The Current Status of the Pathology of Prostate Cancer
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A diagnosis of prostate cancer by current pathology practice is affected by economic and medicolegal forces.

Background: The pathology of prostate cancer in modern day medicine cannot be understood simply in terms of tissue patterns or genetic abnormalities. Efforts to accommodate changes in patient care delivery and reimbursement, combined with an explosion in information, have wrought major changes in pathology.

Methods: The author summarizes the current status of the pathology of prostate cancer in light of these influences. The detection of prostate cancer in needle biopsies, the diagnostic interpretations that tend to confuse clinicians, the prognostic factors in prostate cancer, and the effects of radiotherapy and hormone therapy on prostatic tissue are discussed.

Results: Collegial associations are difficult to maintain when consultants are spatially separated and patients are shuttled between primary care and specialty centers. Economic forces cannot be ignored, regardless of the level of altruism of individual practitioners. A medical environment governed by judgment and wisdom is difficult to maintain when external forces and even patients themselves demand application of the latest information to each case.

Conclusions: Current trends in medicine offer almost as many pitfalls as promises. Information gathering and transfer tend to marginalize anatomic pathologists from patient care. Current pathology is affected by the influences of medicolegal and economic forces.

Introduction

The pathology of prostate cancer in the modern world must be understood in light of the forces impacting on medicine in general. Like clinicians, pathologists practice in diverse settings, each with its own institutional view, pressures, and goals. A common function for anatomic pathologists in all settings is one of medical consultation. Anatomic pathologists render interpretations based on their personal assessments of changes in tissues and cells. Most function as generalists who encounter prostatic specimens among an assortment of other tissues in daily practice. A few have a special interest or expertise in prostate cancer. No one can absorb or even read the vast literature that is currently available.

Regardless of the level of altruism and dedication to patient welfare, the practice of modern-day pathology cannot avoid the influences of medicolegal and economic forces. The typical anatomic pathologist sees more than 3,000 specimens per year; if he or she has a diagnostic accuracy rate of 99.9%, then at least three errors per year can be expected. In an age where error is equal to malpractice, a tendency toward caution in diagnosis is not only understandable, but also probably necessary, lest a career of a successful pathologist’s work founder in the legal system. An increasing use of consultants is an obvious answer. Not so obvious is a growing reluctance to issue unequivocal diagnoses on small foci of prostatic cancer. Our burgeoning methodology has created an overabundance of information paralleled by the means to rapidly communicate it. Histology, still the mainstay of anatomic pathology, can now be supplemented by cytometry, morphometry, immunohistochemistry, in situ hybridization, and other methodologies. Pathologists can now examine the genome on a routine basis. The temptation to exploit these advances is difficult to avoid, especially when many seem to be demanded by clinicians and patients alike.

The modern medical environment encourages competition among pathologists, a situation that may not be totally beneficial to patients. Competition among pathologists takes many forms, not the least being the offer of “added value” testing, visually appealing reports, and “door-to-door” service. The overabundance of currently available information in a competitive atmosphere has eroded the relationship between clinicians and pathologists. Many clinicians apparently view anatomic pathologists as laboratory managers with a menu of diagnostic services from which they can select the most appropriate rather than as consultants whose medical knowledge can be valuable in the care of their mutual patients. Many confuse interpretations performed by doctors on tissues with laboratory tests performed by machines on serum; they cannot understand why the diagnostic precision of these tissue interpretations is not equal to those of the serum-based tests. Many pathologists accept the role of information manager and emphasize their function of service to clinicians. Others attempt to “raise the bar” by expanding the menu of available technical and diagnostic services.

The evolution of these interacting forces has created a virtual Babel of pathologic information that leaves practitioners of all specialties crying out for standardization, greater simplicity, and consultations with practical value for patient care. Unfortunately, the emphasis on standardization in an interpretive discipline leads to its own problems. The following discussion summarizes the author’s view of the current status of the pathology of prostate cancer and focuses on detection of prostate cancer in needle biopsies, diagnostic interpretations that tend to confuse clinicians, prognostic factors in prostate cancer, and the effects of radiographic and hormone therapy on prostatic tissue. In addition, recommendations are presented to improve patient care through closer collaboration among pathologists and clinicians at the local level.

