

Prostate cancer in Port Harcourt, Nigeria: features and outcome

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ABSTRACT

Background: To present the clinical features and outcome of management of patients with prostate cancer in Port Harcourt, Nigeria.

Methods: A retrospective study of patients with prostate cancer managed in 14 years at the University of Port Harcourt Teaching Hospital.

Results: Of 154,594 men above 40 years old who attended the hospital, 177 were treated for prostate cancer, giving a hospital incidence of 114/100,000. Of these, the records of 47 had sufficient data to be included for analysis. Record keeping was poor. The ages ranged from 45 to 88 years with an average of 71.6 years. Forty-three patients (91.5%) presented late with features of advanced disease such as anaemia, spinal cord compression and urinary retention. The diagnosis was made from tissue biopsies, x-rays and biochemical results with clinical findings. The treatment was bilateral subcapsular orchidectomy with or without diethylstilbestrol. The response to treatment in most patients was satisfactory initially but relapse was common and fatal.

Conclusions: Record keeping requires urgent attention. Prostate cancer screening should be adopted in line with trends in industrialised countries. Mortality in our patients was mainly from direct complications of prostate cancer.

Keywords: Prostate cancer, Features, Port Harcourt, Nigeria.

Introduction

Prostate cancer has a high incidence among elderly black males, so much so that it has been declared a public health

epidemic in black American men.^{1,2} In spite of the high level of morbidity and mortality associated with this disease, and the considerable interest among practitioners, the aetiology and natural

history remain enigmatic.³ In the past, several authors reported a low incidence of prostate cancer in Africa including Nigeria.⁴⁻⁷ Recently, a few reports from the southern part of Nigeria have shown a high and rising incidence of the disease.^{8,9} The incidence and mortality in prostate cancer depend on ethnic, racial and national factors.¹⁰⁻¹² Nigeria is the most populous community of black people in the world. Data on prostate cancer in Africans is scanty as can be confirmed from a Medline search. There is no prostate cancer screening policy in Nigeria. Therefore the patients tend to present with symptoms of complications of the disease. Reports on the management of prostate cancer in different localities in Africa will help to build up an information base on the clinical characteristics of this disease. Port Harcourt is a fast growing city in the Niger Delta Area of Nigeria. We present a retrospective report of our experience in the management of prostate cancer in the University of Port Harcourt Teaching Hospital.

Materials and Methods

The case records of patients diagnosed as and treated for prostate cancer in the University of Port Harcourt Teaching Hospital were retrieved from the outpatient, in-patient and operation theatre registers from January 1985 to December 1998. Data on hospital attendance within this period were obtained from the attendance registers and records in the Medical Records Department of the hospital. These included total attendance in the hospital, total number and ages of all males who

attended and the total number of patients treated for prostate cancer.

Data extracted from the case records included the age of the patient, presenting symptoms and signs including findings at digital rectal examination (DRE), investigations such as haemoglobin concentration and erythrocyte sedimentation rates (ESR), total and prostatic serum acid phosphatase, radiology, methods of biopsy and histology reports, treatment modalities and the outcome of treatment. Two patients had their prostate specific antigen (PSA) levels measured abroad as facilities for this investigation are unavailable in Port Harcourt.

Criteria for the analysis of case records included satisfactory evidence of diagnosis, availability of records of relevant clinical evaluation, investigations, treatment and its outcome. Patients with prostates suspected to have cancer and who in addition, had any of anaemia, bone pains, weight loss, bladder outflow obstruction and neurological abnormalities, were considered to have advanced disease.

Results

Presentation

The total number of males aged 40 years and above treated in the hospitals within the period was 154,594. One hundred and seventy-seven (177) patients were treated for prostate cancer, giving a hospital incidence for prostate cancer of 114/100,000 among males aged 40 years and above. However, only 47 case records of patients had sufficient data for analysis and these form the basis of this report. The patients' ages ranged between

45 and 88 years with an average of 71.6 years (Table 1). Thirty-six patients (76.6%) were aged between 61 and 80 years.

Forty-three of the 47 patients (91.5%) presented at first visit with symptoms attributable to prostate cancer and/or its metastases (Table 2). In 4 patients (8.5%) the diagnosis of prostate cancer was incidental from routine histology of specimens from prostatectomy for benign prostatic hyperplasia (BPH).

