THE DIAGNOSTIC VALUE OF FINE NEEDLE ASPIRATION CYTOLOGY FOR PROSTATE LESIONS AT MUHIMBILI NATIONAL HOSPITAL

By

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences the dissertation titled "The Diagnostic value of Fine needle aspiration cytology for prostate lesions at Muhimbili National Hospital" in partial fulfillment of the requirements for the degree of Master of Medicine in General Surgery.

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DECLARATION AND COPYRIGHT

I Josephat Philip Mponji declare that this dissertation is my own original work and has not been submitted for a similar award in any other University.

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DEDICATION

This work is dedicated to my wife Lucy, my son Philip, my father Phillip and my mother Agustina.

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LIST OF ABBREVIATIONS

BPH	-	Benign Prostate Hyperplasia
CT	-	Computed Tomograph
DRE	-	Digital rectal examination
eMRI	-	Endorectal Magnetic Resonance Imaging
FN	_	False Negative
FP	-	False positive
FNAC	-	Fine needle aspiration cytology
HC	-	Cytology
HP	-	Histopathology
MNH	-	Muhimbili National Hospital
MRI	-	Magnetic Resonance Imaging
NPV	-	Negative predictive Value of a test
PVP	-	Predictive Value of a positive test
PSA	-	Prostate Specific Antigen
NPV	-	Negative predictive Value of a test
TP	-	True positive
TN	-	True negative
USS	-	Ultrasonography
TRUS	-	Transrectal ultrasonography
MUHAS	-	Muhimbili University of Health and Allied Sciences

ABSTRACT

This crossectional descriptive study was designed to determine the diagnostic value of FNAC, as compared to Tru Cut biopsy, a method considered as the gold standard for tissue diagnosis for prostate lesions at MNH.

Patients suspected to have cancer of the prostate from abnormal DRE such as nodular, hard, irregular enlarged prostate or from high levels of PSA (4.0ng/ml or more) or from ultrasonography of hypo echoic lesion(s) or having any combination of the three, were included after their voluntary consent had been obtained. They had both FNAC and Tru Cut biopsies performed at the same sitting, FNAC preceded Tru Cut biopsy always. Smears made at FNAC were fixed in 95% alcohol while the core biopsy specimens were preserved in formalin, and both were labeled and submitted to the pathology laboratory. A specific cytologist was given FNAC specimen to interpret while histology specimen where sent to other pathologists so as to avoid bias at reporting results.

A total of 119 patients met the inclusion criteria for the study between first date of March and the last date of December 2006. One hundreds and ten patients (92%) enrolled into the study had PSA levels more than 4 ng/ml ,thirty two patients enrolled had hypo echoic lesion at ultrasonography and of the enrolled patients grade three prostate enlargement was found in 76(63.9%). Cancer was diagnosed by histology in 57(47.9%) patients as compared to 50(42%) cancer diagnoses by cytology. The age most commonly affected by cancer when the gold standard (core needle) biopsy when used was 60-69 years. Cancer of prostate was uncommon in patients below 60 years.

The accuracy of FNAC diagnosis for prostate lesions when compared with histological diagnosis as standard test was calculated from 101 patients who had adequate specimens for comparison. A total of 18 patients had inadequate specimen of which 11 had inadequate cytology and 7 had inadequate histology were not included at calculating the accuracy. Thirty eight cases were found to have True Positive (TP) cancer diagnoses , 41 patients had True Negative (TN) results,12 patients had false negative (FN)results and 10 patients had False positive (FP)results for prostate cancer diagnosis .The sensitivity of FNAC was found to be 76%, specificity of FNAC was 80.3%, positive predictive value (PPV) was 79.2%, negative predictive value (NPV) of FNAC was 77.4% and the overall accuracy of FNAC in study was 78.2%.

The use of FNAC had an overall cost reduction of more than 77.5% of the cost core needle biopsy. When under optimal conditions FNAC would minimize the duration to obtain tissue diagnosis results for about 97% of the duration required for histology diagnosis .The fact that some prostate cancer patients are severely anemic, therefore a more invasive procedure such as core biopsy would worsen the pre existing anemia, this may be avoided by using FNAC instead.

Fine needle aspiration of the prostate should be introduced at MNH and prostate aspiration procedures should be part of training for medical doctors in surgery and histopathology. Also systematic sampling of the prostate should also be introduced so as to increase the diagnostic accuracy of core needle biopsy.

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Introduction and Literature Review

Introduction

Prostate cancer is the most common non cutaneous cancer among males and is the sixth most common cancers in terms of incidence worldwide [1, 2]

The disease is not uncommon in Africa, although the incidence is not exactly known in most countries [3]. In Tanzania the exact magnitude of prostate cancer is not known, however many cases of prostate cancer are seen in clinical practices. A survey carried at Kilimanjaro Christian Medical Centre found that carcinoma of the prostate accounted for 9.6% of all malignancies and ranked third in frequency of all cancers in men [4]. Another study conducted at Muhimbili National Hospital found cancer of prostate in 79 patients out of 103 patients who underwent prostatic core needle biopsy between 2001 and 2003. [5]

Since early 1990s the incidence of prostate cancer has increased and the increase has been attributed by increased detection by prostatic specific antigen testing [6-8]

Several methods have been used for evaluation and screening for prostate cancer. Digital rectal examination of the prostate remains the cornerstone in the clinical diagnosis of prostate cancer owing to its ease, lack of costs, low risk and its contribution to detection in men with normal PSA. The sensitivity and specificity of DRE is low, detection rate of 0.8% to 25% have been reported, along with positive predictive value of 6.3% to 50%. [9-16]Another method used is prostate specific antigen whose sensitivity is more than 80% in detecting prostate cancer. Since the discovery of PSA there has been a revolutionalization in prostate cancer detection and screening.

Imaging studies such as ultrasound, magnetic resonance imaging, and computed tomography scan have been used to evaluate lesions of the prostate. These imaging studies are of minimal value in making a diagnosis; their use is however seen when directing a need for systematic biopsy.

The diagnosis of cancer of prostate can never be absolutely certain without morphological confirmation that is, without microscopic demonstration of material obtained by some form of biopsy. Two techniques are available for obtaining materials for examination under the microscope which includes core needle biopsy and fine needle aspiration techniques. Core needle biopsy obtains a cylindrical fragment of tissue from the prostate using a Tru-Cut needle via a transperineal or transrectal route. Transrectal route is the commonest route and it enables more accurate needle placement into a prostate lesion. However it carries a risk of septic complication and bleeding from haemorrhoidal vessels.[17, 18]

The transrectal prostatic biopsy can be performed either under digital guidance or under transrectal ultrasound (TRUS) guidance. The transrectal biopsy under TRUS guidance enable systematic sampling of prostate gland during biopsy and thus giving a lesser chance for missing a tumor compared to digital guided transrectal biopsy.

Due to lack of facility for TRUS and aspiration gun, Muhimbili National Hospital is obliged to perform prostate core needle biopsy under digital guidance. This provide an opportunity to miss other cases of caner of prostate

a blunt apex directed inferiorly and towards the urogenital diaphragm. The connective tissue stroma of the prostate is in direct continuity with that of the bladder wall thus intimately fusing the two structures.

