CLINICS

CLINICAL SCIENCE

Serum alkaline phosphatase predicts survival outcomes in patients with skeletal metastatic nasopharyngeal carcinoma

Ying Jin, Mei-Qin Yuan, Jun-Qing Chen, Yi-Ping Zhang*

Zhejiang Cancer Hospital, Department of Medical Oncology, Hangzhou, China.

OBJECTIVE: Bone metastasis is frequently associated with nasopharyngeal carcinoma. The diagnosis and follow-up of bone metastatic patients usually relies on skeletal X-ray and bone scintigraphy, which are time-consuming and costly. This study aimed to evaluate whether serum alkaline phosphatase offers clinical value in predicting the clinical response and survival outcome for skeletal metastatic nasopharyngeal carcinoma.

METHODS: Serum alkaline phosphatase was measured at baseline and then before each cycle of treatment in 416 nasopharyngeal carcinoma patients with bone metastasis. The correlations between the pre-treatment and post-treatment alkaline phosphatase levels and the treatment efficacy were analyzed using the chi-square test. Survival was analyzed using the Kaplan–Meier method and then compared using the log-rank test.

RESULTS: Patients with elevated pre-treatment alkaline phosphatase (>110 IU/L) had significantly worse progression-free survival ($P<0.001$) and overall survival ($P<0.001$) than those with a normal level of this marker (≤ 110 IU/L). Patients with elevated post-treatment alkaline phosphatase had worse progression-free survival ($P<0.001$) and overall survival ($P<0.001$) compared with those with a normal level. Patients with normal pre-treatment and post-treatment alkaline phosphatase showed the most favorable prognosis. The Cox multivariate analysis revealed that only the pre-treatment and post-treatment alkaline phosphatase levels were independent prognostic factors for progression-free survival ($HR=1.656$, $P<0.001$; $HR=2.226$, $P<0.001$) and for overall survival ($HR=1.794$, $P<0.001$; $HR=2.657$, $P<0.001$).

CONCLUSIONS: Serum alkaline phosphatase appears to be a significant independent prognostic index in patients with skeletal metastatic nasopharyngeal carcinoma, which could reflect the short-term treatment response of palliative chemotherapy and the long-term survival outcomes.

KEYWORDS: Nasopharyngeal carcinoma; Palliative chemotherapy; Serum alkaline phosphatase; Skeletal metastasis.

Jin Y, Yuan MQ, Chen JQ, Zhang YP. Serum alkaline phosphatase predicts survival outcomes in patients with skeletal metastatic nasopharyngeal carcinoma. Clinics. 2015;70(4):264-272

Received for publication on August 20, 2014; **First review completed on** September 19, 2014; **Accepted for publication on** January 27, 2015

E-mail: zhang_yp999@sina.cn

*Corresponding author

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a leading form of cancer in several well-defined populations, such as the natives of southern China, Southeast Asia, the Arctic, the Middle East, and North Africa (1,2). With advances in radiotherapy techniques, the regional control rate of NPC has increased remarkably (3). In recent years, the combination of targeted medicine with intensity-modulated radiotherapy has also brought promising results for locoregionally advanced NPC (4,5). The majority of deaths occur not because of the tumor in the primary site but rather because of distant metastasis. Different reports have shown that approximately 17% to 54% of patients with NPC failed treatments due to distant metastases and that approximately one-third of patients presented disseminated disease at the primary diagnosis (6). Bone is one of the preferred target sites for cancer metastasis. NPC has a propensity to spread to bone, and most of the patients who present with bone metastasis have an increased risk of skeletal-related events (SREs), including receiving radiotherapy for bone pain, pathological fracture, spinal cord compression and hypercalcemia, all of which result in reduced quality of life and an increased risk of death (7).

Once bony metastasis has been diagnosed, the current standard treatment modality for these patients essentially

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2015(04)08

involves cisplatin-based palliative chemotherapy with or without local radiation therapy according to the symptoms of bone pain (8). Determining the early response to treatment is essential to the subsequent management in disseminated NPC patients. In the past, the tumor evaluation criteria developed by the WHO defined bone tumor response by the change of lesion size in skeletal scintigraphy and plain radiography. However, because the change in osteodestructive lesion size is always slow, this method is not useful in clinical practice (9). Currently, the most scientific and widely used tumor response criteria in the clinical setting are the Response Evaluation Criteria in Solid Tumors (RECIST), but in this system, bone metastasis is classified as 'non-measurable' and a 'non-target lesion' (10). As a result, a readily available biomarker that may enhance the ability to predict the short-term treatment response and long-term survival outcome of NPC patients with bone metastasis is urgently needed.

Serum alkaline phosphatase (S-ALP) has been extensively used to screen patients for bone metastasis because it is a simple and inexpensive routine hospital test that is easily available and yields quick results. The prognostic role of S-ALP has been explored in various types of malignancies with bony metastatic disease. Both the baseline S-ALP and changes in S-ALP have been reported as prognostic factors for treatment effect and survival such as in bony metastatic prostate cancer (11), bony metastatic breast cancer (12), and clear cell chondrosarcoma of the bone (13). In our previous study (14), we showed that elevated pretreatment S-ALP was an independently negative prognosticator for disseminated NPC. However, to the best of our knowledge, there is no previous research that has explored the clinical application of S-ALP changes in patients with skeletal metastatic NPC receiving palliative chemotherapy.

