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Original article

Malignant Bone Tumors in Pediatric Age Groups in Iraq

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SUMMARY

Introduction/Aim. Roughly six percent of all malignancies diagnosed in children are malignant bone tumors. They have a dramatic effect on psychological status of children and their families.
The aim of the study was to analyze the clinico-pathological features of bone tumors in Iraqi children and to assess response to treatment, outcome, and survival.
Patients and methods. Over an eleven-year period, a retrospective study was done for children with bone tumors conducted on patients data that included a battery of pre-treatment investigations including a complete blood count, serum electrolyte, hepatic, and renal profile, bone marrow aspirate and biopsy, fine-needle aspiration, and imaging studies.
Results. Data of 41 children with bone tumor were collected. The most common site of involvement was lower limbs, found in 21 (51.2%) cases.
At the time of diagnosis, 29 patients presented with localized disease (70.7%), while 12 (29.3%) patients presented with metastasis. From 41 patients included in the study, histopathology of 29 (70.7%) patients was Ewing's sarcoma, whereas 12 (29.3%) patients were diagnosed with osteogenic sarcoma.
The most common toxic effect of chemotherapy was febrile neutropenia which was recorded in 22 (59.5%) patients, followed by hemorrhagic cystitis in 3 (8.1%) patients; both febrile neutropenia and hemorrhagic cystitis were recorded in 5 (13.5%) patients, convulsion was found in 1 (2.7%) patient, and no complication were reported in 5 (13.5%) patients. Relapse was found in 8 (21.6%) patients.
Conclusion. High rate of patients were lost to follow-up. Two-year event-free survival (EFS) was 53%, which is lower than that reported in other studies due to late diagnosis, late referral with the presentation in the locally advanced stage of disease.

Keywords: **osteosarcoma, Ewing's tumor, pediatric**

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INTRODUCTION

Roughly six percent of all malignancies diagnosed in children are malignant bone tumors. The most common malignant bone tumors in kids and teenagers are osteosarcoma (56%) and Ewing sarcoma (34%). Bone cancer risks are highest during teenage growth spurt, around the age of 15, with a decline thereafter.

The incidence of osteosarcoma has a bimodal age distribution, with peaks in young adulthood and later life. Rarely seen in adults, Ewing sarcoma mostly affects children and young adults (1).

Cancers that spread to bones, although not uncommon in children, often originate elsewhere in the body. In contrast, leukemias and lymphomas are more prevalent than primary malignant bone tumors in young adults.

Osteosarcoma is the most frequent kind of bone cancer which, along with Ewing sarcoma family of tumors, accounts for more than 90% of malignant bone tumors.

The origin of malignant bone tumors is often unknown but may have a hereditary component. Chemotherapeutic options are many and their results are variable (2, 3).

AIM

1. To study the clinico-pathological features of bone tumors in Iraqi children.

2. To assess the response to treatment, outcome, and survival.

PATIENTS AND METHODS

Over the 11-year period, from January 1, 2009 to December 31, 2019, a retrospective study was done involving 41 children with bone tumors, who were admitted to the pediatric oncology unit in children welfare teaching hospital (CWTH) and were considered eligible for the study. Four cases with Ewing's sarcoma (ES) were excluded (two with ES treated with National Cancer Institution (NCI) protocol, and two patients also with ES treated in another institute).

Age, sex, place of residence, clinical presentation, diagnostic process, staging investigation, treatment modality and its consequences, and outcome data were collected from inpatient medical records and oncology consultation clinical files.

Patients with Ewing sarcoma underwent a battery of pre-treatment investigations including a complete blood count, serum electrolyte, hepatic, and renal profile, bone marrow aspirate and biopsy, incisional or excisional biopsy, fine-needle aspiration (FNA), and radiography (chest x-ray, abdominal ultrasound, x-ray, CT scan and or MRI to the primary site). Bone scan, serum LDH, cytogenetic, and molecular analyses were not accessible throughout the research period. The patients were classified and treated with chemotherapy according to their histopathological results.

