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THE RISK OF SPREAD OF PRIMARY PROSTATE CANCER IN PATIENTS WITH THE DISEASE IN PORT HARCOURT, NIGER DELTA REGION OF SOUTHERN NIGERIA.

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ABSTRACT

Introduction: Prostate cancer has a hospital incidence of 114/100,000 patients at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria. The aim of this study was to determine the prevalence of high, low and intermediate grades of the disease in patients managed at the hospital. **Material and Methods:** The study was cross-sectional and descriptive and carried out at UPTH using secondary data retrieved from case files and computerized databases of consecutive patients with prostate cancer treated at the hospital from 01/01/2017 to 31/12/2022. The modified Gleason's (Minnesota) and the Grade Group grading systems (John Hopkin's Hospital) were used. **Results:** Two hundred and four (204) consecutive patients treated during the study period were analyzed. Their mean age was 70.00 ± 2.73 years (50-101 years). The prevalence of poorly differentiated adenocarcinoma of the prostate among patients aged 50 to 64 years was 40% (26 of 65). Those aged 65 years and above were 139 (68.9%) and had prevalence of 43.17%) of poorly differentiated adenocarcinoma. Thirteen (20.86%) patients had moderately differentiated adenocarcinoma (Gleason's scores 3 + 4 = 7 and 4 + 3 = 7). Of the study population (n=204), 86 patients (42.16%) had poorly differentiated prostatic adenocarcinoma. The tumour in seventy-six patients (37.25%) were well-differentiated. **Conclusion**: Given the high prevalence of primary poorly differentiated adenocarcinoma of the prostate among these patients, irrespective of age groups of the patients, on the ordinal scale of risk stratification, risk of spread of the tumour in them should be high.

KEYWORDS: Adenocarcinoma of the Prostate, Tumour Grades, Prevalence, Port Harcourt, Nigeria.

INTRODUCTION

Prostate cancer is the most common malignancy in middle-aged and elderly men in Nigeria.[1] The hospital incidence of the disease at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria, is 114/ 100000 patients.[2] Not every patient who presents with histopathological diagnosis of the disease may need aggressive invasive treatment. Rather, a number of considerations are made before the commencement of treatment after its diagnosis. Some of these considerations include the grade of the tumor, age of the patient, performance status, fragility scores, life expectancy, patient's will, laboratory investigations, known complications of the untreated disease, or the side effects of the expected treatment modalities. In our patients' population, sometimes the desire to retain fecundity and erectile function can be very strongly expressed by some affected patients. We therefore exercise great caution in making clinical decisions on treatment once a diagnosis has been confirmed.

The tumor's grade is important as it enhances clinical decision-making on which tumor would most likely have high metastatic potential with a poor prognosis.[3] Currently, in UPTH over the years, we have had patients of all age groups above 50 years with the disease. Some of the patients who should probably have been excluded from invasive investigations and treatment, and who should most likely have benefited from active surveillance only had invasive investigations and treatment. All of such patients never had Gleason scoring. These were opposed to other patients who rapidly deteriorated from the time of the first noticeable symptom to the time of the patient's presentation for treatment. One of our strategies has been to individualize approaches to patients' treatment. The choice of therapy was based on clinical judgment on individual patients, histological diagnosis, Gleason scores, stage of the tumor, patient-centered needs and other objective considerations.

The aim of this study is to use internationally approved grading criteria to segregate the patients into possible groups with a view to improving our clinical judgments on the choice of reliable and effective treatment methods once the diagnosis has been made. We hope to also find some explanations for the clinical observation of relatively poor prognosis in some middle-aged and

younger middle-aged patients with primary prostate in our hospital.

MATERIALS AND METHODS

The study was a cross-sectional observational study of hospital records of consecutive patients who had treatment for histologically confirmed prostate cancer at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria within the 5-year-period from 01/01/2017 to 31/12/2022. The institution is a referral center for urological patients (including those with prostate cancer) from most parts of the Niger Delta States of Southern Nigeria. UPTH'S procedures for diagnosis of prostate cancer were followed for each patient. The procedures were as enumerated below.

