FCO • 9(1) • 2018 •3–9
DOI: 10.2478/fco-2018-0001

sciendo

Forum of Clinical **Oncology**

Functional And Survival Outcome Of Egyptian Children And Adolescents With Malignant Bone Tumors: An Experience In A Setting Of Limited Health Resource

Research Article

Mokhtar M Galila[1], Ebeid FS Fatma[1], Ishak Al Sherif[2], Ragab A Iman[1], Yousef AS Khaled[1]

[1]Paediatrics Department, Orthopaedic Surgery
[2]Paediatrics Department, Faculty of Medicine-Ain Shams University

Received 22 March 2018; Accepted 17 March 2019

Abstract: Objective: Evaluate outcome of paediatric malignant bone tumours at Ain Shams University, Egypt, from January 2003 to July 2016. Methods: Retrospective data analysis regarding clinico-epidemiological aspects, treatment outcomes, survival analysis and musculoskeletal tumour society score (MSTS score). Results: The study included 37 patients; 22 had Ewing sarcoma (ES) and 15 had osteosarcoma, male: female ratio 0.85:1, median ages of 11. The overall frequency was 2.3% among all cancers. There is wide range of time lag until diagnosis. Patients with ES were significantly younger than those with osteosarcoma were. Swelling was the most common presenting symptom and femur was the most common affected site. Fifteen patients fulfilled MSTS criteria; most of them had excellent MSTS score, which significantly affected by type of surgery. ES patients were treated with POG#9354/CCG#7942 protocols and osteosarcoma with CCG#7921 protocol. Limb salvage was the most common type for surgical local control. Most common cause of death was relapse, whereas infection was the most common complication of treatment. 1-year, 2-year, 3-year overall-survival of osteosarcoma were 93.3%, 40%, and 13.3% respectively and 77.3%, 40.9%, and 18.2% respectively for ES. 1-year, 2-year, 3-year event-free-survival were 80%, 40%, and 13.3% respectively and 72.7%, 22.7%, and 18.2% respectively for ES patients. Conclusion: Although survival rates for malignant bone tumours are still unsatisfactory, the functional outcome of extremity tumours after limb salvage procedures is promising

Keywords: *Paediatric bone tumour • Egypt • Ewing sarcoma • Osteosarcoma*

1. Introduction

Primary malignant bone tumours are rare cancers among all type of cancers in paediatric populations accounting with an incidence rate of 9.02 per million population compare to 45.36 per million in leukaemia diagnosis in United States from 2001-2009 [1]. They represent 6 % of all cancers in those less than twenty years old with osteosarcoma and Ewing's sarcoma being the most common types [2].

Osteosarcoma is considered the most common malignant bone tumour in paediatric population, with an incidence of 4.4 per million [3]. The main therapies of osteosarcoma include chemotherapy and tumour excision strategies, with a 5-year event-free survival in extremity localized, non-metastatic disease reaching up to 60-70% [4].

The second most common malignant bone tumour is Ewing sarcoma, with an incidence of 2.9 per million [5]. The cure rate for patients with Ewing sarcoma has increased with the introduction of ifosfamide and etoposide to standard chemotherapy regimens [5, 6]. With the advances in orthopaedic surgical approaches and the use of prosthesis [7] , the aim is a survival with

* *E-mail: dr.fatma_ebeid@yahoo.com*

fair functional outcome, yet mild to moderate disability is still reported in 32% of long term survivors [8].

This work was designed to evaluate clinic-demographic characteristics, survival and functional status of Egyptian paediatric patients with malignant bone tumours.

2. Patients and Methodology

The present study is a retrospective study that is conducted at Paediatric Haematology/Oncology department, Ain Shams University, Cairo, Egypt. Paediatric patients with primary malignant bone tumour diagnosed and treated in the period from January 2003 to July 2016 were recruited.

