Evaluating Prostate Needle Biopsy: Therapeutic and Prognostic Importance

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Introduction

Early detection of prostate cancer is an enormous public health issue, accounting for more than 1 million biopsy and surgical specimens annually in the United States. The incidence of prostate cancer has tripled during the past decade, chiefly because of the widespread use of serum prostate-specific antigen (PSA) testing and digital rectal examination, which has created a massive diagnostic and therapeutic burden for physicians.

This burden is compounded by several factors that have increased the difficulty in interpretation of prostate needle biopsy. First, contemporary 18-gauge needle biopsy cores are much narrower than traditional 14-gauge biopsy cores.

Second, many patients now undergo biopsy because they have elevated serum PSA levels but no other clinical evidence of cancer. The result is a great many biopsies that often contain only a small suspicious focus.

Third, numerous diagnostic pitfalls and mimics of prostate cancer have recently been described or refined, including atypical adenomatous hyperplasia, postatrophic hyperplasia, and prostatic intraepithelial neoplasia. The large number of prostate biopsy specimens being generated magnifies the possibility that a rare or unusual lesion will be seen and that small foci will be misinterpreted.

Finally, sextant biopsies (three from each side) have largely replaced the single bilateral cores of a decade ago, so that several specimens are obtained from each patient.

This report reviews the therapeutic and prognostic importance of prostate needle biopsy. Emphasis is placed on clinical biopsy strategies, biopsy handling and reporting of diagnostic results, predictive factors obtained from biopsies, clinical information that can be used to predict pathologic stage and cancer progression, and clinical nomograms for predicting stage and outcome based on biopsy findings.

Clinical Biopsy Strategies

The introduction of the automatic, spring-driven, 18-gauge core biopsy gun in the past decade began a new era in the sampling of the prostate for histologic diagnosis. Current efforts are directed at determining the optimal number and sites of biopsy of the prostate to detect cancer.

Advantages of Contemporary 18-Gauge Needle Biopsy

The 18-gauge needle offers many important advantages over the older 14-gauge needle. The rate of postbiopsy infection, which was 7% to 39%, is now 0.81%, and hemorrhage with urinary clot retention has fallen from 3.2% to less than 1%.1 The false-negative rate, formerly 11% to 25%, is now 11%, and the quality of the tissue sample has improved, usually with little or no compression artifact at the edges of the specimen.

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The 18-gauge needle also allowed sextant biopsies (six cores, usually including three from each side at the apex, midportion, and base) and seminal vesicle biopsies to be done with minimal discomfort. As many as 18 biopsies can be obtained in one session with no complications other than self-limited gross hematuria.

Contemporary biopsy is also less likely to cause cancer tracking, seeding, and implantation through the capsule than was transperineal 14-gauge needle biopsy. A recent study found no cases of tumor tracking in a series of 311 totally embedded radical prostatectomies with cancer after 18-gauge biopsy, suggesting that transrectal biopsy was associated with no risk of local cancer seeding and implantation.

Older reports with 14-gauge biopsy reported tracking in 0.3% to 1.0% of patients with palpable perineal tumor nodules and 0.1% of all patients. Risk factors for tumor tracking, seeding, and perineal implantation included a large volume of tumor within the prostate and high tumor grade. Perineal implantation occurred from 1 month to 7 years after biopsy but usually within 1 year. Perineal tracking, seeding, and implantation carry a poor prognosis despite the use of adjuvant radiation therapy or androgen deprivation therapy.

Rarely, cancer implantation appears after transrectal biopsy of benign tissue, presumably because of cancer tracking that was not identified in the biopsy specimen. Currently, multiple biopsies for detection of small-volume cancers pose virtually no risk of tumor tracking.

The main disadvantage of the 18-gauge needle is that it provides less than half as much tissue per needle core for pathologic examination as the traditional 14-gauge biopsy did. The external diameter of the typical 18-gauge needle is 1.27 mm compared with 2.08 mm for the 14-gauge needle; because the volume of a cylinder is \( \frac{4}{3} \pi r^2 \) times length, the 18-gauge needle makes a wound 2.7 times smaller than that made by the 14-gauge needle.

**Improvements in Cancer Detection Rates**

According to a review by the American College of Physicians, available tests for the early detection of prostate cancer have limited specificity, requiring a high biopsy rate. Biopsies revealed cancer in approximately 4% of men with serum PSA levels more than 4 ng/ml or abnormal digital rectal examination, yielding a positive predictive value of up to 21%.

The use of sextant biopsies has improved the diagnostic yield of prostate sampling in recent years; the increase is up to 43% more than the yield with two or fewer biopsies. However, sextant biopsies have limited accuracy in detecting small-volume cancers, particularly those less than 5.1 cc. Transrectal ultrasound guidance of the biopsy improves the detection rate and is superior to transperineal or blind biopsy, especially in men with normal results of digital rectal and ultrasound examinations. With this method of sampling, significant cancer is found in as many as one in three men with elevated serum PSA levels.

The cancer detection rate can be improved if more biopsies are obtained. The five-region biopsy technique, consisting of at least 13 biopsy cores per prostate, yielded 35% more cancers than the sextant (six-core) approach. The size of the prostate is also an important determinant of biopsy yield; large prostates require more biopsy cores to maintain the same level of diagnostic accuracy. The increased yield of prostate cancer among men with small prostates is apparently not the result of increased detection of low-grade, clinically unimportant cancers.

**Repeat Biopsy**

In many patients, especially those with elevated serum PSA concentration, an initial biopsy may miss the cancer. This is an important consideration in studies of screening, as most are unable to provide the true false-negative level, resulting in
an underestimate of the true cancer rate.

In men with persistent elevation of serum PSA, repeat biopsy revealed cancer in 19%, 20%, and 23% of patients. In untreated men with documented adenocarcinoma, repeat sextant biopsy revealed cancer in 80%, indicating a false-negative rate of 20%. When men with negative repeat biopsy results were compared with those who had positive results, no significant difference was found in PSA concentration or PSA density, although the negative group had larger prostates and lower stages of clinical cancer.

