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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

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We compared the ability to diagnose skeletal metastasis between serum prostate specific antigen (PSA), C-terminal propeptide of blood type I procollagen (PICP), and urine type I collagen-crosslinked N telopeptide (NTx) in prostate cancer patients. In sixty-nine patients with prostate cancer, bone scintigraphy was performed, and serum PSA and PICP and urine NTx were measured. The median level of serum PSA in the osseous metastasis-negative group (n = 33) was 0.80 ng/m*l* being significantly lower as compared to the osseous metastasis-positive group (n = 36, 7.70 ng/m*l*) ($p < 0.0001$). The serum PICP and urine NTx/Cr levels appeared lower in the osseous metastasis-negative group than the osseous metastasis-positive group, but there was no significant difference. Logistic regression analysis showed that ability to diagnose skeletal metastasis of serum PSA was 68.1% and superior to those of serum PICP (56.5%) and urine NTx/Cr (53.6%). Serum PSA improved the ability to diagnose skeletal metastasis when combined with serum PICP or urine NTx/Cr. When patients were grouped according to the extent of disease grade (EOD grade) nomenclature, Spearman's correlation coefficient by rank showed that serum PSA was most significantly correlated with EOD grade ($p < 0.0001$). In 14 patients whose skeletal metastases progressed or regressed, the change of serum PSA more clearly separated the osseous metastasis-regression group and osseous metastasis-progression group than did serum PICP and urine NTx/Cr. Serum PSA was more reliable than bone resorption and formation markers produced by crosslinking of type I collagen.

Key words: prostate cancer, PSA, PICP, NTx, skeletal metastasis

INTRODUCTION

PROSTATE CANCER has a high frequency of skeletal metastasis,[1,2] and accurate diagnosis of skeletal metastasis is an important factor in determining the prognosis. A number of bone metabolic markers that reflect bone resorption and formation have recently been developed. Measurement of metabolites produced by crosslinking of type I collagen in particular provides a sensitive measurement of bone metabolism. Such new markers include the type I collagen-crosslinked N telopeptide (NTx), as a bone resorption marker[3,4] and C-terminal propeptide of blood type I procollagen (PICP) as a bone formation marker[5,6] which have been reported as being useful in the diagnosis of skeletal metastasis in prostate cancer patients.[7–9] Prostate specific antigen (PSA) is known to be a sensitive marker for monitoring prostate cancer and is routinely used clinically.[10,11] Because of its good sensitivity and specificity, serum PSA has been reported to be a useful marker for skeletal metastasis of prostate cancer.[12–18] In the present study, we compared the ability to diagnose skeletal metastasis using serum PSA and PICP and urine NTx.

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SUBJECTS AND METHODS

Subjects

Between April 1998 and October 1999, 69 patients with

prostate cancer who consulted the Jikei Kashiwa Hospital were studied. The patients ranged in age from 50 to 92 years (mean 72.9 ± 9.1). According to the 1987 TNM staging,[19] clinical stages in the first examinations were: T1 in 3 patients, T2 in 5 patients, T3 in 13 patients, T4 in 26 patients, and unclassified in 22 patients due to transfer from other hospitals. Seven patients undergoing radical prostatectomy and ten patients with localized prostate cancer were treated with external beam radiation therapy for the pelvis. The form of androgen deprivation was varied. As for endocrine therapy, 6 underwent bilateral orchiectomy and 56 patients, including patients relapsing after prostatectomy or radiation therapy, received a lutenizing hormone releasing hormone (LHRH) agonist. The period of LHRH agonist treatment ranged from 0 to 10.5 (mean 2.3 ± 2.3) years. Patients who had a history of traumatic fracture or metastases to locations other than the skeletal system during observation were excluded from analysis because evaluation of skeletal metastases in these patients would have been difficult.

METHODS

Blood and urine samples were collected on the same day. Serum PSA was determined by the Tandem-R PSA assay (Beckman Coulter, Inc., Fullerton, California, USA). Serum PICP was assayed by two-antibody RIA using a PICP RIA kit (Orion Cooporation, Farmous Diagnotica, Turku, Finland). Urine samples were collected at the second voiding, and preserved by freezing under −20°C. NTx was assayed by ELISA using an NTx ELISA kit, Osteomark (Ostex International Inc., Seatle, WA). Urine creatinine (Cr) was simultaneously analyzed by a Hitachi 7150 autoanalyzer. The urine NTx was expressed as nMols of bone collagen equivalents divided by the mMol urinary creatinine (nM BCE/mM Cr).[3]

All patients underwent bone scintigraphy within 10 days of blood and urine examination. 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 the energy was set at 140 keV ± 10%.

