Prognostication Studies of Prostate Cancer in Black Africa: Findings from Calabar, South-South, Nigeria

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ABSTRACT

Introduction: Prostate cancer is the commonest cancer in males in Nigeria, a country with the largest concentration of indigenous black patients worldwide. The disease has variable clinical behavior but is noted to have a more aggressive course in blacks. Prognostication is important in detecting which patients have tumours with aggressive invasive potential bringing about proper patient management. This study was carried out to assess the outcomes in patients diagnosed with prostate cancer and the factors determining these outcomes.

Material and Methods: This was a retrospective analysis of all histologically proven cases of prostate cancer at the University of Calabar Teaching Hospital, Nigeria over a 10-year period. Patients' demographic data, clinical condition and PSA at diagnosis and one year after, histologic diagnoses including Gleason's grade and score, AJCC Stage, as well as treatment regimen were extracted. Data obtained was analyzed using Statistical Package for Social Sciences version 20.

Results: One hundred and eleven (111) cases were studied with mean age of 66.7 ± 10.6 years. Most patients (70.2%) were within the 60-79 year age group. Over 64% of patients presented with Gleason grades of 3 or 4 and over 46% of patients had Gleason scores of 6 or 7. Fifty five percent of patients had PSA values greater than 20ng/mL and among these patients mean PSA was 62.3 ng/mL ± 26.6. Over 64% had at least stage 2B disease and above, metastasis was found in over 20% of patients at presentation and the main drug patients were placed on was Antiandrogens. Metastasis at presentation was found to be more common with age less than 60 years, Gleason Grade greater than 3, Gleason Score greater than 6 and AJCC Stage greater than 2B. Better treatment outcomes were recorded in patients older than 60 years of age, without metastasis at presentation and with AJCC Stage 2B or less. No significant difference in outcomes was noted between Gleason Grade less than or above 3 or scores less than or above 6. Significant loss in data was recorded in the study.

Conclusion: A significant proportion of patients in our environment still present with advanced disease. Routine screening for prostate cancer is recommended and efforts at improving access to imaging modalities and electronic medical records should be intensified if better results in the management of prostate cancer must be achieved.

Keywords: Prognostication, Prostate Cancer, Black Africa

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men worldwide accounting for 28% of all incident cases of cancer and more than 1% of all deaths in men[1,2,3] It is also found to be the commonest cancer in males in Nigeria, which has the largest concentration of indigenous black patients in the world.[4,5] Patients with advanced cancer as well as their caregivers frequently want to know their life expectancy. This makes prognostication important as it enables patients to be better prepared for their disease state and possible death.[6,7] In addition, clinicians need to find factors, which could help in detecting which patients would have tumours with aggressive invasive potential in order to help in management decision making[8,9] Prostate cancer has a variable clinical behavior with many cases being clinically indolent and others being clinically aggressive, becoming metastatic and lethal. There is therefore the need for prognostic biomarkers to accurately stratify patients for appropriate risk-adapted therapy.[10] The common prognostic factors in current use include serum prostate specific antigen (PSA), Gleason grade/ score and tumor stage.[11–13] This study was carried out to assess the outcomes in patients diagnosed with prostate cancer and the clinicopathologic factors determining these outcomes.

MATERIAL AND METHODS

This was a retrospective analysis of all histologically proven cases of prostate cancer in which significant data could be obtained at the University of Calabar Teaching Hospital, Calabar from January 2001 to December 2010. Records were retrieved from patients' case notes, clinic and ward registers and histopathology records. Patients' demographic data, histologic diagnoses including Gleason's grade and score, AJCC stage, treatment regimen instituted as well as outcomes, as indicated by biochemical recurrence (higher post-treatment PSA) and clinical progression (worsening post-treatment clinical status) were extracted and analyzed. Study was done after ethical clearance.

STATISTICAL ANALYSIS

Data obtained was analyzed using Statistical Package for Social Sciences (SPSS) version 20.0. Tests of correlation (Chi square statistics and Fisher's exact tests) at 95%

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confidence limit and p-value of ≤ 0.05 were conducted.

RESULTS

Sociodemographic Characteristics

Data was obtained from 111 male patients with histologically proven prostate cancer. The mean age was 66.7 ± 10.6 with age range of 40-100 years. Most patients (78, 70.2%) were within the 60-79 year age group (Figure 1).

Most cases (72, 64.8%) presented with Gleason grades 3 (38, 34.2%) or 4 (34, 30.6%), majority of subjects had Gleason scores of 6 (32, 28.8%) or 7 (20, 18%) (Table 1).

