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Prognostic Value of the Doubling Time of Serum C-reactive Protein and Alkaline Phosphatase Levels in Primary Bone and Soft Tissue Tumors

Kazuo Yudoh,[1,3] Hisao Matsui,[1] Masahiko Kamanori,[1] Kazuo Ohmori,[1] Taketosi Yasuda,[1] Haruo Tsuji[1] and Shin-ichiro Tatezaki[2]

[1]*Department of Orthopaedic Surgery, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01 and* [2]*Department of Orthopaedic Surgery, Chiba Cancer Center, 666-2 Nitona-cho, Chuo-ku, Chiba 260*

We investigated the clinical relevance of doubling time (DT) of serum laboratory data obtained in routine clinical examination of patients with primary bone and soft tissue tumors, in comparison with major clinical and pathological parameters (age at presentation, sex, tumor size, location, clinical stage and histologic grade) by uni- and multivariate analyses. In 64 patients with primary bone and soft tissue tumors (primary bone tumors: 39, primary soft tissue tumors: 25) and 68 cancer patients, the pretreatment DT values of serum C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), calcium (Ca), phosphate (P) levels were measured, as well as the erythrocyte sedimentation rate (ESR: mm/60 min); these values were then compared with overall survival, local recurrence-free survival and metastasis-free survival. Only DT of CRP and ALP (CRP-DT, ALP-DT) were found to be correlated with disease outcome in patients with primary bone and soft tissue tumors. In cancer patients, only CRP-DT showed a relation with clinical stage and histologic grade, but the ALP-DT in patients with bone metastasis was significantly shorter than that in patients with metastases at other sites or in those with no metastasis. Among all tumor patients, those with bone metastasis showed the shortest ALP-DT compared with those with lung, liver and brain metastasis. Univariate analysis showed that shorter CRP-DT and ALP-DT are associated with poor overall survival, and the development of local recurrence and metastasis. These findings suggest that pretreatment CRP- and ALP-DT could be additional prognostic parameters for disease outcome in patients with primary malignant bone and soft tissue tumors. However, in multivariate analysis, only ALP-DT, but not CRP-DT, was an independent prognostic parameter for these disease outcomes.

Key words: Alkaline phosphatase — C-reactive protein — Doubling time — Bone tumor — Soft tissue tumor

Clinical evidence of local recurrence and metastasis is an important factor in the evaluation of the prognosis of patients with malignant tumors. Estimation of the prognosis based on the tumor growth rate or tumor volume doubling time (DT) has been reported in several cancers.[1,2] The growth rate of the tumor, which reflects the degree of malignancy, is closely related to tumor recurrence, metastases and survival.[1,3] It has been reported that patients with a shorter DT have a poor prognosis in several types of cancer.[2,4,5] Tumor growth rate has been investigated using serum tumor markers. The serum level of tumor markers increases exponentially with the tumor volume and with the advance of metastasis formation, and the increase is closely related to the tumor growth rate. The prognosis and survival rate in cancer patients with a shorter DT of serum tumor marker level were found to be significantly worse than those in patients with a longer DT.[2,5–7] DT values of serum tumor markers could thus be useful for the estimation of prognosis.

In primary bone and soft tissue sarcomas, clinical stage and histologic grade have been reported to be correlated with prognosis, and to define the optimal treatment for a given patient.[8,9] It is well known that high levels of serum alkaline phosphatase (ALP) are associated with a worse prognosis in patients with osteosarcoma.[10–12] However, in the case of primary bone and soft tissue tumors except osteosarcoma,[13–15] though some new diagnostic approaches have been reported, specific tumor markers for the estimation of prognosis have not been identified. In renal cell carcinoma, some inflammatory acute phase proteins have been proposed to predict prognosis.[16–18] Some acute phase reactants and enzymes determined routinely in clinical in examination may therefore have prognostic significance in primary malignant bone and soft tissue tumors.

