Limb preservation surgery with extracorporeal irradiation in the management of malignant bone tumor: the oncological outcomes of 101 patients

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Background: En bloc resection, extracorporeal irradiation (ECI) and reimplantation have been used selectively at our centers as part of limb preservation surgery of malignant bone tumors since 1996. We report the long-term oncological outcomes.

Patients and methods: One hundred one patients were treated with ECI at two Australian centers between 1996 and 2011. A single dose of 50 Gy was delivered to the resected bone segments. The irradiated bones were reimplanted immediately as a biological graft. Patients were treated with chemotherapy as per standard protocol. The three main histological diagnoses were Ewing’s sarcoma (35), osteosarcoma (37) and chondrosarcoma (20). There were nine patients with a range of different histologies.

Results: There was one local recurrence (2.86%) in Ewing’s sarcoma and the 5-year cumulative overall survival was 81.9%. There was no local recurrence in osteosarcoma and 85.7%. The local recurrence rate was 20% (4 of 20) in chondrosarcoma, and the 5-year cumulative overall survival was 85.7%.

survival was 80.8%. Limb preservation was achieved in 97 patients. For the 64 patients with disease in the pelvis or lower limb, 53 (82.3%) could walk without aids at the time of last follow-up.

**Conclusions:** This large series of ECI shows an excellent long-term local control. It is a good alternative reconstruction method in selected patients. The overall survival is comparable to other published series.

**Key words:** chondrosarcoma, Ewing’s sarcoma, extracorporeal, osteosarcoma, radiation, sarcoma

**introduction**

The therapeutic goals in the management of primary bone tumors include optimization of disease control in terms of local control and survival, maintenance of long-term function and minimization of late toxic effects. Surgery is a necessary component of curative therapy in most primary bone tumors and the specific surgical procedure is dictated by the location and extent of the primary tumor. The use of extracorporeal irradiation (ECI) was first reported in 1968 [1]. The tumor-bearing bone segment is resected, treated with a single fraction of radiation therapy (RT) extracorporeally and reimplanted. We have previously reported our initial experiences of this technique [2–5]. The potential risk of local recurrence within the reimplanted bone was of concern with this technique. Here we present the long-term oncological outcomes of 101 patients treated with ECI.

**methods patients**

All consecutive patients treated with ECI at Royal Prince Alfred Hospital and The Children’s Hospital at Westmead (Sydney, Australia) between 1996 and 2011 were included in this study. The study was approved by the ethics committees. Clinico-pathological details were retrieved from the hospital databases. Chemotherapy and/or RT were administered as per the standard protocols of our institutions. The chemotherapy protocol for Ewing’s sarcoma was vincristine 1.5 mg/m², cyclophosphamide 1200 mg/m² and doxorubicin 30 mg/m² (OCA), OCA, etoposide 100 mg/m² days 1–5, ifosfamide 1.8 mg/m² days 1–5 (VIM) OCA OCA VIM then surgery followed by OCA OCA VIM.

The chemotherapy for osteosarcoma was cisplatin 100 mg/m² and doxorubicin 60 mg/m² for three 21-day cycles before surgery. Three cycles of adjuvant chemotherapy were given following surgery, using the same regimen, unless the histological assessment of cell kill was <50%. Biopsy of the involved bone was carried for histological assessment before ECI. If the cell kill was <50%, three cycles of methotrexate 3 g/m² and doxorubicin 60 mg/m² were used.

**surgery and ECI technique**

En bloc resection of the involved bone was carried out at a median time of 4 weeks following chemotherapy. A detailed description of the ECI technique has previously been reported [2–5]. All bone segments were given a single fraction of 50 Gy. In 91 patients, ECI was delivered from a linear accelerator. Ten bone segments measuring less than 19 cm in length and 12 cm in thickness were irradiated in a blood product irradiator. The bone was then reimplanted with or without a vascularized autologous fibular graft. Postoperatively, immobilization was continued until there was radiographic evidence of union. For tumors of the lower limb or pelvis, weight-bearing was allowed when there was radiographic evidence of early union at the osteotomy sites. Patients then advanced to full weight-bearing over 3–4 months depending on the clinical and radiographic progress.

