Consolidation of massive bone allografts in limb-preserving operations for bone tumours

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SUMMARY

This study analysed the influence of several factors affecting the consolidation time of 83 massive bone allografts in. 79 patients with malignant bone tumours: osteosarcoma 57; Evving's sarcoma 8; malignant fibrous histiocytoma 3; chondrosarcoma 4; fibrosarcoma 5; and giant cell tumours 2. The mean age of the patients was 19 years and the mean length of the allografts was 18 cm. The minimum follow up was for 12 months. The mean consolidation time for metaphyseal and diaphyseal osteotomies was 6.5 and 16 months respectively. Fifteen diaphyseal osteotomies required autologous cancellous grafting. There were 8 allograft fractures after consolidation. The following factors which might influence consolidation were analysed: age of the host and donor; allograft length and site; type of osteotomy and osteosynthesis; intra-arterial and systemic chemotherapy; intraoperative and external radiotherapy. In diaphyseal osteotomies there were statistically significant differences in consolidation time with the use of systemic chemotherapy, external radiotherapy and the recipient's age.

RÉSUMÉ

Dans le present travail, est analysé le temps de consolidation et les facteurs qui ont pu l'influencer de 83 allogreffes corticospongieuses placées chez 79 patients affectés de tumeurs osseuses primitives malignes (57 ostéosarcomes, 8 sarcomes d'Ewing, 3 HFM, 4 chondrosarcomes, 5 fibrosarcomes et 2 TCG), traités par chirurgie conservatrice, avec un age compris entre 4 et 69 ans (ni = 19). La durée moyenne de consolidation fut 6.5 mois pour les ostéotomies métaphysaires, 16 pour les diaphysaires, avec 1 pseudarthrose métaphysaire et 7 diaphysaires. Quinze allogreffes ont eu besoin d'un apport de greffe autologue pour consolider et 8 eurent une fracture une fois consolidé. On a analysé les différents facteurs qui ont pu influencer la consolidation; âge du donneur et du receveur; longueur et localisation de rallogreffe, type d'ostéotomie et d'ostéosynthése, chimiothérapie (intra-artèrielle ou systémique) et radiothérapie (intraopératoire ou externe). Dans les ostéotomies diaphysaires, la chimiothérapie systémique ($p < 0.05$), la radiothérapie externe ($p < 0.01$) et l'age du receveur ($p < 0.01$) retardent la consolidation.

INTRODUCTION

En bloc resection of all macroscopic disease is necessary in the treatment of primary bone tumours, and the two main surgical procedures are amputation and limb-preserving reconstruction. The development of modern limb-preserving operations [1, 10, 11, 14, 24, 26, 44] has been helped by the introduction of new diagnostic methods [32], the widespread use of preoperative chemotherapy [4, 42, 43, 44], radiotherapy [6, 7, 8] and multiagent adjuvant chemotherapy [6, 7, 10, 18, 25, 29, 30, 32, 33, 35, 45].

Reconstructive surgery with massive allografts has been possible with the development of bone banks [2, 17] and provides a successful alternative to a prosthetic implant in young patients who have a long life expectancy. Allografts offer many advantages compared to metallic implants including joint reconstruction, incorporation of the graft to the host bone, and longevity [18]. There are, however, problems such as the cryopreservation of articular cartilage and articular denervation which may lead to a situation similar to neuropathic arthropathy when osteoarticular allografts are used [11].

Since 1987 we have used more than 150 massive allografts in the conservative management of malignant bone tumours. The purpose of this study is to analyse the factors which might influence the time for consolidation of these allografts.

PATIENTS AND METHODS

We reviewed the first 100 allografts which we had used in limb-preserving operations for bone tumours. We excluded those tumours occurring in the axial skeleton, patients with less than one year's follow up and those who failed to attend. We included 83 allografts implanted in 79 patients; the allograft was removed because of infection in 4, and a second allograft implanted more than a year after the original operation. The histological diagnoses of the resected specimens are shown in Table 1.

Preoperative staging was made after conventional radiography, digitalised angiography, radionucleide scan, CT scan, MRI and biopsy, which was usually by percutaneous aspiration. We did not take into account Enneking's criteria [16] regarding intra- or extracompartmental involvement. Radiographs and a CT scan of the lungs were used to rule out metastases.

Allografts were removed under sterile conditions from cadavers following the guidelines of the American Association of Tissue Banks [17]. Laboratory tests included culture for anaerobic and aerobic bacteria, VDRL, B and C hepatitis and HIV.

