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Review

Diagnosing and Prognosing Bone Metastasis in Prostate Cancer: Clinical Utility of Blood Biomarkers

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Abstract. *Bone metastasis (BM) may occur in any type of cancer. The diagnosis of patients with BM has increased due to improved imaging technologies and advances in cancer drug therapy that have prolonged the survival time of cancer patients. BM may be asymptomatic in the early stages; however, as the disease progresses, it causes pain, fracture, neurological symptoms associated with spinal cord compression, hypercalcemia, and other specific symptoms that significantly impair the patient's quality of life (QOL). Imaging modalities have disadvantages, such as high cost, radiation exposure, and bone pain associated with holding posture for imaging test; further, they are time-consuming. Hence, patients with BM require convenient and useful biomarkers. However, no blood biomarkers generally useful for diagnosis and therapeutic monitoring of BM are established. Prostate cancer (PC) and breast cancer, in particular, are among the most prone to BM because BM occurs in approximately 70% of patients with advanced disease. Herein, we reviewed various potential bone turnover markers and liquid biopsy for diagnosis and prognosis prediction in patients with BM of PC based on PubMed literature search. The usefulness of conventional bone turnover markers of BM in PC is limited, and cut-off values vary. In the future, the creation of algorithms using these conventional markers and multiple tests, such as liquid biopsy and imaging tests, will help to develop highly accurate techniques for the diagnosis of BM.*

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The number of cancer survivors is increasing due to advances in medical technology, and an increase in effectively diagnosing patients with bone metastasis (BM) (1). The incidence of BM varies depending on the primary tumor type, with prostate cancer (PC) at highest risk of developing BM (85%), followed by lung cancer, kidney cancer, and breast cancer, and it is the lowest (13%) for colon cancer (2-4). Although prostate specific antigen screening and new advances in PC treatment improved survival, future projections indicate that by 2040, 379,000 people will die due to PC worldwide (5). Owing to the progression of systematic medical therapies, life expectancy and the number of patients with BM are increasing and will continue to do so (6). Generally, BM may cause skeletal related events (SRE), such as pain, fractures, spinal cord compressions, hypercalcemia, prolonged hospitalization period, and significantly reduce the quality of life (QOL) in patients with short prognosis (7). BM in patients with breast cancer is a mixed osteolytic and osteoblastic type, whereas in PC, it is predominantly osteosclerotic type. Bone metastatic sites of PC undergo osteogenic changes but are more brittle than normal bone (8). Thus, BM is a clinically important and distinctive condition; however, the American Society of Clinical Oncology guidelines state that there are no established bone turnover markers, effective for monitoring BM in clinical practice (9).

In 1889, Paget proposed the seed and soil theory (10), in which cancer cells and remote organs of metastatic sites were regarded as seeds and fertile soil, respectively, for cancer cells to grow. The seed and soil theory fits well with BM because bone matrix is rich in transforming growth factor-β, insulin-like growth factor, fibroblast growth factor, bone morphogenetic protein, *etc.*, which support the progression of cancer (11). These factors interact to form an entire system, forming a feedback pathway that promotes the production of

various cytokines, which induces PC cell metastasis to the bone, further exacerbating cancer growth (4, 11-17); this process is a vicious cycle (Figure 1). Extensive interactions occur between the bone microenvironment and metastatic PC cells via autocrine and paracrine signaling (4). This activation of bone metabolism via this vicious cycle promotes secretion by osteoblasts and osteoclasts, resulting in high levels of bone turnover markers in the blood.

Conventionally, BM in PC is mainly diagnosed using 99mTc-based bone scintigraphy, and recently 68 Ga-prostate-specific membrane antibody (68 Ga-PSMA) positron emission tomography/computed tomography (PET/CT) provided a major advance in the diagnosis and staging by adding functional information reflecting metabolic changes (18). In addition, 68 Ga-PSMA PET/CT images can detect BM earlier than CT or radionuclide bone scans and identify lesions in tissues other than the bone (19). Although there were many studies on the diagnostic performance of 68 Ga-PSMA PET/CT for patients with metastatic PC, the results were inconsistent with sensitivity ranging from 56% to 98% (20). Whole-body magnetic resonance imaging (MRI) detects BM with a sensitivity and specificity of 91% and 96%, respectively (21). However, these imaging tests have disadvantages, such as time consumption, low specificity, high cost, and risk of radiation exposure (22); hence, it is important to find blood biomarkers that are simple, minimally invasive, and easy to monitor treatment efficacy. Because urinary bone turnover markers are strongly influenced by renal function and show diurnal variation, blood biomarkers are more useful for detecting and monitoring BM (23). Even alkaline phosphatase, the most commonly measured bone turnover marker in daily clinical practice, does not have fixed cut-off value in studies about BM, and there are few reports on the diagnosis and prognosis of other bone turnover markers, including stable cut-off values of BM (24). Because the cut-off values of bone turnover markers varied from study to study depending on patient background, such as newly diagnosed patients with BM or treated by systematic therapy, we summarized the cut-off values in this study for those involved in the diagnosis of BM in PC (Table I).

