The Relative Use of Eight Collagenous and Noncollagenous Markers for Diagnosis of Skeletal Metastases in Breast, Prostate, or Lung Cancer Patients

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Abstract

The present study was sought to assess the relative use of eight biomarkers for the detection of bone metastases in cancer forms frequently spreading to the skeleton. Participants were 161 patients with either breast, prostate, or lung cancer. The presence and extent of bone metastases was assessed by imaging techniques (computer tomography and/or magnetic resonance imaging) and Technetium-99m scintigraphy. Serum or urinary level of the bone resorption markers (αα-CTX, ββ-CTX, NTX, and ICTP), formation marker (BSAP), and osteoclastogenesis markers (osteoprotegerin, RANKL, and TRAP5b) was measured by commercially available immunoassays. When assessed on a group basis, all biomarkers, except for osteoprotegerin and RANKL, were significantly elevated in patients compared with those without bone metastases (P < 0.05). Biomarkers had greater diagnostic value in breast and prostate cancer patients, yet αα-CTX, NTX, and ICTP were able to discriminate lung cancer patients with or without bone metastases (P < 0.05). Strong linear associations were seen between the extent of skeletal infiltration and levels of the different biomarkers, except for osteoprotegerin and RANKL. Furthermore, all biomarkers (except for osteoprotegerin and RANKL) were indicative at the early stage of skeletal involvement (one to five metastases). When expressing sensitivity as the percentage increase in biomarker level relative to patients without bone metastases, αα-CTX showed the largest relative increases at each stage of the metastatic disease. These results suggest that closer monitoring of cancer patients with serial measures of biomarkers might facilitate the timely diagnosis of skeletal metastases.

Introduction

Cancers have the ability to metastasize to organs distant from the site of the primary tumor. Breast, prostate, and lung cancer are primary tumors that most frequently metastasize to the skeleton. The presence of a metabolically and hormonally active bone metastasis exerts profound effects on surrounding bone cells. The consequence of this is an alteration of bone resorption, formation, or both, and thereby an interference with the mechanisms ultimately involved in the maintenance of tissue integrity (1). The chronic presence of bone metastases often results in complete pathologic remodeling of the affected bone compartment, making affected bones vulnerable to several complications. Such complications include pathologic fractures (spinal cord compression, hypocalcemia, and severe bone pain), all reducing quality of life and worsening fractures (spinal cord compression, hypocalcemia, and severe bone pain), all reducing quality of life and worsening

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Note: D.J. Leeming and M. Koizumi contributed equally to this work.

Conflict of interest: D.J. Leeming, I. Byrjalsen, B. Li, and P. Qvist are full-time employees of Nordic Bioscience, a company engaged in the development and marketing of bone and cartilage markers.

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Therefore, the aim of this study was to assess the relative indicative value of this new marker for the presence of bone metastasis in patients with breast, lung, and prostate cancer assessed with reference to seven previously proposed biomarkers.

Patients and Methods

Patients and Study Design. A total of 162 cancer patients were referred to the Cancer Institute Hospital, Tokyo between October 2002 and April 2004. All patients underwent bone scanning using a radionuclide (Technetium-99m) scintigraph together with computer tomography and/or magnetic resonance imaging to verify and quantify the presence of bone metastases. All patients with skeletal complications were newly diagnosed, and none had received therapies known to influence bone turnover in the past 2 years before entry to the study. One breast cancer patient also retained Paget’s disease and therefore was excluded from the analysis.

All participants signed an approved written consent; the study was done in accordance with the Helsinki Declaration II and Standards of Good Clinical Practice. The Local Ethical Committee has approved the study protocol.

Severity of Metastatic Bone Disease (Soloway Score). Number of bone metastasis was recorded, and the skeletal load was graded, as previously proposed by Soloway et al. (15). Briefly, Soloway 0 refers to patients without bone metastasis; Soloway 1 refers to patients with <6 bone metastases; Soloway 2 refers to patients with <20 bone metastases; Soloway 3 refers to patients with >20 but less than a ‘super scan’; Soloway 4 refers to patients with ‘super scan’ that is defined by a >75% involvement of the ribs, vertebrae, and pelvic bones.

