

Update the Indicator Role of Serum PSA Level and Gleason Score of the Biopsy for the Presence of Bony Metastases: Bone Scan Findings in a North African Ethnic Group

Janane Abdellatif*, Fouad Hajji, Jean Crepin Elonodo, Mohamed Ghadouane, Ahmed Ameur and Mohamed Abbar

Military university hospital, Rabat, Morocco

Introduction

According to the American cancer society, prostate cancer (CaP) is the most common type of cancer found in American men, other than skin cancer. The estimated number of new cases of CaP in the United States in 2009 is about 192280; the assessed deaths will be 26730. It is known that there is a wide geographic variation in the incidence of clinical prostate cancer. In the african population, the incidence and mortality rates of CaP are strikingly higher than that in chinese or caucasians ethnies [1,2]. There is evidence that genetic, environmental and social factors jointly, often in combination, contribute to the observed differences in various populations. However due to the increasing awareness of the disease entity. The advent of the prostate specific antigen (PSA) testing for screening or early diagnosis and the improvement in life expectancy of the male population, the epidemiology of CaP in north-african ethnies has changed [3]. In our city, the incidence of CaP new cases is rapidly increasing, from 358 new cases registered in 1997 to 1068 cases in 2007, nearly tripling in 10 years. According to our national cancer register, a crude incidence rate is rising and the disease is being found earlier as well. However, the mortality from CaP is relatively static, with the number of deaths at 121 in 1997 and 289 in 2007, respectively. This implies that an increasing number of our citizens are living with cancer of prostate [3].

Considering that the skeleton is the most painful and debilitating site of metastasis from CaP, skeletal screening is crucial in management planning and assessing the prognosis in the early disease state. Skeletal scintigraphy is the investigation of choice in diagnosing bone metastases; it is more sensitive than skeletal radiography and serum alkaline phosphatase levels, is good in its accessibility, non invasiveness, low radiation dose, and above all, its ability to evaluate the entire skeletal system [4,5].

Our purpose is to determine whether the probability of positive bone scan result of newly diagnosed CaP patients can be predicted by serum PSA level in the north-african population, with an attempt to define a particular PSA level under which the group of patients would have low risk of obtaining a positive bone scan, so that the radiologic procedure can be safely omitted.

Moreover, we would like to correlate the Gleason score with PSA level and probability of positive bone scintigraphy results. It is to determine whether there is any relation between the histologic grade, tumour marker level, and the aggressiveness of the tumour itself in our ethnic group.

Patients and Methods

At the university military hospital, all patients aged 45 to 85 years with prostatic symptoms (i.e., obstructive or irritative urinary symptoms and hematuria) would have a baseline serum PSA level taken, together with transrectal ultrasound (TRUS) guided prostate biopsy and bone scintigraphy; according to the european urologic association guidelines.

A retrospective computer search of our urologic department records of the period between January 1997 and December 2007 was performed, reviewing all patients who had undergone TRUS prostate biopsy and had pathologically proven CaP. A total of 348 consecutive patients were included. They all had TRUS prostate biopsies, serum PSA levels, and bone scans within 4 weeks of one another. Patients having previous therapy for prostatic diseases, including androgen ablation therapy, radiation therapy on prostate or prostate surgery were excluded from the study.

Statistical analyses were performed using the Fisher exact test, by statistical software (SPSS, Statistical Package for the Social Sciences, version 11.5.1, Chicago, IL) with differences at $P < 0.05$ considered significant.

The serum PSA level was analyzed with the VITROS Immunodiagnostic Products PSA Calibrators (Ortho-Clinical Diagnostics, Inc., Rochester, NY) with the corresponding VITROS Immunodiagnostic Products PSA Reagent Pack.

Bone scintigrams were performed with technetium-99m HDP. The dose of Tc-99m HDP used was approximately 20 mCi (740 MBq) and scanning was performed by a single head gamma camera (prism 1000; Picker International Inc., Highland Heights, OH). High-resolution collimator was used and whole body anterior and posterior planner images, together with oblique and localized views for areas of interest were reviewed. The bone scintigrams were reviewed by 2 radiologists having experience in radiology of 13 years (WHL) and 7 years (MHYL), respectively.