En bloc resection, including the biopsy scar, was carried out for primary nonmetastatic tumours. The level of the osteotomy was determined by the intramedullary spread as shown by CT and MRI. Our safe margin was 5 cm and we performed intraoperative biopsy of the resected margins. Every patient was given prophylactic cephalosporin. Chemotherapy and radiotherapy was used in every case following the University Clinic of Navarra Cancer Protocol [42, 43], depending on the type of tumour. Table 2 shows the protocol for osteosarcoma. The disease-free survival with the protocol for osteosarcoma is 74.4% at 5 years and 70.3% at 10 years (Kaplan-Meier). Table 3 shows the antitumour treatment given.

The type of allograft depended on the involvement of the growth plate and the possibility of preserving the joint near the tumour. We implanted 35 endoprostheses into a fresh-frozen allograft (Fig. 1) and carried out 29 intercalary allografts, 15 osteoarticular allografts (Fig. 2a, b), and 4 arthrodeses with corticocancellous allografts.

The mean length of the allografts was 18 cm (range 4 to 42 cm) (Fig. 3 a, b). The mean age of the group was 19.6 years (range 4 to 69 years). The mean follow up was 33.7 months (range 12 to 82 months).

The follow up was at monthly intervals during the first year of systemic chemotherapy, with diagnostic studies being made to assess the local and systemic control of the disease. Subsequently, the follow up was 3 monthly for another year, and then every 6 months.

We studied the consolidation of 80 diaphyseal and 32 metaphyseal osteotomies (Table 4). Metaphyseal osteotomies were horizontal in all but one case, and several types of osteosynthesis were used including Kirschner wires, Ender nails, screws and staples (Table 5).

The ISOLS criteria were used to evaluate the consolidation results (Table 6). We considered the age of the host and donor, allograft length and location, type of osteotomy and osteosynthesis, infra-arterial and systemic chemotherapy, intraoperative and external radiotherapy. We used multi-variant statistical analysis with the Statview programme and the functional results were rated according to Mankin's classification [33].

RESULTS

The mean consolidation time for metaphyseal osteotomies was 6.5 months and we did not find any statistically significant correlation with the factors we studied. There was only one malunion, in a patient in whom a tibial allograft was used in an ankle arthrodesis, which had no clinical significance. Consolidation was achieved in many cases with minimal osteosynthesis.

The mean consolidation time for diaphyseal osteotomies was 16 months. There were statistically significant differences with the use of systemic chemotherapy ($p < 0.05$) and the use of external radiotherapy ($p < 0.01$) with both factors delaying consolidation. The older the patient the worse was the influence on consolidation ($p < 0.01$).

There were no statistically significant differences with the use of intra-arterial chemotherapy, intraoperative radiotherapy, the donor's age, the type of osteosynthesis (plates vs intramedullary devices), the type of osteotomy (horizontal vs oblique) or the type and site of the tumour.

Seven (8.7%) diaphyseal nonunions occurred. Further osteosynthesis and autogenous iliac bone grafting was needed in 15 diaphyseal osteotomies. Most of the osteosyntheses were with plates. In order to avoid a large implant some used in children were inadequate. There were 8 (9.6%) allograft fractures, 4 of which consolidated with conventional treatment.

DISCUSSION

Metaphyseal osteotomies consolidated at a mean time of 6 months which is similar to Vander Griend's findings [49]. The mean consolidation time for diaphyseal osteotomies in his series was 9 months, but he did not give the criteria for determining consolidation, Mankin reported 18 months [30], and in our series the time was 16 months. Seventy-three out of 79 of our patients had chemotherapy, whereas in the other two series [30, 49] almost half the patients did not. We believe that chemotherapy plays an important part in delaying consolidation. We found statistically significant differences between those who had intensive adjuvant chemotherapy for a year after the operation and those who had not. Our finding is supported by data in other series [12, 13, 20, 31, 44]. Radiological changes have been seen in the long bones of patients who have had chemotherapy without irradiation [44], and Shinohara found that all grafted bone in patients receiving chemotherapy failed to heal primarily [46]. Glasser reported slowing of growth during the year of intensive chemotherapy given to children with osteosarcoma and Ewing's tumour [20]. Experimental studies have also proved that chemotherapeutic agents impair bone healing and that allogenic cortical bone grafts incorporate more slowly when chemotherapy is given [27, 52].

External radiation also delayed consolidation and ionising radiation is known to have a harmful effect on skeletal growth [15, 21, 23, 33, 46, 47, 48] which results from alterations of chondroblastic [21, 40] and periosteal activity [41]. Radiation also damages the small and medium blood vessels supplying nutrients to the bone, reducing the potential for healing [21]. Retardation of bone growth caused by irradiation is dose-dependent [5, 22, 36, 50]. Clinically measurable growth disturbance can be produced by doses below 500 cGy [5]. Computed tomographic-assisted planning systems and increasingly sophisticated therapy equipment may help to reduce the side effects of radiation.

