ORIGINAL ARTICLE

Role of Prostate-Specific Antigen Level and Prostate Biopsy Gleason Score in Predicting Bone Metastases of Prostate Cancer in North African Population

K. Lmezguidi[1,2], F. Hajji[1], A. Janane[1], A. Ameur[1], M. Ghadouane[1], M. Alami[1]

[1]Department of Urology, Mohamed V Military Teaching Hospital, Rabat, Morocco, [2]Faculty of Médecine , Mohamed V University, Rabat, Morocco

ABSTRACT

Objectives: The objective of this study is to determine the relationship and correlation between the rate of prostate-specific antigen (PSA), Gleason scores, and the presence of bone metastases and to evaluate the ability of these two variables to predict the probability of bone metastases before conducting an isotope imaging. **Materials and Methods:** This is a retrospective study of 384 cases diagnosed with prostate cancer at the Mohammed V Military Teaching Hospital, between January 2001 and December 2010. Patients who had prior therapy for the prostate, androgen deprivation therapy, and surgery of the prostate or bladder resection were excluded from the study. **Results:** The mean patients' age was 68 years (between 49 and 77 years old), and the mean PSA value was 86.63 ng/ml (between 2 ng/ml and 298 ng/ml). Our patients were classified into four groups, depending on their initial PSA level. We found bone metastases in 23.85% of patients, and the prevalence of bone metastases on bone scan tomography gradually increases with the level of PSA and Gleason scores, from 2% in the group with PSA <10 ng/ml to 92% in the group with PSA >100 ng/ml. We found that the mean Gleason scores were 6.48 and 7.89, respectively, for groups with negative and positive bone scan tomography. **Conclusion:** Despite its retrospective nature, our study corroborates the previous results supporting the correlation between the PSA value, the Gleason biopsy score, and the presence of bone metastases in our north-African ethnic group, and further prospective studies are needed to support these findings.

Key words: Bone metastasis, bone scan tomography, gleason score, prostate cancer, prostate-specific antigen

INTRODUCTION

Prostate cancer (PCa) is one of the most common men's cancers. Its incidence has continued to increase in all continents since 1980.

Screening and ultra-early diagnosis of PCa are the most complex and controversial issues between epidemiologists and urologists.[1]

PCa is the second leading cause of cancer-related death in the United States among men. It is the most commonly diagnosed cancer in American men. Most PCa deaths are due to the metastatic course of the disease. It is estimated that 2–3 of 10 men will develop PCa in their lifetime, and this probability increases with age. Since the advent of prostate-specific antigen (PSA) screening, PCa has been detected and treated earlier than in the 1970s and 1980s.[2]

Bone metastases are present in 58–73% of advanced PCa. Skeletal localization is one of the major causes of morbidity and mortality. Synchronous or metachronous metastatic disease is initially managed by androgen deprivation therapy, but the majority of patients will eventually develop a PCa castrate-resistant form.[3]

Considering that the skeleton is the most accessible site for metastasis, rigorous evaluation of the skeleton is crucial in

Address for correspondence:
K. Lmezguidi, Department of urology , military teaching hospital of Rabat Morocco. Tel: +212 671678567,
E-mail :lmezguidikhalid@gmail.com

management planning as well as prognosis estimation at an early stage of the diagnostic procedure.

Bone scan tomography is the test of choice for the bone metastases diagnosis; it is more sensitive than bone radiography and serum alkaline phosphatase. With satisfactory accessibility, it is a non-invasive exploration with low doses of radiation, and especially an ability to instantly evaluate the entire bone system.[4,5]

The aim of our work is to determine, in a North African study, the link and correlation between PSA levels, Gleason scores, and the presence of bone metastases. Are these two variables able to predict the probability of bone secondary localization before performing an isotopic imaging whose sensitivity, specificity, and predictive value are far from perfect?

MATERIALS AND METHODS

We retrospectively exploited the medical records of 348 patients treated for PCa at the Mohammed V Military Teaching Hospital between January 2001 and December 2010.