Detection of Prostate Cancer in Needle Biopsies

Despite a vast experience accumulated over the decade since biopsy sampling was introduced, anatomic pathologists continue to discuss the histopathologic criteria for recognizing prostate cancers in biopsies. The implications of an unequivocal diagnosis are heightened by the ever decreasing age of the patients undergoing biopsy. In simplest terms, one might consider a prostate biopsy to be diagnosable for cancer or not -- i.e., the interpreter being able to recognize unequivocally neoplastic glands or being able to see only normal changes or unusual changes that cannot be interpreted as prostate cancer. The tendency, however, has been for pathologists to "diagnose" any unusual tissue changes in an effort to help the clinician separate patients into levels of risk on the apparent assumption that patients with normal glands in a biopsy are at less risk for cancer than those with abnormal but not unequivocally cancerous changes. Supporters of this approach cite the need for...
more frequent surveillance of patients having atypical glandular changes. Thus, one can receive diagnoses of "atypia," "atypical glands," and more recently, "atypical small acinar proliferation." Previous terms such as "clear-cell hyperplasia," "adenosis," and "atypical adenomatous hyperplasia," now generally considered to describe variants of prostatic hyperplasia (BPH), continue to be used to the further confusion of those not fully conversant with the pathologic literature. While these terms may be descriptively accurate, they do not adequately address the problem at hand -- namely, whether or not the patient has a pathologically diagnosable cancer. Oftentimes, the clinician cannot determine whether the patient has (1) an atypical but benign change, (2) a precursor or risk factor for cancer, or (3) a focus of cancer that the pathologist is unwilling or unable to recognize. Requests for a second opinion in such cases are common. If the second opinion is "prostate cancer," the first pathologist suffers a loss of credibility, whether or not he or she was justified in expressing reluctance to diagnose unequivocal carcinoma. It is not at all clear that the use of equivocal terminology to interpret prostatic biopsies is beneficial in channeling the behavior of clinicians. There seem to be few if any studies addressing this issue.

Is a 60-year-old patient with a normal-sized prostate by digital rectal examination and a serum prostate-specific antigen (PSA) >10 ng/mL more likely to undergo rebiopsy if the initial tissue is interpreted as "atypical" than if it is diagnosed as "no significant pathologic alteration"? What if the patient is 80 years of age with a slightly enlarged prostate and a serum PSA of 7.8 ng/mL? Will follow-up change if the PSA is rising or if <25% is free PSA? The permutations on this theme are considerable. Still, follow-up paradigms might be possible for individual practice groups, based on the proclivities of the diagnosing physicians (pathologists) and the tendencies of the treating physicians (clinicians).

Currently, most anatomic pathologists have developed substantial experience with prostatic needle biopsies. They recognize the major histopathologic features of carcinoma:

- an infiltrative growth pattern
- clusters of large or small glands with features markedly different from those of normal adjacent glands
- large nucleoli (>1.6 µ) in several adjacent nuclei of a gland
- nuclear enlargement with slight increase in chromatin granularity
- slight nuclear pleomorphism and abnormal distribution of nuclei within glands
- absence of basal cells.

Anatomic pathologists are also aware of helpful if not diagnostic features of prostatic carcinoma:

- blue-tinged mucus
- collagenous nodules
- nuclear degeneration in the presence of non-degenerated adjacent nuclei
- crystalloids, not necessarily in neoplastic foci.

The majority of prostatic biopsies are correctly interpreted. In a minority of cases, the histopathologic changes are such that the degree of certainty required for an unequivocal interpretation cannot be achieved. Attempts to relate this uncertainty are often unhelpful. In my opinion, equivocal descriptive terminology should be avoided unless a clear understanding can be developed between pathologists and clinician consultants regarding the specific impact of these terms for patient care. The apprehension of pathologists that an expert witness might identify cancer in a case called "no significant pathologic alteration" and that any adverse consequences of this expert opinion might be ameliorated if the original diagnosis had said something about "atypical glands" may seem to require the use of such terms. Unfortunately, the pathologist is unlikely to be "saved" since the litigants will almost certainly claim that the harm resulted from lack of an unequivocal diagnosis, regardless of how the uncertainty was expressed.

