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Original Article

Pediatric Bone Sarcomas: Outcome of Multimodality Treatment in a Single Institution in South India over a Decade

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Abstract

Context: Pediatric bone sarcoma is a rare entity with low incidence of around 2.5–6 per million population in India. Management of this condition is well standardized, and global survival data are available; however, there is a paucity of data in the Indian perspective. **Aim of the Study:** The aim of this study is to analyze various prognostic factors and survival outcome. The purpose of this study is to assess the role of surgery, multiagent chemotherapy, and radiation in the management of these tumors. **Patients and Methods:** Retrospective analysis of patients aged 18 and less, diagnosed as bone sarcomas and treated in our tertiary cancer center. All the patients received at least one form of therapy depending on stage and site of the primary lesion. **Results:** Twenty-one patients of Ewing sarcoma and 20 patients of osteosarcomas were eligible and were included in the study. In Ewing sarcoma, completing the full course of standard chemotherapy and radiotherapy to the local site was associated with improved survival. In osteosarcoma, limb salvage surgery (LSS) had a significant difference in overall survival compared to amputation. Induction chemotherapy was associated with better percentage of necrosis and showed improved survival. The percentage of necrosis correlated positively with survival which was statistically significant (P = 0.015). **Conclusion:** The median survival in both these bone sarcomas is inferior to global trends. Probable reasons for such discrepancy are lack of compliance to treatment protocols due to age factors and late presentation. Completion of multiagent chemotherapy in both the tumors add to better survival. Radiotherapy in Ewing sarcoma improves survival. In osteosarcoma, LSS is an oncologically safe alternative to amputation. The percentage of necrosis following chemotherapy in osteosarcoma is a reliable predictor of prognosis.

Keywords: *Ewing sarcoma, osteosarcoma, pediatric bone sarcomas*

Introduction

Pediatric bone sarcoma is a rare entity with low incidence of around 2.5–6 per million population in India. Although there are lot of data on these tumours internationally, the data about the management and outcomes of these tumours in Indian perspective is abysmally low. Multimodality management of these tumors including aggressive multiagent systemic therapy, surgery in the form of limb salvage surgery (LSS) and radiation pose a great challenge to the treating multimodality team because patients usually present in an advanced stage in India. Compliance to treatment protocols directly reflect on the outcomes of the management of these tumors. The purpose of this study is to analyze the impact of various prognostic factors on survival outcomes.

Patients and Methods

This is a retrospective study of 10-year duration; data collection was done from previous medical records of patients treated in our institution and patients within the age group of 18 at presentation were included in this study. Totally, 21 patients of Ewing sarcoma and 20 patients of osteosarcoma were included in the study. The data collected were pooled and analyzed for management outcomes and prognostic association. Both these tumours are chemotherapy sensitive, patients were given standard accepted chemotherapy regimens and in some patients with slight alteration in the regimen. Standard regimen used in Ewing sarcoma was vincristine, adriamycin, and cyclophosphamide/ifosfamide etoposide (VAC/IE), some patients received Vincristine, Cyclophosphamide, Methotrexate/Cisplatin, Vincristine, Cyclophosphamide, Etoposide (VCM/

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PVCE). Osteosarcoma patients received AP with or without Ifosfamide, and some patients received PVCE. Although we insisted on strict adherence to the duration of treatment, especially chemotherapy, some patients defaulted treatment.

To analyze the data, SPSS (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp. Released 2013, Armonk, NY, USA) was used. 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 and treatment modalities were analyzed to know about their prognostic significance and their impact on survival. Finally, overall median survival and event-free survival were analyzed.

Results and Discussion

Ewing sarcoma and osteosarcoma account for around 5% of pediatric malignancies. The biological properties of these tumors are different; however, the treatment principles are similar.

Ewing sarcoma

Overall, the incidence of Ewing sarcoma is 2.93 per 1 million population. It is second most common bone tumor next to osteosarcoma. These tumors most commonly arise in the second decade of life. Most commonly, these tumors arise from the bone, but a small proportion, about 30% arises from the soft tissue. These tumors present clinically as localized pain of the affected bone and swelling; other nonspecific symptoms include fever loss of weight and appetite. The most common site of metastasis is lung followed by bone and bone marrow.

