Original Article

A Clinicopathological Analysis of Bone and Soft Tissue Sarcoma in Children and Young Adults: Time to Adapt with the Rapidly Changing Landscape?

Abhishek Basu, Debottam Barman, Shinjini Chakrabarty, Janmenjoy Mondal, Bhukya Swetha, Ansuman Bhattacharjee, Ipsita Chakraborty
Department of Radiotherapy, Medical College Kolkata, Kolkata, West Bengal, India

Abstract

Context: Primary bone and soft-tissue sarcomas (STSs) are rare tumors, comprising <1% of overall adult cancers. Despite its heterogeneous molecular profile, multimodality management of these tumors has led to the 5-year overall survival (OS) benefit, from approximately 50% in 1970 to the range of 75%–80% presently, in the adolescent age group. Various hospital-based registries have tried to address the scarcity of data of bone and STSs in Indian context in the last decade, but the number is not encouraging enough to gauge the pattern of care of the disease in children and young adults. **Aims:** To analyze the predictive and prognostic factors of clinical outcome in bone and STS in children and young adults. **Settings and Design:** This was a retrospective, single-institutional study from a prospectively maintained database. **Subjects and Methods:** We enrolled biopsy-proven patients (aged 3–35 years) of bone and STS, attended at our outpatient department during the period of January 2015 to December 2017 and traced till November 2019. Follow-up time was defined by the period from the date of registration to the date of last attendance or death. **Statistical Analysis Used:** Univariate log-rank analysis and unpaired *t*-test were used to assess the potential prognostic factors for progression-free survival and OS and further validated by multivariate Cox regression analyses. **Results:** Tumor size, stage at presentation, and treatment modality were the significant prognostic factors for both bone and STS. Children had better OS with 3-year OS (89.7% vs. 71.8%). **Conclusions:** We recommend multidisciplinary management with emphasis on early intervention in these tumors.

Keywords: Bone tumors, chemoradiation, local control, progression-free survival, soft-tissue sarcoma

Introduction

Bone and soft-tissue sarcoma (STS) is a heterogeneous group of many rare tumors that comprise more than 50 subtypes.[1] They comprise <1% of overall adult cancers.[2,3] Despite their rarity, bone and STSs are diagnostically and therapeutically challenging tumors. Bone sarcomas constitute as the third most common cause of mortality in adolescents. Despite its heterogeneous molecular profile, multimodality management of these tumors has led to the 5-year overall survival (OS) benefit, from approximately 50% to 75%–80% in the last three decades in the adolescent age group.[4] Various hospital-based registries have tried to address the scarcity of data of bone and STS in Indian context in the last decade, but the number is not encouraging enough to gauge the pattern of care of the disease in children and young adults. A study from Tata Memorial Hospital (Mumbai, India) has recently published their institutional data on bone and STS, which shed some light on the demography and clinical aspects of the disease. Among bone tumors, osteosarcoma and Ewing's sarcoma were the most common ones, while in STS, synovial and spindle cell histology were at the top of the list.[5]

A review by Ramaswamy *et al*. further explored the implications of histology, genetic profile, advanced radiological investigations, and chemotherapy regimen in the management

Submitted: 19-Mar-2020 **Accepted:** 29-Apr-2020 **Published:** 11-Jun-2020

Access this article online

Quick Response Code:

Website: www.actamedicainternational.com

DOI: 10.4103/ami.ami_26_20

Address for correspondence: Dr. Abhishek Basu, Department of Radiotherapy, Medical College Kolkata, Kolkata, West Bengal, India.
E-mail: dr.abhishekbasu123@gmail.com

How to cite this article: Basu A, Barman D, Chakrabarty S, Mondal J, Swetha B, Bhattacharjee A, *et al*. A clinicopathological analysis of bone and soft tissue sarcoma in children and young adults: Time to adapt with the rapidly changing landscape?. Acta Med Int 2020;7:7-12.

of bone and STS on Indian patients.[6] In pediatric and adolescent population, non-rhabdomyosarcoma (RMS) STS has slightly different clinicopathological profile and treatment strategies. In pediatric oncology, risk adaptive therapy has been used as a key strategy. In view of comparison of expected survival and quality of life, more intensified treatment approach is considered in high-risk patients with a grave prognosis, while deescalated therapy often offered in borderline to low-risk patients to prevent the long-term morbidity in many childhood cancers. However, this risk adaptive approach is highly debatable in pediatric non-RMSs with very limited evidence till date.[7,8]

This study is to analyze the predictive and prognostic factors of clinical outcome of bone and STS in children (3–17 years) and young adults (18–35 years) and also compare with their adult counterparts.

