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Full Length Research Paper

Association of Gleason Risk Groups with Metastatic Sites in Prostate Cancer

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ABSTRACT

Prostate cancer is the second most common non cutaneous male malignancy worldwide. Gleason composite score is used for risk classification. The most common site of metastasis in prostate cancer is the bone among others. The site and number of metastasis affect overall survival. The ability to predict the metastatic site at diagnosis can assist in predicting the prognosis. To assess the pattern of bone and visceral organ metastases in prostate cancer and evaluate if the initial Gleason grade at diagnosis can predict metastatic sites in prostate cancer. Records of patients with metastatic prostate cancer seen in an institution in Nigeria were analysed. Imaging examination reports used were Technitium99m bone scan for skeletal metastasis, ultrasonography, chest x-ray and cranial CT scan for evidence of visceral metastasis. The association of the initial Gleason grade and site of metastasis was determined using Chi square test for significance. Eighty two patient's records were analysed. The proportion of patients with low risk Gleason grade (≤6) at diagnosis was 27(32%), Intermediate risk grade (Gleason=7) was 25 (30%) while high risk Gleason grade (8-10) was 30 (38%). Spinal metastasis was 77(94%), pelvis 55(67%) femur 36 (44%) and tibia 1 (1%) while 55(67%) patients had multiple bones affected. Twenty seven patients 33% had visceral metastasis with liver 15(18%) lungs 9 (11%) and brain 3 (4%). There was no significant association between the initial Gleason risk grade with the site of metastasis (x^2 3 =2.411, p=0.491). The spine was the most common site of metastases from prostate cancer in this series. The Gleason risk grade at diagnosis was not predictive of metastatic site.

Key words: Prostate cancer, Gleason grade, metastatic site

INTRODUCTION

Prostate cancer is the second most common non cutaneous cancer of men worldwide. In 2012 about 1.1 Million cases representing 15% of male cancers were diagnosed and it accounted for 6.6% of cancer related mortality in men in 2012 (GLOBOCAN, 2014). Common malignancies such as those of the breast, lung and prostate, frequently metastasize to bone, and in a large number of patients with metastatic disease the skeleton is the site of the most significant tumour burden (Yin et al., 2005). In the past, cancer of the prostate was reported to be uncommon among West African blacks, specifically the Nigerian male. It was also reported in 1973 that prostate cancer ranked 16th and constituted 2.2% of all malignancies in the cancer registry in Ibadan Nigeria (Nkposong and Lawani, 1973) . However, in recent years reports have shown that the incidence of prostate cancer is on the rise. Presently prostate cancer is the most common non cutaneous cancer in Nigeria

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accounting for 32% of all malignancies in men of all ages according to GLOBOCAN estimates for 2012.

Bone metastases are a frequent complications of advanced cancer, occurring in up to 70% of patients with metastatic prostate cancer diagnosed clinically (Roodman, 2004). The most common site of metastatic spread in patients with prostate cancer is the skeleton, which accounts for about 90% of all prostate cancer metastases reported from autopsy studies (Thobe et al., 2011). Prostate cancer has predilection for bone. The reason and mechanism for this is complex and not completely understood. Mechanical and molecular processes have been adduced for this tendency. The prostatic venous plexus is anatomically connected to the vertebral veins through the unique bidirectional valveless veins of Batson (Batson, 1995). Prostate cancer cells can therefore easily enter the vertebral venous circulation especially during increased intra pelvic pressure during straining and therefore get attached to the pelvic and vertebral bones. Molecular mechanisms have also been described linking the tendency of prostate cancer cells to involve bones. There is presence of high levels of chemokine receptors in bone marrow stem cell niches. These receptors are also highly expressed by prostate cancer cells making it easy for the two cell populations to interact. Annexin receptors responsible for cellular adhesion, migration and growth of prostate cancer cells has also been described in osteoblasts and hematopoietic stem cells. These receptors recruit disseminating tumour cells towards the bones (Semenas et al., 2012). The molecular and cellular mechanisms of bone metastasis in prostate cancer have been extensively reviewed by Lin and colleagues (2007) and Semenas (2012) (Ye et al., 2007, Semenas et al., 2012). About 90-95% of bone metastases from prostate cancer are osteoblastic lesions, while 5% are mixture of osteoblastic and osteolytic lesions (Koeneman et al., 1999, Rucci and Angelucci, 2014). There is secondary bone formation occurring in response to lytic bone destruction, this is detected by means of bone scanning which identifies active bone formation. Tc-99m-MDP bone scan is most widely used technique for the detection and surveillance of metastatic spread to the skeleton on account of this (Kakhki et al., 2013). The onset of bone metastasis in prostate cancer is a poor prognostic occurrence as about 90% of the patients will eventually die within 5 years (Ablin, 2008). The Mechanism of death is commonly due to marrow failure and skeletal related events like pathological fracture and cord compression. These skeletal related events drastically reduce patient's quality of life leading to early death (Smith et al., 2007).