The aim of this study was to evaluate whether DT values of common laboratory data, measured in routine clinical examination, are correlated with prognosis in patients with primary bone and soft tissue tumors. Therefore, we examined the pretreatment DT of serum levels of C-reactive protein (CRP), ALP, lactate dehydrogenase (LDH), calcium (Ca) and phosphate (P) levels and the erythrocyte sedimentation rate (ESR: mm/60 min) in patients with primary bone and soft tissue tumors and

[3] To whom correspondence should be addressed.

investigated the relation between pretreatment DT values of these serum parameters and disease outcome. We compared these parameters with several clinicopathologic parameters by performing uni- and multivariate analyses.

MATERIALS AND METHODS

Patients The subjects consisted of patients who underwent follow-up care at the Toyama Medical and Pharmaceutical University Hospital and Chiba Cancer Center for verified primary bone and soft tissue tumors between 1982 and 1989. All patients who met the following criteria were eligible for analysis: (1) newly diagnosed primary tumor; (2) histologically classified; (3) radically resectable; (4) no other disease that would influence serum laboratory data. Patients with apparent hepatobiliary disorders, such as liver cirrhosis or hepatitis were excluded. Sixty-four patients met the study criteria; 39 patients with primary malignant bone tumors, and 25 patients with primary malignant soft tissue tumors. Included were 36 men and 28 women with an average age of 36.6±14.2 years (mean±standard deviation (SD): ranged from 10 to 76 years) at diagnosis. The observation periods ranged from 13 to 115 months (mean±SD, 68±9 months). Surgery with curative intent was performed in all cases. Surgical procedures were marginal resection for 3 (0.46%), wide marginal resection for 50 (78.1%), curative wide marginal for 4 (6.3%), amputation for 6 (9.4%) and unknown for 2 (3.1%). Surgical treatment was preceded by radiotherapy for 11 patients, by chemotherapy for 40 patients, and by radiotherapy and chemotherapy for 4 patients. Surgery was followed by radiotherapy for 12 patients, by chemotherapy for 20 patients, and by radiotherapy and chemotherapy for 6 patients. For comparison with patients with primary bone and soft tissue tumors, we also investigated 68 age- and sex-matched cancer patients including 40 patients

Table I. Characteristics of Tumor Patients

Type	Number of patients	Characteristics			
		Histological grade Malignancy Low/High	Size <5 cm/ >5 cm	Stage I+II/III+IV	Site of primary lesion or metastases
Primary bone tumor					
Osteosarcoma	18	1/17	10/8	9/9	primary: extremity: 18 metastasis: 6 lung, 3 brain
Chondrosarcoma	15	5/10	6/9	8/7	primary: extremity: 15 metastasis: 5 lung, 2 liver
Ewing's sarcoma	4	0/4	2/2	2/2	primary: extremity: 4
Malignant giant cell tumor	2	1/1	1/1	1/1	primary: trunk: 1, extremity: 1 metastasis: 1 brain, 2 liver
Primary soft tissue tumor					
Leiomyosarcoma	8	3/5	4/4	5/3	primary: extremity: 8 metastasis: 4 lung, 3 bone
Synovial sarcoma	8	0/8	3/5	4/4	primary: extremity: 8 metastasis: 3 lung, 2 bone
Liposarcoma	6	2/4	3/3	3/3	primary: extremity: 4, trunk: 2
MFH[a)]	3	1/2	2/1	1/2	primary: trunk: 1, extremity: 2 metastasis; 1 brain, 2 lung
Cancer					
with bone metastasis					metastasis: sites other than bone
Breast cancer	12	6/6	6/6	8/4	4 lung, 2 brain
Prostatic cancer	9	5/4	7/2	4/5	6 lung
Gastric cancer	8	4/4	6/2	4/4	4 liver, 2 lung
Lung cancer	6	3/3	4/2	3/3	2 brain, 1 liver
Colorectal cancer	3	2/1	2/1	1/2	2 lung
Ovarian cancer	2	1/1	1/1	1/1	2 lung
without bone metastasis					
Breast cancer	8	4/4	5/3	4/4	2 lung, 2 brain
Prostatic cancer	8	3/5	6/2	5/3	3 lung, 3 liver
Gastric cancer	6	2/4	4/2	3/3	2 lung, 1 liver
Lung cancer	6	3/3	5/1	2/4	1 lung

a) MFH, malignant fibrous histiocytoma.