Subjects and Methods

This is a retrospective, single-institutional study from a prospectively maintained database. We enrolled biopsy-proven patients (aged 3–35 years) of bone and STS, attended at our outpatient department (OPD) during the period of January 2015 to December 2017 and traced till November 2019. Cases with low-grade STS such as Gastrointestinal stromal tumor (GIST), double primary, gynecological sarcomas such as uterine carcinosarcoma and cases who defaulted treatment and follow-up were excluded from analysis.

All patients of the study cohort underwent radiographic assessment and a magnetic resonance imaging of the affected area. Staging included a noncontrast computed tomogram (CT) of the thorax, along with a bone scan, as a part of the metastatic workup. Positron emission tomogram (PET)-CT scan is performed in cases of Ewing's sarcoma, as a part of the metastatic workup. CT scan/bone scan or F-18 PET scans are performed in cases of chondrosarcoma. Complete blood count, renal function test, DTPA scan in some patients, liver function test, and echocardiography were performed to assess the organ functions. Baseline demographic features (age, gender, and socioeconomic status), tumor burden markers (tumor size, lactate dehydrogenase, and serum alkaline phosphatase), and nutritional parameters (serum albumin, body mass index, and hemoglobin) were tested, and nutritional deficiencies were corrected to improve tolerance which affect compliance to treatment and that might have a bearing on outcome.[9] Postsurgery, histopathologic tumor necrosis was assessed by Huvos grading in cases of osteosarcoma and Ewing's sarcoma.[10]

Follow-up time was defined by the period from the date of OPD registration to the date of last attendance or death. The patient-related data were collected from file archives, subsequent OPD visits, and more than 85% of patients attended physically before the final analysis and the rest contacted over telephone. Response assessment was done in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. Time from OPD registration to progression of disease (progression-free survival [PFS]) or death (OS) was assessed by the Kaplan–Meier method. Univariate log-rank analysis and unpaired *t*-test were performed to evaluate the prognostic factors for PFS and OS and further validated by multivariate Cox regression analyses. A P value < 0.05 was considered significant. All the statistical tests were performed using SPSS 23.0 software (Palo Alto, CA, USA).

Results

Bone tumors

A total 145 cases of bone tumors were registered during the study period, and only 82 patients were finally accrued owing to the inclusion criteria. Median follow-up period was 36 months (7–58 months). Among pediatric population, the incidence of Ewing's sarcoma was the most common followed by osteosarcoma, while chondrosarcoma dominated in young adults [Figure 1]. Ewing's sarcoma was more common in females, while for other histology, there was no sex predilection. Univariate analysis and independent sample *t*-test described stage at presentation, site, tumor size (cutoff 8 cm), treatment modalities, pretreatment hemoglobin, and low serum albumin were the significant prognostic factors for local