Clinical and paraclinical data were collected from a database, available from Urology and Pathology Department archives.

Statistical analysis was performed in patients who had undergone an ultrasound-targeted prostate biopsy and whose histology was in favor of PCa.

These men all had more biopsy, digital rectal examination (DRE), serum PSA values, and bone scan tomography. Patients who had previous therapy for prostate disease, lymph node invasion, prostate, or bladder surgery were excluded from the study.

For statistical analysis, we calculated the statistical significance using the SPSS IBM 20.00 program. A $P < 0.05$ was considered to be statistically significant.

Bone scans were performed, using the same isotopic molecule technetium-99 (Tc-99) m HDP. The dose of Tc-99 m HDP used was about 20 mCi (740 MBq). A single gamma camera head performed scanning. Two senior radio-isotopists examined bone scans and urologists under transrectal ultrasound guidance performed prostatic biopsies.

The cores tissues were sent to the pathology and cell biology department of our hospital, for the diagnosis of cancer, its location, its extent, and its aggressiveness.

RESULTS

In our series, the mean age was 68 years. PSA levels ranged from 2 to 298 ng/ml, with a median value of 32.16 ng/ml.

The median time interval between PSA determination and bone scan tomography was 29 days.

Our patients were classified into four groups, based on their initial PSA level:

- The first group had PSA levels between 2 and 10 ng/ml ($n = 75$).
- The second group had PSA levels between 10 ng/ml and 20 ng/ml ($n = 126$).
- The third group had PSA levels ranging from 21 to 100 ng/ml ($n = 96$).
- And the fourth group had PSA levels >100 ng/ml ($n = 51$).

The bone scan tomography carried out as part of the extension assessment of any diagnosed PCa revealed bone metastasis in 83 of 348 biopsied patients.

On our observational study, we were able to identify the following points:

The prevalence of bone metastases on bone scan tomography increases progressively with the level of PSA, from 2.6% (2 out of 75 cases) for a PSA level <10 ng/ml to 92.15% (47 of 51cas) for the level of PSA >100 ng/ml [Figure 1].

The Gleason score in our series had ranged from 6 to 10, with a mean score of 7.

Comparing the mean value of the Gleason score in the four groups, the biopsy score was significantly higher in patients who had a PSA level >100 ng/ml. Between Groups 1 and 2, there was no significant difference in the Gleason score to predict the existence of bone metastasis. On the other hand, between Group 1 and the two others: Group 3 and 4, the Gleason difference was significant in predicting bone metastases.

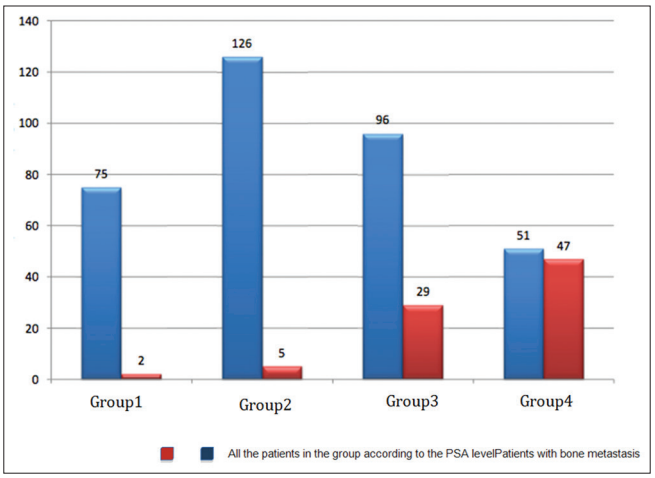

Figure 1: Distribution of 83 patients with bone metastases according to their prostate-specific antigen levels

These differences between groups are illustrated in Table 1.

When comparing Gleason scores to bone scan tomography results, we found that the mean Gleason scores were 6 and 8, for groups with negative and positive bone tomography, respectively [Table 2].

