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Isoenzymes of Alkaline Phosphatase – Useful Parameters for Identification of Bone Metastasis in Prostatic Carcinoma?

R. Paul[a] P. Bottermann[b] J. Breul[a] R. Hartung[a]

[a] Urologische Klinik und Poliklinik und
[b] II. Medizinische Klinik und Poliklinik, Technische Universität München, Klinikum rechts der Isar

Key Words
Bone-specific alkaline phosphatase · Alkaline phosphatase · Prostatic neoplasm · Bone metastasis

Summary
Background: The most frequent sites of metastases in prostatic carcinoma are bones. Bone scintigraphy is the diagnostic tool of first choice for staging bone metastases in cancer of the prostate. But this examination is expensive and time-consuming. Therefore we are looking especially for serum parameters like alkaline phosphatase, the isoenzyme of bone-specific alkaline phosphatase, and prostate-specific antigen (PSA) to replace bone scintigraphy for diagnostic staging. ***Material and Method:*** We compared in 132 prostatic carcinoma patients the results of total alkaline phosphatase, bone-specific alkaline phosphatase, and PSA with the results of the bone scan. ***Results:*** All three parameters demonstrate a lower sensitivity compared to the bone scan. Although the highest specificity was obtained by bone-specific alkaline phosphatase, this parameter cannot replace the bone scan for staging cancer of the prostate because of a lack of sensitivity. In a subgroup of patients with a PSA level below 10 ng/ml and a total alkaline phosphatase within normal range there is no need to obtain a bone scan, because of the very low incidence of bone metastasis in this group. ***Conclusions:*** There is only little additional information if bone-specific alkaline phosphatase instead of total alkaline phosphatase is determined. None of the serum parameters examined can replace bone scintigraphy in staging cancer of the prostate, but PSA and alkaline phosphatase can identify patients who are at low risk for bone metastases.

Schlüsselwörter
Knochenspezifische alkalische Phosphatase · Alkalische Phosphatase · Prostatakarzinom · Knochenmetastasen

Zusammenfassung
Hintergrund: Knochenmetastasierung ist die häufigste Metastasierungsart beim Prostatakarzinom. Das Knochenszintigramm ist die Untersuchung der 1. Wahl beim Staging des Prostatakarzinoms. Dieses Untersuchungsverfahren ist aber teuer und zeitaufwendig. Deswegen suchen wir besonders nach Serumparametern wie die alkalische Phosphatase, das Isoenzym der alkalischen Phosphatase, die knochenspezifische alkalische Phosphatase und das prostataspezifische Antigen (PSA), um das Skelettszintigramm beim Staging zu ersetzen. ***Material und Methode:*** Bei 132 Patienten mit Prostatakarzinom verglichen wir die Ergebnisse der gesamt-alkalischen Phosphatase, der knochenspezifischen alkalischen Phosphatase und des PSA mit dem Ergebnis des Knochenszintigramms. ***Ergebnisse:*** Alle drei Parameter zeigen eine niedrigere Sensitivität im Vergleich mit der Knochenszintigraphie. Obwohl die knochenspezifische alkalische Phosphatase die höchste Spezifität erreicht, kann dieser Parameter die Knochenszintigraphie aufgrund der niedrigeren Sensitivität nicht ersetzen. In der Untergruppe von Patienten mit einem PSA-Wert von unter 10 ng/ml und mit einer gesamt-alkalischen Phosphatase im Normbereich kann auf die Durchführung der Knochenszintigraphie verzichtet werden, da in dieser Gruppe die Inzidenz von Knochenmetastasen vernachlässigbar klein ist. ***Schlußfolgerungen:*** Die Bestimmung der knochenspezifischen alkalischen Phosphatase bringt nur wenig Zusatzinformation im Vergleich zur gesamt-alkalischen Phosphatase. Keiner der untersuchten Serumparameter kann die Knochenszintigraphie beim Staging des Prostatakarzinoms ersetzen, aber durch die Bestimmung des PSA-Wertes und der alkalischen Phosphatase können Patienten mit niedrigem Risiko für das Vorliegen von Knochenmetastasen identifiziert werden.

