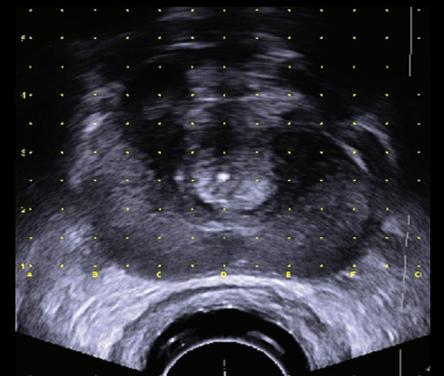
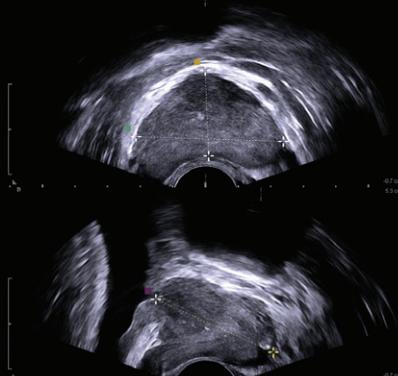
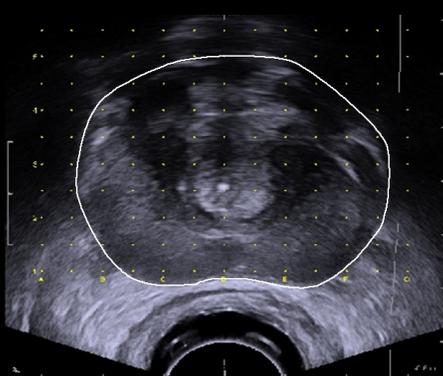
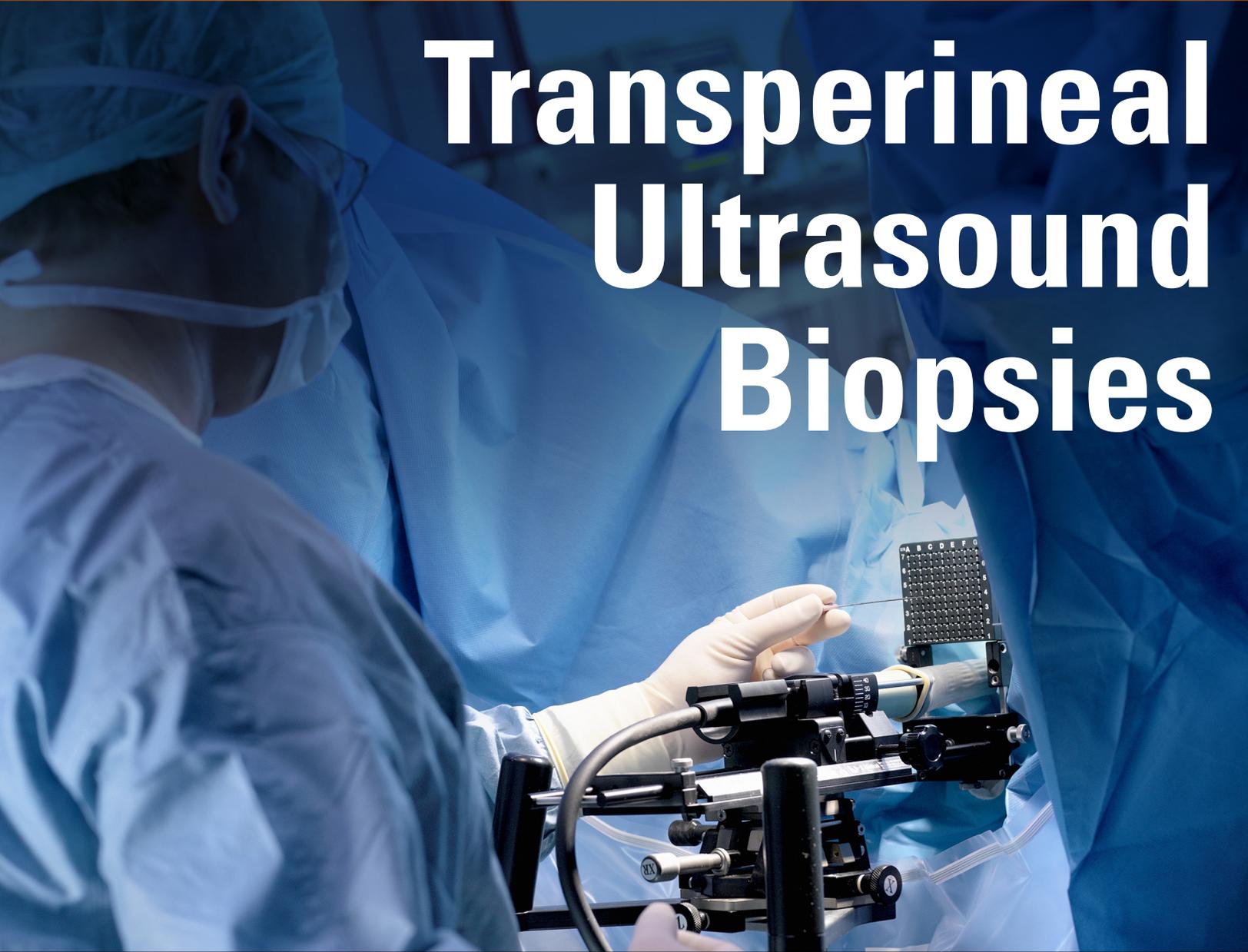


