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Prostate-specific Antigen as a Risk Factor for Skeletal Metastasis in Native Ethnic African Men with Prostate Cancer: A Case-control Study

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Abstract

Prostate cancer is the most common noncutaneous cancer in males. Men of African origin are at a significantly higher risk as reflected in the higher incidence and mortality rates in this racial group. Metastases incidence increases parallel to serum levels of prostate-specific antigen (PSA), contributing significantly to morbidity and mortality. Staging of the disease involves bone scans, which are sensitive in detecting skeletal metastases. Suggestions that these scans may be omitted in some situations in patients with low prostate specific antigen levels have drawn attention to the matter. In this case-control study, using radiology and pathology records, a registry of prostate cancer patients recorded as being of dark-skinned ethnicity was obtained. Images were presented to image reviewers blinded to the PSA level, to determine the presence of skeletal metastases. The risk factor for the outcome of interest (skeletal metastases) was PSA level above 20 ng/mL. The reliability of image reporting was also assessed. Of the 122 patients, skeletal metastases were present in 50 (41%) while these were absent in 72 (59%). The prevalence of metastases among the high PSA group was 55.9% [95% confidence interval (CI) 44.1–67.7%] and among the normal/low PSA group was 22.2% (95% CI 11.1–33.3%). The odds ratio (OR) for skeletal metastases in the exposed (high PSA) group was 4.4 (95% CI, 2.01–9.78.) Intraobserver agreement on image interpretation was 88.5% with a Kappa statistic of 0.76. A relatively higher prevalence of skeletal metastasis is seen in regional dark-skinned African males with prostate cancer at both low and high prostate specific antigen levels. Bone scanning in this population should therefore, be considered even at PSA levels below 20 ng/mL.

Keywords: Bone scan, native ethnic African, prostate cancer, prostate-specific antigen, skeletal metastases

Introduction

Carcinoma of the prostate is the most common noncutaneous cancer in males, and the second most common cause of cancer deaths in males.^[1] Its incidence rises significantly after the age of 50 years, and this cancer is diagnosed in one in six men during their lifetime. Multiple etiological factors are implicated in the development of prostate cancer. Increasing age, a

family history of disease, diet, and genetic factors have all been linked.

Among the most striking factors related to the development of prostate cancer, is race. Significantly, higher rates of prostate cancer are seen in native ethnic African males compared to Caucasian, Hispanic, and Asian males. Age-adjusted incidence rates (between 2002 and 2006) were 231.9 per 100,000 African Americans versus 146.3 per 100,000 in Caucasians.^[1] This made the incidence among the American native ethnic African men

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1.6 times higher than White men. In addition, the death rate among African Americans was 2.4 times higher than Caucasians in the same time period (53.6 versus 26.3 per 100,000.) The differences in the incidence and mortality are greater still, when comparing the rates in African Americans to those among Hispanics, American Indians, and Asians suggesting that African Americans are not just at a higher risk of development of prostate cancer but also appear to develop more aggressive disease.

Prostate cancer is the most common cancer in Africa and sub-Saharan Africa. In Eastern Africa, age-adjusted incidence rates for prostate cancer are the second highest in this region after Kaposi sarcoma and esophageal carcinoma. The disease burden in Africa appears to be significant.^[2]

Prostate-specific antigen (PSA) is produced in the prostatic epithelium but also by tumor cells. A combination of increased cell burden and distorted glandular architecture allowing the escape of prostate specific antigen into systemic circulation is responsible for the increased levels of prostate specific antigen in prostate cancer.

The skeletal system is one of the most common sites of metastasis, found in approximately 85% of patients dying from prostate cancer. These metastases are predominantly osteoblastic.

The bone scan (bone scintigraphy) is the most commonly performed procedure for whole-body screening and assessment of skeletal metastasis [Figure 1]. As a baseline investigation, it stages disease, demonstrates the extent of the disease where metastases exist, and provides a benchmark for follow-up scans when assessing response to treatment. The technique provides complementary information to the anatomical information provided by radiography, by demonstrating the metabolic changes induced by bone pathology. Due to the osteoblastic nature of prostate cancer metastases, metastatic deposits manifest as areas of increased tracer uptake. In extensive metastatic disease burden, diffuse uptake is seen throughout the axial skeleton giving a “superscan” appearance. Although the technique is relatively less specific, it has substantially higher sensitivity compared to radiography. Accurate disease staging can lead to more appropriate decision-making and advice to patients. Management differs significantly in patients with metastatic disease where the goal of therapy is palliative, symptom control, and disease suppression, versus eradication of the disease.

