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Patient-Specific High-Dose Single-Fraction Extracorporeal Irradiation in Osteosarcoma: Technique and Clinical Outcome

ÇİNİ, Nilsu [1], ABUL, Mehmet Süleyman [2], PEKYÜREK VARAN, Melike [1], YETMEN DOĞAN, Özlem [3], ÖZDEN, Ayşe Sevgi [1], GÜMÜŞTAŞ, Seyit Ali [4], KARABULUT GÜL, Şule [1],

[1] Department of Radiation Oncology, Kartal Dr Lütfi Kırdar City Hospital, Istanbul Turkey
[2] Department of Orthopedics and Traumatology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul Turkey
[3] Department of Radiation Oncology, Haydarpaşa Numune Education and Research Hospital, Istanbul Turkey
[4] Department of Orthopedics and Traumatology, Acıbadem Health Group, Fulya Hospital, Istanbul Turkey

Correspondence:
Nilsu Çini Department of Radiation Oncology, Kartal Dr Lütfi Kırdar City Hospital, Istanbul Turkey
nilsucini@gmail.com

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ABSTRACT

Purpose: Osteosarcoma is a rare malignant bone tumor that is difficult to manage with traditional methods. The technique of delivering single fraction high-dose radiation directly to the bone, extracorporeal irradiation (ECI), minimizes radiation-induced damage to adjacent healthy tissues. Planning the ECI technique as patient-specific as possible and mimicking the real radiotherapy process will increase the potential advantages. In this article, we aimed to present our patient-specific designed ECI technique managed by a multidisciplinary team of orthopedics and traumatology and radiation oncology clinics and 6 years follow-up data.

Methodology: As a limb preservation therapy approach, a 14-year-old female patient diagnosed with osteosarcoma underwent en-block resection, ECI with a total prescribed radiation dose of 75 Gray and reimplantation of the left femur bone.

Findings and Conclusion: Our case results revealed that patient-specific ECI is fully effective on 6 years of local recurrence control and disease-free survival, with no postoperative complications and concomitant preservation of limb functionality.

Keywords: *osteosarcoma, extracorporeal irradiation, patient-specific technique, high-dose.*

INTRODUCTION

Malignant bone tumors (MBTs) occur mostly in children and adolescents and account for less than 1% of all cancers diagnosed each year [1]. 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 [2]. The management of MBTs has improved with advances in pathology, radiological imaging, surgical techniques, chemotherapy and radiation therapy technologies. Approximately twenty years ago, patients were evaluated with the option of amputation, but with the developing treatment techniques, most patients are evaluated within the framework of limb preservation protocols [3].

The limb preservation therapy process will be possible with a multidisciplinary approach formed by the effective use of surgery, chemotherapy and radiotherapy. As a multidisciplinary approach method, extracorporeal irradiation (ECI) of the surgically removed tumorous bone fragment followed by reimplantation. Usually, after neoadjuvant chemotherapy, the ECI technique is used in limb salvage therapy for bone sarcoma if the bone is of reasonable quality [4]. Still, Extracorporeal irradiation is a relatively rare method used in the treatment of MBTs [3]. The ECI approach was first reported in 1968 [5]. There is no consensus among previous studies regarding the irradiation dose to be delivered during ECI [4]. Some studies have reported the use of single-fraction doses of 300 Gray (Gy) to ensure that all tumor cells are killed, while others suggest that a single-fraction of 50 Gy is sufficient for this purpose [6–8].

In the external beam radiotherapy technique using photon beam and conventional radiotherapy schemes, irradiating such high doses per fraction defined for MBTs will have serious biological side effects. In the conventional radiotherapy approach for MBTs, applications in the dose range of 1,8 - 2,0 Gy per day and 45 - 70 Gy total have been reported [9]. Malignant bone tumors are resistant to radiation, therefore, studies and techniques that apply high doses both in total dose and dose per fraction have been emphasized. To increase local control, it is possible to increase the fraction / total to high doses in radiotherapy applied to MBTs with Proton or Ion beam therapy [10]. The Children's Oncology Group / American Osteosarcoma Study Group 0331 / EURAMOS-1 study recommended 60 - 66 Gy of radiotherapy after surgery for positive microscopic margins and 70 Gy for definitive local control [9].