Recently, the role of epigenetic regulators of tumor-bone microenvironment interactions, particularly microRNA (miRNA), circulating tumor cells (CTCs), cell free DNA (cfDNA), circulating tumor DNA (ctDNA), and extracellular vesicle (EV) gets importance (4). Because metastatic tissue, especially bone, is often difficult to obtain, this information from liquid biopsy, easily obtained by blood sampling, may be a good choice to characterize BM for more clinical decisions.

Bone Formation Markers

Alkaline phosphatase (ALP). ALP is measured as a nonspecific bone turnover marker since 1936 because serum levels of ALP increased with enhanced osteoblastic activity (39). ALP is a glycoprotein derived from not only the bone but also the liver, kidney, and placenta, and elevated ALP correlates with the amount of BM (24). Serum ALP is a simple and inexpensive method that has long been used as a parameter in diagnosis and prognosis prediction of BM with PC and is expected to be useful in planning routine cancer treatment and follow-up, and to lubricate joint decision-making with patients. However, because ALP is also elevated in liver injury and heart failure, meta-analysis has shown that ALP is not highly accurate in diagnosing BM and is more related to overall survival (OS) than cancer specific survival (CSS) (24).

Bone-specific alkaline phosphatase (BAP). BAP is secreted by osteoblasts and promotes bone mineralization (40). BAP is less sensitive to diet and renal function, hence, there is less variability in measurements, and elevated serum BAP is mainly due to increased osteoblastic activity and secondary bone resorption events. In adults with normal liver function, approximately 50% of the total ALP activity in serum is derived from the liver and 50% from the bone (41).

Osteocalcin (OC). OC is a major non-collagenous protein that makes up approximately 20% of the bone matrix (42). It is synthesized by osteoblasts dependent on vitamin K and active vitamin D3. There are two forms of OC in serum, carboxylated and decarboxylated. Decarboxylated OC is an important determinant of its metabolic activity (43). OC secretion is also increased when osteoblasts are activated by physical stimuli to the bone.

Procollagen type I N-terminal propeptide (PINP) and Procollagen type I C-terminal propeptide (PICP). PINP is a polypeptide produced when type I collagen, a major protein component of the bone matrix, is cleaved from its N-terminal side during the formation of the precursor type I procollagen. As a secreted product produced during the formation of type I collagen during osteogenesis, PINP is a marker that sensitively reflects early metabolic changes. PINP is present in serum as intact trimeric peptides, corresponding to the native isolated products of procollagen during type I collagen synthesis, rather as monomeric peptides, which are degradation products of procollagen (44). Typically, total PINP, the sum of trimeric and monomeric PINP, is measured. Like PINP, PICP is a polypeptide formed when type I collagen is cleaved from the C-terminal side during the formation of its precursor, type I procollagen. In other words, PINP and PICP are derived from the same type I procollagen.

Osteoprotegerin (OPG). OPG is produced by a variety of cells, including osteoblasts, fibroblasts, and hepatocytes, and inhibits osteoclast formation by binding to RANKL (45). Elevated serum OPG levels indicate increased osteogenic bone metabolism (17).

