En bloc resection, intraoperative extracorporeal irradiation and re-implantation of involved bone for the treatment of limb malignancies

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Abstract. Reconstruction of the defect following limb-sparing resection of malignant bone tumors is controversial and extremely challenging. Extracorporeal irradiation (ECI) and re-implantation have been used for limb salvage surgery for patients, with major advantages, including biological reconstruction, ready availability and preservation of bone stock, over replacement with a megaprosthesis. The purpose of the present study was to present our experience and details of all patients treated with this surgery. Between June 2005 and December 2014, we followed-up 23 patients with limb malignancies who were treated with en bloc excision followed by 50-Gy single dose ECI and re-implantation of involved bone segments. All cases were evaluated based on clinical and radiological examinations, complications and Musculoskeletal Tumor Society (MSTS) score. Mean follow-up period was 77.6 months (range, 17-116 months). A total of 17 patients (73.9%) demonstrated no evidence of disease, 5 (21.7%) patients succumbed to the disease and 1 (4.3%) patient was alive with the disease at the final follow-up. Local recurrence occurred in 3 patients (recurrence rate, 13.0%) in the bed outside of the irradiated graft, and 4 of the 5 patients that lost their lives did so due to associated metastatic disease. The mean value of the MSTS score was 78.8% (50-93.3%). The majority of patients demonstrated solid bony union; however, 3 patients had non-union (13.0%) and 1 had a delayed union (4.3%). Early or late complications occurred in 11 patients (47.8%). Although the complication rate (47.8%) and re-operation rate (39.1%) were high, ECI and re-implantation may be a useful and cheap technique following en bloc resection for limb salvage in appropriately selected patients.

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Introduction

The current management of musculoskeletal malignancies is limb sparing, and depending on the specific tumor, chemotherapy, surgery and radiotherapy are used in various combinations (1). Surgery is the mainstay of malignant bone tumor treatment with en bloc resection, followed by implantation of autograft, allograft or prosthesis to ensure skeletal continuity (1). Reconstruction, precise fit and stability of the materials are the main challenges to overcome. Different reconstruction methods have different advantages and disadvantages. Aseptic loosening of prosthesis and fracture of the allograft are common problems in clinical practice (2,3).

In 1968, Spira and Lubin (4) first reported intra-operative extracorporeal irradiation (ECI) and re-implantation of resected bone as a useful method of limb salvage for malignant bone tumors. However, this method does not have a widespread use according to literature; it has only been used in some cases of osteosarcoma, Ewing sarcoma or chondrosarcoma with minimal lytic destruction or predominantly sclerotic changes (5). The dose of radiation produces a dead autogenous bone graft for re-implantation and reconstruction with correct dimensions. Available results have demonstrated excellent oncological outcomes in terms of local control and overall survival (5,6). Previous reports have indicated that ECI and re-implantation of the involved bone were more beneficial than other treatments, including reconstruction using allograft or prosthesis (4-7). ECI and re-implantation is an economic technique that provides an anatomically size-matched graft for a lifelong biological reconstruction and preservation of joint mobility, thus avoiding the problems of revision due to prosthetic wear. Additionally, this technique also removes the requirement for bone banks and other problems associated with allografts, including graft rejection and risk of viral transmission (4-7). ECI and re-implantation of the involved bone was introduced to Southwest Hospital, Third Military Medical University (Chongqing, China) in 2004. The present study reported the results and complications in 23 patients who had undergone this procedure.

Patients and methods

Patients. Between June 2005 and December 2014, ECI and re-implantation of the involved bone was used in 39 patients in Southwest Hospital, Third Military Medical University. The present study retrospectively reviewed the radiographs, histology slides, medical records (history and operative procedure) and follow-up information for each patient. The present study and the treatment protocols were approved by the Research Ethics Committee of Southwest Hospital, Third Military Medical University. The inclusion criteria were as follows: i) Malignant bone tumors involving the limbs; ii) ECI and re-implantation of the involved bone had been performed; and iii) patients had complete follow-up information. Patients with aggressive benign bone tumors were excluded from the present study.

The present study included 23 patients (12 males and 11 females) with an average age of 23.4 years (range, 9-56 years). Patients were followed-up with a mean time of 77.6 months (range, 17-116 months), measured from the date of surgery. The involved bone was the femur in 12 patients, tibia in 10 patients and the humerus in 1 patient. The malignancies included 4 Ewing's sarcomas, 13 osteosarcomas, 1 chondrosarcomas, 2 malignant fibrous histiocytoma and 3 metastatic tumors (Table I). Preoperatively, the stage and extent of the tumor was evaluated using physical examination, plain radiographs, computed tomography, magnetic resonance imaging and bone scans.