Among patients who received radiotherapy, local tumor control and overall survival rates were approximately 78% and 75% when radiotherapy was administered after total or subtotal resection, respectively, compared with only 40% and 25% after biopsy alone [11,12]. In some cases, high rates of complications have been reported due to single-fraction high-dose irradiation of the bone tissue removed from the body for the ECI technique [13]. The main problems relate to mechanical integrity, infection, avascular necrosis and graft resorption on the bone after radiation [14,15].

Case series of centres that applied ECI to increase local control in low radiosensitivity MBTs have been published. It has been reported that ECI is technically feasible in the management of MBTs such as osteosarcoma and Ewing sarcoma and provides good local control and short-term survival rates [3]. A similar study in osteosarcoma, chondrosarcoma, and Ewing sarcoma reported the efficacy of ECI as an alternative reconstruction method with excellent long-term local control in selected patients. Overall survival was comparable to other published series [2].

In addition to these series, a review of 18 patients who received at least 80 Gy single-fraction ECI to tumor-bearing cranial bones to restore skull function and form after resection of bone-invasive meningioma was published. The results reported similar recurrence rates and lower rates of infection requiring explants compared to the largest series of cranioplasty in meningioma [16]. The therapeutic goals in the management of primary bone tumors include optimising local control and overall survival, maintaining long-term function, and minimizing late toxic effects. [2].

In this study, we aimed to present the patient-specific design process of ECI applied to a 14-year-old female patient diagnosed with osteosarcoma as part of a limb-preservation therapy approach, in collaboration with the Orthopedics and Traumatology and Radiation Oncology Clinics, along with the six-year follow-up data.

MATERIAL AND METHODS

A 14-year-old female patient complained of left femur-centered pain for 2 months before diagnosis. Under the Orthopedics and Traumatology clinic follow-up, had a magnetic resonance imaging (MRI) scan in September 2018. The MRI scan reported as; a focus of faint, limited contrast enhancement measuring approximately 37 x 34 x 61 mm, causing heterogeneous signal intensity in the bone structure observed in the lateral localization in the medial metaphysodiaphyseal region of the tibia, is noteworthy. A large-scale periosteal reaction is observed in the immediate vicinity, and it is noted that it is accompanied by cystic soft tissue components measuring 30 x 25 mm and extending towards the soft tissue. At this level, there is a horizontal pathological fracture line in the lateral section of the tibia in the bone structure. Her diagnosis reported with the possibility of Osteosarcoma in the medial of the left femur. See diagnostic preop MRI images in Figure 1. Osteosarcoma was reported in the pathological examination of the sample taken during the operation.

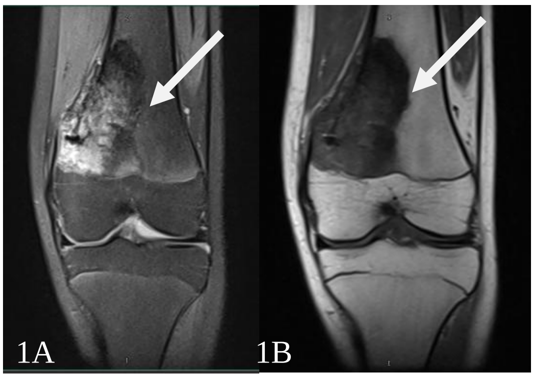

Figure 1: Preop and pre-ECI MRI of the case. 1.A. proton T2 sequence. 1.B. T1 sequence. Reported possible tumoral structure is indicated by the arrow.

The patient received neoadjuvant chemotherapy between September 2018 and December 2018. Limb-sparing surgery was performed approximately four weeks after the chemotherapy cycle. The patient underwent wide local excision surgery followed by an ECI in January 2019. Also, following the operation and ECI, the patient received adjuvant chemotherapy in 2019.

