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Survival analysis and the effects of prognostic factors in patients treated for osteosarcoma

Osteosarkom nedeniyle tedavi edilen hastalarda sağkalım analizi ve prognostik faktörlerin etkileri

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Amaç: Primer osteosarkomlu hastaların uzun vadeli tedavi sonuçları ve çeşitli prognostik faktörlerin sağkalım ve hastalıksız sağkalım üzerine etkileri değerlendirildi.

Çalışma planı: 1991-2005 yılları arasında primer osteosarkom nedeniyle tedavi edilen 180 hasta (111 erkek, 69 kadın; ort. yaş 21±10; dağılım 7-64) çalışmaya alındı. Yüksek dereceli tümörü olan 165 hastada genel ve hastalıksız sağkalım oranları Kaplan-Meier yöntemiyle hesaplandı. Yaş, cinsiyet, yerleşim yeri, tümör büyüklüğü, başvuruda metastaz varlığı, patolojik kırık, nekroz oranı, enfeksiyon gibi faktörlerin prognoz üzerine etkisi araştırıldı. Cerrahi tedaviden önce ve sonra hastalara kemoterapi uygulandı. Ortalama takip süresi 49.7 ay (dağılım 6-185 ay) idi.

Sonuçlar: Altmış dokuz hasta 16 yaşından küçük idi. Tümörler en sık femur distali (%47.2) ve tibia proksimalinde (%25) görüldü. On altı hasta patolojik kırıkla, 12 hasta metastaz ile başvurmuştu. Ortanca tümör büyüklüğü 10 cm idi. Genel sağkalım beş yıl için %68, 10 yıl için %60 olarak belirlendi. Hastalıksız sağkalım beş yıl için %50, 10 yıl için %44 bulundu. İncelenen faktörlerden sadece patolojik kırık ve başvuruda metastaz varlığının prognozu olumsuz etkilediği belirlendi.

Çıkarımlar: Çalışmamızda, en önemli prognostik faktörler olarak belirlenen metastazla başvuru ve patolojik kırık oluşumu genellikle geç başvuru ile ilişkilidir. Her türlü habis hastalıkta olduğu gibi osteosarkomda da erken başvurunun sağlanması ile daha yüksek sağkalım oranları elde edilebilir.

Anahtar sözcükler: Kemik neoplazileri/cerrahi; kemoterapi, adjuvan; tümör metastazı; osteosarkom/cerrahi; prognoz; sağkalım oranı.

Objectives: We evaluated long-term treatment results of patients with primary osteosarcoma and the effect of prognostic factors on overall survival and disease-free survival.

Methods: Between 1995 and 2005, 180 patients (111 males, 69 females; mean age 21±10 years; range 7 to 64 years) were treated for primary osteosarcoma. Overall and disease-free survival rates were analyzed for 165 patients with high-grade osteosarcoma with the Kaplan-Meier method. The effects of potential prognostic factors were assessed, including age, gender, localization, tumor size, primary metastasis on presentation, the presence of pathologic fractures, necrosis rate, and infection. All the patients received chemotherapy before and after surgery. The mean follow-up period was 49.7 months (range 6 to 185) months.

Results: Sixty-nine patients were below 16 years of age. The most frequent involvement was in the distal femur (47.2%), followed by the proximal tibia (25%). Sixteen patients presented with a pathologic fracture, and 12 patients with metastasis. The median tumor size was 10 cm. The overall five- and 10-year survival rates were 68% and 60%, and disease-free survival rates were 50% and 44%, respectively. Only the presence of a pathologic fracture and primary metastasis on presentation were found to affect prognosis.

Conclusion: The two conditions, primary metastasis and a pathologic fracture, found as the most important prognostic factors in our study are mainly associated with late presentation. As in every malignant disease, early admission would provide better survival rates.

Key words: Bone neoplasms/surgery; chemotherapy, adjuvant; neoplasm metastasis; osteosarcoma/surgery; prognosis; survival rate.

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The success of the osteosarcoma treatment is increased by the new chemotherapy regimens. Although the local control of osteosarcomas is provided by surgery, to prevent the losts because of the systemic spread of the disease preoperative and postoperative chemotherapy is used as a standart treatment since 1980's.[1, 2] In large and multicentric studies disease free survival ratios is reported between 55-75%.[3,4,5,6] In our hospital we use standart treatment protocol with the coordination between oncology group since early 1990's.

In this study, we aimed that to evaluate the long term clinical and radiological results, to find out overall survival and disease free survival ratios, the effect of prognostic factors on this ratios on patients who are treated with surgical and oncological methods in our hospital.

