UNDETECTED CARCINOMA OF THE PROSTATE AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any other University

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DEDICATION

1. To my grandmother,Peritah,my father Yowana and my mother Ann for their love and encouragement, which allowed me to learn and achieve.
2. To my wife, Terry for her love, support and understanding which allowed me to succeed.
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STUDY ABSTRACT

Background

The incidence of undetected carcinoma of the prostate has been decreasing in Western Europe after the introduction of PSA and ultrasonography testing for patients with benign prostatic enlargement (BPE), who presents with bladder outlet obstruction. In an earlier retrospective study done in our set up in 1993 before extensive use of PSA and ultrasonography, the incidence of incidental carcinoma of the prostate was 13 %.

Objective

The study was intended to determine the incidence of undetected carcinoma of the prostate at Kenyatta national hospital, in patients presenting with bladder outlet obstruction (BOO) thought to be BPE.

Design

This was a descriptive prospective study, carried out between 15thAugust 2005 and 30th April 2006.

Setting

The study was carried out at Kenyatta National Hospital, which is a teaching and referral hospital.

Subjects

One hundred and six patients were recruited into the study.

Results

The patients' age range was between 60 and 100 years with a mean of 75 years. Seven patients were found to have undetected carcinoma of the prostate, in patients presenting with BOO due to BPE. The incidence was 6.6%. Of the

undetected carcinoma 42% of the patients had adenocarcinoma, 29% had prostate intraepithelial neoplasm (PIN) and 29% had anaplastic carcinoma.

PSA levels were between zero to 4ng/ml and majority of the patients (72%) had PSA between three and 4ng/ml

.

Majority of patients, wth carcinoma were from Central province, 57% followed by 29% from Nyanza and 14% from eastern province.

Conclusion

Incidence of undetected carcinoma of the prostate in patients presenting with BOO at KNH was 6.6% with 50% reduction from previous 13% in our local set up. Study by Reeves H.K. in 1993

INTRODUCTION

Unsuspected carcinoma of the prostate is cancer that is not detected by digital rectal examination (DRE),Ultrasonography nor Prostate Specific Antigen[PSA] screening. The patient presents with symptoms and signs of prostatism and undergoes prostatectomy for the benign disease to relieve bladder neck obstruction. It is called undetected carcinoma when histopathological examination reveals focus or foci of cancer within the resected tissues. This cancer may remain latent and never progress or may progress, metastasize and kill the host, depending on its initial size and grade[1,2,3].

According to Jewett-whitmore American clinical staging system, Stage A1 is a focal disease found in less than 5% of the resected tissues and A2 is a diffuse growth found in more than 5% of the total specimen.

In the 1992 TNM Staging System the counter stages were given as $T1_a$ and $T1_b$. Stage $T1_c$ represents cancer diagnosed by random biopsy of a normally palpated prostate gland because of elevated serum prostate – specific antigen (PSA).

LITERATURE REVIEW

A. HISTORICAL BACKGROUND

Moore and Rich were the first authors to name the undetected carcinoma of the prostate found in autopsies as "occult carcinoma" [1,2]. The term is not appropriate, once it is usually used to refer to carcinomas that appear by metastasis and not by symptoms or signs resulting from their places of origin.

The term latent was initially used by Andrews, but also in an inappropriate way [3]. This and other terms such as dormant and indolent refer to the biological behaviour of tumours [4,5]. The idea of a "latent", "dormant" or "indolent" behaviour of the prostate carcinoma is based on epidemiological features, as it is likely that this carcinoma may develop or not in a slower way when compared to the clinical carcinoma [6,7].

If we compare the frequency of undetected carcinoma to the prevalence and mortality rate of the clinical carcinoma, we can notice a discrepancy. A 50-year-old man with a life expectancy of more than 25 years has a 42% risk of having undetected carcinoma while the risk of developing a clinical cancer is a round 10% and the risk of death due to this cancer is 3% [6,7].

Thus it is necessary to refer to undetected carcinoma found in autopsies, TURP, or open prostatectomy in away that does not implicate the biological behaviour. The carcinoma found like that is purely morphologic and the best terminology is undetectd carcinoma.

In 1980 a review of the topic of undetected prostate cancer concluded that this disease is common but poorly understood [8]

The term prostate cancer is a combination of three entities:

i) Clinical prostate cancer which may become symptomatic and whose diagnosis is made clinically.

ii) Occult prostate cancer in which the primary lesion remains small or hidden, but which produces clinically overt metastases.

iii) Unsuspected prostate cancer which is unrecognizable through signs and symptoms and is generally an incidental finding at prostatectomy for benign prostatic enlargement(BPE), or which is screen-detected in a symptomatic individuals [10].

Therefore the rate of prostate cancer discovery depends also on factors such as a high rate of performing prostatectomies for benign disease and the conduction of population-based screening programs. With an increased population and life expectancy, and advents of tools for early detection of diseases, it is anticipated that more cases of prostate cancer will be reported [9,10]. The two methods of discovering undetected carcinoma of the prostate are prostatectomy, performed for benign disease and PSA based screening.

B. EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

In a review of 253 patients presenting with BPH at Asir Central Hospital (ACH) in the southern region in Saudi Arabia, Ghali et al reported undetected adenocarcinoma of the prostate in 1.7% of 248 prostatectomy specimens obtained [11].

The prevalence varies widely thoughout the world. The lowest incidence of 0.5 per 100,000 men is found in Qidong, China. Sweden has a rate of 55.3 per 100,000 men and the US has a rate of 102.1 per 100,000 men. Black males in the US have the highest incidence of prostate cancer in the world, and present at a younger age with higher grade and stage of disease than white US males [27]

In another study by Richard E. Zigeunev et al at University Hospital Graz Austria of 1127 patients were studied, the rate of undetected prostate cancer in patients with both negative age-specific PSA levels and Negative DRE finding was 6.4% in the above group.

The incidence of prostate cancer detected in specimens after cystoprostatectomy for invasive bladder cancer has been reported to be up to 45% [12,14]. In patients with negative PSA and DRE findings. The rate of Histologic carcinoma of the prostate in autopsies is 36.66% in a study done by Athanase Bills et al at Sa Francisco University Brazil [14].

During 1990s, TURP performance for BPH reached exceptionally high rates in North America [15]. Undetected cancer was found in 10% of patients undergoing a transurethral prostatectomy for bladder outlet obstruction symptoms from presumed benign prostatic hyperplasia [16].

C. AETIOLOGY

As with many cancers the aetiology of prostate cancer is not proven and may be multifactorial. It is clear that testosterone and its active metabolite dihydrotestosterone are essential for its development; castration in prepubertal males blocks development of the prostate and androgen deprivation is an effective albeit temporary, treatment for prostate cancer. [15]

There is increasing evidence that while genetic factors are responsible for some cases, occupation, diet, hormones, sexual habits and sexually transmitted diseases may all play some part in causation of prostate cancer in susceptible males.[15]

1. Genetic factors

Cancer is caused by a complex but incompletely understood interaction between hereditary factors and environmental factors. It is a group of diseases in which certain genes that regulate cell growth and death are abnormal, or their protein products are over or under expressed. The risk of prostate cancer is increased by 2 – 9% if there is any family history of the disease. In such cases, the age of onset is lower than that of sporadic case.
The site of the affected gene or genes is currently the subject of investigation. Loss of the long arm of chromosome 10 and 7 and loss of chromosome 1, 2, 3, and 4 have been suggested. Allele loss on chromosome 8 suggests that a tumour suppressor gene may be involved. Less than 10% of tumour cases appear to be genetic, nonetheless this is a significant number of men at risk.

Glutathiones – transferases (GsTs) is associated with cancer of the prostate risk. Male pattern baldness seems to be risk factors for clinical prostate cancer[9].

2. Diet

Fat intake is associated with prostate cancer. Animal fat and alpha-linoleic acid from vegetable sources may be the most important components, but the mechanisms involved are unclear. Fatty meat, such as beef and lamb has been incriminated. Betacarotene consumption seems to be protective, as in other epithelial cancers [17]. The high soya intake in Japan and China may also be protective and could explain the low rates of prostate cancer in these countries [17]. Soya beans are a dietary source of isoflavone genistein, which is a specific inhibitor of protein tyrosine kinases and inhibits DNA topo. Isomerases as well as other enzymes involved in signaling transduction. Genistein has been shown to suppress proliferation of prostate cancer by two or three fold and is found in high concentration in cooked or crushed tomatoes. "The prostate cancer diet" is the subject of a great deal of research and conjecture.

3. Sexual Habits

Age at first intercourse, number of sexual partners and history of sexually transmitted disease may all be associated with some elevation of risk, but these findings are not consistent across all studies. [19,20]

Correlation between a history of gonococcal infection and prostate cancer, with a 45-year delay period has been reported [18]. However these are conflicting data suggesting an increase in prostate cancer in men with low sexual activity [19] and a study has shown that prostate cancer mortality in 1400 of reputedly celibate catholic priests was comparable to that within the general male population [20]. At present the influence of sexual activity on the development of prostate cancer is uncertain. Sexual morality has changed over the years. The median age at first intercourse for men in the UK, for example has fallen from 20 to 17 years over the last 2 decades. The number of partners during the lifetime of an average man has also increased considerably [21].

4. Hormones

Circulating androgens are an essential prerequisite for the growth of normal prostate and for development of benign prostatic hyperplasia and prostate cancer change. Although the amounts of circulating testosterone are variable from one individual to another, there is apparently no direct correlation between the serum testosterone level and the risk of developing prostate cancer. The results of hormone studies in male with prostate cancer and age-matched controls have been disappointing. Testosterone, dihydrotestosterone, prolactin, follicle stimulating hormone, oestradiol, oestrone, luteinisting hormone and sex hormone binding globulin have all been investigated without conclusive results.[15]

It is interesting to note that although serum testosterone levels gradually decline with advancing age, the incidence of prostate cancer steadily increases. This apparent anomaly may be explained by the lengthy lag period between early neoplastic change and appearance of clinically apparent prostate cancer, as well as changes in androgen receptor levels.

Testosterone is metabolized within the prostate to dihydrotestosterone (DHT) rather than testosterone, which is the major intracellular androgen that promotes growth within the prostate.

The role of DHT in the promotion of prostate cancer is unclear. However prostate cancer does not appear to occur in acohort of pseudohermaphrodite male in whom 5-alpha reductase is absent.[15]

Hormonal factors may be responsible for the different incidence of the disease between ethnic groups. Young adult Afro-American men have 10% greater circulating testosterone levels than young adult white men, so they may have increased cell division and risk of alterations in alleles holding proto-oncogenes or tumour suppression genes. The risk may even be increased in utero since Afro-American women have higher first trimester testosterone levels than white women, which could affect the hypothalamic-pituitary-testicular system.