Performing bone scans in patients with PSA levels below 20 ng/mL remains a gray area in clinical practice. The American Urology Association guidelines in its best

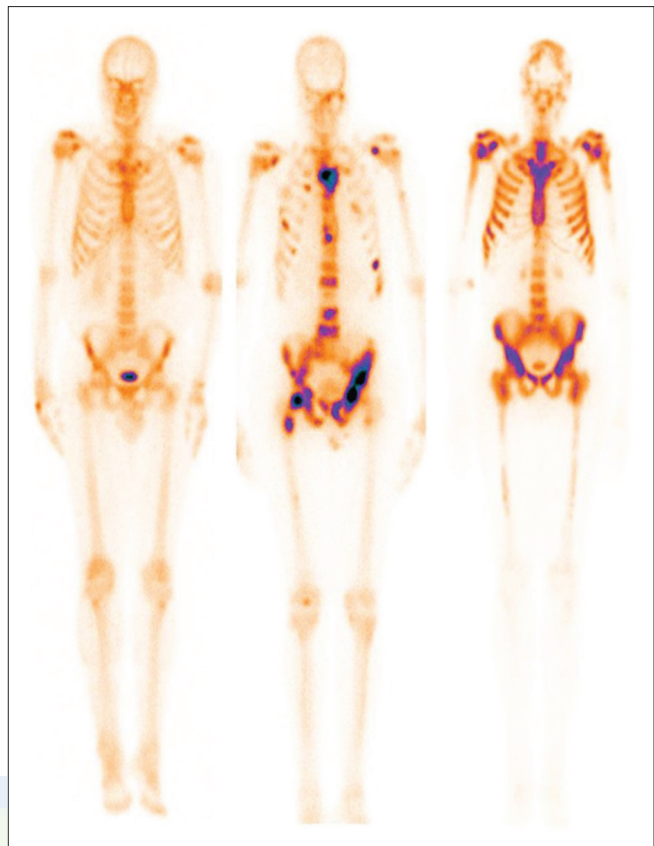


Figure 1: Bone scan images depicting normal uptake (left), metastatic disease (middle), and a superscan (right)

practice statement of 2013 states that bone scans should be considered at PSA levels below 10 ng/mL if the tumor’s Gleason score is 8 or more or there is locally advanced disease ($\geq T3$).^[3] By contrast, guidelines by the European Association of Urology state that in locally advanced disease or poorly differentiated tumors, bone scans should be performed regardless of the PSA value.^[4] The Japanese Urological Association suggests that bone scans may be eliminated when PSA levels are less than 10 ng/mL in patients with well- differentiated to moderately differentiated cancers.^[5] A systematic review examined the findings from 48 research reports, 23 of which correlated baseline bone scan findings as well as PSA levels. Out of 8,644 patients, 16.8% had metastases. Detection rates were 2.3%, 5.3%, and 16.2% in patients with PSA levels less than 10 ng/mL, 10.1–19.9 ng/mL, and 20 to 49.9 ng/mL, respectively.^[6] This meta-analysis may be taken as a global overview. However, men in the east African region may be considered at a higher risk of developing skeletal metastases on the basis of ethnicity or other factors, based on the observation of a higher incidence of and more aggressive prostate cancer in other dark skinned populations worldwide. The present study was undertaken so as to generate data on prostate cancer metastasis to inform local and regional clinical practices.

Materials and Methods

Based on a hypothesis that metastasis is more common than the global estimate in our population, a sample size calculation determined that a sample size of 120 (40 cases and 80 controls) were required to detect an odds ratio (OR) difference of 4 between patients with mildly elevated PSA (<20 ng/mL) and high PSA (≥ 20 ng/mL), at 91% power. This was derived from the pilot study data entered into a power and sample size calculator (<http://biostat.mc.vanderbilt.edu/PowerSampleSize>. Approx. date of last access: 2012 December 20) where it was shown that to detect a low OR at a high power, a moderate number of cases were required [see Appendix 1.] Patients with histologically confirmed prostate cancer who had a bone scan between August 2011 and January 2013 at the Aga Khan University Hospital, Nairobi, Nairobi County, Kenya were consecutively collected for this retrospective case-control study, which was approved by the Research Ethics Committee (Ref No: 2012/REC-08(V2)). Cases were defined as patients with histologically proven prostate cancer with skeletal metastases. Controls were defined as patients with histologically proven prostate cancer without skeletal metastases. The risk factor for outcome of interest (skeletal metastases determined by bone scan) was a PSA level greater than or equal to 20 ng/mL. Inclusion criteria included native ethnic African patients with histologically confirmed prostate cancer and a serum PSA test within 3 months of the bone scan who underwent bone scan for disease staging. Cases with bone metastases due to malignancy other than prostate cancer, posttherapy follow-up bone scans, equivocal cases without complementary images, and bone scans reported by a radiologist other than the nuclear physician were excluded from the study.