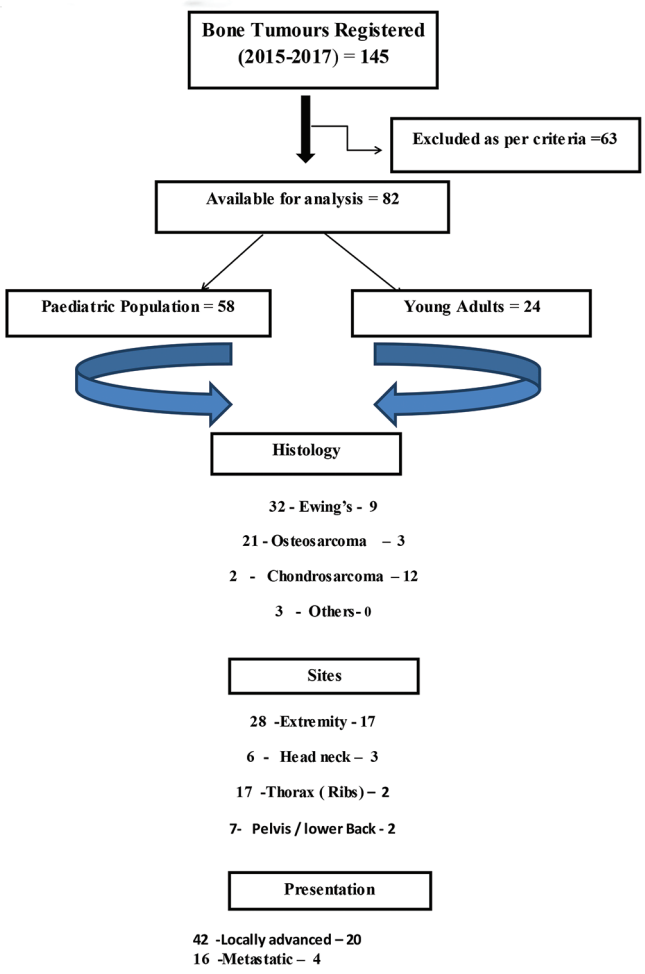

Figure 1: Study cohort of bone tumors

control. Among them, stage at presentation (metastatic), site of disease (pelvic worst), tumor size >8 cm, and treatment modality (multimodality best, palliative worst) turned out to be the significant prognostic markers by multivariate Cox regression analysis [Table 1]. Serum albumin had shown an upward trend with hazard ratio of 0.82, while other tumor-related characteristics had failed to show any significant correlation with recurrence. This study pointed out a trend of better clinical outcome for both osteosarcoma and Ewing's sarcoma in young adults ($P = 0.05$). Overall, locoregional control (LRC) among the two age groups was comparable (61.90% vs. 58.20%). On subset analysis, we found that Ewing's sarcoma and osteosarcoma had poorer local control than others ($P < 0.05$), irrespective of age group. Lung was the most common site of distant metastasis followed by bone and Ewing's sarcoma had the most cases of distant failures.

Majority of the patients received multimodality approach (74.6%), 9.4% received only surgery, while 16% got only palliative care in the form of chemo/radiotherapy (RT) and best supportive care as advised by multidisciplinary tumor board of our institution [Table 2]. On progression or recurrence, 3% of patients received salvage surgery, while 9.4% were offered second-line chemotherapy as per the institutional protocol. Overall, both median PFS and OS have not reached yet; however, in metastatic cohort, they were11 and 22 months, respectively. Three-year LRC and OS were 60.1% and 75.6%, respectively [Table 3].

Soft tissue sarcoma

Ninety-six cases of STS were accrued for final analysis. It was predominant in young adult age group (86%). Extremity location (61%) (lower > upper) and RMS (28%) followed by spindle cell sarcoma (25%) were the most common across the study population [Figure 2].

Young adult age, metastatic stage at presentation, tumor size >8 cm, and palliative or single treatment modality were the significant poor prognostic factors for disease control. Baseline tumor characteristics are depicted in Figure 2 and Table 1. Median follow-up period was 36 months (6–60 months).

Sixty-three percent of patients received multimodality treatment, 12% were treated with single modality (surgery only), while 19.8% got treatment with entirely palliative intent. Doxorubicin-based chemotherapy was the most common regimen; 11% of patients received second-line chemotherapy on progression [Table 2]. Among the radiation cohort, majority were treated in telecobalt machine, while only 7% got image-guided conformal radiation as the later facility was installed lately, precisely in August 2018. Median external beam radiation therapy dose was 60 Gy. Only three patients received interstitial brachytherapy as boost, and two locally recurrent cases were treated with surface mold brachytherapy with customized mold (wax) and plastic catheters. Planning target volume was covered with 100%–150% isodose and the mean doses were 16 Gy/4# and 42 Gy/14#, respectively. In postoperative cases, 2% of the patients had close and/or positive margin which was significant for LRC on univariate analysis but not on Cox regression analysis. In extremity location, 12 patients got that amputated and limb salvage/preservation rate was a meager 5%.

Three-year LRC and OS were 67.1% and 80.5%, respectively [Table 3]. Median PFS and OS have not reached yet in overall population, but they were 9 and 19 months in metastatic cohort, respectively.

