

Review

Handling and Pathology Reporting of Prostate Biopsies☆

Liliane Boccon-Gibod^{a,*}, Th. H. van der Kwast^b, Rodolfo Montironi^c,
Laurent Boccon-Gibod^d, Aldo Bono^e

^aDepartment of Pathology, Hopital Armand-Trousseau. AP-HP, Faculté Saint-Antoine, 26 Av. du Dr. Arnold Netter, 75571 Paris, France

^bDepartment of Pathology, Erasmus MC, Rotterdam, The Netherlands

^cInstitute of Pathological Anatomy and Histopathology, School of Medicine, Polytechnic University of the Marche Region, Ancona, Italy

^dDepartment of Urology, Hopital Bichat, AP-HP, Faculté Paris VII, France

^eDivision of Urology, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Accepted 15 April 2004

Available online 3 May 2004

Abstract

Appropriate handling and processing of prostate needle biopsies is critical for an optimal examination by pathologists. Reporting by pathologists should be accurate, unequivocal and concise, giving the information needed for the urologist. Quality parameters need to be developed to survey the performance of pathology laboratories.

© 2004 Published by Elsevier B.V.

Keywords: Prostate cancer; Needle biopsy; Immunohistochemistry; Quality indicators

1. Introduction

Increasing numbers of prostatic needle biopsies are being sent to pathology laboratories, particularly of men lacking specific symptoms of prostate cancers in order to detect prostate cancer at an early stage. Apart from establishing the presence or absence of cancer, prostate biopsies, when positive, provide along with serum PSA and Digital Rectal Examination a wealth of information critical to the staging. Indeed in the absence of an imaging technique showing the actual tumor, quantitative histology [1,2] remains the best way to indirectly evaluate the volume of the tumor, upon which greatly depend treatment decisions. It is obvious that the amount of information expected by the clinician from the pathologist requires proper handling, adequate processing, followed by an accurate evaluation of prostate

biopsies. The aim of this paper is to provide guidelines to the individual pathologist on how to handle prostatic needle biopsies and what to report in order to give optimal information to the urologist. Furthermore, a proposition is made to establish a few quality parameters by which the adequacy of handling prostate biopsies by a given pathology laboratory can be assessed.

2. The role of the urologist

The role of the urologist is to provide (1) adequate clinical information to the pathologist, i.e. patient identification, PSA level and/or reason for biopsy and—if relevant—clinical history, including data on previous diseases of the genito-urinary tract, (2) provide the pathologist with adequate tissue samples for pathologic evaluation, and (3) handle the biopsies in a way that will help the pathologist to identify and map cancer in the prostate. The pathologist can demand from the urologist that he/she meets the above requirements. The minimum number of biopsies that should be taken from an individual man is controversial. It has been repeatedly shown that sextant biopsies are sub optimal and that at least, 10 biopsies, predominantly on

☆ This publication is made under the auspices of the European Society of Uropathology (a full section office member of the European Association of Urology, EAU) and the Uropathology Working Group (European Society of Pathology, ESP).

* Corresponding author. Tel. +33-1-44-73-61-82;

Fax: +33-1-44-73-62-82.

E-mail address: liliane.boccon-gibod@trs.ap-hop-paris.fr
(L. Boccon-Gibod).

the lateral aspect of the prostate, are now state of the art in order to detect a maximum of cancers [3–5]. The biopsies provided by the urologist or—in some institutions by the radiologist—should be of adequate length and quality. A direct correlation between length of prostatic tissue submitted and the detection rate of prostate cancer has been demonstrated in the European Randomized Screening program of Prostate Cancer (ERSPC) [6]. Undoubtedly, the primary responsibility for the number of biopsies taken and the quality of the tissue samples rests with the clinician. In spite of the associated increase in workload, it is strongly recommended that each biopsy is submitted in a separate container to the pathology laboratory on the basis of the following arguments:

- Laterality of the cancer can be important if nerve sparing surgery is considered.
- Presence of uni- or bilateral cancer is a staging parameter.
- Basal or apical cancer localization may modify the surgical technique (e.g. contra-indication to bladder neck sparing surgery).
- Presence of a focus of a suspect lesion can help to redirect part of the repeat biopsies.

