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PROSTATIC CANCER AFTER PROSTATECTOMY FOR BENIGN PROSTATIC HYPERPLASIA IN NIGERIA
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ABSTRACT

Objectives: **To establish the prevalence of 'prostatic cancer after a previous prostatectomy for benign prostatic hyperplasia (BPH)' and to find out if there are any differences in clinical presentation, histological characteristics and response to treatment, between this type of cancer of prostate and that of prostatic cancer in patients with intact prostate.**
Design: **A prospective study carried out between January 1989 and December 1998.**
Setting: **University of Nigeria Teaching Hospital, Enugu and JAMA Urological Clinic in Enugu, Nigeria .**
Subjects: **All patients presenting with histologically diagnosed carcinoma of the prostate during the study period.**
Interventions: **Transperineal, transurethral and open prostatic biopsies. Hormonal manipulations, transurethral prostatic resections, and ureteroneocystostomies.**
Main outcome measures: **Clinical presentation, histological characteristics of the tumour, and patient survival.**
Results: **Eight hundred and forty seven new cases of cancer of prostate were seen during the study period and 39 of them had had prostatectomy for histologically diagnosed BPH in the past (tissues were cut by step sectioning technique), giving a prevalence rate of 4.6%. Ages of these 39 patients ranged from 64 to 89 years (mean 71.6 years), while that for the rest of carcinoma of prostate ranged from 56 to 87 (mean 70.4 years). Time interval between prostatectomy for BPH and presentation with prostatic cancer ranged from one to 10 years in 36 patients (mean 6.6 years) while the remaining three patients presented after 15, 20 and 22 years respectively. Histology in all the 847 patients showed adenocarcinoma. When the two groups were compared, there were no statistically significant differences in clinical presentation, histological grading, type of treatment and final outcome.**
Conclusion: **Prostatic carcinoma after prostatectomy for BPH is not uncommon. It should be managed in the same line as those with cancer in intact prostate.**

INTRODUCTION

The prostate gland is a major accessory sex gland in the male that is prone to hyperplasia and neoplasia in ageing men. It is separated by the urethra into ventral fibromuscular and dorsal glandular portions(1,2). The glandular portion is further divided into four zones - the peripheral zone, the central zone, the transition zone and the periurethral gland zone(1,2). There is a general acceptance that carcinoma originates from the outer part of the prostate while benign prostatic hyperplasia (BPH) is usually found in the inner part of the gland(3). Prostatectomy for BPH therefore does not confer immunity against subsequent development of prostatic cancer because, in the process of enucleating the adenoma, a substantial but variable prostatic tissue including the peripheral zone generally regarded as the carcinomatous zone, is left behind. The first case of prostatic cancer after prostatectomy for BPH was described in 1929 and many more cases have since been described by other workers(4-6). Low grade carcinomas arising from the prostatic transition zone have also been described(7).

The epidemiology of prostate cancer is complex, with few established risk factors(8-10). Worldwide, there has been a dramatic increase in detection of prostatic cancer since the introduction of prostate specific antigen (PSA) test in the 1980's(11). The incidence in China is less than 2 per 100,000 male population(12). In the United States of America, the age adjusted rates in 1992 for black and white men were 249 and 182 per 100,000 men respectively(12). In Nigeria, a recent study showed the hospital incidence to be 127 per 100,000 men(13), while a startling incidence of 304 per 100,000 men was recorded in Jamaica, the highest rate in the world(12).

The present study reviews the mode of presentation, histological characteristics and treatment of prostatic cancer occurring after prostatectomy for histologically diagnosed BPH in comparison with prostatic cancer in patients with intact prostates, in Enugu.