The gland consists of right and left lobe united in front of the urethra by a fibro muscular strip called the isthmus. A median lobe lies posterior to the lateral lobes and superior to the level of entry of ejaculatory ducts. The prostate has its own capsule, smooth muscle and thick layer of pelvic fascia surrounding it. The capsule and sheath are separated by prostatic plexus of veins. The gland has three histological distinctive glandular zones as defined by Mc Neal which are the peripheral (70% to75%), the central (20% to 25%) and the transitional zone (5% to 10%).Most cancers arise from the peripheral zone. The prostate is supplied by inferior vesical artery and venous drainage to the prostatic plexus of veins thence to the vesical plexus and internal iliac veins. The lymphatic vessels draining the prostate terminate chiefly in the internal iliac and sacral lymphnodes. Some vessels from its posterior surface pass with lymph vessels of the bladder to the external iliac nodes. The prostate is innervated by parasympathetic fibres arising from pelvic splanchnic nerves S1, S2 andS3; and also innervated by sympathetic fibres from the inferior hypogastric plexus

Pathophysiology

Prostate cancer develops when the rates of cell division and cell death are no longer equal; leading to uncontrolled tumor growth. Following the initial transformation event, further mutations of a multitude of genes, including the genes for P53 can lead to tumor progression and metastasis.

Most prostate cancers are adenocarcinoma (95%), about 4% have transitional cell morphology, and very few have neuroendocrine origin. About 70% of cancers arise from the peripheral zone of the prostate, 15-20% arises in the central zone, and 10 – 15% arises in the transition zone. Most prostate cancers are multifocal, with synchronous involvement of multiple zones of the prostate which may be due to clonal or non clonal tumors.

Prostate intraepithelial neoplasm (PIN) represents the precancerous morphology of cellular proliferation within the prostatic ducts, ductules and acini .The predominant location is the periphery zone of the prostate where most cancers arise [24]

PIN refers to morphological appearance extending between histologically "normal" and "frankly" malignant prostatic epithelium. Two grades are identified the low grade PIN and the high grade PIN. The high grade PIN is associated with invasive carcinoma in 80% of cases, whereas the low-grade PIN is associated with invasive carcinoma in only 20% of cases. The high-grade PIN is considered to be a precursor to invasive carcinoma. Therefore, its identification in prostate biopsy specimen warrants further search for concurrent invasive carcinoma. [24-27]

Clinical Features

In the modern era most patients present because of the abnormalities in a screening PSA level or digital rectal examination (DRE) not because of symptoms [28-31].

In the pre-PSA era patients with prostate cancer presented with local symptoms such as urinary retention occurred in 20 – 25%, back or leg pain occurred in 20 – 40%, and haematuria in 10 – 15%.

Currently with PSA screening, patients report urinary frequency (38%), decreased urine stream (23%), urinary urgency (10%) and haematuria (1.4%). These symptoms are not specific to prostate cancer. About 47% of patients are without symptoms.Some patients present with symptoms of metastasis such as bone pain, weight loss, pathological fracture, and adenopathy [32]

Epidemiology of Prostate Cancer and Diagnosis

Cancer of the prostate is the sixth most common cancer in terms of incidence worldwide, and is the fourth most common cancer in men. The life time incidence of prostate cancer in developed countries is approximately 14.3% compared to only 4.3% in the third world [1, 33]. Also prostate cancer is the most common non cutaneous cancer among males [2]. Prostate cancer incidence has increased in many countries since early 1990s. Although much of this increase can be correlated with the introduction of wide spread prostatic specific antigen testing, some of the increase predates prostatic cancer screening. In southern Netherlands prostate cancer incidence increased from 36 per 100,000 in 1971 to 55 per 100,000 in 1989. [6, 7] Similar incidence was found in Denmark, despite the absence of extensive prostate cancer screening, incidence increased from 11 per 100,000 in 1943 to 30.9 per 100,000 in 1998. [8] These findings suggest that some of the worldwide increase in prostate cancer incidence reflects a true increase in the number of the patients with clinical prostate cancer rather than a simple result of increased detection [10]. For two decades leading up to 1993 the age specific incidence rates of prostate cancer were highest for men aged 75 years and older, followed by that for men aged 65 years to 74 years. [32]

The disease is not uncommon in Africa, although the incidence is not exactly known in most countries. Prostate cancer was reported to be number one cancer in Nigerian men and constituted 11% of all males cancer [35] with prevalence of 127 cases per 100,000 men [36] the calculated age adjusted incidence in blacks of Cameroon is 93.8 cases per 100,000 men [37] A survey carried at Kilimanjaro Christian Medical Centre found that carcinoma of the prostate accounted for 9.6% of all malignancies and ranked third in frequency of all cancers in men [38]. Another study conducted at Muhimbili National Hospital found cancer of the prostate in 79 patients out of 103 patients who underwent prostatic core needle biopsy between 2001 and 2003 [39]

Prostate cancer mortality rose at annual rate of 3.1% between 1987 and 1991 (1992 for the African Americans in the USA, then decreased at a rate on 1.9% annually through 1995.[40,41]. The American Cancer Society predicted that the total number of prostate cancer deaths in the USA would decrease from 37,400 in 1999 to 31,900 in 200.It is estimated that in the USA the lifetime risk of developing prostate cancer to be one in six men, where as the lifetime mortality from prostate cancer is on the order of one in thirty men[32]

In contrast to the USA prostate cancer, mortality in the southern Netherlands continued to rise through 1994 at a point it reached a level of 33 per 100,000 .[6, 7] In the southeast region of Sweden, prostate cancer mortality vacillated between 28 and 33 per 100,000 during the years between 1987 and 1995 without any downward trend. [42, 43]

Several methods have been used for evaluation and screening of lesions of the prostate gland. These include digital rectal examination (DRE), prostate specific antigen (PSA),

imaging techniques such as ultrasonography magnetic resonance imaging, computed tomography scan, positron emission tomography and biopsy techniques by core needle or by fine needle.

Digital rectal examination of the prostate remains to be the cornerstone in the diagnosis of prostate cancer owing to its easy, lack of costs, low risk and its contribution to detection of cancer in men with normal PSA levels. DRE has been used for centuries and has a Latin name *palpatio per anum.* The use of the DRE in the diagnosis and staging of prostate cancer was accurately described by Marion in 1921.[44] digital rectal examination findings for cancer include hard in consistent, irregular surface, nodular prostate and obliteration of median sulcus; these features occur in advanced cancer. In early cancer the prostate may appear firm or elastic and diagnosis by digital rectal examination becomes difficult even among experienced urologists.

The presence of nodularity of the prostate do not confirm prostate cancer, studies have shown only 26% - 50% of nodular prostate were confirmed to be cancer by biopsy.[45-47].

When using digital rectal examination to detect cancer of the prostate the detection rate of 0,8% to 25% have been reported, along with positive predictive value (PPV)s of 6.3%to 50% [9-16]

The sensitivity of digital rectal examination of the prostate in the detection of prostate cancer is low, and results vary between examiners. Despite these shortcomings of the test in terms of low sensitivity and specificity up to 25% of prostate cancer are still detected in men with normal PSA levels. A suspicious digital rectal examination should be followed by a prostate ultrasound and biopsy [48]. A routine annual DRE is recommended

by the American Cancer Society, American Urological Association and American Medical Association.

Prostate specific antigen is another investigation used not only for screening purpose but also for follow up of individuals with prostate cancer. Prostatic specific antigen is an organ specific, kallikrein like, serine protease produced by columnar epithelial cells that line ducts of the prostate gland and periurethral glands. [49, 50] Prostatic specific antigen is metabolized by the liver and has serum half life of about two to three days. Secreted into the lumen of prostatic ducts, it is in high concentration in seminal fluid in which it is involved in liquefaction of the seminal coagulum.[51] Prostatic specific antigen is believed to leak from prostatic duct system into the prostatic stroma and then into the blood stream. Prostate cancer cells actually produce less PSA and messenger RNA than do normal prostate epithelial cells and BPH. It remains unclear why there is a higher PSA serum concentrations in settings of cancer of prostate.

