
Research Article

Real World Experience with Osteosarcoma from a Tertiary Cancer Centre in India

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Abstract

Background: Osteosarcoma represents the commonest category of bone tumors in the children and young adults and stability in its incidence rates have been observed throughout the world. The present study evaluated the varied profile of Indian patients with osteosarcoma with a special emphasis on the survival patterns in a tertiary cancer care centre in India.

Methods: A retrospective review of all patients diagnosed with osteosarcoma during the year 2000 to 2020 was included in the study. Details of their demographic, treatment and survival profile were collected from the electronic medical records of the patients.

Results: Among 112 patients, male gender (75.9%), disease in extremity sites (89.3%), conventional histology (95.5%), serum alphas >120U/L (75.9%) and non-metastatic disease at presentation (66.1%) and IAP regime (57.1%) were more commonly reported. The OS of the patients was 51% at 20 years. Statistical associations were observed with respect to age (p-value 0.019), site (p-value 0.017), grade (p-value 0.019), metastatic disease (p-value 0.006) and site of metastasis (p-value <0.0001). The PFS of the patients was 48% at 20 years and correlations were observed with respect to age (p-value 0.021), site (p-value 0.002), grade (p-value 0.016), metastatic disease (p-value 0.001), site of metastasis (p-value <0.0001) and HUVOS grade (p-value 0.026).

Conclusion: With a static pattern in survival, there is an imperative need to characterize the genetic, epigenetic and immunologic basis of the disease in order to look for newer targets, inhibitors and therapies.

Keywords: Real World Experience; Osteosarcoma; Tertiary Cancer Centre

Introduction

Osteosarcoma derived from bone forming mesenchymal cells, represents the commonest category of bone tumors in the children and young adults [1]. Stability in its incidence rates have been observed throughout the world along with a decline in the mortality rates. This has been largely possible with the advent of multi agent chemotherapy [2, 3]. The most widely reported prognostic factors for osteosarcoma include tumor size and site, surgical resectability, response to chemotherapy and presence of metastases [4].

Survival outcomes in osteosarcoma depend to a great extent on the choice of therapy. Induction chemotherapy followed by surgical resection for local tumor control and consolidation local control to metastatic sites is the standard treatment regime for these patients [1]. Studies have reported an improvement

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in the survival outcomes from 17% with surgical resection to 66% with the addition of adjuvant chemotherapy in a multi-institutional randomized trial conducted in the 1980's. Also, with respect to therapy, a meta-analysis has demonstrated the superiority of three drug regimens to two drug regimens, also highlighting the importance of high dose methotrexate [5]. In a Pediatric Oncology Group study by Harris et al, a five year event free and overall survival of 47% and 53% were observed with the use of induction ifosfamide, resection and adjuvant MAP ifosphamide and improvements in outcomes were observed with unilateral lung metastases and limited number of lung metastases [6]. In terms of radiotherapy, a study by Ozaki et al has shown an improvement in overall survival in the patients without resection for pelvic tumors [7].

The present study was conducted to evaluate the varied profile of Indian patients with osteosarcoma with a special emphasis on the survival patterns in a tertiary cancer care centre in India.

Materials and Methods

Patients

A retrospective review of all patients diagnosed with osteosarcoma during the year 2000 to 2020 was included in the study. Patients presenting with secondary osteosarcoma or relapsed disease at diagnosis were excluded from the analysis. Details of their demographic, treatment and survival profile were collected from the electronic medical records of the patients. The study was conducted as per the Declaration of Helsinki and was given a waiver of the informed consent process.

Diagnostic and staging evaluation

Baseline nutritional status (body mass index, haemoglobin, albumin) and tumor burden markers (tumor dimensions, Lactate dehydrogenase) was documented. All

patients underwent baseline plain radiographs and magnetic resonance imaging (MRI) of the primary disease site prior to initial histopathological evaluation and management.

Besides routine blood investigations (complete blood count, renal function and liver function test), echocardiography, staging work up including computed tomography (NCCT) thorax and bone scintigraphy were performed. Core needle biopsy using standard recommended practices with histopathological confirmation and morphological subtyping was performed.

