

APPENDIX H

PROCESSING AND REPORTING PROSTATIC BIOPSIES

By Professor Chris Foster

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 cores¹⁻⁷. 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 taken⁸. In addition, sampling of hypo-echoic areas in the peripheral zone should be made⁹. 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 cancer¹⁰.

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 minimize PSA and age related detection rates. The recommended scheme i.e. a modification of that introduced by Presti et al, comprising 10 biopsies, (6 sextant and 2 lateral and apical on each side)¹¹. This approach limits the biopsy scheme to 6 central cores with an emphasis on the lateral peripheral zones¹². This 10-core biopsy protocol with emphasis on lateral and apical placement to enhance detection of peripheral zone cancers. This is probably because most cancers originate peripherally¹¹. 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. Recommendations to maximise cancer detection have included strategies incorporating more regions such as transition and lateral peripheral zones^{13, 14}.

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 biopsies¹. Thus, it may be 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. Adopting such a protocol is suboptimal and contravenes established WHO¹⁵ and European¹⁶ guidelines. Whatever the employed protocol, it is important to maintain separation of 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.

Although histopathology workloads are deemed to be high in many laboratories, no good case can be made for compromising standards for the sake of speed, brevity, expediency or merely to facilitate technical aspects of specimen processing.

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. Furthermore, 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:

- 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 studied (e.g. immuno-histochemistry).

While apparently pragmatic, it is probable that a cost-benefit assessment of “tissue aggregation” is likely to indicate the compromise of detailed information for the unlikely gain of speed in tissue processing, and hence should be discouraged.

6. 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 difficult¹⁷. Some guidance is suggested that might assist in resolving this dilemma:

The number of biopsies embedded in one cassette

Urologists want to know at which site the prostate cancer is located. This information may help to decide whether a unilateral nerve sparing prostatectomy is possible. In cases of lesions suspect for adenocarcinoma, it is important to know their localization for site-specific repeat biopsy. It is considered preferable that each biopsy core is embedded separately¹⁶. This recommendation was not given explicitly in previous guidelines¹⁵.

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^{18, 19}. However, needle biopsies tend to become curved after fixation and flat embedding of the biopsy cores enhances the amount of tissue that is examined by the pathologist. Strengthening of biopsy cores can be achieved by stretching the

needle biopsy tissue between two nylon meshes or by wrapping them in a piece of paper. This can be done even after initial formalin fixation. Such manipulations are not recommended because manual handling, however minimal, is associated with traumatisation to the tissue and impaired morphology.

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

Earlier reports^{15, 19} 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 unnecessary²⁰. Their study of 200 consecutive cases showed that the initial three 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 rebiopsy. 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.

7. Guidelines for Uniform Reporting of Prostate Lesions

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. The adequacy of prostatic needle biopsies should be mentioned in the pathology report. An inadequate prostatic core biopsy core is defined as a core lacking glandular structures, is traumatized or is fragmented such that a diagnosis of prostate cancer cannot be reliably confirmed or excluded. The underlying terms seem to have proven their value and consistency in 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 variation²¹. Pathologists should make themselves aware of benign prostatic lesions that mimic carcinoma²².

Acute inflammation

This lesion is characterized by damage to glandular structures. This finding might explain increased serum PSA levels.

Chronic granulomatous inflammation

Includes xanthogranulomatous inflammation. This condition can cause strongly elevated PSA levels and cause a false positive digital rectal examination.

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 hyperplasia²³. The latter term is not recommended because the term “atypical” may suggest a relation with malignancy.

Prostatic intra-epithelial neoplasia (PIN)

Although initially low grade and high grade PIN were distinguished, only (high grade) PIN is reported. Cytological and nuclear abnormalities contributing to the various entities recognised as “low grade” PIN has no prognostic relevance. Only “high grade” PIN is associated with an adverse risk of developing prostate cancer. Therefore, HGPIN is now reported simply as ‘PIN’. 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 cancer²⁴. Isolated diagnosis of HG PIN necessitates a repeat biopsy within six months. There is a strong association of previous PIN with cancer²⁵. Men with PIN have been reported to have up to 36% cancer detection rates in subsequent biopsies^{26,27}.

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 disease²⁸. The extent of cancer involvement may be given in percentage of the biopsy core lengths (e.g. > 5%, 10%, 20%, etc).

Appearance 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^{29,30}.

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

Reporting grades of differentiation

It is recommended to use the Gleason scoring system. 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 Epstein³¹ Gleason scores of 2 to 4 to prostatic adenocarcinoma should not be attributed on peripheral zone needle biopsies. It is recommended that 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 biopsies³².

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 irrespective of its extent in the needle biopsy³³. 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 the 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 cytokeratins³⁴⁻³⁸ and to α MeCo racemase³⁹⁻⁴² are principally employed. Antibody 34 β E12 (previously known as “keratin 903” and generated by Gown and Vogel in 1982⁴³ 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.³⁹ occurs in neoplastic prostatic epithelial cells of both luminal and basal types⁴⁴. Both reagents should be used by experienced immunohistochemistry and interpreted with caution by experienced diagnostic pathologists to avoid erroneous interpretation of appearances. 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.

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