Prostatic specific antigen testing provides the means to detect prostate cancer in men with normal digital rectal examination that may otherwise present as so-called incidental cancer at TURP for apparently benign disease or later in the course of its natural history as a locally advanced or metastatic disease. [52] Studies in the USA have shown that 8% to 15% of screened men aged 50 years and older will have PSA level greater than the normal value of 4ng/ml and the positive predictive value of an elevated PSA level with initial biopsy range from 30% to 37%. [53] The probability of detecting prostate cancer at various stages is dependent on serum PSA level and digital rectal findings, and more than 80% of cancer can be detected. [54-59]

The upper limit of normal for PSA is 4ng/ml, however some authors advocate age related cut offs such as 2.5ng/ml for the fifth decade of life and 4.5ng/ml for the sixth decade of life. Some advocate the upper limit of normal PSA being 2.5ng/ml instead of 4ng/ml. [60-62]

Prostatic specific antigen has been found to be the single best test for detection of prostate cancer, but it is non specific that is, up to three- fourths of men with abnormal PSA may not have prostate cancer. Numerous factors can alter the serum PSA level and therefore cancer. PSA may be increased by distraction of prostate epithelium, by disease process such as BPH, urinary tract infections, prostatitis, prostatic stores and instrumentation to lower urinary tract., manipulations y DRE, ejaculation and trans rectal biopsy. [63]

Measurements of bound and free PSA can help discriminate between patients with mildly elevated PSA levels from cancer and those with benign prostatic enlargement. The lower the ratio of free to total PSA, the high the likelihood of cancer. Free PSA is reported as a percentage. When 25% of free PSA is taken as a cut of, more than 95% of cancers can be detected in both whites and blacks. When 22% is taken as a cut off cancer detection is maximized and unnecessary biopsies are avoided. [60, 64-66]

Although imaging studies do not have a place in early detection of prostate cancer, imaging dose play a role in diagnosis and evaluation of the disease.

Transrectal ultrasound (TRUS) is used to guide biopsies of the prostate gland in a patient with abnormal DRE or elevated serum PSA level. Magnetic resonance imaging (MRI) and particularly, combined MRI and three dimensional IH-MR spectroscopic imaging

(proton 3D-IH-MRSI) can be used for patients stratification and targeted biopsies in patients with previously negative biopsy findings. Patients with negative biopsy findings may also be evaluated using endorectal MRI (eMRI) for classification into low, moderate and high risk groups. MRI was found to have overall accuracy of 70% and negative predictive value of 94.4%Combining 3D-MRSI with eMRI further improves the ability to noninvasively identify cancer in a sextant location [65]. Computed tomography scan and bone scintigraph are imaging techniques valuable for depicting distant spread of disease.

The anatomy of the prostate gland is well displayed on high resolution cross-sectional imaging such as TRUS, CT and MRI. These imaging techniques are able to display all the five lobes of the prostate gland. [66] The prostate gland is also divided into three anatomical zones which are central, peripheral and transitional zone. [67]

From radiological view point most commonly used subdivision of the glandular prostate are the peripheral zone and central zone. [68], the central (gland) refers collectively to periurethral, transitional and central zones. There is further anatomical refinement of the prostate into divisions called sextants. These divisions enabled biopsing the prostate systematically. [69] The sextants consist of base, mid gland and apex bilaterally.

The prostate can be visualized by both transabdominal and well as transrectal ultrasound, however detailed assessment of the zonal anatomy is performed by transrectal ultrasound [68]. TRUS can be used to detect prostate cancer located in the peripheral zone of the gland reliably. On TRUS scans prostate cancer most commonly 60% to 70% of cases appear hypo echoic compared to normal peripheral zone. Up to 40% of lesions however,

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are isoechoic and therefore not detected by ultrasonograph. [70,71] About 1% to 5% of cancer may appear hyper echoic. Despite the differences in echo pattern, these cancer share biological behavior [72] Hypoechoegenicity is not specific for cancer always.

CT scan of the prostate lacks soft tissue contrast resolution needed for detection of intraprostatic cancer and offers no advantage over TRUS in biopsy guidance. On the other hand MRI is the best imaging modality for demonstrating normal zonal anatomy of the prostate at present time, it is like TRUS, and has no established role in prostate cancer detection. [73,74]

The diagnosis of cancer of prostate can never be absolutely certain without morphological confirmation that is, without microscopic demonstration of material obtained by some form of biopsy. The techniques that are available for obtaining materials for examination under the microscope include Tru Cut or core needle biopsy and fine needle aspiration techniques.

The core needle biopsy of the prostate is done via transperineal or transrectal route using a Tru Cut or Vim Silverman needle are currently preferred methods of establishing the diagnosis of prostate cancer. However transrectal biopsy has an advantage that it allows more accurate needle placement into a prostatic nodule and does not require anesthesia. Its disadvantage is its association with septic complication in 5 to 36%of patients, also its association with bleeding from hemorrhoid vessels. Blood cultures are positive in 85% of patients following transrectal biopsy; however the incidence of clinically manifest infection is less. It is prudent to administer prophylactic antibiotics before transrectal

biopsy. [17, 18] In general core needle biopsy is a safe procedure. Implantation of tumor cells along the needle biopsy tract is rare. [75,76] Prostate core needle biopsy can be performed as an outpatient procedure. The core needle biopsy has a 10% false negative rate [77].

In performing transrectal biopsy the needle is inserted into the rectum along the vollar aspect of the finger. The needle tip is advanced until it abuts against the prostatic nodule. With Vim Silverman needle, the obturator is withdrawn and the cutting blades are inserted and advanced into the prostate. The outer sheath is then advanced over the cutting blades and twisted. The cutting blades are removed and jaws are separated to remove the tissue. With Tru Cut needle the procedure is similar but the cutting action is different.

With advances in technology core needle biopsy is performed under transrectal ultrasound guidance. Trans rectal ultrasound is not an accurate method for localizing early prostate cancer and it is not recommended for use in prostate cancer screening. [78,79] The primary role of TRUS in prostate cancer detection and diagnosis is to ensure accurate sampling of prostate tissue by prostate biopsies in men suspected of harboring cancer based on serum PSA levels and DRE. [80] This is best achieved by targeting peripheral zone lesions that appear hypo echoic by TRUS, along with performing systemic sampling biopsies of areas without hypo echoic lesions in the prostate periphery zone.[81] Biopsies of transitional zone are recommended for men undergoing repeated prostate biopsies for persistently elevated serum PSA levels when missed cancer is suspected .[82] The optimal biopsy technique ,including the number and placement of biopsies for tissue procurement

that will minimize the chance of missing a relevant cancer remains controversial.[83,84] Trans rectal ultrasound guided prostate biopsies are performed routinely with an 18 gauge needle fixed from a spring loaded gun through a port mounted on ultrasound probe. The discomfort associate with prostate biopsy is minimized by injection of local anesthetic around the periphery of the gland. [85] A minimum of 8 systematic biopsies of the peripheral zone of the prostate including the apex, mid lobar midgland, lateral midgland, and lateral base should be performed routinely. Cancer detection is increase with increase number of biopsies. [86-97]

Transperineal needle biopsy is done first by inserting examining finger into the rectum and the region of indurations is identified. Then the biopsy needle is inserted through the skin of perineum and guided under bimanual control until the tip abuts against the prostatic nodule.

Aspiration biopsy of the prostate can be performed as an outpatient procedure without anesthesia and results are made available within minutes to hours. Aspirates are either air dried and stained with May-Grunwald-Giemsa stain or fixed in alcohol and stained by the Papanicolaou method.

The sensitivity of fine needle aspiration biopsy in making the diagnosis of prostate cancer ranges from 71 to 92% and the test has specificity of more than 80% in most series and that reported false positive rate is almost zero [19-23] Fine needle aspiration biopsy is performed under digital guidance. The accuracy of FNAC when compared with TRUS guided core biopsy and reported to be of superior value with sensitivity of 83.7% versus 74.4% and another series FNAC was more sensitive than core biopsy by 92% and 84%

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respectively [22, 23] In some settings FNAC of prostate was equally effective to core needle biopsy even when core needle biopsy was performed under TRUS guidance. [19,20] Other studies have shown the two investigations to complement one another and in addition FNAC had more advantages to core needle biopsy such as being cheap, safe and quick. [19,20,95] Owing to the high accuracy of FNAC, it is highly recommended to be used in the initial diagnosis of suspected prostate cancer and will continue to be a useful diagnostic tool in the 21st century [21,22].