Patients and methods

One-hundred-and-eighty primary osteosarcoma patients (metastatic or non-metastatic) were treated and followed up regularly between 1991-2005. We included patients who took their definitive diagnosis in our pathology laboratory and who applied our orthopaedics clinic primary or secondary (after biopsy or improper treatment) and whole surgical and/or oncological treatments are given in our institution.

Diagnosis methods

Direct radiography and MRI of the affected whole bone or in first years the computed tomograpy of the whole bone were obtained, Chest CT and Tc99 bone scintigraphy of whole body were used for metastasis work-up. By these methods we staged the patients and in the first referrance we made biopsy for definitive diagnosis. The pathological investigations in outer centers are repeated by our pathologists and in suspicious diagnosis we made an another biopsy. In first years the biopsy intaken by open methods mostly but in recent years we prefer tru-cut method.

After definitive diagnosis the patients are referred to our oncology clinic for neoadjuvant chemotherapy. The patients are admitted to our orthopaedics department after 3 chemotherapy cures and after their blood table status permits surgery. After surgical treatment the patients are referred again to oncology clinic for the adjuvant chemotherapy.

Chemotherapy regimen

Adult patient (>16 years): In this group 2 different protocol is used. Between 1991-1999 years preop neoadjuvant chemotherapy is used by 3 cycle by cisplatin 100 mg/m2, epirubicin 90 mg /m^2 in first day and iphosfamide in 3 divided doses with totaly 6 gr/m^2 (PEI) in 3 weeks intervals. For the toxicity of iphosfamide we added mesna to our treatment. After operation the same treatment chart is used 3 times with 4 week intervals. Total treatment is made by 6 cycles.

In between 1999 and 2005 years preoperatively we give 3 cycle chemotherapy by alternative drugs to the >16 age group. In first cycle cisplatin 120 mg /m^2 in 24 hour infusion, adriablastin 60 mg /m^2 in 48 hour infusion; in the second cycle iphosfomide 6 gr/m^2 divided in 2 days, protecter dose of mesna and cysplatin 120 mg/m^2 in 24 hour infusion; in third cycle iphosfomide 6 gr/m^2 divided in 2 days, protective dose of mesna and adriablastin 60 mg /m2 in 48 hour continiuous infusion is used. All treatments are given in 3 week intervals. In postoperative chemotherapy total 6 cycle, cisplatin 120 mg /mv in 24 hour infusion, adriablastin 60 mg /mv in 48 hour infusion, iphosfamide 10 gr/m^2 with mesna prevention is given. All treatment is made by 9 cycles. Treatments are given with 3 week intervals. When desired necrosis ratios are could not be achieved by neoadjuvant chemotherapy, methotrexate treatment is added to treatment postoperatively. Methotrexate is used in 12 mg/m^2 doses with folinic acid.

Pediatric patients: <16 years patients are referred to pediatric oncology department after staging studies and biopsy results are taken. With 3 week intervals for 4 days preoperatively and postoperatively 3 cycles chemotherapy is given. To give chemotherapy we look for patients have the hemoglobin ≥ 10 gr /dl, absolute neutrophil count ≥ 1000 /mm3, platelet count ≥ 100.000 /mm3, ejection fraction ≥60 % and EKG must be normal.

In treatment intervals when the hemoglobin ≤ 7 gr/dl and platelet ≤ 30.000 /mm^2 RBC and platelet transfusion is given. When tranfusion is needed the blood products are radiated by 1500-2000- cGy. Febrile neutropenia patients are also treated as the protocol algorithm. Because of our protocol we didn't give G-CSF/ GM-CSF prophylaxis but between 1993 and 1997 years we used secondary prophylax-

is . Between 1990 and 2005 years in pediaric patient group we used epirubusin 90µg/mv/1 day, iphosfomide 1.8 gr/m²/l day and cisplatin 100µg/m²/1 day for 4 days, and for antiemesis and bladder prevention urometaxan is used for chemotherapy period at advised doses.

In follow up for relapsed cases we used high dose methotraxate gr/m²/l day and high dose iphosfamide 14 gr/m²/l day 2-4 week intervals with transformation. At first referrence and follow up these datas are documented, these datas are investigated for effects on survival and disease free survival by univariate and multivariate statistical analysis.

The age of patient: The patients ages are documented at first referrance and by the limit of 16 years the patients are divided into groups.

The localization of tumor: First, grouped as lower, upper and trunk. Then documented by the bone name and parts of bones. In multicenter osteosarcoma patients clinically important lesion is documanted basicly.