with bone metastasis. All tumors were histologically confirmed. The histologic grade and clinical stage of primary bone and soft tissue tumors were documented based on the criteria of the TNMG system of the American Joint Committee on Cancer (AJCC).[19] Regarding cancer patients, tumor grading and staging were performed using the World Health Organization (WHO) histologic classification and TNM classification according to the AJCC in cooperation with the International Union Against Cancer.[20, 21] All tumors were graded as high or low malignancy grade using the respective histological classification. The characteristics of tumor patients are summarized in Table I.

Doubling times of serum CRP, ALP, CPK, LDH, Ca, P levels and ESR Serum analyses were performed as a part of routine clinical examination before treatment. An autoanalyzer (Hitachi 7250, Hitachi Medico, Tokyo) was used for measurements of CRP, ALP, CPK, serum Ca, P and LDH. ESR was obtained by Westergren's method. Three or more serum samples (average: 6, range: 3–10) were taken at least 2 weeks apart. The median time period from initial sampling until the final sampling was 28 days (range 14–48 days). No specific treatment for tumors was given between the initial and final pretreatment serum parameter determination. If a biopsy was performed, serum samples obtained within 30 days after the biopsy were not included. After at least three serum level determinations, data were plotted on a semilogarithmic graph; a linear increase was confirmed, the regression line ($Y=aX+b$) was obtained, and DT of each serum parameter was calculated using the following formula[7]:

$$\text{Doubling time} = \frac{\log 2}{a} \text{ (days)}$$

The relationship between pretreatment DT of serum parameters and clinical factors, and survival length was examined. The survival length was defined as the number of days of survival after the first detection of the tumor. Patients who died from diseases other than tumor were excluded from this study.

Statistical analysis Results were expressed as mean$\pm$SD. Variances were analyzed by use of the F test. Student's t test (equal variance groups) and the Wilcoxon U test (unequal variance group) were used for statistical comparisons between groups. A P value of less than 0.05 was considered to indicate a significant difference. Diagnosis was considered as the time of origin. For survival curves, we considered as an event all deaths, whatever their cause. For the local recurrence-free interval, we considered strictly local recurrence as an event. When patients died without local recurrence, they were considered as censored data by the time of their death. For metastasis-free interval, we considered the first metastasis as an event. When patients died without any metastasis, they were considered censored data by the time of their death. Overall observed survival functions and probabilities were estimated using the Kaplan-Meier method. The log rank test was used to detect differences between survival curves for stratified variables. Uni- and multivariate analyses were performed using Cox's proportional hazard model. Univariate analysis resulted in identification of DT values of serum parameters which had an association with overall survival, local recurrence and metastasis of the patients. For the multivariate analysis, these DT values were separately adjusted to the clinicopathologic parameters to determine the independent prognostic value of all the parameters.

RESULTS

In all tumor patient groups, exponential increases of serum parameters, resulting in a linear relationship between the logarithmic serum level and time, could be observed prior to treatment, and pretreatment DT values could be calculated. However, pretreatment DT values of serum CPK, Ca, P, LDH and ESR were not associated with any specific clinical findings. There were positive correlations between pretreatment DT values of serum CRP and ALP levels and several prognostic factors.

In both primary bone and soft tissue tumors, pretreatment CRP-DT and ALP-DT values showed the same response pattern relative to clinical stage and histologic grade as shown in Table II. A significant decrease of both CRP-DT and ALP-DT values corresponding to faster increase in CRP and ALP was observed in going from stage I–II to stage III, and to stage IV disease. There was a significant correlation between the histologic grades and CRP- and ALP-DT, with lower DT values at high grade, as shown in Table II.

