A review of transrectal ultrasound guided prostate biopsies: is there still a role for finger-guided prostate biopsies?

A MINI DISSERTATION SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

MMed (UROLOGY)

IN THE FACULTY OF HEALTH SCIENCES AT THE UNIVERSITY OF CAPE TOWN

by

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DECLARATION

I, Karlheinz Jehle, declare that this research report is based on independent work performed by me and neither the whole work nor any part of it has been submitted for another degree to any other university. This work has been presented in part at the proceedings of the biennial conference of the South African Urological Association held in Durban in 2010.

Signed …….. **Date:** *12 August 2012*

ACKNOWLEDGEMENTS

I would like to extend my gratitude to the following people who contributed in many different but equally important ways towards the completion of this manuscript:

My long suffering wife, Nathalie, who said this is categorically and positively the very last degree she ever wishes to be involved with.

Mr Henri Carrara, Analytical epidemiologist & Biostatistician at the Faculty of Health Sciences, University of Cape Town for being a candle in the darkness that is statistical analysis.

Dr Tony Wu and Professor Dhirendra Govender of the Department of Anatomical Pathology, University of Cape Town & NHLS, Groote Schuur Hospital – for allowing me access to their database and for providing useful comments at the outset.

Prof Dick Barnes, Dr John Lazarus and Prof Johan Naudé for adding helpful comments in the preparation of this document.

The Registrars in the Division of Urology at Groote Schuur Hospital, for tirelessly filling in the data collection sheets.

Professors Alan Pontin and Professor Dick Barnes of the Division of Urology, Groote Schuur Hospital – for being grand masters of the grand round and for being mentors whose love of their discipline inspires a new generation.

LIST OF ABBREVIATIONS:

TRUS	Transrectal ultrasound
DRE	Digital Rectal Examination
PSA	Prostate Specific Antigen
FG	Finger Guided (prostate biopsy)
VAS	Visual Analogue Score
SEER	Surveillance, Epidemiology and End Results program of the US National Cancer Institute
ng/mL	Nanogram per millilitre
cc	Cubic centimetres (volume)
EAU	European Association of Urology

PART A: PROTOCOL

Title:

A review of transrectal ultrasound guided prostate biopsies: is there still a role for finger guided prostate biopsies?

Purpose of the study:

To review our local experience with transrectal ultrasound guided prostate biopsies. A retrospective review of prostate biopsies over the last four years to audit our practice will be performed. We will compare diagnosis and negative biopsy rates, before and after the introduction of transrectal ultrasound in our department. In addition data on clinical, ultrasound and histopathological findings will be analysed. We will also be able to evaluate the disease profile in our population to improve our practice if needed.

Background:

Prostate cancer is the most common male malignancy amongst black males in South Africa and the second commonest amongst white males (1,2). Prostate biopsy, via the rectum, is an essential part of diagnosing and treating this disease. Traditionally needle biopsies of the prostate were performed blindly by digital palpation of the gland per rectum. The use of a transrectal ultrasound probe to guide the biopsy needle has revolutionised the procedure in terms of accuracy, efficiency and safety. The Department of Urology at

Groote Schuur Hospital acquired an ultrasound machine in 2008, enabling us to deliver this service to our patients.

Methodology:

***Study design*:** Retrospective review

Population: All patients presenting to Groote Schuur Hospital Department of Urology for prostate biopsies.

Data collection: Prospectively collected data via standardised proforma at time of biopsy, collated in database. Historical data will be extracted from histology reports from all prostate biopsies submitted to our institution's anatomical pathology department between 2006 and 2008. This information will be supplemented from hospital information systems (eg. Clinicom) and patient folders if necessary.

Data analysis: Using Microsoft Excel with statistical packages from Stata and PAST.

Privacy and confidentiality: Data sheets are kept locked in department with restricted access. Computer access is restricted. Data identifying patients will be removed before analysis to ensure anonymity. Ethics approval will be obtained from the local Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town.

Research Objectives:

We expect to show improved diagnostic accuracy using the transrectal ultrasound guided biopsy technique compared to traditional digital guided biopsies. However, as our patients often present late with advanced disease, there may be a role for finger-guided biopsies as it is easier to diagnose advanced prostate cancer clinically. As a secondary research objective we will evaluate the role of ultrasound findings in diagnosing malignancy in our setting. In addition we will be able to analyse the demographic and disease data to evaluate our local patient profile and current management practices with a view to improving our service.

Dissemination of results:

Results will be presented at departmental and national or international level and will be subject to peer review.

Reference:

1. Kaestner, L-A. Is ethnicity a risk for high-grade prostate cancer? MMed (Urology) Thesis, University of Cape Town, 2010
2. Heyns CF, Lecouna AJ, Trollip GS. Prostate cancer: Prevalence and treatment in African men. JMHG 2005; 2(4): 400-405

Lay Summary (for Ethics protocol)

It is important for doctors to review their service and performance by way of regular internal quality control. This is part of clinical audit. This is especially important when changing one's practice and, in addition to avoiding harm to patients, it often leads to an improvement in service.

Prostate cancer is very common and to diagnose it, the doctor needs to take a sample of the prostate (biopsy), usually by using a needle and directing it with the help of an ultrasound machine. We have introduced this service in our department in 2008 and are now looking back at our results. We want to investigate how many prostate cancers we have diagnosed by way of prostate biopsies.

PART B: LITERATURE REVIEW

INTRODUCTION

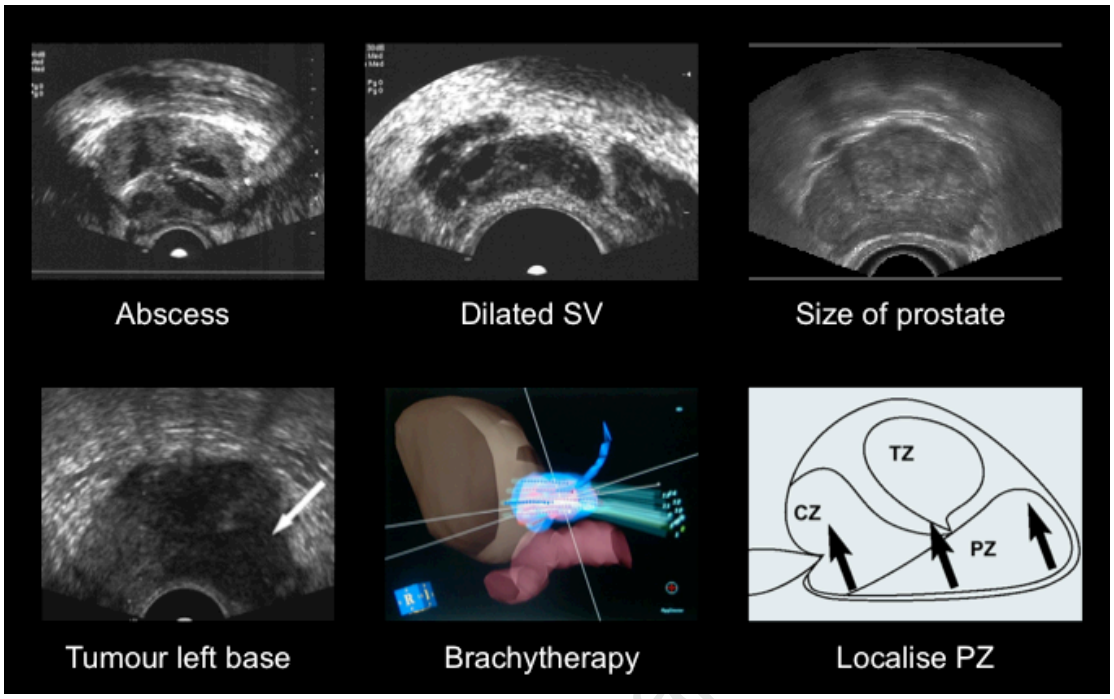
Prostate cancer is the commonest malignancy amongst black males in South Africa and the second commonest amongst white males (1). The incidence of prostate cancer is increasing in the developed world but remains under diagnosed in the developing world where the disease often presents late (2). There has, however, been a dramatic decline in mortality from prostate cancer due to earlier detection and treatment (3). This has been largely due to screening with prostate-specific antigen (PSA) and an increased public health awareness combined with improved prostate biopsy techniques. Both these developments have happened relatively recently and gained widespread clinical acceptance in the 1990s.

Biopsy of the prostate is the cornerstone of the diagnosis and treatment prostate cancer. The first transperineal needle aspiration of cancer cells from the prostate was reported by Ferguson in 1930, followed by Astraldi in 1937 (3) with a transrectal needle biopsy. Historically, biopsies of the prostate were performed only when an abnormal prostate was felt on digital rectal examination (DRE) or if metastases were suspected. Three important developments significantly changed the way the prostate biopsies were performed. Firstly, the introduction of transrectal ultrasound enabled the urologist to visually guide the biopsy-needle. Secondly, the adoption of a systematic rather than random biopsy scheme as described by Hodge (4) in

the landmark paper from the Stanford group. This became necessary because of the increasing use of PSA in patients who had normal feeling prostates on DRE, necessitating a systematic sampling of the gland. Lastly, the use of a mechanical biopsy gun was introduced in the early 1980s, obtaining good quality tissue for pathological review.

