



## Osteosarcoma - The outcomes of neoadjuvant chemotherapy and surgery

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**Abstract :** Objectives To describe an institutional experience of osteosarcoma of extremities and to determine whether neoadjuvant chemotherapy would allow limb salvage surgery yet maintain local disease control. Methods Between April 2011 to April 2013, 41 patients were seen in Department of Radiation Oncology with osteosarcoma. They were retrospectively analysed with respect to age, gender, site of tumor, stage, histology, surgery, post surgical histopathology response and condition on last follow up. Results There were 19 males and 8 females with age ranging from 16 yrs to 60 yrs. The most common site was around the knee joint (distal femur) and uncommon sites were pelvis, L3, scalp and gingiva. The commonest histology was high grade osteosarcoma. 14 patients were excluded from the study as they had no treatment or had metastatic disease. Out of the other 27 patients who were included in the study, 5 had amputation, 18 underwent limb salvage surgery and 4 had wide local excision. The follow up ranged from 3 to 27 months. 7 patients were disease free at the last follow up and 9 patients developed metastases. 1 patient was found to have local recurrence during follow up. The sites of metastases seen were lung, bone, inguinal nodes and right ventricle. Conclusion The combination of advances in surgical techniques, improved imaging modalities to accurately document tumor extent and the effect of neoadjuvant chemotherapy has made limb salvage surgery as the standard of care in the management of osteosarcoma. Comprehensive multidisciplinary approach has transformed it from a disease with a modest long term survival in which at least 23 of the patients will be cured. Successful management of osteosarcoma with limb salvage surgery is a challenging problem in the developing world.

**Keyword :** Osteosarcoma, Neoadjuvant Chemotherapy, Limb Salvage Surgery

### INTRODUCTION

Osteosarcoma is the most common primary bone tumor, defined by the presence of malignant mesenchymal cells which produce osteoid or immature bone. The incidence of osteosarcoma is 2 to 3 million per year worldwide. The most common site is the metaphysis of distal Femur [42%]. Until 1980s, amputation was considered the only way to achieve local control, after which limb sparing surgeries have developed(1). Studies done by Bacci et al comparing limb salvage and amputation showed a median follow-up of 10.5 years. The five-year disease-free survival and overall survival

rates were 60.7% and 68.5%, respectively, with no significant difference between the two groups(2). The incidence of local recurrence was the same for patients treated by either amputation or limb salvage and correlated significantly with the margins of surgical excision and the histological response to chemotherapy. The outcome for patients with local recurrence was significantly worse than those who had recurrent disease with metastasis only. Use of imaging like MRI and CT scan has helped the surgeons in accurately defining the extent of the tumor thereby plan tumor resection. Neoadjuvant chemotherapy (NACT) evolved in Memorial Sloan-Kettering Cancer Center as part of waiting for the making of customized endoprosthetic device in limb salvage surgery(3). Administration of neoadjuvant chemotherapy improved survival rates and has been proven effective in increasing the proportion of limb salvage surgeries. It also helps to prognosticate the patients by assessing the percentage of necrosis in the post-operative histopathology. Multimodality treatment with neoadjuvant chemotherapy followed by limb salvage surgery is the present standard of care. This retrospective study was done to assess the response to neoadjuvant chemotherapy in terms of percentage of tumour necrosis in the post operative specimen which in turn reflected on the prognosis of the disease.

### MATERIALS AND METHODS

#### Patient selection

Retrospective study of patients, diagnosed to have Osteosarcoma between April 2011 and April 2013 who attended the outpatient clinic of the Department of Radiation Oncology.

#### Treatment Details

Data of patients who had completed treatment (either surgery or neoadjuvant chemotherapy followed by surgery with or without radiation therapy) were included in the analysis. Data of the patients with either metastases or those patients who had defaulted was excluded.

#### Data

The data includes details of age, sex, location of the tumour, stage, type of tumour, grade, initial size of the tumour clinically and radiologically, treatment taken, details of neoadjuvant and adjuvant chemotherapy, post operative histopathological response, margin status after surgery and patient's condition at last follow up.

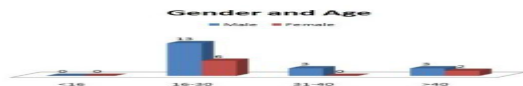
#### Analysis

The percentage of patients who had limb salvage surgery after NACT was calculated. Disease status of the patients at last follow up was documented. Locoregional recurrence and

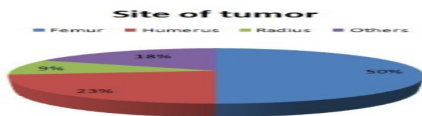
metastases at last follow up was compared between the groups which received NACT and who had upfront surgery.

