



INTRA-OPERATIVE EXTRA-CORPOREAL RADIATION: A LIMB SPARING OPTION IN BONE TUMORS

Surgery

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ABSTRACT

Background: Delivery of lethal dose radiation to resected tumor bearing bone, and reimplantation of the resultant dead autogenous graft, is an option for limb preservation. We report an analysis of patients treated likewise.

Methods: This is an analysis of 25 patients from a prospectively maintained database; who underwent extra-corporal radiation therapy between March 2012 and December 2015. Patients were evaluated for complications, delay in adjuvant therapy, bone union, recurrences, functional outcome and deaths.

Results: The median age of patients was 12 years. 18(72%) had osteosarcoma, 6(24%) had Ewings sarcoma and 1(4%) patient had adamantinoma. The involved bone was femur in 12, tibia in 11, radius in 1 and humerus in 1 patient. 6 patients had complications. Adjuvant chemotherapy was started within 3 weeks of surgery in 20 out of 24 patients requiring adjuvant. There were 5(20%) recurrences: 4 distant and 1 local. Mean time to all recurrence was 13.8 months (3-36). 2 patients died, both due to disease progression. Most patients have a satisfactory functional outcome.

Conclusion: Extracorporeal radiation therapy is an oncologically safe option for bone tumors.

KEYWORDS

INTRODUCTION

Recent years have witnessed major advancements in the multidisciplinary management of bone tumors. Amputations are preferably abandoned and the contra-indications of limb salvage are by and large relative. At the same time the need for a suitable bone and soft tissue reconstruction after resection has become more evident. Various methods have been used for bone reconstruction, including arthodesis, rotation plasty, endoprosthesis replacement, distraction osteogenesis, allografts or alloprosthetic composites and autografts. Autologous sterilized tumor bone provides a perfect fit, avoids problems of prosthesis wear and holds a promise for long term bone longevity. In 1968 Spira and Lubin first described the use of extracorporeally irradiated bone as an autograft in 2 patients¹. Further studies showed that a single dose of 50Gy was sufficient to obtain adequate tumor kill² and that there is a dose dependent reduction in revascularisation and osteoconductive properties of bone, thereby, affecting bone union and incorporation³. It was soon proven by various biomechanical studies that extracorporeal radiation provides the best tumor kill with minimal alteration of structural integrity of bone when compared with other available methods of bone sterilization². Furthermore, the proposed advantages of such an approach include immediate postoperative joint mobilisation, sparing of surrounding normal tissues of radiation, avoidance of second primaries, avoidance of second surgery, and avoidance of need of bone banks or issues with allograft procurements.

We present an analysis of 25 appropriately selected patients treated in a tertiary care centre in South India with resection of tumor bearing bone, curettage of all gross tumor of the bone, delivery of lethal dose of radiation to such bone and its reimplantation.

AIMS AND OBJECTIVES

To report an analysis of patients treated with extra-corporeal intra-operative radiation therapy for bone tumors as a method of limb salvage with focus on surgery related complications, resultant delay in adjuvant therapy, bone union, recurrences, functional outcome using Musculoskeletal Tumor Society (MSTS) scoring system and deaths.

Methodology

Twenty five patients went limb salvage surgery using intra-operative extra-corporeal radiation between March 2012 and December 2015 in a tertiary care centre in South India. A retrospective analysis of these patients was done from a prospectively maintained database. Appropriate staging investigations and histopathological evidence of malignancy were obtained for all patients. Neoadjuvant and adjuvant therapies were administered as per institutional policy. MRI was used pre and post neo-adjuvant therapy to assess extent of tumor in terms of involvement of soft tissues, bone marrow and neurovascular bundle, response to neoadjuvant therapy and to determine line of resection of bone. A gross margin of 2-3 cm was aimed for.

Enblock resection of bone containing tumor was done with appropriate gross margins. Proximal and distal stump marrow was sampled for frozen section analysis to confirm negative marrow margins. Resected bone was then transferred to a separate sterile trolley away from the field and the main operative trolley. The bone was cleared off all the soft tissues including periosteum and marrow under strict surgical asepsis. This soft tissue was sent for pathological analysis to determine percentage viable tumor remaining after neo-adjuvant therapy. When in doubt, the nearest soft tissue was sent for frozen analysis for confirmation of negative margins.

