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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

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Studies show markers of bone turnover can help the clinician in the diagnosis and follow-up of bone metastases. The present study aimed to investigate the value of biochemical markers of bone turnover in the diagnosis and prognosis of bone metastases of malignant tumors.

Material/Methods: The serum levels of C-Telopeptide-Cross-Linked Type I Collagen (CTx), Procollagen Type I N-Terminal Propeptide (PINP), Bone-Specific Alkaline Phosphatase (B-ALP) and Osteocalcin (OST) in patients with bone metastases and control subjects were measured using radioimmunoassay and immunochemiluminescent assay.

Results: The levels of CTx, PINP, B-ALP and OST in the metastasis group were significantly higher than those in both control groups and correlated with the number of bone metastatic sites. The levels of these markers were higher in prostate cancer patients with bone metastasis. The CTX of >426 ng/ml had the highest sensitivity and NPV, and PINP of >51.21 ng/ml had the highest specificity and PPV in healthy subjects. In addition, CTX of >547 ng/ml had the highest sensitivity and OST of >20.34 ng/ml the highest specificity in the non-metastasis group. Furthermore, both B-ALP of >15.55 ng/ml had relatively high negative predictive value and positive predictive value.

Conclusions: Biochemical markers of bone turnover, including CTx, PINP, B-ALP and OST, play important roles in the diagnosis and prognosis of metastatic bone cancer. CTX had a high sensitivity, and PINP had a high specificity in predicting bone metastasis. B-ALP is an ideal biochemical marker of bone turnover for metastatic bone cancer.

key words: **bone metastasis • osteocalcin • Procollagen Type I N-Terminal Propeptide • C-Telopeptide-Cross-Linked Type I Collagen • bone-specific alkaline phosphatase**

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Background

The bone is a common site of metastasis for a number of different cancers; bone metastasis may be observed in approximately 80% of patients with malignant tumors at the advanced stage. Bone metastases of malignant tumors refer to the bone cancer secondary to a primary malignant tumor through blood circulation or in other ways. According to the types of bone lesions, metastatic bone cancer can be classified into osteolytic lesion, osteoblastic lesion and mixed lesion. Clinically, the determination of the type of bone lesions is mainly based on imaging.

In respect to metastatic bone cancer, the clinical diagnosis rate is far lower than the actual incidence. Currently, the cytological characteristics are the criterion standard in the diagnosis of metastatic bone cancer. Other examinations such as X-ray computed tomography (X-CT), magnetic resonance imaging (MRI), and bone scan have their own advantages and disadvantages in the diagnosis of metastatic bone cancer. In recent years, increasing attention has been focussed on the biochemical markers of metastatic bone cancer [1], and several relatively stable and accurate methods have been developed which play an important role in the diagnosis of diseases with abnormal bone metabolism. These bone markers include osteocalcin (OST), total alkaline phosphatase (TALP), bone-specific alkaline phosphatase (B-ALP), procollagen type I N-terminal propeptide (PINP), carboxyterminal propeptide of type I collagen (PICP), pyridinoline crosslinks (PYD), deoxypyridinoline crosslinks (DPD), cross-linked carboxyterminal telopeptide of type I collagen (ICTP), C-telopeptide-cross-linked type I collagen (CTX), N-telopeptide of type I collagen (NTX) and tartrate-resistant acid phosphatase 5b (TRAP 5b). The concentrations of the bone markers TAP, BAP, PINP, PYD, DPD and ICTP were significantly higher in patients with bone metastasis than in those without bone metastasis [2]. In osseous metastasis, even though not statistically significant, TRAP 5b increased in patients with a small bone metastatic burden and NTX increased in patients with extensive bone metastatic burden [3]. Takahashi [4] and Leeming et al. [5] found that biomarkers of bone metabolism seem more important than other tumor markers in predicting the response to treatment of metastatic bone cancer. Bone metabolic markers can also be used to predict the survival and/or incidence of bone- relevant events. Lipton et al. [6] revealed early normalization of elevated baseline NTX while receiving zoledronic acid is associated with longer event-free and overall survival times compared with persistently elevated NTX. These findings demonstrate that bone metabolic markers will be beneficial for monitoring and predicting the prognosis of bone metastasis. In the present study, the serum levels of biomarkers of bone metabolism, including OST, B-ALP, PINP, and CTX, were measured and the value of these biomarkers in the diagnosis and prognosis of metastatic bone cancer was evaluated.

