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Research Article

Evaluation of factors affecting survival rate in primary bone sarcomas with extremity and pelvis involvement

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ABSTRACT

Objective: This study is an evaluation of the overall survival rate and factors affecting survival in patients with osteosarcoma, chondrosarcoma, or Ewing's sarcoma. This study aimed to determine the effect of factors related to the preoperative period, patient, tumor, treatment, and postoperative period on survival.

Methods: A total of 114 patients (64 male and 50 female) with osteosarcoma, chondrosarcoma, or Ewing's sarcoma treated between 2005 and 2013 were included in this study. All the patients received standard treatment and were followed up regularly. In all, 44 cases of (conventional and telangiectatic) osteosarcoma, 30 cases of Ewing's sarcoma, and 40 cases of high-grade chondrosarcoma were identified using the Bone and Soft Tissue Tumor Registry. Gender, age, tumor size and localization, pathological fractures, histopathological type, grade, surgical treatment, adjuvant treatments, relapse of the disease, and postoperative complication data were obtained from follow-up forms. The learning curve of institutional expertise was also evaluated. The patient survival rate was calculated using the Kaplan-Meier method, and log-rank statistical methods were used to compare survival rates.

Results: The mean length of survival of the patients was 72 months. There was a 56% 5-year survival rate, and the event-free survival rate was 53%. The survival of patients with Ewing's sarcoma whose prodromal period was less than 12 weeks was significantly higher than that of the other groups (p=0.031). The survival of patients with tumor size greater than 150 cc, with local recurrence and distant metastases was low for all groups. Survival rates were significantly lower in osteosarcoma and Ewing's sarcoma patients with stage III tumor or metastasis at diagnosis. The survival of patients with osteosarcoma diagnosed between 2010 and 2013 was significantly higher than that of the earlier group (p=0.02).

Conclusion: Decreasing the prodromal period (early diagnosis) can improve survival by preventing the local and systemic spread of the tumor. Increase in the surgical experience is likely to have a positive effect on survival rates, especially for patients with osteosarcoma. The relapse of the disease is a poor prognostic factor for survival despite aggressive surgery and adjuvant therapies.

Level of Evidence: Level IV, Therapeutic study

Primary sarcomas of the bone constitute a heterogeneous group of neoplasms. Osteosarcoma, Ewing's sarcoma, and chondrosarcoma are high-grade tumors in this group. The introduction of chemotherapy has dramatically improved the survival of patients with osteosarcoma and Ewing's sarcoma (1, 2). Despite the development of surgical techniques and adjuvant therapies in subsequent years, no remarkable improvement has been seen in survival rates (3).

Survival is multifactorial and no definitive factor, which can predict survival rates of patients with bone sarcomas, has been found. To increase survival rates in these patients, individual prognostic factors should be correctly evaluated and there should be appropriate interventions throughout treatment.

Various prognostic factors affect survival of patients with primary bone sarcomas. Details about tumor size, tumor grade, age, gender, metastasis at the time of diagnosis, recurrent disease, response to neoadjuvant chemotherapy, surgical margin, axial or pelvic localization of Ewing's sarcoma, central or peripheral localization of chondrosarcoma, and serum lactate dehydrogenase (LDH) levels in patients with osteosarcoma are important in determining the prognosis of bone sarcomas (4-8).

In this study, some factors that were not studied previously but could affect the survival of

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patients with primary bone sarcomas from a single center, were evaluated and compared with literature reports. To the best of our knowledge, there is no study demonstrating the impact of receiving entire treatment in a single center and surgical experience on survival. This study aimed to evaluate the effects of factors related to the preoperative period, patient, tumor, treatment, and postoperative period of primary bone sarcomas on survival. Our hypothesis indicated that early diagnosis, treatment in a single location, and surgical experience would have a significant effect on survival.

Materials and Methods

In all, 114 patients who were admitted to our clinic between 2005 and 2013 with the diagnosis of high-grade (HG) osteosarcoma (conventional, telangiectatic), Ewing's sarcoma, or HG (grade 2-3) chondrosarcoma were included in the study (Table 1). All cases were treated with a multidisciplinary approach based on a decision of the Bone and Soft Tissue Tumors Council of Marmara University Education and Research Hospital, Pendik, İstanbul. There were 50 female and 64 male patients with an average age of 27.2 years (range, 3 to 78 years). All patients received standard treatment and were followed up regularly. Patients with osteosarcoma and those with Ewing's sarcoma underwent routine neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. Patients receiving adjuvant treatment protocols with different chemotherapeutic agents, patients with low-grade (stage I) sarcomas, and patients who had a definitive inadequate surgery at another clinic were not included in the study.

Some patients with osteosarcoma or Ewing's sarcoma and with low tumor necrosis rate received second-line chemotherapy in the postoperative period. Also, some patients with Ewing's sarcoma underwent preoperative or postoperative radiotherapy. Patients with chondrosarcoma were treated with surgery alone. Surgical treatment included resection with wide surgical margins and bone and soft tissue reconstruction. R classification was used to evaluate the surgical margin. According to the R classification, residual tumors are referred to as R0, R1, and R2 (R0: No residual tumor, margin ≥1 mm; R1: no residual tumor [microscopic residual tumor], margin ≤1 mm; R2: macroscopic residual tumor) (9). All of the operations were performed by the same surgeon (B.E) at a single center.