The urinary system was amongst the first organs evaluated by diagnostic ultrasound in the 1950s because of the easily recognisable echostructure of the kidney and the bladder. Even though transrectal ultrasonography (TRUS) was attempted in 1955, it took another decade before Watanabe (5) obtained the first sonographic picture of the prostate in 1967 using a device intended to visualise the heart via the oesophagus. Since then TRUS has been firmly established in urological practice for a variety of indications. They include imaging the prostate, the evaluation of azoospermia and the therapeutic aspiration of prostatic abscesses and cysts. However, it is the ability to perform real-time image guidance, most commonly for performing transrectal prostate biopsies, that has made the investigation so popular. Other uses include the placement of radioactive Iridium brachytherapy seeds, fiducial gold seeds used for accurate positioning in external beam radiation therapy, as well as probe placement for cryotherapy and high-intensity focused ultrasound (HIFU). The indications for prostate biopsy as well as the technical procedural details as described in the manuscript below, are beyond the scope of this literature review and the reader is referred to a standard contemporary textbook (6).

Figure 1: Examples of uses of TRUS in urological practice. Images from Google. (SV, seminal vesicles; PZ, peripheral zone)



OBJECTIVES OF LITERATURE REVIEW

To establish what the role of finger guided (FG) biopsies are and to investigate the body of evidence for FG prostate biopsy in the era where TRUS is the gold standard. Secondly, to review the literature on the evolution and current status of TRUS guided biopsies of the prostate.

LITERATURE SEARCH METHODOLOGY

Primary searches of the English language literature were performed using the PubMed and Medline databases and the Google scholar search engine. Key words included:

Prostate biopsy, Prostate needle biopsy, Transrectal ultrasound guided, TRUS guided, Finger guided, Digitally guided and Digitally directed

Manual searches of the bibliographies of relevant articles were performed. The guidelines of professional associations as well as standard textbooks were consulted.

SUMMARY OF THE LITERATURE

The management of prostate cancer and the role of prostate biopsies

Prostate cancer comprises a heterogeneous disease spectrum and the management thereof depends on a variety of factors, which can be loosely classified into patient factors, tumour related factors and healthcare related factors. Table 1 shows some of the factors to be considered:

Table 1: Factors affecting decision making in prostate cancer management

Patient factors	Tumour factors	Healthcare facility
Age and life expectancy	Clinical stage and presence of metastases	Availability of urologist
Comorbid diseases	Gleason grade	Treatments offered
Performance status	Volume of disease	Funding of treatment
Patient preference	PSA level and prostate size	Accessibility for patient

Standard treatments options offered for patients with organ-confined disease include (7):

- Watchful waiting
- Active surveillance
- Radical prostatectomy (open, laparoscopically or robotic-assisted)
- Brachytherapy
- External beam radiotherapy
- Adjuvant (early) hormonal treatment

Prostate biopsies play an important part not only in the diagnosis of prostate cancer but also the management and treatment decisions. The stage, grade of cancer, volume of disease and size of the prostate (on imaging such as TRUS) impact directly on treatment decisions and as such the prostate biopsy has an important part to play. New treatment modalities such as multimodal treatment for high-risk disease and focal therapy also rely heavily on prostate biopsy findings.

New evidence regarding the outcome of various treatments has shed new light on the long-term survival of patients. Ward et al looked at the survival of men with low risk prostate cancer by analysing the SEER database (8). They found that in men below 60 years of age, the cancer related death rate for patients treated with surgery were comparable to that of brachytherapy (both less than 1%). For patients over the age of 60 years, the corresponding rates were 3.8% for surgery, 5.3% for brachytherapy and 8.4% for no treatment. The difference between brachytherapy and surgery was not statistically significant and they concluded that treatment for carcinoma of the prostate was preferable to no treatment, regardless of the modality used.

Conversely, the results of the PIVOT trial were recently published in the New England Journal of Medicine (9) and suggested that some patients actually did better in terms of survival when they had no treatment. When followed for at least 12 years, patients with clinically localised prostate cancer treated with radical prostatectomy did not have an improved all-cause or prostate cancer specific survival over patients treated with observation only. The trial was critised for being under-powered and for lack of adhesion to the protocol as 20% of participants in the observation group crossed over to receive surgery while 21% of patients randomised to receive surgery did not and were in fact observed for the study period. Nevertheless, the trial argues strongly towards observing these patients with low risk prostate cancer, with what is currently termed active surveillance.

The role of Transrectal Ultrasound in imaging the prostate

Findings on TRUS include both calcifications (including corpora amylacea) and cystic lesions. These include those from Wolffian duct origin (ejaculatory duct and seminal vesicle cysts) as well as the Müllerian duct structures (prostatic utricle). From a prostate cancer point of view, the important structures to identify on TRUS are hypoechoic areas in the peripheral zone, which should be included in the biopsy if visualised, and extracapsular extension (6). Prostate cancer may be isoechoic in 39% of cases and hyperechoic in 1% according to Shinohara et al (10). Hypoechoic lesions themselves are malignant between 17% and 57% of the time and should therefore be included in any biopsy (11). The presence of hypoechoic lesions in a prostate are associated with a higher incidence of cancer per se, even if the specific hypoechoic area is in fact benign. Other causes of hypoechoic lesions include BPH nodules in the transitional zone as well as prostatitis, lymphoma and prostatic infarcts (6).

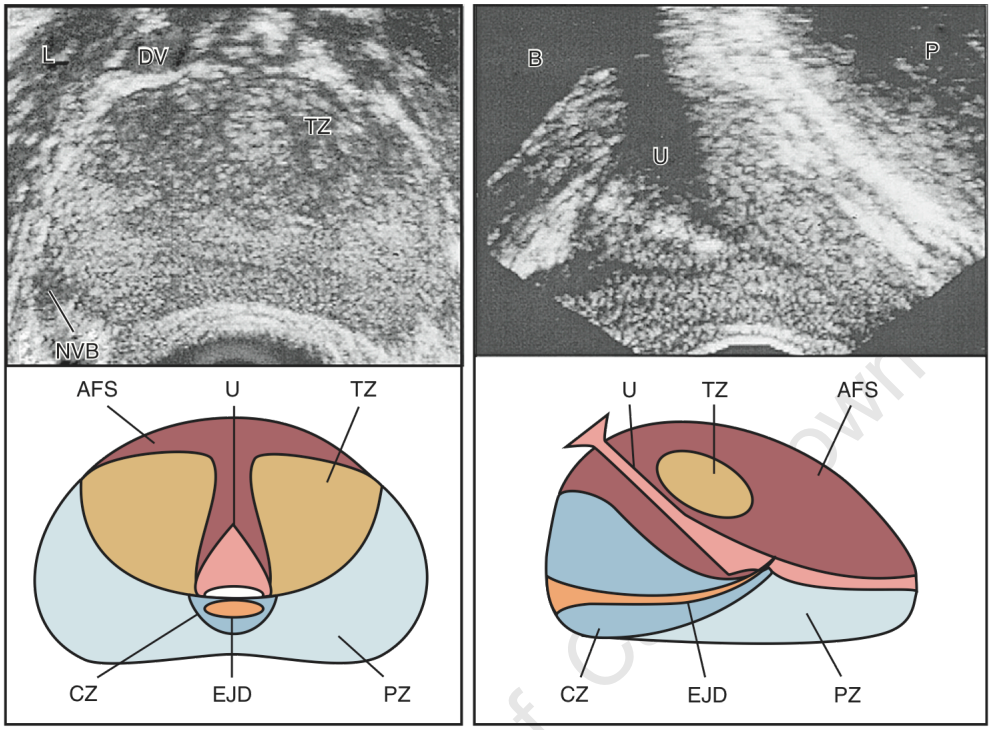
In 2007, Toi et al (10) published a review of 7426 patients where they performed systematic 6 – 10 core TRUS guided biopsies on patients initially with added biopsies if a suspicious lesion was seen on TRUS or if it was a repeat biopsy (in 26%). Not only were biopsies in those patients who had a prostatic lesion identified on TRUS more likely to have cancer diagnosed (57.8% vs 30.8%), but the median percentage of the core involved with cancer, as well as the Gleason scores were greater indicating higher grade and volume cancers which were more clinically significant. This study

emphasised the importance of TRUS, not only in directing the biopsy needle to the appropriate part of the prostate, but also in identifying lesions. In their series, the likelihood of finding cancer increased in older men with smaller prostates and an abnormal DRE or PSA value above 10 ng/mL.

Where to direct the biopsy needle?

McNeal, after whom the zonal anatomy of the prostate is named (11), evaluated prostate glands removed by radical prostatectomy to establish where the cancers originated. In 68% the peripheral zone was thought to be the origin followed by the transitional zone in 24% (12). His work formed the basis for Hodge and Stamey's landmark paper (4), which changed prostate biopsy from random sampling to a standardised systematic sextant biopsy on which all modern biopsy schemes are based. The zones of the prostate are shown in Figure 2. Hodge et al described the sextant method as follows: "These 6 biopsy sites were located approximately 1 cm apart and were taken from the apex, middle and base of the prostate bilaterally. With respect to the coronal plane, the biopsy sites were oriented in the center of each lobe. …. If a suspicious hypoechoic region was located medially or far laterally to this mid lobe parasagittal line of random systematic sampling additional directed biopsies were taken of the specific defects." Figure 3 demonstrates the original Stanford method.

