

Comparison of Transrectal Ultrasound Guided Fine Needle Aspiration Cytology with Core Needle Biopsy in the Diagnosis of Prostate Cancer

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Abstract

Aim and objectives: To compare the diagnostic accuracy of transrectal ultrasound (TRUS) guided Fine Needle Aspiration Cytology (FNAC) protocols against the gold standard (TRUS guided Core Needle Biopsy {CNB}).

Materials and methods: This was a prospective study of 96 patients being investigated for prostate cancer. Inclusion criteria comprised of the presence of one or more of the following: Persistently elevated Prostate Specific Antigen (PSA), abnormal Digital Rectal Examination (DRE) and abnormal prostatic imaging. Patients already on treatment for prostate cancer and those with symptomatic urinary tract infections were excluded. They all had an extended 10-aspiration TRUS –guided FNAC using a 22G Echotip Chiba needle. This was followed by an extended 10 core TRUS guided CNB using an 18G Bard Max-core biopsy gun at the same sitting. The extended protocol entailing traditional sextant aspirations/core needle biopsies as well as four laterally guided aspirations/core needle biopsies taken in the peripheral zone in the middle and base of the prostate were carried out. The cancer detection rates of FNAC and CNB protocols were determined and compared. The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were ascertained. P value <0.05 was taken as being statistically significant.

Results: The overall cancer detection rate was 24.0%. Benign cases were reported in 71.8% of patients and 4.2% reported as suspicious. FNAC overall accuracy rate was 96.7% with PPV of 100% and NPV of 95.7%. Sensitivity and specificity were 88.5% and 100% respectively.

Conclusion: FNAC was comparable with CNB in terms of diagnostic accuracy.

Keywords: FNAC; CNB; PSA; DRE; Prostate cancer; Detection rate

Introduction

Prostate cancer is the commonest male malignancy occurring after middle age [1]. Although most men usually die with the disease rather than from the disease as it is regarded as a slow growing, chronically evolving condition, it is still one of the most common causes of cancer mortality among men [2]. It constitutes a significant health care burden due to its tremendous incidence and mortality rates especially amongst the Afro-Caribbeans as well as the cost associated with the detection and treatment of this disease [2,3].

Indications for prostate biopsy are mainly abnormal findings on digital rectal examination (DRE), persistently raised prostate specific antigen (PSA) and abnormal findings on prostatic imaging.

Initiating early treatment requires early and precise diagnosis. The diagnostic work up includes both noninvasive and invasive procedures. The noninvasive work up includes a good clinical history, digital rectal examination and transrectal ultrasonography. Fine needle aspiration cytology and Core needle biopsy are the major techniques used in tissue diagnosis [4]. The earliest reports on the results of TRUS guided prostate biopsy are attributed to Torp-Pedersen et al. [5]. This was achieved with the aid of an 18 gauge spring action biopsy needle device and this is considered the gold standard. The trauma attributed to CNB as well as the relatively high true negative rates led to consideration of other methods and more studies on the less invasive technique of FNAC to assess the diagnostic accuracy.

FNAC has evolved from the transperineal route first introduced by Ferguson [6] which was popularized by Franzen [7] with the development and introduction of a needle guide for the transrectal route. With the advent of renewed interest leading to more experienced

cyto-pathologists, it has gained increasing popularity in the United States since the 1970s [8]. Studies have subsequently shown that the initial reservations about the technique which included unacceptably high false negative rates no longer apply [9]. The technique can be implemented not just as a method for detecting prostatic carcinoma but also for tumour grading, which is of utmost importance in deciding type of therapy. FNAC can also be utilized for early detection of recurrences of prostatic carcinoma [10]. It also has the advantages of negligible bleeding due to the size of the needle being significantly smaller. It is less traumatic and can be performed with little or no analgesia and thus can be repeated with minimal distress to the patient. It can therefore be a valuable tool in patients requiring repeated biopsies as part of follow up. The result of FNAC is also very rapid as the smear can be stained and read within 30 minutes thus making repeat biopsy possible even before the patient goes home. This is also valuable in patients with advanced disease presenting with impending paraplegia where urgent diagnosis is necessary without further delay. Tijani et al. also undertook a study of digitally guided random FNAB in the Nigerian population-one of

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the first studies in this population [11]. There were however limitations to this study. First, the biopsies were digitally guided, thereby reducing accuracy, secondly, the biopsies were taken randomly and thirdly they were done without a needle guide thereby exposing the operator to the risk of needle injury.