The size of tumor: The size is only documented in extremity tumors. In 3 plane the largest diameter is documented basicly.

Metastasis at referrance(Primary met.): At the time of the osteosarcoma diagnosis by pathology laboratory, any metastatic lesion in any parts of the body which is shown by radiologically or pathologically.

Stage: Patients are graded by Enneking classification with grade, location, and metastasis. Grade I is lower grade, grade II is high grade and grade III is metastatic lesions; The term 'A' refers to intracompartmental and the term 'B' refers to extracompartmental spread.

Radiotherapy: Because of different reasons preoperative and postoperative radiotherapy added and the reasons are documented. We detect, before year 1996 and in patients who are admitted with pathological fractures to increase the local control, preoperative radiotherapy is used.Postoperative radiotherapy is used for cases in local recurrence.

Deviation from chemotherapy: At preoperative period for any reason the cases which there is a deviation from chemotherapy (for more than 3 neoadjıvant treatment) is documented.

Surgery type: The first surgery is taken in principle. When firstly the limb sparing surgery is used but than amputated because of recurrence, we document the first operation basically. Treatment's characteristics like limb salvage /amputation, prosthesis/biological reconstruction is documented.

Surgery complication: Complications are documented as early, mid and long term. Early term is postoperative 1 month, mid is between 1 to 12 months and long term is after 1 year postoperatively.

Necrosis ratio: The tumor necrosis ratios are reported by pathological investigations after the surgery on pathology material is documented. Before 1996's generally this ratios are not used, instead the analysises are reported like low, medium, high or don't reported as qualitatively. For this reason the cases in which the necrosis ratios are reported numerically, this characteristic is used as a prognostic factor. The ratios are classified as 1. degree (<50% necrosis), 2. degree (50-90%), 3.degree (91-99%), and 4. degree (100%).

Metastasis: During the postoperative follow up, metastasis that are detected at lung and other organs and the dates are documented. The patients who have solitary metastasis are operated by thorax surgeons for metastasectomy.

Statistical analysis

From 180 patients that included the study 15 patients who are in low grade class, because of their histopathological diagnosis is parosteal osteosarcoma, they are not included in total survival and disease free survival analysis. The remaining 165 patients age, gender, localization, grade, the metastasis at referrence, pathological fracture, infection, surgery type and necrosis like factors effects on total survival and disease free survival is analysed by SPSS 13.0 (SPSS Corp, USA) statistic program with Kaplan-Meier method. Total survival is from the biopsy date to death date (for any reason); disease free survival is documented time between biopsy date to the date of recurrence of disease (local recurrence or metastasis) or the time of death (which is occurred earlier). In statistical analyses, in %95 confidence interval $p<0.05$ is detected as significant.

Results

111 patients were male and 69 patients were female. The mean age was 21.3±9.7 years (between 7-64 years). The patients were divided into two groups as those younger than 16 years of age (pediatric patients) and those over 16 years of age. 69 patients were younger than 16 years and 111 patients were 16 years old or older. Mean follow-up period was 49.7 (6-185) months.

Chief complaint at presentation: Long term pain which is not activity related and swelling were presenting symptoms at the majority of patients (164 patients, 91.1%). 16 patients (9%) had pathologic fracture at presentation.

Tumor localization: Osteosarcoma was located at the lower extremity in 158 patients, upper extremity in 20 patients and axial skeleton in 2 patients. Most common locatizations were distal femur (85 patients, 47%), and proximal tibia (45 patients, 25%). Detailed information is given at the table and figure below. (Table 1, Table 2, Figure 1).

Metastasis at presentation: 12 patients (6.7%) had metastasis at presentation. Of these patients, 10 patient had lung involvement, 1 patient had metastasis at the 12. thoracic vertebra, and 1 patient had both brain and lung metastasis.

Biopsy: Biopsy was performed at another center to 29 patients (16%); 5 patients (2.8%) received inadequate surgery at another center and referred to our hospital thereafter. 144 patients were treated at our clinic from the beginning.

Table 1. The bone distrubition of upper extremity

	No	%
Upper extremity (n=20)		
Humerus	13	7.2
Ulna	2	1.1
Radius	1	0.6
Skapula	2	1.1
Clavikula	2	1.1
Lower extremity (n=158)		
Proximal femur	2	1.1
Femur diaphysis	3	1.7
Distal femur	85	47.2
Proximal tibia	45	25.0
Tibia diaphysis	3	1.7
Distal tibia	4	2.2
Fibula	7	3.9
Pelvis	9	5.0

Pathologic examination revealed classic osteosarcoma in 112 patients, chondroblastic osteosarcoma in 24 patients, pleomorphic type in 13 patients, fibroblastic type in 6 patients, telangiectatic type in 5 patients, small cell type in 2 patients, secondary tumor in 3 patients (metal-induced in 1 patient, Paget disease related in 1 patient, and in 1 patient due to radiation therapy received for treatment of Ewing sarcoma). 15 patients were detected to have low grade parosteal osteosarcoma.

