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MANAGEMENT AND SURVIVAL IN ADVANCED PROSTATE CANCER IN NAIROBI
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ABSTRACT

Objective: **To evaluate the management and survival of patients with advanced prostate cancer in this locality.**
Design: **A prospective case study.**
Setting: **Kenyatta National Referral Hospital and the Nairobi and Mater Hospitals.**
Patients: **Fifty nine patients with advanced cancer of prostate (extra prostatic locally advanced and metastatic cancer).**
Results: **Transperineal trucut needle biopsies of the prostate revealed 15 patients (25.42%) had poorly differentiated cancers with Gleasons scores greater than 7. Fifteen patients (25.42%) had moderately differentiated cancers with Gleason scores of 6; and twenty nine other patients (49.2%) had well differentiated cancers with Gleason scores of 4 and below. Surgical castration was effected on 15 patients four of whom also had 50 mg of oral bicalutamide (casodex) daily. Thirty six patients were treated with subcutaneous goserelin (zoladex) depot 3.6mg every 28 days. Ten of these patients also had 50 mg oral casodex daily in addition to the zoladex. Three patients in this group also had external radiotherapy for severe bone pains. Only eight patients were treated with oral diethylstilboestrol 3 mg daily. All the 15 patients with undifferentiated cancers died within 12 months. Of the 22 patients surviving at 48 months irrespective of the method of treatment, 20 of them had well differentiated cancers with Gleasons scores of 4 or less.**
Conclusion: **Survival in the undifferentiated and poorly differentiated prostrate cancer Gleasons grades 4 and 5 with a score of over 7 is poor irrespective of the mode of treatment as all the patients in this group were dead within 12 months of diagnosis. Twenty patients (90.90%) of the surviving patients at 48 months had well differentiated cancers Gleasons grades 1 and 2 with scores of 4 or less indicating better prognosis for these tumours which are known to be slow growing with a much longer tumour doubling time.**

INTRODUCTION

Prostate cancer is the most common male cancer and the second leading cause of cancer death in American men(1). The disease is also common in Europe and is the third commonest cause of cancer death in the United Kingdom(2,3). Prostate cancer has also been reported as the most common genitourinary malignancy by African authors(4-8). This is as a result of increased awareness of the disease, increased life expectancy, improved diagnostic techniques and screening procedures which include the use of serum prostate specific antigen (PSA)(l,9). The incidence of prostate cancer is thus increasing worldwide both as a result of organised screening programmes in some countries and an apparent increase in incidence(10,11). Prostate cancer commonly occurs in men above 50 years, with more than 80% of all cases being diagnosed in men over 65 years of age, and less than one per cent in men under 50 years of age. The median age at diagnosis of prostate cancer is 72 years although active screening programmes in some countries may ultimately lead to lowering of the median age of first diagnosis.

The epidemiology of prostate cancer is complex with only a few established risk factors. Those most established are family history, age, race, country and testosterone deficiency(12-14). In the United States of America, the presentation of black Americans with more advanced prostate cancer than white Americans has been attributed in part to the differential use of the available medical resources in that country(15). Only a small proportion of men diagnosed with prostate cancer eventually die from the disease. It has now been established by Stamey *et al*(16) that a tumour volume of less than 0.5mls and a Gleason score of less than 7 would not be life threatening because such prostate cancer has a long doubling time. Prostate needle biopsies which identify microfocal cancer with a tumour volume of less than 3mls and a Gleason score of less than 7 creates a management dilemma for urologist(17).

Many prostate cancers are diagnosed at the stage of bony metastases when treatment can best be palliative. Current population screening techniques are at best controversial(2). The sensitivity and specificity of PSA levels, digital rectal examination (DRE) and transrectal ultrasound of the prostate (TRUS) are low, and no screening

test has been shown to reduce mortality in prostate cancer. Furthermore, studies have shown that clinical staging of prostate cancer frequently underestimates the pathological stage of the tumour(18,19).

MATERIALS AND METHODS

This is a prospective study involving 59 patients with advanced prostate cancer. All patients presented with urinary outflow problems. Twenty nine patients (49.15%) in this group first presented late with acute urinary retention. Digital rectal examination (DRE) was performed on the left lateral position by the same investigator. Transrectal ultrasound of the prostate was performed on 49(83.05%) patients. Transperineal trucut needle biopsy of the prostate was performed under digital guide in all patients. Blood was taken for serum prostate specific antigen (PSA) in 50 patients (84.75%). Plain x-rays of the pelvis and lumbosacral spine were taken in all patients. X-rays of the thoracic spine and chest were taken in 20 patients (33.90%). Intravenous urogram (IVU) was performed in 40 patients (67.80%). Eight patients were treated with oral diethylstilboestrol 1mg three times daily. Fifteen patients (25.42%) had bilateral orchidectomy. Thirty six patients (67.8%) were treated with 3.6mg subcutanous depot of zoladex every four weeks. Oral antiandrogen casodex 50mg daily was given to ten patients on zoladex depot, and four patients who had orchidectomy. Follow up was effected monthly at which all patients were clinically re-evaluated. All data were analysed and tabulated in various tables as seen under the results.

