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ORIGINAL ARTICLE

Analysis of prognostic factors and histopathological response to neoadjuvant chemotherapy in osteosarcoma

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Osteosarcoma is a rare disease characterized by the production of tumoral osteoid or immature bone after the proliferation of malignant osteoblasts.[1] Treatment of osteosarcoma is primarily based on neoadjuvant and adjuvant chemotherapy (CT) and surgical resection. With developments over the years, the combined use of surgical treatment and CT has significantly increased the cure and survival rates of patients.[2] Although multimodal therapy has greatly improved patients' oncological outcomes, the prognosis of metastatic or recurrent osteosarcoma is still unsatisfactory.

Although many prognostic factors affecting the course of the disease have been described in the literature, controversial results have been reported.

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ABSTRACT

Objectives: This study aims to examine the clinical results of patients who underwent medical and surgical treatment for osteosarcoma, to determine the overall survival (OS) and disease-free survival (DFS) rates, and to examine the effects of prognostic factors on these rates.

Patients and methods: Between January 2005 and January 2020, a total of 64 patients (38 males, 26 females; mean age: 20.9±11.5 years; range, 6 to 70 years) who received medical and surgical treatment for osteosarcoma were retrospectively analyzed. Demographic characteristics, follow-up period, tumor location and size, tumor stage and necrosis rate, metastatic disease, surgical treatments, postoperative complications, local recurrence, and metastasis were recorded. The relationship of these factors with the survival was examined.

Results: The median follow-up was 51.6 (range, 3 to 156) months. The most common tumor localization was in the distal femur with 42 (65.6%) patients and the most common histopathological subtypes were conventional osteosarcoma in 50 (78.1%) patients. The OS rates were 91.6% at one year, 65.9% at five years, and 51.6% at 10 years. With the exception of two patients who died during neoadjuvant chemotherapy, all patients underwent surgical treatment. The addition of chemotherapy + radiotherapy in the treatment did not provide any benefits in terms of survival and recurrence compared to the group that was not added, and the five-year OS rate was 79.3% compared to 20.7%, respectively. The overall 10-year survival rates were 83.9% and 37.2% in the group with a good response (≥90%) and poor response (<90%) to treatment (p=0.012). The mean survival time of three patients who presented with pathological fractures was shorter than the others (p>0.05). Surgical margin was ≤2 mm in 27 (42.2%) patients, >2 mm in 30 (46.9%) patients, and surgical margin was positive in five (7.8%) patients. The mean OS in the group with a surgical margin closure of >2 mm was 10.8±1.9 years and was longer than the other groups (p=0.047).

Conclusion: Metastasis at the time of diagnosis, <90% tumor necrosis, a tumor size of ≥10 cm, and metastasis development were significantly associated with poor survival and were found to be independent prognostic factors. The OS rate in the patient group with Stage III-IV response after neoadjuvant chemotherapy given the cisplatin + doxorubicin protocol was found to be better than those given the European and American Osteosarcoma Studies (EURAMOS) protocol. More research is needed to determine the most optimal chemotherapy protocols in this patient population. In addition, a multidisciplinary approach in treatment is of utmost importance to improve oncological outcomes.

Keywords: Chemotherapy, osteosarcoma, prognosis, survival.

Therefore, further research investigating the main risk factors is needed to understand the nature of the tumor and to develop effective treatment plans.

In the present study, we aimed to examine the clinical results of patients who underwent medical and surgical treatment for osteosarcoma, to determine the overall survival (OS) and disease-free survival (DFS) rates, and to examine the effects of prognostic factors on these rates.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ondokuz Mayıs University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2005 and January 2020. A total of 64 patients (38 males, 26 females; mean age: 20.9±11.5 years; range, 6 to 70 years) who received medical and surgical treatment for osteosarcoma were included. The patients in the study group were scanned from the hospital database using file/patient number, and data were obtained on the patient history, physical examination, imaging tests, surgery notes, pathology reports, and outpatient clinic follow-up.

Several characteristics of the patients, such as demographics, tumors, or treatments, were evaluated. Patient characteristics included demographic characteristics such as age and sex, complaints on presentation, and follow-up time. Tumor-related characteristics included tumor location and size, tumor stage, necrosis rate, and presence of metastasis at the time of diagnosis. The treatment-related factors were defined as the CT and radiotherapy (RT) plan applied, surgical plan for limb salvage (prosthesis/biological reconstruction) or amputation, surgical margin, and the presence of postoperative complications, particularly local recurrence (LR) and metastasis. Analyses were, then, made to identify the relationship of these factors with survival and whether they could be accepted as prognostic factors.

