Serum bone alkaline phosphatase levels enhance the clinical utility of prostate specific antigen in the staging of newly diagnosed prostate cancer patients

José A. Lorente[1], Herminia Valenzuela[2], Juan Morote[3], Antoni Gelabert[1]

[1] Department of Urology, Hospital del Mar, Autonomous University of Barcelona, Barcelona, Spain
[2] Department of Nuclear Medicine, Vall d'Hebron University Hospital, Autonomous University of Barcelona, Barcelona, Spain
[3] Department of Urology, Vall d'Hebron University Hospital, Autonomous University of Barcelona, Barcelona, Spain

Received 4 December 1998 and in revised form 15 February 1999

Abstract. The aim of this study was to analyse the clinical utility of serum bone alkaline phosphatase (BAP) in addition to prostate-specific antigen (PSA) in the staging of newly diagnosed untreated prostate cancer patients. A prospective study was conducted, analysing serum BAP and PSA concentrations in 295 consecutive newly diagnosed untreated prostate cancer patients (T1–4, N0–1, M0–1b), 93 of whom had bone metastases on bone scan. The relationship of each marker with extent of bone disease, the influence of several clinical variables on both serum marker levels, the efficiency in predicting bone metastasis through receiver operating characteristic curves and, finally, the clinical utility in avoiding unnecessary bone scans were determined. Significant differences were found in the serum levels of both BAP and PSA between patients with and patients without bone metastases. Multiple regression analysis showed the extent of bone disease to be the only variable that influenced both serum levels. However, while serum BAP levels showed a statistical relationship with extent of bone disease, serum PSA levels did not. The best prediction of bone scan findings was obtained with the combination of both markers using a cut-off of 20 ng/ml, with positive and negative predictive values of 46.5% and 100%, respectively. This greater efficiency could permit 32.2% of initial bone scans to be avoided. False-positive and false-negative rates of BAP were 7.5% and 14%, respectively. This study suggests that serum BAP levels could play a complementary role in the diagnosis of bone metastasis in prostate cancer patients. This marker could provide useful clinical information on the degree of skeletal metastasis and constitute an easy way of enhancing the clinical utility of PSA. The addition of this marker to PSA in the initial evaluation could permit staging bone scan to be avoided at a PSA range of 10–20 ng/ml, with significant implications for cost saving.

Correspondence to: J.A. Lorente, C/ Juan de Mena 5–7, 20–3ª, E-08035 Barcelona, Spain

Key words: Prostate specific antigen – Bone alkaline phosphatase – Prostate cancer – Bone metastasis – Bone scan

Eur J Nucl Med (1999) 26:625–632

Introduction

Prostate-specific antigen (PSA) has become the most clinically useful tumour marker available for the diagnosis of prostate cancer [1]. In the past decade, its extensive application has definitively changed the management and even the prognosis of the disease. Its wide recognition as the gold standard tumour marker in prostate cancer has generated interest in its clinical utility as a screening tool [2]. The application of early diagnosis programmes has revealed an increasing annual incidence of the disease in developed societies, particularly in the initial stages. The finding of different molecular forms of PSA, such as free PSA, has generated investigation into the use of these forms in these programmes [3]. However, this situation has given rise to debate on financial costs in the urological community, and several proposals for improving clinical indications have been put forward. It has recently been suggested that PSA levels might be used as a basis for eliminating some initial staging examinations because of the relationship between serum PSA concentrations and the clinical stage [4]. Among these recommendations, Oesterling et al. have proposed eliminating the staging bone scan owing to the low probability of bone metastasis in patients with low serum PSA levels [5]. Other studies, dealing with a high prevalence of metastatic bone disease, have questioned such an application of PSA [6–9].