Diagnostic Interpretations That Tend to Confuse Clinicians

In addition to any form of the term "atypia" in a pathologic diagnosis, other interpretations tend to be confusing. Prostatic intraepithelial neoplasia (PIN) is a currently popular term to identify patients with putative precursors of prostatic carcinoma. The name grows out of the notion that invasive epithelial malignancies arise through an orderly series of phenotypic changes that can be recognized by knowledgeable observers. Thus, normal PIN progresses to low-grade PIN and low-grade PIN progresses to high-grade PIN, which subsequently progresses to invasive carcinoma. In contrast to various atypias, PIN has been well defined in histopathologic terms (Fig 1). A large amount of data confirms that (1) low-grade PIN is common and is not statistically associated with coexisting prostatic carcinoma, (2) high-grade PIN is composed of cells that are essentially identical to those of certain invasive carcinomas, and (3) high-grade PIN is commonly associated with coexisting prostatic carcinoma. Despite the common belief in PIN as a precursor, there is little evidence that any significant percentage of patients with high-grade PIN do not already have but will subsequently develop prostatic carcinoma. On the other hand, there is some evidence that populations with prostate cancer actually develop the prostatic cancers before the PINs.

As a practical matter, pathologists are discouraged from diagnosing low-grade PIN, and clinicians should question the significance of this interpretation. Tissues with high-grade PIN, if interpreted according to established definitions, have a 70% chance of harboring coexistent prostatic carcinomas, and pathologists should and do make this diagnosis. The chance of coexisting carcinoma probably increases if the high-grade PIN is observed in a prostate biopsy obtained because of an elevated serum PSA or an abnormal digital rectal examination. The frequency of high-grade PIN in the absence of coexisting prostatic carcinoma in needle biopsies has varied depending on the prebiopsy probability of cancer. In unselected series, the frequency is in the range of 5%.

![Fig 1](https://via.placeholder.com/150)

*Fig 1. High-grade prostatic intraepithelial neoplasia (PIN) composed of normally configured glands with a mixture of bland cells and cells having atypia, essentially identical to those of some invasive carcinomas.*
Grading of prostatic carcinoma in a needle biopsy is another source of confusion inasmuch as many pathologists tend to confuse a small focus of cancer with a well-differentiated cancer, not realizing that truly well-differentiated prostatic carcinomas almost always occur in the transition zone. Needle biopsies tend to sample the peripheral zone, a region where carcinomas of Gleason pattern 1 or 2 comprise <5% of cases. Therefore, nearly all carcinomas detected in needle biopsies will be at least Gleason pattern 3 with a score of at least 6 (Fig 2). Undergrading might be a serious consideration in circumstances where the treatment of a Gleason 2-4 tumor would vary from that of a Gleason 5-6 cancer. The recent interest in separating Gleason score 7 prostate cancers into a category with important prognostic implications is likely to be mitigated by data indicating no adverse effects of such lesions compared with Gleason 6 tumors so long as the Gleason 7 cancer is confined to the resection specimen. 

![Image](https://via.placeholder.com/150)

Fig 2 — A small focus of neoplastic glands infiltrating a duct having a normal gland with "normal bridge" formation. Sima Gleason's system is based on the pattern of infiltration rather than the degree of cytopathic change. This photograph documents a pattern 5 tumor. Some experts have recently suggested that small foci of cancer should be based on "typical small gland proliferation," but such terminology is not particularly helpful and should probably be reserved to cases requiring a second opinion.