**statistical analysis**

Times to local failure, death from cancer and death from any cause were calculated from date of diagnosis for those patients who had ECI for primary bone tumor without metastatic disease at diagnosis. For those who underwent ECI for secondary metastasis in the bone, the time to local failure was calculated from the date of ECI. Recurrence was defined as clinical, radiological or pathological evidence of recurrence at the primary site or distant site. Patients who were not observed to experience a given event over the duration of the study were censored at the date of last follow-up, death from any cause (when estimating recurrence-free survival) or death from causes other than the primary bone tumor (when estimating disease-specific survival). The Kaplan–Meier method was used to construct time-to-event curves. Univariate and multivariate time-to-event analyses were undertaken using Cox proportional hazards regression modeling.

**results**

**overall patient characteristics**

A total of 101 patients (53 males and 48 females) with a median age at diagnosis of 23 years (range 3–70 years) were treated between 1996 and 2011. There were 62 pediatric patients (≤18 years old). The median follow-up from ECI was 52.8 months (range 0.4–169 months). For the survivors, the median follow-up was 67 months (range 3.8–169 months). For the deceased patients, the median follow-up was 21.2 months (range 0.4–106.3 months). The main diagnoses were Ewing’s sarcoma (35, 34.7%), osteosarcoma (37, 36.7%) and chondrosarcoma (20, 19.8%). There were nine patients with the following histologies: synovial sarcoma with bony involvement (three), clear cell sarcoma (one), giant cell tumor (one), malignant fibrous histiocytoma (one), metastatic melanoma (one) adamantinoma (one) and myxoid fibrosarcoma with bony involvement (one). There was no local recurrence in these nine patients. The ECI-treated sites were pelvis (35, 34.7%), femur (34, 33.7%), humerus (17, 16.8%), tibia (14, 13.9%) and radius (1, 1%).

**Ewing’s sarcoma**

For the 35 patients with Ewing’s sarcoma, the median age at diagnosis was 14 years (range 0.1–51 years, 25 patients aged ≤18 years) and the median follow-up was 75.5 months (Table 1). The majority (32, 91.4%) had localized disease at the time of diagnosis, and three patients had small volume pulmonary metastasis at the time of diagnosis. The ECI-treated sites were pelvis (16, 45.7%), femur (10, 28.6%), humerus (5, 14.3%) and tibia (4, 11.4%). All patients were treated with chemotherapy before surgery with ECI. Four patients received postoperative RT (50–54 Gy, 3 pelvis and 1 humerus) for positive margins, and they all tolerated the treatment well without an unexpected rate of toxic effect. Thirty-one patients received postoperative chemotherapy. Only one patient (2.86%) developed local
This 17-year-old female had Ewing’s sarcoma of the pelvic ilium. She was initially treated with neoadjuvant chemotherapy and local excision at another institution. She developed local recurrence in the pelvis 18 months later and was referred to our institution for management. She was then treated with chemotherapy followed by local excision with ECI. Postoperative RT (54 Gy in 27 fractions) was given for close surgical margins. She developed a large local recurrence in the pelvis with a large soft tissue component 15 months after ECI and died with local and distant disease 20 months after ECI. Overall, there were eight distant recurrences. The 5-year cumulative overall survival was 81.9% (median not reached).

osteosarcoma

For the Thirty-seven patients, the median age was 15 years (range 3–51 years, 28 patients aged ≤18 years), and the median follow-up was 49 months. Thirty-four patients had first presentation of osteosarcoma without metastatic disease; two had ECI for bony metastasis from a primary osteosarcoma elsewhere and one had ECI for a local recurrence in pelvis (previous chemotherapy and surgery at another institution). The treated sites were femur (17, 46%), humerus (10, 27%), pelvis (5, 13.5%) and tibia (5, 13.5%). All patients except the two who received ECI for osteosarcoma metastasis and two with low-grade parosteal osteosarcoma were treated with chemotherapy before surgery. One patient who had ECI for local recurrence in the pelvis also received postoperative RT (66 Gy in 33 fractions) for involved surgical margins. There was no local recurrence in all 37 patients and six distant recurrences in the 35 patients without distant metastasis at the time of ECI.

