Extracorporeal irradiation for pelvic reconstruction in Ewing’s sarcoma

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We review the treatment of pelvic Ewing’s sarcoma by the implantation of extracorporeally-irradiated (ECI) autografts and compare the outcome with that of other reported methods.

We treated 13 patients with ECI autografts between 1994 and 2004. There were seven males and six females with a median age of 15.7 years (interquartile range (IQR) 12.2 to 21.7). At a median follow-up of five years (IQR 1.8 to 7.4), the disease-free survival was 69% overall, and 75% if one patient with local recurrence after initial treatment elsewhere was excluded. Four patients died from distant metastases at a mean of 17 months (13 to 23). There were three complications which required operative intervention; one was a deep infection which required removal of the graft. The functional results gave a mean Musculoskeletal Tumor Society score of 85% (60% to 97%), a mean Toronto extremity salvage score of 86% (69% to 100%) and a mean Harris hip score of 92 (67 to 100).

We conclude that ECI grafting is a suitable form of treatment for localised and resectable pelvic Ewing’s sarcoma.

Ewing’s sarcoma is the second most common primary malignant bone tumour in children and adolescents and the fourth most common primary malignant bone tumour overall.1,2 The pelvis is the most common site for primary malignant bone tumours (5% to 15%), and particularly for Ewing’s sarcoma in young adults.2-11

Advances in multimodal treatments have improved the survival rates at five years from 5% to 10% 20 years ago to 60% to 75% most recently.2,7,11 The prognosis for Ewing’s sarcoma is poorest in the pelvis2,7,12 with a survival rate at five years of approximately 50%.7,14,15 The pelvis is a deep organ with poor compartmentalisation for the restriction of tumour growth, and a complicated anatomy with major neurovascular and visceral structures. It is difficult to achieve local control, limb salvage and preservation of function.1,4,9,16,17

Wide resection is essential to achieve local control4,18-22 after which there are many methods available for limb salvage, including biological reconstruction (allograft, autoclaved/irradiated autograft), endoprosthetic reconstruction, hip transposition, arthrodesis or the creation of pseudarthrosis.2,3,5,18,23-30

We present an alternative method of biological reconstruction, namely, implantation of an extracorporeally-irradiated (ECI) autograft. The technique consists of wide en bloc resection, ECI with 40 Gy to 60 Gy of irradiation, debulking of the tumour from the resected bone and re-implantation with or without vascularised bone graft.19 To our knowledge, there have been no reports of the treatment of Ewing’s sarcoma using this technique.

Patients and Methods
We reviewed 13 consecutive patients with pelvic Ewing’s sarcoma who underwent re-implantation of ECI autograft after wide resection between 1994 and 2004. There were seven males and six females with a median age of 15.7 years (interquartile range (IQR) 12.2 to 21.7, range 6.5 to 34.1). A total of 12 were referred primarily and one with local recurrence after surgery elsewhere (case 9). The median follow-up was five years (IQR 1.8 to 7.4, range 1.1 to 8.2) for all patients and 6.7 years (IQR 4.8 to 7.4, range 3.1 to 8.2) for the nine survivors. All the tumours were classical Ewing’s sarcoma without macroscopic metastatic disease at diagnosis. The sites are shown in Table I, which was the classification of Enneking and Dunham.31

All the patients also received neo-adjuvant chemotherapy; 11 had a soft-tissue mass which responded to chemotherapy with a reduction in size of at least 50%. There was no significant delay for post-operative chemotherapy; all patients resumed chemotherapy within three to four weeks.
After classification, the surgical plan included wide en bloc resection and complete excision of biopsy scars. All operations were performed by the senior author (PDS) and, depending on the location and extent of the tumour, part or all of an extended sacroiliofemoral or ilioinguinofemoral (triradiate) approach was used. Osteotomies were planned to allow a wide en bloc resection. In patients in whom the ilium was resected, an osteotomy was performed beneath the anterior superior iliac spine if possible, to allow re-attachment of the inguinal ligament and musculature.

Extracorporeal irradiation of the specimen was performed using a single dose of 50 Gy at a rate of 2 Gy per minute. While this was happening, the operation site was prepared for re-implantation and biopsies of the surgical margins at the osteotomy sites were taken. On return, the specimen was cleared of all unnecessary soft tissue, leaving the important muscle insertions for muscle re-attachment, particularly the hip abductors. The ECI graft was washed with betadine solution and re-implanted. Depending on the size of the graft and the osteotomy sites, fixation was performed by AO plates and screws (Fig. 1).

