Intercalary femoral reconstruction with extracorporeal irradiated autogenous bone graft in limb-salvage surgery

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Between 1996 and 2003, 16 patients (nine female, seven male) were treated for a primary bone sarcoma of the femur by wide local excision of the tumour, extracorporeal irradiation and re-implantation. An additional vascularised fibular graft was used in 13 patients (81%). All patients were free from disease when reviewed at a minimum of two years post-operatively (mean 49.7 months (24 to 96)).

There were no cases of infection. Primary union was achieved after a median of nine months (interquartile range 7 to 11). Five host-donor junctions (16%) united only after a second procedure. Primary union recurred faster at metaphyseal junctions (94% (15) at a median of 7.5 months (interquartile range 4 to 12)) than at diaphyseal junctions (75% (12) at a median of 11.1 months (interquartile range 5 to 18)).

Post-operatively, the median Musculoskeletal Tumour Society score was 85% (interquartile range 75 to 96) and the median Toronto Extremity Salvage score 94% (interquartile range 82 to 99). The Mankin score gave a good or excellent result in 14 patients (88%).

The range of movement of the knee was significantly worse when the extracorporeally irradiated autografts were fixed by plates rather than by nails (p = 0.035).

A total of 16 (62%) of the junctions of the vascularised fibular grafts underwent hypertrophy, indicating union and loading.

Extracorporeal irradiation autografting with supplementary vascularised fibular grafting is a promising biological alternative for intercalary reconstruction after wide resection of malignant bone tumours of the femur.

The primary en bloc excision of a bone tumour usually leaves a defect which is too large to reconstruct with autogenous bone. This is particularly true in the lower limb where the problem is addressed either by replacement with a mega-prosthesis or by allograft reconstruction with additional autograft as necessary.

In the last 20 years a variation of the second option has been reported. After wide resection, extracorporeal irradiation of the resected bone segment is performed and the autograft is then re-implanted.

This method was first described by Spira and Lubin in 1968. A single radiation dose of 50 Gy is lethal to all cells and produces a dead autogenous bone graft with the precise dimensions needed for re-implantation and reconstruction. Extracorporeal irradiation was first introduced to Australia in 1996, and since then we have treated more than 50 cases of bony malignancy at various sites without local recurrence.

Our aim in this study was to analyse the survivorship of the irradiated intercalary femoral autografts and to determine their time to consolidation and the incidence of any ensuing complications compared with those previously reported in the literature.

Patients and Methods

We reviewed a consecutive series of 16 patients who had undergone wide local resection and extracorporeal irradiation autograft reconstruction for a primary bone sarcoma between 1996 and 2003. Nine females and seven males were followed for a minimum of two years (mean 49.7 months (24 to 96)). No patient was lost to follow-up.

Their mean age was 17 years (8 to 55). No patient had metastatic disease at the time of the diagnosis; of these, 14 received pre-operative neo-adjuvant chemotherapy and resumed their treatment two to three weeks after operation. One patient with a parosteal osteosarcoma...
received only post-operative chemotherapy. The patient with chondrosarcoma did not receive chemotherapy.

In each case, wide en bloc resection of the tumour was carried out in the standard manner. The median length of the resected bone was 16.2 cm (10.0 to 24.0). Next, the resected segment was tightly wrapped in a wet sterile drape and three sealed sterile plastic bags and delivered to the oncology department where each segment was irradiated with a single midplane dose of 50 Gy at a rate of 1.8 to 2.0 Gy per minute. The mean time between collecting the specimen and returning it to the operating room was 25 minutes (20 to 35). We have previously reported our technique in greater detail.3,6 While waiting for the return of the graft, the operation site was prepared for its re-implantation and biopsies of the surgical margins were taken.

On its return, the autograft was cleaned of all unnecessary soft tissue and necrotic bone, leaving the major muscle insertions for re-attachment. We ensured that good stable bone stock was preserved after debulking. The extracorporeally irradiated autograft was then re-implanted and fixed using intramedullary nails in the nine skeletally-mature patients (mean 21.4 years (13 to 55)). Of these, four had additional plate fixation and two additional screw fixation. In the seven skeletally-immature patients (mean 11.4 years (8 to 14)) blade-plates were combined with additional plates in two, or screws in five. An adjunctive vascularised fibular graft was used in 13 patients, the median length of which was 20 cm (interquartile range (IQR) 18 to 25). It was implanted either in parallel to the extracorporeal irradiation graft or by cutting a trench in the graft to allow it to lie within the intramedullary cavity.

