ORIGINAL ARTICLE

Co-morbid Medical Conditions and Medical Complications of Prostate Cancer in Southern Nigeria

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SUMMARY

Background: Prostate cancer often co-exists with other diseases. It accounts for 11% of all cancers in Nigerian men, and it is the commonest cause of mortality due to cancer in elderly males in Nigeria..

Objective: To present co-morbid medical conditions and medical complications of prostate cancer in patients with the disease in Southern Nigeria.

Patients and methods: The study was carried out prospectively (2002 to2003) at University of Port Harcourt Teaching Hospital (UPTH), and Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi- both in Southern Nigeria. Using common proforma, patients who presented to the urology units of the two teaching hospitals were evaluated clinically and with relevant investigations for prostate cancer and other diseases. Those with histologically confirmed prostate cancer were included in this study.

Data was also collected retrospectively by using the same proforma to obtain information from case files of 37 patients diagnosed with prostate cancer at UPTH. Data from the two institutions were collated and analysed.

Results: Of 189 cases analysed, 73.4% had significant medical co-morbid diseases/complications. These included anaemia (69.8%), urinary tract infection (56.1%), chronic renal failure (33.9%), hypertension (41.8%), diabetes mellitus (9.5%), paraplegia (9.5%), congestive cardiac failure (9.0%) and cerebrovascular disease (5.3%).

Conclusion / Recommendations: These patients had high disease burden. Improved health education and well coordinated interdisciplinary team work are suggested in managing this malignancy.

KEY WORDS:
Prostate Cancer; Medical Complications; Nigeria

INTRODUCTION

Prostate cancer is a public health problem among elderly males world wide. It accounts for 11% of all cancers in Nigerian men, and it is the commonest cause of mortality due to cancer in elderly male Nigerians [1]. Patients with the disease often present late [2] with co-morbid conditions and complications that sometimes may obscure the clinical manifestations of the tumour, probably enhance its pathogenesis, delay diagnosis, increase the cost and complexity of treatment, and probably worsen its prognosis. These conditions usually necessitate interdisciplinary approaches to patients' evaluation and treatment. At present it is not to our knowledge that any common or unified protocol exists in Nigeria or the West African Sub-Region for the management of this malignancy. We wish to present co-morbid medical diseases and medical complications of prostate cancer in Southern Nigerians. We also wish to determine the disease burden represented by these co-morbid medical diseases and complications in these patients' populations.

MATERIALS AND METHODS

The study was carried out prospectively and retrospectively in two centres in Southern Nigeria – Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, and University of Port Harcourt Teaching Hospital, Port Harcourt (2002-2003). Ethics Committee approval of the study was obtained in each institution. Consent was also obtained from each patient evaluated prospectively. A common proforma was prepared and used to evaluate each patient that presented to the urology units of the two hospitals with features of prostatic diseases. Information sought in the proforma included patients' identification numbers, personal data (age, place of origin), symptoms and signs of diseases, results of investigations including full blood count (FBC), serum prostate- specific antigen (PSA), serum electrolyte, urea and creatinine assay (E/U/Cr), liver function test (LFT), fasting blood sugar (FBS), urinalysis, urine microscopy culture and sensitivity, abdominal ultrasonography, ultrasonography of the prostate, and plain radiological examination of the chest, femur, pelvis / axial skeleton. Intravenous urography and plain radiographic skull examinations were done with specific indications. Each patient had digitally guided transrectal Tru- Cut needle® (Cardinal Health) biopsy of the prostate. In five cases incidental histology reports of adenocarcinoma of the prostate were made on prostatic tissue obtained from open prostatectomy for supposedly benign prostatic enlargement. In few patients, the perineal route was used. Anaesthesia for needle biopsy was achieved by the pudendal block [3]. Fifteen patients still had significant pain, needed adjunctive analgesia, and were given intravenous pentazocine 30mg start dose only. Ciprofloxacin

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500mg 12-hourly, metronidazole 400mg 8-hourly and 1g paracetamol 8-hourly for 5 days post biopsy were given to each patient. Each specimen was preserved in 10% formaldehyde and sent with request for histology to the Anatomical Pathologists in each hospital. Each tumour was staged with the Whitmore – Jewett criteria for staging of prostate cancer [4]. Following diagnosis all the patients had androgen deprivation therapy (ADT) except few that never gave consent for treatment during the study period. Patients who presented with castration resistant prostate cancer had second line hormonal treatment using low doses of diethyl stilboestrol (1mg tid) in combination with prednisolone (5).

