Correlation of Urine Type I Collagen-Cross-Linked N Telopeptide Levels With Bone Scintigraphic Results in Prostate Cancer Patients

Nobuyoshi Fukumitsu, Mayuki Uchiyama, Yutaka Mori, Shuuichi Yanada, Takashi Hatano, Hiroshi Igarashi, Kouichi Kishimoto, Jojiro Nakada, Akiko Yoshihiro, and Junta Harada

The diagnostic potential of a new bone resorption marker, type I collagen-cross-linked N telopeptide (NTx), for bone metastasis of prostate cancer was evaluated. Ninty-one prostate cancer patients underwent bone scintigraphy, and urine NTx/creatinine (NTx/Cr) was measured. Urine NTx/Cr levels were compared with bone scintigraphic results. Urine NTx/Cr levels in the bone metastasis-positive group (n = 47) were 92.9 ± 105.1 nmol/L of bone collagen, which is equivalent to per millimole of urinary creatinine (nmol/L BCE/mmol/L Cr), significantly higher than the level of the bone metastasis-negative group (n = 44) (59.0 ± 41.6 nmol/L BCE/mmol/L Cr). When patients were classified by the extent of disease grade (EOD grade) nomenclature, the urine NTx/Cr level of the EOD (4+) group was 209.5 ± 186.5 nmol/L BCE/mmol/L Cr. This level was significantly higher than those of the EOD (-) group (59.0 ± 41.6 nmol/L BCE/mmol/L Cr), EOD (1+) group (59.0 ± 47.8 nmol/L BCE/mmol/L Cr), and EOD (2+) group (81.1 ± 41.3 nmol/L BCE/mmol/L Cr). However, no significant difference was observed between the EOD (-) and EOD (1+) groups. The mean change in urine NTx/Cr level 3 to 17 months after the first bone scintigraphy and urine NTx/Cr examination in the bone metastasis-progression group (n = 8) was 11.0 ± 31.2 nmol/L BCE/mmol/L Cr, significantly higher than that in the bone metastasis-regression group (n = 15) (-26.8 ± 40.7 nmol/L BCE/mmol/L Cr). In conclusion, urine NTx /Cr can be measured noninvasively and reflects the state of bone metastasis. However, the sensitivity of urine NTx/Cr is not as high as that of bone scintigraphy. Therefore, it may provide an auxiliary diagnostic index for bone scintigraphy.

PROSTATE CANCER HAS a high frequency of bone metastasis,[1,2] and accurate diagnosis of bone metastasis is an important factor in determining prognosis. The most widely used test for the diagnosis of bone metastasis is bone scintigraphy. A number of bone metabolism markers that reflect bone resorption and osteogenesis have recently been developed. Measurement of metabolites produced by cross-linking of type I collagen, in particular, provides a sensitive measurement of bone metabolism. Such markers include the C-terminal telopeptide of blood pyridinoline-cross-linked type I collagen (ICTP) and the C-terminal propeptide of blood type I procollagen (PICP).[3] Type I collagen-cross-linked N telopeptide (NTx), as a new bone resorption marker was also recently developed.[4,5] NTx can easily be measured in urine because it is excreted by the kidneys, and this examination is a noninvasive test for patients. Few studies have reported on clinical evaluations of NTx in prostate cancer.[6,7] We deemed it necessary to study in detail the sensitivity of NTx in the diagnosis of bone metastasis, including severity and treatment effects. We studied the diagnostic performance of this new bone resorption marker for bone metastasis and compared it with bone scintigraphy.