The size of the tumor was determined from individual magnetic resonance imaging (MRI) scans as described by Bieling et al.[3] Tumor staging was graded according to the Enneking classification. Chemotherapy regimens were tailored by the medical oncologists in our center, and cisplatin + doxorubicin and European and American Osteosarcoma Studies (EURAMOS) protocols were the most frequently used.[4] The COSS (Cooperative German, Austrian, Swiss Osteosarcoma Study Group) and Rosen T-10 were other protocols used (Table I). Due to cohort heterogeneity, the protocols were grouped as cisplatin + doxorubicin, EURAMOS, and others to better compare CT regimens. Radiotherapy was applied pre- and postoperatively in patients with surgical margin positivity and patients with recurrent and metastatic disease. Surgical complications were documented as an early and late-term. The early period was determined as within one month and the late period as after one month postoperatively.

Treatment management

In the treatment of osteosarcoma in our center, a multidisciplinary approach is applied with the full working collaboration of orthopedic oncology and medical oncology departments. After the relevant imaging methods and clinical evaluation, the treatment management of the patients is determined by the Tumor Council.

In general, after histopathological diagnosis from Tru-cut biopsy, the diagnosis was made according to the predominant cell type, and the patients were treated as neoadjuvant CT-surgery - adjuvant CT.

After approximately three cycles of neoadjuvant CT, surgical treatment was planned, if the general condition of the patient allowed surgery. The response of the mass to neoadjuvant treatment was evaluated histopathologically after the operation and, then, the treatment was completed by giving an adjuvant treatment protocol according to the patient's medical

TABLE I
Neo/adjuvant chemotherapy protocols given in the treatment of patients

Chemotherapy protocols	Tumor response	
T-10		HDMX + P/HDMX + IFO+ ADR
COSS		A + IFO + B
EURAMOS	>90%	M + A + P/I
	<90%	M + A + P/I + E
Doxorubicin + cisplatin	>90%	A + P/A + IFO
	<90%	A + P/M + A + IFO

HDMX: High-dose methotrexate; P: Cisplatin; IFO: Ifosfamide; ADR: Adriamycin; A: Doxorubicin; B: Bleomycin; M: Methotrexate; I: Pegylated interferon; E: Etoposid.

TABLE II
Demographic and tumoral characteristics of the patients

Parameters	n	%
Age (year)		
<18	48	78.2
≥18	14	21.8
Sex		
Male	38	59.4
Female	26	40.6
Metastatic disease		
Yes	5	7.8
No	59	92.1
Localization		
Distal	43	67.1
Proximal	18	28.1
Pelvis	3	4.6
Histological type		
Conventional OS	55	85.9
Surface OS	7	10.9
Secondary OS	2	3.1
Stage		
IIA	13	20.3
IIIB	46	71.9
III	5	7.8
Necrosis (Huvos)		
≥90%	32	51.6
<90%	30	48.4
Surgical margin		
0-2 mm	27	42.1
>2 mm	30	46.9
Positive	5	7.8
Tumor size		
<10 cm	45	70.3
≥10 cm	19	29.6
Metastasis		
Yes	17	26.5
No	47	73.5
Local recurrence		
Yes	9	14.0
No	55	86.0

OS: Overall survival.

condition. These patients were followed regularly at three-month intervals in the first two years after surgery and at six-month intervals in the second two years. During the follow-up of the patients, direct X-ray and contrast-enhanced dynamic MRI of the relevant region were evaluated. After completion of adjuvant CT, chest X-ray and thoracic CT were performed every three months in the first year, and every six months in the following year. Bone metastasis and LR scans were performed with positron emission tomography (PET) examination once a year or when needed. During follow-up, data such as physical examination and imaging findings and the presence of complications were recorded.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The effect of prognostic factors on survival was analyzed using Kaplan-Meier analysis and the log-rank (Mantel-Cox) technique. The independent samples t-test was used to compare two independent groups, and Cox Regression analysis was used to evaluate the variable effects of prognostic factors on survival compared to each other. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Demographic and tumoral characteristics of the patients are shown in Table II. The median follow-up was 51.6 (range, 3 to 156) months.