Diagnostic terms such as "atypical adenomatous hyperplasia," "adenosis," "atypical basal cell hyperplasia," "basal cell hyperplasia," "clear cell intraductal hyperplasia," "sclerosing adenosis," "fibroadenoma," "mucinous metaplasia," and "Paneth cell change" describe variants of the nodular involution that commonly occurs in the aging prostate. Pathologists tend to record these variations to document that they have observed them. Likewise, "chronic prostatitis" merely reflects the presence of a paraglandular lymphocytic infiltrate and is not intended to correlate with clinically important disease.

Prognostic Factors in Prostate Cancer

The search for prognostic factors has become one of the major growth industries in modern medicine, and pathologists have contributed their share. At last count, more than 35 factors had been claimed to have value in predicting the future development of prostate cancer, the likely response to therapy, the pathologic stage, the nature of the tumor, and the likelihood of progression. 10, 11

In nearly all instances, the data actually document associations with phenomena that already exist rather than with situations that might arise de novo in the future. For almost all such factors, one can forecast an often repeated cycle of enthusiasm based on initial data, followed by reassessment based on a wider experience, followed by rejection when the prognostic factor turns out to be just another element in the extraordinary complexity of human cancer.

Amid all the information on putative prognostic factors for prostate cancer, it is perhaps sobering to reflect that there are only three basic outcomes available to a patient: (1) "cure," or no evidence of disease during follow-up (the patient being alive or dead at last contact), (2) progression of disease, essentially unaffected by medical intervention (the patient being either dead of disease or alive but likely to die of disease at last contact), or (3) persistence of disease with little effect on the medical intervention. With only three possible outcomes, it is difficult to understand how there could be more than 35 factors that independently affect prognosis.

The rush to bring new discoveries to the bedside is hard to resist, especially when a slow, carefully reasoned approach may prevent a patient from benefitting from the latest knowledge. Unfortunately, a hasty approach is not without risk. The importance of all but a few of these factors is justified primarily by association, and associations can be misleading. Prior to serum PSA, for example, a strong case could have been made that prostate cancer was a function of age when we now know that a large percentage of relatively young men (35% of 50-year-old men) actually harbor the disease. 7

In addition to the risk of inappropriate treatment and counseling, there is the potential for economic adversity. Most if not all pathology laboratories have suffered adverse financial consequences from molecular biology testing. Patients are impacted as well, since the costs of new information are often passed on to them and third parties are increasingly reluctant to pay. Patients might also question the quality of the statistical data on which these tests are justified. Fifteen years ago, for example, one could have developed P values to show that age accounted for the majority of cases of prostate cancer and that carcinoma of the prostate was unusual prior to age 60. Few would attempt to defend such P values today.

Considering the vast array of data on prognostic factors, it is surprising how little this information has affected patient outcome, unless most of our observations are actually epiphenomena. Among pathologic prognostic factors for the prostate, those that seem to be of proven importance include histological type of tumor, grade, stage, adequacy of excision (expressed primarily as involvement of specimen margins and/or seminal vesicles in prostatectomies), and metastases. 10, 11

Certain pathologic factors have little if any practical prognostic value. Among these are perineural invasion in prostatectomies, percentage of tumor in needle biopsies, and transition zone vs peripheral zone involvement.

Factors such as tumor volume, genetic constitution, and microvessel density as well as DNA ploidy remain controversial. Until further experience can be accumulated, it seems prudent to view the rapidly expanding literature on prognostic factors with the proverbial "grain of salt" and to use caution when passing the costs of this information on to patients.