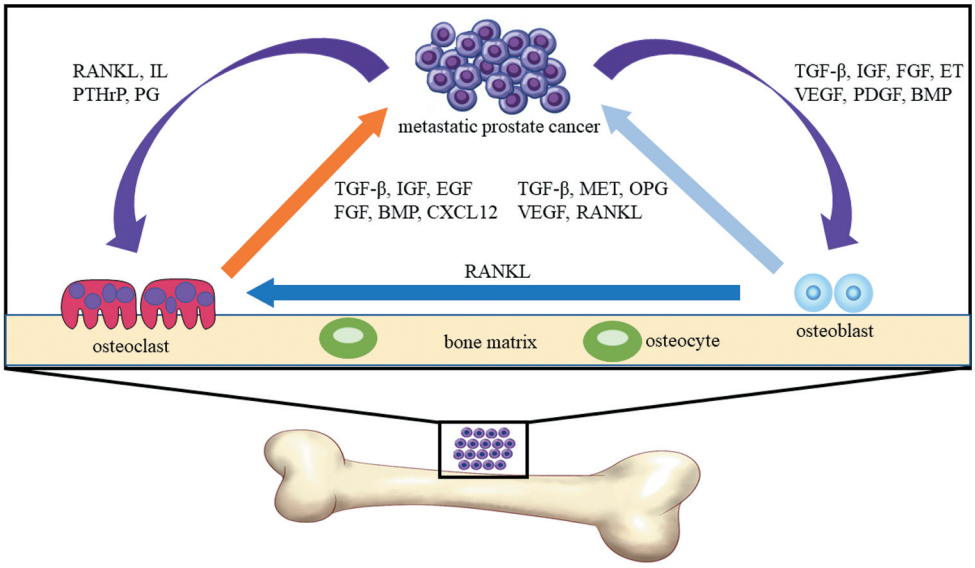

Figure 1. *Major signal pathways and vicious cycle in bone metastasis from prostate cancer.*

Bone Resorption Markers

Type I collagen cross-linked N-terminal telopeptide (NTx), type I collagen cross-linked C-terminal telopeptide (CTx), and C-terminal pyridinoline cross-linked telopeptide of type I collagen (ICTP). Type I collagen accounts for more than 90% of the bone organic matrix. It consists of two α1 chains and one α2 chain forming a helical twisted helix structure, with two non-helical telopeptides at the N-terminus and C-terminus, and a trivalent telopeptide at the helix (46). These cross-linked portions are used as bone resorption markers because they are released into the blood when type I collagen is degraded by bone resorption. The fragment of type I collagen arising from the N-terminus is NTx, and the fragments arising from the C-terminus are CTx and ICTP (46, 47). ICTP is a specific telopeptide, separated from collagen by metalloproteinases (40).

Tartrate-resistant acid phosphatase (TRACP). TRACP 5b was originally discovered in leukocyte extracts of patients with hairy cell leukemia and later, detected in osteoclasts (48). It was first named type 5 acid phosphatase because of its rapid electrophoretic mobility toward the cathode on acidic acrylamide gels using electrophoresis (49); this band was found in human serum, and could be electrophoretically separated into two distinct bands, 5a and 5b (50). Analysis of these two isoforms showed that 5a contained sialic acid, which is absent in 5b, and electrophoretic studies showed that TRAP 5b was derived from osteoclasts. TRACP 5b has high specificity for osteoclasts and is not susceptible to hepatic and renal dysfunction. It is not affected by physiological changes and diet (38).

Liquid Biopsy

Recently, several cellular and molecular components that play a role in cancer were detected via liquid biopsy. These utilities of BM in PC are briefly discussed below.

Circulating tumor cells (CTCs). The number of CTCs varies greatly depending on the type of cancer, and relatively large numbers are detected in breast and prostate cancers (51). The number of CTCs was significantly higher in PC with BM than without BM, and CTC counts of 3 or more out of 7.5 ml blood was associated with a poorer prognosis than a count of less than 3 (52). Patients with PC with BM had higher numbers of CTCs in their blood expressing KLK2/3 than those with no BM (53). Gene expression profiles of paired samples of plasma CTCs and metastatic tissue from the spine of PC patients with BM showed that nine genes (*AGR2, AKR1C3, AR, CDH1, FOLH1, HER2, KRT19, MDK*, and *SPINK1*) were strongly correlated. These results demonstrate the potential of CTC phenotyping as a tool to improve rapid diagnosis and personalized treatment of metastatic PC (54).

