



## Review - Prostate Cancer

# 2005 Update on Pathology of Prostate Biopsies with Cancer<sup>☆</sup>

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### Abstract

**Objective:** To review the diagnostic and prognostic importance of pathologic findings in prostate biopsies.

**Materials and Results:** While the primary goal of the biopsy is to diagnose prostatic adenocarcinoma, once carcinoma is detected, information regarding the type, amount, and grade of cancer forms the cornerstone for contemporary management of the patient and for assessment of the potential for local cure and the risk for distant metastasis.

**Conclusions:** The novelty of this 2005 update is represented by a detailed morphologic and immunohistochemical description of prostatic adenocarcinoma features in biopsies.

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## 1. Introduction

Needle biopsy of the prostate plays a central role in the morphologic evaluation of prostatic adenocarcinoma [1–4]. The pathology report of a biopsy with cancer should include a number of morphologic features to help urologists assess the risk of extraprostatic disease and progression: cancer location, extent and volume of cancer in each specimen, and Gleason score; optional features that may add predictive value include perineural invasion and vascular/lymphatic invasion.

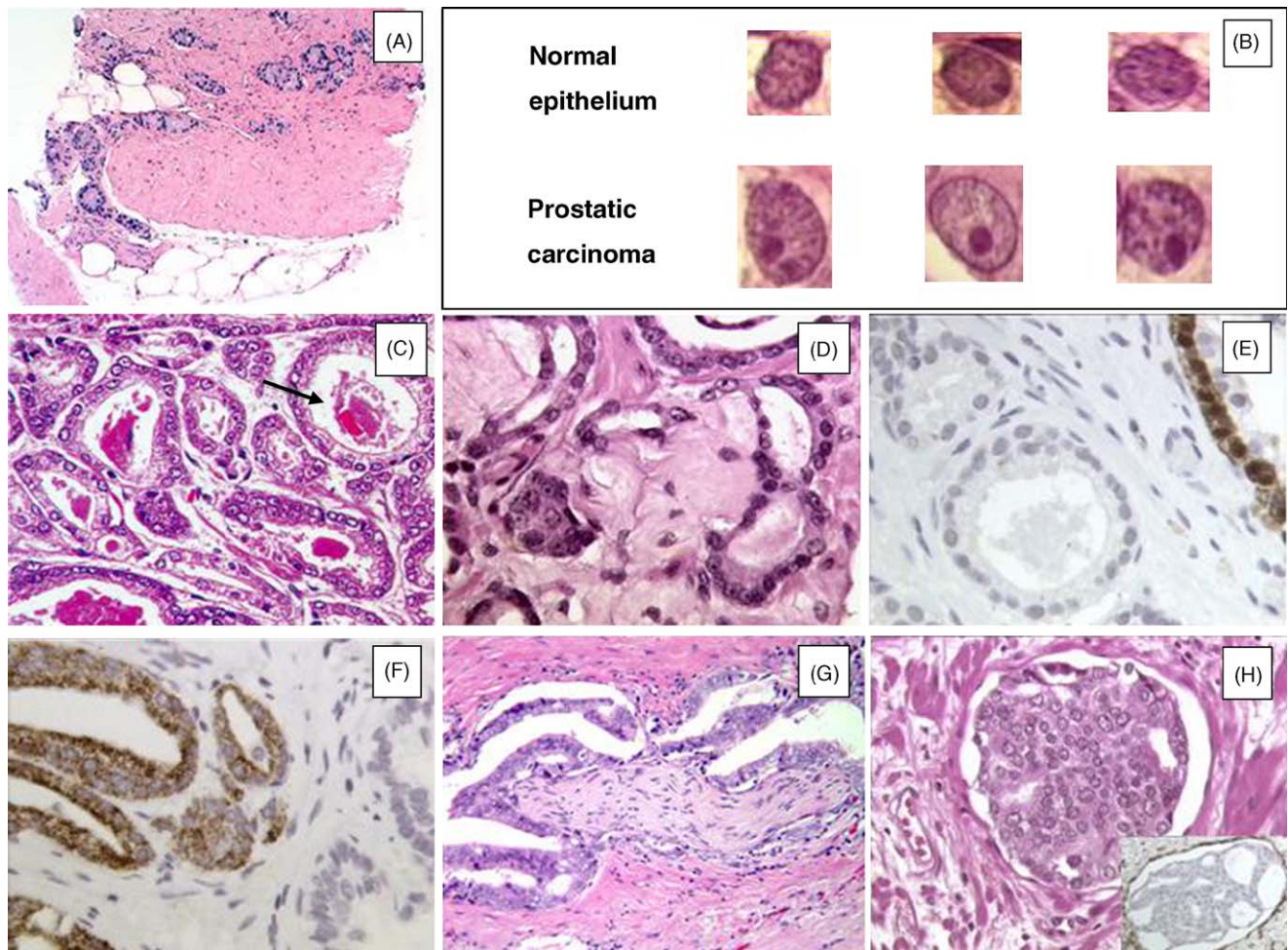
This report specifically focuses on pathologic findings of prostate biopsies with cancer. It is

