Prostate Specific Antigen as a risk factor for skeletal metastasis in Black African men with Prostate Cancer: a Case Control study

ABSTRACT

Prostate cancer is the commonest non cutaneous cancer in males. Men of African origin are at significantly higher risk as reflected in higher incidence and mortality rates in this racial group. Metastases incidence increases in parallel with serum levels of Prostate Specific Antigen (PSA), contributing significantly to morbidity and mortality. Staging of disease involves bone scans, which are sensitive in detecting skeletal metastases. Suggestions they 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 Black African ethnicity was assembled. Images were presented to image reviewers blinded to the prostate specific antigen level, to determine presence of skeletal metastases. The risk factor for the outcome of interest (skeletal metastases) was prostate specific antigen level above 20ng/ml. Reliability of image reporting was also assessed. Of 122 patients, 50 (41%) had skeletal metastases, while these were absent in 72 (59%). The prevalence of metastases among the high prostate specific antigen group was 55.9% (95% CI 44.1% to 67.7%) and 22.2% (95% CI 11.1% to 33.3%) among the normal/low prostate specific antigen group. The Odds Ratio (OR) for skeletal metastases in the exposed (high prostate specific antigen) group was 4.4 (95% CI, 2.01 to 9.78.) Intra-observer agreement on image interpretation was 88.5% with a Kappa statistic of 0.76. Relatively higher prevalence of skeletal metastasis is seen in regional Black 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 prostate specific antigen levels below 20ng/ml.

Keywords: Prostate Cancer, Prostate Specific Antigen, Skeletal Metastases, Bone Scan, Black African

INTRODUCTION

Carcinoma of the prostate is the commonest non-cutaneous cancer in males, and the second most common cause of cancer deaths in males.[1] Its incidence rises significantly after the age of 50, and this cancer is diagnosed in one in six men during their lifetime. Multiple aetiological factors are implicated in the development of prostate cancer. Increasing age, a family history of disease, diet and genetic factors have all been linked.

Amongst the most striking factors related to development of prostate cancer is race. Significantly higher rates of prostate cancer are seen in Blacks compared to Caucasian, Hispanic and Asian males. Age adjusted incidence rates (between 2002 – 2006) were 231.9 per 100,000 (African Americans) versus 146.3 per 100,000 (Caucasians) respectively.[1] This placed incidence among the American Black men 1.6 times higher than white men. In addition, the death rate amongst 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 incidence and mortality are greater still, when comparing rates in African Americans to those among Hispanics, American Indians and Asians suggesting African Americans are not just at higher risk of development of prostate cancer, but also appear to develop more aggressive disease.

Prostate cancer is the commonest 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 oesophageal carcinoma. The disease burden in Africa appears to be significant.[2]

Prostate Specific Antigen is produced in the prostatic epithelium but also by tumour cells. A combination of increased cell burden and distorted glandular architecture allowing 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 commonest 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 disease extent 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 prostatic cancer metastases, metastatic deposits manifest as areas of increased tracer uptake. In extensive metastatic disease burden, diffuse uptake is seen in 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 disease.

Performing bone scans in patients with prostate specific antigen levels below 20ng/mL remains a grey area in clinical practice. The American Urology Association guidelines in their best practice statement of 2009 state that bone scans should be considered at prostate specific antigen levels below 20ng/ml if the tumour's Gleason score is eight or more or there is locally advanced

disease (≥ T3).[3] By contrast guidelines by the European Association of Urology state that in locally advanced disease or poorly differentiated tumours, bone scans should be performed regardless of the prostate specific antigen value.[4] The Japanese Urological Association suggests bone scans may be eliminated when prostate specific antigen levels are less than 10ng/mL in patients with well–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 prostate specific antigen levels. Of 8644 patients, 16.8% had metastases. Detection rates were 2.3%, 5.3% and 16.2% in patients with prostate specific antigen levels less than 10, 10.1 to 19.9 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 higher risk of developing skeletal metastases on a basis of ethnicity or other factors, based on the observation of higher incidence of and more aggressive prostate cancer in other Black populations worldwide. The present study was undertaken so as to generate data on prostate cancer metastasis to inform local and regional clinical practice.

