The clinical outcomes of extracorporeal irradiated and re-implanted cemented autologous bone graft of femoral diaphysis after tumour resection

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Abstract

Purpose We report the outcome of intercalary resection of the femoral diaphysis and extracorporeal irradiated autologous bone graft reconstruction, without the use of vascularized fibular graft.

Methods Six patients with Ewing sarcoma of the mid-shaft femur who were treated by limb sparing tumour resection and reconstruction with extracorporeal irradiated autologous bone graft with intramedullary cement between 2002 and 2010 were studied.

Results Mean age at the time of surgery was ten years (range, four–23). The length of resected femoral bone averaged 23 cm (15–32 cm). The ratio of bone resection length to total femoral length averaged 60 % (56–66 %). The patients had been followed up for between 16 and 79 months (mean, 41 months) at the time of the study. There was no infection nor fracture in this series. Primary union of the distal and proximal osteotomy sites was achieved in three patients. Delayed union of the proximal osteotomy site occurred in one patient that was successfully treated with iliac crest bone grafting. One patient developed non-union at the distal osteotomy site which failed to heal with bone grafting and was therefore converted to endoprosthetic

replacement, and another patient was converted to rotation-plasty at five months post-surgery because of contaminated margins. Function was excellent in all patients with surviving re-implanted bone. Local recurrence arose in one patient.

Conclusion Our experience suggests that cement augmentation of extracorporeal irradiated and re-implanted bone autografts offer a useful method of reconstructing large femoral diaphyseal bone defects after excision of primary malignant bone tumours.

Introduction

There have been considerable advances in the management of patients with primary malignant tumours of the bone over the last 30 years due to improved imaging techniques, effective neo-adjuvant chemotherapy, better radiotherapy planning and delivery, and improved surgical expertise. Primary malignant tumours arising from the diaphysis of the femur are relatively uncommon and the vast majority of these are Ewing's sarcoma [1, 2]. Intercalary resection of the diaphysis for bone tumour has many advantages, as opposed to excision of the end of the long bone, including preservation of joint function, more reliable bone reconstruction and preservation of the epiphyses in children. The options for reconstruction of the defect after intercalary resection in the femur include endoprosthetic replacements [3, 4], biological reconstruction either with allograft [5–8], vascularised or non-vascularised fibular autologous grafting [9], distraction osteogenesis [10] or more recently, sterilisation and re-implantation of the excised bone [11–14].

Intra-operative extracorporeal irradiation and re-implantation of bone sarcomas was first described by Spira

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and Lubin in 1968 [15]. This technique enables biological reconstruction with a precise fit, helps to restore function and avoids long-term complications of endoprosthetic replacement such as loosening and breakage [3, 4]. Previous reports recommended vascularised fibular graft to supplement the reconstruction with extracorporeal irradiated autologous bone graft because there remained an exact fitting scaffold of dead bone for a long time [9, 11, 12]. However, vascularised fibular grafts are associated with considerable donor-site morbidity [9]. We report the clinical and functional outcome of intercalary resection of the femoral diaphysis and extracorporeal irradiated autologous bone graft reconstruction without an added vascularized fibular graft in six patients with Ewing sarcoma.

Materials and methods

Six consecutive patients with Ewing sarcoma of the mid-shaft femur who were treated by limb sparing tumour resection and reconstruction with extracorporeal irradiated autologous bone graft between 2002 and 2010 were studied. Our indications for this procedure were as follows: (a) malignant tumours of the femoral mid shaft, (b) adequate strength of the diseased bone preserved, (c) adequate length of residual bone to allow for fixation using plate, (d) ability to obtain wide margins at the time of surgery as defined by Enneking [16], and (d) good response to neo-adjuvant chemotherapy on imaging.

All the patients were fully staged at the time of diagnosis as recommended by the musculoskeletal tumour society [17]. Histological diagnosis was obtained in all the patients. All the patients received neo-adjuvant chemotherapy consisting of vincristine, ifosfamide, doxorubicin and etoposide according to the EURO EWING protocol [18]. Clinical and radiological records of the patients were reviewed retrospectively. Resection was carried out via a lateral approach to the femur and the bone was divided at least 2 cm distally and proximally from the tumour margin as assessed on the MRI scans at the time of initial presentation. After excision of the bone and tumour, the soft tissue part of the tumour was removed from the bone and sent for histological examination leaving the bone available for extra-corporeal sterilisation. The bone was wrapped in vancomycin antibiotic soaked gauze and placed in two sterile bags before being sent to the radiotherapy suite in a special box. A dose of 90 Gy of radiotherapy was used for sterilisation and the whole process for sterilisation of the bone took about 30 min. The medullary cavity of the bone was then filled with gentamicin containing bone cement to improve the strength of the bone. We ensured that there was no cement in the last 2 cm of the bone ends in order to allow for bony ingrowth at the osteotomy sites. The bone was then re-

implanted and fixed with suitable plate and screws osteosynthesis with compression at the osteotomy sites. Functional assessments were made according to the criteria of the Musculoskeletal Tumour Society Functional Assessment System [10].