CLINICAL USE OF

Transperineal Ultrasound Biopsies



A Q&A WITH DR. RICK POPERT MS FRCS

Prostate cancer continues to be a worldwide health problem and the second most common cancer in men. Statistics from 2008 show that prostate cancer accounts for around 14 per cent of all new cancer cases in men, and it is predicted that the number of cases will almost double (to 1.7 million) by 2030¹. The need for early detection, effective diagnostics and treatment options continues.

For more than 25 years, PSA testing and transrectal ultrasound guided prostate biopsy (TRUS-Bx) has been the primary diagnostic pathway for prostate cancer. But, an increasing number of surgeons are beginning to reconsider the efficacy, potential risks and drawbacks of transrectal biopsies and

are returning to transperineal biopsies (TPUS Bx) as part of a more precise, systematic and targeted method for diagnosing prostate cancer in some patients.

Rick Popert, consultant urological surgeon at Guy's Hospital in London, explains his reasons for using TPUS Bx, and discusses his clinical experience with TPUS Bx and how he views the future of precision diagnosis in prostate cancer.

Rick Popert MS FRCS(Urol),
Consultant Urological Surgeon

Guy's & St Thomas' NHS Foundation Trust
London Bridge Hospital, HCA International

WHAT IS YOUR RATIONALE FOR USING TP BIOPSIES?

We have found that TP biopsies are a better alternative to TR biopsies in certain types of patients. These include:

- Patients with a potential risk of sepsis
- Patients with previous negative TR biopsies, but in whom there is a continuing suspicion of prostate cancer
- Patients being considered for active surveillance
- As a primary diagnostic procedure for patients where the pre-biopsy imaging, such as MRI, indicates that they may have disease anteriorly, or in a specific area that is difficult to target with TR biopsies

TP biopsies enable you to better target and sample the whole of the peripheral zone, where 96% of cancers develop. When doing the standard set of TR biopsies, you are only sampling less than 1% of the whole prostate volume – which is not optimal.

I believe that a pre-biopsy MRI scan is an essential component of prostate diagnostics, and when combined with transperineal biopsies or better targeted transrectal biopsies, finally gives a rationalization of the pathway to prostate cancer diagnosis – a pathway that has not changed in 32 years since the first TRUS biopsies were first carried out.

WHAT IS THE TRADITIONAL DIAGNOSTIC PATHWAY FOR PROSTATE CANCER?

The traditional diagnostic pathway is PSA blood testing as a routine screen, a digital rectal examination, TRUS and biopsy. This hasn't changed much since the introduction of TRUS by Holm in 1981².