The commonest symptoms were lower urinary tract symptoms (LUTS) including dysuria, retention, frequency and poor stream. The commonest sign was 'hard nodular prostate' on digital rectal examination. The findings did not routinely indicate whether the tumour was organ-confined, locally advanced or invaded bony structures. Other signs and symptoms are shown in Table 2.

Anaemia was found in 21 (44.7%) patients whose haemoglobin concentration was less than 10 gm/dl before treatment. It was above 10 gm/dl in 19 patients (40.4%) and there were no records in 7 patients (14.9%). The ESR was markedly raised (above 51 mm in the 1st hour Westergreen) in 22 patients (46.8%). In 10 patients (21.3%), it was above 100 mm. In 6 patients (12.8%), it ranged between 21 and 50 mm and in 4 patients (8.5%); it was less than 20 mm. There were no records of the ESR in 15 patients (31.9%). Twenty-four patients (51%) had normal levels of serum acid phosphatase in spite of their advanced disease. Of these, 10 (41.6%) had histologically proven prostate cancer.

Radiological investigations were recorded in 21 patients (44.7%). Of these 21 patients, 13 (61.9%) had metastases to bones. Six of these (46.2%) had osteoblastic changes, 3 (23.1%) had

osteolytic metastases and 4 had no description of structural changes in the bones involved. Lumbosacral vertebrae were the most commonly involved bones in 9 (69.2%). Other bones included the cervical vertebrae 1 (7.6%), multiple areas of sclerotic changes in all bones 1 (7.6%) and diffuse sclerotic changes with lytic defects all over the pelvic bones 1 (7.6%).

Diagnosis

The diagnosis was made in each case with a combination of findings from clinical examination, including DRE, biochemical investigations, such as acid phosphatase and PSA (in 2 patients) and radiological findings (Table 3). Hardness and/or nodularity of the prostate gland were highly suspicious of prostate cancer. Confirmation of diagnosis was done by tissue histology in only 27 patients (Table 4). In one of these, the diagnosis was made from the histology report on cervical lymph nodes.

Treatment and outcome

Treatment was supportive and palliative in all cases. Hormonal manipulation with diethylstilbestrol or surgical ablation - bilateral subcapsular orchidectomy (BSO) formed the basis of palliative treatment (Table 5).

Thirty-four patients (72.3%) had marked improvement in clinical state within 7 - 60 days of hormonal therapy but some were subsequently lost to follow-up. One patient who presented with paraplegia walked after BSO, but two years later, he relapsed with recurrent paraplegia and died in the hospital. Another patient with quadriplegia fully recovered all movements following BSO and remains well after four years on diethylstilbestrol. Two patients developed

paraplegia after BSO and while on diethylstilbestrol. They died within two weeks after relapse. Twenty-nine patients (64.4%) who showed remarkable initial response to treatment relapsed. The longest survivor after diagnosis lived for 6 years. Eight patients (17.0%) had records of mortality: 2 within 3 weeks of treatment on admission and 6 died within 2 years of treatment. Follow up of patients through hospital visits and verbal communications with relations indicated increasing mortality from prostate cancer. The documentation of deaths outside the

hospital was poor.

Table 1: Age distribution of patients with prostate cancer

Age (Years)	No. (%)
41 - 50	1 (2)
51 - 60	9 (19)
61 - 70	17 (36)
71 - 80	19 (40)
81 - 90	1 (2)
Total	47(100)

Table 2. Presenting features in patients with prostate cancer

Symptoms	No. (%)
1. Difficulty in passing urine	23 (48.8)
2. Joint/bone pains + backache	17 (36.2)
3. Haematuria	17 (36.2)
4. Frequent micturition	14 (29.8)
5. Retention of urine (acute/chronic)	15 (31.9)
6. Poor urinary stream	14 (29.8)
7. Weight loss	10 (21.3)
8. Bleeding per rectum	6 (12.8)
9. Fever	5 (10.6)
10. Abdominal mass	4 (8.5)
11. Constipation/inability to pass stool	3 (6.4)
12. Headaches	3 (6.4)
13. Lower abdominal pain	2 (4.3)
14. Diarrhoea	1 (2.1)
Signs	
15. Hard nodular prostate	19 (40.4)
16. Hypertension	5 (10.6)
17. Paraparesis	2 (4.3)
18. Paraplegia	2 (4.3)
19. Facial palsy	1 (2.1)
20. Atrophic testes	1 (2.1)
21. Scalp nodules	1 (2.1)
22. Cervical lymphadenopathy	1 (2.1)
23. Faecal incontinence	1 (2.1)
24. Hydronephrosis	1 (2.1)

