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Clinical and Prognostic Characteristics in Childhood Osteosarcoma: A Single-Center Experience in Türkiye

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What is already known on this topic?

- *Osteosarcomas are the most common primary malignant tumor of bone in children and adolescents worldwide.*
- *Clinical course and survival of osteosarcoma cases are related to various factors, and these cases require multidisciplinary treatment and post-treatment follow-up.*
- *Survival and quality of life in osteosarcoma cases have improved significantly over the years.*

What this study adds on this topic?

- *In the study, the clinical experience of our center in osteosarcoma cases was presented and compared with literature data.*
- *There are different opinions in the literature regarding the effect of diagnosis time on prognosis. In our study, patients with an interval of 3 months or less from the onset of symptoms to diagnosis had higher rates of multiple surgery, recurrence, and mortality.*
- *There is still a long way to go regarding survival and quality of life in osteosarcoma cases. Therefore, multicenter and multidisciplinary studies on osteosarcoma are needed.*

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ABSTRACT

Objective: In our study, we aimed to share the clinical experiences of our center regarding osteosarcoma cases, the most common primary malignant bone tumor in children and adolescents.

Materials and Methods: With approval from the Clinical Research Ethics Committee of our center, the data of 59 pediatric patients who were followed up in our center with the diagnosis of osteosarcoma between 2007 and 2021 were evaluated retrospectively.

Results: The mean time between the onset of symptoms and diagnosis was 3 months. Although not statistically significant, patients with a diagnostic delay of 3 months or less had a higher rate of recurrence and mortality. 59.3% of patients had metastatic disease, and the presence of metastases was associated with higher rates of recurrence and mortality. Significant number of patients had multiple surgical operations. Amputation as the first operation and the need for multiple surgeries were associated with higher mortality. Pathologically poor response to chemotherapy is associated with mortality. 42.4% of patients died, and the 5-year overall and disease-free survival rates were 47.5% and 30.5%, respectively. Survival rates were highest in non-metastatic and non-relapsed patients, and lowest in metastatic patients and patients with poor response to chemotherapy. Renal problems and cardiotoxicity were most frequently treatment-related complications.

Conclusion: Significant improvements have been achieved in the survival and quality of life in osteosarcoma cases compared to previous years; however, there is still a long way to go, and more multicenter and multidisciplinary studies are needed on osteosarcoma.

Keywords: Osteosarcoma, prognosis, survival, mortality

INTRODUCTION

Osteosarcoma, which is among the malignant bone tumors that constitute approximately 0.2% of all malignancies and approximately 6.0% of all childhood cancers, is the most common primary malignant tumor of bone in children and adolescents worldwide.[1,2] Osteosarcoma, with an overall worldwide incidence of 3.4/1000000 cases per year, can affect individuals of all ages and sexes. It is more common in males and is characterized by a bimodal age distribution, with the first peak between 15 and 19 years of age (8.0/1 000 000 cases per year), the second peak between 75 and 79 years of age (6.0/1 000 000 cases per year), and a flat plateau between 25 and 59 years of age (1.0-2.0/1 000 000 cases per year).[2,3] In Türkiye, according to the data of the Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Society, 2301 (6.4%) of 35 978 cases recorded between 2002 and 2021 were malignant bone tumors and the frequency of osteosarcoma is unfortunately unknown.[4,5]

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Prognosis and survival of osteosarcoma cases is associated with various factors such as diagnosis age, sex, tumor stage (anatomical localization, dimensions, and intraosseous/ex traosseous spread, and presence of regional lymph node and distant organ metastasis), incomplete surgical resection (surgical margin positivity), poor response to neoadjuvant chemotherapy (<90% necrosis), and recurrence within the first 2 years after the end of treatment.[6,7] While survival was around 20% with only surgical treatment in the 1970s, with the inclusion of chemotherapeutic agents in the treatment and the development of surgical techniques, it has increased dramatically over the years, up to 70%. However, increased survival has brought with it the quality of life problem, that is, the problem of the long-term effects of the disease and treatments.[8]

Although it is the most common primary malignant bone tumor in the pediatric population, it is rare and still causes high mortality and poor quality of life, physicians need to have high awareness of osteosarcoma. In this retrospective case series, it is aimed to evaluate the prognosis and survival of osteosarcoma cases followed and treated in our center and to compare them with the literature.