An initial listing of potentially eligible cases was acquired from the departmental patient register. The indication for the scan was confirmed from the radiology request form. In the few instances where this information was not provided, confirmation of the scan indication was made from the patient's file. Following the collection of these data, the listing of cases was cross-referenced with the pathology department records to obtain details of histopathology where it was performed at the hospital. Pathology reports from other hospitals were included where available. Data collection began with the most recently performed bone scans to assess prostate cancer skeletal metastases, and proceeded retrospectively. The sampling of patients was stratified into two groups: those with mildly elevated or normal PSA (less than 20 ng/mL) and those with highly elevated PSA (greater than 20 ng/mL). The total number of patients acquired was only slightly greater than the desired sample size; therefore, sampling was nonrandom, and all eligible cases were included in the analysis. PSA levels were

routinely collected from the patients prior to the bone scan. The patients' ethnicities were confirmed from the patient registration section of the respective patient files where this information is routinely recorded according to hospital administrative procedures.

Data including patient identifiers were collected by one investigator. Details including the patient's name, hospital number, and PSA level were entered into a primary data collection table and each record was coded, providing anonymity of the patient dataset and achieving a blinding of subjects to the image reviewers. Coded images were presented to the image reviewers who entered the data into a separate data collection table.

Technetium-99 methylene diphosphonate (^{99m}Tc -MDP) whole-body bone scans were performed on a dual head gamma camera (Millennium MG, GE Medical Systems, Milwaukee, WI, United States) 3–4 h following intravenous (IV) injection of ^{99m}Tc -MDP.

Image acquisition time for a whole-body scan was typically 20 min (camera speed of 11 cm/s); however, these varied depending on the amount of activity injected. Lower injected activities require a longer scan time. A matrix of 1024×256 was used with a low-energy high-resolution collimator (GE Medical Systems, Milwaukee, WI, United States). If necessary, spot views of an area of interest were acquired. Five hundred thousand counts were obtained of this site.

Images were analyzed by a nuclear physician (expert reviewer) with over 15 years of experience in nuclear medicine, and a registrar with cumulative total of 5 months training in nuclear medicine. The coded images were uploaded onto the hospital picture archiving and communication system (PACS) to a folder specific for the purposes of the study. Through this system, images were presented to the image reviewers using Agfa[®] PACS and image viewing software (Mortsel, Belgium) on a high-resolution viewing monitor. The image reviewers were blinded to the results of the PSA. In cases with metastatic disease, sites of skeletal metastases were listed by the nuclear physician. Results of the nuclear physician's repeat report were compared with the original so as to determine intraobserver variability, and comparison between the registrar's report with the nuclear physicians repeat report to test interobserver variability. For comparison with PSA levels, the analysis was based on the expert reviewer's repeat report. In equivocal cases, the image reviewers were provided with complementary images in the same coded manner.

PSA levels in patients with and without skeletal metastases and summary statistics for the distribution

of PSA levels were calculated. Potential statistical associations between PSA and skeletal metastases were estimated using Chi-square statistics. OR of skeletal metastases between low and high PSA groups were calculated. To determine the prevalence of skeletal metastases in patients with PSA below 20 ng/mL a two-sample test for proportions was applied using the global estimate of 3.5% for comparison.^[6] Assessment of intraobserver and interobserver agreement for bone scans was quantified using Cohen’s kappa and percentage of agreement.

Results

Within the 122 patient data sets included, 50 (41%) were found to have skeletal metastases while 72 (59%) had no skeletal metastases detectable on bone scan. Sixty-eight of the 122 PSA values (55.7%) were greater than or equal to 20 ng/mL while 54 patients (44.3%) were considered “unexposed” on the basis of PSA level of below 20 ng/mL.

Among patients with and without skeletal metastases, the PSA levels are summarized in Table 1 and Figure 2. To illustrate the actual range of PSA values in the sample population, the mean PSA in the “unexposed” group (PSA less than 20 ng/mL) was 10.2 ± 5.0 ng/mL (1–19.9 ng/mL) and the median PSA was 10 ng/mL. Within the “exposed” group (PSA greater than 20 ng/mL), the mean PSA was 441.4 ± 86.0 ng/mL (20–7000 ng/mL). The median PSA value was 86 ng/mL.

