

*Towards a Consensus Protocol on Prostate Biopsies:
Indications, Techniques and Assessment
Report of a Conference held*

at the

Royal College of Pathologists, London

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BACKGROUND

Accurate interpretation of prostatic needle biopsy specimens is currently the “gold-standard” of prostate cancer diagnosis, worldwide. Currently, however, there is no single standardised approach to obtaining or interpreting those tissue biopsies. Transrectal needle-biopsy of the prostate gland is an invasive procedure that is sometimes difficult to perform, uncomfortable if not painful for the patient and is associated with potentially serious consequences of morbidity and even mortality. Thus, the benefits of the procedure must, in each individual patient, significantly outweigh the risks when obtaining the specimens necessary to confirm the diagnosis of prostate cancer.

It was the intention of the conference sponsored by the NHS Prostate Cancer Risk Management Programme, organised by the University of Liverpool and held at the Royal College of Pathologists, London on 6th June 2003, to identify and to discuss in open forum, the most important factors relating to all stages of the prostatic biopsy. These factors ranged from identification of those men who should or should not undergo prostatic biopsy to a detailed appraisal of the optimal methods of handling the obtained prostatic biopsies and their subsequent analysis and interpretation. This conference was intended and perceived to be a first step towards the goal of obtaining a consensus by which all men in whom the differential diagnosis of prostate cancer was being considered might undergo prostatic needle biopsy according to an agreed protocol. It was also understood that this was a complex process in which not all hospitals or pathology laboratories might contain the recommended equipment or levels of staffing expertise. Thus, a significant amount of pragmatism will be required to adapt the protocol ultimately recommended to the resources available in each individual institution. The incidence of prostate cancer is rising year by year. Increased public awareness fuelled by the advent of PSA and the possibility of effective treatment for early confined disease has led to a dramatically increased demand on the urologist to make the diagnosis of prostate cancer by obtaining prostatic biopsies (Carter & Coffey, 1990). Although it is possible to obtain tissue by the trans-urethral and trans-perineal routes, in practice the trans-rectal approach using trans-rectal ultrasound (TRUS) guidance and a spring loaded biopsy gun has proved to be the most effective way in reliably obtaining good cores of tissue from representative parts of the prostate (Ragde *et al*, 1988; Lee, 1989). The ease in which this can be done, either without anaesthetic, or under local anaesthetic has led to the development of TRUS guided biopsy clinics performing the biopsies as an outpatient procedure outside of the operating theatre environment. This has the advantage that patients can be seen, have a biopsy and the diagnoses achieved quickly and at low cost. Taking the biopsies in a place that has not historically been used to dealing with tissue samples can, on occasions however, lead to errors in clinical practice. To overcome these errors, the process of taking prostatic biopsies has been studied and advice given about the steps necessary to minimise the errors.

The argument about at which level of PSA should prompt biopsy and the enhancement or not of PSA by using DRE, PSA density, transitional zone density, free/complexed PSA ratios or complexed PSA alone have been dealt with elsewhere. It is presumed that the referral for biopsy has been made and the aim of this workshop was to determine how best to undertake this procedure while minimising risk to the patient.

INTRODUCTION

Histopathological examination of a needle core-biopsy of prostatic tissue is currently, the “gold standard” modality by which a suspected diagnosis of prostate carcinoma is confirmed. Other investigative techniques (including clinical examination, radiology and radio-immunoassay) merely heighten, or strengthen, the suspicion of prostatic carcinoma by which a suspected diagnosis of a prostatic carcinoma is made. Since many men, in the United Kingdom and throughout the Western world, are now presenting for assessment to exclude the possibility that they might have prostate cancer, there is a growing requirement to develop a single consensus strategy for obtaining, processing, examining and reporting the appropriate prostatic tissue samples. Thereafter, there should be an agreed strategy for the management of all patients including those in whom the prostate biopsy is negative (but in whom the indications that they have prostate cancer remain robust).

The purpose of this Conference was to draw together the most comprehensive evidence from those authorities, internationally, who have demonstrable expertise in the various different aspects of performing and reporting the prostate biopsy, as well as of using the obtained data in managing the patients thereafter. The intention is to publish a set of contemporary guidelines that address the various practical aspects of performing and reporting the prostate biopsy in order that all patients, irrespective of wherever they may present for examination, receive optimally-agreed care and management while undergoing this procedure and whatever treatment might be recommended thereafter.

Although histopathological examination of prostatic tissue is the “gold standard” it may not, in all instances, receive the appropriate tissue with which to make, or exclude, a diagnosis of prostate cancer. The term “gold standard” does not mean “final and incontrovertible evidence” but indicates the best modality currently available. Therefore, it is of utmost importance that all aspects of the procedure are considered and refined in order to optimise the chances of obtaining the appropriate specimen without necessitating a repeat biopsy. The prostatic biopsy, while practically and logistically straightforward, is not without significant risk or discomfort to patients. It should not be undertaken lightly or without due consideration for the risks to which those patients might be subject. Nevertheless, the benefits of obtaining tissue for histopathological diagnosis – and for other types of

cellular and molecular analysis that are currently being developed – significantly outweigh any disadvantages or hazards when the biopsy is performed under appropriate conditions by experienced operators who have been trained appropriately.

For nearly a decade, the “sextant” biopsy approach to obtain six cores, three from each side of the prostate, (apex, middle and base) has been the standard biopsy schema, particularly in the United States of America, for patients suspected of having prostate cancer. In recent years, data have been emerging to suggest that the sextant technique fails to detect a significant proportion of cancers. Due mostly to a persistent suspicion for the presence of prostate cancer following a negative sextant biopsy, several biopsy approaches have been applied to confirm or rule out prostatic cancer. The newer biopsy strategies have two common denominators; increasing the number of cores obtained and equally important, targeting the lateral and apical peripheral zone of the prostate for biopsy since there are the regions in which early abnormalities are most likely to be identified.

Unfortunately, prostate cancer appears to be a heterogeneous disease across national as well as ethnic boundaries. Therefore, the data on incidence in different countries may not translate exactly to the findings in other countries. Thus, the single clear objective of this meeting was to consider, in detail, the individual components of the prostatic biopsy in order to recommend an agreed standard procedure that conforms to current international guidelines, by which to obtain and report each prostatic specimen. Thereafter, there should be a single agreed strategy to manage each individual patient irrespective of whether the diagnosis of prostate cancer is confirmed or not.

[I] MULTIDISCIPLINARY CLINICAL PARAMETERS

As the background clinical/health service environment in which men with prostate cancer are assessed, investigated and managed, it is suggested that the following features should be developed as providing a comprehensive and standard resource:

- All data pertaining to each individual patient should be collected and held in a single cumulative electronic record.
- The data should be constantly available to all those with responsibility for managing investigative diagnostic and therapeutic aspects of the patients.
- The data should be regularly reviewed throughout the management of the patient, preferably by all involved specialties. Such reviews would be most effective when all specialties are simultaneously present, particularly at Multi-Disciplinary Team (MDT) meetings.

[II] CRITERIA TO PERFORM, OR NOT TO PERFORM, A PROSTATIC BIOPSY

Selection of men requiring prostatic biopsy, and their distinction from those men in whom prostatic biopsy either should not, or need not, be performed is of paramount importance. The decisions may be clinical or pathological or both. As a general principle, a prostatic biopsy should be employed as the definitive diagnostic procedure in those instances where confirmation of prostatic malignancy cannot be obtained by another modality, where the information derived from the biopsy outweighs the clinical risks to the patient and only in those patients in whom a definitive line of management will be undertaken. There is no doubt that, worldwide, the PSA test has contributed and remains a significant factor in providing evidence that an individual man requires a prostatic biopsy (Guru *et al*, 2003). To address the valid question of the lack of specificity, and hence the clinical significance of an elevated PSA in an individual patient, a number of different laboratories continue to develop different mathematical algorithms with respect to parameters such as PSA velocity, doubling time, free-total PSA (Zhu *et al*, 2004) or free PSA (Khan *et al*, 2003). As a general principle, all men should have their PSA tested prior to biopsy. This measurement will assist in segregating those men required to undergo prostatic biopsy from those in whom the index of prostatic cancer is sufficiently high that a prostatic biopsy is no longer required. Prostate ultrasonographic appearances of cancer are shared with benign disease; prostate ultrasound alone cannot diagnose early cancer.

1. Indicators for First Biopsy

Clinical parameters

- To identify prostate cancer in men in whom a definitive line of clinical management will be instituted with the intention of modulating the natural course of a prostate cancer identified in each individual, either to increase the *length* of life by annulling of the malignancy or by improving the quality of life, even though the *duration* may not be extended.