HIGHLIGHTS

- Decreasing the prodromal period (early diagnosis) can improve survival by preventing local and systemic spread of the tumor.
- All patients with suspected bone sarcoma should be referred to reference centers where definitive surgery and all adjuvant treatments can be administered with a multidisciplinary approach.
- As the surgical experience increases, the factors that cause comorbidity such as the duration of the operation and the amount of bleeding decrease, and thus, the survival rate improves.

The study data were obtained from the institutional database of medical records and follow-up forms. The overall survival rate of each of the study groups was calculated. Then, as a reference to the surgical learning curve, factors related to the preoperative period, patient, tumor, treatment, postoperative period, and timeframe of diagnosis and treatment were analyzed for the effect on survival. While performing all these analyses, each group of patients was evaluated within itself, i.e., the data of patients with osteosarcoma, Ewing's sarcoma, or chondrosarcoma were compared with data of other patients with osteosarcoma, Ewing's sarcoma, or chondrosarcoma. This study was approved by the ethical committee of the Marmara University School of Medicine (no. 09.2015/055). All patients or their parents gave written informed consent to be included in this study.

Statistical analysis

IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) software was used to analyze the data. The Kaplan-Meier test was used to evaluate survival analyses, and the log-rank method was used to compare survival rates. Results with $p < 0.05$ were considered significant.

Results

There were 44 cases of osteosarcoma (conventional and telangiectatic), 30 of Ewing's sarcoma, and 40 of HG chondrosarcoma identified from the Bone and Soft Tissue Tumor Registry. The mean length of survival of the patients was 72 months (range, 2 to 108 months). The 5-year survival rates for osteosarcoma, Ewing's sarcoma, and chondrosarcoma were 46%, 60%, and 71%, respectively. The overall 5-year survival rate was 56% and the event-free survival rate was 53% (Table 2).

Effect of preoperative factors on survival

The mean duration of the prodromal period was 10±4 weeks in the osteosarcoma group, 12±3 weeks for the patients with Ewing's sarcoma, and 33±13 weeks for those with chondrosarcoma. In all, 39 patients presented to the hospital within 12 weeks of onset of complaints, but 75 were seen after at least 12 weeks. There were no patients with chondrosarcoma with a prodromal period shorter than 12 weeks, so they could not be evaluated with the Kaplan-Meier test. In patients with osteosarcoma, the relationship between survival and the prodromal period was not significant (Table 3). Survival was significantly higher in patients with Ewing's sarcoma who had a prodromal period shorter than 12 weeks (Mantel-Cox log-rank test, p=0.031) (Figure 1).

Table 1. General demographic and clinical data

Parameter		Osteosarcoma (n)	Ewing's sarcoma (n)	Chondrosarcoma (n)	Total (n)
Diagnosis		44	30	40	114
Prodromal period	>12 weeks	19	16	40	75
	<12 weeks	25	14	-	39
Pathological fracture		6	4	1	11
Treatment location	All at study center	37	27	37	101
Age (years)	<15	16	17	2	35
	16-30	20	5	11	36
	≥30	8	8	27	43
Gender	Female/male	23/21	10/20	17/23	50/64
Metastasis	At diagnosis	5	3	1	9
Tumor volume (cc)	≤50	3	4	10	17
	50-150	27	18	22	67
	>150	14	8	8	30
Localization	Lower extremity	41	20	16	77
	Upper extremity	2	6	20	28
	Pelvis	1	4	4	9
Stage	Stage IIA	1	0	7	8
	Stage IIB	38	28	27	93
	Stage III	5	2	6	13
Surgical margin	Positive	3	1	1	5
	Negative	41	29	39	109
Tumor necrosis	≥90%	27	18	-	45
	<90%	17	12	-	29
Chemotherapy	Neoadjuvant	42	29	-	71
	Adjuvant	43	30	2	75
Radiotherapy	Neoadjuvant	-	2	-	2
	Adjuvant	-	6	2	8
Complication	Early (<4 weeks)	6	5	2	13
	Late	6	7	3	16
Relapse	Local recurrence	4	6	4	14
	Distant metastasis	15	11	4	30
Date of treatment	2005-2009	10	7	6	23
	2010-2013	34	23	34	91

Table 2. The survival rate of patients with osteosarcoma, Ewing's sarcoma, and chondrosarcoma

Diagnosis	1-year survival	2-year survival	3-year survival	5-year survival
Osteosarcoma	88%	73%	57%	46%
Ewing's sarcoma	89%	70%	61%	60%
Chondrosarcoma	92%	88%	71%	71%

The entire treatment plan, including biopsy, neoadjuvant chemotherapy, surgery, adjuvant chemotherapy, and adjuvant radiotherapy was performed at our institution for the majority (101 patients = 88.6%) of the study population. Thirteen (11.4%) patients underwent biopsy or were administered adjuvant therapy in another center, but their surgery was performed at our institution. The effect of all treatment steps occurring at the same center was not significant for any group (Table 3).