Sextant prostate tissue biopsies were performed by urologists under ultrasound guidance (C9-5 transrectal US curved array probe, ATL. HDI 5000 system; Philips, Irvine, CA); 20-gauge Temno biopsy puncture needles (Santo Domingo, Dominican Republic, Cardinal Health) were employed. The tissues cropped were sent to the anatomic and cellular pathology department of our university hospital for tissue diagnosis.

Results

The patients were aged 46 to 85 years, with a mean age of 68 years.

***Corresponding author:** Janane Abdellatif, Military university hospital, Rabat, Morocco, E-mail: a.janane@yahoo.fr

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PSA levels ranged from 2 to 998 ng/ml with a mean value of 86.63 ng/ml. The time interval between PSA determination and bone scan was within 27 days.

Bone metastases were identified in 102 patients out of 348 patients. The patients were stratified into 4 groups according to their PSA level: the first group of patients had PSA level ranging from 0 to 10 ng/ml (n = 75), the second group had PSA level ranging from 11 to 20 ng/ml (n = 63), the third group had PSA ranging from 21 to 100 ng/ml (n = 159), and the fourth group was those having serum PSA level more than 100 ng/ml (n = 51). The prevalence of osseous metastases proven by bone scintigrams increased progressively with PSA level, rising from 0% (0 out of 75) for PSA level < 11 ng/ml, to 100% (51 out of 51) for PSA level > 100 ng/ml (P < 0.001). Bone scintigraphy results with respect to PSA levels are summarized in Table 1.

Gleason score ranged from 2 to 10, with the overall mean Gleason score being 6.336. In 3 patients, no Gleason score was given by the pathologist and only the presence of adenomatous carcinoma was stated. These three slides were already destroyed at the time of this study according to storage protocol.

When we compared the mean Gleason score in the four groups of patients with different PSA levels, the mean Gleason score was only slightly higher in the group with PSA more than 100 ng/ml. No statistically significant relationship was established between PSA level and Gleason score (Table 1, P > 0.05).

In comparing the Gleason scores to bone scan findings, we found that the mean Gleason scores were 6.808 and 7.249 for the groups with negative and positive bone scan results, respectively. There was no statistically significant relation between the 2 groups (P > 0.05) (Table 2).

Discussion

Prostate cancer exhibits tremendous difference in incidence in different populations worldwide. Asian men typically have a very low incidence and mortality of CaP in contrast to northern European, African and American populations [1,2]. There is doubt whether the behaviour of CaP in the African population is different from that in western countries. Due to the mortality rate of CaP in African population, many CaP patients may live with the disease for a considerable period of time [3]. Screening out patients with advanced disease or bone metastases, is essential in order to prevent complications from bone destruction, and to improve the quality of life of these patients [4].

PSA level, ng/ml	Bone scan positive for metastases (102)	Bone scan negative for metastases (246)	Mean Gleason score //
0-10	0*	75	6.0
11-20	6	57	6.4
21-100	45	114	6.9
>100	51*	0	7.4

* P value < 0.001

// P value > 0.05

Table 1: Radionuclide bone scan results and Gleason scores based on PSA levels.

Scintigraphy result	PSA mean (range), ng/ml	Gleason score mean (range)*
Positive for metastases (102)	157.09 (17-998)	7.249 (6-10)
Negative for metastases (246)	33.30 (2-91)	6.808 (4-10)

* P value > 0.05

Table 2: Comparison of PSA values and Gleason scores with results of skeletal scintigraphy.

The diagnosis of bony metastasis secondary to prostate cancer significantly alters patient treatment. Currently radionuclide bone scans are the gold standard for detecting osseous metastasis. An ongoing debate surrounds the optimal PSA for recommending a bone scan for nonmetastatic prostate carcinomas. Detecting patients with bone metastases is essential in predicting prognosis, and identifying or preventing complications incurred by disease progression. However, if every patient newly diagnosed with CaP is offered bone scintigraphy as the baseline staging investigation, the increase in incidence would imply a growing burden on the health care system. It is therefore important to seek a balance between cost and benefit, and to develop an algorithm for the indication of a baseline bone scintigraphy [4].