The patients' hospital records were reviewed and personnel interviews with the patients and/or their caregivers were also performed to collect the required data. Special emphasis was laid on demographic characteristics, delay of diagnosis calculated from time of first appearance of complaint until time of diagnosis, residency and family history of bone tumours or other malignancies. Clinical presentation, pathologic diagnosis, disease risk criteria, the used protocol, pathological response, complications occurred while on therapy or after, and causes of death during the defined period of the study were recorded. Baseline laboratory evaluation and initial radiological investigation, type of biopsy, immune histochemistry, pathological diagnosis, and site of tumour were analysed. Enneking surgical staging of musculoskeletal sarcomas was used for staging of bone sarcomas.

Patients with osteosarcoma were treated according to Intergroup Study 0133 (CCG-7921 and POG-9351) and non-randomly assigned to regimen A (cisplatin, doxorubicin, and HDMTX) without muramyl tripeptide, an induction period of chemotherapy lasting 10 weeks, then definitive resection of primary tumor were performed with assessment of necrosis index. Maintenance therapy was scheduled to start at week 12 until week 31 in regimen A [9]. Patients with ES were treated according to protocol POG9354/CCG 7942 standard regimen. Chemotherapy courses were VDC alternating with IE to be administered every three weeks. The standard regimen prescribed seventh cycles of chemotherapy delivered over 48 weeks. Local control of the disease, to be performed after week twelve, consisted of resection or radiotherapy. Those who had close or positive margins received post-resection radiotherapy [6, 10].

Event-free survival (EFS) was calculated from the date of diagnosis to date of events that were identified as resistance, relapse, death, or whichever occurred first, and during analysis patients who neither relapsed, showed resistance, nor died were censored at last assessment before the lost follow-up.. Overall survival (OS) was calculated from the date of diagnosis to date of events that was identified as death from any cause, and during analysis, living patients or patients lost to follow-up were censored on last known date they were alive.

Functional status was assessed by using Musculoskeletal Tumour Society Score (MSTS score) [11]. This MSTS score was established on six items each for upper and lower extremities. Each item was allocated a value from zero to five points, with five demonstrating the best function. The values form each items was added and then the functional score will be presented as a percentage of the maximum possible thirty points score. The MSTS score was then categorised into four categories; poor if less than 25%; fair if from 25% to 49%; good if from 50% to 75% and excellent if the score was above 75% of maximum score [12]. The protocol of the study was approved by the institutional regulatory authority of the Paediatric Department, Faculty of Medicine, Ain Shams University and a verbal informed consent was obtained from patients and/or their legal guardian.

Statistical analysis: Statistical package for social sciences (SPSS), version 20.0 for Windows was used. Quantitative variables were described in the form of mean and standard deviation (SD) or median and interquartile range (IQR: 25th-75th percentiles). Qualitative variables were described as number and percentage. Kaplan-Meier analysis was used to estimate the overall survival and disease-free rates. Log-rank test was used to compare the different prognostic factors. In order to compare two independent groups with quantitative parametric distributed variables, Independent t-test was performed. Pearson correlation coefficients were applied in order to examine the relation between two studied parameters within the same group. The cut-off level for p-value was considered significant if the P value was below 0.05.

3. Results

We revised data for 37 patients with pathology proven primary malignant bone tumour, they were 20 females (54.1%) and 17 males (45.9%) with median age of 11, (IQR) (5 – 14) and range (2 – 18) years. They were diagnosed among 1581 patients of all malignancy (2.3%). Most of patients 77.3% were resident in Great Cairo and Delta; 11 patients (50%) and six (27.3%) respectively, and five (22.7%) in Upper Egypt. 50% were from urban area and the other half from rural ones.

3.1. Clinico-demographic Characteristics of the studied patients:

Four (12.1%) patients had positive parental consanguinity. Two cases with ES had positive family history of malignancy; one of them had her sister diagnosed with brain tumour and the other with bone tumour. None of the recruited patients had previous history of malignancy nor previously treated with radiotherapy. There is wide range of time lag between first presentation and diagnosis (9 - 1065 days), it was caused by misdiagnosis in three cases with median (IQR) time lag of 90 days (45-180). The three misdiagnosed patients were initially diagnosed as osteomyelitis, Guillain-Barre syndrome and rheumatic fever.

