



Original Research Article

The correlation of prognostic factors and clinical outcomes in patients with osteosarcoma – An observational study

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ABSTRACT

Context: Osteosarcoma is characterized by the production of malignant osteoid. It arises typically in the adolescent age group.

Aims: The purpose of this study is to analyze the impact of various prognostic factors on survival in osteosarcoma patient admitted in our institution.

Settings and Design: Retrospective observational study of 10 years duration from 2007 to 2017

Methods and Materials: There were 66 patients in the records. As a part of the staging work up, CT and MRI of the local part and CECT CHEST were performed. All patients received adriamycin and cisplatin with or without Ifosfamide, and PCVE regimen.

Statistical analysis used: IBM SPSS Statistics version 20. Survival and percentage of necrosis was correlated by Spearman Rank correlation.

Results: Sixty six patients were included in this study. The median survival of patient who underwent limb salvage surgery (LSS) was 28 months and that of patient underwent amputation was 17 months. No statistically significant survival advantage present between the two group ($p=0.68$). There is a statistically significant difference in percentage of necrosis in patient who receive neoadjuvant chemotherapy if ifosfamide is added to the regime ($p=0.006$). Spearman Rank correlation revealed that there was a strong positive Correlation (0.418) between the percentage of necrosis and survival. The correlation was statistically significant ($p = 0.02$).

Conclusions: LSS in osteosarcoma is a safe alternative to amputation. Response to chemotherapy, with regards to necrosis correlates well with survival, thus clearly emphasizing the role of chemotherapy in the management of these tumors.

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1. Introduction

Osteosarcoma is a primary mesenchymal tumor that is characterized by the production of malignant osteoid.¹ It arises adjacent to growth plates, typically in children and adolescents.² Osteosarcoma follows a bimodal distribution, with first peak in the late adolescent and young adult period and a second peak during or after the 6th decade of life. Multimodality management of these tumors including aggressive multi agent systemic therapy and surgery in the form of limb salvage surgery (LSS) pose a great challenge

to the treating multimodality team because patients usually present in an advanced stage in India. The purpose of this study is to analyze the impact of various prognostic factors and chemotherapy on survival outcomes in osteosarcoma patient admitted in our institution.

2. Materials and Methods

This is a retrospective observational study of 10 years duration from 2007 to 2017. Data collection was done from previous medical records of patients treated in our institution for osteosarcoma. There were 66 patients in the records. As a part of the staging work up, a routine hematological and biochemical investigation, X-ray, CT

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and MRI of the local part, nuclear bone scan and contrast enhanced computed tomography of chest were performed. In some cases PETCT is done for metastatic work up. PET/CT is more accurate than a bone scan in detecting bone metastasis. Biopsy was done via the planned incision. Osteosarcoma patients received adriamycin and cisplatin with or without Ifosfamide, and some patients received PVCE regimen (Cisplatin, Vincristine, Cyclophosphamide, Etoposide). Adriamycin dose was 75mg/m² in three divided doses for three days and cisplatin 100 mg /m² in three divided doses for three days. Ifosfamide 2000 mg/m² iv over 3 hrs with mesna given. Ifosfamide is added to chemotherapy regimen when there was poor clinical and radiological response post 2 to 3 cycle of adriamycin and cisplatin chemotherapy or if post operative necrosis in the specimen was less. If disease is metastatic at presentation in addition to above regimen etoposide 100mg/m²/day iv is given. In general, preoperatively three cycle of neoadjuvant chemotherapy is given and assessed for limb salvage surgery and post operatively three or more adjuvant cycle are given based on tumour necrosis. Statistical analysis was performed using IBM SPSS Statistics version 20. Correlation between survival time and percentage of necrosis was determined by Spearman Rank correlation. Significance level was fixed as 5% ($\alpha = 0.05$). Various clinical data were analyzed to know about their prognostic significance and their impact on overall median survival and event-free survival.

3. Results

A total of 66 osteosarcoma patients were included in this study, including 43 men (66%) and 23 women (34%), with a median age at diagnosis of 17 years (6–60 years). In our study, 45 patients (70%) were less than 18 year and 21 (30 %) patients were more than 18 years. (Table 1) Median survival among males was 13.5 months and among females it was 10 months which was not statistically significant ($p=0.625$). The median survival of patient less than 18 years was 20 months and that of patient more than 18 years was 13.5 months, there was no statistically significant difference in survival ($p=0.38$). In our study, in 35 cases femur was involved and 19 cases tibia was involved. In other cases humerus ($n=3$), mandible ($n=3$) fibula ($n=2$), sacrum ($n=1$), maxilla ($n=1$), radius ($n=1$), rib ($n=1$). Based on site of disease there was no significant survival difference. Based on type of osteosarcoma, most common was conventional type ($n=62$), Periosteal ($n=2$), Low-grade central osteosarcoma ($n=1$), telangiectatic ($n=1$). In conventional type osteoblastic variant ($n=48$), chondroblastic variant ($n=12$), mixed ($n=1$) both chondroblastic and osteoblastic, fibroblastic ($n=1$). Median survival among patient with osteoblastic type of osteosarcoma was 17.5 months and chondroblastic variant was 36 months. But was not statistically significant