1. Patients with osteosarcoma were treated according to the European Osteosarcoma Intergroup Study Protocol (osteogenic sarcoma (Regimen I)/ without G-CSF protocol) that includes: Doxorubicin 25 mg/m^2 i.v. infusion in 800 ml/m^2 G/S over 4 hours (pre- hydration) at 10:00 a.m. D1-3, CIS platinum 100mg/m^2 i.v. infusion in (2000 ml/m^2 G/S + 5cc KCL in each pint+ 8 gm mannitol in each pint) /24 hours at 2:00 p.m., and post hydration 1800 cc/m^2 G/S + 5cc KCL in each pint+ 2 gm Mannitol in each pint+ Calcium Gluconate one ampoule in each pint/24 hours D2, at total of 6 cycles three weeks apart.

2. Patients with Ewing sarcoma were treated according to the EWING SARCOMA/ VIDE PROTOCOL (EURO 99), which includes:

• Induction treatment: all patients are to receive 6 courses of VIDE chemotherapy as induction; courses should be given at 21 days intervals or on hematological recovery to WBC > = 2 X 10^9/L with ANC > = 1 X 10^9/L; platelets count > = 80 X 10^9/L.

Each VIDE course consists of Vincristine: 1.5 mg/m^2 I.V. bolus, Adriamycin: 20 mg/m^2 I.V. infusion over 4 hours for 3 hours, Etoposide (VP16): 150 mg/m^2 I.V. infusion in N/S over 1 hour for 3 days, Ifosfamide 3000 mg/m^2 I.V. infusion over 1 hour for 3 days, Mesna (urometixan): 3600 mg/m^2/24 hours I.V. infusion and Hydration 3000 ml/m^2/day.

• Consolidation treatment: patients randomized to receive 9 courses of VAC or VAI courses as consolidation treatment; courses should be given at 21 days intervals or on hematological recovery to WBC > = 2 X 10^9/L with ANC > = 1 X 10^9/L; platelets count > = 80 X 10^9/L.

Each VAC course consists of: Vincristine: 1.5 mg/m^2 I.V. bolus, Actinomycin 1.5 mg/m^2 I.V. bolus and cyclophosphamide 1200 mg/m^2 i.v. infusion over 30 minutes, Mesna (urometixan) 800 mg/m^2/24 hours I.V. infusion and hydration 3000 ml/m^2/day.

Each VAI course consists of: Vincristine: 1.5 mg/m² I.V. bolus, Actinomycin 0.75 mg/m² I.V.D1-D2, Ifosfamide 3000 mg/m² I.V. infusion over 1 hour, Mesna (urometixan) 3000 mg/m²/24 hours I.V. infusion and hydration 3000 ml/m²/day.

Response criteria: The first is a complete response (CR), which is defined as the absence of illness symptoms for at least four weeks. Ewing tumor cells must be absent from ≥ 2 locations in individuals with a history of bone marrow involvement (by light microscope).

Partial response (PR): Tumor volumes at solid tumor locations decreased by more than or equal to 50% from the baseline measurements (except bone sites only). The bone marrow examined under a microscope was disease-free. CT-detected reduction in lung lesions of at least 50% in size or number from baseline was found.

Disease stability (SD) is defined as no new tumor growth or progression, bone marrow involvement (but no regression), and a reduction in tumor volume of at least 50% relative to baseline for at least four weeks.

The presence of new lesions or an increase in the total volume of all existing lesions by more than 25% relative to the smallest measurement constitutes progressive disease (PD).

Patients with bone tumors who have completed therapy will get chest x ray (CXR) once a month for the first two years following the diagnosis, then every 4 - 6 months. The examination of the main site will also be performed at this frequency for the first two years. A chest computerized tomography (CT) and bone scan, if possible, should be performed every 4 - 6 months for the first two years following the diagnosis, and then less often afterwards. For the statistical analysis, we used SPSS for Windows Version 15 (Statistical Package for the Social Sciences). Quantitative information is often shown as a mean or median value, whereas qualitative information is typically presented as a frequency distribution. Survival curves were shown using the Kaplan-Meier technique.