Biochemical parameters

- All patients should have had their PSA tested prior to biopsy.
- An elevated PSA may be validated by a repeat measurement prior to biopsy.
- PSA values should be interpreted with respect to age.
- There are no rigid criteria or cut-off levels of PSA above which biopsy is recommended.
- PSA values should not be measured with concurrent UTI infection, or within 6 weeks of relieving acute urinary retention, whether by catheterization or by TURP.
- Numerous studies show that a PSA level of 2.5-10.0 ng/ml is associated with approximately 25% cancer incidence. Greater than 10 ng/ml is associated with a greater than 55-60% cancer incidence.

Abnormal DRE

- An abnormal DRE has been abandoned in the European Randomised Study of Screening for Prostate Cancer. (Schroder *et al*, 2000).
- 14-30% of men with a suspicious DRE and PSA between 1-4ng/ml have been shown to have prostate cancer.
- Overtly malignant prostate (ie >T3).

PSA

- Age adjusted PSA levels should be used to increase sensitivity in younger men and specificity in older men.
- Oesterling showed increased detection of organ-confined cancers in men <50 years (Oesterling *et al*, 1993).
- The use of age adjusted PSA values maybe helpful in patient management, although the relevance of PSA to the management of prostate cancer has been disputed (Stamey, 2004).

Age-adjusted PSA

- In the age range 60-69 years, a 15% decrease in biopsy would result in missing 8% of organ-confined cancers.
- In the age group >70 years, a PSA of 6.5 ng/ml allows 44% fewer biopsies but would miss 47% of the organ confined cancers (Catalona *et al*, 1994).

PSA Doubling Time (PSADT)

- There is an exponential increase of serum PSA over time (Schmid *et al*, 1993).
- Is independent of baseline PSA and assay used.

PSADT is defined as:
$$\frac{\log 2 \times t}{\log (\text{final PSA}) - \log (\text{initial PSA})}$$

PSA density

- Benign enlargement is associated with an increase in PSA (Nadler *et al*, 1995).
- In range 4-10ng/ml PSA density should be <0.15 (Seaman *et al*, 1993).
- Clinically difficult to calculate as TRUS is highly operator dependent. Concomitant BPH or prostatitis may interfere with this.
- Prostatitis interfere (Brawer *et al*, 1993).

2. Relative Contraindication to First Prostatic Biopsy

- A PSA > 100ng/ml, in the presence of an abnormal DRE.
- Abnormal radiographic, scintigraphic or histopathological evidence of metastatic disease.
- Tissue confirmation already obtained by TURP.
- Concomitant anticoagulation therapy (i.e. Warfarin).

3. Indication for Repeat Biopsy - General

- Previous biopsy that did not obtain adequate amounts of prostatic tissue to confirm or exclude prostate cancer.
- Previous biopsy of adequate prostatic tissue that did not include prostate cancer in the circumstance of continuing clinical or biochemical indications of prostate cancer (e.g. abnormal DRE, persistently enhanced or rising PSA).
- Prostate cancer detection on repeat biopsy ranges from 10 to 20% (Fleshner *et al*, 1997; Djavan *et al*, 2000).
- No differences in the stage or grade of tumour detected (Djavan *et al*, 2001b).
- Multiparametric analysis by nomographic evaluation to predict likelihood of positive repeat biopsy (Lopez-Corona *et al*, 2003).

4. Repeat Biopsy - Following Previous Diagnosis of High Grade PIN and/or Previous Suspicious Appearances

- The rate of diagnosing cancer following biopsies with isolated high grade (clinically significant) PIN has declined over the last several years. It is now believed to be reasonable to recommend a repeat biopsy after an isolated diagnosis of high grade PIN, particularly if the lesion was found via a sextant and not an extended (10- or 12-core) biopsy schema. Systematic biopsies should be obtained.
- In case of a suspicious diagnosis, the implications are more immediate and a timely repeat biopsy concentrated in the location of the suspicious region should be performed.

5. Repeat Biopsy – In a Patient with Previous Negative Biopsies - Saturation Biopsy

- A negative biopsy is a common indicator for a repeat, particularly if accompanied by an abnormal PSA and/or DRE.
- If the second biopsy is negative, the chances of missing an aggressive large cancer are small (Chokkalingam *et al*, 2003).

6. Histopathological Indications

PIN

- Strong association of previous PIN with cancer (Meng *et al*, 2003b).
- Adenocarcinoma in 36% of subsequent biopsies from cases with PIN vs 13% in controls (Davidson *et al*, 1995; Goeman *et al*, 2003).

Glandular epithelial atypia

- Lesions suspicious for, but not diagnostic of, malignancy in primary but not repeat biopsies.
- 45% of patients diagnosed with atypia are subsequently found to have prostate cancer (Chan & Epstein, 1999; Park *et al*, 2001).
- Lesions with altered expression of key phenotypic markers (e.g. 34 β E12, α MeCoA racemase, PKC β , HSP27).
- Recommendation for a repeat biopsy at 3-12 months with an extended biopsy schedule (Iczkowski & Bostwick, 1999).

Inflammation

- Histologically-proven chronic prostatitis, but absence of cancer in the presence of strong associated suspicion of cancer (Platz & De Marzo, 2004).

7. Biochemical Indications

Elevated free/total PSA ratio

- Free, bound to α 1-antichymotrypsin, bound to α 2-macroglobulin (Christensson *et al*, 1990).
- Decrease in f/t ratio in cancers (Christensson *et al*, 1993).
- In men with PSA between 4-10ng/ml a cut off of 25% detects 95% of cancer avoiding 20% of biopsies (Catalona *et al*, 1998).
- Should be used to guide the need for further biopsies.

Elevated PSA velocity/doubling time

- Increasingly replaced by PSADT (Cannon *et al*, 2003).
- More effective at low initial PSA level (Smith & Catalona, 1994).
- Increase in excess of 0.75ng/ml/yr suggested as cut off (Carter *et al*, 1992).

Note: PSA should not be repeated within six weeks of biopsy or TURP, but ideally at least three months after either procedure.

Those men with exponentially rising PSA require re-biopsy. If the first repeat biopsy is negative, the chances of finding a more aggressive cancer later are minimal (Philip *et al*, 2004b).

8. Relative Contraindications to Repeat Prostatic Biopsy

- New co-morbid medical conditions rendering performance of the biopsy hazardous.
- Following a negative biopsy, men with an elevated but static (non-rising) PSA over a prolonged period of time (e.g. 4 years) do not warrant a repeat biopsy (Singh *et al*, 2003).
- Cancer detected at initial biopsy or on first repeat appears to differ from tumours found on third and fourth biopsy (Djavan *et al*, 2001b). However, Steiner *et al*. reported no difference in cancer detection from 1st to 5th set of biopsies (Steiner *et al*, 2004).

[III] OPERATOR EFFICIENCY, INCLUDING QUALITY OF THE OBTAINED TISSUE SPECIMENS

1. Minimising the Risks

- The patient is sent written information about the procedure and instructed to bring all medications with him, but to contact the department immediately if taking anticoagulants.
- The PSA level is checked on the hospital system or the GP surgery is contacted and a level of PSA verified from the original lab report.
- On arrival the name, date of birth and address are checked.
- A history is taken in particular looking for symptoms of a UTI at the time of the PSA test estimation and whether the symptom or any infection present was treated with antibiotics.
- Past history of cardiac valvular abnormalities, epilepsy, drug history and allergies.
- A sample of urine is tested with Multistix 19 SG (Bayer). If positive for leukocytes or nitrites an MSSU is sent and the biopsy deferred until a result is available.
- The procedure is explained again and written informed consent obtained.
- The patient is taken through into the biopsy room, which has been cleared of all other patient notes and materials and his name, date of birth and address checked again. The procedure should only be performed in suitable accommodation, in which resuscitation capabilities are immediately available, without the requirement to first remove other equipment.
- Providing no history of allergy to penicillin is elicited 1.2g co-amoxyclav is given IV. Alternatively IV gentamycin and metronidazole PR are given.
- A DRE is performed and local anaesthetic is injected using a spinal needle into the plane between rectum and prostate under ultrasound guidance.
- The volume of the prostate is estimated (Wolff *et al*, 1995).
- Under ultrasound guidance approximately 10 cores of prostate are obtained. If it is the first biopsy then 2 or 3 cores are obtained from the posterolateral peripheral zone and 2 or 3 from the parasagittal plane on each side. For patients in whom the first set of biopsies were benign

the second set of biopsies samples the posterolateral peripheral zone again ,the base of the prostate in the parasagittal section, the transitional zone and the midline peripheral zone.

- The labelling of the samples and pathology form are checked and placed in a sealable polythene bag, which is placed in the pathology collection point.
- The probe is immediately cleaned and sterilised in readiness for the next patient.
- The notes of the patient are removed from the room in readiness for the next patient.
- A pad is given to the patient to place inside his underpants in case of bleeding.
- The details of the TRUS biopsy are inserted into the TRUS biopsy database.
- The patient is given written instructions about the after effects of the biopsy and told to expect blood in the motions, urine and semen. The patient is instructed to seek immediate medical advice if he becomes unwell or has a high temperature or bleeds significantly.
- Ciprofloxacin 500mg b.d. for 2 days is started immediately after the biopsy unless the patient is epileptic or allergic to quinolone antibiotics in which case trimethoprim 200 mg b.d. is used for 5 days.
- Details of when and how the biopsy results will be given to the patient are explained prior to departure.

