Journal of BUON **13:** 69-74, 2008
© 2008 *Zerbinis Medical Publications. Printed in Greece*

ORIGINAL ARTICLE

Association between bone scintigraphy and serum levels of procollagen (I) and PSA in the detection of bone disease in prostate cancer patients

A. Zissimopoulos[1], A. Bantis[2], K. Stellos[3], G. Petrakis[4], D. Matthaios[5]

[1]Department of Nuclear Medicine, and [2]Department of Urology, University General Hospital of Alexandroupolis, Alexandroupolis, Greece; [3]Medizinische Klinik III, Universitatsklinikum Tuebingen, Eberhard-Karls University of Tuebingen, Germany; [4]Department of Pathology, Aristotle University of Thessaloniki, Thessaloniki, Greece; [5]Department of Medical Oncology, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

Summary

Purpose: *To evaluate the clinical usefulness of serum procollagen I carboxyterminal propeptide (PICP) and prostate specific antigen (PSA) in relation to bone scan results in Greek patients with prostate cancer (PC).*

Patients and methods: *108 patients (mean age 58±4.3 years; range 42-81) with PC and 52 healthy blood donors as control group were examined for serum PICP and PSA levels. The diagnosis of PC was confirmed histologically. Bone metastases were diagnosed in 68 of the patients with the use of ^{99m}Tc-MDP bone scan, while 40 patients had no bone metastases. During the one year follow-up new PICP and PSA measurements were obtained along with a new bone scan for all groups studied.*

Results: *The levels of serum PICP and PSA were significantly higher in patients with PC and bone metastases in comparison to patients with no bone metastases. The sensitivity and specificity of the combination of PICP and PSA were 78% and 96%, respectively.*

Conclusion: *PICP could be useful for diagnosing early bone metastases of prostate adenocarcinoma and in combination with PSA and bone scan can be an additional tool in the follow-up of patients with PC.*

Key words: bone metastases, bone scan, procollagen (I) carboxyterminal propeptide, prostate adenocarcinoma, prostate specific antigen

Introduction

Prostate cancer is the 6th commonest cancer worldwide and the 3rd most important to men with 543,000 new cases each year. It is estimated that in USA 1 in every 6 men develops PC during his life, while only 1 out of 32 will die of this disease according to the American Cancer Society's 2004 Cancer Facts & Figures [1]. In Greece PC is the second commonest cancer in men after lung cancer with 2,920 new cases in 2002, comprising 13.2% of all cancers in men [2]. At the time of diagnosis of PC the tumor has advanced beyond the prostatic capsule in 75% of the patients and distant metastases can be detected in nearly half of them. Nowadays, with the wide use of PSA, many PC are detected in early stages and therefore can be treated either surgically or by drugs [3].

Accurate evaluation of bone metastases in patients with PC is significant both for the disease classification at the time of diagnosis and also for a correct decision-making and effective follow up. Although the most common location of metastases from PC is the skeleton, bone metastases cannot always been accurately detected since radiologic imaging modalities, such as x-ray and computerized tomography (CT) can only detect the long-term appearance of bone metastases (osteoblastic lesions) [4]. It is commonly observed and widely accepted that plain x-ray examination has low sensitivity and that substantial osseous destruction sometimes occurs before the appearance of metastatic lesions on plain x-rays films [5]. Radioisotope bone scan is a reliable and established tool for the diagnosis and monitoring of skeletal metastatic status. Although bone scintigraphy is considered very powerful at the initial diagno-

Correspondence to: Dimitrios Matthaios, MD. Department of Medical Oncology, University General Hospital of Alexandroupolis, Dragana, 68 100 Alexandroupolis, Greece. Tel: + 30 25510 21506, Fax: + 30 25510 30470, E-mail: matthaiosdimitr@hotmail.com

Received: 23-07-2007; Accepted: 27-09-2007

sis because of high sensitivity, its specificity is low since several hot spots (especially in skull or cervical spine) give commonly false-positive areas on bone scans [6]. The flare phenomenon (paradoxical deterioration) has also been reported on bone scans after the start of anticancer treatment with estrogens, LHRH agonists, antiandrogens, 5-fluorouracil (5-FU), mitomycin or after orchiectomy. In addition, bone scintigraphy is not suitable for monitoring short-term response of bone metastases to therapy [7].

Immunoassays for measuring the circulating products of both type I collagen synthesis and degradation have been developed and used for the early detection of bone metastases in patients with PC [7].