Material and Methods

Patients

This study was approved by the Ethics Committee of the Sixth People's Hospital, Shanghai JiaoTong University. Informed consent was obtained from each patient before the study began. This trial is a retrospective study and 2 control groups were included in the present study – 1 control group consisted of 330 patients with the history of surgery for malignant tumors but currently without metastasis and/or recurrence (Control group 1), and the other consisted of 246 healthy subjects (Control group 2). The metastasis group included 216 patients (114 males and 102 females) with metastatic bone cancer from January 2007 to December 2009. Follow-up was performed from the first discharge to October 30, 2010. The age and sex of subjects were not significantly different among the 3 groups.

Inclusion criteria: 1) the malignant tumor was proved by cytopathology or histopathology; 2) malignant tumors were at stage III or IV; 3) informed consent was obtained.

Exclusion criteria: 1) with metabolic bone diseases; 2) bisphosphonate, hormone, and calcium were administered within 4 weeks prior to study; 3) traumatic bone fracture within 90 days; 4) radiotherapy within 4 weeks prior to study; 5) pregnant or breastfeeding women; 6) severe comorbidities (eg, hyperglycemia); 7) blood creatinine clearance rate (CCr) >2 mg/dl; 8) corrected serum calcium ⩾12 mg/dl; 9) serum total bilirubin >2.5 mg/dl.

Diagnosis and grouping

Metastatic bone tumors were examined by CT, MRI or X-ray in all patients in the metastasis group. Among them, metastatic cancer was diagnosed by fine needle aspiration biopsy in 158 patients. The diagnosis of metastatic bone cancer in patients without definite pathological findings was made by more than 2 experienced physicians based on findings on imaging. In patients with a history of cancer, metastatic bone tumors were excluded by single photon emission computed tomography (SPECT). Patients with metastatic bone cancer were further divided into 3 subgroups according to the scores of the Visual Analogue Scale (VAS): mild bone pain group (VAS score 0–3), moderate bone pain group (VAS score 4–6), and severe bone pain group (VAS score 7–10). According to the number of metastatic sites (Soloway score) [7] these patients were divided into 4 subgroups: patients with fewer than 6 bone metastatic sites; patients with fewer than 20 bone metastatic sites; patients with more than 20 bone metastatic sites, and patients with more than 20 bone metastatic sites, 75% of which were in costa, vertebra or pelvis.

Laboratory examinations

Sample collection and processing

Fasting venous blood (2 ml) was collected in the early morning and kept for 2~3 h at room temperature followed by centrifugation at 3500 r/min for 10 min. The serum was collected and stored at –20°C.

Measurement of biomarkers related to bone metabolism

PINP was measured with kits (Orion Diagnostica, Finland) by radioimmunoassay according to manufacturer's instructions. Serum OST and CTX were measured with automated electro-chemo-luminescence immunoassay equipment (Elecsys 2010, Roche) and agents were provided by Roche. B-ALP was detected with biotin-avidin ELISA with quantitative assay kits provided by IDS, UK.

Table 1. General Information among the three groups (Pearson Chi-Square test).

	Cancer patients with bone metastases (%)	Cancer patients without bone metastases (%)	Healthy subjects (%)	*P* value
Gender				
Female	102 (47.2)	160 (48.5)	93 (37.8)	0.097
Male	114 (52.8)	170 (51.5)	153 (62.2)	
Age (years)				
<45	25 (11.6)	50 (15.2)	33 (13.4)	0.667
45–55	69 (31.9)	90 (27.3)	69 (28.0)	
>55	122 (56.5)	190 (57.6)	144 (58.5)	
Primary cancer				
Lung	122 (56.48)	162 (49.09)		0.189
Breast	39 (18.06)	57 (17.27)		
Prostate	22 (10.19)	51 (15.45)		
unknown	33 (15.28)	60 (18.18)		

Table 2. Factors affecting bone metabolism.