For all these reasons, individualization of specimens in single containers is of a benefit that outweighs the costs associated with increased workload for the pathology laboratory, even if the number of biopsies is increased from sextant biopsy procedure to 10 or 12.

Each biopsy should be delivered and embedded separately after flattening the cores between nylon sponges (Fig. 1) or a paper. If flattening is not achieved as shown, some segments of prostatic tissues may not be seen on slides and will not be accessible to pathologic evaluation. The higher the number of biopsies included in one cassette, the more likely that the

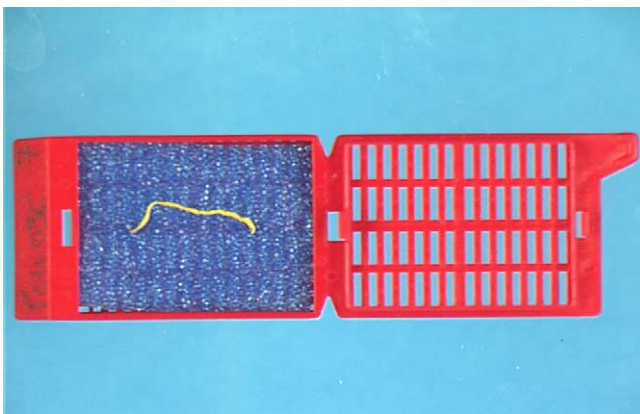


Fig. 1. Embedding of a needle biopsy using nylon sponges in order to flatten the tissue sample.



Fig. 2. At the left side, entanglement of multiple biopsies embedded in a single cassette, while at the right side a single biopsy is embedded after flattening.

entanglement of biopsies leads to loss of tissue for a complete pathologic evaluation (Fig. 2). It has recently been shown that simultaneous inclusion of 3 biopsies in the same cassette can lead to the loss of a mean length of 1.15 cm of assessable tissue which corresponds to the average length of one prostate biopsy [7].

Although in many hospitals in France, Austria, Italy, etc, the urologist (or radiologist) puts the biopsies directly in the tissue cassettes, this may also be done in the pathology laboratory. The advantages of immediate embedding by the urologists or radiologists are: avoidance of a (useless) transfer from containers into cassettes and reduction of the possibility of attribution errors [8].

An interesting and maybe cheaper alternative to separate embedding of needle biopsies in multiple cassettes has recently been proposed: the use of a multi-compartment micro-cassette [9]. Evaluation of this technique by other centres should be of interest.

3. The role of the pathologist

The pathology report of prostate needle biopsies has to be concise, and it should use unequivocal terms [6]. The following prostate needle biopsy diagnoses are described below in detail:

- (1) prostatic adenocarcinoma;
- (2) focus suspicious for cancer (synonyms: (a) atypical small acinar proliferation suspect for malignancy, (b) biopsy suspect for malignancy);

- the acronym ASAP, which is not a diagnosis in itself should be prohibited;
- (3) isolated high grade prostatic intra-epithelial neoplasia;
 - (4) no malignancy detected.

3.1. Prostatic adenocarcinoma

If prostatic adenocarcinoma has been diagnosed the pathology report should include the following items:

- length of each biopsy and involvement of biopsy by cancer in millimetres,
- the Gleason grade(s) and if present, the extent in mm of the high grade (Gleason 4 or 5) component,
- number of biopsy cores positive for cancer,
- the location (and/or mapping) of positive biopsies in the prostate when submitted in separate containers,
- the presence of any tumour in the peri-prostatic fatty tissue,
- the presence of tumoral extension in peri-neural sheaths either intra- or extra-prostatic, while also the approximate calibre of nerve fibres may be recorded.

The above list of biopsy parameters largely follows the recommendation by the College of American Pathologists [10] and by the French Association of Urology [11].