FNAC of the prostate is a very valuable investigation not only in making diagnosis but also at follow up of patients. [90] In contrast to core tissue biopsy which obtains cylinder of tissue for histological examination; FNAB obtains a smear for cytological examination. If the cytologic expertise is unavailable locally, the specimen may be fixed in the office and shipped to a major medical centre for interpretation. [98]

Cytological prostate can be graded into four degrees of malignancy: high grade, medium grade, poorly differentiated and anaplastic carcinoma and this is of prognostic value. [95, 96, 99,100] Despite the high diagnostic values, errors have been reported in up to 30% of cases in some reports outside Scandinavian. [87, 88,101] False negative results may occur in patients having a cytological well differentiated carcinoma and false positive may occur in patients having granulomatous prostatitis or those in whom seminal vesicles are inadvertently aspirated [87,88].

Aspiration of prostate is usually performed with a Franzen needle. The index finger is placed in the needle guide and a finger Cot is placed over the examining finger and needle. The finger is then inserted into the rectum and the nodule is identified. A 22

gauge needle is put through the needle guide and advanced into the nodule. Suction is applied and maintained. The needle tip is moved back and forth within the nodule. Suction is then released and the needle withdrawn from the guide. The aspirate is then injected onto microscope slide and smeared.

The technique of FNAC is not new at MNH and East Africa; it has been practiced for more than twenty years. Of all the aspirations no aspiration to the prostate has been documented. Aspiration from other solid tumors is well known and practiced. The accuracy of FNAC in other tumors other than the prostate ranges from 54% to 96% and it is well documented to be a cost effective investigation [98,101,102]

Problem Statement

Tru Cut biopsy for histology under digital guidance has been used as the gold standard in making tissue diagnosis for prostate cancer at MNH. Despite the fact that the procedure is invasive, accompanied by bleeding, infections and that the processing of histology specimens takes long time, leading to delays in making tissue diagnosis and thus delay in initiating treatment, it has remained as the sole way of making tissue diagnosis for prostate lesions in MNH. In addition at MNH there are no facilities such as TRUS and biopsy gun to enable systematic sampling of the prostate. It is also believed that most prostate cancer patients at MNH present with advanced disease. Fine needle aspiration biopsy for the breast, thyroid, lymph nodes and other solid tumors with exception for the prostate have been established [98,100-102]

Fine needle aspiration biopsy of the prostate a method reported to be safer, quicker, yet accurate, as reported in other places has not been practiced at MNH and its diagnostic value in prostate lesions at MNH is yet to be established.

Rationale

The study looks at the diagnostic value of FNAC when compared with Tru Cut or core biopsy for prostate cancer. If the study finds the diagnostic value of FNAC is almost the same to that of Tru cut biopsy then the extra costs of investigation and delays in initiating treatment will be avoided Also cytologists will gain the experience and expertise in prostate lesions. The procedure may be done at bedside or side room without anesthesia and pain. Core needle biopsy will only be used to complement FNAC when necessary.

Broad Objective

To determine the diagnostic value of fine needle aspiration biopsy for prostrate lesions at MNH.

Specific Objectives

1. To determine sensitivity, specificity, false negative, false positive, negative predictive value, positive predictive value of FNAC as compared to core needle biopsy of prostate lesions at MNH.

2. To determine the duration (in days) from requesting of FNAC to the reporting of results compared with that of Tru Cut biopsy at MNH.

3. To determine the cost effectiveness of FNAC over that Tru Cut biopsy

4. To determine the profile of patients meeting the criteria for prostate biopsy at MNH

Methodology

Study Design

The study design was a crossectional descriptive conducted at Muhimbili National Hospital, from the first day of March 2006 to the last day of December 2006.The study involved men with PSA level of 4ng/ml or more,with abnormal digital rectal findings suggestive of prostate cancer and /or with abdominal ultrasound findings suggestive of prostate cancer.

Description of the Study Area

The study site was Muhimbili National Hospital. The Hospital was selected due to two reasons.

1. The Hospital was selected due to having pathology laboratory and pathologists, where fine needle aspiration biopsies and core needle biopsies could be performed, processed and interpreted by pathologists.
2. Muhimbili National Hospital was also selected due to having a firm specialized in urology. The urology firm performed routine core needle prostatic biopsies in patients with prostate lesions in order to make tissue diagnosis.

Hypotheses

1. Fine needle aspiration cytology has similar diagnostic value to core needle biopsy.
2. Fine needle aspiration biopsy can speed up the diagnosis and management of patients with prostate lesions.
3. Fine needle aspiration biopsy can reduce the cost of diagnosis of prostate lesions.

Training

At the beginning of the study a senior pathologist and a senior urologist at Muhimbili University College demonstrated to the investigator on how to perform fine needle aspiration and Tru Cut prostatic biopsy in six patients respectively; later they supervised the investigator to perform FNAC and Tru Cut biopsy in six other patients. A minimum of three aspirations were taken from cancer suspicious part of prostate and from each aspiration two smears were made which were immediately fixed in 95% ethyl alcohol for less than thirty minutes and later stained using Papanicolaou stain. On the other hand a minimum of three Tru Cut biopsy specimen were taken from the suspicious part of the prostate and they were immediately fixed in formalin before sending to pathology laboratory. During demonstration emphasis was put on the quality of smears and careful handling of tissue specimen to enable making definitive diagnosis.

The questionnaire which was used for registering all patients for the study (appendix 1) was discussed, each item being elaborated thoroughly. Emphasis was made on the need to write a clear and elaborate clinical provisional diagnosis when sending the smears and core biopsy specimen to the pathologist. Errors which arose either during aspiration,

smear preparation, taking core biopsy, specimen fixation and their implication on the ultimate diagnosis of the prostate lesions were discussed.

Glass slides, a pencil for labeling slides, absolute alcohol to be diluted to make a fixative, formalin, coplin jars which were used to keep fixative during smear preparation, special needles gauge 22, disposable 10mls plastic syringes, metal syringe holder and Tru Cut needles were purchased for the study.

Patients Recruitment and Enrollment

Advertisements were put in all adult male clinics and wards to recruit patients suspected of having cancer of prostate to be referred to the Investigator for further evaluation and possible enrollment when criteria were met.

Enrolled to the study were those who presented themselves or referred cases from peripheral hospitals with PSA level of 4ng/ml or more, with abnormal digital rectal findings such as prostate nodule, irregular prostate or hard prostate or with hypo echoic lesion(s) at abdominal ultrasonography or any combination of the three.

Enrolled Patients were prescribed with 120mls of enemax as a cleansing enema to drink the night before prostate biopsy. Also they were prescribed tablets tramadol 100mg, tablets diazepam 10mg stat and two tablets of conaz to come with the day of taking biopsy.

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Inclusion Criteria

Inclusion criteria were one of these three or a combination.

1. A patient with PSA of 4ng/ml or more
2. A patient with abnormal digital rectal examination of the prostate such as with nodular prostate obliterated median sulcus and irregular.
3. A patient with hypo echoic lesion of the prostate as seen by ultrasonography

Exclusion Criteria

1. Patients with cancer of prostate on treatment

Procedure of Prostate Biopsy and Making Smear

The patient with an empty rectum (rectum without stools) received tablets of 100 mg tramadol, 10mg of diazepam and one tablet of conaz an hour prior to the biopsy. The patient was then positioned in either lithotomy or in lateral decubitus position.