Alkaline phosphatase activity has been used as a non-specific marker of bone metastasis from prostate cancer since 1936, when Gutman et al. showed its serum activity increasing with osteoblastosis [10]. Human alkaline

phosphatases are a group of five isoenzymes. Under normal conditions, bone fraction (BAP) represents less than 40% of the total serum concentration. The first immunoradiometric assay incorporating two specific monoclonal antibodies was developed in 1990 [11] (Tandem-R Ostase; Hybritech, Inc., San Diego, Calif.). Since then, several studies have focussed on biochemical markers of bone metabolism in prostate cancer [12–15]. This neoplasm is a unique model for the study of osteoblastic metastasis and BAP is an indicator of the metabolism of the osteoblast. The purpose of this study was to analyse the clinical utility of BAP in addition to PSA in the staging of newly diagnosed, untreated prostate cancer patients.

Material and methods

Patient population. A prospective study including 295 consecutive newly diagnosed untreated patients with histologically proven prostate cancer, was conducted between November 1992 and December 1996. Mean patient age was 72.1 years (range: 42–96 years). Serum concentrations of PSA and BAP were determined in all patients. Clinical assessment included digital rectal examination, transrectal ultrasonography and radionuclide bone scan. Indication for prostatic biopsy was established on the basis of abnormal digital rectal examination and/or a PSA serum level higher than 4 ng/ml. Occasionally, computed tomography, magnetic resonance imaging or bone marrow scintigraphy were performed to clarify doubtful hot spots. When a precise initial clinical status was not determined, patients were excluded from the study.

After bone scan, 202 patients were classified as M0 (non-metastatic bone scan) and 93 as M1b (metastatic bone scan) according to the 1992 TNM classification. Extension of skeletal disease (EOD) was established according to Soloway et al. [16] and yielded a classification of M1 (<6 hot spots) in 29 patients, M2 (6–20 hot spots) in 25, M3 (>20 hot spots) in 27 and M4 (superscan or equivalent patterns) in 12. M0 patients were classified as T1 in 30 cases, T2 in 67, T3 in 89 and T4 in 16. Gleason score ranged from 2 to 4 in 33 patients, 5 to 7 in 159 and 8 to 10 in 103.

PSA and BAP determinations. Both markers were measured in sera that had been stored at –20 C. Previous studies showed that the two markers remained stable during storage. PSA was measured by the Hybritech Tandem-R PSA kit [two-site immunoradiometric assay (IRMA); normal range, 0–4 ng/ml]. The Hybritech Tandem-R Ostase two-site IRMA was used to measure serum BAP, and the normal range in males was 3–20 ng/ml (mean ± standard deviation (SD) 11.3±4.8]. Briefly, the method consisted in incubating 100 µl of standard, control, or sample with 100 µl of tracer (iodine-125 labelled anti-bone alkaline phosphatase mouse monoclonal antibody). After gentle mixing, a bead coated with a second monoclonal antibody directed towards a second site of the molecule was added to each tube. After incubation for 19±2 hours at 2°–80 C, the solid phase was washed 3 times to remove excess tracer and counted. The test had a dynamic range of 2–120 ng/ml, an intra- and inter-assay variation of<7% and 9%, respectively, and a cross-reactivity with liver alkaline phosphatase of <15% (information supplied by the manufacturer).

Statistical methods. Multiple regression analysis was used to determine the influence of several clinical parameters on both serum marker levels. Receiver operating characteristic (ROC) curves were determined to assess the efficiency of PSA and BAP for the diagnosis of bone metastasis. The Hanley and McNeil method was used to compare the areas under the ROC curves. The non-parametric Mann-Whitney *U* test was used to compare means, and predictive values were calculated for different cut-off levels. An SPSS 6.0 program was used for statistical analysis [17].

Results

Mean serum BAP concentration was 12.0 ng/ml [mean 95%; confidence interval (CI) 10.5, 13.6] in 202 M0 prostate cancer patients and 94.0 ng/ml (mean 95%; CI 67.4, 120.6) in 93 M1b patients (P<0.0001). Mean serum PSA concentration was 62.7 ng/ml (mean 95%; CI 43.8, 81.7) in M0 patients, and 758.0 ng/ml (mean 95%; CI 529.5, 987.2) in M1b patients (P<0.0001). (Table 1).