For six patients in whom a partial or total acetabular resection was required, total hip replacement (THR) was performed after re-implantation and fixation of the graft. Four skeletally-immature patients (cases 1, 3, 4 and 7) had a resection through the triradiate cartilage and did not need a THR (Fig. 2). The remaining three had posterior resection without acetabular involvement.

Post-operatively, all patients were rested in bed without traction for six weeks. Prophylactic intravenous antibiotics were given for one week and stopped after all drains and catheters had been removed. A first-generation cephalosporin was given for another six weeks. At this stage, partial weight-bearing on crutches were required. After six to seven months, full weight-bearing with one or two sticks was allowed, provided the radiographs were satisfactory, and continued until the osteotomies had united.

Radiographs were taken at regular intervals and reviewed for evidence of union at the sites of the osteotomies, bone quality, fatigue fractures and loosening of the implants. Chest radiography, CT of the lungs and from 2001, PET-CT, were done to exclude metastatic disease.

Table I. Details and findings in the 13 patients with Ewing's sarcoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Site</th>
<th>Resection classification* THR†</th>
<th>Margins</th>
<th>Scores‡</th>
<th>Follow-up survival (yrs)</th>
<th>Complications</th>
<th>Status§</th>
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<tr>
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<td>6.5</td>
<td>Ilium</td>
<td>PI + PII</td>
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<td>4</td>
<td>100 90 97 96 8.2</td>
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<td>NED</td>
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<tr>
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<td>34.1</td>
<td>Ilium</td>
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<td>- - - 1.2</td>
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<td>DWD (b,br)</td>
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* According to Enneking and Dunham, S, sacrum; PI, ilium from sacroiliac joint of the neck of ilium; PII, periacetabular, PIII, pubic rami
†THR, total hip replacement
‡TES, Toronto extremity salvage score; MSTS, Musculoskeletal Tumor score (society); HHS, Harris hip scores; CHS, combined hindquarter salvage score
§NED, no evidence of disease; DWD, died with metastatic disease; b, bone; br, brain; l, lung
**local recurrence
The nine survivors were evaluated using the Musculoskeletal Tumor Society score (MSTS), the Toronto Extremity salvage score (TESS) and the Harris hip score (HHS). In order to produce meaningful results we formulated a ‘combined hindquarter salvage score’ (CHSS) as the mean of the three established scoring systems, thereby enabling results to be graded as excellent (90 to 100), good (80 to 90), fair (70 to 80) and poor (< 70).

Data and statistical analysis. Description of the data was based on medians, quartiles (IQR) and the minimal and maximal range for continuous endpoints. Event-free and overall survival were calculated from the time of histological diagnosis to the latest uneventful follow-up visit. An event was defined as a relapse or progression of disease, a treatment-related secondary neoplasm, or death. An event affecting the overall survival was defined as death from any cause. Survival rates were based on Kaplan-Meier analyses. The log-rank test was used to evaluate the significance of differences in overall survival between groups of patients. A p-value ≤ 0.05 indicated statistical significance and statistical analysis was performed using SPSS software version 11.5 (SPSS Inc., Chicago, Illinois).

Results

The overall survival and survival rate at five years was 69% compared with 75% for all patients with primary Ewing’s sarcoma presenting to our institution. At the end of our study, nine patients were alive without local recurrence or distant metastases.

The median event-free survival was 6.7 years (IQR 4.8 to 7.4, range 3.1 to 8.2, Table I). Four patients (31%) died from metastatic disease without local recurrence after a median 1.4 years (IQR 1.1 to 1.9). For the survivors the median MSTS was 86% (IQR 68.5 to 91.5, range 60 to 97), the median TESS 85% (IQR 78.5 to 93.5, range 69 to 100) and the median HHS 89 (IQR 82.5 to 96.5, range 67 to 100). The median CHSS was 88 (IQR 78.2 to 93.3, range 65 to 98), with three patients rated excellent, four good, one fair and one poor (Table I). On clinical review of the survivors the functional outcome was excellent and good in seven (78%). All had returned to work or study and to their pre-morbid lifestyle as far as possible. None used a walking aid.