In this study we evaluated the clinical usefulness of serum PICP as an indicator for early detection of bone metastases in Greek patients with PC in combination with PSA levels.

Patients and methods

Patients

The study population consisted of 108 patients aged 42-81 years (mean age 58±4.3) with histologically confirmed PC (Table 1). Disease stage was defined according to the TNM system [8]. Sixty-eight (42.5%) patients had bone metastases assessed by bone scan (group A) with 46 of them having more than 3 hot spots, and 22 with less than 3 hot spots (Table 1, Figure 1). The remaining 40 (25%) patients had no bone metastases (negative bone scans and x-ray) (group B). Fifty-two healthy blood donors (mean age 46±7.3 years, range 40-62) served as control group (group C) to estimate the cut off value of serum PICP and PSA. None of them had a history of disease (such as bone fractures, osteomalacia, Paget's disease, renal or liver failure) or use of drugs (steroids, calcitonin, biphosphonates) which could affect bone metabolism [9-11].

All patients had an initial whole body bone scan with 925 MBq ^{99m}Tc-MDP using tomographic gamma - Camera (GE Millennium MPR, USA) and serum PICP and PSA measurements and entered the follow-up program of our clinic which included new serum PICP and PSA measurement after 6 months and bone scan after one year . All of the patients were under hormone therapy with antiandrogens and LHRH analogues during this one-year period of follow-up.

Table 1. Patient and prostate cancer (PC) characteristics of all groups studied

Characteristic	*Group A (bone scan pos) n (%)*	*Group B (bone scan neg) n (%)*	*Group C (controls) n (%)*
No. of patients	68 (42.5)	40 (25)	52 (32.5)
Age (years), mean (range)	73.5 (65-82)	73 (61-85)	68.5 (53-84)
Initial Gleason score			
2-4	15 (22)	23 (57)	–
5-6	21 (31)	15 (37)	–
≥7	32 (47)	2 (6)	–
Initial TNM stage[1]			
T3N0M0	–	17 (43)	–
T3N1-3M1b	36 (53)	–	–
T4N0M0	–	23 (57)	–
T4N1-3M1b	32 (47)	–	–
Bone scan (T3-4N1-3M1b)[2]			
≤3	46 (67)	–	–
>3	22 (33)	–	–
PC treatment[3]			
Surgical castration	26 (32)	25 (62)	–
Hormonal therapy	42 (62)	15 (38)	–
Initial serum PSA (ng/ml)			
<50	–	12 (30)	52 (100)
≥50	68 (100)	28 (70)	–
Initial serum PICP (μg/l)			
<170	–	9 (22)	52 (100)
≥170	68 (100)	31 (78)	–

[1]T3a-c: unilateral (a), bilateral extraprostatic (b), extension and invasion of seminal vesicles (c); T4a-b: invasion of bladder neck, rectum or external sphincter (a), and invasion of levator muscle or pelvic floor (b); N_{1-3}: lymph node metastasis; M_{1b}: bone metastasis. [2]Bone scan with more or less than 3 hot spots. [3]Androgen deprivation by surgical castration or flutamide with LHRH analogue.