Stage: According to Enneking staging system, 148 patients were stage IIB, 5 patients were stage IIA, 13 patients were stage IB, 12 patients were stage IIIB, and 2 patients were classified as stage IA at presentation.

Radiotherapy: 10 patients in total (8 patients in or before 1996) received preoperative radiotherapy. 5 patients received postoperative radiotherapy due to contaminated margin or local recurrence.

Deviation from chemotherapy program: 30 patients (18%) who received more than 3 sessions of neoadjuvant chemotherapy were regarded as deviation.

Type of surgery: Limb salvage procedures were applied in 158 patients (87.8%). Amputation was performed in 14 patients (7.8%). 8 patients refused surgery. Of the salvaged extremities, 108 limbs were reconstructed with endoprostheses, and 50 limbs by biologic methods.

Tumor size: Examination of maximum diameter of tumors revealed that median diameter was 10 cm (2-26). 95 patients (53%) had a tumor larger than 10 cm.

Percentage of necrosis: Necrosis rate was determined in order to search for excised tumors' response to chemotherapy.

109 patients, whose necrosis rates were recorded numerically in pathology reports, were examined for this criterium. According to Huvos criteria, 1. degree (<50%) was detected in 12% of patients, 2. degree (50-90%) in 41%, 3. degree (91-99%) in 38% and 4. degree (100%) in 9%. For statistical evaluation, patients were divided in 2 groups to those over (32 patients) and below(77 patients) 95%.

Complications of surgical treatment: Complications were examine in 3 groups as early, mid-term and late complications. 28 early complications included transient neuropraxia in 9 patients, superficial wound problem in 6 patients, infection in 11 patients, compartment syndrome at crus in 1 patient and limb length discrepency in 1 patient. Infection, wound problems and neuropraxia was controlled with adequate medical treatment and dressings. Fasciotomy was performed in the patient who had compartment syndrome. 17 patients had mid-term complications. Among these, 9 patients had prosthesis-related problems (early loosening, periprosthetic fracture) and 8 patients were detected to have deep infection. There were 46 late complications. 14 patients had aseptic loosening of the prosthesis, 11 patients had deep infection, 13 patients had limb length discrepancy more than 2 cm, 2 patients had extremity deformity, 4 patients had joint contracture, and 2 patients had problems related with biologic reconstruction (graft resorption and nonunion).

Local control: Local recurrence occured in 14 patients during follow-up. Mean duration until recurrence was 8.1 months. Amputation-disarticulation was performed in 8 patients, resection was performed in 4 patients and 2 patients didn't accept the proposed treatment.

Metastasis: 77 patients (43%) had systemic metastasis during follow-up. 63 of 165 patients were detected to have lung metastasis. 7 patients had multiple metastasis, and 7 patients had metastasis at other sites and organs (liver, brain). Metastatectomy was performed in solitary lung metastases. Of 63 patients with lung metastasis, 52 patients received surgical intervention by chest surgery. 35 of those 65 patients died. Mean duration until metastasis was 23 months. 63 patients had solitary lung metastasis, 7 patients had metastases in other regions (bone, brain, etc.), and 7 patients had multiple metastases.

Survival of prosthesis

Among 180 patients, prosthesis was applied in 109 patients. Mean prosthesis survival was 42.4 months (3.4-162 months).

5-year prosthesis survival was 84.12%; 10-year prosthesis survival was %62.53. Prosthesis survival curve was parellel for septic and aseptic loosening