Remission failure (early mortality, non-responders, and treatment discontinuation) or the end of the first remission phase were considered events (event free survival - EFS) (relapse, second malignancy, death from any cause, and abandonment of treatment before completion of chemotherapy).

Ethical approval for the study was obtained from the scientific and the ethical committee in Al-Kindy College of Medicine; registration number (EAC – 25468).

Statistical analysis

The patient data were compiled and analyzed using SPSS (Statistical Package for the Social Sciences) version 15 for Windows. Qualitative data is represented in terms of frequency and proportion, whereas quantitative data is represented by mean and median.

The survival curves were shown using the Kaplan-Meier technique.

Event-free survival (EFS) was defined as the absence of any events that result in remission failure, such as early death, non-responders, or abandonment of treatment. It also includes the end of the first remission phase due to recurrence, second malignancy, death from any reason, or abandonment of treatment before completing chemotherapy.

RESULTS

A total 41 children with bone tumor were seen at CWTH from January 1, 2009 to December 31, 2019. Patients' data were analyzed.

The patients were referred to CWTH from 10 governorates: 18 patients referred from Baghdad (43.9%) followed by Babil, Ramadi and Diyala - 4 patients (10%), Wasit - 3 patients (7%), as shown in Table 1.

There was an increment in the referral of the patients with bone tumors to CWTH in 2009 reaching seven times the number compared to 1999 (34.1% vs 4.9%), as shown in Table 1.

The minimum age at presentation was 2 years and the maximum age was 14 years, with a median age of 8 years. The most common age at presentation ranged from 5 to 10 years as shown in Table 1.

Male to female ratio was 1.2:1; there were 23 (56.1%) males and 18 (43.9%) females, as shown in Table 1. The minimum duration of symptoms was 30 days and the maximum was 360 days with mean of 123.02 days.

The most common site of involvement was the lower limbs, recorded in 21 (51.2%) cases, in which femur involvement occurred in 13 patients (32%),

Table 1. *Referral pattern of patients with bone tumor to CWTH*

Variable	Frequency	Percentage (%)
Referral pattern of patients with bone tumor to CWTH		
Baghdad	18	43.9
Ramadi	4	9.8
Babil	4	9.8
Diyala	4	9.8
Wasit	3	7.3
Salah-aldain	3	7.3
Dewania	2	4.9
Mousl	1	2.4
Najaf	1	2.4
Nasirya	1	2.4
Total	41	100.0
Year of diagnosis		
1999	2	4.9
2000	1	2.4
2001	5	12.1
2002	1	2.4
2003	1	2.4
2004	1	2.4
2005	4	9.8
2006	2	4.9
2007	7	17.1
2008	3	7.3
2009	14	34.1
Total	41	100.0
Age distribution of patients. Mean age was 8.3 years:		
< 5 years	6	15
5 - 10 years	21	51
> 10 years	14	34
Total	41	100.0
Sex distribution of patients. Male: female ratio = 1.2:1 :		
Male	23	56.1
Female	18	43.9
Total	41	100.0

tibia involvement in 5 patients (12.2%), fibula involvement in 1 patient (2.4%), knee joint involvement in 1 patient (2.4%), and ankle joint involvement in 1 patient (2.4%), followed by trunk (pelvis and vertebra) involvement found in 13 (31.7%) cases, whereas upper limb involvement was noted in 7 patients (17.1%), as shown in Table 2.

The main signs and symptoms were swelling and pain found in 17 patients (41.5%). Pain alone was found in 10 patients (24.4%), swelling alone was reported in 9 patients (22%), swelling and fever were seen in 2 patients (4.9%), pathological fracture was found in 2 patients (4.9%), and one patient (2.4%) presented with pain and fever, as shown in Table 2.

At the time of diagnosis, 29 patients presented with localized disease (70.7%), while 12 (29.3%) patients presented with metastasis, as shown in Table 2.