Bone scintigrams were read by radiologists and classified into an osseous metastasis-positive group and osseous metastasis-negative group. The degree of severity of skeletal metastasis was also evaluated in detail using the extent of disease grade (EOD grade) nomenclature[20] (Table 1). When the results of bone scintigrams differed between radiologists, a majority decision was taken. Furthermore, in some patients, MRI was used to diagnose skeletal metastasis.

The patients who underwent second bone scintigraphy examination and in whom serum PSA and PICP and urine NTx/Cr were measured, were classified into an osseous metastasis-progression group and osseous metastasis-regression group. Subtraction of the first set of values

Table 1 The 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 (one lesion about the size of a vertebral body would be counted as two lesions).
EOD (2+):	number of bony metastases between six 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, i.e., more than 75% or the ribs, vertebrae, and pelvic bones.

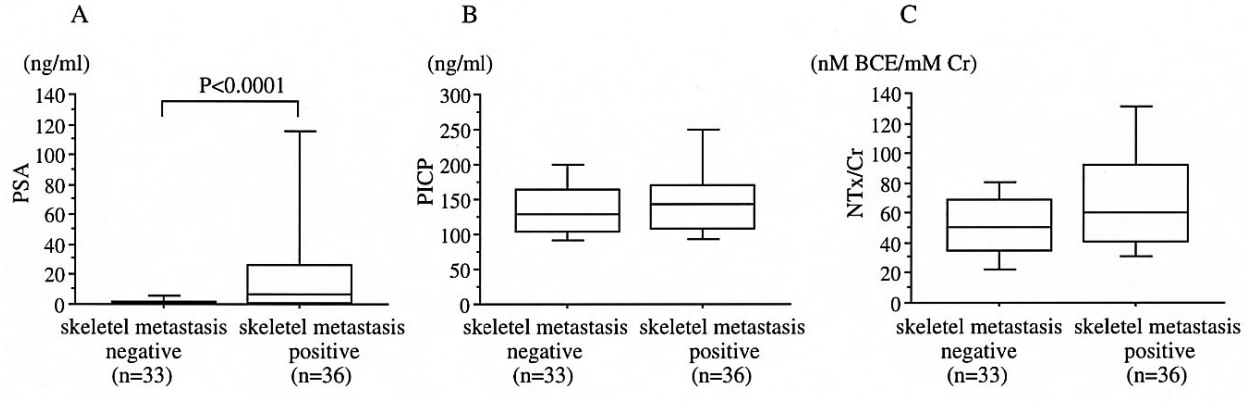

Fig. 1 Comparison of serum PSA and PICP and urine NTx/Cr between the osseous metastasis-negative and osseous metastasis-positive groups (A: serum PSA, B: serum PICP, C: urine NTx/Cr). Serum PSA was significantly higher in the osseous metastasis-positive group ($p < 0.0001$). Serum PICP and urine NTx/Cr appeared to increase in the osseous metastasis-positive group, however there were no significant.

from the second set of values of serum PSA and PICP and urine NTx/Cr data gave serum PSA and PICP and urine NTx/Cr changes. We excluded the patients in whom the interval between the first and second examinations was less than 4 months because flare phenomenon could have affected the evaluation.

We compared the ability to diagnose the skeletal metastasis of these three markers in prostate cancer patients.

Statistics

Values are presented as median : [Q 25%, Q 75%]. The Mann-Whitney U test was applied for comparison of measurements between the two groups. Receiver operating characteristic (ROC) analysis and areas under the ROC curve (AUCs) were used as objective measures to evaluate the three markers. Logistic regression analysis was subsequently applied for comparison of the ability to diagnose the skeletal metastasis of these three markers. From examination of the EOD grade and these markers, Spearman's correlation coefficient by rank was obtained. An unpaired t test was applied and adjusted with Bonferroni/Dunn in comparison with intergroups. A value of $p < 0.05$ was considered to be statistically significant.