Solid bony union was observed at all the osteotomy sites and consolidation was achieved after a median six months (IQR 5 to 7, range 4 to 8). One stress fracture occurred at the sacroiliac joint 15 months after operation, with breakage of a sacroiliac screw.
Local osteolysis was seen in three patients. In two this had not progressed after one year, and the implants and reconstructions remained stable. In the third (case 4) there was collapse of the dome of the acetabulum and a leg-length discrepancy of 5 cm (Fig. 3). The other three patients (cases 1, 3, and 7) whose resection involved the acetabulum and who were skeletally immature, all had an excellent outcome and no further growth was seen in the irradiated segments on follow-up radiographs. None of the THRIs showed osteolysis to any extent but there was loosening of one of the acetabular components (case 11).

There were four complications, three of which required operative intervention. In one patient with a deep infection (case 13), the ECI autograft had to be removed giving a failure rate of 8%. He had an early deep infection and, after finishing chemotherapy, all implants, were removed 1.5 years after the initial operation and replaced with a cement spacer which was finally removed two years after the initial operation leaving him with a pseudarthrosis. There has been no evidence of recurrent disease and, despite a shortening of the affected leg by 5 cm, the overall functional result (CHSS) was fair.

There were two superficial post-operative wound infections involving skin necrosis at the apex of the triradiate incision. One healed with simple dressings and the other required a small split skin graft.

The fourth complication (case 11) was a traumatic fracture through the graft 15 months after the operation, resulting in breakage of a sacral screw. The fracture united with conservative treatment. However, the acetabular component of the THR was found to be loose and was revised 4.2 years after implantation. At five-year follow-up, ten months after revision, the patient was free of pain and had returned to sport.

No other THR required revision or showed signs of loosening and all hips have remained stable without dislocation.

Discussion

Ewing's sarcoma of the pelvis is more aggressive than that at other sites and has an unfavourable prognosis. Delayed diagnosis is associated with larger tumours and micro-metastases, and results in poorer local and systemic control. Surgery in this area is also very difficult, requiring considerable expertise and often a long operating time. Support services are likewise important, with a requirement for large amounts of blood products, specialised post-operative recovery care, and prolonged rehabilitation.\textsuperscript{1,2,4,6-9,11,12,16-18,22,36}

Since Ewing’s sarcoma is sensitive to radio- and chemotherapy, its primary treatment is multi-agent chemotherapy followed by local treatment and neo-adjuvant chemotherapy.\textsuperscript{1,2,10,11,15,32,33,37} Local treatment includes surgery and radiotherapy or a combination of the two.\textsuperscript{1,4,12,15} The reported five-year survival for pelvic Ewing’s sarcoma is between 42% and 75%.\textsuperscript{7,14,15} We observed an overall disease-free survival of 75%, when the patient who presented with local recurrence at the beginning of the study (case 9) was excluded.

Wide resection is the crucial part of local treatment,\textsuperscript{6,7,12,15} and has a much higher survival rate at five years of 75% compared with a rate of 25% in patients with a marginal or intralesional resection.\textsuperscript{15}

Post-operative radiotherapy has been shown to improve local control after an incomplete resection and in patients with a poor histological response.\textsuperscript{1,2,6,7,12,32,38,39} Five patients received post-operative radiotherapy. Two had a contaminated margin and two had clear margins, but with a poor response to chemotherapy. The remaining patient presented with a local recurrence.

Four patients died after a mean 17 months (13 to 23) from distant metastases without local recurrence. Two had an insufficient resection, one presented with local recurrence and the fourth had a poor response to chemotherapy. They also received post-operative radiotherapy. Sarcomas are known to grow locally after inadequate excision and have a poor response to chemotherapy. As distant metastases occur in almost every patient after adequate local treatment it must be assumed that there are micro-metastases at diagnosis in most patients.\textsuperscript{1,4,8,9,16} Patients with primary metastases and recurrent disease have a higher risk of relapse than those with localised disease (case 9).\textsuperscript{1} Some studies have reported a worse prognosis when there are multiple rather than isolated metastases. The prognosis for lung metastases is better than that for metastases elsewhere.\textsuperscript{1,6,18}

Most current treatments emphasise limb salvage and reconstructive surgery rather than amputation.\textsuperscript{2,4,9,11,18,20,22,25,26,37,40-43} After peri-acetabular resection, stable pelvic reconstruction is the main goal.\textsuperscript{3,4,9,21,28,31,42} Also, it is usually impossible to achieve a wide margin of healthy peri-acetabular bone without resection of the hip. CT or MRI cannot predict whether tumour cells have invaded the
joint. The ideal method of peri-acetabular reconstruction remains controversial, especially in growing children with open physes. Functional deficiencies are caused by leg-length discrepancy and pelvic tilt. Operations such as iliofemoral/schiofemoral arthrodesis or pseudarthrosis, modified Girdlestone procedures and hip transpositions are less accepted nowadays and the risks of failed fusion, pain, limb discrepancy and increased instability is high with these methods.