It was therefore appropriate for this study to improve on the previous studies by eliminating the limitations. In this study, systematic extended (10-sites) fine needle aspirations (followed by core needle biopsies) were taken under TRUS guidance with a needle guide.

Materials and Methods

This study was prospectively carried out amongst men who were being evaluated for prostate cancer at our centre. Human Research and Ethics Committee of the hospital's approval was obtained as well as informed consent from all the patients involved. Inclusion criteria were the presence of one or a combination of persistently raised PSA, abnormal DRE findings and abnormal findings on imaging studies (USS, CT or MRI) of the prostate. Patients who declined consent or had symptomatic urinary tract infections or that were already on treatment for prostate cancer were excluded. Patients on antiplatelet therapy or anticoagulants were asked to discontinue the drug(s) for an appropriate period of time prior to the biopsy. All procedures were done as day cases. Prophylactic antibiotics (500 mg ciprofloxacin b.d. and 400 mg metronidazole tds) were also administered according to the hospital's microbiology protocols. All patients had intravenous cannulation before the procedure. No systemic sedatives or analgesic agents were administered.

Bowel preparation was achieved with Dulcolax suppositories inserted by the patients into the rectum the night prior to the procedure. Patients were positioned with knees and hips flexed at 90° in the left lateral decubitus position for biopsies. An arm board was attached parallel to the table and a pillow between the knees allowed patients to remain in this position. It was ensured that the buttocks were flush with the edge of the table to allow instillation of anaesthetic gel and manipulation of the probe with ease. Local anaesthesia (20 ml of intrarectal 2% xylocaine gel) was instilled into the rectum and preliminary DRE was carried out and documented. A condom was worn over the transrectal ultrasound probe (Mindray product, DP-2200 model with a 7.5 MHz transducer, China) then a needle guide was attached. It was lubricated with sonogel and then gently inserted into the rectum. Ultrasound evaluation of the prostate was done and documented. Each patient received injection of 5 ml of 2% plain xylocaine (Rotex Medical brand, Germany) bilaterally at the basolateral region, at the junction between the seminal vesicle and the prostate. A further 5 ml of 2% plain xylocaine was then injected at the apex of the prostate.

Fine needle aspiration cytology as shown in Figures 1 and 2 was carried out in the above stated position with the aid of a 22G, 20 cm long Echotip Skinny needle with a Chiba tip (Cook medical brand) which was inserted through the needle guide on the transrectal probe. Whilst the needle was in the prostate, about 10 small amplitude to-and-fro movements of the needle were done to loosen the target tissue. Negative pressure was developed by pulling on the syringe plunger (20 ml syringe) in order to aspirate the cellular material into the needle. Before withdrawing the needle from the prostate, the negative pressure was then released. This is the most important step in ensuring that the aspirated material remained in the needle and did not enter the barrel of the syringe, where it would have been lost irretrievably. A set of standard sextant aspirations was done. Also two laterally guided aspirations



Figure 1: Materials for procedure: Coplin jars, biopsy specimen bottles, microcopy glass slides and syringes.



