JBUON 2021; 26(3): 1102-1110
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Late effects of osteosarcoma and its treatment in pediatric patients: A single-center experience

Nurdan Tacyildiz[1], Hatice Mine Cakmak[1], Emel Unal[1], Handan Dincaslan[1], Gulsah Tanyildiz[1], Incesoy Ozdemir Sonay[1], Omer Kartal[2], Yasin Yilmaz[1], Yusuf Yildiz[3], Basarir Kerem[3], Gulsan Yavuz[1]

[1]Ankara University School of Medicine, Department of Pediatric Hematology-Oncology, Ankara, Turkey. [2]Gulhane Research and Training Hospital, Department of Pediatric Hematology-Oncology, Ankara, Turkey. [3]Ankara University School of Medicine, Department of Orthopedics, Ankara, Turkey.

Summary

Purpose: *The success of osteosarcoma treatment strategies improved survival rates. The need of diagnosing and managing adverse effects is increasing. We aimed to investigate the outcomes and late results of pediatric osteosarcoma treatment in the survivors.*

Methods: *Out of osteosarcoma patients (n=54), we assessed the long-term outcomes of survivors (n=39) diagnosed from 2002-2018. We compared the survivors' (n=39) health status (cardiac, renal, neurologic, psychiatric, physical limitations), pain, and psychosocial outcomes (education level, smoking history, and alcohol consumption, marital status, parenthood, health care services usage) with their siblings (n=77). The quality of life and overall survival of amputee and non-amputee survivors are also compared. We provided the retrospective data from the files and phone calls and used Kaplan Meier survival analysis, Ki-Kare, and t-test.*

Results: *The overall survival (OS) of children with osteosarcoma (n=54) who survived at 2 years and 5 years from the diagnosis was 90.7 and 77.8%, respectively. These patients achieved 2- year event-free survival (EFS) of 70.4% and 5-year EFS of 57.4%. Thirty-nine survivors of osteosarcoma were compared with 77 sibling controls. Osteosarcoma survivors were more likely than the sibling cohort to report adverse health status containing nephrotoxicity (5.1 vs 0%) (p=0.045), cardiotoxicity (10.3 vs 0%)(p<0.01), neurotoxicity (5.1 vs 1.7%) (p=0.045), activity limitations (64 vs 1.3%)(p<0.01) and pain (12.8 vs 0%) (p=0.002). Survivors' educational status (p=0.014), marital status (5.1 vs 32.5%) (p=0.001), employment (2.6 vs 28.6)(p < 0.001), parenthood (0 vs 29.9%)(p < 0.001) were negatively affected compared with the control group. The prevalence of smoking, alcohol use, psychiatric treatment, and deafness were similar. The amputees (n=9) had an OS rate of 55.6%, and the non-amputees (n=45) had 75.6%. We found similar quality of life results between them.*

Conclusion: *Long-term survivors of pediatric osteosarcoma are at significant risk of chronic health conditions, physical limitations, and pain up to 16 years follow up. Follow-up clinics and clinical guidelines are required for the survivors of children with osteosarcoma.*

Key words: *childhood cancer, long-term outcomes, osteosarcoma, pediatric cancer, late effects*

Introduction

Osteosarcoma is the most common primary bone malignancy in children and accounts for 3- 6% of all childhood cancers [1,2]. The 5-year event-free (EFS) and overall survival (OS) rates for localized osteosarcoma are 60-65% and 75-80%, respectively [2,3]. However, outcomes have been associated with osteosarcoma and treatment-related sequelae. Management and monitoring of acute complications and late effects of therapy are essential for oncologists after osteosarcoma therapy [3].

Corresponding author: Hatice Mine Cakmak, MD. Ankara University School of Medicine, Department of Pediatric Hematology-Oncology, Ankara, Turkey.
Tel: +90 5073796203, E-mail: h.m.tokuc@hotmail.com
Received: 29/10/2020; Accepted: 21/11/2020

The purpose of this study was to evaluate the survival of osteosarcoma patients and the late effects of that cancer and its treatment, comparing the survivors' and their controls' outcomes (health status, psychosocial impairment, chronic health conditions, frequency of health care usage). We also aimed to compare some of these variables between amputees and nonamputees.