The 5-year cumulative overall survival for the 35 patients with localized disease at the time of ECI was 85.7% (median not reached). The 5-year overall survival for the patients with high-grade osteosarcoma was 85.6%.

chondrosarcoma

Twenty patients (median age 43 years, range 13–70 years, seven patients aged ≤18 years) with chondrosarcoma were treated with ECI with a median follow-up of 57.1 months. All patients had localized disease at the time of diagnosis (one patient had multifocal disease in pelvis). The treated sites were pelvis (nine),
femur (six), humerus (two), tibia (two) and radius (one). All patients were treated with surgical excision without neoadjuvant chemotherapy. One patient with multifocal disease in pelvis was given postoperative radiation (54 Gy) for close margins. There were four local recurrences (20%, primary sites: humerus, sacrum, acetabulum and multifocal disease in pelvis) at 3, 11, 14 and 33 months after ECI (Table 2). The corresponding sites of local recurrence were soft tissue mass around drain site, soft tissue mass behind and medial to femoral vessels extending up to psoas muscle, soft tissue mass around sacrum and bony pelvis outside the reimplanted bone and postoperative fields. All were treated by local excision and postoperative RT (50.4–60 Gy) was given to the first three patients who did not receive RT prior. There were six distant recurrences. The 5-year cumulative overall survival was 80.8% (median not reached). The 5-year overall survival for the 16 patients with high-grade chondrosarcoma was 77.9%.

**Limb preservation**

Limb preservation was achieved for 97 patients. The median time to reanastomosis at the osteotomy site was 11 months. Reunion times by site of treated bone were 6 months for humerus and pelvis, 12 months for femur and tibia and 39 month for the single ECI patient with a radial primary. Time to reanastomosis was not influenced by gender, age, lower versus upper limb site of disease or the use of a vascularized fibular graft. There was one case of stress fracture in the irradiated tibia and one case of necrosis in the irradiated acetabulum. There was no case of osteonecrosis in those patients who were treated with postoperative RT.

Four patients were eventually undergoing amputation. Three patients were for osteomyelitis at 6, 14 and 31 months after ECI. One patient, a 14-year-old female, underwent a forequarter amputation for recurrent mesenchymal chondrosarcoma. She presented with a primary lesion in the proximal humerus and underwent surgery with ECI and reconstruction with a Bigliani hemiarthroplasty. She developed a subcutaneous recurrence adjacent to the drain site 3 months after ECI. This was locally excised and postoperative RT (60 Gy in 30 fractions) was given. Seven months later, she developed further recurrence in distal humeral metaphysis with a 3-cm soft tissue mass and underwent shoulder disarticulation 14 months after ECI. She remained disease free 70 months after the initial diagnosis.

The long-term functional outcomes of these patients are being assessed and will be reported separately. Briefly, 60 of 73 patients (88%) with primary disease in the lower limb or pelvis sites could walk unaided at the time of the last follow-up. Three patients were able to mobilize with one walking stick mainly due to incomplete union of the osteotomy sites precluding full weight bearing. In the immediate postoperative period, major wound complication occurred in eight patients (necrosis of split skin graft, debridement myofascial flap, hematoma), and six patients (5.9%) suffered a wound infection. Overall, 36 patients (35.4%) underwent further local surgery for either mechanical reason or delayed osteomyelitis. The need for further local surgery was not associated with primary disease features of histology or site of treated bone, nor was it associated with the use of a vascularized fibular graft.