The aim of this retrospective study was to investigate the prognostic value of S-ALP as a tumor marker in patients with bony metastatic NPC treated with systemic chemotherapy. Pre-treatment and post-treatment S-ALP levels were measured. The correlations of the S-ALP levels to the treatment response evaluation and survival outcome were analyzed.

Patients and methods

Inclusion criteria and enrollment. The charts of 1,380 patients with metastatic NPC admitted to Zhejiang Cancer Hospital between January 2000 and December 2011 were reviewed. The following inclusion criteria were applied: (i) patients with histological confirmation of NPC; (ii) patients with radiological confirmation of bone metastatic lesion(s); (iii) patients with a good performance status (Karnofsky Performance Scores ≥ 80); (iv) patients with the appropriate renal, cardiac and liver function to tolerate chemotherapy; (v) patients with complete pre-treatment and post-treatment S-ALP records; and (vi) patients with complete follow-up data. The following exclusion criteria were applied: (i) patients with other types of malignancy; (ii) patients aged < 18 years; and (iii) patients who were pregnant at the time of diagnosis. Finally, we were able to retrieve the data for 416 patients.

Definition. Metastasis at the time of presentation was defined as patients who presented with distant metastasis when first diagnosed with NPC. This feature was analyzed as a separate category from the patients who presented with localized disease but then developed metastases at a later date. The SREs were classified as fractures, spinal cord compression, radiation to bone, surgery on bone and hypercalcemia. Progression-free survival (PFS) was defined as the time from the first diagnosis of metastasis to disease progression (newly occurring metastatic lesion, recurrence or the expansion of the primary lesion). Overall survival (OS) was defined as the time from the first diagnosis of metastasis to the time of death. Patients whose deaths were not caused by cancer progression were excluded from the study.

S-ALP was estimated using the optimized standard method recommended by the German Society of Clinical Chemistry (15). S-ALP levels lower than 110 IU/L were considered normal because this value corresponds to the extreme range that can be found in a normal population using the method described above. S-ALP >110 IU/L was considered a sign of pathology.

Evaluation protocol. The short-term treatment efficacy in patients with measurable lesions was evaluated by measuring the response every 2 treatment cycles during treatment and then every 3 months until death. The response of the tumor to therapy was evaluated based on computed tomography (CT) or magnetic resonance imaging (MRI) scans. The short-term efficacy, based on the RECIST, was assessed as CR, PR, SD and PD; CR and PR were regarded as responses to treatment. The long-term efficacy was evaluated according to the PFS and OS.

Statistical analysis. Statistical analysis was performed using the SPSS 17.0 package. Correlations between the S-ALP levels and several variables were assessed using the product moment correlation coefficient (r). The relationship between short-term treatment efficacy and S-ALP was analyzed using the chi-square test. Survival was analyzed using the Kaplan–Meier method and then compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportion hazards model. P-values for differences between proportions were calculated using Fisher's exact test (two-tailed). Statistical significance was defined as $P < 0.05$.

RESULTS

Descriptive characteristics

These features are shown in Table 1. All patients were of Chinese ethnicity with a male predominance (85.1%). The mean age at diagnosis of metastatic NPC was 44.9 years (ranging from 18 to 70 years). Approximately one-third of the patients had distant metastasis at presentation, and 63.7% of the patients had vertebral metastases. Two hundred and thirty-one (55.5%) patients had more than one metastatic site, and more than half of the patients had visceral metastasis (lung or liver). Among the 416 patients, the incidence rate of SREs was 39.9%.

Two hundred and thirteen (50.0%) patients showed an increased pretreatment S-ALP. Sex and age, as well as metastases at the time of presentation, did not influence the pretreatment S-ALP levels. The presence of an elevated S-ALP level (>110 IU/L) was significantly correlated with the involvement of more than one metastatic site ($P = 0.001$, $r = 0.167$) and specific liver metastasis ($P < 0.001$, $r = 0.218$), as well as the presence of SREs ($P = 0.016$, $r = 0.118$). The levels

Table 1 - Increased S-ALP according to several variables in the 416 patients.

	No. of cases	Elevated S-ALP	%	r-value	*p*-value
Sex					
Male	354	171	48.3	0.024	0.632
Female	62	32	51.6		
Age					
<45 years	211	109	51.7	−0.058	0.237
≥45 years	205	94	45.9		
Metastasis at presentation					
Present	148	73	49.3	0.008	0.874
Absent	268	130	48.5		
Number of involved sites					
One	185	73	39.5	0.167	0.001
Two or more	231	130	56.3		
Liver metastasis					
Present	154	97	63.0	0.218	<0.001
Absent	262	106	40.5		
Lung metastasis					
Present	114	54	47.4	−0.018	0.721
Absent	302	149	49.3		
Vertebral metastasis					
Present	265	136	51.3	0.067	0.173
Absent	151	67	44.4		
Skeletal-related events					
Present	166	93	56.0	0.118	0.016
Absent	250	103	41.2		

of S-ALP did not correlate with the presence of lung effusion and vertebral effusion.

Treatment

An overwhelming majority (70.9%) of the patients were treated with cisplatin-based doublets. The most frequently used regimens included cisplatin (25 mg/m^2 intravenously on days 1-3 every 21 days) plus 5-fluorouracil (600 mg/m^2 intravenously on days 1-5 every 21 days) and paclitaxel (175 mg/m^2 intravenously over 3 hours on day 1 every 21 days) plus cisplatin (25 mg/m^2 intravenously on days 1-3 every 21 cycles). One hundred and one (29.1%) patients received a triple-drug combination chemotherapy. The most frequently used regimen was paclitaxel (150 mg/m^2 intravenously over 3 hours on day 1 every 21 days) plus cisplatin (25 mg/m^2 intravenously on days 1-3 every 21 cycles) plus 5-fluorouracil (500 mg/m^2 intravenously on days 1-5 every 21 days).