The retrospective aspect of the study was carried out in UPTH by collating hospital numbers and initials of the patients treated for prostate cancer (outside the approved period of the prospective arm of the study) and recorded in surgical and medical out patient clinics. The case files were traced out from the Medical Records Department. These comprised patients that were missed during the approved period of the study as consecutive patients with prostatic diseases were evaluated for prostate cancer. The common proforma was used to obtain information on each patient from his case file. Data obtained were pooled together with the results of the prospective study, analysed using simple descriptive statistics and organised into tables and a pie chart, using Microsoft Excel(2003 version).

RESULTS

Two hundred and two patients were evaluated. One hundred and eighty nine patients with histologically confirmed prostate cancer were studied. Patients who had no histological diagnosis were excluded. One hundred and fifty –two (152) patients were studied prospectively and thirty –six (36) retrospectively. One hundred and twenty –seven patients(67.2%) were aged 60 to 79 years.

Fifty patients (26.6%) had no significant co- morbid diseases / complications, while 139 (73.4%) had. Lower urinary tract symptoms were the most common features at presentation. These included frequency of micturition (62.4%), poor stream of urine (59.2%), urgency (46.6%) hesitancy, nocturia, and feeling of incomplete voiding (31.7%). Bone pain and erectile dysfunction occurred most frequently of non – urinary tract symptoms (Table I).

The most common anatomical changes of the prostrate gland observed on digital rectal examination (DRE) were enlargement of the gland in 171 patients (90.5%) and nodularity in 89 (47.1%). Paraplegia and para paresis frequently complicated the disease from spinal metastases (Table III).

The disease was staged in 172 of 189 patients. Seventeen of them could not afford certain staging investigations, e.g. prostate and pelvic ultrasonography and plain skeletal x-ray examination. These could not be staged accurately. However they satisfied minimum criteria for inclusion in the study which included adequate clinical and histological diagnosis of prostate cancer. The stages of the disease and serum PSA levels are presented in Table V. The least value of serum PSA was 0.5ng/ml and the highest 250ng/ml. Of 152 studied prospectively 85 (55.9%) had urethral catheter in-situ, or had had some form of urethral instrumentation or suprapubic cystostomy at the time of this study. All patients in the series had androgen deprivation therapy.

DISCUSSION

This report highlights the common medical co-morbid diseases and medical complications of prostate cancer in southern parts of Nigeria. Detailed patients' follow –up to determine disease-specific effects of the co-morbid conditions on tumour progression, health related quality of life (HRQoL) and patients' survival will require another study.

The study revealed a high incidence of anaemia (69.8%), urinary tract infection (UTI)(56.1%), chronic renal failure (33.9%) and hypertension (41.8%). These findings are similar to those of Badmus *et al* [6] who observed that prostate cancer in Southwestern Nigeria was associated with anaemia in 45.5%, haematuria 40.7%, renal failure 39.2%, inability to walk 22.2%, and low back pain 50.3% of cases. Our findings

Table I: Symptoms of diseases in Patients with Adenocarcinoma of the Prostrate Urinary tract symptoms

	Number	%
Frequent micturition	118	62.4
Poor Stream of urine	112	59.2
Urgency	88	46.6
Hesitancy	79	41.8
Nocturia	64	33.9
Feeling of incomplete voiding	60	31.7
Straining at micturition	5	23.8
Urge Incontinence	43	22.8
Gross Haematuria	41	21.7
Dysuria	40	21.2
Intermittency	40	21.2
Acute retention of urine	39	20.6
Chronic retention of urine	14	7.4