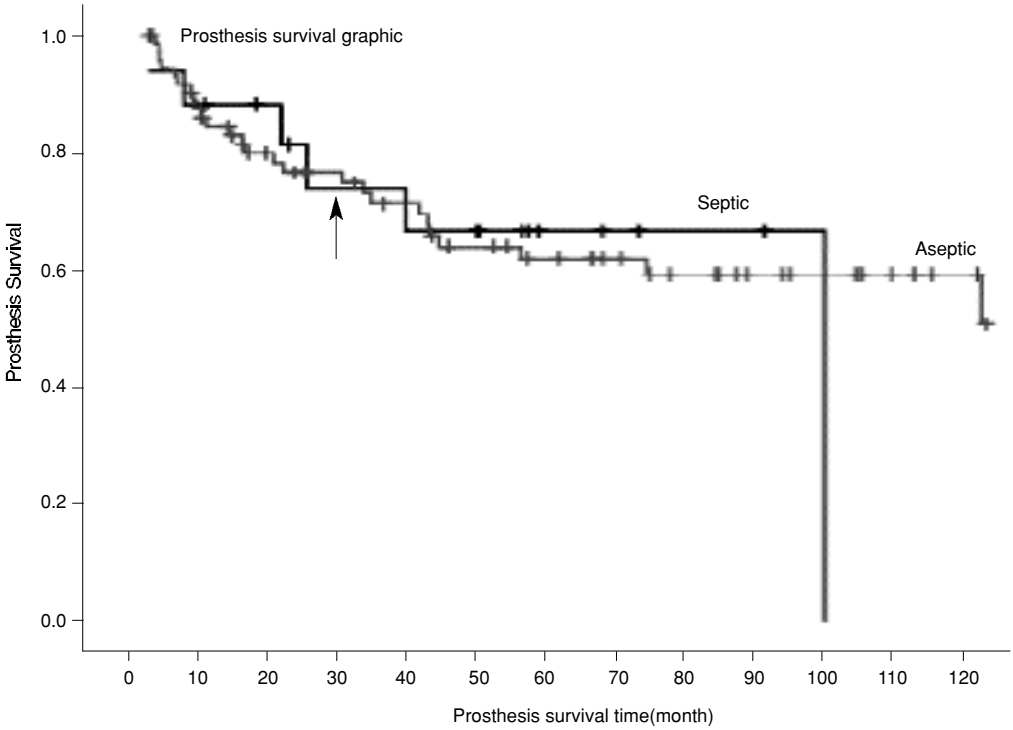

Figure 1. Prosthesis survival curve was parellel for septic and aseptic loosening until 30. month, but septic loosening ratio rised after that. Considering these results, prosthetic infection can be estimated to occur at 30. month approximately.Black arrow shows 30.month. (Blue line shows septic loosening and gren line shows aseptic loosening)

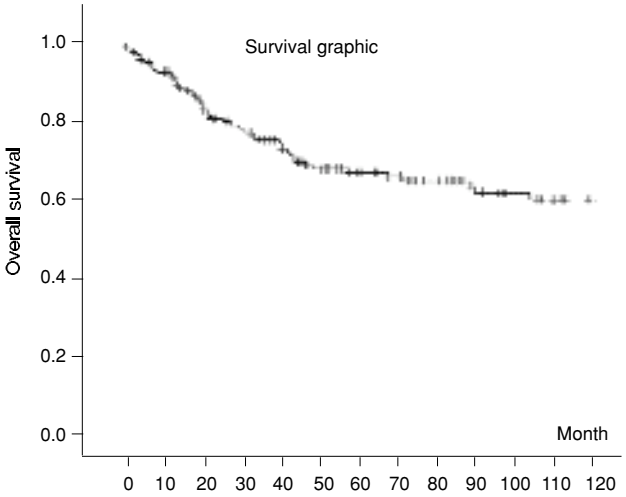

Figure 2. Overall survival graphic of all patients.

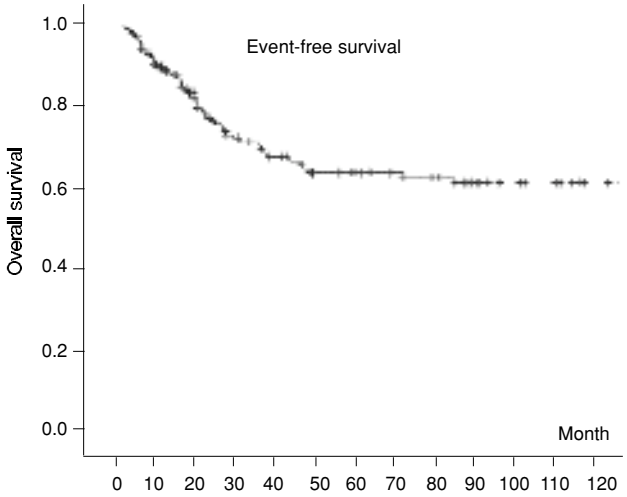

Figure 3. Event-free survival graphic

until 30. month, but septic loosening ratio rised after that. Considering these results, prosthetic infection can be estimated to occur at 30. month approximately (Table 3).

Survival results

Total survival rate was 68% for 5 yeras and 60% for 10 years. Disease-free survival rate was 50% for 5 years and 44% for 10 years (Table 3, Table 4).

