

The Role of the Pathologist in Diagnosing Prostate Cancer and Guiding Therapy

Michael H. Weinstein, MD, PhD

Introduction

The recognition that serum prostate-specific antigen (PSA) concentration is a marker for adenocarcinoma of the prostate and the ability to measure PSA concentration represent major watersheds in the treatment of prostate cancer. Prior to these advancements in the 1980s, enlargement of the prostate gland detected by digital rectal exam, local symptoms, or sequelae of metastatic disease were the usual means of discovery of prostate cancer. In this pre-PSA era, prostate cancers were usually incurable at the time of diagnosis. PSA screening has led to earlier detection and, although interpretation of recent epidemiologic data is still being debated, there is good evidence that PSA screening, prostate biopsy, and therapy with curative intent have led to decreased morbidity and mortality from this disease.¹

Also during the 1980s, refinements in the surgical technique for radical prostatectomy, which is potentially curative, yielded significant advancement in the treatment of prostate cancer by reducing the risk of morbidity associated with the surgery. These refinements hinged on two discoveries. First, elucidation of the venous plexus in the region of the prostate allowed operation in a "bloodless" field. This led to more accurate dissection, especially at the prostatic apex and, thus, greater preservation of urinary continence. Second, understanding the anatomy and function of the network of nerves around the prostate allowed "nerve-sparing" surgery and greater preservation of sexual function following radical prostatectomy.

These advancements required better means of screening and definitive diagnosis. PSA measurement and the thin-needle biopsy technique and equipment, although not perfect, are powerful tools for these purposes. Thin-needle biopsies cause less morbidity than open biopsy or biopsy with larger needles. As the pieces of tissue obtained by biopsy became much smaller, pathologists had to develop new techniques and expertise in interpreting these very thin biopsies.

PSA measurement has limitations, primarily in specificity, making this non-invasive test most useful as a first-line or

screening detection method. While a few patients with prostate cancer have a normal serum PSA concentration, there are a significant number of men without cancer who have an abnormal concentration for whom therapy would not be warranted.

Thin-needle biopsy, by contrast, has essentially 100% specificity. The sensitivity of this test is estimated to be at least 75%, meaning that it will accurately detect three-out-of-four true cancers. Although more than one set of biopsies may be required for diagnosis, the morbidity associated with thin-needle biopsy is very low.

"PSA screening has lead to earlier detection, and... there is good evidence that PSA screening, prostate biopsy, and therapy with curative intent have lead to decreased morbidity and mortality from this disease."

Pathologists have played a crucial role in the accumulation of the data upon which modern therapy is based, and they continue to provide essential information upon which medical oncologists, radiation oncologists, surgeons, and patients base their therapeutic and management decisions. This commentary is meant to outline the ways in which the clinical pathology laboratory and the work of pathologists serve as crucial components of the clinical decision-making process.

Michael H. Weinstein, MD, PhD, is Director of Pathology Laboratories at WakeMed Health and Hospitals in Raleigh, NC. Dr. Weinstein can be reached at MWeinstein@wakemed.org or 3000 New Bern Avenue, Raleigh, NC 27610. Telephone: 919-350-8260.

PSA Testing

Prostate-specific antigen (PSA) is a serine protease enzyme secreted by the glandular epithelium of the prostate into the ducts of the gland. It ultimately contributes to the composition of the seminal fluid. Its normal function is thought to be liquefaction of semen. Much lower concentrations are typically found in the blood, where the majority of PSA is protein-bound. Measurement of PSA concentration is based upon binding of a PSA-specific antibody to the substance. Multiple tests have been developed using different antibodies, and there is a variation in results between laboratories of up to 25% or more in the range of 0-6.0 ng/ml.² Moreover, some methods show greater precision than others. PSA testing has two principal uses. It is widely used to screen for prostate cancer and to monitor individual patients, either following therapy or during a "watchful-waiting" period. The variation between laboratories is of less significance when PSA testing is used for screening purposes than when following an individual patient. In the latter circumstance, it may be helpful to use a single, reliable laboratory for serial testing.

PSA Screening

The "normal" PSA concentration in men has been given as less than 4.0 ng/ml, although there is considerable disagreement over the threshold value that should prompt additional testing for prostate cancer. More recently, age-specific ranges have been given, including an upper limit of 2.5 ng/ml for men under the age of 50.^{3,4} Elevated serum PSA concentration is associated with multiple pathological processes and some situations in which there is no disease. Benign prostatic hyperplasia (BPH), prostatitis, and prostate cancer are the main pathologic states in which increased serum PSA is often seen. Prostate biopsy itself, ejaculation, and, possibly, exercise may also lead to an increase in the PSA.