The prostate was digitally examined and localized first, and then fine aspiration needle gauge 22 was inserted along the vollar aspect of one index finger. The needle was advanced and inserted into the presumed center of the prostate lesion such as a nodule and a minimum of three aspirations were made from the lesion. The plunger in the syringe was drawn out to its maximum length. The 10mls syringe was necessary for attaining negative pressure strong enough to draw the cellular material into the lumen of the needle. The aspirator moved the needle back and forth about 20 times while angling it to sample cellular materials from all areas of the prostate with suspicious lesion at the same time maintaining negative suction pressure. When enough material entered into the hub of the needle, negative pressure was released slowly for about 2 seconds. The slow

release of the negative pressure was important, because sudden release could force the cells back through the needle. The aspirator withdrew the needle from the prostate only after the release of the negative pressure

Preparation of Smears

A minimum of six glass slides were polished and marked with a pencil indicating the cytological number of the patient and the date of aspiration, the same information appeared in the request form and questionnaire. The aspirator quickly detached the syringe from the needle and filled the syringe with air, the needle was reconnected and the aspirate was blown sharply onto two slides depending on the amount of the cellular material. When excess blood or tissue was present, it was sucked back from the slide leaving a predominance of tissue fragments.

To smear the cellular material, the aspirator touched the slide with cellular material with a second empty slide. The empty slide was placed with tip at about sixty degrees angulations touching the edge of cellular material and pulled over the length of first slide. Macroscopic examination of the aspirate aided in assessing the adequacy of the material.

To prevent cells from drying, which could distort the nuclear parameters and prevent accurate cytological interpretation, the aspirator needed to prepare the slides quickly and place them in a coplin jar filled with 95% ethyl alcohol for at most thirty minutes. The slides were placed back to back with cellular material slides facing the outside. Fixed smears were stained by Papaniculaou method for six minutes. There was no special priority given to the prostate smears. The prostate slides were stained together with other tissues smears.

Immediately after completion of FNAB the patient underwent trans rectal digital guided core needle biopsy. The core needle was introduced into the rectum along the vollar aspect of the finger as in FNAB. The core needle tip was advanced until it abutted against the prostatic lesion, then the obturator was withdrawn and the cutting blades were inserted and advanced into the prostate. The outer sheath was then advanced over the cutting blades and twisted. The cutting blades were removed and jaws were separated to remove biopsy tissues which were immediately fixed in formalin and sent to pathology laboratory for processing and interpretation. Tru Cut biopsy specimens were sent to a pathologist different to the cytologist interpreting FNAC.

The fine needle aspiration smears were evaluated for adequacy of cells that is cellularity, cellular distribution, nuclear to cytoplasmic ratio (n: c) whether increased or moderately increased or normal. The smear was also examined for cellular pleomorphism and prominence of nucleoli. Noted also in the smear was the presence of inflammatory cells and presence of mitotic figures.

The cytological report was classified into five categories

1. **Inadequate or unsatisfactory smear**. This was reported when a smear contained no cells, making cytological diagnosis not possible and a repeat of FNAC was advice.
2. **Benign lesion.** This was reported in a smear which contained cohesive groups of epithelial cells with normal nuclear to cytoplasmic ratio and no variation in size of cells.
3. **Suspicious of malignancy**. This report was issued when the smear despite having cohesive groups of epithelial cells, it also had loose cells with moderately increased

nuclear to cytoplasmic ratio, slight hyperchromasia, and slight variation in size of individual cells.

4. **Malignancy.** This was reported when definitive feature of malignancy were seen in most cells such as high cellularity of smears, necrotic background, loose single cells with high nuclear to cytoplasmic ratio, hyperchromasia, prominence of nucleoli, marked variation in size of the individual cells and presence of mitotic figures.
5. **Other lesions**. These were specified by the pathologist. Example in this study schistosomiasis was found.

In those cases of inadequate aspiration the patient was advised to have a repeat aspiration biopsy. For all those with malignancy as a diagnosis on FNAC the Surgeons were advised to carry out definitive treatment as he would carry in cases where core needle biopsy diagnosed carcinoma. Similarly histology results were interpreted for features of malignancy, benign, inflammatory lesions and other lesions such as schistosomiasis. Inadequate core biopsy specimen were recommended to be repeated

Determination of Sample Size:

The required sample size was calculated by using a web based software, and the following assumptions were made; two tailed test was used; a 95% confidence interval was considered; the proportion of cancer patients to be diagnosed using FNAC was assumed to be 84%; an acceptable error of 0.05% was also assumed; and the desired power of the study to detect a difference was assumed to be 80%.It was known that the proportion of cancer patients correctly diagnosed when FNAC was used to be 92%. [(23)]A

minimum required sample size obtained using the software in the study was found to be one hundreds and eleven.

Cost Effective Analysis

For all patients with prostate lesions diagnosed by using FNAC and core needle biopsy, the cost of using FNAC as compared to that of core needle biopsy was considered. The costs for FNAC included, disposable prostate aspiration needles worth 300 shillings, pathology laboratory charges of 25,000 shillings, cost for purchasing slides and fixative of about 1,000 shillings. A total of 26,300 shillings was needed for fine needle aspiration. The cost considered in core needle or Tru-Cut needle biopsy included cost of buying Tru Cut needle of 90,000 shillings, laboratory charges of 25,000 shillings, cost of purchase container for prostate biopsy 200 shillings, cost for purchasing formaldehyde 100 shillings .The total cost for core needle biopsy was 115,300 shillings and that core needle biopsy was more expensive than FNAC by 89000(77.2%) shillings.

All these costs were looked while collecting data and a patient only paid laboratory fee of 25,000 shillings to carter for the core needle biopsy.

Quality Assurance

Before sending the fine needle aspiration slides to central pathology laboratory a date of taking the aspiration biopsy was noted and entered into the structured questionnaire for each patient. After making diagnosis, the reports were typed and sent to the Investigator.

Indicated in the report form were the date of aspiration and the date of making cytological diagnosis. The duration in days from the day of performing fine needle aspiration biopsy to the date of making cytological diagnosis was calculated. Patient with cytological diagnosis of suspicious of malignancy waited for core needle biopsy results before commencing any further investigation. Re aspiration was expected in patients with inadequate smears. For core needle biopsy tissue, a date of performing core needle biopsy was noted usually was similar to that of fine needle biopsy, this date was also entered into a structured questionnaire.

After reception at the pathology laboratory, specimen were processed as routinely done together with other tissue biopsies and then stained with haematoxylin and eosin (H&E) No special priority was given to prostate biopsies as this could defeat the objectives of the study. The core biopsy specimens were interpreted by a pathologist different to that who read the cytology specimens in most cases. This pathologist had no prior information of the FNAC diagnoses and vice versa. The date of diagnosis by core needle biopsy was indicated in the request form of each patient before report was typed. This date was also entered into a structured questionnaire and thereafter was used to calculate the duration needed from request of core needle biopsy to results in days.

Data Analysis

Data was extracted from the structured questionnaire and then filled into computer Microsoft excel spread sheet. Then data was transferred into SPSS spread sheet where

data cleaning and coding was done. Thereafter frequency tables and cross tabulations were performed.

Ethical Consideration

The study was conducted after being granted permission by the department of surgery and obtaining clearance by the college research and publication committee.

Ethical issues and risks involved by the study due to its invasive nature were addressed clearly at requesting ethical clearance as well as when enrolling patients for the study. Patients were informed of having two parallel investigations performed at one sitting, and they were informed that the additional investigation was safer than the standard. Also patients were informed that inclusion into the study was their free will and that they might drop out of the study without adverse effects on their care. Patients were ensured of confidentiality and free consultation from the investigator.