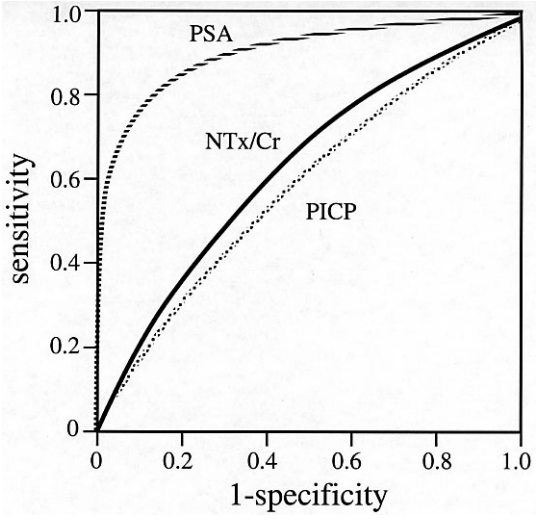

Fig. 2 Comparison of ROC curve of serum PSA, PICP, urine NTx/Cr. The AUC was 0.89 in serum PSA, 0.59 in serum PICP and 0.64 in urine NTx/Cr.

RESULTS

The serum PSA level was significantly lower in the osseous metastasis-negative group than the osseous metastasis-positive group (n = 33, 0.80 [0.80, 0.80] vs. n = 36, 7.70 [0.90, 21.0] ng/m*l*, $p < 0.0001$, respectively, Fig. 1-A). The serum PICP level was lower in the osseous metastasis-negative group than the osseous metastasis-positive group without significance (n = 33, 130.0 [101.0, 166.0] vs. n = 36, 144.0 [107.0, 174.0] ng/m*l*, respectively, Fig. 1-B). The urine NTx/Cr level was lower in the osseous metastasis-negative group than the osseous metastasis-positive group without significance (n = 33, 50.5 [35.1, 69.1] vs. n = 36, 59.9 [40.4, 97.4] nM BCE/mM Cr, respectively, Fig. 1-C).

The AUCs were 0.89 in serum PSA, and superior to those of serum PICP (0.59) and urine NTx/Cr (0.64) (Fig. 2). Logistic regression analysis showed that the ability to diagnose skeletal metastasis of serum PSA was 68.1% and superior as compared to serum PICP (56.5%) and urine NTx/Cr (53.6%). The ability to diagnose skeletal metastasis of serum PICP and urine NTx/Cr was significantly improved when combined with serum PSA ($p < 0.05$, respectively). However, that of serum PSA was not significantly improved when combined with serum PICP and urine NTx/Cr, as shown in Figure 3-A, B, C.

When patients were grouped according to the EOD

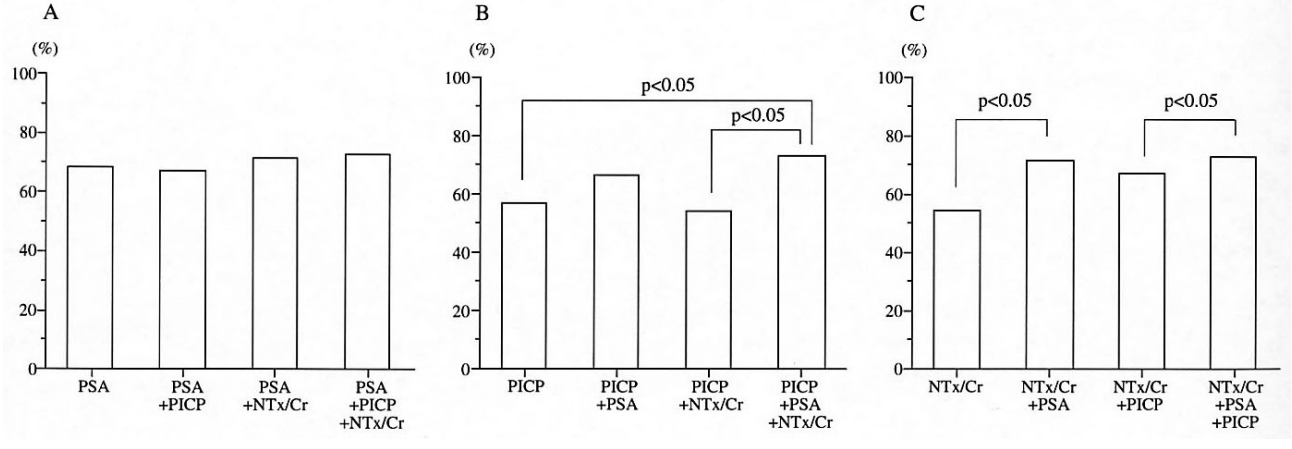

Fig. 3 The ability to diagnose skeletal metastasis (A: serum PSA, B: serum PICP, C: urine NTx/Cr). Logistic regression analysis showed that the ability to diagnose skeletal metastasis was 68.1% in serum PSA, 56.5% in serum PICP and 53.6% in urine NTx/Cr. Those of serum PICP or urine NTx/Cr were significantly improved when combined with serum PSA ($p < 0.05$, respectively).