MATERIALS AND METHODS

Study Design and Population

In this retrospective case series study, patients aged ≤18 years of age at diagnosis, who were followed up and treated between 2007 and 2021 with the diagnosis of osteosarcoma in our center and whose medical data were available, were included. These patients were diagnosed with osteosarcoma clinically and radiologically, and their diagnoses were confirmed pathologically. Cases who continued their follow-up and treatment in another center after diagnosis and whose medical data could not be accessed were excluded from the study.

The data of the patients included in the study were collected retrospectively and analyzed, and the results were interpreted. The data of the patients examined in the study were demographic characteristics, diagnosis and onset of symptoms date, primary tumor localization, presence and localization of metastases, pathology of the tumor, type and number of surgery, recurrence and time of recurrence, treatment-related side effects and long-term effects, disease-free survival, total survival, and mortality.

Ethics Committee Approval

All medical records were pseudo-anonymized for the current study. The study was approved by the Clinical Research Ethics Committee (decision date and number: March 16, 2022, İ04-155-22), and carried out according to the Declaration of Helsinki.

Statistical Analysis

All statistical analysis were performed using the IBM SPSS Statistics 22 (IBM Corp., Armonk, New York, USA). In continuous data, mean ± SD, median, minimum, and maximum values were given, and in categorical data, frequencies and percentages were given. Chi-square statistical method was used to compare categorical variables, and $P < .05$ was accepted as the statistical significance limit.

RESULTS

Demographic Characteristics of the Patients

The study included 59 patients. Male:female ratio was 1:1 and the mean age was 12.9 ± 2.6 years. The time between the onset of symptoms and the diagnosis of osteosarcoma was 3.1 ± 2.2 months. Demographic characteristics of the patients were shown in Table 1.

Primary Tumor and Metastasis Location

The primary tumor was most commonly located in the distal femur, proximal tibia and proximal humerus, thus in the knee and shoulder joint. Also, the primary tumor was located distal to the skeleton in almost all patients (Table 2).

Thirty-five of 59 patients (59.3%), 16 of them (16/33, 45.7%) at diagnosis, had metastatic disease, and the most common sites of metastasis were the lungs and bones. No correlation was found between the age at diagnosis, sex, and time from symptom onset to diagnosis of the patients and the presence of metastatic disease ($P = .4$, $P = 0.91$, and $P = .33$, respectively) (Tables 2 and 3).

Surgery Information

Twenty-four of 59 patients (40.7%) had multiple surgical operations. Most of the patients (51/59) underwent limb-sparing surgery as their first surgery, and over the years, it has been observed that the frequency of amputation as the first surgical operation has decreased importantly [44.4% before 2011 (4/9), 8.0% after 2011 (4/50)]. Multiple surgical operations were required in 50.0% of patients who underwent amputation as the first surgical operation (4/8), and in 39.2% of patients who underwent limb-sparing surgery (20/51); and were performed in 46.3% of patients with ≤3 months of time between the onset of symptoms and diagnosis (19/41), and 27.8% of patients with >3 months (5/18). The maximum number of surgical operations performed was 5. The relationship between the type of first surgical operation and the time from onset of symptoms to diagnosis with the number of surgical operations was not determined ($P = .56$ and $P = .18$, respectively) (Tables 4 and 5).

Table 1. Demographic Characteristics of Patients

	n (%)
Sex	30 (50.9%)
Male	29 (49.1%)
Female	
Age at diagnosis (years)	33 (55.9%)
≤ 13	26 (44.1%)
> 13	
Time from onset of symptoms to diagnosis (months)	41 (69.5%)
≤ 3	18 (30.5%)
> 3	
Age at diagnosis (years)	Mean ± SD (min-max)
All patients	12.9 ± 2.6 (6 – 18)
Male	12.5 ± 3.1 (6 – 18)
Female	13.3 ± 2.1 (9 – 17)
Time from onset of symptoms to diagnosis (months)	
All patients	3.1 ± 2.2 (0.25 – 12)
Male	2.9 ± 2.0 (0.25 – 8)
Female	3.2 ± 2.4 (0.5 – 12)