## RESULTS

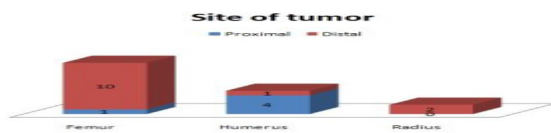
### Patient Characteristics



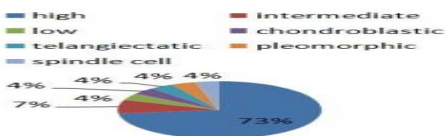
**Fig 1 shows male preponderance and most common age group is between 16-30years (68%) Site of Tumor**



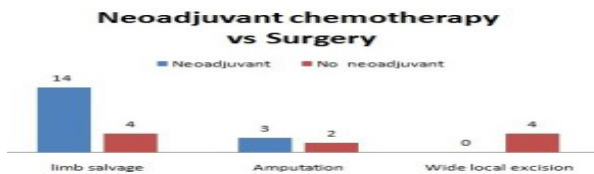
**Fig 2 shows that distal Femur was the commonest site of tumor Histology of Tumor**



**Fig 3 shows that 73% had high grade histology Noadjuvant chemotherapy with surgery**



**Fig 4 shows that limb salvage was maximum with neoadjuvant chemotherapy (14/17 Response of neoadjuvant chemotherapy on post surgical histopathology**



**Fig 5 shows the effect of neoadjuvant chemotherapy on the post surgical histopathology in terms of the percentage necrosis, showing that there was no residual tumor in 2 patients and 80 to 95% necrosis in 6 patient**

### Response on neoadjuvant chemotherapy on the surgical margins



**Fig 6 shows that 14/17 patients who received NACT had negative and close surgical margins and 3 patients had positive margins**

**Fig 8 shows that lung was the most common site of metastasis (62%). In the limb salvage group, 1 patient had local recurrence, 2 patients had metastases on follow up and 2 patients were detected to have metastases while on treatment. In the amputation group 2/5 patients had metastases on Follow up**

The follow up period ranged from 3 to 27 months with the median of 13 months. Seven patients were disease free at the last follow up and 9 patients developed metastases. One patient was found to have local recurrence during follow up.

## DISCUSSION

Studies done by Zhang et al showed that the 5-year-survival rate was 78.5% in the combined therapy. In our study, the most common age group was the 16-30 yrs (68%) with a male preponderance (70%). Studies have shown that the commonest age group is 15-20 yrs and in age group >60 yrs with a higher male to female ratio (4).

The most common site was the distal Femur [41%]. The commonest histology was high grade type [73%]. Studies show that high grade histology is common in the second decade of life (5).

The effect of neoadjuvant chemotherapy was studied with respect to surgery, post surgical histopathology and the surgical margins. The current practice of neoadjuvant chemotherapy with platinum and anthracyclines with/without high dose Methotrexate has been proved to improve the adequacy of surgery leading to feasibility of more limb salvage surgeries thereby decreasing local recurrences (1,2). In our study out of 18 patients who had limb salvage surgery, 14 patients received neoadjuvant chemotherapy (82% vs 18%) showing that neoadjuvant chemotherapy contributes to increased rate of limb salvage surgery. Neoadjuvant chemotherapy regimens with 2 drug and multidrug regimens have been analysed and in the EOJ study and concluded that both have the same effect in non metastatic osteosarcoma (6).

The response of neoadjuvant chemotherapy on post surgical histopathology in terms of necrosis was studied, which showed that there was no residual tumor in 2 patients and 80 to 95% necrosis in 6 patients. Among the patients who received neoadjuvant chemotherapy in our study, 82% had negative or close margins while 18% had positive margins. Response to chemotherapy is defined by histologic appearance in the resected specimen (4). The most important prognostic variable for patients with osteosarcoma of the extremity was tumor necrosis evident following preoperative chemotherapy (5). Five-year survival rates for patients with an extremity sarcoma and a "good" response to chemotherapy (defined as 90% necrosis in the surgical specimen) are significantly higher (71-80%) than for those with a lesser response (45-60%). group (surgery and chemotherapy) and 35.1% in the non-combined therapy group (unfinished surgery or chemotherapy). Local recurrence rate was 16.6% in limb salvage surgery with combined therapy group (90 cases) and 38.1% in limb salvage surgery with non-combined therapy group (42 cases). The local recurrence is related to the surgical margin (7). Our study showed that definitive radiotherapy was received by 9 patients out of the total 12 patients who had close or negative margins after surgery. 3 patients defaulted treatment. 1 patient received palliative radiotherapy for metastases. Studies done have concluded that local control rates for combined surgery and RT were significantly better than those for RT alone (48% vs. 22%,  $p=0.002$ ) (8). For majority of patients surgery remains the local treatment of choice. Radiotherapy is indicated in unresectable tumors and as a palliation for symptomatic metastases. The commonest site of metastases was the lung (62%) in our study. The other sites of metastases were the right atrium, inguinal node and bones. In the limb

salvage group 1 patient had local recurrence, 2 patients had metastases on follow up and 2 patients were detected to have metastases while on treatment. In the amputation group 2/5 patients had metastases on follow up. Clinically detectable metastatic disease at initial diagnosis occurs in less than 20% of patients with high-grade osteosarcoma and predicts a poor outcome with long-term survival rates between 10% and 40%(9). In our study, at mean follow up of 13 months 7 were disease free, 9 had metastases and 1 had local recurrence.

## CONCLUSION

The combination of advances in surgical techniques, improved imaging modalities to accurately document tumor extent and the effect of neoadjuvant chemotherapy has made limb salvage surgery as the standard of care in the management of Osteosarcoma. Adequate surgical margin is important for limb salvage, since local recurrence rates are increased in margin positive patients. Tissue necrosis is an important predictor of systemic disease after chemotherapy thus affecting the survival. Comprehensive multidisciplinary approach has transformed it from a disease with a modest long term survival in which at least 2/3 of the patients will be cured. Successful management of Osteosarcoma with limb salvage surgery is a challenging problem in the developing world.

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