Correlation between S-ALP and treatment response

For the 217 patients who had measurable lesions (with lung or liver metastasis), the overall clinical response rate was 59.0% (CR in 6 patients and PR in 122 patients).

The difference between the response (CR and PR) rate of patients with normal baseline S-ALP levels (CR = 5 and PR = 55) and those with elevated baseline S-ALP levels (CR = 1 and PR = 67) was not significant ($P = 0.217$) (Figure 1A).

Among the 121 patients with elevated pre-treatment S-ALP levels, a drop in the post-treatment S-ALP to a normal level at any time during the treatment was noted in 72 (59.5%) patients. All 6 patients who achieved CR showed a normal post-treatment S-ALP. Thirty-nine of the PR and 14 of the SD patients showed a sharp drop in S-ALP from an elevated level to a normal level. The response rate was significantly higher in patients with a normal post-treatment S-ALP level (CR = 6 and PR = 94) compared with those with sustained high post-treatment S-ALP levels (CR = 0 and PR = 28) ($P < 0.001$) (Figure 1B).

Correlation between S-ALP and survival outcome

The mean PFS and OS for the total 416 patients were 8.3 (0.5-75.5) and 23.3 (2.0-106.0) months, respectively. The mean PFS and OS in patients with a normal baseline S-ALP level were significantly longer than in those with elevated S-ALP levels (the mean PFS was 10.3 vs. 6.1 months, $P < 0.001$; the mean OS was 28.8 vs. 17.6 months, $P < 0.001$) (Figure 2A and 2B). The mean PFS and OS in patients with normal post-treatment S-ALP levels were significantly longer than those with elevated S-ALP levels (the mean PFS was 9.7 vs. 4.8 months, $P < 0.001$; the mean OS was 27.5 vs. 13.4 months, $P < 0.001$) (Figure 2C and 2D).

The 416 patients were divided into four subgroups according to their pre-treatment S-ALP level and post-treatment S-ALP level: 1) elevated pre-treatment S-ALP and elevated post-treatment S-ALP (83 patients); 2) elevated pre-treatment S-ALP and normal post-treatment S-ALP (120 patients); 3) normal pre-treatment S-ALP and elevated post-treatment S-ALP (39 patients); 4) normal pre-treatment S-ALP and normal post-treatment S-ALP (174 patients). The mean PFS for these four subgroups was 4.4, 7.3, 5.7 and 11.3 months, respectively ($P < 0.001$). The mean OS was 11.5, 21.8, 17.5 and 31.4 months, respectively ($P < 0.001$) (Fig. 2E and Fig. 2F).

Prognostic factors for survival outcome

Factors that were incorporated into the analysis included patient factors (age group, gender), disease factors (metastasis at presentation, visceral involvement, vertebral involvement, number of involved sites, pre-treatment and post-treatment S-ALP levels, presence of SREs) and treatment factor (number of drugs for chemotherapy).

The Cox multivariate analysis identified that only the pre-treatment S-ALP level and post-treatment S-ALP level were independent prognostic factors for PFS (HR = 1.656, P < 0.001; HR = 2.226, P < 0.001) and for OS (HR = 1.794, P < 0.001; HR = 2.657, P < 0.001) (Tables 2 and 3).

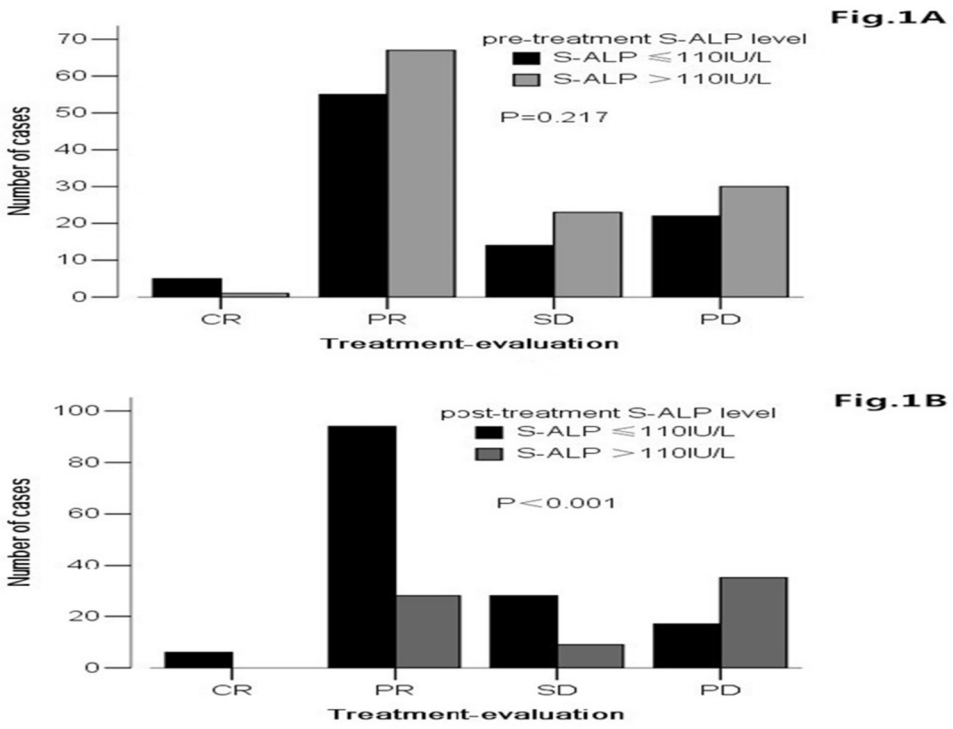

Figure 1 - Correlation between the pre-treatment (and post-treatment) S-ALP level with the treatment responses of the 217 patients who had measurable lesions. **A)** Pre-treatment S-ALP level and the treatment response are shown (chi-square test, P=0.217). **B)** Post-treatment S-ALP level and the treatment response are shown (chi-square test, $P < 0.001$).