Risks anticipated included pain, anxiety and infection which were avoided by giving patients tablets tramadol 100milligrams, diazepam 10 milligrams and one tablet of conaz respectively. Also they were informed about self limiting bleeding which might have presented as haematuria or rectal bleeding in the first 24 to 48 hours. Patients were advised to return to the investigator immediately when they encountered an abnormality, and they were given phone numbers for contact in case of problems. Appendix (1, 2)

Limitation of the Study

1. Difficulties in accessing pathologist when a need to discuss results arose due to physical barrier at the laboratory.
2. Inability of Tru Cut biopsy to sample the whole prostate gland (systematic prostate biopsy) due to absence of TRUS and biopsy gun.
3. Inability of pathologist to perform cytological grading and irregular reporting on histological grading by Gleason for no obvious reasons.
4. Failure to assess complications of prostate biopsy procedures as most patients did not return or report back to the investigator despite being told when they had encountered a problem.

Results

A total of 119 males with suspicious lesions for prostate cancer were studied. The enrolled males had age range from 50 to 90 years and the mean age at enrollment was 70 years. Patients aged less than 60 years were 12(10.1%). Out of 119 men with suspicious prostate lesions, 57(47.9%) patients were diagnosed to have cancer by histology. Of these cancer patients 38(66.6%) were between 60-79years. The age group most commonly affected was 60-69 years and had 21(36.8%) cancer cases. Cancer of the prostate was uncommon (10.5%) below 60 years (table 1a and table1b).

About 92% of patients enrolled into the study had PSA levels more than four nanogram per milliliter (table 2)

Table 3 shows that, seventy six (63.9%) patients with suspicious lesions for prostate cancer had grade three prostatic enlargements at enrollment. A total of 40(70.2%) prostate cancer cases were diagnosed from the 76 patients and, it was also found that cancer prevalence increased with increase of degree of prostate enlargement.

Table 4 shows that, of the119 patients enrolled into the study, hypo echogenicity of the prostate was found in 32(27%) patients. Among those with hypo echoic prostates 23 patient were diagnosed as cancer by histology. These 23 patients contributed to 40% of all cancer patients.

Table 5 shows that, of the 119 aspirations studied 11(9.2%) had inadequate material to permit a meaningful cytological diagnosis, 55 (46.2%) were diagnosed to be benign prostate lesions, 50(42%) were malignant and three (2.5%) were prostatitis. On the other hand core needle biopsy reported inadequate results in 7(5.9%), benign conditions of the prostate in 51(42%), cancer in 57(47%) and prostatitis was reported in 3(2.5%) of patients.

The accuracy of FNAC diagnosis for prostate lesions when compared with histological diagnosis as standard test among 101 patients who had adequate specimen for comparison of the two diagnostic tests is shown in table 6. Thirty eight cases were found to have True Positive (TP)cancer diagnoses results ,41 patients were true negative (TN) results,12 patients were found to have false negative (FN)results and 10 patients were

found to be False positive (FP)for prostate cancer diagnosis. Seven patients diagnosed to have cancer by Tru-Cut biopsy were excluded from the table for accuracy due to having inadequate cytology results. Two patients diagnosed to have cancer by cytology were also excluded from the study due to inadequate histology results. Two other patients with BPH by FNAC were excluded from the table for accuracy due to inadequate histology result. There were 3 patients excluded from the table of accuracy due to inadequate cytology as well as histology. And 4 cases labeled benign by Tru-Cut were inadequate in FNAC and therefore excluded from the study.

From the findings of table 6, the sensitivity of FNAC was calculated by the ratio of true positives (38) cases to a total number of individuals found to have cancer by Tru-Cut biopsy (50) cases, multiplied by one hundred, which was found to be 76%. The specificity of FNAC was calculated by the ratio of true negatives (41) cases and total number of all benign lesions diagnosed by Tru-Cut biopsy (51), multiplied by 100, which was found to be 80.3%.The positive predictive value (PPV) in the study was calculated by dividing true positive (38) cases to total positive test of FNAC for cancer (48) cases multiplied by one hundred this resulted into 79.2%. Moreover the negative predictive value (NPV) of FNAC was calculated by dividing true negatives (41) cases over total test negatives by FNAC (53) cases multiplied by 100 equaled 77.4%.Finally the accuracy of FNAC in this series was calculated by the sum of (TP+TN) divided to total number of patients with adequate specimens to permit meaningful comparison (101) cases, then multiplied by 100, which resulted into 78.2%.

Tables 7a and 7b show the tissue diagnosis by the two tests required a minimum of three days and a maximum of 55 days. It is also shown that under optimal conditions such as having enough well motivated staff and adequate supplies, FNAC was found to be faster than core needle biopsy by more than 97% of the time for histology.

Table 8 shows that, when FNAC was used as a pretreatment diagnostic tool for prostate lesions, it was found to save 89,400 Tanzanian shillings as compared to routinely done core needle biopsy. The percentage of cost reduction by FNAC of prostate lesions at Muhimbili was found to be 77.2 %.

Discussion

Prostate cancer is the most common cancer in men, with incidence and mortality rates that vary markedly among and within different countries.[5] In the present study symptomatic prostate cancer was found to be 47.9% of all men presenting in Surgery department with suspicious lesions for prostate cancer, this finding is less than what was found by Magandi in 2004 in which cancer was diagnosed in 79 cases out 103 patients suspected. Lower proportion of cancer in this study may have been attributed by increased community awareness and possibly most patients attend peripheral hospitals where they can be treated without coming to MNH.

About 92% of patients enrolled into the study had PSA levels more than 4ng /ml .More than 43(75%) of cancer patients had PSA level more than 10ng/ml, this shows that most cancer of prostate patients at MNH are at a higher risk of advanced disease. The high risk cancer patients seen in this study are contributed by the absence of community based screening programs by PSA and DRE. [13,15,34,44,52,55-57,60-65] A total of 15(29.3%) with histological diagnosis of benign prostate conditions had PSA level more than 50ng/ml, these patients could probably be cancer when the prostate was systematically sampled during biopsy as digital guided biopsies are inferior to TRUS guided biopsies The finding concur with the literature. [9-11, 64, 75-80]

The incidence of prostate cancer increases with age. The mean age at diagnosis in the study was 70.6 years and the youngest patient was 50 years old. These figures are comparable with findings from other studies, which reported a mean age of 69.1 years. ([1-8] The study findings also showed that prostate cancer was uncommon below the age of

60 years indicating that even in a setting like ours prostate cancer is still a disease of elderly males.

In the study it was found that adenocarcinoma of the prostate was the only cancer diagnosed. This finding concur with previously reported studies that adenocarcinoma was the predominant cancer in more than 95 %. [5] Mesenchymal tumors, transitional cell carcinoma, rhabdomyosarcoma and squamous cell carcinoma were not found. Due to rare occurrences of other malignancies of prostate the number of patients in this study is small to be compared with for type of cancers as seen in other places. The study found prostatitis in 3(2.5%) of patients by both investigations and this was consistent with findings elsewhere to be the diagnosis of exclusion.

The proportion of inadequate in the study was found to be 9.2% for FNAC and 5.9% in Tru-Cut biopsy. These results concur with other findings from other studies. On correlating Tru-Cut biopsy for histology and FNAC of prostate for cytology only those patient who had adequate cells on both categories were analyzed and they were 101 patients

The study found the accuracy of FNAC among 101 patients with adequate cells for comparison between FNAC and core biopsy in diagnosing prostate cancer to be 78.2%. That was consistent with data reported in the literature ranging from 71-92%.The sensitivity of FNAC was 76% and specificity of FNAC of prostate was found to be 80.3%, the positive predicative value was found to be 77.4%. The results were almost similar to those seen in other places. [19-23] With more training and practices these results could be improved.