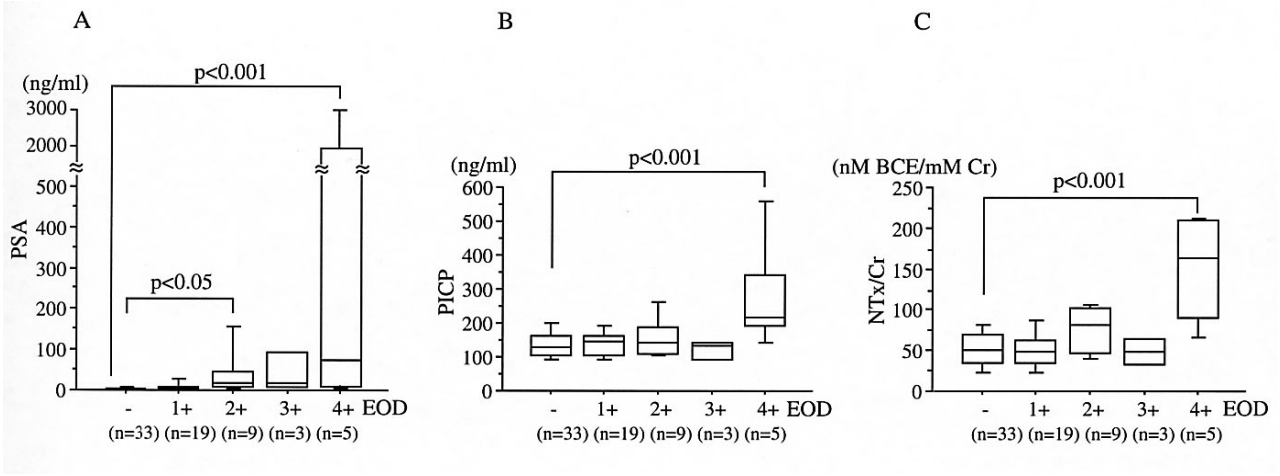

Fig. 4 Comparison of serum PSA and PICP and urine NTx/Cr according to EOD grade nomenclature (A: serum PSA, B: serum PICP, C: urine NTx/Cr). Spearman's correlation coefficient by rank showed that serum PSA and urine NTx/Cr were significantly correlated with EOD grade ($p < 0.0001$, $p = 0.011$, respectively), however serum PICP was not significantly correlated with EOD grade. In serum PSA, the values of EOD (2+) and (4+) were significantly higher than those of EOD (–) ($p < 0.05$, $p < 0.001$, respectively). In serum PICP and urine NTx/Cr, only the values of EOD (4+) were significantly higher than those of EOD (–) ($p < 0.001$, respectively).