Classical radiographic findings are lytic or mixed lytic-sclerotic lesion, multilamellar periosteal reaction, namely onion peel appearance. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are necessary to characterize and to establish the extent of the lesion locally. CT of the chest and bone scan (technetium 99 m) or a positron emission tomography (PET) scan for detecting bone metastasis. Bilateral bone marrow sampling is a must regardless of primary site or tumor size. Biopsy and histopathology are necessary to establish the diagnosis. Histologically, they are characterized by small round blue tumors, expressing CD99, and positive IHC for synaptophysin, Neuron-specific enolase, S100 and CD 57.

Overall, Ewing sarcoma has slight male preponderance. Of the 21 patients included for analysis, 12 were male, and nine were female, the difference in median survival of 2.5 months in favor of female gender was not statistically significant ($P = 0.499$) [Table 1].

Ewing sarcoma is generally distributed equally between axial and appendicular skeleton. Of 21 patients, nine patients had disease in the axial skeleton, and the rest ($n = 12$) in appendicular skeleton. There was no statistical difference in survival between the two sites of presentation ($P = 0.40$) [Table 1].

Table 1: Ewing sarcoma prognostic factors and survival

Factors	Median/maximum survival months	*P*
Gender		
Male (*n*=12)	14.5	0.499
Female (*n*=9)	17.0	
Location		
Axial (*n*=9)	12	0.402
Appendicular (*n*=12)	17	
Stage		
IIB (*n*=14)	16	0.417
III (*n*=1)	3	
IVB (*n*=6)	10.5	
Metastasis		
B/L lung (*n*=1)	32 (maximum)	Lung metastasis better survival
DL spine (*n*=1)	6 (maximum)	
Lung (*n*=2)	32 (maximum)	
Skull (*n*=1)	2 (maximum)	
Skull scapula pelvis (*n*=1)	2 (maximum)	
Chemotherapy 17 cycles (*n*=12)	24	0.004 significant
Incomplete (*n*=9)	8	
Radiation Received (*n*=12)	24.5	0.023 significant
Not received (*n*=9)	13	
Surgery		
Yes (*n*=6)	16	0.704
No (*n*=15)	15	
Recurrence local (*n*=3)	25	0.368
Distant (*n*=5)	15	
Histopathological response after surgery		
Partial (*n*=2)	12.5	0.355
Total (*n*=4)	22.5	
Event-free survival	11 19	
Duration of survival	15 39 (maximum)	

At presentation, 14 patients were in Stage II B (T < 8 cm), one patient in Stage III (T > 8 cm) and six patients in Stage IV B (Metastatic disease) with a median survival of 16 months, 3 and 10.5 months, respectively. Survival of patient Staged III B was less than that of metastatic disease the reason was that patient received only four cycles of VAC chemotherapy and 30 Gy RT to the primary site thus emphasizing the impact of number of cycles of chemotherapy in survival. Site of metastasis in six patients who presented with metastasis was bilateral lung ($n = 1$), dorsal lumbar spine ($n = 1$), unilateral lung ($n = 2$), skull ($n = 1$), and scapula and pelvis ($n = 1$) with median survival of 32, 6, 32, 2, and 2, months, respectively. Although the common site of metastasis is lung generally, followed by bone, our data show

that both lungs and bones were equally common (n = 3) each. Lung metastasis had better survival than skeletal metastasis [Table 1].

Common treatment protocol for Ewing sarcoma is primary treatment by multiagent chemotherapy agents preferably VAC alternating with IE for at least 12 weeks followed by local control therapy by surgery or radiation and finally adjuvant treatment.[1,2] Adjuvant therapy following wide excision indicated between 28 and 49 weeks.[3] Postoperative radiation is recommended for patients with positive or close margins.[2]

Among 21 patients, 11 completed full 17 cycles of chemotherapy and the rest defaulted. Median survival was 24 and 8 months, respectively, and the difference in survival was statistically significant (P = 0.004) [Table 1]. Completion of multiagent chemotherapy had a positive impact on survival while defaulting had detrimental effect on survival. Reason for default being poor compliance among the patients and toxicity associated with chemotherapy in spite using growth factors.

Radiation was a part of local treatment to the primary site in addition to chemotherapy in 12 patients, and nine patients defaulted radiation. The median survival was 24.5 and 13 months, respectively, and the difference was statistically significant (P = 0.023). Radiation as a local treatment has a positive impact on survival [Table 1].

Six patients underwent surgery of the primary site, one case of spine decompression and stabilization, one case of pulmonary metastasectomy, and surgery was not a part of treatment in 13 patients. Surgery was a part of local treatment in six patients, total scapulectomy (n = 3) [Figure 1], fibular resection (n = 1), chest wall resection (n = 1), and shoulder disarticulation (n = 1). Median survival was 16 and 15 months, respectively, between patients managed with and without surgery of the primary site; the difference was not statistically significant (P = 0.704).

