

# Effect of Combination Chemotherapy and Radiotherapy in the Management of a Pathological Fracture in High-grade Osteosarcoma with Limb Salvage Procedure – A Case Report

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## Abstract

**Introduction:** Osteosarcoma (OS), the most common primary bone tumor, is known to be relatively a radioresistant tumor. Pathological fracture in OS denotes its aggressive biological response and so it was considered a contraindication to limb salvage in earlier days. Radiotherapy has its role only in cases that are inoperable or have poor prognostic factors. In recent years, there have been major advances in the management of pathological fractures in high-grade OS (HGOS). This case report is about the effect of combination chemotherapy and radiotherapy in the management of pathological fracture in HGOS with limb salvage procedure.

**Case Report:** A 19-year-old male with pain and swelling in his right lower third of thigh and inability to walk for 3 months was diagnosed as a case of OS right distal femur with a pathological fracture. Open biopsy was done which confirmed the diagnosis as HGOS, staged Enneking IIb. He was treated with a combination of chemotherapy, external beam radiotherapy, tumor resection, and modular resection prosthesis.

**Results:** There were no immediate, early, and late complications. At the end of 1½ years, his functional recovery is good and he has reached more than 70% of the right knee functions. He has no signs of recurrence at present. He has got a better quality of life and functional activity with the prosthesis compared to what an amputated limb can produce.

**Conclusion:** Pathological fracture in OS is not a contraindication to limb salvage. Radiotherapy can be used in combination with chemotherapy and limb salvage surgery in HGOS with a pathological fracture. This combination treatment helps in increasing the chances of limb sparing surgery with good local control and tumor necrosis rate. The new knowledge that radiotherapy can be effective when used with chemotherapy has shown good result in our case.

**Keywords:** Osteosarcoma, pathological fracture, external beam radiotherapy, limb salvage, custom modular prosthesis.

## Introduction

Osteosarcoma (OS), the most common primary malignant bone tumor, accounts for 25–45% of all skeletal malignancies. In OS, pathological fracture can be the mode of presentation in some patients, or it can also occur during the course of treatment. Earlier days, amputation was the standard method for the treatment for OS with pathological fracture. Whereas, in recent years, there have been major advances in the management of pathological fractures in high-grade OS (HGOS). The comprehensive treatment comprising high-dose chemotherapy, limb salvage surgery, especially modular prosthesis, and selective use of radiotherapy has resulted in a significant reduction in limb

amputation rate. Here, we present a case of HGOS with pathological fracture treated successfully in our hospital with combination of neoadjuvant chemotherapy and pre-operative external beam radiotherapy (EBRT) followed by custom modular prosthesis.

## Case Report

A 19-year-old male patient, with complaints of pain and swelling in his right lower third of thigh and inability to walk for 3 months, underwent native treatment and was later diagnosed as a case of OS right distal femur (right). X-ray right femur distal third showed mixed osteosclerotic and osteolytic lesion with periosteal reaction with fracture line

extending obliquely. He was diagnosed as a case of OS distal femur right with pathological fracture.

Computed tomography (CT) and magnetic resonance imaging of the affected part, CT chest, and open biopsy were done. Biopsy report showed tumor tissue composed of spindle cells with pleomorphic hyperchromatic nuclei, islands of cartilage with malignant osteoid formation, which confirmed the diagnosis as HGOS, and staged Enneking IIb. Although bone scan is mandatory, as the facility is not available in our hospital, it was not done. The patient was immobilized with POP-above-knee cast initially, later replaced with detachable splint. Preoperatively, 3 cycles of chemotherapy

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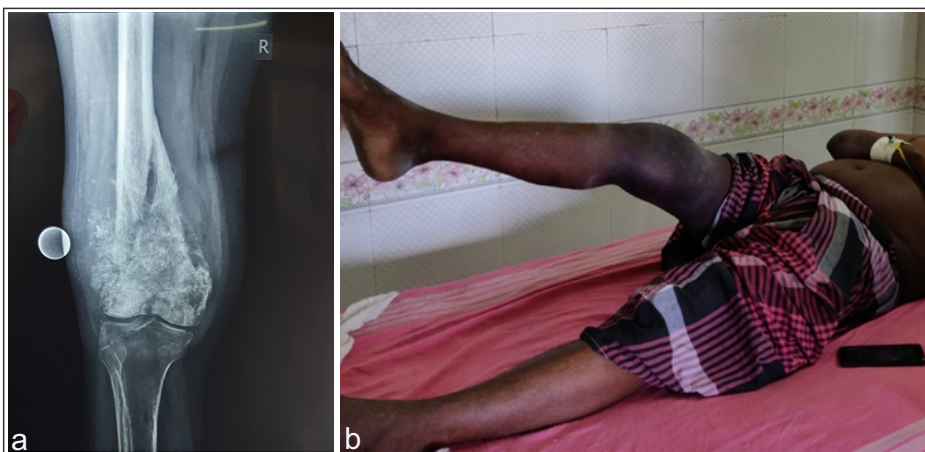


**Figure 1:** X-ray right thigh showing osteosarcoma with a pathological fracture.



**Figure 4:** Post-operative scanogram.

(IAP regime – ifosfamide, adriamycin, and cisplatin) and EBRT of total 5000 CGy (200 CGy for 5 sittings/week, total 5 cycles) were



**Figure 2:** (a and b) X-ray and clinical picture after pre-operative chemo and external beam radiotherapy showing fracture union and consolidated antitumor effects.