Table III shows the CRP- and ALP-DT values in relation to clinical stage and histologic grade in cancer patients. A significant decrease of CRP-DT values was observed with advancing clinical stage and histologic grade. No significant difference in CRP-DT was found between patients with bone metastasis and those with metastasis other than bone. Regarding ALP-DT values, there were significant differences between stage IV with bone metastasis, and stage I–II, and stage III disease, but no significant difference was observed between stage IV without bone metastasis, and stage I–II, and stage III, or between stage I–II and stage III disease (Table III). Higher histologic grades were significantly correlated with lower CRP- and ALP-DT (Table III).

In both primary bone and soft tissue tumor patients and cancer patients, those with bone metastasis showed the shortest ALP-DT compared with those with lung, liver and brain metastasis, but no significant difference of CRP-DT values was found depending on the region of metastasis (Table IV).

Table II. Levels of CRP- and ALP-doubling Time in Relation to Clinical Stage and Histologic Grade in Patients with Primary Bone and Soft Tissue Tumors

Variable	Number of patients	Doubling time (days, mean±SD)	
		CRP	ALP
Primary bone tumor			
Stage			
I+II	20	163.5±38.5	199.5±30.5
III	10	98.8±20.5	138.5±32.5
IV	9	61.9±13.5	98.4±18.5
Grade			
low+moderate	17	141.5±28.5	155.4±26.5
high	22	92.8±22.8	111.5±30.5
Primary soft tissue tumor			
Stage			
I+II	11	187.6±34.5	205.5±28.5
III	6	103.5±18.5	144.2±36.5
IV	8	67.9±20.5	101.4±22.5
Grade			
low+moderate	12	140.5±30.5	165.5±26.5
high	13	95.5±30.5	118.5±35.6

CRP, C-reactive protein; ALP, alkaline phosphatase.
* $P<0.05$; ** $P<0.01$; SD, standard deviation.

Table III. Levels of CRP- and ALP-doubling Time in Relation to Clinical Stage and Histologic Grade in Cancer Patients

Variable	Number of patients	Doubling time (days, mean ± SD)	
		CRP	ALP
Stage			
I+II	8	188.5±31.5	205.5±32.8
III	7	102.5±31.5	195.5±27.4
IV bone metastasis	40	66.2±23.5	98.4±18.5
IV metastasis other than bone	13	70.3±25.5	189.8±42.5[a]
Grade			
1+2	26	144.5±42.5	202.5±22.5
3	21	98.6±27.5	146.6±32.6
4	22	68.8±28.5	102.5±31.5

CRP, C-reactive protein; ALP, alkaline phosphatase; SD, standard deviation; NS, not significant.
a) NS compared with stage III disease. * $P<0.05$; ** $P<0.01$.

The mean CRP-DT values in patients with the development of local recurrence and metastasis were 69.6± 22.3 and 68.6±14.5 days in primary bone tumor patients, and 66.8±19.5 and 70.3±23.8 days in primary soft tissue tumor patients, respectively. The mean ALP-DT in patients with the development of local recurrence and metastasis were 96.8±28.6 and 98.5±31.8 days in primary bone tumor patients, and 94.6±28.5 and 95.7± 31.6 days in primary soft tissue tumor patients, respectively. We classified these DT values into two subgroups: the short doubling time group, in which doubling times were shorter than 70 days for CRP and shorter than 100 days for ALP, and the long doubling time group, in which doubling times were 70 days or more for CRP, and 100 days or more for ALP. Table V show the univariate analysis of prognostic parameters for overall, local recurrence-free and metastasis-free survival. The tumor size, clinical stage, histologic grade, CRP-DT and ALP-DT values had a significant influence on overall mortality and metastasis ($P<0.01$). Clinical stage, histologic grade, CRP-DT and ALP-DT significantly affected local recurrence-free survival ($P<0.01$), and there was a trend ($P=0.05$) for two variables: tumor size and localization (Table V). The prognosis of 64 patients with primary bone and soft tissue tumors was studied. As shown in Fig. 1, A and B, the prognosis of the short CRP- and

ALP-doubling time group was significantly worse than that of the long CRP- and ALP-doubling time group. The effects of variables presumably associated with prognosis were then studied by multivariate analysis. Tumor size, ALP-DT and histologic grade were significantly correlated with poorer overall, local recurrence-free and metastasis-free survival, while CRP-DT, age, sex, tumor localization and clinical stage showed no significant correlation. Among these parameters, tumor size was the most important factor for predicting overall, local recurrence-free and metastasis-free survival, followed by ALP-DT and histologic grade (Table VI).