PSA Characteristics

Most patients (61, 55.0%) had PSA values >20ng/mL and among patients with PSA>20ng/mL, mean PSA was 62.3 ng/mL± 26.6 (22-145), with the commonest PSA group (33, 29.7%) being 40.0-79.9 (Table 2)

Variable	Frequency	Percentage
Tumor grade		
1	12	10.8
2	4	3.6
3	38	34.2
4	34	30.6
5	19	17.1
Missing	4	3.6
Total	111	100
Tumor score		
2	1	0.9
3	1	0.9
4	3	2.7
5	5	4.5
6	32	28.8
7	20	18.0
8	16	14.4
9	15	13.5
10	2	1.8
Missing	16	14.4
Total	111	100

Table-1: Gleason Grade and Score of Patients

General PSA values		
PSA group (ng/mL)	**Frequency**	**Percentage**
<4	7	6.3
4-10	14	12.6
11-20	19	17.1
>20	61	55.0
Missing	10	9.0
Total	111	100
PSA among patients with PSA>20		
<40	11	9.9
40.0-59.9	17	15.3
60.0-79.9	16	14.4
80.0-99.9	7	6.3
100.0-120	4	3.6
>120	1	0.9
Missing	55	49.5
Total	111	100

Table-2: PSA group characteristics

AJCC Stage	Frequency	Percentage
Stage 1	9	8.1
Stage 2A	13	11.7
Stage 2B	53	47.7
Stage 4	19	17.1
Missing	17	15.3
Total	111	100
Presence of Metastasis at time of diagnosis		
Metastasis detected	**Frequency**	**Percentage**
Yes	23	20.7
No	67	60.4
Missing	21	18.9
Total	111	100.0
Treatment type commenced		
Drug commenced	**Frequency**	**Percentage**
Antiandrogens only	56	50.5
Estrogens only	14	12.6
Combination therapy	18	16.2
GnRH agonists	8	7.2
Missing	15	13.5
Total	111	100.0

Table-3: AJCC stage, presence of metastasis at diagnosis and treatment commenced

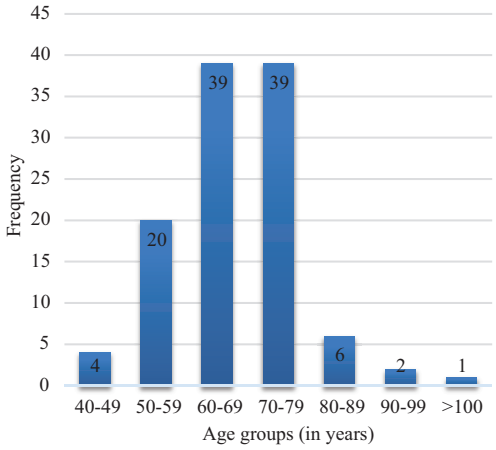

Figure-1: Age Distribution of Patients

Most subjects (72, 64.8%) had at least stage 2B and above, metastasis was found in one-fifth of patients (23, 20.7%) at the time of diagnosis and over half of the patients were placed on antiandrogens for treatment (Table 3)

A higher percentage of patients less than 60 years, patients with Gleason grade higher than 3, Gleason Score greater than 6 and AJCC stage greater than 2B presented with metastatic disease (Table 4).

Better treatment outcomes were recorded in patients older than 60 years of age, without metastasis at presentation and with AJCC Stage 2B or less (Table 5).

DISCUSSION

In the GLOBOCAN 2012 report, prostate cancer incidence and mortality rates in Africa were reported to be 23.2 and 17.0 per 100,000, respectively. This is relatively lower than those of some other world regions, but evidence shows that mortality rates from prostate cancer are generally higher in predominantly black African populations compared to

Relationship between Age and Metastasis at presentation (n=90)					
Age group	**Metastasis**			**Chi-square statistic**	**P-value**
	Present n (%)	**Absent n (%)**	**Total n (%)**		
<60	5 (33.3)	15 (66.7)	20 (100)	0.01	0.95
≥60	18 (25.7)	52 (74.3)	70 (100)		
Relationship between Gleason grade and Metastasis at presentation (n=86)					
Grade	**Metastasis**			**Chi-square statistic**	**P-value**
	Present n (%)	**Absent n (%)**	**Total n (%)**		
≤3	8 (18.2)	36 (81.8)	44 (100)	2.6	0.11
>3	14 (33.3)	28 (66.7)	42 (100)		
Relationship between Gleason score and Metastasis at presentation (n=76)					
Score	**Metastasis**			**Chi-square statistic**	**P-value**
	Present n (%)	**Absent n (%)**	**Total n (%)**		
≤6	6 (17.7)	28 (82.3)	34 (100)	3.1	0.08
>6	15 (35.7)	27 (64.3)	42 (100)		
Relationship between AJCC Stage and Metastasis at presentation (n=79)					
AJC stage	**Metastasis**			**Chi-square statistic**	**P-value**
	Present n (%)	**Absent n (%)**	**Total n (%)**		
≤2B	3 (5.2)	55 (94.8)	58 (100)	51.3	0.00
>2B	18 (85.7)	3 (14.3)	21 (100)		