effective treatment for relapse after medical or surgical castration.^{18,47,48}

Recurrence after a successful endocrine treatment connotes escape of prostate cancer from endocrine control and is associated with a poor prognosis.⁴⁹ This was confirmed in this study.

Conclusions and Recommendations

It used to be said that patients with prostate cancer die with the disease rather than from it^{50,51}. From this study, even with the limited availability of records, a sizeable proportion of the patients died from the direct complications of prostate cancer. Dawan and his associates in Nigeria reported that 0.7% of their patients with BPH compared with 26% of those with prostate cancer died within 6 months of diagnosis and treatment.³⁷ These suggest that many patients with prostate cancer die, not only with it, but also from it.

Epidemiological and prospective clinical studies on prostate cancer are needed in Nigeria. Notwithstanding the apparently poor economic situation in the country, we advocate for public health education, a national prostate cancer screening programme, an active national cancer registry and improved facilities for diagnosis and treatment of the disease. Efficient recording, storage and retrieval of patients' hospital data are urgently desired.

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References

1. Pienta KJ, Demers R, Hoff M, Kau TY, Montie JE, Severson RK. Effect of age and race on the survival of men with prostate cancer in the metropolitan Detroit tricounty area, 1973 to 1987. *Urology* 1995; 45:93-101.
2. Boring CC, Squires TS, Heath CW Jr. Cancer statistics for African Americans. *CA Cancer J Clin* 1992; 42:7-17.
3. Severson RK, Grove JS, Nomura AMY, Stemmermann GN. Body mass and prostatic cancer: a prospective study. *BMJ* 1988; 297:713-715.
4. Wynder EL, Mabuchi K, Whitmore WF Jr. Epidemiology of cancer of Prostate. *Cancer* 1971; 28:344-360.
5. Ahluwalia BS, Jackson MA, Jones GW, Williams AO, Rao MS, Rajguru S. Blood hormone profiles in prostate cancer patients in high-risk and low-risk population. *Cancer* 1981; 48:2267-2273.
6. Levine RL, Wilchinsky M. Adenocarcinoma of the prostate: a comparison of the disease in blacks versus whites. *J Urol* 1979; 121:761-762.
7. Jackson MA, Ahluwalia BS, Herson J et al. Characterization of prostate carcinoma among blacks: a continuation report. *Cancer Treat Rep* 1977; 61:167-172.
8. Osegbe DN. Prostate cancer in Nigerians: facts and nonfacts. *J Urol* 1997; 157:1340-1343.
9. Ogunbiyi JO, Shittu OB. Increased

19 of the above patients (40.4%), the prostate was described as hard and nodular. These figures suggest that hardness and nodularity, very often relied upon as clinical signs of malignancy, are not constant findings as has been noted previously.³⁴ They however, would serve to increase the index of suspicion. As the DRE reports did not routinely describe whether the tumour was organ-confined or otherwise, the T stage of the cases could not be determined. In spite of the hopes of Osegbe,⁸ PSA estimation is not yet generally available in Nigeria either as a screening or as a diagnostic tool. We still employ acid phosphatase estimations in our centre because we lack the resources for PSA estimation and TRUS biopsy. The diagnosis of prostate cancer is anchored on tissue histology. Twenty patients (42.6%) did not have a biopsy probably because they could not afford it. The histology of prostate cancer in this series was adenocarcinoma only. Other histological types including non-epithelial tumours such as leiomyosarcomas and rhabdomyosarcomas³⁵ were not seen. The diagnosis in 10 out of 47 (21.3%) of these was based on classical radiological appearances of bone deposits, as has been done before.³⁶

Factors contributory to late presentation in our environment include absence of routine screening programs including PSA estimation, inadequate diagnostic facilities such as TRUS biopsy technique, abject poverty and lack of health education. A previous report from Nigeria attributed late presentation to the assumption by patients that lower urinary tract symptoms are part of the normal ageing process.³⁷

Early diagnosis of localized prostatic cancer is expected to improve cure rates where facilities for cure are available.

