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Research Article

The Prognostic Importance of Clinicopathological Factors in Patients with Osteosarcoma Who Received Neoadjuvant Therapy; A Single Center Experience

Fatih Şimşek, Nargiz Majidova, Muhammed Fatih Kırcalı, Nadiye Sever, Abdussamet Çelebi, Rukiye Arıkan, Selver Işık, Murat Sarı, İbrahim Vedat Bayoğlu, Osman Köstek

Division of Medical Oncology, Department of Internal Medicine, Marmara University Faculty of Medicine, İstanbul, Türkiye

Abstract

Objectives: Osteosarcoma has worse prognosis in adult patients but cure is possible even in the metastatic stage. Survival rates have been significantly improved with systemic chemotherapy. We aimed to investigate the effects of clinicopathological factors on overall-survival (OS) and disease-free-survival (DFS) in 77osteosarcoma who received neoadjuvant treatment and were treated in our center.

Methods: The patients were 18 years of age and over, applied to the Marmara University of Medical Oncology outpatient clinic between 2001-2022.

Results: The overall 5-year DFS rate is 35.5%. Patients with primary tumor location in the pelvis had 5-year DFS rate of 20.0%, whereas patients with a primary location outside the pelvis had a DFS rate of 36.6%. After neoadjuvant therapy, patients with a necrosis rate of 90% or more had a 5-year DFS rate of 54.0%, while patients with a necrosis rate of less than 90% had rate of 31.6%.

Conclusion: Significant prognostic indicators for DFS were found to be female gender, primary pelvic location, and completion of adjuvant therapy in patients who underwent surgery after neoadjuvant therapy. The completion of adjuvant chemotherapy in patients who underwent surgery after neoadjuvant therapy and a necrosis rate of 90% or more in the pathology report were discovered to be significant prognostic markers for OS.

Keywords: Disease-free survival, neoadjuvant, osteosarcoma, overall survival

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Less than 1% of cancer diagnoses each year in western countries are osteosarcoma. It accounts for 3% of all pediatric cancers.[1] Under the age of 20, it accounts for 56% of all cases of bone malignancy. The incidence of osteosarcoma has a bimodal age distribution. It's incidence is the highest in adults over the age of 65.[2] In both children and adults, males are slightly more likely to develop osteosarcoma than females (ratio: 1.4:1).[2-4] In the 2020 World Health Organization bone tumor classification, conventional osteosarcoma comprises the largest group by making up 90% of cases.[5,6] Conventional osteosarcomas are divided into osteoblastic (76–80%), chondroblastic (10–13%), and fibroblastic (10%) subtypes.[6,7] They have similar clinical behavior and management despite histological differences. One

Address for correspondence: Osman Köstek, MD. Division of Medical Oncology, Department of Internal Medicine, Marmara University Faculty of Medicine, İstanbul, Türkiye
Phone: +90 212 657 06 06 **E-mail:** osmankostek@hotmail.com

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of the most crucial prognostic factors is disease stage. While patients with overt metastatic disease have a less than 20% expectancy of long-term survival, chemotherapy can cure up to 50% of those with limited pulmonary metastases. Adults have a worse prognosis than children.[8–10] Patients with primary pelvic tumors have a worse prognosis.[11]

Multimodality therapy, which includes systemic chemotherapy, significantly improved survival in osteosarcoma patients even in the metastatic stage. Surgery is the standard treatment for osteosarcoma. A major prognostic factor is the tumor response to neoadjuvant chemotherapy.[12] While methotrexate + doxorubicin and cisplatin (MAP) regimen is recommended for children and adolescents, doxorubicin + cisplatin regimen is mostly preferred in adults.[14–16] For both children and adults, neoadjuvant and adjuvant therapy are the gold standard components of treatment that have a significant impact on survival. In our study, we sought to determine the effects of epidemiological and clinicopathological factors on overall survival (OS) and disease-free survival (DFS) in 77 osteosarcoma patients who underwent neoadjuvant therapy among total 112 osteosarcoma cases. All patients were 18 years of age and older and monitored in our center.

Methods

Patients

Our study was planned in accordance with the Patient Rights Regulation and ethical rules. Written approval for the study was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine with the protocol code of 09.2022.1009 on 22.07.2022.

In our study, 124 patients with known osteosarcoma diagnosis who applied to the Marmara University Faculty of Medicine's Medical Oncology outpatient clinic between 2001 and 2022 had their file records retrospectively reviewed. Twelve of these patients were excluded as their files and electronic records lacked sufficient information, and further 25 patients were excluded as they had not received neoadjuvant therapy. Totally, the study excluded 37 patient files because they didn't fit the requirements. Retrospective analysis of 77 patients over the age of 18 who received neoadjuvant therapy was performed (Appendix 1). 21 of these patients were diagnosed at the Pediatric Oncology outpatient clinic of Marmara University Faculty of Medicine, their treatment was started, and since they were 18 years of age or older, their follow-up and treatment continuation was carried out by our Medical Oncology clinic and they were included in the study.