Intra-arterial chemotherapy and intraoperative radiotherapy did not influence graft consolidation since both are given before the graft is implanted and do not cause sufficient soft tissue damage to delay bony healing.

Our incidence of nonunion was similar to that reported in other series [18, 30, 34, 35, 49]. Seven of 8 nonunions occurred at diaphyseal osteotomies. The routine addition of autogenous bone graft at the allograft-host junction has been advocated when the graft is implanted [3, 51], but we only used autogenous graft in patients with delayed consolidation to avoid morbidity from the donor site.

We thought that oblique osteotomies would heal more quickly than transverse due to the larger contact area [53]. However, we did not find any statistically significant difference in the consolidation time between the 2 types. We now only use an oblique osteotomy to avoid rotation when using non-locked intramedullary systems.

We prefer to use intramedullary devices for fixation as they allow weightbearing immediately after operation [28, 49] in contrast to plates. Plate fixation was associated with a higher incidence of fracture of the allograft [49] and with the need for further osteosynthesis, particularly in children when we used minimal fixation.

Some authors advise replacement after fracture through the shaft of the allograft because of the limited potential for healing of the graft, but we were able to achieve consolidation in these circumstances with conventional treatment, as has been reported by others [47].

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Table 1. Histological diagnosis

Histological diagnosis	**No.**
Osteosarcoma	
Osteoblastic	36
Chondroblastic	11
Fibroblastic	6
Telangiectasic	2
Parosteal	2
Ewing's sarcoma	8
Fibrosarcoma of bone	5
Chondrosarcoma	4
Malignant fibrous histiocytoma of bone	3
Aggresive giant cell tumour	2
Total	79

Table 2. Therapeutic protocol for osteosarcoma in our Department

1. Neoadjuvant chemotherapy:

   CDPP: 40 mg/m^2IAx3 days, every 3 weeks for 3 cycles

   ADR: 30 mg/m^2IVx2 days, every 3 weeks for 3 cycles

   MTX: 8 mg/m^2IV/days 7, 14, 29 and 36

2. Surgery

3. Postoperative chemotherapy (9 to 12 months): MTX, CDPP, ADR, bleomycin, actinomicin D, cyclophosphamide and vincristine

Table 3. Antitumour therapy

Systemic chemotherapy	73
External radiotherapy	24
Intraoperative radiotherapy	53
Intra-arterial chemotherapy	57

Table 4	
Allografts	83
Patients	79
Metaphyseal osteotomy only	3
Diaphyseal osteotomy only (TKR, some osteoarticular allografts, etc)	51
Metaphyseal and diaphyseal osteotomy (intercalary allografts)	29

Table 5. Diaphyseal osteotomies and osteosynthesis	
Osteotomy	
Horizontal	46
Oblique	34
Osteosynthesis	
Plates	42
Intramedullary	38

Table 6. ISOLS criteria for the fusion of allografts
Excellent: fusion with osteotomy line not visible
Good: fusion > 75% with osteotomy line still visible
Fair: fusion 25-75%
Poor: no evidence of callus or fusion <25%

Figure 1. An endoprosthesis has been inserted into a fresh frozen allograft of the right distal femur with excellent consolidation.