Each patient who presented to the Urology Clinic of the hospital was evaluated for a history of prostate cancer, which included lower urinary tract symptoms, bone pain, history of familial or hereditary prostate cancer, and clinical examination noting unilateral or bilateral pitting lower limb edema. Digital rectal examination findings that suggested prostate malignancy included nodularity of the gland, absence of bulbocavernosus reflex, asymmetrical enlargement, hardness and nodularity of the gland, absence of the median sulcus, and fullness of the lateral sulci. Each patient had serum PSA assay, transrectal ultrasonography (TRUS) or transabdominal ultrasonography of the prostate, and abdominal ultrasonography. Confirmation of diagnosis was by histology of core needle (Tru-Cut) prostate biopsy. Few cases were diagnosed incidentally from histology of chips obtained from transurethral resection of the (TURP), or open prostatectomy specimens. Some patients had prostate biopsies incidentally on the finding of elevated serum prostate-specific antigen assay. Details of clinical and laboratory findings were entered into designated pathology request forms with the specimens presented in 10% formaldehyde and sent to the hospital's anatomical pathologists for confirmatory histopathological diagnosis with Gleason's scoring.

Staging investigations included an abdominopelvic CT scan, plain skeletal X-ray examinations of the pelvis, and lumbosacral spines, and plain chest X-ray examination. Magnetic resonance imaging was done in patients scheduled for radical prostatectomy to evaluate extra prostatic lymph node spread and in patients with suspected vertebral metastasis with spinal compression. Such patients often presented with back aches, paraparesis, or paraplegia.

A cross-sectional study of the records of all the patients was done. The Gleason's scores for all patients with prostate cancer were matched against the Grade Group classification[4,5] endorsed by the World Health Organization and the International Society of Urological Pathologists (ISUP), and presented in tables and prose form. The patients were grouped according to their ages, and the grades of prostate cancer detected in each of them by the pathologists, using the Grade Group grades and corresponding Gleason scores.

In line with recommendations of ISUP[6] tumors with Gleason scores of ≤ 6 (Grade Group 1) were taken as having slow growth, those with (3+4 = 7, Grade Group 2) were adjudged tumors with predominantly slow growth, but having some tumor tissues that might have grown moderately fast; those with Gleason score 4+3 = 7 (Grade Group 3) were considered to be tumors that predominantly could grow moderately fast with some slow-growing tumor tissues.[7] Tumors with Gleason scores 4+4 = 8 (Grade Group 4) were considered tumors that might grow moderately fast. Tumors with a Gleason score of 4+5 = 9 (Grade Group 5) were tumors with predominantly moderately fast-growing components, and vice versa for 5+4 = 9. Tumors with a Gleason score 5+5 were considered to be fast-growing tumors. Some of these tumors were described by our pathologists as forming no glands but had sheets of invasive cells.[7]

Consent was obtained from individual patients involved in this study during routine hospital investigations and treatment. Microsoft Word was used to organize data obtained into tables, and the Karl Pearson's Chi-square test was used to test for the significance of observations.

The grading Systems used: The Grade Group Grading System and the Gleason's Grades/Scores.

Two prostate cancer grading systems were used. **(i) The ISUP- approved modification of the original Gleason's Grading System and** (ii) The Grade Group System of grading prostate cancer: In 1974, Dr. Donald Gleason (Chief of Pathology, Veteran's Hospital, Minnesota, USA) and Millinger GT published a grading system in which prostate adenocarcinoma was scored based on its glandular histopathological architectural patterns.[8] This was said to have been based on a 5-year-study by the Veteran Affairs Cooperative Research Group (VACORG) 1959-1964.[8] This grading system is known as the Gleason's Grading System. In the original Gleason's System, prostate cancer, depending on the tumour grade, was assigned total scores of 2 to 10 and partly became the subject of a number of consensus conferences including conferences of the International Society of Urologic Pathologists ISUP]. One consensus recommendation of ISUP was the categorization all adenocarcino mas of the prostate with total Gleason's score of 6 or less as well differentiated.[9]

The Grade Group Grading System was developed by another research group from John Hopkins Hospital in 2013: In this system the tumor was categorized into 1 to 5 grades.[4] In our current study, a combination of the modified Gleason's grades (≤ 6,7, 8, 9, and 10), and the Grade Group systems, in line with the ISUP consensus recommendations.