MATERIALS AND METHODS

Between January 1989 and December 1998, all new cases of cancer of the prostate that presented to two busy health establishments in Enugu metropolis - University of Nigeria Teaching Hospital and JAMA Urological Clinic, were studied. The diagnosis of carcinoma of prostate was reached after history, physical examination including digital rectal examination (DRE), relevant investigations including serum electrolytes, urea and creatinine, serum acid phosphatase, skeletal survey, trans-abdominal ultrasonography and prostatic biopsy (transperineal or transurethral, and open biopsies in those whose bladders were explored incidentally). All the cases of carcinoma of the prostate after previous prostatectomy for BPH had their original slides reviewed by our pathologists before being classified as such. When the original slides of the cases of carcinoma of prostate after prostatectomy were reviewed, those in two patients revealed suspicious areas of prostatic cancer and these were promptly excluded from this category. Out of all the 847 patients with clinical prostate cancer, 21(2.5%) presented with incidental cancer. Serum prostate specific antigen (PSA) and transrectal ultrasonography (TRUS) were not done as these facilities were not available at the time of study. All the patients were started on treatment and reviewed monthly for as long as possible. From this total number of carcinoma of prostate, those who had had prostatectomy for histologically diagnosed BPH in the past, were identified and their features compared with the rest of the prostate cancers with intact prostate. The variables collected and compared were age, clinical presentation, tumour stage and grade, treatment methods and outcome. Also noted was the interval between prostatectomy for BPH and presentation with cancer of the prostate. Tumour staging was by modified Whitmore method(14) and the grading system was according to Mostofi(15). In the unclassified group, the histological differentiation was not stated. Chi-square analysis of the variables in the two groups was done by Computer using the Epi Info Version 5 Software.

RESULTS

During the study period, 847 new cases of histologically diagnosed carcinoma of the prostate were encountered. Out of these, 39 patients had had prostatectomy for histologically diagnosed BPH in the past. This gives a prevalence rate of 4.6% for this type of prostatic cancer. The ages of these 39 men ranged from 64 to 86 years (mean 71.6 years) while that for the rest of carcinoma of prostate with intact prostate was from 56 to 87 years (mean 70.4 years).

Table 1 shows the clinical presentation compared in the two groups of patients. Raised erythrocyte sedimentation rate (ESR) was present in all the patients. Metastatic symptoms and signs included lower back pains, paraplegia, haemoptysis, palpably enlarged abdominal and supraclavicular lymph nodes, visible metastases to skull and chest wall. One hundred and two patients first presented with symptoms and signs of renal failure as a result of obstructive nephropathy. In 31 patients, the clinical diagnosis was suspected on routine examination by physicians for general ill health. Statistical analysis of the clinical features at presentation showed no significant difference in the two groups of prostatic cancer patients (Chi-square = 13.1 , DF = 8, P value = 0.09).

Table 1

Clinical presentation

Presentation	Post-prostatectomy carcinoma Number (%)	Carcinoma in intact prostate Number (%)	Total No. (%)
Raised ESR	39 (100.0)	808 (100.0)	847 (100.0)
Abnormal digital rectal examination	32 (82.1)	756 (93.6)	788 (93.0)
Irritative symptoms	34 (87.2)	714 (88.4)	748 (88.3)
Weight loss	35 (89.7)	687 (85.0)	722 (85.2)
Dysuria	19 (48.7)	489 (60.5)	508 (60.0)
Haematuria	28 (71.8)	457 (56.6)	485 (57.3)
Metastatic signs and symptoms	16 (41.0)	391 (48.4)	407 (98.1)
Chronic constipation	16 (41.0)	343 (42.5)	359 (42.4)
Urinary retention	17 (43.6)	278 (34.4)	295 (34.8)
Renal impairment	6 (15.4)	96 (11.9)	102 (12.0)
Incidental finding	5 (12.8)	26 (3.2)	31 (3.7)

Chi square=13.71, DF=8, p value=0.09

Table 2 shows the interval between prostatectomy for BPH and presentation of carcinoma of prostate in 39 patients. Thirty six patients (92.3%) presented within 10 years of the prostatectomy with a mean of 6.6 years. Among these, ten showed mild anaplasia, eleven moderate anaplasia and five marked anaplasia, while in ten, the histological differentiation was not classified.

Table 2

Interval between prostatectomy for BPH and presentation with prostatic cancer

Interval (years)	No. of patients	%
1-2	2	5.1
3-4	3	7.7
5-6	10	25.6
7-8	10	25.6
9-10	11	28.2
>10 (15, 20 and 22 years respectively)	3	7.7

The remaining three patients presented at 15, 20 and 22 years respectively. Table 3 shows the clinical stage of the tumour at presentation in all the patients. Three patients who had had prostatectomy in the past for BPH, presented with enlarged prostates after 8, 10 and 15 years respectively. Digital rectal examination and available investigations pointed to the benign nature of the recurrent growths and these shelled out very well at open prostatectomy. However, histology showed foci of carcinoma. Generally, patients with cancer of the prostate presented more with late stage disease. When the stage at presentation in the two groups were compared statistically (Chi-square = 6.48, DF = 3 and P value = 0.09), there was no significant difference. Similarly Table 4 shows the histological grading in the two groups, and when compared (Chi-square = 5.4, DF = 3 and P value = 0.11), there was no significant difference. In 122 patients, the histological differentiation was not stated (unclassified).