The diagnosis of bone tumors was based on biopsy in 40 patients (97.6%), of which incision biop-

Table 2. *The main site of involvement, main signs and symptoms, extension of disease at the time of diagnosis and method of diagnosis*

Main site of involvement		
	Frequency	Percent %
Lower extremities	21	51.2
Trunk	13	31.7
Upper extremities	7	17.1
Total	41	100.0
Main signs and symptoms		
	Frequency	Percent
Swelling and pain	17	41.5
Pain alone	10	24.4
Swelling alone	9	22.0
Swelling and fever	2	4.9
Pathological fracture	2	4.9
Pain and fever	1	2.4
Total	41	100.0
Extension of disease at the time of diagnosis		
	Frequency	Percent
Localized	29	70.7
Metastasis	12	29.3
Total	41	100.0
Method of diagnosis		
	Frequency	Percent
Incision biopsy	30	73.2
Excision biopsy	10	24.4
FNA	1	2.4
Total	41	100.0

sy in 30 patients (73.2%) and excision biopsy in 10 patients (24.4%), and FNA diagnosis from the swollen mass of bone tumor in 1 patient (2.4%), as shown in Table 2.

From 41 patients included in the study, the histopathology of 29 (70.7%) patients pointed to Ewing's sarcoma, whereas 12 (29.3%) patients were diagnosed with osteogenic sarcoma.

Laboratory and radiological results

Table 3 shows the initial BM involvement at the time of diagnosis which was found in 3/30 (10%) patients; normal BM was found in 27/30 (90%) patients, and no results were recorded in 11 (26.8%) patients.

Chest x-ray was normal in 35/38 (92.1%) patients, abnormal finding was found in 3/38 (7.9%) patients, and no results were recorded in 3 patients.

Local US to the affected area was normal in 26/34 (76.5%) patients, abnormal findings were found in 8/34 (23.5%) patients, and no results were recorded in 7 patients.

Abnormal CT chest findings in the form of cannon ball, mediastinal and hilar lymph adenopathy were recorded in 10/16 (62.5%) patients, normal in 6/16 (37.5%), while in 25 patients it was not performed.

Abnormal CT abdomen findings were found in 6/7 (85.7%) patients, normal in 1/7 (14.3%) patient, whereas in 34 patients it was not performed.

Table 3. *Laboratory and radiological results*

		Frequency	Percent %
BMA			
	Normal	27	90
	Involved	3	10
	Not recorded	11	
CXR			
	Normal	35	92.1
	Abnormal	3	7.9
	Not recorded	3	
US of the involved area			
	Normal	26	76.5
	Abnormal	8	23.5
	Not recorded	7	
CT chest			
	Normal	6	37.5
	Abnormal	10	62.5
	Not done	25	
CT abdomen			
	Normal	1	14.3
	Abnormal	6	85.7
	Not done	34	

Treatment results

From the total of 37 patients with bone tumors, 22 (59.5%) patients were treated with chemotherapy alone, 9 (24.3%) patients were treated with chemotherapy and then surgery, 3 (8.1%) patients were treated with chemotherapy and radiotherapy, and 3 (8.1%) patients were treated with surgery (amputation in one patient with osteosarcoma and excision of clavicle and radius in 2 patients with Ewing's sarcoma), chemotherapy and radiotherapy, as shown in Table 4.

The most common toxic effect of chemotherapy was febrile neutropenia which was recorded in 22 (59.5%) patients, followed by hemorrhagic cystitis in 3 (8.1%) patients. Both febrile neutropenia and hemorrhagic cystitis were recorded in 5 (13.5%) patients, and convulsion was recorded in 1 (2.7%) patient, and no complications were seen in 5 (13.5%) patients, as shown in Table 4.

Relapse was found in 8 (21.6%) patients. The outcome in relapsed patients was as follows: 1 (12.5%) patient died, 1 (12.5%) patient was lost to follow up, and 6 (75%) patients were alive.