More recent data from the United States shows that the cancer detection rate for patients with an elevated PSA of about 4 or between 4 and 10 with 6 core biopsies from the base, mid and apical prostate is about 25%. And, when the number of biopsies increases to 12 core and the biopsies are optimized to sample the lateral peripheral zone, then the number of biopsies with cancer detection rate increase to about 44%³.

So the recommendation across the world today – as the standard of care – is 10-12 core biopsies directed to the lateral peripheral zone – what we call laterally targeted biopsies. And at best you will have a 40% cancer detection rate. That's about as good as it gets.

IN ADDITION TO THE LOW DETECTION RATE, WHAT DO YOU SEE ARE THE DISADVANTAGES OF TR BIOPSIES AS A DIAGNOSTIC PATHWAY?

TR biopsies can lead to uncertainty, and there are several reasons for this:

First, there is a problem with the PSA test because it is not prostate cancer-specific.

Second, TR biopsies are known to both under-diagnose and misdiagnose prostate cancer, which results in over-treatment because patients tend to opt for radical treatment because of the uncertainty. Their surgeon can't say whether they have high-grade or high-volume disease, so the default position tends to be radical prostatectomy.

Third, you may mischaracterize the cancer as being low-grade when it is in fact intermediate to high-grade, and then offer the patient some form of focal or localized treatment that is insufficient or active surveillance that is destined to fail.

Finally, there are about 4% of patients who suffer from life-threatening sepsis (Fig. 1) in association with admission to hospital. This is one of the disadvantages of TR biopsies – the antibiotics being used and the potential for sepsis⁴(Fig. 1).

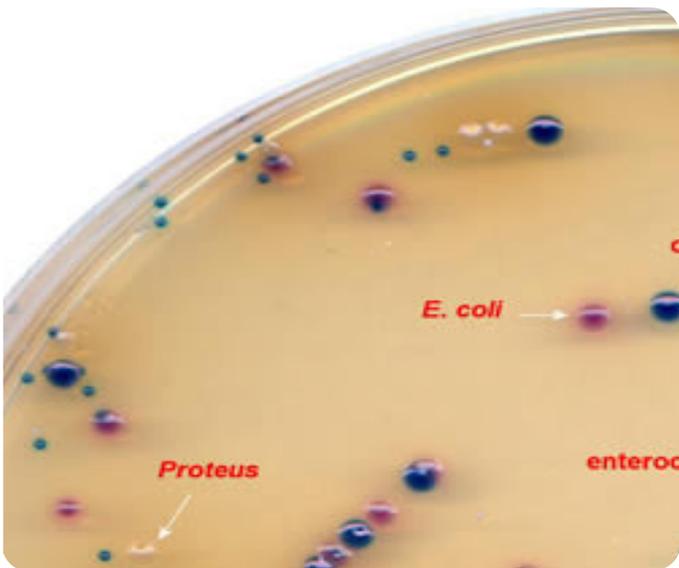


Fig. 1 Problems with diagnostic pathway - sepsis

All of these things make TR biopsies a problem, but by far the most important to me clinically is that TRUS

biopsies can under-assess the disease burden and lead to diagnostic and management uncertainty.

WHAT DO YOU THINK ARE THE REASONS FOR THE FALSE NEGATIVES AND UNDERASSESSMENT OF THE DISEASE IN CONNECTION WITH TRUS BX?

Over 30% of patients with negative transrectal biopsies will be found to have cancer on subsequent transperineal biopsies. Most of these will have anterior disease and we know 20% of radical prostatectomy specimens have isolated anterior cancers. The problem with TR prostate biopsies is that the sampling of the anterior peripheral zone of the prostate, particularly the apex, is poor. Also, the posterior peripheral zone either side of the midline is under-sampled by transrectal biopsies (Fig. 2).