Current indications for repeat biopsy include the presence of high-grade prostatic intraepithelial neoplasia (PIN); microscopic foci suggestive but not diagnostic of malignancy (discussed later) and high clinical risk because of serum PSA elevation, digital rectal examination abnormality, and ultrasound abnormality. Selective measurement of the percentage of free PSA may significantly improve the specificity of prostate cancer screening with PSA.

PATHOLOGIC CHANGES AFTER NEEDLE BIOPSY

Transrectal 18-gauge needle biopsy of the prostate induces a predictable inflammatory response along a very narrow track. The biopsy track consists of a partially collapsed cavity, often filled with red blood cells and rimmed by mixed acute and chronic inflammation, including lymphocytes, macrophages, and occasional eosinophils (Fig. 1). Variable amounts of hemosiderin pigment, granulation tissue, and fibrosis are present, usually limited to the edge of the cavity. Venous thrombosis and foreign body giant cell reactions are seen infrequently.

Biopsy tracks in prostatectomy specimens obtained 6 weeks after biopsy contain fewer red blood cells and less acute inflammation than seen in those obtained earlier, but no other histologic differences are noted. No evidence of florid granulomatous prostatitis or fibrinoid necrosis is found after needle biopsy, although these are often seen after transurethral resection.

Handling Specimens and Reporting Findings of Needle Biopsy

HANDLING SPECIMENS

Most laboratories employ 10% neutral buffered formalin for prostate biopsy fixation, but equivalent or superior results may be obtained with other fixatives such as zinc formalin, alcoholic formalin, and Bouin’s fixative.

Rapid immersion of the biopsy specimen in fixative is most important; this avoids rapid drying of the surface of the cores, which creates substantial artifacts. Specimens from different sites in the prostate should be submitted in separate containers for processing and histopathologic examination so that the location and extent of cancer can be determined; this is crucial information for estimating stage and planning therapy.

Although inking the needle biopsy is useful for identifying the tissue cores in paraffin blocks, it is done infrequently. Laboratories vary in the number of serial sections obtained from the tissue blocks for routine examination; in practice, up to 48 sections can be obtained from a single needle core. The rate of cancer detection in needle biopsy specimens is maximized by procurement of a total of five slides with three sections per slide (15 sections) or three slides with about four sections per slide (12 sections).

We routinely obtain at least three sections on each of two slides, yielding a minimum of six sections. It may be useful to have three slides routinely made, submitting slides 1 and 3 for hematoxylin and eosin stain and retaining slide 2 for special studies such as immunohistochemistry for keratin 3βE12 or digital image analysis for DNA ploidy analysis. In our experience, refacing and recutting the block to obtain additional levels is
useful in about half of cases; usually no more than four additional slides can be obtained before the biopsy tissue is exhausted. Consequently, contingency planning for additional studies or levels may be useful before initial cutting of the block.

**Diagnostic Criteria for Carcinoma in Biopsy Specimens**

Most prostatic adenocarcinomas are composed of acini arranged in one or more patterns. The diagnosis relies on a combination of architectural and cytologic findings. The light microscopic features are usually sufficient for diagnosis, but rare cases may benefit from immunohistochemical studies.

**Architectural Features of Carcinoma**

Architectural features are assessed at low to medium power magnification. Noting the arrangement of the acini is diagnostically useful and is the basis of the Gleason grade. Malignant acini usually have an irregular, haphazard arrangement, randomly scattered in the stroma in clusters or singly (Fig. 2A) (p. 303). The spacing between malignant acini often varies widely. Variation in acinar size is a useful criterion for cancer, particularly when small, irregular, abortive acini with primitive lumens are seen at the periphery of a focus of well-differentiated carcinoma.

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

The stroma in cancer frequently contains young collagen, which appears lightly eosinophilic, although desmoplasia may be prominent. Muscle fibers in the stroma sometimes split or are distorted. However, this is a difficult feature to appreciate and cannot be relied upon because of the resemblance to benign acini. An understanding of the Gleason grading system is valuable in interpretation of small foci because of its reliance on architectural patterns, as discussed later.

**Cytologic Features of Carcinoma**

The cytologic features of adenocarcinoma include nuclear and nucleolar enlargement, which occurs in most malignant cells (Fig. 2A). Every cell has a nucleolus, so “prominent” nucleoli (at least 1.50 in diameter or larger) are sought. Because we do not routinely measure nucleoli for diagnosis, this determination is based on comparison with benign epithelial cells elsewhere in the specimen.

Artifacts often obscure the nuclei and nucleoli, and overstaining of nuclei by hematoxylin creates one of the most common and difficult problems in the interpretation of suspicious foci. Differences in fixation and handling of biopsy 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, which are often enlarged. In specimens with nuclear hyperchromasia and pale eosinophilic staining, we often increase the light source and magnification of suggestive foci to identify hidden enlarged nucleoli.