Figure 2: Normal prostate ultrasound images with diagrams indicating the zonal anatomy at the level of the veru montanum. A: transverse view and B: sagittal view. From Trabulsi et al, Campbell Walsh Urology (6)



Legend: AFS - anterior fibromuscular stroma, U – urethra, TZ – transition zone, CZ – central zone, EJD – ejaculatory duct, PZ – peripheral zone

The reasoning behind the position of the 6 cores as described is unclear and possibly relates to symmetry. This protocol was adhered to until Stamey suggested in an editorial (13) to place the needles more laterally to obtain better samples of the anterior horns of the peripheral zone.

Figure 3: The original plaster cast of a radical prostatectomy specimen used to illustrate the biopsy sites and direction of the needle. From Hodge et al, J Urol 1989 (4)

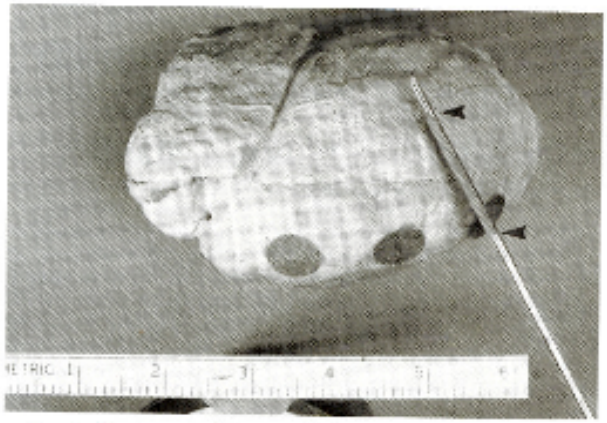


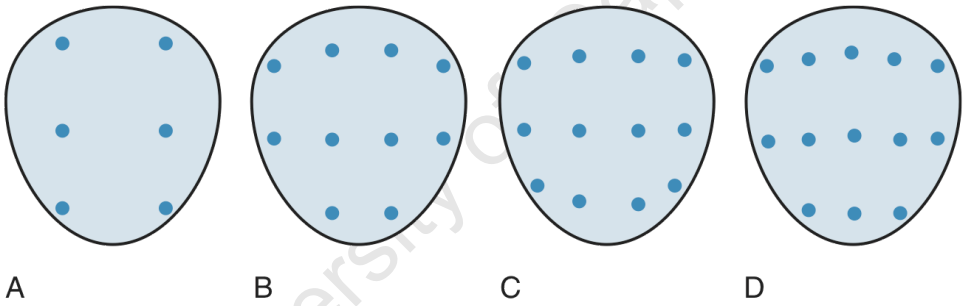
FIG. 1. Plaster cast of 40 gm. radical prostatectomy specimen. Rectal surface is located posteriorly, apex to right side. Arrowheads indicate 1.6 cm. crypt area for core biopsy. Core (1.6 cm.) would include full thickness of peripheral zone and part of transition zone of prostate. Angle of biopsy, determined by computer generated trajectory of Bruel and Kjaer 8537 sector scanner, is approximately 45 degrees.

FIG. 2. Posterior (rectal) surface of 40 gm. prostate seen in figure 1. Apex is at bottom and vesical neck is at top. Three dots over each lobe mark site of 6 random systematic biopsies. Longitudinal distance between center of each dot is 1 cm.

The number of biopsy cores

The number of cores taken during prostate biopsy remains controversial. Whilst the aim of a biopsy is to diagnose cancer, the urologist is reluctant to diagnose clinically insignificant cancer and wants to minimize morbidity. The initial sextant biopsy as described by Hodge (4) comprised 6 cores but has been superseded by the modern TRUS guided biopsy schemes. See Figure 4 for illustration.

Figure 4: Various reported systematic biopsy schemes with base at the top and apex at bottom of picture. From Campbell Walsh Urology 10th Edition (6)



A – sextant biopsy proposed by Hodge et al (1989)

B – 10 core biopsy from Presti et al (2000)

C – 12 core scheme

D – 13 core or 5-region scheme after Eskew et al (1997)

An early prospective randomised trial reported by Naughton et al (14) built on previous non-randomised findings (15,16) and suggested that 12 cores were better than 6 cores although this finding was on the basis of a subgroup analysis which showed a 21% increase in cancer detection by obtaining

additional lateral 6 cores. The trial was however critised as it was underpowered to detect a 10% or less difference in cancer between the study groups. Further randomised trials evaluated the number of cores by comparing cancer detection. Results are shown in Table 2. Of note is the work from Presti et al (17) where they showed that traditional sextant biopsies may miss up to 20% of cancers and that lesion-directed biopsies provide little additional cancer identification when used in addition to extended peripheral zone biopsies.

Table 2: Trials showing increased cancer detection rates with extended biopsy schemes. From Campbell-Walsh Urology 10th edition (6)

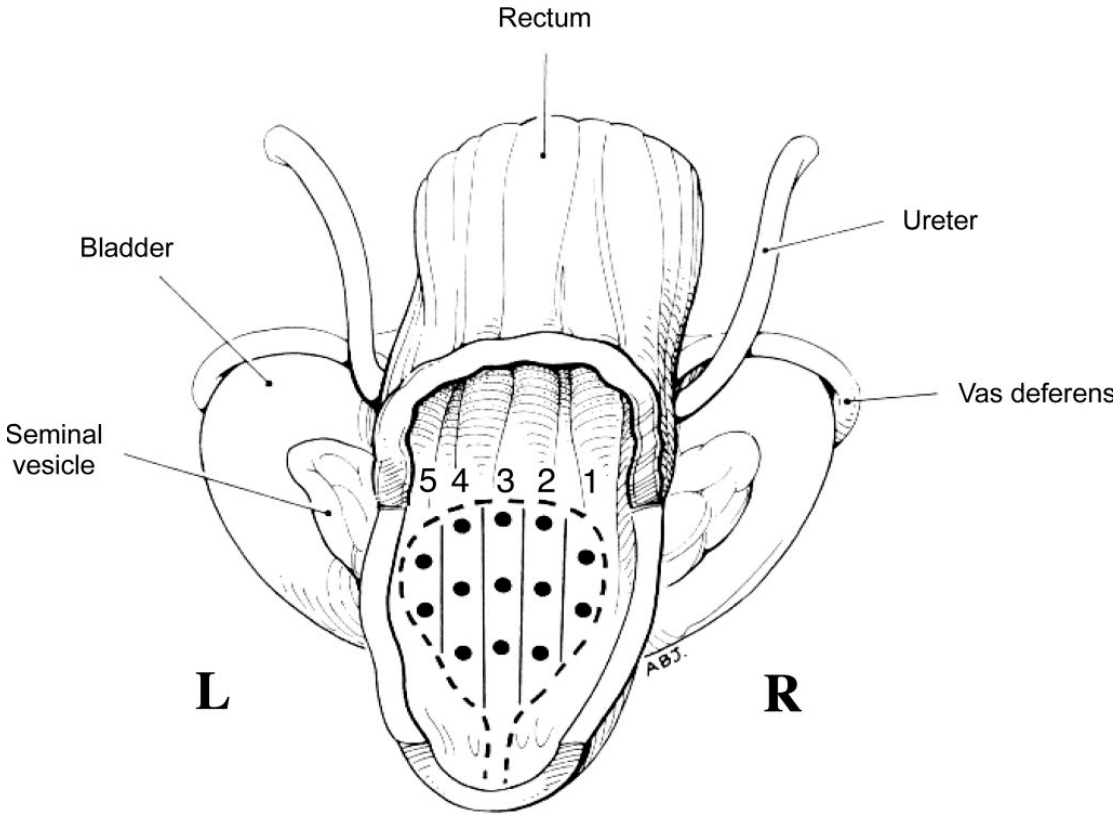
Author	Number of cores	Cancer detection rate
Eskew 1997 (16)	6	26.1%
	13	40.3%
Naughton 2000 (14)	6	26%
	12	27%
Presti 2003 (18)	6	33.5%
	8	39.7%
	10	40.2%
Babaian et al (2000)	6	20%
	11	30%

A Mexican group performed a prospective randomised trial (21) of 150 patients comparing 12 to 18 core biopsies and found cancer in 30.7% and

48% respectively. The groups were well matched and there was no difference in the complication rates. The biopsies were however performed under sedation. Extended biopsy schemes using more than 18 cores, so-called saturation biopsies, are reserved for patients in whom a high suspicion of prostate cancer exists and previous biopsies have proved negative (23). In a study by Ashley et al (24) from the Mayo Clinic, no more abnormal pathology was detected when the initial biopsy involved more than 24 cores, compared to a standard 12 to 18-core biopsy. Scattoni et al (25) similarly reserves saturation biopsies (which they classify as more than 20 cores) for repeat biopsies where there is suspicion of cancer, but also includes active surveillance protocols as an indication.

A review by Eichler (18) included 20698 patients in 87 studies showed that biopsy schemes comprising 12 cores in the standard sextant pattern with additional cores directed more laterally were optimal in balancing cancer yield versus complications. This has formed the basis for the European Association of Urology (EAU) guidelines (19), which state that a minimum of 8 cores should be sampled in small prostates (30-40cc) whilst 10 to 12 cores are recommended. The American Urology Association agrees with this but allows for additional anterior and transitional zone biopsies (20). See Figure 5.