Table II: Non- Urinary Tract Symptoms associated with Prostate Cancer observed in the Patients

	Number	%
Bone Pain	60	31.7
Poor penile erection	55	29.1
Inability to walk	42	22.2
Gross Haematuria	41	21.7
Poor appetite	37	19.6
Lethargy	36	19.0
Weight loss	33	17.4
Numbness in lower limbs	30	15.9
Constipation	29	15.3
Headaches	24	12.7
Tremors	20	10.9
Fever	17	9.0
Chest Pain	13	6.9
Dizziness	12	6.3
Pruritus	3	1.6
Partial deafness	3	1.6
Generalized body pain	2	1.0

Table III: Findings on Physical examination of Patients with Prostate Cancer in Southern Nigeria.

Digital Rectal Examination Findings		
Sign	**Number**	**%**
Enlarged prostate	171	90.5
Nodular Prostate	89	47.1
Hard prostate	87	46.0
Firm prostate	82	43.4
Laxed anal sphincter	44	23.3
Asymmetrical enlargement of the prostate	39	20.6
Obliterated median Sulcus	32	16.9
Haemorrhoids	11	5.8
Tender prostate	4	2.1
Other findings		
Pallor	95	50.3
Pedal oedema	28	14.8
Paraplegia	18	9.5
Paraparesis	14	7.4
Ascites	12	6.3
Osteoporosis	10	5.2
Pathological fractures	5	2.6
Gallop rhythm	3	1.6
Rectal Bleeding	2	1.1
Jaundice	2	1.1
Rectal prolapse	1	0.5

Table IV: Complications/medical Co-morbid Conditions in Patients with Adenocarcinoma of the Prostate in Southern Nigeria

Disease	Number	%
Anaemia	132	69.8
Urinary tract infection	106	56.1
Hypertension	79	41.8
Chronic renal failure	64	33.9
Diabetes mellitus	18	9.5
Paraplegia	18	9.5
Congestive cardiac failure	17	9.0
Cerebrovascular disease	10	5.3
Parkinsonism	5	2.6
Dilated Cardiomyopathy	2	1.0
Allergic dermatitis	2	1.0
Liver cirrhosis	2	1.0
Schizophrenia	1	0.5
Hepatorenal syndrome	1	0.5
Bronchopneumonia	1	0.5

Table V: Stages of Tumours and Serum PSA levels in Patients with Prostate Cancer in Southern Nigeria.

Stage:	Serum PSA (ng/ml)						
	0-4	**5-10**	**11-20**	**21-50**	**51-100**	**101 and above**	**Total (%)**
A	3	2	5	1			11 (6.4)
B		3	17	7			27 (13.7)
C		1	11	34	17		63 (36.6)
D			4	15	28	24	71 (43.3)
Total	3	6	37	57	45	24	172(100.0)

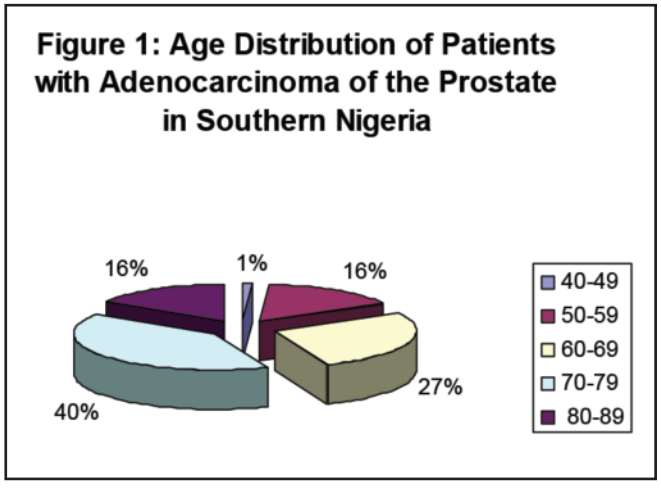

Fig. 1

parallel the advanced tumour stages (stages C and D) observed at presentation in 77.9% of the patients. This high disease burden resulted partly from late presentation of the patients for treatment and is in agreement with findings of others elsewhere in Nigeria [7, 8]. Anaemia in the patients was probably multifactorial. These factors include poor nutrition, haematuria which occurred in 21.7% of the patients, bone marrow invasion by the tumour, and chronic renal failure observed in 33.9% of them (Table III). Androgen deprivation therapy (ADT) which was the mode of treatment in almost all the patients has also been associated with anaemia as a complication [9].

