Diagnostic and Prognostic Use of Bone Turnover Markers

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Abstract

The use of bone turnover markers in oncology includes monitoring of anticancer treatment in patients with malignant disease metastatic to the bones (*therapeutic monitoring*), predicting the risk of bone relapse in patients with a first diagnosis of potentially curative, early-stage malignant tumors (*prognostic use*), and making an early diagnosis of (microscopic) malignant bone disease in patients with a known malignant tumor to start early bone-targeted treatment and avoid skeletal-related events (*diagnostic use*). Concerning *prognostic use*, there is limited evidence for bone turnover markers to predict the occurrence of metachronous bone metastases in patients with early-stage malignant tumors, with serum PINP (N-terminal propeptide of procollagen type 1), ICTP (Carboxyterminal cross-linked telopeptide of type I collagen), bone sialoprotein (BSP), and tumor immunoexpression of BSP being the most promising candidates. Concerning *diagnostic use*, serum bone-specific alkaline phosphatise (BSAP), PINP and osteoprotegerin (OPG) were repeatedly shown to be associated with synchronous bone metastases in patients with breast or lung cancer, but sensitivity of these markers was too low to suggest that they might be preferred over conventional bone scans for the diagnosis of bone metastases. A somewhat higher sensitivity for the diagnosis of bone metastases was found for urinary NTx (N-terminal cross-linked telopeptide of type I collagen) and serum ICTP in solid tumor patients, serum TRAcP-5b (Tartrate-resistant acid phosphatase type 5b) in patients with breast cancer and serum BSAP, PINP and OPG in prostate cancer patients. Both prognostic and diagnostic use of bone turnover markers are reviewed in this chapter.

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Contents

1 Introduction

The majority of solid malignant tumors have a strong propensity to spread to the bone. The mechanisms involved in cancer dissemination to bone are complex, and the changes in bone metabolism are very profound, once bony metastases have occurred. The use of bone markers in oncology covers mainly three topics. The first is monitoring of anticancer treatment in patients with established malignant disease metastatic to the bones. However, this is not the topic of the present chapter. The second application is to use bone turnover markers as a prognostic tool for patients with a first diagnosis of potentially curative, early-stage malignant disease, to predict the risk of disease relapse in the bones, and potentially apply preventive measures such as adjuvant chemotherapy or bisphosphonates. The third application is to use bone markers for an early diagnosis of (microscopic) malignant bone disease in patients with a known malignant tumor, and potentially start early bone-targeted treatment to delay overt malignant bone disease with subsequent complications such as pain, fractures and immobility.

Diagnostic procedures for metastatic bone disease traditionally focus on the localization and characterization of the lesion, using different imaging techniques such as radiographs, computed tomography, magnetic resonance imaging (MRI),

^{99}technecium bone scans and positron-emission tomography (PET) scans. These diagnostic tools have been proven to be effective in identifying established metastatic spread. However, earlier (microscopic) stages of malignant bone disease cannot be diagnosed with conventional radiological or radionuclide imaging. In such cases, bone markers might be of particular value to enable early diagnosis of malignant bone disease, or even provide some information on the future risk of developing bone metastases in patients with early malignant disease. Under normal conditions, bone remodeling is a balanced, lifelong continuum of resorption of old bone (through the action of osteoclasts) and replacing the removed tissue by an equal amount of newly formed bone (through the action of osteoblasts). The presence of bone metastases greatly perturbs this balance. Driven by a number of tumor-derived factors, the osteoclasts surrounding cancer metastases become activated and start resorbing bone substance. By contrast, bone formation may be increased or decreased, but is usually inadequate to compensate for the increase in bone resorption. Radiographically, this results in predominantly lytic or mixed lytic–sclerotic lesions, as typically seen in breast cancer metastases to bone. By contrast, sclerotic lesions are typically found in prostate cancer, characterized at the cellular level by a relative excess of bone formation as compared to bone resorption. However, even the skeletal metastases of prostate cancer are characterized by an increased rate of both bone resorption and formation. Therefore, high bone turnover is a general feature of metastatic bone disease, and is accompanied by a respective increase of both markers of bone formation and bone resorption.

There are some practical and important issues for the analysis and interpretation of bone markers, including diurnal variation of serum concentrations, that might reach 20% of the absolute values, potential seasonal variation and gender differences. These various reasons for diagnostic variability have recently been reviewed by Coleman et al. (2008). Although bone markers may have the potential as diagnostic or prognostic tools in cancer patients, the available data do not allow final conclusions regarding the accuracy and validity of any of the presently used markers in the primary or secondary prevention of bone metastases. Still, available data allow to give an overview on the potential diagnostic and prognostic use of bone markers in patients with solid malignancies or multiple myeloma, as outlined in this chapter.

2 Overview on Bone Markers

2.1 Bone Formation Markers

By-products of osteogenesis or osteoblast-secreted factors can provide insight into the activity of bone formation (Table 1).

2.1.1 Bone-Specific Alkaline Phosphatase

Bone-specific alkaline phosphatase (BSAP) hydrolyses pyrophosphates, thereby removing an inhibitor of osteogenesis while creating the inorganic phosphate that is required for generation and deposition of hydroxyapatite. BSAP is secreted from

Table 1 Markers of bone formation

Marker	Specimen	Normal range	Diagnostic use for bone metastases	Prognostic use for bone metastases
BSAP	Serum	PreM. women: 2.9–14.5 μg/L (Coleman et al. 2008) PostM. women: 3.8–22.6 μg/L (Coleman et al. 2008) Men: 3.7–20.9 μg/L (Coleman et al. 2008)	High values associated with bone metastases in 200 cancer patients (Oremek et al. 2003) High values associated with bone metastases in 295 prostate cancer patients (Lorente et al. 1999)	
OC	Serum	PreM. women: 1.0–36 μg/L (Heuck and Wolthers 1998) Men: 1.0–35 μg/L (Heuck and Wolthers 1998)	Low values associated with bone metastases in lung cancer patients (Karapanagiotou et al. 2010)	Low values predict relapse in bone in 79 patients with newly diagnosed NSCLC (Terpos et al. 2009)
PICP	Serum	Women: 50–170 μg/L (Caillot-Augusseau et al. 1998; Puistola et al. 1993) Men: 38–202 μg/L (Caillot-Augusseau et al. 1998; Puistola et al. 1993)	High values associated with bone metastases in 200 cancer patients (Oremek et al. 2003) High values associated with bone metastases in 276 cancer patients (Koizumi et al. 2003)	High values predict tumor relapse in bone in 373 early breast cancer (Jukkola et al. 2001)
PINP	Serum	Women: 31.7–70.7 μg/L (Bauer et al. 2006) Men: 21–78 μg/L (Nguyen et al. 2007)	High values associated with bone metastases in breast cancer patients (Luftner et al. 2005) High values associated with bone metastases in prostate cancer patients (Koizumi et al. 2001; Thurairaja et al. 2006; Koopmans et al. 2007)	