Results

Six patients were studied and all had histological diagnosis of Ewing's sarcoma. None of the patients had metastases at diagnosis and all the tumours were Enneking stage IIB at diagnosis. The mean age of the patients at the time of surgery was ten years (range, four–23). There were three males and three females. The length of the resected femoral bone varied from 15 cm to 32 cm (mean, 23 cm). The ratio of bone resection-length to total femoral length varied from 56 % to 66 % (mean, 60 %). The patients had been followed up for between 16 and 79 months (mean, 41 months) at the time of the study. Tumour response to chemotherapy was estimated histologically from the resected soft tissue and bone marrow. Complete necrosis (100 %) was obtained in five patients but only 50 % in one patient. Surgical margins were adjudged to be wide in five patients but contaminated in one patient. The patient with contaminated margin was advised to undergo rotationplasty which was performed at completion of chemotherapy five months after the initial surgery (case 6). Although no residual tumour was identified in the resected limb and the patient had a satisfactory functional outcome he has now developed metastatic disease.

All the patients were alive at the time of our study. Local recurrence in the soft tissue developed in one patient who initially had clear margins and 100 % necrosis. He is currently receiving second line chemotherapy. No patient developed local recurrence in the re-implanted bone. There was no infection or fracture of the graft in this series. Primary union of the distal and proximal osteotomy sites was achieved in three patients, specifically, at seven months in two patients and ten months in the third, with these patients achieving full weight bearing within seven months post-surgery (Fig. 1). One patient developed non-union at the distal osteotomy site which failed to heal with bone grafting and was therefore converted to endoprosthetic replacement (case 2). Delayed union of the proximal osteotomy site occurred in one patient and this was successfully treated with iliac crest bone grafting; full union and full weight bearing was achieved in this patient by six months post-surgery (case 3). One patient had a femoral neck fracture, away from the re-implanted graft, after falling from a bicycle 33 months after surgery, which required fixing with screws. The leg length of this patient was 2.5-cm short because the distal epiphysis did not grow as planned (case 4).

Fig. 1 Radiograph showing Ewing sarcoma of the right mid femur (case 1). **a** MRI showing pre-operative Ewing sarcoma of the right mid femur. **b** Immediate postoperative radiographs showing cement augmentation and

plate fixation of the graft. **c** Sound union of the proximal and distal grafts after ten months

Function was excellent in all the patients with surviving re-implanted bone. At the last follow-up, functional score in the four patients with surviving autografts varied from 87 % to 100 % but was 40 % in the patient with failed autograft salvaged with endoprosthesis. The clinical and functional results of all the patients are summarised in Table 1. The leg lengths were equal in four patients at the last follow-up but limb length discrepancy was 2.5 cm in one patient (case 4).

Discussion

Reconstruction of segmental bone defects after intercalary resection of the femur may be performed with endoprostheses [3, 4], distraction osteogenesis [10], allografts [5–8] and autologous grafts [11–14]. Custom-made intercalary endoprostheses have the advantage of allowing early mobilisation and return to function. However, loosening, wear and breakage have been reported and its long-term survival is still of great concern, thereby limiting its use in young

patients [3, 4]. Distraction osteogenesis can provide bone which will develop sufficient biomechanical strength and durability. However, the procedure is relatively time-consuming and demanding, particularly for very long defects as seen in our series and when patients require chemotherapy [10]. Reconstruction with allograft is currently the most frequent type of intercalary reconstruction performed [5–8]. However, there are significant complications associated with the use of large bone allografts, such as fracture, non-union and infection. The rate of non-union in intercalary reconstructions with allografts has been reported as being between 15 % and 71 % [5–8]. There is also the potential for transmission of infectious disease [16, 19, 20].

The advantage of re-implanting an extracorporeal irradiated autologous bone graft over allograft is that the autograft fits the defect exactly and the muscle attachment can be preserved. This advantage may contribute to the excellent functional scores in our patients. Contrary to autograft, it is relatively difficult to obtain perfect cortical apposition between the allograft and host cortices at the junction because

Table 1 Patients' characteristics and outcomes

Case/ sex/ age (years)	Diagnosis	Fixation	Resection of length (cm)	Cut length/ total length (%)	Bone union (time)	Follow-up (months)	Outcome	MSTS score	Comments
1/M/16	Ewing	LCP	27	57	Yes (7 months)	20	AWD	30	Soft tissue recurrence
2/F/4	Ewing	DCP	19	66	No (distal)	46	CDF	12	Non-unionEndoprosthesis
3/M/23	Ewing	DCP	32	60	Delay (distal)	65	CDF	28	Delay unionIliac bone graft
4/F/8	Ewing	DCP	22	61	Yes (seven months)	79	CDF	26	2.5 cm shortFemoral neck fracture
5/F/7	Ewing	LCP	21	61	Yes (ten months)	22	CDF	28	
6/M/4	Ewing	LCP	15	56	–	16	CDF	NA	Resection margin positiveRotationplasty

M male, *F* female, *LCP* locking compression plate, *DCP* dynamic compression plate, *AWD* Alive with disease, *CDF* continuous disease free, *NA* not applicable, *MSTS score* Musculoskeletal Tumour Society score

of their different sizes and trabeculae orientation. We believe that perfect anatomical reduction and stable fixation are the most important factors in promoting healing of the junction.