Survival analysis for only bone metastasis

The mean PFS and OS for the 199 patients with only bony involvement were 9.9 (1.0-75.5) and 24.4 (2.0-106.0) months, respectively. The mean PFS and OS in patients with a normal baseline S-ALP level were significantly longer than those with an elevated S-ALP level (the mean PFS was 12.3 vs. 6.3 months, $P < 0.001$; the median OS was 29.3 vs. 17.5 months, $P < 0.001$) (Figure 3A and 3B). The mean PFS and OS in patients with a normal post-treatment S-ALP level were significantly longer than in those with an elevated S-ALP level (the mean PFS was 11.6 vs. 4.6 months, $P < 0.001$; the mean OS was 28.6 vs. 12.0 months, $P < 0.001$) (Figure 3C and 3D).

The 199 patients were divided into four subgroups according to the pre-treatment S-ALP level and the post-treatment S-ALP level: 1) elevated pre-treatment S-ALP and elevated post-treatment S-ALP (34 patients); 2) elevated pre-treatment S-ALP and normal post-treatment S-ALP (48 patients); 3) normal pre-treatment S-ALP and elevated post-treatment S-ALP (16 patients); 4) normal pre-treatment S-ALP and normal post-treatment S-ALP (101 patients). The mean PFS for these four subgroups was 4.0, 8.0, 6.1 and 13.3 months, respectively ($P < 0.001$). The mean OS was 10.3, 22.5, 15.7 and 31.4 months, respectively ($P < 0.001$) (Figure 3E and 3F).

DISCUSSION

Among the distant metastatic sites from NPC, the skeleton is one of the most common organs found to be involved (16). Bone metastasis is a pathological status of bone metabolism in which the normal balance between resorption of old bone and formation of new bone is destroyed (17). Following up changes in bone metabolism is crucial because it can provide information for treatment evaluation in patients with skeletal metastases. However, bone density changes occur too slowly to allow the clinician to use an acceptable imaging test to monitor the early response to treatment. X-ray has low sensitivity and can only detect lesions when the diameters of the bone metastatic sites are bigger than 1 cm. Bone scans can detect bone lesions earlier than can X-ray, but this method has low specificity and a high false-positive rate. CT is radiative, PET/CT is expensive, and MRI also suffers from limitations. It is therefore unpractical to use the above means to dynamically monitor the changes in bone metabolism.

In recent years, serum markers of bone formation and resorption processes have held great promise as a new means of obtaining the required information. Effective chemotherapy for patients with skeletal metastatic NPC likely has a favorable effect on serum biomarkers of bone turnover, but this impact is still unknown (18–20). Alkaline phosphatase (ALP) is a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids. The process of removing the phosphate group is called dephosphorylation. In humans, almost all tissues throughout the entire body contain this enzyme, but it is particularly concentrated in the bone, liver, bile duct, kidney, and placenta. Although ALP is abundant in tissue cells, blood levels of the enzyme are normally low. However, in some pathological and specific physiological situations, they release more ALP into the bloodstream. Conditions that can cause increased ALP in the serum include pregnancy, bile duct obstruction, kidney disease, hepatocellular carcinoma, and bone metastasis (11,21-24).