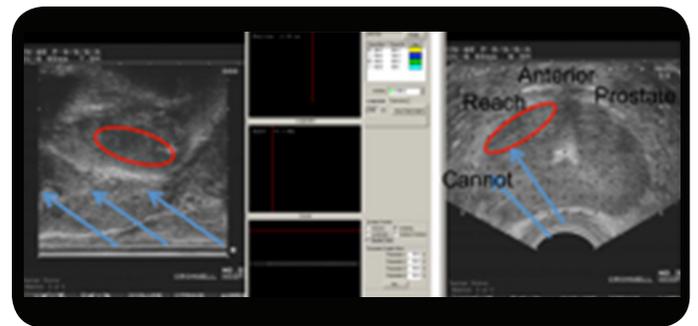


Fig. 2 TRUS Bx under-sample the anterior prostate

WHAT ARE THE SIDE EFFECTS OR CONSEQUENCES FOR PATIENTS FOLLOWING TRUS BX, AND HOW DO THEY AFFECT FURTHER TREATMENT?

A study in the UK⁵ surveyed how patients were doing 7 days and 35 days after a TR biopsy. The typical side effects after 7 days were pain (42%), fever (13.8%), shivers (14.5%), infection (37%), and 12% of the participants surveyed said they would decline further biopsy.

After 35 days, the results were similar with the exception of the number of patients that declined further biopsy – this number increased to 22%.

This is the undisclosed morbidity associated with TR biopsies, and what's interesting is that so many of the patients refuse to have a further biopsy.

IS IT POSSIBLE TO CARRY OUT TR BIOPSIES WITH MRI SCANNING?

There are many urologists who use TRUS Bx with MRI, but there are problems with that. There is still the risk of sepsis, and under-assessing the rest of the peripheral zone.

You can target a lesion very easily, but if you only target the lesion, you have to be sure that there is no significant cancer within the rest of the prostate gland, and the problem is that it is not possible to see everything on an MRI scan.

WHAT IS A TRANSPERINEAL BIOPSY?

Transperineal biopsy is (Fig. 3):

- A day case procedure carried out under general or spinal anaesthetic
- The legs are in the lithotomy position
- Perineum is exposed by elevation of scrotum
- US probe is fixed in a cradle and lined up to a grid
- Systematic biopsies of the prostate are taken according to a defined protocol (mapping)

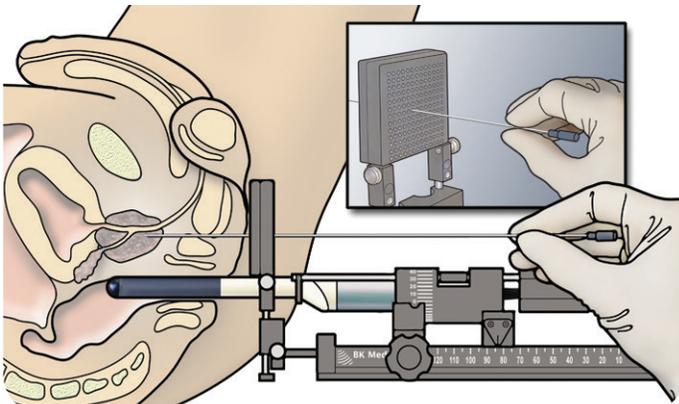


Fig. 3 Transperineal biopsy with transducer placed in rectum

CLINICAL APPLICATIONS – WHAT PATIENTS ARE SUITABLE FOR TPUS BX?⁶

Patients in whom I would use TPUS Bx rather than TRUS Bx include:

- Those who are at risk of urosepsis, diabetics and the immune-compromised
- Patients who have travelled to Asia or Africa in the last 3 months
- Patients with exposure to quinolones in the last six months
- Any patient with a previous negative TRUS Bx and a rising PSA
- Patients who have a large prostate (greater than 50cc)
- To confirm a patient's suitability for our Active Surveillance program
- Primary TP Biopsy is commonly carried out in the private sector to minimize the risk of sepsis, patient discomfort and to provide diagnostic certainty. It can also be carried out by patient's choice

HOW ARE TPUS BX TRADITIONALLY PERFORMED?

The classical way of doing transperineal biopsies was first described by Barzell as the Template Mapping Biopsy. These biopsies were designed to evaluate patients who were thought to have low-risk prostate cancer suitable for focal therapy with cryotherapy. The aim was to identify patients who had disease just on one side and freeze that area. They needed to be as sure as possible that there was no disease elsewhere.

