Acta orthop. scand. *50*, 129–138, 1979

ALLOGENEIC TRANSPLANTATION IN LOW-GRADE MALIGNANT BONE TUMOURS

A New Operative Technique to Avoid Amputation

ERKKI V. S. KOSKINEN, PENTTI SALENIUS & ANTTI ALHO

Department of Orthopaedics and Traumatology, University Central Hospital, Helsinki, Finland

A massive allografting of deep-frozen cadaver bone or hemi-joint was performed in 11 patients with tumours which were diagnosed as aggressive, low-grade malignancies. One patient died from a pre-existing hepatic insufficiency. The other 10 patients have been followed up from 1 to 8 years. These patients received two bone grafts and eight hemi-joint grafts around the knee joint. The operative procedure consisted of fixation of the graft by stable osteosynthesis, surrounding the graft-host junction with an autogeneic iliac chips cuff and, in cases of hemi-joint grafts, reconstruction of the ligaments. X-ray, scintigraphy and biopsy were used to judge the incorporation of the graft. The patients had to be prepared to face a considerable morbidity with long non-weight-bearing periods and possibly further operations.

A full restitution of function was achieved in the bone graft cases. The patients with hemi-joint grafts were also able to retain their limb with a good or satisfactory function. No metastases or recurrences were experienced. The allograft procedure appears to be useful for younger adults, whose long life expectancy makes this operation justifiable, although the fate of cartilage still is unpredictable.

Key words: bone neoplasms; bone neoplasms, surgery; chondroblastoma, surgery; giant cell tumours, surgery; parosteal osteosarcoma, surgery; bone transplantation; allogeneic

Accepted 1.x.78

Clinical experience in using allogeneic bone-cartilage transplants dates back to the beginning of this century (Lexer 1908). However, it was only in the 60's, after asepsis and osteosynthesis techniques had been improved, that this method gained a broader clinical use (Parrish 1966, Nilsonne 1969, Volkov 1970, Ottolenghi 1972). One of the cornerstones in the development was deep-freezing of the graft as a means of preservation (Imamaliev 1969).

The indication for allograft replacement has been a locally aggressive bone tumour, where the tendency to metastasis formation is minor and where the therapeutic alternative is in most cases a mutilating amputation (Mankin et al. 1976). The present report relates the experiences gained in the treatment of 11 low grade malignant bone tumours using a technique (Koskinen 1978) in which cadaver grafts of bone and bone-cartilage are combined with fresh autogeneic cancellous bone grafts.

PATIENTS AND METHODS

During 1970–1977 eleven patients received an osseous or osteoarticular allograft as replacement

0001–6470/79/020129–10$02.50/0

Table 1. Eleven cases of bone and hemi-joint allotransplantation

Case	Sex	Age	Tumour	Type of replacement (1)	Duration of plaster immobilization (months)	Period of non-weight-bearing (months)	Complications	Radiological joint degeneration	Functional result and working ability (2)	Follow-up period (years + months
1	M	34	Giant cell tumour	DFHJ	3	9	Progressive deterioration of the joint	+++	Stable, 10°–120°; disabled	8 + 2
2	F	20	Fibrosacroma	TMD	6	12	Fatigue fracture; united		Normal; at work	7 + 7
3	M	24	Osteosarcoma	HMD			Died from polycystic hepatic degeneration (see text)			
4	F	37	Fibrosarcoma	TMD	7	14	None		Normal; at work	4 + 3
5	M	32	Giant cell tumour	DFHJ	6	9	Collateral ligament insufficiency	+	5° varus, stable, 0°–85°; undergoing re-education	3 + 6
6	M	34	Giant cell tumour	DFHJ	5	10	None	++	Stable, 0°–50°; undergoing re-education	3 + 2

7	F	17	Chondro-blastoma	DFHJ	8	8	None	–	Stable, 0°–100°; at work	2 + 7
8	M	23	Giant cell tumour	PTHJ	6 (3)	12	Fatigue fracture at 5 months, united	+	Stable, 0°–70°; undergoing re-education	2 + 3
9	M	42	Parosteal osteosarcoma	DFHJ	3	9	None	–	Stable, 0°–70°;	1 + 9
10	M	26	Giant cell tumour	DFHJ	2	9	None	++	Stable, 0°–70°; undergoing re-education	1 + 9
11	M	23	Parosteal osteosarcoma	DFHJ	4	6	Fracture at the graft-host junction, united	–	Mobilized; gradual weight-bearing	1 + 3