Chinese and Japanese men have a lower 5-alpha reductase activity than Caucasians and Afro-Americans.

5. Environmental Factors

Industrial chemicals have been associated with particular malignancies. Workers exposed to chemicals in rubber, textile, chemical drug, fertilizer and atomic energy industries have an increased risk of developing prostate cancer.[9]

6. Smoking

Tobacco smoking has been implicated in many malignant tumours such as carcinoma of the lung and bladder no corelation has yet been found with prostate cancer.[15]

7. Viruses

Viruses are known to be the cause of carcinogensis in genital malignancy such as cervical cancer. Viruses may have an environmental potential to trigger for prostate cancer but this has not been proved. A possible candidate for aetiolgy of prostate cancer is Herpes simplex virus type 2. Antibodies to this virus were detected within the serum of 71% of prostate cancer cases but only 66% controls of benign prostatic hyperplasia [(22)]. The virus has also been demonstrated in prostate cancer cells by electron microscopy [(23)].

It is interesting to note that wives of men with prostate cancer were reported to have increased incidence of cervical carcinoma in one study [(24)].

RNA viral particles have also been identified within prostate cancer cells [(25)]. Further support for an aetiological role of RNA viruses is the presence of H-vas oncogen P21 within prostate cancer cells. This seems to be associated with less well-differentiated prostate cancer [(26)].

D. ANATOMY

The term prostate was originally derived from Greek word prohistani meaning to stand in front of and has been attributed to Herophilus of Alexandria who used the term in 335 BC to describe the organ located in front of the urinary bladder.

The male prostate gland is located below the bladder. The seminal vesicles are located posterior to the prostate. The urethra exits from the bladder and traverses the prostate before exiting to the penile urethra.

The normal prostate is composed of glands and stroma. The glands are seen in cross-section to be rounded to irregularly branching. These glands represent the terminal tubular portions of long tubuloalveolar glands that radiate from the urethra. The glands are lined by two cell layers: An outer low cuboidal layer and an inner layer of tall columnar mucin-secreting epithelium. These cells project inward as papillary projections. The fibromuscular stroma between the glands account for about half of the volume of the prostate. The prostate is surrounded by a thin layer of connective tissue that merges with surrounding tissues, including nerves. There is no distinct capsule.

McNeal first proposed the histological division of the prostate into:-

i) Outer peripheral zone
ii) A central zone
iii) An inner transitional zone

In the young adult prostate, approximately 5% of prostate glandular tissue is in the transitional zone located on both sides of the prostatic urethra. This is the area where benign hyperplasia develops in older patients. The transitional zone is separated from the peripheral zone and central zone by the surgical capsule in which calcified corpora amylacea may be found. The central zone is relatively resistant to disease process and constitutes approximately 25% of the glandular tissue of the prostate in the young adult. The central zone is situated at the base of the prostate and the ejaculatory ducts reach the verumontanum by passing through the central zone. The peripheral zone constitutes 70% of the prostate and lies on the posterior and lateral aspects of the gland surrounding the transitional zone. Its ducts drain into the urethra distal to the verumontanum.

Of all prostate cancers, 70% occur in the peripheral zone and approximately 20% occur in the transitional zone.[27]

E. PATHOPHYSIOLOGY

Approximately 95% of prostate cancers are adenocarcinomas, developing in the acini of prostatic ducts [(27)]. Other rare histopathologic types of prostate carcinoma occur in 5% of patients these include [(27)].

- Small cell carcinomas
- Mucinous carcinoma
- Endometrioid carcinomas (prostatic ductal carcinomas)
- Transitional cell cancer
- Squamous cell carcinoma
- Basal cell carcinoma
- Adenoid cystic carcinoma (basaloid)
- Signet-ring cell carcinoma
- Neuroendocrine cancer

The development of prostate cancer appears to be a slow, gradual process, the histological cellular architecture passing from normal, through dysplasia, to cancer. Some cases develop prostatic intraepithelial neoplasia, which is a significant precursor of aggressive malignancy and is detected occasionally on Biopsy [(10)].

Prostate cancer can co-exist with BPH but there is no link between the two and BPH is not a precursor of cancer. While the cancer can be slow growing and incidental to an elderly man's co-morbidity, some cases are aggressive and life threatening. In the younger age group, even the slow growing type has time to progress and metastasize and is likely to be the cause of death if untreated [(10)].

Most of the carcinomas have their origin in the peripheral zone (pz) [(28, 29)]. Some authors admit the evidence of a different biological behaviour depending on the origin of prostate carcinoma [(30, 31, 32, 33)].

Greene et al [32, 33] observed that in radical prostatectomies the carcinomas, which originated in the transitional zone, were well differentiated, even if large in volume. These authors have also observed that 93% of the peripheral zone tumours were associated to a high-grade prostate intraepithelial neoplasm (PIN), while none of the tumours found in the transitional zone had this association.

Studying radical prostatectomies, Lee et al [34] observed that 22% of neoplasms originated in the transitional zone presented extraprostatic extension (PT3 stage), while 48% of the tumours originated in the peripheral zone presented this extension. Besides, they observed that the average score according to Gleason's system was 6.2 ± 1.6 and 7.4 ± 0.9 respectively to tumours that originated in the transitional and peripheral zone.

Grignon and Sakr [30] observed that the proliferation index for tumours originated in the peripheral and transitional zone was 5.0 to 1.6% respectively. The Gleason's system was 6.7 and 5.6 respectively.

The morphologic results of this study show that the carcinoma presents a better behaviour only when located exclusively in the transitional zone. In this unique site all neoplasias had low grade and were less extense.

About PT1a stage. Whenever a low grade and less extense (less than 5% of fragments examined) undetected carcinoma is found in prostatic transurethral resection or open prostatectomy, i.e. surgeries which ressect the transitional zone, it is likely that the carcinoma is also present in the peripheral zone, more extense and of higher histologic grading [35]. Thus the need for Needle Biopsy in peripheral zone in evaluation of the therapeutic approach in PT1a stage.

Undetected prostate cancer numbers are similar in many countries. However its progression is rather irregular and depends on genetic, racial and environmental factors.

The racial genetic factors are the most interesting ones and are predominantly related to the polymorphism of the gene, which codifies the androgen receptor located in the x

chromosomes. The Asians have a long repetitive region while the Blacks have a very short one and Caucasians an intermediate one. The longer this polymorphic repetition, the less the sensibility of the receptor [36, 37].

F. CLINICAL PRESENTATION OF PROSTATE CANCER

Even though the incidence of prostate cancer had been increasing before the introduction of serum PSA testing the manner in which the disease is diagnosed today is different from that of ten years ago. In the past, prostate cancer was first detected by digital rectal examination or because the patient had urinary symptoms. In the 1990s, prostate cancer is often diagnosed after a man has been found to have a high serum PSA concentration.

Prostate cancer is usually a symptomatic at presentation and detected either by abnormalities on routine rectal examination or, with increasing frequency by a high serum PSA concentration. While symmetric enlargement and firmness of the prostate is most typical of benign prostatic enlargement (BPH), asymmetric areas of induration or frank nodules are more suggestive of prostate cancer.

When it is symptomatic, prostate cancer can cause urinary urgency, nocturia, frequency, and hesitancy; these symptoms are also present in men with BPH, and are more likely to be caused by BPH than cancer.
The new onset of erectile dysfunction should always raise suspicion of prostate gland pathology since an enlarging gland may encroach upon periprostatic tissue, which contains the neurovascular bundle that is involved in erectile function. A small percentage of men present with symptoms due to metastatic disease such as bone pain or rarely, spinal cord compression.

G. DIAGNOSIS

The diagnosis of undetected prostatic carcinoma depends upon the histopathological detection of focus or foci of cancer in the resection or biopsied prostatic tissue of patients with normal (unsuspected for cancer on palpation) glands on DRE [9-11,38]. Once cancer is diagnosed, a complete staging procedure should be carried out. Currently, the staging

procedure involves in addition to DRE and serum, PSA measurement, transrectal ultrasonographic (TRUS) examination of the prostate, MRI or CT Scan of the pelvis looking for pelvic lymph node involvement and bone Scan [10-13]. Pelvic lymphadenoctomy by open or laparotomy or laparascopically is the most accurate method to detect metastasis to pelvic lymph nodes [9-11,38]. This definitive surgical staging procedure precedes a planned curative measure, either radical prostatectomy or radical external beam radiotherapy. Both are indicated for localized prostate cancer.

H. SERUM PSA ELEVATION

Malignant prostate tissue generates more PSA than normal or hyperplastic tissue. In addition, cancerous tissue may disrupt the prostate-blood barrier, further increasing the serum concentration of PSA.

A total serum PSA concentration >4.0 ng/mL is considered abnormal in most assays, and is suspicious for prostate cancer. However, some men with prostate cancer have a serum PSA concentration below 4.0 ng/mL. In three studies of men aged 50 years and older, 136 out of 319 men (43%) with prostate cancer had values below 4.0 ng/mL [39, 40]. Furthermore, in the Prostate Cancer Prevention Study, which compared finasteride to placebo in over 18,000 men at risk for prostate cancer, 21% of cancers diagnosed for reasons other than an elevated PSA had a serum PSA level between 2.6 and 3.9 ng/mL [39]. Normal fluctuations in serum PSA further complicate the use of serum PSA to select men for prostate biopsy. In one series of 972 unscreened men who had serum collected during their participation in a polyp prevention trial, 44% of 154 participants found to have a PSA level >4 ng/mL had a normal PSA at one or more subsequent visits over a four-year period [40]. Thus, confirmation of an elevated PSA is advisable prior to proceeding to prostate biopsy.

The positive predictive value (PPV) of an elevated serum PSA for detecting prostate cancer depends upon the PSA concentration. As an example, in one series, the PPV for serum PSA levels 4 to 10 ng/mL, and >10 ng/mL were 21, and 42 to 64%, respectively [40]. Several refinements in the PSA levels assay have been introduced (e.g., PSA density, PSA velocity, age-specific reference ranges, free versus bound PSA values) in an effort to improve test specificity at intermediate PSA concentrations (i.e., 4 to 10 ng/mL) and reduce the number of

unnecessary prostate biopsies. In practice, however, these techniques have not resulted in superior diagnostic outcomes compared with simple PSA testing.[46]

Unfortunately, there is no absolute elevation in serum PSA that accurately distinguishes between malignancy and benign disease, Prostatic biopsy is advised if the serum PSA concentration is greater than 4 ng/mL, even in the presence of a normal rectal examination. The management of men with smaller elevations in PSA is less clear since the majority will have negative biopsies. Most men are referred to a urologist to assist with decision making and to help rule out other causes of an elevated PSA.
Most men who have a diagnosis of prostate cancer will have already had a serum PSA concentration. This value is not used for staging, but may help to predict the local extent of disease in men with prostate cancer.[46]

- There is a higher likelihood of finding organ-confined disease when the serum PSA concentration is less than 4.0 ng/mL. as an example, in one report, 332 asymptomatic men with a normal rectal examination and a serum PSA between 2.6 and 4.0 ng/mL underwent multiple prostate biopsies [(45)]. Cancer was detected in 73 men (22%), all cancers detected were clinically localized, and 42 out of 52 that were surgically staged were organ confined.