RESULTS

The age range was 49 to 82 years with a mean of 65.1 ± 2.0 years (Table 1). Digital rectal examination (DRE) revealed hard or multinodular prostates with obliterated median sulci and fixed rectal mucosae in all the 59 patients. Transrectal ultrasound of the prostate was performed on 49 (83.05%) patients and revealed extracapsular tumour in all these patients. Transperineal trucut needle biopsy of the prostate was effected in all patients under local anaesthesia and the histopathological findings are illustrated in Table 2. Blood was taken for serum prostate specific antigen (PSA) and was found to be elevated above 20ng/ml in 92% of the 50 patients in which it was measured Table 3. Plain x-rays of the pelvis and lumbosacral spine showed evidence of osteosclerotic metastases in 35 patients (59.32%) and osteolytic metastases in three patients (5.08%). Distant metastasis in the thoracic spine, the chest wall including the lungs was present in five patients(8.47%).

Table 1

Age distribution in advanced prostate cancer

Age group in years	No. of patients	% of total
4-49 years	1	1.6
50-59 years	6	10.17
60-69 years	32	54.24
70-79 years	17	28.81
80-89 years	3	5.10
Total	59	100

Table 2

Histological degree of differentiation in advanced prostate cancer

Degree of differentiation (Gleasons grade)	Gleasons score	No. of patients	% of total
Grade 1	2	10	16.95
Grade 2	4	19	32.25
Grade 3	6	15	25.42
Grade 4	8	7	11.86
Grade 5	10	8	13.56

Table 3

Serum prostate specific antigen levels in advanced prostate cancer

Serum PSA level	No. of patents	% of total
0-4 ng/ml	1	2.0
5-10 ng/ml	1	2.0
11-20 ng/ml	2	4.0
Over 20 ng/ml	46	92.00

Table 4

Methods of treatment in advanced prostate cancer

Method of treatment	No. of patients	% of total
Total orchidectomy	2	3.39
Subcapsular orchidectomy	9	15.25
Oral diethylstilboestrol	8	13.56
3.6 mg zoladex depot monthly	23	38.98
3.6 mg zoladex depot and external radiotherapy	3	5.10
3.6 mg zoladex depot and oral casodex 50 mg daily	10	16.95
Orchidectomy and oral casodex 50 mg daily	4	6.78

Table 5

Survival of patients with advanced prostate cancer

Survival	No. of patients dead	No. of patents alive	% alive of Total
6 months	3	56	94.91
12 months	12	37	79.66
18 months	20	39	66.10
24 months	24	35	59.32
30 moths	29	30	50 85
36 months	31	28	47.46
42 months	35	24	40.68
48 months	37	22	37.29

Ureteric obstruction was observed in seven of the 40 patients (17.5%) who had intravenous urograms performed. Six of the obstructions were unilateral with only one being bilateral. The various methods of treatment effected for patients are illustrated in Table 4. Survival of various patients from 6-48 months is illustrated in Table 5.

DISCUSSION

The rising incidence of and mortality from prostate cancer has generated great interest in proving the results of current methods available for treatment. Hormonal manipulation in the treatment of advanced cancer was first described by Higgins and Hodges in 1941(20) using orchidectomy or oestrogen injections. Oestrogen inhibits lutenizing hormone (LH) and follicular stimulating hormone (FSH) secretion by the pituitary, in turn inhibiting testosterone secretion by the testis. The most commonly used oestrogen has been diethystilboestrol. The administration of diethystilboestrol one milligramme three times daily produces castrate levels of testosterone within 7-21 days (21). In this study, only eight patients (13.56%) were treated with diethystilboestrol. This was because these patients refused orchidectomy and could not afford the high cost of lutenizing hormone releasing hormone (LHRH) analogues. Stilboestrol is not the preferred treatment of choice for advanced prostate cancer in this locality because of the associated side effects which include thrombosis, pulmonary embolism, myocardial infarction, tenderness and enlargement of breasts, nausea, vomiting and hot flushes. Parenteral administration of oestrogens like diethylstilboestrol diphosphate intravenously has however been shown to reduce cardiovascular side effects(22).

In this study bilateral orchidectomy was performed on 15 patients (25.42%). Bilateral orchidectomy was considered the gold standard as it caused a 95% reduction of the circulating testosterone. However, this may not accurately reflect the intraprostatic concentration of dihydrotestosterone DHT originating from other estragonadal sources after surgical castration, intraprostatic DHT remains at 40% of measured levels in intact men (23). The importance of non testicular sources, for example, the adrenal androgens in adult men is the basis of adding antiandrogen therapy to castration regardless of how it is achieved.

Lutenizing hormone releasing hormone LHRH is a decapeptide. Substitutions at the sixth, ninth and tenth positions results in the production of analogues with greater than 100 times the potency of the naturally occurring LHRH agonist, for example, goserelin (zoladex) interferes with its pulsatile release from the hypothalamus and desensitises the pituitary with subsequent suppression of LH release. Suppression of LH release results in a decrease in testosterone to castrate level (24,25). The majority of patients in this study (61.01%), were treated with 3.6mg subcutanous zoladex depot every four weeks. Side effects of LHBH agonists include hot flushes and sexual dysfunction, none of which was reported in this study.