**Figure 3:** (a and b) Intraoperative resection of tumor and fitting of femoral modular resection prosthesis.

given to the local part.

Considering the favorable response to pre-operative chemo and radiotherapy assessed, clinically by decrease in pain and size of the swelling, no tenderness or yielding at the fracture site, ability to do straight leg raising without splinting, radiologically by sclerosis, and new bone formation at the fracture site, we planned for limb salvage procedure in the form of modular resection prosthesis surgery for the affected bone.

The limb salvage procedure was done successfully through an anteromedial approach to the right thigh and knee area. The entire tumor area along with 4 cm of normal bone from proximal stump was resected assuring tumor clearance. Distally, the knee joint and 0.5 cm of proximal tibia were resected. Intraoperative frozen section study from the proximal stump confirmed a satisfactory tumor clearance. The resected tumor was replaced with femoral modular resection prosthesis and fixed with bone cement. Resected specimen – macroscopic study showed 16 × 11 × 10 cm sized tumor, occupying medullary cavity extending to all surfaces, without muscle involvement, lying 4 cm from the proximal resected margin which means adequate clearance. Microscopically, there was no residual tumor tissue. There was more than 90% necrosis of tumor cells. The patient was given 3 more cycles of the same drug (adjuvant chemotherapy).

Physiotherapy and mobilization were done for 3 weeks. Static quadriceps exercises from the 3rd POD, non-weight-bearing walking with walker and knee brace from the 8th POD, suture removal on the 16th POD, and full weight-bearing by the end of 3 weeks. Continuous passive mobilization was started from the 2nd week, 0–30° initially and gradually increased by 10° per week and attained 60° flexion at the time of discharge.

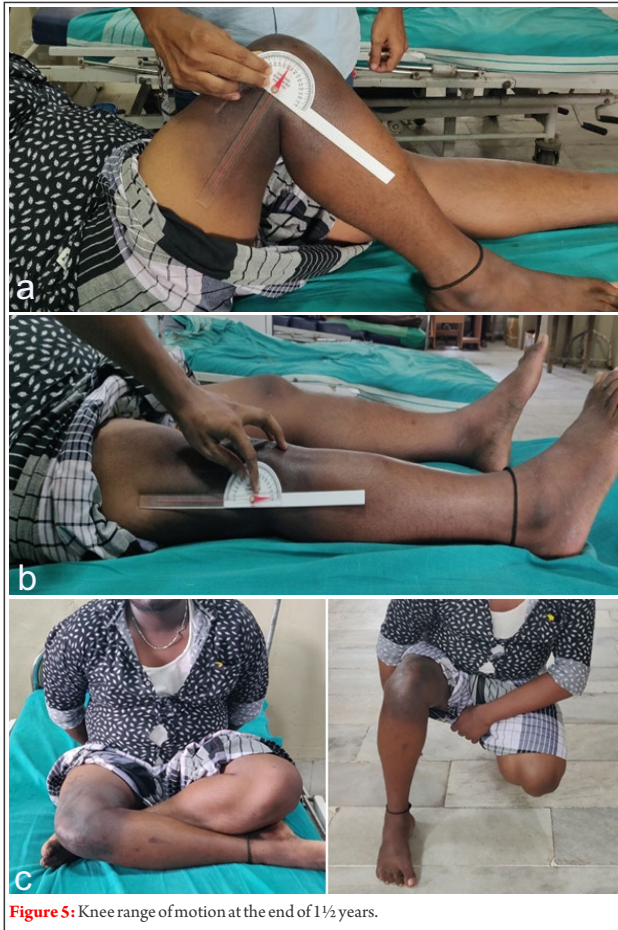
The patient was followed with monthly visits for the first 6 months and then once in 3 months, to be continued up to 2 years. Later, it will be annual check-up periodically. In each visit, he was assessed for any evidence of local recurrence or metastasis by means of proper history taking, clinical, radiological assessment of the operated area, laboratory investigations, and CT chest.

At the end of 1½ years, his functional recovery is good and he has reached more than 70% of the right knee functions. The patient is satisfied completely with the procedure and has no signs of recurrence at present.

## Discussion

Pathological fracture in OS denoted aggressive biological response and so for a long time, it was considered a contraindication to limb salvage for two reasons: (1) Dissemination of tumor cells into adjacent tissues and adjacent joints, from





**Figure 5:** Knee range of motion at the end of 1½ years.

the hematoma and (2) damage to the microcirculation facilitating metastases [1]. The 5-year survival in these patients was lower than those without a fracture [2]. Hence, historically, amputation was the procedure of choice for these injuries to ensure optimal outcome in terms of recurrence and survival.