Quantification of Biochemical Markers. Second morning void urine and blood samples were collected from each patient and stored at −40°C until assaying. Second morning void urine was used for estimation of bone resorption by measuring the level of ALP and CTX, BETA CTX, and NTx. The concentration of osteocalcin and βCTX fragments was measured by the urinary ALPHA CTX ELISA (13) and Serum CrossLaps ELISA (Nordic Bioscience, Herlev, Denmark), respectively. Urinary samples were diluted at least 1:25 in incubation buffer. The concentration of NTx fragments was determined using the Osteomark NTx ELISA (Wampole Laboratories, Princeton, NJ). Urinary excretion was corrected for creatinine levels measured by an automated urine analyzer (Hitachi-912, Roche, Mannheim, Germany).

Serum samples were used for measuring ICTP, BSAP, TRAP5b, osteoprotegerin, and RANKL. The concentration of ICTP fragments was determined using the Osteomark ICTP ELISA (Immundiagnostik AG, Bensheim, Deutsland). All samples were tested in a blinded manner.

Statistical Analysis. Data shown are mean ± SD, unless otherwise indicated. Basic demographic characteristics were compared with Student’s t test for unpaired observations. The values of each of the biochemical markers were logarithmically transformed to obtain normality. Comparison between cancer types of the level of the marker in patients without bone metastasis was done by ANOVA using the General Linear Models Procedure of the Statistical Analysis System (SAS, Cary, NC). The same statistical procedure was used for comparison of the level in patients without and with bone metastasis for each cancer type. In the comparison of the levels for each Soloway score against the level in patients without metastasis, the Dunnett’s adjustment of the level of significance was employed to correct for multiple comparisons. Differences and associations were considered statistically significant if P < 0.05.

Results

Demographic Characteristics of Subjects. Table 1 shows the basic demographics of 161 cancer patients stratified according to bone metastasis and cancer type. There were no statistically significant differences between patients with or without bone metastasis.

Collagenous Resorption Markers. Figure 1 shows mean values of the different resorption markers (αCTX, βCTX, NTx, and ICTP) in patients stratified according to cancer type and the presence or absence of bone metastasis. There was a uniform pattern of significantly increased levels of the resorption markers in patients with bone metastasis compared with those without. Differences between patients with or without bone metastasis were more pronounced in patients with breast or prostate cancer compared with differences in lung cancer patients. Nevertheless, only βCTX could not discriminate lung cancer patients with or without bone metastasis.

Noncollagenous markers

Bone Formation Marker. Data obtained with the use of the formation marker BSAP are summarized in Fig. 1. In both breast cancer and prostate cancer patients but not in lung cancer patients, skeletal involvement was associated with significantly elevated levels of the formation marker. Judging from the magnitude of differences, the formation marker was particularly indicative for the presence of bone metastasis in prostate cancer patients.

Osteoclastogenesis Markers. TRAP5b, an indicator of osteoclast number, was significantly elevated in the presence of bone metastasis when measured in breast and prostate cancer patients. However, no significant differences were noted between lung cancer patients with or without bone metastasis. The bone-regulatory proteins, osteoprotegerin and RANKL

Table 1. Demographic data on cancer patients stratified by cancer type and presence or absence of bone metastases

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer</th>
<th>Lung cancer</th>
<th>Prostate cancer</th>
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<tbody>
<tr>
<td></td>
<td>−BM</td>
<td>+BM</td>
<td>−BM</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
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<tr>
<td>Age (y)</td>
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<td>14</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>53.6 ± 10.5</td>
<td>53.1 ± 11.5</td>
<td>59.4 ± 11.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>155.2 ± 5.7</td>
<td>155.6 ± 6.4</td>
<td>160.9 ± 8.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>53.2 ± 8.7</td>
<td>56.6 ± 9.8</td>
<td>59.4 ± 8.0</td>
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<td>Gender (n)</td>
<td>45 F</td>
<td>45 F</td>
<td>23.0 ± 3.1</td>
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</table>

