime de cryopréservation, la fixation et la remise en contrainte des greffes influencent ces facteurs ainsi que la disposition de lamelles d'autogreffe à la jonction hôte-allogreffe et l'existence de radio ou chimiothérapie. La rupture de la greffe peut être récupérée dans la plupart des cas, contrairement à l'infection qui demeure la complication la plus grave qui peut se produire à tout moment. Même avec le développement des prothèses massives pour tumeur l'utilisation des allogreffes reste une option intéressante spécialement chez les patients jeunes.

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Introduction

The use of massive bone allografts, including osteoarticular and structural grafts, has a long tradition in Czech orthopaedics [11, 18]. In a similar way, other surgeons have used various types of allografts to cover different bone defects [1, 7, 9, 14]. In bone tumour surgery, massive allografts were used initially to fill defects after resection of aggressive benign lesions and low-grade malignant tumours [7, 11]. With the introduction of effective postoperative and, especially, preoperative chemotherapy, bone allografts could also be safely used in high-grade malignant tumours [4, 10]. The correct indication, application and long-term fate of these large allografts still remain questionable.

Materials and methods

We refer to our experience with 72 allografts in patients operated on or controlled personally by at least one of us at the Orthopaedic Clinics of the 1st Medical School in Prague 2 and Prague 8 during 1961 to 1990. There were 23 large osteoarticular grafts (Table 1), 28 intercalary grafts (Table 2) and 20 fibular grafts (Table 3). We implanted one composite hip endoprosthesis in 1988 after a 16 cm proximal femur resection for Ewing's sarcoma in a 10-year-old girl.

The grafts were either ordered from the Brno bone bank or had been harvested since 1958 by members of the clinic from donors who died suddenly. Most of them were also donors for organ transplantations. No cryoprotection was used, and the grafts were deep frozen between -50°C and -80°C and stored at temperatures between -20°C and -80°C . The graft harvesting was performed under sterile conditions or a 0.9% solution of sodium chloride with antibiotics was applied. No sterilization through radiation or boiling was performed.

Grafts were evaluated for complications and survival.

Results

From the 23 osteoarticular grafts, 14 (60%) are long-term survivals, including one after fracture salvage. Six had to be removed because of infection. Three patients died of complications related to the disease and one from a cause unrelated to the tumour (Table 1). Two patients with pelvic tumours died within 2 months of surgery. One with a tumour in the proximal femur died after 2 years from lung metastases. One of the distal femoral grafts fractured after 24 years but it could be salvaged, and one was removed after 17 years because of infection. Another distal femoral graft became infected early after surgery and was removed after 1 year of treatment. One proximal tibia graft treated with radiation became infected early after surgery. One patient with this type of graft died 8 years after surgery from causes unrelated to the tumour. One distal tibia became infected 5

years after surgery and was salvaged by an arthrodesis with fibular allografts. In the humerus the intramedullary nail had to be removed, and the graft continued to resorb.

Of the 28 intercalary grafts, 16 (57%) have survived for over 15 years (Table 2). Infection occurred in six patients who were undergoing chemotherapy. Two of them had intra-arterial CDDP and one additional radiation. All infections were early except for one that developed after 3 years. The infection in a patient who had not received chemotherapy occurred 4 years after surgery. None of the infected grafts could be salvaged. One extremity could be salvaged with external fixation and cancellous autografts.

Re-osteosynthesis was necessary in four patients who had received chemotherapy: two within 1 year and, in the other two, after 3 and 4 years. One re-osteosynthesis in a patient who had not undergone chemotherapy was performed 15 years after the initial surgery.

Two patients had abbreviation osteotomies after growth arrest. One patient with a locally recurrent low-grade parosteal osteosarcoma had an amputation 5 years after initial surgery.