One-year OS rate was 91.6% (95% CI: 86.7-94.8), five-year OS rate was 65.9% (95% CI: 56.9-78.2), and 10-year OS rate was 51.6% (95% CI: 36.2-64.7). The one-, five- and 10-year DFS rates were 79.4% (95% CI: 55.2-82.6), 60.9% (95% CI: 46.4-74.3), and 48% (95% CI: 23.1-70.2), respectively.

A total of 42 (65.6%) patients had distal femur, 12 (18.8%) patients had proximal tibia, five (7.8%) patients had proximal humerus, three (4.6%) patients had pelvis, one (1.5%) patient had proximal femur, and one (1.5%) patient had distal tibia involvement. In terms of localization, 10-year OS rates in the proximal, distal, and pelvis groups were 52.8%, 60.3%, and 0%, respectively, indicating no statistically significant difference (p=0.341) (Figure 1a).

Thirty-five of 54 patients were diagnosed with unclassified conventional osteosarcoma, and no histological subtypes were recorded in the final histopathological report. Other subtypes were osteoblastic and chondroblastic osteosarcoma in seven patients, small cell and giant cell osteosarcoma in two patients, and telangiectatic osteosarcoma and fibroblastic osteosarcoma in one patient each. As surface osteosarcoma, four patients had parosteal and three patients had periosteal osteosarcoma. Two patients had secondary osteosarcoma. Secondary osteosarcoma cases developed after RT following previous breast and cervical malignancies. In terms

of 10-year OS, the best rate was found for parosteal osteosarcoma with 100%, followed by 64.8% for unclassified osteosarcoma. The worst survival results were in chondroblastic osteosarcoma with 22.9% and secondary osteosarcoma with 0% (p=0.137).

Pathological fractures were detected in three (4.7%) patients at the time of hospital admission. The patients presenting with pathological fractures had a shorter mean OS time compared to the others (3.5±1.5 years *vs.* 8.6±1.8 years, respectively), and all patients who developed fractures died during follow-up. Metastasis at the time of diagnosis was present in five (7.8%) patients; four with isolated pulmonary metastasis and one with pulmonary + bone metastasis.