Treatment Effects on Prostatic Tissues

Treatment options for prostate cancer are limited. One can surgically excise the tumor, irradiate it, or deprive it of hormonal support. Attempts to freeze, burn, or vaporize it remain experimental. Surgery causes few alterations in cancerous glands, and most pathologists and clinicians involved with this treatment have considerable
experience in what to expect. Radiation therapy has been used for many years, but the pathologic changes directly associated with this form of treatment remain controversial.13 X rays have the potential to prevent division without killing the cell, thus creating cells with abnormal nuclei similar to what one might expect in a cancer. Our inability to distinguish cancerous from reactive phenotypes under these circumstances has rendered recognition of abnormal nuclear changes of relatively little value in the diagnosis of residual cancer after radiotherapy. More important to the diagnosis of cancer after radiotherapy is the preservation of an infiltrative growth pattern. Characteristically, residual neoplasms are composed of small glands with clear or vacuolated cytoplasm and nuclei essentially identical to those in non-irradiated neoplasms. Even so, it has not been possible to confirm the viability of these glands in individual cases. DNA synthesis, as demonstrated by a positive immunohistochemical reaction for MIB-1 (Ki67) or proliferative cell nuclear antigen (PCNA), might be helpful, but prostatic carcinomas are notorious for a slow cell turnover rate. As a practical matter, the majority of patients with histologically recognizable prostatic carcinoma occurring at least 12 months after radiotherapy will have clinical progression. Assessment for residual carcinoma can probably be improved by factoring in the serum PSA, especially if it is rising.14

Androgen deprivation therapy with various drugs as well as castration produces a more characteristic pattern of tissue changes than does radiotherapy. Basically, androgen deprivation therapy results in atrophy of both prostatic glands and stroma.15 Neoplastic glands tend to shrink away from one another, a phenomenon that results in both increased collagen separating them and an apparent lack of lumina within them. This plus a tendency for cytoplasmic clearing have caused many to overgrade carcinomas exposed to androgen deprivation. If grading of a hormonally treated prostate cancer is an issue, these factors must be kept in mind. Androgen deprivation therapy with leuprolide results in a statistically significant decrease in the frequency of positive specimen margins after prostatectomy for clinically organ-confined disease. The reasons are speculative but do not include failure of pathologists to recognize atrophic tumor. To date, the frequency of serum PSA levels >0.2 ng/mL after prostatectomies in such patients has not changed compared to patients without leuprolide pretreatment.16

Conclusions

The current status of pathology and anatomic pathologists in prostate cancer is a complex issue. The old paradigm, where pathology was relied on to define the nature of disease and anatomic pathologists functioned as a resource to clinicians, is breaking down. Responsibility for patient care is increasingly devolving on clinicians alone, as often as not radiotherapists rather than urologists, with pathology being asked to fulfill certain expectations and anatomic pathologists being expected to "read slides" and report results with a precision similar to that of a serum test. At the same time, pathology has developed impressive technological advances that enable anatomic pathologists to not only assess tumor DNA, cell and nuclear shape, antigenic composition, and genetic constitution, but also calculate a number of indices based on these parameters. Many clinicians and even patients demand this information, and pathologists are offering results based on these methods, justifying them by their added value to diagnosis or prognosis.

While an ever widening database seems good, the concentration on information gathering and transfer tends to marginalize anatomic pathologists from patient care, thus functionally depriving patients of one of their doctors while, if anything, potentially increasing costs. More functional alternatives should be explored. One such option might be to recognize that just as patients are treated locally, they should be evaluated and monitored in the same way. Patients with prostate cancer have at least two doctors and may acquire as many as five (pathologist, urologist, radiotherapist, radiologist, primary care physician). When assessing the value of prognostic information on treatment options, the medical knowledge of each doctor can be pooled to create a coordinated approach to patient care at the point of delivery. Paradigms for evaluation and utilization of information in the literature can be developed and records of results kept locally, thus allowing patients to evaluate the benefits and risks that have been achieved by the doctors directly responsible for their care. Patients should be informed that a pathology report is a medical consultation and that no one can attain 100% diagnostic accuracy. If necessary, patients may be asked to attest to their understanding that a finite error rate in pathologic diagnosis must be accepted. With the threat of litigation thus partially alleviated, anatomic pathologists should be expected to gain and maintain sufficient expertise to accurately assess prostatic biopsies and to refrain from the use of equivocating terminology. As at nearly all times, current trends in medicine offer almost as many pitfalls as promises. Despite seeming to want magic from their medicine, it is likely that patients are actually wishing for wisdom from their doctors, a wisdom that is difficult to achieve in the information age.

References

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Back to Cancer Control Journal Volume 5 Number 6