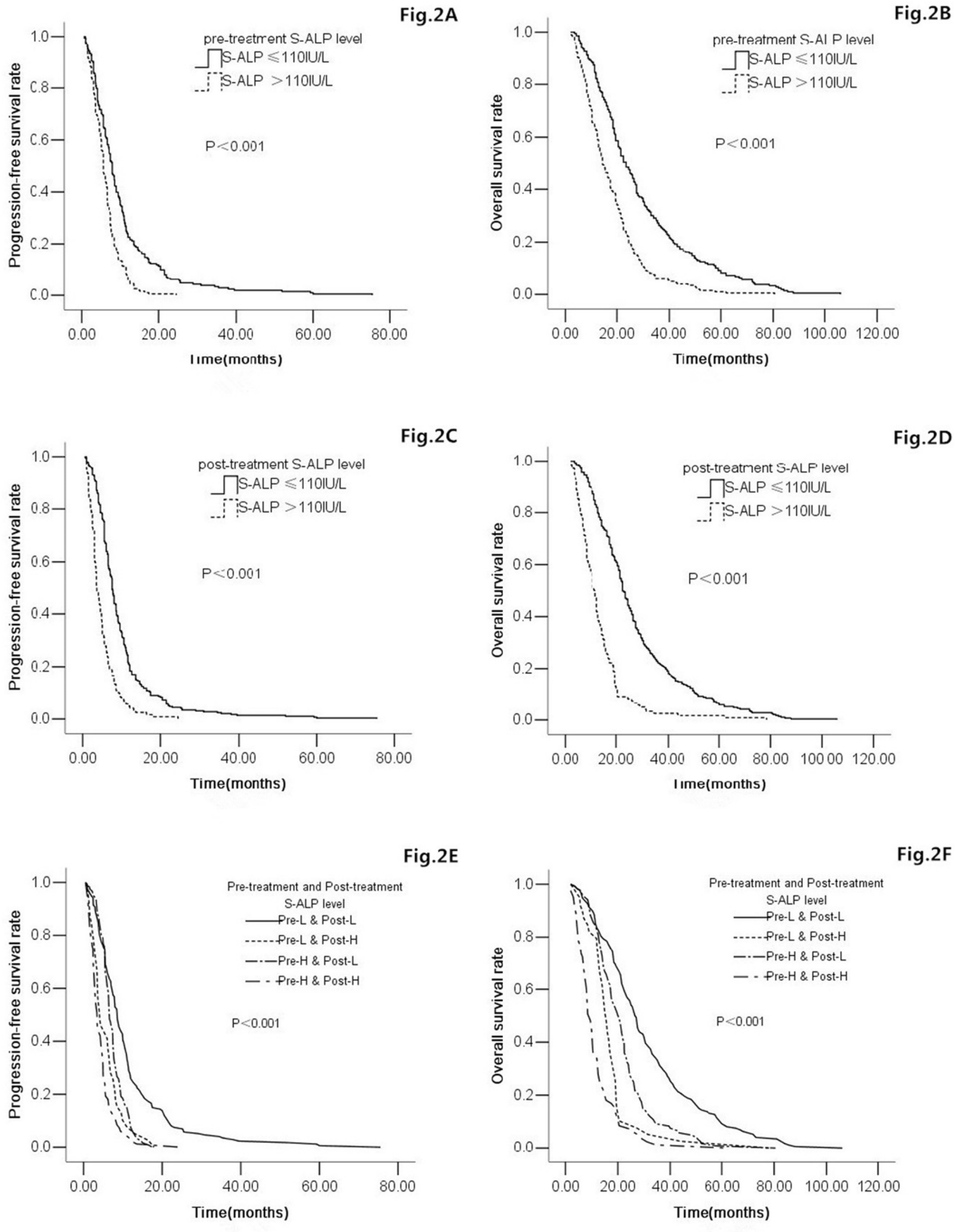

Figure 2 - Kaplan-Meier survival curves are shown for the total sample of 416 patients according to the pre-treatment (and post-treatment) S-ALP level. **A)** PFS according to the pre-treatment S-ALP ($P<0.001$). **B)** OS according to the pre-treatment S-ALP ($P<0.001$). **C)** PFS according to the post-treatment S-ALP ($P<0.001$). **D)** OS according to the post-treatment S-ALP ($P<0.001$). **E)** PFS according to the combination of pre-treatment and post-treatment S-ALP ($P<0.001$). **F)** OS according to the combination of pre-treatment and post-treatment S-ALP ($P<0.001$).

Table 2 - Univariate and multivariate analysis of progression-free survival.

Factors	Univariate analysis		Multivariate analysis	
	P-value	*HR* (95% CI)	*P*-value	*HR* (95% CI)
Sex: Male or female	0.345	0.871 (0.654-1.160)		
Age: <45 years or ≥ 45 years	0.904	0.988 (0.808-1.208)		
Metastasis at presentation: Present or absent	0.023	1.284 (1.035-1.594)		
Liver metastasis: Present or absent	0.122	1.284 (0.936-1.760)		
Lung metastasis: Present or absent	0.060	1.336 (0.987-1.808)		
Pre-treatment S-ALP level: Normal or elevated	<0.001	1.602 (1.294-1.985)	<0.001	1.656 (1.345-2.040)
Post-treatment S-ALP level: Normal or elevated	<0.001	2.254 (1.784-2.848)	<0.001	2.226 (1.780-2.783)
Number of drugs for chemotherapy:Two or three	0.047	0.802 (0.645-0.997)		
Number of involved sites: 1 or ≥ 1	0.704	0.928 (0.629-1.367)		
Vertebral metastasis: Present or absent	0.984	1.002 (0.816-1.231)		
Skeletal-related events: Present or absent	0.899	0.980 (0.723-1.329)		

HR: hazard ratio; 95% CI: 95% confidence interval.

Table 3 - Univariate and multivariate analysis of overall survival.

Factors	Univariate analysis		Multivariate analysis	
	P-value	*HR* (95% CI)	*P*-value	*HR* (95% CI)
Sex: Male or female	0.256	0.845 (0.632-1.130)		
Age: <45 years or ≥ 45 years	0.385	1.094 (0.894-1.338)		
Metastasis at presentation: Present or absent	0.523	1.074 (0.862-1.338)		
Liver metastasis: Present or absent	0.995	1.001 (0.736-1.361)		
Lung metastasis: Present or absent	0.894	0.980 (0.724-1.325)		
Pre-treatment S-ALP level: Normal or elevated	<0.001	1.794 (1.453-2.214)	<0.001	1.794 (1.462-2.201)
Post-treatment S-ALP level: Normal or elevated	<0.001	2.777 (2.195-3.514)	<0.001	2.657 (2.122-3.327)
Number of drugs for chemotherapy: Two or three	0.881	1.017 (0.820-1.261)		
Number of involved sites: 1 or ≥ 1	0.811	0.954 (0.645-1.409)		
Vertebral metastasis: Present or absent	0.069	1.210 (0.985-1.486)		
Skeletal-related events: Present or absent	0.657	0.933 (0.688-1.265)		

HR: hazard ratio; 95% CI: 95% confidence interval.