The Marmara University Medical Faculty Hospital's automation system and patient files in the Medical Oncology archive were used to collect patient data. As the date of diagnosis, the date of the bone tru-cut biopsy report in non-operated cases and, if applicable, the primary tumor operation pathology report were used. Age, height, weight, ECOG score, primary tumor site, tumor size, surgical margin, metastasis information discovered at admission or later, treatments administered, treatment evaluation outcomes during follow-up, type of progression (local recurrence and/or metastasis) and dates of death were retrospectively scanned through patient files.

Relationship Analysis

A combined chemotherapy regimen was used as the most frequent neoadjuvant treatment, involving administration of cisplatin 100 mg/m^2 on the first day of every three-week cycle and doxorubicin 25 mg/m^2 on the first, second, and third days of each cycle. A pathological complete response was defined as the absence of any residual tissue in the surgical specimen obtained following neoadjuvant chemotherapy or the presence of 1% residue.

Primary outcome, disease-free survival, was defined as the time between diagnosis and first progression, death, or the duration of the last disease-free visit. Overall survival was calculated as the time from diagnosis to death or last visit.

Statistical Analysis

All data was analyzed through the software SPSS 23.0. Univariate and multivariate analysis were conducted. Standard deviation is expressed as (±). The independent variable t test was used to compare parametric variables between groups. The chi-square test was used to assess relations of non-parametric variables with each other. For the multivariate analysis, Cox Regression analysis was conducted. For a survival analysis, the Kaplan-Meier test was employed. The 95% confidence interval was used, and a p value of <0.05 was regarded as statistically significant.

Results

Study Patient

In our study, 77 patients who received neoadjuvant treatment were included among 112 osteosarcoma patients over the age of 18. Clinical characteristics of patients who received neoadjuvant therapy showed; the gender distribution of the patients was 44 (57.1%) men and 33 (42.9%) women. The median age of patients at diagnosis was 18 (range, 10-75) years. There were 74 (96.1%) patients with an ECOG-performance score of 0 and with 3 patients (3.9%) with a score of 1-2. Body surface area (BSA, m^2) of the patients had a mean ± standard deviation of 1.73±0.27.

The median primary tumor size of patients was 9 cm (range, 2.5-17.0). There were 48 patients (62.3%) whose tumor size

Table 1. Clinical characteristics of patients receiving neoadjuvant therapy

	n	%		n	%
Age at diagnosis, year, median (min-max)	18 (10-75)		Neoadjuvant cisplatin dose, mg/m²/cycle	98.3 (90.5-101.2)	
Gender			Neoadjuvant cisplatin x cycle, median (min-max)	3 (2-6)	
Male	44	57.1	Duration of surgery with neoadjuvant final therapy, weeks, median (min-max)	3.0 (0.8-23.4)	
Female	33	42.9	Surgical margin		
ECOG score			R0	67 (87.0)	
0	74	96.1	R1/2	2 (2.6)	
1-2	3	3.9	Unknown	8 (10.4)	
BSA, m² (mean±SD)	1.73±0.27		Pathological response		
Primary tumor size, cm, median (min-max)	9.0 (2.5-17.0)		Complete response	9	11.7
<8	27	35.1	Presence of residual	59	76.6
≥8	48	62.3	Unknown	9	11.7
Unknown	2	2.6	Rate of necrosis ≥%90	24	31.2
Extrapelvic location, median (min-max)	8.5 (2.0-18.0)		Cisplatin+doxorubicin	6	25.0
T1 (<8)	27	37.5	PEI	17	70.8
T2 (≥8)	43	59.7	Other	1	4.1
Unknown	2	2.8	Adjuvant treatment		
Pelvic, median (min-max)	9.8 (8.3-11.0)		Yes	66	85.7
T1a (<8)	0	0.0	No	7	9.1
T1b (≥8)	5	100.0	Unknown	4	5.2
Neoadjuvant treatment			Adjuvant cisplatin x cycle, median (min-max)	3 (1-6)	
Cisplatin+doxorubicin	44	57.1	Recurrence or progression	38	49.4
Epirubicin+cisplatin+ifosfamide	25	32.5			
Others	8	10.4			

ECOG: Eastern cooperative oncology group; BSA: Body surface area; SD: Standard deviation.

was over 8 cm and 27 patients (35.1%) had tumors under 8 cm. The primary tumor sizes of 2 (2.6%) patients were unavailable. For the primary tumors outside the pelvis, the median primary tumor size was 8.5 cm (range, 2.0-18.0). Of them, 27 (37.5%) were T1 (under 8 cm), and 43 (59.7%) were T2 (8 cm and above). The primary tumor size of 2 (2.8%) patients was unavailable. For the primary tumors in the pelvis, the median primary tumor size was 9.8 cm (range, 8.3-11.0). All of these 5 patients were T1b (8 cm and above).