Chemotherapy. All cases of osteosarcomas and Ewing sarcomas were treated with similar neoadjuvant chemotherapy protocols of three cycles at three-week intervals with the drugs of cisplatin (Qilu Pharmaceutical Co., Ltd., Haikou, China) and Adriamycin (Zhejiang Haizheng Pharmaceutical Co., Ltd., Fuyang, China). In each cycle, the patient was administered intravenously with Adriamycin (60 mg/m^2) and cisplatin (120 mg/m^2) for 2 days. Following completion of the neoadjuvant chemotherapy, re-evaluation of the stage and extent of the tumor was performed using the same preoperative imaging studies. No radiotherapy was given prior to surgery. In 1 patient, post-operative radiotherapy was given due to marginal resection (patient 3).

Surgical procedure. Informed consent was provided by the patients and/or their guardians, who were aware of the risks of the surgery and the availability of other standard methods for surgical reconstruction. Senior surgeon (Xu-quan Wang) performed all surgical procedures, with the purpose of removing the tumor with satisfactory margins. The surgical procedure included three main steps. The first step was en bloc resection of the tumor and the involved bone, along with soft tissues, through the MRI scan as far as possible (Fig. 1). Following resection, the second step involved a thorough debridement of all the tumor and soft tissues from the resected bony segment, leaving only the insertions of important ligaments and tendons. All tissue removed from the tumor was sent for histopathological examination, performed by a pathologist. Then the bone was placed into two sterile plastic bags and delivered for radiotherapy. Bone segments were irradiated with 4-6 MV photons from a linear accelerator, having a single midplane dose of 50 Gy at a rate of 1.8-2.0 Gy per min (6,7). For irradiation, each segment was placed in the center of a cylindrical plastic canister and water-equivalent material was used to fill the remaining space. The mean time from collection of the bone to its return to the operating room was 40 min. During ECI, the surgical site was prepared for re-implantation, and biopsy was performed at all osteotomy sites by the surgeon to assess the resection margins for safety. The irradiated bone segments were then re-implanted in the excision site using fixation methods, such as plates and intramedullary nailing (Fig. 2). When ECI and re-implantation was first introduced into our hospital, some irradiated bone tissue was taken for pathological examination to ensure that the inactivated bone had no live tumor cells. In recent years, cancellous bone graft harvested from the iliac crest is applied at the osteotomy site to promote bone healing, which was performed in some cases in the present study.

Each patient was managed with the standard perioperative protocol, including intravenous antibiotics until all drains and catheters were removed, prophylaxis against venous thrombosis, physical therapy and pain control. Post-operatively, patients were usually kept in bed for 5-7 days, and were then allowed to walk without weight-bearing on crutches for ~3 months. After this stage, partial weight-bearing was allowed, progressing to full weight-bearing for another 3 months according to the plain radiographs, albeit protected by one or two crutches until both osteotomies had united. Some patients were immobilized in a brace for the first 6-8 weeks to maintain knee stability and protect the implants. The majority of patients received a course of physiotherapy for 4-6 weeks following surgery.

Follow-up. Patients were followed-up at 3-month intervals within 3 years of surgery, and at 6- or 12-month intervals 3 years later, for local control, metastatic spread, function of the limb, graft union and side effects. Meanwhile, the patients keep in touch with us via email or telephone. Functional outcome was evaluated by the Musculoskeletal Tumor Society (MSTS) system at the final follow-up, which is based on six parameters, including walking ability, pain, emotional acceptance, functional activities, the use of external support and gait (8). All patients with Ewing sarcomas and osteosarcomas received postoperative chemotherapy.

Results

Oncologic outcome. The details and functional outcome of patients are summarized in Table I, which includes the notable incidence of complications and problems. At the final follow-up, the living patients had a mean follow-up time of 77.6 months (range, 17-116 months), measured from the date of surgery. Of the 23 patients included in the present study, 17 (73.9%) demonstrated no evidence of disease, 5 (21.7%) succumbed to the disease and 1 (4.3%) was alive with the disease at the final follow-up. Local recurrence occurred in 3 patients (13.0%), with the recurrence site in the bed outside of the irradiated graft, and amputation surgery was performed. A total of 3 of the patients who lost their lives with osteosarcoma (patients 3, 12 and 22) all presented with a large soft tissue swelling and unsatisfactory response to the neoadjuvant chemotherapy, and 1 had a metastatic tumor of ovarian carcinoma of the humerus shaft (patient 13). Of the 5 patients who lost their lives, 4 demonstrated disseminated disease,

Table I. Characteristics and results of the 23 patients.