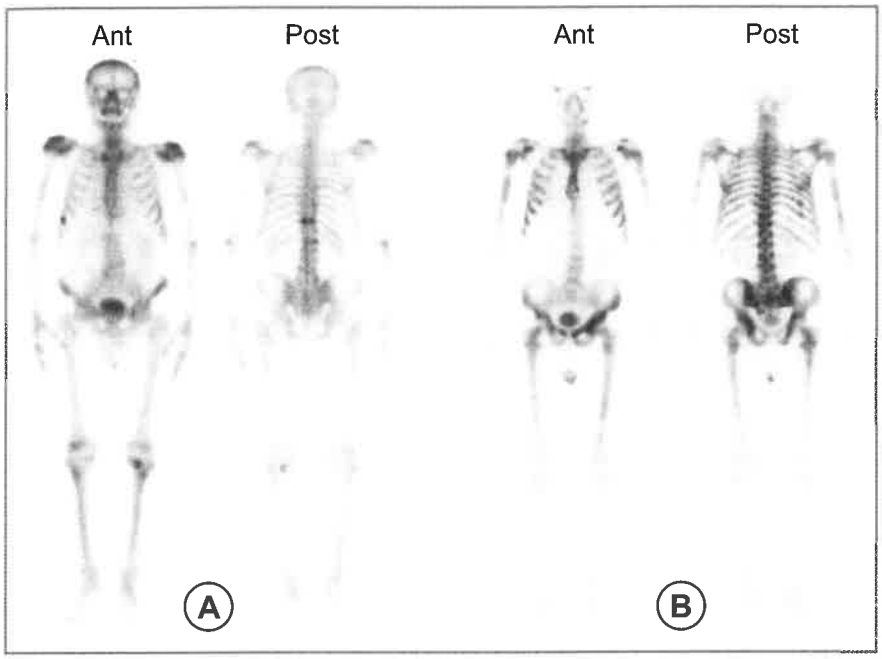


Figure 1. Whole body bone scan with 925 MBq ^{99m}Tc-MDP in patients with bone metastasis of prostate cancer. A: less than 3 hot spots; B: more than 3 hot spots at bone scan.

The diagnosis of bone involvement was performed with whole body scintigraphy, followed by confirmation with a plain x-ray along with CT scan to discriminate lesions that appeared positive at scintigraphy and negative at x-ray. The extent of metastases in bone scintigraphy was established according to the Soloway criteria [12].

Assays

Blood samples were drawn in the morning after overnight fasting and the serum was separated and frozen at –70° C until assayed. Serum levels of PICP were assayed by RIA (Orion Cooperation, Farmos Diagnostic, Finland) and serum PSA was determined with Tandem-R PSA assay (Hybritech Inc, San Diego, Calif, USA). The reference normal levels of PICP were considered to be < 170 µg/l according to our measurements in group C of healthy blood donors, in agreement with other studies [13]. The accepted upper limit of normal level for PSA was set at 4.0 ng/ml.

Statistical analyses

Statistical analyses were performed using the statistical package SPSS V.11. We compared the PICP and PSA serum values between PC patients with multiple bone metastases (>3 hot spots) with those with limited bone metastases (≤ 3 hot spots) and those without bone metastases. Chi-square test was considered as appropriate. The specificity, sensitivity and accuracy were calculated using ROC curve analysis (PICP, PSA). A p-value of less than 0.05 was considered statistically significant.

Results

The patient and control groups characteristics are summarized in Table 1. PICP levels in group A (Figure 2) were 380±89 µg/l (range 178-580), in group B 128±43 µg/l (range 98-195) and in group C 90± 45 µg/l (range 60-120).

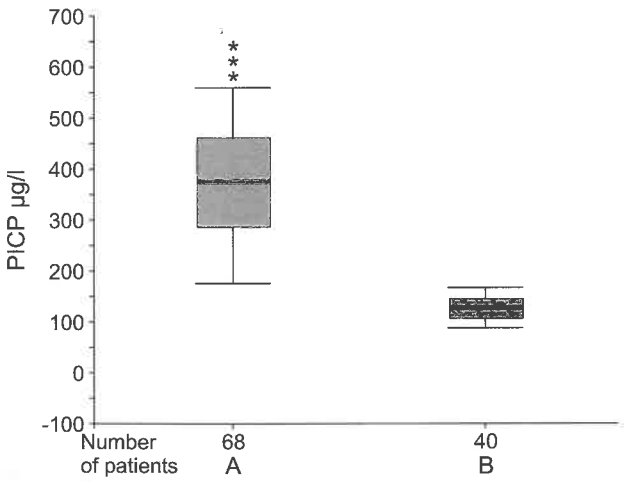


Figure 2. Observed values of serum procollagen (I) in group A of patients with bone metastases assessed by bone scan, and group B with negative bone scans and x-ray (range 178-580 µg/l in group A and 98-195 µg/l in group B).

PSA levels in group A were 158± 85 ng/ml (range 73-243), in group B 6.2±5.8 ng/ml (range 0.4-12.0), and in group C 2.8±1.9 ng/ml (range 0.9-4.7) (Figure 3).

The levels of PICP and PSA were significantly higher in patients with PC and bone metastases (T1-3N1-3M1b) in comparison to patients with PC without bone metastases ($p < 0.005$). PICP and PSA serum levels were significantly higher in patients with PC and bone metastases than in those without bone metastases ($p < 0.005$). Very high values of PICP, higher than those of PSA, were found in patients with multiple (>3 hot spots) bone metastases ($p < 0.005$).