Treatment and toxicity

Multimodality treatment including surgery, systemic chemotherapy and/or radiation therapy was adopted for patients with nonmetastatic osteosarcoma. Surgical management protocol ensured the complete safe resection of tumor with functional preservation including limb salvage and adequate surgical margin with enbloc excision of biopsy tract by dedicated orthopedic oncology surgeon. Two standard chemotherapy protocols followed at our centre and evaluated in this study are summarized in Table 1. Granulocyte colony-stimulating factor (G-CSF) products were administered as primary prophylaxis following each cycle of chemotherapy. Planned dose reductions in subsequent cycles were based on occurrence of clinically significant hematological and/or non-hematological toxicities. Toxicities were documented according to Common Toxicity Criteria for Adverse Events (CTCAE v4.0) recommendations. Histological evaluation of extent of tumor necrosis was assessed using Huvos grading system. Chemotherapy treatment was not adopted for good or poor histological responders.

Follow up

Post-treatment follow-up included physical examination, complete blood count, chest imaging and local imaging of the primary site every three months for two years, every

MAP (high-dose methotrexate + cisplatin + doxorubicin)

Cycle length: 5 weeks (cycles 1 through 4), 4 weeks (cycle 5 and 6) Duration of therapy: 6 cycles.			
Drug	Dose and route	Week of treatment	Given on days
Cisplatin	120 mg/m ² (4 h infusion of 60 mg/m ² per day for 2 days)	Preoperative: Weeks 1 and 6 Postoperative: Weeks 12 and 17	Days 1 and 2
Doxorubicin	37.5 mg/m ² per day on days 1 and 2 as 4-hour infusion	Preoperative: Weeks 1 and 6 Postoperative: Weeks 12, 17, 22, and 26	Days 1 through 2
Methotrexate	12 g/m ² over 4 h (maximum dose 20 gm) with hyper-hydration, alkalinisation	Preoperative: Week 4, 5, 9, and 10. Postoperative: Week 15, 16, 20, 21, 24, 25, 28, and 29.	Day 1
Leucovorin	15 mg orally, IV, or IM every six hours Dose adjusted according to serum methotrexate concentrations.	Preoperative: Week 4, 5, 9, and 10. Postoperative: Week 15, 16, 20, 21, 24, 25, 28, and 29.	Starting 24–48 h from methotrexate infusion and continuing until methotrexate concentration was less than 0.1 µM.
Surgery		Week 11	

Ifosfamide, Adriamycin and Cisplatin (IAP)

Table 1: Two standard chemotherapy protocols (MAP and IAP) followed at our centre.

Cycle length: 21 days		
Duration of therapy: 6 cycles.		
Drug	Dose and route	Given on days
Ifosfamide	1.8 gm/m ² per day IV	Days 1 to 5
Doxorubicin	25 mg/m ² per day IV	Days 1, 2 and 3
Cisplatin	37.5 mg/m ² per day IV	Day 1 and 2

Table 2: Profile of 112 patients with osteosarcoma on the basis of age group.

Characteristics	Total patients N=112	Age group <20 years; N=50	Age group 20-40 years; N=47	Age group >40 years; N=15	p-value**
Gender					0.280
Male	85	40	36	9	
Female	27	10	11	6	
Site					<0.0001
Extremity	100	49	42	9	
Axial	12	1	5	6	
BMI					0.003
<18.5 Underweight	34	22	12	0	
18.5-24.9 Healthy	56	22	26	8	
≥25 Overweight	22	6	9	7	
Histology					0.175
Conventional	107	49	45	13	
Extraskeletal	5	1	2	2	
Grade					0.325
1-2	24	8	11	5	
3-4	88	42	36	10	
<i>S. alphos</i>					0.123
30-120U/L	27	8	13	6	
>120U/L	85	42	34	9	
Stage					0.241
Non metastatic	86	42	34	10	
Metastatic	26	8	13	5	
Site of metastasis					0.688
No metastasis	74	35	29	10	
Lung	38	15	18	5	
Chemoprotocol					<0.0001
IAP	64	16	36	12	
MAP	48	34	11	3	
HUVOS grade					0.045
1-2	43	15	24	4	
3-4	43	26	13	4	
Not available*	26	-	-	-	
Progression					0.012
Yes	53	16	27	10	
No	59	34	20	5	
Status					0.018
Alive	69	38	23	8	
Dead	43	12	24	7	

BMI, body mass index; MAP, methorexate-adriamycin-cisplatin; IAP, ifosfamide-adriamycin-cisplatin.

*Not available cases were not considered for p-value calculation.

**p-value <0.05 was considered as significant.

four months for year 3, every six months for years 4 and 5, and annually thereafter or as clinically indicated; in line with the recommendations by National Comprehensive Cancer Network (NCCN) and Children’s Oncology Group (COG) guidelines. Tumor surveillance was continued for longer time as late metastases may occur 10 years after diagnosis. Further investigations to monitor the possible cardiac, renal, pulmonary, cognitive, developmental and late side effects of therapies were included in follow up visits. In suspected relapse/metastatic presentation, management was planned after biopsy confirmation of malignancy. Patients who were lost to regular follow up were communicated telephonically.