The distribution of neoadjuvant therapy regimens among the patients was as follows: epirubicin + cisplatin + ifosfamide in 25 patients (32.5%), and cisplatin + doxorubicin in 44 patients (57.1%). Other neoadjuvant regimens used in our study were doxorubicin + ifosfamide + methotrexate, cisplatin + doxorubicin + methotrexate + etoposide + ifosfamide (EURAMOS 1), ifosfamide + epirubicin, methotrexate + carboplatin + topotecan, cisplatin + cyclophosphamide, cisplatin + etoposide + ifosfamide and they were used in 8 patients (10.4%). In neoadjuvant therapy, the median cisplatin dose (mg/m²/cycle) was 98.3 (range, 90.5-101.2). The median number of neoadjuvant cisplatin cycles administered was 3 (range, 2-6). A median of 3 (range, 0.8-23.4) weeks separated the last neoadjuvant treatment from the time of surgery. Among the patients who received neoadjuvant therapy; 66 (85.7%) of them also received adjuvant therapy, 7 (9.1%) patients did not and the adjuvant treatment status of 4 (5.2%) patients is unknown. The median number of adjuvant cisplatin cycle was 3 (range, 1-6).

Following neoadjuvant therapy, surgical margin, pathological response, and necrosis rate were assessed in the surgical material. 67 (87%) of the patients had negative surgical margins (R0), 2 (2.6%) had positive surgical margins (R1/2), and surgical margin status of 8 (10.4%) patients were unknown. Pathological complete response was achieved in 9 patients (11.7%), but 59 patients (76.6%) still had residuals. The pathological response remained undetermined in 9 patients (11,7%). There were 6 (25.0%) patients who received cisplatin + doxorubicin and 17 (70.8%) patients who received PEI (epirubicin + cisplatin + ifosfamide) among the 24 (31.2%) patients with a necrosis rate of 90% or more following neoadjuvant therapy. There was 1 (4.1%) patient who underwent other neoadjuvant regimens with a necrosis rate of 90% or higher. Among the 77 patients who received neoadjuvant therapy, 38 (49.4%) of the patients experienced recurrence or progression. Table 1 displays the clinical traits of patients underwent neoadjuvant therapy.

Table 2. Factors associated with 5-year DFS and OS in patients receiving neoadjuvant therapy -Univariate analysis

	DFS		OS	
	5-years DFS (%)	p	5-years OS (%)	p
General (n=77)	35.5		52.7	
Age				
<30	44.4	**0.06**	58.1	**0.01**
≥30	22.6		31.9	
Gender				
Male	20.9	**0.02**	37.0	**0.01**
Female	53.2		71.2	
Primary tumor size				
<8 cm	44.4	0.36	62.6	0.18
≥8 cm	33.2		44.3	
Bone location				
Extra-pelvic	36.6	**0.02**	54.4	**0.01**
Pelvic	20.0		26.7	
Neoadjuvant treatment				
Cisplatin+doxorubicine	28.2	0.25	36.7	**0.04**
Epirubicin+cisplatin+ifosfamide	47.4		67.3	
Others	28.6		57.1	
Surgical margin				
R0	40.5	**0.07**	54.0	**<0.001**
R1/2	0		0	
Pathological response				
Complete response	55.6	0.24	72.9	0.09
Presence of residue	34.5		47.0	
Rate of necrosis ≥%90				
Yes	54.0	**0.04**	71.9	**0.002**
No	31.6		35.4	
Postoperative treatment				
Yes	39.6	**<0.001**	56.8	**<0.001**
No	0		0	

DFS: Disease-free survival; OS: Overall-survival.

Survival Analysis

Table 2 displays the results of the univariate analysis of the variables influencing 5-year DFS and OS. Overall, 5-year DFS rates of patients were 35.5%. Those under 30 years old at diagnosis had a 5-year DFS rate of 44.4%, whereas those over 30 at diagnosis had a rate of 22.6%. There was statistically significant difference among gender for DFS as the 5-year DFS rate was 20.9% for men and 53.2% for women. Those with a primary tumor size of less than 8 cm had a 5-year DFS rate of 44.4%, whereas those with a primary tumor size of 8 cm or more had a rate of 33.2% in which difference was statistically significant. In this study, the 5-year DFS rate was 20.0% in patients with the primary tumor location in the pelvis and 36.6% in patients with the primary tumor location outside the pelvis in which difference was statistically significant. There was no difference in the 5-year DFS rates when the patients were assessed based on their neoadjuvant treatment plans, surgical margin status, and pathological response to treatment. The 5-year DFS rates for those who received cisplatin and doxorubicin were 28.2%, epirubicin plus cisplatin plus ifosfamide was 47.4%, and other neoadjuvant therapies were 28.6%. In patients with negative surgical margins, the 5-year DFS rate was 40.5%, while it was 0% in patients with positive surgical margins. Regarding the pathological response, the 5-year DFS rate was 34.5% in the patients with residuals while it was 55.6% for the cases of complete response. It was statistically significant that after neoadjuvant therapy, the 5-year DFS rate was 54.0% in patients with a necrosis rate of 90% or higher and 31.6% in patients with a necrosis rate of less than 90%.