(1) DFHJ – Distal femoral hemi-joint graft
TMD – Tibial metaphysial-diaphysial graft
HMD – Humeral metaphysial-diaphysial graft
PTHJ – Proximal tibial hemi-joint graft

(2) Joint stability, degree of extension-flexion
(3) Primary immobilization for 2 months, immobilization was reinstated after the fatigue fracture.

for a radically removed bone tumour. The tumours were: giant cell tumour – 5, fibrosarcoma – 2, parosteal osteosarcoma – 2, chondroblastoma – 1, and osteosarcoma – 1 (Table 1). The osteosarcoma had arisen from a giant cell tumour. Two of the giant cell tumours had shown their aggressiveness by a local recurrence after earlier surgery. Three tumours presented themselves clinically as pathological fractures. The diagnosis was verified by open biopsy and the extent determined by angiography and ^{99m} technetium diphosphonate scanning. Metastases were excluded by chest films supplemented by planigraphy and lymphography.

In seven cases the operation consisted of a distal femoral hemi-joint replacement and in one case of a proximal tibial hemi-joint replacement. Metaphysial-diaphysial grafting was performed on the humerus in one patient and on the tibia in two. The donors were patients who had died suddenly from subarachnoidal haemorrhage or accident. Their ages varied from 16 to 50 years. Their histories were checked for chronic diseases, malignancies, infections and medication. The size of the graft bone was taken into consideration, but not the sex, blood group or tissue typing of the donor. The grafts were removed within 6 hours of death, and in accordance with Finnish law. The removal was performed in the operating room. All soft parts, muscles, ligaments and periosteum were removed and the bone marrow curetted. Bacterial cultures were taken from the transplant surfaces after the removal and immediately before the transplantation. In one case a positive saprophyte culture (*Aspergillus nigra*) was obtained before the planned operation. This did not affect the postoperative course under antibiotic coverage. The graft was preserved in a sterile plastic bag at a temperature of −70°C for 48 hours and at −20°C for 30–180 days. Before the transplantation the graft was thawed for 12 hours at +8°C and rinsed with antibiotic solution (Koskinen 1973).

The removal of the tumour was performed as a radical *en bloc* resection including the scar after the previous biopsy and the diseased bone with a large bone and soft tissue margin. The knee ligaments could be saved except in one case with involvement of the medial collateral ligament, which was reconstructed. In no case was the main vessel-nerve bundle affected.

In eight hemi-joint replacements the graft was cut to match the resection level and a stable AO/ASIF osteosynthesis (Müller et al. 1970) was performed (Figure 1). A cuff of autogeneic iliac bone was invariably built-up around the host-graft contact plane. This was done in order to stimulate the process of bony union and to promote bone regeneration in the graft itself (Koskinen 1978). The host ligaments were connected with the graft using nonresorbable sutures in bone tunnels. The posterior tendon-capsule envelope was not specially attached. Suction drainage, systemic antibiotics and plaster immobilization were used in the aftertreatment.

In cases of massive metaphysial-diaphysial resection a corresponding technique was used, extending the osteosynthesis plate over the graft and grafting iliac bone chips around both junctions (Figure 2).

At the time of reporting (May 1978), the follow-up times varied from 8 years 2 months to 15 months (median 2 years 10 months). During the first year the patients were examined at 1- to 3-month intervals and thereafter usually at half-year intervals. To check the incorporation of the grafts X-rays were taken regularly, and biopsies in seven cases between 3 months and 7 years (Holmström et al. 1978). Furthermore, chest films and haematological studies were done at regular intervals.

The postoperative plaster immobilization period varied from 3 to 8 months. Full weight-bearing was allowed between 6 and 14 months.