Previous reported studies of intercalary reconstructions of the femur with re-implanted extracorporeal sterilised bones have largely combined the re-implanted bone with vascularised fibular autografts [11–14], and we ourselves have done this when resecting the mid tibia [21].

While a vascularised fibula has the advantage of bringing vascularity to an otherwise dead sterilised bone, the procedure time is much prolonged and there is the associated risk of donor site morbidity. The fibula does not significantly increase the mechanical strength of the re-implanted bone [9]. The advantages of cement augmentation of the re-implanted bone over vascularised fibula include reduced operating time, avoidance of donor site morbidity, improved mechanical strength of the re-implanted bone, better screw hold and pull out strength of the screws fixed to bone cement, and the ability to deliver high concentration of antibiotics to the graft and local tissues [22–24]. We believe this is the reason why fracture of the graft did not occur in any of the patients in our series. In long resections the fibular may not even be long enough for augmentation as we noticed in two of our patients.

Non-union in intercalary reconstructions with extracorporeal irradiated autologous bone grafts with vascularised fibular grafts has been reported to occur in between 7 % and 31 % of patients [11–13]. Chen et al. reported that reconstruction with extracorporeal irradiated autologous bone graft had a significantly lower rate of non-union than that with segmental allograft [12]. The rates of non-union noted in our series are therefore similar. Fracture of femoral intercalary allografts and extracorporeal re-implanted bone autograft with vascularised fibular occurred in about 5–20 % [11–13]. We have not noticed fracture of the graft in any of our patients due to the improved mechanical strength offered by cement. Similarly, in the study by Puri et al. [14], fracture did not occur in all 32 patients with extracorporeal irradiated and re-implanted cemented autologous bone graft of diaphyseal bone tumour, including 17 femoral bone tumours. Studies have shown that addition of intramedullary cement reduces the risk of fractures in patients with allografts [24]. We consider that perfect anatomical reduction and stable fixation play an important part in the healing of the osteotomy junctions, and use of cement in the graft and adequate control of weight bearing can prevent fracture. Our experience suggests that addition of antibiotics to the bone cement placed inside the graft is useful in reducing the risk of infection. None of our patients have

developed infection compared to 24 % graft infection requiring total removal of the re-implanted graft of the patients with femoral reconstruction by Puri et al. [14] where antibiotic was not added to the cement.

The leg lengths were equal in four patients at the last follow-up, but limb length discrepancy was 2.5 cm in one patient. In this case the distal osteotomy was just a few centimetres above the growth plate and in order to achieve sound fixation and thus early union, the plate on the side of the bone was extended to the epiphysis and screws were inserted here. Even though the screws were removed once union had taken place the growth plate failed to grow normally.

The main problems in this series were oncological. The first challenge was in the child aged four (case 6) who had a small Ewing's tumour which appeared to respond well to chemotherapy. The bone was resected along with a generous cuff of vastus intermedius around it, but histology of this muscle showed extensive pockets of viable tumour cells extending to the margin. It was agreed that this meant that there was almost certainly residual tumour in the leg and so a rotationplasty was advised and performed. Histology showed no residual tumour either in the irradiated bone or the residual soft tissue. Despite this we felt that this further surgery was the only safe option as the alternative of giving radiotherapy to the thigh would almost certainly have led not only to non-union of the re-implanted bone but also to growth arrest in the epiphyses.

The other problem was in the young man who developed local recurrence in the soft tissues of the thigh, 20 months after undergoing resection and re-implantation. This was most unexpected as he had 100 % necrosis of the tumour following neo-adjuvant chemotherapy with clear margins.

These two cases do however illustrate the challenge of surgically resecting Ewing's sarcoma. Local recurrence can be a real risk even with a good response to chemotherapy and clear margins of excision. Whilst radiotherapy can decrease this risk, this would also be detrimental to bone healing. Thus, very careful patient selection is needed prior to this surgery being considered, but even then local recurrence can arise (as it did in case 1).

Furthermore, this method is not recommended when a postoperative adjuvant radiotherapy is included as a treatment protocol.

Although this is a small case series with relatively short follow up time, our experience suggests that cement augmentation of extracorporeal irradiated and re-implanted bone autografts offer a useful method of reconstructing large femoral diaphyseal bone defects after excision of primary malignant bone tumours.

Conflict of interest statement We declare that we have no conflicts of interest.

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