beyond the scope of this review to deal with specific features of atypical small acinar proliferations that are suspicious for cancer, including the minimal requirement to make a definitive diagnosis of cancer. The reader is referred to comprehensive reviews recently published [1–4].

## 2. Diagnosis

### 2.1. Architecture

Architectural features are assessed at low to medium magnification, with emphasis on spacing,



**Fig. 1 - (A)** Biopsy with cancer: acini with an irregular, haphazard arrangement, randomly scattered in the stroma. Extraprostatic extension is present. **(B)** The cytologic features of adenocarcinoma include nuclear and nucleolar enlargement (nuclei from normal are shown). **(C)** Cancer with crystalloid (arrow). **(D)** Collagenous micronodules. **(E)** Cancer lacks basal cells (a non-neoplastic duct with basal cells) (cocktail 34betaE12 and p63). **(F)** Cancer with racemase expression (non-neoplastic duct without racemase). **(G)** Perineural invasion. **(H)** Lymphovascular invasion (insert: CD34 immunostain).

size, and shape of acini. The arrangement of the acini is useful diagnostically and is the basis of the Gleason grade. Malignant acini have an irregular, haphazard arrangement, randomly scattered in the stroma in clusters or singly (Fig. 1A). The spacing between malignant acini varies widely. Variation in acinar size is a useful criterion for cancer.

The acini in suspicious foci are in general small or medium sized, with irregular contours that contrast with the typical smooth, round to elongated contours of benign acini. Comparison with the adjacent benign prostatic acini is of value in cancer diagnosis. Well-differentiated carcinoma and the large acinar variant of Gleason grade 3 carcinoma are difficult to separate from benign acini in needle biopsies because of the uniform size and spacing of acini;

in such cases, greater emphasis is placed on cytologic features, immunohistochemical findings, and the presence of smaller diagnostic acini at the edge of the focus. Retraction clefts surrounding the carcinoma glands often are encountered in cancer.

The basal cell layer is absent in prostatic adenocarcinoma (PCa), whereas an intact basal cell layer is present in benign acini. This is an important diagnostic feature that is not easy to evaluate in routine tissue sections owing to false-negative findings with atrophy and other mimics of cancer. Fibroblasts may mimic basal cells but are seen only focally at the periphery of acini. Small foci of adenocarcinoma sometimes cluster around larger benign acini that have an intact basal cell layer.

## 2.2. Cytology

The cytologic features include nuclear and nucleolar enlargement, which occur in most malignant cells (Fig. 1B). Every cell has a nucleolus, so “prominent” nucleoli (at least 1.50  $\mu\text{m}$  in diameter) are sought. This determination is based on comparison with benign epithelial cells.

Artifacts obscure the nuclei and nucleoli, and overstaining of nuclei by hematoxylin creates one of the most difficult problems in the interpretation of suspicious cells. Differences in fixation and handling of specimens influence nuclear size and chromasia, so comparison with cells from the same specimen is useful as an internal control. Many pathologists prefer pale staining with eosin, but this approach fails to accentuate nucleoli. In specimens with nuclear hyperchromasia and pale eosinophilic staining, we increase the light source and magnification of suggestive foci to identify hidden nucleoli.