All of the proximal humerus fibular allografts showed complete resorption of the proximal head within 3 years (Table 3). Only two patients with chondrosarcoma and one each with Ewing sarcoma and clear cell renal carcinoma metastasis survive. Even though the proximal part is missing, the function is sufficient for daily activities. The diaphyseal reconstructions with additional cancellous autografts had incorporated within 3 years. Two knee arthrodesis patients died from tumour progression at 14 months and 36 months. The ankle arthrodesis was a salvage procedure after a failed osteocartilaginous allograft shown in Table 1.

The patient with the composite stem had two cup revisions, but the stem is doing well and we observed only mild osteolysis at the proximal part of the graft between the second and fifth year, which remained stable.

Allografts in the proximal tibia of a 23-year-old woman with a giant cell tumour and in the left acetabular region of the pelvis of a 21-year-old woman with osteosarcoma are illustrated in Figs. 1 and 2.

Table 1 Massive osteoarticular grafts

Location	BT	GCT	LG MT	HG MT	Total	Survival	Survival time (years)	Complications
Pelvis		1	1	2	4	2	15, 40	0
Femur (proximal)	1		1		2	1	26	0
Femur (distal)		5	1		6	4	22, 23, 32, 44	I 2, F 1
Tibia (proximal)	1	6		1	8	6	21, 21, 34, 24, 24, 31	I 1
Tibia (distal)		2			2	1	34	I 1
Humerus		1			1	0		Resorption 1
Total	2	15	3	3	23	14	15–40	6

BT benign tumour, GCT giant cell tumour, LG MT low-grade malignant tumour, HG MT high-grade malignant tumour, I infection, F fracture

Table 2 Intercalary grafts

Surgery	Diagnosis	Location	Survival ^a	Complications	Died	Total
Knee res.AD	OSA	Femur 9, tibia 7	9 (21.5 years)	I 4, LR 1, F/R 4	3 Met	16
	MFH	Femur 1, tibia 1	0	I 1	1 Met	2
	EWS	Tibia 2	1 (16 years)	I 1		2
	Agr. BT	Femur 1, tibia 1	3 (32 years)	I 1		4
Diaphyseal	EWS	Femur	1 (17 years)			1
	CHS	1st MTC	1 (32 years)			1
	ABC	Ulna	1 (34 years)			1
Resection	CHS	Pelvic wing	0		1 Met	1
Total			16	12	4	28

res.AD resection arthrodesis, *OSA* osteosarcoma, *MFH* malignant fibrous histiocytoma, *EWS* Ewing sarcoma, *Agr.BT* aggressive benign tumour, *CHS* chondrosarcoma, *ABC* aneurysmatic bone cyst, *MTC* metacarpal, *I* infection, *LR* local recurrence, *F/R* graft fracture or re-osteosynthesis, *Met* metastases

^a Number of surviving patients and average survival time

Discussion

The way of preserving the grafts can influence the immune reaction of the recipient and preservation of different types of cells [13, 18]. Different concentrations of cryoprotecting agents such as dimethyl sulphoxide (DMSO) or glycerol, as well as regimes for deep freezing and for thawing, have been advised, especially for preservation of vital chondrocytes [3, 13]. We have not used any such agents, and the freezing regimes were different over the time. Nevertheless, all grafts were deep frozen to at least -40°C and then kept in temperatures of at least -20°C . This stops the enzymatic reactions and preserves the graft for a period of at least 6 to 12 months. Friedlaender gave a nice overview of immunological processes in bone grafts [5]. Chondrocytes, on the other hand, are not expected to survive, even if the cartilage can stay functional for several years [3, 5]. Even though some authors advise the use of fresh osteochondral allografts with immunosuppressive drugs [3], we do not believe that this is the ideal solution for tumour patients, as the reaction of the host could be severe and immunosuppressive drugs are not recommendable for oncological patients. At present, we are applying the standards of the European Union for allograft harvest and preservation even though they are still not technically perfect. We found the sterilization of massive grafts through radiation [8] or heating [1] really disturbing, as their strength decreases

immensely and immunological reaction of the host against protein fragments of the graft can be expected after radiation, including an increased risk of infection [10].