										Oncologic outcome			
Case	Sex	Age, years	Diagnosis	Bone involved	Location	Resected segment length, cm	Follow-up, months	Complications	Re-operation	Relapse	Patient status	Time for graft union, months	MSTS, %
1	M	17	Malignant fibrous histiocytoma	Femur	Distal	16	76	None	None	None	NED	8	90.0
2	M	13	Ewing sarcoma	Tibia	Shaft	10	89	Part of the graft resorption	None	None	NED	13	93.3
3	M	9	Osteosarcoma	Tibia	Proximal	10	9	None	Amputation	Local recurrence, metastasis	STD	NA	66.7
4	M	32	Chondrosarcoma	Femur	Shaft	17	24	None	None	None	NED	12	86.7
5	F	15	Ewing sarcoma	Femur	Distal	12	7	None	None	None	STD	NA	70.0
6	F	25	Osteosarcoma	Femur	Distal	16	74	Non-union, Failure of metalwork	Revision fixation + graft planned	None	NED	15	80.0
7	M	15	Ewing sarcoma	Tibia	Shaft	16	116	None	None	None	NED	12	93.3
8	F	13	Osteosarcoma	Tibia	Proximal	15	92	4 cm short	Limb lengthening, resection of the metastatic lesion	Metastasis	AWD	7	70.0
9	F	18	Osteosarcoma	Tibia	Proximal	15	87	Peroneal nerve palsy, part of the graft resorption	None	None	NED	9	50.0
10	F	17	Osteosarcoma	Tibia	Distal	14	96	Minor resorption of the graft	None	None	NED	11	86.7
11	F	19	Osteosarcoma	Tibia	Proximal	15	135	Deep vein thrombosis, part of the graft resorption	None	None	NED	8	83.3
12	M	12	Osteosarcoma	Tibia	Distal	10	18	None	Amputation	Local recurrence, metastasis	STD	10	63.3

Table I. Continued.

Case	Sex	Age, years	Diagnosis	Bone involved	Location	Resected segment length, cm	Follow-up, months	Complications	Re-operation	Oncologic outcome		Time for graft union, months	MSTS, %
										Relapse	Patient status		
13	F	56	Metastatic tumor of ovarian carcinoma	Humerus	Shaft	11	43	None	None	Metastasis	STD	13	86.7
14	F	17	Osteosarcoma	Femur	Distal	18	79	Delayed healing of proximal osteotomy	Graft planned	None	NED	14	86.7
15	M	16	Osteosarcoma	Femur	Proximal	14	66	None	None	None	NED	6	90.0
16	M	49	Metastatic tumor of pulmonary carcinoma	Femur	Shaft	18	17	None	None	None	NED	11	83.3
17	F	38	Malignant fibrous histiocytoma	Femur	Distal	16	41	Non-union, stress fracture	Revision fixation + graft planned	None	NED	16	80.0
18	F	47	Osteosarcoma	Femur	Distal	17	135	None	None	None	NED	6	93.3
19	M	16	Ewing sarcoma	Femur	Proximal	17	84	None	None	None	NED	7	86.7
20	M	15	Osteosarcoma	Femur	Distal	14	83	Non-union, failure of fixation fracture	Revision fixation + graft planned	None	NED	14	43.3
21	F	52	Metastatic tumor of thyroid carcinoma	Femur	Shaft	19	38	None	None	None	NED	10	83.3
22	M	11	Osteosarcoma	Tibia	Proximal	10	23	Wound infection	Wound debridement, amputation	Local recurrence, metastasis	STD	13	70.0
23	M	16	Osteosarcoma	Tibia	Shaft	13	64	Wound infection, partial skin edge necrosis	Wound debridement, skin flap transfer	None	NED	12	76.7

AWD, alive with disease; STD, succumbed to disease; MSTS, musculoskeletal tumor society score; NED, no evidence of disease; NA, not available; M, male; F, female.

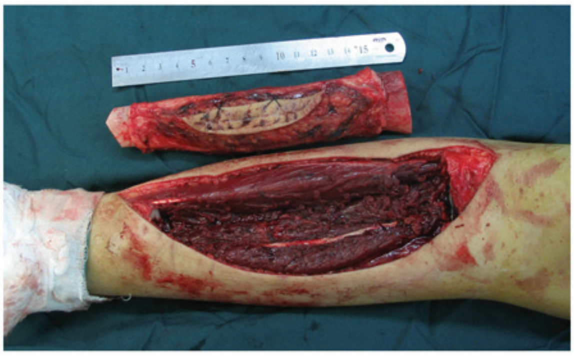

Figure 1. En bloc excision of the affected area.