Methods

This retrospective study included 54 children with osteosarcoma diagnosed between 2002 and 2018 in the Department of Pediatric Hematology and Oncology at Ankara University School of Medicine. Out of 54 patients, 39 were survivors. The data of these pediatric osteosarcoma survivors (n=39) and their healthy siblings (n=77) were compared.

Patient medical records from the institutional database were examined for the outcome categories of OS, EFS, second malignant neoplasms (SMNs), and chronic health conditions (cardiac disease, renal failure, neurotoxicity, hearing loss). Survivors' health status data (general and mental health, functional limitations, pain) and health care usage, psychosocial outcomes (educational status, smoking, alcohol use, marital status, employment, having children), and deafness were acquired via a questionnaire. Survivors completed that 3-page questionnaire.

Treatment data

All patients received high-dose methotrexate (HDMTX)-based chemotherapy, and most of the survivors (n=31) (79.5%) received the Euramos chemotherapy protocol (Table 2)[4]. This protocol contains two regimens MAP (methotrexate, adriamycin, cisplatin) and MAP + IE (methotrexate, adriamycin, cisplatin + ifosfamide, etoposide) (Table 1)[4]. The patients in the high-risk group with necrosis >95% took Euramos+IE chemotherapy. The previous regimens of the survivors (n=8) [non-Euramos] included various chemotherapeutics. Five survivors received bleomycin, actinomycin D, cyclophosphamide (BCD) with methotrexate and other chemotherapy drgs. Three survivors took other protocols containing methotrexate, ±cisplatin, ±etoproside, ±ifosfamide, ±doxorubicin, ±carboplatin, ±vincristine in different combinations.

Statistics

The Kaplan-Meier survival analysis estimated OS and the significance of the risk for adverse events was determined with the log-rank test. We evaluated the test's variables using the Mann-Whitney U test, Chi-square test, and Fisher's exact test and accepted a p value of 0.05 and lower as significant.

Results

Demographics

Out of 54 patients with osteosarcoma, 15 died of pulmonary metastasis and respiratory failure. Our cohort consisted of 39 survivors (15 female, 24 male) with a mean age of 17.42±3.15 years and 77 siblings (43 male, 34 female) with a mean age of 18.85±8.48 years at the last contact (p=0.31). Time since diagnosis ranged between 0-5 years (n=22) (56.4%) (Table 2).

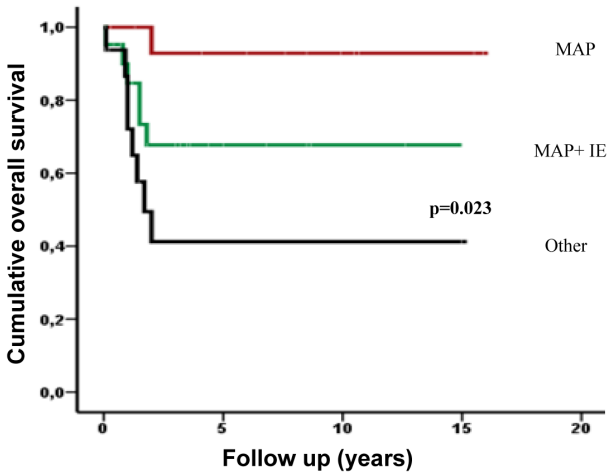

Figure 1. Cumulative overall survival of Euramos MAP, Euramos MAP + IE, and other previous regimens.

Table 1. Euramos treatment schedule

Treatment (T)	AP	M	M	AP		M	M	Surgery								
Weeks (W)	1	4	5	6		9	10									
A																
T	AP	M	M	AP	M	M	A	M	M	A	M	M				
W	12	15	16	17	20	21	22	24	25	26	28	29				
OR **B**																
T	AP	M	IE	M	Ai	M	IE	M	AP	M	IE	M	Ai	M	M	
W	12	15	16	21	22	25	26	29	30	33	34	35	36	39	40	

A= doxorubicin 75 mg/m²/course, P= Cisplatin 120 mg/m²/course, M= Methotrexate 8-12 g/m²/course, E= Etoposide 500 mg/m²/course, I= Ifosfamide 14 g/m²/course, i= Ifosfamide 9 g/m²/course