Barzell & Whitmore developed a procedure that sampled the whole of the prostate gland, taking biopsies proximally and distally - taking a biopsy in every single hole where the prostate gland is overlaid by the grid. You would generally take between one and two cores per cc of prostate⁷.

For a 40 cc prostate 40-60 cores would be taken, for a 120 cc of prostate – 120 cores. This approach involved sampling the entire prostate, including the transition zone, which you do not really have to do, because 96% of cancer exists within the peripheral zone.

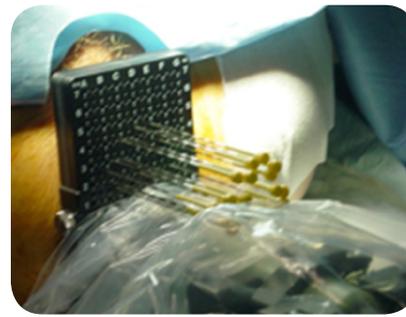
This over-sampling increases morbidity from swelling of the prostate and it does have pathological implications, including increased processing and reporting times and cost (Figs. 4 & 5).

WHEN DID YOU START CONDUCTING TPUS BX?

We started doing systematic transperineal sector biopsies in 2007 and we do over 300 TP biopsies a year.

WHAT IS YOUR APPROACH?

We started by doing transperineal needle insertions with brachytherapy. Generally, I would insert between 20 and 28 needles to do a brachytherapy implant, and preferentially targeting the peripheral zone and the central prostate at the base and apex but avoiding the transition zone.



Guy's Transperineal Sector Mapping Biopsies (TPSMB). Placement of brachytherapy needles in perineum

Our biopsy technique was based upon this distribution of needles, targeting the anterior, mid and posterior peripheral zones by these sectors. In prostates larger than 30cc, we incorporated a basal sector as well – allowing us to sample this area much more accurately. The advantage of our approach is that it preferentially targets the peripheral zone anteriorly at the apex and the posterior peripheral zone in the midline at the base, and so avoids the under-sampling inherent in TRUS biopsy⁸ (Fig. 6).

GUY'S SECTOR MAPPING PROTOCOL

With this technique we can systematically sample McNeal's peripheral and central zones, avoiding over-sampling of the transition zone, which reduces morbidity (Fig. 7).

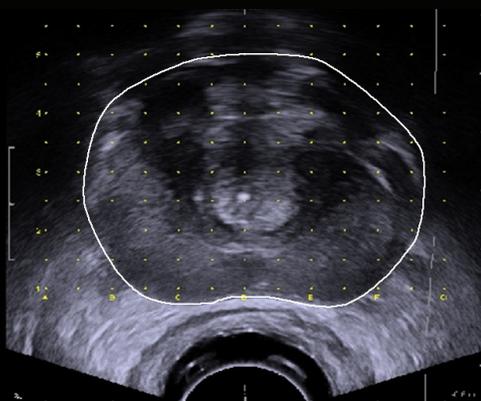


Fig. 4 Transverse image with transition zone and peripheral zone demonstrated

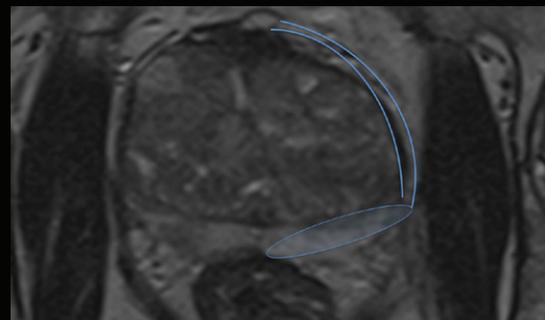


Fig. 5 Template mapping biopsies - over-sample in transition zone and under- sample in peripheral zone