- A serum PSA concentration of 4.1 to 10.0 ng/mL at the time of diagnosis of prostate cancer increases the likelihood of finding an organ-confined tumour larger than 0.5 mL, but also increases the odds of finding extracapsular extension by 5.1 – fold [(46,47)].

- A serum PSA concentration higher than 10.0 ng/mL increases the likelihood of finding extraprostatic extension by 24 to 50-fold [(46, 48)].

I. ABNORMAL DRE

Digital rectal examination (DRE) can detect tumours in the posterior and lateral aspects of the prostate gland. Tumours not detected by rectal examination include the 25 to 35% that occur in other parts of the gland, and stage T1 cancers, which are not palpable by definition.

The PPV of an abnormal DRE for prostate cancer varies from 5 to 30 percent [41]. This variability depends in part upon the serum PSA concentration. As an example, in one study of 129 men with a serum PSA less than 4.0 ng/mL and an abnormal DRE or transrectal ultrasound (TRUS), the PPV of an abnormal DRE was approximately 2% for men with serum PSA levels < or = 1.9 ng/mL, compared with 19% and 44% in men with a serum PSA of 2 to 2.9 ng/mL and 3.0 to 4.0 ng/mL, respectively [38].

Despite the relatively low positive predictive value of an abnormal DRE, all men with induration, asymmetry, or palpable nodularity of the prostate gland require further diagnostic studies to rule out prostate cancer, particularly if they are over the age of 45 or have other risk factors for the disease. A serum PSA should be obtained prior to biopsy, both for diagnostic and prognostic purposes. Although serum PSA concentrations rise slightly during the first several hours after a rectal examination in some men [44], the rise is so small that the blood sample for PSA testing can be obtained at any time.

Even if the serum PSA is in the normal range (i.e., <4 ng/mL), prostate biopsy may be indicated in men with a DRE examination that is suspicious for cancer. As many as 43% of patients with prostate cancer have normal serum PSA values [40]. Furthermore, in one large study of prostate cancer screening, a diagnostic DRE was reported in 18% of men who had a normal serum PSA [40].

Transrectal ultrasonography (TRUS) may be used to evaluate abnormalities detected by DRE. However, many investigators recommend prostate biopsy in this setting, regardless of the results of ultrasonography, since TRUS may miss a substantial number of tumours [48]. Cancers typically appear hypoechoic, but some may be hyperechoic or isoechoic, leading to false negative studies. The main utility of ultrasonography is to guide prostate biopsy.[50]

J. PROSTATE BIOPSY

Prostate biopsy is the gold standard for prostate cancer diagnosis. Transrectal biopsy is a relatively simple office technique that requires no sedation or analgesia. The location of the biopsy is often determined by findings on rectal examination or ultrasonography. However,

in many men, these tests are normal, and the diagnosis of prostate cancer may be made by blind prostate biopsies.

In the standard ultrasound-guided sextant biopsy, a specimen is removed with a biopsy gun from any suspicious areas (e.g., by rectal examination or TRUS) followed by six tissue cores from the base, midzone, and apical areas of the right and left lobes of the gland. The most common procedure-related complications in one series of 5802 TRUS guided sextant biopsies were hematospermia (51%), hematuria (23% longer than three days), fever (3.5%) and rectal bleeding (1.3%) [46]. Less than 1% developed urinary retention or required hospitalization, which was usually for urosepsis [46].

In many parts of the developed countries, the sextant biopsy has been largely replaced by extended biopsy schema that sample more areas of the gland, particularly the lateral aspects. When more than six biopsies are taken, some investigators have reported improved prostate cancer detection rates [39, 40, and 48]. As an example, in one study of 483 men with serum PSA concentrations 4.0 ng/mL or higher who underwent routine sextant biopsies plus lateral biopsies of the peripheral zone at the base and mid gland for a total of 10 biopsies [49]. The ten-biopsy scheme detected 96% of the cancers while traditional sextant biopsy missed 20%. Eliminating the midlobar base biopsies, an eight-biopsy scheme, maintained a detection rate of 95%. A standard ten-core biopsy scheme has been suggested by some [39], while others recommend a 12-site biopsy scheme to optimize cancer detection [41]. Compared to sextant biopsies, more extensive biopsy schemes are not associated with more abdominal or rectal pain, although hematochezia and hematospermia may be more frequent [42].

Transrectal prostate biopsy is an imperfect test. A substantial number of men who have negative results on an initial biopsy but persistently high serum PSA concentrations will have cancer diagnosed on subsequent biopsies [43].

K. REPEAT BIOPSY

Because prostate cancer is often a multifocal disease and the sampled volume is small with a standard needle biopsy, repeat evaluation may be appropriate in the face of a persisting suspicion of prostate cancer if the initial set of biopsies is negative. Many urologists recommend a repeat ultrasound-guided biopsy at six or eight weeks in such patients. In one report, cancer was detected in 83 of 820 (10%) second biopsies [48]. Third and fourth biopsy attempts at six or eight-week intervals yielded a cancer diagnosis in 4 to 5% of cases. In other series, up to one-fourth of cancers are missed on the initial biopsy [48].

L. MOLECULAR DETECTION IN URINE

Several urinary assays to detect transitional cell cancer of the urinary tract rely upon the presence of molecular alterations or other biomarkers that are specific for bladder cancer. Molecular assays for urinary detection of prostate cancer are beginning to be explored. Initial studies suggest that these tests have very high specificity, thereby permitting the identification of men with a high serum PSA concentration due to BPH.

Promoter hypermethylation of the glutathione S-transferase (GSTP1) gene is one of the earliest molecular changes in prostate cancer, and a test has been developed for urinary detection after prostatic massage [50]. In one study of 45 men with BPH and 40 men with prostate cancer, the overall sensitivity and specificity for the detection of cancer were 73 and 98%, respectively. The sensitivity was similar in men with early-stage disease).[52]

Others have evaluated an assay for telomerase in urine as a molecular marker of prostate cancer. In one series of 36 men undergoing either radical prostatectomy or prostatic needle biopsies, urine specimens were obtained following prostate massage, and the results correlated with histologic findings. The sensitivity and specificity for prostate cancer were 58% and 100%, respectively.[53]

M. COMPLETING THE DIAGNOSTIC AND STAGINGEVALUATION

If a prostate biopsy specimen is interpreted as containing carcinoma, additional evaluation or clinical staging is required to determine the extend of spread. Determining the correct stage of prostate cancer is critical. All of the potentially curative therapies are associated with major complications; these risks can be justified only if the treatment has a reasonable chance of achieving a cure.

Overall survival at ten years after radical prostatectomy or radiation therapy is high, but the likelihood of remaining disease free (as evidenced by an undetectable serum PSA) at ten years following treatment is related to whether the cancer is specimen confined, the extent of extracapsular extension, and whether the surgical margins of excision are positive. Thus, the primary goal of the staging evaluation is to rule out the presence of disease outside of the prostate gland, and to assess the likelihood of finding potentially respectable, organ-confined disease.

N. TNM STAGING SYSTEM

The tumour-node-metastasis (TNM) system is the most popular method of staging prostate cancer. Men are assigned a clinical stage, or stage is determined after a pathologist has evaluated a radical prostatectomy specimen. A man who has a palpable nodule on one side of the prostate gland, but on biopsy has cancer found on both lobes is still given the clinical stage of T2, even though further evaluation of the biopsy may demonstrate more extensive cancer. Impalpable lesions that are visible on TRUS are designated T2 rather than T1c [54].

The definition of T stage by the American Joint Committee on Cancer (AJCC) staging criteria has evolved over the last 15 years. The 1992 revision of the AJCC staging criteria defined the following tumour stages:[55]

- T1 tumours are microscopic and neither palpable nor visible on TRUS.
- T2 are palpable and appear confined to the gland
- T3 tumours protrude beyond the prostate capsule or into the seminal vesicles.

❖ T4 tumours are fixed and have extended well beyond the prostate.

The 1997 revision of the AJCC staging system, T3a disease was defined by extracapsular extension, and T3b tumours involved one or both seminal vesicles. The 1997 revision subdivided T2 disease into two (T2a and T2b) rather than three (T2a, T2b, T2c) groups, a consolidation that obscured a significant difference in outcome between patients with stage T2a and T2b disease [56]. As a result, the most recent 2002 AJCC staging system once again subdivides stage T2 disease into three categories .[56]

O. GLEASON GRADE

Analysis of tumour histology (Gleason grade) provides some index of prognosis and may also guide local therapy. With the Gleason histological scoring system, tumours are graded from one to five based on the degree of glandular differentiation.

A primary score and a secondary score is reported, and combined to form the Gleason score. As an example, if a biopsy consists of predominantly grade three and secondarily grade four disease, the combined score is "three plus four" or seven. The most differentiated cancers have a score of "one plus one" or two; the most undifferentiated cancers are scored as "five plus five" or ten. Combined scores (primary and secondary scores) of two, three, and four usually represent well-differentiated or low-grade cancers; scores of five, six or seven represent moderately differentiated cancers; and scores of eight, nine or ten represent poorly differentiated (high-grade) cancers. The prognosis is directly related to the pattern score.[58]

P. CT SCAN

Although a CT scan of the abdomen and pelvis is often recommended as part of the staging evaluation for newly diagnosed prostate cancer, the inability of CT scans to diagnose extracapsular extension and seminal vesicle invasion accurately is well known [66]. Most staging CT scans are negative for metastasis. In a series of 588 men with early-stage prostate cancer, only 7% had a positive scan [51]. Further, all 244 men with Gleason score two to seven, serum PSA values<15 ng/mL, and clinical stage T2b or less had negative CT scans.[67]

Staging CT scans should be considered in men who are going to be treated with external beam radiation therapy to design the treatment portals, and in men who have a high serum PSA concentration (>10 to 15 ng/mL) or Gleason score (greater than six), who have an increased likelihood of pelvic lymph node metastasis compared to men with lower serum PSA and Gleason score values.