Figure 5: The prostate and bladder viewed from posterior via the rectum to show the 5 zones for the systematic extended biopsy protocol. The 10-core biopsy excluded the 3 biopsies in zone 3. From Eichler et al. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006; 175(5): 1605-1612 (19)



The role of finger guided prostate biopsies in an abnormal feeling prostate

Despite the widespread acceptance of TRUS guidance as the gold standard in prostate biopsy and the global adoption of systematic biopsy protocols, a few papers have investigated the role of FG biopsies in the TRUS era. Current literature suggests that a palpable nodule or abnormality felt on DRE can be seen on TRUS and therefore more accurately biopsied than by digital direction only (50).

Following Hodge's 1989 publication (4), a number of papers were published evaluating FG biopsies. Huynh et al (37) performed TRUS and FG biopsies of 240 palpably abnormal prostates and found an increased yield of cancer from 47.9% to 55.4%. Furthermore, they found that 7.5% of the cancers were only detected in the FG biopsies and that in 27% of those patients that had malignancy in both FG and TRUS, the FG biopsies added more information in terms of the tumour volume. Van Emery et al (38) found that TRUS guidance was comparable to FG biopsies. On the contrary, Türkeri and his colleagues (39) compared FG to TRUS guided biopsies in a small group of 40 patients, all with a palpably abnormal prostate and found systemic TRUS guided biopsies to diagnose 21 cases of cancer compared to the 18 cases of FG biopsies, concluding that FG biopsies are unnecessary.

Figueiredo et al (40) performed both FG and TRUS guided biopsies on 52 patients at the same sitting, randomly assigning the first method. They found

the two techniques to be equivalent in terms of cancer detection. Resnick et al (41) also compared FG with TRUS guided biopsies in 45 men with an overall cancer yield of 31% but no difference between the two methods in patients with an abnormal DRE.

In 2001 Garcia (42) published their experience with a group of 51 patients who had both TRUS guided and FG transperineal prostate biopsies at the same sitting, albeit with only 6 cores with each route. They concluded that while it was possible to perform systematic biopsies with FG via a transperineal route, the yield of prostate cancer was indeed related to the increased number of cores taken rather than the technique or approach used. Weaver et al (44), on the other hand, compared FG biopsies of palpable nodules or abnormal feeling areas with simultaneous TRUS biopsies in 51 patients with abnormal DRE and found that 23 lesions (45.1%) were adenocarcinoma while the FG biopsies only diagnosed 9 cancers (17.6%). They concluded that TRUS is of benefit even if a nodule is felt.

In the same year two urologists from Nova Scotia in Canada published a series of 145 patients in whom they performed 189 prostate biopsies using a FG systematic 8-core protocol (43). The cancer yield was 53% in men with an abnormal DRE (25%, 43% and 84% had PSA values below 4 ng/mL, 4-10 ng/mL and >10 ng/mL respectively). In patients with a normal feeling prostate the yield was 22% and 28% for PSA values below 4 ng/mL and 4-10 ng/mL respectively. The authors compared their findings with the published literature at the time and concluded that the two techniques were equivalent in efficacy,

attributing the success of TRUS biopsy to the systematic nature and larger numbers of sampling.

More recently, Chiang and colleagues (45) in Taiwan retrospectively compared prostate cancer detection rates in 148 patients who presented over a 4 year period with palpable nodules by performing both systematic 12 core TRUS-guided as well as 3 digitally directed FG biopsies of the nodule. They wanted to see if adding FG biopsy of the nodule to the standard biopsy protocol would increase the yield of cancer. Cancer was detected in 44.6% of patients with the highest detection rates from using both systematic random biopsies and FG biopsies together. The histology obtained from FG biopsies led to an increase in the Gleason grading in a number of patients but this did not reach statistical significance.

In a study from Australia, Mancuso et al (46) also reported on 500 consecutive patients, all with an abnormal DRE, who had both TRUS and FG biopsies over a 6-year period. The cancer detection rate overall was 53.6% with 14.6% positive on FG biopsies but negative on TRUS. In this subgroup, there were 38.5% who had a PSA < 4 ng/mL and 27.7% who had prostates larger than 50 cc. Among those patients who returned positive histology on both the FG and TRUS biopsies, the FG cores gave additional information on tumour grade and stage in 59.3% of cases, showing that in patients with an abnormal DRE there is a benefit in performing FG biopsies in terms of cancer detection and grading.

In summary, the literature surrounding the use of finger-guided biopsies in the diagnosis of prostate cancer is sparse and consists of retrospective case series with no prospective trials found. This is not unsurprising, as the major body of evidence (81% of studies) taken into account during the development of the 2007 AUA guidelines on prostate cancer were retrospective case series, with controlled clinical trials only accounting for 6% (47).

Initially the trials comparing FG with TRUS guided biopsies after Hodge's (4) publication consisted of small retrospective series, showing conflicting results. Most trials investigating FG biopsies involved only patients with abnormal DRE findings. Among these, there is evidence to show that FG biopsies have a role to play in the era of TRUS guided biopsies, especially in patients presenting with an abnormal DRE. However, the gold standard of TRUS guided systematic biopsies have been shown to be superior to targeted FG biopsies only.

What needle to use?

The advent of TRUS guided biopsies together with the spring loaded biopsy gun enable the urologist to use thinner needles than the older manually operated Tru-cut needles, but still obtain better quality cores of tissue for pathological review. Whilst much has been published in the literature to assess where prostate biopsies should be directed to effectively yet randomly sample the prostate, in the absence of having any imaging to guide biopsies, very little has been written about the length of the biopsy cores. In a recent

publication from Istanbul, Öbek et al (26) evaluated the hypothesis that longer and better quality cores will improve the sampling and thus the yield of prostate cancer. They found that there was a significant difference in the mean core length in patients with cancer and that a core length of greater than 11.9mm serves as a minimum to ensure quality biopsies.

The importance of prostate size when looking for cancer

Several authors have investigated the logical question that the size of the gland is inversely related to the yield of cancer because of the inherent problem of sampling. Karakiewics et al (27) demonstrated that, using sextant biopsies, the yield of cancer was 40% in glands less than 20cc, dropping steadily to 12% in glands sized 70cc. In a study from Canada, Al-Azab et al (28) found that with the benefit of TRUS in patients with PSA below 9 ng/ml, the strongest predictor on multivariate analysis, above PSA level and age, was prostate volume. When evaluating patients who have had at least one previous negative biopsy, Novara et al (29) demonstrated using transperineal saturation biopsies that size was the only predictor of a positive biopsy. His group from Italy reported cancer diagnoses in 47% of prostates smaller than 40cc and only 14% in prostates larger than 60cc. A recent study from Israel reported similar results, stating prostates larger than 72cc should benefit from more than 12 cores when biopsied (30).

The above findings prompted investigators to create a guide to determine the number of biopsies. One of these is the Vienna nomogram designed for

patients with a PSA value between 2 and 10 ng/mL and taking into account the prostate volume and age of the patient. The paper by Remzi et al (31) showed that biopsies using the nomogram-detected cancer in 36.7% compared to 22% in a historical control group using 8 biopsies. The study was critised for not being randomised and the groups were not comparable. In a prospective randomised trial, Lecuona and Heyns (32) showed that there was in fact no advantage in using the Vienna nomogram over an 8-core protocol.

Does it matter who performs the biopsy?

The literature is not uniformly clear as to what the experience or grade of the relevant clinicians (junior trainees vs senior trainees vs qualified specialists) are who perform the prostate biopsies in their studies. Whilst some clinicians present their personal case series, those studies from larger institutions have many clinicians performing the biopsies.

Karam et al (33) investigated the impact of training level on the detection of prostate cancer on TRUS biopsy in a study of 627 patients over 3 years. The patients had a raised PSA between 4 and 10 ng/mL and underwent their first biopsy by residents in their first to fourth year of training. A senior resident supervised the residents for “up to five sessions” before performing the biopsies unsupervised. They found no difference in the cancer detection between the different years of residency, concluding that there was no learning curve associated with the TRUS biopsy of the prostate.

Addressing the same issue, a group from Toronto evaluated their database of 9072 initial biopsies performed over 8 years by 4 different uroradiologists (34). The overall yield of cancer was 49.3% and varied between 43.8% and 52.4% between the operators. They concluded that there was no learning curve involved in the acquisition of the skill and that the volume of prostate biopsies performed does not impact the positive cancer detection rate.

Nguyen et al (35) from Cleveland evaluated the patients' experience of their biopsy by recording a Visual Analogue Score (VAS) for pain and discomfort during the ultrasound probe insertion, the injection of local anaesthetic and the taking of the biopsies. They found that the mean VAS scores were higher for residents, but questioned themselves whether their findings were clinically meaningful as the absolute differences in pain were very small.

The literature therefore suggests that trainees rapidly become adept at performing adequate biopsies. These findings were reaffirmed in a recent study published in the British Journal of Urology (36) where investigators compared a large series of prostate biopsies performed by an experienced consultant urologist with those performed by a trained nurse practitioner. The incidence of cancer in the urologist cohort was 57.3% compared to 52.7% in the nurse practitioner's cohort, leading the authors to conclude that a trained nurse can perform TRUS biopsies as effectively as an experienced urologist after an initial learning curve of 50 biopsies.

FURTHER RESEARCH

Beyond TRUS – modern imaging techniques used with prostate biopsy

Despite the significant improvements made over the last 20 years in diagnosing prostate cancer, the stage migration of the disease has exposed significant gaps in our current practice and technology. The current gold standard, TRUS guided systematic biopsies, does however have several advantages over other imaging modalities. It is safe, devoid of ionising radiation, relatively cheap and accessible with a short learning curve. The prostate is amenable to imaging, lying in close proximity to the rectum. It also allows real time imaging enabling clinicians to perform interventions such as biopsy, brachytherapy seed implantation and focal therapy. Greyscale ultrasound does however lack sensitivity and specificity in the detection of prostate cancer (50).