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Fax +49 761 4 52 07 14
E-mail Information@Karger.de
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Dr. Roger Paul
Urologische Klinik und Poliklinik der Technischen Universität München,
Klinikum rechts der Isar
Ismaninger Str. 22, D-81675 München (Germany)
Tel. +49 89 41 40-25 07, Fax -25 85
E-mail R.Paul@lrz.tu-muenchen.de

Introduction

The most frequent sites of metastases in prostatic carcinoma are bones. Before prostate-specific antigen (PSA) was introduced into the diagnostics of cancer of the prostate, up to 70% of all cancers detected presented with bone metastases at the time of diagnosis [1]. Nowadays, this number has dropped to about 30% (cases with bone metastases out of all new cases with prostatic carcinoma; Tumor Center Munich, 1994). To determine which therapy should be applied it is mandatory to know whether the stage is localized or metastatic. Therefore, examination of bone metastases in cancer of the prostate must be highly sensitive and should be reasonably specific. Additionally, staging should be simple and unexpensive.

Up to now the diagnostic tool of the first choice is bone scintigraphy, which is a highly sensitive but time-consuming and expensive examination. A further disadvantage of bone scans is the low specificity; therefore, new markers of bone metastases are needed.

As reported previously, total alkaline phosphatase (AP) and the skeletal isoenzyme of AP – bone-specific alkaline phosphatase (bAP) – are promising new markers [2–4].

Our intention is to establish the value of AP and bAP as well as PSA in the staging of newly diagnosed cancer of the prostate.

Method

Between 1995 and 1999 we studied 132 patients with histologically proven carcinoma of the prostate. All patients were examined by PSA, total AP, bAP, and bone scan.

For PSA evaluation we used the Hybritech Tandem-E assay; blood samples were obtained before any manipulation of the patient like digital rectal examination. Total AP in blood serum was photometrically determined by enzymatic dephosphorylation of nitrophenol phosphate (fig. 1) at 405 nm. Upper limit of the normal range is 170 IU/l. The wheat germ agglutination method was used for bAP. Added wheat germ agglutinin precipitated bAP; after precipitation the residual AP activity in the supernatant was determined by enzymatical dephosphorylation as described above. bAP was calculated by the difference total AP minus AP activity of the supernatant. Upper reference value of bAP is 100 IU/l. Additionally, we calculated the ratio of bAP and total AP to look for any improvement of these parameters.

Bone scan was performed by Technetium-99m skeletal scintigraphy as reference examination for diagnosing bone metastases. Suspicious lesions on bone scan were controlled either by plain X-ray or, if there was any doubt of metastatic origin of the focus, by magnetic resonance imaging. Statistical analysis was performed using StatView 4.0 software, statistical significance was accepted at $p = 0.05$.

Patient Population

132 patients with a mean age of 70.6 (range 48–88) years were evaluated between 1995 and 1998. All 132 patients had histologically proven prostatic carcinoma. 80 patients were negative on bone scan – localized prostatic carcinoma group (M0 subgroup), 52 patients proved to have bone metastasis (Moss subgroup). 108 patients were evaluated before any kind of treatment was initiated, 16 patients had hormonal therapy, and 6 patients had a radical prostatectomy before they were included.

Results

PSA Values

PSA values ranged between 0.9 and 544 ng/ml, with a mean value of 66.5 ng/ml; the median value was calculated to be 19.1 ng/ml. 22 patients who previously had hormonal therapy or radical prostatectomy were excluded from PSA evaluation in diagnosing bone metastasis.