RESULTS

Primary operative results. All transplantations were technically successful and resulted in stable osteosyntheses where infections were not experienced. One early postoperative death from previous liver disease will be discussed later under complications (Case 3). Thus the follow-up study consists of 10 cases with tumours in the vicinity of the knee or in the diaphysis of the tibia.

The total number of operative procedures in the series was 20, five of these being separate biopsies. In two cases the osteosynthesis implant has been removed.

Immobilization and weight-bearing. The length of the plaster immobilization always exceeded the time expected for healing of the soft tissues and even with the shortest immobilization time no adverse effects were observed. In all but one case (Case 11) weight-bearing was gradually increased to full load between 8 and 14 months. The criterion for increasing loading was radiological consolidation at the autogeneous sleeve area

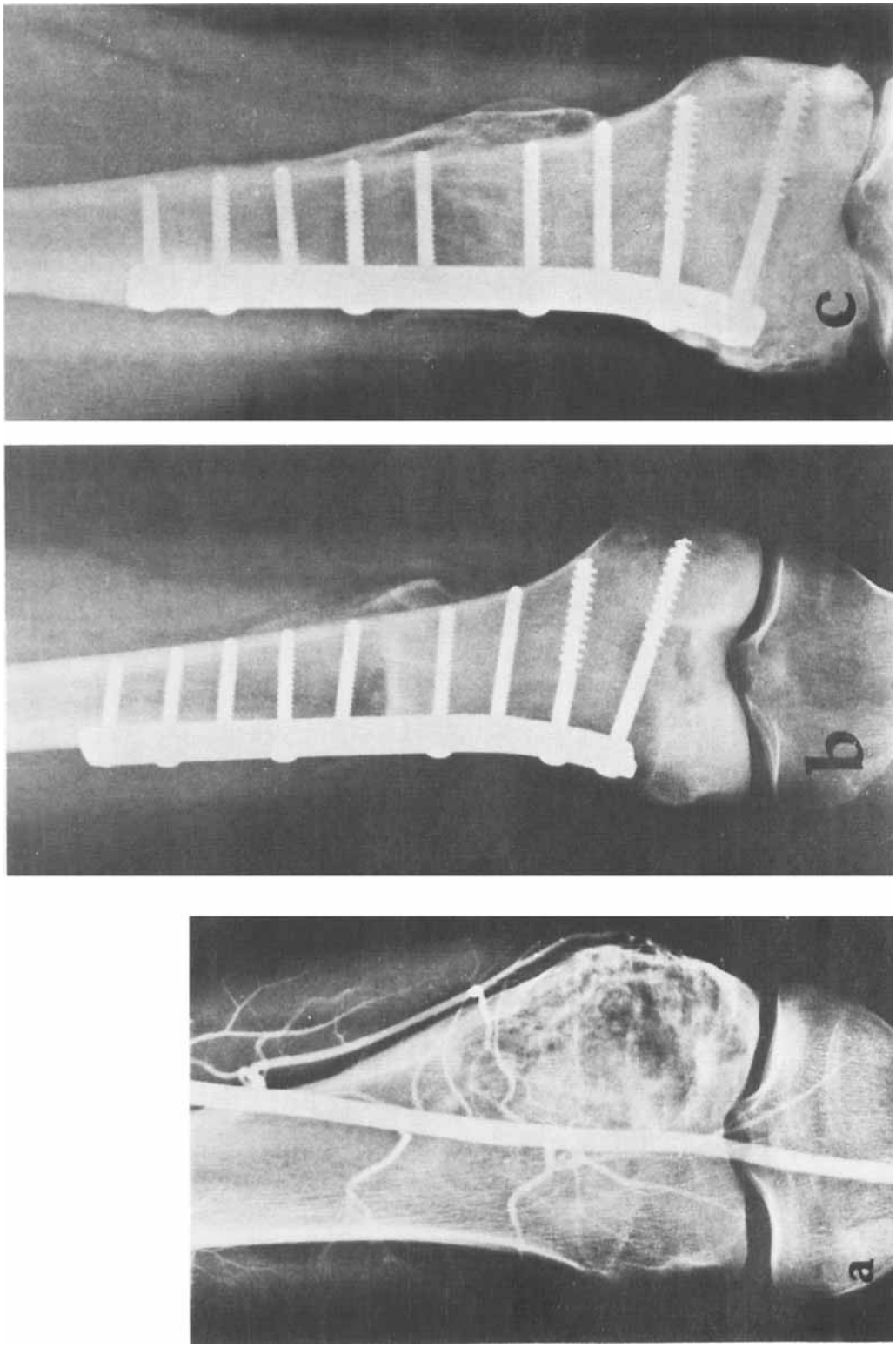

Figure 1. Case 7. Distal femoral chondroblastoma in a 17-year-old girl (a). Distal femoral allograft 6 months postoperatively. Fusion is progressing between the cadaver graft and femur with a callus sleeve from autogeneic bone around the junction (b). Solid union 1.5 years after the operation (c).

between host and graft. In Case 11 weight-bearing was obviously allowed too early. At 6 months the plate and bone fractured at the host-graft junction, which shows the importance of bone consolidation in this area. In Case 8, where the progress of healing was very rapid, partial weight-bearing was attempted 2 months after the transplantation. A fracture of the graft, considered a fatigue fracture, occurred 3 months later. With reosteosynthesis and plaster immobilization for a further 4 months, and non-weight-bearing for a total of 1 year, consolidation was finally achieved.