Most prostate adenocarcinomas are multifocal in origin and sometimes this leads to the presence of distinct populations of malignant cells in the tissue. These different populations are usually at different stages of differentiation which imposes various degrees of aggressiveness. Five levels of cellular differentiation described by Gleason (Gleason, 1966) can be identified. The most prominent two in an H&E stained tissue sample slide is summed up to give the Gleason composite score which is used in assessing prognosis for treatment classification (Iczkowski and Lucia, 2011, Gleason, 1966). In this scoring system, a predominantly well differentiated histology followed by a moderately well differentiated histology will have a score of 1+2 giving a composite score of 3 (Humphrey, 2004) though this composite score of 3 is not commonly seen clinically but in autopsy series. Similarly, if the predominant histological differentiation is Grade 3 followed by grade 4, the composite score is 3 plus 4 which is equal to 7. Another tumour will also be graded as 7 if the predominant differentiation is 4 followed by 3 (Chan et al., 2000; Lau et al., 2001). The Gleason composite score gives degree of aggressiveness of the tumour as shown in Table 1 (Gleason and Mellinger, 2002, Egevad et al., 2002).

Table 1:
Gleason composite score and corresponding degree of differentiation

Gleason Score	Grade	Degree of differentiation
2-4	1	Well differentiated
5-6	2	Moderately differentiated
7-10	3-4	poorly differentiated/undifferentiated

Prostate cancer is divided into three prognostic risk groups, (i) low risk, (ii) intermediate risk and (iii) high risk for clinical management decisions (D'Amico et al., 1998). Low risk patients are defined as PSA level ≤10, Gleason score ≤ 6, and tumour size (T) ≤2b). Intermediate group are patients with PSA>10≤20 with Gleason score of 7 while high risk group includes patients with PSA>20, T2b/T3 with Gleason score from 8-10. This grouping has been used in assigning patients to various treatment modalities / clinical trial groups by various guidelines like The National Comprehensive Cancer Network (NCCN). The risk group at presentation is used to assign patients to either conservative or radical treatment based on the expected aggressiveness of the disease. Low risk class of diseases are noted to behave indolently with slower rates of progression whereas those in the high risk class with poorly differentiated

histological types progress faster and have tendency to involve visceral and soft tissue organs as well as bones (Beltran et al., 2014).

Based on the above facts, we hypothesised that the Gleason based risk classification at diagnosis of prostate cancer may be associated with site of metastasis in the metastatic phase of the disease. The objective of this study was to assess the pattern of bone and visceral organ metastases in prostate cancer and evaluate if the initial Gleason grade at diagnosis can predict metastatic sites in prostate cancer.

MATERIALS AND METHODS

Data collection

This is a retrospective study of patients diagnosed with adenocarcinoma of the prostate treated at the department of Radiation Oncology University College Hospital (UCH) Ibadan, South West Nigeria who had Tc99m-MDP bone scan done as well as routine abdomino-pelvic ultrasonography and chest x-ray examinations. Cranial CT scan was done if there was clinical suspicion of cerebral metastasis. Ethical approval for the study was obtained from the Institutional Ethical Review Committee.