Twenty-two patients were diagnosed as Ewing sarcoma (59.5%) and 15 patients as osteosarcoma (40.5%). Patients with ES were significantly younger than those with osteosarcoma with median age of 13 years for osteosarcoma and 5 years for Ewing sarcoma.

As regards clinical presentation, as illustrated in Table1, swelling was the most common presenting symptom (48.5%), followed by pain (45.4%); and (80%) of patients presenting with swelling had associated pain. Patients with osteosarcoma presented more frequently with swelling, pain and bone fracture than patients with ES. Femur was the most common affected site for ES and osteosarcoma 35% and 59.90% respectively. Tibia was the second most common site for osteosarcoma and chest wall for Ewing sarcoma.

Most of patients (89.2%) presented at stage II; 80.0% and 95.4% for osteosarcoma and ES respectively. Two patients with osteosarcoma presented with stage I. Two patients only presented with metastasis at time of presentation (5.4%), one patient with left distal femur osteosarcoma presented with skip metastasis at left proximal femur, small soft tissue component at the costo-vertebral junction of left 4th and 12th ribs and sclerotic soft tissue at the right 3rd rib. The other patient with left hemi-thorax ES presented with lung metastasis. There was no statistical difference between type of bone tumour either and staging (P=0.197)

3.2. Treatment Modalities of the Studied Patients

Patients with Ewing sarcoma were treated with regimen A (POG #9354/CCG #7942 protocol), the standard dosing regimen. Nine out of 13 patients (69.2%) with osteosarcoma were treated with regimen A (protocol CCG 7921), two patients (15.4%) were shifted to regimen B (protocol CCG 7921) with the addition of ifosfamide due to disease progression and two patients refused treatment. Most of osteosarcoma patients had tumour necrosis <90% (83.3%), and only two patients had tumour necrosis >90% (16.7%).

Limb salvage was the most common surgical local control modalities (59.26%) and two patients underwent amputation (7.4%) both of them had osteosarcoma. One of them had amputation due to aggressive behaviour of the tumour, and the other patient had amputation due to osteomyelitis after limb salvage operation.

3.3. Complications of therapy

Infection was the most common complication of treatment, 22 patients (59.5%) had infection, six patients (27.2%) of them had febrile neutropenia. 11 (29.7%) suffered from other complications; three patients (8.1%) had haemorrhagic cystitis, and four patients (10.8%) had interstitial nephritis, renal failure or SIADH.

3.4. Musculoskeletal Tumour Society scoring system

Fifteen (48.4%) patients (9 with osteosarcoma and six with ES) had extremity tumours and underwent the MSTS with range from 50 to 87 and mean± SD (74.53 ± 10.39). 60% of patients had excellent MSTS >75 (5 patients (55.6%) with osteosarcoma and 4 (66.6%) with ES); 40% had MSTS 50-75 (4 patients with osteosarcoma and 2 with ES). None of patients had poor or fair MSTS. Table 2 showed statistical difference between MSTS with type of surgery and staging. There was no significant statistical correlation between MSTS with age at presentation (r=0.274, P=0.323) or delay in diagnosis (r=-0.202, P=0.488).

3.5. Survival of the studied patients

At one-year evaluation, eighteen patients are living (66.7%) while nine patients (33.3%) died. Most common cause of death is relapse in four patients (44.4%), disease progression in two patients (22.3%) and complications of treatment in three (33.3%). Seven patients (25.9%) had relapse after end of treatment and 20 patients (72.1%) were relapse free. Ten patients had lost follow-up.