Table 2. Primary Tumor and Metastasis Location and Frequency

Primary Tumor Location	n (%)
Distal femur	36 (61.0%)
Proximal tibia	13 (22.0%)
Proximal humerus	5 (8.5%)
Proximal femur	1 (1.7%)
Proximal fibula	1 (1.7%)
Posterior iliac wing	1 (1.7%)
Distal tibia	1 (1.7%)
Distal ulna	1 (1.7%)
Presence and locations of metastases	n (%)
Non-metastatic	24 (40.7%)
Sex	
Male	12 (50.0%)
Female	12 (50.0%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	15 (62.5%)
> 3	9 (37.5%)
Age at diagnosis (years)	
≤ 13	15 (62.5%)
> 13	9 (37.5%)
Metastatic	35 (59.3%)
Sex	
Male	18 (51.4%)
Female	17 (48.6%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	26 (74.3%)
> 3	9 (25.7%)
Age at diagnosis (years)	
≤ 13	18 (51.4%)
> 13	17 (48.6%)
Time of metastasis	
At diagnosis (+), new metastasis on follow-up (−)	4 (11.4%)
At diagnosis (−), at follow-up (+)	19 (54.3%)
At diagnosis (+), new metastasis on follow-up (+)	12 (34.3%)
Location of metastasis	
Lung	33 (94.3%)
Bone	18 (51.4%)
Liver	1 (2.9%)
Lymph node	1 (2.9%)

Pathology Results

In the post-operative pathology results, almost all of the patients were evaluated as conventional type osteosarcoma. The pathology results of 4 patients were not available, it was observed that 54.5% of the other patients (30/55) had a >90% necrosis response to neoadjuvant chemotherapy, and 45.5% (25/55) had a ≤90% necrosis response. Patients' sex, age at diagnosis, and time from onset of symptoms to diagnosis were not associated with chemotherapy response (P = .96, P = .84, and P = .31, respectively). Twenty patients (20/25, 80.0%) with ≤90% necrosis response to chemotherapy and 12 patients (12/30, 40.0%) with >90% necrosis response had metastatic disease, and a poor necrosis response to neoadjuvant chemotherapy was associated with metastatic disease (P = .004) (Tables 6 and 7).

Table 3. The Relationship Between Demographic Characteristics and the Presence of Metastatic Disease

Demographic Characteristics		Presence of Metastasis		P*
		Metastatic	Non-metastatic	
Age at diagnosis	≤13 years	18	15	0.4
	> 13 years	17	9	
Sex	Male	18	12	.91
	Female	17	12	
Time to diagnosis	≤ 3 months	26	15	.33
	> 3 months	9	9	

*P values were calculated using chi-square.

Table 4. Surgical Operation İnformation

First Surgical Operation	n (%)
Limb-sparing surgery	51 (86.4%)
Amputation	8 (13.6%)
Amputation by years	
2007-2010	4 (50.0%)
2011-2015	2 (25.0%)
2016-2020	2 (25.0%)
Number of surgical operations	n (%)
Only one operation	35 (59.3%)
First operation	
Limb-sparing surgery	31 (88.6%)
Amputation	4 (11.4%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	22 (62.9%)
> 3	13 (37.1%)
Multiple operations	24 (40.7%)
First operation	
Limb-sparing surgery	20 (83.3%)
Amputation	4 (16.7%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	19 (79.2%)
> 3	5 (20.8%)

Relapse Status

Eleven patients (11/59; 18.6%) died before adjuvant chemotherapy could be completed, and 45.8% of the remaining patients (22/48) developed relapse during follow-up. Chemotherapy was started in all patients who developed relapse, except for one patient who refused treatment. Age at diagnosis, sex, time from onset of symptoms to diagnosis, and the type of first surgical operation were not associated with the development of relapse (P = .26, P = .63, P = .12, and P = .45, respectively). Twenty-one patients who developed relapse (21/22; 95.4%) had metastatic disease, and the presence of metastatic disease

Table 5. The Relationship Between the First Surgical Operation Type and the Time to Diagnosis with the Number of Surgical Operations

First Operation Type and Time to Diagnosis		Number of Surgical Operation		P*
		1	> 1	
Surgical operation	Limb-sparing surgery	31	20	.56
	Amputation	4	4	
Time to diagnosis	≤ 3 months	22	19	.18
	> 3 months	13	5	

*P values were calculated using chi-square.