According to a number of large scaled studies in USA and Canada [5,6], a progressive rising relationship in the prevalence of skeletal metastases with PSA level has been proved. Several papers advocated bone scan is not indicated when pre-treatment PSA levels are low, and when patients are rather D'Amico low risk [7,8]. However, different studies established different cut-off levels for indication of bone scintigraphy.

In newly diagnosed cases the incidence of positive bone scans in patients with PSA less than 20 ng/ml is low. According to Chybowski: in a group of 521 American subjects with untreated newly diagnosed prostate cancer, bone scan finding showed that bone metastasis did not occur in patients with PSA levels of 15 ng/ml or less, but it did occur in 1 patient (0.3%) with a PSA level of 15-20 ng/ml [9]. Rhoden et al studied a group of 214 patients with 35 positive bone scans: only 1 of those was in the group with a PSA less than 20 ng/ml. Studies such as led to a recommendation to avoid staging bone scans in patients with PSA less than 20 ng/ml [8].

Despite many recent numerous studies and reviews citing 10 ng/ml as a threshold PSA for omitting bone scans, others still believe that the small but measurable risk is sufficient to warrant continued scanning [6,10]. Therefore, there is a reluctance to make an absolute recommendation and bone scan continue to be used by many physicians and urologists in the staging process of the disease.

Oesterling examined the relationships among bone metastases, PSA, pathohistologic differentiation and local findings in 852 subjects with untreated prostate cancer. The likelihood of bone metastases in men with PSA levels < 10 ng/ml was 0.5% (4/852). In those with levels < 20 ng/ml, the incidence of bone metastases was only 0.8% (7/852), and of these 7 men, 5 had bone pain. Of the four patients in their study with PSA levels of 10 ng/ml or less, only 1 patient had bone metastasis without bone pain [10].

According to a multicenter retrospective study in Japan, the incidence of positive bone scan in the patient group with low PSA levels in their mass population screening is much higher than that in the other studies performed in Western countries. This raises the suspicion that the behaviour of CaP is different in Asian population compared with Caucasians, and the PSA might not be a good indicator for predicting bone scintigraphy results in some ethnic groups [6].

In another study performed by Gleave et al, a group from Canada, only 6% of 490 patients with newly diagnosed CaP had positive bone scan on initial evaluation. Scans were positive in none of the 290 patients with PSA levels below 10 ng/ml, 4 of 88 (4.5%) with PSA levels between 10 and 20 ng/ml, and 24 of 122 (21%) with PSA levels between 21 and 100 ng/ml [11].

However, in contrast to the other studies done in western countries,

a multi-center retrospective study in Japan has revealed that bone metastasis is common in Japanese patients with newly diagnosed, untreated prostate carcinoma, with an overall positive rate of 24.2% on bone scans [6]. The positive rate is approximately double that reported in United States and Canada (8.9%) [12]. Besides, according to Ito et al, of the 303 patients identified to have CaP in a mass screening program in 9671 subjects, 36 had bone metastasis. Thirteen (36%) of the 36 patients had PSA levels of 10 ng/ml or less [13]. The incidence of having positive bone scan in a patient group with low PSA levels is much higher than the other studies in the western countries. It is therefore certain that the behaviour and histopathologic characters of CaP are different according to the continent, the geographic origin, the race and the ethnic [13,14].

In our study, the prevalence of bone metastases in newly diagnosed CaP patients is 102 out of 348 (29.3%), with a rate much higher than that in the reports done by researchers in the western countries. It could be partly explained by our sample selection. There is no population-based screening program for CaP in our nation. Our hospital adopted symptomatic screening instead, in order to ensure early diagnosis. All cases in our series presented with lower urinary tract symptoms and subsequent digital rectal examination, PSA, and TRUS were done to screen for CaP. This might have contributed to the higher incidence of advanced disease, i.e., having bone metastases, in those newly diagnosed CaP patients.

A positive relation between the PSA level and presence of bone metastasis on bone scan was demonstrated in our study, having a trend in line with the other studies [11,14]. With PSA 10 ng/ml or less, none of the patients had a positive bone scan. If we take serum PSA value of 10 ng/ml or less as a threshold, the negative predictive value of a positive bone scan result would be 100% ($P < 0.01$), i.e., no false negative case. Radionuclide bone scans may therefore be omitted as a routine baseline staging tool in patients with such a negligible risk for positive bone scan results.