Table-4: Correlation statistics with Metastasis at presentation

Relationship between Age and Treatment Outcome (n=73)								
Age group	**Post-treatment PSA**			**Test statistic**	**Post-treatment Clinical**			**Test statistic**
	Better	**Worse**	**Total**		**Better**	**Worse**	**Total**	
<60	15 (66.7)	5 (33.3)	20 (100)	X2=0.1	16 (80.0)	4 (20\.0)	20 (100)	Fisher's Exact
≥60	38 (71.7)	15 (28.3)	53 (100)	p=0.78	41 (77.4)	12 (22.6)	53 (100)	p=0.92
Relationship between Gleason grade and Treatment Outcome (n=71)								
Grade	**Post-treatment PSA**			**Test statistic**	**Post-treatment Clinical**			**Test statistic**
	Better	**Worse**	**Total**		**Better**	**Worse**	**Total**	
≤3	25 (69.4)	11 (30.6)	36(100)	X2=0.21	28 (77.8)	8 (22.2)	36 (100)	X2=0.00
>3	26 (74.3)	9 (25.7)	35 (100)	p=0.65	27 (77.1)	8 (22.9)	35 (100)	p=0.95
Relationship between Gleason score and Treatment Outcome (n=66)								
Score	**Post-treatment PSA**			**Test statistic**	**Post-treatment Clinical**			**Test statistic**
	Better	**Worse**	**Total**		**Better**	**Worse**	**Total**	
≤6	21 (67.7)	10(32.3)	31 (100)	X2=0.34	24 (77.4)	7 (22.6)	31 (100)	X2=0.01
>6	26 (74.3)	9 (25.7)	35 (100)	p=0.56	27 (77.1)	8 (22.9)	35 (100)	p=0.92
Relationship between Metastasis at Presentation and Treatment Outcome (n=60)								
Metastasis	**Post-treatment PSA**			**Test statistic**	**Post-treatment Clinical**			**Test statistic**
	Better	**Worse**	**Total**		**Better**	**Worse**	**Total**	
Detected	7 (58.3)	5 (41.7)	12 (100)	Fisher's Exact	7 (58.3)	5 (41.7)	12 (100)	Fisher's Exact
Not detected	40 (83.3)	8 (16.7)	48 (100)	p=0.06	41 (85.4)	7 (14.6)	48 (100)	p=0.04
Relationship between AJCC Stage and Treatment Outcome (n=67)								
AJCC Stage	**Post-treatment PSA**			**Test statistic**	**Post-treatment Clinical**			**Test statistic**
	Better	**Worse**	**Total**		**Better**	**Worse**	**Total**	
≤2B	45 (80.4)	11 (19.6)	56 (100)	Fisher's Exact	46 (82.1)	10 (17.9)	56 (100)	Fisher's Exact
>2B	7 (63.6)	4 (36.7)	11 (100)	p=0.22	7 (63.6)	4 (36.7)	11 (100)	p=0.11

Table-5: Treatment Outcome Statistics

other races.[14,15] Most patients in our study were found to have Gleason grades of 3 and above and tumor scores of 6 and above. In a study by Freedland et al, the blacks in his study had higher mean Gleason scores than their white counterparts (6.2 as against 5.9).[16] A similar finding was recorded by Sanchez Ortiz in Texas, USA.[17] Our results further prove the earlier reports that black patients present with more advanced disease. Gleason grades and scores are established prognostic markers in prostate cancer and higher values are synonymous with more aggressive disease. Our finding of higher Gleason values in a greater percentage of patients in our study group tallies with the earlier studies that blacks tend to have a more aggressive disease. Most patients had PSA values greater than 20ng/ml (55%) at presentation with the mean value being 62.3ng/ml amongst those with PSA greater than 20ng/ml. Previous studies have shown blacks to have higher PSA values that the whites but the values recorded in our study were significantly higher than the values in these studies.[16,18,19] In a study on patients with advanced-stage prostate cancer by Hoffman et al, 28.4%