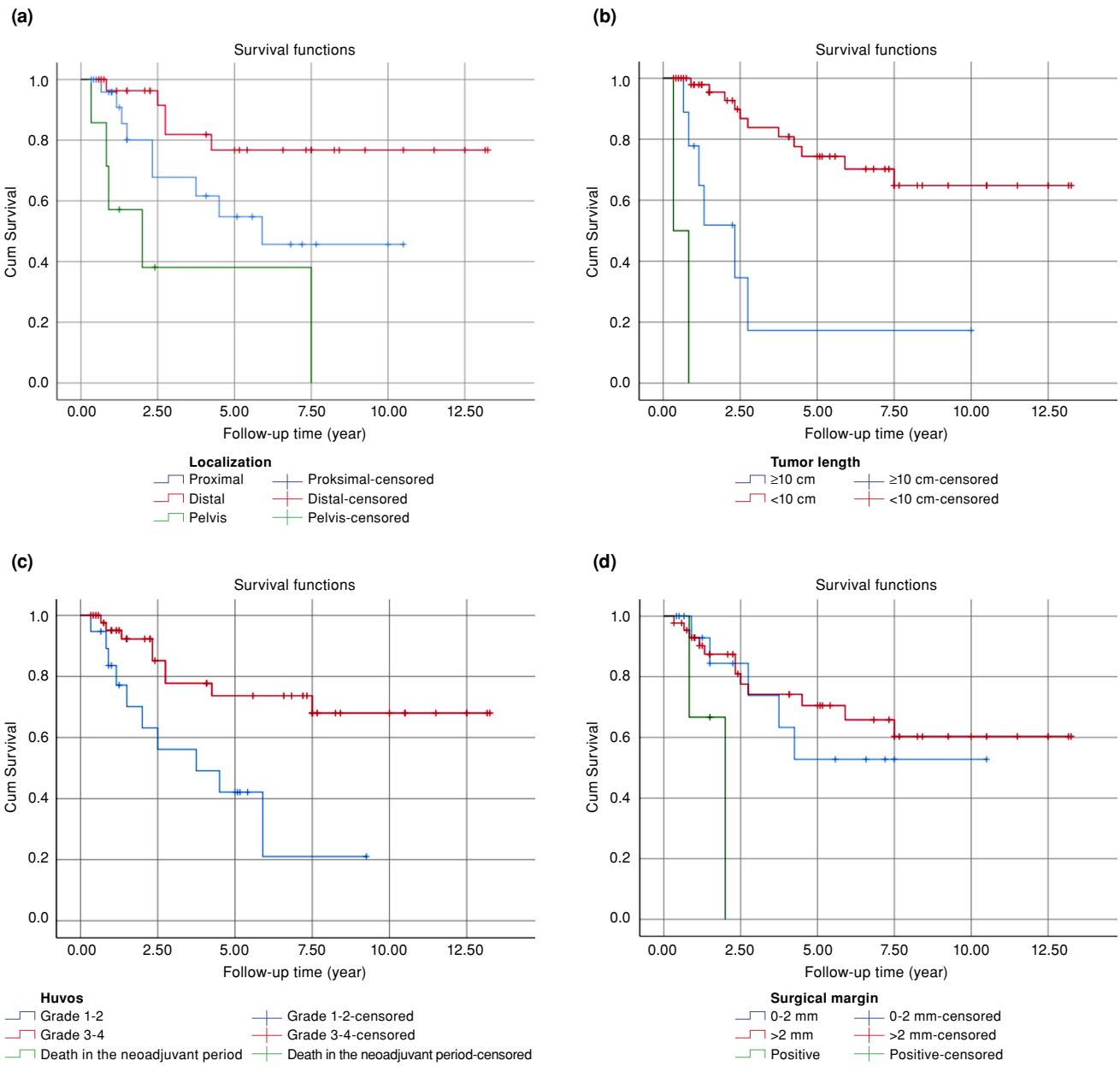


FIGURE 1. Kaplan-Meier curves showing overall survival rates in osteosarcoma patients. **(a)** Graph of overall survival rates by mass localization. **(b)** Graph of overall survival rates by mass size. **(c)** Graph of overall survival rates by necrosis rates. **(d)** Graph of overall survival rates by surgical margin status

TABLE III
Analysis of treatment-related factors

Parameters	n	%
Chemotherapy protocol		
EURAMOS	19	29.7
Cisplatin + doxorubicin	35	54.7
Others	6	12.5
Not given	4	3.1
Primary surgery		
Limb salvage	59	92.2
Endoprosthesis reconstruction	54	84.3
Autograft bone reconstruction	3	4.6
Distraction osteogenesis	2	3.1
Amputation	3	4.7
Not performed	2	3.1
Radiotherapy		
Yes	16	25.8
No	46	74.1
Other complications		
Periprosthetic infection	12	
Aseptic loosening	10	
Implant failure	1	
Nonunion	2	
Stem extension	2	

EURAMOS: European and American Osteosarcoma Studies.

The largest diameter was considered to be the tumor length and the mean tumor size was measured as 8.6±8.3 (range, 3 to 22) cm. Based on OS according to the tumor size parameter, the mean OS time was 5.6±2.1 years in the group with ≥10 cm and 10±1.8 years in the group with <10 cm (p=0.029) (Figure 1b). According to the Enneking classification, 13 (20.3%) patients were Stage IIA, 46 (71.9%) patients were Stage IIB, and five (7.8%) patients were Stage III. The 10-year OS rate was found to be 40% in the lowest Stage III disease (p=0.039).

Surgical resection was planned for 62 (96.9%) patients after the neoadjuvant CT regimen. Two (3.1%) patients died during neoadjuvant CT. Of the patients who underwent surgery, 59 (92.2%) had limb salvage surgery and three (4.7%) had amputation. The types of surgery performed are given in Table III. Four-quarter amputation and hip disarticulation were performed in two of our patients with proximal humerus and proximal femur localization, respectively. Surgical margins were positive after surgery due to its proximity to important vascular and nerve structures and the massiveness of the masses and important vascular-nerve neighborhoods. These patients were lost during follow-up.