BSAP bone-specific alkaline phosphatase, *OC* osteocalcin, *PICP* C-terminal propeptide of procollagen type 1, *PINP* N-terminal propeptide of procollagen type 1, *PreM* premenopausal, *PostM* postmenopausal

osteoblasts to the bone matrix to allow for bone mineralization. There are different alkaline phosphatase isoforms secreted by various organs into the serum, with predominant isoforms originating from the bone, liver or intestines. The bone-specific isoform (BSAP) is a relatively specific marker for osteogenesis. However, elevated serum concentrations of BSAP might also be found in patients with liver dysfunction, as BSAP is normally cleared from the serum by the liver.

2.1.2 Osteocalcin

Osteocalcin (Bauer et al. 2006) is the major non-collagen protein in the bone matrix, and is produced by osteoblasts among other cells. Osteocalcin serum or urinary concentrations reflect both osteolysis and osteogenesis, and concentrations can also be increased in patients with renal dysfunction or hyperlipidemia. Multiple isoforms of osteocalcin are found in the serum or in urine, and current assays might not detect them all (Ivaska et al. 2005).

2.1.3 Propeptides of Procollagen Type I

Collagen type I comprises approximately 90% of the organic bone matrix. After extracellular excretion of the N-terminal propeptide of procollagen type 1 (PINP) and C-terminal propeptide of procollagen type 1 (PICP), these peptides are coupled to collagen and released into the serum. Therefore, levels of PINP and PICP reflect the activity of osteogenesis. Both PINP and PICP are removed by the liver. Other than PICP, PINP can also be deposited directly into the bone matrix, and has been found to constitute 5% of the non-collagenous protein in bone. Data from the literature suggest that PINP has a greater diagnostic validity as compared to PICP (Brasso et al. 2006).

2.2 Bone Resorption Markers

By-products of osteolysis or osteoclast-secreted factors can provide insight into the activity of bone resorption (Table 2).

2.2.1 Pyridinoline and Deoxypyridinoline

Pyridinoline (PYD) and deoxypyridinoline (DPD) are products of the posttranslational modification of lysine and hydroxylysine. They stabilize mature type-1 collagen in bone, cross-linking the telopeptide domain of a collagen fibril to the helical region of an adjacent collagen fibril. Bone resorption results in a release of PYD and DPD into the blood, followed by renal excretion. DPD is found almost exclusively in bone. The contribution from soft tissues to the systems pool of PYD might make the latter less accurate than other bone markers.

2.2.2 C-telopeptide and N-telopeptide of Type I Collagen

C-terminal cross-linked telopeptide of type I collagen (CTx) and N-terminal cross-linked telopeptide of type I collagen (NTx) are the carboxyterminal and

aminoterminal peptides, respectively, of mature type I collagen, and both are released during bone resorption. Degradation products of collagen are of various sizes, i.e. osteoclast-derived fragments are different from those formed in non-skeletal tissues. The CTx peptide exists as α or β-isoforms, with β-isoforms found more often in mature bone. Both CTx and NTx can be analyzed in serum or urine, but urinary concentrations must be adjusted for urine dilution, which may add to the analytical error. Because CTx levels were less elevated in patients with Paget's disease as compared to NTx, and more elevated in patients with hyperthyroidism (Calvo et al. 1996), serum concentrations of NTx might be more specific to processes in the bone as compare to CTx.

2.2.3 Carboxyterminal Cross-Linked Telopeptide of Type I Collagen

Carboxyterminal cross-linked telopeptide of type I collagen generated by metalloproteinases (ICTP) is another metabolic product of mature type I collagen resorption, that is usually detected by immunoassays against the telopeptide portion of the collagen fragment between the two α1-chains. Increased levels of serum ICTP correlate with bone resorption. Importantly, cathepsin K-mediated bone resorption by osteoclasts cleaves the collagen at the antigenic site, and the resulting ICTP fragment is not detected by conventional immunoassays (Sassi et al. 2000). This might explain why ICTP is less sensitive for more physiological changes in bone turnover such as those accompanied by treatment with estrogen or bisphosphonates (Coleman et al. 2008).

2.2.4 Tartrate-Resistant Acid Phosphatase Type 5b

Tartrate-resistant acid phosphatase type 5b (TRAcP-5b) is secreted primarily by activated osteoclasts and is one of two isoforms detected in human serum. Activated macrophages secrete the TRAcP-5a isoform. Osteoclasts secrete the active enzyme TRAcP-5b, before it enters the circulation, where it is inactivated. Serum TRAcP-5b levels are analyzed by immunoassays, and they have been shown to be a good surrogate for bone resorption.

2.3 Osteoclast Regulators: Receptor Activator of Nuclear Factor-κB Ligand/Osteoprotegerin

Receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL) are required for osteoclastogenesis. RANKL (also referred to as OPGL, TRANCE or ODF) is a member of the tumor necrosis factor (TNF) family of cytokines that binds to its receptor RANK to control osteoclast differentiation, activation and survival (Jones et al. 2006). Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL that blocks ligand binding to RANK, thereby preventing the signaling required for osteoclast differentiation and activation (Teitelbaum 2000). In preclinical models of bone metastases secondary to melanoma or prostate cancer, neutralization of RANKL by OPG resulted in a marked reduction in tumor burden

in bones, but not in other organs (Jones et al. 2006). These data revealed that local differentiation factors, such as RANKL, play an important role in cell migration in a metastatic tissue-specific manner (*reviewed in* Mori et al. 2009). In a retrospective analysis, Santini et al. analyzed RANK immunoexpression in tissue from bone metastases from 74 patients with solid tumors, and found a high concordance between RANK immunoexpression in bone metastases and the corresponding primary tumor (Santini et al. 2011). These data support the central role of the RANK/RANKL/OPG pathway in the development of bone metastases in solid tumor patients.