The basal cell layer is absent in adenocarcinoma, an important feature that is often difficult to evaluate in routine tissue sections. Compressed stromal fibroblasts may mimic basal cells but are usually seen only focally at the periphery of acini. An intact basal cell layer is present with benign acini, whereas carcinoma entirely lacks a basal cell layer. Small foci of adenocarcinoma sometimes cluster around large benign acini that have an intact basal cell layer, compounding the difficulty.
Luminal and Stromal Findings in Carcinoma

Luminal Mucin
Acidic sulfated and nonsulfated mucin is often seen in acini of adenocarcinoma, appearing as amorphous or delicate, threadlike, faintly basophilic secretions in routine sections (Fig. 2B). This mucin stains with alcian blue and is best displayed at pH 2.5, whereas normal prostatic epithelium contains periodic acid–Schiff (PAS)-reactive mucin that is neutral. Acidic mucin is not specific for carcinoma; it may be found in prostatic intraepithelial neoplasia, atypical adenomatous hyperplasia, sclerosing adenosis, and, rarely, nodular hyperplasia.24

Crystalloids
Crystalloids are sharp, needle-like eosinophilic structures that are often present in the lumens of well-differentiated and moderately differentiated carcinoma (Fig. 2C).25 They are not specific for carcinoma and can be found in other conditions. The presence of crystalloids in metastatic adenocarcinoma of unknown site of origin is strong presumptive evidence of prostatic origin, although it is an uncommon finding and not conclusive.26

Special stains highlight the presence of crystalloids that otherwise cannot be seen by light microscopy.26 Crystalloids stain red with trichrome stain, blue with toluidine blue, and violet with Mallory’s phosphotungstic acid–hematoxylin. No staining is observed with PAS, alcian blue, Prussian blue, and Congo red. Immunohistochemical stains for PSA and prostatic acid phosphatase (PAP) are negative.

The pathogenesis of crystalloids is not known, but they probably result from abnormal protein and mineral metabolism within benign and malignant acini. Ultrastructurally, they are composed of electron-dense material that lacks the periodicity of crystals. Radiographic microanalysis reveals abundant sulfur, calcium, and phosphorus and a small amount of sodium.25 Hard, proteinaceous secretions are almost always present in adjacent acini and are probably the source of the crystalloids.

Collagenous Micronodules
Collagenous micronodules are a specific but infrequent and incidental finding in prostatic adenocarcinoma. They consist of microscopic nodular masses of paucicellular eosinophilic fibrillar stroma that impinge on acinar lumens (Fig. 2D).27 They are usually present in mucin-producing adenocarcinoma and result from extravasation of acidic mucin into the stroma. Collagenous micronodules are present in about 13% of cases of adenocarcinoma; they are not observed in benign epithelium, nodular hyperplasia, or PIN. They are an infrequent finding, present in 0.6% of needle biopsies and 12.7% of prostatectomies. Collagenous micronodules may be particularly valuable in challenging needle biopsy specimens.27

IMMUNOHISTOCHEMICAL FINDINGS
The most important immunohistochemical markers in prostate pathology are PSA, PAP, and high-molecular-weight keratin 3βE12. Promising new markers include prostate-specific membrane antigen (Bostwick et al, unpublished data) and human glandular kallikrein 2 (hK2).28

Prostate-Specific Antigen
Immunohistochemical expression of PSA is useful for distinguishing high-grade prostate cancer from urothelial carcinoma, colonic carcinoma, granulomatous prostatitis, and lymphoma.29,30 PSA also facilitates identification of the site of tumor origin in metastatic adenocarcinoma. PSA can be detected in frozen sections, paraffin-embedded sections, cell smears, and cytologic preparations of normal and neoplastic prostatic epithelium (Fig. 3A)(p. 308). Staining is invariably heterogeneous. Microwave antigen retrieval is usually not necessary, even in tissues that have been immersed in for-
malin for years. Formalin fixation is optimal for localization of PSA, and variation in staining intensity is only partially the result of fixation and embedding effects. Immunoreactivity is preserved in decalcified specimens and may be enhanced.

Prostatic Acid Phosphatase

PAP is a valuable immunohistochemical marker for identifying prostate cancer when used in combination with PSA. The intensity of PAP immunoreactivity correlates with patient survival, probably because immunoreactive cancer has greater androgen responsiveness.

Keratin 3βE12

In problem cases, using monoclonal antibodies (for example, clone 3βE12) directed against high-molecular-weight cytokeratin may be useful for evaluation of the basal cell layer. We use this infrequently (in fewer than 5% of cases), however, and only as an adjunct to the light microscopic findings. The findings with this immunohistochemical stain should not be the basis for a diagnosis of malignancy, particularly in small suggestive foci. It is most useful in confirming the benignancy of a suggestive focus by showing an immunoreactive basal cell layer (Fig. 3B).

Antikeratin 3βE12 stains nearly all of the normal basal cells of the prostate; no staining occurs in the secretory and stromal cells. The basal cell layer is disrupted in 56% of cases of high-grade PIN, more commonly in glands adjacent to invasive carcinoma than in distant glands. The amount of disruption increases with increasing grades of PIN, and more than one-third of the basal cell layer is lost in 52% of foci of high-grade PIN. Early carcinoma occurs at sites of acinar outpouching and basal cell layer disruption. Prostate cancer cells do not react with this antibody, although it may stain other cancers. The basal cell layer is disrupted also in inflamed acini, atypical adenomatous hyperplasia, and postatrophic hyperplasia.

Despite the clinical utility of high-molecular-weight keratin, caution is urged in interpretation because negative results must be relied on to separate adenocarcinoma from its mimics. Many confounding factors can interfere with staining, including poor tissue preservation and fixation and lack of enzyme predigestion.

Differential Diagnosis of Cancer

In recent years, the diversity of acinar changes in the prostate that mimic adenocarcinoma has received growing recognition. The diagnostic difficulty has been compounded by the success of early detection methods, which often yield biopsy specimens with small foci. The most common mimics of cancer are PIN, postatrophic hyperplasia, atypical adenomatous hyperplasia, and basal cell hyperplasia. This section emphasizes the two mimics most difficult to distinguish from prostate cancer in needle biopsies, PIN and foci suggestive of malignancy.