Factors	Number (%)	CTX P value	OST P value	B-ALP P value	PINP *P* value
Gender		0. 004	0. 420	0. 548	0. 153
Female	102 (52.8)				
Male	114 (47.2)				
Metastasis in visceral organs		0. 143	0. 309	0. 311	0. 611
Yes	159 (73.6)				
No	57 (26.4)				
Nature of bone destruction		0. 481	0. 531	0. 544	0. 236
Osteogenesis	151 (69.91)				
Osteolysis	46 (21.30)				
Miscibility	19 (8.80)				

Statistical analysis

Statistical analysis was performed with SPSS version 13.0 and MedCalc 7.2 (Mariakerke, Belgium). The means (standard deviation) in each group were analyzed and compared with LSD's test of one-way ANOVA. The multivariate survival analysis was done with log rank test of the Kaplan-Meier product-limit method. A value of $P<0.05$ was considered statistically significant.

Results

General Information

The distribution of patients with different numbers of metastatic sites is shown in Table 1. Previous studies found that the levels of bone metabolic markers were correlated with age, sex, and metastasis in visceral organs. The correlations of bone metabolic markers with age, sex, etc were analyzed in the subjects of this study (Table 2).

Results showed there were no significant correlations between factors affecting bone metabolism and bone metabolic markers, which indicates the consistency of statistical homogeneity.

Bone metabolic markers in different groups

Sex, age and pre- or post-amenorrhea for females was matched between the metastasis group and 2 control groups, showing no statistically significant differences (Table 3).

Table 3. Bone metabolic markers in different groups.

Group	CTX (ng/ml)	OST (ng/ml)	B-ALP (ng/ml)	PINP (ng/ml)
Metastasis group	725.51±37.35*,#	18.65±1.18*,#	35.01±2.39*,#	114.7±14.79*,#
Non-metastasis group	379.68±31.40	16.10±1.53	13.81±1.61	45.44±6.87
Healthy group	261.89±12.40	11.50±0.33	13.48±0.33	33.10±1.11

* *P*<0.001 *vs.* non-metastasis group; # *P*<0.001 *vs.* healthy group.

Table 4. Primary cancer and bone metabolic markers.

	n (%)	CTX (ng/ml)	OST (ng/ml)	B-ALP (ng/ml)	PINP (ng/ml)
Lung	122 (56.48)	629.35±47.28	16.64±1.59	34.84±3.14	82.32±13.72
Prostate	39 (18.06)	1044.70±153.55*	32.10±6.82*	67.34±12.85	345.71±98.29*
Breast	22 (10.19)	882.7±130.81*	23.32±2.63*	32.94±5.41	206.8±81.36*
unknown	33 (15.28)	774.27±62.19	17.19±2.08	26.69±12.85	89.45±14.11

* *P*<0.05 *vs.* Prostate cancer patients.

Table 5. Bone metabolic markers and amount of bone metastatic sites.

Parameter (ng/ml)	Amount of bone metastatic sites					
	1	2	3	4	Correlation coefficient	P
CTX	604.83±44.29	719.77±38.64*	779.02±74.59	972.25±115.84	0.228	0.003
OST	15.04±1.56	18.79±1.26*	22.38±2.34*	24.61±3.36*	0.297	0.000
B-ALP	30.43±3.04	34.62±4.71*	35.87±2.53*	54.96±7.20*	0.237	0.001
PINP	73.80±10.29	120.85±16.60*	165.26±39.38*	214.13±16.60*	0.328	0.000

* *P*<0.05 *vs.* grade 1; CTX, OST, PINP and B-ALP were associated with the number of metastatic sites.

As shown in Table 3, when compared with the non-metastasis group and the healthy group, the levels of bone metabolic markers were significantly increased in the metastasis group (*P*<0.001).

Bone metabolic markers and characteristics of primary cancer

The patients in the metastasis group were subdivided based on the primary cancer: lung cancer (n=122); prostate cancer (n=39); breast cancer (n=22), and metastatic bone cancer of unknown cause (n=33). Analysis showed the levels of CTX, OST and PINP in prostate cancer patients were markedly higher than those in breast cancer patients and lung cancer patients (Table 4) (*P*<0.05).

Number of bone metastatic sites and bone metabolic markers

According to the Soloway score, patients were subdivided into 4 groups: group 1 patients had <6 metastatic sites in the bone; group 2 patients had <20 metastatic sites; group 3 patients had >20 metastatic sites; group 4 patients had >20 metastatic sites and 75% of sites were in the ribs, vertebrae and pelvis. As shown in Table 5, the levels of bone metabolic markers increased with the increase in the number of metastatic sites. When compared with group 1, the levels of CTX, OST, PINP and B-ALP were significantly increased (P<0.05). Furthermore, the levels of CTX, OST, PINP and B-ALP were related to the number of metastatic sites.