In Table 4, the outcome of patients included in the study was as follows: 21 (56.8%) patients were alive, 9 (24.3%) patients died and 7 (18.9%) patients were lost to follow up.

The presumptive causes of death in 9 (24.3%) patients were respiratory failure in 2 (5.4%) patients, progressive disease in 2 (5.4%) patients, heart failure in 1 (2.7%) patient, sepsis in 1 (2.7%) patient, CNS complications in 1 (2.7%) patient, and 2 (5.4%) patients died at home, as shown in Table 5. The maximum period of follow-up of 35/37 patients was 60 months with a mean of 15.80 months.

Progressive disease was found in 16 patients (43%), and their outcome was as follows: 7 patients (44%) died, 3 patients (19%) were lost to follow-up and 6(37%) patients were alive.

The overall survival (OS) at 20 months was 69%, 60% at 24 months and 50% at 36 months, as shown in Figure 1.

The event free survival rate (EFS) at 24 months was 53%, as shown in Figure 2.

Table 4. *Treatment modalities, complications, and outcome of the studied group (37 patients)*

Treatment modalities		
	Frequency	Percent %
Chemotherapy alone	22	59.5
Chemotherapy and surgery	9	24.3
Chemotherapy and radiotherapy	3	8.1
Chemotherapy, surgery and RT	3	8.1
Total	37	100.0
Complications		
	Frequency	Percent
Febrile neutropenia	22	59.5
Febrile neutropenia and hemorrhagic cystitis	5	13.5
No complication	5	13.5
Hemorrhagic cystitis	3	8.1
Convulsion	1	2.7
Others	1	2.7
Total	37	100.0
Outcome of the studied group (37 patients)		
	Frequency	Percent
Alive	21	56.8
Died	9	24.3
Lost to follow-up	7	18.9
*Total	37	100.0

* Four patients were excluded (2 were treated with different protocols and 2 were treated in other institutes)

Table 5. *Presumptive cause of death in (9/37) patients*

	Frequency	Percent %
Respiratory failure	2	5.4
Progressive disease	2	5.4
Died at home (terminal cases)	2	5.4
CNS involvement	1	2.7
Sepsis	1	2.7
Heart failure	1	2.7
Total	9	24.3

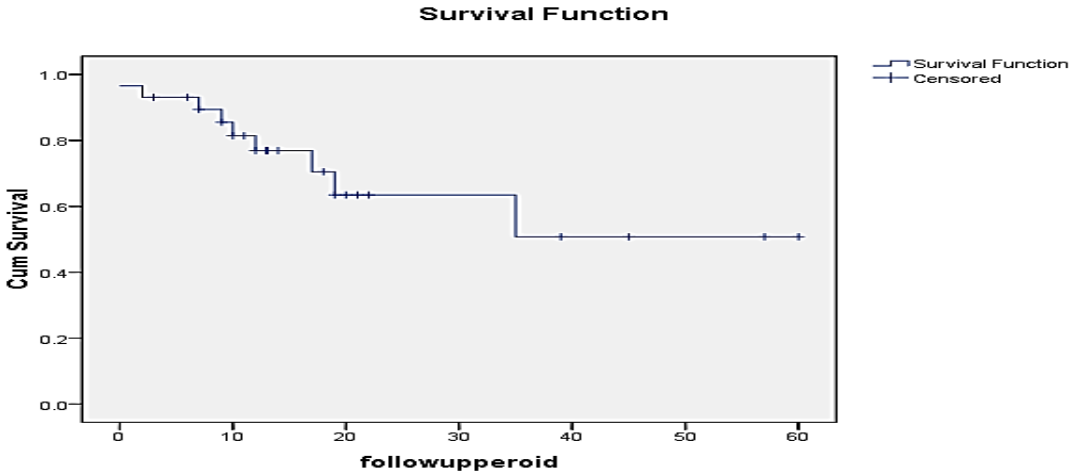

Figure 1. *Figure 1. Overall survival (OS) at 20 months was 69%, 60% at 24 months, and 50% at 36months*