Table 2. The influence of prognostic factors on survival is summarized below.The bold written pathologic fracture and metastasis at presantation are the ones that are statistically significant.(p<0.01)

			Overall survival (%)			Event-free survival (%)		
		Sayı	5 year	10 year	p	5 year	10 year	p
Total		165*	68±4	60±4		50±4	44±4	
Gender	Male	105	69±4	65±5	0.88	52±5	47±5	
	Female	60	69±4	56±4		50±7	40±7	
Age	<16	65	69±7	58±7		50±6	44±7	
	≥16	100	66±5	59±5	0.89	51±5	44±6	0.67
Loc.	Upp ext.	20	76±10	48±14	0.74	42±12		
	Low ext.	143	68±4	64±4		52±4	45±4	0.17
	Axial	2						
Pat.frc	Yes	149	69±4	65±4	0.08	55±4	48±4	
	No	16	57±13	14±12		12±8		**<0.01**
Met.at pres.	Yes	12	26±15	13±12	<0.01	12±8		
	No	153	70± 4	63±4		52±4	46±4	**<0.01**
Stage	IIA	5						
	IIB	148	71±4	67±4	0.03	55±4	51±4	
	IIIB	12	50±12	28±14		29±11		0.002
Enf.								
	Yes	139	68±4	58±5		49±4		
	No	26	67±9		0.89	54±10	54±10	0.57
Surg. type	Limb salv.	146	70±3	62±4		50±4	44±4	
	Amp.	13	56±14		0.5	43±14		0.85
	No	6						
Necrosis (%)	0-94	77	63±6	60±6		46±6	46±6	
	95-100	32	72±9	66±9	0.39	57±9	57±9	0.2

*From 180 patients that included the study 15 patients who are in low grade class, because of their histopathological diagnosis is parosteal osteosarcoma, they are not included in total survival and disease free survival analysis

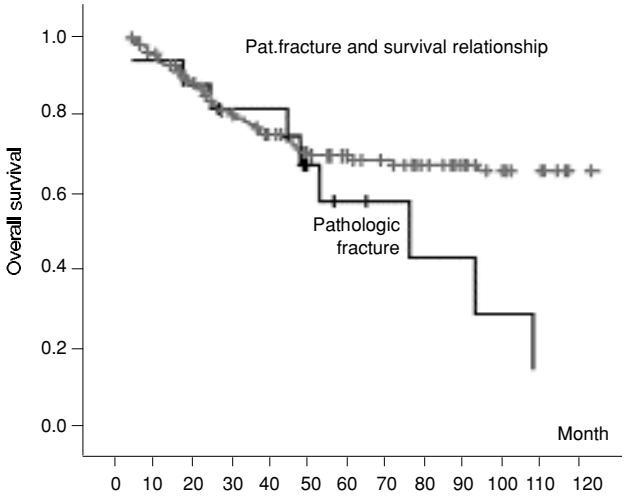

Figure 4. This graphic shows the relationship between pathologic fracture and survival

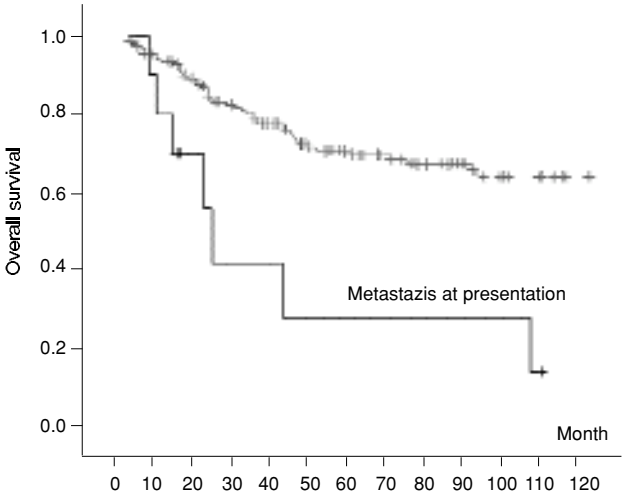

Figure 5. This graphic shows the relation between netastasis at presentation ann survival.