Table IV. CRP- and ALP-doubling Time and Region of Metastasis in All Patients

Region of metastasis	Doubling time (days, mean±SD)	
	CRP	ALP
Primary bone and soft tissue tumor		
Lung ($n=18$)	70.2±23.4	111.6±28.7
Liver ($n=4$)	67.7±21.7	96.7±23.8
Brain ($n=7$)	65.8±18.7	103.5±27.8
Bone ($n=5$)	69.8±22.4	61.4±18.4
Cancer		
Lung ($n=24$)	66.5±22.5	105.6±31.4
Liver ($n=9$)	70.6±18.5	92.8±36.5
Brain ($n=6$)	69.8±26.5	116.5±34.7
Bone ($n=40$)	74.5±24.4	56.5±24.4

CRP, C-reactive protein; ALP, alkaline phosphatase.
* $P<0.05$.

DISCUSSION

The natural history of malignant bone and soft tissue tumors is complicated, making it difficult to predict the prognosis. It is necessary to determine prognostic parameters to enable selection of a suitable therapeutic program and to allow evaluation of the efficacy of the therapy used. Clinical stage, histologic grade and clinical factors such as tumor size and depth have been examined as predictors of prognosis in bone and soft tissue sarcomas.[2, 5, 6, 22, 23] Tumor growth potential may be an important factor for predicting prognosis. It is known that tumor nodules grow exponentially for considerable periods. Tumor volume DT was shown to be an important

Table V. Univariate Analysis of Clinicopathologic Parameters and CRP- and ALP-doubling Times in Relation to Overall, Local Recurrence- and Metastasis-Free Survival in Patients with Malignant Bone and Soft Tissue Tumors

Parameter	Number of patients	Overall 5-year survival rate (%)	P value	Recurrence-free 5-year survival rate (%)	P value	Metastasis-free 5-year survival rate (%)	P value
Age (year)							
<50	30	68.8	0.3	61.5	0.6	68.6	0.8
≥50	34	61.5		64.7		61.5	
Sex							
Male	36	65.5	0.8	68.9	0.9	60.5	0.4
Female	28	64.3		70.8		65.5	
Tumor size							
<5 cm	28	82.5	<0.001	76.8	0.05	78.5	<0.001
≥5 cm	36	54.2		64.4		45.5	
Localization							
extremity	52	63.3	0.07	70.6	0.05	69.5	0.5
trunk	12	58.5		58.8		67.5	
Stage							
I+II	33	81.7	<0.001	76.4	0.004	82.3	<0.001
III+IV	31	51.6		59.6		51.6	
Grade							
low+moderate	16	76.0	0.0015	87.5	0.04	81.3	<0.001
high	51	41.2		70.6		45.1	
CRP-DR (days)							
<70	29	51.7	<0.001	65.2	0.001	45.8	<0.001
≥70	35	77.1		87.1		71.4	
ALP-DT (days)							
<100	34	41.2	<0.001	67.1	<0.001	47.1	0.002
≥100	30	76.4		88.4		66.6	

CRP, C-reactive protein; ALP, alkaline phosphatase; DT, doubling time.