Serum levels of OPG and both soluble and total RANKL are assessed by immunoassay. Elevated levels of either protein alone or increases in the ratio of RANKL to OPG have been investigated as a prognostic tool in patients with bone metastases, with rather controversial results (Jung et al. 2004; Leeming et al. 2006).

2.4 Bone Sialoproteins

Histological studies have shown that the two sialoproteins, bone sialoprotein (BSP) and osteopontin (OPN) are induced in multiple types of cancer, and that serum concentrations of BSP and OPN are significantly higher in patients with various solid tumors as compared to healthy controls (Fedarko et al. 2001). BSP is a member of the Small Integrin-Binding Ligand N-linked Glycoprotein (SIBLING) family of proteins that also includes OPN, dentin matrix protein 1 (DMP1), dentin sialophosphoprotein, and matrix extracellular phosphoglycoprotein (Fisher and Fedarko 2003). BSP is a non-collagenous bone matrix protein secreted by osteoclasts, and is present in all mineralized tissues. Recent evidence suggests that—in the presence of RANKL—BSP might synergistically induce osteoclastogenesis (Valverde et al. 2005). BSP contributes to osteoclast survival and decreased apoptosis. Regulation of BSP activity is achieved through dephosphorylation by TRAcP (Ek-Rylander et al. 1994). Serum BSP levels are measured by immunoassays. Elevated serum BSP levels have been reported in patients with various solid malignancies (Jung et al. 2004; Fedarko et al. 2001) and in multiple myeloma (Woitge et al. 2001). Although many of the SIBLING proteins are predominately expressed in bone, several of these proteins have been shown to be aberrantly expressed in a variety of malignant tumors (Fisher et al. 2004), and expression of BSP in these tumors has been proposed to play a role in the homing of tumor cells to the bone, and in the enhanced survival of tumor cells in the bone microenvironment (Jain et al. 2002). Bone sialoprotein is expressed by many malignant tissues, including breast, prostate (Waltregny et al. 2000), lung (Bellahcene et al. 1997) and several other cancer types (Fisher et al. 2004), and BSP expression is markedly lower in visceral metastases as compared to bone metastases in human breast and prostate cancers, suggesting some role of BSP in the pathogenesis of bone metastases (Waltregny et al. 2000). BSP-integrin interactions are important to stimulate the migration of tumor-derived cells. Although

the specific mechanisms by which BSP stimulates migration are not known, it has been reported that BSP can increase the invasiveness of cancer cells by forming a trimolecular complex with integrins and the matrix metalloproteinase MMP-2 (gelatinase A), increasing localized matrix degradation (Karadag et al. 2004). While BSP may play an important role as an adaptor molecule participating in the attachment of proteins to the cell surface of migrating cells, the protein may also play a more direct role, stimulating molecular signals at the focal adhesion resulting in expression of pro-metastatic factors.

Serum concentrations of BSP have been shown to correlate with markers of bone resorption in malignant bone disease and are often elevated in patients with tumors metastatic to bone (Seibel et al. 1996). Of particular interest, the highest levels seemed to occur in patients with bone metastases from cancers that are known to express BSP ectopically, such as breast, prostate or thyroid cancers (Bellahcene et al. 1996).

3 Prognostic Use of Bone Markers

There are accumulating data describing the association between specific bone markers and the outcome with respect to skeletal-related events (SRE) in patients with bone metastases from malignant tumors. At the same time, there are only limited data on the prognostic value of bone markers in patients with early-stage cancer where no metastatic spread to the bones has been diagnosed. The term "prognostic markers" is used here for clinical studies that focus on the clinical outcome in patients receiving either no or standard anticancer treatment, in contrast to "predictive markers" that look at the clinical outcome with respect to a well-defined, often newer or experimental treatment. In 2005, Brown et al. studied 441 patients with bone metastases from various solid malignancies, and found high levels of urinary N-telopeptide (NTx) at the time of diagnosis to predict an increased risk of skeletal-related events (relative risk of 3.25 for prostate cancer, 1.79 for lung cancer and other tumors), disease progression (relative risk of 2.02 for prostate cancer, 1.91 for lung cancer and others), and death (relative risk of 4.59 for prostate cancer, 2.67 for lung cancer and others) as compared to patients with low NTx urinary levels (Brown et al. 2005). The authors concluded that high urinary NTx levels should prompt more aggressive treatment to prevent skeletal-related morbidity in patients with bone metastases from solid tumors (Brown et al. 2005). These data in patients with various malignant tumors suggest that bone markers such as urinary NTx are early surrogates for clinical outcome, and clinical studies on early prevention of skeletal events in cancer patients should stratify patients according to these markers. However, prospective validating studies are necessary if bone turnover markers are to be implemented into daily clinical practice. Below, clinical evidence on the prognostic value of various bone markers in breast-, prostate-, lung cancer and multiple myeloma is summarized.

Table 2 Markers of bone resorption und osteoclast regulators

Marker	Specimen	Normal range	Diagnostic use for bone metastases	Prognostic use for bone metastases
PYD	Urine	Adults: 19.5–25.1 nM/mM Cr (Coleman 2002)	High values associated with bone metastases in 153 cancer patients (Pecherstorfer et al. 1995) High values associated with bone metastases in prostate cancer patients (Ikeda et al. 1996)	
DPD	Urine	Adults: 1.8–15.5 µmol/mol (Pecherstorfer et al. 1997)	High values associated with bone metastases in 153 cancer patients (Pecherstorfer et al. 1995) High values associated with bone metastases in prostate cancer patients (Ikeda et al. 1996; Wymenga et al. 2001) High values associated with bone metastases in lung cancer patients (Dane et al. 2008)	
CTx	Urine	3.9–4.9 nM/mM Cr (Coleman 2002)	High values associated with bone metastases in breast cancer patients (Voorzanger-Rousselot et al. 2006)	
	Serum	PreM women: 0.29 ± 0.14 ng/mL (Souberbielle 2004) PostM women: 0.56 ± 0.23 ng/mL (Souberbielle 2004) Men: 0.30 ± 0.14 ng/mL (Souberbielle 2004)	High values associated with bone metastases in lung cancer patients (Kong et al. 2007)	

(continued)

Table 2 (continued)

