Original Research

The Clinicopathologic Pattern of Prostatic Carcinoma in Lagos, Nigeria

M. Olatokunboh Odubanjo, MBBS;[1]* Adekunbiola AF. Banjo, MBBS;[1] Shonibare Ayoola, MBBS;[2] Fatimah B. Abdulkareem, MBBS;[1] Chidozie C. Anunobi, MBBS;[1] Afolabi A. Olayinka, MBBS[2]

[1] *College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria*
[2] *Vantage Medical Centre (VMC), Lagos, Nigeria*

This is a review of the clinicopathological pattern of prostatic carcinoma in Lagos, Nigeria. The mean age was 68.48 years. 20% of our patients were asymptomatic at presentation, significantly higher than values from most previous Nigerian studies, likely due to an established PSA screening program. This however did not appear to translate to better disease outcomes, likely because radical prostatectomy was not offered as a treatment option for early disease. 68.6% of symptomatic patients presented with lower urinary tract symptoms, and 4.4% had a family history of prostate cancer. The median PSA value at presentation was 58.90ng/ml. Clinical stages II and III disease were most common, 42.5 and 30% respectively. Gleason scores 6 and 8 were the most common (23.3 and 20% respectively). The clinical stage and the age showed the best correlation with disease progression evidenced by increased PSA 2 months after treatment (PSA progression) and metastasis during follow up. The Gleason score also showed good correlation with these parameters while the pre-treatment PSA showed poor correlation, possibly due to the high incidence of urogenital infections and prostatitis in this environment. The incidence of PSA progression and metastasis were 0.35 and 0.54 per patient year of follow up respectively.
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INTRODUCTION

Prostate cancer is now the sixth most commonly diagnosed cancer in the world.[1] The estimated number of new cases was 513,000 in the year 2000.[1] This represents 9.7% of cancers in men[1]. It is a less prominent cause of death from cancer, with 201,000 deaths.[1] The low fatality means that many men are alive following a diagnosis of prostate cancer, making this the most prevalent form of cancer in men.[1]

In Nigeria, prostate cancer has been shown to be the most common cancer in men.[2] According to the GLOBOCAN 2008 report of the International Agency for Research in Cancer (IARC), prostate cancer is the most important cause of morbidity and mortality among men in Nigeria.[3]

The objective of this study is to review the clinicopathologic pattern of prostatic carcinoma among Nigerians in Lagos, Nigeria with a view to identifying any factors which could contribute towards improving the management of our patients in the future.

METHODS

This is a retrospective review of cases of prostatic carcinoma diagnosed at the Lagos University Teaching Hospital (LUTH), Lagos. All the patients were managed at Vantage Medical Centre (VMC), Lagos, Nigeria between December 2003 and July 2010. Each patient with multiple biopsies was regarded as one case only with the details of the various biopsies being evaluated for the relevant areas of the study as appropriate, often depending on whether the indication for the biopsy was diagnosis or treatment.

Patients lacking records of specific clinical details are excluded from all statistical evaluations for which those details are required. For example, any patient with no documented date of first diagnosis or onset of disease is excluded from follow-up studies. Patients with inaccurate or incomplete data for a parameter are excluded from all statistical studies involving the parameter. For example, cases with Gleason score 2-4 on needle biopsy are excluded from all statistical analyses involving the Gleason score.

Needle Biopsy Protocol

Transrectal ultrasound (TRUS) guided prostate needle biopsy was performed in men with an abnormal DRE and or an elevated PSA (defined as PSA>4.0 ng/ml).[4]

The prostate was sampled with the A1820 Programmable Automatic Biopsy system, 18Gx20cm, Cardinal Health, USA

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*__Corresponding Author:__ College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria. (Email: todubanjo2002@yahoo.com)

under transrectal ultrasound guidance, using the Shimadzu (Shimadzu Corporation, Japan) SDU-350A Diagnostic ultrasound system, Australia.

The locations of these biopsies are shown in **Figure 1**.