A higher sensitivity for detecting nodal metastases (particularly within nodes between 5 and 10 mm in diameter) has been achieved using magnetic resonance imaging (MRI) with lymphotropic superparamagnetic iron oxide nanoparticles.[67] overall sensitivity compared to conventional MRI imaging 91 versus 35.4%) [67]. Although this method is promising for the preoperative identification of men with nodal metastases, it is not widely available,

Q. ENDORECTAL COIL MRI

MRI of the prostate gland utilizing an endorectal probe can determine with reasonable accuracy the likelihood of either seminal vesical involvement or extracapsular extension in patients who are thought to have clinically localized prostate cancer.

R. TRANSRECTAL ULTRASONOGRAPHY AND STAGING BIOPSY

Three dimensional transrectal ultrasonography is superior to 2-D imaging for staging localized prostate cancer. As an example, one study of 36 men compared standard 2-D and three-dimensional ultrasonography in patients with newly diagnosed clinically localized prostate cancer that then underwent radical prstatectomy [58]. Three-dimensional imaging correctly identified extracapsular extension in nine men but missed seminal vesicle invasion in one of two men.

Staging biopsies of either the seminal vesicles or extraprostatic tissue have been used to diagnose non-organ-confined prostate cancer. In one study of 100 ultrasound-guided seminal vesicle biopsies in 50 men with clinically localized prostate cancer who underwent radical prstatectomy, only six of 40 men (7.5%) with negative preoperative seminal vewsicle

biopsies had a positive biopsy at the time of surgery). However, at present, this is not a standard component of the diagnostic workup.[68]

S. PROSTASCINT SCAN

Single-photon emission computed tomography (SPECT) imaging uses a murine monoclonal antibody that targets prostate specific membrane antigen (PSMA) a membrane-bound glycoprotein that is highly restricted to the prostate (ProstaScint). This study is scored based upon a ratio of antigen detected in the prostate to muscle background (P/M). The use of the ProstaScint scan increases the detection of pelvic lymph node spread in men with prostate cancer. However, recognition of involved disease sites can be difficult, especially if involved nodes are near blood vessels. The sensitivity of the ProstaScint study for detection of malignant lymph nodes is 62%, markedly better than the sensitivity of CT scans of the pelvis 4%. The use ProstaScint combined with other predictors of lymph node involvement such as serum PSA value and Gleason score, may improve its diagnostic accuracy.[62]

JUSTIFICATION

Bladder outflow obstruction is common in the elderly and most of this is managed as benigh prostatic enlargement. Some of these patients also have undetected carcinoma of the prostate. Prostate cancer is the most common cancer in elderly Men above 60 years. The need for this study:

- To be able to detect the disease early especially in the young age group and decide on the mode of management.
- The need to do a local study to determine the incidence.
- In the era of PSA and ultrasonography if the incidence has changed locally.

OBJECTIVES

Primary objective

- To determine incidence of undetected carcinoma of the prostate

Secondary objective

- To determine histological types of undetected carcinoma of the prostate
- To determine PSA levels in patients with undetected carcinoma of the prostate
- To determine minimum age at which undetected carcinoma of the prostate was found.
- To determine the population distribution within our country of the patients affected.

PATIENTS AND METHODS

Study design

This was eight months hospital based descriptive prospective study carried out between August 2005 and April 2006, to determine the incidence of undetected carcinoma of the prostate. The main outcomes of interest were incidence of undetected carcinoma, histological types, and age of patients with undetected carcinoma, , PSA levels, residence of the patients.

Selection of patients

Patients with Bladder Outlet Obstruction (BOO) caused by benign prostatic enlargement were taken as study population. Patients were evaluated with DRE, ultrasonograph and PSA testing to rule out malignancy. One hundred and eight patients were admitted through surgical outpatient clinic and consultant clinics to general surgical wards and private wing of the hospital for prostatectomy. Those who did not meet inclusion criteria as set out were not included into the study.

Those who were admitted were clerked, examined including DRE and the investigator confirmed diagnosis of BPE. Patients were prepared for theatre, blood for U/E; HB were taken. Informed consent for participation into the study plus consent for surgery was taken. The patients were prepared and taken to theatre. The consultant urologist selected choice for the type of prostatectomy.

On prostatectomy there was no evidence of intra-operative malignancy as each enucleated adenoma was macroscopillary examined and there was no evidence of malignancy. Specimens were taken for histology. We managed to get histology results for 106 patients. These were the patients who were included into the study we were not able to trace histology results for two patients. These patients were excluded from the study, remaining with 106 patients.

After prostatectomy, patients were taken to the ward on continuous bladder irrigation. After the irrigation was clear, catheter was removed and patients observed, if they were stable, they

were discharged from the hospital for follow-up in the clinic. Histology results were collected from the laboratory and results explained to the patients.

Data was recorded by using pre-designed data collection forms including age, date of admission, physical finding, including DRE, investigations, type of prostatectomy and place of birth.

Setting

The study was carried out at Kenyatta National Hospital, which is a public tertiary care teaching hospital, that also house the University of Nairobi Medical School. It serves as a referral hospital-receiving patients from provincial, district and mission hospitals in Kenya.

The hospital has a capacity of 2000 beds. It also serves as a general hospital for an estimated population of 3 million people in cosmopolitan Nairobi area.

SAMPLE SIZE

The sample size was based on the patients presented in Kenyatta National Hospital, who were to undergo prostatectomy for BPE.

The sample size (n); is derived by the formula $n = Z^2Pq /d^2$

Where p is the incidence, d the confidence limit,

q = (1-p) and Z is the standard deviation of the 95^{th} percentile (1.96).

N= sample size

P= estimated prevalence

D= desired width of confidence interval

Z^2 (1-a) = square of the normal standard deviation corresponding to 95% confidence interval

Using incidence of 6.4%

$$N = \frac{1.962 \times 0.064(1-0.064)}{0.05}$$

$$= \frac{3.8416 \times 0.064 \times 0.936}{0.25} = \frac{0.2301272}{0.0025}$$

= 92

SURGICAL TECHNIQUE

The three main surgical techniques were.

i) Millins prostatectomy

ii) Freyer's prostatectomy

iii) Transurethral resection of the prostate.

CRITERIA FOR ENTRY

1. Patients of all age group presenting with symptoms of BPE.
2. Patients with PSA less than 10ng/l
3. Patients with ultrasound findings not suspicious of carcinoma of the prostate.
4. Patients with normal findings on Digital rectal examination (DRE).

EXCLUSION CRITERIA

Patients with no histology results.

ETHICAL CONSIDERATION

The Kenyatta National Hospital ethical research committee (ref KNH-ERC/01/2725) approved the study protocol.

Informed consent was sought in all the patients.

LIMITATION OF THE STUDY

- The study was not an analytical study and therefore it is difficult to make conclusions on some findings
- Ultrasound reporting is user dependent some of the finding could have been labeled negative and yet they were positive and vice versa
- Histology reports could not give full histological classification.
- In some histology report Gleason score was not indicated making it difficult to grade the disease

DATA ANALYSIS

Data collected was carefully studied and entered into computer. Data was analysed by statistician using SPSS and Microsoft excel.

RESULTS

Out of 106 patients entered into the study seven(7) patients were found to have undetected carcinoma of the prostate. These patients had PSA levels ranging from 0-4ng/ml. This is *shown in the figure 1 below.*

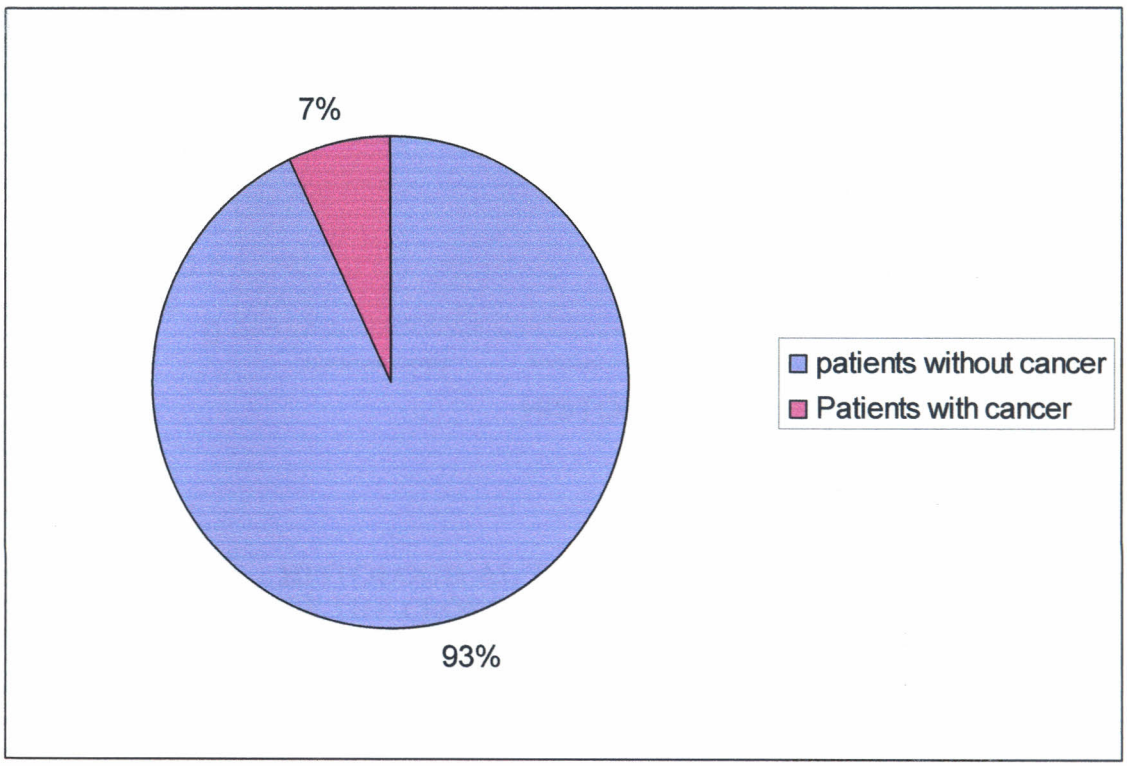

FIGURE I INCIDENCE OF UNDETECTED CARCINOMA OF THE PROSTATE PSA<= 4 WAS 6.6%

Figure 2 below presents histological classification of undetected carcinoma of the prostate.