Marker	Specimen	Normal range	Diagnostic use for bone metastases	Prognostic use for bone metastases
NTx	Urine	PreM women: 5–65 nM BCE/mM Cr (Osteomark 2008) Men: 3-63 nM BCE/mM Cr (Osteomark 2008)	High values associated with bone metastases in 276 cancer patients (Koizumi et al. 2003) High values associated with bone metastases in 97 cancer patients (Costa et al. 2002) High values associated with bone metastases in lung cancer patients (Chung et al. 2005)	High values predict SRE in 441 patients with predominantly prostate and lung cancer (Brown et al. 2005)
	Serum	Women: 6.2–19 nM BCE (Osteomark 2008) Men: 5.4–24.2 nM BCE (Osteomark 2008)		High values predict TTP and OS in 250 patients with metastatic breast cancer (Ali et al. 2004)
ICTP	Serum	Adults: 0.76–5.24 ng/mL (Shimozuma et al. 1999)	High values associated with bone metastases in 97 cancer patients (Costa et al. 2002) High values associated with bone metastases in breast cancer patients (Ulrich et al. 2001; Wada et al. 2004) High values associated with bone metastases in lung cancer patients (Aruga et al. 1997) High values associated with bone metastases in lung cancer patients (Kong et al. 2007)	High values predict OS in 141 patients with mainly early-stage NSCLC (Ylisirnio et al. 2001) High values predict OS in 313 patients with multiple myeloma (Fonseca et al. 2000)
TRAcP-5b	Plasma/serum	PreM. women: 0.5–3.8 U/L (Terpos et al. 2004) PostM. women: 0.5–4.8 U/L (Terpos et al. 2004)	High values associated with bone metastases in 276 cancer patients (Koizumi et al. 2003) High values associated with bone metastases in breast cancer patients (Voorzanger-Rousselot et al. 2006; Capeller et al. 2003; Chao et al. 2004; Korpela et al. 2006)	Low values predict relapse in bone in 79 patients with newly diagnosed NSCLC (Terpos et al. 2009)

(continued)

Table 2 (continued)

Marker	Specimen	Normal range	Diagnostic use for bone metastases	Prognostic use for bone metastases
BSP	Serum	Men: 0.5–3.8 U/L (Coleman 2002) Adults: 8.0–9.4 ug/L (Coleman 2002)		High values predict relapse in bone in 388 early breast cancer patients (Diel et al. 1999) High values predict OS in 62 patients with multiple myeloma (Woitge et al. 2001)
	Tumor tissue			High tumor expression in 454 early breast cancer patients predicts relapse in bone and OS (Bellahcene et al. 1996) High tumor expression in 180 patients with prostate cancer predicts biochemical relapse (Waltregny et al. 1998) High expression predicts relapse in bone in 180 patients with resected NSCLC (Zhang et al. 2010)
RANKL	Plasma/serum	Adults: 0.80 ± 0.40 pmol/L (Morena et al. 2006)	High values associated with bone metastases in lung cancer patients (Karapanagiotou et al. 2010)	RANKL/OPG ratio in serum predicts OS in 121 patients with multiple myeloma (Terpos et al. 2009)
OPG	Plasma/serum	Adults: 2.42 ± 0.26 ng/L (Guang-da et al. 2005)	High values associated with bone metastases in prostate cancer patients (Jung et al. 2001; Narita et al. 2008; Aruga et al. 1997)	

Abbreviations *PYD* Pyridinoline, *DPD* Deoxypyridinoline, *CTx* C-telopeptide of type 1 collagen, *NTx* N-telopeptide of type I collagen, *ICTP* Carboxyterminal cross-linked telopeptide of type 1 collagen, *TRAcP-5b* Tartrate-resistant acid phosphatase type 5b, *BSP* bone sialoprotein, *RANKL* Receptor activator of nuclear factor-kB ligand, *OPG* Osteoprotegerin, *PreM* premenopausal, *PostM* postmenopausal

3.1 Prognostic Use of Bone Markers in Breast Cancer

Some interesting results have been published that assessed the prognostic value of various bone markers in patients with early or metastatic breast cancer. In 2001, Jukkola et al. assessed the prognostic value of PINP, PICP and ICTP in 373 patients with node-positive early breast cancer (Jukkola et al. 2001). Mean levels of PINP in serum were significantly elevated in patients who developed metastatic disease *in the follow-up* as compared to patients without tumor relapse in the bones. When patients with only bone metastases were compared with those not exhibiting bone metastases, PINP concentrations in serum were significantly higher in the group with recurrence in the bone, but there were no significant differences in serum PINP, PICP or ICTP values between patients with only bone metastases and those who developed soft or visceral metastases during the follow-up (Jukkola et al. 2001). These data were recently confirmed by a subgroup analysis of a randomized, double-blind placebo-controlled study in women with early breast cancer receiving either standard adjuvant therapy plus oral clodronate ($n = 419$) or placebo ($n = 432$) for 2 years (McCloskey et al. 2010). In the 230 women receiving oral clodronate and having paired measurements of PINP at baseline and after one year, there was a significant relationship between changes in serum PINP and the subsequent development of bone metastases. Women experiencing increasing serum PINP levels after one year of oral clodronate had a 20.8% risk of subsequent development of bone metastases (McCloskey et al. 2010). In 2004, Ali et al. found serum NTx levels to predict the time to progression (TTP) and overall survival (OS) in 250 patients with metastatic breast cancer (Ali et al. 2004). Time to progression was significantly shorter in patients with elevated serum NTx concentrations as compared to those with low NTx levels (139 as compared to 220 days, $p < 0.001$).

Recently, BSP has emerged as a new marker of bone resorption in breast cancer patients with bone metastases. Using a retrospective study design, Bellahcene et al. found that the amount of BSP expressed in breast cancer tissues (as assessed by semiquantitative immunohistochemistry) correlated with the propensity of the cancer to metastasize to the bones (Bellahcene et al. 1996). Some years later, Diel et al. performed a two-year prospective study, showing that serum BSP concentrations were highly predictive of future bone metastases in women with newly diagnosed, early breast cancer (Diel et al. 1999). Women with breast cancer and elevated serum BSP levels at baseline (i.e. before surgical tumorectomy) had a significantly increased risk of developing bone metastases as compared to patients with normal baseline BSP concentrations. Furthermore, these clinical data are supported by preclinical data, in that the expression of BSP has been demonstrated to be sufficient to promote skeletal metastasis in non-osteotropic cells (Zhang et al. 2004). A recent study by Tu et al. has demonstrated that the transgenic overexpression of BSP resulted in increased skeletal as well as systemic metastases in a murine breast cancer model (Tu et al. 2009). This evidence would strongly implicate BSP in promoting skeletal metastases in malignant tumors.

