Abstract. Background: The aim of this study was the investigation of the diagnostic value of the amino-terminal propeptide of type I collagen (P1NP) and the tumour markers, CA 15-3 and CA 125, in patients with breast and ovarian cancer. Patients and Methods: Serum levels of P1NP, CA 15-3 and CA 125 were analyzed using specific immunoassays. Baseline serum samples of 66 patients with metastatic breast cancer and 34 patients with metastatic ovarian cancer under chemotherapy were investigated. Results: P1NP concentrations were elevated in up to 70% of patients with confirmed bone metastases. The P1NP levels were significantly higher in patients with bone metastases (median: 134 ng/ml) than in those without bone spread (median: 58.5 ng/ml). Conclusion: Markers of biochemical bone remodeling can be used in assessing and managing patients with malignancies that metastasize to bone. These markers are abnormally raised in the blood of patients with metastatic bone disease.

Biochemical markers of bone are direct or indirect products or enzymes of active osteblasts (1-4). Tumour markers are still disappointing in diagnosis and follow-up (5). A malignant tumour can destroy bone mass by local invasive growth or by producing enzymes which act in systemic bone resorption (6-8, 11). Local spread or systemic bone resorption products of malignant tumours may also lead to bone destruction. Beside organ systems such as the liver and lungs, the skeleton is one of the most common organs affected by metastases. The majority of bone metastasis is caused by carcinomas of the breast, prostate, lung, kidney, ovary, and multiple myelomas (9-10, 12, 13).

Several laboratory methods and markers have been developed to assist the diagnosis of bone lesions. The accurate diagnosis of bone metastasis and early induced antiresorptive and cancer therapy are essential for reducing morbidity and mortality. Bone is a tissue which undergoes continual resorption and formation. Malignant tumours which are spread to bone cause osteolytic, osteoblastic or mixed lesions. Bone is resorbed by osteoclasts rather than through the tumour cells. Under these circumstances, bone turnover is elevated and some of the involved enzymes and metabolic products can be measured. Several markers of bone turnover with different sensitivity and specificity have been described so far.

Patients and Methods

Tumour markers CA 15-3 and CA 125, as well as P1NP, were measured in 100 patients with malignancies. All patients were informed and gave consent. Serum samples were obtained from 66 patients with metastatic breast cancer and 34 patients with metastatic ovarian cancer. Serum samples of 100 patients with benign diseases served as the control group. All serum samples were taken prior to chemotherapy or radiation. The sera were separated from blood by centrifugation at +4°C less than 1 h after sample collection, then frozen and stored at –20°C until assayed. Serum levels of CA 15-3, CA 125 and P1NP were measured using an electrochemiluminescence method (sandwich principle, with streptavidin labeled microparticles and monoclonal antibodies labeled with a ruthenium complex) with the Elecsys 2010 analyzer (ROCHE Co., Mannheim, Germany). Bone marker levels of P1NP were tested for association with the presence or absence of bone scan-documented metastases.

Results

The serum stability of P1NP at different temperatures is shown in Table I. The median values for a healthy volunteer were 48 ng/ml for P1NP, 25 U/ml for CA 15-3, and 35 U/ml for CA 125. In 46 breast cancer patients, a significant increase of P1NP and CA 15-3 was seen. In all of these patients, the skeletal scintigram after the increase was
demonstrated, showed skeletal metastases. Patients with metastasizing breast carcinoma had elevated P1NP (median 134 ng/ml) and CA 15-3 concentrations (median 234 U/ml). Patients with more than 7 bone lesions had a significantly higher P1NP level (median 134 ng/ml, \( p = 0.005 \)). The ROC curves for P1NP, CA 15-3 were 0.683 and 0.769 respectively. The most accurate sensitivity and specificity was 48.9% and 92.4% for CA 15-3, and 49.2% and 91.5% for P1NP, respectively.

Patients with metastasizing ovarian cancer had elevated P1NP (median 128 ng/ml) and CA 125 concentrations (median 370 U/ml). The sensitivity and specificity was 69.4% and 99% for CA 125, and 52.4% and 89.4% for P1NP, respectively. The ROC curves for P1NP and CA 125 were 0.692 and 0.798, respectively.

The concentrations of P1NP and tumour markers in gynecological carcinomas are shown in Table II. P1NP levels were associated with the number of bone metastases.

### Conclusion

This study demonstrates the role of the tumour markers CA 15-3 and CA 125 as independent prognostic factors in breast and ovarian cancer. Both tumour-associated antigens have the advantage of a test with low invasiveness during the usual preparation for surgery. Without obtaining tumour tissue preoperatively, they offer high prognostic validity. Biochemical markers of bone resorption and bone formation are abnormally increased in the samples of patients with metastatic bone disease. Thus, markers of osteoblast function, such as P1NP, appear to be useful in assessing and managing patients with malignancies that metastasize to bone. In our study, the bone marker P1NP was significantly associated with the presence of bone metastases and the level of skeletal participation. In conclusion, when skeletal metastases are suspected in patients with breast or ovarian carcinoma, a combination of skeletal scintigam and evaluation of P1NP as a sensitive marker seems to be advantageous.

### References


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Table I. Stability of P1NP in serum samples.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Room temperature</td>
<td>24 hours</td>
</tr>
<tr>
<td>+4° -8°C</td>
<td>6 days</td>
</tr>
<tr>
<td>-20°C</td>
<td>6 months</td>
</tr>
<tr>
<td>-80°C</td>
<td>12 months</td>
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Table II. P1NP and tumour marker concentrations in breast and ovarian cancer patients.

<table>
<thead>
<tr>
<th>Tumour</th>
<th>P1NP (ng/ml)</th>
<th>CA 15-3 (U/ml)</th>
<th>CA 125 (U/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mean range</td>
<td>mean range</td>
<td>mean range</td>
</tr>
<tr>
<td>Ovarian</td>
<td>187.2 58.6-587.3</td>
<td>365.4 100-1403</td>
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<tr>
<td>Breast</td>
<td>224.4 56.0-923.1</td>
<td>758.7 103-6817</td>
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