Table 1: Evaluation of prognostic factors by multivariate Cox regression analysis

Prognostic factors	Median	Hazard ratio (95% CI)		*P*
		Bone tumors	STS	
Age (years)	24	0.16	2.5 (0.9-7.8)	0.2, 0.03
Sex				
Male	1.78	0.20	0.8	0.6, 0.4
Female	1			
ECOG PS				
0, 1	-	0.43	0.65 (0.1-3.7)	0.8, 0.7
≥2				
Stage	-	4.01 (1.1-14.2)	2.4 (0.4-12.4)	0.03, 0.04
Site	-	2.54 (1.2-5.03)	0.84	0.01, 0.7
Tumor size (cm)	9.5	2.45 (1.1-7.4)	3.5 (1.8-11.4)	0.07, 0.02
Treatment received	-	3.30 (1.3-5.2)	1.81 (0.3-5.2)	0.02, 0.03
Pretreatment hemoglobin (g/dl)	11.0	0.41	0.16	0.01, 0.08
Serum albumin (g/dl)	3.7	0.82	0.73	0.05, 0.06
Serum LDH (U/L)	180	0.02	0.04	0.98, 0.76
Serum alkaline phosphate (IU/L)	212.50	0.21	0.23	0.73, 0.65
Pretreatment NLR	1.60	0.34	0.44	0.34, 0.87
BMI	20.5	0.40	0.33	0.71, 0.42

BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio, LDH: Lactate dehydrogenase, ECOG PS: Eastern Clinical Oncology Group performance status, CI: Confidence interval

Table 2: Different treatment modalities received

Primary	Radical surgery	Combined modality	Palliative chemotherapy	Palliative RT	Brachytherapy	Salvage surgery/CT
Bone tumor (%)	9.4	74.6	8	8	0	3 and 9.4
STS (%)	12	63	11	8.8	5.2	5 and 11

STS: Soft tissue sarcoma, Combined modality: Surgery + EBRT or chemotherapy, RT: Radiotherapy, CT: Chemotherapy, Salvage treatment is offered at recurrence, percentage is depicted, respectively (calculated separately from treatment-naïve cases). EBRT: External beam radiation therapy

Table 3: Pattern of care in bone and soft tissue sarcoma

Primary	Stage	3-year LRC (%)	3-year OS (%)	PFS (months)		Overall survival (months)
				Mean	Median	Median
Bone tumors	Locally advanced	67.8	93.3	41.3	-	-
	Metastatic	39.8	27.3	22.4	11	22
	Overall	60.1	75.6	36.3	-	
STS	Locally advanced	69.1	91.2	47	-	
	Metastatic	40.5	40	30	9	19
	Overall	67.1	80.5	43	-	
Overall		62.4	76.4	39	-	

STS: Soft tissue sarcomas, LRC: Locoregional control, OS: Overall survival, PFS: Progression-free survival

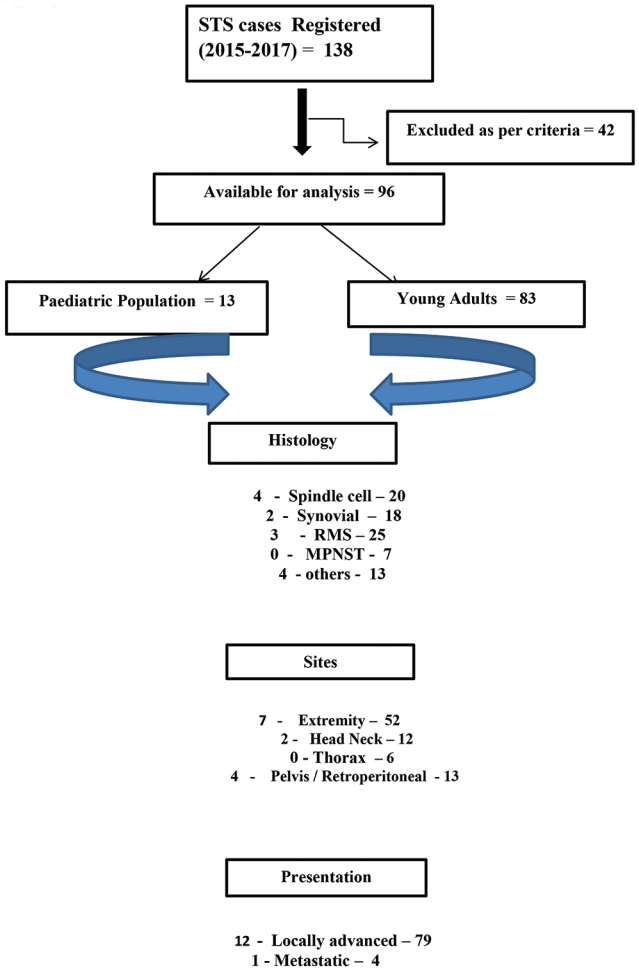

Figure 2: Study cohort of soft tissue sarcoma

Kaplan–Meier analysis showed that PFS in bone and STS was related to tumor size significantly [Figures 3 and 4] and children had better OS with 3-year OS in all cases analyzed together (89.7% vs. 71.8%) [Figure 5].