[IV] OPERATIVE PROTOCOL AND IMAGE GUIDANCE

1. Physical Environment

- The procedure should only be performed in suitable accommodation, in which resuscitation capabilities are immediately available, without the requirement to first remove other equipment.
- The patient is taken into the biopsy room, specifically designated and/or constructed, which has been cleared of all other patients' notes.
- The patient's name, date of birth and address are checked again, before any further part of the procedure is initiated.

2. Manpower Requirements

- Operators are required to demonstrate appropriate training and skills to be deemed competent in performing prostatic biopsies.
- Their practice should be supported by ongoing audit and regular retraining.
- Clinicians responsible for managing patients should maintain an interest in the prostate biopsy to ensure continuous advancement and refining of the technique, particularly following regular audit assessment.

3. Machine and Instrumentation Requirements

- Measurement of prostatic volume at the time of initial imaging is likely to assist with later management and will avoid repeating these studies at a later date.
- Transrectal ultrasound equipment must provide satisfactory resolution of the zonal anatomy of the prostate.
- Equipment must allow both targeted biopsy and volume assessment.
- Transrectal ultrasound technology can be adequately performed with dedicated end-fire probes with curved array or side firing transducers.
- Machines must have the capability of using disposable guides. Instrument manufacturers should produce equipment of the required specifications.
- Preferably use only sterile disposable guides.
- The probe must be covered using a sheath.
- It is possible to biopsy the prostate of patients who have had an abdomino-perineal resection using trans-cutaneous ultrasound and trans-perineal biopsy.

4. Diagnostic and Procedural Parameters

- Hypoechoic areas in the peripheral zone, particularly those that correspond with abnormal digital rectal examination are noted. In more advanced cancer, prostatic internal architecture may be completely distorted (Greene *et al*, 1992).
- Absence of a hypo-echoic area in the prostate does not exclude the presence of prostate cancer.
- Spring-loaded biopsy guns are used to take cores from suspicious areas on TRUS. The majority of patients with elevated PSA do not have hypo-echoic areas in the peripheral zone of the prostate. Therefore, if no sonographic abnormality is detected, a biopsy strategy needs to be followed to allow the best possible chance of cancer detection.
- Any hypo-echoic area in the peripheral zone should be included in the random biopsy strategy.
- The biopsy needle should be placed at the margin of the prostatic capsule to sample peripheral zone tissue. The optimal site for cancer detection is in the peripheral zone, adjacent to the capsule. The capsule seen on TRUS is actually an interface between the gland and the periprostatic fat. Introduction of the needle into the gland may sample tissue in the transition zone
- Lateral needle placement increases sampling of the peripheral zone and increases cancer detection rates. Lateral needle placement also increases the possibility of detecting clinically significant cancer.
- The optimal biopsy protocol most suited to prostate biopsy in the absence of any hypoechoic area in the prostate is a 10- or 12-core technique (Philip *et al*, 2004b) laterally directed biopsy

described by Presti et al. (Presti *et al*, 2000). This maximises the detection rate with the least number of biopsies, making the procedure more tolerable for the patient.

- There should be a written proforma to document the following:
 - i. Any discrete hypo-echoic lesion in the peripheral zone (PZ) of the prostate gland should be sampled.
 - ii. Any diffuse hypo-echoic lesion in the PZ.
 - iii. Any hypo-echoic lesion with distortion of the capsule of the gland in the PZ.
 - iv. Any focal lesion with increased vascularity.
 - v. Disruption of the capsule of the gland.
 - vi. Any hypoechoic lesion in the central part of the gland.
- There should be a written record of the number and location of each biopsy, preferably by diagram that is also made available to the pathologist reporting the biopsies.
- A single national consensus proforma to record all salient features could be constructed along internationally agreed guidelines.
- Occasional patients cannot tolerate a probe in the rectum usually either due to pain or a rectal stenosis. Sedation or general anaesthesia may be needed.

5. Identifiable Dangers and Risks Incurred During Prostatic Biopsy

- The patient is subjected to unnecessary biopsy.
- The wrong patient is biopsied or the samples are incorrectly labelled or the samples are lost.
- The patient develops an infection after the biopsy.
- The patient haemorrhages after the biopsy.
- A significant cancer is missed at the biopsy or an insignificant cancer, which is not a threat to the patient, is discovered.
- Analgesia is inadequate so that the patient experiences unnecessary pain.

6. Audit

In each biopsy centre, a rolling audit should be performed to identify:

- Rates of detection.
- Sampling of non-prostatic tissues.
- Post-biopsy infections – severity and type.
- Other complications (e.g. haemorrhage).

[V] PATHOLOGICAL ASPECTS: ORIGIN OF TISSUE CORES

1. Number of Cores

Multiple reports from the U.S. and Europe have confirmed that “sextant” sampling methods “misses” a significant percentage of cancers in the first biopsy procedure and that an extended biopsy approach yields higher detection rates. The number of cores recommended in these studies is variable ranging from a minimum of 8 cores to extensive biopsy schema. Most reports have advocated 10-12 cores (Fink *et al*, 2001; Stewart *et al*, 2001; Bott *et al*, 2002; Durkan *et al*, 2002; Haggarth *et al*, 2002; Taylor *et al*, 2002; Matlaga *et al*, 2003). It might be argued that the precise technique adopted in an individual patient depends upon whether radiographic abnormalities have been identified within the prostate or whether prostatic biopsy is being employed as a “blind” screening procedure following detection of an elevated PSA or digital rectal abnormality. However, if performed correctly, a standard protocol-based procedure should identify, locate and map all the essential information with respect to the majority of prostate cancers. At the initial biopsy, a minimum of 8 cores should be taken (Damiano *et al*, 2003). In addition, sampling of hypo-echoic areas in the peripheral zone should be made (Lee *et al*, 1985). The use of two lateral biopsies in addition to the previous sextant biopsies detects a further 15% of prostate cancers. It is recommended, on the basis of current evidence, that a standard 10-core biopsy procedure provides optimal detection of a new prostate cancer (Philip *et al*, 2004b).

2. Location, Anatomic Source of the Cores

All the above-cited studies reported significantly improved cancer detection when the most lateral “subcapsular” peripheral zone of the prostate including the anterior “horns” and the apex were biopsied. Sampling these compartments according to different studies results in reducing the sextant false negative rates by 20-35%, with a recent report indicating that the extended biopsy schemes minimizes PSA and age related detection rates. The recommended scheme is a modification of that introduced by Presti *et al*, comprising 10 biopsies, (6 sextant and 2 lateral and apical on each side) (Presti *et al*, 2000). This approach limits the biopsy scheme to 6 central cores with an emphasis on the lateral peripheral zones (de la Taille *et al*, 2003). This 10-core biopsy protocol places emphasis on lateral and apical placement to enhance detection of peripheral zone cancers. Any hypoechoic areas in the peripheral zone should be included in the biopsy strategy. In addition, it may be necessary to perform digitally guided biopsies of an indurated or suspicious area.

3. Considerations for Gland Volume

Detecting prostate cancers in larger prostates is often more difficult than in smaller glands. While more studies suggest that obtaining more cores from larger prostates can increase the rate of cancer detection, a recent report on 750 patients acknowledged the inverse relationship between gland

volume and ability to detect prostate cancer in larger glands, disputes the value of more core biopsies (Durkan *et al*, 2002). Thus, it maybe beneficial to obtain more biopsy cores from large volume glands. However, there are no objective evidence-based data to support such a presumption.

4. Length and Diameter of Cores, Type of Needles Used

It is important to provide adequate diagnostic material with an effort to obtain intact cores. This is directly dependent on the type of needle biopsy gun employed and the training and dexterity of the operator. Assessment of training and efficiency should be monitored by audit.

5. Maintaining Source Identification of Individual Cores When Sent for Pathological Examination

To alleviate workload in the laboratory, it has been suggested that cores from the apex, mid and base from one side of the prostate can be submitted in one container and reported collectively. However, it is important however to maintain the separation of the biopsy samples according to side (right/left) throughout submission and pathology reporting. Samples obtained via modifications of the sampling protocol (such as few cores from a palpable abnormality), need to be oriented and kept separately for processing and reporting.

Assessment of a patient as a potential candidate for locus-specific treatment (i.e. radical prostatectomy or selective radiotherapy) requires the comprehensive accumulation of data from several distinct clinical, radiological and pathological sources. Key to this assessment is a detailed understanding of the precise location, and possible extent, of an identified prostate cancer. Therefore, individual prostatic tissue core biopsies, taken separately, should be retained and processed separately and not “lumped together” in single cassettes. The practice of attempting to arrange multiple needle-cores of tissue into single cassettes in some sort of sequence marked by the presence of some identifiable agent, or non-prostatic tissue (e.g. mouse liver has been suggested) should be discouraged as unnecessary for the following reasons:

- i. Introduction of unwarranted complexity.
- ii. Increased likelihood of error with respect to identification of individual cases.
- iii. Increased handling of tissues.
- iv. Increased need to cut multiple sections to fully examine each of the tissue cores with consequent loss of tissue for additional studies (e.g. immunohistochemistry).