NOTE: Results shown are means ± SD.
Abbreviations: F, female; M, male; BM, bone metastases; BMI, body mass index.
showed no significant differences with relation to the presence or absence of bone metastasis in any of the three cancer types, except for a modest yet statistically significant elevation of osteoprotegerin in breast cancer patients with bone metastasis ($P = 0.04$).

Relation to the Extent of Metastatic Bone Disease. Because most measured biomarkers carried little potentials for providing sufficient diagnostic value in lung cancer patients, this subpopulation was excluded from further analyses seeking associations between the extent of skeletal involvement and circulating/urinary levels of the biomarkers. Accordingly, data from breast and prostate cancer patients were pooled together for these analyses ($n = 132$). The demographic data for patients stratified according to Soloway score is indicated in Table 2. There were no linear associations between Soloway score and the demographic characteristics of patients.

Figure 2 shows associations between Soloway score and the different markers. All bone turnover markers and TRAP5b indicated linear increases with advancing severity of the metastatic involvement of the skeletal system. In contrast, levels of osteoprotegerin and RANKL were fairly uniform across the different categories.

Diagnostic Value at the Early Stage of Metastatic Bone Disease. Importantly, the level of bone turnover markers in patients with Soloway score 1 (one to five metastases) was significantly elevated compared with those in patients without...
bone metastasis (Fig. 2). The most consistent elevations were revealed by αCTX (P = 0.002) and NTx (P = 0.007) assays. The osteoclastogenesis marker TRAP5b was also able to differentiate patients with Soloway 1 from those without bone metastasis (P = 0.04), which was however not true for osteoprotegerin and RANKL.

**Relative Responsiveness of Markers.** To obtain initial insights into the relative sensitivity of the different markers to signal skeletal involvement, we plotted relative increases in the markers on an individual basis as a function of the Soloway score. The plot indicated a trend toward greater relative increases in the level of the αCTX marker compared with other markers; differences becoming more evident with increasing Soloway score (Fig. 3).

**Discussion**

This is the first study describing parallel evaluation of αCTX with other promising candidate biomarkers proposed for the diagnosis of bone metastases in a study population, including all three cancer types that are known to spread into the skeletal system. The main findings were as follows: (a) Different degradation fragments of collagen type I were generally best to differentiate patients with or without bone metastasis regardless of cancer type. (b) The formation marker, BSAP was particularly useful to indicate the presence of bone metastasis in prostate cancer patients. (c) Osteoclastogenesis markers in general had a poor diagnostic value, except for TRAP5b, an indicator of osteoclast number, that was able to indicate the presence of bone metastasis in breast and in particular in prostate cancer patients. (d) The level of all markers, except for osteoprotegerin and RANKL, was linearly associated with the severity/extent of metastatic bone disease. (e) The significant increases in patients with Soloway 1 compared with those without bone metastasis suggest that biomarkers carry notable potentials for monitoring and early detection of bone metastasis in cancer patients. In this latter regard, our preliminary findings suggest that αCTX is the most sensitive of collagen type I–derived biomarkers.

Currently, the diagnosis of bone metastasis in cancer patients relies predominantly on imaging techniques, such as plain radiography or Technetium-99m scintigraphy. Although these techniques provide useful diagnostic tools, their use to provide early diagnosis or for close monitoring of patients is not without limitations. Routine radiography only gives definitive diagnosis when the bone is already substantially damaged by the tumor. Although scintigraphy is more sensitive and even can give quantitative information regarding skeletal involvement (i.e., number of “hotspots”), this examination is also a more expensive, invasive, time-consuming, and exposes cancer patients to irradiation, limiting its use for monitoring purposes. Thus, these weaknesses of current methodology point out an unmet need for establishing supplementary diagnostic tools.