Statistical analysis

SPSS version 23 for Windows (SPSS Inc, Chicago IL, USA) was used for the statistical analysis of the data obtained. Pearson chi square or Fisher’s Exact Test, whichever appropriate, was used for the analysis of categorical variables. Kaplan Meier method was used for survival analysis [8]. Overall survival was calculated as the time duration between the date of diagnosis and the last date of follow up whereas progression free survival was calculated on the basis of the time duration between the date of diagnosis and the date of progression, if occurred. The differences in survival among the groups were compared using the Log Rank test. A two sided p-value <0.05 was considered as significant.

Results

A total of 112 patients were included in the study. Of these, 85/112 (75.9%) patients were males. The disease was more commonly observed in the extremity sites (89.3%, 100/112). Conventional histology (95.5%, 107/112), serum alphos >120U/L (75.9%, 85/112) and non-metastatic disease at presentation (66.1%, 74/112) were more commonly reported in the patients. MAP regime was given to 48 (42.9%) patients whereas IAP regime was given to 64 (57.1%) patients in the study. Differences in the profile of patients were observed on the basis of age group as shown in Table 2.

Patients were also compared on the basis of disease progression (Table 3). Statistical associations were observed with age group (p-value 0.012), site of disease (p-value 0.042), grade of disease (p-value 0.013), stage of disease (p-value 0.003), site of metastasis (p-value <0.0001), HUVOS grade (p-value 0.048) and vital status of the patient (p-value <0.0001).

The OS of the patients was 51% at 20 years. At 5 years, improved OS was seen in patients with age group <20 years (74%), male gender (58%), disease in extremities (62%), conventional histology (59%), grade 1-2 (82%), *S alphos* 30-120U/L (73%), non-metastatic disease (63%), MAP chemoprotocol (53%) and HUVOS grade 3-4 (73%).

Table 3: Profile of 112 patients with osteosarcoma on the basis of disease progression.

Characteristics	Total patients N=112	Yes N=53	No N=59	p-value**
Age group				
<20 years	50	16	34	0.012
20-40 years	47	27	20	
>40 years	15	10	5	
Gender				
Male	85	39	46	0.588
Female	27	14	13	
Site				
Extremity	100	44	56	0.042
Axial	12	9	3	
BMI				
<18.5 Underweight	34	13	21	0.417
18.5-24.9 Healthy	56	28	28	
≥25 Overweight	22	12	10	
Histology				
Conventional	107	50	57	0.561
Extraskelatal	5	3	2	
Grade				
1-2	24	6	18	0.013
3-4	88	47	41	
S. alphos				
30-120U/L	27	9	18	0.095
>120U/L	85	44	41	
Stage				
Non metastatic	86	34	52	0.003
Metastatic	26	19	7	
Site of metastasis				
No metastasis	74	20	54	<0.0001
Lung	38	33	5	
HUVOS grade				
1-2	43	22	21	0.048
3-4	43	13	30	
Not available*	26	-	-	
Chemoprotocol				
IAP	53	33	31	0.299
MAP	59	20	28	
Status				
Alive	69	13	56	<0.0001
Dead	43	40	3	

BMI, body mass index; MAP, methorexate-adriamycin-cisplatin; IAP, ifosfamide-adriamycin-cisplatin.

*Not available cases were not considered for p-value calculation.

**p-value <0.05 was considered as significant.

Using the Log Rank test, statistical associations were observed with respect to age (p-value 0.019), site (p-value 0.017), grade (p-value 0.019), metastatic disease (p-value 0.006) and site of metastasis (p-value <0.0001). The PFS of the patients was 48% at 20 years. A similar trend was observed in the case of PFS and statistical correlations were observed with respect to age (p-value 0.021), site (p-value 0.002), grade (p-value 0.016), metastatic disease (p-value 0.001), site of metastasis (p-value <0.0001) and HUVOS grade (p-value

0.026). The OS and PFS status of the patients with respect to the various characteristics is depicted in Table 4.

Comparisons were also made on the basis of the vital status of the patients and statistical correlations were observed with respect to the age group, site of disease, grade, S alphos and the site of metastasis as shown in Figure 1.

Table 4: Five year survival profile of 112 patients with osteosarcoma.