The mean values, ranges and medians of PSA for subgroups M0 and Moss are depicted in table 1. There was a highly significant difference of PSA values for M0 and Moss patients for a cutoff value of 50 ng/ml ($p < 0.01$). The cutoff value was determined by ROC (Receiver operator characteristics) curve analysis (table 2). The cutoff value of 50 ng/ml demonstrated best

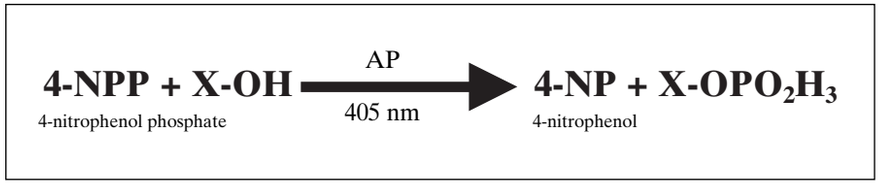

Fig. 1. Chemical reaction of enzymatic dephosphorylation by AP with nitrophenol phosphate dye.

Table 1. Prostate-specific antigen (PSA), total alkaline phosphatase (AP), and bone-specific alkaline phosphatase (bAP) of prostatic carcinoma patients with and without bone metastases

	PSA, ng/ml		Total AP, IU/l		bAP, IU/l		Ratio bAP/total AP	
	mean (range)	median	mean (range)	median	mean (range)	median	mean (range)	median
M0 subgroup	35.2 (0.9–390)	16.6	110.0 (61.5–196.5)	101.5	39.0 (11–93)	36.5	0.34 (0.06–0.99)	0.42
Moss subgroup	233.4 (10–544)	99.0	607.0 (72–5,588)	101.5	371.0 (11–4,048)	125.0	0.49 (0.08–0.82)	0.49
Total	66.5 (0.9–544)	19.1	290.6 (61.5–5,588)	120	156.0 (11–4,048)	45	0.38 (0.06–0.99)	0.42

Table 2. Sensitivities and specificities of PSA at different cutoff levels in detecting bone metastases in prostatic carcinoma patients

Cutoff level ng/ml	Sensitivity %	Specificity %	Positive predictive value, %
0.5	100.0	0.0	20.5
1.0	100.0	2.9	20.9
4.0	100.0	8.3	21.4
10.0	88.9	34.3	25.8
20.0	88.9	54.3	33.3
50.0	77.8	77.1	46.7
100.0	66.7	91.4	66.7
500.0	12.5	97.1	50.0

Table 3. Sensitivities and specificities of PSA, total AP, and bAP in detecting bone metastases in prostatic carcinoma patients

Parameter	Cutoff level			Sensitivity %	Specificity %
	ng/ml	IU/l	–		
PSA	50			77.8	77.1
AP		250		50.0	97.7
		200		56.4	96.3
		170		63.6	88.4
		160		63.6	83.7
		140		72.7	74.4
bAP		120		54.6	100.0
		100		59.1	97.7
		80		68.2	90.7
		60		77.3	83.7
bAP/AP ratio			0.40	63.6	69.8

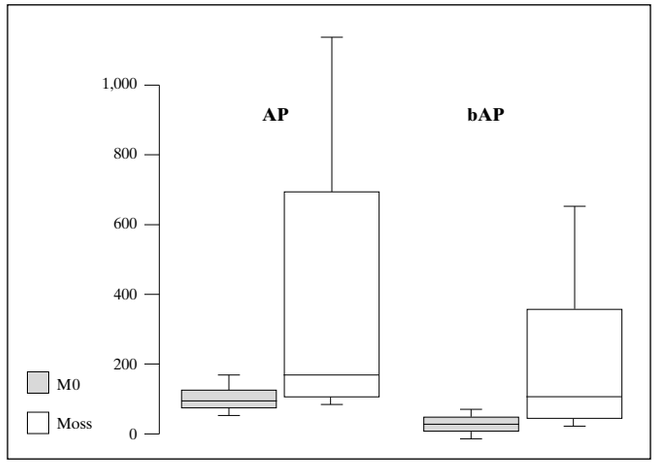

Fig. 2. Box-plot diagram of AP and bAP for the subgroups M0 and Moss.