Patients with low levels of PICP (< 90 μg/l) had no bone metastases. High levels of PICP (>170 μg/l) were predictive for bone metastases with sensitivity, specificity and accuracy of 54%, 93% and 84%, respectively. PSA values > 4 ng/ml were predictive for bone metastases with sensitivity 75%, specificity 94% and accuracy 88%, while when PSA levels were < 4 ng/ml sensitivity was 68%, specificity 91% and accuracy 88%.

Sensitivity, specificity and accuracy of the combination of PICP plus PSA were 78%, 96% and 97%, respectively (Figure 4).

After one year of follow-up serum PICP, PSA and bone scan for all groups studied were repeated (Table 2). Eight (20%) patients of group B presented with bone metastases, of whom 5 (12.5%) had >3 hot spots and 3 (7.5%) < 3 hot spots. All patients with new metastatic lesions had initial PSA level > 50 ng/ml and PICP level >170 μg/l. Besides, 12 (17.6%) patients of group A increased their bone metastases from < 3 hot spots to > 3 hot spots on bone scan, while 5 (7.3%) patients with > 3 hot spots on bone scan, serum PSA >50 ng/ml and PICP >170 μg/l died during this period (one year).

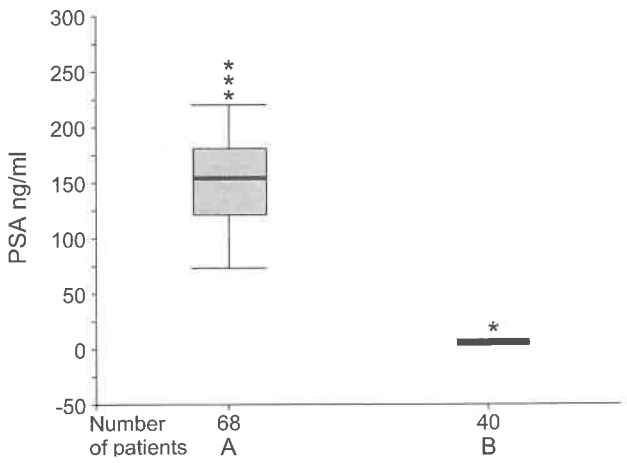


Figure 3. Variations of serum PSA values (box plots) of all groups studied (group A range 73-243 ng/ml, and group B range 0.4-12.0 ng/ml).

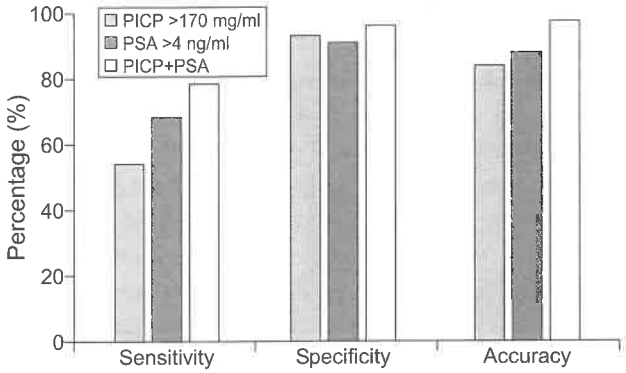


Figure 4. Percentages of sensitivity, specificity and accuracy for bone scan, PICP more than 170 μg/l and serum PSA more than 4 ng/ml.

Table 2. Characteristics of all groups studied after one year of follow-up

Characteristic	*Group A n (%)*	*Group B n (%)*
No. of patients	76 (100)	32 (100)
TNM stage		
T3-4N0M0	–	32 (100)
T3-4N1-3M1b	76 (100)	–
Bone scan (no. of hot spots)		
≤3	37 (49)	–
>3	39 (51)	–
Serum PSA (ng/ml)		
< 50	–	7 (22)
≥ 50	76 (100)	25 (78)
Serum PICP (μg/l)		
< 170	–	6 (18)
≥170	76 (100)	26 (82)

Discussion

It is known that metastatic bone lesions interfere with normal bone regeneration due to the local release of cytokines and growth factors which increase osteoblastic and/or osteolytic activity [14]. Bone metastases occur in 85% of the patients who die of PC [5]. Although most patients with bone metastases respond well to hormonal therapy, the median survival is between 2 and 3 years, and only 30% of the patients are alive after 5 years [15]. The early detection of bone metastases is therefore considered to be very important and decisive for the prognosis of patients with PC.