Osteocartilaginous grafts must permit motion. At the beginning we used only adaptive osteosynthesis, and plaster of Paris was applied for 2 months after surgery. From then on limited passive motion was advised, with partial weight bearing starting at 6 months and full weight bearing after 2 years, when the osteosynthetic material was removed, without evidence of graft collapse (Fig. 1). This is in accord with the finding of Enneking and Campanacci, that the graft unites first at 2 years [3]. We also found narrowing of the joint space in nearly all of the cases within the first 2 to 3 years and then after 20 to 30 years. This was without clinical relevance, as the allograft is a dead bone with no neurological feedback, so the patient does not feel any pain. As the cartilage on the allograft probably rebuilds into a pannus of fibrovascular repair tissue [3], this is probably softer than the cartilage of the host, and, therefore, severe changes in the host cartilage are not to be expected unless the joint has significant signs of incongruence. In this way we try to explain the long-lasting pain-free course of the surviving patients, even if we observed a slowly decreasing range of motion within time. The main risk in large pelvic resections is the peri-operative mortality also observed by others [2]. Once healed, the pelvic allograft functions surprisingly well [2, 15]. We observed necrosis in the adjacent healthy bone in

Table 3 Fibular grafts

Location	Number	Complications	Survival	Diagnosis
Humerus (proximal)	15	LR 2, F 3, res. 12	4 (27 years)	Met 7, MM 3, CHS 4, EWS 3
Femur (diaphyseal)	2		2 (20.5 years)	CHS 1, EWS 1
Femur (distal AD)	2	PA 2	0	OSA 2
Tibia (distal AD)	1		1 (16 years)	GCT 1

LR-local recurrence, *F* graft fracture, *res.*-resorption of graft, *PA*-pseudoarthrosis, *Met*-bone metastases, *MM*-multiple myeloma, *CHS*-chondrosarcoma, *EWS*-Ewing sarcoma, *OSA*-osteosarcoma, *GCT*-giant cell tumour

Fig. 1 **a** Osteolytic lesion in the proximal tibia of a 23-year-old woman with a giant cell tumour; **b** After intralesional resection of the proximal tibia, preserving only the cortical bone on both sides, an osteocartilaginous allograft was fixed with two screws; **c** 24 years after surgery the patient walks symmetrically without support. Knee flexion is limited only by 15° in comparison with the healthy side

two cases: patient in Fig. 2 had a femoral head necrosis and one patient with distal tibia graft had a talus necrosis 34 years after surgery. We did not consider this a graft complication as only the normal bone was affected.

Large structural intercalary allografts showed good results in diaphyseal locations [4, 6, 17]. Nevertheless, we prefer the use of autologous fibular grafts in young patients with primary malignant or benign tumours or the use of cement spacers in bone metastases. Arthrodesis around the knee with an allograft is a good solution, especially as a secondary procedure after a temporary cement spacer in combination with an intramedullary nail. We prefer this procedure in primary malignant bone tumours where endoprosthesis is not an option. In a one-stage procedure we prefer the Putti–Juvara type of arthrodesis, which combines autologous and allogeneous bone grafts with plating, as the healing is more rapid and additional cancellous bone chips can improve the vascular supply and graft remodelling. In these procedures we did not remove the osteosynthetic material as we considered further extensive surgery a high risk of infection.

The allogeneous fibular grafts showed bad results in the proximal humerus, where the massive allograft also failed. This can be due to either adverse biomechanical and nutritive conditions around the humeral head or the fact that the fibular head has separate vascularization and becomes necrotic within time. At present, we do not use fibular allograft in contrast to the fibular autograft, especially since the fibula can be used as a vascularised bone graft.

The healing of the graft took, in our experience, about 6 months, and the graft was incorporated at around 2 years. During the course of chemotherapy no remodelling occurred, but this resumed when the chemotherapy ended. This is in accordance with the histological findings of Enneking and Campanacci [3]. In children the remodelling was faster and took about 12 to 18 months [6]. In adults the remodelling was rarely complete. We did not find any clinical correlation with the length of graft and extent of remodelling, even though this would have to be verified histologically for clear evidence. Throughout the whole observation periods the grafts remodelled slowly but gradually deteriorated, especially in joint locations. Because of this we can say that, even though the allografts offer a long term solution they can fail even after more than 30 years of use, and that a permanent solution by the allograft is, therefore, questionable.