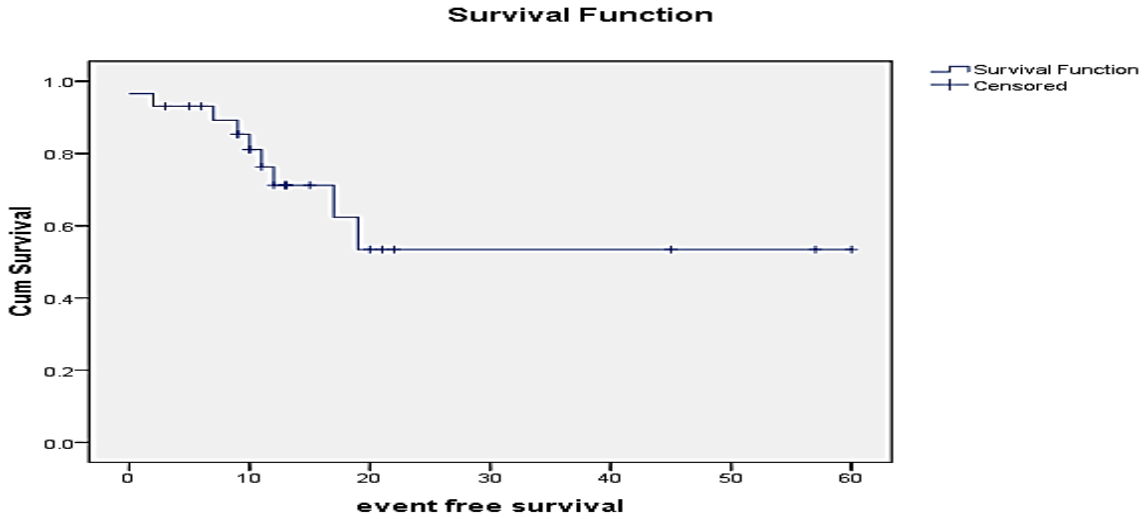

Figure 2. *Event-free survival at 24 months was 53%*

DISCUSSION

The five-year relative survival rate for pediatric patients diagnosed with bone cancer increased from 49% during the time frame of 1975-1984 to 63% during the period 1985-1994. Survival rates showed enhancement in both osteosarcoma and Ewing's sarcoma throughout the two time periods.

The survival rates for osteosarcoma were superior to those for Ewing's sarcoma, particularly during the initial time period (4).

The peak age incidence was in the age group 5-10 years, which is different than that mentioned in Obalum DC's study from Nigeria (5), which was 11-20 years. This may be due to higher percentage of Ewing's sarcoma which is more common in children younger than 10 years of age.

Regarding sex distribution, male:female ratio was 1.2:1, which is slightly lower than that mentioned in Omololu et al.'s study from Nigeria (6), in which male:female ratio was 1.4:1.

The mean duration of illness was 4.1 months, which is shorter than that mentioned in Guerra et al.'s study from São Paulo (7), which was 6.6 month.

Local pain was reported in 10 (24.4%) patients, which is less than that mentioned in Guerra et al.'s

study from São Paulo (7) (89.5%) and that mentioned in the reference literature (1) (93%).

Advanced stage (metastasis at diagnosis) was found in 12 (29.3%) patients, which was higher than that mentioned in Sluga et al.'s study from Germany (8) (9%). The high percent in the current study may be attributed to late diagnosis referral because of poor diagnostic facilities, lack of index of suspicion, and poor socioeconomic state.

Osteosarcoma was found in 12 (29.3%) patients, and Ewing's sarcoma was found in 29 (70.7%) patients, which is different from that mentioned in Haidar et al.'s study from Lebanon (9), in which osteosarcoma constituted 93% and Ewing's sarcoma 3%. This is different from that mentioned in Sluga et al.'s study from Germany (8) in which osteosarcoma constituted 73% and Ewing's sarcoma 27%, and also different from that mentioned in Körholz et al.'s study from Germany (10) in which osteosarcoma constituted 60.5% and Ewing's sarcoma 39.5%.