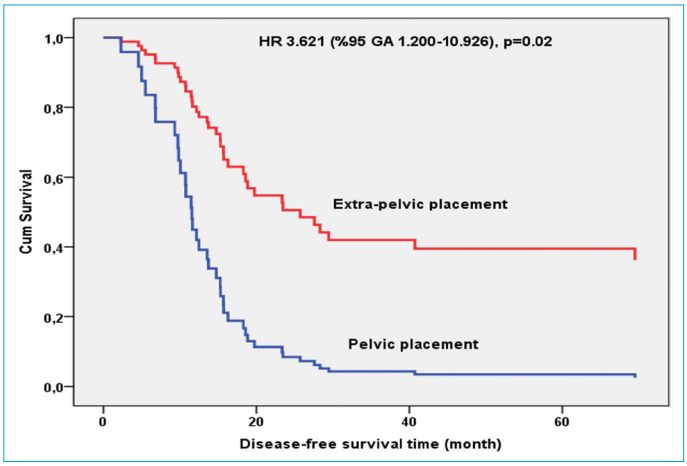


Figure 1. Multivariate Cox regression analysis DFS and tumor placement.

HR: Hazard ratio; DFS: Disease-free survival.

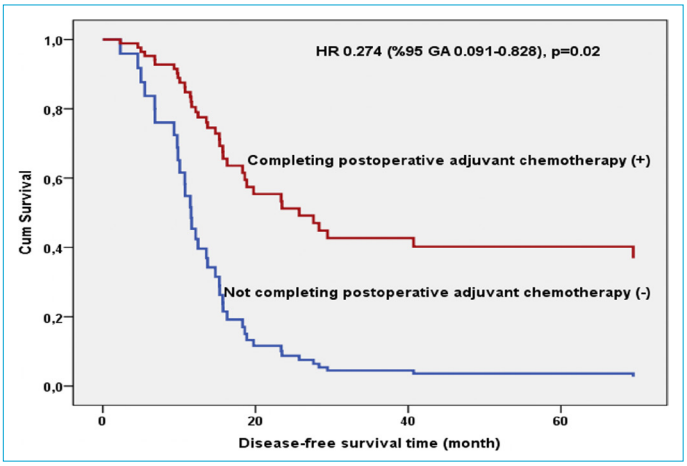


Figure 2. Multivariate Cox regression analysis DFS and adjuvant chemotherapy.

HR: Hazard ratio; DFS: Disease-free survival.

In this study, a statistically significant difference was observed in the 5-year DFS based on postoperative treatment as the 5-years DFS rate was 39.6% in those who received postoperative care and rate was 0% in those who did not.

The overall 5-year survival rate was 52.7%. The 5-year OS rate in men was 37.0%, while this rate was 71.2% in women, which was statistically significant. The 5-year OS rate for those under 30 at diagnosis is 58.1%, while the rate for those 30 and older at diagnosis is 31.9%. With a primary tumor size of less than 8 cm, the 5-year OS rate was 62.6%, while the rate for primary tumors larger than 8 cm was 44.3%. While the 5-year OS rate was 26.7% in patients with a primary pelvic location, it was statistically significant to note that this rate was 54.4% in patients with a primary location outside the pelvis. In those who received cisplatin + doxorubicin as neoadjuvant therapy, the rate of 5-year OS was 36.7%; in those who received epirubicin + cisplatin + ifosfamide, the rate was 67.3%; and in those who received other neoadjuvant therapy, the rate was 57.1%. Patients with negative surgical margins had a 5-year OS rate of 54.0%; those with positive surgical margins had a 5-year OS rate of 0%; and those who had pathological responses had 5-year OS rates of 72.9% for complete responses and 47.0% for residuals. After neoadjuvant therapy, the 5-year OS rate was statistically significant at 71.9% in patients with a necrosis rate of 90% or higher and 35.4% in patients with a necrosis rate of less than 90%. In the neoadjuvant group, the 5-year OS rate was 56.8% in those who received postoperative treatment and 0% in those who did not (Table 2).

Female gender, pelvic primary lesion, and completion of adjuvant chemotherapy in patients undergoing surgery following neoadjuvant therapy were discovered to be statistically significant prognostic markers for disease-free survival (DFS) in the multivariate Cox regression analysis.

On the other hand, for the overall survival time (OS), multivariate Cox regression analysis revealed that the necrosis rate of 90% or more in the pathology report after neoadjuvant therapy and the completion of adjuvant chemotherapy in patients who underwent surgery after neoadjuvant therapy were found to be statistically significant prognostic markers.

In the multivariate Cox regression analysis, female gender was found to be a statistically significant prognostic predictor for DFS (HR 0.475 (95% CI 0.227-0.993), p=0.04) (Appendix 2). Pelvic origin of the primary lesion was found to be a statistically significant prognostic marker for DFS (HR 3.621 (95% CI 1200-10926), p=0.02) (Fig. 1). The completion of adjuvant chemotherapy in patients who had undergone surgery after neoadjuvant therapy was found to be a statistically significant prognostic marker for DFS (HR 0.274 (95% CI 0.091-0.828), p=0.02) (Fig. 2). A necrosis rate of 90% or more in the pathology report after neoadjuvant therapy was found to be a statistically significant prognostic marker for the OS (HR 0.238 (95% CI 0.087-0.650), p=0.005) (Appendix 3). The completion of adjuvant chemotherapy in patients who had undergone surgery after neoadjuvant therapy was found to be a statistically significant prognostic marker for the OS (HR 0.098 (95% CI 0.023-0.426), p=0.02) (Fig. 3). (Appendix 4).