Figure 2: Chiba needle for Fine needle aspiration cytology.

were taken in the peripheral zone at the middle and the base (lateral aspirations) in each lobe. This constituted the extended 10 aspiration protocol. Suspicious nodules were aspirated and sent off separately. Each aspiration was then smeared on two slides and immediately fixed in 95% alcohol and transported to the cyto-pathologist. A spring loaded size 18 gauge, 25 cm length and 22 mm penetration depth Bard Max-core Disposable core biopsy gun was then attached to the transrectal probe. An extended 10-core biopsy was taken from the same area as the FNAC. Nodules were also biopsied separately. The specimens were stored in 10% formalin, processed at the anatomic and molecular pathology department by a histopathologist. The cytology stains used were Papanicolou, Haemoxilyn and Eosin. The FNAC slides were then analysed by a single uro-cytopathologist. The results of the FNAC were reported as per the Royal College of Pathologists scheme. This scheme classification is reported as: positive for malignant cells, negative for malignant cells, suspicious or insufficient sample. The CNB was also assessed for malignant cells and graded according to the Gleason grading system. The findings on the FNAC were then compared with the histopathological diagnosis. All the cytology slides were reported by a single cytopathologist (CCA) while the histopathology slides were reported by the pathologist to whom the specimen was officially allotted by the hospital and did not include the cytopathologist.

Patients not on indwelling urethral catheters were monitored for haematuria or urinary retention before discharge. All patients were discharged home after observations were completed especially if no complication(s) warranting admission for further care was noticed. They were advised to note the onset, type and duration of any problem(s) arising following the procedure. Completing the course of earlier prescribed antibiotics was also emphasized.

The first clinic visit was 1 week after the procedure to review and document any complication(s). The second clinic visit after the procedure was two weeks after the procedure and was dedicated to the review of their investigation results. The data was analysed using SPSS. A p value <0.05 was taken as being statistically significant. True positives (A), False positives (B), False negatives (C) and False positives (D) were determined as shown in Table 1.

Results

Ninety-six patients were recruited for the study. The age range of the patients was from 47 to 80 years with a mean age of 64.96 ± 7.53 years. The peak age range was 61-70 years and this accounted for 52.1% of the entire study population as shown in Figure 3. The PSA values ranged from 2.33 to 161.45 with a mean of 14.89 ± 20.34 ng/ml.

Cytopathology of 23(24%) of the 96 patients was reported as malignant, 69(71.8%) as benign and 4 (4.2%) as suspicious as shown in Figure 4.

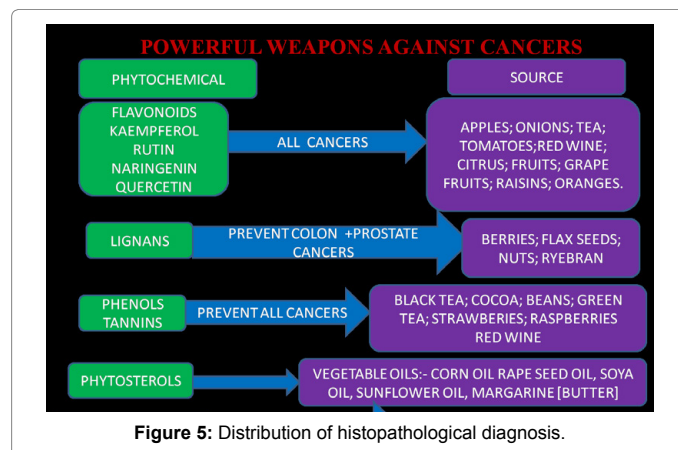
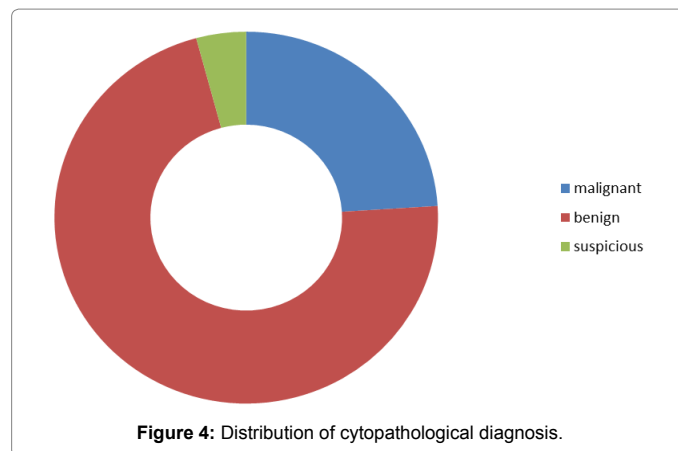
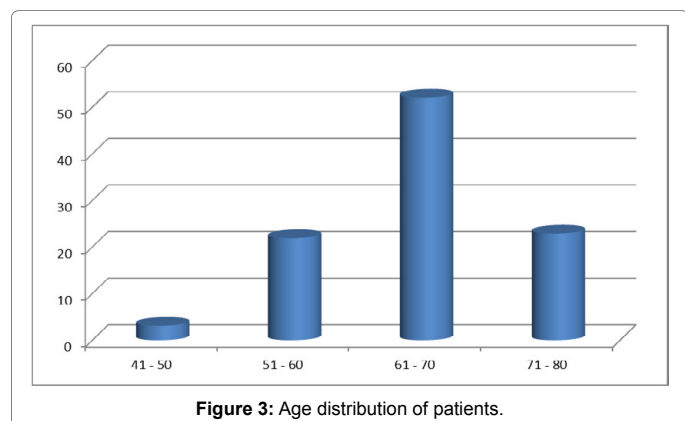
Twenty seven of the 96 patients had malignant histology accounting for 28.1% while 71.9% were benign. All malignant biopsies were adenocarcinomas as shown in Figure 5.