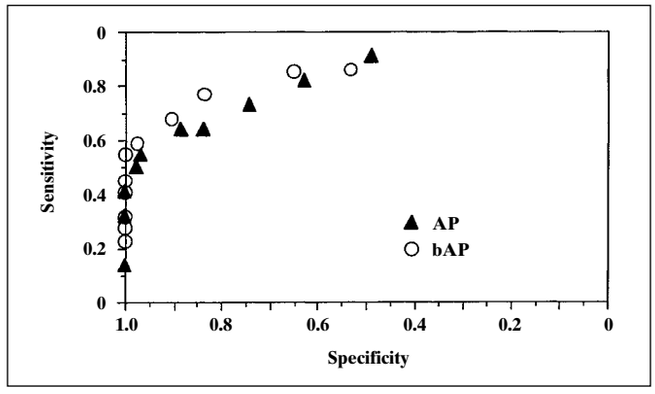

Fig. 3. Receiver operator characteristics (ROC) for the parameters AP and bAP.

results concerning sensitivity (77.8%) and specificity (77.1%) for PSA values (table 3).

Total Alkaline Phosphatase

The mean values, ranges and medians of total AP for subgroups M0 and Moss are shown in table 1. The difference between patients of subgroup M0 and those of subgroup Moss was statistically highly significant ($p < 0.01$). As mentioned above, the cutoff value was calculated by ROC curve analysis (fig. 2). Sensitivity was determined to be 63.6%, with a high specificity of 88.4% at a cutoff value of 170 IU/l.

Bone-Specific Alkaline Phosphatase

The mean values, ranges and medians of bAP for subgroups M0 and Moss are denoted in table 1. bAP also showed a significantly different value for metastasized and non-metastasized patients; again this difference was statistically highly significant ($p < 0.01$). The ROC curve analysis for bAP demonstrated a slight improvement compared with total AP (fig. 3). The ideal cutoff level was calculated at 100 IU/l, with a specificity of 97.7% but a lower sensitivity of 59.1%. With the cutoff level of 100 IU/l, 31 of 52 patients with metastases of prostatic carcinoma would have been detected correctly in our study.

Ratio of Bone-Specific Alkaline Phosphatase/Total Alkaline Phosphatase

The mean values, ranges and medians of the ratio bAP/total AP for subgroups M0 and Moss are shown in table 1. The calculated ratio of bAP and AP with mean values of 0.34 and 0.49 for both subgroups showed the difference reported for AP and bAP above as well. But the information gained could not enhance the results obtained from one of these two parameters. As demonstrated on the box plot diagram (fig. 2), both parameters are able to discriminate between M0 and Moss patients and the mean values demonstrate large differences between these two groups, but for both parameters an overlapping range for both parameters in both groups is shown.

Combination of Parameters

Combining PSA levels with the results of total AP or bAP shows a minor increase in sensitivity and specificity (table 4). Interestingly, the best combination seems to result if the PSA level is over 10 ng/ml *and* the total AP level is above 170 IU/l. This combination entails an increased specificity of 91.1% and a sensitivity of 68.4%. In this setting, total AP is even better than the bone-specific isoenzyme, but the specificity of bAP is

Table 4. Sensitivities and specificities of combinations of the parameters PSA, total AP, and bAP for different cutoff levels in detecting bone metastases in prostatic carcinoma patients