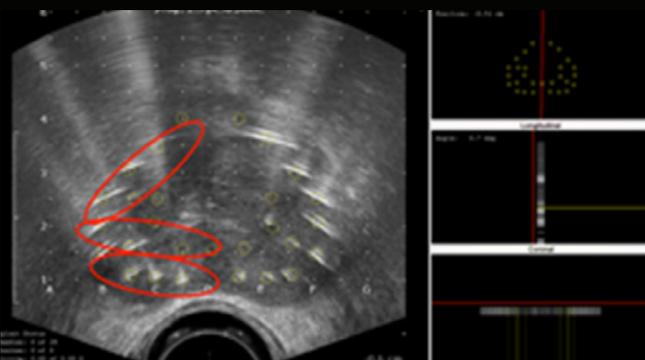


Fig. 6 Needle placement defines anterior, mid and posterior sectors

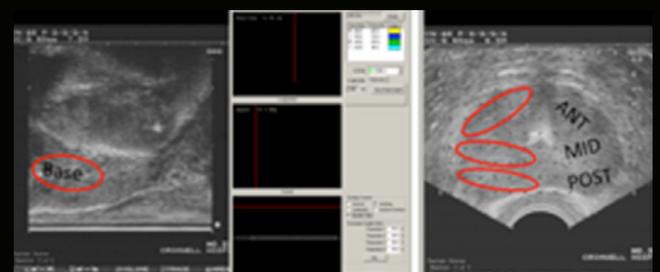
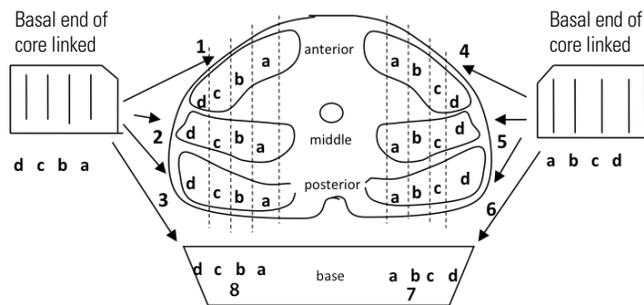


Fig. 7 Sampling of McNeal's peripheral and central zones avoiding the transition zone

The number of cores taken depends upon the size of the prostate. We rarely take more than 38.

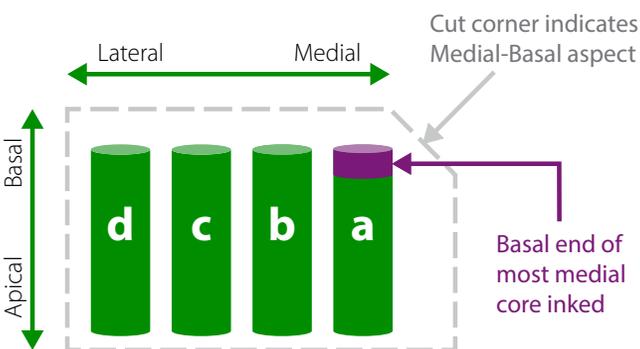
Transperineal Sector Biopsy (TPSB) Core Number Protocol					
Prostate Volume (cc)	No of Cores taken per sector (Right + Left)				Total No. of Cores
	Anterior	Mid	Posterior	Basal	
0 - 30	4 + 4	4 + 4	4 + 4	0	24
>30 - 50	4 + 4	4 + 4	4 + 4	4 + 4	32
>50	5 + 5	5 + 5	5 + 5	4 + 4	38 - 40

Biopsies are taken systematically by sector and laid onto sponges (one sponge per sector). The most medial core is inked at its basal end to provide accurate pathological localisation.



Cores are placed on sponges medial to lateral at basal end, placed in cassette and placed in labelled numbered formalin pots as below:

- 1. Right Anterior Sector 2. Right Middle Sector 3. Right Posterior Sector
- 4. Left Anterior Sector 5. Left Middle Sector 6. Left Posterior Sector
- 7. Left Base Sector 8. Right Base Sector



PATHOLOGICAL OUTCOMES

We have been impressed with our positive pick-up rate in both the repeat and the primary biopsy setting.