There was a statistically significant difference between the two groups that corroborated with the literature data regarding the linear relationship between Gleason score and metastatic potential.

DISCUSSION

PCa has disparate incidences and remains a real public health problem. His mass screening remains controversial between epidemiologists and urologists. On the other hand, its ultra-early diagnosis through individual screening, using PSA and DRE, remains strongly recommended. The diagnostic approach, therapeutic alternatives, and monitoring are currently well codified.

Asian men generally have low incidence and high PCa mortality, in contrast to the European, African, and North American populations.[6,7]

In the various reports of the AUA since 2000–2015, it has been established that the behavior of PCa in the African population is different from that of Western countries. The death rate in the African population and the proportion of aggressive cancer are higher than in the European and North American ethnic groups.[8]

Table 1: Comparison of the mean value of the Gleason score in the four groups $P>0.05$

Group	PSA level (ng/ml)	The mean Gleason score
1	0–10	7
2	11–20	7
3	21–100	8
4	>100	9

PSA: Prostate-specific antigen

Table 2: Comparison of PSA values and Gleason according to bone scan tomography

Bone scan results	Mean PSA value (interval)	Mean Gleason score value (interval)
Positive	57.09 (7–298)	8 (7–10)
Negative	23.30 (2–81)	6 (6–7)

PSA: Prostate-specific antigen

Screening patients with this localized or metastatic disease are essential to prevent skeletal-related events, improve quality of life, avoid disease complications, and optimize prognosis.[4]

The occurrence of bone metastases in the natural history of cancer significantly changes the therapeutic attitude and disease prognosis. Currently, bone scan tomography is the gold standard for the detection of secondary bone sites.

A debate and a controversy remain current concerning optimal PSA value to recommend this examination as an evaluation of a prostatic cancer extension. The detection of patients with metastases, or bone micrometastases, is essential to adopt a suitable therapeutic protocol, to predict the evolution and prognosis of the disease, and to prevent the progression disease complications.

Several works and recommendations of the Europeans and North American's Urological Societies specified the indication Bone scan tomography in detecting bone metastases.

The challenge was to find a balance and a compromise between the potential risk of metastasis, the utility, and the cost of radiological imaging. This allowed developing a BST indication algorithm.

The first studies of this topic in the USA, Japan, Canada, and Norway had published work specifying the prevalence of bone metastases according to the PSA level with a reliable statistical methodology.[9,10]

The recent EAU and AUA guidelines stipulate that BST remains an optional examination for patients with D'AMICO low-risk PCa. The risk of having secondary bone localization is <2% for this category of patients.

According to Chybowski *et al.*, in a newly diagnosed 521 PCa patient group, this isotopic analysis showed the presence of bone metastasis in 1.8% of patients with a PSA level <10 ng/ml. In contrast, for patients with PSA between 10 ng/ml and 20 ng/ml, the rate of bone metastasis was 4.3%.[11]

A Canadian study of 214 patients had shown that the probability of bone metastasis was 0% in patients with PSA <10 ng/ml. This rate was 0.75% in patients with a PSA level between 10 ng/ml and 20 ng/ml.[12]

After these results, the authors conclude that BST is optional for PSA levels <10 ng/ml, except for the presence of Gleason biopsy score 4 or a tumor volume >1/5 of the biopsy core.

Many recent comments set 20 ng/ml as PSA cutoff, and to recommend BST, other recent work justifies the need for axial bone scanning for PSA between 10 ng/ml and 20 ng/ml.[10,13]

As the macroscopic metastase detection rate is 5%, the percentage of false negatives for micrometastases detection can reach 10–12% for the PSA interval between 10 ng/ml and 20 ng/ml.