Table 1: Summary statistics for distribution of PSA in patients with and without skeletal metastases

	Mean	Median	SD [†]	Min	Max
No	68.4	15.2	226.4	1	1,800
Yes	512.8	100	1101.5	1.02	7,000

[†]SD: Standard deviation

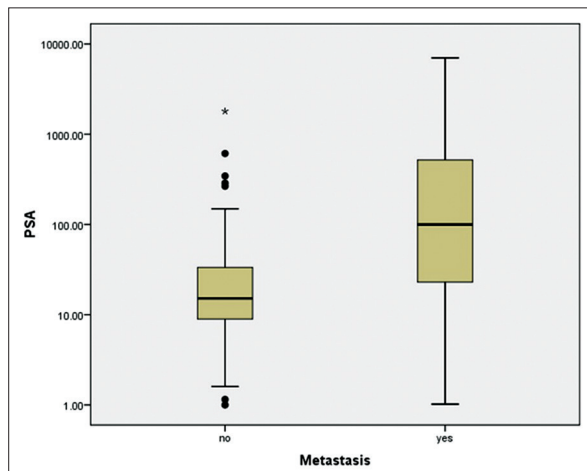


Figure 2: Box plot displaying summary statistics for PSA in cases with and without metastasis

In the present study, the OR for skeletal metastasis was 4.4 [95% confidence interval (CI), 2.0–9.8] in the exposed (high PSA) group. The prevalence of metastases among this high PSA group was 55.9% (44.1–67.7%) and 22.2% (11.1–33.3%) among the normal or low PSA group. A two-sample test of proportions was used to compare these proportions with global estimates of 42.6% and 3.5%, respectively, for the high PSA group and the normal or low PSA group. The prevalence of metastases among the high PSA group differed by 13.3% (95% CI, 1.2–25.4%; *P* = 0.031) compared to the global estimate. Among the low PSA group, the prevalence differed by 18.7% (95% CI, 7.6–29.8%; *P* = 0.001) from the estimated global average.

The sites of skeletal metastases varied, with the spine, pelvis, and rib cage representing the most common sites. These data are summarized in a bar graph format [Figure 3].

Intraobserver and interobserver agreement of reporting was performed using kappa statistics. There was an 88.5% agreement between the expert reviewer’s original and repeat reports, giving a kappa value of 0.76, indicating substantial agreement. Agreement between the registrar and expert reviewer reports was 85.3%, with a kappa value of 0.70, also indicating substantial agreement.

Discussion

The increasing role of PSA as a screening tool for prostatic disease has led to an increase in the diagnosis of prostate cancer, with more cancers being detected at an earlier stage. The need for staging of prostate cancer is important for optimal management, which includes radical prostatectomy for organ-confined disease and androgen deprivation therapy for metastatic disease.

Forty-one percent of the patients in our study had skeletal metastases as assessed on bone scans using methods for which good reliability was demonstrated. This is over

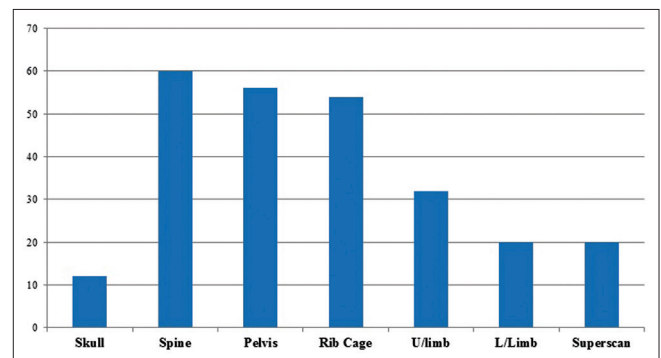


Figure 3: Summary of frequency and percentage involvement of various sites of skeletal metastases

twice the proportion seen in the systematic review by Abuzallouf *et al.* where 1,453 out of 8,644 patients (16.8%) had positive bone scans. The inclusion of solely native ethnic African patients in the present study may be a possible explanation for the large difference. Data from other dark skinned populations have shown higher prostate cancer incidence and mortality within men of African descent that is consistent with a truly greater prevalence of the disease in this group.^[1] Fifty-six percent of the patients in our study had a PSA level greater than or equal to 20 ng/mL while 44.3% had a PSA level below 20 ng/mL. A considerable difference is seen between the present findings, compared to those from the meta-analysis where 27.8% of the patients had a PSA level of greater than or equal to 20 ng/mL, and 72.2% had a PSA level of less than 20 ng/mL. This reflects the case mix and inclusion criteria in reported studies, with many reporting the results of evaluation for skeletal metastases at PSA levels less than 20 ng/mL.