($p=0.08$). (Table 1) The mean post operative necrosis in osteoblastic type of osteosarcoma cases was approximately 50 percent and that of chondroblastic variant was 60 percent, though not statistically significant. Based on grade of osteosarcoma, high grade osteosarcoma ($n=64$) and low grade osteosarcoma ($n=2$). Mean necrosis was more in chondroblastic variant. Median duration of survival for stage 1b ($n=1$), Stage II A ($n=11$), II B ($n=45$), III ($n=2$), IV A ($n=6$), and IV B ($n=1$) were 16, 23, 23.5, 18, 10.5 and 12 months respectively. No significant survival difference based on stage of disease was present in our study.

Based on the type surgery which patient underwent 32 patients had limb salvage surgery with custom mega prosthesis reconstruction, 14 patients underwent curative amputation, 5 patients underwent palliative amputation, 3 patients underwent hemimandibulectomy, 1 patient each underwent fibulectomy, sacrectomy, maxillectomy, rib resection and VanNess rotationplasty. Median survival of patient underwent limb salvage surgery with custom mega prosthesis reconstruction was 28 months and that of patient underwent amputation was 17 months. No statistically significant survival advantage present between the two groups ($p=0.68$). Average percentage of necrosis in patients receiving adriamycin and cisplatin was 53 % and IAP based chemotherapy was 68% which was statistically significant ($p = 0.006$). Spearman Rank correlation revealed that there was a strong positive correlation (0.418) between the percentage of necrosis and survival. The correlation was statistically significant ($p = 0.02$). The percentage of necrosis correlating with the survival was well established in our data too. But Ifosfamide addition to AP regimen dose not influence overall survival compared to other regimens ($p=0.214$). In our study the average overall survival was 26.89 months and median overall survival was 13.5 months. In our study the average event free survival was 22.34 months and median event free survival was 13 months. Three cases developed local recurrence after a median of 12 months. Out of three patients one patient underwent above knee amputation and other two underwent hip disarticulation. Post operative complication occurred in 11 patients out of 28 patients who underwent limb salvage surgery with custom made prosthesis reconstruction (40%). The post operative complications are graded according to Clavien-Dindo Classification. Out of 11 cases, three patients had vascular complication, two patients had re exploration and vascular reconstruction and one had above knee amputation. One case had prosthesis fracture underwent prosthesis replacement, two patients had dislocation of prosthesis one underwent open reduction and other with close reduction. Four patients had prosthesis infection, one patient underwent above knee amputation due to uncontrolled infection and other three were conservatively managed, all 4 cases had methicillin sensitive staphylococcus aureus in culture. One patient who was hepatitis B positive had acute

Table 1: Clinical and histological characteristics vs survival

	Number of patients	Months	P value
1)gender			
male	43	13.5	0.625
female	23	10	
2)Site			
Femur	35	20.5	0.669
Tibia	19	20	
3)Age			
Less Than 18 Years	45	20	P=0.3833
More Than 18 Years	21	13.5	
4)Histology			
A)Conventional			
Osteoblastic osteosarcoma	48	17.5	P=0.081
Chondroblastic	12	36	
Mixed osteoblastic and chondroblastic	1	70(max)	
Fibroblastic	1	84 (max)	
B)Periosteal	2	16(max)	
C)Telangiectatic	1	15(max)	
D)Low-grade central osteosarcoma	1	5(max)	
4)Response to chemotherapy (percentage of necrosis)			
Osteoblastic variant		49%(mean)	P=0.433
Chondroblastic variant		60%(mean)	
5)Stage			
IB	1	16	
IIA	11	23	P=0.87
IIB	45	23.5	
III	2	18	
IVA	6	10.5	
IVB	1	12	

hepatic encephalopathy and death on POD15. Maximum overall survival in non metastatic patient, who underwent limb salvage with custom made prosthesis reconstruction was 80 months .

4. Discussion

Osteosarcoma is common in the appendicular skeleton, with the most prevalent sites are distal femur (32%), proximal tibia (15%), proximal humerus (8%), and proximal femur (5%).³ This distribution corresponds to activity of the growth plates. Even in our study distal femur was the most common site of osteosarcoma. In order of occurrence distal femur (47%), proximal tibia (24%), proximal humerus (5%), proximal femur (4%), mandible (4%), distal tibia (4%), mandible (4%), fibula (2%), maxilla (1%), sacrum(1%), radius (1%), radius (1%), rib(1%), middle third femur(1%). At diagnosis, osteosarcoma is classically localized in 80% of cases, and pulmonary metastases are evident in 20%.⁴ In this study, 7 (10%)patients were metastatic at presentation , of which 6 had pulmonary metastasis.