Table 2. Demographic data of survivors

	n (%)
Time since diagnosis, years	
0-5	22 (56.4)
5-10	12 (30.8)
>10	5 (12.8)
Chemotherapy	
Euramos MAP	16 (41)
Euramos MAPIE	15 (38.5)
Other	8 (20.5)
Surgery	
Amputation	5 (12.8)
Extremity-sparing surgery	34 (87.2)
Total anthracycline dosage, mg/m^2	
209	4 (10.3)
210-358	8 (20.5)
359-450	24 (61.5)
No dose	1 (2.6)
Unknown dose	2 (5.1)
Total cisplatin dosage, mg/m^2	
1-362	5 (12.8)
362-489	14 (36)
≥490	16 (41)
No dose	2 (2.8)
Unknown dose	2 (2.8)
Total methotrexate dosage, g/m^2	
< 96	18 (46.2)
96-144	18 (46.2)
No dose	0 (0)
Unknown dose	3 (7.6)

MAP: methotrexate, adriamycin, cisplatin; MAPIE: methotrexate, adriamycin, cisplatin, ifosfamide, etoposide

Survival

Among 54 osteosarcoma patients, the subsequent survival at 2 and 5 years since diagnosis was 90.7 and 77.8%, respectively, and the cumulative OS was 70.4%. The cumulative OS rates of the Euramos MAP regimen (94.1%), Euramos MAPIE regimen (71.4%), and the previous regimens (50%) were statistically different (p=0.023) (Figure 1).

Recurrences

The cumulative incidence of recurrences at 2 and 5 years were 29.4% (n=16) and 42.6% (n=23), respectively. Only one recurrence occurred in 5.5 years of diagnosis. EFS at 2 years and 5 years was 70.4 and 57.4%, respectively, and the cumulative EFS was 55.6% (Figure 2).

Late effects of chemotherapy and osteosarcoma

Survivors who developed cardiotoxicity (n=4; 10.3%) had received cumulative doxorubicin dose of 180 mg/m^2, 300 mg/m^2, 375 mg/m^2 and 450 mg/m^2. When compared to their controls (0%), cardiotoxicity (concentric hypertrophy (n=1), left ventricular dysfunction (n=1), and mild mitral regurgitation (n=2) were more common in osteosarcoma survivors (n=4; 10.3%; p<0.01) (Table 3). Out of survivors who received cumulative doxorubicin dose of 450 mg/m^2 (n=24), 23 had normal cardiac function.

The prevalence of hearing loss was similar in survivors (n=2) and the control group (n=1) (5.1 vs. 1.3%, respectively) (p=0.22). These two survivors with hearing loss received a total platinum