## 2.3. Lumens

Crystalloids are sharp, needle-like eosinophilic structures present in the lumens of well-differentiated and moderately differentiated carcinoma (Fig. 1C) [5]. They are not specific for carcinoma. Hard, proteinaceous secretions are present in adjacent acini and are probably the source of the crystalloids.

Luminal acidic sulfated and nonsulfated mucin often is seen, appearing as amorphous or delicate, threadlike, faintly basophilic secretions in routine sections. This mucin stains with Alcian blue, whereas normal prostatic epithelium contains periodic acid Schiff-reactive mucin that is neutral. Acidic mucin is not specific for carcinoma; it may be found in prostatic intraepithelial neoplasia (PIN), atypical adenomatous hyperplasia (AAH), sclerosing adenosis, and benign prostatic hyperplasia (BPH) [5].

## 2.4. Stroma

The stroma in cancer frequently contains young collagen, which appears lightly eosinophilic, although desmoplasia may be prominent. Muscle fibers in the stroma are sometimes split.

Collagenous micronodules (mucinous fibroplasia) are a specific but infrequent finding in PCa. They consist of microscopic nodular masses of paucicellular eosinophilic fibrillar stroma that impinge on acinar lumens (Fig. 1D). They are present in mucin-producing adenocarcinoma and result from extravasation of mucin into the stroma. Collagenous micronodules are present in about 13% of adeno-

carcinomas; they are not observed in benign epithelium, BPH, or PIN.

## 2.5. Immunohistochemistry

Expression of prostate-specific antigen (PSA) is useful for distinguishing high-grade PCa from urothelial carcinoma, colonic carcinoma, granulomatous prostatitis, and lymphoma [5]. PSA is helpful in distinguishing prostatic adenocarcinomas from other neoplasms secondarily involving the prostate and in establishing prostatic origin in metastatic carcinomas of unknown primary. PSA also is helpful in excluding benign mimics of prostatic carcinoma, such as seminal vesicle/ejaculatory duct epithelium, nephrogenic adenoma, mesonephric duct remnants, Cowper's glands, granulomatous prostatitis, and malakoplakia. Prostatic acid phosphatase is a valuable marker in combination with PSA.

Using antibodies against high molecular weight cytokeratin (34 $\beta$ E12) may be useful for evaluation of the basal cells. We use this in fewer than 5% of cases. The findings with this immunohistochemical stain should not be the basis for a diagnosis of malignancy, particularly in small suggestive foci. The stain is most useful in confirming the benignancy of a suggestive focus by showing an immunoreactive basal cell layer.

Since uniform absence of a basal cell layer in acinar proliferations is one important diagnostic feature of PCa and basal cells may not be apparent by hematoxylin and eosin stain, basal cell-specific immunostains may help to distinguish PCa from benign small acinar cancer-mimics that retain their basal cell layer (eg, glandular atrophy, post-atrophic hyperplasia, AAH, sclerosing adenosis and radiation induced atypia) [5]. Because the basal cell layer may be not demonstrable in small numbers of benign glands, the complete absence of a basal cell layer in a small focus of acini cannot be used alone as a definitive criterion for malignancy; rather, absence of a basal cell layer is supportive of carcinoma only in acinar proliferations that exhibit suspicious cytologic and/or architectural features on hematoxylin and eosin stain. Conversely, some early invasive prostatic adenocarcinomas (eg, microinvasive carcinomas arising in association with or independent of high-grade PIN) may have residual basal cells [6]. Intraductal spread of PCa and entrapped benign glands are other proposed explanations for residual basal cells [5,6].

p63 is a nuclear protein encoded by a gene on chromosome 3q27–29 with homology to p53. Specific isoforms are expressed in basal cells of stratified/pseudostratified epithelia, reserve cells of simple columnar epithelia, and myoepithelial cells [6].

An antibody is active in paraffin-embedded tissue. p63 has similar applications to those of high molecular weight cytokeratins in the diagnosis of PCa, with the advantages that p63

- stains a subset of 34 $\beta$ E12 negative basal cells.
- is less susceptible to the staining variability of 34 $\beta$ E12.
- is easier to interpret because of its strong nuclear staining intensity.