In our study sample, if bone scans were omitted for patients having a level of PSA 10 ng/ml or less, 75 out of 348 men (21.6%) of the routine staging bone scans would be avoided.

On the other hand, if imaging had been denied only to those men with a PSA level of 20 ng/ml or less, imaging sensitivity would have decreased to 94%, but 63 more men could have been omitted from bone scan, i.e., 138 out of 348 (39.7%) routine staging bone scans would be avoided.

Currently, performing bone scintigraphy is time-consuming, taking several hours to complete; and it costs about US\$ 100 per examination. Time and resources for radionuclide bone scans could be saved for other purposes if the request could be more selective. This could be a significant source of savings in the present climate of economic constraints and managed health care.

Our recommendation is to delay the radionuclide bone scans in this group of patients having PSA < 10 ng/ml until PSA level rises or when symptoms (e.g. bone pain) arise.

Conversely, for PSA levels more than 100 ng/ml, all subjects in our study had proven to have skeletal metastases on radionuclide bone scan. The positive predictive value using a cut off point of a serum PSA more than 100 ng/ml is 100% ($P < 0.001$). This implies that arranging an early appointment for bone scintigraphy is necessary, for planning local treatment (e.g. radiotherapy) in order to prevent complications such as pathological fracture and spinal cord compromise. The radionuclide

bone scan could also act as a baseline to indicate treatment response and, later, presence of recurrent metastatic disease [14,15]. In our hospital, clinical urologists would actually plan for orchidectomy and chemotherapy for this group of patient without waiting for the bone scan results.

In studying the correlation of the Gleason score with bone scan findings and PSA levels, no statistically significant relationship was established. No clinical value has been added to this study.

The major limitation of this study is that it is retrospective, and the patients were not recruited from a population based screening program. The vast majority of men in our series presented with lower urinary tract symptoms. The patient sample is different from that of the other studies with which we have made a comparison. On the other hand, the presence or absence of metastases is not tissue biopsy proven, and bone scan is actually not the true gold standard.

According to the last report of the European Association of Urology (EAU), in Barcelona (April-2010): skeletal scintigraphy with doubtful lesions must be explored by functional MR imaging of the axial skeleton; to attach fixation abnormalities to their inflammatory, traumatic or neoplastic aetiology. In some few cases remaining in diagnosis litigation (e.g. unique bone lesion in an unusual area of prostatic metastases), a biopsy is recommended to carry a certain histologic diagnosis [15].

In the most European and American centres, axial skeleton MRI is a fast exam, which can be coupled to lymph node staging evaluation during the same sequences (T1-T2). Both its sensibility and specificity are better than scintigraphy accuracy in all bone's types and areas except for skull's arch and ribs [15,16]. However, this technique is not widely standardized; this limitation can explain varied sensibility (42 to 100%) and specificity (82 to 94%). The usefulness of a detection whole body MRI "Scinti-MRI" is still being tested in the perspective of a large validation.

To reach compromise between adapting our practise to the EAU guidelines and our university hospital's economic conjuncture, skeletal scintigraphy remains the investigation of choice in diagnosing bone metastases; it is appropriate because of its accessibility, non invasiveness, low radiation dose, and above all, its ability to evaluate the entire skeletal system [4,15].

Bone scans have also been an important tool in monitoring disease progression after definitive therapy. However, the same controversy exists about the optimal post-treatment PSA at which to recommend this test [7,14]. To date only small series have been published which correlate the prevalence of bone metastases with PSA after local therapy.

In the face of increasing health care costs, clinicians are constantly expected to reevaluate the diagnosis tools and the treatment of patients with regard to economic considerations as well as best practise.

Conclusion

Progressive rising incidence of bone metastasis on radionuclide bone scan in relation to the PSA levels in patients newly diagnosed of CaP is proven. Very high negative predictive value (100%) could be achieved by using a PSA level of 10 ng/ml as a cut off point for indication of bone scan in our ethnic. The positive predictive value using a cut off point of a serum PSA more than 100 ng/ml is 100%.

Using PSA as an indicator for the presence of bony metastases rather than routine bone scans would have large economic savings given the population size. However, our recommendations are restricted only to

symptomatic screening and cannot extrapolate to population-based screening program due to the sample selection of the study.

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