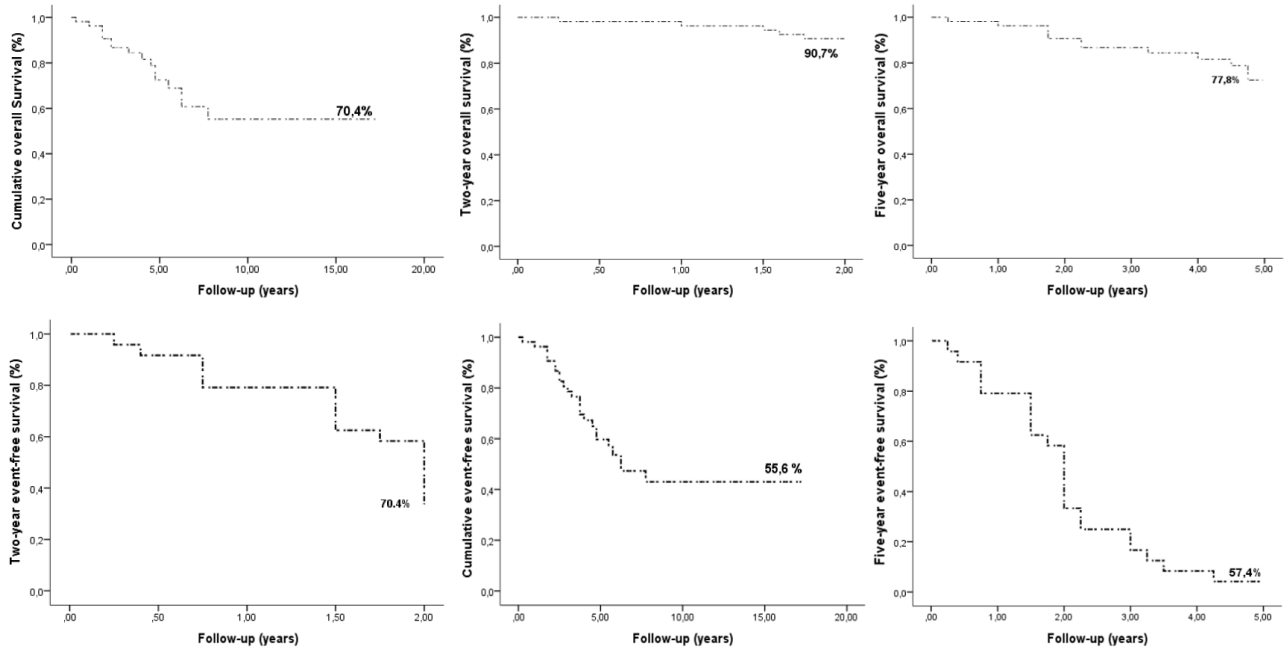

Figure 2. Overall survival and event-free survival rates at 2, 5 and 10 years since diagnosis and their cumulative values.

dose between 362-489 mg/m². The renal failure rate of survivors (5.1%) was significantly more common than the siblings (0%) (p=0.045); two had undergone dialysis (one for methotrexate toxicity, one for cisplatin toxicity). However, renal function improved. None of them is an end-stage renal failure in the long-term follow-up (Table 3). SMN (acute myeloid leukemia), was detected in one survivor who is still in remission. Two of 39 survivors reported having peripheral neuropathy (paresthesias) (5.1%), compared with the siblings (0%), and neuropathy incidence was significantly higher (p=0.045) in the survivor group (p=0.045). These two patients received a cumulative dose of methotrexate of 104 g/m² and 108 g/m² (Table 2).

Overall, 5.1% of survivors reported having been married compared to 32.5% of siblings (p=0.01). Parenthood data were 29.9% in the siblings and 0% in the survivors (p<0.001). Employment rates were low, and more siblings (28.6 %) worked versus survivors (2.6%) (p<0.001). Compared with their siblings (0%), survivors (15.4%) were more likely to have visited an outpatient clinic and/or been hospitalized as an inpatient in the last year (p<0.001) (Table 4).

The siblings' educational status was better than the survivor group; 10.3% of survivors could graduate at least from high school, while 44.5 % of siblings could (p=0.014) (Table 4).

Among the survivors, 25 (64.1%) reported a physical limitation (difficulty in routine daily activities, difficulty in walking, extremity movements, severe difficulty in physical activity), and 5 (12.8%) reported having pain due to late surgical effects. When compared to siblings (1.3%), survivors of osteosarcoma (64.1%) showed significantly more limited results in physical functioning (p<0.001) (Table 3). Survivors reported more bodily pain (12.8 vs. 0%) during the past four weeks compared with the siblings (p=0.02) (Table 4).

Renal failure was reported in 0 (0%) of 15 patients in the MAP group (n=15) and 1 (6.3%) in the MAPIE group (n=16). Echocardiography was performed in two (13.3%) patients in the MAP group (n=15) and 1 (6.3%) in the MAPIE group (n=16). Hearing loss was reported in one patient in the MAPIE group and no patient in the MAP group (p=0.325). Neuropathy was reported in 2 of the patients in the MAPIE group while it did not develop in the MAP group (p=0.164). Education

Table 3. Demographics and clinical data of survivors and healthy siblings of the control group