Surgical techniques

The patient was placed in the supine position under general anesthesia, and after appropriate preparation with an antiseptic solution and covering for embolism and infection prophylaxis, an anteromedial incision was made starting from the distal left thigh and ending at the medial side of the proximal tibia. After passing the skin, subcutaneous tissue and fascia, the distal femur was exposed. The epiphyseal line was preserved and the distal femur was resected with osteotomes. The soft tissues were sent to the pathology laboratory for pathological examination. The resected distal femur was sent to the Radiation Oncology department for extracorporeal radiotherapy.

Since the pathological examination resulted in negative surgical margins, a graft was taken from the same side with an approximately 13 cm fibula osteotomy for autograft application. Then, the irradiated distal femur and the fibula were fixed to their anatomical location with a distal femur medial plate. Hemostasis control was provided. A Hemovac drain was placed. The skin, subcutaneous tissue and fascia were closed. The operation was terminated.

Postoperatively, the patient was allowed full weight bearing according to clinical and radiological progression.

ECI techniques:

The surgery consisted of en-bloc resection of the tumor and bone along with the soft tissues. The bone flap was then wrapped in wet sterilised gauze, placed in a sterile plastic package and transferred to the Radiation Oncology Clinic. The sterile package containing the bone flap was embedded and placed in the middle of the rice-filled box.

The rice embedding process helps immobilize the bone material at the same position during computerized tomography (CT) imaging and irradiation on the linear accelerator table, and to perform high-accuracy dose calculations in a stabilized volume, especially for the ECI technique.

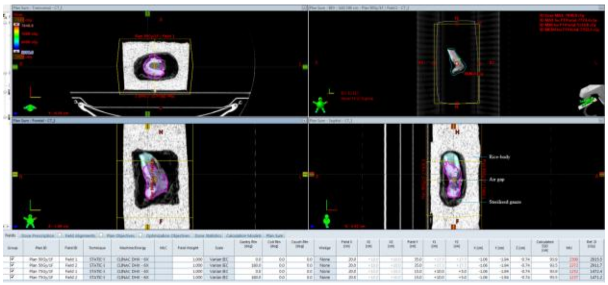

Figure 2: The sum of the patient-specific designed plans and the beam angle, field size, SDD and MU information corresponding to each irradiation field. Plan 50 Gy / 1F initiates the Primer plan. Plan 75 Gy initiates the Boost plan. Sections from 3 different axis and the image of structure outlines in beam eye view of Primer plan 50 Gy /1F on gantry angle 0. Contour lines for CTV (Magenta), PTV (Cyan) and Body (skin default rendering).

For irregular surfaces compensator / bolus materials are used to simulate tissue and modulate the dose distribution around the target [17]. Rice packing as a tissue equivalent compensator is used in many cases to achieve a homogenous dose distribution and dose buildup at the skin surface [18]. A study designed to investigate the contribution of rice-compensators to dose homogeneity in total body irradiation. It was reported that dose measurement in phantom with compensator-rice indicates that ±5% uniformity is attainable throughout the body [19]. Also studies revealed that rice-filled medium provides dose homogeneity for the target coverage, as well as reproducibility and immobilization for the irradiation design with highly irregular surfaces, like extremity and digit involvement [17,18].

In this case, we created a rice-based body simulation and thickness to provide distance for dose build-up and to increase the dose enough to cover the bone flap entirely.

Simulation CT images of the box had been taken by General Electric Bright Speed CT with a 2,5 mm slice thickness to be used in the treatment planning system (TPS). These images were transferred to the TPS. The rice-filled box was introduced to the system as the body volume and the radiation oncologist defined the Clinical Target Volume (CTV) and Planning Target Volume (PTV) on the CT images. Magenta for the CTV, Cyan for the PTV, and the default skin rendering for the Body were selected colours for the contours.