A multiple regression model was used to analyse the influence of several clinical variables on both serum marker levels. Extent of disease (EOD) measured by bone scan, as proposed by Soloway et al., was the only variable that statistically influenced both serum levels (Table 2).

Thus, mean serum BAP and PSA concentrations were analysed in 93 M1b prostate cancer patients according to skeletal involvement (EOD). Analysis of serum BAP concentrations revealed that mean BAP levels increased significantly from M1 to M4 (P<0.0001), showing a relationship with the degree of skeletal involvement. Although the mean serum PSA concentration increased

Table 1. Details of BAP and PSA levels in prostate cancer patients according to bone scan result

	BAP (ng/ml)		PSA (ng/ml)	
	M0	M1b	M0	M1b
Patients	202	93	202	93
Mean±SD	12.0±11.2	94.0±129.4	62.7±136.2	758±1111.3
Mean 95% CI	10.5,13.6	67.4,120.6	43.8,81.7	529.5,987.2
Median	10.8	49.7	20.1	355
Range	0.5–151	3.3–895	1.3–1500	8.9–5164
25–75th percentile	7.5–15	22.7–106	10–61.8	110–1000
95th percentile	20.8	360.9	285.7	3723.8
	P = <0.0001		P = <0.0001	

Table 2. Result of multiple regression analysis of the influence of various clinical variables on serum BAP and PSA levels

	B	SE B	*P*
a)	BAP		
PSA	–0.0035	0.0059	0.5533
Gleason score	2.7257	6.1944	0.6602
Age	0.4819	0.3990	0.2281
EOD	47.709	4.1809	0.00001
T local stage	–5.8516	4.9702	0.2400
Constant	–18.6278	32.6914	0.5693
b)	PSA		
BAP	–0.3432	0.5783	0.5533
Gleason score	–33.0193	60.9247	0.5883
Age	7.2674	3.9116	0.0642
EOD	249.6316	47.3082	0.00001
T local stage	93.4530	48.7009	0.0560
Constant	–603.0506	319.8094	0.0603

from M1 to M4, no significant differences were found among groups (Table 3).

BAP and PSA efficiency in predicting bone scan findings was studied at different cut-off values in 295 newly diagnosed untreated prostate cancer patients. The ability of BAP and PSA, alone or combined, to predict a metastatic bone scan is reflected in Table 4. When the two markers were considered individually, a bone scan revealing metastases was presented by no patients with a PSA value lower than 8 ng/ml, by only one with a PSA value lower than 10 ng/ml and by three with a PSA value lower than 20 ng/ml. Positive predictive values (PPV) were 35.9%, 37.5% and 46.1%, respectively, while negative predictive values (NPV) were 100%, 98% and 97%, respectively. Similarly, 13 patients with a BAP value lower than the proposed normal cut-off level of 20 ng/ml presented a metastatic bone scan with PPV and NPV of 84.2% and 93.5%, respectively. However, when the combination of both markers at 20 ng/ml was evaluated, no patient had a metastatic bone scan, with PPV and NPV of 46.5% and 100%, respectively.

Multiple logistic regression models were used to estimate the relationship between each serum marker and

Table 3. Serum BAP and PSA levels in prostate cancer patients according to the extent of bone disease

a) BAP levels

	BAP (ng/ml)			
	M1	M2	M3	M4
Patients	29	25	27	12
Mean±SD	24.7±13.1	61.7±48.7	126.7±114.9	255±239.2
Mean 95% CI	19.7,29.7	41.7,81.8	81.2,172.1	103,407
Median	21.8	50	95	201
Range	3.3–61	20–210	18–545	36–895
25–75th Percentile	16.7–34.9	35.4–63.2	54.7–163	74.5–371.2
95th Percentile	55	205.2	466.6	746.2
		P = <0.0001		
	P = <0.0001			
		P = 0.0057		
			P = 0.05	