We do not consider fracture of the graft as an absolute indication for graft removal. On the contrary, we prefer a stable re-osteosynthesis with autologous cancellous bone grafting, such as in pseudoarthrosis. Surprisingly, such fractures healed well, not only in our experience [16]. Another possibility is an onlay vascularised fibular graft. This we used only in one case. An exception is the proximal humerus

Fig. 2 a Osteolytic lesion in the left acetabular region of the pelvis in a 21-year-old woman. Diagnosis from the biopsy was malignant fibrous histiocytoma. The final histological diagnosis was osteosarcoma with more than 90% tumour necrosis after preoperative chemotherapy. **b** Sixteen years after surgery the allograft is well integrated, with no tumour recurrence. Femoral head necrosis and limited range of motion are the only problems. The patient married and gave birth to two healthy children by caesarian section

where the fractures do not heal, and we strongly recommend the use of endoprostheses in these locations or the vascularised clavicle if biological reconstruction is indicated.

Surprisingly, the rate of local recurrences was low. This was also due to the histological spectrum of the tumours where the majority was benign or low-grade malignant tumours.

Infection is the most severe complication that leads to the loss of the graft and, in most cases, also to the loss of the extremity. In contrary to the findings of Mankin et al. [10], chemotherapy clearly, in our experience, increases the risk of early infection, especially in locations with decreased soft tissue covering or in combination with radiotherapy either before or after tumour resection. In cases of planned radiotherapy, allografts should not be used, or, if necessary, primary muscle flaps should be added in order to improve soft tissue coverage and vascularisation. On the other hand, late infections are, in our experience, unrelated to chemotherapy and can occur at any time. The risk of infection is always increased, as the graft contains areas of necrotic bone. Only one infected graft was salvaged by distal tibial arthrodesis. Moor et al. also use arthrodesis as salvage in this location [12].

The biomechanical properties of the graft are a very interesting subject, i.e. the loading of the graft and the type of fixation that is connected with this. When plate fixation is used, the graft must be situated either in the centre of the bone or on the opposite side to the plate, but never under the plate. Usually, we observed an increased gap at the junction between the allograft and host bone that fractured between 1 and 2 years after surgery. Additional osteosynthesis with bone grafting leads to the healing of the graft. Intramedullary fixations, especially with interlocking nails that are rotationally stable, are probably the best biomechanical solutions in cases where they can be applied. Dynamisation of such nails can be performed between 6 and 12 months. In young children with preserved growth plates, external fixators can

be an option, even with chemotherapy, but the pins must be put outside the graft. Dynamisation of the external fixator after 3 to 6 months increases the remodelling.

Whenever possible we try to add morcelised autologous bone chips around the junction of the allograft and the host bone. In children it is also possible to resect 1–2 cm more of the host bone and use the thick sleeve of the periosteum to cover the allograft–host junction.

The 60% long-term survival rate is comparable to that of other studies [7, 17]. At mid-term follow-up the results are inferior to those of endoprostheses, but, in the long term, they justify their use. On the other hand, the time till full activity is achieved is much longer than that of the tumour endoprostheses. Because of this they should be indicated in young patients with good prognosis for permanent survival or in cases of arthrodeses in patients who need a fully weight-bearing extremity.

Conclusion

Even with the gradual improvement of endoprostheses, the use of allografts remains an option in the treatment of large defects after tumour resections. Especially in young patients and in intercalary locations they offer a good long-term solution. The remodelling of massive osteocartilaginous allografts should be studied further in relation to their cryoprotection, chondrocyte preservation, biomechanics and type of fixation. If infection can be prevented they offer a long-term, even if probably not a permanent, solution.

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