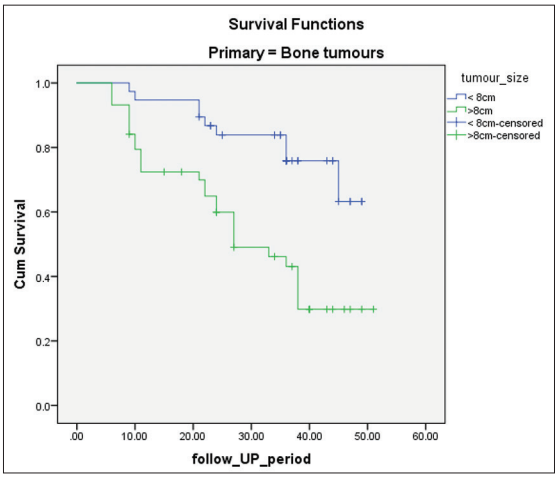

Figure 3: Progression free survival in bone tumors in view of tumor size. Log rank $P < 0.01$

Discussion

Both rarity and heterogeneity make bone and STS a challenging disease entity to study. Our study correlates fairly not only with Indian data on the these tumors but also with slight difference as rightfully so, because of the age stratification.[6,11,12] Tumor size, stage at presentation, and treatment modality were the significant prognostic factors for both bone and STS. Overall 48% of population presented with tumor size >8 cm. Pelvic location was worst for disease control in bone tumors in accordance with previous evidence.[13,14] Few studies had shown adjuvant radiation (in non-RMS STS) in poor light, when it comes to PFS; however, our study did not find such association.[15,16] In fact, adjuvant radiation was indispensable

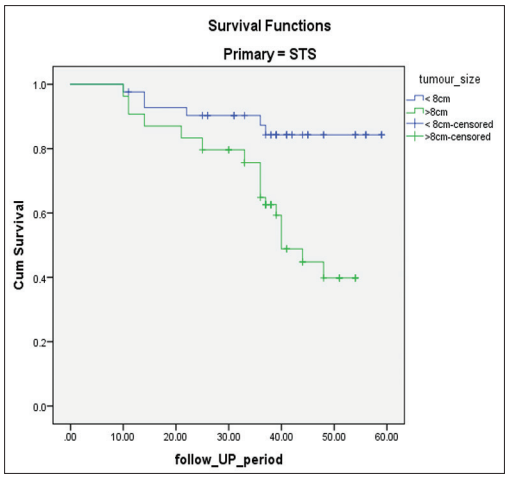

Figure 4: Progression free survival in soft tissue sarcoma in view of tumor size. Log rank $P = 0.01$

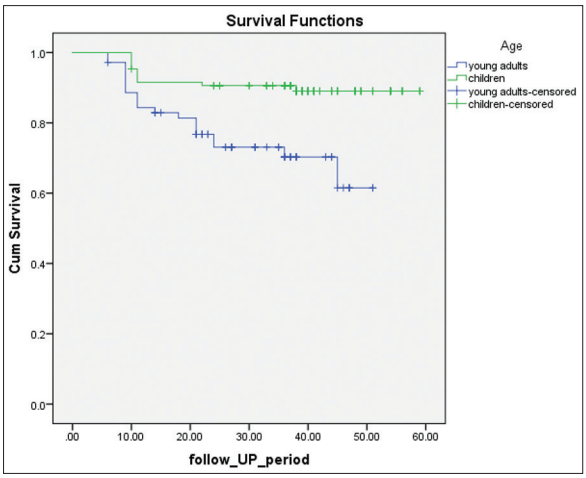

Figure 5: Overall survival in children and young adults in bone and soft tissue sarcoma together. Log rank $P = 0.03$

in limb-preserving cases and radical RT was offered in inoperable tumors barring retroperitoneal sarcomas, owing to unavailability of linear accelerator machine in earlier part of the study period. Foulon *et al*.[17] had described that the benefit of adjuvant radiation was even more profound in Ewing's sarcoma with tumor volume more than 200 cc, which is indirectly supported by our analysis too. Hypoalbuminemia and anemia were the independent prognostic factors of treatment tolerance and local control but not with OS, which also supports the published literature.[18] Acute hematologic and gastrointestinal toxicity was more with multiagent chemotherapy but was not life-threatening. Ten percent of the patients had Grade 2/3 late skin toxicity in the form of fibrosis, edema, and impaired joint mobility.