of African Americans had PSA values greater than 20 ng/ml. Other racial groups had fewer patients with PSA greater than 20 ng/ml.[18], much fewer than what we recorded. Most patients had Stage IIB disease and above with over one-fifth of patients presenting with metastatic disease. Petrovich and colleagues had noted that about 50% of cases are diagnosed at a locally advanced stage, and about 30% have bone metastases at the time of diagnosis.[20] Results of our study further buttresses the results earlier obtained indicating that a significant number of patient in our environment and indeed of blacks present with advanced disease.[18,21] A very significant challenge with staging in this study was the absence of facilities for imaging. CT and MRI are commonly unavailable in our environment and when available are usually very expensive such that most patients cannot afford it. As at when these patients were seen neither CT nor MRI was available for staging of the patients, hence a number of patients could not be properly staged. Over thirty-three percent (33.3%) of the patients under 60 years presented with metastatic disease which was higher than the 27.5% in the patients above 60 years. Prostate cancer is considered a disease of elderly men (aged >65 years) and when diagnosed at age ≤55 years it is regarded as early-onset prostate cancer. This is generally a more aggressive disease associated with a higher cause-specific mortality than in men diagnosed at an older age. It is also found to have a strong genetic component.[22] Hence the finding that a significant number of patients in this age group had metastasis at presentation was not surprising.

The biochemical response (as measured by PSA)one year post treatment commencement was found to be better in 66.7% of the patients less than 60 years and in 71.7% of those 60 years and older. Better clinical outcome was recorded in 80% of those less than 60 years and in 77.4% of those 60 years and above. Conflicting results have been recorded by researchers in the past regarding the impact of age on the outcome of prostate cancer. Hamstra and colleagues found that prostate cancer was less aggressive in older men in their study and that they were more likely to die from other causes.[23] Conversely Bechis et al concluded in their own study that older patients were more likely to have high-risk prostate cancer at diagnosis and ultimately a more aggressive disease.[24] Our study showed no significant difference in the response to therapy based on age even though a significant proportion of the younger patients presented with more advanced disease.

Gleason score has been noted to be the strongest clinical predictor of prostate cancer progression by Gleason and colleagues.[25] Tumorswith Gleason grade 7 or higher are at increased risk of extra-prostatic extension, recurrence after initial therapy, and death from the disease.[26] However, no significant difference was found between the treatment outcomes in cases with Gleason grade values of 3 or less and above 3 or score values of 6 or less and above 6. The reason for this is not readily available but may be accounted for by the small sample size of 71 and 66 for Gleason grade and score respectively making the power of the study low.

Over 41% of the patients with metastasis at presentation had both worse biochemical (41.1%) and clinical (41.1%) outcome despite androgen deprivation therapy showing that metastasis at presentation is a poor prognostic factor. Over eighty percent(80.4%) of patients with AJCC stage 2B or less had better biochemical outcomes one year after commencement of androgen deprivation therapy while 63.6% of patients with stage >2B had better outcomes. Clinically, 82.1% had better outcomes among the Stage 2B or less group while 63.6% of those with Stages greater than 2B had better clinical outcomes. Extra-prostatic extension of prostate cancer has been noted to be a significant prognostic factor previously by Jeffrey et al[27] and this was evident in our study.

The major limitations highlighted by this study were:

1. Limited/ absent information on imaging studies on the patients. Majority of the patients did not have routine imaging investigations done. Using the AJCC staging, any grade higher than 2B could only be assigned based on imaging information except for cases of Stage 4 which were assigned to obviously metastatic cases. This is still a significant problem in many countries in black Africa.[28–30] Modern imaging equipment are frequently unavailable and where they are available are of prohibitive cost to patients making it difficult to properly manage patients and subsequently to carry out prognostication research. The need therefore exists for government and private organizations to have collaborations that can bring about the availability of these equipment.
2. The large number of unavailable data (34.2%) on outcomes (biochemical recurrence or clinical progression). This is due to the fact that a very large number of patients were lost to follow up.
3. A significant number of cases had incomplete data. This is a major challenge especially with retrospective studies mainly because of poor record keeping. There's a high dependence on paper records which makes it easy to lose data in transit. This could be a direct result of lack of preservation and conservation policy,[31,32] poor funding of ICT upgrades and absence of a policy on digitalization of data. This has greatly hampered the carrying out of quality research as data is not readily available and where available is frequently incomplete.

CONCLUSION

A significant number of our patients still present with advanced prostate cancer with resultant poor prognosis. Awareness about prostate cancer though increasing needs still to improve. Routine screening for prostate cancer should be adopted so that cases can be identified early and overall prognosis would be better.

Major challenges faced in carrying out these kinds of prognostication studies include limited ability to stage the disease due to limited imaging capacity, limited outcome data as a result of loss to follow-up as well as incomplete and lost data due to poor record keeping. Efforts at improving

access to imaging modalities and electronic medical records need to be intensified both by governmental and non-governmental organizations. There needs to be a shift from paper to electronic record keeping.

There is also a need to adopt a protocol for documenting prostate cancer cases as well as a need to adopt a deliberate policy on follow up in order not to lose too many patents to follow up. These will all have tremendous positive impact on improving the quality of research on prognostication studies in Black Africa.

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