Table 6. Post-operative Pathology Results

Necrosis Responses to Chemotherapy	n (%)
> 90%	30 (54.5%)
Sex	
Male	17 (56.7%)
Female	13 (43.3%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	19 (63.3%)
> 3	11 (36.7%)
Age at diagnosis (years)	
≤ 13	16 (53.3%)
> 13	14 (46.7%)
Presence of metastases	
Metastatic	12 (40.0%)
Non-metastatic	18 (60.0%)
≤ 90%	25 (45.5%)
Sex	
Male	14 (56.0%)
Female	11 (44.0%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	19 (76.0%)
> 3	6 (24.0%)
Age at diagnosis (years)	
≤ 13	14 (56.0%)
> 13	11 (44.0%)
Presence of metastases	
Metastatic	20 (80.0%)
Non-metastatic	5 (20.0%)

was associated with the development of relapse ($P < .001$). In the pathology results, 53.3% of patients with ≤90% necrosis response to chemotherapy (8/15) and 37.9% of patients with >90% necrosis response (11/29) developed relapse, and poor necrosis response to chemotherapy was not associated with relapse ($P = .33$) (Tables 8 and 9).

Treatment-Related Side Effects and Long-Term Complications

Complications of the disease and the treatments were seen in 32.2% of the patients, and the most common complications were renal problems (10.2%), cardiotoxicity (8.5%), and reversible acute hepatotoxicity (8.5%). Complications that occurred less frequently in patients were methotrexate-related acute encephalopathy (3.4%), peripheral neuropathy (3.4%), bilateral mixed hearing loss (3.4%), reversible acute pancreatitis (1.7%), and secondary malignancy (acute myeloid leukemia) (1.7%).

Table 7. The Relationship Between the Demographic Characteristics and Presence of Metastasis with the Necrosis Response to Neoadjuvant Chemotherapy

Demographic and Metastatic Characteristics		Response to Chemotherapy		*P**
		≤ 90% Necrosis	> 90% Necrosis	
Age at diagnosis	≤ 13 years	14	16	.84
	> 13 years	11	14	
Sex	Male	14	17	.96
	Female	11	13	
Time to diagnosis	≤ 3 months	19	19	.31
	> 3 months	6	11	
Presence of metastasis	Metastatic	20	12	.004
	Non-metastatic	5	18	

*P values were calculated using chi-square.

Table 8. Patients According to Relapse Development

Relapse Status	n (%)
Relapsed	22 (45.8%)
Sex	
Male	16 (72.7%)
Female	6 (27.3%)
Age at diagnosis (years)	
≤ 13	10 (45.5%)
> 13	12 (54.5%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	18 (81.8%)
> 3	4 (18.2%)
Presence of metastases	
Metastatic	21 (95.5%)
Non-metastatic	1 (4.5%)
Necrosis responses to chemotherapy	
> 90%	11 (50.0%)
≤ 90%	8 (36.4%)
(–)	3
Number of surgical operations	
Only one operation	2 (9.1%)
Multiple operations	20 (90.9%)
First surgical operation	
Limb-sparing surgery	20 (90.9%)
Amputation	2 (9.1%)
Non-relapsed	26 (54.2%)
Sex	
Male	12 (46.2%)
Female	14 (53.8%)
Age at diagnosis (years)	
≤ 13	16 (61.5%)
> 13	10 (38.5%)
Time from onset of symptoms to diagnosis (months)	
≤ 3	16 (61.5%)
> 3	10 (38.5%)
Presence of metastases	
Metastatic	3 (11.5%)
Non-metastatic	23 (88.5%)
Necrosis responses to chemotherapy	
> 90%	18 (69.2%)
≤ 90%	7 (26.9%)
(–)	1
Number of surgical operations	
Only one operation	26 (100.0%)
Multiple operations	0 (0.0%)
First surgical operation	
Limb-sparing surgery	25 (96.1%)
Amputation	1 (3.9%)

Mortality and Survival Rates

In total, 42.4% of patients (25/59) died. Patients' age at diagnosis [39.4% of patients ≤13 years old (13/33), 46.1% of patients >13 years old (12/26)] and sex [36.7% of male patients (11/30)

Table 9. The Relationship Between Demographic, Clinical, and Pathological Characteristics and the Development of Relapse