Neoadjuvant CT was planned for 58 (90%) patients by a medical oncologist in our hospital, and was not considered appropriate for four (6.2%) patients due to the diagnosis of parosteal osteosarcoma. Neoadjuvant CT treatment was completed by two patients at an external center. The most commonly used neoadjuvant CT regimens were cisplatin + doxorubicin in 35 patients and EURAMOS in 19 patients. The COSS and T-10 regimens were given to the other four patients. After neoadjuvant CT, there was no statistically significant difference in survival between the protocols given to the patient group with Grade 1-2 response (p=0.47). The survival rate of patients with Grade 3-4 and cisplatin + doxorubicin regimen was statistically significantly higher than that of patients who received the EURAMOS regimen (p=0.042). When the treatment protocol groups were analyzed as cisplatin + doxorubicin, EURAMOS, and others, no significant difference in OS was observed in patients who responded well and poorly to treatment (p=0.351). The addition of CT + RT in the treatment did not provide any benefit in terms of survival and recurrence compared to the group that was not added, and the 10-year OS rates were 79.3% compared to 20.7%, respectively (p=0.01).

According to the Huvos Grading System, the histological response to treatment was 83.9% in the ≥90% group and 37.2% in the <90% group, with a significant difference in 10-year OS (p=0.012) (Figure 1c). The surgical margin was ≤2 mm in 27 (42.2%) patients, >2 mm in 30 (46.9%) patients, and the surgical margin was evaluated as positive in five (7.8% patients). While the mean OS was 10.8±1.9 years in the group with a surgical margin closure of >2 mm, it was approximately similar and shorter in the other margin groups where the surgical margin was 2 mm and positive (6.9±3.6 years and 6.3±1.8 years, respectively) (p=0.047) (Figure 1d).

Twelve LRs were detected in nine (14%) patients. The mean time to LR was 7.8±10.9 months, and the mean OS in the patient group with LR was 3.6±1.2 years, with OS rates at one and five years determined as 90% and 13%, respectively. The mean OS in the patient group without LR was 9.7±1.6 years, with OS rates at one and five years of 89% and 78%, respectively (p=0.036).

In the postoperative period, 23 distant organ metastases developed in 17 (26.5%) patients. The patients with metastases were 11 (64.7%) with isolated lung metastasis and six with more than one metastasis

TABLE IV
Comparison of overall survival rate among osteosarcoma patients from Kaplan-Meier estimates and log-rank statistics

	Mean survival time (year)	95% CI	% Overall survival rate	*p*
Age				0.749
<18	7.9	5.6-10.3	57.9	
≥18	9.5	7.3-11.3	54.1	
Sex				0.591
Male	8.3	6.2-10.4	53.3	
Female	9.2	6.9-11.5	59.5	
Metastatic disease				0.026
Yes	2.5	0.4-4.7	20.0	
No	9.2	7.6-10.9	59.9	
Localization				0.341
Proximal	6.8	4.4-9.2	52.8	
Distal	9.2	7.4-11.2	60.3	
Pelvis	1.6	0.7-2.4	0.0	
Pathologic fracture				0.006
Yes	3.5	2.1-5.1	0.0	
No	8.6	7.4-10.2	60.2	
Histological type				0.137
Secondary OS	1.41	0.2-2.5	0	
Chondroblastic OS	4.28	1.3-7.2	22.9	
Others	9.60	7.9-11.2	64.8	
Enneking stage				0.039
IIA	10.4	8.5-12.3	90	
IIB	7.95	6.1-9.8	46.7	
III	3.34	0.4-6.2	40.1	
Necrosis (Huvos)				0.012
≥90%	11.4	9.6-13.2	83.9	
<90%	7.10	4.9-9.2	37.2	
Surgical margin (cm)				0.047
>2	10.8	8.9-12.8	76.7	
0-2	6.39	4.4-8.3	45.6	
Positive	6.31	4.2-8.1	0	
Tumor size (cm)				0.029
≥10	4.30	2.6-6.1	21	
<10	10.1	8.2-11.8	58	
Chemotherapy protocol				0.351
EURAMOS	10.7	7.3-14.8	79.9	
Cisplatin + doxorubicin	7.82	6.2-10.1	54.1	
Others	4.61	2.6-6.6	48.2	
Treatment				0.001
Surgery + CT	10.9	9.5-12.6	79.3	
Surgery + CT + RT	3.72	2.1-5.3	20.7	
Metastasis				0.001
Yes	1.82	2.5-4.7	23.1	
No	11.6	10.3-12.9	74.6	
Local recurrence				0.036
Yes	3.8	2.4-5.3	16.2	
No	9.5	7.8-11.2	63.8	

CI: Confidence interval; OS: Overall survival; EURAMOS: European and American Osteosarcoma Studies; CT: Chemotherapy; RT: Radiotherapy.