The presence of tumor cells in bone tissue may have a strong effect on the mechanisms of bone turnover maintaining tissue integrity and function. Tumor cells are able to secrete soluble factors, such as hormones, cytokines, and growth factors, which directly or indirectly stimulate osteoclast and osteoblast proliferation and function. The main mechanism by which bone metastases evoke dysregulation of bone turnover is the ability of tumor cells to stimulate the secretion of RANKL in osteoblastic stromal cells via release of parathyroid hormone–related protein (16, 17) or directly stimulate osteoclast by secretion of tumor necrosis factor-α, colony-stimulating factor-1, interleukin-1, interleukin-6, interleukin-8, interleukin-10, and RANKL (18). RANKL activates its specific receptor RANK on osteoclasts precursors and promotes cellular maturation in the presence of macrophage colony stimulation factor. The ultimate consequence is an increased survival rate and number of mature osteoclast and thus generation of an osteolytic metastasis, involving collagen type I degradation. During osteoclastic resorption, growth factors, such as bone morphogenetic protein-2 and transforming growth factor-β, are released from the bone matrix that can activate tumor cells, thereby setting up the vicious cycle. Less is known about osteoblastic metastases that also are associated with increased bone turnover, which in contrast to that in osteolytic lesion, is predominated by bone formation. Thus, in this case, tumor cells stimulate osteoblast function via endothelin, bone morphogenetic proteins, and insulin-like growth factors. Appearance of bone metastases occurs in 70% of patients with advanced breast and prostate cancer. Breast cancer metastases are predominately osteolytic (70-85%; ref. 19), whereas the majority of prostate cancer metastases are osteoblastic (65%; ref. 20), although mixed lesions exists in both cancer types (21). Collectively, these mechanisms provide rational for investigating the use of different biomarkers [bone regulatory proteins (RANKL and osteoprotegerin), indicators of osteoclast number (TRAP5b) and indicators of bone formation (BSAP), or different degradation fragments of collagen type I (CTX, NTx, and ICTP)] for their ability to indicate skeletal involvement in cancer patients.

**Resorption Markers.** Our findings indicated that measuring serum or urinary levels of different degradation fragments of collagen type I was a useful approach to differentiating patients with or without bone metastasis. When comparing the use of each marker in different cancer types, somewhat more consistent elevations were found in breast and prostate cancer patients with bone metastasis, although the biggerender composition of the group of lung cancer patients has implications in this regard. Furthermore, when comparing the pattern of differences obtained on a group basis, virtually no major differences were seen, despite a notably weaker indicative value of βCTX compared with αCTX and the other collagen-derived markers. Two recent studies undertaken in prostate or breast cancer patients support the higher sensitivity of αCTX for detecting the presence of bone metastases compared with βCTX (4, 13).

### Table 2. Demographic data of breast and prostate cancer patients stratified according to the severity of metastatic bone disease (i.e., Soloway score)

<table>
<thead>
<tr>
<th>Soloway score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>n</td>
<td>70</td>
<td>26</td>
<td>13</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.0 ± 13.1</td>
<td>60.0 ± 12.1</td>
<td>51.0 ± 11.0</td>
<td>60.0 ± 18.2</td>
<td>62.8 ± 11.2</td>
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<tr>
<td>Body height (cm)</td>
<td>157.6 ± 6.9</td>
<td>156.5 ± 5.9</td>
<td>155.9 ± 6.2</td>
<td>158.5 ± 7.0</td>
<td>155.9 ± 8.7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>56.5 ± 10.1</td>
<td>56.9 ± 11.2</td>
<td>57.9 ± 7.3</td>
<td>57.6 ± 5.6</td>
<td>58.4 ± 11.4</td>
</tr>
<tr>
<td>BMF (kg/m²)</td>
<td>22.7 ± 3.2</td>
<td>23.2 ± 4.0</td>
<td>23.8 ± 3.2</td>
<td>22.9 ± 2.4</td>
<td>23.9 ± 3.0</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>45 F, 25 M</td>
<td>20 F, 6 M</td>
<td>12 F, 1 M</td>
<td>12 F, 3 M</td>
<td>5 F, 3 M</td>
</tr>
</tbody>
</table>