SUBJECTS AND METHODS

Subjects

Ninety-one patients with prostate cancer who visited the Jikei Kashiwa Hospital between April 1998 and October 1999 were studied. The patients ranged in age from 50 to 92 years (mean, 72.7 ± 9.1), and tissue types (World Health Organization [WHO] classification) were well-differentiated in 8 cases, moderately differentiated in 31 cases, poorly differentiated in 37 cases, and unclassified in 15 cases. The latter 15 cases had been transferred from other hospitals where their tumors had not been classified. According to TNM staging 1987,[8] clinical stages in the first examinations were stage A in 2 cases, stage B in 6 cases, stage C in 18 cases, stage D in 41 cases, and unclassified in 24 cases. Seven patients were undergoing radical prostectomy. Another seven patients with localized prostate cancer were treated with external beam radiation of the pelvis. The forms of androgen suppression were variable. As for endocrine therapy, 14 underwent bilateral orchiectomy, 76 with relapse after prostatectomy or radiation therapy received luteinizing hormone-relapsing hormone (LHRH) agonist, and 1 patient was not treated. The periods of LHRH agonist treatment ranged from 0 to 10 (mean 1.9 ± 2.1) years. Cases with a history of traumatic fracture during observation were excluded from the present clinical evaluation.

Methods

All patients underwent bone scintigraphy. A total of 555 MBq of ^{99m}Tc-hydroxymethylenediphosphonate (^{99m}Tc-HMDP) was injected intravenously, and front and back images of the whole body were taken after 3 hours. The apparatus used was a double-detector gamma camera (RC-2600I, Hitachi Corp, Japan) with a low-energy high-resolution collimator, and energy was set at 140 keV ± 10%. Bone scintigrams were read by radiologists and classified into a bone metastasis-positive and a bone metastasis-negative group. The degree of severity of bone metastasis was also evaluated in detail using the extent of disease (EOD) grade nomenclature[9] (Table 1). When the bone scintigraphic results differed among radiologists, the majority decision was accepted. Furthermore, in some cases, magnetic resonance imaging (MRI) was used to diagnose bone metastasis.

Urine NTx was measured within 10 days after the bone scintigraphic examination in all cases. Urine samples were collected at the second void and preserved by freezing at -20°C. NTx was measured with an enzyme-linked immunosorbent assay (ELISA) kit, Osteomark (Ostex International, Seattle, WA). The ELISA kit was used following the manufacture's instructions. The Osteomark immunoassay detects NTx using monoclonal antibody, 1H11, which specifically binds to

From the Departments of Radiology and Urology, Jikei University School of Medicine, Tokyo, Japan.

Submitted June 12, 2001; accepted January 31, 2002.

Address reprint requests to Nobuyoshi Fukumitsu, MD, Department of Radiology, Jikei University School of Medicine, 3-25-8, Nishi-shinbashi, Minato-ku, Tokyo, 105-8461, Japan.

0026-0495/02/5107-0008$35.00/0

doi:10.1053/meta.2002.33344

Table 1. EOD Grade Nomenclature

EOD (−): Normal, or abnormal due to benign bone disease
EOD (1+): Number of bony metastases less than 6, each of which is less than 50% the size of a vertebral body (1 lesion about the size of a vertebral body would be counted as 2 lesions)
EOD (2+): Number of bone metastases between 6 and 20, size of lesions as described above
EOD (3+): Number of metastases more than 20, but less than a "super scan"
EOD (4+): "Super scan" or its equivalent, ie, more than 75% or the ribs, vertebrae, and pelvic bones

the$\alpha 2(I)^N$ Telopeptide chain of type I collagen. Urine creatinine (Cr) was simultaneously analyzed with a Hitachi 7150 autoanalyzer. Urine NTx was expressed as nanomoles of bone collagen equivalents per millimoles urinary Cr (nmol/L BCE/mmol/L Cr).[4]

Among the patients who underwent a second bone scintigraphic examination and simultaneous urine NTx/Cr measurement 3 to 17 months after the first bone scintigraphy, 23 were classified into a bone metastasis-progression group or a bone metastasis-regression group. Forty-one patients who showed no difference between first and second bone scintigraphic findings were excluded. Subtracting the first urine NTx/Cr from the second yielded the mean change (Δ) in urine NTx/Cr.

