ORIGINAL RESEARCH

Predictive value of standard serum markers for bone metastases in prostate cancer

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Abstract

Background: The early detection of bone metastases is very important in prostate cancer follow-up. This study aimed to compare conventional tumor markers, namely free prostate-specific antigen (free PSA), total prostate-specific antigen (total PSA), free PSA/total PSA ratio, alkaline phosphatase (ALP) values, Gleason scores and ^{99m}Tc-MDP bone scintigraphy findings in the prediction of bone metastases in prostate cancer.

Methods: In total, 175 patients with prostate cancer who underwent whole-body bone scintigraphy were included in the study. All selected scintigraphic studies were reprocessed. Free PSA, total PSA, free PSA/total PSA ratio, alkaline phosphatase (ALP) values and Gleason scores of patients were recorded.

Results: The results of our study show that the presence of bone metastasis correlates very weakly with free PSA/total PSA ratio (rho = 0.179), weakly with total PSA (rho = 0.318) and Gleason score (rho = 0.382), moderately with ALP (rho = 0.539), free PSA (0.416). Only ALP variable had a diagnostic value and ALP cutoff value was 76.50 IU/L, with 80% sensitivity and 82.1% specificity.

Conclusion: According to the results of our study; the free PSA, total PSA, free PSA/total PSA ratio and Gleason score values were not considered as a reliable parameter in the prostate cancer cases follow-up for bone metastasis development. Only ALP had a diagnostic value and ALP cutoff value was 76.50 IU / L with 80% sensitivity and 82.1% specificity in predicting bone metastases in prostate cancer.

Keywords: Bone scintigraphy, Free/total PSA, Prostate cancer

1 Background

Prostate cancer is the second-most commonly diagnosed cancer among men worldwide after lung cancer and ranks fifth for cancer-related mortality rates. Definitive prostate cancer diagnoses are made by biopsy. Patient selection for biopsy is important to prevent unnecessary diagnosis/treatment. The most important marker used to decide which patients should be considered for biopsy is the serum prostate-specific antigen (PSA) value [1–3]. However, PSA, which is a glycoprotein produced by the prostate tissue, increases not only in the case of prostate cancer but also in the case of a variety of benign diseases such as benign prostate hypertrophy (BPH), prostatitis and urinary infections [4]. In addition, the specificity and positive predictive value of PSA, as a commonly used marker in prostate cancer screening, is low and an exact cutoff value has not yet been defined [5]. In clinical routine, the differentiation of BPH and prostate cancer in patients with PSA levels between 4.0 ng/mL and 10.0 ng/mL is difficult [6, 7].

Due to these limitations, the use of different forms or kinetics of PSA has been recommended. However, recent studies have revealed that no biomarker alone is sufficient in diagnosis and a multivariable diagnostic approach is more eligible [5, 8, 9]. Nevertheless, due to some disadvantages of these markers, the free prostate-specific antigen/total prostate-specific antigen (free PSA/total PSA) ratio has become the most frequently used value in clinical practice [9, 10]. Recently, it has been reported in the

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Ozdemir *et al. Afr J Urol*   (2021) 27:69

Page 2 of 6

literature that the free PSA/total PSA ratio is more significant than PSA alone in differentiating prostate cancer and BPH in patients with serum total PSA levels between 4.0 and 10.0 ng/mL [11, 12].

Prostate cancer mainly causes osteoblastic bone metastasis. The number of metastases in the bones is important in predicting the response to therapy and is generally associated with decreased survival rates [13]. Therefore, the early diagnosis of bone metastasis is substantial. Bone scintigraphy is frequently used as a non-invasive, inexpensive and easily accessible imaging method to detect bone metastasis. In addition, bone scintigraphy has been recommended in major urology guidelines as an imaging method for bone metastasis screening in medium-to-high risk patient groups and symptomatic patients. PSA values, Gleason Scores and the clinical stage of the lesion have been known to affect the success rate of this method [14, 15]. This study aimed to investigate the prognostic significance of the free PSA/total PSA ratio, which has been recently reported to be a more sensitive marker in detecting bone metastasis in prostate cancer.

2 Methods
2.1 Patient group
The patient group of this study consisted of a total of 175 caucasian (white) male patients with a mean age of 71.36 ± 8.61 years. The patients were selected retrospectively from those who had prostate cancer and had been sent to the Department of Nuclear Medicine of the Faculty of Medicine for a whole-body bone scintigraphy between 2016 and 2019. The patient population consisted of patients with various stages of prostate cancer who were referred to be further investigated to determined the presence of bone metastasis preoperatively or bone metastasis due to increased PSA at follow-up. The bone scintigraphy results were evaluated by two nuclear medicine specialists, and the number of bone metastases was recorded. In cases with more than 30 bone metastases, the number of metastases was recorded as 30. In addition to bone scintigraphy, the free PSA/total PSA and alkaline phosphatase (ALP) values measured over the last month were screened retrospectively and recorded along with the age, date of cancer diagnosis and Gleason scores of the patients.