Cutoff level			Specificity %	Sensitivity %
PSA ng/ml	*and*	total AP IU/ml		
> 10		> 170	91.1	68.4
> 20		> 170	94.4	57.9
> 50		> 170	97.1	52.6
PSA ng/ml	*and*	bAP		
> 10		> 100	100.0	57.9
> 20		> 100	100.0	52.6
> 50		> 100	100.0	47.4
> 10		> 80	94.1	63.2
> 20		> 80	94.1	57.9
> 50		> 80	97.1	52.6
PSA ng/ml	*or*	total AP IU/ml		
> 10		> 170	39.1	97.3
> 20		> 170	63.9	73.7
> 50		> 170	76.5	68.4
PSA ng/ml	*or*	bAP IU/ml		
> 10		> 100	38.2	89.5
> 20		> 100	64.7	79.0
> 50		> 100	82.4	68.4
> 10		> 80	38.2	89.5
> 20		> 80	64.7	79.0
> 50		> 80	82.4	73.7

again higher than that for total AP. The highest sensitivity, with a value of 97.3%, is achieved from the combination PSA level > 10 ng/ml *or* total AP > 170 ng/ml.

Discussion

Bone metastases in cancer of the prostate are usually osteoplastic metastases [5]. Therefore, markers originating from the osteoplasts may be a predictor of metastases in prostatic carcinoma. AP is an enzyme which is located within the osteoplast and chondroplast. In case of increased osteoplastic activity, AP will be increased in serum. But AP is an enzyme which is also located in a variety of tissues, for example the liver, the biliary system and the mucosa of small intestine. Increased AP is therefore also influenced by diseases of the organs and tissues mentioned above. For these reasons the sensitivity of total AP in our investigation reached just 63.3%, with a specificity of 88.4%. Merrick et al. [6] calculated the sensitivity as high as 94%, but they found a specificity for this cutoff of just 50%. According to our result, if specificity is increased to 97.7% (table 3), the sensitivity drops to 50.0% at a cutoff level of 250 IU/l. Similar to our results, Cowan and co-workers [7] described a sensitivity of 62%.

Increased AP is not specific, but there are three isoenzymes of AP which are genetically determined, so that we are able to measure the isoenzyme which is located in the skeletal system – bAP. Increased bAP is a specific marker for increased osteoplastic activity, like trauma, tumor, Morbus Paget or bone metastasis. Therefore, bAP shows the same restrictions as bone scintigraphy. Our data confirm that bAP is a specific skeletal marker but not a marker of bone metastasis. As demonstrated on the ROC curves (fig. 3), there is a slight improvement of bAP compared to total AP. We can show, compared to total AP, an enhancement of the specificity from 88.4 to 97.7%, but no improvement in the sensitivity, which is calculated at 63.6 and 59.1%, respectively. Lowering the specificity of bAP into the range of the optimal cutoff level of total AP improves the sensitivity to 68.2% which is then slightly better than that of total AP (63.6%).

Compared to the literature, Desoize et al. [5] found a sensitivity of 75% and a specificity of 90%; they also used the wheat-germ agglutination reaction for determining bAP. Whereas Cooper et al. [8] used the Ostase method, an immunoradiometric assay, for determining the bone isoenzyme. They describe a sensitivity of 86% and a specificity of 94%, but they had excluded patients with Morbus Paget from these results. If we look up our ROC data (fig. 3) as well as the data from Wirtz et al. [9], we see that these studies confirm each other; there may be a little improvement using the Ostase kit, but that would have to be shown in a study comparing both methods.

Imai et al. [10] tried to estimate the extent of disease by combining the results of bone scan and AP, and they showed a positive correlation. Akimoto et al. [11] confirmed the correlation of AP levels with the extent of disease. Interestingly they found that bone AP is an even better marker to estimate the extent of bone metastases. In the contrary, Akimoto and co-workers [12] recently published new data demonstrating that the extent of bone metastases can be evaluated more precisely by using the results of the bone scintigram.