In the study false positive was found in 10(20.8%) patients when compared with histological diagnosis. False positive in the literature ranged from 0-30%.Reasons for the false positive results include aspiration from seminal vesicles and aspiration in individuals with granulomatous inflammations. Also false positive results might have occurred when a pathologist used insufficient material for making diagnosis. [87, 88,101]

False negative from the study was found to be 12(22.2%) patients. Reasons for false negative rate being such high include poor sampling, small tumor size and fibrosis. The fact that DRE guided aspiration was performed make a higher chance of poor sampling. [74-78]

In the study the time lapse from requesting FNAC to reporting of result was a minimum of one day a maximum of 55 days. Similarly the duration from requesting to results of Tru-Cut biopsy was a minimum of 3 days and a maximum of 55 days. Under standard conditions FNAC would require lesser than 97% of the time needed for histology .These results show that at MNH processing of tissue specimen took a longer duration by more than twenty folds than when conditions were to be optimal, this might have been attributed by inadequate pathologists and cytologists at the hospital as well as lack of adequate and sustainable supplies. The study found at MNH it was not possible to obtain FNAC results within minutes as stated by literatures. [19-23,101]

The use of FNAC found to reduce the cost of tissue diagnosis by more than 77 percent when compared with the gold standard .An overall cost reduction of 89,400 shillings will be obtained when FNAC of prostate when used. The findings are consistent with the literatures that FNAC is cheaper than core biopsy ([19-23, 97]).

Conclusions

Fine needle aspiration biopsy is as accurate as core needle biopsy in prostate lesions. Introducing FNAC to prostate lesions will minimize resources expenditure, will provide more safety to patients and will provide results at a shorter time interval when conditions are optimized. The fact that some prostate cancer patients are severely anemic; therefore worsening of anemia by bleeding due to a more invasive procedure such as core needle biopsy will be avoided.

Recommendations

(1) Fine needle aspiration cytology of the prostate to be established as first line investigation for tissue diagnosis of prostate lesions.

(2) Systematic prostate biopsy should be introduced at MNH so that prostate cancer can be more accurately diagnosed.

(3) Fine needle aspiration of the prostate should be part of training for medical students and medical doctors in surgery and histopathology.

(4) When FNAC report no cancer in a patient with high risk for malignancy, then it should be repeated together with core needle biopsy.

(5) Pathologist should speed up their ability to interpret slides so as to avoid unnecessary delays.

Tables

Table 1a Age distribution of 119 patients at the time of Diagnosis

AGE GROUP IN YEARS	FREQUENCY	PERCENTAGE	COMMULATIVE PERCENTAGE
< 49	0	0	0
50 – 59	12	10.1	10.1
60 – 69	42	35.3	45.4
70 – 79	39	32.8	78.2
>80	26	21.8	100
Total	119		

- The commonest age group was 60-69.
- The minimum age was 50 years and the maximum age was 90 years.

Table 1 b Age distribution of 57 patients with prostate cancer on histology

AGE GROUP IN YEARS	FREQUENCY	PERCENTAGE	COMMULATIVE PERCENTAGE
< 49	0	0	0
50 – 59	6	10.5	10.5
60 – 69	21	36.8	47.3
70 – 79	17	29.8	77.1
>80	13	22.8	100
Total	57	100	

- Cancer of the prostate was at its peak at age group 60-69
- No Cancer was detected before the age of 50

Table 2. PSA level at the time of diagnosis among 119 patients.

PSA LEVEL NG/ML	FREQUENCY	PERCENTAGE
< 4n	9	7.6
4 – 10	24	20.2
11 – 20	21	17.6
21 – 50	23	19.3
51-100	32	26.8
>100	10	8.4
Total	119	100

- About 92% of patients had PSA more than 4nglml and met the criteria for inclusion into the study by abnormal high PSA level

Table 3. Cross tabulation of DRE and histology diagnosis among 119 patients.

DRE GRADING	BPH	CANCER	PROSTATITIS	BILHAZIA	INADEQUATE	TOTAL
GRADE1	6(12%)	5(8.7)	0	0	0	11(9.2%)
GRADE11	17(34%)	12(21%)	0	0	3	32(26.9%
GRADE111	28(56%)	40(70.2%)	3	1	4	76(63.9%)
TOTAL	50(100%)	57(100%)	3	1	7	119(100%)

- A total of 76(63.9%) patients had grade three prostate enlargements, out of these, 40(70.2%) of cancer cases were diagnosed.

Table 4. Cross tabulation between abdominal ultrasound of the prostate and histological diagnosis among 119 patients.

HISTOLOGY DIAGNOSIS	HOMOGENOUS ENLARGEMENT	HETEROGENOUS ENLARGEMENT /HYPOECHOIC	TOTAL
BPH	43(84.3%)	8(15.7%)	51(100%)
CANCER	34(60%)	24(40%)	57(100%)
INADEQUATE	6	1	7
PROSTATITIS	3	0	3
SCHISTOSOMIASIS	1	0	1
TOTAL	87(73%)	32(27%)	119

- .Sixty percent of prostate cancer patients had homogenous prostatic enlargement.

Table 5 Histology and cytology diagnoses among 119 patients

DIAGNOSES	CYTOLOGY		HISTOLOGY		TOTAL
CANCER	50	42%	57	47.9%	
BPH	55	46.2%	51	42.9%	
PROSTATITIS	3	2.5%	3	2.5%	
SCHISTOSOMASIS	0	0%	1	0.8%	
INADEQUATE	11	9.2%	7	5.9%	
TOTAL	119	100%	119	100%	

- Prostatitis is a rare disease of the prostate and in this study accounted for about 2.5% .The diagnosis was equally made by the two diagnostic tests

Table 6. The accuracy of FNAC diagnosis of prostate lesions when compared with definitive Tru Cut biopsy among 101 patients

CYTOLOGICAL DIAGNOSIS	DEFINITIVE HISTOLOGICAL DIAGNOSIS BY TRU-CUT		TOTAL
	MALIGNANCY	BENIGN	
MALIGNANCY	TP 38	FP 10	48
BENIGN	FN 12	TN 41	53
TOTAL	D^+ 50	D^- 51	101

- Sensitivity of FNAC in making Cancer of prostate diagnosis

$$= \frac{TP}{D^+} \times 100 = \frac{38 \times 100}{50} = 76\%$$

- Specificity of FNAC for making an exclusion of diagnosis of Cancer of prostate =

$$\frac{TN}{D^-} \times 100 = \frac{41}{51} \times 100 = 80.3\%$$

- Positive Predictive value -= $\frac{TP}{\text{Total FNAC}^{+VE}} \times 100$

$$= \frac{38}{48} \times 100$$

$$= 79.2\%$$

- Negative predictive value = $\frac{TN}{\text{Total FNAC}^{-VE}} \times 100$

$$= \frac{41}{53} \times 100$$

$$= 77.4\ \%$$

- False positive rate = $\frac{FP}{\text{Total FNAC positive}} \times 100$

  $= \frac{10}{48} \times 100$

  $= 20.8\%$

- False negative rate = $\frac{FN}{\text{Total FNAC negative}} \times 100$

  $= \frac{12}{53} \times 100$

  $= 20.6\%$

- Accuracy of FNAC $= \frac{TN+TP}{N} \times 100 = \frac{(41 + 38)}{101} \times 100 = 78.2\%$

- 7 Patients diagnosed to have Cancer by Tru-cut biopsy were excluded for analysis the study due to having inadequate cytology result.
- Two patients diagnosed to have CA by cytology where also exclude from the study due to inadequate Histology results.
- Two other patients diagnosed to have BPH by FNAC were excluded from study due to inadequate Histology.
- Three other patients were excluded from analysis due to adequate cytology as well as Histology.
- Four cases labeled benign by Tru Cut biopsy were inadequate at FNAC also excluded.