Categories	*Groups*		*p value*
	Survivor (n=39) *n (%)*	*Control (n=77)* *n (%)*	
Age (years) (Mean±SD)	17.42±3.15	18.85±8.48	0.31
Gender			0.55
Male	24 (61.5)	43 (55.8)	
Female	15 (38.5)	34 (44.2)	
Renal failure			0.045
No	37(94.9)	77 (100)	
Yes	2 (5.1)	0(0)	
Cardiotoxicity			0.04
No	35 (89.7)	77 (100)	
Yes	4 (10.3)	0(0)	
Neuropathy			0.045
No	37 (94.9)	77 (100)	
Yes	2 (5.1)	0(0)	
Hearing loss			0.22
No	37 (94.9)	76 (98.7)	
Yes	2 (5.1)	1(1.3)	
Psychiatric drug therapy			0.77
No	37 (94.9)	72 (93.5)	
Yes	2 (5.1)	5 (6.5)	
Psychotherapy			1
No	39 (100)	77 (100)	
Yes	0 (0)	0 (0)	

status, marital status, parenthood, physical limitations, smoking, and alcohol consumption did not differ significantly between the MAP and MAPIE groups (Table 5). We detected no secondary cancer in the Euramos regimen.

The health status and psychosocial conditions among amputees (extremity sparing surgery group) (n=9) were similar to nonamputees (n=45). Education status, marital status, parenthood, physical limitations, admitting to health services, smoking, and alcohol consumption did not differ significantly between the groups (Table 6).

Discussion

Five-year EFS and OS for localized osteosarcoma are 60-65% and 75-80%, respectively. Consequently, acute complications and late effects of therapy are essential for oncologists because the number of osteosarcoma survivors is increasing [3]. Our results are similar to the literatüre where OS and EFS at 5 years since diagnosis were 77.8% and 57.4%.

In Children Cancer Survivor Study (CCSS) in 2005, the cumulative incidence of recurrences was relatively stable after 5 years (24.5% at 5 years and 28.1% at 25 years), with only 24 subjects having relapsed >5 years after diagnosis [5]. Bielack et al reported an extensive study of 576 patients with relapsed osteosarcoma, where only 5.7% of the relapses occurred after 5 years [6]. In our research, most recurrences (n=23, 95.8%) occurred in the first 5 years since diagnosis; only one relapsed at 5.5th year since diagnosis.

Table 4. Psychosocial conditions of survivors and healthy siblings in the control group

Categories	*Groups*		*p value*
	Survivor (n=39) *n (%)*	*Control (n=77)* *n (%)*	
Current smoker	1 (2.6)	7 (9.1)	0.19
Current drinker	0 (0)	0 (0)	1
Education			0.014
Illiterate	5 (12.8)	6 ((7.8)	
Student	26 (66.7)	34 (44.1)	
Drop out from school	4 (10.2)	3 (3.9)	
High school	3 (7.7)	26 (33.7)	
University	1 (2.6)	8 (10.5)	
Marital status			0.001
Ever married	2 (5.1)	25 (32.5)	
Having children			<0.001
Yes	0 (0)	23 (29.9)	
No	39 (100)	54 (70.1)	
Employment			<0.001
Yes	1 (2.6)	22 (28.6)	
No	38 (97.4)	55 (71.4)	
Use of health services			<0.001
No or <3 in the last 3 months	32 (82)	76 (98.7)	
≥3 in the last 3 months	1 (2.6)	1 (1.3)	
Hospitalized as an inpatient in the last 1 year	6 (15.4)	0 (0)	
Limitation in physical functioning			<0.001
No	14 (35.9)	76 (98.7)	
Difficulty in routine daily activities	2 (5.1)	1 (1.3)	
Difficulty in walking/extremity movements	9 (23.1)	0 (0)	
Severe difficulty in physical activity	14 (35.9)	0 (0)	
Pain in the last four weeks			0.002
No	77 (100)	34 (87.2)	
Mild	0 (0)	2 (5.1)	
Severe	0 (0)	3 (7.7)	

The majority of second malignant neoplasms occurred after 10 or more years from diagnosis of osteosarcoma. A 10-year cumulative incidence was 5.4% in CCSS (2005), 6.3% in the Italian Sarcoma Group study, and 5.3% in the report of Hagleitner et al [5,7,8]. Additionally, in an Italian cancer center research, osteosarcoma survivors were 1.8-fold more likely to experience second malignant neoplasm, and 4.5-fold more likely to experience leukemia [9]. We detected acute myeloid leukemia in one survivor (2.5%). The majority of our survivors (n=22, 56.4%) are in the first 5 years of follow-up since diagnosis.