Table 3. Univariate analysis of variables in patients with primary bone sarcomas using the Kaplan-Meier method with Mantel-Cox log-rank test

Variable	Osteosarcoma (Log-rank p value)	Ewing's sarcoma (Log-rank p value)	Chondrosarcoma (Log-rank p value)
Prodromal period	0.302	0.031*	-
Pathological fracture	0.138	0.232	-
Treatment at same location	0.493	0.102	0.21
Age	0.082	0.133	0.264
Gender	0.093	0.241	0.201
Localization	0.193	0.109	0.256
Metastasis at diagnosis	0.004*	0.001*	-
Tumor volume	0.001*	0.001*	0.02*
Stage	0.005*	0.02*	-
Surgical margin	0.116	0.138	-
Necrosis rate	0.085	0.253	-
Second-line chemotherapy	0.232	0.142	-
Early complication	0.488	0.564	0.071
Local recurrence	0.044*	0.03*	0.016*
Distant metastasis	0.001*	0.002*	0.02*
Radiotherapy	-	0.096	-
Surgical experience	0.02*	0.089	0.102

*Significant p values

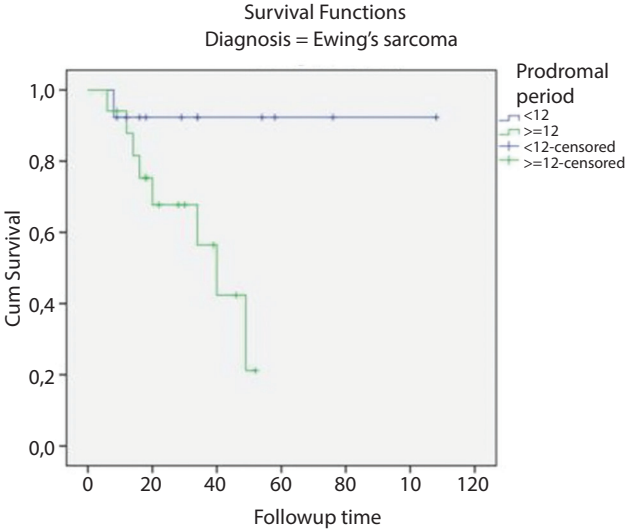

Figure 1. Prodromal period and survival rates in patients with Ewing's sarcoma (Kaplan-Meier)

The mean survival rate of 6 patients with osteosarcoma with pathological fracture was 21 months (range, 12 to 46 months), whereas the mean survival rate of 4 patients with Ewing's sarcoma with pathological fracture was 24 months (range, 12 to 30 months). One patient with chondrosarcoma with a pathological fracture died at 64 months. The relationship between survival and a pathological fracture at diagnosis or during the preoperative period was not significant for any group (Table 3). Only 1 patient in our study had an intra-articular tumor spread following a pathological fracture, and this patient underwent extra-articular resection.

Effect of factors associated with the patient on survival

There were 35 patients under the age of 15 years, 36 patients were between ages 16 and 30 years, and 43 patients were older than 30 years. In our study, age and gender had no significant effect on survival in all three groups (Table 3).

Effect of tumor-related factors on survival

In our patients, 77 (67.5%) had a tumor localization in the lower extremities, 28 (24.6%) in the upper extremities, and 9 (7.9%) in the pelvis. Localization did not have a statistically significant effect on survival for all three groups in this study (Table 3).

Nine patients had metastasis at the time of diagnosis. In our study, the survival rate of patients with metastasis at the time of diagnosis was significantly lower for both osteosarcoma (p = 0.004) and Ewing's sarcoma (p=0.001) (Figure 2. a, b).

Tumor volume was measured with a preoperative magnetic resonance image and a postoperative pathology specimen. The tumor volume was less than 50 cc in 17 patients (14.9%), between 50-150 cc in 67 (58.7%), and more than 150 cc in 30 (26.3%). The survival rate of patients with a tumor vol-

ume >150 cc was significantly lower than that of patients with a tumor volume of ≤150 cc for osteosarcoma (log-rank test, p=0.001), Ewing's sarcoma (log-rank test, p=0.001), and chondrosarcoma (log-rank test, p=0.02) (Figure 3. a-c).

Eight patients were evaluated as stage IIA according to the Enneking staging system, 93 as stage IIB, and 13 as stage III (10). Among patients with osteosarcoma and Ewing's sarcoma, the length of survival of those with stage III tumors was significantly lower than that of patients with stage IIB tumors (log-rank test, p=0.005, and p=0.02, respectively) (Figure 4. a, b).

Effect of treatment-related factors on survival

In 109 patients (95.6%), R0 surgical margin was achieved, whereas in the remaining 5 patients (4.4%), the surgical margins were reported to be R1. Of these 5 patients, 3 had osteosarcoma, 1 had Ewing's sarcoma, and 1 had chondrosarcoma (Table 1). One patient with osteosarcoma underwent amputation and the other two patients had adjuvant chemotherapy without any further surgery. Amputation was performed in 1 patient with chondrosarcoma. Finally, 1 patient with Ewing's sarcoma had adjuvant chemotherapy and radiotherapy. Lung metastasis was detected in the 12th month of follow-up, and the patient died of the disease in the 16th month.