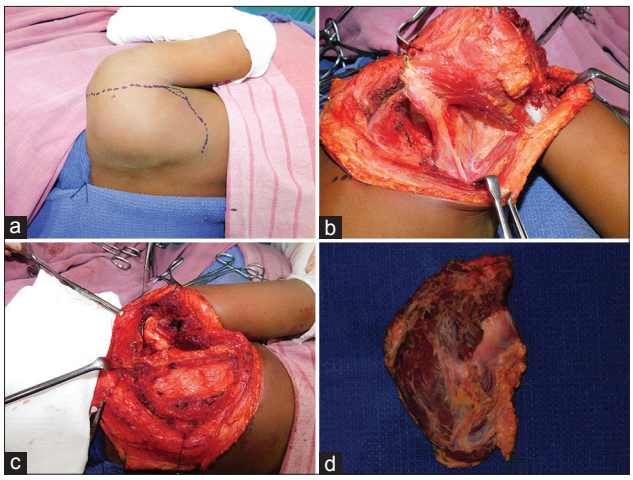

Figure 1: (a) Ewing Sarcoma of Scapula- after 6 cycles of chemotherapy. (b) Scapula with muscle attachments. (c) Humeral head suspended to the clavicle. (d) Scapula Specimen

Among the patients treated with surgery, four patients had complete response, and two had partial response. Although there was a difference in median survival of 10 months (22.5 and 12.5 months respectively) between the two, it was not statistically significant (P = 0.355). The survival difference was due to the response of the tumor to chemotherapy rather than surgery.

Totally 8 patients progressed to develop recurrence either local (n = 3) and distant (n = 5) with median survival of 25 and 15 months, respectively (P = 0.368). Local recurrence had better median survival compared to distant recurrence though the difference was not statistically significant [Table 1].

Median event-free survival was 11 months and maximum of 19 months. Most of the recurrences were during this period of 1–1.5 years. Overall, median survival of Ewing sarcoma in our patients was 15 months with maximum survival of 39 months.

According Esiashvili *et al.*, the 5 years survival of localized disease increased from 44% to 68% in the period after 1993 whereas 5 years survival of metastatic disease increased from 16% to 39%.[4] However, survival in our group of patients is less compared to standards. The overall median survival is 15 months, and maximum survival is 39 months. Poor compliance on the part of patients, greater proportion of patients presenting with metastatic disease, and tumor biology in this age group are reasons for inferior survival outcomes. Completion of multiagent chemotherapy (VAC/IE) with the support of growth factors can improve survival.

Osteosarcoma

Osteosarcoma is the most common primary bone tumor. The peak incidence corresponds with the time of most rapid bone growth. The second peak of incidence after 60 years commonly referred to as secondary osteosarcoma. The disease is slightly more prevalent in males. From our observation, osteosarcoma is common in the second decade and common in males, 13 were male, and 7 were female, and there was no significant difference in survival between the two (P = 0.812) [Table 2].

Clinically, osteosarcoma presents as pain and soft-tissue swelling. Around 5%–10% presents with a pathological fracture. Preferentially involves metaphysis of bones and nearly 80% of them arise from extremity. Distal femur is the most common site followed by proximal tibia. In our group of patients, lower end of femur (n = 10) was the most common site followed by upper end of tibia (n = 7). However, there was no significant median survival difference statistically between the sites (P = 0.769) [Table 2].

Apart from physical examination, radiograph and a CT or MRI should be done to assess the local extent of the tumor. Classical radiological findings include mixed sclerotic and

lytic appearance, periosteal new bone formation, codman triangle, and radial sunburst appearance. MRI is slightly preferred over CT as joint involvement, marrow, and soft tissue extension are better delineated by MRI. CT can also be helpful in surgery and planning purposes. Staging requires bone scan, CT chest, or PET/CT. PET/CT is more accurate than a bone scan in detecting bone metastasis.

Conventional osteosarcomas are most frequently encountered pathology. Osteoblastic 50%, chondroblastic 25%, and fibroblastic 25% are variants of conventional osteosarcoma depending on the type of matrix. Other variants include parosteal, telangiectatic, small cell, periosteal, low-grade central, and high-grade surface. Among 20 patients, four were chondroblastic variant, and the rest of the 16 were osteoblastic variant. Median survival was 38 and 16.5 months, respectively, the difference was not statistically significant (P = 0.072). The mean response to chemotherapy regarding percentage of necrosis in chondroblastic variant, and osteoblastic variant was 61.5% and 43.3%, respectively, and the difference in the percentage of necrosis is not statistically significant (P = 0.323) [Table 2].