[VI] PROCESSING AND REPORTING PROSTATIC BIOPSIES

1. Guidelines for Adequate Prostatic Needle Biopsy Processing

Irrespective of any screening programme, heightened awareness of prostate cancer in the general population, together with increased digital rectal examination and use of PSA testing has increased the detection of early prostatic neoplasia. By definition, many of these lesions tend to be smaller in size and to approximate closer to the normal range of morphological appearances, thus making diagnosis more difficult (Epstein, 2004). Some guidance is suggested that might assist in resolving this dilemma:

The number of biopsies embedded in one cassette

Urologists need to know the precise site at which the prostate cancer is located. This information may help to decide whether a unilateral nerve sparing prostatectomy is possible. In cases of lesions suspected of being adenocarcinoma, it is important to know their localization for site-specific repeat biopsy. It is therefore preferable that each biopsy core is embedded separately (Boccon-Gibod *et al*, 2004). This is not an explicit recommendation in the RCPATH guidelines (Bostwick *et al*, 2000; The Royal College of Pathologists, 2000) but at the very least samples from the right and left side of the gland should be kept separate.

The procedure of embedding of needle biopsies into paraffin wax

The objective is to achieve a maximum amount of tissue for microscopic evaluation since this correlates with the cancer detection rate (Iczkowski *et al*, 2002; van der Kwast *et al*, 2003). Since needle biopsies tend to become curved after fixation, flat embedding of the biopsy cores enhances the amount of tissue that is examined by the pathologist. Flattening of biopsy cores can be achieved by stretching the needle biopsies between two nylon meshes or by wrapping them in a piece of paper. This can be done even after initial formalin fixation.

The number of sections from each biopsy core (levels of sectioning)

Earlier reports (Bostwick *et al*, 2000; Iczkowski *et al*, 2002) have demonstrated that it is mandatory to cut several sections of each biopsy core at different levels in order not to miss small foci of adenocarcinoma. Cutting biopsy cores at different levels may allow a definite diagnosis of adenocarcinoma when a small focus is found at a single level. Practically, laboratories need to agree a single strategy for cutting and staining prostatic needle biopsy specimens. Reyes and Humphrey provide strong evidence that complete histologic sampling with serial sections entirely through the paraffin wax block is unnecessary (Reyes & Humphrey, 1998). Their study of 200 consecutive cases showed that the three initial slides, each containing several sections, identified all of the contained cancers, thus making further work redundant. Furthermore, after an initial diagnosis of pure high-

grade PIN, generation of additional sections is also unnecessary. Rather the patient should undergo clinical follow-up and full re-biopsy should be considered. It is recommended that sections of a core at two different levels are sufficient. Ribbons between the two levels can be stored for cases where additional histologic slides or immunohistochemistry are required.

The length of each biopsy core should be recorded as an integrated part of the macroscopic description for comparison with the length on the glass slide.

2. Guidelines for Uniform Reporting of Prostate Lesions

Differential Diagnoses

Reporting of the histopathology of prostatic needle biopsies should be as unequivocal and concise as possible. This means that the nomenclature of prostatic lesions in pathology reports should be uniform. Terms like “atypical glands”, “glandular atypia”, “probably malignant”, but “benign not excluded” should be avoided, since it is not clear to the urologist which further action should be taken. Adequacy of prostatic needle biopsies should be mentioned in the pathology report. An inadequate prostatic core biopsy core is defined as a core lacking prostatic (glandular) epithelial structures. Where prostatic epithelial structures are present, a salient distinction of the prostatic biopsy is between those features that are benign and those masquerading as malignant. Pathologists should make themselves aware of benign prostatic lesions that mimic carcinoma (Foster & Sakr, 2001a; Foster & Sakr, 2001b). With respect to the latter, the following terms have proven their value and consistency over the last several years:

Benign

This includes fibromuscular or glandular hyperplasia, various forms of atrophy as well as foci of chronic (lymphocytic) inflammation. Although multiple biopsies with post-atrophic hyperplasia may be reported as such, in itself this finding has no clinical consequence. Distinctions between the above entities are of limited clinical relevance and subject to considerable inter-observer variation (Oppenheimer *et al*, 1997).

Acute inflammation

This lesion is characterized by damage to glandular structures. This finding might explain increased serum PSA levels. The presence of epithelial glandular destruction should be recorded together with its proximity to morphologies suspicious for cancer or adjacent to foci of sclerosing adenosis.

Chronic granulomatous inflammation

Includes xanthogranulomatous inflammation. This condition can cause strongly elevated PSA levels and cause a false positive digital rectal examination. The nature of the granulomatous inflammation

should be assessed together with the history to identify those cases of bladder cancer where BCG might be employed therapeutically.

Adenosis

Adenosis, fortunately is a very rare finding in peripheral zone derived needle biopsies. Adenosis which is characterised by a condensation of small glands surrounded by sporadic basal cells is also known as atypical adenomatous hyperplasia (Bostwick *et al*, 1993). The latter term is not recommended because the term “atypical” may suggest a relation with malignancy.

Prostatic intra-epithelial neoplasia (PIN)

Although initially low and high grade PIN was distinguished, now only (high grade) PIN is reported. The extent and architectural pattern of PIN may also be reported, since some of these variants (solid, comedo and cribriform) may be associated with unfavourable prostate cancer as they may represent intraductal spread of high-grade cancer (Cohen *et al*, 2000).

Adenocarcinoma

The location(s) of the foci of adenocarcinoma should be recorded. In this way the number of positive biopsies is implicitly known to the clinician. If a small focus (< 3 mm) of adenocarcinoma is present in only one needle biopsy this may be recorded in the conclusion as “*focal adenocarcinoma*”. It is also recommended to estimate the proportion of tumour involvement of the needle biopsies, particularly with the advent of quantitative prostate biopsy for prediction of organ confined disease (Haese *et al*, 2003). The extent of cancer involvement may be given in percentage of the biopsy core lengths (e.g. > 5%, 10%, 20%, etc).

Suspicious, but not diagnostic, of adenocarcinoma

If the lesion is too small and/or lacks sufficient criteria to be able to make a definite diagnosis of adenocarcinoma (Cheville *et al*, 1997; Epstein, 1999).

The possibility of other malignancies, including *carcinosarcoma*, *sarcoma*, *adenocarcinoma of the colon* etc. masquerading as prostatic carcinoma should be considered. When adenocarcinoma, high grade PIN, or lesions suspected as being adenocarcinoma are present at separate sites, they should also be reported separately.

Reporting of differentiation grade

It is recommended that the **Gleason scoring** system be used. Advantages of this grading system are its general use and the large amount of data in the literature on its prognostic impact and accuracy. As advocated by Epstein (Epstein, 2000) we should not attribute Gleason scores of 2 to 4 to prostatic

adenocarcinoma on peripheral zone needle biopsies. The lowest Gleason growth pattern that can be assessed in needle biopsies is growth pattern 3, implying that a Gleason score of 6 is the lowest possible on peripheral zone needle biopsies.

An important feature of the Gleason system is that it takes into account the heterogeneity of prostate cancer by including the two most prominent growth patterns. Thus, in sextant needle biopsies the Gleason score can range from 6 to 10. The **location** of a separate area of **high grade** (Gleason growth pattern 4 or 5) cancer should always be reported (when '5' is included as a tertiary grade), irrespective of its extent in the needle biopsy (Srigley *et al*, 2000; Epstein *et al*, 2005). In radical prostatectomy specimens a second growth pattern that comprises less than 5% of the tumour area is not included in the Gleason score. This rule does not apply for high-grade cancer in prostatic needle biopsies: Irrespective of the amount of the second growth pattern it is included in the Gleason score. If, in addition to growth pattern 3, both pattern 4 and 5 are present in the needle biopsies then pattern 5 will be included in the Gleason score (i.e. $3 + 5 = 8$).