Of the 74 patients with osteosarcoma or Ewing's sarcoma, 45 (60.8%) had a tumor necrosis rate ≥90%, and 29 (39.1%) had a necrosis rate <90%. The effect of surgical margin positivity and necrosis rate for both osteosarcoma and Ewing's sarcoma on survival was not statistically significant in this study (Table 3).

In the postoperative period, second-line chemotherapy was administered to 5 patients with osteosarcoma and 4 patients with Ewing's sarcoma who were associated with low (<90%) tumor necrosis rate. There was no statistically significant effect of second-line chemotherapy on the survival of patients with osteosarcoma and Ewing's sarcoma (Table 3).

Effect of postoperative factors on survival

The overall complication was 25.4%. In 29 patients, early (infection, wound problem, hematoma, etc.) or late (infection, implant failure, etc.) complications were detected. We specifically researched the effect of early (in first 4-6 weeks) postoperative complications on survival because early infections

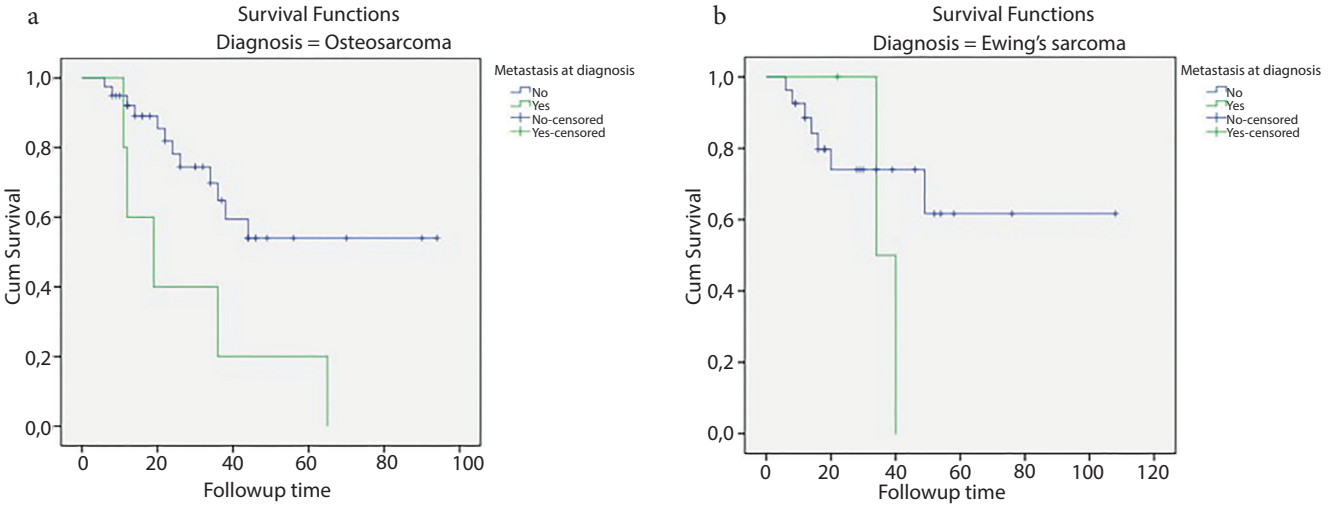

Figure 2. a, b. Metastasis at the time of diagnosis and survival rates in patients with (a) osteosarcoma, (b) Ewing's sarcoma (Kaplan-Meier)

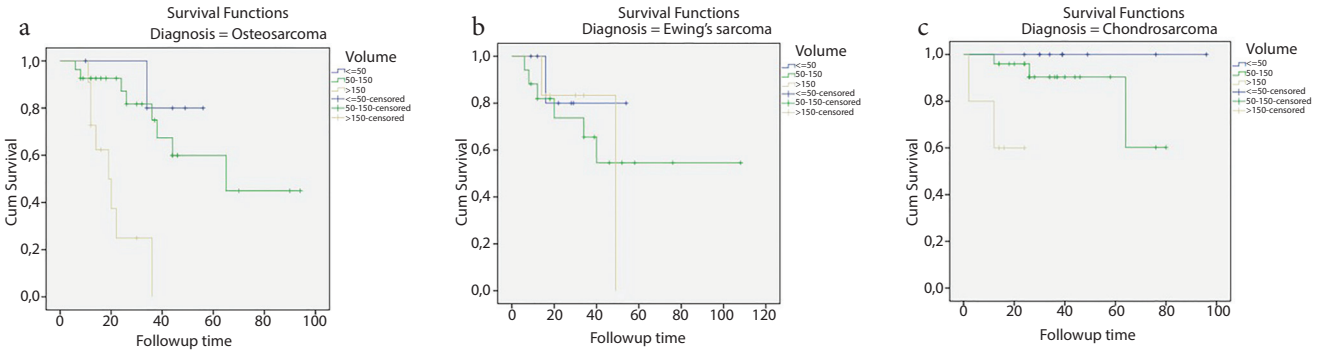

Figure 3. a-c. Tumor volume and survival rates in patients with (a) osteosarcoma, (b) Ewing's sarcoma, and (c) chondrosarcoma (Kaplan-Meier)