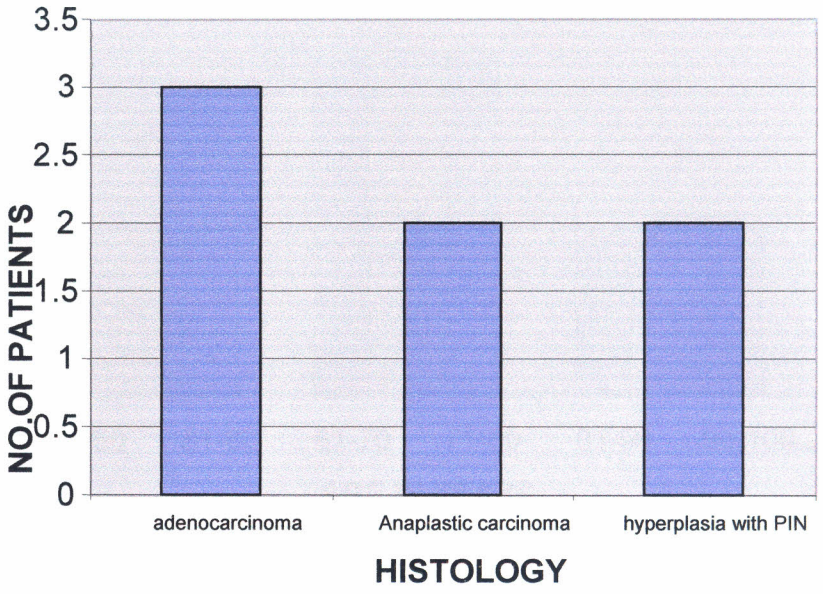

FIGURE 2: HISTOLOGICAL TYPE FOR UNDETECTED CARCINOMA OF THE PROSTATE

The bar chart above shows Histological types. Out of the seven patients who had undetected carcinoma of the prostate 3 had Adenocarcinoma, 2 were found to have Anaplastic Carcinoma and another 2 had hyperplasia with PIN.

Fig 3 shows proportion of patients in each age group

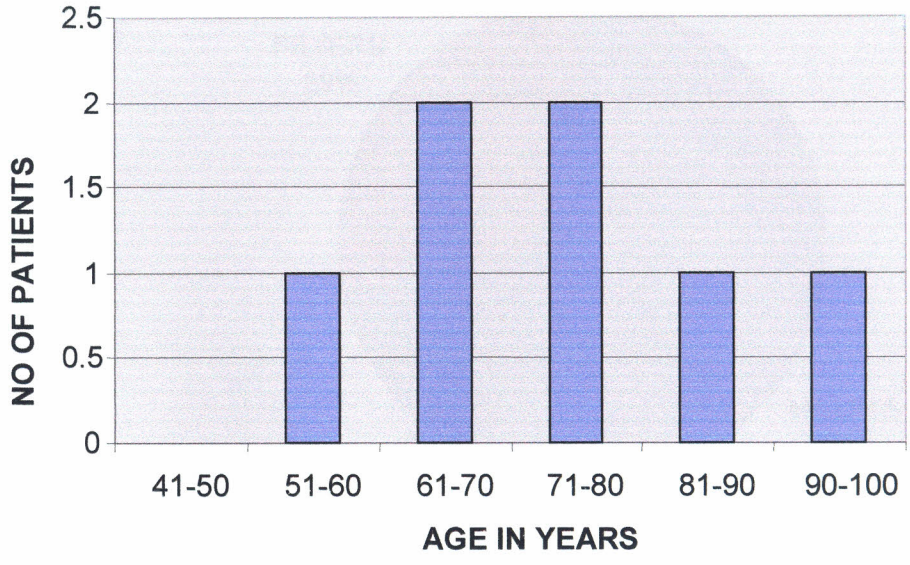

FIGURE 3: AGE RANGE FOR UNDETECTED CARCINOMA OF THE PROSTATE

Of the seven patients with undetected carcinoma of the prostate, majority of them were in the age range of between 61-80 years. That is 4 out of 7 patients. Other age ranges of 51-60 years, 81-90 years and 90-100 years, had one patient each.

The pie chart below depicts the types of prostatectomy

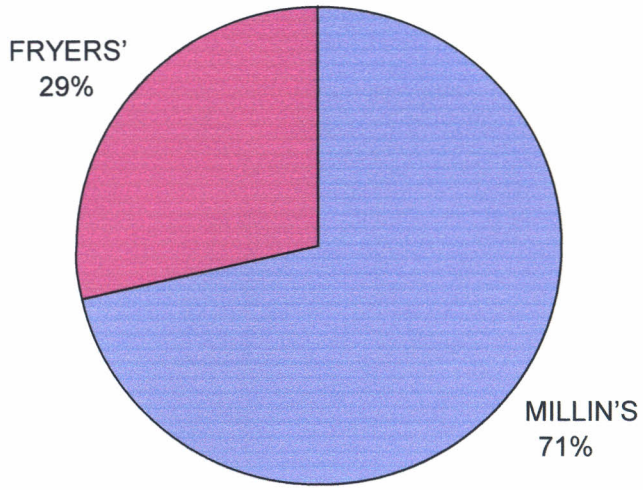

FIGURE 4: TYPE OF PROSTATECTOMY FOR PATIENTS WITH UNDETECTED CARCINOMA OF THE PROSTATE

Of the seven patients whose Histology revealed undetected carcinoma of the prostate, 71% underwent Millin's prostatectomy and 29%, underwent Fryers' prostatectomy.

Fig 5: below shows the PSA range for patients with cancer

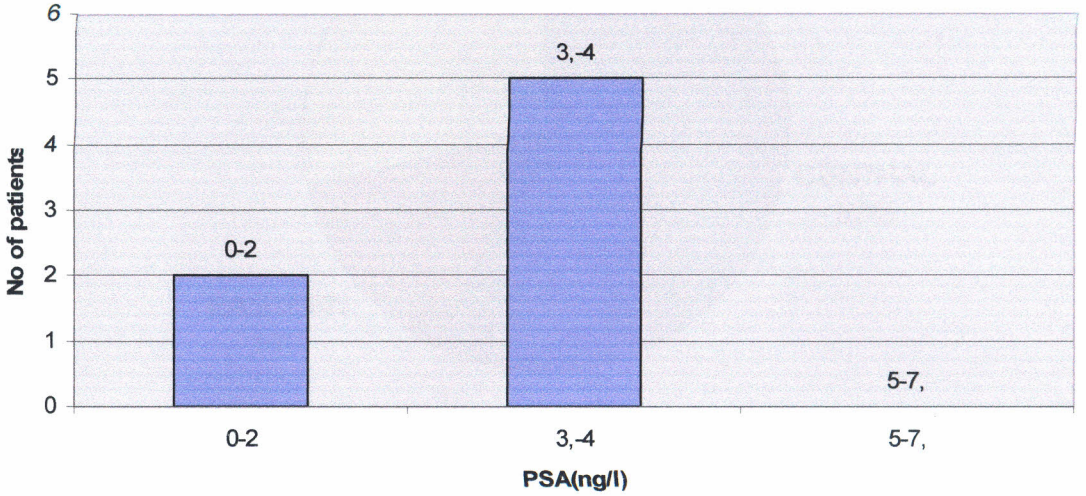

FIGURE 5 PSA FOR PATIENTS WITH UNDETECTED CARCINOMA OF THE PROSTATE

PSA for all the patients entered into the study was below 4ng/l. Of the seven patients who had undetected Adenocarcinoma, 5 had PSA of between 3-4ng/l, and 2 patients had PSA of between 0-2ng/l.

The pie chart below shows the distribution of patients in each province

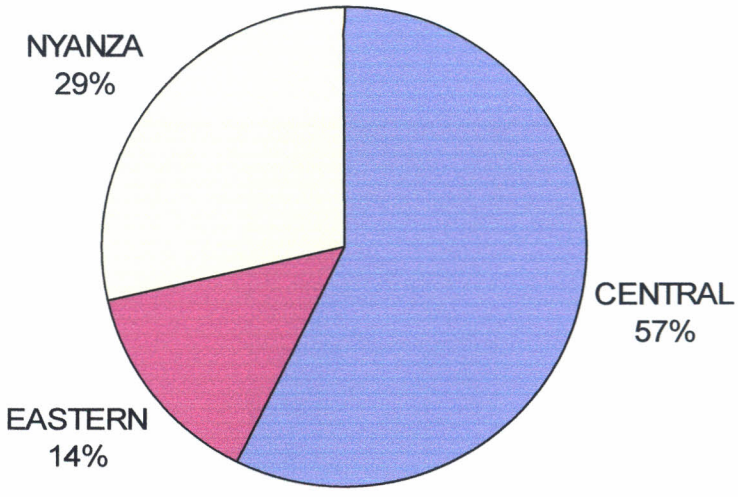

FIGURE 6 RESIDENCE OF PATIENTS WITH UNDETECTED CARCINOMA OF THE PROTATE

Majority of the patients with undetected carcinoma of the prostate came from Central Province 57%. Followed by Nyanza Province 29% and lastly Eastern Province 14%.

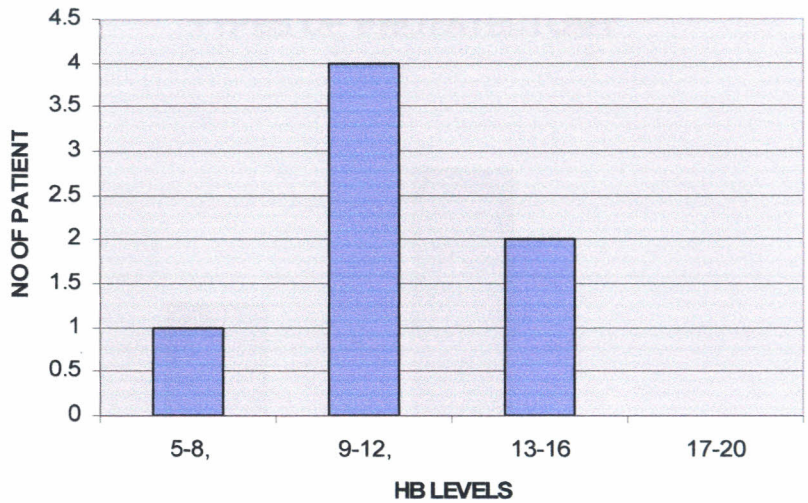

FIGURE 7 HB FOR PATIENTS WITH UNDETECTED CARCINOMA OF THE PROSTATE

Four patients with approximately 57% of the patients with cancer had Hb levels of between 9-12g/dl. Followed with by 2 patients (28.6%) with Hb levels of between 13-16g/dl and only 1 patient had Hb levels below 8g/dl.