Table 3

Clinical stage at presentation (Whitmore)

Stage	Carcinoma after prostatectomy (n=39) Number (%)	Carcinoma in intact prostate (n=808) Number (%)
A	3 (7.7)	18 (2.2)
B	2 (5.1)	76 (9.4)
C	14 (35.9)	228 (28.2)
D	20 (51.3)	486 (60.1)

Chi square = 6.48, DF = 3, P value = 0.09

Table 4

Histological grading of tumours (Mostofi)

Histological grade	Carcinoma after prostatectomy Number (%)	Carcinoma in intact prostate Number (%)
Grade I (mild anaplasia)	10 (25.6)	282 (34.9)
Grade II (moderate anaplasia)	12 (30.8)	203 (25.1)
Grade III (marked anaplasia)	7 (17.9)	211 (26.1)
Unclassified	10 (25.6)	112 (13.9)

Chi square = 5.94, DF = 3, P value = 0.11

Table 5 shows the mode of treatment in the two groups of patients. Hormonal manipulation was the sole mode of treatment in 643 patients (75.9%). In the remaining 204 patients (24.1%), in addition to hormonal manipulation, other modes of treatment were employed. Hormonal manipulations included bilateral orchidectomy and drugs like stilbestrol, cyproterone acetate, flutamide, bicalutamide and leutinising hormone releasing hormone analogues, depending on what the patient could afford. Ureteroneocystostomy was added when the patient presented with obstructive uropathy secondary to obstruction of the lower end of the ureters by the tumour.

Table 5

Type of treatment

Type of treatment	Carcinoma after prostatectomy Number (%)	Carcinoma in intact prostate Number (%)	Total No. (%)
Hormonal manipulation alone	24 (61.5)	619 (76.6)	643 (75.9)
Hormonal manipulation + TURP	10 (25.6)	146 (18.1)	156 (18.4)
Hormonal manipulation + Uretero-neocystostomy	3 (7.7)	34 (4.2)	37 (4.4)
Hormonal manipulation + TURP + uretero-neocystostomy	2 (5.1)	9 (1.1)	11 (1.3)
Total	39	808	847

Chi square = 7.92, DF = 3, P value = 0.05 (borderline)

Generally, most patients were followed up for one year, thereafter, follow up was very irregular. In the 39 patients with cancer of prostate after prostatectomy for BPH, 28 were alive at the end of one year, eight were reported dead while three were lost to follow up. In the 808 patients with cancer in the intact prostate, 416 were alive at the end of one year, 98 were reported dead while 294 were lost to follow up.

DISCUSSION

We have presented 847 new cases of cancer of prostate whom we saw over a period of ten years. Out of these, 39 patients have previously had prostatectomy for histologically diagnosed BPH. This gives a prevalence rate of this type of cancer of the prostate (cancer of prostate after prostatectomy for BPH) to be 4.6% which compares with a figure of five per cent in a similar study by Schwartz *et al*(5). It was not possible to deduce from this study the impact, if any, prostatectomy for BPH had on the risk for subsequent development of prostatic cancer. This would entail follow up of the same number of age-matched control with histologically proven BPH for the same period and determining the incidence of prostatic cancer in the two groups. Two previous studies on this gave conflicting results(16). However, during our ten-year study period, a total of 1419 prostatectomies were done for histologically diagnosed BPH. If it is assumed that approximately this number is done every ten years, a rough incidence of 2.7% of occurrence of cancer of prostate after prostatectomy for BPH would be deduced from this study, which compares with 2.0% of Schwartz *et al*(5) and 0.4 -8.7% of Armenian *et al*(l7).

We are aware that lack of thoroughness in the examination of the enucleated prostatic specimen after the original prostatectomy for BPH, could lead to a missed cancer of the prostate at the time of the original surgery. This error was minimised by the review of the original slides by our pathologists before inclusion.