**Discussion**

This is the largest reported series of extracorporeal irradiation and demonstrates a comparable long-term local control and survival to other published series using conventional limb preservation reconstruction methods. In the 35 patients with Ewing’s sarcoma, our results showed a very low local recurrence rate of 2.86%, and the only local recurrence occurred in a patient who was treated with ECI as a salvage procedure of her recurrent pelvis disease. A review of 1058 patients from three cooperative trials in Ewing’s sarcoma showed the local recurrence rate was 26.3% for those who had RT alone [6]. For those who had surgery as the definitive local treatment, the local recurrence for large central primaries was 12.9%. Ewing’s sarcoma located in the axial skeleton is known to have a poorer prognosis than those arising in the nonaxial skeleton and a local relapse rate of 18% was reported in the Cooperative Ewing’s Sarcoma Study [7]. Local treatment of pelvic Ewing’s sarcoma is often a tradeoff between functional outcomes after surgery and potential side-effects of external beam RT. Our overall local control rate of Ewing’s sarcoma in the pelvis was 93.8%. In the extremity, we have a 100% local control rate. The 5-year cumulative overall survival of 81.9% is comparable to results from other trials [8] and excellent in comparison to results based on analysis of the US National Cancer Database [9].

There was no local recurrence in the 37 patients with osteosarcoma. Other large series of limb preservation surgery reported 5-year local recurrence-free rates of 95%–96% [10, 11]. The 5-year cumulative overall survival for the patients with localized disease at the time of ECI was 85.7%, which is consistent with results from recent prospective trials [10, 12]. For localized chondrosarcoma, surgical treatment offers the only chance for cure. The optimal type of surgical management depends upon histological grade, location and tumor extent. Wide en bloc local excision is the preferred surgical treatment [13]. Our local recurrence rate after ECI in chondrosarcoma was 20% which was higher than Ewing’s sarcoma and osteosarcoma. The recurrences were in the surrounding soft tissues in three patients and another location in the bony pelvis in the patient with multifoci primary in the pelvis. This higher rate of local recurrence may in part be related to often the larger size and pelvic location.

Limb preservation has changed from being an exception to a standard practice in the management of primary malignant bone tumors. Limb preservation can improve functional outcomes without sacrificing local disease control as long as complete tumor resection is anatomically possible. Bony defects created by limb sparing procedures may be reconstructed by a variety of methods. Large osteoarticular defects can be replaced by tumor prostheses, allograft or allograft-prosthesis composites [14]. High complication rates such as failed reconstruction (31.5%) have been reported [15, 16]. In our series of 101 patients, major wound complication occurred in eight and six patients (5.9%) suffered a wound infection which is at the lower end of the range reported in the literature for comparable major surgery involving allograft and/or large tumor prostheses [17, 18]. Ultimately only three patients underwent amputation because of osteomyelitis. The vast majority (88%) of patients with primary sites in the pelvis or lower limb were able to mobilize without aids at the time of last follow-up.
A major advantage of ECI is the precise anatomical fit of the reimplanted bone segment and preservation of joint mobility. Reimplantation of the irradiated bone also obviates some of the other problems associated with allograft, such as the availability of suitable grafts from a bone bank especially in pediatric patients, graft rejection and risk of viral transmission. In pediatric patients, limb preservation surgery needs special consideration to avoid later limb length discrepancy. ECI can potentially avoid the growth discrepancy commonly seen in prosthetic replacement by avoiding resection of the normal growth plate and appositional bone growth from surrounding healthy bones. The risk of infection acquired during ECI is low as the bone segment is irradiated in a sterile condition. In this series, the incidence of wound infection (5.9%) was not higher than the reported rate involving allograft or prosthesis [16, 17]. The risk of radiation-induced malignancy in the low-dose region in the surrounding normal tissue is a concern when standard RT is used as the definitive therapy [19]. The technique of ECI does not have a low-dose region and with the extreme high dose to the irradiated bone, the risk of radiation-induced malignancy after ECI will be expected to be less than standard external beam RT. To date, none of our patients had developed a radiation-induced malignancy and we are continuing to monitor this end point. From a health economics point of view, ECI is a relatively low-cost technique compared with the high initial cost of tumor prostheses and the cost of future revision surgery or proton beam therapy (as an alternative treatment of large pelvis sarcoma) [20].

This series is the largest in the literature with long-term follow-up. Our results confirmed the excellent oncological outcomes in terms of local control and overall survival. ECI is an excellent form of reconstruction in appropriately selected patients who are suitable for limb preservation surgery. Tumor location and extent are the most important determinants of the feasibility of ECI.

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Disclosure

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References