High-Grade Prostatic Intraepithelial Neoplasia

Prostatic intraepithelial neoplasia refers to the putative precancerous end of the morphologic continuum of cellular proliferations within preexisting prostatic ducts, ductules, and acini. PIN is divided into two grades (low and high) to replace the previous three-grade system.
PIN 1 is considered low grade; PIN 2 and 3 are considered high grade) (Fig. 4A) (p. 312). The continuum from low-grade PIN to high-grade PIN and early invasive cancer is characterized by basal cell layer disruption; progressive loss of markers of secretory differentiation; and increasing nuclear and nucleolar abnormalities, proliferative activity, microvessel density, genetic instability, and DNA content. Autopsy studies indicate that PIN precedes carcinoma by 10 years or more; low-grade PIN first emerges in men in the third decade of life. The incidence of PIN in needle biopsies is not known; it probably varies according to the patient population under consideration (screening population versus urology office population). The American Cancer Society National Prostate Cancer Detection Project identified PIN and cancer in 17 (5.2%) and 58 (15.8%) men, respectively, from a series of 330 biopsies from men participating in an early detection project. High-grade PIN is seen in up to 16.5% of contemporary needle biopsy specimens in urology office practice (Fig. 4B). High-grade PIN has a high predictive value as a marker for adenocarcinoma. Davidson et al found adenocarcinoma in 35% of subsequent biopsies from patients with a previous diagnosis of PIN, compared with 13% in a control group without PIN. High-grade PIN, patient age, and serum PSA concentration were all highly significant predictors of cancer, but PIN alone increased the risk 15-fold and provided the highest

Fig. 2. Diagnostic findings of prostatic adenocarcinoma. (A) Biopsy core partially replaced by cancer; right, the cytologic features are evident, including nuclear and nucleolar enlargement. (B) Cancer acini contain mucin. (C) Needle-like crystalloids are more common in cancerous than in benign acini. (D) Collagenous micronodules are virtually diagnostic of cancer.
risk ratio. Others have reported a high predictive value of PIN for cancer, ranging from 38% to 100%. These data underscore the strong association of PIN and adenocarcinoma and indicate that diagnostic follow-up is needed.

Biopsy is the only definitive method for detecting PIN and early invasive cancer. If all procedures fail to identify coexistent carcinoma, close surveillance and follow-up are indicated. Follow-up is suggested at 3- or 6-month intervals for 2 years and then at 12-month intervals for life. Identification of PIN in the prostate should not influence or dictate therapeutic decisions.

**Foci Suggestive of Malignancy**

In up to 2.5% of needle biopsies, small acini proliferate locally, which suggests carcinoma but falls below the diagnostic threshold (Fig. 4C and D). This problem is often the result of the small size of the focus. Although we do not use quantitative criteria for malignancy in the prostate, very small foci with only a few malignant acini are evaluated cautiously and invariably with intradepartmental consultation. We have rarely diagnosed adenocarcinoma with as few as three malignant acini, but only when frank cytologic anaplasia was present in stark contrast with the adjacent benign epithelium, no inflammation was near the focus of concern, serial sections were obtained, and the possibility of seminal vesicle or ejaculatory duct epithelium was excluded.

Other causes of difficulty with small suspicious foci include the presence of distorted acini that lack convincing cytologic features, prominent inflammation in which the adjacent benign acini show distortion, and inflammatory reactive atypia with nuclear and nucleolar enlargement. Calling such a case “atypical small acinar proliferation suggestive but not diagnostic of malignancy” is appropriate. We consider this a valid diagnostic category based on our “absolute uncertainty” regarding the diagnosis. In such cases, the diagnosis of carcinoma cannot be made, but the possibility cannot be definitively excluded.

Because the diagnosis of carcinoma has serious consequences, rendering the diagnosis of malignancy only when one has absolute confidence in the histologic findings is prudent. Other supportive evidence is useful—including patient age, serum PSA concentration, and keratin 3E12 expression—but not a substitute for the light microscopic findings. We usually evaluate these other findings only after microscopic examination to avoid bias.

We classify suspicious small acinar proliferations as “suspicious, favor benign,” “suspicious,” and “highly suspicious.” The expected clinical response to each of these diagnoses is identical, and we recommend patient follow-up with consideration of a repeat biopsy. This classification may appear cumbersome, but we find it useful to stratify our level of suspicion as a teaching tool.

**NEEDLE BIOPSY REPORT**

The Cancer Committee of the College of American Pathologists and other groups have described the essential features that should be included in prostate needle biopsy reports (Table 1). These recommendations have been incorporated in the Mayo Clinic abbreviations system for prostate specimen interpretation (Table 2). These abbreviations are used to shorten pathologists’ transcription time, accelerate secretarial transcription time, reduce typographic errors through computerization, create uniform nomenclature and style for the benefit of clinicians and pathology quality assurance, and standardize the approach to common prostate biopsy problems.

The disadvantages of this abbreviation system are the potential for misinterpretation and incorrect reporting of the abbreviations and simplification of histopathologic findings by forcing all cases into the diagnostic “bins” of the abbreviation template. The abbreviations are meant only as a guide; some cases do not
## Table 1
Protocol for Examination of Biopsy Specimens

| Patient identification |
|------------------------|
| Name                   |
| Age                    |
| Race                   |
| Identification number  |

### Clinical history
(appropriate clinical information should be provided to the pathologist for optimal pathologic evaluation)

- Previous diagnosis
- Treatment
- Clinical stage (digital rectal examination findings)
- Serum prostate-specific antigen concentration
- Findings of imaging studies (transrectal ultrasonography)

### Type of operation

### Gross examination

- Specimen fresh or in fixative
- Size, number of pieces, and orientation*
- Recognizable gross features
- Amount submitted for histologic processing (total or partial)

### Microscopic features/diagnosis

- Tumor (versus no tumor)
  - Histologic type (indeterminable or as appropriate; include mixtures)
  - Gleason grade (score)
  - Extent of tumor (amount of specimen involved)
  - Perineural invasion (we exclude this because of recent data<sup>100</sup>)
  - Extraprostatic extension

- Other lesions
  - High-grade prostatic intraepithelial neoplasia
  - Therapy-associated changes

- Special studies
  - Immunohistochemistry
  - DNA ploidy analysis (flow cytometry, digital image analysis)
  - Other (histochemistry, morphometry)

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*Amount in transurethral resection of the prostate specimens is at least 12 g (about six cassettes for the first 30 g and one cassette for every 10 g thereafter).