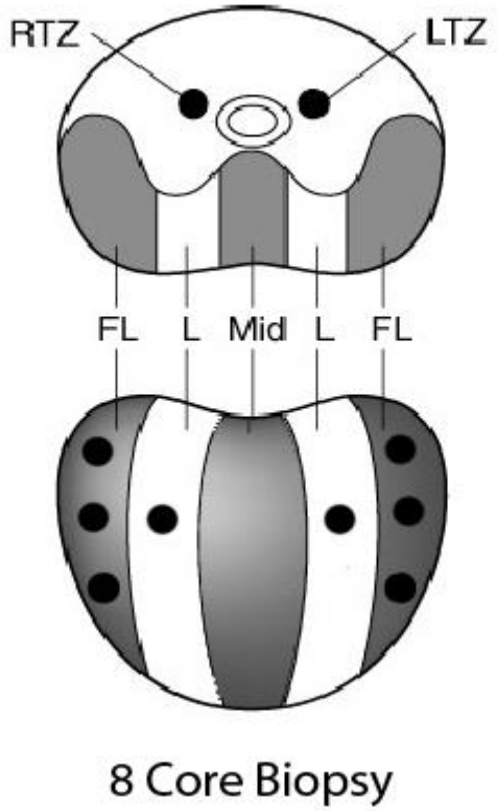

Figure 1. A picture illustrating the locations of the biopsies taken in these patients (FL-Far lateral region, L- Lateral region, Mid- Midline, RTZ- Right transitional zone, LTZ- Left transitional zone).

Processing of Prostatic Tissue
All specimens are fixed in 10% buffered formalin.

Gross examination of prostatic tissue obtained at needle biopsy: All biopsies from the left peripheral zone (3 biopsies), the right peripheral zone (3 biopsies) and the transitional zone (2 biopsies) are labeled and embedded separately. Three histological slides are prepared from each block, each with 4 serial sections cut at 3 micron thickness.[5]

Gross examination and tissue sampling of prostatic chips from TURP procedure: Specimens weighing 12 g or less are submitted entirely. For specimens weighing more than 12g, at least 12 of tissue, equivalent to 6-8 blocks each containing 1-2g of tissue, is submitted to include all grossly suspicious chips. An additional cassette is submitted for every 5g of tissue. The entire tissue is submitted if the microscopic examination of partially submitted chips revealed carcinoma in less than 5% of tissue.[5]

Gross examination and tissue sampling of prostatectomy specimens: The specimen is weighed and the surgical margins are inked. The specimen is serially sectioned at intervals of 3-5mm perpendicular to its posterior surface, to include any hard nodules.[5]

Microscopic examination: All histopathological slides were reviewed and graded/ scored by MOO and AAFB using the Gleason grading system.[1,6]

The Clinical Evaluation and Management of Patients
All the patients were managed by AS.

Clinical staging was done by the use of digital rectal examination (DRE). Patient were placed into stage grouping I-IV according to the cancer staging of the American Joint Committee on Cancer (AJCC) 6th Edition.[6] Needle biopsies were requested for diagnosis in all cases of suspected prostate cancer.

The patients were treated with bilateral orchitectomy, hormonal therapy and or external beamradiotherapy (EBRT). TURP was done to relieve bladder outlet obstruction. No patient was managed with active surveillance alone.

We studied three of the four established prognostic factors recommended by the World Health Organization (WHO) and College of American Pathologists (CAP) for routine use in providing information about disease progression and clinical outcomes in prostate cancer patients [6,8] viz. the clinical stage, the Gleason score, and the pretreatment PSA. The fourth prognostic factor, the surgical margin status could not be studied as none of the patients had treatment by radical prostatectomy. The age and the treatment given were also studied as possible prognostic factors.

Follow-up: The patients are seen at routine pre-scheduled follow-up visits every 2 months for the first year. Subsequently, they are seen every 3 months to 1 year depending on the patient's PSA values and clinical findings on DRE.

For the evaluation of patients for the presence of disease progression, the following markers are used: the presence of metastatic disease and PSA progression.