TABLE V
Predictive factors for overall survival among osteosarcoma patients using multivariate Cox regression analysis

	Regression coefficient (b)	Hazard Ratio	95% CI	*p*
Metastatic disease				
Yes	2.38	10.8	1.5-74.1	0.046
No	Ref.	Ref.		
Pathologic fracture				
Yes	Ref.	Ref		
No	-0.51	0.6	0.14-3.38	0.567
Necrosis (Huvos)				
≥90%	-1.8	6.5	1.4-29.1	0.015
<90%	Ref.	Ref.		
Surgical margin (cm)				
>2	-1.47	0.23	0.21-1.33	0.102
0-2	-0.39	0.67	0.13-3.49	0.639
Positive	Ref	Ref.		
Tumor size (cm)				
≥10	1.08	2.9	1.06-8.21	0.041
<10	Ref.	Ref.		
Metastasis				
Yes	2.45	11.6	1.61-84.1	0.015
No	Ref.	Ref.		
Local recurrence				
Yes	0.41	0.96	0.96-6.37	0.482
No	Ref.	Ref.		

CI: Confidence interval.

(bone, brain, lung). The mean time for metastasis development in the patients after surgery was 12±8.5 months. The median OS of the patients with metastasis was 1.8 years (95% CI: 2.5-4.7), which was significantly shorter than the patient group without metastasis (11.6 years, 95% CI: 2.5-4.7). The one-year and five-year OS rates of the patients with metastasis were 94% and 24%, respectively (p=0.001).

During clinical follow-up after surgery, complications developed in 40 patients (63%). Early wound problems were seen in only two patients as an early complication. The remaining 38 patients (59.3%) developed late complications and 21 patients (32.7%) had more than one complication. The most common complications were metastasis in 17 cases, infection (prosthesis + wound site) in 14 cases, LR in 12 cases, and aseptic loosening in 10 cases. Two of the patients developed neutropenic fever due to adjuvant CT and two patients died during follow-up. Less common late complications were tissue necrosis in three patients, bone graft resorption and non-union development after biological reconstruction in two patients, and neuropraxia, flexion contracture in the joint, and prosthesis fracture in each of these patients. The development of complications was not found to affect patient survival (p=0.181).

In the univariate analysis, risk factors affecting the OS rates were <90% necrosis, ≥10-cm tumor size, Stage III disease, pathological fracture, LR, metastatic status, and ≤2-mm surgical margin (Table IV). In the multivariate analysis, independent prognostic factors affecting the OS were found to be metastatic disease, <90% tumor necrosis, ≥10-cm tumor size, and development of metastases (Table V).

DISCUSSION

In the present study, we evaluated the clinical results of patients who underwent medical and surgical treatment for osteosarcoma and determined the OS and DFS rates. Our study results showed that metastatic disease, <90% tumor necrosis, and tumor size ≥10 cm were found to be independent prognostic factors. However, the OS rate in the patient group with high-grade response after neoadjuvant CT containing cisplatin + doxorubicin regimen was better than those given the EURAMOS protocol.

In a study using the Surveillance, Epidemiology and End Results (SEER) program data of 2,849 osteosarcoma patients, the one-, five- and 10-year OS rates were reported as 83.6%, 71.8%, and 65.8%, respectively.[5] In a recent study using the data of 4,430 patients on the National Cancer Database, these rates were reported as 91.1%, 64.4%, and 58.5%, respectively.[6] The current study results are approximately in line with those of other countries.

Many studies in the literature have shown that pathological fractures affect survival negatively.[7,8] Zhong et al.[7] reported in their study on the oncological outcomes of osteosarcoma patients with pathological fractures that they significantly reduced the survival rates and increased the risk of developing distal metastases. Similarly, in our study, patients who presented with pathological fractures had a shorter mean survival time, and all of the patients died. Since our patients in this group had LR and metastasis, it may have affected the survival rates. Although pathological fracture had a dramatic negative effect on survival in the univariate analysis, this result was statistically weak ($p>0.05$). However, no effect on survival was found in the multivariate analysis ($p>0.05$).