The overall survival rate of 69%, which is higher than that mentioned in the Sluga et al.'s study from Germany (8), which is 63%, may be due to higher percentage of Ewing's sarcoma which has a better outcome.

At a median follow-up of 12 months, the two-year event free survival is 53%, a rate which is lower than that mentioned in literature (1), due to late diagnosis, late referral with presentation in locally advanced stage of disease, in addition to high rate of patients lost to follow up.

CONCLUSIONS

- The majority of cases were in the age group between 5 - 10 years.
- Pain and swelling were the most common presentations, which was different from that mentioned in literature in which local pain is the main presentation in bone tumors.
- Ewing's sarcoma was more frequent than osteosarcoma.
- High percentage of locally large size tumor was found due to late diagnosis.
- Inadequate diagnostic imaging study and treatment modalities like radiotherapy and salvage surgery were applied.
- There was a high rate of patients lost to follow-up.
- A two-year EFS was 53%, which is lower than that reported in other studies due to the above-mentioned reasons.

RECOMMENDATION

1. To improve diagnostic facilities for accurate diagnosis.
2. Treatment should involve all therapeutic methods, including salvage surgery, chemotherapy, and radiation in a well-equipped specialist facility.
3. Physicians should take their role in the process of education of families, particularly the mother, regarding the important and dangerous signs and complications that may arise after each course of chemotherapy, and the importance of treatment compliance.

Conflict of interest

The authors declared no conflict of interest.

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Author contribution

Authors contributed equally in the study.

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Maligni tumori kostiju kod dece u Iraku

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SAŽETAK

Uvod/cilj. Oko šest posto svih maligniteta dijagnostikovanih kod dece čine maligni tumori kostiju, koji imaju dramatičan efekat na psihološko stanje dece i njihovih porodica. Cilj ove studije bila je analiza kliničko-patoloških karakteristika tumora kostiju kod dece u Iraku, kao i procena odgovora na lečenje, ishode i preživljavanja.

Bolesnici i metode. Retrospektivna studija o deci sa tumorima kostiju, bazirana na podacima bolesnika koji su bili podvrgnuti brojnim analizama pre lečenja, trajala je jedanaest godina. Ispitivanje je obuhvatilo kompletnu krvnu sliku, elektrolite seruma, profil jetre i bubrega, biopsiju i aspirat koštane srži, aspiraciju tankom iglom i snimke.

Rezultati. Sakupljeni su podaci o 41 bolesniku sa tumorima kostiju. Najčešće su bili zahvaćeni donji ekstremiteti – to je potvrđeno kod 21 (51,2%) deteta.

U vreme postavljanja dijagnoze, kod 29 bolesnika bolest je bila lokalizovana (70,7%), a kod 12 (29,3%) bolesnika javile su se metastaze. Od 41 bolesnika uključenog u studiju, histopatologija je kod 29 (70,7%) bolesnika ukazala na Juingov sarkom, dok je kod 12 (29,3%) bolesnika dijagnostikovan osteosarkom.

Najčešći toksični efekat hemoterapije bila je febrilna neutropenija, zabeležena kod 22 (59,5%) bolesnika; pratio ju je hemoragijski cistitis, potvrđen kod tri (8,1%) bolesnika. Febrilna neutropenija i hemoragijski cistitis zabeleženi su kod pet (13,5%) bolesnika, konvulzija je utvrđena kod jednog (2,7%) bolesnika; kod pet (13,5%) bolesnika pak nije bilo komplikacija. Recidiv je potvrđen kod osam (21,6%) bolesnika.

Zaključak. Veliki broj bolesnika nije se pojavio za dalje praćenje bolesti. Dvogodišnji period preživljavanja bez značajnijih dešavanja iznosio je 53%, što je procenat niži od onog u drugim studijama; do toga je došlo zbog kasnog postavljanja dijagnoze i kasnog upućivanja lekaru, onda kada je bolest već bila uznapredovala.

Ključne reči: **osteosarkom, Juingov tumor, pedijatrijski**