Incorporation of the graft. As judged radiologically, a reliable bridge formation over the host-graft junction was obtained between 8 and 14 months. At that time full weight-bearing was usually allowed. Concerning the organic incorporation of the graft as a whole, no conclusive information could be obtained by X-ray studies.

In the scintigraphic studies using ^{99m} Tc diphosphonate, increased activity at the host-graft contact plane could be observed as late as 2.5 years after operation. In one patient (Case 7) a large isolated patch of increased activity was observed in the distal femoral graft metaphysis as early as 3 months post-grafting. From 5 months (Figure 3) to 2.5 years a diffusely increased uptake was observed on the host side adjacent to the junction. Seven years after the grafting in Case 1, no elevation of isotope uptake could be observed, indicating a stabilized state. At no time were any large areas of increased activity observed in the graft nor could any time sequence be demonstrated indicating the incorporation of the graft by creeping substitution. Evidence of slow but steady progress in new bone formation and remodelling of the graft is given by the radiological disappearance of the drill holes made for ligament reconstruction in the femoral condyles.

In connection with a secondary onlay grafting after fatigue fracture of the

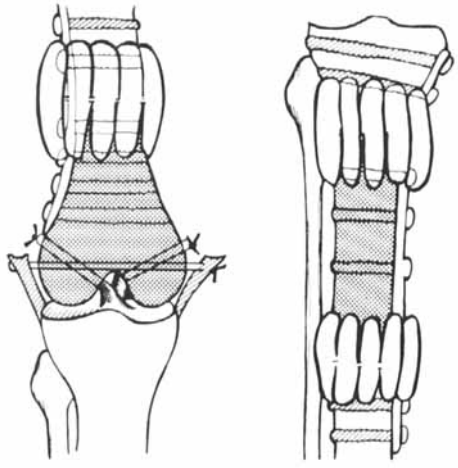

Figure 2. Schematic presentation of the operative techniques. Distal femoral hemi-joint replacement and tibial metaphysial-diaphysial grafting. The junctions of allograft and host bone were surrounded by autogeneic iliac bone chips, rigid AO osteosynthesis was used and the knee ligaments were fixed by sutures through burr canals.

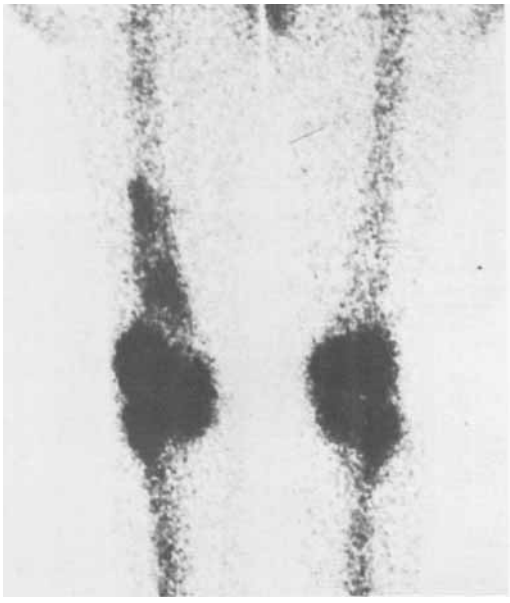

Figure 3. ^{99m}Tc diphosphonate scintigraphy of the transplant shows increased activity 5 months post-operatively as a sign of early creeping substitution in the right distal femur (Case 9).