There are reports that proximal location in the appendicular skeleton and localization in the pelvis may be poor prognosis factors.[9,10] Brown et al.[9] reported one-, five-, and 10-year OS rates for primary OS of the pelvis as 45.6%, 26.5%, and 21.4%, respectively, for the entire cohort of the SEER database. In their study, the most important factor on survival was the presence of metastasis at presentation, while advanced age and other factors affected the surgical removal of the tumor. A previous study found patients with axial skeletal osteosarcoma to have the highest metastasis and worst outcomes, and three-year survival rates for axial skeletal tumors were 13%.[10] In our study, the 10-year OS rates were 52.8% in the proximal location, 60.3% in the distal location, and 0% in the pelvis. Despite similar results, no statistically significant difference was found ($p=0.34$). However, the surgical margins of two patients with a pelvic mass who died after surgery were positive. The relatively small number of the patients with pelvic location and the positive surgical margins in most of them may have caused the cohort to be heterogeneous, thereby affecting the outcome. However, it is important to remove the tumor with clean surgical margins, as well as localization of the osteosarcoma.

Systemic metastases are considered to be one of the most important causes of loss in osteosarcoma.[9,11,12] While long-term survival rates vary from 65 to 70% in patients with localized disease, these rates range between 20 and 30% in patients with metastatic disease.[11] In this study, the five-year OS rate in the group with metastasis at the time of diagnosis was 20%, while it was 68.3% in the group without metastasis. There was a significant difference in the univariate and multivariate analyses ($p<0.05$).

Tumor size is another factor affecting the prognosis of osteosarcoma patients.[13-15] In a study of 1,702 patients, Colding-Rasmussen et al.[13] reported the five-year OS rate as 42% in patients with a primary tumor of ≥10 cm in diameter, while it was 64% in the group with smaller tumors. In a recent study, the tumor size greater than 10 cm was reported to have a hazard ratio (HR) of 2.06 compared to the tumor size less than 10 cm (95% CI: 1.16-3.64; $p=0.01$).[16] The current study showed similar results. The five-year OS rates were 53.1% in the ≥10 cm group and 72.4% in the <10 cm group. A negative effect of ≥10 cm size on cumulative survival was found to be significant in the univariate analysis ($p=0.029$) and multivariate analysis ($p=0.041$).

Parosteal osteosarcoma is known to have a better prognosis than traditional osteosarcoma. Therefore, this subtype was excluded from the analysis for survival with other types, as it can be treated only by extensive surgical resection.[17,18] In our study, all of these patients were alive during follow-up and their prognosis was excellent, except for revision surgery due to infection and prosthesis problems. It has been reported in the literature that chondroblastic osteosarcomas have worse outcomes in terms of CT response and survival among conventional OS.[19,20] Tsagozis et al.[19] found the five-year OS rate to be 51% in patients with chondroblastic osteosarcoma, while Sun et al.[20] found it to be 56.2%. When conventional osteosarcomas were compared among themselves, the five-year OS rate was the lowest (45.7%) in chondroblastic osteosarcoma and the highest (68.9%) in mixed type, and it was not statistically significant ($p=0.137$). However, no statistically significant difference was observed between the necrosis rates and histological types after CT.

There are many clinical and methodological studies on neoadjuvant CT in the literature.[4,21,22] In our study, there was no significant difference in OS between cisplatin + doxorubicin/ifosfamide and EURAMOS(MAP+IE) treatment groups in patients who responded poorly to CT (≥10% viable tumor) ($p=0.351$).

Interestingly, patients with a good response (<10%) who received the cisplatin+doxorubicin/ifosfamide regimen had a higher OS rate than the patients who received the EURAMOS (MAP+ pegylated IFN) regimen (58% *vs.* 48%, respectively), indicating a statistically significant difference (p=0.047).[23]

In their cohort, Bielack et al.[4] administered MAP+IE to patients with a poor response to treatment (≥10% viable tumors), and MAP or MAP+ IFN to patients with a good response (<10%). They found no beneficial effect of the experimental treatment in either group. However, the aforementioned authors did not report a significant difference in the prognostic survival of osteosarcoma between the MAP and MAP+ regimens. Yu et al.[21] reported that the incidence of CT toxicities was lower in the MAP regimen and it was still a suitable option in the treatment. In our study, MAP+IE and COSS treatments were given to patients with neutropenic fever and sepsis. Therefore, even if our statistical power is limited, it is conceivable that the use of combination therapy in poor responders is associated with the increased toxicity without improved survival.