Several new developments are being investigated to improve both the imaging and sampling of prostates where there is a clinical suspicion of malignancy. They fall beyond the scope of this literature review and are mentioned here for the sake of completeness, being well documented in several recent review articles (48,49):

(i) *Quantification*: This method uses computer algorithms to analyse greyscale ultrasound data with the aim to increase cancer diagnosis. Systems being investigated include AUDEX, C-TRUS

and Histoscanning, the latter claiming sensitivity and specificity of 90 and 72% respectively and able to diagnose lesions larger than 0.2ml.

(ii) Doppler: The use of both colour and power Doppler relies on the imaging of flow in blood vessels. This limitation of this technology is the low flow rate of blood in the small calibre vessels associated with tumour angiogenesis.

(iii) Elastography: This technology uses the differences in the reflection of sound waves between different (benign and malignant) tissues. A further development in this field is the shear wave elastography (SWE) in which quantification is possible, thereby minimising the inter-operator variability.

(iv) MRI-transrectal ultrasound fusion: Although 3.0 Tesla T2-weighted MRI has been used for some time to visualise prostate tumours, the cumbersome nature of the equipment, together with the inconsistent accuracy, has made it an unpopular choice for intervention. A fusion of multiparametric MRI with TRUS however is a more workable option and has recently shown promising results.

(v) 3D and 4D ultrasound: although these machines allows imaging in two planes simultaneously in addition to computer generated reconstruction of the prostate gland, the increased visualisation of hypoechoic areas in the prostate does not negate the need for systematic biopsies to exclude cancers that are not characterised by hypoechoic areas.

(vi) Contrast enhanced ultrasound: Contrast enhanced ultrasound uses intravenous micro-bubble agents to increase Doppler signal in areas of high vascularity as found in tumours.

Whilst many of these technologies are still in the early stages of development, the mere fact that they exist, heralds a new era in the search for a reliable way to diagnose prostate cancer. The improved imaging could, in time, lead to targeted biopsies and then to targeted or focal therapies. At present, however, the multifocal nature of prostate cancer and the limitations of greyscale ultrasound dictates that we persevere with extended biopsy schemes and focus on how we interpret biopsy findings in order to treat our patients appropriately.

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PART C: MANUSCRIPT

TITLE

A review of transrectal ultrasound guided prostate biopsies: is there still a role for finger guided prostate biopsies?

JOURNAL

African Journal of Urology - the official journal of Pan African Urological Surgeons Association (PAUSA)

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KEY WORDS

prostate cancer, prostate biopsy, transrectal ultrasound, finger-guided prostate biopsy

WORD COUNTS

Abstract: 306 words Manuscript: 2743 words

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ABSTRACT

Objective: We compared our institution's initial experience with transrectal ultrasound-guided (TRUS) prostate biopsies in a single arm prospective study to a historical cohort of finger guided (FG) biopsies. The primary outcome measure was prostate cancer detection. We documented our findings on TRUS including the findings of peripheral calcifications, hypoechoic lesions and capsular distortion and evaluated whether these had any significance in prostate cancer detection.

Patients and Methods: All patients presenting to our institution for prostate biopsy were included. Indications included raised PSA and/or abnormal DRE or other suspicion of prostate cancer. Data on 12-core TRUS guided biopsies were prospectively collected and compared to a historical cohort of 6-core FG biopsies obtained from the pathology database of all prostate biopsies performed at Groote Schuur Hospital within the study period.

Results: One hundred ninety two patients were included in the TRUS group over a 25-month period (2008 – 2010) and 262 FG biopsies were reviewed between 2006 and 2008. Abnormal DRE findings were present in 56.2% of FG and 43.3% of TRUS biopsies. Histology was available in 97.8% of cases. The incidence of prostate cancer was 42%. Malignant or suspicious histology was found in 45.6% of the FG group compared to 48.6% in the TRUS group (p=0.27). In patients with a normal DRE there was a trend that favoured TRUS for improved cancer detection, which is significant if the PSA was below 10 ng/mL.

Conclusion: Our study did not show superiority of TRUS over FG biopsies except when the patient had a low PSA (below 10 ng/mL) and a normal DRE. Systematic FG biopsies may be underutilised in the TRUS era, and may be of benefit in patients presenting with a PSA over 10 ng/mL or an abnormal DRE. This may be of value in a limited resource setting where access to TRUS is restricted.

INTRODUCTION

Prostate cancer is the commonest malignancy amongst black males in South Africa and the second commonest amongst white males (1,2). Although the incidence of prostate cancer is increasing in the developed world, it remains under-diagnosed in the developing world where it often presents late (3). Biopsy of the prostate forms the cornerstone in diagnosing and treating this disease. Historically, needle biopsies of the prostate were performed either transrectally or trans-perineally, with digital palpation of the gland and guidance of the biopsy needle per rectum (4). Three important developments significantly changed the way the prostate cancer was diagnosed in the early 1990's. Firstly, the adoption of a systematic rather than random biopsy scheme as described by Hodge et al (5). Secondly, the use of a biopsy gun as opposed to hand-operated Tru-cut needles and thirdly, the advent of the transrectal ultrasound (TRUS) probe enabling the clinician to visually guide the biopsy needle (6).

Over the last two decades, TRUS has become the gold standard in performing prostate biopsies (7,8). The initial work from Stanford University demonstrated that TRUS biopsies diagnosed cancer in 23 of 43 patients who had previous negative FG biopsies while confirming previously digitally diagnosed cancer in 94% (9). In a further publication in the same journal, they showed that the yield of prostate cancer was better with six systematic random biopsies than FG biopsies of abnormal areas in the prostate (5). The benefits of ultrasound in guiding biopsy needles became more apparent as

the understanding of prostate anatomy and distribution of carcinoma improved, assisted by McNeal's description of the different zones (10). Since then much work has been done to determine the optimal sites and numbers of prostate biopsies to maximise cancer detection of what remains a test with a significant sampling error. The consensus today for initial biopsies are to use a minimum of 10 to 12 laterally directed biopsies from the peripheral zones with the use of TRUS (11,12).

Our institution only acquired a transrectal ultrasound probe in 2008, enabling us to perform TRUS guided biopsies. We prospectively collected data on all TRUS guided prostate biopsies since the inception of this service, using a standard proforma (cf Appendix 2). The aim of this review was to investigate our hypothesis that TRUS would increase the yield of our prostate biopsies which were previously performed with 6 finger-guided (FG) cores. At the same time we wanted to evaluate the extent to which the trainees were able to detect abnormalities of the prostate on TRUS by recording the findings and correlating them with cancer diagnoses.

PATIENTS AND METHODS

Approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. (cf. Appendix 1)
The study population included all patients undergoing prostate biopsy at our institution during the study period July 2006 to February 2010. The first group was the FG biopsy group identified from pathological records of needle

biopsies of the prostate performed in the time period immediately preceding the introduction of TRUS at our hospital. The second group was the TRUS guided biopsy group where data was prospectively collected since the start of TRUS, on a standardised proforma at the time of biopsy and combined with the histological findings. Only patients with complete data sets were included in the study. Patients who underwent FG biopsy during the TRUS period were excluded.

Clinical parameters included patient demographics including age, reason for intervention (screening or symptoms), PSA value, and clinical findings on DRE. DRE findings were classified from clinical stage 1 to 4 according to the AJCC staging system as found on initial examination by a member of our Urology Department (cf. Appendix 3). Absolute PSA values were recorded and subsequently subdivided for the purposes of analyses into 5 groups: 0-4, 4-9.9, 10-19.9, 20-99.9 and >100 ng/mL.

TRUS was performed using a Toshiba diagnostic ultrasound machine with a 7.5-MHz transrectal probe. Informed consent was obtained and antibiotic prophylaxis administered orally 30 minutes before the procedure. Local anaesthetic with intrarectal instillation of 20ml 2% lignocaine jelly (Remicaine®, AI Generics, South Africa) was used without periprostatic needle infiltration. The findings on TRUS were documented for both the right and left lobe as follows: the presence of hypoechoic areas and/or calcifications in the periphery and the centre of the glands as well as the presence of capsular distortion or the visualisation of a palpable irregularity.

The prostate gland was assessed in the axial plane where the transverse and antero-posterior measurements were taken at the point of maximum diameter, followed by a paramedian longitudinal measurement in the sagittal plane. The volume was calculated using a standard pre-programmed formula {π/6 × (transverse diameter) × (antero-posterior diameter) × (superior-inferior diameter)} based on an ellipsoid shape. The number of biopsies taken was documented prospectively in the TRUS group as either the routine 12 cores (2 cores from apex, mid-zone and base of prostate on the periphery of either lobe) or the routine 12 cores plus additional biopsies of suspicious areas (on ultrasound or digital examination). Biopsies were taken using a Magnum Biopsy Instrument (C.R. Bard Inc, USA) with 18G 25cm Tru-cut needles. Cores were transferred in 2 specimen bottles for FG biopsies (left and right lobes) and in 6 pots for TRUS biopsies (left and right apex, mid-zone and base respectively).