transplant in Case 2, a biopsy was taken from the middle of the graft. It revealed well-organized lamellar bone with regular osteones and living osteocytes and osteoblasts 5 years after the allogeneic grafting. These findings were also noted in an arthroscopic biopsy at 2.5 years.

Changes in the cartilage. Varying stages of cartilage degeneration were seen on X-ray examination at follow-up. These changes were not distinctly time-dependent (Table 1). However, the most noticeable changes were found in the earliest case, and even this patient did not experience any pain in the knee. Moderate changes were observed in two cases and slight changes in a further two cases between 1.5 and 3 years. Three patients showed no cartilage deterioration, the longest follow-up being 2 years and 5 months.

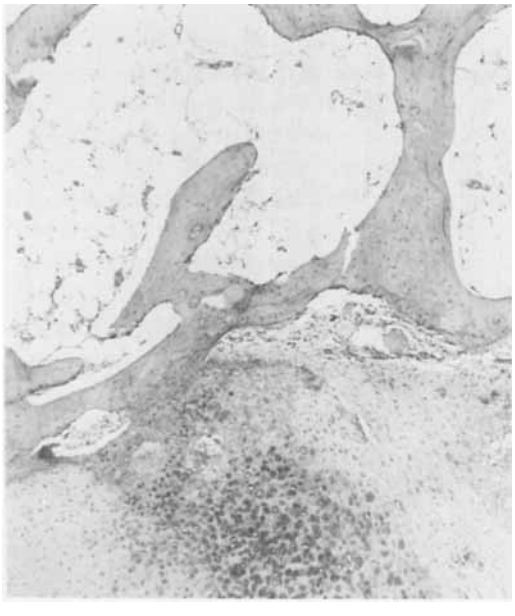

Figure 4. Biopsy specimen (Case 1) shows new viable bone with large vascular spaces and osteoblast activity. A few nests of unreplaced graft bone can also be seen. The cartilage is degenerated, but new, viable, mature hyaline cartilage can also be seen in the midst of fibrous cartilage. The follow-up period was 7 years.

In the biopsies, varying degrees of cartilage death and degeneration were observed, but there were also changes indicative of regenerative activity in the grafted cartilage (Figure 4).

Functional results. In ten cases a useful extremity was obtained and in six cases the patients returned fully to their pre-treatment activities. One patient continued working for 4 years and then retired due to low back problems. Another patient applied for re-education after a 2-year period in his previous occupation. In three cases re-education was started immediately. One patient is still in the process of mobilization and gradual weight-bearing.

Histocompatibility. No efforts were made to match the grafts. Many patients had an unexplained fever shortly after the operation. In some cases a transient eosinophilia was recorded. A biopsy at 18 months in Case 6 revealed a slight lymphocyte infiltration in the subchondral bone. This case also showed distinct radiological signs of cartilage degeneration 3 years after the transplantation. No manifest rejection reactions were observed.

Complications. Two fatigue fractures of tibial grafts were experienced, one at 5 months and the other at 5 years. One insufficient medial collateral ligament was reconstructed 3 years after the primary operation, the degenerated medial meniscus being removed. In the first case a distinct femoral cartilage deterioration was observed. However, 8 years after the grafting the knee was painless and had an extension-flexion range of 10°–120°.

No local recurrences or metastases occurred in the series. No infections were experienced.

One patient (Case 3) developed a parenchymatous type of icterus. He had negative blood cultures for bacteria and did not have hepatitis antigens. In controlled studies no blood transfusion dyscrasias were found. The

patient had in his history a period of hepatic insufficiency at the age of 14. He died from hepatic coma 5 weeks postoperatively and the necropsy revealed a polycystic cirrhotic liver.