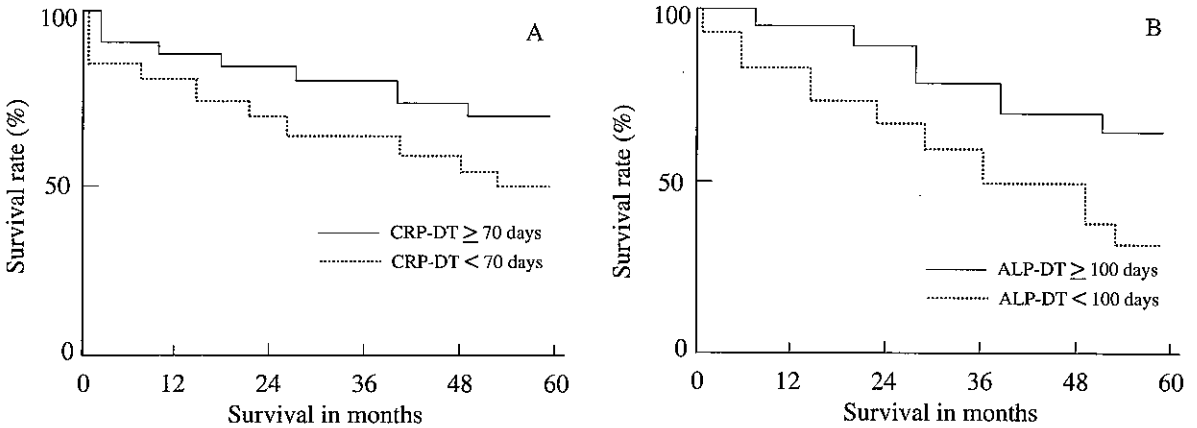

Fig. 1. A, Overall survival curves according to high and low C-reactive protein-doubling time (CRP-DT) in patients with primary bone and soft tissue tumors. B, Overall survival curves according to high and low alkaline phosphatase-doubling time (ALP-DT) in patients with primary bone and soft tissue tumors. For both CRP- and ALP-DT, the survival rate in the group with a short doubling time is significantly shorter than that in the group with a long doubling time ($P=0.003$, $P<0.001$, respectively).

Table VI. Multivariate Analysis for Overall Survival, Local Recurrence and Metastasis Rate

Parameter	Cox's hazard ratio (95% CI) and *P* value		
	Overall survival	Local recurrence	Metastasis
Age (year) (<50 vs. 50≤)	1.2 (0.7–2.3) 0.08	1.6 (0.9–3.4) 0.07	1.3 (0.7–2.6) 0.08
Sex (male vs. female)	1.1 (0.5–2.1) 0.07	0.9 (0.6–1.9) 0.06	1.2 (0.8–2.3) 0.08
Tumor size (<5 cm vs. 5 cm ≤)	0.3 (0.1–0.8) 0.01	0.5 (0.3–1.1) 0.02	0.3 (0.2–0.8) 0.01
Localization (extremity vs. trunk)	1.3 (0.7–3.4) 0.07	1.4 (0.7–2.5) 0.07	1.3 (0.6–2.9) 0.08
Stage (I+II vs. III+IV)	1.5 (0.7–2.9) 0.06	1.3 (0.8–3.8) 0.07	2.8 (0.9–4.8) 0.08
Grade (low+moderate vs. high)	0.4 (0.3–1.1) 0.03	0.5 (0.3–1.3) 0.04	0.4 (0.2–0.9) 0.04
CRP-doubling time (<70 days vs. 70 days ≤)	1.8 (1.0–7.0) 0.05	2.6 (0.9–7.7) 0.08	0.5 (0.2–1.0) 0.05
ALP-doubling time (<100 days vs. 100 days ≤)	0.4 (0.2–0.8) 0.02	0.3 (0.1–0.9) 0.03	0.5 (0.2–0.9) 0.03

CRP, C-reactive protein; ALP, alkaline phosphatase; CI, confidence interval.

determining factor for survival, and histopathological findings indicated that DT of tumor volume is related to the prognosis of patients with malignant tumors.[1, 3, 4] Furthermore, it has been reported that tumor volume DT is correlated with the DT of serum tumor marker level in the exponentially increasing phase. In patients with colon cancer or hepatocellular cancer, the DT values of carcinoembryonic antigen and alpha-fetoprotein were found to be correlated with the prognosis.[2, 5–7] The DT values of serum tumor markers might be useful in evaluating the prognosis, although the factors influencing disease outcome are very complex.