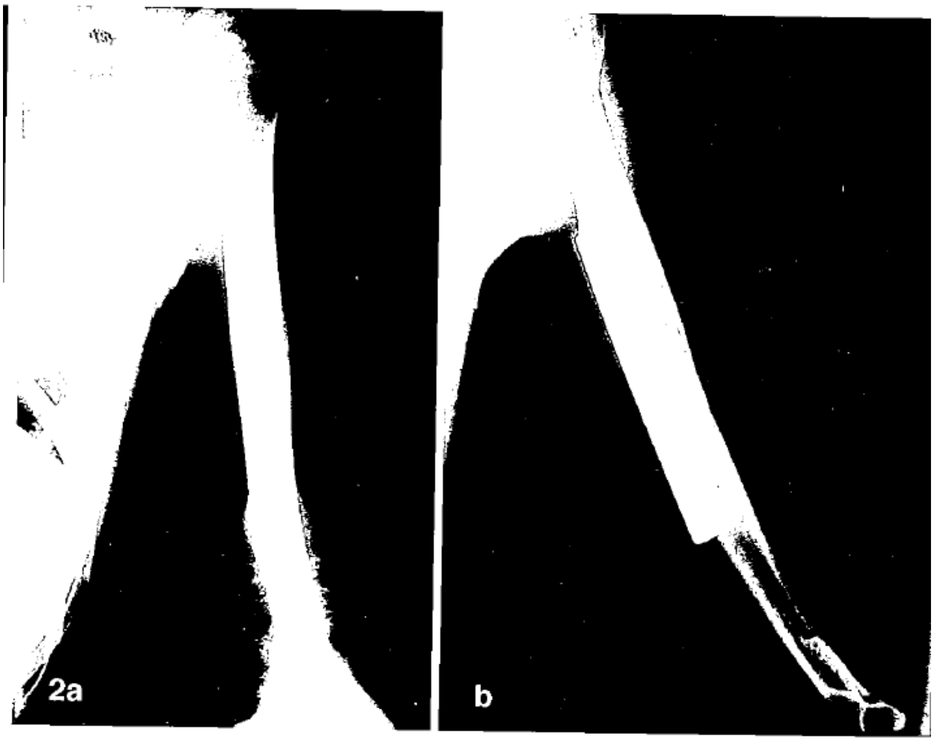

Figure 2. a Osteosarcoma of the distal end of the humerus. **b** Osteoarticular allograft of the elbow with a perforation for muscle attachment. Consolidation was at 3 months which was the fastest in the series.

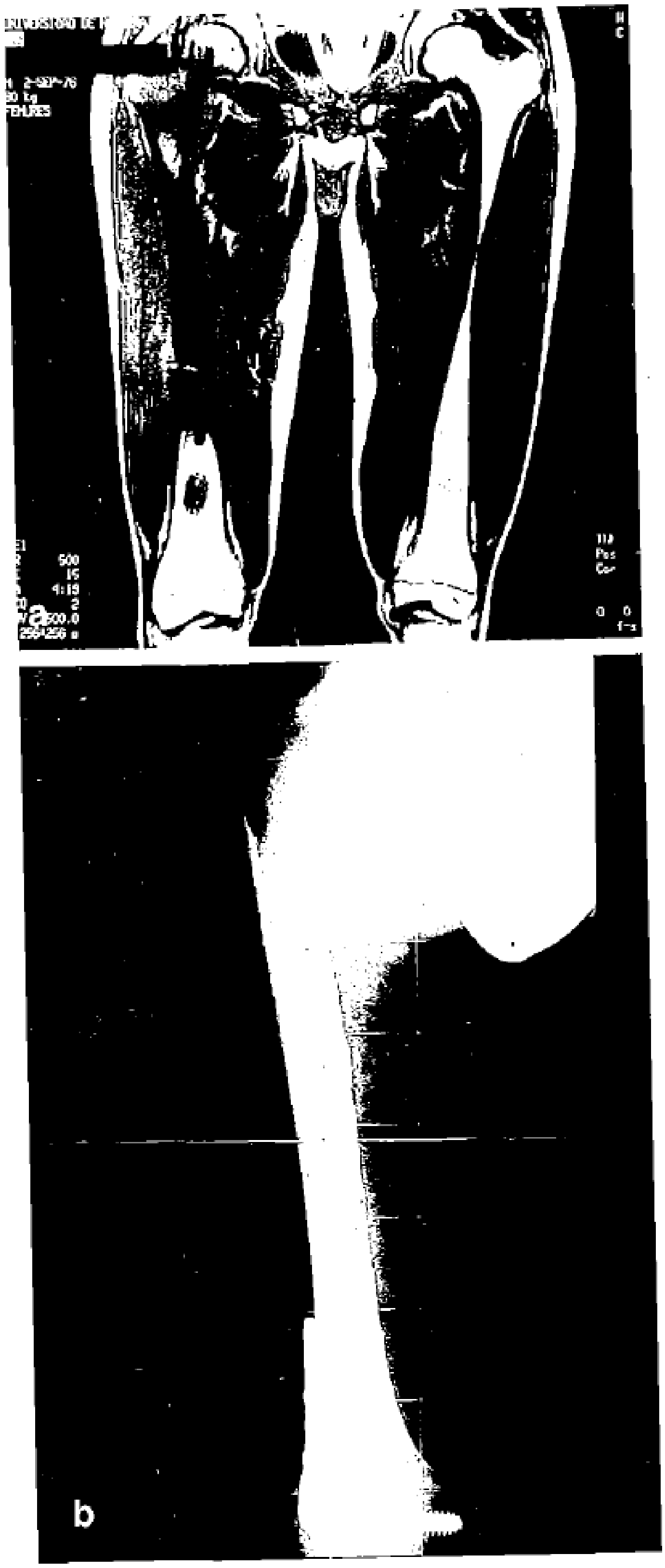

Figure 3. a Osteosarcoma involving almost the whole of the right femur with a skip metastasis in the distal metaphysis. **b** An osteoarticular allograft 42 cm long (the longest in the series) was inserted from the proximal epiphysis to the distal metaphysis. Consolidation of the metaphyseal osteotomy occurred in 6 months.