Bone pain and bone metabolic markers

Patients were classified into those with mild bone pain, moderate bone pain and severe bone pain according to VAS score. There was no significant correlation between bone metabolic markers and the bone pain intensity (*P*>0.05).

Specificity and sensitivity of each bone metabolic marker

The cut-off curve was used to analyze the sensitivity and specificity of each bone metabolic marker – "1" represents cancer patients without metastasis and "2" represents healthy controls. When compared with patients without metastasis, the CTX had the highest sensitivity and PINP had the highest specificity. When compared with healthy controls, CTX

Table 6. Specificity and sensitivity of bone metabolic markers in control groups.

Parameter	Cut-off value (ng/ml)	Sensitivity (%)	95% CI	Specificity (%)	95%CI	PPV (%)	NPV (%)
B-ALP	>19.1*	52.24	45.1–59.3	89.55	84.7–93.3	81.3	68.2
	>15.55**	59.20	52.1–66.1	86.67	59.5–98.0	74.5	76.4
CTX	>426*	68.06	60.9–74.6	85.80	79.6–90.7	80.7	75.5
	>547**	59.64	51.3–65.7	84.21	68.7–93.9	71.4	76.2
OST	>18.56*	39.04	32.0–46.4	89.47	85.0–93.0	76.5	62.7
	>20.34**	33.16	26.5–40.4	87.50	67.6–97.2	63.5	66.6
PINP	>51.21*	56.69	47.6–65.5	90.56	85.3–94.4	84.0	70.6
	>57.61**	51.18	42.2–60.1	79.17	57.8–92.8	61.4	71.2

* Healthy group; ** non-metastasis group; PPV – positive predictive value; NPV – negative predictive value.

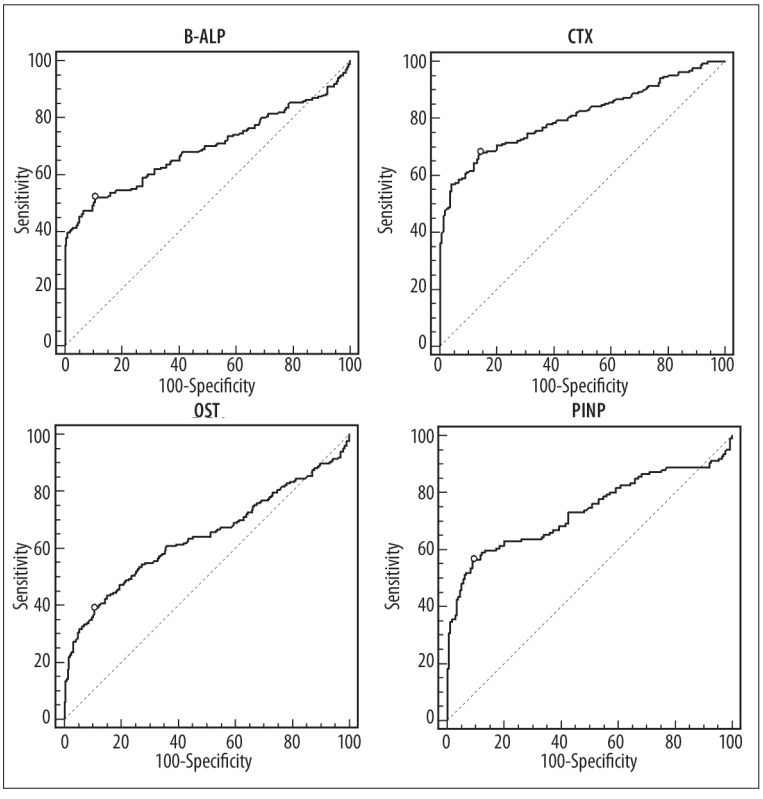

Figure 1. ROC cruves of B-ALP, CTX, OST and PINP.

had the highest sensitivity and OST had the highest specificity (Table 6, Figure 1). According to the receiver operating characteristic (ROC) curve, the cut-off value of each marker was obtained, based on which the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. As shown in Table 6, in healthy subjects CTX of >426 ng/ml had the highest sensitivity and NPV, PINP of >51.21 ng/ml had the highest specificity and PPV. In the non-metastasis group, CTX of >547 ng/ml had the highest sensitivity, OST of >20.34 ng/ml had the highest specificity, and B-ALP of >15.55 ng/ml had the highest NPV and PPV. Therefore, CTX was considered as a sensitive biochemical marker of bone turnover and PINP was considered as a specific marker. Based on the NPV and PPV, B-ALP may be an ideal marker of bone metabolism.