b) PSA levels

	PSA (ng/ml)			
	M1	M2	M3	M4
Patients	29	25	27	12
Mean±SD	550±1212.6	674.9±887.3	958±1253.6	984.8±932.7
Mean 95% CI	89.1,1011.6	308.6,1041.1	462.5,1454.3	392.1,1577.4
Median	151	355	623	765
Range	8.9–5164	14.5–3434	26.8–4983	28.5–2972
25–75th Percentile	49.0–389.5	93.9–785	180–1000	195–1708.2
95th Percentile	4782	3228.5	4983	2741.3
		P = 0.0102		
	P = 0.0924			
		P = 0.1996		
			P = 0.6	

Table 4. Ability of different cut-off values of BAP and PSA, alone or combined, to predict bone scan results

	M0			M1b			PPV	NPV
	+	–	Sp%	+	–	Sens%		
PSA 8[a]	36	166	17.8	93	0	100	35.9	100
PSA 10	49	153	24.2	92	1	98.9	37.5	98
PSA 20	97	105	48	90	3	96.7	46.1	97
BAP 20	187	15	92.5	80	13	86	84.2	93.5
BAP 20 + PSA 20	95	107	47	93	0	100	46.5	100

Sp, Specificity; Sens, Sensitivity; PPV, positive predictive value; NPV, negative predictive value

[a] PSA and BAP units: ng/ml

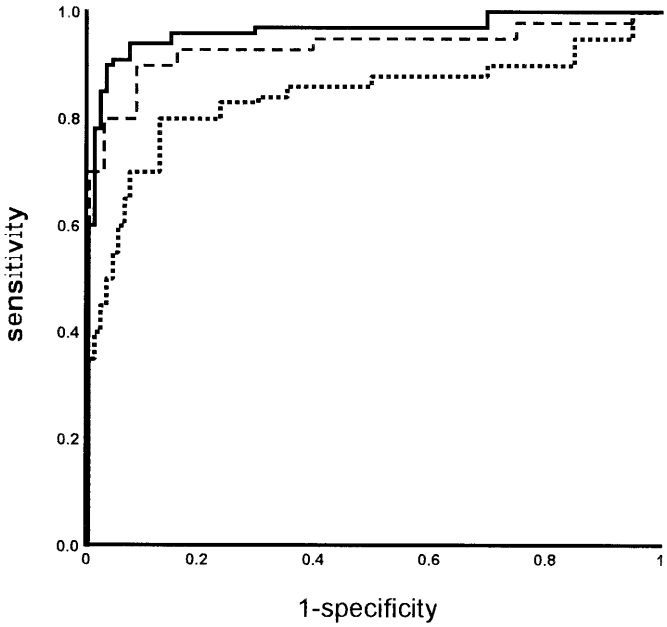

Fig. 1. ROC curves for detecting bone metastases in bone scans. Areas under the curves represent the efficiencies. *Continuous line*, BAP+PSA; *broken line*, BAP; *dotted line*, PSA

the probability of metastatic bone involvement. The value of each marker was considered a predictive variable. Models with PSA, BAP and BAP+PSA were applied and a theoretical probability of bone metastasis was estimated from each model. Sensitivity and specificity were plotted in ROC curves and the predictive value of each model estimated from the area under the respective curve. The area under the PSA curve was 0.8527 (SE = 0.0275), that under the BAP curve, 0.9355 (SE = 0.0186) and that under the BAP+PSA curve, 0.9551 (SE = 0.0159). Differences between areas for BAP+PSA and BAP compared with PSA models were significant (P = 0.001 and 0.005, respectively). Nevertheless, differences between areas were not significant for BAP+PSA and BAP models (P = 0.1858) (Fig. 1).