Prostate-specific antigen (PSA) was measured in 77 cases on the same day that urine NTx/Cr was measured. Patients were then classified into 3 groups on the basis of their PSA levels. In group A patients, PSA was under 4.0 ng/mL. In group B patients, PSA was more than 4.0 ng/mL, but less than 10.0 ng/mL. In group C patients, PSA was more than 10.0 ng/mL.

Tests

(1) Urine NTx/Cr was compared with bone scintigraphic results in all cases. (2) Δ urine NTx/Cr values were compared between bone metastasis progression and regression groups. (3) Urine NTx/Cr was compared with bone scintigraphic results on the basis of PSA levels.

Statistical Analysis

Values are presented as means ± SD. Student's *t* test was applied for comparison of measurements between 2 groups. Scheffes F test was used for comparisons among groups. A value of $P < .05$ was considered to indicate a statistically significant difference.

RESULTS

Correlation Between Urine NTx/Cr and Bone Scintigraphic Results

Patients were divided into 2 groups based on the the presence or absence of bone metastasis. The mean urine NTx/Cr was significantly lower in the bone metastasis-negative group (n = 44) than in the bone metastasis-positive group (n = 47), (59.0 ± 41.6 *v* 92.9 ± 105.1 nmol/L BCE/mmol/L Cr, respectively) (Fig 1; $P < .05$). Correct diagnosis of bone metastasis was highest when the urine NTx/Cr cutoff level was set at 70 to 75 nmol/L BCE/mmol/L Cr, assuming bone scintigraphy finding is the most reliable. At this cutoff level, diagnosis reached a sensitivity of 51.1%, a specificity of 79.5%, and an accuracy of 64.8% (Table 2). When patients were grouped according to EOD grade, the urine NTx/Cr level did not differ between the EOD (-) (n = 44) and EOD (1+) (n = 27) groups (59.0 ± 41.6 *v* 59.0 ± 47.8 nmol/L BCE/mmol/L Cr, respectively). Urine NTx/Cr in the EOD (4+) group (n = 9; 209.5 ± 186.5 nmol/L BCE/mmol/L Cr) was significantly higher than those in the EOD (-), (1+), and (2+) groups (n = 44; 59.0 ± 41.6 nmol/L BCE/mmol/L Cr, n = 27; 59.0 ± 47.8 nmol/L BCE/mmol/L Cr, n = 10; 81.1 ± 41.3 nmol/L BCE/mmol/L Cr, respectively) (Fig 2; $P < .001$). Statistical analysis was not performed for the EOD (3+) group as there were too few patients.

Correlation Between Δ Urine NTx/Cr and Bone Scintigraphic Results

The intervals between the first and second bone scintigraphy were 5 to 17 months in the bone metastasis-regression group (n = 8) and 3 to 16 months in the bone metastasis-progression group (n = 15). The mean Δ urine NTx/Cr was significantly lower in the bone metastasis-regression group than the bone metastasis-progression group, (-26.8 ± 40.7 *v* 11.0 ± 31.2 nmol/L BCE/mmol/L Cr, respectively) (Fig 3; $P < .05$). There was no significant difference between the bone metastasis-regression group and the bone metastasis-progression group as to the manner of treatment.

Correlation Between Urine NTx/Cr and Bone Scintigraphic Results Based on PSA Levels

In group A, the urine NTx/Cr level was beyond 100 nmol/L BCE/mmol/L Cr in 4 patients (bone metastasis-negative group (3/28), bone metastasis-positive group (1/13)). In group B, the urine NTx/Cr level exceeded 100 nmol/L BCE/mmol/L Cr in 1 patient (bone metastasis-negative group (0/5), bone metastasis-positive group (1/12)). In group C, the urine NTx/Cr level was over 100 nmol/L BCE/mmol/L Cr in 6 patients (bone metas-