Assessment of other methods for detecting and evaluating bone metastases, such as monitoring of urinary hydroxyproline, urinary pyridinoline and deoxypyridinoline, urine calcium, serum osteocalcin and serum alkaline phosphate levels have been performed [11,16,17], but they seem incomplete without clinical

usefulness. It is noteworthy that there are highly malignant PCs that produce less PSA than low malignancy PCs. Such cases call for the development of new biological markers [18].

As a consequence of bone involvement a variety of biochemical markers are altered and monitoring these markers in the blood and urine can provide an indirect indication of the disease activity [19,20]. The measurement of the markers is cheaper than other methods, more easily determinable and with negligible disturbance to the patients [21].

Type I collagen is the most abundant collagen in many soft tissues and accounts for more than 90% of the organic matrix of the bone. The precursor molecule, procollagen, contains both aminoterminal and carboxyterminal extension peptides which are cleaved before collagen becomes incorporated as a fibrin into the bone matrix. The amount of PICP released into the circulation is directly related to the rate of *de novo* synthesis of collagen molecules, since PICP normally does not come from soft tissues. PICP is not incorporated into the bone matrix and thus circulating levels of PICP indicate the rate of bone collagen synthesis, and consequently of osteoblastic activity [8,9]. Therefore, monitoring of the collagen type 1 metabolism can be used to detect the activity of bone metastases [22]. PICP is a marker of bone metabolism and its levels are known to be elevated in other diseases such as bone fracture, osteomalacia and Paget's disease [9-11]. Therefore, careful assessment of PICP levels is required in patients with combinations of these diseases.

PSA is the marker most widely used for the diagnosis and follow-up of PC [18]. There is a general agreement that PSA takes its highest prognostic value for PC when it is estimated in relation to age, prostate size, the relation to free PSA and the rhythm by which it increases within one year [13]. In a study 10-27% of men aged 62-91 years with PSA 4.0 ng/ml or slightly less had PC [18]. Younger individuals with PSA 2.6-6 ng/ml have higher possibilities than elders to have curable PC, while elders have higher possibility to have highly malignant PC. In addition, PSA levels are not always related to the PC extent [23]. Also, given that PSA is under androgen regulation, it is worth mentioning that after hormonal therapy 34% of patients with clinical stage D2 disease show normal PSA values despite the progression of bone metastases [24]. These findings underline the need of additional measurement of PICP levels in these categories of PC patients.

In the present study the combination of PICP and PSA showed sensitivity and specificity of 78% and 96%, respectively.

The high levels of PICP found in patients with PC without bone metastases can be attributed to the presence of micrometastases undetectable by conventional methods [25]. The results of our study are in agreement with similar studies [21,22,26-30].

In conclusion, our findings validate the usefulness of PSA in the diagnosis of metastatic bone disease and indicate PICP as a reliable marker of bone metastatic changes in PC patients. Their combination improves the accuracy, sensitivity, and specificity for the diagnosis of bone metastases in PC, especially in early disease stages.

References

1. Eble J, Sauter G, Epstein J, Sesterhenn I. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon, IARC Press, 2004.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Cancer Incidence, Mortality and Prevalence Worldwide, Globocan 2002, American Cancer Society. CA Cancer J Clin 2005; 55: 74-108.
3. Elder JS, Catalona WJ. Management of newly metastatic carcinoma of the prostate. Urol Clin North Am 1984; 11: 283-295.
4. Stoll BA. Natural history, prognosis and staging of bone metastases. In: Stoll BA, Parbho S (Eds): Bone metastases monitoring and treatment. New York: Raven Press, 1983, pp 1-4.
5. Jacobs S. Spread of prostatic cancer to bone. Urology 1983; 21: 337-344.
6. Smith PH, Bono A, Calais da Silva F et al. Some limitations of the radioisotope bone scan in patients with metastatic prostatic cancer. A subanalysis of EORTC trial 30853. The EORTC Urological Group. Cancer 1990; 66 (5 Suppl): 1009-1016.
7. Akimoto S, Koichiro A, Shimazaki J. Clinical usefulness of serum carboxyterminal propeptide of type I procollagen and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen in patients with prostate cancer. J Clin Oncol 1996; 26: 157-163.
8. Fleming I, Cooper J, Henson D et al (Eds): AJCC Cancer Staging Handbook (5th edn). Lippincott, Williams & Wilkins, Philadelphia, 1998, p 203.
9. Joerring S, Jensen LT, Andersen GR, Johansen JS. Types I and III procollagen extension peptides in serum respond to fracture in humans. Arch Orthop Trauma Surg 1992; 111: 265-267.
10. Li F, Iqbal J, Wassif W, Kaddam I, Moniz C. Carboxyterminal propeptide of type I procollagen in osteomalacia. Calcif Tissue Int 1994; 55: 90-93.
11. Simon LS, Krane SM, Wortman PD, Krane IM, Kovitz KL. Serum levels of type I and III procollagen fragments in Paget's disease of bone. J Clin Endocrinol Metab 1984; 58: 110-120.
12. 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; 61: 195-202.
13. Grammaticos P. Diagnostic and prognostic value of serum prostate specific antigen in prostate carcinoma. Hell J Nucl Med 2004; 7: 146-148.
14. Mundy GR. Mechanisms of osteolytic bone destruction. Bone 1991; 12 (Suppl 1): S1-S6.