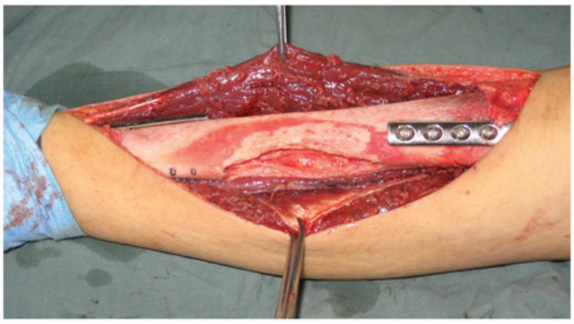

Figure 2. Re-implantation of the irradiated bone segment into the excision site using a plate.

while the remaining patient lost their life due to coagulopathy and myocardial damage due to postoperative chemotherapy (patient 5). Osteosarcoma of the proximal tibia was observed in 1 patient (patient 8) who had pulmonary metastases 72 months after surgery. This was managed by surgical resection at another hospital and chemotherapy. At the last follow-up, this patient was still alive with the disease.

Orthopedic outcome. The marginal biopsies obtained intraoperatively were adequate for assessing the resection margin, and histopathological study revealed no viable tumor cells in the irradiated bone. The mean value of the MSTS score was 78.8% (range, 50-93.3%). The majority of patients demonstrated solid bony union (Figs. 3-5); however, 3 patients (patients 6, 17 and 20) had non-union (13.0%) and were revised by exchange of the fixation implant and additional bone grafting, 2 patients (patients 3 and 5) had no union due to amputation and mortality, respectively, and 1 patient (patient 14) had a delayed union (4.3%) and underwent re-operation with autogenous bone graft. Radiological union at the osteotomy site was assessed according to literature, with graft union defined as uninterrupted external bony borders between the graft and the recipient bone except obscured or absent osteotomy lines at both junctions (9). According to this criterion, the host-irradiated bone junctions healed after a mean time of 10.8 months (range, 6-16 months) in all but 2 patients who lost their lives or required amputation before union. In the present study, it was observed that bony union tended to occur more rapidly in cases of the use of bone graft at the osteotomy site, or secure reduction and fixation using plates or intramedullary nailing.

Complications. Complications occurred in 11 patients (47.8%), including early or late complications related to tumor resection and irradiated bone reconstruction with implant. The main complications were non-union, delayed union and failure of fixation, and 3 of the 4 patients who experiences these complications were revised by exchange of the fixation device and a bone graft. All non-unions and delayed unions had united 3-5 months after re-operation, whereas resorption of the irradiated bone was observed (patients 2, 9, 10 and 11), particularly in the long follow-up cases. A total of 2 patients sustained deep vein thrombosis caused by stretching during the surgery and a long bedridden time, and a neuropraxia of the peroneal nerve potentially caused by stretching during the surgery, respectively. Both patients recovered, and partial limb function was preserved following conservative treatment for 6 months. Superficial skin infection was observed in 2 patients, and 1 patient was treated with intravenous antibiotics, debridement, frequent dressing and immobilization without removal of the irradiated bone. In the other patient, the skin necrosis was large and healed by debridement and skin flap transfer.

Discussion

The incidence of malignant bone tumor is low and usually occurs in the limbs; however, the morbidity and mortality is high (10). Currently, limb salvage is usually the first choice for treatment, which may result in increased survival rates and disease-free periods that equal those achieved with amputation, and may also offer an improved psychological acceptance and an intact limb (11). Although it is generally believed that limb-sparing surgery may lead to an increased risk of recurrence and metastasis, there is no convincing evidence that en bloc resection of the tumor leads to decreased survival time, and any higher rate of recurrence and metastasis, even in the cases with inadequate margins of resection or inappropriate adjuvant chemotherapy and radiotherapy (12). Along with the advancements in imaging and reconstruction methods, chemotherapy or radiotherapy has made limb salvage an alternative to amputation for limb malignancies.

The ideal reconstruction of the defect created following en bloc resection of the bone tumor is controversial. Tumor prostheses provide advantages, such as convenience, rapid mobilization and weight bearing capabilities (13). However, tumor prostheses incur a high financial cost and involve various complications, including infection, aseptic loosening, breakage during the long-term follow-up and a higher probability of revision surgery being required within 10 years, as reported in some studies (13-15). Allografts are a common reconstructive method utilized in some western countries, whereas this technique is forbidden in some Asian and African countries due to religious reasons (16). Although it is a biological reconstructive method, it carries a high risk of transmission of infectious diseases, fracture, tissue rejection, articular cartilage degeneration and poor union rate (3). In addition, bone banking requires substantial time, energy and money. Furthermore, as the concept of bone donation is not widely accepted in some Asian countries, allografting may be difficult to carry out.