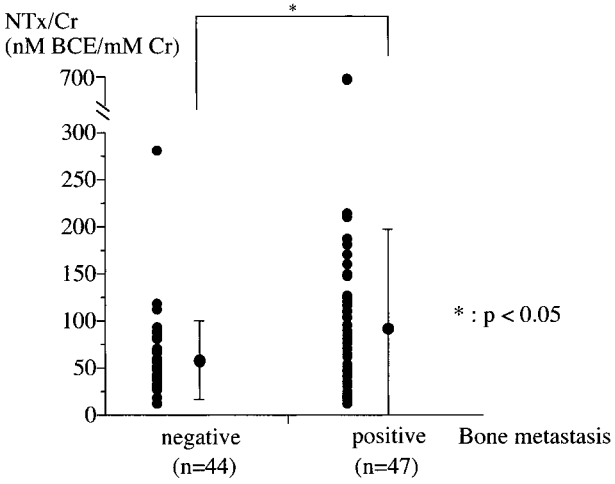

Fig 1. Comparison of urine NTx/Cr between the bone metastasis-negative and bone metastasis-positive groups. Urine NTx/Cr was significantly higher in the bone metastasis-positive group.

Table 2. Diagnostic Ability of Bone Metastasis

Cutoff Level (nmol/L BCE/mmol/L Cr)	Sensitivity (%)	Specificity (%)	Accuracy (%)
95	31.9	93.2	61.5
90	34.0	90.9	61.5
85	38.3	84.1	60.4
80	44.7	81.8	62.6
75	51.1	79.5	64.8
70	51.1	79.5	64.8
65	53.2	65.9	59.3
60	57.4	63.6	60.4
55	57.4	50.0	53.8
50	63.8	45.5	54.9

tasis-negative group (0/4), bone metastasis-positive group (6/15) (Fig 4A-C).

DISCUSSION

Bone scintigraphy is based on the highly specific accumulation of ^{99m}Tc-HMDP in bone tissue. It has been widely used to facilitate imaging of the whole body and for accurate detection of lesion sites. However, bone scintigraphy is limited by several factors: its inability to resolve differences between benign and malignant bone lesions, the cost of the procedure, frequent patient exposure to radiation, and subjectivity in image interpretation.

To compensate for these limitations, various markers of bone metabolism have recently been developed and applied clinically.[10-15] ICTP and PICP examinations were already reported to be useful for assessing bone metastasis of prostate cancer clinically.[3] However, ICTP and PICP data are affected by renal dysfunction, hepatitis, and hepatic fibrosis.[15-18] The requirement for frequent blood collections to monitor these markers is not always well accepted by patients, adding to the desire for a less invasive and more sensitive marker of bone metabolism.

The presence of NTx, a metabolite of bone resorption

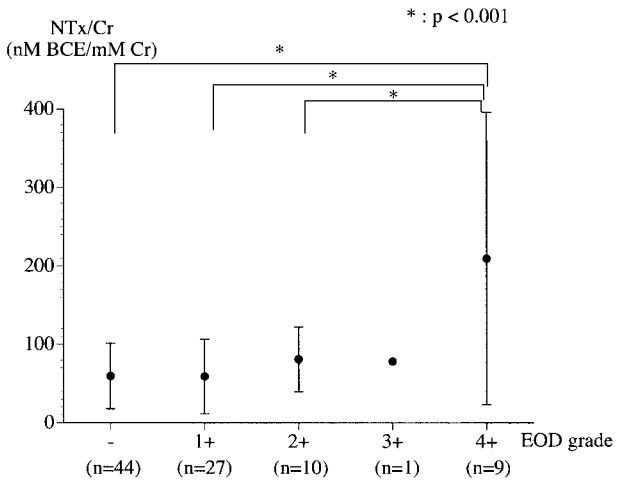

Fig 2. Comparison of urine NTx/Cr according to EOD grade nomenclature. Urine NTx/Cr was significantly higher in the EOD (4+) group than in the EOD (-), (1+), and (2+) groups.