Majority of the patients had obstruction of the bladder outlet (BOO) due to prostatic enlargement. This was evidenced by predominance of voiding lower urinary tract symptoms (LUTS), poor stream of urine (59.2%), hesitancy (41.8%), feeling of incomplete voiding (31.7%), intermittency (21.2%), straining at micturition (23.8%), acute retention of urine, and chronic retention of urine (Table I).The high incidence of BOO observed in this patents agrees with findings of others in different Nigerian hospitals [10,11,12]. We would probably have improved this observation if we had facilities for urodynamic investigations. We would then have inter-alia been able to measure detrusor pressure and determine likelihood and severity of obstruction in each case. Complications of obstruction include of urinary tract infections (56.1%) and nephropathy (33.9%) . Another factor that increased the rate of UTI among the patients was that 55.9% of 152 studied prospectively had some form of instrumentation of the urinary tract or the other. Majority of those catheterised in the two centres had prolonged catheterization either per urethram or via suprapubic cystostomy to relieve obstruction of the lower urinary tract. Such catheters were usually

changed monthly. Indwelling catheters with their retention devices in the urinary bladder provide surfaces for the formation of biofilms [13]. These are structured communities of pathogens and their extra cellular polysaccharide products [14], as opposed to their plank tonic co-pathogens which exist freely in urine surrounding the catheter [15]. Pathogenic bacteria (especially Pseudomonas aeruginosa) that inhabit the biofilm have been known to posses certain characteristics that confer on them far more antibiotic resistance than their planktonic forms. These include the physico-chemical nature of the extracellular polysaccharide they secrete, "their slow growth and stress response [16], as well as gene expression and development of biofilm- specific resistant phenotypes [17]". These may partly explain the observations of Banadio *et al* [18] that, especially in male patients, prolonged in-dwelling catheters were associated with emergence of multi-drug resistant pathogens. UTI will continue to be a very significant problem with the current method of prolonged catheterization as observed in this study.

Hypertension constitutes 28.2% of all medical admissions in UPTH [19] and was observed to have an incidence of 16% among male residents of the University Village in the area [20]. It was the most common cardiovascular co-morbid condition in these patients, occurring in 41.8% of them. Congestive cardiac failure and cerebrovascular diseases were frequent (Table IV). Other conditions such as myocardial infarction and cardiomyopathies were rare. Although these diseases are known to have high incidence in geriatric populations [21], some of the cases probably arose as complications of the pathological process, investigations and treatment of prostate cancer. As a source of cardiovascular complications in prostate cancer patients, androgen deprivation therapy (ADT) is important. ADT is the mainstay of current treatment of advanced prostate cancer. It may also be an appropriate mode of treatment for some patients with localized or recurrent prostate cancer. In this study, almost all the patients except those who had active surveillance alone, or who had not given consent for treatment at the time of assessment had ADT. This was in the form of bilateral total or subcapsular orchidectomy alone, bilateral orchidectomy with anti-androgen (total androgen blockage), or leuteinising hormone- releasing hormone (LHRH) agonist with anti-androgens. Selected patients who presented with castration refractory or resistant prostate cancer had second line endocrine therapy. Although these patients were not followed up for treatment- specific complications, ADT has been widely reported as causing cardiovascular and other complications [22,23,24]. The use of estrogens alone or in combination with nitrogen mustard in the treatment of prostate cancer has been associated with ischaemic heart disease, venous thrombo-embolism, cardiac decompensation and cerebral depression [25]. Leuteinising hormone- releasing hormone (LHRH) agonists e.g. goserelin are used for ADT for advanced prostate cancer. Only few patients in this study could afford these drugs because of their high cost and scarcity. Although GnRH agonists have been associated with increased risk of cardiovascular morbidity when used for prostate cancer ADT [26], others observed that they do not seem to increase cardiovascular mortality in men with locally advanced prostate cancer [27]. However, the severity of the induced cardiovascular disease may be an important factor in its effects on HRQoL and post treatment recovery of function. In the radical management of early prostate cancer, severe induced cardiovascular diseases have been associated with decreased pre-treatment HRQoL and more prolonged post-treatment recovery of physical and sexual functions [28].