Interpretative limitations related to presence or absence of basal cells in small numbers of glands for 34 $\beta$ E12 apply to p63 [6]. A cocktail containing antibodies to 34 $\beta$ E12 and p63 is an effective basal cell stain (Fig. 1E).

$\alpha$ -Methyl-CoA racemase (AMACR) mRNA is over-expressed in PCa [7]. This mRNA encodes a protein. Studies on biopsy material with an antibody directed against the AMACR (P504S) protein demonstrate that greater than 80% of PCAs are labeled. Subtypes of PCa, such as foamy gland carcinoma, atrophic carcinoma, pseudohyperplastic, and treated carcinoma, show lower expression. AMACR is not specific for PCa and is present in BPH (12%), atrophic glands (36%), high-grade PIN (>90%), and AAH (17.5%). AMACR is used as a confirmatory stain for PCa, in conjunction with morphology and a basal cell-specific marker (Fig. 1F).

Approximately 30% of the foci suspicious for cancer can be diagnosed correctly when AMACR immunohistochemistry is applied. Foci suspicious for cancer can greatly benefit from using an immunoperoxidase cocktail containing monoclonal antibodies to AMACR and p63 [2]. From a practical standpoint, it is important that the suspicious focus is indeed present in the slides studied by immunohistochemistry. The best way to achieve this result is, from the beginning, to cut a series of 3 slides (with different levels), to submit slides 1 and 3 to standard staining, and keep a reserve slide of level 2 for immunohistochemistry [2].

### 3. Prognosis

#### 3.1. Site of sampling

Knowing the location of the biopsy and the cancer is important in the following processes [1-4]:

- *Correlation with digital rectal examination and imaging studies.*
- *Prognosis.* Tumor involvement of base biopsies may influence bladder neck-sparing radical

prostatectomy (RP); extensive cancer in base biopsies correlates with extraprostatic extension (EPE); and dominant side of prostate biopsy correlates with ipsilateral positivity of surgical margins and EPE.

- *Planning of therapy.* Mapping distribution of the cancer in biopsies may help plan the field of radiation therapy or may influence nerve-sparing or bladder neck-sparing during RP.
- *Subsequent sampling.* In a patient with atypical small acinar proliferations, knowledge of the site allows for more-focused repeat biopsies.
- *Subsequent prostate gland sampling.* Knowledge of cancer location may help target additional tissue sampling in cases with no apparent cancer in RP sections.
- *Recognition of potential pitfalls.* Pitfalls include seminal vesicle epithelium or central zone epithelium, seen most frequently in base biopsies and the Cowper's glands in apex biopsies.

#### 3.2. Histologic type

Greater than 99% of prostate carcinomas seen in biopsies are referred to as "acinar," "microacinar," or "conventional type." It is not necessary to specify such cancers as acinar or conventional type.

PCa with architectural or cytologic variations, such as atrophic, pseudohyperplastic, hypernephroid, are descriptive terms used to describe variations in PCa to help pathologists recognize diagnostic pitfalls, but the terms have no known prognostic significance. They may be commented upon in a microscopic description and do not deserve specific mention in the final diagnosis.

Several variants have been described, including ductal, mucinous, signet ring cell, adenosquamous, small-cell carcinoma, and sarcomatoid carcinoma [5]. The first three variants are diagnoses tenable on examination of RP or transurethral resection specimens. If seen in biopsies, the diagnostic terminology used must be: "PCa with ductal features," "PCa with signet ring cell features," and "PCa with mucinous differentiation." Small-cell carcinoma, sarcomatoid carcinoma, and adenosquamous carcinoma may be diagnosed on biopsies. No formal studies have demonstrated that the presence of these variants in biopsies is of prognostic importance, although the aggressive outcome associated with such tumors suggests the value of this exercise [1].

#### 3.3. Cancer grade

The Gleason score (GS) is a scalar measurement that combines primary and secondary patterns (grades)

into nine groups (scores 2–10). GS should be reported as the composite score and its components (Gleason 7 = 4 + 3). The method of reporting in biopsies has been addressed recently [1,8–10].