MATERIALS & 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 prostate specific antigen (<20 ng/ml) and high prostate specific antigen (≥ 20 ng/ml), at 91% power. This was derived from pilot study data entered into a power and sample size calculator (http://biostat.mc.vanderbilt.edu/PowerSampleSize) where it was shown that to detect a low Odds Ratio 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 the months of August 2011 to January 2013 at the Aga Khan University Hospital, Nairobi, 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 prostate specific antigen level greater than or equal to 20ng/ml. Inclusion criteria included Black African patients with histologically confirmed prostate cancer and a serum prostate specific antigen test within 3 months of the bone scan who underwent bone scan for disease staging. Cases with bone metastases due to malignancy other than prostatic cancer, post-therapy 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 circumstances where this information was not provided, confirmation of the scan indication was made from the patient's file. Following collection of these data, the listing of cases was cross-referenced with Pathology department records to obtain details of histopathology where this had been carried out at the hospital. Pathology reports from other hospitals were included where available. Data collection began with the most recently performed bone scans to assess for prostate cancer skeletal metastases, and proceeded retrospectively. Sampling of patients was stratified into two groups: mildly elevated or normal prostate specific antigen (less than 20ng/mL,) and those with highly elevated prostate specific antigen (greater than 20 ng/mL.) The

total number of patients acquired was only slightly greater than the desired sample size therefore sampling was non – random, and all eligible cases were included in the analysis. Prostate specific antigen levels are routinely collected from patients prior to the bone scan. Patient ethnicity was confirmed from the patient registration section of 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 patient name, hospital number and prostate specific antigen level were entered into a primary data collection table and each record was coded providing anonymity of the patient dataset and achieving blinding of subjects to the image reviewers. Coded images were presented to the image reviewers who entered data into a separate data collection table.

Technetium-99 metastable Methylene Diphosphonate (99mTc-MDP) whole body bone scans were carried out on a dual head gamma camera (Millennium MG, GE Medical Systems) 3 - 4 hours following IV injection of Technetium-99 metastable Methylene Diphosphonate.

Image acquisition times for a whole body scan were typically 20 minutes (camera speed of 11cm/sec) however these varied depending on the amount of activity injected. Lower injected activities require longer scan times. A matrix of 1024 x 256 was used with a Low Energy High Resolution collimator. If necessary, spot views of an area of interest were acquired. Five hundred thousand counts were obtained of this site.

Images were analysed 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. 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® picture archiving and communication system and image viewing software, on a high resolution viewing monitor. The image reviewers were blinded to the results of the prostate specific antigen. In cases with metastatic disease sites of skeletal metastases were listed by the nuclear physician. Results of the Nuclear Physicians repeat report were compared with the original so as to determine intra-observer variability, and comparison between the registrar's report with the Nuclear Physicians repeat report to test inter-observer variability. For comparison with prostate specific antigen 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.

Prostate specific antigen levels in patients with and without skeletal metastases and summary statistics for the distribution of prostate specific antigen levels were calculated. Potential statistical associations between prostate specific antigen and skeletal metastases were estimated using Chi – square statistics. Odds ratio of skeletal metastases between low and high prostate specific antigen groups were calculated. To determine the prevalence of skeletal metastases in patients with prostate specific antigen below 20ng/ml a two-sample test for proportions was applied using the Global estimate of 3.5% for comparison.[6]Assessment of intra-observer and inter-observer 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 prostate specific antigen values (55.7%) were greater than or equal to 20 ng/ml, whilst 54

patients (44.3%) were considered ‘unexposed’ on the basis of a prostate specific antigen level of below 20 ng/ml.