Limb preservation rate in our patient series is not at par with national (85%) or international (80%)[5,19] data due to lack of advanced techniques such as extracorporeal radiation, image guided radiotherapy (IGRT), nonuniform chemotherapy regimen, and diagnostic delay.

Although we believe that our data are robust, certain drawbacks could impact our results. First, retrospective design is itself a caveat, but still we have to keep in mind both the rarity and age restriction of the disease under evaluation. Attempts had been made for a prospective trial, many a times before but were closed due to poor accrual.[20,21] Second, this study does not focus on symptom burden, pretreatment delay, or immunohistochemistry stratification, neither it analyzes the psychological distress[22] among the patients. Moreover, we also admit that comprehensive molecular characterization has sharpened the prognostication of bone and STSs in recent years,[23,24] but heterogeneous laboratory reports, small sample size, and nonavailability have led to its omission in our analysis. Finally, detailed analysis of tumor necrosis postneoadjuvant chemotherapy is lacking due to poor accrual.

Having that said, we believe that this single-institutional audit on bone and STS among children and young adults from Eastern India evaluates the unmet needs of the disease and will be helpful for future evidence. Head-to-head comparisons in similar groups in these tumors are very scarce for obvious reasons.

Recent evidences and future direction

Immunotherapy along with targeted molecules has paved its way in the management of bone and STS of late. ANNOUNCE trial[25] failed to show OS benefit in addition of olaratumab in STS which further scrutinized concept of the Food and Drug Administration-accelerated approval. SARC 028 study[26] also could not establish the role of pembrolizumab in pleomorphic-undifferentiated sarcoma and liposarcoma. However, these results are not discouraging as more accessible targets are yet to be explored. Another study (STRASS) has envisaged the role of preoperative radiation in retroperitoneal sarcoma. It was only beneficial in liposarcoma subgroup which may be confounded by histopathological heterogeneity.[27]

Better OS in children in our study cohort is in accordance with the review published by Winette *et al*.,[28] and further studies are required to investigate the factors behind it.

Conclusions

Locally advanced stage, low tumor volume, and preferably extremity site along with chemo/radiosensitive histology make a favorable outcome for bone and STS in children and young adults. We recommend multidisciplinary management with emphasis on early intervention in these tumors. Histology-specific multi-institutional studies will answer the unmet needs that we could not interpret. The landscape of sarcoma is changing, and we need to document more multi-institutional long-term data to gauge the nuances as well.