The influence of prognostic factors on survival is summarized below. (Table5)

Sex: For the 105 male patients, 5-year total survival rate was 69±4% and 10-year survival rate was 65±5%. For the 60 female patients the 5-year total survival rate was the same as the male patients but 10-year survival rate decreased to 56±4 (p=0.44). Disease- free survival rate for males was 52±5% for 5 years and 47±5% for 10 years; for females 5-year survival rate was 50±7% and 10-year survival rate was 40±7%. (p=0.9)

Age: Among the 65 patients below 16 years of age, 18 patients died while 34 out of 100 patients over 16 years of age died. Considering survival, no statistically significant difference was detected between two groups (p=0.89). Below 16 years of age, 5-year survival was 69±7%, 10 year survival was 58%; over 16 years of age 5-year survival was 66±5% and 10 year survival was 59±5%.

Localization: Although the difference was not statistically significant at sutvival analysis (p=0.74), the total survival for upper extremity osteosarcoma was found to be more than lower extremity osteosarcoma at long term follow-up. Total survival for upper extremity was 76±10% for 5 years and 48±14% for 10 years; disease-free survival rates for upper extremity were 42±12% for 5 years, and those for lower extremity they were 52±4% for 5 years and 45±4% for 10 years.

Tumor size: Total survival rates for tumors <10 cm. were 71±6% for 5 years and 67±8% for 10 years; for tumors >10 cm. they were 736% for 5 years and 65±8% for 10 years. There was no statistically significant difference (p=0.67).

Pathologic fracture: There was a pathologic fracture in 16 cases. For those without pathologic fracture the total survival rate was 69±4% for 5 years and 65±4% for 10 years; for patients who presented with pathologic fracture it was 57±13% for 5 years and 14±12% for 10 years (p=0.08). Considering disease-free survival, however, there is a significant difference. 5- year disease-free survival was 55±4% for patients without pathologic fracture and 12±8% for patients with pathologic fracture (p<0.01). (Table 6)

Metastasis at presentation: For the 12 patients who had metastasis at first presentation, the 5-year total survival rate was 26±15% and 10-tear total survival rate was 13±12% (p<0.01). Disease-free survival was found to be 12±8% for 5 years (p=0.01). (Table 7)

The statistical analysis of the groups with stage IIA, IIB, IIIA and IIIB osteosarcoma according to Enneking staging system was not possible because 148 patients were stage IIB and the number of patients belonging to other groups was not enough for the analysis to be carried out.

Type of surgery: Total survival rate for patients who had limb-salvage surgery was 70±3% for 5 years and 62±4% for 10 years; and for patients who had amputation it was 56±14% (p=0.5). 5-year dis-

ease-free survival rate was 50±4%, 10-year disease free survival rate was 44±4%; for amputation group 5-year disease free survival was 43±14% (p=0.85).

Deviation from chemotherapy: 30 out of 165 patients were found to have deviated from the chemotherapy program. 8 out of 30 patients died. For patients without deviation, 5-year total survival rate was 69±4% and 10-year total survival rate was 60±5%; for those with deviation 5-year total survival rate was found to be 62±10%. There was no statistically significant difference (p=0.8).

5-year total survival rate for 10 patients with high-grade osteosarcoma who received preoperative radiotherapy was found to be 50±15%; but there was no reliable statistical evaluation because of the small size of the group.

Discussion

Treatment of osteosarcoma is standardized globally. However, disease free survival rates of 55-65% which were achieved 10 years ago have not been improveddespite best effort.[3,4,5] The most extensive study in this area is the series of 1702 patients of th Germany-Austria-Switzerland study group; in this study the 10 year total survival rate is found to be %59.8 and the 10 yera disease free survival rate is found to be 48.9%.[3] The study of Rizzoli Orthopedic Institute, which evaluated patients with no metastasis at presentation, has given the total survival rate as 70% and disease free survival rate as 59% for 10 years.[4] The results we achieved with our more heterogenous study group are close to these rates (10-year total survival rate 60%, disease-free surviva 44%).[3,4,5] Systemic metastases are the most imported cause of death in osteosarcoma. In our study, metastasis at presentation has significantly diminished total and disease-free survival rates. As shown in previous studies conducted at various centers, metastasis at presentation significantly aggravates prognosis.[3,5,6] For this reason studies for developing neoadjuvant chemotherapy usually include patients without metastasis.[4,7,8]

Another evidence that patients present to the hospital late after the first symptom is the great number of patients presenting with pathologic fracture. In our study, 16 patients, constituting 10% of patients with high grade osteosarcoma, had significantly lower survival rates. The unfavorable effect of pathologic fracture on prognosis was reported before.[9] The same study showed that limb salvage surgary didn't aggravate the prognosis any further.[9] In our study, 13 patients out of 16 received limb salvage surgery.