However, there is as yet no standard therapy for advanced prostate cancer.^{38,39,40} Total androgen deprivation by bilateral subcapsular orchidectomy supplemented occasionally with oral diethylstilbestrol was the treatment in the above patients, who invariably presented with advanced prostate cancer. Early hormonal treatment for advanced disease is expected to reduce the occurrence of serious complications like spinal cord compression but these complications may still occur in spite of treatment⁴¹ as observed in this series. The cost of anti-androgen drugs such as bicalutamide, flutamide and goserelin is prohibitive in the underdeveloped world economic environment. This probably accounts for why they were not used. However, the advantage of these drugs over conventional medical or surgical castration is doubtful.^{42,43} The statement that there has been no new basic or innovative concepts in the treatment of prostate cancer since the description of retropubic radical prostatectomy in 1945⁴⁴ remains true. There is usually a good initial response to hormonal manipulation in advanced prostate cancer^{17,18} as shown in some of our patients with spinal cord compression. Unfortunately, such responses are often temporary, with relapse occurring within two years followed by death in a few months⁴⁵. The reasons advanced to explain this behaviour of prostate cancer include the heterogeneous composition of clones of prostate cancer cells in one individual.⁴⁶ Pulsed hormonal treatment by intermittent androgen suppression (IAS) at all stages of the disease has been advocated in order to take advantage of this biological situation and provide prolonged symptom-free intervals in patients.⁴⁷ There is usually no further

Discussion

The prevalence of prostate cancer among black men is emphasised by data indicating that the prostate cancer risk among United States black men is twice that of their white counterparts, 4 times that of Europeans and 20 times that of native Japanese.^{8,10,13} Although the high incidence in the US blacks has been reported in Nigerians,^{8,9} valid conclusions from this present study are hindered by the poor record keeping noted. This is underscored by the finding in this study that only 47 out of 177 patients with prostate cancer had sufficient records to be analysed. Furthermore, histological confirmation was obtained in only 60% of the patients. Several case notes could not be retrieved from the Medical Records Department. These handicaps form part of the relevant lessons from the study.

The hospital incidence of 114/100,000 in this series is high. The earlier reported low incidence of prostate cancer in Africans in Africa^{4,5,7} is now believed to have resulted from under-reporting or lack of awareness of the disease.⁸ The finding of a prostate cancer locus on chromosome 1 supports the importance of race as an aetiological factor in prostate cancer.¹⁴ But there is as yet no evidence that this chromosome finding predominates in blacks. While the black race is a risk factor in prostate cancer^{15,16} it is probable that the increasing incidence in Nigeria is partly due to worsening environmental pollution associated with increasing industrialization and urbanization. This is worthy of research. Androgens have been associated by 'exclusion' as the disease does not develop in eunuchs castrated before puberty.¹ In spite of a significant

response of prostate cancer to androgen ablation as in this series and others,^{17,18} the role of hormones may be merely permissive rather than causative.¹⁹

Prostate cancer is the most common malignant tumour in men over the age of 65 years.¹ Thirty-seven patients (78.7%) in this series were above 60 years old. The average age at presentation of 71.6 years (Table 1) conforms to previous Nigerian reports.^{8,9} We observed this increase up to the age of 80 years. Among our patients, 43 (91.5%), who presented with anaemia, weight loss, paraparesis, paraplegia, bone pain and urinary retention (Table 2), were deemed to have advanced disease,²⁰ while 4 (8.5%) were found to have latent disease (Table 3). The predominant clinical features on presentation were mainly those of voiding such as poor stream and retention (Table 2). Retention of urine as a presenting symptom occurred in 14 patients (29.8%). Higher figures of urinary retention associated with prostate cancer have been reported in the past in our environment.^{8,21,22} One patient presented with scalp secondaries and cervical lymph node metastasis from where the histopathological diagnosis was made. He responded satisfactorily to BSO. Lymphadenopathy in prostate cancer may confer increased survival in patients following hormonal manipulation.²³ Other rare metastatic sites for prostate cancer reported elsewhere include the penis,²⁴ breast,^{25,26} the skin,²⁷ the appendix²⁸ and the orbit.^{29,30} Rectal involvement presenting with obstruction, or bleeding as in one of the patients in this series, may lead to a misdiagnosis and inadvertent colonic surgery.^{31,32,33}