Acknowledgment

We acknowledge the efforts of our colleagues from medical and surgical oncology.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med 2005;353:701-11.
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, *et al*., editors. SEER Cancer Statistics Review. Bethesda, MD: National Cancer Institute; 1975-2014. Available from: http://www.seer.cancer.gov/csr/1975_2013/. [Last accessed on 2019 Dec 01].
3. Dinshaw KA, Ganesh B. Hospital Based Cancer Registry. Annual Report 2001. Mumbai: Tata Memorial Hospital; 2005. p. 90-1.
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30.
5. Bajpai J, Khanna N, Vora T, Gulia A, Laskar S, Puri A, *et al*. Analysis of bone and soft-tissue sarcomas registered during the year 2012 at Tata Memorial Centre, including clinical outcomes. Indian J Cancer 2018;55:37-44.
6. Ramaswamy A, Rekhi B, Bakhshi S, Hingmire S, Agarwal M. Indian data on bone and soft tissue sarcomas: A summary of published study results. South Asian J Cancer 2016;5:138-45.
7. Pui CH, Gajjar AJ, Kane JR, Qaddoumi IA, Pappo AS. Challenging issues in pediatric oncology. Nat Rev Clin Oncol 2011;8:540-9.
8. Pappo AS, Rao BN, Jenkins JJ, Merchant T, Poquette CA, Cain A, *et al*. Metastatic nonrhabdomyosarcomatous soft-tissue sarcomas in children and adolescents: The St. Jude Children's Research Hospital experience. Med Pediatr Oncol 1999;33:76-82.
9. Bajpai J, Puri A, Shah K, Susan D, Jambhekar N, Rekhi B, *et al*. Chemotherapy compliance in patients with osteosarcoma. Pediatr Blood Cancer 2013;60:41-4.
10. Huvos AG. Bone Tumors: Diagnosis, Treatment and Prognosis. Philadelphia, USA: W. B. Saunders; 1991. p. 122-8.
11. Biswas B, Agarwala S, Rastogi S, Khan SA, Mohanti BK, Sharma DN, *et al*. High burden of metastases and poor outcome in pelvic PNET. Pediatr Blood Cancer 2013;60:E97-9.
12. Biswas B, Deo SV, Agarwala S, Sharma DN, Vishnubhatla S, *et al*. Evaluation of outcome and prognostic factors in extraosseous Ewing sarcoma. Pediatr Blood Cancer 2014;61:1925-31.
13. Laskar S, Basu A, Muckaden MA, D'Cruz A, Pai S, Jambhekar N, *et al*. Osteosarcoma of the head and neck region: Lessons learned from a single-institution experience of 50 patients. Head Neck 2008;30:1020-6.
14. Puri A, Gulia A, Pruthi M. Outcome of surgical resection of pelvic osteosarcoma. Indian J Orthop 2014;48:273-8.
15. Waxweiler TV, Rusthoven CG, Proper MS, Cost CR, Cost NG, Donaldson N, *et al*. Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Children: A Surveillance, Epidemiology, and End Results Analysis Validating COG Risk Stratifications. Int J Radiat Oncol Biol Phys. 2015;92:339-8.
16. Cheung MC, Zhuge Y, Yang R, Ogilvie MP, Koniaris LG, Rodríguez MM, *et al*. Incidence and outcomes of extremity soft-tissue sarcomas in children. J Surg Res 2010;163:282-9.
17. Foulon S, Brennan B, Gaspar N, Dirksen U, Jeys L, Cassoni A, *et al*. Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group. Eur J Cancer 2016;61:128-36.
18. Biswas B, Rastogi S, Khan SA, Shukla NK, Deo SV, Agarwala S, *et al*. Hypoalbuminaemia is an independent predictor of poor outcome in metastatic Ewing's sarcoma family of tumours: A single institutional experience of 150 cases treated with uniform chemotherapy protocol. Clin Oncol (R Coll Radiol) 2014;26:722-9.
19. Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. Lancet Oncol 2003;4:335-42.
20. Parsons HM, Penn DC, Li Q, Cress RD, Pollock BH, Malogolowkin MH, *et al*. Increased clinical trial enrollment among adolescent and young adult cancer patients between 2006 and 2012-2013 in the United States. Pediatr Blood Cancer 2019;66:e27426.
21. Reed DR, Naghavi A, Binitie O. Sarcoma as a model for adolescent and young adult care. J Oncol Pract 2019;15:239-47.
22. Smith AW, Parsons HM, Kent EE, Bellizzi K, Zebrack BJ, Keel G, *et al*. Unmet support service needs and health-related quality of life among adolescents and young adults with cancer: The AYA HOPE study. Front Oncol 2013;3:75.
23. Panagopoulos I, Mertens F, Isaksson M, Limon J, Gustafson P, Skytting B, *et al*. Clinical impact of molecular and cytogenetic findings in synovial sarcoma. Genes Chromosomes Cancer 2001;31:362-72.
24. Ladanyi M, Antonescu CR, Leung DH, Woodruff JM, Kawai A, Healey JH, *et al*. Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: A multi-institutional retrospective study of 243 patients. Cancer Res 2002;62:135-40.
25. Tap WD, Wagner AJ, Papai Z, Ganjoo KN, Yen CC, Schoffski P, *et al*. Announce: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS) J Clin Oncol 2019;37(18 Supp l):LBA3. [Google Scholar].
26. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, *et al*. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18:1493-501.
27. Bonvalot S, Gronchi A, Pechoux CL, Swallow CJ, Strauss DC, *et al*. STRASS (EORTC 62092): Aphase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. JClin Oncol 2019;37:11001.
28. Winette T, van der Graaf A, Orbach D, Judson IR, Ferrari A. Soft tissue sarcomas in adolescents and young adults: A comparison with their paediatric and adult counterparts. Lancet Oncol 2017;18:e166-75.