Immunohistochemistry

Of all special investigations available to diagnostic surgical pathologists only immunohistochemistry has yet found a regular place in the compendium of techniques routinely-accepted techniques. Antibodies to detect high-molecular weight cytokeratins (Brawer *et al*, 1985; Purnell *et al*, 1987; Grignon *et al*, 1988; Hedrick & Epstein, 1989; Devaraj & Bostwick, 1993) and to α MeCo racemase (Xu *et al*, 2000; Jiang *et al*, 2001; Luo *et al*, 2002; Rubin *et al*, 2002) are principally employed. Antibody 34 β E12 (previously known as "keratin 903" and generated by Gown and Vogel in 1982 (Gown & Vogel, 1982) reveals absence of basal cells from glandular epithelial structures to be indicative (but not diagnostic) of malignant change. Conversely, enhanced expression of α MeCo racemase (identified as P504S and first reported by Xu *et al*. (Xu *et al*, 2000) occurs in neoplastic prostatic epithelial cells of both luminal and basal types (Evans, 2003). Both reagents should be used by experienced immunohistochemists and interpreted with caution by experienced diagnostic pathologists to avoid erroneous interpretation of appearances. Loss of expression of nuclear protein p63 by prostatic basal cells (Weinstein *et al*, 2002; Stefanou *et al*, 2004) is a powerful marker of dysplasia that may be used in conjunction with AMACR. Full assessment of the uses and potential benefits of a range of new markers has been considered in detail (Dodson & Foster, 2005). It cannot be emphasized strongly enough that underpinning such diagnostic adjuncts is the "gold standard" of good morphological assessment.

Quality control indicators

The standardization of processing and reporting on prostate needle biopsies, will be increasingly important in order to assure quality and to avoid medico-legal complications.

As a quality indicator the average length of needle biopsies and the percentage of inadequate biopsies can be used. The frequency of suspect lesions might give an indication as to the level of certainty reached by the pathologist. This is of course related to several factors, including the population under study, the quality of needle biopsies and their processing as well as the staining and the confidence of the pathologist. The percentage of suspect lesions should not rise above 5% since this will lead to a too frequent indication of repeat biopsies.

[VII] ANALGESIA AND ANAESTHESIA FOR TRUS GUIDED PROSTATE BIOPSY

It is generally accepted that without some form of analgesia, some pain (discomfort) is experienced during prostatic biopsy and that this pain is unnecessary. Only one study is known that has examined the severity of pain when prostatic biopsy is performed in the absence of analgesia, and has provided useful information on the sequence of prostatic sites biopsied in order to minimise the discomfort experienced (Bastide *et al*, 2003).

1. To Control Pain: Five Different Approaches are Currently Employed, Either Alone or in Combination.

Periprostatic Local Anaesthesia (LA)

Seven randomised studies are available (Pareek *et al*, 2001; Seymour *et al*, 2001; Wu *et al*, 2001; Lynn *et al*, 2002; Schostak *et al*, 2002; Walker *et al*, 2002). Two were double blinded (Wu *et al*, 2001; Walker *et al*, 2002), all but one (Wu *et al*, 2001) showed LA to be benefit, with between 1-4 point improvement in a 10 point visual analog scale (VAS) pain scores immediately after biopsy. The only one that showed no benefit was double blinded but under-powered with 40 patients only. No increased complication rate, particularly sepsis or lignocaine toxicity were reported. Nevertheless, 7.5% would not consent to repeat biopsy on self-answered questionnaires (Seymour *et al*, 2001).

At least three different infiltration techniques have been described and comprising apical injection, neurovascular bundle injection or injection around the base of the seminal vesicle. One study suggested that apical injection was more effective than neuro-vascular injection (Schostak *et al*, 2002), although this was not confirmed in the most recent evaluation of 98 men (Philip *et al*, 2004a).

Rectal Anaesthetic gel

Five randomised studies have been reported (2 double blind). Three compared gel *versus* no gel – the larger two studies (108 and 109 patients, both double blind) reported no benefit, (Desgrandchamps *et*

al, 1999; Chang *et al*, 2001) the other (50 patients) said gel was better (Issa *et al*, 2000). Five further studies compared gel versus LA injection (Alavi *et al*, 2001; Lynn *et al*, 2002; Stirling *et al*, 2002; Adamakis *et al*, 2003; Rodriguez *et al*, 2003) all found LA injection to be superior, but one (Stirling *et al*, 2002) reported that gel was better at improving the discomfort due to probe introduction. No significant complications were reported in any of the five studies.

Analgesic Suppositories

Although used in some departments, there are no robust controlled data to support its value.

Entonox

- One double blind, randomised study (110 patients) showed that Entonox significantly improved pain tolerance.
- Entonox provides equivalent analgesia to periprostatic infiltration with 1% lidocaine (Manikandan *et al*, 2003).
- However, Entonox alone requires post-procedure patient care since 14% of men complained of transient drowsiness. Otherwise, no major complications have been reported (Masood *et al*, 2002).

Intravenous sedo-analgesia

Used in some departments. There are no controlled data to support its value, but it is likely to be of benefit. This technique requires a higher level of patient care and facilities (recovery room etc.)

2. Recommendations

Some form of pain control should be provided during TRUS guided prostate biopsy. Local anaesthetic infiltration has been most thoroughly studied to date, is of proven benefit, is safe and is recommended.

3. Further Studies Needed

- Do more men agree to repeat biopsy after LA injection? If not, might the addition of gel or analgesic suppository help?
- Confirm that local anaesthetic is better than Entonox and that both are significantly better than Gel.
- Longer experience with LA- the gland has a rich blood supply and there is a theoretical risk of vascular injection and cardio-toxicity.

Between 10-24% of patients report moderate or severe pain after sextant TRUS guided prostate biopsy (Clements *et al*, 1993; Collins *et al*, 1993; Crundwell *et al*, 1999) and 7.5-19% (Irani *et al*,

1997; Seymour *et al*, 2001) would refuse a repeat biopsy. More recently 47.6 % complained of pain after 10 biopsies (Peyromaure *et al*, 2002); study methods may account for apparent increase but it is possible that as more biopsies are taken per gland, pain is more prevalent.

The pain/discomfort of the procedure may arise from:

- introduction of the probe through the anal sphincter
- pressure of the probe tip on the rectal wall
- needle puncture of the rectal wall/prostate capsule
- by the impact/propulsion forces of the biopsy needle as it is ‘fired’ by the spring driven biopsy gun.

Any one or more of these factors may play a part.

Although the sensory innervation of the prostate is not well described, the prostatic nerves lateral to the gland are believed to be important. Many men find TRUS guided biopsy unpleasant or painful. This may become more so as more biopsies and repeat biopsies become necessary. Some sort of pain control helps during prostate biopsy. Rectal anaesthetic gel may have some effect on pain related to probe introduction, but not on the biopsy pain. There are no reliable data about analgesic (or non-steroidal) suppositories. The value of Entonox needs to be confirmed, it also requires some bulky equipment and possibly monitoring. Local anaesthetic injection helps, as supported by good quality evidence, and seems to be safe.

[VIII] IMAGE CONTROL AND 3D SCANNING

Imaging has two main purposes:

1. To guide transrectal needle prostate biopsy
2. As an adjunct to clinical examination in staging prostate cancer prior to intervention. No radiological technique makes an incontrovertible diagnosis of prostate cancer. Histopathological examination remains the “gold standard” procedure for the diagnosis of prostate cancer.

Summary

- Conventional TRUS has largely replaced digitally guided biopsy in acquiring prostate tissue to diagnose cancer. Digitally-guided biopsy is inaccurate and therefore not appropriate for diagnosing organ confined prostate cancer, although DRE remains a core modality of clinical staging. Optimally all prostate biopsies should be under TRUS guidance (Linzer *et al*, 1996).
- Imaging has no role in screening for prostate cancer but does have a place in the diagnosis and staging of the disease. Needle biopsy following transrectal ultrasonography (TRUS)

remains the “gold standard” procedure for the diagnosis of prostate cancer. 2D or gray scale TRUS is a ‘real time’ imaging modality, which is easily manipulated to allow targeted biopsy for histological staging (e.g. to seminal vesicles). 2D TRUS is highly operator dependent but in experienced hands can yield accuracies in staging of up to 86% (Aarnink *et al*, 1998).

- Adjuncts to gray scale imaging are colour power doppler (PDI), contrast agents (e.g. Eghogen, Levovist, Imavist) and harmonic enhancement. In research settings each may increase the sensitivity of conventional TRUS (Forsberg *et al*, 1996; Calliada *et al*, 1998; Shigeno *et al*, 2000) for cancer detection and staging. However, to date, they have no place in the routine diagnosis of prostate cancer.
- CT is neither sufficiently sensitive nor specific in the diagnosis or staging of localised prostate cancer. At present it is only recommended in patients with clinical stage T3-4, Gleason score 8-10 or PSA >20ng/ml; where there is particular concern about nodal status (Emory *et al*, 1983; Yu & Hricak, 2000).
- MRI has no role in directly guiding prostate biopsy (Kurhanewicz *et al*, 2000).
- In some countries, including the USA, MRI is the most favoured imaging modality for staging prostate cancer prior to intervention. This trend has not been reproduced in the UK since MRI is not routinely available and is vastly more expensive when compared to transrectal ultrasound. Interpretation of scans is expertise-dependent. There is a tendency for MRI to over-stage. Therefore, MRI should only be performed and analysed by radiologists who have adequate experience in interpreting these scans, with state-of-the-art equipment.
- Several techniques are being developed in an attempt to improve staging. PET (Positron Emission Tomography) and MRSI (Magnetic Resonance Spectroscopy) have yet to establish a place in routine clinical imaging of prostate cancer. Although recent evidence suggests that MRSI may be a useful adjunct to MRI, providing additional metabolically driven diagnostic information that can, if indicated, aid further TRUS guided biopsy (Kurhanewicz *et al*, 2000). 3D TRUS is a newly-emerging modality. Initial results show improved staging for biopsy-diagnosed prostate cancer. However, images are not yet ‘real time’ and therefore have no place in directing biopsy. Presently these developing modalities remain under investigation and have no place beyond a research context in specialised centres.