In our study, survival was higher and the LR rate was statistically significant in the group with a surgical margin >2 mm in the univariate analysis. The five-year OS rates were found to be >2 mm (76.7%) in the 0-2 mm group (54.8%) and in the positive group (38.1%) (p=0.031). Bertrand et al.[24] reported that surgical margin >1 mm was an independent predictor of LR and OS. Jeys et al.[25] reported in their series that tumor resection with at least 2-mm normal tissue margin was a better predictor of prognosis. They reported that a net 2-mm margin of normal tissue in a tumor that responded poorly to CT had a 16% risk of LR at five years without compromising survival. In our study, the risk of LR at five years was 22% in these patients with a margin greater than 2 mm. However, the effect of surgical margin on OS was not found in the multivariate analysis (p>0.05). Therefore, it can be speculated that more findings are needed to tailor adequate treatment and minimize the risk in patients having a poor response to CT.

It is usually accepted that there is a negative association between LR and survival in patients with osteosarcoma.[26-28] Similarly, the five-year OS was dramatically lower in the LR group in our study (16.1% *vs.* 73.2%, respectively). In terms of cumulative survival, the negative effect of LR was found to be significant in the univariate analysis (p=0.036). Weeden et al.[28] proposed the view that it was not possible to differentiate whether LR caused a poor outcome by reducing survival or was merely a marker of poor prognosis. Local recurrence may not be a cause, but a secondary consequence of poor histopathological response to CT. In a study, patients with a poor response to CT predicted poor survival independent from the development of LR.[26] However, the only controllable factor for LR during tumor resection can be considered as the surgical margin at the present salvage procedures. Although the proximity of the surgical margin increased the likelihood of LR in our study, this was not statistically significant (p=0.64). Similarly, the effect of LR on survival was not found to be significant in the multivariate analysis (p=0.482).

In the present study, when surgical methods were compared in terms of OS rates and LR risk, the patients with amputation had a shorter survival time and a higher risk of LR compared to the other surgical groups (p=0.51). This result can be attributed to the fact that patients with tumors requiring amputation were in a worse condition before surgery compared to those who underwent limb-sparing surgery, rather than there being any advantage of limb-sparing surgery. Traven et al.[29] reported that the mean survival rate of patients who underwent limb-sparing surgery was 20% higher than those who underwent amputation.

A meta-analysis by Papakonstantinou et al.[30] showed that although limb-sparing surgery was associated with a higher five-year OS rate, the probability of LR increased compared to amputation. Evans et al.[31] also reported that similar LR rates of limb salvage surgery and amputation could be achieved in carefully selected patients. However, our patient population is insufficient to make this comparison, and there are controversial results in the literature. It is obvious that since amputation is performed less frequently currently, it would create difficulties in terms of the definitive outcome for future randomized studies.

In the current study, surgical resection was performed following CT/RT due to LR and metastasis development in two of the three patients with aseptic loosening in the first year. Subsequently, these patients underwent revision due to aseptic loosening in the following period. Thus, it can be thought that CT and RT given to the patients in the early period may have increased the risk of aseptic loosening. It has long been known that the multi-agent CT plan affects bone-prosthesis osseointegration.[32,33] There are reports of less bone formation, particularly in the first year of CT.[34]

Nevertheless, our study has several limitations. The patient group size and heterogeneity of the

cohort limit statistical power and may have caused a selection bias that has the potential to affect the results of the study. However, all patients in our study were operated by a single surgeon at a single institution, but our experience covers times when imaging, surgery, and CT modalities have changed dramatically. Therefore, treatment modalities are not standardized in the management of the disease, which can be considered another limitation.

In conclusion, metastasis at the time of diagnosis, <90% tumor necrosis, a tumor size of ≥10 cm, and metastasis development were found to be significantly associated with poor survival and were found to be independent prognostic factors. However, a surprising result is that the OS rate in the group of patients with Grade 3-4 response after neoadjuvant CT given the cisplatin + doxorubicin regimen was better than those given the EURAMOS protocol. Many studies continue in the literature to determine the most optimal CT protocols in a randomized-controlled manner. Further investigation of histogenetic features such as the detection of gene rearrangements, variations and genome, sequencing disorders has been increasingly becoming important in terms of diagnosis and treatment in the management of OS. In this way, the most optimal treatment would be provided with standardized CT regimens after the use of molecular targeting agents. However, multidisciplinary approach in which surgeons, pathologists, medical oncologists and radiotherapists are involved and treatment management is tailored jointly is of utmost importance to improve oncological outcomes.

Ethics Committee Approval: The study protocol was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (date: 16.01.2020, no: 2020/07). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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