Metastatic disease was defined as clinical evidence (discovered during follow-up) of prostate cancer found in any organ adjacent to the prostate (apart from the seminal vesicles) on DRE or cancer in a distant organ discovered on X-rays, CT or MRI.[9]

PSA progression was defined as PSA levels 2 months after treatment higher than the value at presentation plus 3ng/ml. Our definition of PSA progression was based on the American Society for Therapeutic Radiology and Oncology (ASTRO)'s definitions of recurrent disease in prostate cancer.[10] The term recurrent disease was not appropriate for most of these patients as they were not treated with full curative intent.

Duration of follow up was defined as the time period between the onset of disease and the date of this study. The

onset of disease is the date of first diagnosis with prostate cancer, often with needle biopsy but also as an incidental finding in prostatic chips/ simple prostatectomy specimens for benign prostatic disease.

Data Analysis

The data obtained was analyzed using the SPSS statistical package version 18.0. P value < 0.05 was taken as significant.

RESULTS

Two hundred and thirty-two (232) patients had prostatic biopsies during the period of the study. One hundred and thirty-nine (139, 59.9%) of these patients were diagnosed with benign prostatic hyperplasia (BPH), 92 (39.7%) with cancer, 1 patient (0.4%) with acute and chronic prostatitis and 1 patient (0.4%) with atrophy. In this study, the 92 patients with prostate cancer were further evaluated. The mean age was 68.48 ± 9.893 years with peak occurrence in the 65-74 year age group.

A total of 68.6% of the patients presented with irritative and or obstructive lower urinary tract symptoms. 11.4% presented with hematuria, 2.9% with acute urinary retention, 4.3% with weight loss, 2.9% with weakness, and 1.4% each with abdominal pain and swelling, anorexia and marked pallor. 20% of the patients were asymptomatic with elevated PSA levels on routine checks. 21.4% of the asymptomatic patients had enlarged prostate gland on DRE. 4.4% of the patients with clinical documentation of information about family history of prostate cancer had a positive history while 95.6% had no family history of this disease.

The median value of PSA at presentation was 58.90ng/ml, range 1.0 to 15,500ng/ml. The median value for PSA two months after treatment was 3.9ng/ml, range 0.1 to 1520ng/ml. There was a statistically significant difference in PSA values at presentation and PSA values 2 months after treatment. The P value for the Wilcoxon Signed Ranks test was less than 0.0005. Most patients (42.5%) presented with Stage II disease. Only 10% presented with Stage I cancer. 30% and 17.5% of the patients presented with Stages III and Stage IV disease respectively.

The diagnosis was obtained from needle biopsies in 83 cases (90.2%), simple prostatectomy specimens in 2 cases (2.2%), and from prostatic chips obtained at TURP procedure in 7 cases (7.6%). Of the 83 patients who had needle biopsies, 62 of them had records of needle biopsies alone while twenty-one (21) patients had histological records of both needle biopsies and prostatic chips. 21.1% of the patients had Gleason scores 2-5, 23.3% had Gleason score 6, 18.9% had Gleason score 7 and 36.7% had Gleason scores 8-10.

Twenty-eight (28) patients were managed surgically. Nine (9) patients had bilateral orchitectomy while 21 patients had TURP. Of the 9 patients who had orchitectomy, 7 had orchitectomy alone while 2 had the procedure along with TURP. 48 patients (52.2% of 88 patients) had hormonal therapy. A total of 6 patients had EBRT. 2 patients had EBRT alone while 4 had EBRT along with TURP.

The clinical stage and the age showed the best correlation with the occurrence of PSA progression and metastasis during follow up. The Gleason score also showed good correlation with these parameters. The clinical stage showed good correlation with the leason score ($p < 0.0005$). The pre-treatment PSA values showed poor correlation with PSA progression or metastasis. PSA progression showed good correlation with the incidence of metastasis ($p = 0.001$).

Table 1. Results of logistic regression analyses.