All available treatment records of patients with histologically diagnosed adenocarcinoma of the prostate treated at the Department of Radiation Oncology, University College Hospital Ibadan Nigeria from 2006 to 2010 and had bone scan examinations were retrieved. This period was chosen because regular bone scan facilities were available from 2006 in the institution. Patients with metastatic disease were selected for analysis. The data obtained from patients' records were patients' bio-data and clinical data. Pathological features of the disease such as stage of disease, histology, and Gleason's score at presentation and PSA results were extracted. The symptoms preceding skeletal related events in relevant patients were also documented. The bone scan protocol consisted of intravenous injection of 15- 25 mCi of Tc99m- MDP depending on the patient's weight. The scan of the whole body was performed using a single head Gamma Camera system (Siemens E-cam, signature series). Images were acquired about 4 hours after injection. High resolution collimators was used and whole body anterior and posterior planner images, together with oblique and localized views for areas of interest were obtained. Sites of bone metastases were identified on the images from the Gamma camera. Bone scan results were reported by Nuclear Medicine physicians. Patients with positive report of skeletal involvement were selected for analysis. Other radiological investigations for the selected patients reviewed were ultrasound and chest x-ray reports for radiological evidence of metastasis. These imaging procedures were reported by Board Certified Radiologists. All the above pieces of information were extracted using data extraction form.

Data analysis

The data were analysed using SPSS version 17.0. Descriptive methods were used to present the data in forms of graphs and tables of frequency, proportions and percentages. t-Test was used to compare the frequency of soft tissue versus bone metastasis for significant differences while Chi square test was used to test the association of Gleason risk classes with sites of metastasis..

RESULTS

A total of 82 patients with histologically diagnosed adenocarcinoma of the prostate with positive radiological evidence of metastasis results were analysed. All the patients were indigenous African blacks. The age group distribution of the patients is presented in Figure 1. The age range was 47-87 years with a mean age of 67 years (SD ±1.8). The modal age group being 60-69 years. Three percent of the patients were less than 50 years in age.

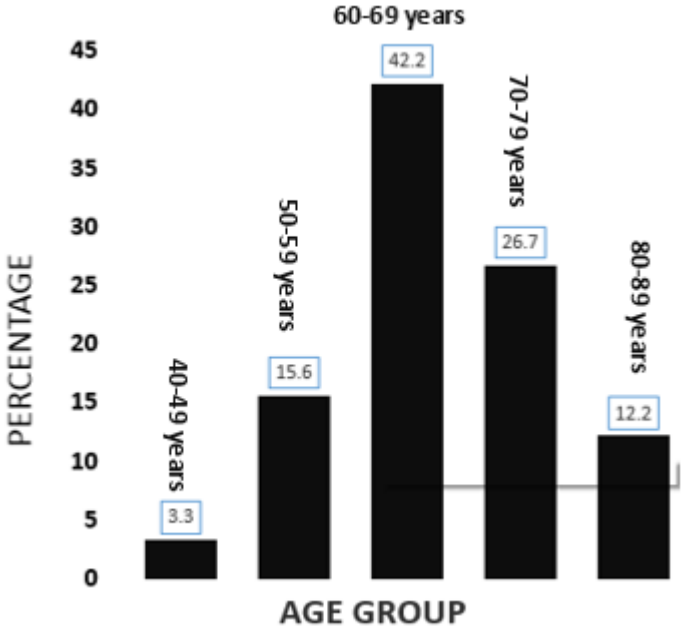

Figure 1:
Age distribution of 82 prostate cancer patients with metastatic disease. Age group 40-49 years have the lowest frequency of 3 (3.4%) and the highest number of patients was in the 60-69 years age group accounting for 46.2% of all the patients.

Table 2:
Gleason's composite score of 82 patients with metastatic prostate cancer. A: Gleason composite score. B: Classification into risk groups based on Gleason grades.