PSA is not a bone marker and it is not a tumor marker, but it is a marker of prostatic tissue. Increased PSA values correlate with the risk of bearing metastatic disease, therefore a PSA value above 50 ng/ml is associated with a high risk of metastasized prostatic carcinoma in our study. More than 80% of all patients with PSA values above 50 ng/ml in our study demonstrated bone metastases at the time of diagnosis. On the other hand, a PSA value below 10 ng/ml before therapy is associated with localized disease in all but 1 case (0.9%) in our study. Oesterling [13] also described a positive bone scan for patients with PSA values below 10 ng/ml in just 0.5%. Other authors report that PSA is the best predictor to differentiate clinical stages, although PSA levels are not useful for stratifying the extent of bone disease [14]. After therapy, PSA values are altered, and PSA is not a useful marker to monitor for bone metastasis, but it is a very useful marker for progressive disease. Especially after radical prostatectomy PSA elevation may be the first sign of progressive disease over years [15, 16]. Thus, monitoring PSA levels can be sufficient after treatment for cancer of the prostate, and only if rising PSA values are noted, further workup with AP and/or bAP or a bone scan should be performed.

However, for newly diagnosed prostatic carcinoma, patients should be examined very carefully because the prove of distant metastasis in prostatic carcinoma will completely alter the treatment strategy. If no metastasis can be detected, patients will be eligible for curative therapy, either radical prostatectomy or radiotherapy, but in case of systemic disease patients should receive hormone therapy. Therefore a high sensitivity is mandatory for staging examinations. Our results suggest that the combination of a PSA value above 10 ng/ml or a total AP value >170 IU/l are suspicious for bone metastasis (sensitivity 97.3%), although these parameters are very unspecific (specificity 39.1%). Using the combination of either a PSA value above 10 ng/ml or a total AP value above 170 IU/l leads to the detection of nearly all metastasized patients. On the other hand, our recommendation is that patients with untreated prostatic carcinoma with normal total AP levels (<170 IU/l) and a PSA value below 10 ng/ml do not need to have further workup for bone metastasis, but patients at risk with a PSA value above 10 ng/ml or an AP above 170 IU/l should have a bone scan for further skeletal staging. Stokkel et al. [17] are defining a similar subgroup at risk for prostatic carcinoma, but they found that PSA was the best overall predictor, and they are using a higher cutoff value of 20 ng/ml.

Other parameters like acid phosphatase, tartrate-resistant acid phosphatase, and prostatic acid phosphatase have been evaluated, but none of these parameters proved to show better results in detecting bone metastasis in cancer of the prostate [5, 18, 19].

New biomarkers of bone resorption are under consideration, such as urine pyridinoline [20, 21] or the carboxy-terminal telopeptide of type I collagen (ICTP) as well as new bone formation markers: carboxy-terminal propeptide of type I collagen (PIPC). Up to now the best parameter seems to be bAP as reported by Akimoto et al. [11]. New parameters are needed to replace bone scintigraphy in the future, because sensitivity and specificity of bAP are not sufficient for decision-making for further therapy based on bAP alone.

We conclude that up to now obtaining a bone scan before treatment is the most useful examination to rule out bone metastasis in cancer of the prostate, but it is not necessary for a subgroup of patients with low risk of bone metastasis. This subgroup is defined by a PSA value below 10 ng/ml and a total AP value within normal limits (<170 IU/l) in our hands. In patients with a PSA value above 10 ng/ml we would recommend obtaining a bone scan prior to curative therapy, also if the PSA value is below 10 ng/ml. But if total AP is above 170 IU/l we recommend skeletal scintigraphy to exclude bone disease. On the other hand, there is no need to obtain the total AP or even bAP in patients with a PSA value above 10 ng/ml, because these patients need a bone scan since the suspicion of bone metastases is already raised from the obtained PSA value.

None of the three parameters – total AP, bAP, and PSA – is as sensitive as the bone scan. Therefore, patients at risk for bone metastasis need to be investigated by bone scintigraphy. In the monitoring of disease, PSA values seem to be sufficient, because the PSA level after therapy is probably the best marker of relapse and progressive disease. Only if rising PSA values are detected, further examinations are necessary.

Because there is only little improvement using bAP compared to total AP, we do not recommend to measure bAP in the staging or monitoring of prostatic carcinoma.

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