[IX] MANAGEMENT FOLLOWING A NEGATIVE CORE BIOPSY

PSAD (prostate specific antigen density) and PSAT (prostate specific antigen transition zone) reflect the volumetric component of PSA, and are not of particular interest. DRE and TRUS do not have predictive value especially in the lower PSA ranges.

The histology of the initial biopsy might be directive for a repeat procedure. The presence of carcinoma after high grade PIN in the initial biopsy has recently been reported to be less frequent (Hoedemaeker et al, 2001) compared to former studies (Zlotta et al, 1996). However, as suggested earlier (see p10. Repeat Biopsy) it is reasonable to perform an extended biopsy (10- or 17-core) at 3 – 12 months after an initial biopsy that identified only PIN, particularly in the presence of a persistently-elevated PSA. Other pathologic findings, like atypical small acinar proliferations (ASAP), may urge a repeat biopsy (Vis et al, 2001).

Nearly all detectable cancers will be found in three series of subsequent sextant biopsies (Djavan *et al*, 2002). The optimal biopsy interval is determined arbitrarily by the patient with his doctor. In the absence of symptoms, intervals up to four years are considered safe, but biannual repeat biopsies in men with PSA > 4 ng/ml have been advised (Etzioni *et al*, 1999).

In summary it might be concluded that:

- The performance of the repeat biopsy is dependent on the method of initial biopsy
- Repeat biopsies are acceptable and safe
- Repeat sextant biopsies are no longer adequate but an initial series of 10 or 12 cases, repeated in the event that the first series is histologically negative should be considered.
- Any interval between 6 weeks to 4 years is safe, 2 years or more after an initial procedure seems efficient.

Indicators for repeat biopsy which might be considered include:

- *Persistently elevated PSA > 3*
- *histologic lesions (ASAP, but not HGPIN)*
- *PSADT < 10 months*
- *PSAV of > 0.1 ng/ml annually, although this is rarely used and PSADT is preferred*
- *watchful waiting / screening protocols.*

Summary

- Routine audit of defined aspects of biopsy outcome and effectiveness is essential.
- Prostate cancer appears to be a heterogeneous disease across national as well as ethnic boundaries. Therefore, the data on incidence in different countries may not translate exactly to the findings in all other countries.
- Audit of methods of analgesia is essential to ensure that patients in each unit are receiving optimal pain/discomfort management, particularly as prescribes rise to increase patient numbers undergoing prostatic biopsy.

Repeat prostate biopsies to detect prostate cancer are performed in the scope of trial protocols, or in the outpatient setting as the result of the patient's desire to exclude cancer or diagnose it early and the urologist's advice. There must be the intention to treat should relevant disease be detected.

Repeat biopsies detect relevant cancers, according to the criteria of Epstein, in screening as well as in clinical series (Rietbergen *et al*, 1998; Hugosson *et al*, 2003). Tumour characteristics are identical to those of tumours found during initial biopsy. (Djavan *et al*, 2002) The efficacy of detection during repeat biopsy procedures is dependent on the performance of the initial procedure (Fleshner *et al*, 1997; Djavan *et al*, 2000). Optimising of the both procedures is required, as the repeat biopsy often serves to correct the sampling error of the initial procedure (Eskew *et al*, 1997; Chang *et al*, 1998; Bauer *et al*, 1999). The questions raised at repeat biopsy are identical to those for initial biopsy

Various parameters might be monitored after an initial negative biopsy, including PSA and isoforms, prostate volume, DRE and initial histology. Nearly all studies perform repeat biopsies on a persistently elevated PSA. Men with persistently elevated PSA and a small gland (< 20 ml) are likely to have cancer, while men with volume > 70 ml have BPH (Zackrisson *et al*, 2003). Annual PSA increases of 0.1 ng/ml may discriminate between men with minimal likelihood on prostate cancer, and those with of over 60% (Fang *et al*, 2002). While PSA is correlated to prostatic volume, F/T ratio can be regarded as independent. The F/T ratio is significantly lower in cancer patients compared to controls, and remains so in repeat biopsy rounds in which cancer is ultimately diagnosed (Zackrisson *et al*, 2003).

[X] IDENTIFIABLE DANGERS AND RISKS OF PROSTATIC BIOPSY

1. That the patient be subjected to an unnecessary biopsy

Prostatic biopsy is undertaken to exclude or make the diagnosis of prostate cancer. Therefore, it should only be performed on patients in whom the diagnosis of cancer would lead to a change in their management. For instance an asymptomatic 95-year man with severe congestive cardiac failure and a PSA of 4.1 is unlikely to benefit from prostatic biopsy and biopsy should be avoided in patients in whom it would not change their management. The decision to perform or avoid biopsy is often a matter for clinical judgement. However, protocols should be developed to indicate where 'no biopsy' may be the most appropriate course of management and/or where senior colleagues' judgement might be sought. Such protocols would also assist GPs and others in advising men about PSA testing which should not be undertaken if there is no intention to treat.. This is particularly important in 'one-stop' biopsy clinics based on a GP referral letter.

Biopsy is generally indicated either if the patient has an elevated PSA or if the prostate feels abnormal at digital rectal examination. The main reason for an elevated PSA or abnormal DRE, other than cancer and benign prostatic hyperplasia (BPH) are urinary tract infection (UTI) and retention with catheterisation where PSA levels in excess of 100 ng/ml have been regularly recorded in such patients (Dalton, 1989; Neal *et al*, 1992; Ulleryd *et al*, 1999; McNeill & Hargreave, 2000; Kiran, 2001).

A history should be obtained from the patient to elicit symptoms of a UTI currently and at the time the elevated PSA was estimated. Infection should be excluded prior to biopsy as the presence of infection in the urine prior to biopsy is of dual concern to the doctor looking after the patient. Firstly, the reason for the biopsy should be questioned as the elevated PSA or DRE could be due to the infection rather than cancer. Secondly, it is likely that the patient is at increased risk of post biopsy sepsis if infections is already present at the time of the biopsy

The urine of patients should be tested either by sending a mid-stream specimen of urine (MSSU) to the laboratory and having the results available, or by testing the urine with dipstix that is capable of detecting leukocytes and nitrites, prior to the biopsy. If the dipstix test is positive then the biopsy should be delayed pending the MSSU results.

In all patients, a urinary tract infection (UTI) should be treated with antibiotics prior to biopsy. To achieve good prostatic levels of antibiotic within the prostate, the antibiotic should be given for sufficient time to eradicate prostatic infection. In patients with acute bacterial prostatitis a 4 week course seems the minimum length of time needed reliably to eradicate the infection (Lipsky, 1999). The quinolone group of antibiotics and, to a lesser extent trimethoprim, have been shown to be good candidates for treating prostatic infections (Madsen *et al*, 1976; Frimodt-Moller *et al*, 1979; Sabbaj *et al*, 1986; Gerding & Hitt, 1989; Naber, 1989). Unless there is very strong clinical evidence for the presence of cancer it seems reasonable to allow sufficient time for the PSA to fall to normal levels and/or the DRE return to normal before undertaking the biopsy. The rate of fall of PSA has been shown to be very variable. Ulleryd *et al* showed that although over 50% of patients have normalised their PSA by six weeks a small proportion will take up to a year to fall below 4.0 after an acute UTI (Ulleryd *et al*, 1999). They have shown, however, as have others (Ulleryd *et al*, 1999; Kiran, 2001) that a small proportion of patients who present with a definite UTI end up by having a positive biopsy for cancer. This may be due to chance, with the UTI acting as a trigger for screening, but the possibility that in some circumstances prostate cancer can predispose to infection (or vice versa) must be entertained just as lung cancer predisposes to pneumonia. It seems reasonable, however, given that over 80% of patients will normalise their PSA levels with sufficient time, to monitor the rate of fall of PSA. Judgement as to how long one should delay the biopsy if the PSA/DRE do not return rapidly to normal requires a balance between the desire not to delay the diagnosis of cancer versus the desire not

to subject the patient to an unnecessary biopsy. This is a matter of clinical judgement based on the rate of fall of PSA, the DRE findings and the age and frailty of the patient. Although it has not been reported it would seem likely that the shape of the graph produced by plotting PSA against time could predict the nadir of PSA.