**NOTE:** Data shown are mean ± SD. Abbreviations: F, female; M, male; BMI, body mass index.

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Studies focusing on the use of αCTX showed consistent elevation of the marker in prostate cancer patients with bone metastasis compared with healthy male controls (22) or cancer patient without bone metastasis (23). In contrast, only one study described significant elevation in βCTX in male lung cancer patients with bone metastasis (9), but in light of our negative findings, it remains to be established whether this biomarker is a selective indicator of lung metastasis in bones of males. Collectively, when assessed on a group basis, collagen degradation fragments are generally informative indicators of bone metastasis in particular in breast and prostate cancer patients.

**Figure 2.** Resorption (αCTX, βCTX, NTx, and ICTP), formation (BSAP), and osteoclastogenesis (TRAP5b, OPG, and RANKL) marker levels in 132 breast and prostate cancer patients stratified according to the extent of metastatic bone disease described by the Soloway score 0 (−BM) and 1 to 4 (+BM). Columns, mean; bars, SE.
that the diagnostic value may vary with ethnical background were undertaken in Caucasians, it is tempting to speculate included Japanese patients only, whereas previous studies ascribed to methodologic issues. Because the present study as the aforementioned studies did (26, 28, 29), which seems to offer universally applicable diagnostic tools for the detection of bone metastases.

Traditionally, TRAP5b has been classified as a resorption marker, but recent observations suggest that it is more closely related to osteoclast number (10). In light of the earlier described direct and indirect effect of tumor cells on osteoclastogenesis, it is not surprising that on a group basis TRAP5b revealed trends similar to those indicated by the resorption markers. Our findings are in accordance with previous studies showing that TRAP5b can differentiate breast cancer but not lung cancer patients with or without bone metastasis (9, 10, 30). Collectively, estimating osteoclast number with TRAP5b can be a useful approach, but it does not seem to be a superior diagnostic tool compared with collagen-derived markers.

Severity of Metastatic Load. Few studies have addressed the question whether bone turnover markers can give quantitative information about the extent of skeletal involvement in cancer disease. When using the Soloway score system defining four stages of metastatic involvement in breast and prostate cancer patients, the present study revealed linear increases in bone formation and resorption markers as well as the indicator of osteoclast number with advancing severity, which is in accordance with previous findings (7, 24). Our findings are also in line with the study by Jung et al., indicating the inability of osteoprotegerin and RANKL to reflect the severity of metastatic bone disease (28).

A possible explanation to these latter findings could be that tumor may secrete these bone regulatory proteins regardless of their location, and thus circulating levels maybe elevated even when skeletal involvement has not emerged.

Indicative Value in the Early Phase. Because early diagnosis of bone metastasis is the ultimate aim of improving the diagnostic approach to cancer patients, we dedicated particular interest to the ability of the different markers to differentiate between patients with Soloway score 0 or 1. Except for osteoprotegerin and RANKL, all evaluated markers indicated elevated circulating/urinary levels in patients with a Soloway score of 1. When comparing the increases in the level of biomarkers relative to the values seen in patients without bone metastasis, αcCTX was consistently the most responsive biomarker at all stages of the metastatic disease (i.e., in each Soloway category). This latter marker was followed by BSAP and NTx, which were characterized by virtually identical sensitivities; however, whereas NTx provided comparable diagnostic value in both cancer types, the apparent high sensitivity of BSAP was mainly driven by its good indicative value in prostate cancer patients. Although this is the first systematic comparative study, including αcCTX, observations regarding the other markers seem to be in line with previous observations. For example, our findings confirm previous findings that NTx levels are a more sensitive indicator of bone metastasis than ICTP in breast, lung, and prostate cancer patients (7). In addition, the results are also in line with the previous report that showed TRAP5b is able to identify breast cancer patients with extensive bone metastasis but has limited sensitivity to point out patients with limited bone metastasis (10, 30).