The resected bone was then lavaged with vancomycin and normal saline. It was then transferred to radiation suite wrapped in vancomycin soaked mops, draped in sterile surgical drape in a special plastic container. All empty space in the container was filled with saline soaked surgical cotton pads to eliminate air. A single fraction of 50 Gy radiation was delivered to the specimen by 2D conventional technique, using two parallel-opposed antero-posterior and postero-anterior fields with 6 MV photons. The specimen then transferred back to operative suite.

The marrow was then removed by reaming and the specimen was lavaged using pulsed lavage system to remove any residual marrow. Fibular graft was used till December 2013. Following an incidence of vascular injury while harvesting fibular graft in one patient, the institution policy was changed and bone cement was used in the later period. Bones were then approximated using extra-medullary internal fixation using minimal possible screws in the treated bone.

Post operatively the joint was mobilised immediately and weight bearing started as appropriate to the site and fixation used.

Patients were then followed up as per standard follow up protocol for bone tumors.

Patients were evaluated for surgery related complications, resultant delay in adjuvant therapy, bone union, recurrences and deaths. Mann Whitney U test was used to assess difference in bone union times.

The functional status was assessed at follow up visit using the Musculoskeletal Tumor Society (MSTS) scoring system.

RESULTS:

The median age of study patients was 12 years (1-34). There were 10(40%) males and 15(60%) females.

18(72%) patients had osteosarcoma, 6(24%) had Ewings sarcoma and 1(4%) patient had adamantinoma.

The involved bone was femur in 12(48%) [osteosarcoma -11(91.67%); ewings sarcoma- 1(8.33%)]; tibia in 11(44%) [osteosarcoma - 5(45.45%), ewings sarcoma -5(45.46%), adamantinoma -1(9.09%)]; radius in 1(4%) (ewings sarcoma) and humerus in 1(4%) (osteosarcoma) patient.

Figure 1: Bone involved with histology

	Osteosarcoma	Ewings sarcoma	Adamantinoma
Femur 12(48%)	11(91.67%)	1(8.33%)	
Tibia 11(44%)	5(45.45%)	5(45.45%)	1(9.10%)
Radius 1(4%)	1(100%)	-	
Humerus 1(4%)	1(100%)	-	
Total 25(100%)	18(72%)	6(24%)	1(4%)

7 patients had previous local surgery (curettage- 1, incision biopsies-5, trial excision-1). Trucut biopsy was used for tissue diagnosis in all other patients.

24(96%) patients received neoadjuvant chemotherapy. The mean preoperative hemoglobin was 11.3g/dl (8.8-14.9).

The mean length of bone resected was 18.57cm (9-30). Fibular graft was used in 11(44%), and bone cement was used in 14(56%) patients. 3(12%) patients required gastrocnemius cover. Femoral nerve was sacrificed in 1 case due to tumor encasement.

Bone and marrow margins were free of tumor in all cases.

6 patients had surgery related complications.

1. Implant fracture occurred in a patient with osteosarcoma of femur, 5 months after ECRT. Refixation was done with a 6 hole plate across fracture line.
2. A girl with adamantinoma of lower third tibia with history of

curettage twice before developed non- union at proximal diaphyseal end. It was treated with contra-lateral iliac crest bone graft around 14 months after ECRT.

3. Non union, skin breakdown and exposure of plate occurred in a 9 year old girl with Ewings sarcoma of tibia. Plate removal and gastrocnemius flap had to be done in her 6 months following ECRT. Healing occurred uneventfully in cast following the procedure. She also developed a bed sore which responded to conservative measures.
4. Wrist dropped occurred in a girl in whom the radial nerve was shaved off the tumor leading to planned positive margin. Almost whole of proximal 2/3rd of radius was involved by tumor in this patient, including head. Annular ligament was cut and fixation was done using K wire. She was also diagnosed to have implant resorption at a later date.
5. A 12 year old child with osteosarcoma of tibia was diagnosed to have hematoma at surgical site 3 months after ECRT. It was drained and a gastrocnemius flap used for cover.
6. There were a total of 3 cases of surgical site infections (2 of which were reported in above mentioned patients- a. in patient with adamantinoma of tibia with non union and b. in patient with Ewings sarcoma with skin break down and non- union). One patient required secondary suturing for wound gaping. All infections settled with appropriate antibiotics.