Survival analysis

The median survival time was 16.00 months (95% CI: 13.23–18.77 months) for 216 patients until the end of follow-up (Figure 2).

Correlations between biomarkers and survival time

Regression analysis was conducted to analyze the relationships between bone metabolic markers, sex, location of

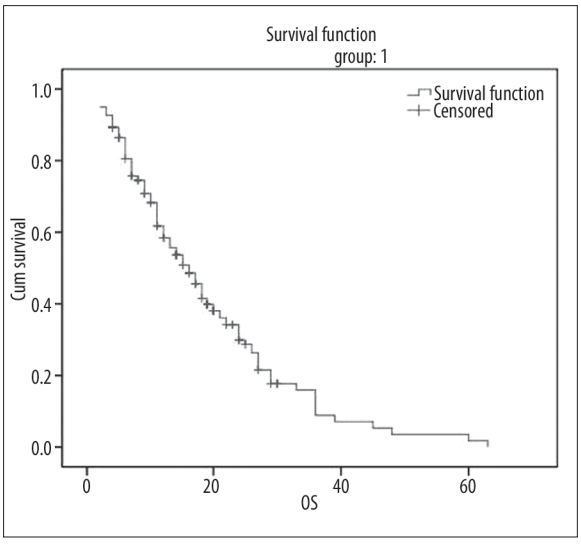

Figure 2. The survival curve of metastatic bone cancer patients.

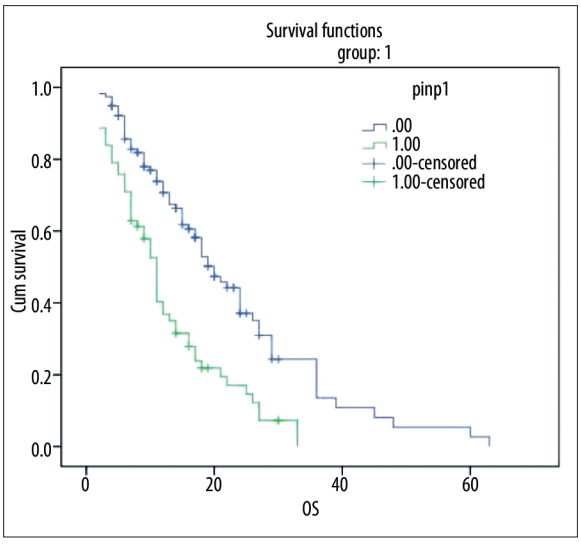

Figure 4. PINP and survival time.

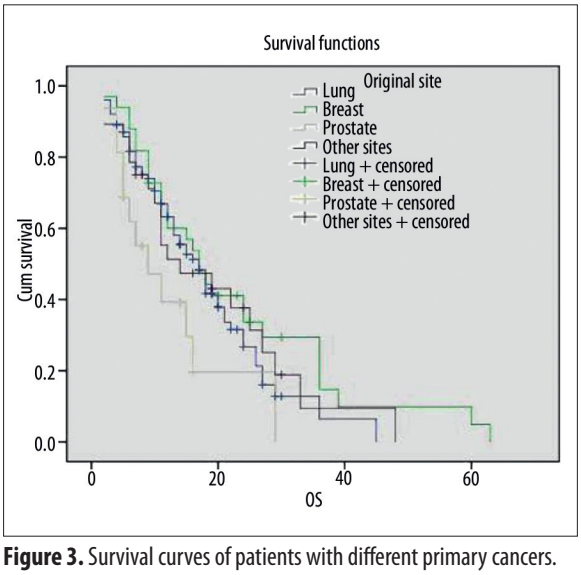

Figure 3. Survival curves of patients with different primary cancers.

primary cancer, number of bone metastatic sites, or characteristics of metastatic bone cancer versus survival time. Results showed the location of primary cancer and PINP could affect the survival time.