The mean PSA level was five times higher in patients with skeletal metastases than those without skeletal metastases in the current study--a finding that is expected, considering that the incidence of skeletal metastases increases with an increase in the PSA level. Of the patients without metastases, most were in the low PSA group, as indicated by a median PSA value of 15.2 ng/mL. Within the high PSA group, the median PSA was 86 ng/mL. An important observation with clinical implications in our sample is the wide distribution of PSA levels among patients with skeletal metastases, including those below 20 ng/mL.

We documented a higher prevalence of skeletal metastasis in the regional native ethnic African population relative to the typical global pattern, especially those with a low PSA level. Indeed, the prevalence of metastasis was considerably greater than that seen in East Asian studies and among Arab populations, which is consistent with the existing data that indicate that these ethnic groups have a lower incidence and mortality from prostate cancer.^[7-10] Five studies from the systematic review reported a prevalence of skeletal metastases above 10% at PSA levels below 20 ng/mL, with reported ranges from 11.7% to 15.9%.^[11-15] The prevalence of skeletal metastasis in these studies is still noted to be somewhat lower than the current study population. A possible reason for this is the ethnic differences of patients in these studies from the current study, which exclusively evaluated native ethnic African males. Our findings are consistent with the conclusion that skeletal metastases from prostate cancer occur earlier in men of African descent, and that the biological aggressiveness of prostate cancer within this population may be higher than that seen within non-native ethnic African male populations.

These findings are parallel to reports showing that the incidence of and mortality rates from prostate cancer within the east African region are high.^[2]

In the current study, the spine, pelvis, and ribs were the most common sites of skeletal metastasis. The probable reasons for this include the fact that the above sites are abundant in cancellous bone, which has a rich blood supply. During the passage of blood through tight sinusoids in this bone structure, there is a slowing of blood flow allowing deposition of tumor cells. In addition, tethering proteins such as vascular cell adhesion molecule 1 (VCAM-1) are moderately expressed and interact with neoplastic cells, anchoring them to the bone.^[16] This pathophysiological mechanism also explains why the upper and lower limbs are affected (32% and 20%, respectively); however, it does not explain why this is less than the previously described regions. A possible explanation is the conversion of red marrow, and subsequent reduction in blood supply to the bone marrow compared to the previously described areas where residual red marrow exists in relative abundance.

Conclusions

The results from the present study suggest that prostate cancer within the East African native male population demonstrates aggressive biological behavior, similar to that seen in African American populations. Based on our findings, we consider bone scans should be ordered for prostate cancer patients with PSA levels less than 20 ng/mL, and in our setting those with levels less than 10 ng/mL should also be investigated. The need for scanning is obviously greater if patients have coexisting risk factors for skeletal metastasis such as high Gleason's scores or extra prostatic disease extension, and there is therefore, a role for further research in this field locally.

Establishing the infrastructure and logistics required to run a nuclear medicine facility are challenging in low-resource settings. Aspects of this are training and retention of specialist personnel, consistent procurement of radionuclide generators and radiopharmaceuticals, the maintenance of infrastructure that meets radiation safety standards, and the ability to sustain the service through realistic cost recovery and adequate volume of cases referred for investigation. We consider that the appropriate way forward is to concentrate such services within larger tertiary referral centers alongside arrangements to enable a wide access through effective referral linkages that deal with practical arrangements such as travel and accommodation. In sub-Saharan Africa, resourcing such developments may be best undertaken *via* public-private collaboration on cancer services using mechanisms such as service level agreements involving

partners at the regional as well as national levels, as for many countries undertaking these developments would be unrealistic. Furthermore, some countries are currently developing or implementing national cancer strategies so that related regional collaboration would be timely.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1

No. of cases	OR [†] desired to be detected	Power to detect the desired OR
50	2	0.434
	3	0.841
	4	0.967
40	2	0.347
	3	0.740
	4	0.916
30	3	0.592
	4	0.805
	5	0.910
20	4	0.590
	5	0.728
	6	0.819
	7	0.879
	8	0.917
18	6	0.765
	7	0.832
	8	0.878
	9	0.910
15	10	0.933
	8	0.788
	9	0.830
	10	0.863
	11	0.888
	12	0.907

[†]OR: Odds ratio