All complications were noticed in patients who were operated before December 2013, except for the case in which implant fracture occurred, which was operated in May 2015.

Second surgery was required in 5 patients, including one for illizarov removal in a 1 year child with Ewings sarcoma tibia. She developed complete graft resorption and eventually underwent tibialization of fibula.

Figure 2: Complications and second surgery

Complication	N	Diagnosis	Bone augmentation	Second surgery
Implant fracture	1	Osteosarcoma femur	Bone cement	Refixation with 6 hole plate
Non-union	2	a) Adamantinoma tibia (diaphyseal end) # b) Ewings sarcoma tibia (both diaphyseal ends)^	a) Fibular graft b) Fibular graft	a) Contralateral iliac crest bone grafting b) Plate removal and gastrocnemius flap
Wrist drop	1	Ewings sarcoma radius*	Nil	-
Wound hematoma	1	Osteosarcoma tibia	Fibular graft	Hematoma drainage and gastrocnemius flap
Wound gaping	1	Osteosarcoma femur\$		
Implant resorption	2	a) Ewings sarcoma radius* b) Ewings sarcoma tibia+		
Wound infections	3	a) Osteosarcoma femur\$ b) Adamantinoma tibia# c) Ewings sarcoma femur^	a) Fibular graft b) Fibular graft c) Fibular graft	a)Secondary suturing
Bedsore	1	Ewings sarcoma femur^	Fibular graft	
				Illizarov removal (Ewings sarcoma tibia)+ : n=1
				Total -5
#- same patient, *- same patient, ^- same patient, \$- same patient, +- same patient				

The mean bone union time was 29.93 weeks (6-118) for diaphyseal end and 15 weeks (6-44) for metaphyseal end. When fibular graft was used the mean bone union time was 58.8 weeks (20-118) for diaphyseal end and 19.33 weeks (8-30 weeks) for metaphyseal end. When bone cement was used for bone augmentation the mean bone union time was 15 weeks (6-25) for diaphyseal end and 13.92(6-44) for metaphyseal end.

Figure 3: Bone union at diaphyseal and metaphyseal ends

	Diaphyseal or metaphyseal end	Mean bone union time range Weeks(range)
All patients (n=25)	Diaphyseal end (n=30)	29.93 weeks (6-118)
	Metaphyseal end (n=20)	15 weeks (6-44)
Fibular graft (n=11)	Diaphyseal end (n=14)	58.8 weeks(20-118)
	Metaphyseal end (n= 8)	19.33 weeks(8-30 weeks)
Bone cement (n=14)	Diaphyseal end (n=16)	15 weeks(6-25)
	Metaphyseal end (n=12)	13.92(6-44)

When bone unions at diaphyseal end was considered, there was a statistically significant difference between fibular graft and bone cement (p=0.036). However, the result could have been affected by data of single patient with Ewings sarcoma who had non union at both diaphyseal ends of tibia (118 weeks for each end) with delayed healing after plate removal and gastrocnemius flap. When data of this single

patient was excluded, the difference was not significant statistically (p=0.234).

When union at metaphyseal end was considered, there was no statistically significant difference in time required between the use of fibular graft or bone cement (p=0.520).

Adjuvant chemotherapy was started within 3weeks of surgery in 20 of the 24 patients requiring adjuvant chemotherapy.

3(12%) patients received adjuvant radiation.

Mean follow up was 14.14 months at the time of analysis (1-36 months). One patient had lost to follow up after being diagnosed to have distant recurrence There were 5 (20%) recurrences: 4(16%) distant and 1(4%) local. Mean time to all recurrence was 13.8 months (3-36).

Of the patients who developed a distant recurrence one had solitary lung metastasis and underwent metastatectomy; one was lost to follow up. Two patients died both due to disease progression at last follow up. The patient who developed local recurrence underwent wide excision for the same and was disease free at last follow up.