Each patient received intravenous antibiotics according to a standard protocol of intravenous ciprofloxacin until all drains and catheters were removed. Post-operatively, patients rested in bed for a minimum of a week and were then allowed to walk non-weight-bearing on crutches. This continued for three months and was followed by partial weight-bearing for another three months. The younger patients were also immobilised in a cast or brace for the first six to eight weeks. After six months, full weight-bearing was allowed, albeit protected by one or two crutches until both osteotomies had united. The median time to full weight-bearing without aids was eight months (IQR 6 to 9).

Functional evaluation was carried out using the Musculoskeletal Tumour Society scoring system9,10 and the Toronto Extremity Salvage score.11 For comparison with the findings of earlier series we also used the Mankin score.12 We also measured the range of movement (ROM) of the hip and knee around the reconstruction.

Radiographs were taken regularly and were reviewed for evidence of union or nonunion of the 32 graft-host junctions, hypertrophy of the vascularised fibular graft and for complications such as fatigue fracture. We used the hyper-trophy index of De Boer and Wood12 to assess the biological response of the fibular graft (n = 13; 26 junctions). The time to consolidation and the incidence of fatigue fractures and nonunion were analysed in relation to the age of the patient, the type of stabilisation and the length of the autograft.

Statistical analysis. Our description of the data was primarily based on medians and quartiles for continuous endpoints. Binary end-points were characterised by frequencies. Interindividual comparisons between patient subgroups were assessed using Fisher's exact test for binary end-points and by the Wilcoxon two-sample test for continuous end-points. A p-value ≤ 0.05 was taken to indicate statistical significance. Statistical analysis was performed using SPSS software version 11.5 (SPSS Inc., Chicago, Illinois).

Results

Clinical findings. Every patient was alive and free from disease at the end of the follow-up period.

The median Musculoskeletal Tumour Society score was 85% (IQR 75 to 96) and the median Toronto Extremity Salvage score 94% (IQR 82 to 99). Excellent or good results were achieved in 14 patients (88%) according to the Mankin score.

There was a significant difference in the ROM of the knee between the fixation groups. Five patients who had plate fixation of the extracorporeal irradiation graft had restricted flexion of that knee (mean reduction 30°) compared with one who had fixation with an intramedullary nail (p = 0.035). There was no loss of movement at the hip.

Three patients required epiphysiodesis of the opposite limb for leg-length discrepancy. All three had a level pelvis at skeletal maturity.

Radiological findings. Primary union was achieved in 27 of the 32 graft-host junctions (84%). These were consolidated after a median of nine months (IQR 7 to 11). Primary union occurred faster (94% (15 of 16) at a median of 7.5 months (IQR 4 to 12)) at the metaphyseal junction than at the diaphyseal junction (75% (12 of 16) at a median of 11.1 months (IQR 5 to 18)). There was no difference in the median consolidation time between the junctions fixed by plates in younger patients (median 10 months (IQR 6 to 12)) and those fixed by nails in older patients (median 9 months IQR 8 to 11). Two of 14 plated junctions (14.3%) developed a nonunion compared with three of 18 (16.6%) nailed junctions.

The consolidation time in patients with longer (≥ 20 cm) autografts was less: median nine months (IQR 7 to 11) than in those with shorter (< 20 cm) autografts (median 12 months (IQR 9 to 12)). There was no significant difference in the rate of union between the groups (union rate ≥ 20 cm, 88% (16 of 18) vs < 20 cm, 79% (11 of 14); Fisher's exact test, p = 0641).
Radiologically, the bone quality of the extracorporeal irradiation autografts, assessed from standard radiographs, was generally good. Reduced bone density, assessed in the same way as bone quality, with some osteolysis was noted in only two autografts. In both, the implants were stable and did not show any sign of loosening. The osteolysis had not progressed after a year.

Vascularised fibular grafts were added to 13 reconstructions. Significant hypertrophy (> 20%) was found in 16 (62%) of the 26 graft-host junctions (Fig. 1). There was no evidence of atrophy.