Once the behaviour of both markers in predicting bone scan findings had been assessed, the clinical utility in cost-effectiveness of BAP and PSA was analysed to eliminate bone scan staging in newly diagnosed untreated prostate cancer patients. If a bone scan had not been performed in all patients with a PSA level below 8 ng/ml, 12.2% of examinations could have been avoided, with a correct diagnosis in all cases. The same situation would have been achieved by applying the criterion of not performing a bone scan when initial BAP and PSA values were below 20 ng/ml. This last combination

Table 5. Characteristics of patients with non-metastatic or metastatic bone scans and BAP higher or lower than the normal range

PSA (ng/ml)	BAP (ng/ml)	Bone scan results	BAP mean±SD
MO patients			
22.3	24.0	Paget's disease	
376.0	151.0	Paget's disease	
60.0	35.0	Paget's disease	52.2±55.4
20.0	22.9	Paget's disease	
91.0	28.0	Paget's disease	
4.2	23.7	Other benign features	
140.0	20.0	Other benign features	
21.0	20.0	Other benign features	21.6±1.8
22.0	23.6	Other benign features	
101.0	21.0	Other benign features	
5.0	28.0	Normal appearance	
23.0	20.0	Normal appearance	
384.0	21.8	Normal appearance	21.9±3.4
14.8	20.0	Normal appearance	
99.0	20.0	Normal appearance	
M1b patients			
248.0	18.5	M1	
184.0	16.0	M1	
446.0	17.4	M1	
91.0	11.8	M1	
395.0	19.0	M1	
99.0	3.3	M1	
4400.0	12.8	M1	12.6±4.9
54.6	7.8	M1	
33.7	9.7	M1	
46.1	9.0	M1	
3434.0	14.0	M1	
623.0	18.0	M3	
1045.0	18.8	M3	

would have been more cost-effective since it would have permitted 2.6 times more examinations to be saved than with the first criterion.

Finally, false-positive and false-negative rates of serum BAP in predicting bone scan results were analysed and are shown in Table 5. A false-positive rate of 7.5% was found, mainly due to benign bone disease. The false-negative rate was 14%, mainly because of prostate cancer patients classified as having minimal metastatic bone disease (M1), three of whom had solitary bone scan lesions; however, all had serum PSA levels higher than 20 ng/ml.

Discussion

The extensive clinical use of serum PSA determination has changed the diagnosis as well as the staging of prostate cancer. Because of the relationship between serum PSA level and tumour burden, a high probability of normal bone scan with a low PSA level has been proposed. Firstly, for a PSA concentration of 20 ng/ml, Chybowski et al. [18] reported a negative predictive value of 99.7%. Likewise, Oesterling et al. [5] proposed not performing staging bone scan in all asymptomatic patients with PSA below 10 ng/ml because of their low probability of having metastases. However, this recommendation has been questioned, particularly in populations with a high prevalence of bone metastasis. A number of series analysing this aspect are presented in Table 6, where the number of patients with bone metastases and PSA cut-offs between 10 and 20 ng/ml can be seen [18–34].

To improve the clinical utility of PSA in this application, the measurement of several bone metabolic serum markers has been proposed. As bone metastases of prostate cancer are mainly osteoblastic, a marker reflecting osteoblastosis could be a good indicator of bone involvement. This finding was initially described in bone metastasis in breast cancer. Our group has reported this idea previously and it has also been demonstrated in different series [32, 35–37]. As PSA determination correlates significantly with clinical stage and tumour burden, it seems obvious to seek differences between M0 and M1b patients. Similarly, as BAP reflects osteoblastic activity, significant differences were also observed according to the existence or absence of bone disease. Thus, a multiple regression analysis was performed to verify the influence of different clinical variables on both serum levels. For PSA, local stage was nearly significant, but EOD measured by bone scan was the only variable that statistically influenced both serum levels (P = 0.00001). In recent studies, EOD has been described as a useful prognostic tool and M1 patients appear to have a higher specific cancer survival rate [38]. We analysed the relationship between mean serum BAP and PSA concentration and EOD. Analysis of serum BAP concentrations showed that mean BAP level increased significantly from M1 to M4 (P<0.0001), thereby establishing a relationship with the degree of skeletal involvement. Although mean serum PSA concentration increased from M1 to M4, no significant differences were found among groups. Maeda et al. [39] found a BAP concentration of 25.7 ng/ml in eight M1 patients, 87.3 ng/ml in 17 M2,