Figure 3. Relative increases in bone resorption, bone formation, and osteoclastogenesis markers as a function of the extent of skeletal involvement assessed in 132 breast and prostate cancer patients. Relative increases are expressed as percentage of levels in patients with Soloway score 0.

**Formation Markers.** In the present study, the biomarker of bone formation, BSAP, was most indicative for the presence of bone metastases in prostate cancer patients. These observations are in accordance with previous reports (8, 24) and the general perception that bone metastasis arising from prostate frequently induces abnormal bone formation when invading bone tissue. Indeed, prostate cancer cells were shown to release a number of factors, such as transforming growth factor-β, bone morphogenetic proteins, fibroblast growth factor, and endothelin-1, that all can evoke osteoblast activation (25). Despite its advantages in the diagnosis of bone metastases in prostate cancer patients, BSAP has been reported as the least sensitive to point out bone metastasis when compared with a number of collagen-derived markers in studies, including breast cancer patients (5, 7). Similar to findings with βCTX, BSAP also was indicative for the presence of bone metastasis in male lung cancer patients (9). Collectively, when assessed on a group basis, the bone formation marker BSAP seems to be a powerful diagnostic tool for drawing attention to bone metastasis in prostate cancer patients.

**Osteoclastogenesis Markers.** In a published study by Jung et al., the bone-regulatory protein osteoprotegerin was the best to indicate the presence of bone metastasis in prostate cancer patients compared with TRAP5b, RANKL, BSAP, and a number of resorption markers (8). The advantages of osteoprotegerin in prostate cancer patients are supported by independent groups (27-29). However, the present study did not find significant differences between prostate cancer patients with or without bone metastasis. We used the same commercially available assay for measuring osteoprotegerin as the aforementioned studies did (26, 28, 29), which seems to exclude the possibility that the apparent discrepancies can be ascribed to methodologic issues. Because the present study included Japanese patients only, whereas previous studies were undertaken in Caucasians, it is tempting to speculate that the diagnostic value may vary with ethnic background of the patient, which needs to be evaluated in multiethnic cohorts. Despite these apparent discrepancies, our findings are in accordance with previous reports showing modest to no indicative value of osteoprotegerin in breast cancer patients (8, 11). Although the presence of RANKL mRNA and protein in skeletal metastases of breast and prostate cancer have been shown (16), circulating RANKL failed to differentiate prostate cancer patients from those without bone metastasis (28), which is similar to our results revealing poor indicative value of this bone regulatory protein. Collectively, these findings suggest that circulating levels of the bone regulatory proteins (osteoprotegerin and RANKL) do not seem to offer universally applicable diagnostic tools for the detection of bone metastases.
In conclusion, the present study provide further support for the emerging concept that bone turnover markers carry notable potentials for the early detection of bone metastasis in patients with diagnosed cancer disease. Whereas the non-collagenous formation marker BSAP is a powerful indicator of metastatic bone disease in prostate cancer patients, the collagenous markers carry similar diagnostic value in both prostate and breast cancer patients. These preliminary analyses suggest that αCTX is the most sensitive collagenous marker to reflect accelerated bone resorption induced by bone metastases. However, to fully establish the role of biomarkers in clinical practice, prospective studies are needed. The ultimate question is whether serial measurements of biomarkers in patients with diagnosed cancer disease could replace imaging techniques for monitoring purposes and capturing the increase of skeletal invasion. However, to establish the use of biomarkers for such purposes, we need prospective studies using parallel monitoring of cancer patients with both imaging techniques and biochemical markers.

References
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