Dependent variable	Covariate(s)	P value	Statistical significance (P<0.05)
Metastasis	PSA value at presentation, PSA value at 2 months, Gleason score, Clinical stage, Age and Treatment	0.342	Not significant
Metastasis	Gleason score, Clinical stage, Age, Treatment	0.021	Significant
Metastasis	Gleason score, Clinical stage, Age	0.019	Significant
Clinical stage	Gleason score	<0.0005	Significant
Metastasis	Gleason score and PSA value at presentation	0.009	Significant
Metastasis	Gleason score and PSA value at 2 months	0.110	Not significant
Metastasis	PSA progression	0.001	Significant
PSA progression	PSA value at presentation, PSA value at 2 months, Gleason score, Clinical stage, Age and Treatment	0.01	Significant
PSA progression	PSA value at presentation, PSA value at 2 months, Gleason score, Clinical stage, and Age	<0.0005	Significant
PSA progression	Gleason score and PSA value at presentation	0.25	Not significant
PSA progression	Gleason score and PSA value at 2 months	0.004	Significant

19 patients (33.3%) of the patients with complete follow up information showed clinical evidence of metastatic disease during follow-up. 7 patients (12.5%) of the patients had PSA progression after the first 2 months, and 5 patients (8.9%) had both PSA progression and metastasis.

The rate of development of metastasis was 0.54 per patient year of follow up while the incidence of PSA progression was 0.35 per patient year of follow-up. Median follow up period in this study was found to be 1.5 years, range of 1 month to 9 years.

DISCUSSION

Prostate cancer constituted 39.7% of all patients who had prostate biopsies sent to LUTH from VMC within the study period. Previous studies showed prostate cancer constituted 13.0%,[11] 14.8%,[12] and 22.4%[3] of all prostatic biopsies. The ratio of cancer to BPH in our study was 0.66, and in the previous studies cited above, 0.15 in 1984,[11] 0.17 in 2000,[12] and 0.29 in 2003.[3] These figures show a progressive increase in the incidence of prostate cancer over the years. In developed nations, a similar increase due to increasing life expectancy and a Western lifestyle has been described[1]. In Nigeria, the introduction of PSA screening and increasing awareness about prostate cancer is a likely reason.[14]

The mean age of patients in this study was found to be 68.48 ± 9.893 years. Several articles from Nigeria have shown a mean age ranging between 61.2 and 71.4 years.[3,11,13,14,15] In the United States, the median age at diagnosis is 67 years of age.[16] Most of our patients presented with lower urinary tract symptoms. This corroborates the findings from several previous studies from igeria.[11,14,15] Hematuria was fairly common (11.4%), as in some previous Nigerian studies.[11,14,15,17] In most of these previous studies, features of advanced or metastatic disease such as enlarged hard, craggy prostate, acute urinary retention, features of metastasis such as low back pain, paraparesis/ paraplegia, abdominal swelling were also found to be common.[12,14,15,18,19]

Our findings differ from those from previous studies in that acute urinary retention was much less common (2.9% as against 56 and 78% described by 2 previous studies),[11,14] less than half of the patients belonged to clinical stages III and IV(47.5% as against the value of 75% described by Jackson MA et al),[20] a relatively higher proportion of patients (20%) presenting with asymptomatic disease and discovered on routine checks (20% as against 4.4% in a previous study),[21] and the finding of a lower proportion of Gleason score 8-10 than in previous Nigerian studies. These features suggest a relatively earlier presentation in our patients. This is likely due to the established protocol for routine PSA screening of patients over 40 years for prostate cancer at this hospital.

In this study, the distribution of Gleason grade among prostate cancer patients show a proportion of patients with Gleason scores 8-10 that is significantly higher than that described by studies from the United States (36.7% versus <20%),[22] thus suggesting a high prevalence of aggressive disease as expected of a Black African population.[23] The study by Jackson MA et al[20] demonstrates comparable distribution by grade among black patients with prostate cancer in Ibadan, South-west Nigeria and in Washington DC, thus underscoring the greater significance of genetic factors over environmental factors in determining the aggressiveness of prostate cancer disease.