The sterilised gauze was at least 2,8 - 3,0 cm thick, 1,0 - 1,65 cm air gap between the bone and the sterilised gauze, and there was 0,2 cm air space around the sterilised gauze package. Rice-body thickness around the package was varying 2,5 to 4,5 cm corresponding to treatment fields. (Figure 2)

Two plans were designed with 6 MV photon beams to be irradiated in the Varian DHX linear accelerator device. Treatment plans were calculated with PBC - version 10.0.28. Primer plan, with a larger irradiation field, designed to irradiate the PTV with 50 Gy. Two gantry angles, at 0 and 180 degrees, were defined and the intensity of doses was divided equally between these angles. Dimensions of the Primer plan were, Field X = 20 cm, Field Y = 35 cm. Source skin distance (SSD) was 93.9 at the gantry angle 0. Monitor units (MU) calculated for each field: gantry 0 was 2398 MU, gantry 180 was 2372 MU. (Figure 2)

The second plan was the Boost plan, with a smaller irradiation field, designed to irradiate the CTV with an additional 25 Gy and to increase the dose to 75 Gy. Two gantry angles, for 0 and 180 degrees, were defined and the intensity of doses was divided equally between these angles. Dimensions of the Boost plan were, Field X = 20, Field Y = 15. The primary plan was closed in the Y direction up to the CTV boundary. Source skin distance was 93.9 cm at the gantry angle 0. Monitor units calculated for each field: gantry 0 was 1252 MU, gantry 180 was 1237 MU. Presented in Figure 2.

Plan normalizations for both plans were set at 100%. We summed the two plans and examined the doses received by the target volumes in the dose-volume histogram (DVH). Defined CTV was 194,3 cc; minimum dose 64,05 Gy, maximum dose 77,24 Gy and mean dose 74,80 Gy. Defined PTV was 214,2 cc; minimum dose 51,10 Gy, maximum dose 77,24 Gy and mean dose 73,52 Gy. (Figure 3) Global maks dose of the sum plans was 78,49 Gy and was placed on the rice-body. We neglected this while CTV and PTV were receiving adequate doses.

Total irradiation time consists of placement of the bone flap embedded rice-filled box on the table, SSD set-up on the box and irradiation of the two plans took 12-17 minutes. During ECI, the operative site was prepared for reimplantation and biopsies were performed at all osteotomy sites to assess the status of the resection margins. After ECI was completed, the sterile package of the bone flap was opened in the operating room.

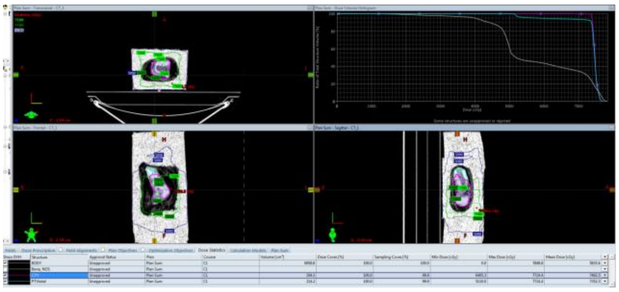

Figure 3: Dose-volume histogram (DVH) and dose distributions of the sum of the patient-specific designed plans. Sections from 3 different axis and DVH. Isodose lines for 50Gy, 74 Gy and 75Gy. Contour lines for CTV (Magenta), PTV (Cyan) and Body (skin default rendering).

RESULTS

The patient was followed up with an MRI at the 7th month and 5th year postoperatively. Post-op 7th-month MRI important highlights are reported as follows. There is effusion in the left coxofemoral joint space. In a case with an operation history, edematous changes in the skin and subcutaneous tissue and T2 signal increases are also present. (Figure 4.A. and 4.B.) And the post-op 5th year MRI reported as follows. Instrument material placed in surgery is observed in the distal diaphyseal section of the femur. Heterogeneous, increased signal and fluid intensity are observed in the prepatellar area, and the appearance is compatible with prepatellar bursitis. Effusion was observed in the intra-articular distance. (Figure 4.C.)