Finally, a large ongoing phase III clinical study assesses the value of "fixed" versus "marker-directed" dosing of zoledronic acid in 1400 patients with advanced breast cancer metastatic to bones, with SRE being the primary study endpoint (Coleman et al. 2008, BISMARK trial). In this study, zoledronic acid is given at 3–4 weekly intervals in patients with serum Ntx > 100 nM, at 8–9 weekly intervals in patients with serum Ntx between 50 and 100 nM, and in 15–16 weekly intervals in patients with serum Ntx < 50 nM. In the conventional study arm, zoledronic acid is given at 4 mg i.v. every 3–4 weeks.

3.2 Prognostic Use of Bone Markers in Prostate Cancer

Similar to studies in breast cancer (Bellahcene et al. 1996; Diel et al. 1999), tissue expression of BSP in prostate cancer might enable the identification of subgroups of patients who are at high risk for developing bone metastases or disease recurrence (De Pinieux et al. 2001). In 2001, Waltregny et al. analyzed immunohistochemical expression of BSP in 180 prostatectomy specimens for localized prostate cancer (Waltregny et al. 1998). Most of the prostate cancer lesions examined expressed BSP (78%), compared with no or low expression in the adjacent normal glandular tissue. Although a significant association was found between BSP expression and biochemical progression of prostate cancer, follow-up was too short to determine whether overexpression of BSP was also a predictor for the development of bone metastases (Waltregny et al. 1998). A recent study by Ramankulov et al. suggests that plasma concentrations of another non-collagenous bone protein, OPN, alone or in combination with other bone markers, may be useful as a diagnostic and prognostic marker in the detection of bone metastases in patients with prostate cancer (Ramankulov et al. 2007).

3.3 Prognostic Use of Bone Markers in Lung Cancer

In 2001, Ylisirnio et al. assessed serum concentrations of PINP, PICP and ICTP in 141 patients with mainly early-stage non small-cell lung cancer (NSCLC) (Ylisirnio et al. 2001). Patients with elevated serum concentrations of ICTP (>5ug/L) had a 64% higher risk of dying from lung cancer as compared to patients with low ICTP serum concentrations. However, the inclusion of patients with various stages of lung cancer makes interpretation of this study difficult. In a recent clinical study, Terpos et al. assessed the prognostic value of several bone markers in serum from 79 patients with newly diagnosed NSCLC (Terpos et al. 2009). Patients who later developed bone metastasis had decreased osteocalcin (Bauer et al. 2006) and TRAcP-5b concentrations as compared to those patients who never developed bone metastases (Terpos et al. 2009). In a case-control study, 30 patients with NSCLC who subsequently developed bone metastases were matched for clinicopathologic parameters to 30 control patients with resected NSCLC

without any metastases and 26 patients with resected NSCLC and non-bone metastases, and the immunohistochemical expression of BSP in the primary cancer was reported to be associated with the progression of distant bone metastases (Papotti et al. 2006). This suggests that measuring BSP expression levels in lung cancers may be helpful in identifying patients at high risk to develop bone metastases (Papotti et al. 2006). However, this comes with the necessity of cross-laboratory validation of the immunohistochemical bioassay. This hypothesis is further supported by very recent data from Zhang et al., who showed BSP immunohistochemical expression in resected primary tumors from 180 Chinese NSCLC patients to be stronger in 40 out of the 180 patients who later developed bone metastases as compared to the other patients (Zhang et al. 2010). At the same time, tumor expression of OP was not a significant predictor of the development of bone metastases.

3.4 Prognostic Use of Bone Markers in Multiple Myeloma

In 2003, Tian et al. showed expression of dickkopf 1 (DKK1), an inhibitor of osteoblast differentiation, in myeloma cells from lytic tumors to inhibit osteoblasts (Tian et al. 2003). Additionally, myeloma cells express the receptor activator of nuclear factor κB ligand (RANKL), a major driver of osteoclastogenesis. Therefore, the simultaneous overexpression of RANKL and DKK1 by myeloma cells greatly increases bone resorption while inhibiting osteoblast differentiation and bone formation. In 1997, Pecherstorfer et al. published a study were they looked at urinary PYD in 50 patients with newly diagnosed and untreated MM, 40 patients with MGUS, 40 untreated patients with osteoporotic vertebral fractures, and 64 healthy adults (Pecherstorfer et al. 1997). Patients with MM had significantly higher levels of urinary DPD as compared to healthy adults, patients with monoclonal gammopathy of undetermined significance (MGUS) or patients with postmenopausal osteoporosis. In one of three patients progressing from initial MGUS into stage I MM, urinary DPD increased above the upper limit of the normal range, while it remained normal in 13 patients with stable MGUS. In general, urinary DPD had low sensitivities to predict the changes in monoclonal protein in stage I and II MM (<50%), but increased to 93% in stage III MM. Although urinary DPD correctly identified patients with advanced MM (stage III), the test did not discriminate between patients with MGUS, or with early (stage I) MM or osteoporosis, probably because bone resorption rates are similarly low in MGUS and early stage MM (Pecherstorfer et al. 1997).

There is a role for serum osteocalcin (Bauer et al. 2006) and BSP as prognostic markers in patients with MM, as suggested by some clinical studies. Back in 1990, Bataille et al. quantified OC in bone marrow tissue from crest biopsies and in serum from 19 patients with MM (Bataille et al. 1990). Reduced serum OC levels were shown to be associated with rapid disease progression and poor survival, probably as a consequence of impaired osteoblast activity (Bataille et al. 1990).

However, this association was not confirmed in other studies (Carlson et al. 1999; Mejjad et al. 1996), and more recent studies indicate that serum ICTP concentrations are a better prognostic marker in MM as compared to other biochemical indices (Abildgaard et al. 1998; Fonseca et al. 2000). Furthermore, Woitge et al. studied serum BSP in 62 patients with newly diagnosed MM followed over a period of four years, in 46 patients with monoclonal gammopathy of undetermined significance MGUS, in 71 patients with untreated benign vertebral osteoporosis and in 139 healthy controls (Woitge et al. 2001). Serum BSP concentrations increased with disease progression and higher serum concentrations of BSP distinguished between MM and benign osteoporosis, and were associated with shorter survival time in those patients suffering from MM (Woitge et al. 2001). Finally, Terpos et al. studied the prognostic value of serum RANKL and OPG in 121 patients with newly diagnosed MM to evaluate their role in bone disease and patient survival.