Based on the Practice Protocol of the Cancer Committee of the College of American Pathologists<sup>50</sup> with modifications suggested at the International Consultation on Prostatic Intraepithelial Neoplasia and Pathological Staging of Prostate Cancer.<sup>19</sup>
Table 2
Prostate Biopsy Abbreviations Used at Mayo Clinic

| Abbreviation | Description |
|--------------|-------------|
| **Tissue sites normal** | |
| P            | Prostate |
| SV           | Seminal vesicle |
| EJ           | Ejaculatory ducts |
| SK           | Skeletal muscle |
| BPT          | Benign prostatic tissue |
| FO           | Fragments of |
| NEON         | No evidence of neoplasm |

| **Inflammation** | |
|------------------|------------------|
| CINF1, CINF2, CINF3 | Chronic inflammation (mild, moderate, severe) |
| AINF1, AINF2, AINF3 | Acute inflammation (mild, moderate, severe) |
| GRAN1, GRAN2, GRAN3 | Granulomatous inflammation (mild, moderate, severe) |

| **Atrophy and hyperplasia** | |
|-----------------------------|-----------------------------|
| A1, A2, A3                  | Atrophy (mild, moderate, severe) |
| AAH                         | Atypical adenomatous hyperplasia |
| BCH                         | Basal cell hyperplasia |
| ABCH                        | Atypical basal cell hyperplasia |
| BPH                         | Nodular hyperplasia |
| PAH                         | Postatrophic hyperplasia |

| **Prostatic intraepithelial neoplasia** | |
|----------------------------------------|-------------------------------|
| HGPIN                                  | High-grade prostatic intraepithelial neoplasia present |

| **Atypical small acinar proliferations** | |
|------------------------------------------|--------------------------------------------------------|
| ASAPB                                   | Atypical small acinar proliferation, favor benign; malignancy cannot be definitively excluded |
| ASAPS                                   | Atypical small acinar proliferation suggestive but not diagnostic of malignancy |
| ASAPH                                   | Atypical small acinar proliferation highly suggestive but not diagnostic of malignancy |
| R*                                      | Repeat biopsy may be valuable if clinically indicated |

| **Carcinoma** | |
|---------------|------------------|
| CA            | Adenocarcinoma |
| CAG           | Adenocarcinoma (Gleason grade) involving ___% of the specimen |

| **Needle biopsy examples** | |
|---------------------------|--------------------------------------------------|
| BPT, A1, AINF1            | Benign prostatic tissue; mild atrophy; mild acute inflammation. |
| CAG 3 + 4, 20%            | Adenocarcinoma (Gleason grade 3 + 4 = 7) involving about 20% of the specimen. |
| ASAPS, HGPIN, CINF1       | Atypical small acinar proliferation suggestive but not diagnostic of malignancy. High-grade prostatic intraepithelial neoplasia; mild chronic inflammation. |

| **Transurethral resection of the prostate examples** | |
|------------------------------------------------------|--------------------------------------------------|
| BPH, AAH                                              | Nodular hyperplasia with atypical adenomatous hyperplasia |
| CAG 2 + 2, < 5% BPH                                   | Adenocarcinoma (Gleason grade 2 + 2 = 4) involving less than 5% of the specimen. Nodular hyperplasia. |

*This code is rarely used.*
Biopsy After Therapy

**Value of Needle Biopsy After Therapy**

**Biopsy After Radiation Therapy**

For about 12 months after external beam irradiation, needle biopsy is of limited value because of delayed and continuing tumor cell death. After this period, however, biopsy is the best method for assessing local tumor control. The level of sampling error is low and can be reduced by obtaining multiple specimens. Histopathologic changes of radiation injury in the prostate include acinar atrophy, shrinkage, and distortion; marked cytologic abnormalities of the epithelium; basal cell hyperplasia; stromal fibrosis; and decreased ratio of acini to stroma. Vascular sclerosis is also prominent and may involve small and large vessels. Recent results with interstitial brachytherapy reveal that biopsies are negative in 80%, indeterminate in 17%, and positive in 3%; as follow-up time increased, many indeterminate cases converted to negative on repeat biopsy.

No definitive method exists for assessment of tumor viability after irradiation. PSA and PAP expression persist, suggesting that tumor cells that can produce protein probably retain the potential for cell division and consequent metastatic spread. Keratin 3βE12 expression also persists after radiation therapy and is often valuable in separating treated adenocarcinoma from some of its mimics. If prostatic carcinoma is not histologically ablated by external beam radiotherapy after 12 months, it is probably biologically active. Pretreatment PSA serum concentration and posttreatment PSA nadir are the most important predictors of outcome.

Cancer grading after radiation therapy has yielded conflicting results. Some observers noted no difference between pretherapy and posttherapy grades; others found an increase in grade. Up to 31% of pretreatment diploid tumors may shift toward aneuploid DNA content, indicating increasing histologic and biologic tumor aggressiveness. The consensus opinion is that grading should not be relied upon after radiation therapy.

**Biopsy After Androgen Deprivation Therapy**

Androgen deprivation is used to shrink tumors preoperatively and to treat prostatic hyperplasia; it may be effective for cancer prophylaxis, although this remains speculative. Androgen deprivation of normal, hyperplastic, and dysplastic epithelial cells causes acceleration of programmed cell death of single cells (apoptosis), with fragmentation of tumor DNA, emergence of apoptotic bodies, and inhibition of cell growth.