Antiandrogens like bicalutamide (casodex) act peripherally by blocking androgen uptake and/or nuclear binding of testosterone at the target prostate cancer tissue. In this study 10 patients were treated with oral casodex 50 mg daily in addition to the monthly 3.6 mg zoladex depot. Another four patients who had bilateral orchidectomy were treated with oral casodex 50 mg daily. More evidence is now available to support the benefit of the combination of an antiandrogen such as casodex with orchidectomy or medical castration with LHBH agonists in patients with advanced prostate cancer (26,27). Continuous double blind trials with combination of antiandrogens and medical or surgical castration have shown improvements in objective response rates, progression free survival and overall survival for maximum androgen blockade compared with castration alone (28,29). The only significant limiting factor concerning the use of combined androgenic blockade is the issue of high cost to the patient. Perhaps one possibility that may help address the economic concerns in future could be the application of intermittent androgenic blockade which may be expected to increasingly emerge as a potential treatment if proved effective.

There are many unresolved issues in the diagnosis and treatment of both early and advanced prostate cancer (3,30). The clinical course of localised prostate cancer is unpredictable while some patients die within one to two years of diagnosis, others develop no symptoms during their lifetime indicating a highly variable biological potential for prostate cancer (31,32). In this study fifteen (25.42%) patients had poorly differentiated and undifferentiated cancers, Gleasons grades 4 and 5 on histopathological examination. Fifteen patients (25.42%) had moderately differentiated Gleasons grade 3 cancer while another twenty patients (49.15%) had well differentiated Gleasons grade 1 and 2 cancer (Table 2). All the fifteen patients in this study with poorly differentiated and undifferentiated cancers died within 12 months of diagnosis irrespective of the mode of treatment (Tables 4 and 5). This is in conformity with the well known fact that the prognosis in prostate cancer is dependent on both the clinical stage of tumour according to the tumour node and metastasis (TNM) classification(33) at the time of first presentation, and the histopathological degree of differentiation as determined by Gleasons grades(34). Apart from Gleasons grades, many other tumour grading systems have been proposed including the Mostofi system(35), the Gaeta system(36), the Bocking system(37), and the Anderson hospital system(38). Today, the Gleasons grading system remains the most commonly utilised and widely accepted. The Gleason system utilises glandular configuration and the amount of tumour showing specific histologic patterns to develop a scoring system (from 1-5) that lends equal weight to the dominant and secondary areas of the neoplasm (38). Furthermore, it is now believed that most prostate cancers progress from small well differentiated tumours to large poorly differentiated tumours which disseminate with subsequent poor prognosis(39). The rate of progression and probable clinical outcome in any given case are reflected by the clinical stage of tumour as determined by digital rectal examination, histological grade and volume of tumour, and the serum levels of prostate specific antigen (PSA) which has turned out to be the most sensitive tumour marker in human prostate cancer. PSA is widely used in early detection of prostate cancer and in the follow up of patients after radical prostatectomy in which its elevation indicates residual disease and progression. Although poorly differentiated prostate cancer tissue produces less PSA per unit volume, this is thought to be compensated for by the generally larger volume and greater cellularity of tumours with high Gleasons grades(40,41). PSA however is not a

useful marker for the presence or absence of metastatic disease. The Veterans Administration Co-Operative Urological Research Group, the National Prostate Cancer Group, and the European Organisation for Research on Treatment of Cancer Genitourinary G Group (EORTC-GU) have all performed analyses to identify prognostic variables in patients with advanced prostate cancer. They reported the prognostic factors to include elevated serum phosphates, upper urinary tract obstruction, tumour grade and stage, the performance status, and other variables such as serum PSA(42).

Most of patients who died had hormone resistant tumours. The treatment objective in hormone resistant prostate cancer should be palliation, particularly the relief of pain especially in the bones during the usual average of 11-12 months survival from the time of diagnosis. Quality rather than duration of life is the main objective in dealing with this group of patients. Pain relief is often achieved by radiotherapy which may be local wide field or systemic with complete relief reported in upto 80% of the patients thereby improving significantly their quality of life(43,44). Administration of chemotherapeutic agents may also be considered in some cases although a significantly greater toxicity and highly increased cost treatment should be weighed against the potential clinical benefits before reaching the decision.

Twenty patients (90.9%) of the 22 patients still surviving at 48 months during the study had well differentiated cancers with low Gleasons grades 1 and 2 which were all hormone responsive, confirming good prognosis for these group of tumours (Table 5) . The ideal of combined androgen blockade using a non steroidal antiandrogen and surgical or medical castration should be initiated as gold standard therapy for patients with metastatic well differentiated and moderately differentiated hormone resposive prostate cancer. From this study it is concluded that survival in the undifferentiated and poorly differentiated prostate cancer Gleasons grades 4 and 5 with a score of over 7 is poor irrespective of mode of treatment.

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