Hudson et al reported that survivors of childhood cancer were significantly more likely to report general adverse health statuses, mental health, activity limitations, and functional impairment than siblings. Compared to those with leukemia, an increased risk of at least one negative status among those with bone tumors was repeated [10].

Compared with the general population, osteosarcoma survivors were more likely to develop at least one chronic disease [5,11]. In the CCSS study in 2005, 19 reported having congestive heart failure, with 13 of the 19 having received greater than 360 mg/m^2 of anthracyclines. In addition to congestive heart failure, 11 reported having cardiovascular disease [5]. In another report of CCSS (2018), the 75th and the 90th percentile of cumulative doses

Table 5. Demographics and clinical data of survivors in the MAP and MAPIE groups

Groups	*MAP (n=15)* *n (%)*	*MAPIE (n=16)* *n (%)*	*p value*
Renal failure			0.325
No	15 (100)	15 (93.8)	
Yes	0 (0)	1 (6.3)	
Cardiotoxicity			0.51
No	13 (86.7)	15 (93.8)	
Yes	2 (13.3)	1 (6.3)	
Neuropathy			0.045
No	37 (94.9)	77 (100)	
Yes	2 (5.1)	0 (0)	
Hearing loss			0.325
No	15 (100)	15 (93.8)	
Yes	0 (0)	1 (6.3)	
Current smoker	0 (0)	0 (0)	1
Current drinker	0 (0)	0 (0)	1
Psychiatric drug therapy			0.30
No	14 (93.3)	16 (100)	
Yes	1 (6.7)	0 (0)	
Limitation in physical functioning			0.246
No	5 (33.3)	4 (31.3)	
Difficulty in routine daily activities	1 (6.7)	1 (6.3)	
Difficulty in walking/extremity movements	1 (6.7)	8 (50)	
Severe difficulty in physical activity	8 (53.3)	2 (12.5)	
Marital status			
Ever married	0 (0)	1 (6.3)	
Parenthood			
Yes	0 (0)	0 (0)	1
No	39 (100)	54 (70.1)	
Education			0.444
Illiterate	2 (13.3)	3 (18.8)	
Student	9 (60)	11 (68.81)	
Drop out from school	2 (13.4)	0 (0)	
High school	2 (13.3)	2 (12.5)	
University	0 (0)	0 (0)	

Table 6. Psychosocial conditions of amputees and extremity sparing

Groups	*Amputees (n=9)* *n (%)*	*Extremity sparing surgery (n=45)* *n (%)*	*p value*
Current smoker	0 (0)	1 (2.2)	0.659
Current drinker	0 (0)	(0)	1
Education			0.736
Illiterate	5 (55.6)	13	(28.9)
Student	2 (22.2)	25	(55.6)
Drop out from school	1 (11.1)	4	(8.9)
High school	0 (0)	3	(6.7)
University	1 (11.1)	0 (0)	
Marital status			
Ever married	0 (0)	2 (4.4)	0.528
Parenthood			1
No	0 (0)	0 (0)	
Use of health services			0.635
No or <3 in the last 3 months	5 (55.6)	27	(60)
≥3 in the last 3 months	0 (0)	2 (4.4)	
Hospitalized as an inpatient in the last 1 year	4 (44.4)	16 (35.6)	
Limitation in physical functioning			0.099
No	0 (0)	14 (31.1)	
Difficulty in routine daily activities	4 (44.4)	13 (28.9)	
Difficulty in walking/extremity movements	1 (11.1)	8 (17.8)	
Severe difficulty in physical activity	4 (44.4)	10 (22.2)	

of doxorubicin were 383.2 mg/m^2, 467.7 mg/m^2, respectively [13]. In our study, 4 (10%) patients had cardiotoxicity (concentric hypertrophy (n=1), left ventricular dysfunction (n=1), mild mitral regurgitation, (n=2); three of these patients received anthracycline ≥300 mg/m^2. Compared with their siblings (0%), the incidence of cardiotoxicity (10.3%) was significantly superior in survivors (p=0.04).