Characteristic involutional changes occur in the prostate after androgen deprivation therapy (Fig. 5) (p. 313). Benign acini show marked lobular and acinar atrophy, epithelial vacuolation, basal cell hyperplasia, squamous metaplasia, transitional metaplasia, and acinar rupture with extravasation of secretions. Androgen deprivation therapy also causes a marked reduction in the presence and extent of high-grade prostatic intraepithelial neoplasia. Cancer shows an increase in Gleason grade and a substantial reduction in nuclear and nucleolar size, accompanied by prominent cytoplasmic clearing. These changes are rarely seen in benign acini and untreated carcinoma, and the combination of features after therapy is sufficiently distinctive to allow recognition of this morphologic change. Androgen deprivation therapy causes an apparent increase in the Gleason grade of the tumor, accompanied by reduction of nuclear size, loss of recognizable nucleoli, chromatin condensation, nuclear pyknosis, and cytoplasmic vacuolation (“nucleolus-poor clear cell adenocarcinoma”). This uncoupling of the architectural and cytologic pattern is vex-
ing because of the presence of small, shrunken nuclei within malignant acini, particularly in lymph nodes submitted for frozen section evaluation.

Grading systems have been proposed for therapy-induced adenocarcinoma regression, chiefly by German investigators, but have not been widely adopted. Armas et al consider grading after therapy to be potentially misleading and recommend against it.

Immunohistochemical studies for PSA, PAP, and basal cell–specific keratin 3ßE12 are useful in identifying carcinoma after therapy. PSA and PAP are retained in tumor cells after therapy, and keratin 3ßE12 remains negative, indicating that the basal cell layer is absent. No differences are found in expression of neuroendocrine differentiation markers such as chromogranin, neuron-specific enolase, ß-human chorionic gonadotropin, and serotonin. Proliferative activity according to proliferating cell nuclear antigen immunoreactivity decreases after androgen deprivation therapy.

**Biopsy After Cryosurgery**

Cryosurgical ablation refers to freezing of the prostate. Several cryoprobe needles filled with circulating liquid nitrogen transform the prostate into an ice ball, resulting in substantial tissue destruction and the death of benign and malignant cells. The flow of liquid nitrogen through the probes is adjusted to create the desired freezing pattern and extent of tissue destruction in the prostate; no liquid nitrogen comes in contact with the tissue. Preliminary results with cryoablation for prostate cancer are encouraging, but the method is still considered experimental.

After cryosurgery, tissue is completely ablated in some areas of the prostate. Other areas show typical features of tissue repair, including marked stromal fibrosis and hyalinization, basal cell hyperplasia with epithelial regeneration, squamous metaplasia, and stromal hemorrhage and hemosiderin deposition. Coagulative necrosis is present between weeks 6 and 30 of therapy, but patchy chronic inflammation is more common. Focal granulomatous inflammation is associated with epithelial disruption caused by corpora amylacea. Dysrophic calcification is infrequent and usually appears in areas with the greatest reparative response. Atypia and PIN are not seen in areas that otherwise show changes of postcryoablation therapy.

**Predictive Factors in Prostate Needle Biopsy Specimens**

Studies of tissue biopsy samples that provide additional prognostic information beyond the usual light microscopic findings are greatly needed. Recent reviews provide details about new predictive fac-

Fig. 3. Immunohistochemistry of prostatic adenocarcinoma. (A) Cancer cells display intense immunoreactivity for prostate-specific antigen. (B) Keratin 3ßE12 reactivity is limited to the basal cells present in benign acini.
tors in prostate cancer and their limitations.40,72 None of these predictive factors is currently recommended for general use in practice by the College of American Pathologists, although DNA ploidy may be useful in specific clinical settings.73 This question will be reevaluated by a consensus group in the next year.

**LOCATION AND EXTENT OF CARCINOMA**

Transrectal ultrasound guidance allows precise anatomic sampling of the prostate, including sites other than the peripheral zone. Controversy exists regarding the utility of transition zone and seminal vesicle biopsies, but these are useful for select patients. Routine transition zone biopsy has a low yield of cancer, ranging from 0.6%74 to 1.0%,75,76 with differences resulting from different patient selection criteria. Accordingly, transition zone biopsies are discouraged except in patients in whom negative sextant biopsies fail to reveal cancer but whose PSA level is markedly elevated or rising.74

Seminal vesicle biopsies are most valuable in patients with PSA level more than 15 ng/ml to 20 ng/ml or abnormal or enlarged seminal vesicles according to clinical or ultrasonographic findings.77-80 For some urologists, routine seminal vesicle biopsy is advocated because positive results have a significant impact on patient management.77,78 The yield of seminal vesicle biopsy is about 15% in patients with biopsy-proven clinically localized prostate cancer79 and 69% in patients with metastases.81

The presence of cancer within adipose tissue in needle biopsy specimens shows extraprostatic extension of cancer, which should be documented by the pathologist.80

**VOLUME OF CANCER IN NEEDLE BIOPSY**

Can the amount of cancer in the needle biopsy predict the volume of tumor in the prostate?

The volume of cancer in a biopsy specimen depends on many factors, including prostate volume, cancer volume, cancer distribution, technical procedure, number of biopsy cores obtained, and cohort of patients being evaluated. The combined results of several studies show that the biopsy extent of tumor has some predictive value for the extent in radical prostatectomy specimens and probably should be reported. Its predictive value for the individual patient is limited, however.2-4,12,81-89 Reliance on this measure alone often may be misleading.90 Consequently, the volume of cancer in the needle biopsy should not influence therapeutic decisions.

A fair84 to good4 correlation exists between the amount of cancer in biopsies and that in radical prostatectomy specimens, but this correlation is greatest for large cancers. High cancer burden on needle biopsy is strongly suggestive of large-volume, high-stage cancer.2-4 In one study, lymph node metastases were identified in 52 of 57 patients (91% specificity) and 10 of 14 patients (71% sensitivity) when adenocarcinoma completely replaced two cores and 80% of a third core from the sextant sample.3

Unfortunately, low tumor burden on needle biopsy does not necessarily indicate low-volume, low-stage cancer. We found that patients with less than 30% of needle cores replaced by cancer had mean volumes in the radical prostatectomy of 6.1 cc (range, 0.19 cc to 16.8 cc), showing that the amount of tumor on transrectal needle biopsy was not a good predictor of tumor volume.84

In another report, patients with less than 10% cancer in the biopsy had a 30% risk of positive surgical margins, a 27% risk of extraprostatic extension, and a 22% risk of PSA biochemical progression; these risks were higher in patients with more than 10% cancer.89 Patients with less than 3 mm of cancer and Gleason scores 6 or less on needle biopsy had a 59% risk of cancer volume exceeding 0.5 cc.2 Those with less than 2 mm of cancer had a 26% risk of extraprostatic
cancer, and those with less than 3 mm had 52% risk.