Studies [3, 4] have shown that OS patients with pathological fractures have a high rate of local recurrence and a low survival rate and the occurrence of a pathological fracture in a primary bone tumor was associated with an impaired survival rate. The fracture probably might have been due to the aggressive nature of the tumor and early amputation was advised due to the risk of local and distant tumor spread, Finn et al. [5, 6].

Bacci et al. [7] and Kim et al. [8] proved that the tumor volume is higher in patients with a pathological fracture than in patients without pathological fracture and it was concluded that tumor volume is an independent negative survival predictor in OS [9].

Many other surgeons believed that immediate aggressive removal of the tumor might halt the fracture-induced disease

progression and the surgical option for all OS patients with a pathological fracture was early amputation [10, 11]. Even with early limb ablation, the patient's long-term survival rate was only 10–20%. The amputation surgery also brought serious physical dysfunction to patients, seriously affecting their quality of life [12].

In recent years, there have been major advances in the management of pathological fractures in HGOS by the way of comprehensive treatment comprising high-dose chemotherapy, limb salvage surgery, especially custom modular prosthesis, and selective use of radiotherapy which have resulted in a significant reduction in limb amputation rate.

### **Role of neoadjuvant chemotherapy and limb salvage in OS with pathological fractures**

Most of the surgeons accept limb salvage as a treatment for localized HGOS (such as Enneking Stage IIa OS), but the presence of a pathological fracture (Stage IIb OS) makes the surgical decision difficult. Recently, neoadjuvant chemotherapy and limb salvage have become an acceptable alternative for treating non-metastasizing HGOS with pathological fracture due to the acceptable clinical outcome [13, 14, 15, 16].

Recent studies [17] and from a meta-analysis [18], comparing limb salvage with ablative surgery for pathological fractures in HGOS, there was no difference in the outcome after limb salvage, including tumor recurrence, the development of metastases, and overall survival in patients who presented with a fracture.

Jaffe et al. [9] and Ebeid et al. have shown that 84% of the pathological fractures have potential to heal during the preoperative chemotherapy. Furthermore, the fracture union correlated with a high tumor necrosis percentage, thus indicating good response to chemotherapy.

Many studies conclude that the pathological

fracture is usually a low-energy process with less soft-tissue contamination than conventional fractures, and surgery within certain tissue planes is possible. The efficacy of chemotherapy and healing of fractures in these special cases are considered as supportive factors for limb salvage surgery [19].

Hence, pathologic fractures of primary bone sarcoma should not be considered as an absolute indication for amputation. Patients should be treated with neoadjuvant chemotherapy coupled with limb salvage surgery. On comparing limb salvage group with amputation group, the quality of life, function, and physical limitations were superior in the former group.

### **Role of radiotherapy in OS**

Although OSs are known to be relatively radioresistant, definitive radiotherapy has a role in cases that are unresectable or those with poor prognostic factors or as an alternative in patients in whom definitive surgery is not possible or is refused. However, recently, neoadjuvant chemotherapy followed by local therapy (surgery alone and/or radiotherapy) and maintenance chemotherapy remain the current standard of care for the treatment of non-metastatic HGOS.

Machak et al. [20], the largest study by far, where modern neoadjuvant chemotherapy and EBRT were given in combination for local control of non-metastatic OS of the extremities. The study included 31 patients treated with definitive radiotherapy to a median dose of 60 Gy and concluded that when used after effective induction chemotherapy, radiotherapy can be a reliable modality to control local disease and preserve limb function in OS of the extremities.

Further, after initial chemotherapy, the potential usefulness of radiotherapy for non-metastatic OS of the extremities may be predicted to be high, medium, or low. Our case belongs to the high usefulness category as the primary tumor was sensitive to induction chemotherapy, and the radiotherapy effectively consolidated antitumor effects. The chances to achieve durable local control and excellent limb function were highest (100%) in this subgroup of patients.

Caceres et al. [21] noted complete pathological response in 80% of patients of

OS treated by chemotherapy and 60 Gy of radiation therapy (RT) and noted excellent functional outcomes in 86% of the patients. Dincbas et al. [22] used a pre-operative RT dose of 35 Gy in 10 fractions followed by limb sparing surgery in 44 patients. The tumor necrosis rate was 90% in most of his patients and the 5-year overall survival and local recurrence in his patients were 48.4% and 97.5%, respectively.

### Limitations of the study

1. The individual contribution of RT to the

total tumor necrosis cannot be assessed separately.

2. Addition of radiotherapy distorts the anatomical planes, thus making the surgical access difficult.

3. The success of reproducibility depends on various patient factors and is possible only in a tertiary care center with a skilled surgical team, experienced pathologist, and radiation oncology unit.

4. It is premature to determine the outcome of our study without a long follow-up period.

### Conclusion

Thus, this combination of neoadjuvant chemotherapy and external beam radiotherapy, followed by limb salvage procedure and proper adjuvant chemotherapy helped us for this successful outcome in our case. This combination treatment helps in increasing the chance of limb sparing surgery with good local control and tumor necrosis rate. The new knowledge that radiotherapy can be effective when used with chemotherapy for OS awaits further study.

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