The literature reports that the incidence and magnitude of hearing loss increases with increasing cumulative cisplatin doses with a threshold between 240-400 mg/m^2 with younger age associated with greater risk. In the study of Hangleitner et al, of the 62 survivors with an audiogram, 31 (50%) had hearing loss [8]. As reported in the Italian cancer center experience [9], hearing loss, as evaluated by audiograms, was detected in about 40% of our patients after a cumulative cisplatin dose of 600 mg/m^2. Bertolini et al reported that ototoxicity occurred after a total cisplatin dose of at least 400 mg/m^2. In another report of CCSS (2018) about cancer survivors, the 75th and the 90th percentile of cumulative doses of cisplatin were to be 607.6 mg/m^2 and 807.1 mg/m^2, respectively [13]. In our current study, both of the survivors with hearing loss (n=2) received cisplatin dose between 362-489 mg/m^2.

As previously reported, bone sarcoma survivors were more likely than the siblings to have chronic and adverse health conditions [5,13]. Our survivors were more likely than the sibling cohort to report unfavorable health status (echocardiography abnormality of 10.3 vs. 0%, renal failure of 5.1 vs. 0%, peripheral neuropathy of 5.1 vs. 0%) similar to other studies. Out of 4 survivors, two of them had undergone dialysis (one with methotrexate and the other with cisplatin toxicity). Later their renal function improved.

In the Euramos 1 trial, the OS at 3 years since diagnosis was 72% for the MAP group and 77% for the MAPIE group, and the prevalence of cumulative nonhematological events was significantly higher in the MAPIE group vs MAP group (p=0•0024) [14]. We found that the cumulative OS was 94.1% in the MAP group, 71.4% in the MAP+IE group, and 50% in the previous chemotherapy regimens of osteosarcoma (p=0.023). In our study, late effects of osteosarcoma (nephrotoxicity, cardiotoxicity, hearing loss, neuropathy), psychosocial outcomes (marital status, education, parenthood, physical limitations) were statistically similar between MAP (n=15) and MAPIE groups (n=16).

In 2011, Nagarajan et al observed that general health, mental health, and osteosarcoma survivors'

anxiety were not different compared to their siblings. However, functional status, activity limitations, and pain were more likely to be problems (all with a p<0.001). Survivors were less likely than expected to obtain some types of educational qualification, marital status, employment (all with a p<0.01) [5].

In the Children Cancer Group (CCG) study in 2018, bone sarcoma survivors' (n=309) death rates were 7-fold the number of deaths expected from the general population. Bone sarcoma survivors were almost 3 times more likely to have visited an outpatient hospital department in the previous 3 months. However, survivors were significantly less likely to be current smokers and consume alcohol over recommendations than the general population sample. Fifty-four % and 61% of survivors were limited in moderate activities and walking more than one mile, compared with the 8 and 11% expected from the general population sample, respectively. As for the pain, survivors reported more bodily pain (12 vs. 5%) and more pain interference (16 vs. 5%) during the past 4 weeks compared with the general population sample [15].

Consistent with these studies, survivors had severely limited health status. Compared with the siblings, survivors were more likely to have experienced reduced physical functions (p<0.001) and increased pain (p=0.02). Our findings suggest that survivors were significantly less likely than expected to obtain some types of educational qualification (p=0.014), marital status (p=0.01), parenthood (p<0.001) and employment (p<0.001).

Our survivors were significantly more likely to have visited an outpatient hospital department in the previous 3 months and been hospitalized as an inpatient during the last year (p<0.001). The incidence of smoking and alcohol consumption were similar between survivors and their siblings.

Out of 694 survivors, amputees' marital status, employment, and educational qualifications were identical to those of nonamputees [16]. In MD Anderson Childhood Cancer Center study, amputees and nonamputees had similar physical functions, psychiatric health, employment, and marital status [17]. Meta-analyses of quality of life showed no differences in outcomes between patients who underwent limb-sparing vs amputation for local control [18]. As mentioned in previous studies, we suggest that physical limitation, health care usage, parenthood, smoking, and alcohol habits among amputees were similar to nonamputees. However, in the CCG study, amputees were more likely to experience physical dysfunctions than nonamputees [15].

The results of high-dose chemotherapy and autologous stem cell transplantation in the treatment of relapsed osteosarcoma are not consistent in the literature [19]. We do not suggest this treatment in this group of patients. Aggressive local and medical therapies (chemoradiotherapy, surgical removal of primary and or metastatic disease) are currently available for these patients [20].