Tumor size is another factor which is reported to affect prognosis of patients with osteosarcoma unfavorably.[3,6] In our series, survival rates of tumors smaller and bigger than the median size of 10 cm. were not significantly different. In other studies which quantitatively evaluated tumor size, this factor was found not to affect prognosis.[4,8] However, in an extensive study which evaluated tumor size by the ratio of the tumor to the involved bone showed unfavorable prognostic effect.[3]

The treatment and prognosis of low grade superficial osteosarcoma, which is not included in the survival analysis in our study, is different from classic osteosarcoma. Surgical resection is rcommended as the only treatment and chemotherapy is not required.[10, 11] In our series, all such patients have been treated according to this approach. Only one patient from this group had recurrence of the tumor which had transformed to high grade metastatic osteosarcoma, and died.

Among the controversial prognostic factors, age, sex, and tumor localization didn't influence survival in our study. In an study, presentation at an age younger than 40 years and tumor localized at the upper extremity have been shown to indicate better prognosis.[3]

The best method indicating the efficacy of chemotherapy is the necrosis ratio at the resected tumor. In our series, necrosis ratios varied widely. In statistical analysis, necrosis ratio was found not to have a significant effect on survival.Although necrosis ratio is shown to affect prognosis in many studies,[3,5,6] there are also ather studies reporting that this factor doesn't influence the results.[4,8]

Some patients deviated from standard three sessions of chemotherapy because of problems with social security system and providing the prosthesis. In patients who received four or five sessions of neoadjuvant chemotherapy, the survival rate wasn't shown to significantly differ from those patients who received standard therapy.

Surgical site infection is shown to have a good prognostic effect in dogs with osteosarcoma.[12] No such data is present for man. In our series, total survival rates of patients with infection was not different from others. However, prosthesis survival in these patients is shorter when compared with patients without infection.

The weaknesses of our study are the limited number of cases despite our best effort, insufficiency while collecting data and thus acquiring unhealthy results at statistical analysis. The strength of our study is that this analysis is performed for the first time at our national orthopedic literature and is leading the way to other studies.

In conclusion, osteosarcoma treatment is performed at our hospital with strong multidisciplinary collaboration, achieving success rates close to internationally accepted rates. Metastasis at presentation and pathologic fracture, which were found to be the most important prognostic factors in our study, are usually related with late presentation. Higher rates can be achieved by providing early presentation in osteosarcoma, like any other malignancy.

References

1. Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986;314:1600-6.
2. Winkler K, Beron G, Kotz R, Salzer-Kuntschik M, Beck J, Beck W, et al. Neoadjuvant chemotherapy for osteogenic sarcoma: results of a Cooperative German/Austrian study. J Clin Oncol 1984;2:617-24.
3. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, 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;20:776-90.
4. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli /osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000;18:4016-27.
5. Meyers PA, Gorlick R, Heller G, Casper E, Lane J, Huvos AG, et al. Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol. J Clin Oncol 1998;16:2452-8.
6. Petrilli AS, de Camargo B, Filho VO, Bruniera P, Brunetto AL, Jesus-Garcia R, et al. Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: prognostic factors and impact on survival. J Clin Oncol 2006;24: 1161-8.
7. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin Orthop Relat Res 1993;(286): 241-6.
8. Bacci G, Ferrari S, Mercuri M, Longhi A, Capanna R, Tienghi A, et al. Neoadjuvant chemotherapy for extremity osteosarcoma-preliminary results of the Rizzoli's 4th study. Acta Oncol 1998;37:41-8.
9. Wilkins RM, Cullen JW, Odom L, Jamroz BA, Cullen PM, Fink K, et al. Superior survival in treatment of primary nonmetastatic pediatric osteosarcoma of the extremity. Ann Surg Oncol 2003;10:498-507.
10. Scully SP, Ghert MA, Zurakowski D, Thompson RC, Gebhardt MC. Pathologic fracture in osteosarcoma: prognostic importance and treatment implications. J Bone Joint Surg [Am] 2002;84:49-57.
11. Kaste SC, Fuller CE, Saharia A, Neel MD, Rao BN, Daw NC. Pediatric surface osteosarcoma: clinical, pathologic, and radiologic features. Pediatr Blood Cancer 2006;47: 152-62.
12. Okada K, Frassica FJ, Sim FH, Beabout JW, Bond JR, Unni KK. Parosteal osteosarcoma. A clinicopathological study. J Bone Joint Surg [Am] 1994;76:366-78.
13. Lascelles BD, Dernell WS, Correa MT, Lafferty M, Devitt CM, Kuntz CA, et al. Improved survival associated with postoperative wound infection in dogs treated with limb-salvage surgery for osteosarcoma. Ann Surg Oncol 2005;12: 1073-83.