Oesterling was the first to examine the relationship between the probability of bone metastases, PSA, and the degree of cancer differentiation in 852 patients. The probability of metastases in the PSA group <10 ng/ml was 0.5% (4/852), and for the group with PSA between 10 ng/ml and 20 ng/ml, the incidence of bone metastasis was only 0.8% (7/852).[13]

Nevertheless, a recent Japanese multicenter study found slightly elevated incidences of bone metastasis, whether in the PSA <10 ng/ml group or in the PSA group between 10 ng/ml and 20 ng/ml, suggesting the following facts.

The cell cycle, proliferation, cell turnover, and biocellular behavior of CaP are different in the Asian population compared to the Caucasian, European, African American men, and Indian population.[10]

In the different statistics observed according to ethnicity and race, the behavior of PCa is linked to the factors involved in carcinogenesis (viral factor, environmental factors, dietary factors, body mass index, basal metabolism of the tumor cell, the autocrine and paracrine growth mechanisms, cancer diffusion, and differences in angiogenesis intensity).

Gleave *et al.* found in a Canadian study of 490 patients, 6% bone metastasis, 0% for PSA <10 ng/ml, 4.5% for PSA between 10 ng/ml and 20 ng/ml, and 21% bone metastasis for PSA between 20 ng/ml and 50 ng/ml. In other words, BST is strongly recommended for PSA >20 ng/ml and for PSA <20 ng/ml if patients had PCa with gleason score 7(4+3).[14]

The same author recommends in case of diagnostic dispute, an axial magnetic resonance imaging (MRI) which is able to detect with high accuracy bone metastasis for PSA <20 ng/ml.

In addition, according to a new retrospective Korean study of 579 newly diagnosed patients, 14.3% of patients had bone metastases, 0.2% for a PSA level <10 ng/ml, 4.6% with a PSA level between 10 and 20 ng/ml, and 9.5% with PSA >20 ng/ml.[15]

A positive relationship between PSA level and the presence of bone metastasis had been demonstrated in our study; this trend is linear compared to other Western studies.

For serum PSA >10 ng/ml, we have found a negative predictive value (NPV) of 97%; however, it seems difficult to made exact rational synthesis, concerning the non-necessity of bone scan tomography for patients with PSA <10 ng/ml.

The prediction of bone metastases in this interval could be compelling due to the heterogeneous aggressiveness of cancer, the variable rate of Grade 4, and tumor volume that can range from micro focus to 30% of the whole gland volume.

The mechanisms of cancer growth are different from one individual to another; this could be explained by epidemiological and genetic factors, resulting from a large ethnical mixture between Berbers, Phoenicians, Romans, Gulf Arabs, Moorish, Andalusian, and African Blacks.

In our series, the only VPP that was 100% was the relevance of BST for PSA >100 ng/ml, and it is from this value that the axial MRI and the BST have the same accuracy.

Otherwise, the axial skeleton MRI has become more efficient for the detection of micrometastases for PSA between 10 and 50 ng/ml, for which the BST NPV can reach 8–34%.

Isotope imaging detects bone metastasis at a late stage; it risks missing a micrometastasis due to the biological characteristic of radiotracer which detects only metastases with active metabolism and a diameter >6 mm.

It does not distinguish between degenerative, post-traumatic, or neoplastic lesions.

The international guidelines recommend axial skeleton MRI whenever there is a perceptible disease in the DRE, a major biopsy grading score of 4, a tumor volume >20%, an mpMRI suspicious extracapsular extension, a nodes, or seminal vesicle invasion, even for PSA <10 ng/ml.

The MRI PPV and NPV are superior to BST for PSA value <10 ng/ml or between 10 ng/ml and 20 ng/ml.

We can conclude that, for a strong suspicion of PCa aggressiveness, on the DRE, the biopsy, and mpMRI, a negative BST does not exclude the presence of bone metastases and using axial MRI is strongly recommended [Table 3].