Serum levels of sRANKL were elevated in patients with MM and correlated with the extent of bone disease. Additionally, the RANKL/OPG ratio in serum, C-reactive protein (CRP), and β2-microglobulin were the final prognostic factors for overall survival within multivariate analysis. The authors generated a prognostic index based on these factors, categorizing patients into three risk groups (Terpos et al. 2003). These data suggest bone markers to be of distinct clinical value in predicting outcome in patients with multiple myeloma. Presently, a U.S. clinical study is assessing the optimal dosing schedule of bisphosphonates in patients with multiple myeloma according to urine NTx concentrations.

4 Diagnostic Use of Bone Markers

The early diagnosis of metastatic spread to the bones in patients with known malignant disease might be beneficial, as this allows the early initiation of bone-targeted treatment, which may avoid or delay secondary complications such as bone pain and immobility. We might call this secondary prophylaxis or prevention of skeletal-related events (SRE) due to malignant bone disease. Most studies in this area have compared biochemical markers of bone turnover between groups of cancer patients with or without established bone metastases. While this is a sensible and straightforward approach, its validity largely depends on a correct diagnosis in the "negative" group, that is the group of cancer patients declared to be free of skeletal disease. Given the different techniques used to prove the absence of malignant bone lesions, the assumption of a "negative status" might not always be correct. Additionally, many studies have included patients with various solid malignancies, and this might also lead to some bias. Lastly, the potential association between total tumor burden and the respective bone markers is usually not reported, although this would substantially support the rational for using bone turnover markers in the clinic. Not surprisingly, the available information on the diagnostic use of bone markers in metastatic bone disease is

controversial. However, the picture becomes more consistent when comparisons are made between a marker of bone turnover and specific imaging techniques, in particular bone radioisotope scans in well-defined groups of patients (Ebert et al. 2004; Meijer et al. 2003).

4.1 Diagnostic Use of Bone Markers in Various Tumors

In 2003, Oremek et al. published a study that assessed the diagnostic value of serum BSAP and PICP in 200 patients with various newly-diagnosed or progressive solid tumors (Oremek et al. 2003). Both BSAP and PICP were elevated in patients with confirmed metastases to the bone, and the quantitative elevation of PICP and BSAP was correlated with tumor burden in the bones. Similarly, Koizumi et al. found serum NTx and TRAcP-5b to be of value for the diagnosis of bone metastatic disease in 75 cancer patients with as compared to 201 cancer patients without skeletal metastases (Koizumi et al. 2003). Pecherstorfer et al. performed a similar cross-sectional study of 153 patients with various solid tumors and an equal number of matched healthy controls, and analyzed serum levels of calcium, total AP, urinary excretion of calcium, PYD and DPD (Pecherstorfer et al. 1995). Within the total of cancer patients, individuals with skeletal metastases had higher serum concentrations of calcium, total AP, urinary PYD and DPD, as compared to patients without evidence of malignant bone disease. Urinary calcium however did not differ between cancer patients with or without bone metastases (Pecherstorfer et al. 1995). However, a significant proportion of cancer patients without any evidence of malignant bone involvement also had elevated urinary levels of DPD, and it remains unclear if these patients later developed overt metastatic disease of the bone (Pecherstorfer et al. 1995). Finally, Costa et al. studied serum bone-specific alkaline phophatase (BSAP), C-telopeptide of type-I collagen (ICTP) and urine levels of NTx in 97 cancer patients with either metastases to the bones or extraskeletal tissues (Costa et al. 2002). There was a marked and significant increase of urinary NTx by 152%, and serum ICTP of 144% in patients at the time of disease progression in the bones, and this was independent of bisphosphonate treatment. At the same time, extraskeletal disease had no effect on bone markers. The studies by Oremek and Costa suggest that there is a consistent rise of bone-specific alkaline phosphatase (BSAP) in patients with various malignant tumors and newly detected bone metastases (Oremek et al. 2003; Costa et al. 2002). However, this has not been confirmed in another study by Jung et al. (Jung et al. 2006). In the latter study, NTx, TRAcP-5b, OPG and RANKL were analyzed in the serum of 72 patients with renal-cell carcinoma and in 68 healthy controls. No bone marker led to the differentiation between patients with bone and those with non-bone metastases (Jung et al. 2006).

4.2 Diagnostic Use of Bone Markers in Breast Cancer

In 1991, Paterson et al. compared urinary PYD and DPD in 10 patients with bone metastases with 10 breast cancer patients without bone metastases, and found a non-significant difference for the bone markers between the groups (Paterson et al. 1991). Eight out of the 10 patients with metastases had above average urinary crosslinks, but sensitivity was low. Therefore, the analysis of urinary PYD/DPD is not recommended for diagnostic purposes in patients with breast cancer. In another clinical study, Keskikuru et al. analyzed preoperative serum levels of PINP, PICP and ICTP in 138 women with breast cancer and 94 women with benign breast disease, both before undergoing local tumorectomy, and 100 healthy controls (Keskikuru et al. 1999). While the sensitivity of these bone markers was low for discriminating breast cancer patients from non-cancer patients, a tendency toward higher serum levels of PINP and low PICP/PINP ratio was found in patients with advanced stage IV breast cancer (Keskikuru et al. 1999). Ulrich et al. compared urinary NTx, serum ICTP and serum BSAP in 106 breast cancer patients with ($n = 19$) and without ($n = 87$) bone metastases as diagnosed by bone scintigraphy (Ulrich et al. 2001). Serum ICTP best discriminated between patients with bone metastases compared to those without bone metastases, with a specificity of 91%, but a sensitivity of only 65%. The authors concluded that the sensitivity of these three markers did not seem to be sufficient enough for early identification of patients with subclinical bone metastases from breast cancer. Similar results were reported by Wada et al. who compared serum ICTP, TRAcP, urinary NTx and serum AP in 114 breast cancer patients without bone metastases, 23 patients with bone metastases and 19 patients with extraosseous metastases (Wada et al. 2004). Serum concentrations of ICTP and TRAcP were significantly higher in patients with bone metastases, and there was also a positive association between the amount of metastatic bone disease in bone scintigraphy and the concentrations of ICTP and TRAcP (Wada et al. 2004). In 2005, Lüftner et al. analyzed serum PINP as a potential marker of metastatic spread to the bones in 38 breast cancer patients with bone metastases and 24 patients without bone metastases (Luftner et al. 2005). The authors found a sensitivity of 50% for serum PINP to predict bone metastases at the threshold concentration of 95 ng/mL, and there was a positive association between elevated serum PINP and the amount of metastatic bone involved. The authors hypothesized that the low sensitivity for the diagnosis of bone metastases might be biologically related to ineffective bone repair in certain patients (Luftner et al. 2005). A further study compared various serum biochemical markers of angiogenesis, tumor invasion and bone turnover in 29 breast cancer patients without bone metastases, 28 patients with bone metastases and 15 healthy women (Voorzanger-Rousselot et al. 2006). Importantly, the authors were also able to assess these markers over a time of three years in 34 patients, of whom 15 patients developed bone metastases and 19 remained free of bone metastases. All bone markers were significantly higher in patients with bone metastases as compared to patients without bone metastases and healthy controls. The bone