Conclusions

Osteosarcoma survivors are at significant risk of having chronic health conditions (cardiac, renal, neuronal, hearing loss), unemployment, chronic pain, and physical limitation. The incidence of using health care services was significantly more common in survivors compared with their siblings. The marital status, and parenthood of the survivors were affected considerably. Multidisciplinary studies and risk-based life guidelines are warranted to control the osteosarcomas' long-term adverse effects and improve survivors' health conditions.

Conflict of interests

The authors declare no conflict of interests.

References

1. Simpson E, Brown HL. Understanding osteosarcomas. Journal of the American Academy of Physician Assistants 2018;31:15-9.
2. Megan E, Anderson MD. Update on survival in osteosarcoma. Orthop Clin N Am 2016;16:283-92.
3. Janeway KA, Grier HF. Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects. Lancet Oncol 2010;11:670-78.
4. Whelan JS, Bielack SS, Marina N et al. EURAMOS-1, an international study for osteosarcoma: results from pre-randomization treatment. Ann Oncol 2015;26: 407-14.
5. Nagarajan R, Kamruzzaman A, Ness KK et al. Twenty Years of Follow-Up of Survivors of Childhood Osteosarcoma. Cancer 2011;117:625-34.
6. Kempf-Bielack B, Bielack SS, Jurgens H et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol 2005; 23:559-68.

7. Longhi A, Ferrari S, Tamburini A et al. Late Effects of Chemotherapy and Radiotherapy in Osteosarcoma and Ewing Sarcoma patients. The Italian Sarcoma Group Experience (1983-2006). Cancer 2012;118:5050-9.
8. Hagleitner MM, Eveline SJ, De Bont M et al. Survival Trends and Long-Term Toxicity in Pediatric Patients with Osteosarcoma. Sarcoma 2012;2012:1-5.
9. Ferrari S, Palmerin E, Staals EL et al. The Treatment of Nonmetastatic High-Grade Osteosarcoma of the Extremity: Review of the Italian Rizzoli Experience. Impact on the Future. Cancer Treat Res 2009;152:275:87.
10. Hudson MM, Mertens AC, Yasui Y et al. Health status of adult long-term survivors of childhood cancer: a report from the childhood cancer survivor study. JAMA 2003; 290:1583-92.
11. Bertolini P, Lassalle M, Mercier G et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 2004;26:649-55.
12. Stohr W, Langer T, Kremers A et al. Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system. Cancer Invest 2005;23:201-7.
13. Gibson TM, Mostoufi-Moab S, Stratton KL et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 197099: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 2018;19:1590-601.
14. Neyssa MM, Smeland S, Bielack SS et al. Comparison of MAPIE Versus MAP in Patients With a Poor Response to Preoperative Chemotherapy for Newly Diagnosed High-Grade Osteosarcoma (EURAMOS-1): An Open-Label, International, Randomised Controlled Trial. Lancet Oncol 2016;17:1396-1408.
15. Fidler MM, Frobisher C, Guha J et al. Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study. Br J Cancer 2015;112:1857-65.
16. Nagarajan R, Neglia JP, Clohisy DR et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report from the Childhood Cancer Survivor Study. Cancer 2003;97:2554-64.
17. Ottaviani G, Robert RS, Huh WW et al. Functional, Psychosocial and Professional Outcomes in Long-Term Survivors of Lower-Extremity Osteosarcomas: Amputation Versus Limb Salvage. Cancer Treat Res 2009;152:421-36.
18. Stokke J, Sung L, Gupta A et al. Systematic Review and Meta-Analysis of Objective and Subjective Quality of Life among Pediatric, Adolescent, and Young Adult Bone Tumor Survivors. Pediatr Blood Cancer 2015;62:1616-29.
19. Karadurmus N, Sahin U, Bahadir Basgoz B et al. . Is there a role of high dose chemotherapy and autologous stem cell transplantation in the treatment of Ewing's sarcoma and osteosarcomas? JBUON 2018;23:1235-41.
20. Mavrogenis AF, Rossi G, Palmerini E et al. Palliative treatments for advanced osteosarcoma. JBUON 2012;17:436-45.