Lee *et al.* reported a series of 579 patients, 29 patients had bone metastases with a Gleason score <7, and 1.2%, 10.8%, and 22.9% of patients had positive results for Gleason 5, 6, and 7, respectively.[15]

In the Mcarthur *et al.* series of 672 patients, 54 (8%) had bone metastasis, the mean Gleason scores were, respectively, 7 and 8 for groups with negative and positive results at BST, and the author reported a statically significant relationship between the Gleason score and the occurrence of bone metastasis.[17]

Table 3: Comparative table of bone metastasis prevalence according to the PSA level regarding several studies conducted in different countries

Study	Country	Cases number	PSA<10 ng/ml (%)	10<PSA <20 ng/ml	20<PSA <50 ng/ml (%)
Chybowski *et al*.[11]	United States	521	1.8	4.3	-
Oesterling *et al*.[13]	United States	852	0.5	0.8	-
Gleav *et al*.[14]	Canada	490	0	4.5	21
Rhoden *et al*.[12]	Canada	214	0	0.75	41.5
Lee *et al*.[15]	South Korea	579	0.2	4.6	9.5
O'Sullivan *et al*.[16]	London	420	4	8	13
Our study	Morocco	348	2.6	3.96	30

PSA: Prostate-specific antigen

Table 4: Comparative table of bone metastasis prevalence according to the biopsy Gleason scores regarding of several studies conducted in different countries

Study	Patients number	Gleason score<7	Gleason score=7	Gleason score>7
Mcarthur *et al*.[17]	672	3.7	9.3	47
Lee *et al*.[18]	631	2.8	10	29.6
Lee *et al*.[15]	579	2	10	70
Our study	348	2.6	3.96	51.7

Another study by Lee *et al*. in a series of 631 patients found 88 (14%) bone metastases cases: 2.8% for a GS <7; 10% for a GS =7 and 29.6% for a GS >7.[18]

This study demonstrated that the Gleason score and PSA are predictors of bone metastases in newly diagnosed patients.

Our results are in perfect agreement with the results of previous work,[15,17,18] showing a progressive increase in bone metastasis prevalence according to the Gleason score [Table 4].

The main limitation of our study is its retrospective nature, with a limited population cohort, and the majority of our patients did not meet standardized criteria of the WHO screening program. In fact, the vast majority of our patients had lower urinary tract symptoms. The ethnic mixing of the Maghreb makes that comparison with other Western studies difficult. However, our statistical evaluated parameters allowed results close to the Italian, Spanish, and Turkish series.

Despite its cost and non-availability in all centers, according to EAU (2014), axial skeleton MRI remains more efficient than BST for detecting early-stage metastases, and it also helps to detect nodes invasion. Its sensitivity and specificity are, respectively, 62–96% and 71–94%. The only limitation of MRI is poor accuracy at the ribs and cranial vault.

To reach a compromise and an adaptation of our practice, to the guidelines of the EAU and AUA, and to the economic situation of our university hospital, the BST remains the diagnostic tool of choice for bone metastases.

Our study corroborates data from the recent literature. The initial PSA and Gleason score remain strong predictors of tumor volume, aggressiveness of the neoplasm, and its ability to disseminate through pelvic nodes and lymphovascular invasion. These three pathways of dissemination are the most incriminated in secondary bone localizations.

The perspectives of the future are the cell adhesion molecules, a real marker of molecular biology (integrin, catenin, cadherin), monoclonal antibodies, and angiogenic growth factors (vascular endothelial growth factor, HiP, PD6F, and insulin-like growth factor).

These indicators will allow us 1 day to accurately predict the synchronous or metachronous metastatic potential of localized or locally advanced PCa.

CONCLUSION

The use of PSA and Gleason score,rather than Bone scan tomography to predict bone metastases, would have an economic importance.

Our results, corroborated by the literature data, show the power and predictive relevance of PSA and Gleason in predicting bone metastases existence.

The moderate sensitivity and false negative rate of BST for PSA between 10 ng/ml and 50 ng/ml make skeleton MRI a lawful tool for skeletal secondary localizations early detection.

Metastatic prediction could benefit in the future from the contribution of molecular biology.