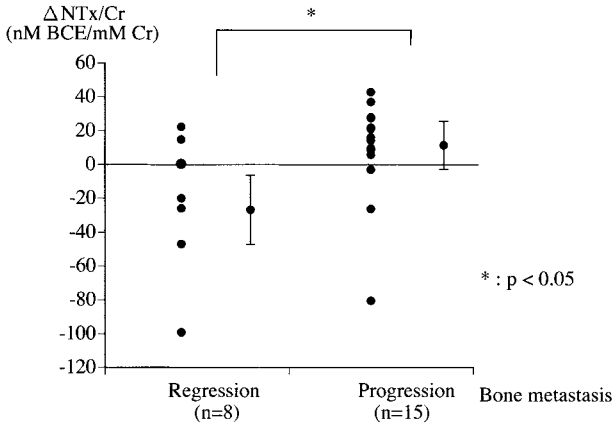

Fig 3. Comparison of Δ urine NTx/Cr between bone metastasis-regression and bone metastasis-progression groups. Δ urine NTx/Cr was significantly higher in the bone metastasis-progression group.

derived from type I collagen in humans, in urine has been reported.[5] The diagnostic performances of urine NTx, blood ICTP, urine pyridinoline (PYD), and deoxypyridinoline (DPD) have been compared, and urine NTx was found to be the most sensitive marker of bone metabolism.[7] One advantage of NTx examination is that it can easily be repeated. It is also noninvasive, which is important to patients. We examined the effectiveness, limitations, and significance of NTx as a marker for clinical application. In this report, we divided the urine NTx level by the urine Cr concentration.[4,19]

Levels of urine NTx/Cr have been investigated in healthy patients by Sone et al.[19] Urine NTx/Cr excretion levels were determined in 452 healthy Japanese subjects. Urine NTx/Cr values in healthy subjects ranged from 5.1 to 150.0 (31.6 ± 16.7) nmol/L BCE/mmol/L Cr. While a marked variation was observed between pre- and postmenopausal women, urine NTx/Cr values did not vary greatly according to age in male study subjects. Urine NTx/Cr values in our bone metastasis-negative group showed a wide range from 9.6 to 278.6 nmol/L BCE/mmol/L Cr (mean, 59.0 ± 6.1). We will discuss the reason for our bone metastasis-negative group data being higher than that of Sone et al.[19] The exact reasons for this discrepancy are not known. However, it is likely that there relatively large differences exist in the urine of NTx/Cr individuals. In addition, bone resorption and urine NTx/Cr values are reportedly significantly elevated in patients undergoing androgen ablation therapy.[20,21] Our previous results demonstrated an increase in urine NTx/Cr beyond 20 nmol/L BCE/mmol/L Cr in patients without bone metastasis due to androgen suppression for at least 12 months.[22] In our study, most of the patients were undergoing androgen suppressive treatments (bilateral orchiectomy, 14 cases; LHRH agonist, 76 cases). The reason for the urine NTx/Cr values of the bone metastasis-negative group being higher than those of healthy Japanese subjects reported by Sone et al[19] could be related to androgen deficiency. Because of the higher baseline NTx excretion in androgen-suppressed prostate cancer patients, the sensitivity of urine NTx/Cr for bone metastasis might be lower than in men with normal testosterone levels. However, many patients un-