Graft-host junctions in the intramedullary nailing group were more likely to develop significant hypertrophy (75%; 9 of 12) than those in the plate fixation group (50%; 7 of 14). Complications. The main complication was nonunion (Figs 2a to 2c) and five of 32 (16%) host-donor junctions did not initially unite. Four of these were revised by exchange of the fixation implant and additional bone grafting (3 autologous, 1 allogenic) (Figs 2d and 2e). In the fifth case, debridement and stable fixation of the hypertrophic nonunion were sufficient to promote union. All the nonunions had united three to five months after revision, and all junctions had united after a median of ten months (IQR 7 to 12). The rate of nonunion was less clinically relevant at the host-donor junctions where fibular hypertrophy had occurred (1 of 16) than at those where it had not, or where no vascularised fibula had been implanted (4 of 16).

There were no cases of infection. There was one fatigue fracture of an autograft through the proximal junction after an injury nine months after operation. We replated the femur and added autologous bone graft. After four months the fracture healed and the autograft united.

Another patient needed a revision after a fall which fractured the proximal end of her intramedullary nail. The autograft, however, remained intact and only the nail had to be changed. Consolidation had occurred by ten months.

Discussion
Intercalary reconstruction of the femur using allograft has been extensively documented. However, until now only 19 cases of reconstruction with extracorporeal irradiation autograft have been reported, consequently, we believe that the 16 patients whom we describe form the largest single series to date.

If an extracorporeal irradiation autograft is to be used safely for reconstruction, a wide resection must be carried out so that the whole tumour is contained within the resected bone. Irradiation must then completely eradicate the tumour.

In a histological study, Hatano et al confirmed the complete eradication of tumour cells in grafts by a single radiation dose of 60 Gy. We used a radiation dose of 50 Gy which is equivalent to 250 Gy administered conventionally. This dose is significantly higher than that obtained using standard fractionated external-beam irradiation. Experience of more than 70 cases without local recurrence and metastatic disease suggests that the dose is sufficient. Higher doses (> 250 Gy) have been shown to reduce the revascularisation and osteoconductive capability of the graft, thereby increasing the time to union and incorporation. One local recurrence has occurred in an extracorporeal irradiation autografting of the femur over the last 15 years. The local rate of recurrence in allograft reconstruction of the lower limbs is reported to be 9% to 12%,.

Autoclaving excised bone tumours as a method of eradicating the neoplastic cells has been described but has the great disadvantage of causing a marked deterioration in the biological and biomechanical properties of the resected bone. An advantage of an extracorporeal irradiation autograft over allograft is that the autograft fits exactly and the muscle attachments can be preserved. We believe that this contributed to the excellent functional scores in our series.

The functional outcomes and complication rates for extracorporeal irradiation autograft and allograft procedures are compared in Table I.
The means by which the extracorporeal irradiation autograft is fixed has a considerable effect on movement of the knee which was more likely to be restricted when the graft had been plated.

Nonunion occurred in five of the 32 host-donor junctions (16%). The rate of nonunion in intercalary reconstructions with allografts has been reported as being between 15% and 71%\(^\text{16,17,28}\) and is higher in the diaphysis than in the metaphysis.\(^\text{16,17,28}\) This corresponds to our experience of extracorporeal irradiation autografting of the femur. Union occurred faster at the metaphyseal than at the diaphyseal junction. Consolidation occurred after a median of nine months. The consolidation time for allografts has been reported as being 9 to 15 months.\(^\text{19,28}\) Aranguren et al\(^\text{11}\) have also observed faster consolidation in the metaphysis than in the diaphysis in allografting (6.5 vs 16 months). Ceruso et al\(^\text{12}\) reported a similar mean consolidation time of eight months with allografts combined with a vascularised fibular graft. The biological remodelling of the extracorporeally irradiated autografts takes time and is limited. Taking our mid-term results and overall experiences\(^\text{3}\) into consideration we suggest that complete remodelling or replacement with living bone will take a long time. Only long-term follow-up with biopsies could properly answer this question.

After extracorporeal irradiation there remained an exact fitting scaffold of dead bone which required the long-term support of metal implants. This is why we recommend the vascularised fibular graft as a biological bridge to support the reconstruction in most cases and to reduce the nonunion rate at the osteotomy sites.