Discussion

Osteosarcoma is a rare tumor that accounts for less than 1% of all newly diagnosed cancers each year. It accounts for 3% of all pediatric cancers.[1] Patients with osteosarcoma have experienced a marked improvement in survival times since the introduction of multimodal therapy, which includes systemic chemotherapy. While less than 20% of patients with extensive metastatic disease can be expected to survive in the long term, multimodality therapy can cure up to 50% of patients with limited pulmonary metastases. In

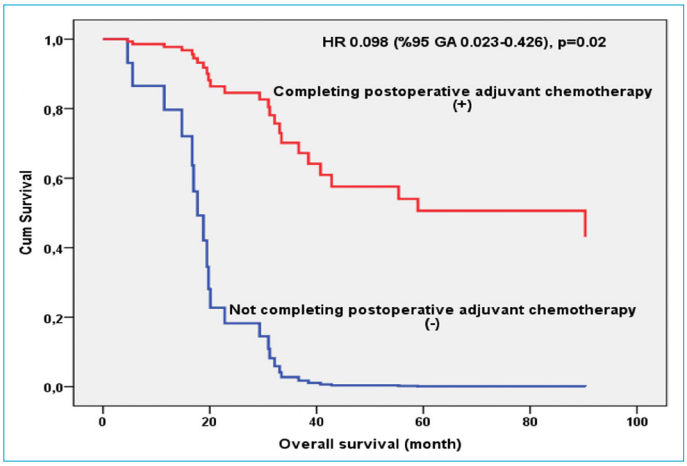


Figure 3. Multivariate Cox regression analysis OS and adjuvant chemotherapy.

HR: Hazard ratio; OS: Overall-survival.

our research, we identified primary pelvic osteosarcoma, female gender, and successful completion of perioperative systemic chemotherapy is important prognostic indicators for DFS. Additionally, it was discovered that the completion of perioperative systemic chemotherapy and a necrosis rate of 90% or higher in the pathology report following neoadjuvant therapy are important prognostic indicators for OS.

Between 1973 and 2004, a total of 3482 osteosarcoma patients from the population-based Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute were examined. Age groups (0–24 years, 25–59 years, and 60–85 years) were studied for disease survival rates. Young-onset (0–24 years old) osteosarcoma had a relative 5-year survival rate of 61.6%, 25–59 years had a relative 5-year survival rate of 58.7%, and 60–85 years had a relative 5-year survival rate of 24.2%.[2] In our study, patients under the age of 30 at diagnosis who received neoadjuvant therapy had a 5-year OS rate of 58.1%, whereas patients over the age of 30 at diagnosis had a rate of 31.9% (p=0.01). In our study, it was discovered that the rates of DFS and OS were higher in the population under 30 at diagnosis.

The mean male-to-female ratio of osteosarcoma cases in the same SEER program study was 1.22:1.[2] In our study, there were also more male patients. The male to female ratio among the patients was 1.33:1, with 44 (57.1%) men and 33 (42.9%) women making up the patient population. This rate might suggest that, as in earlier studies, men are more likely to develop osteosarcoma than women. Considering that bone growth rate plays a role in the pathogenesis of osteosarcoma, the fact that males grow faster than females during adolescence may explain the male dominance in osteosarcoma.

Same study from the SEER program examined the gender differences in 5-year survival rates. The 5-year DFS rate found to be higher in women as reaserch showd; in the 0-24 age range, the 5-year DFS rate was 65.8% for women and 58.4% for men; in the 25-59 age range, rate was 64% for women and 54.6% for men; and in the 60-85 age range, rate was 27% for women and 19.9% for men.[2] The 5-year DFS rate for male patients in our cohort was 20.9%, whereas the rate for female patients was 53.2%, which presented statistically significant difference (p=0.02). Similarly, the five-year OS rate was 37.0% in men and 71.2% in women, which was statistically significant difference (p=0.01). Female gender was discovered to be a statistically significant prognostic marker for DFS in the multivariate Cox regression analysis of these patients who received neoadjuvant therapy (HR 0.475 (95% CI 0.227-0.993), p=0.04) (Appendix 2). The higher rate of survival in women may indicate that hormonal factors are involved.

The ECOG performance score is one of the crucial factors we consider when choosing a course of treatment. Regarding the tolerability of the treatment, its low level is important. 96.1% (74) of our patients had an ECOG score of 0, and 3.9% (3) had a score of 1-2 or higher on the ECOG-performance scale.

Approximately 90% of osteosarcomas are the histopathological subtype known as conventional osteosarcoma.[5,6] In our study, the majority of the patients had conventional osteosarcoma.

The optimal chemotherapy regimen for adults (at least those over 40) has not yet been determined; older patients are typically advised to take doxorubicin plus cisplatin regimen. In fit patients, doxorubicin 25 mg/m^2 daily on days 1 through 3, cisplatin 100 mg/m^2 daily on day 1 for six cycles.[14–16] In our study, the majority of patients (57.1%) received cisplatin plus doxorubicin.