Survival time and location of primary cancer

The median survival time of patients with primary lung cancer, breast cancer, prostate cancer, or other cancers was 17 months (95% CI: 13.854~20.146), 17 months (12.901~21.099), 9 months (2.464~15.536) and 14 months (2.464~15.536), respectively. There was no significant difference in the survival time among metastatic bone cancer patients with different primary cancers (P=0.094>0.05) (Figure 3).

Correlation between each bone metabolic marker and survival time

According to the cut-off value (the standard) from the ROC curve, data of each group were classified into 2 groups – group 0 and group 1. Group 1 was higher than the cutoff value and group 0 was lower than the cutoff value. Results showed the PINP could affect the survival time (P<0.001) (Figure 4).

There were no significant differences between other bone metabolic markers, amount of bone metastatic sites, characteristics of metastatic bone cancer and survival time.

Discussions

Currently, the criterion standard for the clinical diagnosis of metastatic bone cancer is cytological characteristics, but this method is invasive. Each radiological examination has its own advantages and disadvantages [7]. X-ray has low sensitivity and can only detect lesions in the trabeculae when the diameters of bone metastatic sites are ⩾1~2 cm. Bone scan can detect bone lesions 3–6 months earlier than X-ray, but has low specificity and high false positive rate. Thus, it cannot be used as a standard to evaluate the therapeutic efficacy. CT is radiative, MRI also has limitations, and PET/CT is expensive. It is therefore impractical to apply the above examinations for dynamically monitoring the changes in bone metabolism.

In recent years, new biomarkers of bone metabolism have been identified, having relatively high sensitivity and specificity, and can reflect the bone turnover at an early stage, predict the risk for bone fracture, and monitor the therapeutic efficacy. Some markers have already been widely applied in clinical practice [8]. However, there is no consensus on the application of these biomarkers in the clinical diagnosis of metastatic bone cancer. The present study investigated the bone metabolic markers in 216 patients with metastatic bone cancer in Shanghai, and the value of these markers in the diagnosis and prognosis of metastatic bone cancer was evaluated.

Our results showed the levels of B-ALP, BINP, OST, and CTX in the metastasis group were significantly higher than those in both control groups. However, there were no significant differences in the levels of B-ALP, PINP, OST and

CTX among patients with osteolytic lesions, osteoblastic lesions and mixed lesions. The correlation analysis showed the number of bone metastatic sites was strongly correlated with each bone metabolic marker. In addition, CTX >426 ng/ml had the highest sensitivity in patients without metastasis, whereas PINP >51.21 ng/ml had the highest specificity in healthy subjects in the prediction of bone metastasis, CTX >547 ng/ml had the highest sensitivity, and OST >18.56 ng/ml had the highest specificity. Additionally, the survival time of patients with bone metastasis of breast cancer was longer than patients with other primary cancers, whereas there were no significant differences among patients with other primary cancers. Correlation analysis revealed that PINP was related to the survival time. Regression analysis showed the number of bone metastatic sites, the characteristics of bone metastasis (osteolytic, osteoblastic or mixed), sex and extraskeletal metastasis did not significantly affect the survival time.

The maintenance of bone metabolism requires a balance between bone resorption by osteoclasts and bone formation by osteoblasts. The bone metabolism can be reflected by biochemical markers through which the viability of osteoblasts and osteoclasts can be indirectly observed [9–11]. The markers of bone formation include B-ALP, PINP and OST, and the markers of bone absorption include CTX.

OST is a non-collagen protein synthesized and secreted by osteoblasts and can accumulate in the bone matrix. The level of OST in the serum is positively correlated with that in the bone. OST can reflect the bone turnover and the metabolic activity of the whole skeletal system and has been used as a specific biomarker of bone formation [12]. Currently, the intact OST is able to be measured in China with ELISA. However, the intact OST varies from different subjects, which may lead to a false negative result [13]. The electro-chemoluminescence assay has excellent stability and was used in the present study to measure OST, which can reflect the state of bone formation more accurately [14]. The alkaline phosphatase is synthesized in the liver and osteoblasts, and has been used as a specific marker for the liver and the bone, respectively. B-ALP mainly concentrates at the ossification sites and is involved in bone formation [15]. It has become one of the best markers for the evaluation of bone formation and bone turnover [16,17]. Moreover, B-ALP can accurately reflect the bone alteration at an early stage. In the present study, in healthy subjects and patients without metastasis, B-ALP of >15.55 ng/ml had the highest NPV and PPV, suggesting B-ALP is an ideal biomarker of bone turnover for the prediction of metastatic bone cancer.