Fig 8 shows the number of patients who underwent prostatectomy

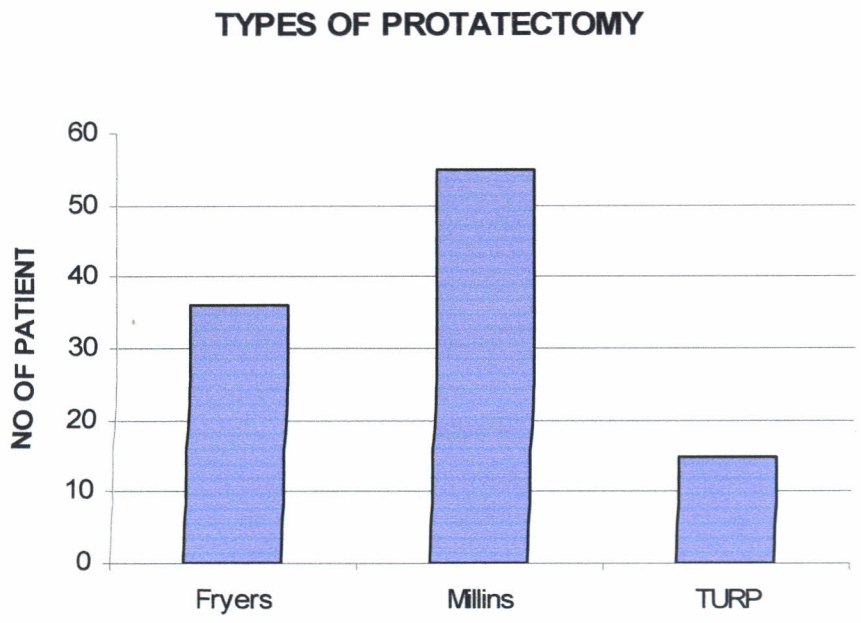

Figure 8 Type of prostatectomy done for patients with BPE

Of the 106 patients who underwent prostatectomy for BPE, Millin's prostatectomy was performed on 56 patients (53%). Followed by Fryers (33%) and lastly TURP (14%).

Fig 9 shows age distribution for patients with *BPE*

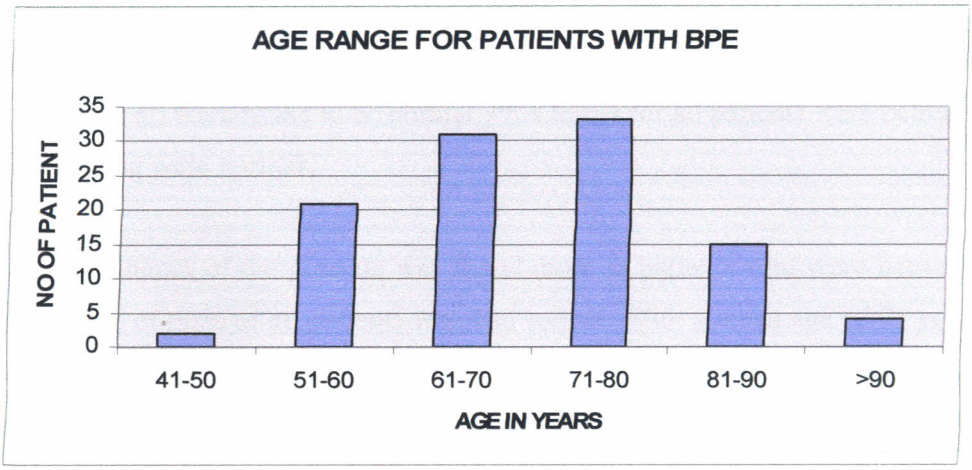

FIGURE 9 THE AGE RANGE OF PATINTS DONE PROSTATECTOMY FOR BPE

As shown above, majority of the patients who underwent prostatectomy for *BPE were in the* age range of 71-80years consisting of 35 patients. Followed by age range of 61-70 years 32 patients. Others of age range 51-60 years 21 patients, 81-90 years 15 patients, less than 50 years 1 patient and greater than 90 years 2 patients. Majority of the patients were in the age range of 61-80 years comprising of 59.4% of all patients.

DISCUSSION

This study of undetected carcinoma of the prostate was carried out on men who presented with lower urinary tract symptoms. Malignancy had been ruled out on, clinical examination, ultrasonography and prostate specific antigen (PSA). Digital rectal examination was done to assess the size, consistency, fixity to the pelvic walls, state of median sulcus and rectal mucosa of which all were found to be normal. PSA levels for all patients were below 4g/l and ultrasound finding were normal.

Undetected carcinoma of the prostate was found more in patients who were between 61-80 years comprising of 60% of all patients who had cancer. With a mean age of 75 years. Only one patient with cancer of the prostate was below the 61- 100 years range. This one patient was actually 60 years old. All our patients with undetected carcinoma of the prostate were 60 years and above. Ghali et al in a similar study in Saudi Arabia found that all their patients with undetected carcinoma of the prostate were older than 70 years of age.[13] In another study in Brazil done by Bill et al found that 66% of the patients were above a 60 years of age.[29] In the earlier study done here in KNH by Reeves HK, 66% of the patients with incidental carcinoma of the prostate were between 60- 79-age range and 82% were above 60 years of age. Majority of our patients with undetected carcinoma of the prostate are above 60 years of age although our patients are younger than those patients in Saudi Arabia. Studies done elsewhere, show that the highest reported incidence is in blacks in the USA, South American, and Scandinavian countries, the disease occurs in younger age groups and is more aggressive . While Asian countries, such as Japan and China report low incidence of this disease [27]

The study revealed incidence of undetected carcinoma of the prostate to be 6.6% at Kenyatta National Hospital, based on negative DRE,normal ultrasonography and PSA below 4ng/ml. The incidence dropped to 6.6% from a previous one of 12.3% in a study done by Reeves H.K.[71] in pre-PSA and ultrasonography era representing 50% drop. This study compares well with a similar study done by Richard EZ et al in Karl university hospital in Austria in 2003, which showed an incidence of 6.4 (a drop of more than 50% from pre- PSA era where the incidence was 13%.) [63] . A similar study done in Saudi Arabia by Hishman et al reported incidence of undetected carcinoma of the prostate to be 1.6% [13]. Yet in Another study done in University hospital in Madrid by Herranz AF et al, 1997 incidence of undetected carcinoma

of the prostate in PSA era was 6%. [66] Our results of incidence of undetected carcinoma of the prostate compare well with other international findings.

The incidence of prostate cancer detected in specimen after Cystoprostatectomy for invasive bladder cancer in patients with negative PSA and DRE findings has been reported to be 45% greater than rates reported in Autopsies (30%- 40%).[70]

The histological pattern of undetected carcinoma of the prostate show adenocarcinoma is the commonest type with 42% followed by prostatic intraepithelial neoplasm (PIN) at 29% and anaplastic carcinoma also at 29%. Many pathologist consider PIN to be a pre invasive stage of some prostate cancer. In some instance it is recorded as carcinoma in situ and classified a high grade or low grade. In the previous study by Reeves HK. adenocarcinoma was the commonest with 60%. Others were not classified. A study done in Brazil by Bills et al put figures for Adenocarcinoma to range between 42-92% [29] in histopology reporting our pathologist only reported 2 specimen as a Gleason score 5 and 8 respectively hence. This Gleason score has not been included in our results, but it is important for us to encourage our pathologist to include Gleason score in their reporting of histology results.
Our histology pattern of 42% of adenocarcinoma being the commonest followed by PIN and anaplastic compared well with other studies done [70]

Figures 4 and 8, shows the type of prostatectomy done, patients who underwent prostatectomy for BPE, open prostatectomy was performed on 86% of patients while TURP accounted for 14%. Millins prostatectomy was done almost as twice as freyers prostatectomy. All the seven patients with undetected carcinoma 71% had undergone millins prostatectomy and 30% freyers none had TURP. This in different world over now TURP is the Gold standard for prostatectomy.[63]

In this study all the seven patients with undetected carcinoma of the prostate had a PSA less than 4 ng/L, which is a normal reference level. This shows that with negative DRE ultrasonography and PSA < 4mg/dl you will still miss 6.6% of cancers. Routine biopsy in this patients would represent invasive overdiagnosis in more than 93%. Routine biopsy should be

done in those patients where PSA is rising up even if DRE, and ultrasonography are normal. In three studies of men aged 50 and above 136 out of 319 (43%)with prostate cancer had PSA below 4.0ng/ml, in prostate cancer prevention study 21% of cancers diagnosed had serum levels between 2.6 and 3.9ng/ml.[39] PSA in now important in monitoring response to treatment. Some investigators recommend a second TURP or biopsy after they find undetected carcinoma.[66]

Majority of patients with incidental carcinoma came from Central province followed by Eastern as shown in Fig 6. This is not clear; it could be due to proximity of central province to Kenyatta National Hospital however, this does not explain why Eastern province, which is closer to Nairobi, has fewer patients i.e. 14% as compared to Nyanza, which is further away from Nairobi. Aetiology of carcinoma of the prostate being multifactoral could be due to diet as Betacarotene consumption as well as Soya intake are protective [17]. Still environmental factors such as chemical, in rubber, textile and drugs play a role [9]. The two areas seem to have more factories with above chemicals. We need further studies in epidemiology of prostate cancer in Kenya.

Haemoglobin in patients with cancer of the prostate was within normal ranges pre-operatively. One would expect this disease process being neoplasm patients to have low HB. This was not the case in this study. Probably there is no relationship between pre-operative HB and undetected carcinoma of the prostate but further studies need to be done.

CONCLUSION

1. This incidence of undetected carcinoma of the prostate was 6.6%, in the Age group of 60-100 years with mean of 75 years and peak 70-80 years. This incidence is similar to others observed in other countries being significantly higher in older patients.
2. In the era of PSA screening and ultrasonography studies before surgery the rate of undetected carcinoma of the prostate has decreased by more than 50%
3. Adenocarcinoma is the commonest histological type of undetected carcinoma of the prostate.
4. Undetected carcinoma of the prostate is rare below the age of 50 years.