Demographic, Clinical, and Pathological Characteristics		Relapse Status		P*
		Relapsed	Non-relapsed	
Age at diagnosis	≤13 years	10	16	.26
	>13 years	12	10	
Sex	Male	16	12	.63
	Female	6	14	
Time to diagnosis	≤3 months	18	16	.12
	> 3 months	4	10	
First operation type	Limb-sparing surgery	20	25	.45
	Amputation	2	1	
Presence of metastasis	Metastatic	21	3	<.001
	Non-metastatic	1	23	
Chemotherapy response**	≤90% necrosis	8	7	.33
	> 90% necrosis	11	18	

*P values were calculated using chi-square.
**The pathology results of 4 patients were not available.

and 48.3% of female patients (14/29)], time from symptom onset to diagnosis [48.8% of patients with elapsed time ≤3 months (20/41), 27.8% of patients with elapsed time >3 months (5/18)], and location of the primary tumor [42.9% of patients with proximal tumors (3/7) and 42.3% of patients with distal tumors (22/52)] were not associated with mortality (P = .6, P = .37, P = .13, and P = .98, respectively). All patients who died were metastatic patients, and metastatic disease is associated with mortality (P < .001). In the post-operative tumor material, 23.3% of patients with >90% necrosis response (7/30) and 60.0% of patients with ≤90% necrosis response (15/25) died, and poor response to chemotherapy was associated with mortality (P = .007). Seven patients who underwent amputation as the first operation (7/8, 87.5%) and 18 patients who underwent limb-sparing surgery (18/51, 35.3%) died. Nine patients (9/35, 25.7%) who had only one surgical operation died, and this rate rises to 66.7% (16/24) for patients who had multiple operations. Amputation as the first operation and the need for multiple operations were associated with mortality (P = .021 and P = .003, respectively). In total, 63.6% of the patients who developed relapse (14/22) died. The mortality rate was 64.7% in patients who developed relapse within 2 years after the completion of treatment (11/17), and 60.0% in patients who developed relapse after more than 2 years (3/5), and no effect of the time of relapse on mortality was detected (P = .85) (Tables 10 and 11).

Table 10. The Relationship Between Demographic, Clinical, and Pathological Characteristics and the Development of Mortality

Demographic, Clinical, and Pathological Characteristics		Mortality		P*
		Exitus	Alive	
Age at diagnosis	≤13 years	13	20	.6
	>13 years	12	14	
Sex	Male	11	19	.37
	Female	14	15	
Time to diagnosis	≤3 months	20	21	.13
	> 3 months	5	13	
Primary tumor location	Proximal	3	4	.98
	Distal	22	30	
Presence of metastasis	Metastatic	25	0	<.001
	Non-metastatic	0	24	
First operation type	Limb-sparing surgery	18	33	.021
	Amputation	7	1	
Surgical operation number	Only one	9	26	.003
	Multiple	16	8	
Chemotherapy response**	≤90% necrosis	15	10	.007
	>90% necrosis	7	23	

*P values were calculated using chi-square.
**The pathology results of 4 patients were not available.

Table 11. The Relationship Between Time to Relaps and the Development of Mortality

Patients Who Developed Relapse		Mortality		P*
		Exitus	Alive	
Time to relapse	0-2 years	11	6	.85
	>2 years	3	2	

*P values were calculated using chi-square.

Two- and 5-year overall survival rates were 74.6% and 47.5%, respectively, and 2- and 5-year disease-free survival rates were 44.1% and 30.5%, respectively, in our patients. Survival rates reached their highest levels in non-metastatic and non-relapsed cases and declined to the lowest levels in patients with poor necrosis response to neoadjuvant chemotherapy and metastatic patients (Table 12).

DISCUSSION

Diagnosis of childhood malignancies, especially of malignancies that start with non-specific signs and symptoms such as osteosarcoma, continues to be a challenging process and, therefore, delay in diagnosis is unfortunately an important problem today. Although delay in diagnosis is associated with poor prognostic outcomes in many childhood malignancies, there are different results in the literature regarding delayed diagnosis in osteosarcoma cases. In a systematic review by Brasme et al (2012), it has been shown that the mean total time to diagnosis for osteosarcoma is 12.4 weeks, and there is no significant relationship between the time to diagnosis and the presence of metastases, response to chemotherapy, limb preservation, recurrence, or survival.[9] However, in a study by Yoshida et al (2021), it was shown that patients with less than 4 weeks between the onset of symptoms and diagnosis had significantly better results in terms of 5-year survival than patients with longer than 4 weeks.[10] On the other hand, Bacci et al (2002) and Ferrari et al (2016) reported in their studies that the time between the onset of symptoms and the final diagnosis was significantly shorter in metastatic patients than in patients with localized tumors, and the short symptom duration until diagnosis was associated with poor prognosis. They explained this situation with the biological characteristics of the tumor.[11,12]