2A

Gleason's Composite score	Frequency	Percent
4	5	6
5	3	3
6	19	23
7	25	30
8	22	27
9	7	9
10	2	2

2B

Gleason risk grades	Frequency	Percent
Low risk (Gleason ≤6)	27	32
Intermediate risk (Gleason 7)	25	30
High risk (Gleason 8-10)	30	38

Table 3:
Distribution of sites of skeletal metastasis in 82 patients showing the frequency of involvement of each site.

Skeletal site	Frequency	Percent
Spine	77/82	94
Cervical	22/77	28.6
Thoracic	64/77	83.1
Lumbar	71/77	92.2
Sacrum	48/77	62.2
Coccyx	15/77	19.5
Flat bones		
Pelvis	55/82	67
Skull	18/82	22
Ribs	33/82	40
Scapula	12/82	15
Sternum	26/82	32
Lower extremities		
Femur	36/82	44
Proximal	35/36	97.2
Shaft	19/36	52.7
Distal	10/36	27.8
Tibia	1/82	1
Upper extremities		
Humerus	31/82	38
Proximal	27/31	87.1
Shaft	11/31	35
Distal	3/31	10
Ulna	1/82	1
Clavicle	23/82	28

The Gleason composite score of the patients were also extracted (Table 2A). Gleason 7 represents the highest number of composite Gleason score assigned to patients. These were sorted into the three prognostic groups. Patients with high risk group were more (38%) in this series (Table 2B).

The frequency of involvement of the different bone sites is presented in Table 3. Spine was the commonest site of metastases seen in 77 (94%) of the patients. The lumbar vertebrae was the spinal section most affected [71 (92.2%)]. Ulna and tibia were least affected with only 1 (1.1%) patient each. The number of patients with multiple bone involvement was 55(67%) while 27 (33%) had single bone involvement.

The presenting symptoms relating to bony involvement among the patients varied. Pain was the most common presenting complain in 57 (70%) of the 82 patients with bone metastases. Eight patients (9.3%) were however asymptomatic (Table 4).

Information on visceral metastasis from radiological reports was also extracted and is presented in Table 5. The liver was the most common visceral organ affected.

Table 4:
Presenting symptoms of 82 patients with bone metastases from prostate cancer

Symptoms	Frequency	Percent
Pain	57/82	70
Cord compression	13/82	16
Asymptomatic	8/82	9.3
Fracture	4/82	4.7

Table 5:
Distribution of visceral metastases in 82 patients with metastatic prostate cancer.

Site of metastasis	Frequency	Percent
Liver	15/82	18.8
Lungs	9/82	11.1
Brain	3/82	3.7
Total	27/82	33.6

All the patients with visceral and bone metastasis had loco regional lymph node involvement of the disease as well. Twenty three patients (28%) had both visceral and bone involvements. The frequency of bone metastasis was compared with visceral sites using t-Test. Skeletal metastasis was significantly higher than soft tissue sites in this series (Figure 2)

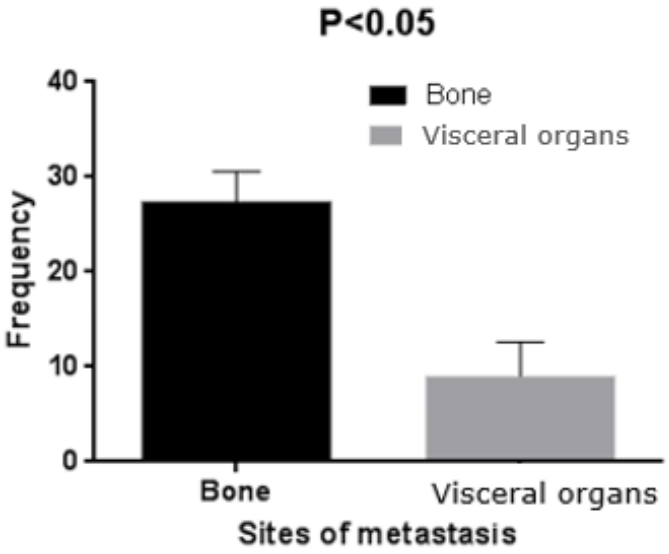

Figure 2:
Frequency of bone and visceral involvement in 82 prostate cancer patients with metastatic disease. Bone metastasis is significantly higher than soft tissue (visceral) sites in prostate cancer patients analysed. Columns are mean ± SEM of number of patients. (p<0.0028 by t-Test).