REFERENCES

1. Cuzick J, Thorat MA, Andriole G, Otis W. Brawley-prevention and early detection of prostate cancer. Lancet Oncol 2014;15:e484-92.
2. Terris MK, Kim ED. Metastatic and Advanced Prostate Cancer-mars. Medscape; 2015.
3. Suzman DL, Boikos SA, Carducci MA. Bone-targeting agents in prostate cancer. Cancer Metastasis Rev 2014;33:619-28.
4. Koizumi M, Maeda H, Yoshimura K, Yamauchi T, Kawai T, Ogata E, *et al.* Dissociation of bone formation markers in bone metastasis of prostate cancer. Br J Cancer 1997;75:1601-4.
5. Schulman CC, Irani J, Morte J, Langley RE, Price P, Abel PD. Androgen deprivation therapy in-prostate cancer: An European expert panel review. Euro Urol Suppl 2010;9:675-91.
6. Meng E, Sun GH, Wu ST, Chuang FP, Lee SS, Yu DS, *et al.* Value of prostate-specific antigen in the staging of Taiwanese patients with newly diagnosed prostate cancer. Arch Androl 2003;49:471-4.
7. Farkas A, Marcella S, Rhoads GG. Ethnic and racial differences in prostate cancer incidence and mortality. Ethn Dis 2000;10:69-75.
8. Janane A, Hajji F, Ismail TO, Elondo JC, Ghadouan M, Ameur A. Endorectal MRI accuracy and its staging evaluation contribution: A North-African ethnic group. Int Urol Nephrol 2010;112:9853-61.
9. Langley RE, Price P, Abel PD. Re: Claude C. Schulman, Jacques Irani, Juan Morote, *et al.* Androgen-deprivation therapy in prostate cancer: A European expert panel review. Eur urol suppl 2010;9:675-91. Eur Urol 2011;59:e24-5.
10. Warren KS, Chodak GW, See WA, Iverson P, McLeod D, Wirth M, *et al.* Are bone scans necessary in men with low prostate specific antigen levels following localized therapy? J Urol 2006;176:70-3.
11. Chybowski FM, Keller JJ, Bergstralh EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: Prostate specific antigen is superior to all other clinical parameters. J Urol 1991;145:313-8.
12. Rhoden EL, Torres O, Ramos GZ, Lemos RR, Souto CA. Value of prostate specific antigen in predicting the existence of bone metastasis in scintigraphy. Int Braz J Urol 2003;29:121-5.
13. Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. JAMA 1993;269:57-60.
14. Gleave ME, Coupland D, Drachenberg D, Cohen L, Kwong S, Goldenberg SL, *et al.* Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. Urology 1996;47:708-12.
15. Lee SH, Chung MS, Park KK, Yom CD, Lee DH, Chung BH, *et al.* Is it suitable to eliminate bone scan for prostate cancer patients with PSA ≤ 20 ng/mL? World J Urol 2012;30:265-9.
16. O'Sullivan JM, Norman AR, Cook GJ, Fisher C, Dearnaley DP. Broadening the criteria for avoiding staging bone scans in prostate cancer: A retrospective study of patients at the royal marsden hospital. BJU Int 2003;92:685-9.
17. McArthur C, McLaughlin G, Meddings RN. Changing the referral criteria for bone scan in newly diagnosed prostate cancer patients. Br J Radiol 2012;85:390-4.
18. Lee N, Fawaaz R, Olsson CA, Benson MC, Petrylak DP, Schiff PB, *et al.* Which patients with newly diagnosed prostate cancer need a radionuclide bone scan? An analysis based on 631 patients. Int J Radiat Oncol Biol Phys 2000;48:1443-6.

How to cite this article: Lmezguidi K, Hajji F, Janane A, Ameur A, Ghadouane M, Alami M. Role of Prostate-Specific Antigen Level and Prostate Biopsy Gleason Score in Predicting Bone Metastases of Prostate Cancer in North African Population. J Clin Res Oncology 2018;1(1):1-6.