The quantitative data on involvement of the biopsies by cancer will easily allow the determination of the ratio of the total length of cancer to the total length of biopsies. The measurement of the amount of cancer in mm is considered a better parameter than its quantitation in percentage of cancer as it is less precise. The percentage of cancer can in fact always be easily calculated later. The importance of quantitative histopathology in reporting prostate biopsies has been emphasized by many authors [2,5,12,13]. The length of the cancer which usually is in direct relationship with tumour volume in the prostate and Gleason score is probably the most important feature on multivariate analysis [11–13]. All above-mentioned parameters are extremely useful as several studies have shown that the prostate biopsy features are an essential part of clinical staging: in the absence of any imaging tool able to document the tumor volume, and its relationship with surrounding structures, biopsy features give an indirect evaluation on tumour volume and therefore on the stage of the disease. Furthermore, the presence of carcinoma in the peri-prostatic tissue visible on the biopsies is diagnostic of extra-prostatic extension or stage pT3. Synthesis of all these information can be transmitted as a short written summary or on a synoptic report with use of a template. The reports could be

standardized from one pathology department to the other, thus helping to check the presence of all important parameters on each report.

The use of the Gleason score is mandatory: The community of urologists and uropathologists agrees that the Gleason grading and scoring system is the international standard, being most clearly related to prognosis. It was reported that among biopsies with Gleason score 7 those with dominant Gleason pattern 4 (4 + 3) indicate the presence of more adverse pathological findings compared to those with Gleason score 7 with a smaller pattern 4 component (3 + 4) [14]. Consequently, when reporting a Gleason score of 7, the pathologists should make a clear distinction between Gleason scores of 7 (3 + 4 versus 4 + 3).

At the other end of the spectrum, it has now been agreed that it was not possible to report a Gleason score 2 to 4 on peripheral zone prostate biopsies, implying that the minimum Gleason score that should be reported is 5 [15].

Several prognostic markers have been described in the literature: p53, Bcl-2, Ki-67, p27, CD44, etc.; none of these markers used on biopsy material have ever been shown to have an independent prognostic value on multivariate analysis. Therefore, their use should be restricted to research protocols; using them in routine clinical practice is a waste of time and money.

3.2. Focus suspicious for malignancy

If a lesion is detected which does not meet the criteria for a definite diagnosis of adenocarcinoma or for high grade prostatic intra-epithelial neoplasia the pathologists should avoid two unwanted situations:

- over-diagnosis of cancer leading to major treatment procedures with potentially devastating side effects,
- under-diagnosis of cancer leading to a delay in the treatment of a potentially lethal condition.

First of all, pathologists should be able to report such a lesion as suspect for but not definite cancer. Since such a diagnosis generally leads to a repeat biopsy the frequency of this diagnosis should be limited as much as possible. In order to do so several procedures can be followed:

- (1) intra-departmental consultations with a specialist in urogenital pathology,
- (2) immunohistochemistry using basal cell markers, e.g. high molecular weight keratins and/or p63 and p504S.

A recent study looking at 16,000 biopsies pooled from non-specialized laboratories has shown that the best way to reduce the percentage of “suspicious

focus” (7% in the study), were intra- and extra-departmental consultation and the use of immunohistochemistry (high molecular weight cytokeratin) which drastically reduced the percentage of suspicious cases from 7 to 2.1% [16]. More recently, the marker racemase (p504S) has been described which might be useful for a positive identification of prostate cancer or HG-PIN in combination with microscopic findings, although its results are not superior to immunohistochemistry with high molecular weight keratins [17]. Some authors reported good results with a combination of the nuclear basal cell marker p63 and the cytoplasmic marker for neoplasia, racemase [18].

From a practical standpoint, it is of the utmost importance that the suspicious focus is indeed present in the slides studied by immunohistochemistry. The best way to achieve this result is from start to cut a series of 3 slides (with different levels), to submit slides 1 and 3 to standard staining and to keep a reserve slide of level 2 for immunohistochemistry. The increase in cost due do additional slides can be by-passed by storing ribbons of unstained levels until standard stains are examined. Even, if this procedure leads to a small increase in costs as far as slides and technician time are concerned, there is a definite benefit in that there is no need to recut new sections, no delay in pathology report, and furthermore, a less frequent disappearance of the suspicious focus on subsequent pathology sections. Provided immunohistochemistry is interpreted with the surrounding benign glands as an internal control and confronted to the aspect of the suspicious focus in routine pathological staining, the diagnostic yield of this technique is highly significant. However, doubt may still remain and the pathology report should mention in the conclusion in unequivocal terms the presence of a lesion suspicious for cancer. Depending on where the first biopsy has been interpreted, if the diagnosis “lesion suspicious for cancer” is made, repeat biopsies can find a cancer in up to 40% of the cases [19]. Although for this reason the diagnosis “suspicious for cancer” will generally be followed by a (set of) repeat biopsies, the final decision to perform a repeat biopsy procedure depends upon the urologist. The frequency of lesions suspicious for cancer in needle biopsies may be employed as a quality indicator of a given pathology laboratory. It may for instance be considered that the proportion of suspicious cases should not exceed 3% of biopsies in any good pathology department.