Three techniques are favoured after peri-acetabular resection, namely, a saddle prosthesis, a computer-designed custom prosthesis and cemented hip arthroplasty with or without autograft or allograft support. The youngest acceptable age for these techniques is 14 years because there is insufficient bone stock before this.

THR with a composite prosthesis was performed. For six of our patients, aged between 13 and 29 years, after whole or partial resection of the acetabulum, The mean CHSS was 81.3%. Three cases in the THR group died from metastatic disease.

In four skeletally-immature patients, aged between six and 13 years, resection was performed through the triradiate cartilage, assuming that this was a barrier to extension of the tumour. When part of the acetabulum is preserved, there is no stability after fixation of ECI bone.

Verma, Kuo and Gitelis reported the case of a four-year-old girl who underwent resection and reconstruction of the acetabulum with a trimmed, adult-size allograft. This allowed proper cover of the femoral head in a stable position and showed that the oversized acetabulum produced enough space for expansion of the femoral head during growth. At follow-up after two years she had a stable, painless gait with good movements.

In the remaining three cases, without acetabular involvement and with a stable pelvis we performed posterior resection alone fixing the ECI graft with AO devices. One of these patients had a positive margin and died following a poor response to chemotherapy.

ECI can be used in the treatment of all bone tumours when, following excision, there is enough stable bone stock for fixation and reconstruction. The advantages of this technique include restriction of irradiation to the resected bone, an ideal fit of the graft, preservation of bone stock, re-attachment of tendons and ligaments, no risk of transmission of disease or immunological reactions, cost-effectiveness and convenience in any institution with radiotherapeutic equipment. These advantages also give better conditions for THR.

One of the criticisms of ECI is the lack of material for the histological assessment of the chemotherapeutic effect. However, we believe that our marginal biopsies were satisfactory for assessing resection. Our oncologists base post-operative chemo- and radiotherapy on the clinical and radiological responses and marginal biopsies. The low rates of recurrence and mortality in our series and the findings of earlier publications support this view.

The most common complications of the ECI-graft technique with 50 Gy are nonunion of the osteotomies, fractures and, in the skeletally immature, limb-length discrepancy. Non-progressive bone osteolysis is also seen and usually appears within two years after operation. Higher rates of infection, bone resorption and fracture are seen with higher doses of radiation and usually occur three to four years after operation. These are a result of irreversible radiation-induced osteopaenia with decrease in bone strength. Other considerations include the adverse effects of chemotherapy on the host-immune system and a long operating time.

Liptak et al., in an animal model, showed that radiation induced a decrease in osteoprogenitor cells. This may be caused by a direct cytotoxic effect or by obstruction of blood vessels. Ischaemia and loss of cellular mass increase the porosity of the bone and reduce its mechanical strength and the capacity for formation of new bone. With a large single dose of radiation these changes are accentuated and bone repair is further delayed. Osteolysis and the radioluent gaps seen on plain radiographs are explained by this phenomenon. Bone resorption occurs mainly in the grafted bone furthest from revascularisation. The porosity increases considerably within 24 weeks, the weakest time for irradiated bone, after which remodelling takes place and bone strength improves over the following 30 weeks and probably beyond.

The application of 50 Gy is not enough to inactive the proteins in the bone matrix. Thus, graft osteoconductivity and the induction of local osteoprogenitor cells work to incorporate the ECI-bone. Bone irradiated with higher doses (> 250 Gy) has a reduced stability, vascularisation and osteoconductive properties, thereby increasing the time to union and incorporation.

Four patients had complications and three required further surgery. One had a deep infection and the ECI graft had to be removed. These complication rates are comparable with or better than other biological reconstruction methods in the pelvis and better than other prosthetic techniques.

Instability, aseptic loosening, wear and failure of the implant are the most common failure of prostheses and depend on the age, level of activity and the bone stock. Other reported complications include leg-length discrepancy and nerve damage, which are sometimes inevitable when trying to achieve a clear margin.

We believe that our study supports ECI and reconstruction as a method of treatment for pelvic Ewing’s sarcoma. We support the view that most complications in the treatment of pelvic Ewing’s sarcoma are caused not by the type of reconstruction, but by the type of resection and that the best predictors for survival include a localised lesion amenable to wide resection and when surgery is performed at a centre with access to excellent oncological, radiotherapeutic and radiological support.
References