Circulating tumor DNA (ctDNA), cell free DNA (cfDNA). The presence of cell-free nucleic acid fragments in human blood was first reported in 1948 (55). In healthy individuals, there are small amounts of DNA fragments mainly derived from the death of hematopoietic cells. In patients with cancer, ctDNA is mixed with a part of cfDNA due to apoptosis of cancer cells or destruction of CTCs leaked into the blood by autoimmunity. This ctDNA can be easily and

Table I. *Utility of bone turnover markers for bone metastasis of prostate cancer.*

Bone turnover marker	Diagnosis				Survival	Reference
	Cut-off value	Sensitivity (%)	Specificity (%)	AUC		
Bone formation markers						
ALP	129 (U/l)	81	93	-	CSS, OS	(25)
	275 (U/l)	-	-	0.76	CSS	(26)
	288 (U/l)	69	90	0.82	-	(27)
	335 (U/l)	50	100	-	-	(28)
	115 (U/l)	57	65	0.74	-	(29)
	67 (U/l)	-	-	-	OS	(30)
	227 (U/l)	91	100	0.98	-	(31)
BAP	15.2 (ng/ml)	75	93	-	CSS, OS	(25)
	24.2 (ng/ml)	-	-	0.73	CSS	(26)
	18.3 (ng/ml)	-	-	-	OS	(30)
	34 (U/l)	-	-	-	OS	(32)
	18.4 (ng/ml)	92	92	-	-	(33)
	164.7 (ng/ml)	-	-	-	OS	(34)
	29.6 (U/l)	68	90	0.81	-	(35)
OC	11.3 (μg/l)	24	95	-	-	(25)
PINP	50.6 (μg/l)	76	90	-	CSS, OS	(25)
	30.3 (μg/l)	-	-	-	OS	(30)
	120 (μg/l)	-	-	-	OS	(32)
	84 (μg/l)	100	100	-	-	(33)
	148.5 (μg/l)	-	-	-	OS	(34)
	47.0 (μg/l)	72	90	0.85	-	(35)
	106.3 (μg/l)	65	78	0.71	-	(36)
PICP	150.0 (μg/l)	57	90	0.40	-	(35)
	-	-	-	0.59	-	(37)
OPG	3.4 (pmol/l)	93	94	-	CSS, OS	(25)
Bone resorption markers						
NTx	26.9 (nmol/l BCE)	61	96	-	CSS, OS	(25)
	12.8 (nmol/l BCE)	-	-	-	OS	(30)
CTx	0.627 (μg/l)	30	93	-	CSS, OS	(25)
	54 (ng/l)	-	-	-	OS	(30)
	0.25 (μg/l)	-	-	-	OS	(32)
ICTP	3.3 (ng/ml)	-	-	0.85	CSS	(26)
	5.0 (ng/ml)	79	88	-	-	(28)
	4.3 (ng/ml)	69	77	0.82	-	(29)
	4.37 (ng/ml)	-	-	-	OS	(30)
	5.2 (ng/ml)	100	79	-	-	(33)
	4.6 (ng/ml)	67	90	0.75	-	(35)
	5.73 (ng/ml)	37	90	0.64	-	(36)
TRACP	10.4 (U/l)	69	86	0.81	-	(27)
TRACP 5b	4.62 (U/l)	77	85	-	CSS, OS	(25)
	105.5 (mU/dl)	-	-	0.64	CSS	(26)
	4.98 (U/l)	71	96	0.82	-	(31)
	335 (mU/lL)	71	90	0.87	CSS	(38)

AUC: Area under the curve; CSS: cancer specific survival; OS: overall survival; ALP: alkaline phosphatase; BAP: bone-specific alkaline phosphatase; OC: osteocalcin; PINP: procollagen type I N-terminal propeptide; PICP: procollagen type I C-terminal propeptide; OPG: osteoprotegerin; NTx: cross-linked N-terminal telopeptides of type I collagen; CTx: cross-linked C-terminal telopeptides of type I collagen; ICTP: carboxy-terminal pyridinoline cross-linked telopeptide parts of type I collagen; TRACP 5b: tartrate-resistant acid phosphatase type 5b.

repeatedly used to detect cancer-specific genetic mutations. In a healthy donor, most cfDNA is released from hematopoietic cells, and the concentration of cfDNA in healthy individuals ranges from 1 to 10 ng/ml; however, the concentration of cfDNA is elevated in cancer patient serum (56, 57). An integrated radiographic and liquid biopsy study found that CT images of BM sites have features associated with CTC number and cfDNA levels (58). The tumor

fraction, the percentage of ctDNA in the plasma cfDNA of castration-resistant PC patients, was strongly correlated with the number of BM and serum ALP levels (59).