Written informed consent was obtained from all patients. This retrospective study was approved by Canakkale Onsekiz Mart University Clinical Research Ethics Committee (Date: 07.05.2020, No:2020–07).

All patients read and signed the informed consent forms and were properly prepared for the procedure. For the bone scintigraphy, 15–30 mCi (doses were adjusted to weight) Tc-99 m-tagged diphosphonate compounds (MDP or HMDP) were injected into the

patients intravenously. Approximately, 2–3 h after the injections were given, the whole-body images in the anterior and posterior projections and—if necessary—spot planar images of the suspicious regions were acquired. The whole-body bone scintigraphy imaging was realized with a dual-head gamma camera (Infinia; General Electric Medical Systems, Milwaukee, Wisconsin, USA) using an image matrix of 1024×1024 with a speed of 8 cm/min for 10 min for each static. The prior surgery and trauma history of the patients were carefully noted. Asymmetric and multiple focal lesions, especially located in the axial skeleton, were evaluated as bone metastasis.

2.2 Statistical analysis
All data were analyzed using statistical package software SPSS (Statistical Package for Social Sciences) version 20.0. The descriptive data analysis included number, percentage, mean, standard deviation, minimum and maximum values. In the analytical data presentation, the conformity of the variables to the normal distribution was assessed using the Kolmogorov–Smirnov normality test, due to the fact that the number of patients included in the study was more than 50. The Pearson correlation test was used to analyzed the continuous variables with normal distribution, while the Spearman correlation test was used to analyze the continuous variables without normal distribution. The cutoff, sensitivity and specificity values were determined by the receiver-operating characteristic (ROC) curve analysis. A value of $p < 0.05$ was considered statistically significant.

3 Results
The study population of the present study consisted of 175 male patients with prostate cancer who underwent whole-body bone scintigraphy to investigate the presence of bone metastasis. The mean age of the patients was 71.36 ± 8.61 years (minimum–maximum: 48.0–88.0). The mean free PSA and total PSA values of the patients were 19.21 ± 43.02 ng/ml and 87.84 ± 299.83 ng/ml, respectively. The mean value of the free PSA/total PSA ratio was calculated as 0.026 ± 0.731. The mean ALP and Gleason score of the patients were 181.87 ± 283.46 IU/L and 7.75 ± 1.43, respectively. The demographic and clinical characteristics of the case groups are summarized in Table 1. The bone scintigraphy images of three prostate cancer patients at different stages are illustrated in Fig. 1.

When the free PSA, total PSA, free PSA/total PSA ratio, ALP values and Gleason scores were compared with number of bone metastases, the following were determined:

Ozdemir *et al. Afr J Urol*   (2021) 27:69

Page 3 of 6

Table 1 Demographic and clinical parameters

Clinical parameters	Patients cohort (n = 175)		
	Mean ± SD	Median	Min.–Max.
A.ge (years)	71.36 ± 8.61	71.00	48–88
Free PSA (ng/ml) (n = 95)	19.21 ± 43.02	2.93	0–235
Total PSA (ng/ml) (n = 175)	87.84 ± 299.83	14.95	0–2934
Free/total PSA (n = 96)	0.236 ± 0.220	0.18	0–1.67
Alkaline phosphatase(U/L) (n = 57)	181.87 ± 283.46	91.00	12.80 ± 1722
Gleason score (n = 120)	7.75 ± 1.43	8.00	4–10
Number of metastatic foci (n = 175)	9.68 ± 12.13	2.00	0–30

1. A very weak correlation was observed between the number of bone metastases lesions and the free PSA/ total PSA ratio (rho = 0.179).
2. A weak correlation was found between the number of bone metastatic lesions and total PSA (rho = 0.318) and Gleason scores (rho = 0.382).
3. A moderate correlation was observed between the number of bone metastatic lesions and, ALP values (rho = 0.539) and free PSA (0.416) (Table 2).

The ROC curve of sensitivity versus the specificity of free PSA, total PSA, free PSA/total PSA ratio, ALP and Gleason scores was performed to detect bone metastases in prostate cancer. It was determined that only the ALP variable was statistically significant and had a high diagnostic value (AUC = 0.907, p = 0.004). The ALP cut-off value was found to be 76.50 IU/L, with a sensitivity rate of 80% and a specificity rate of 82.1%. The obtained results also showed that there was a moderate correlation between bone metastasis and ALP values. On the other hand, according to the results, the free PSA (AUC = 0.657, p = 0.269), total PSA (AUC = 0.661, p = 0.259), free PSA/total PSA ratio (AUC = 0.521, p = 0.880) and Gleason score (AUC = 0.529, p = 0.841) values were not considered as reliable parameters for the detection of bone metastasis in prostate cancer cases. (Fig. 2, Table 3).