The PET report dated April 2024, at the post-op 5th year, was interpreted as "No findings were detected that could be evaluated in favor of recurrence-metastasis of the primary tumor." (Figure 4.D.) In April 2025, the 6th postoperative year, we contacted the patient, and she reported using the limb with full weight-bearing and had no complaints. The patient also reported that she went to another hospital close to her home for follow-up. The patient completed 6 years postoperative and post-ECI with disease-free survival and local control, with no postoperative complications and concomitant full preservation of limb functionality. Patient data were collected between September 2018 and April 2025.

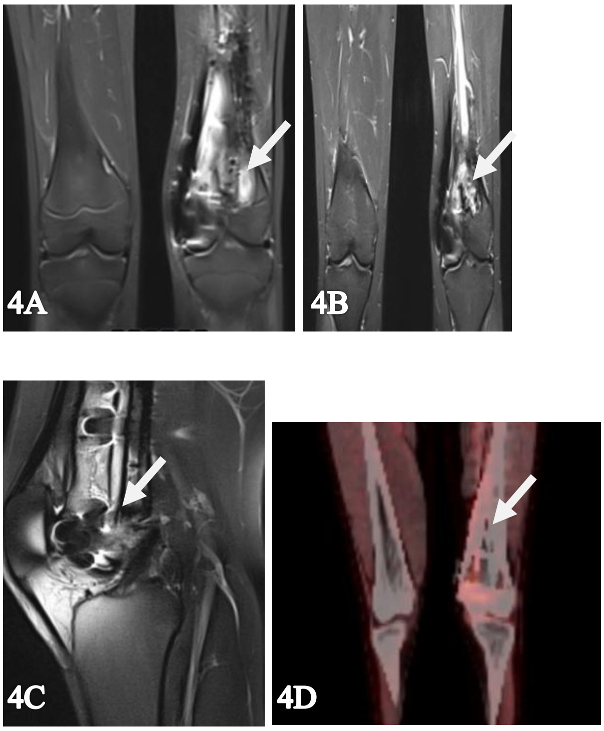

Figure 4: Sections from different postoperative imaging of the case. 4.A. Postop 7th month MRI coronal (proton T2 sequence). 4.B. Postop 5th year MRI coronal (proton T2 sequence). 4.C. Postop 5th year MRI sagital (proton T2 sequence). 4.D. Postop after 5th year PET coronal (proton T2 sequence). ECI-applied target-bone indicated by the arrow.

DISCUSSION

Since MBTs are frequently observed in children and adolescents, the limb preservation approach, instead of amputation, is a more moderate and safer option from an oncological perspective. Extracorporeal irradiation technique offers a limb preservation approach for the management of MBTs. The ECI technique, which allows high-dose radiation to be delivered directly to the affected bone in a single fraction, minimizes the damage to the surrounding healthy areas. It helps to protect the soft tissue, lymphatic and vascular structures, and the muscular system around the bone from early and late radiation side effects.

Many studies have been designed to optimize the dose to be prescribed in the ECI approach. A study was conducted with mature cattle bones to observe the mechanical side effects of the ECI technique at different doses. They hypothesised that increasing the dose of radiation applied to the autograft might have adverse effects on the collagen found within bone, causing adverse changes in its elastic and viscoelastic mechanical properties. Bones irradiated from 50 Gy to 300 Gy were examined for these properties in line with the hypotheses. They reported no significant changes in all of these mechanical properties with an increasing level of irradiation dose. And concluded that the overall mechanical effect of high-dose ECI on bone, even at 300 Gy, is negligible. Consequently, the ECI dose can be maximised to reduce the risk of local tumour control [4,17].

Although the irradiation dose range allows high doses in many studies, we used a maximum dose of 75 Gy in our ECI application. As recommended at the Children's Oncology Group American / Osteosarcoma Study Group 0331 / EURAMOS-1 study, 60 - 66 Gy of radiotherapy after surgery for positive microscopic margins and 70 Gy for definitive local control [9]. While doses reaching 300 Gy are being discussed, other studies have also been conducted on these radioresistant tumors.