An elevation of S-ALP is most frequently reported in bone metastasis from certain malignancies, such as lung cancer, breast cancer, and prostate cancer (25-27). Until now, the clinical application of S-ALP in patients with skeletal metastatic NPC has rarely been mentioned. This is the first time the prognostic role and dynamic changes in the significance of S-ALP in disseminated NPC with bone involvement has been explored.

The results of this study are consistent with those several of previous studies indicating that the activity of S-ALP is an important prognostic factor for patients with bony malignancies (28,29). In our report, elevated S-ALP levels were significantly correlated with the presence of liver metastasis and skeletal-related events, as well as the involvement of more than one metastatic site. The median PFS and OS in patients with a normal pre-treatment S-ALP level were significantly longer than those with an elevated pre-treatment S-ALP level. The same results were observed as a correlation between the post-treatment S-ALP level and survival outcome. Previous reports have also demonstrated that elevated S-ALP levels are present in both primary and metastatic liver tumors (30). Because the majority of S-ALP consists of isoenzymes derived from liver and bone, it is reasonable that patients with bony metastasis associated with liver involvement have higher S-ALP levels than those with only bone metastasis. The association between increased pretreatment S-ALP activity and skeletal-related events and the involvement of more than one metastatic site also provide a rationale that the negative clinical prognosis associated with elevated pretreatment S-ALP may simply be attributed to a greater initial tumor burden and consequently more advanced tumor stage.

As described above, practical imaging techniques for evaluating the treatment response of bone metastases in a timely manner are still lacking. Therefore, we have investigated the predictive value of S-ALP and found that it could serve as a marker to reflect the degree of regression or progression during chemotherapy for the 217 patients who also presented with measurable lesions (with lung or liver metastasis). All 6 patients who achieved CR showed a normal post-treatment S-ALP. Thirty-nine of the PR and 14 of the SD patients showed a sharp drop in S-ALP from an elevated level to a normal level. The response rate was significantly higher in patients with a normal post-treatment S-ALP level compared with those with a sustained high post-treatment S-ALP level. S-ALP levels have been demonstrated to reflect the growth and regression of various malignant neoplasms. Guru Sonpavde et al evaluated the association between changes in the S-ALP within 90 days with OS in men with castration-resistant prostate cancer and bone metastases treated with docetaxel or mitoxantrone in the TAX327 trial. The results showed that the normalization of S-ALP by day 90 predicted better survival and that an increase in S-ALP by day 90 predicted poor survival (11). Maisano R et al reported that in 103 consecutive patients with metastatic colorectal cancer treated with chemotherapy, only 3 patients in the high alkaline phosphatase group obtained a partial response (9.4%) compared to 3 complete