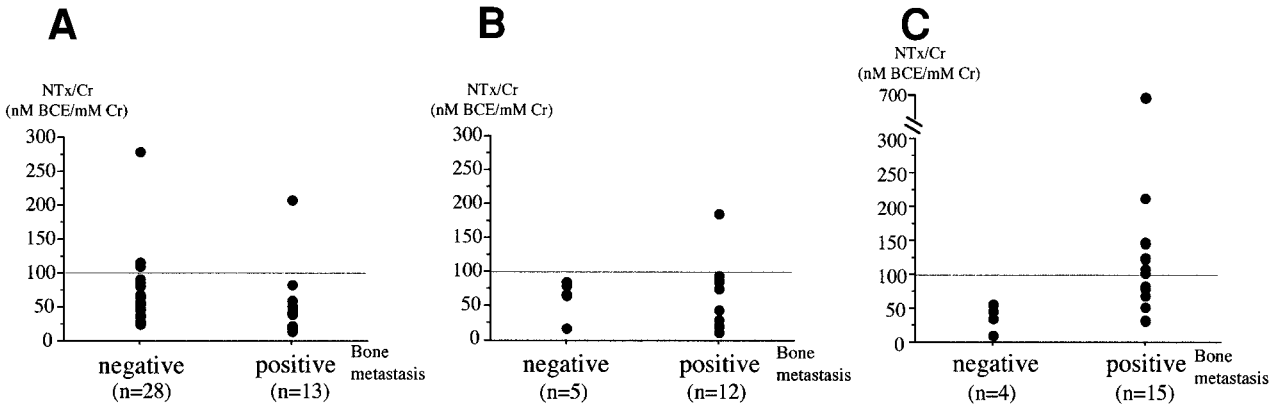

Fig 4. Diagnostic ability combining urine NTx/Cr with PSA. (A) Group A (PSA < 4), (B) group B (4 ≤ PSA < 10), and (C) group C (PSA ≥ 10). All of the patients whose urine NTx/Cr levels were over 100 nmol/L BCE/mmol/L Cr in group C had bone metastasis.

dergoing androgen suppressive treatments are included among bone metastasis-negative patients in some hospitals. For a marker to be used clinically, its diagnostic ability should be investigated, keeping in mind potential disadvantages. For this reason, we selected bone metastasis-negative patients as our control group.

In 1 patient in the bone metastasis-negative group who received an LHRH agonist for 8 months, both urine NTx/Cr (278 nmol/L BCE/mmol/L Cr) and alkaliphosphate (ALP) (481 IU/L) were very high. Over the following month, urine NTx/Cr decreased to 62 nmol/L BCE/mmol/L Cr, while ALP increased to 581 IU/L. This patient had neither hepatic nor pancreatic disease. The origin of the increase in ALP in this case is unclear. Thus, we are still monitoring the course of this patient.

Yamamoto et al[6] reported the efficiency of diagnosing bone metastasis to be greatest with the cutoff level for urine NTx/Cr set at 40 to 50 nmol/L BCE/mmol/L Cr. In the present study, correct diagnosis was highest with the urine NTx/Cr cutoff level set at 70 to 75 nmol/L BCE/mmol/L Cr. At this cutoff level, diagnosis reached a sensitivity of 51.1%, a specificity of 79.5%, and an accuracy of 64.8%, as shown in Table 2. Significant differences in urine NTx/Cr levels were observed between the bone metastasis-negative and positive groups, but the variance in values between the 2 groups overlapped, as shown in Fig 1. These results illustrate the difficulties associated with diagnosing the presence or absence of bone metastasis by urinary analysis of NTx/Cr alone.

When EOD grade nomenclature was used to classify the degree of bone metastasis, urine NTx/Cr increased relative to the EOD grade, and urine NTx/Cr levels in the EOD (-), (1+), and (2+) groups were significantly lower than that of the EOD (4+) group. No significant difference was observed between the EOD (-) and EOD (1+) groups, indicating the urine NTx/Cr level to be elevated in patients in whom bone metastasis had progressed. However, urine NTx/Cr may not be suitable for early diagnosis of bone metastasis. The small number of cases in the EOD (3+) group prevented comparisons between this group and the EOD (-) group.

These results indicate that a single examination of urine NTx/Cr values is not sufficient for determining the state of bone resorption in an individual, and that repeated urine NTx/Cr measurements appear to be necessary to detect variations. In this study, we found the mean Δ urine NTx/Cr in the bone metastasis-progression group to be significantly higher than that in the bone metastasis-regression group. However, further studies are needed to provide more detailed information and confirm our results.