It is not possible to distinguish BPH from malignancy without a biopsy. It is, however, important to make sure that, if the decision to perform a prostatic biopsy is taken on the basis of an elevated PSA, then the result is reported accurately. A written copy of the report or access to the computerised report should always be obtained.

The risk of the laboratory giving an erroneous reading is possible but it is a rare occurrence (Dejter *et al*, 1988).

2. The wrong patient is biopsied or the samples are incorrectly labelled or lost

It is possible that the appointment for a prostatic biopsy has been sent to the wrong patient or, when two patients with the same name live at the same address (e.g. father and son) that the patient himself has made an error. Although it might be assumed that the patient would not submit to biopsy under these circumstances the elderly or timid patient may allow a biopsy to be performed if told that it was necessary by a doctor. The name, date of birth and address of the patient should be checked prior to the biopsy. It is also important that the history in the hospital notes or in the letter from the general practitioner (GP) tallies with the patients understanding of his condition.

In a busy clinic where several patients follow on from one another there is always the risk that samples will be incorrectly labelled or the form from one patient be put with the specimen from another. This is particularly so with the increasing use of pre-printed adhesive labels which are sometimes misfiled in the notes of the wrong patient or are easily taken from the wrong notes (Cummins *et al*, 2000; Orser *et al*, 2001). Using “on-demand” printed bar-coded forms and specimen containers with information taken directly from the patient database and with specimen details referred to the database is now the most reliable and preferred option.

Strict protocols must be adopted to minimise the risk of such errors and the division of labour and responsibility between the person performing the biopsy and his/her assistant determined. It is advisable that the hospital notes of the person being biopsied are the **only** notes out at the time of the biopsy. At the end of the biopsy the labelling of the specimens and the pathology form should be checked with the patient by the person performing the biopsy and placed together in a sealed polythene bag ready for collection to be sent to pathology.

3. The patient develops an infection after the biopsy

Sepsis, which may be severe, is well documented after prostatic biopsy (Gustafsson *et al*, 1990; Enlund & Varenhorst, 1997; Rodriguez & Terris, 1998; Crundwell *et al*, 1999) and deaths have been reported (Brewster *et al*, 1993; Borer *et al*, 1999). Anyone who has readmitted a patient with sepsis will be struck by how ill patients can become. Gustafsson *et al* (1990) reported a 3.5% readmission rate when using an 18G trucut needle without antibiotic cover (Gustafsson *et al*, 1990). Enlund and Varenhorst, however, reported that 0.7% of patients required hospitalisation for septicaemia after biopsy using a spring-loaded gun (Enlund & Varenhorst, 1997). In addition for every patient treated in hospital four more were treated by their general practitioner for an episode involving pyrexia or rigor. The need to take a quinolone antibiotic for at least 2 days after biopsy seems to be established (Roach *et al*, 1991; Aus *et al*, 1996; Sieber *et al*, 1997; Isen *et al*, 1999; Janoff *et al*, 2000). Alternatives must be sought in patients who are allergic to these antibiotics. Epileptics pose a problem as quinolones may reactivate previously stable epilepsy. Trimethoprim, which also achieves high prostate levels, is a less effective alternative in these patients (Ruebush *et al*, 1979; Fong *et al*, 1991; Isen *et al*, 1999). The vast majority of infections are due to gram negative septicaemia (Gustafsson *et al*, 1990; Enlund & Varenhorst, 1997). Although the risk of anaerobic infection is low, when it does occur, it appears to be particularly serious (Harris *et al*, 1978) and two deaths in the literature (Brewster *et al*, 1993; Borer *et al*, 1999) encourage use of co-amoxycylav or metronidazole when the patient is allergic to penicillin. Pre biopsy enemas do not appear to reduce the rate of infection (Carey & Korman, 2001).

Patients who are at risk of bacterial endocarditis are particularly susceptible due to the bacteraemia that almost inevitably follows the biopsy (Ruebush *et al*, 1979). A careful history should be taken to exclude cardiac valvular defects and indwelling pacemakers. If such a history is forthcoming then full endocarditis prophylaxis must be given in addition to the routine antibiotic cover (Taubert & Dajani, 2001).

It is self evident that the ultrasound probe or biopsy guide might transmit infection (e.g. HIV or hepatitis) from patient to patient if not protected, for example with a condom, or sterilised in between patients. The sterilisation or protection process depends on the type of probe used and generally the companies that make the ultrasound equipment issue guidelines based on national authority (in the UK the Medicines and Healthcare products Regulatory Agency (MHRA) and in the USA the Centre for Disease Control, Atlanta). The person setting up the biopsy clinic has a duty to ensure the correct sterilisation of the equipment or protection of the patient by covering the probe with a condom or similar protective. Frequently a local hospital committee with responsibility for sterilisation of equipment will advise. Generally needles should be disposable, needle guides either disposable or autoclaved and the probe either protected with a condom or chemically sterilised.

Although there has been no reported case of variant CJD being contracted after TRUS guided biopsy in the UK it remains a theoretical possibility (Bernoulli *et al*, 1977; Brown *et al*, 2001). Prion proteins have been identified in the rectum of both sheep with scrapie and patients with vCJD (van Keulen *et al*, 1999; Wadsworth *et al*, 2001).

4. The patient haemorrhages after biopsy

Minor bleeding in the urine and semen and from the rectum is common and patients should be warned to expect it (Djavan *et al*, 2001c). More profuse bleeding may complicate prostatic biopsy. Djavan *et al* reported a severe haematuria rate of 0.5 - 0.7% and although this is usually self-limiting there have been rare cases where it has been life threatening (Dunn *et al*, 2000; Djavan *et al*, 2001c; Strate *et al*, 2001). The main preventable reason for bleeding is anticoagulation. This is particularly relevant if the patient is taking anticoagulants without the knowledge of the person performing the biopsy. Although a recent survey indicated that it is not universal practice amongst doctors who perform TRUS guided biopsies to stop warfarin prior to biopsy (Connor & Wingate, 1999) this policy seems needlessly risky given the known incidence of bleeding. Unless there are strong medical reasons to continue full anticoagulation the risk to the patient should be minimised by stopping the anticoagulant prior to the biopsy. If the clinical decision is that anticoagulation cannot be stopped for longer than a few hours e.g. in patients with a metal heart valve, then conversion to intravenous heparin prior to the biopsy affords the most control.

A drug history should be taken prior to the biopsy to exclude the possibility that the patient is on anticoagulants. It should be remembered that patients may be receiving alternative medications to warfarin (e.g. Dindavan). Numbers of patients are self-medicating with aspirin at various doses.

The risk of bleeding due to aspirin or non-steroidal anti-inflammatory drugs is less clear cut. Although there is some evidence that, generally, patients do bleed more when taking aspirin or non steroidal anti-inflammatory (NSAI) agents with anti-platelet activity, (Zhu *et al*, 1995) there is no direct evidence to show that there is an increased incidence of bleeding in these patients undergoing transrectal prostatic biopsy (Rodriguez & Terris, 1998; Herget *et al*, 1999) and it is a matter of clinical judgement therefore whether to stop or continue these drugs prior to biopsy.

Where major bleeding does occur it can be managed either by endoscopic banding or injection of adrenaline (Strate *et al*, 2001) or by direct suture (Dunn *et al*, 2000).

5. Where a significant cancer is missed at biopsy

When TRUS guided prostatic biopsy was first used to diagnose prostate cancer, only abnormal areas either on DRE or TRUS were biopsied (Lee, 1989). It rapidly became clear that this regime missed a large number of cancers and the addition of random biopsies enhanced the detection rate (Hodge *et al*, 1989a). The sextant biopsy protocol advocated by Hodges *et al* whereby six biopsies were taken in the para-sagittal plane at the apex, middle and base of the gland on each side became the standard in most centres (Hodge *et al*, 1989a). More recently however it has become clear that, even when using this protocol, a significant number of cancers can be missed (Norberg *et al*, 1997; Levine *et al*, 1998; Brossner *et al*, 2000; Cookson, 2000; Niemann & Bahnson, 2001). Recently reports of ‘saturation biopsies’ of up to 45 biopsies has yielded cancer detection rate in patients with previous negative biopsies of up to 34% (Borboroglu *et al*, 2000; Stewart *et al*, 2001). The feasibility and desirability of such a protocol as a routine is uncertain but it has become clear that six biopsies is inadequate as a standard technique and that about ten should be the norm. The exact number of biopsies that should be taken has to be determined by weighing the desire not to miss a cancer on the one hand with what the patient can reasonably be expected to tolerate, and the risks of detecting cancers which are not a threat to the patient on the other. The cancers detected by performing repeat sextant biopsies in those with initial negative biopsies appear to be similar to those detected on the first set as judged by pathological stage and Gleason grade (Stroumbakis *et al*, 1997; Djavan *et al*, 2001a). Djavan *et al*, however, have shown that the 3rd and 4th sets of sextant biopsies yield tumours that are significantly smaller and better differentiated than those on the first and second set (Djavan *et al*, 2001b).