Early detection strategies in prostate cancer include DRE, PSA, transrectal ultrasound scan (TRUS) and biopsy. In

Table 3. Methods of diagnosis of prostate cancer

Method	No. (%)
Transrectal Trucut Needle biopsy	21 (44.7)
Incidental findings from prostatectomy (for BPH) specimen	4 (8.5)
Biopsy of prostate via a proctoscope	1 (2.1)
Cervical lymph node biopsy	1 (2.1)
Acid Phosphatase + clinical findings with DRE	12 (25.5)
Acid Phosphatase + Radiological findings	2 (4.3)
Clinical findings, DRE and radiological features of metastasis	2 (4.3)
Clinical findings alone	2 (4.3)
PSA and Clinical findings	2 (4.3)
Total	47 (100)

Table 4. Histological diagnosis

Histology	No. (%)
Adenocarcinoma	
Poorly differentiated	4 (8.5)
Well-differentiated	15 (31.9)
No details of differentiation	8 (17.0)
No Records of histology	20 (42.6)

Table 5. Treatment options offered

Option	No. (%)
BSO + Diethylstilbestrol	18 (38.3)
BSO alone	14 (29.8)
Diethylstilbestrol alone	10 (21.3)
Supportive treatment alone	3 (6.4)
Retropubic prostatectomy + Diethylstilbestrol	1 (2.1)
Diethylstilbestrol + Goserelin + Radiotherapy	1 (2.1)

- incidence of prostate cancer in Nigerians. *J Natl Med Assoc* 1999; 91:159-164.
10. Zaridze DG, and Boyle P. Cancer of the Prostate: Epidemiology and aetiology. *Br J Urol* 1987; 59:493-502.
 11. Angwafo FF. Migration and prostate cancer: an international perspective. *J Natl Med Assoc* 1998; 90(11 Suppl): S720-723.
 12. Farkas A, Marcella S, Rhoads GG. Ethnic and racial differences in prostate cancer incidence and mortality. *Ethn Dis* 2000; 10:69-75.
 13. Pienkos EJ, Meisner LF. Adenocarcinoma of the Prostate in a 41 year old man with XXY karyotype and chronic lymphocytic leukaemia; report of a case. *J Urol* 1991; 145:148-150.
 14. Smith JR, Freije D, Carpten JD et al. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* 1996; 274:1371-1374.
 15. Moul JW, Douglas TH, McCarthy WF, McLeod DG. Black race is an adverse prognostic factor for prostate cancer recurrence following radical prostatectomy in an equal access health care setting. *J Urol* 1996; 155:1667-1673.
 16. Schmidt JD, Mettlin CJ, Natarajan N et al. Trends in patterns of care for prostatic cancer, 1974-1983: results of surveys by the American College of Surgeons. *J Urol* 1986; 136:416-421.
 17. Magoha GA. Subcapsular orchidectomy in the management of prostatic carcinoma in Nigerians. *East Afr Med J* 1989; 66:400-403. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics 1997. *CA Cancer J Clin* 1997; 47:5-27.
 18. Carter BS, Carter HB, Isaacs JT. Epidemiologic evidence regarding predisposing factors to prostate cancer. *Prostate* 1990; 16:187-197.
 19. Rana A, Chisholm GD, Rashwan HM, Salim A, Merrick MV, Elton RA. Symptomatology of metastatic prostate cancer: prognostic significance. *Br J Urol* 1994; 73:683-686.
 20. Onuigbo WIB. Carcinoma of prostate: indigenous patterns. *J Natl Med Assoc* 1984; 76:373-375.
 21. Nkposong EO, Lawani J. Primary carcinoma of the prostate in Ibadan. *West Afr Med J* Dec 1973:108-111.
 22. Sandhu DPS, Mayor PE, Sambrook P, George NJR. Increased survival of patients with massive lymphadenopathy and prostate cancer: evidence of heterogeneous tumour behaviour. *Br J Urol* 1990; 66:415-419.
 23. Sciarra A, D'Eramo G, Casale P et al. Penile metastasis from carcinoma of the prostate in a patient with high serum prostate specific antigen levels. *Minerva Urol Nefrol* 1999; 51:157-158.
 24. Choudhury M, de Rosas J, Papsidero L, Wajsman Z, Beckley S, Pontes JE. Metastatic prostatic carcinoma to breast or primary breast carcinoma? *Urology* 1982; 19:297-299.
 25. Wilson SE, Hutchinson WB. Breast masses in males with carcinoma of the prostate. *J Surg Oncol* 1976; 8:105-112.
 26. Katske FA, Waisman J, Lupu AN. Cutaneous and subcutaneous metastases from carcinoma of prostate. *Urology* 1982; 19:373-376.
 27. Stein A, Sova Y, Almalah I, Lurie A. The appendix as a metastatic target