In our study, the mean time from the onset of symptoms to diagnosis was 3.1 months. Although a statistically significant relationship was not detected, a higher rate of patients in whom the time from onset of symptoms to diagnosis is 3 months or

Table 12. Survival Rates

Survival Rates	Overall Survival (%)	Disease-free Survival (%)
All patients		
2-year	74.6	44.1
5-year	47.5	30.5
Sex		
Male		
2-year	76.7	43.3
5-year	53.3	30.0
Female		
2-year	72.4	44.8
5-year	41.4	31.0
Age at diagnosis (years)		
≤13		
2-year	75.7	39.4
5-year	51.5	27.3
> 13		
2-year	73.1	46.1
5-year	42.3	26.9
Time to diagnosis (months)		
≤ 3		
2-year	75.6	41.5
5-year	51.2	26.8
> 3		
2-year	72.2	50.0
5-year	33.3	27.8
Presence of metastases		
Metastatic		
2-year	72.4	20.0
5-year	34.5	5.7
Non-metastatic		
2-year	95.8	79.2
5-year	75.0	66.7
Necrosis responses to chemotherapy		
>90%		
2-year	83.3	63.3
5-year	60.0	50.0
≤ 90%		
2-year	64.0	20.0
5-year	32.0	10.0
Number of surgical operations		
Only one operation		
2-year	82.9	60.0
5-year	57.1	51.4
Multiple operations		
2-year	62.5	20.8
5-year	33.3	(-)
Relapse status		
Relapsed		
2-year	72.7	22.7
5-year	36.4	(-)
Non-relapsed		
2-year	96.1	80.8
5-year	76.9	69.2

less compared to patients for whom is longer than 3 months, it was observed that they had undergone multiple surgical operations, developed recurrence, and died. These results suggest that osteosarcoma cases with a biologically more aggressive tumor are admitted to the hospital earlier with more severe symptoms.

Surgical resection is essential for local disease control in the treatment of osteosarcoma. Surgical margin positivity leads to a higher risk of recurrence; therefore, it is of great importance to apply a wide resection with surgical margin negativity to patients. The type of surgery is determined by the location, size, and spread of the tumor, presence of metastases, and patient's age, skeletal development, and lifestyle preferences.[13] Surgical approaches in osteosarcoma still remain a subject on which studies and comparisons continue. In a review by Papakonstantinou et al (2020), 5-year overall survival in patients who underwent limb-sparing surgery was 2 times higher than in patients who underwent amputation, but there was no difference in disease-free survival between patients who underwent limb-sparing surgery and amputation.[14] In addition, it was shown that patients who underwent limb-sparing surgery had a higher recurrence rate than patients who underwent amputation, but this was not statistically significant. In another study by Wang et al. (2022), it was shown that the 5-year survival rate was higher in patients who underwent limb-sparing surgery than in patients who underwent amputation.[15] In the study, it was suggested that amputated patients had tumors that were larger, more aggressive, and less responsive to chemotherapy, and this may be associated with higher survival rates in patients who underwent limb-sparing surgery.

In our study, although a higher rate of recurrence was observed in patients who initially underwent amputation compared to patients who underwent limb-sparing surgery, this situation was not statistically significant. The mortality rates of patients who underwent amputation as the first operation were found to be statistically significantly higher than those who underwent limb-sparing surgery. However, similar to the study of Wang et al. (2022), patients who underwent amputation in our study had higher rates of metastatic disease and poor response to chemotherapy, and this could be explained by the higher recurrence and mortality rates of these patients.