PSA has been widely used as an index of metastasis to bone and other organs in prostate cancer patients.[11-14] As shown in Fig 4, those patients whose urine NTx/Cr levels exceeded 100 nmol/L BCE/mmol/L Cr in the C group all belonged to the bone metastasis-positive group, based on bone scintigraphy. These results suggested that combining urine NTx/Cr with PSA would facilitate making an exact diagnosis of bone metastasis. However, we speculate that further studies, including consideration of other bone metabolism markers, are needed to clarify this issue.

In general, bone metastasis of prostate cancer is composed mainly of osteoblastic type cells. The reason for the increase in bone resorption markers correlating with the progression of prostate cancer is not clear at present. It has been well documented that excessive osteoid formation occurs adjacent to metastatic bone lesions in prostate cancer, and that active osteoblast numbers increase in parallel with the rate of bone resorption.[23,24] Increased osteoclast activity can be promoted by tumor-derived factors, such as epidermal growth factor, tumor necrosis factor-α, and transforming growth factor-α.[25,26] It is interesting that elevation of bone resorption markers, such as blood ICTP, urine PYD, and DPD have been reported in prostate cancer patients with bone metastasis.[27-29] It was argued, based on such results, that bone resorption markers increase as bone is resolved, despite osteoblastic activity being enhnaced. It is probable that our finding of elevated urine NTx/Cr in these types of cancer cases is attributable to similar mechanisms.

CONCLUSION

(1) Bone scintigraphy and urine NTx/Cr measurements were performed for 91 prostate cancer cases. (2) Urine

NTx/Cr was significantly higher in the bone metastasis-positive group than in the bone metastasis-negative group. (3) Urine NTx/Cr was significantly higher in the EOD (4+) group than in the EOD (-), (1+), and (2+) groups. However, no significant difference was observed between the EOD (-) and (1+) groups. (4) Changes in urine NTx/Cr in the bone metastasis-progression group were significantly greater than those in the bone metastasis-regression group. (5) The ability to diagnose bone metastasis was improved by combining urine NTx/Cr with PSA. (6) Urine NTx is potentially useful as an auxiliary diagnostic index, used in conjunction with bone scintigraphy.