Table 7a: Duration in days from requesting to reporting of cytology and histology results among 119 patients

DURATION IN DAYS	HISTOLOGY	CYTOLOGY
<3 days	4	9
4 – 7 days	36	23
8 – 14 days	40	42
15 – 21 days	23	22
22 – 55 days	16	23

- A minimum of three days and a maximum of 55 days were required to report histology as well as cytology specimen. The mean duration for reporting histology was 13.7 days and that for cytology was 14.8 days.

Table 7b.Optimal duration in hours to process cytology and histology specimen for each patient

PROCEDURE	CYTOLOGY DURATION	HISTOLOGY DURATION
Tissue fixation	30 minutes	24 hours
Automated tissue processing and microtome	0	24 hours
Paraffin embedding, dewaxing and cooling	0	3 hours
Staining and mounting	30 minutes	30 minutes
Reporting	30 minutes	30 minutes
Total duration	90 minutes	52 hours

Percentage duration reduction by FNAC=$\frac{\text{Duration for (histology - cytology)}}{\text{Duration for histology}} \times 100$

$=\frac{52-1.5}{52} \times 100$

$=97\%$

Table 8 to show cost analysis of using FNAC as a diagnostic tool for prostate lesions compared to core needle biopsy at MNH

COST OF CYTOLOGY	SHILLINGS
Syringe and needle	300/-
Pathology FNAC report	25,000/-
Microscope slides	200/-
95% alcohol	400/-
Total	25,900

COST OF HISTOLOGY	SHILLINGS
Tru-cut needle equipment	90,000/-
Pathology HP report	25,000
Container for specimen	200/-
Formalin 100%	100/-
Total	115,300

$$\text{COST REDUCTION BY FNAC} = \frac{\text{COST OF HP} - \text{COST OF HC}}{\text{COST OF HP}}$$

$$= \frac{(115{,}300 - 25{,}900)}{115{,}300} * 100$$

$$= 77.5\%$$

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Appendix 1

INFORMED CONSENT FORM

ID-NO.

- **Consent to participate in** FNAC of prostate lesion

- **Greetings:** My name is Dr. J. P. Mponji a postgraduate student investigating the use of FNAC for prostate lesions in MNH.

- **Purpose of the Study:** To determine the diagnostic value of FNAC of prostate to diagnose prostate lesions suspicious of malignancy.

- **What participation involves:** if you agree to join the study you will be required to be examined and if found to have a suspicious lesions suspicious lesion for cancer of prostate on either DRE, PSA level of ultrasound you will be included in the study.

- **Confidentiality:** The investigation results once provided you will be sent to your referring doctor. The information obtained from investigations will be entered into computers with only study identification number.

- **Risks:** You may have mild bearable pain, self limiting bleeding and infection which will be avoided by antibiotics and analgesics.

- **Right to withdraw and alternative**
  - Involvement into this study is completely your choice
  - You may opt out of the study without any adverse consequence to the management of your condition.

- **Benefits:** You will benefit having a shorter waiting time for the investigation and thorough evaluation by Dr. Mponji without paying consultation fee. Also information learnt from this study will benefit others.

- **In case of injury:** No harm is anticipated as a result of this study. It is happens you will be treated accordingly. There will be no additional compensation.

- Who to contact: If you have a question about this study you should contact Dr. Mponji cell phone No. 0713-434344. If you ever have questions about your rights as a participant you may call Prof. A. Y. Massele, Chairman of the college research and publication committee, P. O. Box 65001, Dar es Salaam, Tel. 21150302-6.

Signature_____

Do you agree?

Participant agrees .....participant does not agree.....

I ..... have read the contents in this form. My questions have been answered. I agree to participate in this study.

Signature of Participant .....

Signature of Witness .....

Kukubali Kushiriki Kwenye Utafiti

- Namba ya utambulisho.

- Kukubali kushiriki utafiti wa kipimo cha FNAC ya kuchunguza saratani ya PROSTATE.

- Kukubali kushiriki utafiti.

- **Ushiriki unahusu nini?**

  Ukikubali kuwa sehemu ya utafiti huu utatakiwa upimwe na daktari wa kidole njia ya haja kubwa, kupima damu kwa ajili ya kipimo cha PSA, na kufanya sonagrafi ya tumbo. Na ikionekana tezi la prostate linahisiwa kuwa saratani utatakiwa uchukuliwe kipimo cha FNAC na Tru-cut biopsy.

- **Siri**

  - Taratibu zote za mgonjwa zitatunzwa kwa siri kubwa na mgonjwa ataelezwa majibu ya vipimo vyake ili ampeleke Mganga aliyemtuma.

  - Namba ya utambulisho itatumika kwenye kutathmini matokeo ya utafiti.

- **Hatari zinazoweza kutokea**

  Unaweza kupata maumivu kidigo wakati wa kipimo, pia unaweza kutokwa damu kidogo wakati wa kipimo. Hathari hizi zitaisha muda mfupi baada ya kipimo.

- **Faida ya utafiti**

  - Utafaidika kufanyiwa uchunguzi wa maradhi yako mapema bila kusubiri, na Dr. J.P. Mponji atakupima bila kumlipa ada ya kumwona.

  - Matokeo ya utafiti yatasaidia kuchunguza wagonjwa wengine wa aina hii.

- **Madhara ya utafiti**

Sitegemei kumdhuru mtu yeyote kutokana na utafiti huu. Yakitokea madhara yoyote utatibiwa mara moja. Lakini hakutakuwa na fidia ya ziada.

- **Mawasiliano**

  Ikiwa unalo swali juu ya utafiti huu wasiliana na **Dr. J. P. Mponji** kwa simu namba **0713-434344**. ikiwa bado hujaridhika juu ya haki kuhusu ushiriki wako unaweza kuwasiliana na **Prof. A. Y. Masele,** Mwenyekiti wa baraza la utafiti la chuo na majarida, **P. O. Box 65001, Dar es Salaam Simu, 2150302-6.**

Sahihi_____

Nakubali ushiriki..... Nakataa ushiriki.....

Mimi.....nimesoma na kuelewa fomu hii na maswali yangu yamejibiwe, Nakubali kuwa sehemu ya utafiti.

Sahihi yangu..... Sahihi ya Shahidi.....

Appendix I1

DETERMINATION OF DIAGNOSTIC VALUE OF FNAC FOR PROSTATE LESSIONS IN MNH:

QUESTIONAIRE:

A: INTRODUCTION:

- Serial No. _____
- Hospital case files No. _____
- Patient Age in years _____
- Patients PSA level _____

DRE findings:

Grade of prostate enlargement:

(i) _____

(ii) _____

(iii) _____

USS findings:

(i) Hypo echoic lesion

(ii) Homogenous

B: MAIN THEME:

(i) FNAC

- Date of requesting
- Date of reporting
- Duration (in days) from time FNAC was requested to when report was made available.
- Diagnosis according to FNAC

a. Cancer _____

b. No cancer _____

c. Suspicious _____

d. Indeterminate _____

(ii) CORE BIOPSY

(i) Date of requesting core biopsy

(ii) Date of reporting core biopsy

(iii) Duration (in days) from the time Trucut/core biopsy was taken to when reported _____

(iv) Was the diagnosis made following FNAC similar to the one make by core biopsy: YES/NO

(v) Was the positive result in FNAC also positive in Tru cut biopsy histological result YES/NO.?

(vi) Was a negative result in FNACE also negative in core biopsy histological result: YES/NO.

(vii) FNAC – Suspicious result:

a. Confirmed by core biopsy YES/NO

b. Refuted by core biopsy result YES/NO

c. Open biopsy result also inconclusive YES/NO

(viii) Was the positive result in FNAC found to be negative in core biopsy YES/NO.?

(ix) Was the negative result in FNAC found to be positive in core biopsy, YES/NO.?

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