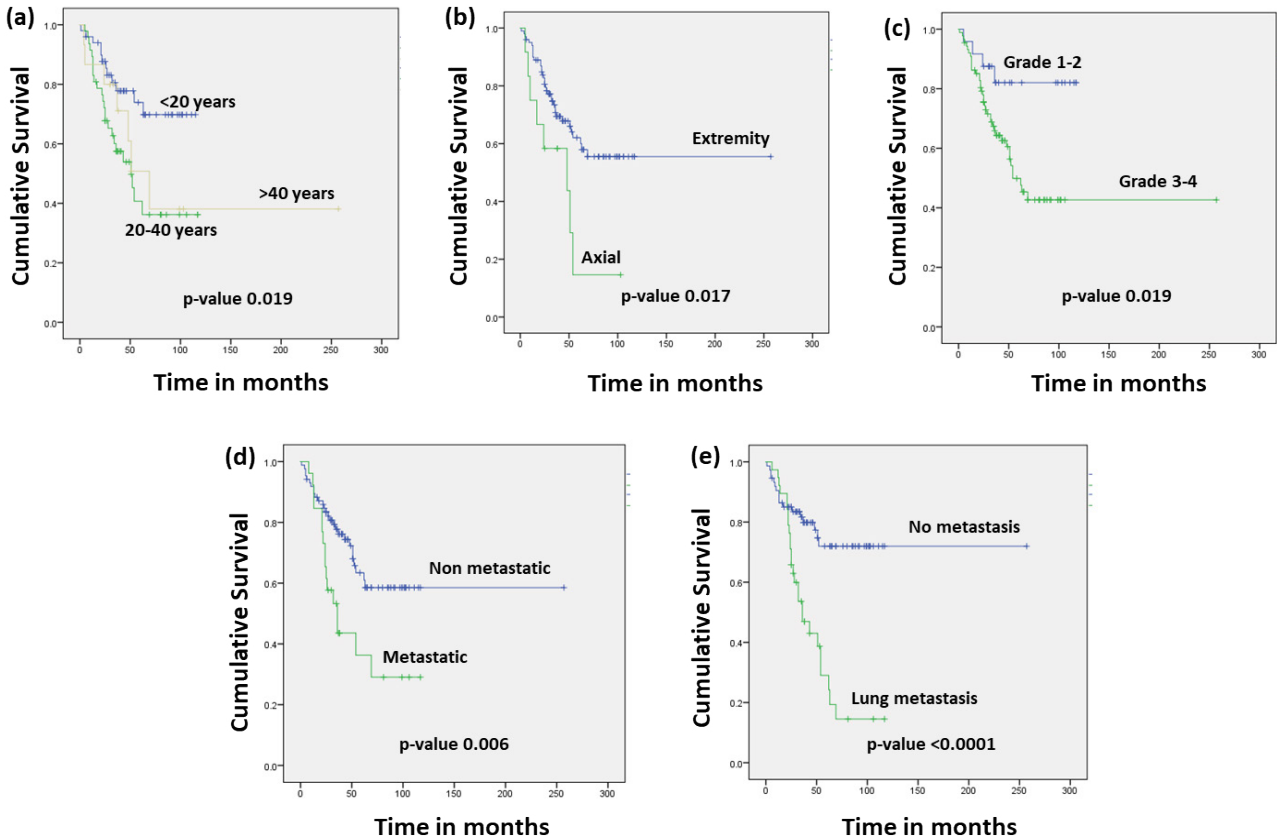
Characteristics	Total patients N=112	OS (%)	p-value	PFS (%)	p-value**
Age group					
<20 years	50	74	0.019	65	0.021
20-40 years	47	41		42	
>40 years	15	51		27	
Gender					
Male	85	58	0.367	50	0.302
Female	27	52		47	
Site					
Extremity	100	62	0.017	53	0.002
Axial	12	15		19	
BMI					
<18.5 Underweight	34	59	0.880	55	0.565
18.5-24.9 Healthy	56	54		48	
≥25 Overweight	22	59		42	
Histology					
Conventional	107	59	0.735	50	0.765
Extraskelatal	5	40		40	
Grade					
1-2	24	82	0.019	78	0.016
3-4	88	50		42	
S. alphos					
30-120U/L	27	73	0.055	70	0.064
>120U/L	85	52		43	
Stage					
Non metastatic	86	63	0.006	57	0.001
Metastatic	26	36		24	
Site of metastasis					
No metastasis	74	72	<0.0001	70	<0.0001
Lung	38	29		13	
HUVOS grade					
1-2	43	54	0.066	42	0.026
3-4	43	73		68	
Not available*	26				
Chemoprotocol					
IAP	53	53	0.307	45	0.314
MAP	59	62		54	

BMI, body mass index; MAP, methorexate-adriamycin-cisplatin; IAP, ifosfamide-adriamycin-cisplatin; OS, overall survival; PFS, progression free survival.