Table 2: Osteosarcoma prognostic factors and survival

Factors	Median/maximum survival months	*P*
Gender		
Male (*n*=13)	17	0.812
Female (*n*=7)	16	
Site		
Femur (*n*=10)	20.5	0.769
Tibia (*n*=7)	17	
Variant		
Osteoblastic (*n*=16)	16.5	0.072
Chondroblastic (*n*=4)	38	
Response to chemotherapy (percentage of necrosis)		
Osteoblastic variant	43% (mean)	0.323
Chondroblastic variant	61% (mean)	
Stage		
IIA (*n*=1)	46	0.577
IIB (*n*=14)	18	
III (*n*=2)	13.5	
IVA (*n*=2)	14	
IVB (*n*=1)	12	
Metastasis bone (*n*=1)	12	
*LSS (*n*=2)	14	
Surgery LSS (*n*=12)	20	0.044
Amputation (*n*=5)	19	significant
No surgery (*n*=3)	3	
Percentage of necrosis and correlation with survival	Correlation 0.596	0.015 significant
Chemotherapy complete (*n*=13)	24	0.021 significant
In complete (*n*=7)	12	
Chemotherapy regimen percentage of necrosis		
**IAP (*n*=12)	70%	0.048
Others (*n*=4)	15%	significant
Event-free survival	4 months (minimum) 17 months (maximum)	
Duration of survival (months)	17 (median) 58 (maximum)	

*LSS – Limb salvage Surgery; **IAP Ifosfamide, Adriamycin and Cisplatin

Median duration of survival for Stage II A (n = 1), II B (n = 14), III (n = 2), IV A (n = 2), and IV B (n = 1) were 46, 18, 13.5, 14, and 12, respectively. Lung metastasis (n = 2) at initial presentation had better maximum survival of 25 months compared to 12 months in bone metastasis (n = 1) [Table 2]. In general, the presence of metastatic disease (10%–20%) at presentation is associated with poor prognosis. Lung metastasis had better survival compared to bone metastasis. In addition, our data show that lung metastasis had better maximal survival compared to bony metastasis.

Twelve patients underwent LSS, amputation in five patients, and 3 patients had no surgery in the treatment with a maximum survival of 58 months, 30 months and 12 months, respectively, and the difference was statistically significant (P = 0.044). There was a significant survival difference, and LSS was associated with better survival. The reason was that amputations were done in all the five patients with ulcerative and fungating lesions. We used custom-made stainless steel prosthesis for all patients except for a 6-year-old male child, titanium expandable prosthesis was used [Figure 2].

Among patients undergoing LSS, eight patients had no complications 66.7%. The remaining four had complications.

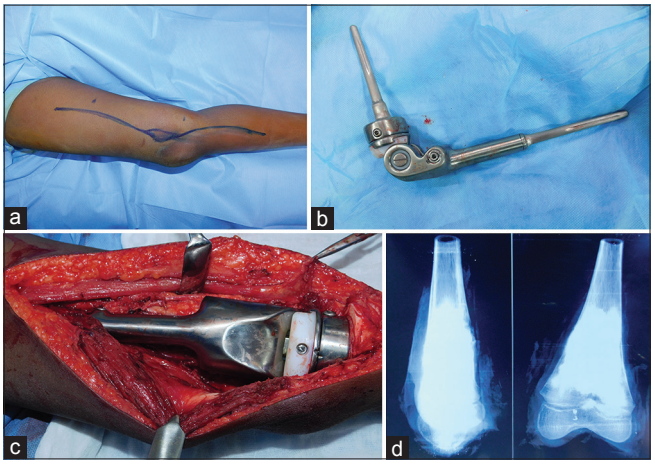

Figure 2: (a) Osteosarcoma of Distal Femur - after 3 cycles of neoadjuvant chemotherapy. (b) Expandable titanium distal femoral prosthesis. (c) Prosthesis secured by bone cement. (d) Specimen X-ray showing tumor response and margin

Table 3: Percentage of necrosis with different chemotherapeutic regimen

Chemotherapy	Response 0–20 (%)	21-40	41-60	61-80	81-100
*AP ± Ifosfamide (*n*=17)	3	1	1	7	1
**PVCE (*n*=3)	3	-	-	-	-