It is the association of elevated PSA concentration with prostate cancer that has led to its utility in screening. The test is non-invasive (requiring only a blood sample through venipuncture) and is relatively inexpensive. Unfortunately, the range of PSA concentrations seen in patients with prostate cancer overlaps with the range seen in benign processes. The essential limitation is that there is no single value separating men with cancer from those without.

The *sensitivity* of a test is defined as the fraction of individuals with a specific disease for whom the test will yield a positive result. The *specificity* of a test is defined as the fraction of all abnormal results that represent individuals who do have the disease for which they are being tested. Decreasing the maximum PSA value that is considered "normal" increases the sensitivity of the test in detecting prostate cancer. However, this also leads to an increase in the number of men who are labeled "abnormal" who do not have this disease (decreased specificity). Thus, while measurement of serum PSA concentration has proved to be a powerful tool in the ability to detect prostate cancer, appreciation of its limitations is critical for maximization of its utility. In fact, average PSA concentration in men without prostate cancer increases with age. This is largely due to BPH, which increases in

incidence and severity. In truth, the PSA test is best used to estimate the chance that an individual has carcinoma of the prostate. PSA testing cannot be used to render a definitive diagnosis.

In an effort to increase sensitivity and specificity, derivative PSA tests have been developed. These include measurement of free PSA and calculation of the ratio of free/total PSA. These methods have yielded some increase in sensitivity and specificity with increased cost, but still suffer from an overlap in ranges in the populations of men with and without prostate cancer.^{5,6} They may provide additional guidance in difficult circumstances, such as when PSA levels are significantly elevated, multiple sets of biopsies have been negative, and no other explanation for the elevation in PSA level is apparent.

The ratio of free/bound PSA is considered abnormal by many when it falls below 25%. This cutoff is associated with sensitivity and specificity of approximately 90% and 25%, respectively, for the detection of prostate cancer.

PSA velocity is the rate at which the serum PSA concentration rises over time. This calculation is of some use in men with borderline elevated PSA.⁷ A PSA velocity greater than or equal to 0.75 ng/ml per year with measurements spanning at least 18 months has sensitivity and specificity of approximately 70% and 90%, respectively. Specific measurement of bound PSA has not been demonstrated to offer a significant improvement in detection.

PSA density, which is defined as the serum PSA concentration divided by the volume of the prostate as measured by transrectal ultrasound, has proven to have limited value.

Other tests potentially on the horizon include pro-PSA and human kallikrein-2, but these are not ready for routine clinical use in screening for prostate cancer.

PSA Monitoring

Serum PSA concentration is also useful for monitoring patients for progression of disease. Until late in the disease when the tumor may become so poorly differentiated that its ability to produce PSA protein becomes impaired, increasing PSA concentration is associated with advancing disease. Thus, the serum PSA typically falls to near zero following prostatectomy, since all of the prostate tissue, both benign and malignant has usually been removed. Minute amounts of tumor that may have spread beyond the prostate prior to surgery may not produce enough PSA to be detected until they grow, at which time the PSA concentration begins to rise.

The PSA often does not fall to zero in patients who have received radiation therapy without surgery. However, the PSA does fall for months following the treatments. In fact, the lower the nadir (lowest concentration detected) in PSA, the greater the chance of cure or long-term remission. Moreover, the longer the time it takes to reach the PSA nadir, the better the prognosis.⁸

Some patients with proven prostate cancer choose "watchful waiting" over therapy in order to avoid the morbidity associated with prostatectomy, radiation therapy, and hormonal therapy. A significant rise in serum PSA concentration may prompt physicians to recommend therapy to avoid morbidity and mortality associated with progression of the disease.

Prostate Biopsy

The thin-core needle biopsy technique and equipment allow multiple biopsies to be performed in the doctor's office with minimal morbidity (significant complications less than 0.5%) and provide material for definitive diagnosis of prostate cancer. The sensitivity of this procedure is very difficult to gauge. In the absence of metastatic disease, there is no way to tell with certainty whether a man has prostate cancer without pathologic examination of the entire prostate gland, which requires removal. Moreover, the sensitivity likely varies with the prevalence and type (i.e., grade, stage) of prostate cancer in the population being studied. However, based on data that do exist, a reasonable estimate for the sensitivity of needle biopsy of the prostate in patients with elevated PSA is at least 75%, if cancers detected on a second or later set of biopsies are included.