- *General applications.* A GS of 1 + 1 = 2 is a score that should not be diagnosed regardless of the type of specimen, with extremely rare exception. The diagnosis of Gleason 2–4 should not be made on biopsies. The reasons for not making this diagnosis are compelling: GS 2–4 cancer is extraordinarily rare in biopsies, compared with transurethral resection specimens; there is poor reproducibility among experts for lower-grade tumors; the correlation with the prostatectomy score for Gleason 2–4 tumors is poor; a “low” GS may misguide clinicians into believing that there is an indolent tumor. “Individual cells” would not be allowed within Gleason pattern 3. The vast majority of cribriform patterns are diagnosed as Gleason pattern 4, with rare cribriform lesions satisfying criteria for pattern 3C.
- *Grading variations of acinar adenocarcinoma.* One should grade the tumor on the basis of the underlying architecture.
- *Grading variants of adenocarcinoma.* Ductal adenocarcinomas should be graded as GS 4 + 4 = 8, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathologic findings. There is no consensus on the way colloid (mucinous) carcinoma should be scored. Some authors think that all colloid carcinomas should be assigned a GS of 8, while others say that one should ignore the extracellular mucin and grade the tumor on the basis of the underlying architectural pattern. Small-cell carcinoma should not be assigned a Gleason grade.
- *Reporting secondary patterns of lower grade when present to a limited extent.* In the setting of high-grade cancer, one should ignore lower-grade patterns if they occupy less than 5% of the tumor area.
- *Reporting secondary patterns of higher grade when present to a limited extent.* High-grade tumor of any quantity, as long as it was identified at low to medium magnification, should be included within the GS.
- *Tertiary Gleason patterns.* The typical situation includes tumors with patterns 3, 4, and 5 in various proportions. Such tumors should be classified overall as high grade (GS 8–10) given the presence of high-grade tumour (patterns 4 and 5) on biopsy. On biopsies with patterns 3, 4, and 5, both the primary pattern and the highest grade

should be recorded. For an RP, specimen one assigns the GS on the basis of the primary and secondary patterns with a comment as to the tertiary pattern.

- *Percentage of Gleason 4 pattern in GS 7 tumors.* In recently generated nomograms, patients with GS 4 + 3 versus 3 + 4 are stratified differently, underscoring the importance of the relative amount of pattern 4.
- *Percentage of patterns 4 and 5.* Whether the actual percentage of 4 pattern tumor should be included in the report is not clear, and meaningful discriminatory cutoff points for percentage of pattern 4 need to be defined. Whether one wants to include this information in addition to the routine GS is optional.
- *Biopsy with different cores showing different grades.* The pathologist should assign individual Gleason scores to separate cores as long as the cores are submitted in separate containers or the cores are in the same container yet specified by the urologist as to their location (by different color inks). One has the option to give an overall score. If more than one core contained cancer in the setting of multiple cores per container, some authors think that each core should still be graded separately, while others say that one should give an overall grade for the involved cores per specimen container. In cases in which a container contains multiple cores and one cannot be sure if an intact core is being viewed, only an overall score should be given for that container.
- *Other grading systems.* In addition to the GS, another grading system may be used according to institutional preference (eg, World Health Organization; The University of Texas M.D. Anderson Cancer Center, Houston, Texas). The use of an alternative system is discouraged, but, if used, the system must include the GS to facilitate comparison of data.

### 3.4. Extent of involvement

The extent of involvement of needle cores by PCa has been shown to correlate with the GS, tumor volume, surgical margins status, and pathologic stage in RP specimens [1,2]. The extent of core involvement, including bilateral involvement, has been shown to predict biochemical recurrence, postprostatectomy progression, and radiation therapy failure. It is a parameter included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and radiation therapy failure [11–13].

The report should provide the number of involved cores. In addition, one or both of the following methods of tumor extent should be applied:

- linear length of cancer in mm (total tumor length in all biopsies; longest single length of tumor)
- percentage estimate of involvement of each of the cores derived by visual estimation (overall percentage of cancer in all biopsies, percentage of each core involved) [1,14].