- for male urogenital tumours. *Br J Urol* 1996; 78:647-648.
28. Tertzakian GM, Herr HW, Mehta MB. Orbital metastases from prostatic carcinoma. *Urology* 1982; 19:427-429.
 29. Usui T, Ishibe T, Nihira H. Orbital metastasis from prostatic carcinoma. *Br J Urol* 1975; 47:458.
 30. Winter CC. The problem of rectal involvement by prostatic cancer. *Surg Gynecol Obstet* 1957; 105:136-140.
 31. Fry DE, Amin M, Harbrecht PJ. Rectal obstruction secondary to carcinoma of the prostate. *Ann Surg* 1979; 189:488-492.
 32. Foster MC, O'Reilly PH. Carcinoma of the prostate masquerading as rectal carcinoma. *Br J Urol* 1990; 66:193-195.
 33. Schröder FH, van der Maas P, Beemsterboer P et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomised Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 1998; 90:1817-1823.
 34. Akang EE, Shittu OB. Prostatic carcinoma: a review. *Nigerian Journal of Surgical Sciences* 1996; 6:42-47.
 35. Bridwell KH. Treatment of metastatic prostate cancer of the spine. *Urol Clin North Am* 1991; 18:153-159.
 36. Dawan D, Rafindadi AH, Kalayi GD. Benign prostatic hyperplasia and prostate carcinoma in native Africans. *BJU Int* 2000; 85:1074-1077.
 37. Samdal F, Vada K, Lundmo PI, Mjølnerod OK. Orchidectomy or LHRH-analogue? LHRH-analogue? *Scand J Urol Nephrol* 1991; 25:197-199.
 38. Savage P, Bates C, Abel P, Waxman J. British urological surgery practice: 1. Prostate cancer. *Br J Urol* 1997; 79:749-755.
 39. Emberton M. What urologists say they do for men with prostate cancer. *BMJ* 1999; 318:299.
 40. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br J Urol* 1997; 79:235-246.
 41. Gittes RF. Carcinoma of the prostate. *N Engl J Med* 1991; 324:236-245.
 42. Walsh PC. Benign and malignant neoplasms of the prostate. *J Urol* 1992; 147:289-290.
 43. Gil-Vernet JM. Prostate cancer: anatomical and surgical considerations. *Br J Urol* 1996; 78:161-168.
 44. Beynon LL, Chisholm GD. The stable is not an objective response in hormone-escaped carcinoma of the prostate. *Br J Urol* 1984; 56:702-705.
 45. Isaacs JT. The biology of hormone refractory prostate cancer: why does it develop? *Urol Clin North Am* 1999; 26:263-273.
 46. Theyer G, Hamilton G. Current status of intermittent androgen suppression in the treatment of prostate cancer. *Urology* 1998; 52:353-359.
 47. Newling DW. Second-line treatment of metastatic prostatic carcinoma. *Urol Res* 1997; 25 Suppl 2:S73-S78.
 48. Bonkoff H, Romberger K. Differentiation pathways and histogenic aspects of normal and abnormal prostatic growth: a stem

- cell model. Prostate 1996; 28:98-106.
49. Byar DP. The Veterans Administration Cooperative Research Group's studies of cancer of the prostate. Cancer 1973; 32: 1126-1130.
50. Kozlowski JM, Ellis WJ, Grayhack JT. Advanced prostatic carcinoma. Early versus late endocrine therapy. Urol Clin North Am 1991; 15:15-24.