3.3. High grade prostatic intra-epithelial neoplasia

A diagnosis of isolated high grade prostatic intra-epithelial neoplasia (HG-PIN) should only be rendered

if cells with a luminal phenotype and dysplastic features are detected within a pre-existing gland. The diagnosis of HG-PIN should be separated from lesions suspicious for malignancy, since in most series the likelihood to detect an adenocarcinoma in a subsequent biopsy is considerably lower after an initial diagnosis of HG-PIN as compared to lesion suspicious for cancer. In about 15–25% of the patients harbouring HG-PIN on an initial series of biopsy prostate cancer may be present on a subsequent biopsy, [19,20]. Atypical hyperplasia (or adenosis) is not to be mentioned, as their pre-neoplastic nature has not been demonstrated and reporting them can cause confusion to the urologist.

3.4. No malignancy

The following information should be given by the pathologist if no cancer, H-PIN nor lesions suspicious for cancer have been documented on the biopsy:

- (1) The total length of prostatic tissue submitted to evaluation. There should be at least 10 mm of prostatic tissue evaluable per biopsy. Below average length, the biopsies should be considered inadequate which may suggest a repeat biopsy.
- (2) The presence of inflammatory lesions suggestive of prostatitis should be documented as they may be associated with an elevation of serum PSA. This holds particularly true for granulomatous inflammation. Since in most prostate needle biopsies some lymphocytic infiltrates are present, the term prostatitis should be reserved for those cases where damage to prostatic glands by inflammatory cells or luminal granulocytes can be seen. It should be noted that upon careful review of needle biopsies initially diagnosed as “no malignancy”, in up to 10% of cases a potentially malignant lesion can be detected [21–23].

PROPOSED SET OF QUALITY INDICATORS OF PROSTATIC NEEDLE BIOPSIES

- Average length of prostatic needle biopsies measured on glass slide >10 mm
- Frequency of lesions suspect for malignancy less than 3% (good) or less than 5% (fair)
- Less than 3% false negative diagnoses of prostate cancer after review

Acknowledgements

This paper is one of the seven dedicated to standardization of handling and pathology reporting in

uropathology. The additional six deal with adrenal gland, kidney, bladder, radical prostatectomy, testis and penis.

It is based on the Uropathology Workshop held in Sesto Fiorentino (Ely Lilly Italia Headquarter), Florence, Italy, June 15, 2003.