Recycling of the resected bone segment is a beneficial alternative method that is more economic than the prosthetic

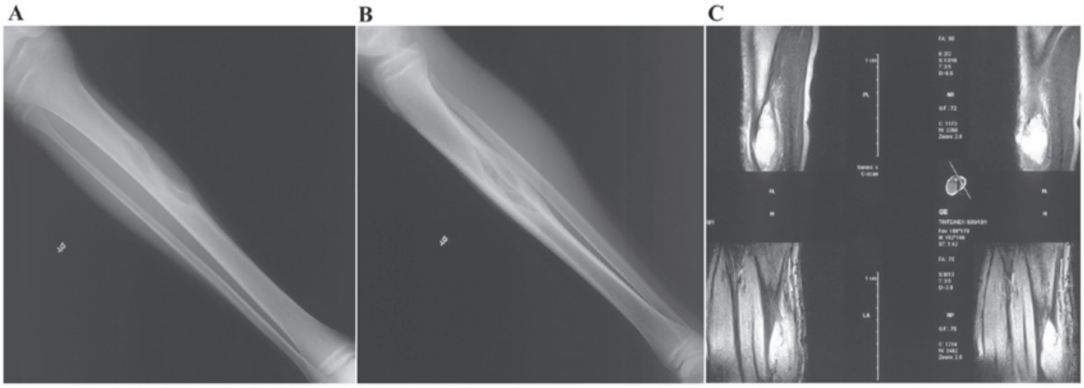

Figure 3. Radiograph and MRI scans of a 15-year old girl who had pain in the leg for 2 months. Radiographs of (A) anteroposterior view and (B) lateral view, and (C) MRI showing Ewing's sarcoma in the diaphysis of the tibia. MRI, magnetic resonance imaging.

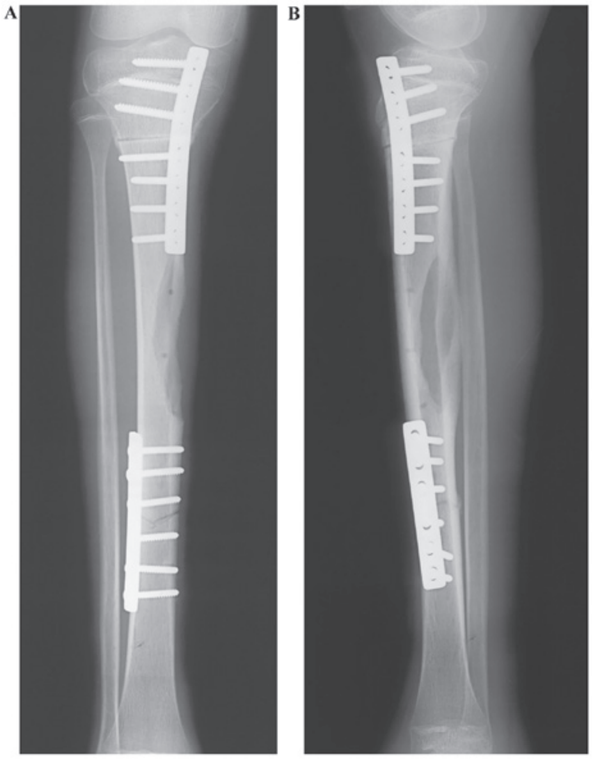

Figure 4. Post-operative radiographs following wide resection and extracorporeal irradiation. Stabilization was achieved by two plates and screws. Radiographs of the (A) anteroposterior and (B) lateral view.

Figure 5. Radiographs 3 years after surgery demonstrating union at the osteotomy site and removal of the implant. Radiographs of the (A) anteroposterior and (B) lateral view.

devices, as well as durable and more psychological accepted because of its biological nature, and may be achieved by irradiation, freezing or heating (17-19). Various methods of sterilization of tumor-bearing bone have been described. Autoclaving and boiling lead to the complete destruction of bone cells, but have the disadvantage of leading to considerable decrease in the biological and biomechanical properties of the graft compared to pasteurization and irradiation, causing severe injury to the collagen matrix and bone proteins (17). Liquid nitrogen as an effective and available cryogenic agent may be used for either tissue preservation or destruction. A quick freeze and slow thaw lead to tissue destruction, while a slow freeze and quick thaw allow for tissue preservation (18). Two studies have reported the use of liquid nitrogen to inactivate and re-implant the resected tumor-bearing segment following en bloc resection (20,21). Among them, a study by Abdel *et al* (21) questioned the effectiveness of reconstruction by re-implanting the tumor-bearing segment after recycling in liquid nitrogen in a prospective clinical study. A total of 10 patients with osteosarcoma of the femur or tibia were treated using this technology. At the final follow-up, all patients were alive and free from any signs of local or systemic recurrence, with the graft united at both junctions (21). Therefore, the authors recommend this technique as an appropriate method of reconstruction in properly selected patients. However, a larger series and a longer follow-up are required to verify the long-term efficacy of this technique. Currently, to the best of our knowledge, re-implantation of the resected tumor-bearing segment following recycling using freezing by liquid nitrogen has been described in a limited number of studies.