Histological diagnoses were classified for the purposes of analysis into benign if reported as normal prostate or benign prostatic hyperplasia or inflammation and as suspicious for malignancy if reported as atypical, atypical small acinar proliferation (ASAP) or high grade prostatic intraepithelial neoplasia (PIN). Gleason scores below 6 were classified as suspicious for malignancy and 6 and higher were classified as malignant. To differentiate between negative biopsies and those with pathological findings, patients with suspicious findings were grouped together with the confirmed carcinomas.

Data were compiled using MicroSoft Excel® and statistical analysis was performed by a biostatistician on Stata® software using the Mann–Whitney U test for continuous variables and the Pearson's chi-squared test for categorical variables. A two-tailed P-value <0.05 was accepted as significant with a power of 80%.

RESULTS

Over a 25-month period complete data sheets and pathology reports were collected in 192 patients who underwent TRUS guided biopsies at one hospital. The FG cohort comprised 262 patients over a 17-month period preceding the start of TRUS guided biopsies.

Presenting features: Patients in the TRUS group presented mostly with obstructive lower urinary tract symptoms (65.2%) followed by referral with raised PSA (21.5%), irritative or mixed lower urinary tract symptoms (11.6%) and other symptoms (1.6%) such as haematuria or paralysis.

Patient age, presenting PSA value and clinical findings are presented in Table 1 together with diagnosis of biopsy. Twenty-four patients had a PSA value less than or equal to 4 and 399 patients a raised PSA. Between the FG and TRUS guided groups, the normal PSA (4 ng/mL and lower) were 12 (5%) and 12 (6.6%) respectively with raised PSA (more than 4 ng/mL) in 229 (95%) and 182 (93.4%) patients respectively. Statistically however, when looking at the whole group, both age and PSA values were significantly different.

Table 1: Patient age, PSA and histology

	Finger guided n = 262	TRUS guided n = 192	p-value
Age (mean ± SD)	68.4 ± 8.38	65.6 ± 7.87	p=0.0005
PSA (median + IQR)	12 (8.8 – 52.8)	17.5 (6.5 – 24.2)	p=0.0001
DRE suspicious or malignant	109/194 (56.2%)	78/180 (43.3%)	p=0.013
Benign histology	141 (54.4%)	94 (51.4%)	p=0.32
Malignant histology	118 (45.6%)	89 (48.6%)	p=0.27
Gleason 6	31.3%	41.3%	
Gleason 7	23.6%	30.7%	
Gleason 8-10	45.3%	28%	

Biopsies performed: Biopsies were performed by an equal number of trainees (6) and specialists (2) with similar level of experience in both finger guided and TRUS guided biopsy groups, as shown in Table 2. Trainees performed 97.9% of the TRUS guided biopsies during the study period.

Table 2: Clinicians (A-P) performing prostate biopsies with finger guidance (FG) and transrectal ultrasound (TRUS) guidance

Clinician	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
FG (262)	10	53	27	24	74	24	18	6	3	7	10	5	0	0	0	0
TRUS (181)	0	0	3	0	31	15	15	3	11	4	0	30	21	13	30	5

The number of biopsies taken differed in the 2 groups. In the finger guided group the average number of cores were 6.24 (range 2 – 12). In the TRUS

group all but 15 patients had 12 or more cores, taken in a systematic sextant fashion as described above. All but 3 patients (due to technical failure of biopsy gun and patient being unable to tolerate biopsy under local anaesthetic) who had less than 12 cores taken with TRUS guidance had raised PSA above 50 ng/mL, with a clinically malignant feeling prostate.

Histology: Histology was available in 444 cases. The incidence of prostate cancer was 42% overall, followed by benign prostatic hypertrophy, prostatitis (mostly chronic) and atypia, ASAP and PIN. Results are shown in Figure 1. When comparing the FG with the TRUS group, there was no difference in the incidence of malignancies between the two groups. When analysing the results according to DRE findings, more patients with a normal feeling prostate in TRUS group had carcinoma ($p = 0.03$). Among the patients with an abnormal DRE and a PSA value of less than 10 ng/mL, there was statistically an advantage in using TRUS guided over FG biopsies.

Prostatitis was diagnosed in 69 (15.2%) patients, evenly distributed between the 2 groups. The mean age (± SD) for patients with histological evidence of prostatitis was 69.4 (± 8.1) years with a mean PSA of 16.9 ng/mL (IQR 7.1 – 19.8 ng/mL).

Eighty-eight patients had a palpable nodule on rectal examination of which 48.9% were diagnosed with malignancy. When analysing patients with an abnormal DRE in whom carcinoma was diagnosed, the yield using TRUS was significantly better only if the PSA was less the 10 ng/dL.

Figure 1: Histological findings in FG and TRUS guided groups

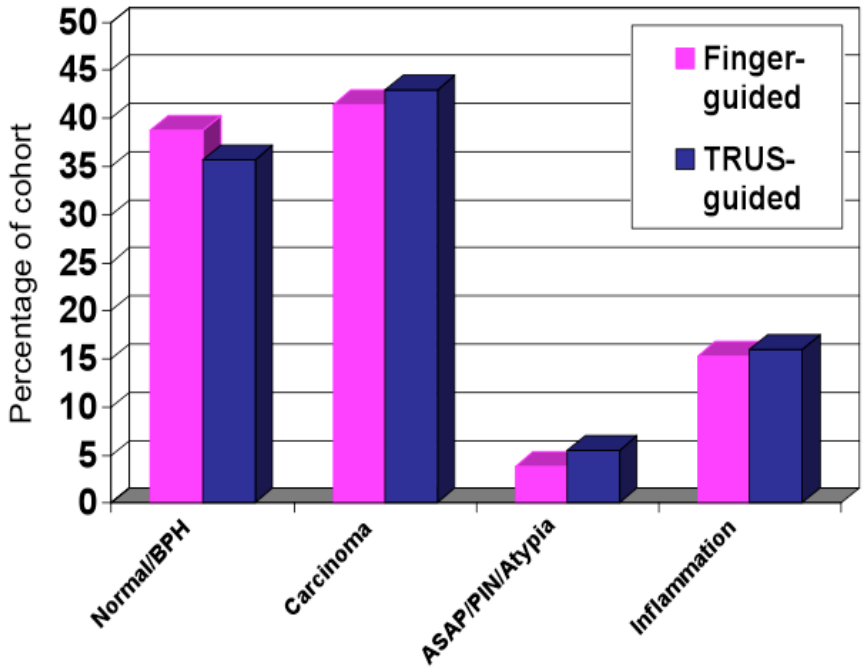


Figure 2: Incidence of cancer in patients presenting with a benign feeling prostate gland shown by PSA categories.

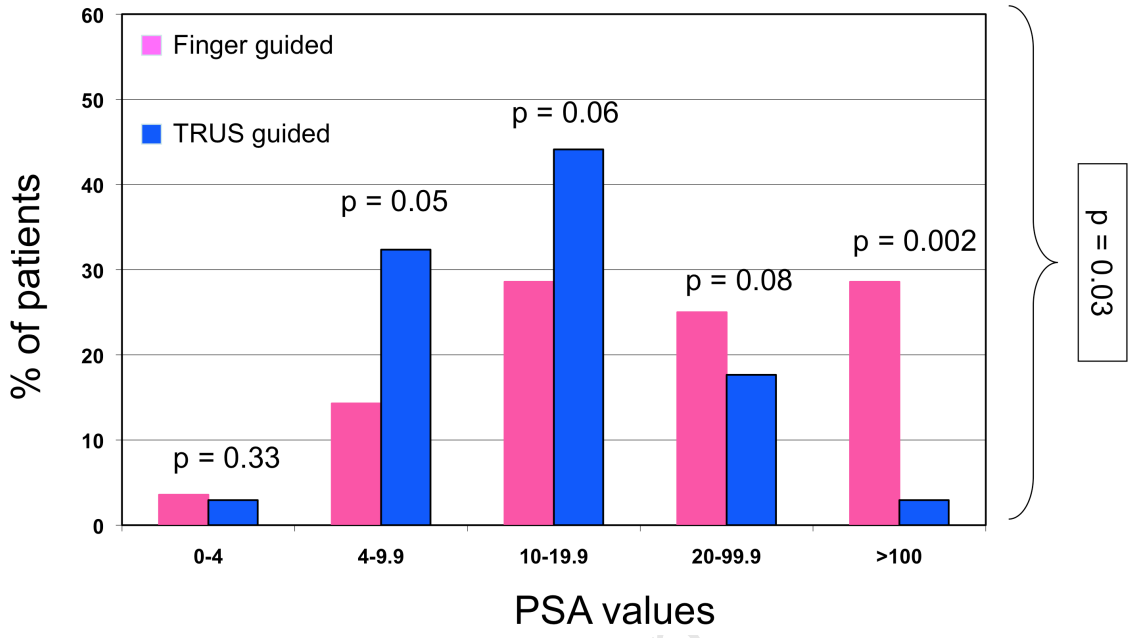
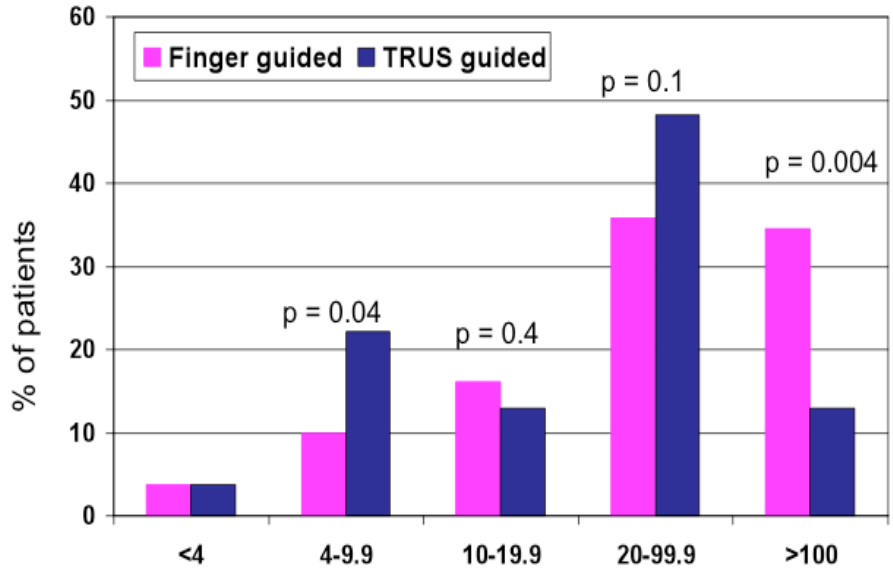


Figure 3: Incidence of cancer in patients presenting with an abnormal DRE shown by PSA categories.