Cytology had an overall accuracy of 92.7% when compared to histology in terms of diagnosis with sensitivity of 88.5% and specificity of 100.0%. PPV and NPV were 100.0% and 95.7% respectively. Among the 23 cases diagnosed as malignancy on cytology, all (100.0%) were confirmed to be malignant on histology. Three benign cases on cytologic evaluation proved to be carcinomatous on histology giving a false negative rate of 4.3%. Conversely, among the 69 benign cases, 66 cases were correctly diagnosed cytologically as benign hyperplasia but in the remaining 3 cases, they were considered suspicious on cytology as seen in Table 2. Patients with suspicious cytologic results were found to have malignant histology in 1 (25.0%) and benign histology in 3 (75.0%). Of 92 patients with definitive cytologic diagnosis, 89 (96.7%) correlated with histology as seen in Table 3. None of the cytology specimens was classed as an insufficient sample.

	Histology positive for malignancy	Histology negative for malignancy
Cytology positive for malignancy	True positive (A)	False positive (B)
Cytology negative for malignancy	False negative (C)	True negative (D)

Sensitivity was then calculated as $A/(A+C) \times 100$. Specificity: $D/(D+B) \times 100$, Positive predictive value: $A/(A+B) \times 100$, and Negative predictive value: $D/(D+C) \times 100$ were also calculated.

Table 1: True positives (A), False positives (B), False negatives (C) and False positives (D).



Discussion

A lot of advances have been made in the past century especially as regards PSA measurement [12]. This has, in turn, led to a rapid increase in the number of prostate biopsies being performed with a resultant dramatic increase in diagnosis of prostate cancer at an early stage. The gold standard for diagnosis remains tissue biopsy. With evolution over the years, at present, techniques involving the use of semi-automated Tru-Cut core biopsy needles and transrectal ultrasound are currently employed. Nevertheless, this is associated with a number of deleterious effects and complications leading to a need and search for less invasive techniques.

In the hands of experienced cytopathologists, many studies have shown that fine needle aspiration cytology (FNAC) may be as helpful as core needle biopsy (CNB) [13]. In this study, the role of TRUS guided FNAC was evaluated by comparing it with an established gold standard, TRUS guided CNB in terms of diagnostic accuracy. The peak age group of the patients was in the 61-70 years age range (52.1%) with a mean age of 64.9 years. This is similar to a study by Osegbe et al. among Nigerians which reported a mean age of 68 years [14]. This emphasises the fact that prostate cancer is a disease of ageing males. Various other studies have also noted a similar distribution. The overall accuracy of TRUS guided FNAC for malignant lesions were 92.7%. This shows that FNAC correlates well with the gold standard, CNB, with specificity and PPV of 100% each recorded in this study. This correlates with various studies as seen in Table 4 in which diagnostic accuracy range from 91% to 94% [15,16]. The role of an experienced cytopathologist can therefore not be overemphasized.