With the development of treatment modalities, survival in osteosarcoma cases has increased importantly over the years. According to the EURAMOS-1, the largest osteosarcoma study to date, 5-year overall and disease-free survival rates were 71% and 54%, respectively. In cases with metastatic disease; 5-year overall survival was 45%, and 5-year disease-free survival was 28%. In non-metastatic cases, 5-year overall and disease-free survival rates were 76% and 60%, respectively; and in cases where complete surgical remission is achieved, post-operative 5-year overall and disease-free survival rates increased to 79% and 64%, respectively.[7] According to The National Cancer Institute Surveillance, Epidemiology, and End Results (NCI SEER) data, 5-year overall survival was observed as 71.8% in the age group 0-9 without any sex difference, and 65.9% in the age group 10-24 and it was higher in women than men. In metastatic cases, this rate decreased to 35.5% for 0-24 years old.[16] In addition, it has been shown in the literature that

5-year disease-free survival is 75-93% in cases with ≥90% necrosis response to neoadjuvant chemotherapy, and this rate regresses to 45-67% in cases with <90% necrosis response.[17]

In our study, the 2- and 5-year overall survival rates were 74.6% and 47.5%, respectively, and the 2- and 5-year disease-free survival rates were 44.1% and 30.5%, respectively. It was observed that the survival rates reached the highest levels in non-metastatic and non-recurring cases, and decreased to the lowest levels in patients who had poor necrosis response to chemotherapy and had undergone multiple surgical operations. These survival rates, which oncologists could not have imagined 50 years ago, both show the point reached in the treatment of osteosarcoma and remind that there is still a long way to go.

The important increase in survival in osteosarcoma cases over the years has brought along long-term complications of the disease and the treatments. Cardiotoxicity and heart failure are one of the most severe treatment complications and may occur even decades after the end of treatment.[18] Another long-term complications is secondary malignancies. These secondary malignancies may be leukemias that are expected to develop within the first 10 years after osteosarcoma and secondary solid tumors that can occur at any time. Chemotherapeutic agents, radiation exposure, and individual factors that predispose to cancer are factors that may contribute to the development of secondary malignancies.[19] Nephrotoxicity is also one of the common problems caused by osteosarcoma treatment. Glomerular or tubular dysfunction caused by cisplatin, ifosfamide, and methotrexate is responsible for treatment-associated nephrotoxicity, which may be reversible or irreversible.[18] In our study, renal problems were detected in 6 patients. Five patients developed cardiotoxicity and 2 of them died. Other long-term complications peripheral neuropathy, bilateral mixed hearing loss, reversible acute pancreatitis, and secondary malignancy occurring within the first 5 years after the diagnosis of osteosarcoma. All these results remind that the follow-up of osteosarcoma cases should be multidisciplinary.

Studies on osteosarcoma have shown that; male sex, adolescent diagnosis age, presence of metastatic disease at diagnosis, incomplete surgical resection, poor necrosis response to chemotherapy, primary tumor located in the axial skeleton or proximal of extremity, larger tumor sizes, recurrence within 2 years after the end of treatment, multiple pulmonary nodules or bilateral pulmonary involvement and pleural damage caused by metastases are among the poor prognostic factors.[7] Similarly, in our study, the presence of metastatic disease was found to be statistically associated with the development of recurrence; presence of metastatic disease, poor necrosis response to chemotherapy, amputation as the first operation and need for multiple surgical operations were found to be statistically associated with mortality. In addition, although not statistically significant, a higher rate of recurrence was observed in cases of male sex, diagnosed over 13 years old, primary tumor located proximal of the skeleton, had a poor response to chemotherapy, amputation as the first operation and the need for multiple operations; a higher rate of mortality was observed in cases of diagnosed over 13 years old and recurrence within 2 years after the end of treatment. Information on other factors related to poor prognosis is not included in this study.

The main limitation of this study was that it was a single-center. A multi-center osteosarcoma study, perhaps on a national scale, could most accurately reveal the survival and quality of life of osteosarcoma patients in our country and the areas we need to focus on to improve them. In addition, various difficulties experienced in accessing patient data, especially the data of patients diagnosed before the electronic data recording system, are among the limitations of the study.

CONCLUSION

In conclusion, significant improvements have been achieved in the survival in osteosarcoma cases compared to previous years, however there is still a long way to go. Additionally, increased survival also brings with it quality of life problems, so follow-up of these cases should be multidisciplinary and care should be taken about long-term effects of the disease and/or treatments in the follow-up. Finally, although it is the most common primary malignant tumor of the bone in children and adolescents, multicenter, perhaps national, studies are needed on osteosarcoma because it is a relatively rare malignancy.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara University (approval number: İ04-155-22; date: March 16, 2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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