4 Discussion

Serum PSA is currently the most commonly used marker in the diagnosis and follow-up of prostate cancer. The use of PSA for prostate cancer screening was approved in 1994 by the US Food and Drug Administration [16, 17]. However, PSA is not a cancer-specific marker, leading to unnecessary biopsies, especially in the range of
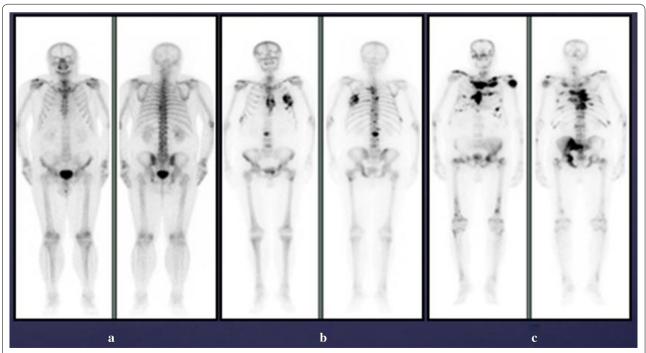

Fig. 1 Bone scintigraphy images of three prostate cancer patients at different stages. **a:** An example patient without bone metastases; free PSA: 2.53 ng/ml, total PSA:17.54 ng/ml, free/total PSA ratio: 0.144, ALP: 43 U/L, **b:** An example patient with numerous metastases; free PSA: 3.11 ng/ml, total PSA:18.30 ng/ml, free/total PSA ratio: 0.169, ALP: 114 U/L. **C:** An example patient with multiple metastases; free PSA: 12.90 ng/ml, total PSA:121.20 ng/ml, free/total PSA ratio: 0.106, ALP: 109 U/L

Table 2 Spearman's correlation coefficients of bone metastases lesion number and some laboratory parameters.

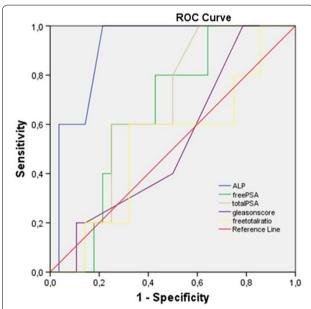| Parameters	Bone metastases lesion number
Free PSA ($n = 96$) Spearman's correlation rho p	0.416 <0.001
Total PSA ($n = 175$) Spearman's correlation rho P	0.318 <0.001
Free/total PSA ($n = 96$) Spearman's correlation rho p	0.179 0.082
ALP ($n = 57$) Spearman's correlation rho p	0.539 <0.001
Gleason Score ($n = 120$) Spearman's correlation rho p	0.382 <0.001

Fig. 2 Receiver-operating characteristic (ROC) curve of sensitivity versus specificity of ALP, free PSA, total PSA, Gleason score, and free/total PSA in prostate cancer bone metastases

4.0–10.0 ng/mL, which is defined as the gray zone. In this range, the most commonly used parameter to increase the specificity of PSA is the free PSA/total PSA ratio. While 5% of serum PSA is found to be free, this level decreases in patients with prostate cancer. Therefore, free PSA measurement is used to increase the sensitivity of cancer detection in patients with normal PSA values and increase specificity in patients with high total PSA (2.5–10 ng/mL) [18, 19].

An increasing number of reports published in recent years have demonstrated that the free PSA/total PSA ratio can be used for determining the necessity of biopsy in prostate cancer diagnoses [12, 20]. Erol et al. conducted a study on 4955 patients with total PSA values between 4 and 10 ng/ml and determined that a free PSA/total PSA ratio of <0,10 had the highest specificity, while a ratio of >0,30 had the highest sensitivity in prostate cancer diagnosis. In addition, this study demonstrated that the free PSA/total PSA ratio varied according to age [21].