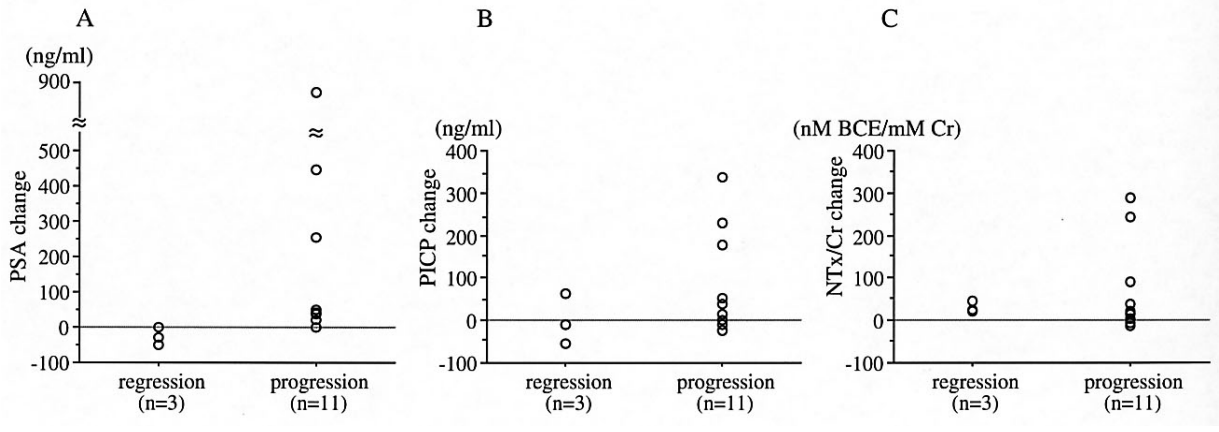

Fig. 5 Comparison of serum PSA and PICP and urine NTx/Cr changes between osseous metastasis-regression and osseous metastasis-progression groups (A: serum PSA, B: serum PICP, C: urine NTx/Cr). Serum PSA change was clearly lower in the osseous metastasis-regression group than the osseous metastasis-progression group. Serum PICP and urine NTx/Cr changes appeared to be lower in the osseous metastasis-regression group than the osseous metastasis-progression group, however some patients overlapped between the two groups.

grade, Spearman's correlation coefficient by rank showed that serum PSA was most significantly correlated ($p < 0.0001$) and urine NTx/Cr was significantly correlated ($p = 0.008$), whereas serum PICP was not significantly correlated ($p = 0.14$) (Fig. 4-A, B, C). In serum PSA, the values of EOD (2+) and (4+) were significantly higher than that of EOD (–) ($p = 0.021$, $p < 0.001$). In serum PICP and urine NTx/Cr, only the values of EOD (4+) were significantly higher than those of EOD (–) ($p < 0.001$). There were no significant differences between EOD (–) and (1+) groups for any markers. As shown in Figure 4, the serum PSA levels appeared to be elevated in parallel with the EOD grade. However, the values of EOD (–), (1+), (2+), and (3+) groups were approximately equivalent in serum PICP and urine NTx/Cr.

A second bone scintigraphy was performed in 58 of the 69 patients and serum PSA and PICP levels and urine NTx/Cr levels were measured. Three patients were in the osseous metastasis-regression group, 11 patients were in the osseous-metastasis-progression group, and 44 patients had no interval changes. The interval between the first and second bone scintigraphy ranged from 4 to 12 months in the osseous metastasis-regression group and 5 to 15 months in the osseous metastasis-progression group.

There was no significant difference between the osseous metastasis-regression group and the osseous metastasis-progression group in the manner of treatment. The serum PSA change was clearly lower in the osseous metastasis-regression group than the osseous metastasis-progression group. The serum PICP and urine NTx/Cr changes appeared to be lower in the osseous metastasis-regression group than the osseous metastasis-progression group, although some patients overlapped between the two groups as shown in Figure 5-A, B, C. Statistical analysis was not done because of the small number of patients.

DISCUSSION

Prostate cancer has a high frequency of skeletal metastasis.[1,2] In patients dying of prostate cancer, skeletal metastasis reportedly occurred in 85% and was the only site of metastases in 65%.[21] Bone scintigraphy has been widely used for easy imaging of the whole body and accurate detection of lesion sites.[22] However, bone scintigraphy is limited by several factors: its inability to resolve differences between benign and malignant bone lesions, quantitative assessment, cost of the procedure, frequent exposure of patient to radiation, and subjectivity of image interpretation.

To compensate for these limitations, various markers of bone metabolism have been developed recently, and applied clinically.[23–26] NTx and PICP have been relatively sensitive and specific biochemical markers of bone turnover, and development of these markers has generated interest in their potential use for monitoring skeletal metastasis and assessing the response to treatment of prostate cancer patients.[7–9]

Serum PSA is an extremely reliable marker of prostate cancer and routinely used clinically.[10,11] Because prostate cancer often metastasizes to bone, serum PSA has been used as a marker of skeletal metastasis with prostate cancer patients.[12–18]

As shown in Figures 1–3, our results indicated that serum PSA was more sensitive than serum PICP or urine NTx/Cr to diagnose skeletal metastasis. Our result was similar to previous comparative studies between serum PSA and bone metabolism markers.[7,27] Logistic regression analysis in this study clearly showed that serum PSA improved the ability to diagnose skeletal metastasis when combined with serum PICP or urine NTx/Cr, but serum PICP or urine NTx/Cr did not much improve the ability to diagnose skeletal metastasis when combined with serum PSA in prostate cancer patients.