resorption markers TRAcP-5b, CTx and ICTP and the marker of angiogenesis VEGF were independently associated with bone metastases within multivariate analysis. These four markers correctly distinguished 85% of breast cancer patients with bone metastases from patients without bone metastases or healthy controls. Patients with primary breast cancer who developed bone metastases during follow-up had higher serum levels of TRAcP-5b (+95%,) at the time of primary diagnosis and higher increases of ICTP during follow-up as compared to patients who did not progress to bone metastases (Voorzanger-Rousselot et al. 2006). Overall, markers of bone resorption had the highest independent diagnostic value for detecting and potentially predicting bone metastases in breast cancer patients. Three studies in breast cancer patients assessed serum TRAcP-5b (Capeller et al. 2003; Chao et al. 2004; Korpela et al. 2006), a more specific marker as compared to TRAcP. In the studies by Chao et al., Capeller et al. and Korpela et al., serum TRAcP-5b was found to be a good surrogate for bone metastases in breast cancer patients when compared to patients without bone metastases and healthy controls (Capeller et al. 2003; Chao et al. 2004; Korpela et al. 2006). In the study by Chao et al., the sensitivity of TRAcP-5b to identify bone metastases in breast cancer was 73%, while specificity was 83% (Chao et al. 2004).

4.3 Diagnostic Use of Bone Markers in Prostate Cancer

In patients with prostate cancer, Ikeda et al. studied the diagnostic value of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) for bone metastases in 15 patients with benign prostatic hypertrophy (BPH) versus 17 patients with carcinoma clinically confined to the prostate and 26 patients with overt bone metastatic disease (Ikeda et al. 1996). Urinary PYD and DPD clearly discriminated between patients with or without bone metastases, and patients receiving successful endocrine treatment for metastatic prostatic cancer had suppressed urinary PYD and DPD levels (Ikeda et al. 1996). Further studies in patients with prostate cancer showed that bone markers such as BSAP increased the diagnostic value of PSA for the diagnosis of bone metastases in patients with prostate cancer (Lorente et al. 1999; Wymenga et al. 2001). In the study by Lorente et al., serum BSAP showed a statistically significant association with the extent of malignant bone disease in 295 patients with newly diagnosed, untreated prostate cancer, 93 of whom had bone metastases on bone scan (Lorente et al. 1999). Interestingly, serum PSA concentrations did not show a significant association with the extent of bone metastases, but the combination of both serum BSAP and PSA was still the best predictor for malignant bone disease in multivariate logistic regression analysis, with a positive predictive value of 46.5% and a negative predictive value of 100% (Lorente et al. 1999). By adding BSAP to PSA for diagnosing metastatic spread to the bones, 32% of initial bone scans could be avoided. Similarly, Wymenga et al. showed that patients with newly diagnosed prostate cancer and bone metastasis had higher urinary DPD levels, and higher serum PSA and AP concentrations as

compared to patients with localized prostate cancer (Wymenga et al. 2001). In the latter study, bone scans were taken as the "gold standard" for the diagnosis of bone metastases. Importantly, bone markers were more specific toward pathological bone processes as compared to PSA that is also dependent on extraosseous malignant disease, and is also subjected to hormonal manipulation. In 2001, Koizumi et al. analyzed various markers such as PINP, PICP, BSAP, OP, ICTP and PSA in 40 patients without and 25 untreated patients with bone metastases from prostate cancer (Koizumi et al. 2001). The levels of serum PINP correlated best with the extent of malignant bone disease, with a sensitivity of 72% and a specificity of 90%, using a threshold level of 47 ng/mL (Koizumi et al. 2001). Similar results were found in 36 patients with early or advanced prostate cancer, were PINP was a potent discriminator of bone metastases, with mean serum PINP concentrations being 18.3, 24.9 and 122.5 ng/mL in patients with negative ($n = 24$), equivocal ($n = 5$) or positive ($n = 7$) bone scans (Thurairaja et al. 2006). This is supported by a further study from Thurairaja et al., who assessed PINP in serum of prostate cancer patients with ($n = 12$) or without ($n = 24$) bone metastases (Thurairaja et al. 2006). The authors found patients with positive bone scans to have significantly higher serum concentrations of PINP as compared to those not having positive bone scans (112 ng/ml as compared to 18.3 ng/ml). This is further supported by the study of Koopmans et al., who assessed serum PINP concentrations in 64 patients with prostate cancer treated between 1999 and 2004 (Koopmans et al. 2007). While serum PINP was a good discriminator of bone metastatic disease, increased PINP levels in patients with bone metastases were detectable up to 8 months before the first positive bone scintigraphy (Koopmans et al. 2007). These data would support the use of PINP concentrations in serum as an early marker for the risk of developing bone metastases from prostate cancer.

In 2001, Brown et al. assessed the diagnostic value of serum OP concentrations in 24 patients with advanced prostate cancer as compared to 25 patients with recurrent prostate cancer, 25 patients with early prostate cancer, 25 patients with benign prostate hyperplasia and 6 healthy volunteers (Brown et al. 2001). Serum OP concentrations were significantly higher in patients with advanced prostate cancer as compared to the other groups, but there was no correlation between serum OP and PSA values (Brown et al. 2001). More explicit results for OP have been reported by Jung et al., who found a significant association between serum OP and bone metastatic spread in 93 patients with prostate cancer as compared to 35 patients with BPH and 36 male healthy controls (Jung et al. 2001). In the study by Jung et al., the diagnostic sensitivity of serum OP for bone metastases was 88%, while specificity was 93%. These results were later confirmed by the same group in 117 patients with prostate cancer, including 44 patients with bone metastases (Jung et al. 2003). Serum OP was increased in patients with bone metastases, with a sensitivity of 95% and a specificity of 89% at a threshold concentration of 2.86 pmol/L. Additionally to serum OP concentrations, Narita et al. also assessed the influence of the two germline genetic polymorphisms 149T/C and 950T/C in the promoter region of the OP gene in 161 patients with prostate cancer as compared to 195 healthy controls (Narita et al. 2008). While there was no

significant difference in the genotype frequencies between prostate cancer patients and healthy controls, serum OP concentrations increased with age in both prostate cancer patients and healthy controls. Additionally, OP serum concentrations were significantly higher in age-matched patients with metastatic prostate cancer as compared to patients without metastatic disease and healthy controls. These results suggest that aging and bone metastasis have a major effect on OP serum concentrations (Narita et al. 2008).