*Not available cases were not considered for p-value calculation.

**p-value <0.05 was considered as significant.

Figure 1: Survival graphs of 112 patients with osteosarcoma on the basis of vital status with respect to (a) age group (b) site of disease (c) histological grade (d) metastatic disease and (e) site of metastasis. p-value <0.05 was considered as significant.



Discussion

Osteosarcoma is a mesenchymal malignancy, mainly affecting the children and adolescents. Outcomes of patients with localized, progressive, recurrent or metastatic disease still remains unchanged in the last few decades. Advancements in surgery, newer chemotherapeutic targets, novel immunomodulators, and improved diagnostic facilities have all together reinstated the hopes for improved outcomes in the future which have yet not translated into improvements in progression free/ overall survival.

The present study reflects the data of young, adolescents, middle age and older age group patients with osteosarcoma and profiles the experience of a single tertiary care cancer centre in India.

Overall, in a total of 112 patients, the patients presenting in the age group of <20 years and 20-40 years were nearly equal and much more than the age group >40 years. It has also been highlighted in other studies where it has been shown that osteosarcoma is the most common primary bone tumor in the children and adolescents [1, 9]. It was observed in our study that it occurred most commonly in the males and extremities were the commonest site of disease occurrence which also

reciprocates with the published literature [1, 9]. Metastatic disease was observed in 26/112 patients, which highlights the fact that the disease largely goes unnoticed in our population leading to potential delay in its diagnosis. Further, Huvo's grade III/IV was observed in 43/86 patients and a statistical correlation was well evident among the different age groups viz a viz <20 years, 20-40 years and >40 years. Differences on the basis of chemotherapy have been observed in trials including MSKCC (65%), INT0133 (48%) and Cooperative German-Austrian-Swiss osteosarcoma study group (COSS) protocol (43%) [10-12].

A large number of clinical trials have been initiated in the European population on pediatric patients with osteosarcoma focusing on multiagent chemotherapy and surgical resection for local control wherever possible. MAP is the routine multiagent chemotherapy schedule in the European and North American populations in the pediatric patients [13, 14]. Although numerous trials have investigated the effect of dose intensification, no substantial benefits of using MAP chemotherapy has been shown [15, 16]. The EURAMOS-1 trial was conducted to test the improvement in outcomes if any, upon the addition of ifosfamide and etoposide to MAP in the postoperative setting in patients with < 90% histologic response to preoperative chemotherapy [16].

Further, studies from different settings has shown comparable results with three-drug regimen without using HDMTX [9, 17-20]. However, the feasibility of testing non-HDMTX triple-drug therapy against HDMTX containing triple-drug therapy which requires meticulous training and monitoring is a matter of grave concern, especially for the clinicians in the developing countries.

In terms of survival, a study by Lee et al assessing the survival trends of adolescents and young adults and comparison with the other age groups, a 5 year OS of 61% was observed in a total of 3017 patients. Further, an inverse correlation with age was reported. Also, a 5% difference in the OS rate among the children and the adolescents and young adults was also observed [9]. In our study, an OS of 51% and PFS of 48% at 20 years were seen. This remains the biggest strength of the study with a large follow up period of patients around 20 years, thus depicting their factual survival rates. Statistical associations were observed with location & extent of disease and age group. Similarly, in our study, correlations were observed with age group, site and metastatic disease in terms of OS (p-value <0.05). An association with these factors was also seen with respect to the PFS (p-value <0.05). In another retrospective study conducted at our institution including all patients up to the age of 18 years with a confirmed diagnosis of osteosarcoma, the 5-year OS and EFS was 55% and 52% respectively [21]. Our results are very similar to the study even though it includes a much varied age group and with a much longer follow up period, thus clearly pointing towards the fact that the survival rates of patients with osteosarcoma have remained largely the same over the years.

The study has certain inherent biases due to its retrospective nature and hence complete data was not available in certain cases. However, the greatest strength of this study is the long follow up period of the patients which truly reflects the survival patterns over a long period of time. Given the fact that the survival of these patients has remained nearly the same over the years, hence, there is an imperative need to characterize the genetic, epigenetic and immunologic basis of the disease in order to look for newer targets, inhibitors and therapies.

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