Of the 22 patients who were available for analysis at last follow up, the mean follow up was 15.05 months (1-36 months). 20 out of the 22 patients had full range functional limb mobility without additional

support. One patient with tumor involving upper end of tibia with cortical break and who underwent knee arthodesis underwent limb lengthening procedure.

DISCUSSION:

Surgery for local control is an important integral part of management of bone tumors. Management of bone tumors has witnessed a great change over time. We have traversed from an era where amputation was the norm, to an era where almost all contra-indications for limb salvage are relative. Reconstruction after resection of bone involved by tumors is challenging in young immature skeletons with dynamic growth and narrow marrow cavity. Of all the available options in reconstructive armamentarium, reimplantation of extracorporeally irradiated bone belonging to the patient itself is quite lucrative.

In our series extracorporeal bone irradiation has been done in almost all indismissible bones so far of the body with satisfactory results. Bone as long as 30 cm could be resected and incorporated. Residual disease on assessment of tumor cleared from bone before subjecting it to radiation was found to be present in 4.17% patients. This is inclusive of a case of adamantinoma and is comparable to the percentage residual disease reported in literature of around 11%⁶.

Non union occurred in 2(8%) of our patients, inclusive of 3 (6%) junctions between healthy bone and graft. This is comparable to reported rates of non-union in literature of around 16%^{7,8}. Krieg et al., in his series of 16 patients treated with extra-corporeal radiation reported that union is faster at metaphyseal ends compared to diaphyseal ends⁷. Similar finding was seen in our series. All non-unions occurred at diaphyseal ends. This was similar to reported 3 non-unions, all at diaphyseal ends in a series of 12 patients analysed by Ajay puri et al⁸. Both of our patients were salvaged – one with contra-lateral iliac crest bone graft and the other with plate removal and gastronemius flap. The reported rates of non –union with allograft, after inter-calary resection has been as high as 63%^{9,10}.

There was no significant difference in union time at diaphyseal or metaphyseal ends, when augmentation with fibular graft was compared with that with bone cement (ignoring union time of a of single patient with fibular graft, in whom healing was significantly delayed at both diaphyseal ends). There is a paucity of trials addressing this. However successful use of bone cement, thereby with avoidance of fibular graft will prevent an extra surgical procedure on contra-lateral limb with its associated risks and results from our series seem fairly encouraging.

Implant fracture is another feared complication in irradiated grafts. In our series, it happened in one patient. It was treated with internal fixation and the patient is doing well after that. This phenomenon is also known to happen with the use of allografts with a variable incidence^{8,11}. However long term follow up of these patients is required for long term integrity and strength of graft.

Implant resorption was diagnosed radiologically occurred in two patients (8%). Minor and severe osteolysis following extra-corporeal radiation is known. It is probably due to inadequate replacement of dead graft with live bone^{12,13,14}. In our series graft osteolysis occurred in a patient with Ewings sarcoma of radius, in whom whole of proximal 2/3rd of bone was involved. Revascularisation is likely to be inadequate in view of relatively large segments of graft. The other patient was a year old child with Ewings sarcoma tibia, who was treated with ECRT and Illizarov. Use of vascularised graft in selected patients would probably avoid this complication. Surgical site infection can be quite disastrous with the consequence of graft loss⁸. It is known to occur with allografts as well as autografts. Incidence ranges from 0-17% for autografts and 6-17.6% for allografts^{8,9,10,15,16,17,18,19}. Wound infection occurred in three (12%) of our patients, one with wound gaping. All settled with appropriate antibiotics. Re-suturing was done for patient with gaping. Local recurrence following extra-corporeal radiation should not occur in the irradiated graft^{8,13,15}. Most solitary local recurrence after extra-corporeal radiation, in literature, were salvageable^{8,13}. There was a single local recurrence in our series. It was in soft tissues away from the graft. It was successfully treated with wide excision.

None of the patients in our series required subsequent amputation in view of complication or recurrence.

CONCLUSION:

Extracorporeal radiation therapy is an oncologically safe option for limb salvage in appropriately selected patients with bone tumors. It achieves effective tumor kill and has satisfactory functional outcome. Long term follow up is required for assessment of the viability of graft in long run.

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