For bone tumors with minimal lytic destruction or predominantly sclerotic changes, ECI and re-implantation of the involved bone has several potential advantages over other methods of limb reconstruction (6,19). Firstly, the affected bone segment is removed from the body and irradiated and therefore, avoidance of radiation injury to the un-irradiated bone, muscles, joint and other healthy tissues of the body is achieved. Secondly, it is an economic technique that provides an anatomically size-matched graft for a lifelong biological reconstruction and preservation of joint mobility, thus avoiding the problems of revision due to prosthetic wear. Thirdly, this technique also removes the requirement for bone banks and some of the other problems associated with allografts, such as graft rejection and risk of viral transmission (22). Fourth, in pediatric patients, this technique may potentially avoid the growth discrepancy commonly observed in prosthetic replacement by avoiding resection of the normal growth plate and appositional bone growth from surrounding healthy bone (23).

Currently, the optimal dose of radiation has not been determined. Radiation doses of 50-300 Gy have been used in some centers with no evidence of local recurrence from irradiated bone segments (6,7,10,16,19,24,25). In a histological study, Davidson *et al* (6) demonstrated the complete eradication of tumor cells in grafts by a single radiation dose of 50 Gy, which is equivalent to 250 Gy in the conventional fraction using the linear quadratic model. They believed the radiation dose was immensely higher than that of the standard fractionated external-beam irradiation treatment for bone tumors, and there was no risk of local recurrence or of radiation-induced malignancy. They also believed that higher doses were unnecessary, take longer to administer and may increase detrimental effects to bone. Other studies have also conformed this point of view and believe this dose should be sufficient to produce a tumor elimination rate of 100% (23,26). Studies by Sabo *et al* (27) and Currey *et al* (28) have demonstrated a radiation dose-dependent reduction in strength and also suggested reduced revascularization and osteoconductive properties, thereby increasing the time to union and incorporation. Therefore, the present study used a radiation dose of 50 Gy.

When compared with other methods of limb preservation, such as megaprosthesis replacement and allograft reconstruction, there was no evidence of increased rate of recurrence with ECI in the present study or other similar studies (5,16,19,24). Furthermore, local recurrence in the irradiated segments was not observed in the present study, and seldom local recurrence has occurred in an ECI autografting over the last 20 years. In the present study, 3 recurrent cases were observed; however, the local recurrence occurred in the bed outside of the irradiated graft, most likely attributable to inadequate resection. In agreement with a study by Uyttendaele *et al* (29), the risk of local recurrence may be minimized by careful preoperative planning and staging by imaging techniques, intraoperative marginal biopsies, and the use of appropriate chemotherapy or radiotherapy regimens.

Non-union (13.0%) and delayed union (4.3%) occurred in 4 of the 23 patients in the present study. The rate of non-union and delayed union corresponded with other reports of ECI autografting of the limb (6,10,16,25,26), and were lower than those observed with reconstructions using allografts (22,30,31). Union occurred faster at the metaphyseal than at the diaphyseal junction in some cases; however, statistical tests were not performed to determine whether these differences were significant. This phenomenon was also observed in a study by Krieg *et al* (32) in ECI autografting. The authors of the present study are in agreement with Chen *et al* (24) and believe that perfect anatomical reduction, stable internal fixation and proper muscle coverage are the most important factors in promoting healing of the graft-host junction. In order to promote bone healing, cancellous bone graft harvested from the iliac crest was applied at the osteotomy site in some of the cases in the present study. Theoretically, radiological remodeling of the large ECI graft is limited, complete replacement with living bone does not occur and the graft remains a framework of dead bone that requires the long-term support of the metal implants. For these reason, some studies recommend a vascularized fibular graft to supplement the reconstruction and promote healing of the graft-host junction (6,10,33). In the present study, resorption of the irradiated bone was observed, particularly in the long follow-up cases. Therefore, it may not be appropriate to remove the implants following bone union in some of our cases, which was strongly required by patients because of religious reasons. Only longer follow-up with biopsies of the irradiated autografts could properly answer this question.