4.4% of the patients in this study had a family history of prostate cancer. From 5% to 10% of prostate cancer cases are believed to be due primarily to high-risk inherited genetic factors or prostate cancer susceptibility genes, family history is known to be a major risk factor for prostate cancer.[1]

The median PSA value at presentation was found to be quite high at 58.90ng/ml. Abbiyesuku et al[24] showed a median PSA value of 92ng/ml. Moul JW et al showed that pretreatment PSA values were higher in black men than in white men in the US.[25]

In our study, 3% of the patients with prostate cancer showed PSA values less than 4ng/ml at presentation. This finding corroborates those from some previous studies.[14,24] There is no clear consensus regarding the optimal PSA threshold for recommending a prostate biopsy to men of any racial or ethnic group. In the past, most doctors considered PSA levels of 4.0 ng/mL and lower as normal, and doctors would recommend a prostate biopsy in a man with PSA value above 4.0 ng/mL to find out if prostate cancer is present.[26] More recent studies have shown that some men with PSA levels below 4.0 ng/mL have prostate cancer and that many men with higher levels do not have prostate cancer. [26] Factors such as prostatitis, urinary tract infections, prostate biopsies and prostate surgery increase the PSA level while drugs including finasteride and dutasteride, which are used to treat nodular hyperplasia of the prostate decrease a man's PSA level.[26] In general, the higher a man's PSA level, the more likely it is that he has prostate cancer. A continuous increase in a man's PSA level over time may signify prostate cancer.[26]

In this study, hormonal therapy was the most common treatment modality. Bilateral orchitectomy has been the most common treatment option for Nigerian patients, likely because most of them present with advanced disease,[12,15,18,19,27] and medical castration incurs higher total costs than surgical castration. In many developed nations, orchitectomy is no longer often used.[28] A recent article from Nigeria also shows increasing use of medical castration.[16]

The overwhelming majority of patients in this study (90.2%, 83 out of 92) had diagnosis made on needle biopsy in keeping with VMC's management protocol of requesting needle biopsies for diagnosis.

All the cases with Gleason score 2-4 on needle biopsy were excluded from all studies involving the Gleason score including bivariate and multivariate analyses to prevent the introduction of bias due to possible inaccurate grading and scoring. It has been proposed that Gleason scores of 2–4 should not be assigned to adenocarcinoma on needle biopsy because it usually represents an undergrading of higher-grade carcinoma, it is not reproducibly diagnosed and it can adversely impact on patient care.[29]

In this study, the clinical stage showed good correlation with the Gleason score as it was first described by Gleason, Mellinger and The Veterans Administration Cooperative Urological Research Group (VACURG) in 1974,[30] and by several other studies since then.[4]

The clinical stage and the Gleason score were found to be good correlates for disease progression as evidenced by PSA progression and metastasis. This is as previously described

by Dr Gleason.[30] The pretreatment PSA showed poor correlation with disease progression in our patients possibly due to the high prevalence of urinary tract infections and prostatitis in this environment.

Median follow up period in this study was found to be 1.5 years. Several previous studies from Nigeria have described similar dismal prognosis.[12,14,15,18] In spite of a relatively high percentage of patients presenting with asymptomatic disease in this study, disease outcomes did not appear to differ significantly from those described by previous studies with median follow-up periods of 19.5 months[12] and 83.7 weeks.[15]

We suggest that this is likely due to the fact that radical prostatectomy was not offered as a treatment option for early stage disease.

CONCLUSION

The clinical stage and the Gleason score were found to be good prognostic factors in our patients. While the Gleason score is routinely used in most centers in Nigeria, we found that the clinical stage was not documented for the patients in any of the previous Nigerian studies that we reviewed.[11-13,14,15,32] The clinical stage is important in that it plays a crucial role in deciding the primary line of management. It is recommended that the clinical stage be routinely used in the management of patients with prostate cancer in Nigeria and other resource-limited settings, preferably in combination with the Gleason score and the pretreatment PSA to determine the risk of disease progression.[33]

In Nigeria, there continues to be difficulties with the paucity of early detection and treatment Programs.[18] We have shown that even though it is important for routine PSA screening to be made readily available, the benefits may not readily translate to better patient outcomes unless there is commensurate availability of adequate expertise and institutional support for radical prostatectomy.

CONFLICT OF INTEREST

None.

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