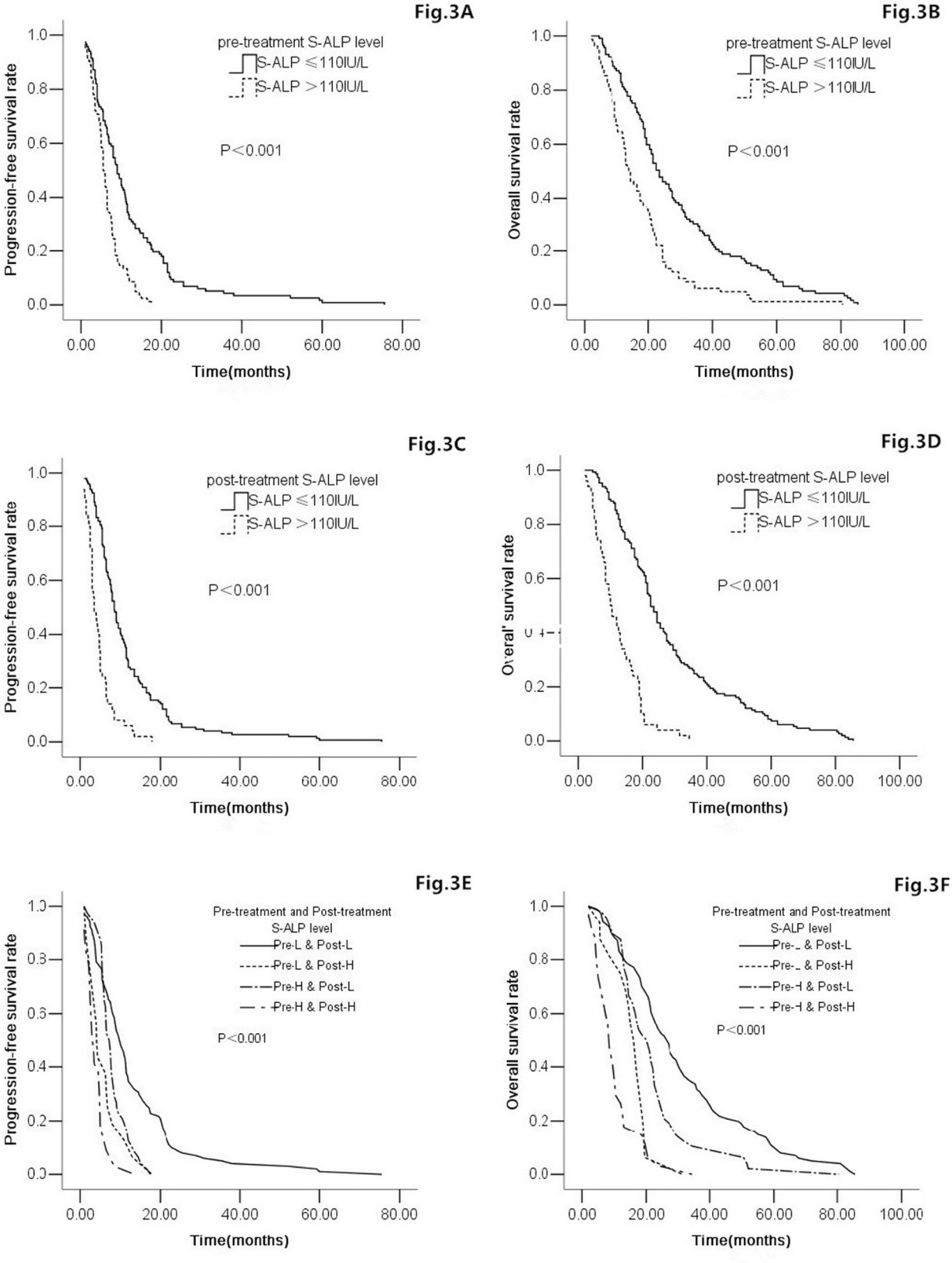

Figure 3 - Kaplan-Meier survival curves are shown for the 199 patients with only bony involvement according to the pre-treatment (and post-treatment) S-ALP level. **A)** PFS according to the pre-treatment S-ALP ($P<0.001$). **B)** OS according to the pre-treatment S-ALP ($P<0.001$). **C)** PFS according to the post-treatment S-ALP ($P<0.001$). **D)** OS according to the post-treatment S-ALP ($P<0.001$). **E)** PFS according to the combination of pre-treatment and post-treatment S-ALP ($P<0.001$). **F)** OS according to the combination of pre-treatment and post-treatment S-ALP ($P<0.001$).

responses and 24 partial responses (41.5%) in the low alkaline phosphatase group (31).

The Cox proportional hazard regression model revealed that only the pre-treatment S-ALP level and post-treatment S-ALP level were independent prognostic factors for overall survival. Notably, when both the pre-treatment and post-treatment S-ALP were considered during analysis, SREs and vertebral involvement were no longer found to be independent negative factors, as described in our previous research (7). As we reported previously (14), one reasonable explanation is that serum tumor markers can reflect the tumor burden more sensitively and precisely than can the specific site of metastases. Additionally, the various sizes and quantities of the lesions may have different prognostic implications. Numerous large lesions may represent a more extensive spread than that of fewer small lesions. These findings provide a rationale for why S-ALP levels have stood out as an independent prognostic factor for survival outcome.

After confirming the prognostic role of S-ALP, we further separated the patients into four subgroups according to their survival outcomes by analyzing the pre-treatment and post-treatment S-ALP in combination. The results revealed that the combination of pre-treatment and post-treatment S-ALP was able to discriminate patients with good prognosis from those with poor prognosis in bony metastatic NPC with or without visceral involvement.

There are several limitations in this study. First, because it is a retrospective study, the patients may have had other nonspecific causes of S-ALP elevation. Second, S-ALP is not fractionated to a specific phenotype in the routine test in our center, and therefore, a bone-specific alkaline phosphatase is not available. However, the inclusion criteria of this study required patients with normal renal, cardiac and liver function; hence, it is unlikely that hepatic dysfunction or renal disease is a significant confounding cause of the observed elevations in S-ALP. Another caveat is that the normal ranges of S-ALP differ slightly in different laboratories. We choose a conventionally accepted normal range for ALP of 110 IU/L in this study.

In conclusion, S-ALP appears to be a useful marker to predict survival and monitor the response to treatment for bony metastatic NPC. Given that the measurement of S-ALP is a simple, readily quantifiable, inexpensive, and established routine diagnostic test that is easily available with quick results, further prospective research on the usefulness of S-ALP determination for the monitoring of bone metastases is certainly worthwhile.

■ ACKNOWLEDGMENTS

This work was supported by Zhejiang Provincial Health Bureau Foundation (Grant No. 2012KYB035).

■ AUTHOR CONTRIBUTIONS

Jin Y contributed to the study design and manuscript preparation. Yuan MQ contributed to data acquisition. Chen JQ contributed to the statistical analysis. Zhang YP contributed to the quality control of the data and manuscript review.