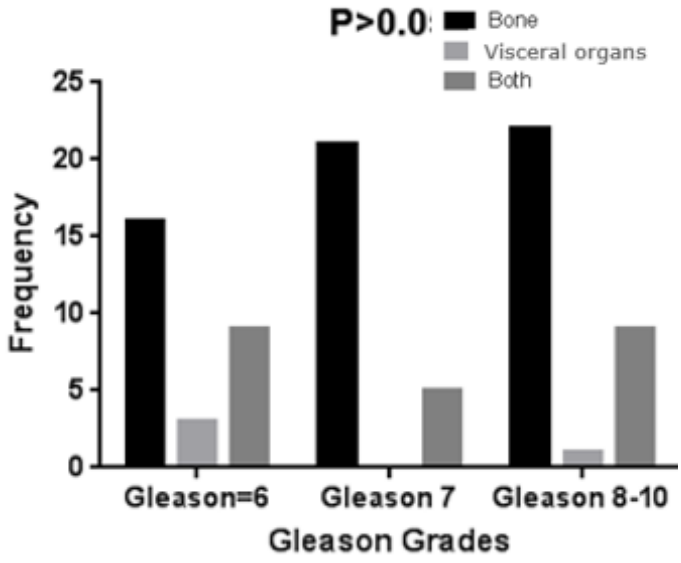

Figure 3:
The association of metastatic sites with Gleason grade at diagnosis. Gleason grade at diagnosis is not significantly associated with metastatic sites in prostate cancer (x^2 3, =2.411, p=0.491)

The possible association of the three Gleason risk groups at diagnosis with predilection of metastatic sites was assessed using Chi square test for contingency tables. The result shows there is no significant association between the Gleason grades at diagnosis with metastatic site. (Figure 3)

DISCUSSION

The consequences of bone metastases are often devastating with bone destruction as a major cause of morbidity in prostate cancer (Mundy, 2002). Bone metastases are frequent events in advanced prostate cancer, 80% of advanced prostate cancer is accompanied by the development of skeletal metastases[7,8]. The mean age at prostate cancer diagnosis in this study was 67±1.8 years (range 47-87 years). This is similar to the study by Badmus and colleagues (2010) in Ile-Ife South West Nigeria who reported a mean age at diagnosis of 68 years in a hospital based study similar to this study (Badmus et al., 2010) and is similar to the age group in other underserved regions (Winer et al., 2014). Nkposong and Lawani (1973) reported a mean age of 61.2 years in Nigeria about 40 years ago. This would have altered possible due to improvement in life expectancy over the time. The age group 60-69 years had the highest frequency of 37.8% in this study. The age group with highest frequency of detection can be influenced by the increasing use of PSA for testing. In such situations, prostate cancer can be diagnosed more in younger age groups (Brewster et al., 2000). In Nigeria like in most developing countries, the routine use of PSA is limited (Delongchamps et al., 2007) and hence the age group with greatest incidence might be affected. All the patients in this study had adenocarcinoma. It is reported that over 95% of cancers arising from the prostate gland are adenocarcinomas (Hammerich et al., 2008). A study in Calabar, Nigeria reported that adenocarcinoma constituted 98.6% of prostate cancer histological types (Ekwere and Egbe, 2002).