DISCUSSION

Bone tumours with a low grade of malignancy and signs of local aggressiveness can be treated by a radical *en bloc* resection with a safe margin of healthy bone. An autogeneic grafting is possible in most cases, but in a large resection special reconstruction problems arise, especially in cases where the tumour is located close to a joint (Koskinen 1973). Reconstruction of the joint with artificial materials can seldom be recommended because most of these patients are relatively young. Therefore, biological material appears to be preferable. The knee region, which is a site of predilection for aggressive tumours, presents a most complicated replacement problem. Arthrodesis using split femoral and tibial grafts (Merle d'Aubigné & Dejouany 1958) is a major and not completely attractive operation. Allogeneic hemi-joint transplantation has been reported from several centres as a solution to this difficult problem (Parrish 1966, Nilsonne 1969, Volkov 1970, Ottolenghi 1972, Mankin 1976).

In the present study, a deep-freezing procedure recommended by Imamaliev (1969) was used for the preservation of the grafts. The experimental evidence of the need for deep-freezing to reduce the antigenicity of allogeneic bone is intriguing (Langer et al. 1975), while the clinical experience speaks for a minimum freezing time of 3 weeks (Parrish et al. 1973). We experienced no distinct rejection reactions. However, sporadic eosinophilia, subchondral lymphocyte infiltration and early cartilage degeneration may be signs of incompatibility.

Apparently, the draw-back of deep-freezing is the death of cartilage cells. In three out of eight hemi-joint transplantations clear degenerative changes were seen on the X-ray films. In agreement with the report of Parrish et al. (1973), this problem was not clearly time-dependent. No changes, or only slight changes, were seen in the other five cases during an observation time extending to over 3 years. However, in the earliest case the deterioration was marked. Pain was not a feature of this degenerative process, indicating a denervated state in the joint. On the basis of experimental studies, Mankin et al. (1976) tried to improve the chondrocyte survival by impregnating the graft cartilage with glycerol prior to freezing.

The fate of the cartilage need not be totally predetermined by the death of the chondrocytes. The matrix receives its nutrients from the synovial fluid. Contrary to some earlier findings, living chondrocytes could be found in some biopsy specimens (Holmström et al. 1978). The importance of this phenomenon in conjunction with progressing degeneration in the other parts of the cartilage is not clear at the present time. Thus, the preservation of the cartilage, in particular, needs further study.

The union of the graft was enhanced by an autogeneic bone chip sleeve taken from the iliac crest (Figure 5). It seems evident that this procedure accelerates the incorporation of the allogeneic graft itself. Radiologically solid union ensued in 8 to 12 months and full weight-bearing could be allowed at that time. Using stable osteosynthesis, the necessary plaster immobilization period was gradually reduced as experience was gained. During a trial of partial weight-bearing, a fatigue fracture occurred in the presumably dead graft. Even total incorporation was no guarantee against this problem, as indicated by another case, where a viable graft fractured 5 years after transplantation.

At no time was any distinctly increased ^{99m}technetium diphosphonate uptake observed, but patches of augmented activity deep in the graft were seen as early as at 3 months and as late as at 2.5 years. In arthroscopic biopsies no living subchondral bone was seen before 2.5 years. This may therefore be the time required for total incorporation of the graft.