In four studies between 1993 and 2005, 1054 osteosarcoma patients were retrospectively examined, and 26 patients (2.5%), had a primary pelvic tumor. Nine patients already had metastatic disease at the time of diagnosis. 2 of the 9 patients with metastatic disease and 5 of the 17 patients with localized disease were still alive at the time of diagnosis. For localized and metastatic disease of the pelvis, 5-year DFS rates were 22% versus 23%; OS rates were 47% versus 22%. 5-year DFS was 57% and OS 69% in patients with primary osteosarcoma in extra-pelvic locations.[11] 5 (6.5%) of the patients in our study had primary tumor pelvic localization. The rates of OS and DFS were calculated without categorizing these patients as localized or metastatic. While patients with a primary pelvic location had a 5-year DFS rate of 20.0%, patients with a primary location outside the pelvis had a rate of 36.6%, which was statistically significant (p=0.02). The five-year OS rate was 26.7% among cases of primary pelvic localization while among the cases of primary tumor outside the pelvis, this rate was 54.4%, which was statistically significant (p=0.01). In our study, multivariate Cox regression analysis revealed that the pelvic origin of the primary lesion was a

statistically significant prognostic marker for DFS (HR 3.621; 95% CI 1200-10926; p=0.02) (Fig. 1). In our study, the pelvis localized group also had lower rates of OS and DFS.

In 19 studies evaluating neoadjuvant therapy, mean 5-year DFS rates ranged from 48% for 2-drug regimens to 58% for regimens containing 3 and higher drugs with 5-year overall survival (OS) rates of 62% and 70%, respectively. Three-drug regimens that included methotrexate, adriamycin, cisplatin, and ifosfamide (MAP) had significantly better outcomes, according to their meta-analysis (DFS: HR=0.701 (95% CI: 0.615-0.799); OS: HR=0.792 (95% CI: 0.677-0.926)).[17] In our study, those who received cisplatin + doxorubicin as neoadjuvant treatment had a 5-year DFS rate of 28.2%, those who received epirubicin + cisplatin + ifosfamide had a rate of 47.4%, and those who received other neoadjuvant treatments had a rate of 28.6% (p=0.25). There was no statistically significant difference between the 5-year DFS rates among different neoadjuvant regimens. In those who received cisplatin + doxorubicin as neoadjuvant therapy, the rate of 5-year OS was 36.7%; in those who received epirubicin + cisplatin + ifosfamide, the rate was 67.3%; and in those who received other neoadjuvant therapy, the rate was 57.1% (p = 0.04). Different neoadjuvant regimens were statistically significant for 5-year OS rates. The triple regimen higher rate of OS may be related to the triple regimens preference among young patients. Other neoadjuvant regimens used in our study are doxorubicin + ifosfamide + methotrexate, cisplatin + doxorubicin + methotrexate + etoposide + ifosfamide (EURAMOS 1), ifosfamide + epirubicin, methotrexate + carboplatin + topotecan, cisplatin + cyclophosphamide, cisplatine + etoposide + ifosfamide; these regimens were used in 8 patients (10.4%). These other regimens include both 2-drug and 3 or higher drug regimens. As the distribution of the neoadjuvant therapy regimen in our study was cisplatin + doxorubicin in 44 patients (57.1%) and epirubicin + cisplatin + ifosfamide in 25 patients (32.5%), the DFS and OS rates were calculated directly for these regimens.

One study examined 881 patients with non-metastatic extremity osteosarcoma treated at the same facility between 1983 and 1999 using five different neoadjuvant chemotherapy and surgical protocols. The histological response to chemotherapy was significantly correlated with the 5-year DFS and OS rates. In good and poor responders, the five-year DFS and OS rates were, respectively, 67.9% versus 51.3% (p<0.0001) and 78.4% versus 63.7% (p<0.0001). The histological good response criterion was accepted as necrosis greater than 90%. Total necrosis versus 90 to 99% necrosis did not significantly differ among the good responders.[18] In a different study, patients with extremity sarcoma who had surgical specimens with 90% or more necrosis and responded well to chemotherapy had significantly higher five-year survival rates than those with poorer responses (71-80% vs. 45-60%).[19-22] In our study, the effect of 90% or more necrosis after neoadjuvant therapy on the rate of DFS and OS was evaluated. It was statistically significant (p=0.04) that the 5-year DFS rate was 54.0% in patients with a necrosis rate of 90% or higher and 31.6% in patients with a necrosis rate of less than 90%. The 5-year OS rate was 71.9% in patients with a necrosis rate of 90% or higher, and 35.4% in those with a necrosis rate of less than 90%, which was statistically significant difference (p=0.002). Necrosis rates of 90% or higher in the pathology report following neoadjuvant therapy for OS were discovered to be a statistically significant prognostic marker in the multivariate Cox regression analysis (HR 0.238 (95% CI 0.087-0.650), p=0.005).