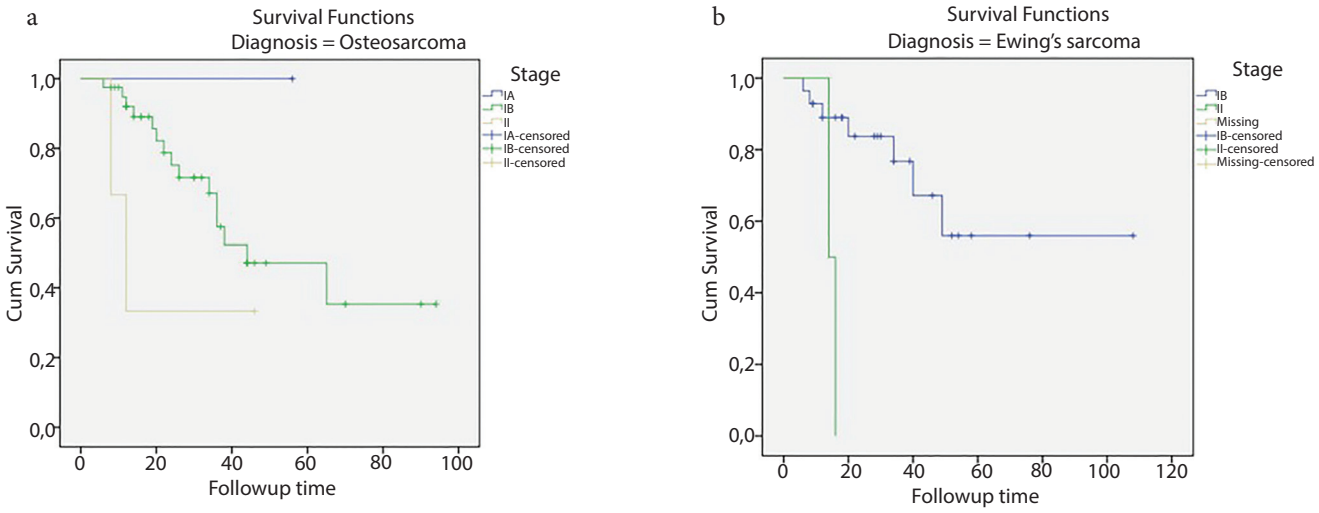

Figure 4. a, b. Tumor stage and survival rates in patients with (a) osteosarcoma, (b) Ewing's sarcoma (Kaplan-Meier)

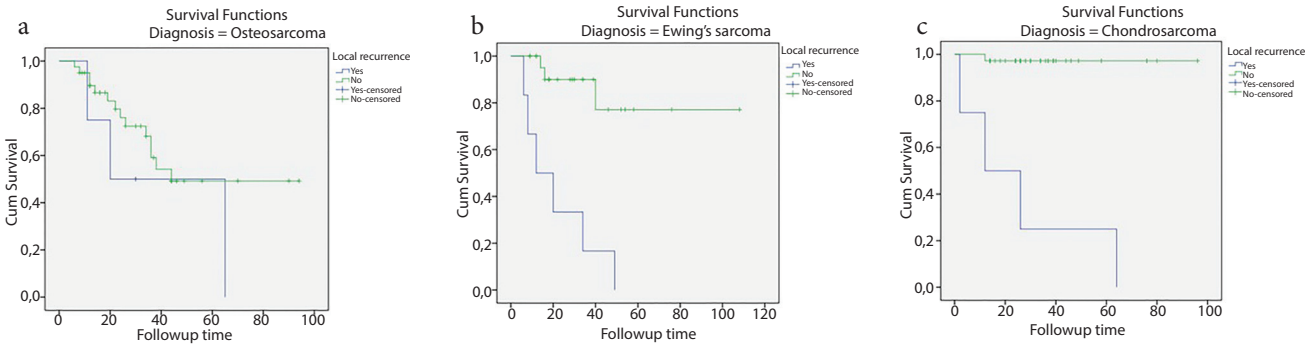

Figure 5. a-c. Local recurrence and survival rates in patients with (a) osteosarcoma, (b) Ewing's sarcoma, and (c) chondrosarcoma (Kaplan-Meier)

caused disruptions in the routine treatment of patients. Early complications including superficial or deep infection, wound dehiscence or skin necrosis were observed in 13 patients. These complication were managed by surgical or conservative treatments. The effect of early complications on overall survival was not statistically significant in the current study for all three groups (Table 3).

Disease relapse was observed in 44 (38.6%) patients. Four patients with osteosarcoma, 6 with Ewing's sarcoma, and 4 with chondrosarcoma had a local recurrence, and 15 patients with osteosarcoma, 11 with Ewing's sarcoma, and 4 with chondrosarcoma had distant metastasis. Local recurrence and metastasis data were analyzed and indicated that the length of survival of patients with a local recurrence was significantly lower than the survival of the patients without relapse for all three groups (log-rank test, p=0.044, 0.03, and 0.016, respectively) (Figure 5. a-c). Similarly, the survival rates of patients with distant metastasis were significantly lower than those of patients without metastasis (log-rank test, p=0.001, 0.002, and 0.02, respectively) (Figure 6. a-c).