How should the volume of cancer in the needle biopsy be measured? We undertook a comparative study that measured cancer volume four different ways: (1) percentage of biopsy cores involved; (2) percentage of cancer area in each biopsy specimen; (3) millimeters of adenocarcinoma in the entire biopsy; and (4) millimeters of adenocarcinoma per core. All measures were essentially equivalent in their predictive value for cancer volume in the prostatectomy. Consequently, we and others recommend use of the percentage of cancer area because it is easy to apply and will probably be accepted by most pathologists, similar to the method for measuring cancer volume in transurethral resection specimens.

**Grade**

In prostate cancer, grade is one of the strongest predictors of biologic behavior, including invasiveness and metastatic potential. It is not sufficiently reliable when used alone, however, for predicting pathologic stage or patient outcome for individual patients. The subjective nature of grading precludes absolute precision, no matter how carefully the system is defined. Yet, the significant correlation of prostate cancer grade with virtually every outcome measure attests to the predictive strength and utility of grading in the hands of most investigators.

The Gleason score is a scalar measurement that combines discrete primary and secondary groups (patterns or grades) into nine groups (scores 2 to 10). Interobserver and intraobserver variabilit-

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**Table 3**

Correlation Between 18-Gauge Needle Biopsy and Gleason Score of Radical Prostatectomy Specimen

| Authors         | No. patients | Setting          | Pathologists* | Correlation with Gleason Unit (%) |
|-----------------|--------------|------------------|---------------|----------------------------------|
|                 |              |                  |               | Exact | ± 1 | > 1 |
| Bostwick⁹²      | 316          | Academic         | 1             | 35    | 39  | 26  |
| Spires et al⁹³  | 67           | Academic         | 3             | 58    | 36  | 6   |
| Kojima et al⁹⁴  | 135          | Academic         | 1             | 48    | 43  | 9   |
| Thickman et al⁹⁵| 124          | Community        | Multiple       | 28    | 24  | 38  |
| Cookson et al⁹⁶| 226          | Academic         | Multiple       | 31    | 43  | 26  |
| Steinberg et al⁹⁷| 499         | Community        | Multiple       | 34    | 32  | NA  |
| **Means**       |              |                  |               | 39    | 36  | 21  |

*Number of pathologists involved in grading.

NA = not available.
ty have been reported with the Gleason grading system and other grading systems. Gleason himself noted exact reproducibility of score in 50% of needle biopsies and a variance of ±1 score in 85%, similar to the findings of others.

Needle core biopsy underestimates tumor grade in up to 45% of cases and overestimates grade in up to 32%. Exact correlation is present in about one-third of biopsies and variance of ±1 Gleason unit in another third (Table 3). Grading errors are common in biopsies with small amounts of tumor and low-grade tumor, probably because of tissue sampling variation, tumor heterogeneity, and undergrading of needle biopsies.

In recent years, I and others have noted a decline in the percentage of low-grade cancers diagnosed, probably because pathologists are more aware of the errors of undergrading. The accuracy of biopsy is highest for the primary Gleason pattern, but the secondary pattern also provides useful predictive information, particularly when combined with the primary pattern to create the Gleason score. Gleason grading should be used for all needle biopsies, even those with small amounts of tumor, according to the recommendations of Gleason.

On the average, 2.7 different Gleason primary patterns or grades (range 1 to 5) are found in prostate cancer treated by radical prostatectomy, and more than 50% of cancers contain at least three different grades. Also, the number of grades increases with greater cancer volume. The most common finding is high-grade cancer within the center of a larger well or moderately differentiated cancer (53% of cases). Grade is an invariable component of most clinical nomograms in prostate cancer, as discussed later in this article.

**Perineural Invasion**

Perineural invasion, which occurs in up to 38% of biopsies, is common in adenocarcinoma and may be the only evidence of malignancy in a needle core. This finding is strong presumptive evidence of cancer but is not pathognomonic because it occurs rarely with benign acini. Complete circumferential growth, intraneural invasion, and ganglionic invasion are found only with cancer. Perineural invasion usually indicates tumor spread along the path of least resistance; it does not represent lymphatic invasion.

Only half of patients with perineural invasion on biopsy have extraprostatic extension. In univariate analysis, perineural invasion was predictive of extraprostatic extension, seminal vesicle invasion, and pathologic stage in patients treated by radical prostatectomy. In multivariate analysis, however, perineural invasion had no predictive value after consideration of Gleason grade, serum PSA level, and amount of cancer on biopsy.

Perineural invasion has limited utility as a diagnostic test for the prediction of extraprostatic extension, with a sensitivity of only 51%, a specificity of 71%, and a positive predictive value of 49%. The negative predictive value was 71%, showing that the absence of perineural invasion was associated with extraprostatic extension in 29% of cases; perineural invasion on biopsy is even less useful as a diagnostic test for the prediction of seminal vesicle invasion. Based on these data, we no longer routinely report this finding in biopsies.

Perineural invasion was a significant independent predictive factor for adverse outcome at 3 years for patients treated by external beam radiation therapy; however, its value was associated only with a pretreatment PSA level of less than 20 ng/ml, suggesting that the poor prognosis associated with a high PSA level overrides any additional information that perineural invasion may provide.