Histologic Diagnosis	Number	Cytologic Diagnosis	Number
Malignant	27	Malignant	23
		Benign	3
		Suspicious	1
Benign	69	Benign	66
		Suspicious	3

Table 2: Correlation of histologic and cytologic diagnosis.

	Histology positive	Histology negative	Total	
Cytology positive	True positive(A)=23	False positive (B)=0	A+B=23	PPV: $A/(A+B) \times 100=100\%$
Cytology negative	False negative (C)=3	True negative (D)=66	C+D=69	NPV: $D/(D+C) \times 100=95.7\%$
Total	A+C=26	B+D=66	A+B+C+D=92	
	Sensitivity: $A/(A+C) \times 100=88.5\%$	Specificity: $D/(D+B) \times 100=100\%$	Accuracy= $A+D/(A+B+C+D) \times 100=96.7\%$	

Table 3: Sensitivity, Specificity, PPV and NPV correlation.

Study series	Number of Patients	Sensitivity	Specificity	Overall Accuracy
Esposti	137	91	97	95
Lin	428	68	78	73
Hosking	74	75	84	81
Zattoni	195	98	92	96
Carter	94	82	97	88
Whelan	26	100	85	92
Brenner	120	87	96	93
Tijani	41	95	100	93
This study	92	88.5	100	96.7

Table 4: Comparison of similar studies.

There were no false positives, this is similar to Carter and associates whose study showed a 91% correlation between aspiration and biopsy, as well as no false positive diagnosis [17]. The experience of the pathologist in cytopathology of prostatic lesions could have contributed to this outcome.

There were 3 false-negative aspirations in adequate samples in this study. As stated by Ljung, Cherrie, and Kaufman, differentiating atypia from low-grade malignancy can be difficult. This could result in falsely negative interpretations. A faulty direction of the needle may also be responsible in each of these cases. False negative rates were thus 4.35% and this compared favorably with other studies with ranges from 3.03 to 8% [18].

Suspicious results which are inconclusive are most commonly due to atypia (without frank evidence of carcinoma), prostatitis, or poor cellularity of the sample. It is likely that suspicious results will lessen with increasing experience of the pathologist, as well as good communication of the clinical findings between the clinician and pathologist. If on repeated aspiration the findings remain non-diagnostic, tissue for histologic examination should be obtained.

One patient in this study had cytologically malignant aspirates that could not be histologically shown to harbor carcinoma. However, persistently elevated PSA despite a course of antibiotics led to a repeat biopsy at a later date (10 weeks after the initial procedure) thereby revealing malignant histology. In numerous series, initial false-positive cytologic aspirates were subsequently proved accurate with repeated core biopsies, surgery, or autopsy [19-23]. It was the initial biopsies that were falsely negative.

Conclusion

The slow acceptance of fine-needle aspiration in routine urological practice is likely due to the concerns about its diagnostic accuracy. In

this study, the sensitivity of the test was 88.5% while the specificity was 100%. Overall agreement with core biopsy was 96.7%. The results are compared with those of other similar studies as shown in Table 4 above. These figures were computed to take into account sensitivity, specificity, and overall agreement only when a definitive diagnosis of either "malignant" or "benign" was made by the pathologist as regards the cytologic aspirates and histologic confirmation was also obtained. Samples that were suspicious were excluded. These figures are in good agreement with those of the other series and reflect the success that has been documented with fine-needle aspiration of the prostate. These are also indicative of a clinically valid test.

Fine needle aspiration cytology is shown to be highly reliable with an overall accuracy rate of 96.7%, a false negative rate (FNR) of 4.35% and a positive predictive value (PPV) of 100%. Extended fine needle aspiration cytology protocol can therefore be regarded as a reliable, safe and tolerable procedure with an acceptable degree of accuracy. The findings from this study indicate that TRUS guided FNAC of the prostate is a well-tolerated and safe procedure which can complement or substitute for CNB.

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