Two patients with Ewing's sarcoma underwent radiotherapy in the preoperative period and 6 patients postoperatively. The effect of radiotherapy administered preoperatively or postoperatively on survival was not statistically significant (log-rank test, p=0.096).

Effect of surgical experience on survival

Of the study group, 23 patients were operated on between 2005 and 2009 and 91 were operated on between 2010 and 2013. The institutional learning curve in cases of chondrosarcoma and Ewing's sarcoma was not statistically significant. Patients with osteosarcoma who underwent surgery between 2010 and 2013 had a significantly higher survival rate (log-rank test, p=0.02) (Figure 7).

Discussion

Prognostic factors that can affect survival in cases of primary bone sarcoma, such as osteosarcoma, Ewing's sarcoma, and chondrosarcoma, have been investigated individually or as multicenter studies in the literature. In our study, we examined all of these primary bone sarcomas in a single center and added some parameters to those previously evaluated. The main findings of this study can be summarized as follows: (a) patients with Ewing's sarcoma with a short prodromal period had higher survival rates; (b) survival rates of patients with

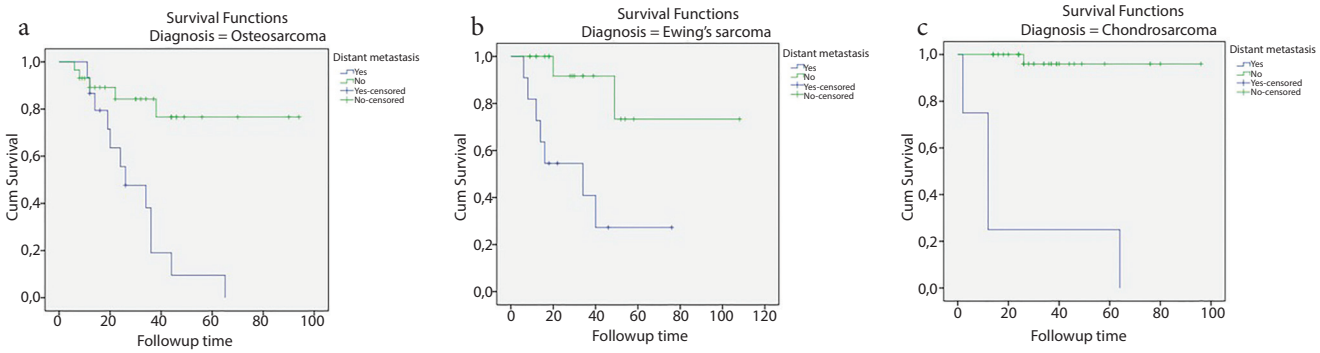

Figure 6. a-c. Distant metastasis and survival rates in patients with (a) osteosarcoma, (b) Ewing's sarcoma, and (c) chondrosarcoma (Kaplan-Meier)

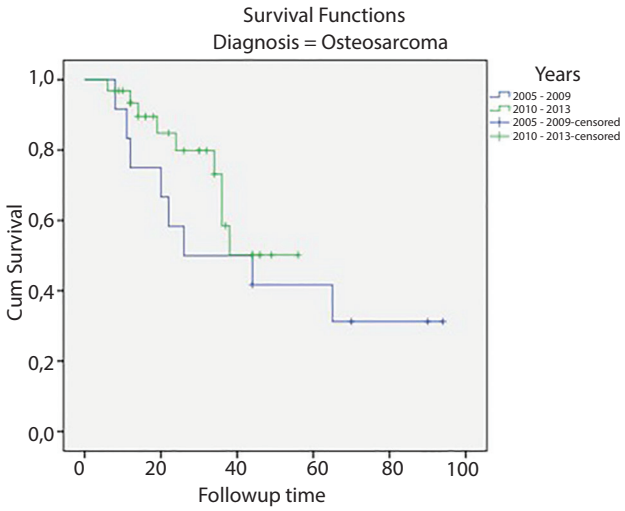

Figure 7. Survival rate of patients with osteosarcoma by year (Kaplan-Meier)

metastasis at the time of diagnosis were significantly lower; (c) survival rates of patients with a tumor size >150 cc and those with stage III tumors were low; (d) survival rates were low in patients with local recurrence and distant metastasis; (e) survival rates were high in patients with osteosarcoma who were operated upon during the period that the institutional learning curve increased.

The duration of the prodromal period, single-center treatment, and pathological fracture occurrence were examined as preoperative period factors. Decreasing the prodromal period (early diagnosis) can improve survival by preventing local and systemic spread of the tumor. Some studies in the literature have reported a median duration of symptoms about 16 weeks before the diagnosis of bone sarcomas (11). In our study, patients with Ewing's sarcoma who had a prodromal period shorter than 12 weeks had improved survival rates. Goedhart et al. showed that in a series of 102 patients, there was a very long delay in the diagnosis of patients with chondrosarcoma, but the delay in diagnosis did not affect survival (12). Kim et al. reported that a doctor-related delay harmed survival rates in patients with osteosarcoma (13). Abou Ali et al. stated that a delay of more than 4 weeks decreased survival rates in osteosarcoma (14). Widne et al. showed that doctor-related delay was significant for Ewing's sarcoma (15). This was consistent with the current study. In the pre-hospital period (at the general practitioner stage), the patients with persistent pain lasting 4-6 weeks and a suspicious lesion on radiographs should immediately be referred to orthopaedic oncologist to decrease the prodromal period. To be able to minimize patient-related delays, studies must be conducted to raise awareness about the importance of persistent pain.