Features identified on TRUS of the prostate: The average size of prostates measured was 38.6g. The findings are presented in Table 3 below. The probability ratios (with a 95% confidence interval) are presented to show the association between TRUS findings and the incidence of malignancy on biopsy. Findings included hypoechoic areas, peripheral calcifications, and a distorted or irregular capsule with probability ratios of 1.34 (0.98-1.8), 0.9 (0.7-1.3) and 29.0 (4.0-210.5) respectively. The findings of hypoechoic areas or calcifications were therefore not associated with a higher probability of finding malignancy in the prostate biopsy. However, when a distorted capsule is seen on TRUS, the probability was at least 4 times higher, and on average 29 times higher than the general population. In all the cases where capsular distortion or irregularity was seen on TRUS, the DRE was also documented as abnormal.

Table 3: Findings on Transrectal Ultrasound with histological diagnosis

(PZ – peripheral zone, calcif – calcification)

TRUS findings	Total	Cancer	No cancer
Capsule distorted	22 (13.0%)	21	1
Capsule intact	147 (87.0%)	50	97
Calcification PZ	108 (60.3%)	27	81
No calcification PZ	71 (39.7%)	21	50
Calcification centre	36 (21.3%)	17	19
No central calcif	133 (79.7%)	55	78
Hypoechoic PZ	100 (54.6%)	54	46
No hypoechoic PZ	83 (45.4%)	24	59

DISCUSSION

Cancer detection: The yield of prostate cancer overall was 42% in our study population with no difference in the incidence between the FG and the TRUS guided groups. This is in keeping with published figures, in spite of the fact that there were on average double the number biopsies done in the TRUS group (12 cores) compared to the FG group (6 cores) (14,15). This finding was contrary to our expectations, as we believed TRUS not only to be sampling the prostate more precisely, but also obtaining double the number of cores.

We also postulated that TRUS might be of more benefit where the DRE was normal but when analysing these patients, there was a trend favouring TRUS only if the PSA was lower than 20 ng/mL, which was statistically significant only when the PSA was below 10 ng/mL. The subgroup of "normal" PSA below 4 ng/mL did not reach significance, likely because of the small number of patients in this group.

Digital rectal examination: The DRE was found to be abnormal in 50%. Among the patients who had a normal DRE, 63 were diagnosed with carcinoma and these patients were equally distributed between the FG and TRUS groups. However, when stratifying these results according to PSA values as shown in Figures 2 and 3, this difference in diagnosis only approaches statistical significance when the PSA value is less than 10 ng/mL. This trend is maintained whether or not the diagnoses of PIN and ASAP are

included in the malignant group. This finding suggests that TRUS biopsy is not superior to FG biopsies for patients with a PSA value of more than 10 ng/mL, irrespective of the DRE findings. According to our data, TRUS should be reserved for patients with a normal DRE and a PSA value below 10 ng/mL.

Of note is the finding that patients were either screened with PSA once they presented to the urological service with urinary symptoms or were referred with a raised PSA. No patient was referred with an abnormal DRE despite almost 50% of patients having a palpable nodule. We found that, in keeping with the literature, a nodule has a 49% chance of being malignant. In a resource limited setting the performance of DRE is cost-effective and may prompt earlier detection of disease and thus earlier referral for assessment.

Study population: In our single arm prospective study of TRUS there were less biopsies performed over a 25-month period than was the case with the 17-month retrospective control group. Two factors can account for this: excluded patients who underwent FG biopsies in the TRUS era, and secondly, the increased time needed to perform TRUS compared to FG biopsies. One weakness of this study is that our two study groups were found to be statistically different in terms of age and PSA value at presentation, even though our department's clinical indication for prostate biopsy have not changed over the course of this study period. Although the age of patients in the FG biopsy group revealed a statistically significantly older population, the median PSA in this group was paradoxically significantly lower than in the TRUS guided biopsy group. This might be accounted for by the higher

percentage of high Gleason grade cancers (Grade 8-10) in the retrospective group. Whether the statistical difference in age and PSA is clinically relevant, is debatable.

Number of biopsies: Although the current guidelines from leading professional bodies (7,16) suggest at least 10-core biopsies, there is evidence to suggest that fewer cores are adequate (17,18). The literature has however shown that 6-core biopsies, in contrast to our findings, are inferior to 10 and 12-core biopsies (19-21). Although urology trainees performed both FG and TRUS biopsies, with equal experience in both approaches, the learning curve associated with TRUS biopsy might impact the quality of the TRUS biopsies in our study. Investigators have, however, found no learning curve associated with the procedure in studies that assessed the cancer detection rate (22,23).

Finger guided targeted biopsies: Initially the trials comparing FG with TRUS guided biopsies after Hodge's publication (5) consisted of small retrospective series, showing conflicting results. Most trials investigating FG biopsies involved only patients with abnormal DRE findings. Among these, there is evidence to show that FG biopsies have a role to play in the era of TRUS guided biopsies, especially in patients presenting with an abnormal DRE (24-27).

CONCLUSION

In centres where TRUS is not available, a systematic finger guided biopsy with a minimum of 6 cores, is a suitable alternative in patients who present with a raised PSA, especially if it is more than 10 ng/mL, especially if the patient has an abnormal feeling prostate gland on DRE. In the absence of a prospective randomised controlled trial directly comparing TRUS with FG biopsies, the role of FG biopsies remains unproven. However, the benefits of FG biopsies are: that it is quick, requires fewer cores and is more readily available than TRUS in the resource limited setting.

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PART D: APPENDICES

1. Ethics Committee letter of approval

2. Data collection sheet

3. Example of consent form

4. AJCC prostate cancer staging

5. Author Guidelines from African Journal of Urology

APPENDIX 1: RESEARCH ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Faculty of Health Sciences Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

27 August 2010

HREC REF: 395/2010

Dr K Jelhe
Department of Urology
E26
New Groote Schuur Hospital

Dear Dr K Jehle

PROJECT TITLE: REVIEW OF TRANSRECTAL ULTRASOUND GUIDED PROSTATE BIOPSIES AT GROOTE SCHUUR HOSPITAL

Thank you for submitting your study to the Health Science Faculty Research Ethics Committee for review

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th September 2011.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010)if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
sAriefdien

APPENDIX 2: DATA COLLECTION SHEET

Patient Name _____ Hospital no. _____	Date: _____/_____/_____ Surgeon: _____

○Informed consent ○Information leaflet	○Ciprofloxacin 500mg stat	OPD appt date _____