It may also be necessary to consider the size of the prostate. Theoretically larger glands may need more biopsies, as obviously a smaller portion of the prostate is sampled. There is also evidence that in practice more cancers may be missed in glands over 50ccs (Uzzo *et al*, 1995; Letran *et al*, 1998). Furthermore Rietbergen *et al* report that prostate volume was the most important factor that correlated with failure to diagnose prostate cancer at the first biopsy (Rietbergen *et al*, 1998).

The site from which the biopsies are taken also seems to be important. The lateral part of the peripheral zone seems to be particularly important as this has the highest detection rate (Chang *et al*, 1998; Aus *et al*, 2001; Epstein *et al*, 2001; Mazal *et al*, 2001). A new protocol seems to be emerging based on the sextant biopsies with additional lateral biopsies using a minimum of 8 cores (Presti *et al*, 2000; Gore *et al*, 2001). However, more reliable is a standard 10- or 12-core biopsy procedure.

Although 20% of prostate cancers are thought to arise in the transitional zone the value of transitional zone biopsies, as a routine, is uncertain and the detection rate is low (<2%) as reported by Liu *et al* (Liu *et al*, 2001) and Fowler *et al*. (Fowler *et al*, 1999). Even Lui *et al*, who reported a higher pick up

rate recommended that transition zone biopsies be reserved for patients with prior negative biopsies and a persistent clinical suspicion for prostate cancer (Liu *et al*, 2001).

In line with previous recommendations, 10- or 12-core biopsies are regarded as routine. In the event that such a series misses a cancer, then a repeat series is recommended after 6 months. It must be remembered that even when using newer biopsy protocols, some cancers will be missed and repeat biopsies are likely to be necessary. This dictates the need for a different strategy for 1st time and repeat biopsies and for this to be possible people who perform the biopsies have to work to a set protocol to avoid repetition or missing areas that may contain a significant cancer.

6. The patient experiences unnecessary pain

There can be little doubt that undergoing a TRUS guided biopsy is at best an uncomfortable and at times a painful or even a very painful experience (Crundwell *et al*, 1999; Naughton *et al*, 2000; Djavan *et al*, 2001c; Manseck *et al*, 2001). Young patients are at particular risk from suffering pain (Djavan *et al*, 2001c). As has been discussed previously, if patients are being increasingly requested to undergo more biopsies per session, and more repeat sessions, more concern must be taken over pain control. It is only recently that sufficient attention has been paid to this, but recent trials have shown that local anaesthetic can reduce the pain of the procedure (Alavi *et al*, 2001; Seymour *et al*, 2001; Vaidya & Soloway, 2001). Technique seems to be important. Injection lateral to the seminal vesicles has little effect (Wu *et al*, 2001) whereas injection in the plane between rectum and prostate at the apex produces good analgesia if not anaesthesia. Lignocaine gel given into the rectum does not appear to be effective (Alavi *et al*, 2001). Even using local anaesthesia, some patients will tolerate the procedure poorly and general anaesthesia is occasionally required although sedo-anaesthesia is a possible alternative (Peters *et al*, 2001). The benefits of the latter in terms of pain relief and amnesia must be weighed against the remote chances of respiratory arrest in a place that might be poorly equipped to deal with the emergency. Given the good pain relief that can be obtained using local anaesthesia it seems an unnecessary risk to take as a routine.

[XI] CONCLUSIONS

Early models of prostate anatomy were misleading and gave rise to a misconception of anatomical prostate lobes which have no basis in prostate histology. Following original work in 1968, McNeal's subsequent description of a zonal anatomy of the prostate based on the duct pattern in adult prostates, has become widely accepted. Pragmatically, it provides a useful conceptual framework within which to locate identified prostatic cancer (McNeal, 1968; McNeal, 1981). Development of high quality transrectal ultrasound in the 1980s helped popularise the zonal anatomy of the prostate and clinicians could identify separate zones on ultrasound and perform needle-guided biopsy of the prostate as a simple out-patient procedure. Transrectal ultrasound and biopsy rapidly replaced digitally guided biopsy.

In the mid-to-late 1980's, prostate specific antigen (PSA) was increasing in popularity as a marker in the detection of prostate cancer in combination with digital rectal examination, PSA and TRUS and has become the standard method of evaluation of men with suspected prostate cancer (Carter & Partin, 2002). The majority of prostate cancers arise in the Peripheral Zone (PZ) and central zone, these cancers are more frequently associated with histological evidence of progression than cancers arising in the Transition Zone (TZ) (Greene *et al*, 1992). A good knowledge of the distribution of cancer is available from studies of radical prostatectomy specimens and is essential for clinicians undertaking TRUS and biopsy. Following the performance of digital rectal examination, an overall sonographic examination of the prostate is performed followed by infiltration of the basal and apical neurovascular bundle areas by lignocaine injection. Many patients referred for TRUS are stage T1c and do not have discrete hypoechoic areas in the peripheral zone; a number of problems arise in deciding on the best biopsy strategy. Among the difficulties faced by the clinician are the initial number of biopsies needed, the exact areas of the prostate to be biopsied, and the decision to repeat a biopsy when the initial result is negative and there is an ongoing suspicion of underlying cancer. Prostate cancer contains fewer sonographically detectable interfaces and therefore appears hypoechoic to the surrounding tissue. In general, the more extensive and more poorly differentiated the cancer, the more hypoechoic it appears on TRUS. A standard systemic biopsy protocol had been shown to be superior to a lesion directed biopsy strategy (Hodge *et al*, 1989b) and for many years this sextant biopsy protocol became the "gold standard" for patients with suspected prostate cancer. The sextant biopsy protocol involved a sample from the base, mid and prostate apex on each side approximately mid-way between the mid-line of the prostate and the edge of the gland. Biopsy of hypoechoic lesions in the transition zone has a much lower yield of cancer than in the peripheral zone (Hodge *et al*, 1989b; Egawa *et al*, 1991). Formerly, transition zone biopsies were reserved for patients who had an initially negative biopsy and where there was an ongoing suspicion of underlying cancer based on a rising serum PSA. However, it is clinically preferable to exclude transition zone cancer at the time of initial biopsy that to repeat the biopsy procedure because of initial incomplete sampling.

The requirements and philosophy of prostatic needle-core biopsies have changed during the past 20 years. Formerly, the procedure was used to confirm a substantive carcinoma suspected following digital rectal examination. Now, however, the procedure is used to locate a carcinoma that is suspected because of an elevated PSA. Furthermore, it is now known that prostate cancer is multifocal such that individual lesions may not alter the physical consistency of the prostate gland yet together contribute to an elevated PSA. Therefore, the strategy is often to fulfil a sampling protocol, based upon the regions within the prostate gland where malignancy occurs most frequently, with the expectation of sampling at least one of the foci. To this end, standardized 10- and 12-core biopsy protocols have been devised with the intention of detecting cancer located in the apex, at the base or

in the transition zone as well as in the lateral and medial compartments of the lower, middle and upper zones of the gland.

THE FUTURE

Procedures for diagnosing prostate cancer are evolving. Practitioners must be prepared to modify their techniques according to a developing evidence-base. Providing significant resistance to quinolone antibiotics does not emerge then transrectal prostatic biopsy is a safe out-patient procedure that can be reduced to being uncomfortable and unpleasant rather than excruciatingly painful and intolerable. In view of the necessity to biopsy many patients, it is vital to work to strict protocols to minimise risks to each patient. The possibility of human error must be considered and minimised. However, patients should understand, that although morbidity can be minimised it probably cannot be eliminated. With respect to diagnostic accuracy, pathologists should be assisted and encouraged to recognise morphological appearances that mimic carcinoma (Foster & Sakr, 2001b) by a process of continuing education. Use of specific markers (in addition to 34 β E12 and α MeCoA racemase) should assist in understanding the biology of evolving prostate cancer (De Marzo *et al*, 2004) and hence identify more specific markers of behaviourally-important prostate cancer genotypes or phenotypes. Additional markers for routine analysis of prostatic neoplastic lesions are also receiving consideration (Cornford *et al*, 1999; Cornford *et al*, 2000; Hlavaty *et al*, 2003; Kaplan, 2003; Nakamura *et al*, 2003). Nevertheless, these and all markers to be used clinically and/or pathologically must be employed correctly by those trained in their interpretation (Meng *et al*, 2003a).

It is already becoming apparent from on-going marker studies that “field changes” occur both prior to the development of a carcinoma and in the vicinity of an established carcinoma. While molecular biological techniques are yet in their infancy, these methodologies are sufficiently sensitive to confirm the presence of a cancer adjacent to a “negative” biopsy or by detection of cancer cells within the peripheral vascular circulation. It is anticipated that the expressed molecular genetic patterns are likely to predict the behaviour and therapy of individual cancers as well as confirming their diagnosis – providing a truly “patient-specific” diagnosis followed by individualised management of prostate cancer.

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