RESULTS

Two hundred and four patients aged between 50 and 101 years were diagnosed with primary prostate cancer and had Gleason's scores for their tumors. Their mean age at diagnosis of prostate cancer was 70.00 ±2.73 years. The modal age group was 70 to 74 years (Table 1)

Levels of tumor differentiation in the patients

(i) Patients aged 50 to 64 years were 65 (31%) (Table 1) of the 204 patients. Twenty-six (40%) of them had poorly differentiated adenocarcinoma of the prostate with Gleason scores (GL 8 to10), Grade Group grades 4 and 5). (ii) Elderly prostate cancer patients (those aged 65years and above) were 139 (68.9% of 204). Of these, those with poorly differentiated adenocarcinoma of the prostate with Gleason total scores of 8 to 10 (Grade Group grades 4 and 5), were 60 (n = 139; 43.17%), while patients with moderately differentiated adenocarcinoma with Gleason's scores 3 + 4 = 7 and 4 + 3 = 7, Grade Group grades 2 and 3 respectively, were thirteen (20.86%). Of the study population (n=204), 86 patients (42.16%) had poorly differentiated prostatic adenocarcinoma. The same type of tumors in 76 patients (37.25%) were well-differentiated.

The patients' 5-year- interval age groups were tabulated. Group specific frequencies, cumulative frequencies, relative frequencies and cumulative relative frequencies were tabulated (Table 1).

Poorly differentiated high grade supposedly fast-growing adenocarcinoma of the prostate was found highly prevalent in the studied population of patients with prostate cancer in Port Harcourt. This finding was irrespective of ages of the patients.

Table 1: Age and frequency distribution of the patients with prostate cancer in Port Harcourt, Nigeria.

Age(Years)	Frequency	Cumulative Frequency	Relative Frequency (%)	Cumulative Relative Frequency (%)
50- 54	12	12	5.9	5.9
55 – 59	22	34	10.8	16.7
60 – 64	31	65	15.2	31.9
65 – 69	36	101	17.6	49.5
70 – 74	57	158	27.9	77.7
75 – 79	21	179	10.3	87.7
80 – 84	9	188	4.4	92.1
85 – 89	12	200	5.9	98.0
90 – 94	3	203	1.5	99.5
95 – 99	0	203	0.0	99.5
≥ 100	1	204	0.5	100.0

Age Range = 50 – 101 years; CF, cumulative frequency; RF, relative frequency; CRF, cumulative relative frequency.

The age groups of the patients were tabulated against the modified Gleason's grades and corresponding Grade Group grades (Table 2)

Table 2: Age and Grade Group grades with corresponding Gleason's scores/ grades of prostate cancer in UPTH, Port Harcourt, Nigeria.[4]

AGE/YEARS	GRADE GROUP 1 GLEASON ≤ 6	GRADE GROUP GRADES 2-3; GLEASON 3+4=7, 4+3=7	GRADE GROUP GRADE 4; GLEASON 4+4=8	GRADE GROUP GRADE 5; GLEASON 4+5=9, 5+4=9 and 5+5=10	TOTAL
45-49	0	0	0	0	0
50-54	8	3	1	0	12
55-59	6	3	8	5	22
60-64	12	7	5	7	31
65-69	16	6	5	9	36
70-74	21	13	9	14	57
75-79	5	4	7	5	21
80-84	2	2	1	4	9
85-89	5	2	3	2	12
90-94	1	1	1	0	3
95-99	0	0	0	0	0
≥100	0	1	0	0	1
TOTAL	76	42	40	46	204

The grade of primary prostate cancer in the patients were tabulated with levels of glandular differentiation (Table 3)

Table 3: Distribution of tumor grades, (Grade Group and Gleason's Grades), frequencies and percentages of patients' distribution, with degrees of cellular and glandular differentiation of prostate cancer in Port Harcourt.

GRADE GROUP GRADE	GLEASON'S GRADE	FREQUENCY	PERCENTAGE (%)
1	≤ 6	76	37.3
2	3+4=7	21	10.3
3	4+3=7	21	10.3
4	4+4=8	40	19.6
5	4+5=9 5+4=9 5+5=10	21 17 8 (46)	10.3 8.3 3.9
Total		204	100.0
LEVEL OF CELLULAR/GLANDULAR DIFFERENTIATION OF THE PROSTATE GLAND	GRADE GROUP GRADE/ (GLEASON'S GRADE)	FREQUENCY	PERCENTAGE (%)
Well differentiated	Grade 1/ (≤ 6)	76	37.3
Moderately differentiated	Grades 2 and 3 /(3+4=7; 4+3=7)	42	20.6
Poorly differentiated	Grades 4 and 5/ (4+4=8; 4+5=9; 5+5=10)	86	22.5
Total		204	100.0

DISCUSSION

Finding the most effective and reliable methods of predicting the future malignant behaviour of newly diagnosed adenocarcinoma of the prostate shall continue to engage the attention of urologists, uropathologists and other concerned clinicians. This is because, as observed in different studies in the literature, majority of latent prostate cancer diagnosed at autopsy had remained innocuous or indolent until the affected patients died of other causes at old age.[10,11] Some of those with only slow-growing or indolent primary prostate cancers would need less aggressive treatments, watchful waiting or active surveillance.