The incidence of pathological fracture in osteosarcoma is from 5% to 12%.⁵

In our study seven cases (10%) had pathologic fracture. Previously pathological fracture was considered contra indication for limb salvage surgery with development in neoadjuvant chemotherapy this concept is under debate. It is argued that pathological fracture results in loss of the surgical border of the tumor; thus, radical or wide resection cannot be performed. But Xie et al study proves the contrary, that there no difference in overall survival and local recurrence rates between patients with or without pathological fracture.⁶ In our study we did total femoral resection with custom made prosthesis reconstruction and patient was disease free for 24 months later developed pulmonary metastasis and survived for 30 months on palliative chemotherapy.

In POG-8651 trial , patients with newly diagnosed localized resectable osteosarcoma were randomized at study entry to undergo immediate surgical resection followed by adjuvant 42 weeks chemotherapy or to receive 10 weeks of neoadjuvant chemotherapy followed by surgery and then 32 weeks of adjuvant chemotherapy. Overall survival and event-free survival were similar between the two arms of the trial, showing that timing of surgical resection did not impact outcomes.⁷ Even in this study ,seven patients underwent upfront surgery, there was no

significant difference in overall survival ($p=0.98$) and event free survival ($p=0.924$) between the group (localised disease at presentation without metastasis). The Italian Sarcoma Group conducted a randomized trial evaluating the role of ifosfamide both as neoadjuvant and adjuvant therapy. Patients who do not receive ifosfamide preoperatively could have ifosfamide added postoperatively if they had a poor histologic response to neoadjuvant therapy without ifosfamide. Of 246 patients who were randomized, the proportion of patients with a good histologic response, overall survival and event-free survival were similar between randomized groups. In our study, in contrary to above study histological response in terms of post chemo necrosis was significantly higher in patients who were given ifosfamide preoperatively ($p=0.006$), but both event free ($p=0.18$) and overall survival ($p=0.63$) were similar to rest of the patients.⁸

The main treatment for osteosarcoma historically was radiation therapy, which was omitted latter because osteosarcomas were thought to be radio resistant. Chambers et al. in their reported out of 43 cases of craniofacial osteosarcomas, 33 pts had preoperative radiation and resection. They reported an overall survival rate of 73% at 5 years.⁹ In our series one case of mandibular osteosarcoma due to poor response to chemotherapy, was given 50 grays preop radiation therapy and had 100 percent necrosis of tumour and overall survival of 20 months.

Osteosarcoma of the sacrum is a rare disease that accounts for only 4% of all primary sacral tumors. Sacrectomy with adequate margin can significantly improve the recurrence rate and event free survival rate.¹⁰ In our series, one case of osteosarcoma sacrum, misdiagnosed as giant cell tumour of sacrum underwent sacrectomy via anterior and posterior approach in a staged manner. Post operative his confirmed osteosarcoma and was given chemotherapy. Patient had no major functional morbidity.

The most important factor in the treatment of malignant bone tumour of distal tibia is to achieve an adequate margin of resection. Below-knee amputation has been the standard surgical procedure for malignant bone tumours involving the distal tibia and fibula. Custom-made prosthetic reconstruction of the ankle following resection of a bone tumour is a treatment in carefully selected patients.¹¹ In our series, one patient underwent distal tibial resection with custom mega prosthesis reconstruction with good functional result, with overall survival of 40 months.

Salah et al study showed pulmonary metastasectomy is associated with improved survival of osteosarcoma patients with resectable lung metastases.¹² In our series one case under went pulmonary metastasectomy with above knee amputation with overall survival of 22 months.

Lung is the most common site of metastasis in osteosarcoma followed by bone. even in our study 14 cases who were initially non metastatic develop lung metastasis despite treatment with surgery and chemotherapy with a

median event free period survival 11 months. The overall survival is significantly low compared to other cases who were non metastatic at presentation ($p=.001$)

Osteosarcoma occurring as a primary tumour in the ribs is rare.¹³ The most common presentation of osteosarcoma of the rib is pain and a palpable chest wall mass. In our series one case presented with mass in left 7 th rib and underwent rib resection with post operatively 6 cycle adriamycin and cisplatin based chemotherapy was given.

5. Conclusion

Limb salvage surgery in osteosarcoma is a safe alternative to amputation. Response to chemotherapy regarding necrosis correlates well with survival, thus clearly emphasizing the role of chemotherapy in the management of these tumors. Chemotherapy with adequate doses and supportive care in high dependency units to be given. Patients who do not comply with treatment had worse survival.

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8. Conflicts of interest

There are no conflicts of interest.

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