15. Thompson IM, Phyllis MD. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003; 3: 215-224.
16. Body JJ, Delmas PD. Urinary pyridinium cross-links as markers of bone resorption in tumor-associated hypercalcemia. J Clin Endocrinol Metab 1992; 74: 471-475.
17. Cooper EH, Whelan P, Purves D. Bone alkaline phosphatase and prostate-specific antigen in the monitoring of prostate cancer. Prostate 1994; 25: 236-242.
18. Masanori N, Shinshi N. Pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen as a useful marker for monitoring metastatic bone activity in men with prostate cancer. J Urol 2001; 166: 1106-1110.
19. Risteli J, Elomaa I, Niemi S, Novamo A, Risteli L. Radioimmunoassay for the pyridoniline cross-linked carboxy-terminal telopeptide of type 1 collagen: a new serum marker of bone collagen degradation. Clin Chem 1993; 39: 635-640.
20. Francini G, Gonnelli S, Petrioli R et al. Procollagen type I carboxy-terminal propeptide as a marker of osteoblastic bone metastases. Cancer Epidemiol Biomarkers Prev 1993; 2: 125-129.
21. Nakashima J, Sumitomo M, Miyajima A et al. The value of serum carboxyterminal propeptide of type 1 procollagen in predicting bone metastases in prostate cancer. J Urol 1997; 157: 1736-1739.
22. Kylmala T, Tammela TL, Risteli L, Risteli J, Kontturi M, Elomaa I. Type I collagen degradation product (ICTP) gives information about the nature of bone metastases and has prognostic value in prostate cancer. Br J Cancer 1995; 71: 1061-1064.
23. McNeal JE, Bostwick DG, Kindrachuck RA et al. Patterns of progression in prostate cancer. Lancet 1986; 1: 60-63.
24. Lorente JA, Morote J, Raventos C, Encabo G, Valenzuela H. Clinical efficacy of bone alkaline phosphatase and prostate specific antigen in the diagnosis of bone metastasis in prostate cancer. J Urol 1996; 155: 1348-1351.
25. Koizumi M, Yamada Y, Takiguchi T et al. Bone metabolic markers in bone metastases. J Cancer Res Clin Oncol 1995; 121: 542-548.
26. Hosoya Y, Arai K, Honda M, Sumi S, Yoshida K. Serum levels of the carboxy-terminal propeptide of type I procollagen and the pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen as markers of bone metastases in patients with prostate carcinoma. Eur Urol 1997; 31: 220-223.
27. Santi I, Monti M, Vigano A et al. Serum levels of procollagen type I carboxyterminal extension peptide in cancer patients with bone metastases. Int J Biol Markers 1995; 10: 107-112.
28. Fukumitsu N, Uchiyama M, Mori Y, Kishimoto K, Nakada J. A comparative study of prostate specific antigen (PSA), C-terminal propeptide of blood type I procollagen (PICP) and urine type I collagen-crosslinked N telopeptide (NTx) levels using bone scintigraphy in prostate cancer patients. Ann Nucl Med 2003; 17: 297-303.
29. Noguchi M, Yahara J, Noda S. Serum levels of bone turnover markers parallel the results of bone scintigraphy in monitoring bone activity of prostate cancer. Urology 2003; 61: 993-998.
30. Thurairaja R, Iles RK, Jefferson K, McFarlane JP, Persad RA. Serum amino-terminal propeptide of type 1 procollagen (P1NP) in prostate cancer: a potential predictor of bone metastases and prognosticator for disease progression and survival. Urol Int 2006; 76: 67-71.