One of the drawbacks of the use of ECI autografts is the lack of material available for histopathological examination of the effects of chemotherapy and the adequacy of the resection margins. As the bone is re-implanted, the pathologist cannot examine the whole material and only has access to soft tissues, bone marrow and some small bone fragments. The surgeon must perform biopsies from the margins of the bone to overcome the issue and to define the status of the surgical margins.

In the present study, early or late complications, such as infection, non-union, fracture and resorption of the irradiated graft, occurred in 11 patients. The complication rate (47.8%) and re-operation rate (39.1%) were high; however, the functional results of patient survival were acceptable. To reduce the complication rate, several techniques, such as irradiated autograft prosthesis composites (24), use of a vascularized fibular graft to supplement the reconstruction, vancomycin prophylaxis and adequate cover of the irradiated bone, were proposed. Preoperative treatment, surgical technique, postoperative support and follow-up by a dedicated team are also major factors in achieving successful outcomes.

In conclusion, when considering the present mid-term results and overall experiences, ECI is a useful technique following en bloc resection for limb salvage when there is reasonable residual bone stock in appropriately selected patients. The patient's own bone fits perfectly to the resection site, risk of local recurrence due to tumor re-implantation is not possible with current radiation doses and complications are usually manageable. In order to confirm this, this technique should be used as part of a multidisciplinary approach, using a larger series with a longer follow-up.