RECOMMENDATIONS

1. All specimens after prostatectomy should be taken for histology as there is a significant incidence of undetected carcinoma .
2. Possibly patients with histologically confirmed BPE should undergo regular follow up because later development of prostate cancer cannot be excluded
3. Need to do a study to determine incidence of undetected carcinoma of the prostate by performing open prostatectomy and TURP.
4. Need for a study that will examine whether the incidence of undetected carcinoma of the prostate correlates with PSA levels

REFERENCES

1. **Moore R.A:** The morphology of small prostatic carcinoma. *J. Urol, 1935; 33-234*
2. **Rich A.R.:** On the frequency of occurrence of occult carcinoma of the prostate. *J. Urol, 1935; 215-223*
3. **Andrews G.S.:** Latent carcinoma of the prostate. *J. Clin Pathol, 1949; 2:197-208*
4. **Isaacs J.T.:** Molecular markers for prostate cancer metastasis: developing diagnostic methods for predicting the aggressiveness of prostate cancer. *A. M. J. Pathol, 1997; 150:1511-1521*
5. Clark O., Clark L.G.O., Ferreira U., Denardi F., Rodriques Netto J. N.: Uro-oncologia beseada em evidencias. Volume 1-prostata, sao Paulo, Sociedade Brasileira de urologia 2001; 22
6. **Scardino P.T., Weaver R, Hudson M.A.:** Early detection of prostate cancer. *Hum Pathol, 1997; 23:211-222*
7. **Whitnore W.F.:** Localised prostatic cancer: management and detection *issues lancet, 1994; 343: 1263-126*
8. **Sheldom C.A., Williams R.D. etal incidental carcinoma of the prostate:** a review of the litrature and critical reappraisal of the classification *J. Urol 1980; 124:626-631*
9. **Boyle P., Maisonneuve P., Napalkov P:** Geographical and temporal patterns of incidence and mortality from prostate cancer, urology 1945; 46 (Suppl 3A): 47-55.
10. **Mottet A. N. et al:** Cancer of the prostate. I. Epidemiol prog urol 1995; 31-7.
11. **Levy 1G et al.** Prostate **cancer in Canada:** Rising incidence or increased detection; Can Med Ass J 1993; 617-24.
12. **Catalona W. J. et al:** Detection of the organ confined prostate cancer is increased through prostate specific antigen based screening JANA 1993; 270: 948-54.
13. **Ghali A. N., et al:** Clinical features and surgical outcome of benign prostatic hyper plasia. Ann Saudi Med 1996; 166-70.
14. **Anthanase B. et al:** Histologic Carcinoma of the prostate in Autopsies Brazilian Journal of urology. Vol. 28 (3) 2002; 197-206
15. **Relly P.H.O:** Aetiology and pathology of prostate cancer. Special feature 1999 volume 6

16. **Smith J.A. Cho Y.H. Management** of stage A prostate cancer. Urol Clin North A.N. 1990; 17:769-777

17. **Stamey T.A., Yemoto C.M., McNeal J.E., Sigal B.M., Johnstone I.N:** Prostate cancer is highly predictable; Prognostic equation based on all Morphological variables in radical prostatectomy specimens J. Urol, 163: 1155-1160, 2000.

18. **Heshmat, M.Y; Kovi, J. Herson, J.** Epidemiologic association between gonorrhea and prostatic carcinoma. *Urolog 1975; 6:457*

19. **Rotkin I.D.** Studies in the epidemiology of prostate cancer expanding sampling. Cancer treatment report, 1977;61:163

20. **Ross, R.K; Deapen, D; Casagrade I. et al.** A Cohort of mortality from cancer of the prostate in catholic priests. *Brit. J. of Cancer 1981, 43: 223 – 235.*

21. **Epitoriah.** Sex education in schools: peers to the rescue? *Lancet 1994; 344: 899-900.*

22. **Herbert, J.T; Birkoff, J.D; Feorino, P.M. et al.** Herpes simplex type 2 and cancer of the prostate *urology, 1976, 116: 1008 – 1911.*

23. **Cerifano, Y.M; Kaufman, D.E; Zam, Z.S. et al.** Herpes virus in prostate cancer cells. *Virology, 1973, 12: 1608.*

24. **Feminella, J. J; Lattimer, J.K.** An apparent increase in genital carcinomas among men with prostatic carcinoma. *Pirquent Bulletin of Clinical Medicine, 1974; 20: 3- 9.*

25. **McCombs, R.M.** Role of oncarnaviruses in carcinoma of the prostate. *Cancer treatment report 1977; 61: 13.*

26. **Viola, M.V; Fromowitz, P; Oravex, et al.** Latent carcinoma of the prostate autopsy in seven areas. *International J. of cancer 1977, 20: 680 – 688.*

27. **Richard Clements et al.** Prostate carcinoma. *E.Medicine, February 3, 2004.*

28. **Moore, R.A.** The evolution and involution of prostate gland. *A.M. J. Pathol, 1936; 12: 599 – 624.*

29. **Billis, A.** Prostatic atrophy: An autopsy of a histologic mimic of adenocarcinoma. *Med. Pathol, 1998, 11: 47 – 54.*

30. **Grignon D.J; Sakr, W.A.** Zonal origin of prostatic adenocarcinoma; are there biologic differences between transition zone and peripheral zone adenocarcinoma of the prostate gland: *J. Cell Biochem (SUPPL.) 1994; 19: 267 – 269.*

31. **Bostwick Da**. Neoplasms of the prostate, In: Urologic Surgical Pathology, Botswick Da, Eble JN (eds), *St. Louis, Mosby,* 1991; *386.*

32. **Greene, D.R; Wheeler, T.M; Egawa S; Dunn, J.K; Scardino, P.T**. A comparison of the morphological features of cancer arising in the transition zone and in the peripheral zone of the prostate. *J. Urol, 1991; 146: 1069 – 1076.*

33. **Greene, D.R; Wheeler, T.M; Egawa, S; Weaver, R.P; Scardino P.**T. Relationship between clinical stage and histological zone of origin in early prostate cancer: Morphometric analysis. *Br. J. Uro, 1991; 68: 499 – 509.*

34. **Lee, F; Siders, D.B; Torp Pedersen, S.T; Kirscht, S.L; McHugh, T.A; Mitchell, A.E.** Prostate cancer: Transrectal ultrasound and pathology comparison. A preliminary study of outer gland (peripheral and central zone) and inner gland (transition zone) cancer. *Cancer, 1991; 67: 1132 – 1142.*

35. **Presti, J.C. Jr; Chang, J.J; Bhargava, V. et al**. The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: results of a prospective clinical trial. *J. Urol. 2000; 163:163.*

36. **Chamberkain, N.I; Driver E.D; Miesfeld R.L**. The length and location of CAG tricucleotide repeats in the androgen receptor N- terminal domain affect transactivation function. *Nucleic acids Res. 1994; 22: 3181 – 3186.*

37. **Nam R.K; Echaji Y; Krahn M.D; Hakimi J; Ho M; Chu W. et al**. Significance of the CAG repeat polymorphism of the androgen receptor gene in prostate cancer progression. *J. Urol, 2000; 164: 567-572.*

38. **Steinberg G.D. et al:** An analysis of watchful waiting for clinically localized prostate cancer J. Urol, 1998; 159: 1431-1436.

39. **Brasso K, et al:** Mortality of patients with clinically localised prostate cancer treated with observation for 10 years or longer: a Population based study J. Urol, 1999;161: 524-528.

40. **Coley, C.M; Barry, M.J; Fleming, C. et al**. Early detection of prostate cancer. Part 1:prior probability and effectiveness of tests. *Ann Intern Med 1997; 126:394*

41. **Pedersen, K.V, Carlsson, P.; Varenhorst, E.; Lofman, O**. Screening for carcinoma of the prostate by digital rectal examination in a randomly selected population. *BMJ 1990; 300:1041.*

42. **Chodak, G.W; Keller, P., Schoenberg, H.W.** Assessment of screening for prostate cancer using the digital rectal examination. *J. Urol 1989; 141:1136.*

43. **Richie, J.P, Catalona, W.J, Ahmann, R.R, et al.** Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology 1993; 42:365.*

44. **Partin, A.W; Carter, H.B; Chan, D.W. et al.** Prostate specific antigen in the staging of localized prostate cancer: Influence of tumour differentiation, tumour volume and benign hyperplasia. *J. Urol 1990; 143:747.*

45. **Lange, P.H; Ercole, C.J; Lightner, D.J. et al.** The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J. Urol 1989; 141:873.*

46. **Hudson, M.A; Bahnson, R.R; Catalona, W.J.** Clinical use of prostate specific antigen in patients with prostate cancer. *J. Urol 1989; 142:1011.*

47. **Thompson, I.M; Goodman, P.J; Tangen, C.M. et al.** The influence of finasteride on the development of prostate cancer. *N. Engl. J. Med. 2003; 349:215.*

48. **Gustafsson, O; Norming, U, Almgard, L.E. et al.** Diagnostic methods in the detection of prostate cancer: A study of a randomly selected population of 2,400 men. *J. Urol 1992; 148:1827.*

49. **Catalona, W.J; Richie, J.P; Ahmann, F.R; et al.** Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer:Results of a multicenter clinical trial of 6,630 men. *J. Urol 1994; 151:1283.*

50. **Yamamoto, T; Ito, K; Ohi, M; Kubota, Y.** Diagnostic significance of digital rectal examination and transrectal ultrasonography in men with prostate-specific antigen levels of 4 ng/l or less. *Urology 2001; 58:994.*

51. **Roehl, K.A; Antenor, J.A.; Catalona, W.J.** Serial Biopsy Results in Prostate Cancer Screening Study. *J. Urol 2002; 167:2435.*

52. **Goessl, C; Muller, M; Heicappell, R. et al.** DNA-based detection of prostate cancer in urine after prostatic massage. *Urology 2001; 58:335.*

53. **Meid, F.H; Gygi, C.M; Leisinger, H. J. et al.** The use of telemerase activity for the detection of prostatic cancer cells after prostatic massage. *J. Urol. 2001; 165:1802.*

54. **Augustin, H; Graefen, M; Palisaar, J. et al.** Prognostic significance of visible lesions on transrectal ultrasound in impalpable prostate cancers: implications for staging. *J. Clin. Oncol. 2003; 21:2860.*

55. **Han, M; Walsh, P.C; Partin, A. W; Rodriguez, R.** Ability of the 1992 and 1997 American Joint Committee on cancer staging systems for prostate cancer to predict progression-free survival after radical prostatectomy for stage T2 disease. *J. Urol 2000; 164:89.*

56. **Greene, F.L; Page, D.L; Fleming, I.D. et al (Eds).** AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 6th Ed. *Springer-Verlag, New York, 2002; 310-311.*

57. **Kleer, E; Larson-Keller, J.J; Zincke, H; Oesterling, J.E.** Ability of preoperative serum prostate-specific antigen value to predict pathologic stage and DNA ploidy: influence of clinical stage and tumour grade. *Urology 1993; 41:207.*

58. **Partin, A.W; Yoo, J; Carte, H.B. et al.** The use of prostate specific antigen clinical stage and Gleason's core to predict pathological stage in men with localized prostate cancer. *J. Urol 1993; 150:110.*

59. **Chybowski, F.M; Larson Keller, J.J; Bergstralh, E.J; Oesterling, J.E.** Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J. Urol 1991; 145:313.*

60. **Zincke, H; Oesterling, J.E; Blute, M.L. et al.** Long-term (15 years) results aftewr radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. *J. Urol 1994; 152:1817.*

61. **Murphy, G.P; Mettlin, C; Menk, H. et al.** National patterns of prostate cancer treatment by radical prostatectomy: Results of a survey by the American College of Surgeons Commission on Cancer. *J. Urol. 1994; 152:1817.*

62. **Sodee, D.B; Ellis, R.J et al.** Prostate cancer and prostate bed SPECT imaging with ProstaScint; Semiquantitative correlation with prostatic biopsy results. Prostate 1998; 37:140

63. **Richard, E.Z. Et al**; Did the rate of incidental prostate cancer change in the era of PSA testing. Urology 2003; 62:451-455,

64. **McNeal JE,et al**: Stage A versus B adenocarcinoma of the prostate: morphological comparison and biological significance. J. Urol 1988;139: 61-65

65. **Andren O. et al:** Incidental prostate cancer prognostic factors. A population based study from orebro Sweden Department of urology and pathology university hospital of Orebro Sweden.