Table 6. Predictive values of different PSA cut-offs in series of prostate cancer patients with bone metastases

Author	No.	M1b	Prev.	PSA <10 ng/ml	PSA <20 ng/ml	NPV10	NPV20
Levran, et al. [19]	861	8	0.9	0	0	100	100
Huncharek, et al. [20]	265	10	3.7	2	3	98.2	97.4
Gleave, et al. [21]	490	28	6	0	4	100	98.9
Wolff, et al. [22]	359	40	11.1	7	10	96	93
Chybowski, et al. [18]	521	71	14	0	1	100	99.7
Puppo, et al. [23]	327	53	16.2	–	16	–	86
Vijayakumar, et al. [24]	90	17	18.8	0	1	100	97.5
Gerber, et al. [25]	277	61	22	0	0	100	100
Miller, et al. [26]	146	34	23	5	10	91	88
Kemp, et al. [27]	98	26	26.5	0	0	100	100
Barichello, et al. [28]	108	30	27.7	5	–	77	–
Present study	295	93	31.5	1	3	98	97
Haukaas, et al. [29]	128	48	37.5	0	3	100	939
Ruiz la Roja, et al. [30]	50	19	40	0	2	100	86
Rudoni, et al. [31]	118	54	45.7	0	7	100	80
Morote, et al. [32]	140	68	48.5	1	2	91.7	87.5
Pertusa, et al. [33]	152	79	52	1	8	88.5	70.3
Morote, et al. [34]	144	83	57.6	2	7	87.1	73.9
	4569	842	18.4	24/789 3%	77/812 9.5%		

Prev., Prevalence

81.3 ng/ml in 11 M3 and 435.0 ng/ml in three M4, whereas Murphy et al. [40] found 12.9 ng/ml in seven M1 patients, 31.5 ng/ml in eight M2, 152.7 ng/ml in five M3 and 378.9 ng/ml in three M4. The different relationship with EOD between these works and ours may be due to different population composition. In fact, our group had previously reported increasing BAP levels from M1 to M4 in 68 prostate cancer patients with bone metastases [32]. However, like Murphy et al. [40] and Kylmälä et al. [41], we found no relationship between EOD and PSA level, since bone disease represents only a part of total tumour burden.

Multiple logistic regression models were used to estimate the relationship between each marker and the probability of metastatic bone involvement. The best model, with the highest area under the ROC curve (0.9551), proved to be BAP+PSA, but no significant differences were obtained compared with the BAP curve (0.9355) (P = 0.1858). In the original study of Chybowski et al. [18], the area under the PSA curve was 0.949 and significant differences were observed with all other parameters analysed. Moreover, the association of any other clinical parameter did not increase the predictive value of PSA. These results have not been reported in other studies. Wolff et al. [22] reported an area under the PSA curve of 0.77. Amico et al. [42] found significant differences in areas under the PSA and BAP curves of 0.81 and 0.93 respectively (P<0.01).

A false-positive rate of 7.5% was found when using serum BAP to predict bone scan results. Garnero et al. [43] reported a high serum BAP concentration in several benign bone diseases such as Paget's disease, renal osteodystrophy, hyperparathyroidism, hyperthyroidism and osteoporosis. On the other hand, without hepatic disease, a 15% cross-reaction has been found with the hepatic fraction of alkaline phosphatase, thereby explaining some false-positive cases. Moreover, increases in bone markers with normal bone scan have been described which, during follow-up, turned precociously into metastasis [44]. In our study, no patients had this pattern on follow-up and their BAP values were continuously higher than 20 ng/ml, perhaps reflecting a constitutional metabolic status of high turnover. A false-negative rate of 14% was found. Eleven patients had M1 disease and three of these had a single hot spot. Several hypotheses have been proposed to explain a metastatic status with low bone marker levels. Firstly, the different metastatic burden in EOD categories. In fact, the M1 category included from a single to five hot spots. Moreover, there could be great variability in the metabolic bone turnover of each individual. Finally, the different phase of metastatic focus could be another qualitative factor. Metastases are dynamic processes that may have different biochemical expression according to their activity. No osteoclastic resorption and collagen proliferation processes have been demonstrated at the same time, in the same focus [45]. If these changes are not very active, they could have poor biochemical serum expression. This phenomenon has been proposed in the 3% of patients with bone metastases whose bone scans are normal. Nevertheless, all false-negative patients had serum PSA levels higher than 20 ng/ml.