Guy’s Transperineal Sector Biopsies Outcomes from 709 Cases, 2007 – 2012:

- 63/174 (36%) with previous negative biopsy had cancer - most of whom chose definitive treatment
- 131 / 350 (37%) thought suitable for Active Surveillance on TRUS - had higher grade or volume of disease - early definitive treatment
- 116 / 185 (63%) with Primary TP biopsy had cancer - 15% had disease exclusively in anterior sectors

WHAT ARE THE COMPLICATIONS OF TPUS BX?

Overall the procedure is very well tolerated despite the need for anesthetic. Rates of urinary retention are very low and we have had no admissions for sepsis.

Complications - 709 cases:

- Acute Urinary Retention - 14 (2%)
- Clot Retention - 2 (0.3%)
- Haematuria Admission - 3 (0.4%)
- UTI (requiring oral abx) - 4 (0.6%)
- Significant Urosepsis - 0 (0%)
- Overall - 23 (3.2%)

TREATMENT CHOICES

The greatest advantage for me clinically is that this method allows better stratification of an individual patients suitability for a particular treatment.

- Active surveillance: 29%
- Brachytherapy: 32%
- Radical prostatectomy: 27%
- Hormones and/or ERBT: 13%

Although concern has been expressed about the risks of over diagnosis and over-treatment, that is not the case. 75% of these patients have disease of clinical significance

and can be better stratified to the most appropriate treatment option, the remainder with low risk disease can enter an active surveillance program with confidence.

TPUS BIOPSY AND MULTIPARAMETRIC MRI

However, the future of prostate cancer diagnosis undoubtedly will be the increased use of mpMRI earlier in the pathway. In my view no patient should be subjected to prostate biopsies without the information available from MRI. Although a normal MRI cannot completely exclude prostate cancer, it can confidently indicate which patients are not suitable for transrectal biopsy because of the size of the prostate or the presence of a focal abnormality within the anterior peripheral zone. If the MRI is normal and the prostate volume greater than 40cc but there is continued suspicion with a high PSA, strong family history, positive urinary PCA3 etc then I would recommend systematic transperineal ultrasound guided biopsies. If the prostate is small (less than 40cc) then a standard 12 core TRUS biopsy may still be the most appropriate choice (Fig 8).

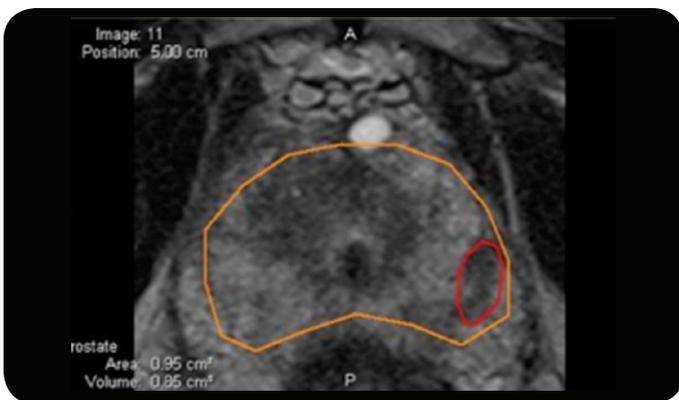


Fig. 8 Peripheral zone lesion (red) outlined on MRI of prostate (orange) (Varian brachytherapy software, Variseed 8.0.2 with image fusion license)

MRI/US FUSION TARGETED BIOPSIES

If the mpMRI indicates a focal abnormality then the urologist is in a much better position to carry out a targeted biopsy of the lesion. A number of systems are becoming available, both transrectal and transperineal, and incorporate MRI – US fusion techniques. The critical link within the system is the quality of the ultrasound platform, which must be able to integrate with the MRI Fusion platform. I am convinced that this will be the way in which urologists will deliver both precision prostate diagnostics and treatments in the near future (Fig. 9).