Metastatic bone cancer will also affect the balance between the anabolic and catabolic processes at the local site of invasion. The measurement of CTX may thus provide clinically useful information for diagnosing and monitoring bone metastasis in cancer patients [18]. Osteoblasts can synthesize procollagen type I and secrete it into the extracellular space. After digestion by specific enzymes, the polypeptides at both terminals are removed, thus forming collagen type I and aggregated collagen fiber. The peptide on its amino-terminal is PINP, which is a specific and sensitive marker of bone formation. It is not affected by hormones and is relatively stable, and thus can be used as a marker in the long-term follow-up of patients with metastatic bone cancer [19–21]. Kong et al. [22] found that the increased CTX level had the specificity and sensitivity of 65.6% and 68.8%, respectively, in the diagnosis of bone metastasis in non-small cell lung cancer patients, and they speculated that CTX could be used to screen the bone metastasis of lung cancer, which was supported by Ebert et al. [2]. Brasso et al. [23] showed the levels of PINP, B-ALP, and CTX increased significantly in patients with bone metastasis of prostate cancer, and were correlated with poor prognosis of prostate cancer.

The simultaneous increases of bone formation markers and bone absorption markers indicate that the bone formation and bone absorption occur at the same time in patients with bone metastasis. That is to say, the 2 processes – old bone being eliminated by osteoclasts and the mineralization and bone formation by osteoblasts – are closely coupled. In the bone metastasis of malignant tumors, the growth and invasion of cancer cells result in imbalance between these 2 processes, and regulators relevant to bone turnover thus changes, as do bone turnover markers. In fact, the osteolytic process and osteoblastic process occur simultaneously during the bone metastasis of malignant tumors. Therefore, the markers of bone turnover in these lesions were not significantly different.

It was found that some markers of bone turnover in patients with bone metastasis of prostate cancer increased significantly when compared with patients with bone metastasis of breast cancer except for OST. However, the level of OST in patients with bone metastasis of prostate cancer was significantly higher than that in patients with bone metastasis of lung cancer. Among the 26 prostate cancer patients, 16 had grade 4 cancer according to Soloway score, and 7 had grade 3 cancer. The grade in Soloway score was higher in prostate cancer patients when compared with patients with other primary cancers.

Meanwhile, as the grade in Soloway score increased, the level of each bone metabolic marker increased significantly. However, there was no significant correlation between the bone pain intensity and bone metabolic markers. It may be that the bone pain is caused by more than 1 factor, and that the location of metastatic cancer, periosteum involvement and nerve compression (besides bone metabolism abnormality) are all contributing factors.

Moreover, in the prediction of bone metastasis, CTX was relatively sensitive. For patients with bone metastasis of malignant tumors, CTX can be considered as a relatively ideal marker, with high sensitivity and favorable specificity, but further studies are required to strengthen this conclusion. PINP and B-ALP were relatively specific markers. To determine the bone metastasis, taking the above markers into account might increase the sensitivity and specificity [24].

In addition, patients with bone metastasis of breast cancer had longer survival time. For these patients, physicians should pay more attention to the observation and treatment, in order to achieve better outcomes, extend survival time and improve the quality of life.

Conclusions

In summary, the bone metabolic markers in the present study can used to predict bone metastasis of malignant

tumors to a certain extent. CTX is a marker with relatively high sensitivity, and OST and PINP are markers with relatively high specificity. These markers can be used to monitor patients with malignant tumors in order to observe and monitor the bone metastasis.

Competing interests

The authors declare that they have no competing interests.