In our study, no patient with a PSA level below 8 ng/ml and an NPV of 100% had bone metastases. Oesterling et al. [5] also failed to find bone metastases in 852 patients with a PSA level below 20 ng/ml; however, metastases were found in one patient with a PSA level between 8 and 10 ng/ml, in two with a PSA level of 10 ng/ml and in four with PSA levels between 10 and 20 ng/ml. In our group, the NPV of PSA levels of 8, 10 and 20 ng/ml were 100%, 98% and 97%, respectively. Although with PSA below 10 ng/ml, bone metastatic dissemination was infrequent in the analysed series (3%), a real risk does exists. Moreover, rare cases of bone metastases with a normal PSA level have been reported [26]. The combination of BAP and PSA, both set at a 20 ng/ml cut-off value, yielded an NPV of 100%. Thus, the combination of BAP and PSA could assist in eliminating bone scans at a PSA range of 10–20 ng/ml, with important cost-saving implications. The 1996 statistics regarding prostate cancer in the United States, where 317 000 new cases were diagnosed, can be used to ascertain this impact. If bone scans had not been performed when PSA was below 10 ng/ml, approximately 187 000 bone scans would have been avoided, with a $ 94 million saving. Patients whose PSA ranges from 10 to 20 ng/ml represent a risk group for bone metastases. Gleave et al. [21] pointed out that this group may represent 18% of screened patients. In our experience, 95% of patients with PSA ranging between 10 and 20 ng/ml have BAP below 20 ng/ml. The application of this criterion could lead to 55 000 more bone scans being avoided and then, finally, only 25% of staging bone scans would be required, with a saving of $ 120 million.

Traditionally, the recommendations of U.S. authors have been carefully considered. The prevalence of metastatic disease is higher in Spain, and early detection programmes are less developed. For this reason, an increasing number of patients are currently being diagnosed with PSA levels between 10 and 20 ng/ml. Among the patients investigated in this study, if bone scans had not been performed when the PSA level was less than 8 ng/ml, 12.2% of scans could have been avoided without causing failure to diagnose matastasis. If bone scans had not been performed when the PSA level was below 10 ng/ml, 17% of scans could have been avoided, though one patient with metastases (1.1%) would not have been correctly diagnosed. If bone scans had not been performed at PSA levels of less than 20 ng/ml, 33.9% of examinations could have been avoided, but three patients with metastases (3.2%) would have remained undiagnosed. However, if a BAP level of less than 20 ng/ml had been employed in addition to the latter criterion, 32.2% of bone scans could have been avoided without loss of diagnoses. This last criterion is clinically most important since inappropriate radical therapy could be

avoided in metastatic patients, with evident individual clinical benefits; with 10 000 estimated new cases of prostate cancer expected next year in Spain, a saving of around 386 400 € would result.

In conclusion, this study suggests that BAP could be a complementary marker in prostate cancer. The addition of BAP determination to PSA in the initial evaluation of newly diagnosed untreated prostate cancer patients could assist in establishing a rationale for the indication of staging bone scan. Its clinical utility could have important cost-saving implications by avoiding bone scan in the grey PSA zone of 10–20 ng/ml. The combined use of both markers at cut-off levels of 20 ng/ml had an NPV of 100% in our series. Thus, this double marker model could provide useful clinical information regarding the degree of skeletal metastatic involvement.

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