It is reported that a pathological fracture through a bony sarcoma can worsen prognosis by spreading the tumor via the fracture hematoma or by spreading micro-metastases (16). In their study, Bramer et al. stated that the overall survival rate is worse in patients with osteo- or chondrosarcoma who had a fracture, and fracture is an independent predictor of survival in osteosarcoma only (16). However, Wang et al. showed that a pathological fracture at the time of presentation did not have a significant effect on survival, and this was consistent with the current study (17). The pathological fracture may lead to an intra-articular spread in lesions close to the joint. In our study, intra-articular tumor spread was observed in one patient following a pathological fracture. Extra-articular resection should be performed in these patients to reach a clean surgical margin and prolong survival.

Literature shows that there is a negative effect on survival when patients with sarcoma present to non-specialized centers and where the first operation performed is an inadequate procedure (18). Survival is significantly low in patients where wide surgical margins have not been obtained and local control has not been achieved (18). Patients who had a definitive inadequate surgery at another institution were not included in this series. There were only 13 patients undergoing biopsy procedures and/or adjuvant therapy in another center. Therefore, this factor did not have a negative effect on survival, i.e., the relation between single-center treatment and survival was not significant in the current study. All patients with suspected bone sarcoma should be referred to reference centers

where definitive surgery and all adjuvant treatments can be administered with a multidisciplinary approach (19).

Gender and age were considered as patient-related factors. It has been reported in the literature that malignant bone tumors are usually seen in patients of ages between 11 and 20 years (20). Some studies have shown that advanced age is a negative factor in the survival of malignant bone sarcomas. Age has been described as a negative prognostic factor for survival in cases of Ewing's sarcoma (21). Craft et al. reported a 5-year survival rate of 55% in patients over the age of 10 years and 86% in younger patients (22). Ferrari et al. found that age under 18 years was a weak factor in prognosis (23). For osteosarcoma, it should be kept in mind that there is generally a good prognosis in girls before the age of 15 years (24). Because our study group included patients of different ages and tumor biology, survival analysis according to gender and age was not significant.

Metastasis at the time of diagnosis, localization, volume, and stage was considered as a tumor-related factor. Metastasis present at the time of diagnosis is a sign of poor prognosis in malignant bone tumors. Overall survival of patients with metastasis at the time of diagnosis was found to be low by Wang et al. in osteosarcomas and by Nagano et al. in all bone sarcomas (17, 25). The results in the current study were consistent with the findings of these studies. Zhan et al. reported higher survival rates following primary tumor resection in metastatic chondrosarcoma (26). In contrast, Grimer et al. reported that life expectancy was low when there is metastasis at the time of diagnosis in dedifferentiated chondrosarcoma (27). Surgical excision is standard in chondrosarcoma, and when there is metastatic disease, the addition of adjuvant treatments can increase survival (27).

Pelvic and axial tumors may be more aggressive. There are also reports describing tumors of the axial skeleton in the literature. All the patients in our study had tumors located in the extremities or the pelvis. Craft et al. reported an event-free survival rate of 41% for patients with pelvic tumors, 55% for those with tumors in other axial localizations, and 73% for those with extremity tumors (22). Serlo et al. found a significantly lower survival rate in patients with axial skeletal Ewing's sarcoma compared with those with tumors in an extremity site (4). The mean survival rate of patients with chondrosarcomas with appendicular localization is better than that in patients with axial localization (82.7% vs. 61.6%) (28). The prognosis of chondrosarcomas with pelvis localization is worse than that of chondrosarcomas with peripheral localization (28). Contrary to the literature, localization did not demonstrate a statistically significant effect on survival in the current study. We attribute this to the fact that our patient population was heterogeneous. Because the patients with tumors in the axial skeleton were not included in the study, we concluded that localization did not yield significant results for survival.

Serlo et al. reported that tumor tissue larger than 10 cm in size harmed survival (4). Albergo et al. reported that survival rate increased and the risk of local recurrence decreased for an Ewing's sarcoma <80 mm (29). Zhan et al. showed that chondrosarcoma <10 cm was significant for survival (26). In the current study, survival was significantly reduced in patients with a large tumor volume, which was comparable with findings in the literature. The larger the size of the tumor, the greater the amount of intact tissue that must be sacrificed to achieve a clear surgical margin. Functional outcomes and low survival rates should be kept in mind while limb salvage surgery is planned for a large volume of tumors.