In Ewing Sarcoma, 28.5% of the treated patients had relapse and 71.1% were relapse free, four (28.5%) died and ten (71.1%) were alive and eight patients lost follow-up. In Osteosarcoma patients treated with regimen

Table 1: Clinico-demographic Characteristics of the studied patients

Demographic data	Total No (%)		Osteosarcoma No (%)		Ewing Sarcoma No (%)		X2	P-value
Sex: Female: Male	20 (54.1%):17(45.9%)		5 (33.3%):10(66.7%)		15 (68.2%): 7 (31.8%)		4.361	0.037
Age (Yrs):Median (IQR)[Range]	11 (5 – 14) [2 – 18]		13 (12 - 15)[3 – 18]		5 (4 - 11)[2 – 15]		-2.785*	0.005
Presenting symptom	Total No (%)		Osteosarcoma No (%)		Ewing Sarcoma No (%)		X2	P-value
Bone pain	15	45.4%	10	66.67%	5	27.78%	4.991	0.025
Swelling	16	48.5%	11	73.33%	5	27.78%	6.798	0.009
History of trauma	4	12.1%	3	20.00%	1	5.56%	1.603	0.205
Systemic manifestation	5	15.2%	1	6.67%	4	22.22%	1.540	0.215
Fever	5	15.2%	1	6.67%	4	22.22%	1.540	0.215
Loss of weight	2	6.1%	0	0.00%	2	11.11%	1.774	0.183
Loss of appetite	1	3.0%	0	0.00%	1	5.56%	0.859	0.354
Neurological manifestation	7	21.3%	2	13.33%	5	27.78%	1.021	0.312
Sphincter Dysfunction	4	12.1%	1	6.67%	3	16.67	0.768	0.381
Inability to walk	5	15.2%	1	6.67%	4	22.22%	1.540	0.215
Headache	1	3.0%	0	0.00%	1	5.56%	0.859	0.354
Bone fracture	3	9.1%	3	20.00%	0	0.00%	3.960	0.047
Eye proptosis	1	3.0%	0	0.00%	1	5.56%	0.859	0.354
Site of tumour	Total No (%)		Osteosarcoma No (%)		Ewing Sarcoma No (%)		X2	P-value
Femur	16	45.71%	9	59.90%	7	35%	2.159	0.141
Chest wall	5	14.28%	1	6.60%	4	20%	1.244	0.265
Tibia	3	8.57%	3	20%	0	0%	4.375	0.036
Dorsa vertebrae	2	5.71%	1	6.60%	1	5%	0.044	0.834
Lumbo-sacral area	2	5.71%	0	0%	2	10%	1.591	0.207
Mandible	2	5.71%	1	6.60%	1	5%	0.044	0.834
Brain	1	2.85%	0	0%	1	5%	0.772	0.379
Clavicle	1	2.85%	0	0%	1	5%	0.772	0.379
Humerus	1	2.85%	0	0%	1	5%	0.772	0.379
Maxillary bone	1	2.85%	0	0%	1	5%	0.772	0.379
Paraspinal	1	2.85%	0	0%	1	5%	0.772	0.379

A, two relapsed (22.2%) and seven were relapse free (77.8%), four died (44.4) and five are still alive (55.6%). Two patients (15.4%) treated with regimen B; one of them relapsed and both are alive. Two patients refused treatment, one died and one lost follow up. In addition two patients lost follow-up.

Overall survival and event-free-survival for osteosarcoma and ES is illustrated in Figure 1. Associations between both OS and EFS and demographic (age and sex), functional (MSTS), and therapy (chemotherapy regimen and surgical procedures) of Ewing and osteosarcoma patients were not statistically significant except that overall survival for osteosarcoma patients was better for those who did not underwent amputation (P=0.004) and those who had excellent MSTS (P=0.007).