■ REFERENCES

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2006;15(10):1765-77.
2. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol*. 2002;12(6):421-9.
3. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol*. 2007;25(31):4873-9.
4. Niu X, Hu C, Kong L. Experience with combination of cetuximab plus intensity-modulated radiotherapy with or without chemotherapy for locoregionally advanced nasopharyngeal carcinoma. *J Cancer Res Clin Oncol*. 2013;139(6):1063-71.
5. Ma BB, Kam MK, Leung SF, Hui EP, King AD, Chan SL, et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulate-dradiotherapy in locoregionally advanced nasopharyngeal carcinoma. *Ann Oncol*. 2012;23(5):1287-92.
6. Yoshizaki T, Ito M, Murono S, Wakisaka N, Kondo S, Endo K. Current understanding and management of nasopharyngeal carcinoma. *Auris Nasus Larynx*. 2012;39(2):137-44.
7. Jin Y, An X, Cai YC, Cao Y, Cai XY, Xia Q, et al. Zoledronic acid combined with chemotherapy bring survival benefits to patients with bone metastases from nasopharyngeal carcinoma. *J Cancer Res Clin Oncol*. 2011; 137(10):1545-51.
8. Bensouda Y, Kaikani W, Ahbeddou N, Rahhali R, Jabri M, Mrabti H, et al. Treatment for metastatic nasopharyngeal carcinoma. Eur Ann Otorhinolaryngol. *Head Neck Dis*. 2011;128(2):79-85.
9. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization Offset Publication; 1979.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-47.
11. Sonpavde G, Pond GR, Berry WR, de Wit R, Armstrong AJ, Eisenberger MA, et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men withcastration-resistant prostate cancer and bone metastasis receiving chemotherapy. Urol Oncol. 2012;30(5):607-13, http://dx.doi.org/10.1016/j.urolonc.2010.07.002.
12. Kanakis I, Nikolaou M, Pectasides D, Kiamouris C, Karamanos NK. Determination and biological relevance of serum cross-linked type I collagen N-telopeptide and bone-specific alkaline phosphatase in breast metastatic cancer. *J Pharm Biomed Anal*. 2004;34(4):827-32.
13. Ogose A, Hotta T, Kawashima H, Hatano H, Umezu H, Inoue Y, et al. Elevation of serum alkaline phosphatase in clear cell chondrosarcoma of bone. *Anticancer Res*. 2001;21(1B):649-55.
14. Jin Y, Cai XY, Cai YC, Cao Y, Xia Q, Tan YT, et al. To build a prognositc score model containing indispensible tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area. *Eur J Cancer*. 2012; 48(6):882-8.
15. Bergmeyer HU, Bowers GN, Jrhorder M, Moss DW. Provisional recommendations on IFCC methods for the measurement of catalytic concentration of enzymes.Part 2. IFCC method for aspartate aminotransferase. *Clin Chem Acta*. 1976;70(2):F19-29.
16. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec*. 2001;63(4):214-6.
17. Guise TA, Mohammad KS, Clines G, Stebbins EG, Wong DH, Higgins LS, et al. Basic mechanisms responsible for osteolytic andosteoblastic bone metastases. *Clin Cancer Res*. 2006;12(20 Pt2):6213s-s.
18. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer*. 2002;2(8):584-93.
19. Suva LJ, Washam C, Nicholas RW, Griffini RJ. Bone metastasis: mechanisms and therapeutic opportunities. Nat Rev Endocrinol. 2011;7(4):208-18, http://dx.doi.org/10.1038/nrendo.2010.227.
20. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med*. 2004; 350(16):1655-64.
21. Mamari AS, Djordjevic J, Halliday JS, Chapman RW. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol*. 2013;58(2):329-34.
22. Damera S, Raphael KL, Baird BC, Cheung AK, Greene T, Beddhu S. Serum alkaline phosphatase levels associate with elevated serum C-reactive protein in chronic kidney disease. *Kidney Int.* 2011;79(2): 228-33.
23. Lu Y, Lu Q, Chen HL. Diagnosis of primary liver cancer using lectin affinity chromatography of serum alkaline phosphatase. *J Exp Clin Cancer Res*. 1997;16(1):75-80.
24. Bashiri A, Katz O, Maor E, Sheiner E, Pack I, Mazor M. Positive placental staining for alkaline phosphatase corresponding with extreme elevation of serum alkaline phosphatase during pregnancy. *Arch Gynecol Obstet*. 2007;275(3):211-4.
25. Facchini G, Caraglia M, Santini D, Nasti G, Ottaiano A, Striano S, et al. The clinical response on bone metastasis from breast and lung cancer during treatment with zoledronic acid is inversely correlated to skeletal related events (SRE). *J Exp Clin Cancer Res*. 2007;26(3):307-12.
26. Sonpavde G, Pond GR, Berry WR, de Wit R, Armstrong AJ, Eisenberger MA, et al. Serum alkaline phosphatase changes predict survival independent of

PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. *Urologic Oncology.* 2010;30(5):607-13.
27. Kanakis I, Nikolaou M, Pectasides D, Kiamouris C, Karamanos NK. Determination and biological relevance of serum cross-linked type I collagen N-telopeptide and bone-specific alkaline phosphatase in breast metastatic cancer. *J Pharmaceut Biomed*. 2004;34(4):827-32.
28. Sternberg RA, Pondenis HC, Yang X, Mitchell MA, O'Brien RT, Garrett LD, et al. Association between absolute tumor burden and serum bone-specific alkaline phosphatase in canine appendicular osteosarcoma. *J Vet Intern Med*. 2013;27(4):955-63.
29. Zhao H, Han KL, Wang ZY, Chen Y, Li HT, Zeng JL, et al. Value of C-telopeptide-cross-linked Type I collagen, osteocalcin, bone-specific alkaline phosphatase and procollagen Type I N-terminal propeptide in the diagnosis and prognosis of bone metastasis in patients with malignant tumors. *Med Sci Monit*. 2011;17(11):CR626-33.
30. Li X, Mortensen B, Rushfeldt C, Huseby NE. Serum gamma-glutamyl-transferase and alkaline phosphatase during experimental liver metastases. Detection of tumour-specific isoforms and factors affecting their serum levels. *Eur J Cancer*. 1998;34(12):1935-40.
31. Maisano R, Azzarello D, Del Medico P, Maisano M, Bottari M, Egitto G, et al. Alkaline phosphatase levels as a prognostic factor in metastatic colorectal cancer treated with the FOLFOX 4 regimen: a monoinstitutional retrospective study. Tumori. 2011;97(1):39-42.