The effect of postoperative chemotherapy on survival was examined in a study from the 1970s, and it was found that the five-year survival rates rose from less than 20% to 40-60%.[23] In our study, patients who received neoadjuvant had a DFS rate of 39.6% for those who also received postoperative care, versus 0% for those who did not (p<0.001). In those who received postoperative care, the 5-year OS rate was 56.8%, compared to 0% in those who did not (p<0.001). In patients who underwent surgery after neoadjuvant therapy, multivariate Cox regression analysis revealed that completion of adjuvant chemotherapy was a statistically significant prognostic marker for both OS and DFS.

Considering the limitations and disadvantages of our study, it was not a randomized controlled study. The patient distribution could not be homogeneous because the study was retrospective. Real-world data, however, were presented because the patients were attended to and monitored in our clinic. Although there are very few patients with vertebral and pelvic involvement, those who do were accepted as T1 according to their general condition, and those in the pelvis were divided into T1a and T1b according to their size. This is because it is impossible to determine the number of vertebral and pelvic segmental involvement in these patients. Being a rare tumor, osteosarcoma had additional limitations brought on by the small patient population. Analysis of cancer-specific survival was not feasible because clinical records for every patient could not be consulted to determine the cause of death.

Conclusion

Female gender, primary pelvic location of lesion, and completion of postoperative adjuvant therapy were found to be significant prognostic indicators for DFS in the patients treated with neoadjuvant chemotherapy. In addition, the completion of adjuvant chemotherapy in patients who underwent surgery after neoadjuvant therapy and a necrosis rate of 90% or more in the pathology report were discovered to be significant prognostic markers for OS.

Disclosures

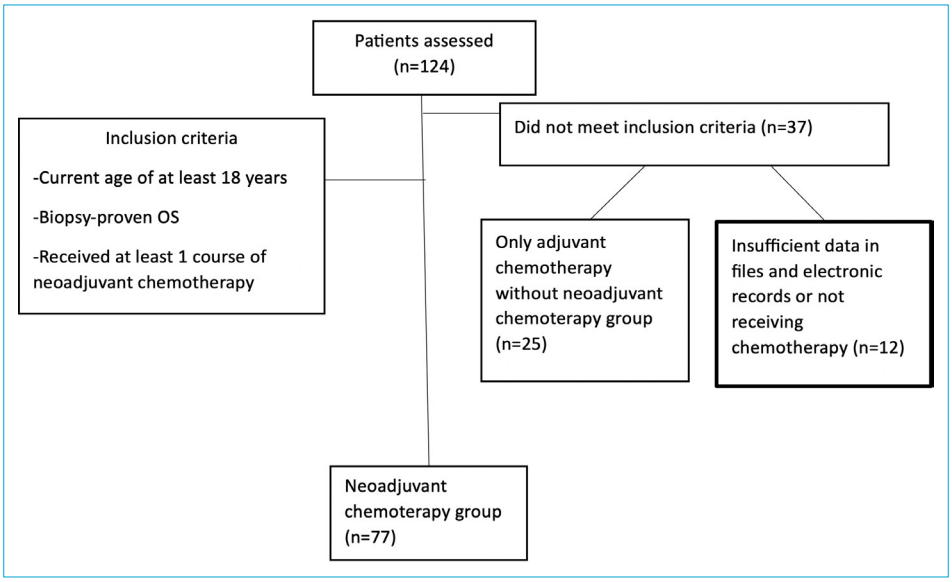
Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Commitee (date: 22.07.2022, no: 09.2022.1009).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