Catalona et al. reported that the free PSA/total PSA ratio significantly decreased in the presence of aggressive prostate cancer (Gleason score ≥ 7, presence of metastasis). In addition, they determined that the 0,25 cutoff value for the free PSA/total PSA ratio would have a sensitivity of 95% in prostate cancer diagnosis and therefore prevent 20% of unnecessary biopsies [22]. The National Comprehensive Cancer Network (NCCN) guideline recommends using the free PSA/total PSA ratio for TRUS-guided prostate biopsy decisions in patients with no prior biopsy history, those with a PSA value of >3 g/ml or high-risk patients with prior negative biopsy results [23]. Similarly, The European Urology Association (EUA) guideline reported that the free PSA/total PSA ratio could be used to avoid unnecessary biopsies in patients with total PSA values between 2 and 10 ng/ml [24]. Likewise, Bjork et al. determined a low free PSA/total PSA ratio in male patients with prostate cancer [25]. The free PSA/total PSA ratio, calculated using simultaneous immune determination of both free PSA and total PSA, has been reported to yield better results than PSA or its derivations alone in prostate cancer diagnosis. This ratio

Table 3 Sensitivity and specificity percentage of ALP, free PSA, total PSA, Gleason score, and free/total PSA values

		Free PSA $n = 96$	Total PSA $n = 175$	Free/total PSA $n = 96$	ALP $n = 57$	Gleason $n = 120$
Bone metastases number	p	0.269	0.259	0.880	0.004	0.841
	AUC	0.343	0.339	0.479	0.093	0.471
	Cutoff	5.77	25.1	0,15	76.5	8.5
	Sensitivity %	60	60	60	80	40
	Specificity %	60.7	60.7	60.7	82.1	50

Ozdemir *et al. Afr J Urol*   (2021) 27:69

Page 5 of 6

is recommended to be used especially in cases where total PSA levels are low.

On the other hand, various studies have reported that the free PSA/total PSA ratio is not as significant as expected. For example, Agnihotri S et al. concluded that the value of free PSA/total PSA in symptomatic males and found a very limited value to improve specificity of total PSA [26]. Moreover, Huyghe E et al. claimed that the calculation of the free PSA/ total PSA ratio did not appear to provide any decisional criteria in favor of radical prostatectomy [27].

Although [68] Ga-PSMA PET-CT imaging is in the gold standard position as it can evaluate the whole body (bone, soft tissue, lymph node, etc.) in the follow-up of prostate cancer, it is expensive and not always accessible [28]. ^{99m}Tc-MDP whole-body bone scintigraphy is still a highly sensitive imaging method in cases that only bone metastases are investigated due to its availability and low cost [29]. A meta-analysis reported a patient-level sensitivity rate of 79% and a specificity rate of 82% and a lesion-level sensitivity of 59% and specificity of 75% [30]. The correlation between bone metastasis and PSA level, ALP level and Gleason score has been previously investigated, and the presence of correlation at different levels has been mentioned in the literature [31–33]. Some studies have recommended the use of bone scans in symptomatic patients or if the alkaline phosphatase levels of the patients are > 90 U/l [34]. Singh et al. claim that there was a PSA cutoff of 10 ng/ml for negative bone scans and a correlation between PSA and the presence and number of metastases [35]. On the other hand, a recent study suggested that the staging of bone scans may not be performed in patients with a PSA level of < 20 ng/mL [36]. However, no clear results were obtained in these studies that focused on determining a cutoff value for the aforementioned parameters in detecting bone metastasis.

The objective of the present study was to compare conventional tumor markers, namely free PSA, total PSA, free PSA/ total PSA ratio, ALP values, Gleason scores and 99 m Tc-MDP bone scintigraphy findings in terms of the detection of bone metastasis. According to the obtained results, a very weak correlation was observed between the number of bone metastases lesions and the free PSA/total PSA ratio (rho = 0.179); a weak correlation was found between the number of bone metastatic lesions and total PSA (rho = 0.318) and Gleason scores (rho = 0.382); a moderate correlation was observed between the number of bone metastatic lesions and, ALP values (rho = 0.539) and free PSA (0.416). As bone scintigraphy is a highly sensitive technique used to detect bone metastases, the results of this study led to the conclusion that free PSA, total PSA, free PSA/total PSA ratio and Gleason score values were not reliable parameters

in the follow-up of bone metastases in prostate cancer cases. On the other hand, the 76.50 IU/L cutoff value for ALP values showed a sensitivity ratio of 80.0% and a specificity ratio of 82.1% for the prediction of bone metastases.

5 Conclusion

The results of this study showed that the free PSA, total PSA, free PSA/total PSA ratio and Gleason score values were not reliable parameters for determining the bone metastases of prostate cancer. It was determined that only the ALP variable had a diagnostic value in predicting bone metastases in prostate cancer. On the other hand, it was thought that routine control and patient complaints maintained their importance in the follow-up of bone metastases.

Declarations

Ethics approval and consent to participate
Ethics committee approval was received for this study from the Canakkale Onsekiz Mart University Clinical Research Ethics Committee local ethics committee (Date: 07.05.2020, No:2020–07).

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

Informed consent
Informed written consent was obtained from all patients.

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Ozdemir *et al. Afr J Urol*   (2021) 27:69

Page 6 of 6

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