Composite Gleason 7 was the most common Gleason grade assigned to the patients (Table 2A). This is consistent with earlier reports that Gleason grade 7 is the most commonly assigned Gleason grade to prostate cancer patients (Sakr et al., 2000). Higher Gleason grades were also assigned to most patients supporting other reports that Black Africans generally have higher grades of disease with associated poor prognosis (Taksler et al., 2012, Sapira and Obiorah, 2012, Ikuerowo et al., 2013).

The most frequently involved area of bone metastases in this study was the spine in 77 patients (85.6%) followed by pelvis with 55(61.1%) of the

patients. This is similar to a study done in Taiwan where bone metastases were found more frequently in the spine (83.5%), then pelvis (73.3%). Others in report are ribs (68.0%), femur (39.2%), scapula (26.8%), skull (21.6%), humerus (20.6%), clavicle (13.4%), and tibia (1.1%) (Huang et al., 2006). However, these differ from the series done in Pakistan by Memon and colleagues (2006) where they found that thoracic vertebrae were the commonest site of bone metastases with 32%. This is followed by shoulder joint (28.0%), and sacroiliac joint (21.0%) (Memon et al., 2006). Though the spine was the most common site of bone metastases in all series, lumbar vertebrae was more common in our study. There were more multiple sites metastases in 63.3% of the patients while the others (27.8%) had single site metastases. More multiple site metastases were found in the report from Taiwan consisting 86.6% and 13.4%[14]. Pain was the most common symptom of bone metastases in 92.6% of patients. The possible mechanisms of pain include structural damage of nerves, periosteal irritation and nerve entrapment (Jimenez-Andrade et al., 2010). Others were cord compression 17.1%, fracture (4.8%), while 4.8% of the patients were asymptomatic. Palmer and colleagues (1998) reported asymptomatic bone metastases in 22% of patients in their study (Palmer et al., 1988) which is very similar to the findings in the Taiwan study[14]

The liver was more affected in this study than the lungs (Table 5). In a report by Adewuyi and colleagues (2013), the lungs were more affected than the liver Table 6 (Adewuyi et al., 2013). However the low rate of visceral involvement 30% in this study supports the report that in most cases of prostate cancer, bone is the only site of distant metastasis (Jimenez-Andrade et al., 2010).

A summary of some studies with pattern of distribution of metastases in prostate cancer is provided in Table 6 (Cereceda et al., 2003, Wang et al., 2013).
There was a significant tendency for the disease to involve bones compared with visceral organs in this study (Figure 2). This is in line with the known preference of prostate cancer cells to metastasize to skeletal sites. This study also highlights that there was no significant association between the Gleason grades at diagnosis with the site of metastasis (Figure 3). With the high proportion of high risk, poorly differentiated tumour characteristics, it would have been expected that the tendency to affect the viscera would have been significant with the higher grade classes than with the low grades. The reason for this might be due to the observations that prostate cancer cells undergo de-differentiation along the course of the disease to more aggressive histological types (Beltran et al., 2014). Trans-differentiation to neuroendocrine characteristics has also been reported on some hormone resistant prostate cancer cells during the course of the disease thus changing their behaviour from what it was at the initial diagnosis (Aggarwal et al., 2014). In addition, the rate of clinical under-grading in prostate cancer has been put at 20-30% (Dall'Era et al., 2012, Iremashvili et al., 2012) . This is because men who were initially assessed as having low grade disease but underwent radical prostatectomy were discovered to have higher grade disease. The presence of high tertiary Gleason grade in tumour tissues can also confer aggressive characteristics to low risk composite Gleason grades leading to poor prognostic features (Patel et al., 2007). The effects discussed above, may imply that at the metastatic stage, the tumour cells are similar in terms of degree of differentiation and aggressiveness hence no difference in predilection to metastatic sites.

In conclusion, the axial skeleton especially the spine is the most common site of bone metastases from prostate cancer. Due to predilection for bone by prostate cancer, it is important to ensure radio-isotope bone scan as a baseline investigation in the management of prostate cancer. The initial Gleason based risk classification at diagnosis, does not predict site of metastasis in prostate cancer in the study population.

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