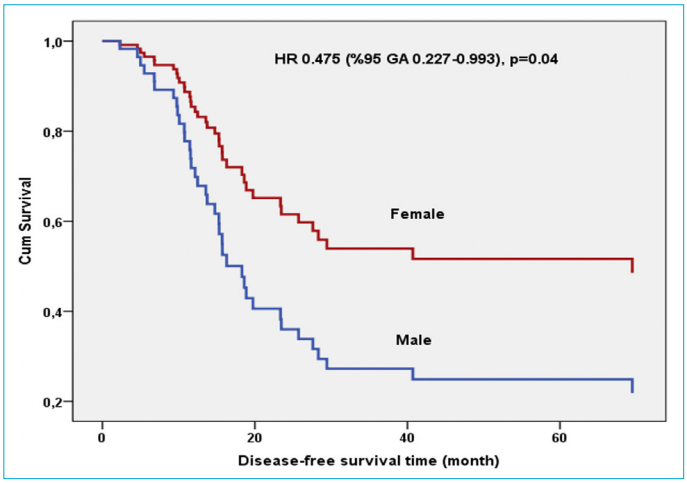
References

1. Data from the American Cancer Society. Available at: https://www.cancer.org/cancer/osteosarcoma/about/key-statistics.html (Accessed on April 17, 2021).
2. Mirabello, L., R.J. Troisi, and S.A. Savage, Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer, 2009. 115(7): p. 1531-43.
3. Kumar, R., et al., Primary Osteosarcoma in the Elderly Revisited: Current Concepts in Diagnosis and Treatment. Curr Oncol Rep, 2018. 20(2): p. 13.
4. de Pinieux, G., et al., Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PLoS One, 2021. 16(2): p. e0246958.
5. Inwards, C.Y. and K.K. Unni, Classification and grading of bone sarcomas. Hematol Oncol Clin North Am, 1995. 9(3): p. 545-69.
6. Soft tissue and bone tumours. In: WHO Classification of Tumours, 5th ed, WHO Classification of Tumours Editorial Board (Ed), IARC Press, 2020. 2020.
7. Papagelopoulos, P.J., et al., Current concepts in the evaluation and treatment of osteosarcoma. Orthopedics, 2000. 23(8): p. 858-67; quiz 868-9.
8. Aljubran, A.H., et al., Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. Ann Oncol, 2009. 20(6): p. 1136-41.
9. Longhi, A., et al., Osteosarcoma in patients older than 65 years. J Clin Oncol, 2008. 26(33): p. 5368-73.
10. Janeway, K.A., et al., Outcome for adolescent and young adult patients with osteosarcoma: a report from the Children's Oncology Group. Cancer, 2012. 118(18): p. 4597-605.
11. Isakoff, M.S., et al., Poor survival for osteosarcoma of the pelvis: a report from the Children's Oncology Group. Clin Orthop Relat Res, 2012. 470(7): p. 2007-13.
12. Marina, N.M., 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(10): p. 1396-1408.
13. Protocol information available online at http://www.clinicaltrials.gov/ct2/show/NCT00134030?term=AOST+0331&rank=1 (Accessed on July 19, 2011).
14. Bramwell, V.H., et al., Neoadjuvant chemotherapy with doxorubicin and cisplatin in malignant fibrous histiocytoma of bone: A European Osteosarcoma Intergroup study. J Clin Oncol, 1999. 17(10): p. 3260-9.
15. Souhami, R.L., et al., Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet, 1997. 350(9082): p. 911-7.
16. Bramwell, V.H., et al., A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol, 1992. 10(10): p. 1579-91.
17. Anninga, J.K., et al., Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? Eur J Cancer, 2011. 47(16): p. 2431-45.
18. Bacci, G., et al., Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. Eur J Cancer, 2005. 41(14): p. 2079-85.
19. Bacci, G., et al., Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. Cancer, 2006. 106(5): p. 1154-61.
20. Bacci, G., et al., Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity. Histologic response to preoperative chemotherapy correlates with histologic subtype of the tumor. Cancer, 2003. 97(12): p. 3068-75.
21. Bielack, S.S., et al., Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol, 2002. 20(3): p. 776-90.
22. Hauben, E.I., et al., Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. Eur J Cancer, 2002. 38(9): p. 1218-25.
23. Rosen, G., et al., Primary osteogenic sarcoma: eight-year experience with adjuvant chemotherapy. J Cancer Res Clin Oncol, 1983. 106 Suppl: p. 55-67.



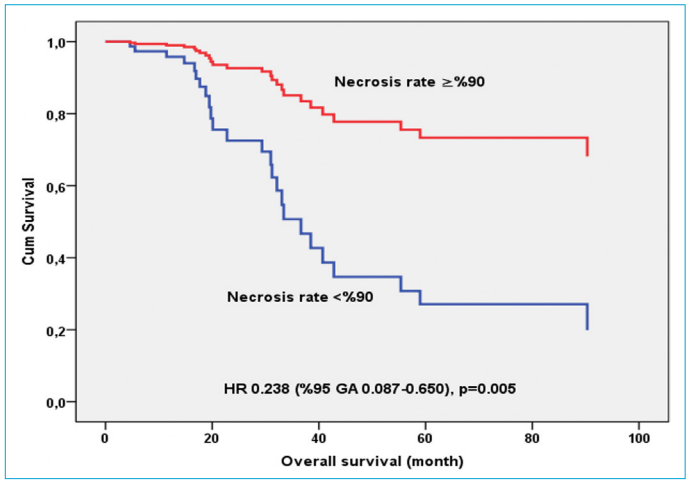
Appendix 1. Trial profile.

OS: Overall-survival.



Appendix 2. Multivariate Cox regression analysis DFS and gender.

HR: Hazard ratio; DFS: Disease-free survival.



Appendix 3. Multivariate Cox regression analysis OS and necrosis rate.

HR: Hazard ratio; OS: Overall-survival.

Appendix 4. Multivariate Cox regression analysis for DFS and OS in patients receiving neoadjuvant therapy

	Multivariate analysis			
	DFS		OS	
	HR (%95 CI)	p	HR (%95 CI)	p
Gender				
Female	0.475 (0.227-0.993)	**0.04**	0.441 (0.183-1.061)	0.06
Primary location				
Pelvic	3.621 (1.200-10.926)	**0.02**		
Rate of necrosis ≥%90				
Yes			0.238 (0.087-0.650)	**0.005**
Completion of postoperative treatment	0.274 (0.091-0.828)	**0.02**	0.098 (0.023-0.426)	**0.02**

DFS: Disease-free survival; OS: Overall-survival; HR: Hazard ratio; CI: Confidence interval.