Symptoms:		○ Obstructive ○ Irritative ○ Screening
PSA	Age	DRE

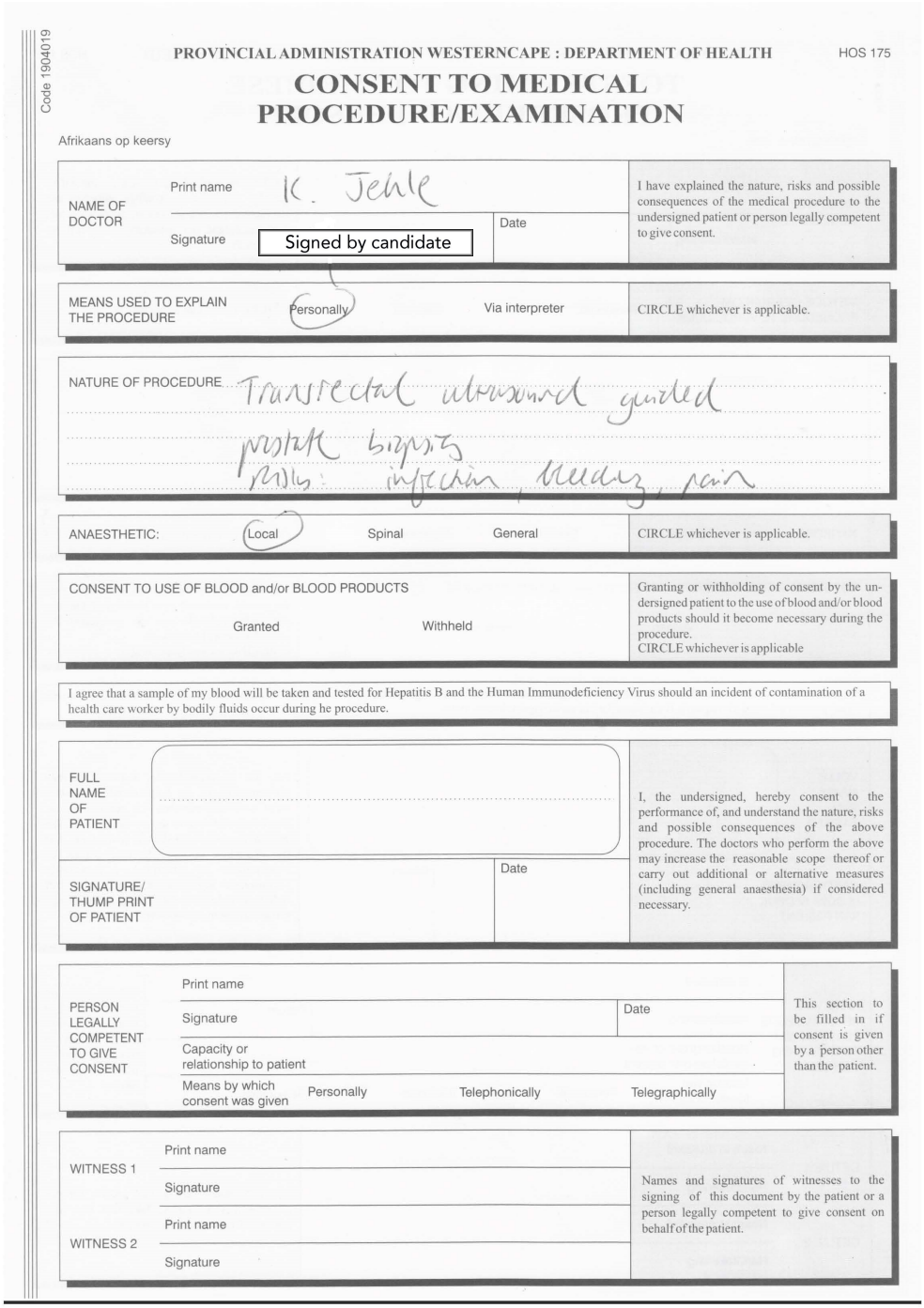
Discrete hypoechoic PZ	○ Yes	○ No	○ Left	○ Right
Diffuse hypoechoic PZ	○ Yes	○ No	○ Left	○ Right
Capsule distorted PZ	○ Yes	○ No	○ Left	○ Right
Capsule intact	○ Yes	○ No	○ Left	○ Right
Calcifications PZ	○ Yes	○ No	○ Left	○ Right
Calcifications central	○ Yes	○ No	○ Left	○ Right
Central hypoechoic areas	○ Yes	○ No	○ Left	○ Right
Increased vascularity	○ Yes	○ No	○ Left	○ Right
Prostate size	_____ grams			

(Photo of ultrasound)

Biopsies: ○ First ○ Re-biopsy	○ Standard 12 core ○ Added biopsies of abnormal areas

Histology:	○ Adeno-Ca ○ Gleason grade ____ + _____ = ____

APPENDIX 3: EXAMPLE OF CONSENT FORM



Code 1904019

PROVINCIAL ADMINISTRATION WESTERNCAPE : DEPARTMENT OF HEALTH HOS 175

CONSENT TO MEDICAL PROCEDURE/EXAMINATION

Afrikaans op keersy

NAME OF DOCTOR — Print name: K. Jehle; Signature: Signed by candidate; Date

I have explained the nature, risks and possible consequences of the medical procedure to the undersigned patient or person legally competent to give consent.

MEANS USED TO EXPLAIN THE PROCEDURE — Personally / Via interpreter (CIRCLE whichever is applicable.)

NATURE OF PROCEDURE: Transrectal ultrasound guided prostate biopsies
risks: infection, bleeding, pain

ANAESTHETIC: Local / Spinal / General (CIRCLE whichever is applicable.)

CONSENT TO USE OF BLOOD and/or BLOOD PRODUCTS — Granted / Withheld

Granting or withholding of consent by the undersigned patient to the use of blood and/or blood products should it become necessary during the procedure. CIRCLE whichever is applicable

I agree that a sample of my blood will be taken and tested for Hepatitis B and the Human Immunodeficiency Virus should an incident of contamination of a health care worker by bodily fluids occur during he procedure.

FULL NAME OF PATIENT

SIGNATURE/ THUMP PRINT OF PATIENT — Date

I, the undersigned, hereby consent to the performance of, and understand the nature, risks and possible consequences of the above procedure. The doctors who perform the above may increase the reasonable scope thereof or carry out additional or alternative measures (including general anaesthesia) if considered necessary.

PERSON LEGALLY COMPETENT TO GIVE CONSENT — Print name; Signature; Date; Capacity or relationship to patient; Means by which consent was given: Personally / Telephonically / Telegraphically

This section to be filled in if consent is given by a person other than the patient.

WITNESS 1 — Print name; Signature

WITNESS 2 — Print name; Signature

Names and signatures of witnesses to the signing of this document by the patient or a person legally competent to give consent on behalf of the patient.

APPENDIX 4: AJCC STAGING OF PROSTATE CANCER

American Joint Committee on Cancer

Prostate Cancer Staging

7th EDITION

T4

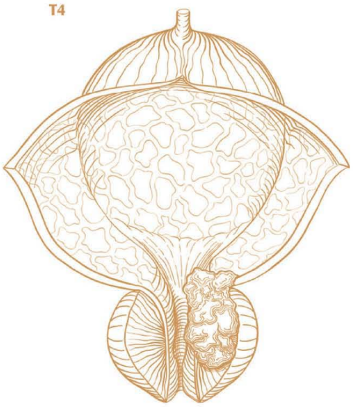


Figure A. T4 tumor invading adjacent structures other than seminal vesicles, such as bladder, rectum, levator muscles, and/or pelvic wall.

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]					
Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

Definitions

Primary Tumor (T)

CLINICAL

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **T1** Clinically inapparent tumor neither palpable nor visible by imaging
- **T1a** Tumor incidental histologic finding in 5% or less of tissue resected
- **T1b** Tumor incidental histologic finding in more than 5% of tissue resected
- **T1c** Tumor identified by needle biopsy (for example, because of elevated PSA)
- **T2** Tumor confined within prostate[1]
- **T2a** Tumor involves one-half of one lobe or less
- **T2b** Tumor involves more than one-half of one lobe but not both lobes
- **T2c** Tumor involves both lobes
- **T3** Tumor extends through the prostate capsule[2]
- **T3a** Extracapsular extension (unilateral or bilateral)
- **T3b** Tumor invades seminal vesicle(s)
- **T4** Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure A)

Pathologic (pT)[3]

- **pT2** Organ confined
- **pT2a** Unilateral, one-half of one side or less
- **pT2b** Unilateral, involving more than one-half of side but not both sides
- **pT2c** Bilateral disease
- **pT3** Extraprostatic extension
- **pT3a** Extraprostatic extension or microscopic invasion of bladder neck[4]
- **pT3b** Seminal vesicle invasion
- **pT4** Invasion of rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)

CLINICAL

- **NX** Regional lymph nodes were not assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in regional lymph node(s)

PATHOLOGIC

- **pNX** Regional nodes not sampled
- **pN0** No positive regional nodes
- **pN1** Metastases in regional node(s)

Distant Metastasis (M)[5]

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Nonregional lymph node(s)
- **M1b** Bone(s)
- **M1c** Other site(s) with or without bone disease

Notes

[1] Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

[2] Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

[3] There is no pathologic T1 classification.

[4] Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

[5] When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

[6] When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

APPENDIX 5: AUTHOR GUIDELINES FOR AFRICAN JOURNAL OF UROLOGY

The African Journal of Urology welcomes original papers, case reports and letters to the editor from any country of the world, particularly from Africa.

Format: Articles are accepted in English or French language. They should be carefully reviewed for accuracy of typing, spelling and grammar before they are submitted, since these mistakes might delay the acceptance of the article. They should be written in double spacing. The computer program used should be MS Word, and the articles should be sent as Word documents. Authors should retain a copy of the article for references.

Organization: Original articles on clinical and scientific aspects of urology and its associated specialities should be organized as follows:
The title page should give the following information: (a) title of article (b) names and initials of authors (c) institution to which the work should be attributed. (d) 1 - 5 key words should be typed at the bottom of the page (e) name and full postal address, telephone, fax number and Email address of the author to whom the reviewers‘ comments and requests for reprints should be sent (f) running title. The title should be concise and clear and should not contain abbreviations.

The abstract should consist of a brief summary of the article and should be subdivided into objective, patients/material and methods, results, conclusion. The abstract should be self-explanatory, without reference to the text. Abbreviations may be included, provided they are defined in the abstract as well as in the main text.

The introduction should be short and include both a brief review of the data in the literature, which are strictly related to the subject and express the exact aim of the work.

Material/Patients and Methods: The patients' characteristics and the technique(s) applied should be described in detail. The statistical analysis method should be exactly defined and its reference should be mentioned.

Results: The results of the work should be presented in detail. The number of patients should be followed by the percentage. Results that are presented in tables should not be repeated in the Results section.

The Discussion should be limited to the reported findings and their implications.

References: References should conform to the Vancouver style and should be numbered consecutively in the order in which they appear (and not listed alphabetically). They should be indicated by Arabic numerals in parentheses. Only the first six authors should be listed. If there are more
than six then the first six should be listed followed by et al. Note that journal titles are abbreviated in accordance with Index Medicus.