An ongoing clinical study looks at changes in serum PINP, ICTP and PSA in roughly 100 men with early prostate cancer, receiving weekly zoledronic acid for 3 months. The primary study endpoint is to assess the relationship between changes in bone parameters, PSA and bone scans with respect to bone metastases. This study will give some insight on whether bone turnover markers may spare bone scans in patients with early prostate cancer, although the study does not answer the question whether any such effect is independent on the administration of bisphosphonates.

4.4 Diagnostic Use of Bone Markers in Lung Cancer

In 1997, Aruga published a study comparing 47 lung cancer patients with bone metastases with 44 patients without bone metastases (Aruga et al. 1997). The authors found serum ICTP to have the highest sensitivity (71%) for the diagnosis of bone metastases, with a specificity of 88% and a threshold for serum ICTP of 4.9 ng/mL (Aruga et al. 1997). A similar analysis compared the diagnostic value of urinary NTx, urinary DPD and total AP in serum from 33 lung cancer patients with bone metastases as compared to 118 patients without bone metastases (Chung et al. 2005). The authors found urinary NTx to have the highest sensitivity (73%) and specificity (84%) for the diagnosis of bone metastases, with a threshold level of 73 μmol/mol creatinine. Finally, Kong et al. analyzed serum ICTP, BSAP, CTx and osteocalcin (Bauer et al. 2006) in 96 male patients with NSCLC and 30 male patients with other pulmonary diseases (Kong et al. 2007). Serum concentrations of both CTx and ICTP were significantly higher in 61 lung cancer patients with bone metastases as compared to 35 lung cancer patients without bone metastases, and significantly correlated with the extent of bone disease. Although ICTP had a better sensitivity (75% versus 66%) and accuracy (73% versus 69%) as compared to CTx, they had a similar area under the receiver operating characteristic curve (0.85 vs. 0.83, respectively). In a Chinese study, Kong et al. analyzed CTx and ICTP, OC and BSAP in 96 male patients with NSCLC and 30 male patients with other pulmonary diseases (Kong et al. 2007). Serum concentrations of CTx and ICTP were significantly higher in 61 lung cancer patients with bone metastases as compared to 35 patients without bone metastases ($p < 0.001$), and significantly correlated with the extent of malignant bone disease. Sensitivity was 75% and 72% for ICTP and CTx, respectively; accuracy was 65% and 68% for ICTP and CTx, respectively. Obviously, sensitivity is too low to justify using these bone markers

for diagnostic purposes. In 2008, Dane et al. measured urinary DPD, calcium, serum osteocalcin and total AP in 60 lung cancer patients (Dane et al. 2008). When bone scintigraphy was performed on all patients, 22 patients turned out to have bone metastases, and urinary DPD levels were significantly higher in patients with bone metastases as compared to those without bone metastases (Dane et al. 2008). As a note of caution, both small-cell and non small-cell histologies were included into the study of Dane et al.. In a recent study, Karapanagiotou et al. analyzed the diagnostic value of serum turnover markers OC, RANKL and OPG in 22 NSCLC patients with bone metastases, 18 NSCLC patients without bone metastases, 28 small-cell lung cancer (SCLC) patients and 29 healthy volunteers (Karapanagiotou et al. 2010). Decreased OC serum levels and increased osteopontin and RANKL serum levels were found in NSCLC patients with bone metastases (Karapanagiotou et al. 2010).

5 Conclusions

Available information on the prognostic and diagnostic use of bone turnover markers in cancer patients is from small retrospective studies, and this does not allow to recommend their use in daily clinical practice at present. Many bioassays for bone turnover markers have not been validated, and this makes inter-study comparison difficult. Additionally, circadian variability may also render the correct interpretation of clinical studies difficult. However, there are some promising retrospective data on the prognostic and diagnostic value of bone turnover markers that should be validated in future clinical studies.

5.1 Prognostic Use of Bone Turnover Markers

There is some limited evidence for bone turnover markers to predict the occurrence of metachronous bone metastases in patients with early-stage malignant tumors, with serum PINP and ICTP being the most promising candidates (Jukkola et al. 2001; Voorzanger-Rousselot et al. 2006; Koopmans et al. 2007). Another promising bone turnover marker is BSP that is expressed in primary cancer tissues of various tumors, and is excreted into serum. Accordingly, serum concentrations of PINP, ICTP or BSP should prospectively be evaluated at the time of tumorectomy in patients with early solid tumors, to define the sensitivity and specificity of these markers in predicting tumor relapse in the bones. If validated, specific bone turnover markers may be implemented into clinical practice to enable clinicians to tailor adjuvant treatment to avoid bone metastatic seeding in patients with early solid tumors. Immunohistochemical expression of BSP in tumor tissue may be a valid alternative to serum markers, but proper validation of the respective assays is mandatory before evaluation in prospective clinical studies.

5.2 Diagnostic Use of Bone Turnover Markers

While serum BSAP, PINP and OP were repeatedly shown to be associated with synchronous bone metastases in patients with breast or lung cancer, sensitivity of these markers usually was too low to suggest that these bone turnover marker might be preferred over conventional bone scans for the diagnosis of bone metastases. A somewhat higher sensitivity for the diagnosis of bone metastases was found for urinary NTx and serum ICTP in solid tumor patients, serum TRAcP-5b in patients with breast cancer and serum BSAP, PINP and OPG in prostate cancer patients. Available data suggest that the most promising application would be to add BSAP, ICTP, PINP or OPG to PSA in prostate cancer patients with suspected bone metastases to spare conventional bone scans. This should be validated in adequately powered prospective clinical studies.

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