miRNAs. miRNAs are single-stranded RNA molecules, 21-25 bases pair, involved in the post-transcriptional regulation of gene expression. Transcriptional repression mediated by miRNA plays an important role in a wide range of biological processes, such as development, cell proliferation and differentiation, apoptosis, or metabolism. Expression of miR-218-5p was decreased in PC tissue and patient serum samples with BM, and ROC curve analysis of miR-218-5p in PC patient serum showed an area under the curve of 0.86, suggesting that miR-218-5p may be a novel serum biomarker for BM from PC (60). In serum exosomes of patients after radical prostatectomy, miR-375 and miR-141 were significantly increased in metastatic PC compared with non-recurrent PC (61). Elevated plasma miR-141-3p levels are a predictor of metastatic PC, and monitoring plasma miR-141-3p levels in patients with PC may predict metastatic risk (62, 63). Furthermore, miR-466-mediated suppression of RUNX2 has been shown to inhibit PC metastasis to the bone (64).

Extracellular vesicle (EV). Exosomes are granule-like substances with a diameter of 50-150 nm that are secreted by cells, and contain nucleic acids (miRNA, mRNA, DNA, *etc*.), proteins, and other substances. Exosomes are a type of extracellular vesicle. In addition to exosomes, there are microvesicles and apoptotic bodies, each with a different production mechanism and size. ITGA3 and ITGB1 were selected by mass spectrometry from exosomes secreted by LNCaP and PC3, and ITGA3 and ITGB1 were more abundant in urinary exosomes from metastatic patients than in patients with benign prostatic hyperplasia and non-metastatic PC (65). Exosomal miR-141-3p and miR-375, secreted by PC cells, promote osteoblast activity, regulate the BM microenvironment, and induce BM of PC (66, 67). Similarly, the exosome hsa-miR-940 secreted by PC cells acts on the BM microenvironment to induce bone marrow mesenchymal stem cells to become osteoblasts, promoting osteogenic BM of PC (68). Exosomal miR-21, miR-141, and miR-375 are involved in BM of PC because they help cancer cells overcome hypoandrogenic conditions in distant metastatic organs (69). There are still many unanswered questions, such as how the contents of blood exosomes differ between non-metastatic PC and PC with BM, and which biosynthetic pathways of what exosomes are activated in response to bone niche (70).

Conclusion and Future Perspectives

In general, the utility of blood bone turnover markers in the diagnosis of BM from various cancers, including PC, is limited. The cut-off values of conventional bone turnover markers for BM in PC vary widely, and which biomarker is useful for the diagnosis and prognosis of BM depends largely on the patient background. BM is complex and involves not only disease progression, but also various coordinated interactions of osteoblasts, osteoclasts, and osteocytes with their microenvironment through a vicious cycle. Liquid biopsy is a simple, non-invasive method to detect cells, exosomes, nucleic acids, and proteins released or detached from tumor tissue in a liquid outside the tissue (58). Recent rapid advances in molecular profiling techniques using liquid biopsy contributed to the advancement of precision medicine. Genomic data obtained from CTCs and ctDNA are also tools that can be analyzed throughout the course of a disease to reveal how tumor phenotypes change in real time during treatment and how these changes ultimately affect clinical outcomes. However, these technical developments remain unidentified as clinically useful biomarkers specific to BM in PC.

One of the major problems with liquid biopsy is that, due to the lack of implementation of uniform standards for collection and measurement, results can vary depending on locus design, depth of gene sequence, and choice of bioinformatical analysis code, even for detection of the same disease. In addition, the low sensitivity resulting from the small sample volume presents the biggest problem in the clinical application of liquid biopsy. Moreover, false-negative cases often occur in clinical practice. Compared with conventional blood bone turnover markers, liquid biopsy is a high cost and time-consuming method. Although there are many in vitro reports of liquid biopsy about BM in PC using cell lines, there are few reports using patient blood, and the actual clinical use has not yet reached the stage of clinical trials. In addition, there are many reports of biomarkers secreted from PC cells, but few reports of biomarkers secreted from the bone matrix through the vicious cycle. Future work may include the development of a diagnostic model for BM using machine learning algorithms that combine conventional blood bone turnover marker data with liquid biopsy and imaging tests. The clinical usefulness of new biomarkers in the diagnosis of BM of PC needs to be examined in prospective studies. Advances in liquid biopsy research and imaging technologies in BM of PC will lead to earlier diagnosis and improved patient prognosis and QOL.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Gaku Yamamichi conceived the presented idea and wrote the manuscript. Taigo Kato, Motohide Uemura and Norio Nonomura supervised the work. All Authors discussed, verified, and approved the final version of the manuscript.

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