REFERENCES

1. Koizumi K, Uchiyama G, Komatsu H: Scintigraphic changes in bone metastasis from prostate cancer after hormonal therapy-comparison with tumor markers and bone X-ray. Ann Nucl Med 8:225-230, 1994
2. Slack NH, Lane WW, Priore RL, et al: Prostate cancer. Urology 27:205-213, 1986
3. Koizumi M, Yamada Y, Takiguchi T, et al: Serum concentration of pyridinoline cross-linked carboxy-terminal telopeptide of type-I collagen (ICTP) and carboxyterminal propeptide of human type I procollagen (PICP) in the diagosis of bone metastases. Kaku Igaku 33:77-84, 1996
4. Hanson DA, Weis MAE, Bollen AM, et al: A specific immunoassay for monitoring human bone resorption: Quantitation of type I collagen cross-linked N-teropeptides in urine. J Bone Miner Res 7:1251-1258, 1992
5. Eyre DR: New biomarker of bone resorption. J Clin Endocrinol Metab 74:470A-470C, 1992
6. Yamamoto I, Morita R, Konishi J, et al: Clinical studies using measurement of N-telopeptides of type I collagen (NTx) in patients with bone metastasis-comparison with bone scintigraphy and other metabolic bone markers. Kaku Igaku 32:501-510, 1995
7. Demers LM, Costa L, Chinchilli VM, et al: Biochemical markers of bone turnover in patients with metastatic bone disease. Clin Chem 41:1489-1494, 1995
8. Union Internationale Contre le Cancer: TNM Classification of Malignant Tumors (ed 4). Geneva, Switzerland, International Union Against Cancer, 1987
9. 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 61:195-202, 1988
10. Imai K, Tomaru Y, Ohnuki T, et al: Significance of a new stratification of alkaline phosphatase and extent of disease in patients with prostate carcinoma with bone metastasis. Cancer 69:2983-2989, 1992
11. Gleave ME, Coupland D, Drachenberg D, et al: Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. Urology 47:708-712, 1996
12. Freitas JE, Gilvydas R, Ferry JD, et al: The clinical utility of prostate-specific antigen and bone scintigraphy in prostate cancer follow-up. J Nucl Med 32:1387-1390, 1991
13. Nguyen-Pamart M, Caty A, Feutrie ML, et al: The diagnostic value of urinary crosslaps and serum alkaline phosphatase in patients with prostate cancer. Br J Urol l70:299-303, 1992
14. Rudoni M, Antonini G, Farvo M, et al: The clinical value of prostate-specific antigen and bone scintigraphy in the staging of patients with newly diagnosed, pathologically proven prostate cancer. Eur J Nucl Med 22:207-211, 1995
15. Mutou S: Prostatic carcinoma: Pyridinoline, deoxypyridinoline and PICP. Hinyouki Geka 10:795-797, 1997
16. Koda K: Purification of carboxyterminal extension peptide of human type I procollagen and diagnosis of liver fibrosis by radioimmunoassay for it. Kanzo 25:192-203, 1984
17. Fukunaga M, Otsuka N, Ono S, et al: Measurement of its concentration in blood by carboxytermin1al propeptide of type I procollagen (PICP) assay kit. Kidney Metab Bone 6:237-245, 1993
18. Elomaa I, Virkkunen P, Risteli L, et al: Serum concentration of the cross-linked carboxyterminal telopeptide of type I collagen (ICTP) is a useful prognostic indicator in multiple myeloma. Br J Cancer 66:337-341, 1992
19. Sone T, Miyake M, Takeda N, et al: Urinary excretion of type I collagen crosslinked N-telopeptides in healthy japanese adults: Age- and sex-related changes and reference limits. Bone 17:335-339, 1995
20. Stoch SA, Parker RA, Chen L, et al: Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. J Clin Endocrinol Metab 86:2787-2791, 2001
21. Smith MR, McGovern FJ, Zietman AL, et al: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 345:948-955, 2001
22. Fukumitsu N, Uchiyama M, Mori Y, et al: A change in the bone metabolism marker (NTx) with hormone therapy in the prostate cancer. Kidney Metab Bone 14:245-248, 2001
23. Kylmala T, Tammela TLJ, Risteli L, et al: Type I collagen degradation product (ICTP) gives information about the nature of bone metastases and has prognostic value in prostate cancer. Br J Cancer 71:1061-1064, 1995
24. Clarke NW, McClure J, George NJ: Disodium pamidronate identifies differential osteoclastic bone resorption in metastatic prostate cancer. Br J Urol 69:64-70, 1992
25. Bertolini DR, Nedwin GE, Bringman TS, et al: Stimulation of bone resorption and inhibition of bone formation in vitro by human tumor necrosis factor. Nature 319:516-518, 1986
26. Vaes G: Cellular biology and biological mechanisms of bone resorption. Clin Orthop 231:239-271, 1988
27. Samma S, Kagebayashi Y, Yasukawa M, et al: Sequential change of urinary pyridinoline and deoxypyridinoline as markers of metastatic bone tumor in patients with prostate cancer: A preliminary study. Jpn J Clin Oncol 27:26-30, 1997
28. Takeuchi S, Arai K, Saitoh H, et al: Urinary pyridinoline and deoxypyridinoline as potential markers of bone metastasis in patients with prostate cancer. J Urol 156:1691-1695, 1996
29. Hosoya Y, Arai K, Honda M, et al: 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 cancer. Eur Urol 31:220-223, 1997