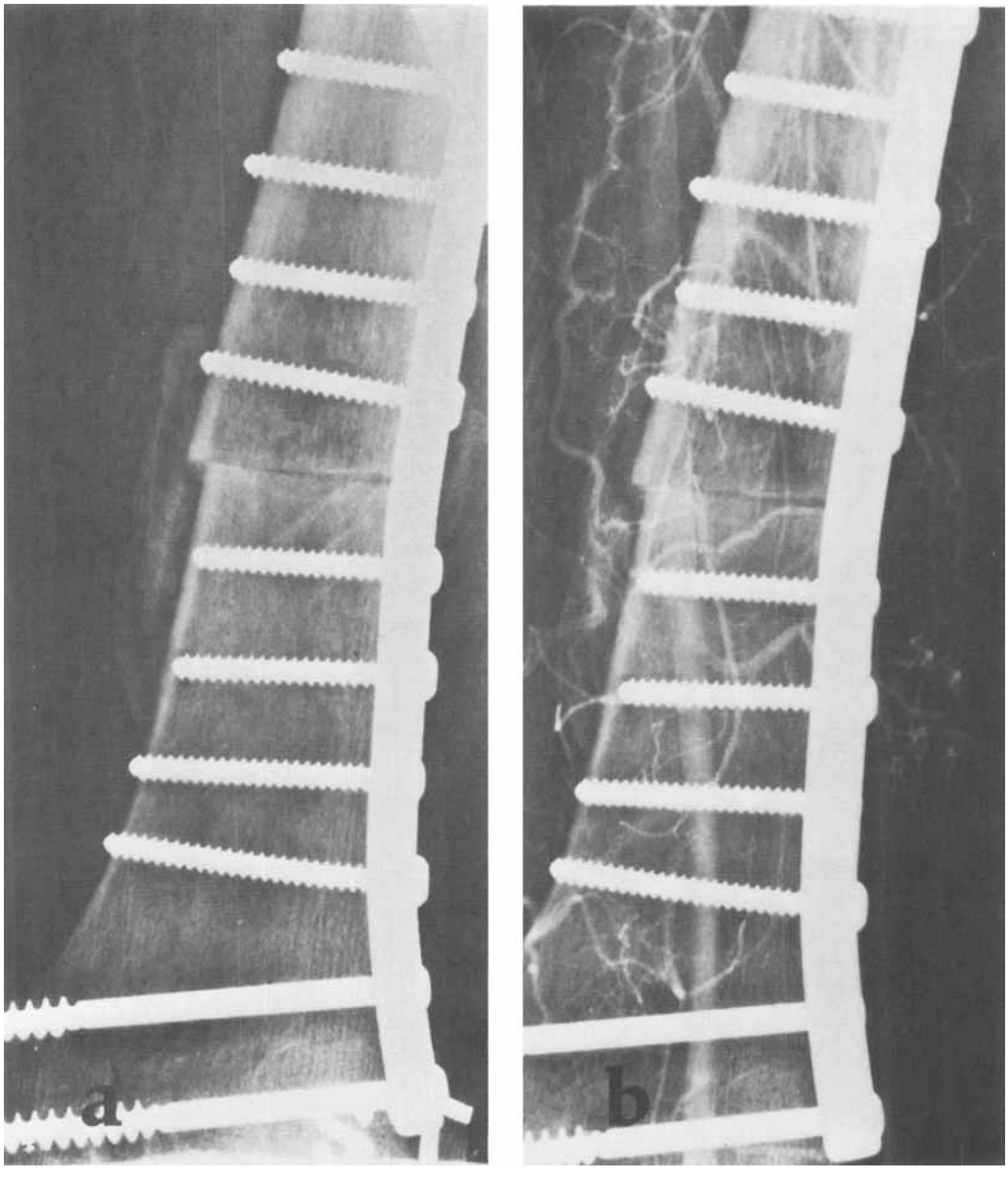

Figure 5. Case 6. Early stage of incorporation, 6 months postoperatively (a). Angiography shows small calibre vessels in the area of autologous chips and allografts (b).

The allotransplantation method of replacing large bone and joint defects seems to be the only choice in selected cases of aggressive, low-grade malignant bone tumours. The patient has to be prepared to face a considerable morbidity with a long non-weight-bearing period, the possibility of further operations and later cartilage degeneration. However, the method appears to be justifiable, since the alternative is often an amputation. No major risks are involved. The death of one patient in the series was obviously a result of a pre-existing condition and not of the allografting itself. So far, there

have been no subsequent amputations and no metastases have been experienced. All patients have retained the limb with a good or satisfactory function. In the cases with bone grafting alone the result was full restoration.

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Correspondence to: Prof. E. V. S. Koskinen, M.D., Anmas Lindgrenintie 15D, SF–00570 Helsinki 57, Finland.