Different protocols for the identification of such indolent subclinical prostate cancers have been developed for clinical application. They have different levels of sensitivities, specificities, positive and negative predictive values. These include the Indolent Prostate Cancer Nomogram by Kattan MW et al;[12] the use of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer; and the use of repeated prostate biopsy after an initial biopsy and histological diagnosis by Patel MI, and DeConcini DT et al.[13] All prostate cancers seen in this study were adenocarcinomas of different variants. This made the application of the two grading systems possible.

A relative increase in the number of patients with prostate cancer from the 5th to the 8th decades of life in this region has been observed in a previous study.[2] In this study, the modal age group with the disease was 70 to 74 years, constituting 23.5% of the study population (n = 204). A sharp decline in the number of prostate cancer patients after the age of 79 years in the study population suggests a sharp decline in patients' survival after this age. It is possible that this sharp decline in survival resulted mainly from this malignancy, its comorbidities or that it was related to a low life expectancy in this population.

Another valuable observation in this study is the relatively high prevalence of high-grade (Grades 4 and 5) prostate cancer in the study population. There were 65 middle-aged patients and 139 (68.14%; n= 204) elderly ones (aged 65 years and above). There was a high prevalence of poorly differentiated moderately fast-growing and fast-growing prostate cancers among the study population. These ranged from 40.0% among middle-aged patients (50 to 64 years old) to 43% of 139 elderly patients. This high prevalence of fast-growing adenocarcinoma of the prostate among the study population was perhaps what gave the impression that adenocarcinoma among the younger population (aged 50 to 64 years) had predominately poor prognosis. Another 40% (26 of 65patients) of middle-aged patients had well differentiated supposedly slow-growing tumors. The clinical significance of this finding is that the prevalence of slow-growing primary prostate cancer (well differentiated) was equally high (40%) among the middle-aged population in this study. This finding suggests that an almost equal mix of fast-growing and slow-growing prostate cancer occurred among the study population. This high prevalence is irrespective of the age of the patients as the same proportion of poorly differentiated prostate cancer was found between middle-aged and elderly patients. Gleason's scoring also revealed the existence of adenocarcinomas of different growth characteristics in the individual patients (for instance a patient with 5+3 = 8 or that of 4+3 = 7).

The result of this study suggests that there is a high risk of metastasis in all age groups with prostate adenocarcinoma in Port Harcourt, a referral centre for prostate cancer in the Niger Delta States of Southern Nigeria. Because of the high prevalence of poorly

differentiated, fast-growing adenocarcinoma within the middle-aged and elderly populations, the choice of active surveillance only as a method of management of patients in the study population should not be based on considerations of age of the patient alone. It suggests a mandatory grading of each tumour after confirmation of diagnosis.

CONCLUSION AND RECOMMENDATIONS

Poorly differentiated (fast-growing) variants of adenocarcinoma of the prostate were highly prevalent in these patients seen with prostate cancer in Port Harcourt. Irrespective of their age groups, well-differentiated grade 1 (modified Gleason's grade $\leq$ 6) were also almost equally prevalent in all the age groups. In most of the patients foci of low-grade and high-grade adenocarcinoma of the prostate co-existed in each individual patient, an occurrence that might account for the variable behaviour of prostate cancer in this population. Given the high prevalence of primary poorly differentiated adenocarcinoma of the prostate among these patients, irrespective of age groups of the patients, on an ordinal scale of risk stratification, risk of spread of the tumour in them should be high. Despite the fallibilities of the grading systems, routine grading is recommended for every patient considered well enough for histopathological diagnosis and treatment intervention. The tumour grade along with other parameters may be considered for active surveillance or watchful waiting as a mode of management of patients with prostate cancer. However, a comparative study of survival of patients with high-grade (Grades 4 and 5) versus low-grade adenocarcinoma of the prostate (grade 1) is recommended for this population.

Compliance with ethical standards

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Disclosure of conflict of interest: There is no conflict of interest

Statement of informed consent: Informed consent was obtained from all individual participants included in this study. No direct or indirect human and animal experimentations were involved in the study.

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