The correlation is with greater involvement of the cores. Low tumor burden in biopsies is not necessarily an indicator of low-volume and low-stage cancer in RP.

One problem encountered with this otherwise straightforward method is when a specimen is fragmented, making assessment of the number of cores and the percentage of cancer within each core difficult. This problem may be overcome by providing a composite percentage of involvement of cancer in all biopsy tissue. This method may be a slightly more accurate correlate of the amount of cancer in the prostate gland.

Bilateral cancer, which indicates multifocality, is indirectly suggestive of greater tumor volume. This parameter is easily deduced from the pathology report findings of each of the cores submitted.

### 3.5. Local invasion

Routine biopsy sampling occasionally may contain extraprostatic fat or seminal vesicle tissue. If cancer is noted in these structures, the finding would indicate pT3 disease. (Incidentally, there is no pT1c category when cancer is seen in a biopsy in patients with elevated PSA). The presence of seminal vesicle invasion or extraprostatic fat involvement in the staging biopsy is highly correlative of similar findings at radical prostatectomies. Extraprostatic fat invasion (Fig. 1A) at biopsy is highly predictive of biochemical recurrence.

Rarely is fat present within the normal prostate. Hence, tumor in adipose tissue in a biopsy specimen can be interpreted safely as EPE [1,2]. Ganglion cell and skeletal muscle involvement by tumor is not equivalent to EPE as they may be found within the prostate.

Distinction between the seminal vesicle epithelium and ejaculatory duct epithelium may be impossible in limited samples, although occasionally the seminal vesicle can be distinguished if its smooth muscle wall is present. In contrast, ejaculatory duct epithelium has a rim of fibrous tissue rich in thin blood vessels. If the distinction between

seminal vesicle tissue/ejaculatory duct is not feasible, diagnostic terminology such as "adenocarcinoma of the prostate with invasion of seminal vesicle/ejaculatory duct tissue" may be used.

In biopsies targeting seminal vesicles or extraprostatic fat, it is important to not only diagnose cancer but also to determine whether the targeted tissue is represented. In a positive biopsy, if the intended tissue is not present and its absence is not specified in the report, an erroneous interpretation of presence of locally advanced disease is highly likely.

### 3.6. Perineural invasion

Perineural, circumferential or intraneural invasion (PI) is defined as the presence of PCa juxtaposed intimately along, around, or within a nerve (Fig. 1G). Other descriptors of PI that may strengthen the prognostic significance of this parameter include extensive (multifocal) PI and greater nerve diameter [1]. Involvement of nerves present within adipose tissue (extraprostatic nerves) by cancer indicates EPE.

Although perineural invasion in biopsies is not an independent predictor of prognosis when the GS, serum PSA, and extent of cancer are factored in, most studies indicate that its presence correlates with EPE (38–93%) [15,16]. Recent data suggest that this finding may independently predict lymph node metastasis and postsurgical progression. This parameter may be used to plan nerve-sparing surgery [1]. Data from radiation oncology literature suggest that it is an independent risk factor for predicting adverse outcome after external beam radiation therapy and in patients with high GS and PI in whom adjuvant hormonal therapy or dose escalation has been advocated.

### 3.7. Lymphovascular invasion

Microvascular invasion consists of tumor cells within endothelial-lined spaces. We do not differentiate between vascular and lymphatic channels because of the difficulty [17]. Immunohistochemical stains directed against endothelial cells, such as CD34, increase the detection. Since lymphovascular invasion (Fig. 1H) in RPs correlates with lymph node metastasis, biochemical recurrence, and distant metastasis, its presence in the biopsy is likely to have similar correlations [1].

## 4. Conclusions

While the primary goal of the biopsy is to diagnose PCa, once carcinoma is detected, further informa-

tion regarding the type, amount of cancer, and grade forms the cornerstone for contemporary patient management and assessment of the potential for local cure and the risk for distant metastasis. The information regarding the attributes of the carcinoma is used to determine whether any form of treatment is indicated and, if so, the type of therapy.

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