Amongst patients with and without skeletal metastases, prostate specific antigen levels are summarised in Table 1 and Figure 2.To illustrate the actual range of prostate specific antigen values in the sample population, the mean prostate specific antigen in the ‘unexposed’ group (prostate specific antigen less than 20ng/ml) was 10.2 ± 5.0 ng/ml (1 – 19.9 ng/ml) and median prostate specific antigen was 10ng/ml. Within the ‘exposed’ group (prostate specific antigen greater than 20ng/ml), the mean prostate specific antigen was 441.4 ± 86.0ng/ml (20 – 7000 ng/ml.)The median prostate specific antigen value was 86ng/ml.

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

Sites of skeletal metastases varied, with the spine, pelvis and rib cage representing the commonest sites. These data are summarised in a bar graph format (Figure 3.)

Intra and inter-observer 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 prostate specific antigen as a screening tool for prostatic disease has led to an increase in 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 patients in our study had skeletal metastases as assessed on bone scans using methods for which good reliability was demonstrated. This is over twice the proportion seen in the systematic review by Abuzallouf and colleagues where 1453 of 8644 patients (16.8%) had positive bone scans. Possible explanations for the large difference may be due to inclusion of solely Black African patients in the present study. Data from other Black populations has shown higher prostate cancer incidence and mortality within men of African descent consistent with a truly greater prevalence of the disease in this group.[1]Fifty six percent of patients in our study had a prostate specific value greater than or equal to 20 ng/ml, whilst 44.3% had a prostate specific antigen level of below 20 ng/ml. A considerable difference is seen between the present findings, compared to those from the meta-analysis where 27.8% of patients had a prostate specific antigen of greater than or equal to 20 ng/ml, and 72.2% had a prostate specific antigen of less than 20 ng/ml. This reflects the case mix and inclusion criteria in reported studies, with many reporting results of evaluation for skeletal metastases at prostate specific antigen levels less than 20 ng/ml.

The mean prostate specific antigen level was 5 times higher in patients with skeletal metastases than those without skeletal metastases in the current study, a finding expected, considering the incidence of skeletal metastases increases with an increase in prostate specific antigen levels. Of the patients without metastases, most were in the low prostate specific antigen group, as indicated by a median prostate specific antigen value of 15.2 ng/ml. Within the high prostate specific antigen group the median prostate specific antigen was 86 ng/ml. An important observation with clinical implications in our sample is the wide distribution of prostate specific antigen levels amongst patients with skeletal metastases, including those below 20 ng/ml.

We documented a higher prevalence of skeletal metastasis in the regional Black African population relative to the typical global pattern, especially those with a low prostate specific antigen. Indeed, the prevalence of metastasis was considerably greater than that seen in East Asian studies and among Arab populations which is consistent with existing data which 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 prostate specific antigen levels below 20ng/ml, with reported ranges from 11.7% to 15.9%.[11 – 15]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 Black African males. Our findings are consistent with a 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 Black African male populations. These findings parallel reports 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 commonest sites of skeletal metastasis. Probable reasons for this include the fact that the above sites are abundant in cancellous bone, which has a rich blood supply. During passage of blood through tight sinusoids in this bone structure, there is slowing of blood flow allowing deposition of tumour cells. In addition, tethering proteins like Vascular Cell Adhesion Molecule – 1 (VCAM – 1) are moderately expressed and interact with neoplastic cells, anchoring them to bone.[16] This pathophysiological mechanism also explains why the upper and lower limbs are affected (32% and 20% respectively), however 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 suggests that prostate cancer within the East African native male population demonstrates aggressive biological behaviour, similar to that seen in African American populations. We consider our findings to require that bone scans are ordered for prostate cancer patients with prostate specific antigen 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 centres alongside arrangements to enable 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 around cancer services using mechanisms such as service level agreements involving partners at regional as well as national level, as for many countries undertaking these developments would be unrealistic. Furthermore, some countries are currently developing or implementing national cancer strategies so related regional collaboration would be timely.

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