4. Discussion

The cumulative frequency of malignant bone tumours (Ewing sarcoma and Osteosarcoma) among all malignancy at our centre was 2.3%. Similarly, Li et al. found that primary bone tumour represented about 2% to 5% of all cancer in those age 0-19 years in SEER data [13] and 3.2% in a national study in Thailand [14] . Ewing sarcoma was found to be the most common primary bone tumour in our studied patients (59.5%). This is in contrast to findings of other authors, who stated that osteosarcoma is considered the most common type of primary bone tumour in childhood and adolescence [15, 16].

We recorded wide range of time lag until diagnosis, this could be explained mostly by difference in

Table 2: Comparison between MSTS and some studied variables

Variables		MSTS system		Independent t-test	
		Mean ± SD	Range	t	p-value
Sex	Female	73 ± 11	50 – 87	0.533	0.603
	Male	76 ± 10	65 – 87		
Type	Ewing sarcoma	75 ± 7	62 – 82	0.53	0.601
	Osteosarcoma	73 ± 13	50 – 87		
Staging	II	76.29 ± 8.18	62 – 87	3.106	0.008
	III	50.0 ± 0.0	50 – 50		
Type of surgery	Limb salvage operation	76.29 ± 8.18	62 – 87	4.435	<0.001
	Amputation	57.5 ± 10.61	50 – 65		

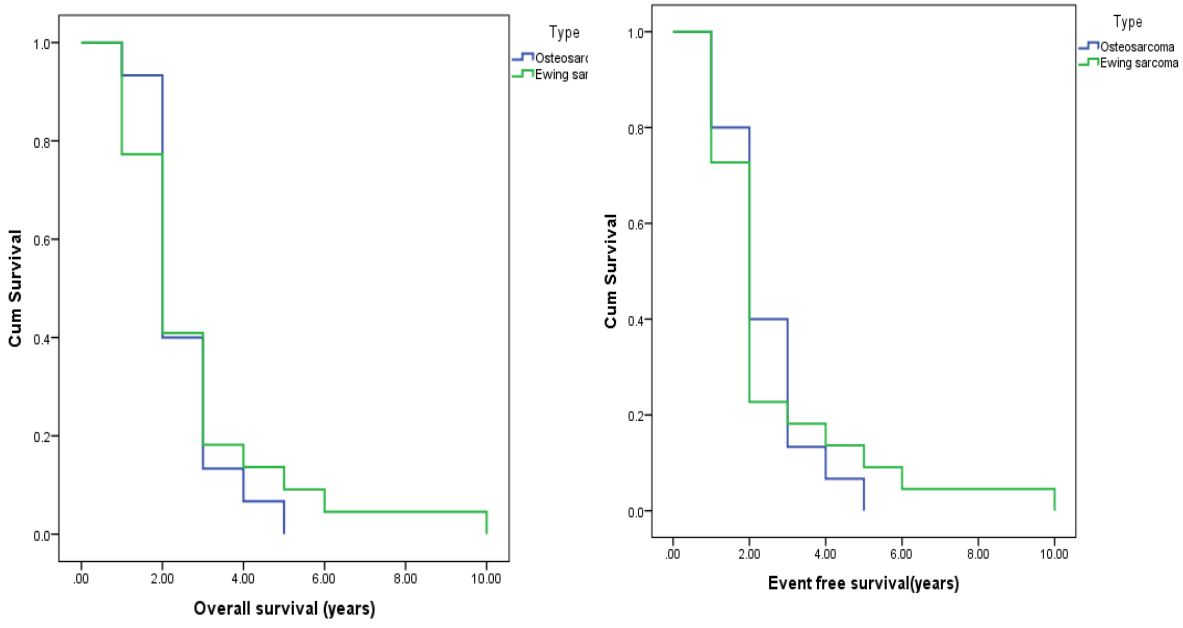

Figure 1: Overall and event free survival of the studied patients with osteosarcoma and Ewing sarcoma

healthcare system , healthcare providers misdiagnosis and the presence of pain may lead to misdiagnosed as strains or tendinitis, which finally lead to delay in diagnosis more than 6 months [17]. Some laboratory findings can also promote misdiagnosing the tumour as osteomyelitis as many Ewing's patients will have high inflammatory markers [18]. These factors highlighted the importance of improve the awareness about paediatrics bone tumour among physicians, especially those in the primary care centres.