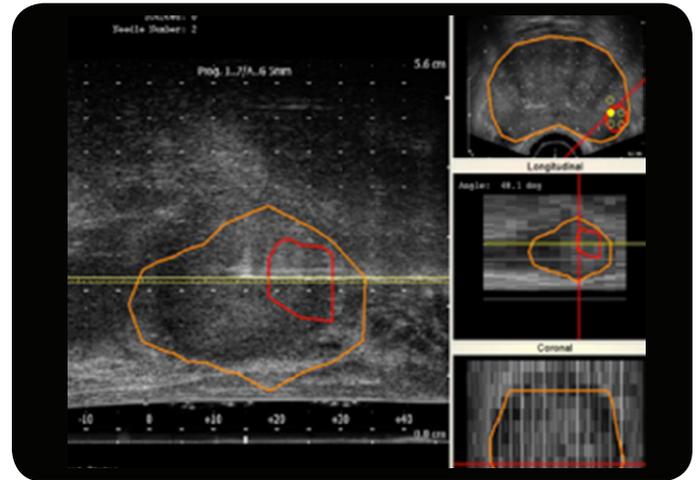


Fig. 9 US Fusion targeted biopsy (Varian brachytherapy software, Variseed 8.0.2 with image fusion license)

CONCLUSION

Our most recent data presented at the EAU and AUA 2014 confirm that targeted biopsies improve detection rates, the majority of visible lesions represent clinically significant disease, but there is clinically significant disease in 30% of areas apparently normal on MRI. Only 10% of patients had disease that was truly focal to the lesion. There is a field effect and this has implications for treatment planning.

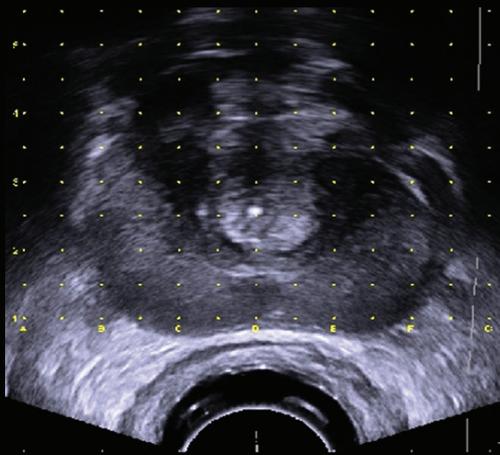
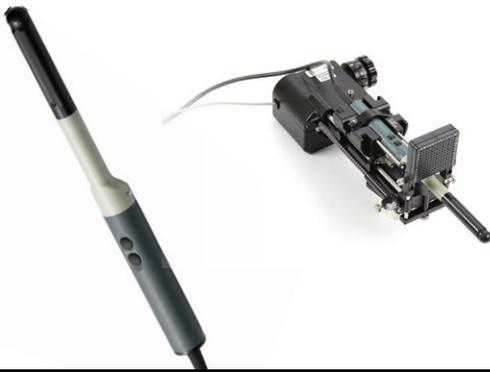
RECOMMENDED EQUIPMENT

The BK Ultrasound Flex Focus 500 is a powerful and flexible ultrasound system for urology, colorectal, urogynecology, vascular, general imaging and other applications.



TRANSPERINEAL BIOPSIES

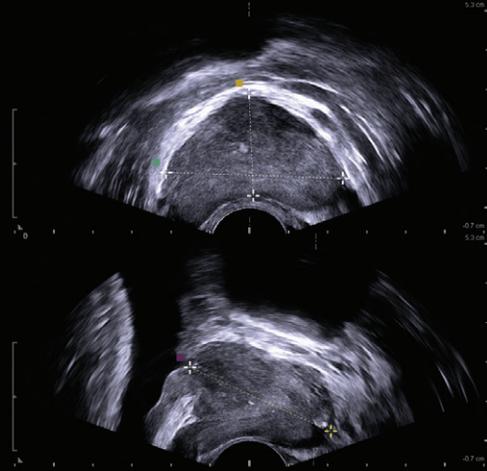
Endocavity Biplane Transducer 8848



Transverse Prostate with Brachy Matrix Template
- Endocavity Biplane Transducer 8848

TRANSRECTAL BIOPSIES

Prostate Triplane Transducer 8818



Prostatic Volume Measurements using Simultaneous
Biplane Imaging - Prostate Triplane Transducer 8818

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