**Vascular/Lymphatic Invasion**

Microvascular invasion consists of tumor cells within endothelial-lined spaces. We do not require the presence of a cellular
reaction in the adjacent stroma for diagnosis. Also, we do not differentiate between vascular and lymphatic channels because of the difficulty and lack of reproducibility among different observers by routine light microscopic examination. Microvascular invasion may be confused with perineural invasion and fixation-associated retraction artifact of acini.

Microvascular invasion is present in 38% of radical prostatectomy specimens. It is commonly associated with extraprostatic extension and lymph node metastases (62% and 67% of cases, respectively), and its presence correlates with histologic grade. Also, microvascular invasion appears to be an important predictor of outcome: it carries a fourfold greater risk of tumor progression and death. It is not an independent predictor of progression, however, when stage and grade are included in the analysis.

The Cancer Committee of the College of American Pathologists recommends reporting microvascular invasion in all prostatic specimens, presumably using routine light microscopic examination. Despite this recommendation, this finding is not evaluated in prostatic biopsies by most laboratories, including ours. Immunohistochemical stains directed against endothelial cells such as factor VIII-related antigen or *Ulex europaeus* may increase the detection rate.
MICROVESSEL DENSITY (ANGIOGENESIS)
A significant increase in microvessel density occurs in prostatic intraepithelial neoplasia and carcinoma compared with normal prostatic tissue. Mean blood vessel count is higher in tumors with metastases than in those without metastases, and most studies, but not all, show a correlation with pathologic stage. Microvessel density appears to be an independent predictor of cancer progression. Increased microvessel density in prostatic carcinoma is probably related to the production of angiogenesis-associated growth, which is similar to what occurs in other organs. The cumulative data suggest that increased microvessel density contributes to extraprostatic spread of adenocarcinoma, perhaps by facilitating microvascular invasion.

DNA PLOIDY
DNA ploidy analysis of prostate cancer by flow cytometry and digital image analysis provides important prognostic information that supplements histopathologic examination. Controversy exists, however, about whether it is a significant predictor above Gleason score in multivariate analysis. DNA ploidy pattern correlates with cancer grade, tumor volume, and stage. Most low-stage tumors are diploid, and high-stage tumors are nondiploid, but many exceptions occur.

Patients with diploid tumors have a more favorable outcome than those with aneuploid tumors; for example, among patients with lymph node metastases treated with radical prostatectomy and androgen-deprivation therapy, those with diploid tumors may survive 20 years or more, whereas those with aneuploid tumors die within 5 years. The 5-year cancer-specific survival is about 95% for those with diploid tumors, 70% for those with tetraploid tumors, and 25% for those with tumors that have multiple aneuploid cell lines. However, the ploidy pattern of prostate cancer is often heterogeneous, creating potential problems with sampling error. Most studies use matched benign or hyperplastic prostatic tissue as controls.

Until recently, flow cytometry was the most common method of DNA ploidy analysis for prostate cancer, but it was limited by the need for a large amount of tissue with a great number of cells. The minimum amount of needle-core tissue necessary to yield satisfactory results with flow cytometry is a 0.2-cm length of malignant acini, which corresponds to about 2,500 to 5,000 nuclei. Digital image analysis overcomes this limitation and is gaining popularity despite a lack of standards for this method. Concordance of digital image analysis on needle biopsy and flow cytometry from radical prostatectomy specimens is 82%. Sensitivity is 87% and specificity is 74% in predicting the presence of cancer. An international DNA Cytometry Consensus Conference reviewed the literature in 1993 and concluded that the clinical significance and biologic basis of DNA ploidy needed further investigation.

OTHER PREDICTIVE FACTORS
Other preoperative factors may improve the predictive accuracy for pathologic stage, including androgen receptors, magnetic resonance imaging, nuclear
and nucleolar morphometry, and polymerase chain reaction–based assay of PSA-synthesizing cells in the peripheral blood.40,72,73

Clinical Nomograms in Prostate Cancer: Value of Needle Biopsy Findings

Accurate preoperative prediction of the anatomic extent of cancer would be clinically useful in planning treatment, especially for patients being considered for treatment in which no additional tissue specimens are obtained, such as radiation therapy and watchful waiting. Preoperative PSA concentration has been shown to correlate with pathologic stage but by itself is not able to predict stage on an individual basis. The predictive accuracy of PSA is enhanced by the addition of other factors, many of which are derived from needle biopsies, including clinical stage, Gleason score, and percent of cancer in the needle biopsy specimen.81, 124-134

The combination of predictive factors provides the greatest accuracy in predicting stage and outcome. Probability estimates derived from nomograms can be used to determine the likelihood of extraprostatic extension and seminal vesicle invasion for individual patients. For example, a patient with a serum PSA level of 4 ng/ml and 10% cancer in the biopsy specimen has an estimated 11% chance of extraprostatic extension (confidence intervals, 7% to 17%) and a 5% chance of seminal vesicle invasion (confidence intervals, 3% to 9%).128

Probability curves for preoperative prediction of prostate cancer stage may be useful guides for patient management, but they are based on estimates subject to tissue biopsy sampling variation and many modeling assumptions.

First, the reliability estimates are optimistic because the models are usually optimized to fit the data set. Second, logistic models estimate the probability of an event occurring (e.g., the patient does or does not have extraprostatic extension), but the clinician needs to decide what probability cut-point to use to manage patients. Third, the estimates often have wide 95% confidence intervals, indicating imprecision for individual patients. Finally, in most studies, no independent data set was used to validate the models, dictating the need for confirmatory studies. The use of artificial neural networks is expected to improve the accuracy of predictions of cancer survival.135

Summary

Needle biopsy of the prostate plays a central role in the diagnosis of prostate cancer and the prediction of outcome. Strategies for sampling the prostate are being refined, which will increase the diagnostic yield. In combination with other clinical factors, the pathologic findings obtained from the biopsy specimen provide enhanced predictive accuracy for stage and individual outcome.

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