Bone tumours commonly manifest with pain and swelling and are often attributed to sports injuries in active adolescents. Failure of symptoms to resolve after several weeks of conservative management should alert the clinician to a more serious underlying cause and prompt further investigation[19]. In our cohort, the systemic symptoms were not common and that is in agreement with other published studies [20, 21].

The MSTS score evaluates the functional condition after completed tumour treatment [22]. The fifteen patients subjected to MSTS scoring system had good to excellent scoring. The amputee had lower MSTS score than patients who had limb-sparing surgery; this is in agreement with previous published data [23].This highlights the importance of limb salvage procedures on the functional status of those young population that may affect their quality of life. The limb salvage surgery was the mainstay of treatment of extremities at our centre over the last 20 years, and apart from the psychological impact, it may be more cost effective in countries with limited health resources.

Current management of osteosarcoma comprises preoperative chemotherapy followed by surgical resection of all tumour including metastases, and postoperative chemotherapy[4]. In our study the chemotherapy used for treatment of osteosarcoma was based on high dose methotrexate, adriamycin, cisplatin (MAP) with shift to regimen B adding ifosfamide in two patients following aggressive disease progression. However, a different approach in poor responders and those showing progression is warranted as the addition of ifosfamide to standard chemotherapy did not result in improve EFS [9] .

The standard treatment for ES includes the use of multi-agent regimens [20]. We used the standard three weekly regimen; however, it was more recently proven that the interval compression of chemotherapy every two weeks is more effective than the three weekly regimen, without increase in toxicity for those with localized Ewing sarcoma [24] and we planned to change the treatment accordingly although this may portend extra costs due to routine use of growth factors.

With chemotherapy and surgery, OS and EFS at 5-years for patients with non-metastatic osteosarcoma can be expected to be approximately 75% and 65%, respectively [25].We recorded a much lower 3-year EFS in osteosarcoma and ES of 13.3% and 18.2% respectively. This necessitates a re-evaluation of possible aetiologies, including raising awareness for clinical presentation to reach to an earlier diagnosis, interval compression of chemotherapy in ES and different approaches to poor responders' osteosarcoma including immunomodulation. Improvements in clinical outcomes may largely been attributable to a multidisciplinary team-based approach consequently at 2014, a multidisciplinary teamwork (paediatrician, orthopaedic surgeon, and nuclear medicine physician) evolved and finally succeeded in establishment of a weekly multidisciplinary solid tumour clinic at Paediatric haematology/ oncology clinic to improve the management and outcome of paediatric bone tumour through better communication and rapid decisions. Furthermore in the developing world, the care of children with cancer could be improved by expand the National financial coverage for treatment and supportive care.

5. Conclusion

Paediatric bone tumours are rare type of cancer that necessitates improvement of awareness. Our survival results are still lagging behind mostly due to late referral and a large number of poor responders. The functional outcome for survivors of extremity tumours is satisfactory.

References

[1] Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J: Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. Pediatrics 2014, 134(4):e945-955.

[2] Heare T, Hensley MA, Dell'Orfano S: Bone tumors: osteosarcoma and Ewing's sarcoma. Current opinion in pediatrics 2009, 21(3):365-372.

[3] Mirabello L, Troisi RJ, Savage SA: Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 2009, 115(7):1531-1543.

[4] Luetke A, Meyers PA, Lewis I, Juergens H: Osteosarcoma treatment - where do we stand? A state of the art review. Cancer treatment reviews 2014, 40(4):523-532.

[5] Esiashvili N, Goodman M, Marcus RB, Jr.: Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. Journal of pediatric hematology/oncology 2008, 30(6):425-430.

[6] Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, Gebhardt MC, Dickman PS, Perlman EJ, Meyers PA et al: Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. The New England journal of medicine 2003, 348(8):694-701.