REFERENCES:

1. Demers LM, Costa L, Lipton A: Biochemical markers and skeletal metastases. Cancer. 2000; 88(Suppl.12): 2919–26
2. Ebert W, Muley T, Herb KP, Schmidt-Gayk H: Comparison of bone scintigraphy with bone markers in the diagnosis of bone metastasis in lung carcinoma patients. Anticancer Res, 2004; 24(5B): 3193–201
3. Koizumi M, Takahashi S, Ogata E: Comparison of serum bone resorption markers in the diagnosis of skeletal metastasis. Anticancer Res, 2003; 23(5b): 4095–99
4. Takahashi S: Evaluation of cancer-induced bone diseases by bone metabolic marker. Clin Calcium, 2006; 16(4): 581–90
5. Leeming DJ, Koizumi M, Byrjalsen I et al: The relative use of Eight collagenous and noncollagenous markers for diagnosis of skeletal metastases in breast, prostate, or lung cancer patients. Cancer Epidemiol Biomarkers Prev, 2006; 15(1): 32–38
6. Lipton A, Cook RJ, Major P et al: Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. Oncologist, 2007; 12(9): 1035–43
7. Soloway MS, Hardeman SW, Hickey D et al: Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer, 1988; 16: 195–202
8. Fontana A, Delmas PD: Markers of bone turnover in bone metastases. Cancer, 2000; 88(Suppl.12): 2952–60
9. Wada S, Fukawa T, Kamiya S: Bone metabolic markers available in daily practice. Clin Calcium, 2009; 19(8): 1075–82
10. Guise TA, Mohammad KS, Clines G et al: Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. Clin Cancer Res, 2006; 12(20 Pt 2): 6213–16s
11. Yuan J, Ossendorf C, Szatkowski JP et al: Osteoblastic and osteolytic human osteosarcomas can be studied with a new xenograft mouse model producing spontaneous metastases. Cancer Invest, 2009; 27(4): 435–42
12. Lee NK, Sowa H, Hinoi E et al: Endocrine regulation of energy metabolism by the skeleton. Cell, 2007; 130: 456–69
13. Lee AJ, Hodges S, Eastell R: Measurement of osteocalcin. Ann Clin Biochem, 2000; 37: 432–46
14. Chang YS, Kim HJ, Chang J: Elevated circulating level of osteopontin is associated with advanced disease state of non-small cell lung cancer. Lung Cancer, 2007; 57(3): 373–80
15. Nakayama H, Yano T, Sagara Y et al: Clinical usefulness of urinary CrossLaps as a sensitive marker of bone metabolism. Endocr J, 1997; 44(4): 479–84
16. Coleman R, Brown J, Terpos E et al: Bone markers and their prognostic value in metastatic bone disease: clinical evidence and future directions. Cancer Treat Rev, 2008; 34(7): 629–39
17. Le Bricon T, Gay-Bellile C, Cottu P et al: Lectin affinity electrophoresis of serum alkaline phosphatase in metastasized breast cancer. J Clin Lab Anal, 2010; 24(1): 20–24
18. Cloos PAC, Fledelius C, Christgau S et al: Investigation of bone disease using isomerized and racemized fragments of type I collagen. Calcif Tissue Int, 2002; 72: 8–17
19. Koopmans N, de Jong IJ, Breeuwsma A: Serum bone turnover markers (PINP and ICTP) for the early detection of bone metastases in patients with prostate cancer: a longitudinal approach. J Urol, 2007; 178(3 Pt 1): 849–53
20. Hernandez MV, Guanabens N, Alvarez L et al: Immunocytochemica evidence on the effects of glucocorticoids on type I collagen synthesisin human osteoblastic cells. Calcif Tissue Int, 2004; 74: 284–93
21. Klepzig M, Sauer-Eppel H, Jonas D et al: Value of procollagen type 1 amino-terminal propeptide in patients with renal cell carcinoma. Anticancer Res, 2008; 28(4C): 2443–46
22. Kong QQ, Sun TW, Dou QY et al: Beta-CTX and ICTP act as indicators of skeletal metastasis status in male patients with non-small cell lung cancer. Int J Biol Markers, 2007; 22(3): 214–20
23. Brasso K, Christensen IJ, Johansen JS: Prognostic value of PINP, bone alkaline phosphatase, CTX-I, and YKL-40 inpatients with metastatic prostate carcinoma. Prostate, 2006; 66 (5): 503–13
24. Klepzig M, Jonas D, Oremek GM: Procollagen type 1 amino-terminal propeptide: a marker for bone metastases in prostate carcinoma. Anticancer Res, 2009; 29(2): 671–73