66. **Herranz A F.**et al: Incidental Prostate cancer servicio de urologia, H.G.U Grigonio Maranon Madrid.

67. **Lee, N; Fawaaz, R; Olsson, C.A.et al:** Which patients with newly digonised prostate cancer need a radionuclide bone scan? An analysis based on 631 patients. Int. J. Radiant. Oncol. Biol. Phys. 2000; 48:1443.

68. **Lee, N; New House, H.H; Olsson, C.A. et al.** Which patients with newly digonised prostate cancer need a computed tomography scan of the abdomen and pelvis? An analysis based on 588 patients. Urology 1999; 54:490.

69. **Monda JM et al:** Prostate specific antigen cannot distinguish stage Tia(AI) prostate cancer from benign prostatic hypoplasia Department of Urology, Mayo clinic Minnesota 55905.

70. **Reeves H K :** Incidental carcinoma of the prostate at Kenyatta national hospital 1993; M. Med. Dissertation

APPENDICES

A. APPENDIX 1: INFORMED CONSENT –EXPLANATION

Title of study: Undetected carcinoma of the prostate

Institution: Kenyatta National Hospital University of Nairobi

Principle investigator: Dr Maurice N. Wakwabubi MBchB (Nrb)

It is important for you to understand the following general principles that apply to the participants in this study.

i. Participation is voluntary
ii. You are at liberty to withdraw from this study or any part of this study at any time
iii. Refusal to participate will involve no penalty or loss of benefits

After the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of this study.

Introduction

Prostate cancer is the most common cancer in men. The incidence of the disease has been increasing. It is important to do a study that will determine the incidence of undetected carcinoma of the prostate, in order to sensitise medical profession, the importance of thorough pathological evaluation of prostate specimen in order to detect early carcinoma and decide on the mode of management.

Procedure to be followed

(i) Questionnaire

If you agree to participate in this study, you will answer some questions about your symptoms

(ii) Clinical examination

You will then be required to have a thorough body examination

(iii) Lab test

You may be requested to undergo some laboratory tests like prostatic specimen antigen to rule out or confirm the state of your disease

(iv) Radiological test

You may be required to do prostatic ultrasonography

(v) If your prostate is enlarged and causing lower urinary tract symptoms you will berequired to undergo prostatectomy, specimen will be taken for histological evaluation and you will be told of the results

FOR INFORMATION OR ANSWER TO QUESTIONS CONCERNING YOUR RIGHTS AS A RESEARCH SUBJECT YOU MAY CONTACT

The chairperson of Kenyatta National Hospital ethical Committee

Acknowledge receipt of this informed consent explanation

SUBJECT'S NAME .....

SUBJECT'S SIGNATURE .....

STUDY NUMBER .....

DATE .....

KISWAHILI

Kiini cha utafiti: saratani ya uvunde(prostate) ambayo haijagunduliwa

Chuo: Hospitali kuu ya Kenyatta Chuo kikuu cha Nairobi.

Mhusika mkuu: Dr. Maurice N. Wakwabubi MBchB (Nrb)

Ni muhimu wewe kuelewa mambo yafuatayo ambayo ni ya maana sana na itatumika kwa washiriki wa utafiti huu:

i. Kushiriki ni kwa kujitolea.

ii. Una uhuru wa kujiondoa kutoka kwa utafiti huu au katika sehemu ya utafiti wakati wowote.

iii. Kukataa kushiriki hakuwa na uadhibifu au kukosa ufanisi.

Baada ya kuelezwa kwa dhadi, tafadhali uwe na uhuru wa kuuliza swali lolote ambalo litakuezesha kuelewa vizuri kuhusu hali ya utafiti.

Kitangulizi

Saratani ya uvunde ni saratani ambayo ina wapata sana waume. Vitokezi vya ugonjwa huu vimekuwa vikiongezeka.

Ni muhimu kijimbua kimasomo ya kuezesha kujua kusudi ya vitokezi vya saratani ya uvunde ili kuapasa habari wasomi maalum wa udaktari, umuhimu wa kufanya uchunguzi kwa dhadi viini vya specimen ya uvunde ili kutambua mapema seratani na kuamua mwenendo wa kuudhabidi.

Mtindo utakaofuatwa

i. Stakabathi ya maswali (questionnaire) Ikiwa unakubali kushiriki kwa utafiti huu, utajibu maswali kadhaa kuhusu dalili yako.
ii. Uchunguzi wa kiliniki. Utahitajika kufanyiwa uchunguzi dhabiti kwa mwili wako.
iii. Uchunguzi wa maabaraUnaweza kuhitajika kufanyiwa uchunguzi kwa maabara kujua kama viini kutokana na uvunde ili kutupilia mbali au kutambua hali ya ugonjwa wako.
iv. Uchunguzi wa radiologiaUnaweza takiwa kufanyiwa uchunguzi wa picha ya uvunde (prostatic ultrasonography.)
v. Ikiwa uvunde wako umeongezeka kwa kiwango cha kusababisha mishipa ya chini ya mikojo kuwa na dalili, utatakiwa kuenenda upasuaji (prostatectomy.) Specimeni itachukuliwa ili kufanyiwa uchunguzi wa histologia (histological examination) na utaambiwa matokeo.

KWA UJUMBE AU JIBU LA SWALI KUHUSU HAKI YAKO KAMA MCHUNGUZWA UNAWEZA KUASILISHA KWA:

Mwenye kiti Hospitali kuu ya Kenyatta (ethical committee)

Udhibitishe baada ya kupokea ujumbe huu kwa kuelezwa kwa ufasaha.

JINA LA MUHUZISHWA.....

SAHIHI YA MUHUZISHWA.....

NUMBARI YA UTAFITI.....

TAREHE.....

B. APPENDIX 2: CONSENT FORM

I have understood the explanation by Dr M.N. Wakwabubi and hereby give informed consent to participate in the study:

1. I accept to participate in the study on my own free will
2. I accept to be interviewed concerning my illness and the answers to be recorded by Dr Wakwabubi.
3. I accept to be examined physically.
4. I understand that my participation is strictly voluntary and I can withdraw my consent at any point of the study; and that such withdrawal will not affect my treatment in any way.
5. I understand that the information I give will be treated with utmost confidence and that my name will not be published in the results.
6. I understand that I may raise any issues relating to the study through the contact number given by Dr Wakwabubi.

PARTICIPANTS NAME (RELATIVE/GUARDIAN'S NAME) **SIGNATURE/THUMB PRINT**

....

WITNESS ***SIGNATURE/THUMB PRINT***

....

INVESTIGATOR SIGNATURE

DR MAURICE N. WAKWABUBI

TEL: 0721238411 .....

KUKUBALI KWA MGONJWA

KUKUBALI KWA MGONJWA

Nimeelewa maelezo yote kutoka kwa Daktari Maurice Nyongesa Wakwabubi na ninatoa kibali kuhuzishwa kwenye utafiti.

1. Kwa hiari yangu binafsi bila kulazimishwa

2. Nakubali kutoa habari kuhusu ugonjwa wangu na majibu yake kurekodiwa na Daktari Maurice Nyongesa Wakwabubi.

3. Nakubali kupimwa kudhibitisha ugonjwa wangu.

4. Nimeelewa kwamba kuhuzishwa kwangu ni kwa hiari yangu na naweza kujiondoa wakati wowote bila masharti, na kujiondoa kwangu hakutadhuru matibabu yangu kwa njia yeyote.

5. Nimeelewa kwamba habari yeyote nitakayoitoa kuhusu ugonjwa wangu itahifadhiwa kwa siri na kwamba jina langu halitachapishwa hadharani.

6. Nimeelewa kwamba naweza kuuliza swali lolote kuhusiana na utafiti kupitia nambari ya simu Daktari Wakwabubi atakayonipa hapa chini.

Jina la mgonjwa Sahihi/Kidole

....

Shahidi Shahidi/kidole

....

Mtafiti Shahidi/Kidole

Daktari Wakwabubi .....

Nambari ya simu: 0721238411

C. APPENDIX 3: DATA COLLECTION

1. Patient's personal details

- Name .....
- Age .....
- Sex .....
- Place of birth .....
- Occupation .....
- Marital status

    (i) Single .....

    (ii) Married .....

2. Blood

- Full Haemogram.
- PSA.....

3. Histology

(a) Benign ☐

(b) Malignant ☐

❖ If b above

(I) Adenocarcinoma ☐

(II) Anaplastic ☐

(III) PIN ☐

(IV) Others. ☐

4. Type of Prostatecomy

(I) Millins ☐

(II) Fryers ☐

(III) TURP ☐

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: "MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/01/2932

Date: 15th August 2005

Dr. Maurice Nyongesa Wakwabubi
Dept. of Surgery
Faculty of Medicine
University of Nairobi

Dear Dr. Wakwabubi

RESEARCH PROPOSAL: "UNDETECTED CARCINOMA OF THE PROSTATE AT KENYATTA NATIONAL HOSPITAL." (P35/3//2005)

This is to inform you that Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** revised version of your above cited research proposal for the period 15th August 2005 to 14th August 2006. You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

Prof. A. N. GUANTAI
SECRETARY – KNH-ERC

c.c: Prof. K. M Bhatt, Chairperson, and KNH-ERC
The Deputy Director (C/S), KNH
The Dean, Faculty of Medicine,UON
The Chairman, Dept. of Surgery, UON
The HOD, Medical Records, KNH
Supervisor: Mr.P.N. Mungai, Dept. of Surgery, UON
Mr. F.Owilla, Dept. of Surgery, UON