Table I. Comparative outcome of extracorporeal irradiation (ECI) autografting in our series and studies on allografting in the literature

<table>
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<tr>
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<th>ECI autografting (%) (n = 16)</th>
<th>Segmental femoral allografting (%)</th>
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<tr>
<td>Excellent and good functional outcome</td>
<td>14 (88)</td>
<td>55 (18/33)(^\text{14,16})</td>
</tr>
<tr>
<td>Nonunion (per junction)</td>
<td>18</td>
<td>28 (44/160)(^\text{16,17,21,33,36})</td>
</tr>
<tr>
<td>Fracture</td>
<td>6</td>
<td>18 (21/120)(^\text{16,17,21,33,36})</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>14 (10/69)(^\text{16,17,21})</td>
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A 17-year-old boy who had a painful swelling of the left thigh for three months. Figure 2a – Radiographs and MRI showing Ewing’s sarcoma of the diaphysis. Figure 2b – Radiographs showing extracorporeal irradiation after wide resection and stabilisation with a vascularised fibular graft and intramedullary nail. Figure 2c – Radiographs showing consolidation of the distal junction after six months. There is nonunion at the proximal site. Figure 2d – Radiographs showing revision 17 months after operation with additional plate fixation and bone grafting. There was consolidation five months after revision. Figure 2e – Radiographs at follow-up at 44 months (2.5 years after revision). The Musculoskeletal Tumour score is 100%, the Toronto Extremity Salvage score 100% and the Mankin score is excellent.
Vander Griend\textsuperscript{33} has reported a significant association between a problem in the achievement of stable fixation and the development of nonunion at the allograft-host junction. In his series no significant difference was found between the rate of union after fixation by an intramedullary nail or a plate. In this study five of 32 junctions (16\%) developed nonunion. Two of 14 (14.3\%) plated junctions developed a nonunion compared with three of 18 (16.6\%) nailed junctions. In a series of 69 intercalary femoral reconstructions Donati et al\textsuperscript{17} also found no difference between the different fixation groups. The rate of union can, however, be improved by using a vascularised fibular graft. Ceruso et al\textsuperscript{32} achieved a high rate of union of 96\% in 59 reconstructions when using allograft combined with a vascularised fibular graft. In our graft-host junctions in which the vascularised fibular graft hypertrophied (62\%), we found a significantly lower rate of nonunion (6\%) than in the cases (25\%) in which there was no hypertrophy of the vascularised fibular graft or no fibula had been implanted. We recommend the use of the vascularised fibular graft as a biological bridge to support the autograft reconstruction because the main part of the extracorporeal irradiation autograft remains as a scaffold of dead bone for a long time.

Removal of the allograft is usually required in the case of deep infection. In the last 15 years only one case of deep infection has been reported in 19 cases.\textsuperscript{1,20-22} This was in a patient with severe diabetes. No infections occurred in our series. The reported rate of deep infection in allograft reconstruction of the lower limb is between 16.6\% and 17.6\%,\textsuperscript{16,17} In a large series of 282 cases recently published by Mankin, Hornicek and Raskin\textsuperscript{34} the primary rate of infection for intercalary allografts was 6\%, but 11 patients developed an infection after a fracture operation resulting in an overall rate of infection of 10\%.

The bone quality of the extracorporeal irradiation autografts was good. The bone density was reduced in two cases with some osteolysis. Berrey et al\textsuperscript{35} described rapid dissolution of two of 43 allografts associated with fractures. Their overall rate of fracture was 16\%. Both allografts had to be replaced.

Only one of our autografts fractured. This may have been related to the irradiation dose. Previous reports of autografts which had received a higher radiation dose documented a rate of fracture of 23\%.\textsuperscript{20-22} Chen et al\textsuperscript{21} successfully treated their two fractures by immobilisation in a cast. This constitutes another indication for the use of a supplementary vascularised fibular graft.

The rate of fracture for intercalary femoral allografts is quoted as being 16\% to 71\%,\textsuperscript{17,28,30,36} Slow asymmetrical revascularisation of the cortex, possibly associated with an immune response, is thought to be responsible for fractures in allografts. Reimplantation of the irradiated bone also bypasses the problem of graft rejection due to the absence of antigenic potency.\textsuperscript{37,38} One disadvantage of the use of extracorporeal irradiation autografts is the lack of material available for histopathological examination of the effects of chemotheraphy and the adequacy of the resection margins. In our opinion, the marginal biopsies and the debulked tumour material should be sufficient to assess both. The low recurrence and mortality rates in our series and the results reported in our previous paper would appear to support this view.\textsuperscript{3}

These results suggest that the use of an extracorporeally irradiated autograft is an acceptable method of reconstructing an intercalary defect in the femur and may offer better results than allografting. Longer follow-up of a larger series is needed to confirm this.

\section*{Supplementary Material}
A supplementary table showing the clinical details and results is available with the electronic version of this paper at www.jbjs.org.uk

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\section*{References}

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