In a cranium ECI study, doses of 80 Gy and above were not associated with high rates of complications such as bone resorption [16]. In particular, it is known that tumorous long bones are completely cleared of living osteosarcoma tumor cells with 50 Gy [20, 21]. Hence, higher doses may not be necessary despite the anoxic irradiation conditions, while increasing the risk of radiation-induced complications [22, 23] On the other hand, dose range between 50-80 Gy provides a short irradiation time, which reduces detrimental effects in bone strength or revascularization [1]. Prescribing within this dosage range is considered most effective for ECI technique and clinical outcomes; like side effects and overall survival.

Some studies have shown good survival and tumor control rates and reduced complications with similar and lower dose ECI. A review of previous studies applied the ECI technique in the MBTs reported postoperative complications ranging from 13% to 40% and local recurrence ranging from 4% to 26%, respectively [1,2,15].

A study applying 50 Gy ECI to a series of 101 patients with Ewing sarcoma reported overall local control rates of 93.8% in the pelvis and 100% in the extremities. The 5-year cumulative overall survival was 81.9% [2]. Another study applying 50 Gy ECI to a series of 14 patients with MBT reported local control of 79% [3]. In our case, patient-specific designed ECI showed an effectiveness on local recurrence control, no postoperative complications, and 6 years of disease-free survival.

In most reported ECI techniques, the bone flap in a sterile package is placed directly on the linear accelerator patient irradiation table, and a bolus material is placed on top of the sterile package sometimes, the field size opened to cover the entire package and SDD was set to 100 cm. Irradiation is performed for a time period corresponding to the prescribed dose and at the appropriate dose rate. Same irradiation procedure defined and applied for limb bones and skull bones [1,2,16,18]. In these cases, there is no CT simulation or patient-specific treatment planning data obtained for the ECI protocol.

In our case study we simulated the entire external radiotherapy process, immobilization, CT simulation, target volume definition, treatment planning in TPS, DVH reading, set-up and irradiation. For the patient-specific ECI plan, the total dose delivered in two segmented plans. The primer plan delivered 50 Gy to the PTV. The Boost plan delivered 25 Gy to the tumor resection area defined as the CTV. Total dose at CTV was increased to 75 Gy. When a high dose was desired for a smaller tumor volume, the boost plan design proved to be a good solution and shortened the application time.

In the era of high technology and personalized precision oncology, patient-specific designed ECI technique will have a great impact on treatment precision and quality. The time spent where the bone tissue remains separate from the body during the ECI application process is important. However, with a professional organization and up-to-date technology, the entire ECI can be designed with high accuracy within 20-25 minutes.

We presented the patient-specific ECI technique design for a 14-year-old patient diagnosed with osteosarcoma on the left femur and effects on local control and overall survival. As a limitation of our study, only telephone communication with the patient was possible, as she currently continues her follow-up at another healthcare institution closer to her residence. Our study has presented good disease and survival control consistent with the literature. Additionally, it has demonstrated a patient-specific ECI design adapted to all real radiotherapy processes, and a practical ECI workflow.

CONCLUSION

Extracorporeal irradiation helps minimize the damage to surrounding healthy tissue while delivering high-dose radiation directly to the target tissue, the bone. It is also an optimal technique that offers significant therapeutic advantages such as improved local tumor control, prolonged disease-free survival, and preservation of limb functionality. In the future, focus should be on innovations that will enable the application of patient-specific ECI techniques in more advanced radiotherapy devices, deliver higher doses to the target more safely and in a shorter time, and develop faster workflows.

Conflict of Interest

There are no conflicts of interest and no acknowledgements.

ACKONOWLEGMENT

This article was presented as an oral presentation at the V. Bilsel International Korykos Scientific Research and Innovation Congress, and only the abstract was published in the congress booklet.

ETHICAL APPROVAL

Ethical approval has been received from the scientific research ethics committee of City Hospital. Ethical approval no: 2025/010.99/16/10. The patient has been informed and has agreed to be included in this article.

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