The mean age at presentation in the patients with cancer of the prostate after a previous prostatectomy for BPH was similar to that for patients with intact prostate - 71.6 years and 70.4 years respectively. Also, the clinical presentation was not different in the two groups. The patients who presented solely with waist pains had received various treatments for arthritis at some peripheral hospitals without improvement before presenting to us. This pattern of presentation was also observed by Osegbe(13) in a study on prostate cancers in Nigerians.

The earliest time of presentation of cancer of prostate after prostatectomy for BPH was 16 months while the longest interval was 22 years. Thirty six patients presented within ten years of prostatectomy with a mean interval of 6.6 years while only three patients presented after an interval of more than ten years. Schwartz *et al*(5) noted two patterns on examination of the interval between prostatectomy for BPH and diagnosis of prostatic cancer. They noted that ten patients (50%) had cancer diagnosed within four years and another 10 patients (50%) had prostatic cancer diagnosed between seven and 28 years

after prostatectomy for BPH. It is assumed that these cancerous lesions arose from the peripheral zone since the adenoma had been enucleated. Previous studies on small prostate cancers concluded that non-hypertrophied senile tissue and sclerotic atrophic glands outside the expanding nodules of hypertrophy are sites of origin of the carcinoma(3). The different time intervals of presentation after prostatectomy for BPH could be explained by Eschenbach trilogy(18). This postulates that: (a) the tumour can remain indolent throughout the patient's lifetime and never progress to clinically significant disease; (b) that the tumour grows slowly and remains confined within the prostate for an ample time to allow for detection and; (c) that *ab nitio,* the tumour is virulent and invasive in biological behaviour, thus manifesting early. All the poorly differentiated tumours in this study were in stages C and D. However, there was no relationship between the histological grading of the tumour and the interval between the time of prostatectomy and presentation with cancer, thus emphasising the diverse nature in malignant expression of prostatic cancer. This was also noted by Schwartz *et al*(5).

When the patients with cancer of prostate after previous prostatectomy were compared with the other patients with carcinoma in the intact prostate, with regards to the stage at presentation, it was observed that most patients (87.2% and 88.3% respectively) presented late with stages C and D disease. A similar late presentation of carcinoma of prostate in Nigerians was observed by Osegbe(13) who noted that 86.4% of cases presented late. However, this contrasted with a figure of 40 - 50% in Europe and 20% in USA reported by Newling(19). This is no doubt due to increased health awareness and better diagnostic facilities in these developed countries.

The grade of the tumour at presentation in patients who had had prostatectomy for BPH was similar to those who had intact prostate. The poorly differentiated tumours were in stages C and D as noted above. Fowler *et al*(20) noted that locally advanced prostate cancers are often poorly differentiated with about 50% associated with regional lymph node metastasis. This same pattern also featured in African American males who presented clinically with higher prostate specific antigen levels, tumours of greater stage, grade and volume, early in the disease(21).

All the patients were subjected to hormonal manipulations. This stems from the work of Huggins and Hodges(22,23) emphasising the hormone dependence of prostatic cancer. All the patients benefitted initially from the therapy. The regression in the tumour experienced by all the patients is attributable to androgen deprivation. Civantos *et al*(24) noted some architectural pattern changes in the prostate as a result of androgen deprivation which include decrease in size and density of neoplastic glands associated with increased stroma between the dispersed small glands. Another pattern noted by the same workers included branching clefts lined by a few scattered tumour cells with pyknotic nuclei and degenerated tumour cells with foamy vacuolated cytoplasm. None of these patterns was confirmed in our patients since no repeated prostatic biopsy was done after the commencement of treatment.

Long term follow up was difficult in most of our patients. In the majority of cases, follow up was very irregular after one year and even in the first year, a good number of patients were lost to follow up. This same pattern had earlier been observed and the probable reasons outlined, in a previous study on bladder tumours in Enugu, Nigeria(25).

In conclusion, prostatic cancer after prostatectomy for histologically diagnosed BPH is not uncommon. The pattern of presentation is the same as in those who have not had an earlier prostatectomy. Patients who present with micturition problems or backache after prostatectomy for BPH should be fully re-evaluated. Primary hormonal manipulation is a reasonably safe and rewarding treatment option in the elderly with this type of cancer who may have a significant comorbid disease that may require therapeutic intervention.

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