Surgical margin positivity and tumor necrosis rates were evaluated as treatment-related factors. Tumors remaining at the surgical margin and a tumor necrosis rate below 90% generally increase local recurrence and metastasis rates. A positive surgical margin adversely affects prognosis (30). In our study, the rate of surgical margin positivity, which was only at the microscopic level, was 3.5%. Serlo et al. reported positive margins in 4 (4.6%) of 88 patients (4). The effect of surgical margin status and necrosis rate on survival was not statistically significant in our study. Cates et al. showed that local recurrence was reduced in osteosarcoma where the distance between the surgical margin and the tumor was greater than 2 mm (31). Loh et al. concluded that decreasing the resection margin from 5 to 1.5 cm did not significantly reduce survival (32). According to the Birmingham classification, which includes the response to chemotherapy, a 2 mm cutoff value is significant with regard to survival and local recurrence risk for osteosarcoma (33). In most patients in the current study, negative margins were obtained. Resection was performed by leaving a safe margin of 2 cm when making the bone cut in patients with sarcoma. However, in the pathology reports of 5 patients with proximity to a neurovascular structure, microscopic positivity was determined in the surgical margin. In these patients with microscopic residual tumor, survival was not affected statistically.

A good response to chemotherapy (necrosis rate>90%) has been shown in the literature to be effective in reducing local recurrence and increasing survival rates (14, 29). Second-line chemotherapy can be administered to some patients with disease recurrence and a low necrosis rate despite the first treatment. This treatment aims to improve the quality of life for the patient and reduce disease-related symptoms. Second-line chemotherapy may prolong patent survival but rarely provides a cure.

Early-stage complications and relapse of the disease were evaluated as postoperative period factors. Early complications may delay the routine postoperative adjuvant chemotherapy regimen. A wound problem or an infection may delay postoperative chemotherapy or radiation treatment. In contrast, in some recent studies, the survival rate of pa-

tients with infection was greater than that of other patients. Yu-Chen et al. observed that of 125 patients with malignant tumors, the 5-year survival rate of patients with a postoperative infection was 100% (34). Jeys et al. reported that survival could be long in patients with infected osteosarcoma (35). However, Lee et al. found that there was no significant relationship between survival rates in infected and non-infected patients (36). In the current study, early complication was not associated with survival.

The prognosis of patients with local recurrence is poor, and the risk of distant metastasis is also increased (14, 25). Wang et al. showed that life expectancy was reduced in patients with local recurrence and distant metastasis of osteosarcoma (17). Albergo et al. also found that local recurrence of Ewing's sarcoma affected overall survival (29). In our study, local recurrence and distant metastasis were found to decrease survival time. The relapse of the disease is a poor prognostic factor despite aggressive surgery and adjuvant therapies. Besides, it has been reported that local recurrence and metastasis are related to inadequate surgical margins and poor chemotherapeutic response (37).

The effect of surgical experience over time on survival rates was evaluated according to the diagnosis. Similar patients were selected from the diagnostic groups and the effect of surgery performed by a single surgeon on survival was analyzed. Wu et al. analyzed survival of patients diagnosed with osteosarcoma between 1984 and 2013, and reported that survival rates had significantly increased over the years (38). Kollár et al. performed statistical evaluations of survival rates of all bone sarcomas between 1996 and 2000 and 2001 and 2015 and reported a significant increase in the period between 2001 and 2015 (39). The results of the current study are consistent with those findings. Among patients with osteosarcoma, the survival of patients who were operated on between 2010 and 2013 was significantly higher than those who underwent surgery between 2005 and 2009. As the surgical experience increases, the factors that cause comorbidity such as the duration of the operation and the amount of bleeding decrease, and thus, the survival rate improves.

We acknowledge some limitations to this study. The major limitation is the underpowered statistical analysis. The statistical evaluations of some factors affecting survival could not be accurately interpreted as the sample size was low. Despite a heterogeneous study group, this analysis presents the survival data of these rarely seen bone sarcomas in a single center separately. Another limitation is the surgical margin. Our pathology reports do not give an actual exact surgical margin but just state the R classification. Thus, any cutoff value of surgical margin as a means of higher survival cannot be understood with these pathology reports. Although this study has provided useful information about the survival of patients with bone sarcomas, it is lacking data related to tumor subtypes, treatment details, and comorbidities. Some factors associated with possible prognostic impact such as surgical procedure and times of recurrence were not investigated in the current study. The information from follow-up forms partly relies on the accuracy of the individuals. Many factors may contribute to survival when examining it as associated with the year of treatment; however, similar patients were selected for analysis, and the experience of the surgeon was prioritized. In contrast, we think that the effect of the prodromal period before diagnosis and the increased learning curve of the sarcoma surgery on survival may provide some contribution to the literature.

In conclusion, it is obvious that in patients with bone sarcoma, the success of treatment is likely to increase when a multidisciplinary approach is used after detection of the disease, with emphasis on early diagnosis. We believe that patient survival will also increase as surgical experience increases. Longer patient follow-up and increasing success with adjuvant treatment options also contribute to survival time. Studies with larger patient groups and long-term follow-up are needed. Greater awareness of primary malignant bone tumors among both orthopedic specialists and the general public would also help to increase survival rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of the Marmara University, School of Medicine (no. 09.2015/055).

Informed Consent: Written informed consent was obtained from the patients and patients' parents who participated in this study.

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