In bone and soft tissue tumors, no specific tumor marker is yet available. Some acute phase proteins such as ESR, CRP and ferritin have been proposed to be useful in predicting the prognosis in renal cell carcinoma.[16–18] It was the aim of this study to investigate whether DT values of serum parameters, measured in routine clinical examination, can be used as predictors of prognosis in bone and soft tissue tumor patients. In all cases in this study, DT values could be obtained for all serum factors examined, CRP, ALP, CPK, serum Ca, P and LDH. However, the DT values of serum CPK, Ca, P, and LDH were not associated with any clinical findings. Only CRP- and ALP-DT were associated with disease outcome in the tumor patients studied.

In patients with primary bone and soft tissue tumors, both CRP-DT and ALP-DT were correlated with clinical stage and histologic grade, with lower values in advanced stages and higher grades. When we investigated the relation between these DT values and disease outcome in cancer patients, we also found that there was a significant correlation between CRP-DT values, and clinical stage, and histologic grade. CRP-DT value may have potential

as a prognostic parameter for disease outcome in cancer patients. Regarding ALP-DT in cancer patients, although no significant correlation was observed between ALP-DT value and clinical stage, ALP-DT value in patients with stage IV disease with bone metastasis was the shortest. Furthermore, patients with bone metastasis showed the shortest ALP-DT compared with those with lung, liver and brain metastasis, whereas CRP-DT value showed no correlation with the region of the metastasis in both primary bone and soft tissue tumor and cancer patients. Thus, pretreatment ALP-DT value may be useful in identifying the location of metastasis.

In humans, elevated serum CRP and ALP levels are associated with several conditions. CRP is an acute phase plasma protein and its serum level is extensively used in routine clinical practice to monitor the acute phase response and tissue damage in trauma, inflammation, infection and tumor.[18, 23–25] Many researchers have concluded that the elevated serum ALP activity originates in the liver or bone, or both, based on observations of ALP isoenzymes.[26, 27] The reason why exponential increases of serum CRP and ALP were observed in the current study is not known. Further investigation of the biochemical regulation of CRP and ALP release and clearance is necessary.

It is well known that patients with osteosarcoma have high serum ALP levels and the increase of this enzyme is related to the osteoblastic activity of osteosarcoma cells.[10–12, 28] Eilber and Canlikins have reported that no relation existed in osteosarcoma between pretreatment value of serum ALP and prognosis.[28] Although there is a consensus that the increase in serum ALP values is correlated with prognosis in osteosarcoma, little is known concerning the relation of serum ALP to overall survival. We confirmed here that serum ALP level is significantly associated with local recurrence and metastasis in primary bone and soft tissue tumors (data not shown). However, there was no correlation between serum ALP level and overall survival. Regarding serum CRP level, although it tended to be associated with disease outcome, no significant correlation was observed (data not shown).

In the present study, we evaluated the clinical relevance of pretreatment CRP-DT and ALP-DT in patients with primary bone and soft tissue tumors, in comparison with major clinicohistologic parameters by uni- and multivariate analyses. Univariate analysis revealed that a shorter CRP-DT and ALP-DT were significantly correlated with a poor overall survival, and the development of local recurrence and metastasis in primary bone and soft tissue tumors. However, multivariate analysis showed that ALP-DT, but not CRP-DT, was an independent prognostic factor for overall survival, local recurrence, and metastasis. Recently, it has been reported that clinical factors such as clinical stage, histologic grade, tumor size and tumor depth are independent prognostic factors for overall survival, local recurrence or metastasis in bone and soft tissue sarcoma.[22, 23] However, laboratory data or serum tumor markers were not considered as prognostic parameters. This study, like others, confirms that clinical stage, histologic grade and tumor size are significantly correlated with prognosis in primary bone and soft tissue tumors. Furthermore, we have shown that pretreatment ALP-DT is an independent prognostic factor for primary malignant bone and soft tissue tumors, for which no specific tumor markers for the estimation of prognosis have previously been available.

In conclusion, multivariate analysis indicates that pretreatment ALP-DT, but not CRP-DT, is an independent prognostic parameter for overall survival, local recurrence and metastasis in primary malignant bone and soft tissue tumors.

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