References

- [1] Graefen M, Karakiewicz PI, Cagiannos I, Quinn DI, Henshall SM, Grygiel JJ, et al. International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2002;20:3206–12.
- [2] Lewis JS, Vollmer RT, Humphrey PA. Carcinoma extent in prostate needle biopsy tissue in the prediction of whole gland tumour volume in a screening population. *Am J Clin Pathol* 2002;118:442–50.
- [3] Ravery V, Moulinier F, Blanc E, Toublanc M, Delmas V, Boccon-Gibod L. Diagnostic improvement of prostate cancer using an extensive biopsy protocol. *Prostate Cancer Prostatic Dis* 1999;2:S28.
- [4] Peyromaure M, Ravery V, Messas A, Toublanc M, Boccon-Gibod L, Boccon-Gibod L. Pain and morbidity of an extensive prostate 10-biopsy protocol: a prospective study in 289 patients. *J Urol* 2002;167:218–21.
- [5] Presti JC. Prostate biopsy: how many cores are enough? *Urol Oncology* 2003;21:135–40.
- [6] Van Der Kwast TH, Lopes C, Santonja C, Pihl CG, Neetens I, Martikainen P, et al. Guidelines for processing and reporting of prostatic needle biopsies. *J Clin Pathol* 2003;56:336–40.
- [7] Yfantis HG, Loffe OB, Silverberg SG. Prostate Core Biopsies Processing: Evaluating Current Practice. USCAP annual meeting, Chicago, 2002, p 347 A., Abstract 1447.
- [8] Rogatsch H, Moser P, Volgger H, Horninge W, Bartsch G, Mikuz G, et al. Diagnostic effect of an improved preembedding method of prostate needle biopsy specimens. *Hum Pathol* 2000;31:1102–7.
- [9] Laniado ME, Mc Mullen I, Walker MN, Patel NA. Use and rationale of a multicompartiment microcassette for site-specific biopsies of the prostate in a consecutive cohort of men. *Prostate Cancer Prostatic Dis* 2003;6:50–2.
- [10] ftp://ftp.cap.org/cancerprotocols/prostate03_p.doc.
- [11] Molinie V, Vieillefond A, Cochand-Priollet B, Dauge-Geffroy MC, Lefrere-Belda MA, de Fromont M, et al. Recommandations pratiques pour les prélèvements prostatiques. *Ann Pathol* 1999;19:549–56.
- [12] Ravery V, Chastang C, Toublanc M, Boccon-Gibod L, Delmas V, Boccon-Gibod L. Percentage of cancer on biopsy cores accurately predicts extracapsular extension and biochemical relapse after radical prostatectomy for T1-T2 prostate cancer. *Eur Urol* 2000;37:449–55.
- [13] Srigley JR, Amin MB, Bostwick DG, Grignon DJ, Hammond ME. Updated protocol for the examination of specimens from patients with carcinomas of the prostate gland: a basis for checklists. *Arch Pathol Lab Med* 2000;124:1034–9.
- [14] Makarov DV, Sanderson H, Partin AW, Epstein JI. Gleason grade 7 prostate cancer on needle biopsy: is the prognostic difference in Gleason score 4 + 3 and 3 + 4 independent of the number of involved cores. *J Urol* 2002;167:2440–2.
- [15] Epstein JI. Gleason score 2–4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. *Am J Surg Pathol* 2000;24:477–8.
- [16] Novis DA, Zarbo RJ, Valenstein PA. Diagnostic uncertainty expressed in prostate needle biopsies. A College of American Pathologists Q-probes. Study of 15,753 prostate needle biopsies in 332 institutions. *Arch Path Lab Med* 1999;123:687–92.
- [17] Beach R, Gown AM, De Peralta-Venturina MN, Folpe AL, Yaziji H, Salles PG, et al. P504S immunohistochemical detection in 405 prostatic specimens including 376 18-gauge needle biopsies. *Am J Surg Pathol* 2002;26:1588–96.
- [18] Luo J, Zha S, Gage WR, Dunn TA, Hicks JL, Bennett CJ, et al. Alpha-methylacyl-CoA racemase: a new molecular marker for prostate cancer. *Cancer Res* 2002;62:2220–6.
- [19] Vis AN, Van Der Kwast TH. Prostatic intraepithelial neoplasia and putative precursor lesions of prostate cancer: a clinical perspective. *BJU Int* 2001;88:147–57.
- [20] Kronz JD, Allan CH, Shaikh AA, Epstein JI. Predicting cancer following a diagnosis of high-grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow-up biopsy. *Am J Surg Pathol* 2001;25:1079–85.
- [21] Kronz JD, Milord R, Wilentz R, Weir EG, Schreiner SR, Epstein JI. Lesions missed on prostate biopsies in cases sent in for consultation. *Prostate* 2003;54:310–4.
- [22] Van der Kwast TH, Lopes C, Martikainen PM, Pihl C-G, Santonja C, Neetens I, et al. Report of the pathology committee: false positive and false negative diagnoses of prostate cancer. *BJUI Supplement* 2003;92:62–5.
- [23] Montironi R, Mazzucchelli R, Scattoni V, Bostwick DG. Pathological findings in TRUS prostatic biopsy. Diagnostic, prognostic and therapeutic importance. *Eur Urol Suppl* 2002;1(6):60–75.