[7] Benedetti MG, Bonatti E, Malfitano C, Donati D: Comparison of allograft-prosthetic composite reconstruction and modular prosthetic replacement in proximal femur bone tumors: functional assessment by gait analysis in 20 patients. Acta orthopaedica 2013, 84(2):218-223.

[8] Stish BJ, Ahmed SK, Rose PS, Arndt CA, Laack NN: Patient-Reported Functional and Quality of Life Outcomes in a Large Cohort of Long-Term Survivors of Ewing Sarcoma. Pediatric blood & cancer 2015, 62(12):2189-2196.

[9] Meyers PA, Schwartz CL, Krailo M, Kleinerman ES, Betcher D, Bernstein ML, Conrad E, Ferguson W, Gebhardt M, Goorin AM et al: Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. Journal

of clinical oncology : official journal of the American Society of Clinical Oncology 2005, 23(9):2004-2011.

[10] Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, Marina N, Leavey P, Gebhardt M, Healey J et al: Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009, 27(15):2536-2541.

[11] Davis AM, Wright JG, Williams JI, Bombardier C, Griffin A, Bell RS: Development of a measure of physical function for patients with bone and soft tissue sarcoma. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 1996, 5(5):508-516.

[12] Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ: A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clinical orthopaedics and related research 1993(286):241-246.

[13] Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL: Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics 2008, 121(6):e1470-1477.

[14] Wiangnon S, Veerakul G, Nuchprayoon I, Seksarn P, Hongeng S, Krutvecho T, Sripaiboonkij N: Childhood cancer incidence and survival 2003-2005, Thailand: study from the Thai Pediatric Oncology Group. Asian Pacific journal of cancer prevention : APJCP 2011, 12(9):2215-2220.

[15] Lietman SA, Joyce MJ: Bone sarcomas: Overview of management, with a focus on surgical treatment considerations. Cleveland Clinic journal of medicine 2010, 77 Suppl 1:S8-12.

[16] Choi EY, Gardner JM, Lucas DR, McHugh JB, Patel RM: Ewing sarcoma. Seminars in diagnostic pathology 2014, 31(1):39-47.

[17] Widhe B, Widhe T: Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. The Journal of bone and joint surgery American volume 2000, 82(5):667-674.

[18] Nakamura T, Grimer RJ, Gaston CL, Watanuki M, Sudo A, Jeys L: The prognostic value of the serum level of C-reactive protein for the survival of patients with a primary sarcoma of bone. The bone & joint journal 2013, 95-B(3):411-418.

[19] Arndt CA, Rose PS, Folpe AL, Laack NN: Common musculoskeletal tumors of childhood and adolescence. Mayo Clinic proceedings 2012, 87(5):475-487.

[20] Moore DD, Haydon RC: Ewing's sarcoma of bone. Cancer treatment and research 2014, 162:93-115.

[21] Moore DD, Luu HH: Osteosarcoma. Cancer treatment and research 2014, 162:65-92.

[22] Tunn PU, Pomraenke D, Goerling U, Hohenberger P: Functional outcome after endoprosthetic limb-salvage therapy of primary bone tumours--a comparative analysis using the MSTS score, the TESS and the RNL index. International orthopaedics 2008, 32(5):619-625.

[23] Aksnes LH, Bauer HC, Jebsen NL, Folleras G, Allert C, Haugen GS, Hall KS: Limb-sparing surgery preserves more function than amputation: a Scandinavian sarcoma group study of 118 patients. The Journal of bone and joint surgery British volume 2008, 90(6):786-794.

[24] Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, Marcus K, Sailer S, Healey JH, Dormans JP et al: Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012, 30(33):4148-4154.

[25] Bielack SS, Kempf-Bielack B, Branscheid D, Carrle D, Friedel G, Helmke K, Kevric M, Jundt G, Kuhne T, Maas R et al: Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009, 27(4):557-565.