As shown in Figure 4, serum PSA mostly correlated with the EOD grade and appeared to be elevated in parallel with the EOD grade. On the other hand, in serum PICP and urine NTx/Cr, the values of EOD (–), (1+), (2+), and (3+) groups were approximately equivalent. This result indicated that serum PSA was most affected by the severity of skeletal metastasis in prostate cancer patients. However it was difficult to diagnose minimal skeletal metastasis by these markers, because it was difficult to discriminate between EOD (–) and (1+) groups.

As shown in Figure 5, serum PICP and urine NTx/Cr changes appeared to be elevated in the osseous metastasis-progression group. This result indicated that both bone resorption and formation were activated in patients with osseous metastasis progression, although skeletal metastasis of prostate cancer was mainly of the osteoblastic type. The value of serum PSA change more clearly separated the osseous metastasis-regression and progression group than did serum PICP and urine NTx/Cr. This result suggested that of these three markers, serum PSA most sensitively reflected the activity of skeletal metastasis, but a definite conclusion could not be reached because of the small number of patients.

From our results, we realized again that serum PSA was the most reliable marker to diagnose skeletal metastasis including the severity, activity and treatment effect, as reported in some previous studies.[7,27]

We previously examined the ability to diagnose skeletal metastasis using urine NTx/Cr in 91 prostate cancer patients, and reported that the value of the osseous metastasis-positive group was significantly higher than that of the osseous metastasis-negative group.[28] This discrepancy is thought to be due to the lower number of patients. In this study, 69 prostate cancer patients (91 patients in the previous study) were studied. However, a similar result whereby the value of the osseous metastasis-positive group was much higher than that of the osseous metastasis-negative group was seen again.

Because bone metabolism markers do not signficantly improve the ability to diagnose skeletal metastasis combined with serum PSA, they might appear to be unnecessary. However, bone metabolism markers and serum PSA do not always demonstrate a close or definite correlation. There are a few prostate cancer patients who produce less PSA, even when they have high-grade tumors.[29,30] In our study, three patients with skeletal metastasis showed high values of bone metabolism markers, such as values of serum PICP above 200 ng/m*l* or of urine NTx/Cr above 100 nM BCE/mM Cr, despite a normal value of serum PSA, for example lower than 2 ng/m*l* as follows; (EOD (1+); serum PSA 0.8 ng/m*l*, serum PICP 203 ng/m*l*, urine NTx/Cr 84.3 nM BCE/mM Cr, EOD (4+); serum PSA 1.8 ng/m*l*, serum PICP 215 ng/m*l*, urine NTx/Cr 208.7 nM BCE/mM Cr, and EOD (1+); serum PSA 0.8 ng/m*l*, serum PICP 209 ng/m*l*, urine NTx/Cr 133.5 nM BCE/mM Cr). Serum PICP and urine NTx/Cr are therefore sometimes useful in detecting skeletal metastasis in prostate cancer patients whose serum PSA values are not elevated.[31]

The first change seen in bone metastasis is osteoclastic proliferation distant from the tumor. As the tumor edge approaches the endosteal surface of the cortex, localized destruction occurs in which osteoclasts are prominent.[32] Bone resorption markers thus retain the possibility as an

effective index of the early diagnosis of skeletal metastasis. More sensitive markers which complement serum PSA need to be developed to more accurately diagnose skeletal metastasis in prostate cancer patients.

CONCLUSIONS

1. Serum PSA was more sensitive for monitoring skeletal metastasis than serum PICP and urine NTx/Cr. Serum PSA could statistically improve the ability to diagnose skeletal metastasis combined with serum PICP or urine NTx/Cr, but serum PICP or urine NTx/Cr could not statistically improve them when combined with serum PSA.
2. Minimal skeletal metastasis was difficult to diagnose with serum PSA. The ability to diagnose skeletal metastasis using serum PSA did not exceed that of bone scintigraphy.
3. In some patients with skeletal metastasis, urine NTx/Cr and/or serum PICP values were elevated although no elevation was seen in serum PSA values (3/69).
4. The reliability of serum PSA and PICP and urine NTx/Cr rose in the EOD 4 group.

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