The crude and standardized prevalence rates for males with diabetes mellitus in Port Harcourt were observed by Nnyenwe *et al* [29] as 7.7% and 7.9% respectively. The finding of 9.5% diabetics suggests a high incidence of the disease in our prostate cancer patients. This seems to suggest that the reported [30] protective effects of the diabetic genotype against prostate cancer may not be true of these patients. However, certain observations in other populations are salient. A notable genetic finding in diabetic prostate cancer patients is the observation in a German study [31]" that fathers of patients suffering from type 2 diabetes mellitus were diagnosed less frequently with prostate cancer compared with non- diabetic controls". Also separate studies in Germany and Japan [32, 33] reported decreased risk of prostate cancer and lower prostate-specific antigen in diabetic men. The cause of the seemingly protective effect of diabetes mellitus against prostate cancer does not seem established. Baradaran *et al* [34] found that sex hormones (e.g. testosterone) were not involved. Effectiveness of the treatment of diabetes mellitus appears important in the progression of prostate cancer, as the glycaemic control, assayed by HbA1c level, has been reported to be a "useful pre-operative predictor of aggressive tumour profile among diabetics with localized prostate cancer [35]". However a different study [36] could not establish such a causal relationship between diabetes mellitus and prostate cancer adverse pathological features. Some of the cases of diabetes encountered in the patients might have been primarily caused by ADT. Large *et al* [37] observed that among patients with prostate cancer," those initiating androgen deprivation therapy were more likely to develop diabetes mellitus within 1 year of commencement of therapy."

Some less frequent observations in these patients included ascites which was seen in 12 (6.3%) of them (Table III). This was detected in most of the patients with cardiac failure, and in one patient resulted from liver cirrhosis. Rectal bleeding due to malignant prostatic invasion of the rectal wall was not observed in this series. However, bleeding per rectum occurred in two patients with haemorrhoids. Malignant axial skeletal invasion contributed to the causes of chronic back pain and caused paraparesis, pathological fractures and paraplegia (Table III).

Serum PSA studies were done in different laboratories in each of the two study centres and cities. Some of the serum PSA values are higher than expected for the corresponding stages of the tumours (Table V), especially between stages B and C, and C and D. Probable reasons for these were observer errors, differences in methods of serum PSA assay and some associated undetected inflammatory conditions of the prostate which caused increased serum PSA levels.

The high disease burden observed in this study, that 73.4% of the patients had either significant medical complications of prostate cancer and / or medical co-morbid diseases, justifies alternative approaches to management of this malignancy in this sub- region.

CONCLUSION

Some of the co-morbid diseases were actually complications of the pathological process, evaluation and treatment of prostate cancer. There was a high disease burden in these patients, characterized by high incidence of obstruction of the lower urinary tract. This was frequently complicated by urinary tract infections, chronic renal failure, acute and chronic retention of urine and cardiovascular morbidity. It appears the problems of a well planned screening programme for cancer of the prostate may be less in effect on the individual patient and our society (and may be more easily improved by periodic auditing and improved facilities and capacity) than those due to the high disease burden observed in this study. These observations necessitate increased health education aimed at increasing the awareness of the population on problems of prostate cancer in our communities. We also recommend better coordinated interdisciplinary team work in the management of this malignancy.

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