Note: Four of 17 patients who received AP+/- Ifosfamide regimen were not operated so percentage of necrosis could not be measured.. AP – Adriamycin, Cisplatin; PVCE – Cisplatin, Vincristine, Cyclophosfamide, Etoposide

Dislocation after a total femoral prosthesis for which open reduction was done (n = 1), Fracture of prosthesis and replacement (n = 1), surgical site infection (n = 1), vascular injury (n = 1) for which an immediate reconstruction was done. One case of total femoral resection, during the postoperative period, developed dislocation of head of femur. As closed reduction failed, open reduction was done. Another patient had a fracture of the prosthesis, replacement of prosthesis was done. One patient had tumor abutting the proximal popliteal artery, LSS was done. Postoperatively, the patient had feeble distal pulse. Reexploration showed a thrombosed popliteal artery; a vein graft was done with contralateral saphenous vein. One more patient had surgical site infection which was then managed conservatively.

Thirteen patients completed full course of chemotherapy (Ifosfamide, Adriamycin and Cisplatin [IAP] based chemotherapy) and had a median survival of 24 months and those who defaulted chemotherapy had a median survival of 12 months the difference in survival was statistically significant (P = 0.021) [Table 2]. Usually, we follow two drug regimens (doxorubicin, cisplatin with or without ifosfamide) with growth factors. The survival difference between those who received complete chemotherapy and those who did not was statistically significant, emphasizing the role of completeness of chemotherapy.

Average percentage of necrosis in patients receiving IAP-based chemotherapy was 70% and for those who received alternate regimen (PVCE) was 15% which was statistically significant (P = 0.048). Spearman Rank correlation revealed that there was a strong positive correlation (0.59) between the percentage of necrosis and survival. Moreover, the correlation was statistically significant (P = 0.015) [Tables 2 and 3]. We were able to achieve median percentage of necrosis of 70% with (doxorubicin and cisplatin) compared to 15% in other regimens which was statistically significant. The reason for not achieving higher percentage of necrosis can be basically due to the biology of tumor or avoidance of high dose of methotrexate and at times Ifosfamide. The percentage of necrosis correlating with the survival was well established in our data too.

Median duration of survival in patients developing metastasis was 15.5 months and maximum was 26 months. Median event-free survival was 6 months and maximum of 17 months in patients who developed metastatic disease after completion of treatment. Overall median survival in osteosarcoma was 17 months and maximum of 58 months. Five years survival of localized osteosarcoma is around 60%–80% and that of metastatic disease is around 15%–30%.[5] In our group of patients, the overall median survival was 17 months and maximum survival 58 months. The reason for such a huge difference regarding survival was because, five patients developed metastatic disease, and 2 patients presented with metastatic disease.

Biology of these tumors

Chemotherapy is a critical component in the management of these tumors. Comparing outcomes of pediatric (Age up to 18 years) and adult bone sarcomas (age 18–40 years), survival is poor in adults. A lot of hypotheses are being said to explain these results such as intrinsic differences in tumor biology between pediatric and adult patients with similar sarcoma histologies and ability to tolerate maximal cytotoxic chemotherapy. However, investigators concluded that the receipt of high-dose chemotherapy and the manner of its metabolism by the host was the key driver of outcome rather than tumor biology.[6] Tumor biology or difference in the metabolism of chemotherapeutic agents in Indian population may be the reason for inferior survival outcomes. This has to be addressed in future research.

Limitations of the study

We have limited our study to pediatric age group. Bone sarcoma in this age group is a rare entity, and so the sample size is very small. Both the tumors are chemotherapy sensitive and compliance of this age group of patients to chemotherapy is poor. The toxicity associated with chemotherapy is very high even with the use of growth factors and this contributes to poor compliance. None of the patients in our study received high-dose chemotherapy which may be one of the factors for low survival rates compared to standard survival rates for these tumors. Locally advanced and systemic disease at presentation are reasons for inferior survival outcome.

Conclusion

Pediatric and adolescent bone sarcomas are a rare entity, which needs multimodality treatment for better survival. In managing Ewing sarcoma, strict compliance to aggressive multi-agent chemotherapy with the help of growth factors along with local therapy in the form of radiation adds to better survival. Even with multimodality therapy, the survival rates are dismal. LSS 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

can improve survival rates. In addition, the role of local treatment is questionable in the absence of response to chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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