References

1. Gitelis S, Bayne CO, Frank JM, Fillingham YA and Kent PM: Surgery in malignant bone tumors. Curr Probl Cancer 37: 192-197, 2013.
2. Unwin PS, Cannon SR, Grimer RJ, Kemp HB, Sneath RS and Walker PS: Aseptic loosening in cemented custom-made prosthetic replacements for bone tumours of the lower limb. J Bone Joint Surg Br 78: 5-13, 1996.
3. Matejovsky Z Jr, Matejovsky Z and Kofranek I: Massive allografts in tumour surgery. Int Orthop 30: 478-483, 2006.
4. Spira E and Lubin E: Extracorporeal irradiation of bone tumors. A preliminary report. Isr J Med Sci 4: 1015-1019, 1968.
5. Böhm P, Fritz J, Thiede S and Budach W: Reimplantation of extracorporeal irradiated bone segments in musculoskeletal tumor surgery: Clinical experience in eight patients and review of the literature. Langenbecks Arch Surg 387: 355-365, 2003.
6. Davidson AW, Hong A, McCarthy SW and Stalley PD: En-bloc resection, extracorporeal irradiation, and re-implantation in limb salvage for bony malignancies. J Bone Joint Surg Br 87: 851-857, 2005.
7. Hong A, Stevens G, Stalley P, Pendlebury S, Ahern V, Ralston A, Estoesta E and Barrett I: Extracorporeal irradiation for malignant bone tumors. Int J Radiat Oncol Biol Phys 50: 441-447, 2001.
8. Enneking WF, Dunham W, Gebhardt MC, Malawar M and Pritchard DJ: A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin Orthop Relat Res: 241-246, 1993.
9. Hsu RW, Wood MB, Sim FH and Chao EY: Free vascularised fibular grafting for reconstruction after tumour resection. J Bone Joint Surg Br 79: 36-42, 1997.
10. Muramatsu K, Ihara K, Hashimoto T, Seto S and Taguchi T: Combined use of free vascularised bone graft and extracorporeally-irradiated autograft for the reconstruction of massive bone defects after resection of malignant tumour. J Plast Reconstr Aesthet Surg 60: 1013-1018, 2007.
11. Sluga M, Windhager R, Lang S, Heinzl H, Bielack S and Kotz R: Local and systemic control after ablative and limb sparing surgery in patients with osteosarcoma. Clin Orthop Relat Res: 120-127, 1999.
12. Bacci G, Ferrari S, Bertoni F, Rimondini S, Longhi A, Bacchini P, Forni C, Manfrini M, Donati D and Picci P: Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: Analysis of 359 patients at the Istituto Ortopedico Rizzoli. J Clin Oncol 18: 4-11, 2000.
13. Heller L and Kronowitz SJ: Lower extremity reconstruction. J Surg Oncol 94: 479-489, 2006.
14. Kawai A, Muschler GF, Lane JM, Otis JC and Healey JH: Prosthetic knee replacement after resection of a malignant tumor of the distal part of the femur. Medium to long-term results. J Bone Joint Surg Am 80: 636-647, 1998.
15. Natarajan MV, Annamalai K, Williams S, Selvaraj R and Rajagopal TS: Limb salvage in distal tibial osteosarcoma using a custom mega prosthesis. Int Orthop 24: 282-284, 2000.
16. Araki N, Myoui A, Kuratsu S, Hashimoto N, Inoue T, Kudawara I, Ueda T, Yoshikawa H, Masaki N and Uchida A: Intraoperative extracorporeal autogenous irradiated bone grafts in tumor surgery. Clin Orthop Relat Res: 196-206, 1999.
17. Singh VA, Nagalingam J, Saad M and Pailoor J: Which is the best method of sterilization of tumour bone for reimplantation? A biomechanical and histopathological study. Biomed Eng Online 9: 48, 2010.
18. Bickels J, Meller I, Shmookler BM and Malawer MM: The role and biology of cryosurgery in the treatment of bone tumors. A review. Acta Orthop Scand 70: 308-315, 1999.
19. Puri A, Gulia A, Agarwal M, Jambhekar N and Laskar S: Extracorporeal irradiated tumor bone: A reconstruction option in diaphyseal Ewing's sarcomas. Indian J Orthop 44: 390-396, 2010.
20. Tsuchiya H, Wan SL, Sakayama K, Yamamoto N, Nishida H and Tomita K: Reconstruction using an autograft containing tumour treated by liquid nitrogen. J Bone Joint Surg Br 87: 218-225, 2005.
21. Abdel Rahman M, Bassiony A and Shalaby H: Reimplantation of the resected tumour-bearing segment after recycling using liquid nitrogen for osteosarcoma. Int Orthop 33: 1365-1370, 2009.
22. Donati D, Capanna R, Campanacci D, Del Ben M, Ercolani C, Masetti C, Taminiau A, Exner GU, Dubousset JF, Paitout D, *et al*: The use of massive bone allografts for intercalary reconstruction and arthrodeses after tumor resection. A multicentric European study. Chir Organi Mov 78: 81-94, 1993 (In English, Italian).
23. Hong AM, Millington S, Ahern V, McCowage G, Boyle R, Tattersall M, Haydu L and Stalley PD: Limb preservation surgery with extracorporeal irradiation in the management of malignant bone tumor: The oncological outcomes of 101 patients. Ann Oncol 24: 2676-2680, 2013.
24. Chen WM, Chen TH, Huang CK, Chiang CC and Lo WH: Treatment of malignant bone tumours by extracorporeally irradiated autograft-prosthetic composite arthroplasty. J Bone Joint Surg Br 84: 1156-1161, 2002.
25. Sabo D, Bernd L, Buchner M, Treiber M, Wannenmacher M, Ewerbeck V and Parsch D: Intraoperative extracorporeal irradiation and replantation in local treatment of primary malignant bone tumors. Orthopade 32: 1003-1012, 2003 (In German).
26. Kotb SZ and Mostafa MF: Recycling of extracorporeally irradiated autograft for malignant bone tumors: Long-term follow-up. Ann Plast Surg 71: 493-499, 2013.
27. Sabo D, Brocai DR, Eble M, Wannenmacher M and Ewerbeck V: Influence of extracorporeal irradiation on the reintegration of autologous grafts of bone and joint. Study in a canine model. J Bone Joint Surg Br 82: 276-282, 2000.
28. Currey JD, Foreman J, Laketić I, Mitchell J, Pegg DE and Reilly GC: Effects of ionizing radiation on the mechanical properties of human bone. J Orthop Res 15: 111-117, 1997.
29. Uyttendaele D, De Schryver A, Claessens H, Roels H, Berkvens P and Mondelaers W: Limb conservation in primary bone tumours by resection, extracorporeal irradiation and re-implantation. J Bone Joint Surg Br 70: 348-353, 1988.
30. Donati D, Di Liddo M, Zavatta M, Manfrini M, Bacci G, Picci P, Capanna R and Mercuri M: Massive bone allograft reconstruction in high-grade osteosarcoma. Clin Orthop Relat Res: 186-194, 2000.
31. Cara JA, Laclériga A and Cañadell J: Intercalary bone allografts. 23 tumor cases followed for 3 years. Acta Orthop Scand 65: 42-46, 1994.
32. Krieg AH, Davidson AW and Stalley PD: Intercalary femoral reconstruction with extracorporeal irradiated autogenous bone graft in limb-salvage surgery. J Bone Joint Surg Br 89: 366-371, 2007.
33. Muramatsu K, Fukano R, Ihara K, Iwanaga R and Taguchi T: Reconstruction of the proximal humerus by combined use of extracorporeally-irradiated osteochondral graft and free vascularized fibula following resection of Ewing sarcoma. J Plast Reconstr Aesthet Surg 63: 2177-2180, 2010.