There is little debate about which areas of the prostate to biopsy, at least on the initial attempt to demonstrate tumor. However, the optimal number of biopsies to perform is not clear. The sextant biopsy technique (six biopsies) was considered adequate and was, by far, the most commonly used technique for approximately a decade. In recent years, it has become clear that performing more biopsies improves the chances of detecting cancer on the first attempt.⁹ This is especially true when the prostate is markedly enlarged due to BPH. However, more biopsies are associated with greater discomfort, a greater chance of complications, and greater cost. Moreover, the incremental increase in sensitivity with each additional biopsy diminishes progressively. At the present time, there is no agreement on how many biopsies more than six should be performed.

In addition to identifying the presence of cancer, the pathologist interpreting the biopsies routinely provides other indispensable information regarding the tumor. The following diagnostic categories should be included in the pathologist's report. The clinical significance of each is summarized in Table 1.

Tumor Grade

Tumor grade is probably the single most important tumor characteristic assessed on needle biopsy of the prostate. The Gleason grade, also termed Gleason score or Gleason sum, is very useful in predicting the behavior of a given patient's tumor. Thus, it is used in planning therapy and estimating prognosis. Although the grade of the tumor in the biopsies is not a perfect predictor of the grade of the tumor in the prostate as a whole, the correlation is good. The lack of perfect correlation is not surprising, since the volume contained in an entire set of biopsies usually comprises less than one thousandth of the volume of the entire prostate gland.

It is worth noting that each type of cancer specific to an organ in the body has its own histopathologic (microscopic) grading scheme. The Gleason grading scheme is very unusual in that it ignores the appearance of the individual cancer cells and concentrates purely on the patterns of growth of the malignant prostate glands. The method takes into account the common occurrence of multiple glandular patterns of cancer being present in a single patient's tumor. Numerals 1-5 have been assigned to recognized categories of tumor patterns, and, traditionally, the two most prevalent pattern types are given as well as the numeric sum. Thus, a Gleason grade of 3+4 = 7 might be reported, where "3" represents the tumor pattern most prevalent in a specimen and "4" represents the second most prevalent pattern. The Gleason score of a homogeneous tumor will simply have the same number repeated in the sum (e.g., 3+3 = 6). A consensus of genitourinary pathologists has recommended long-overdue modifications to the original scheme, which was devised around 1970, but the essential concepts remain unchanged. It is now recommended that small amounts of high-grade tumor (i.e., Gleason pattern 4 or 5) be reported even when they represent neither the first nor second most prevalent pattern, as this finding correlates with more aggressive tumor behavior.¹⁰

The combination of PSA concentration, findings from digital

Table 1.
Pathologic Parameters Assessed on Thin-Needle Core Biopsy of the Prostate and the Clinical Significance of Each Parameter.

Parameter	Clinical Importance
Tumor Grade	Used to predict aggressiveness of tumor, stage, response to non-surgical therapy, and chance of cure with various types of therapy.
Location and Extent of Tumor in Biopsy Cores	Used to predict stage and response to some types of therapy (e.g., radiation therapy).
Perineural Invasion	May be used to plan extent of surgery (e.g., whether to sacrifice neurovascular bundle).
Atypical Glands	Re-biopsy should be performed—indicate ~50% chance of finding cancer on re-biopsy.
High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)	~30% or less chance of finding cancer on re-biopsy, depending on how many biopsies originally performed. HGPIN may represent a precursor of prostate cancer.
Tumor Characteristics Following Therapy: Grade of tumor and whether therapy effect is present.	Used to assess prognosis and predict whether additional therapy is likely to be of benefit.

rectal exam, and biopsy Gleason grade has been used to estimate the stage of the tumor. The likelihood that the tumor is confined to the prostate, the chance of local spread into the surrounding fibroadipose tissue, the chance of invasion into the seminal vesicles, and the chance of local lymph node metastases can be estimated. These data have been compiled in the "Partin Tables,"¹¹ providing useful summary information to help each patient and his physician to make sensible decisions regarding choice of therapy.

Location and Extent of Tumor

The pathologist should report the amount of cancer present in the biopsy core(s) originating from each biopsy site. This information can be useful in estimating stage and predicting long-term outcome following therapy (e.g., prostatectomy, radiation therapy), especially when combined with other parameters, such as PSA concentration and tumor grade.^{12,13}

Perineural Invasion

The presence of invasion of small nerves in the biopsy cores by the cancer is predictive of spread beyond the prostate when viewed in univariate analyses.¹⁴ The reasoning behind these initial studies stemmed from the hypothesis, which is still accepted, that one of the main routes of tumor escape from the prostate is by tracking along nerves that traverse the surface of the prostate and comprise a portion of the periprostatic neurovascular bundles. However, most of the predictive power of the finding of perineural invasion on needle biopsy disappears in multivariate analyses when other variables, such as Gleason grade, are taken into account. Still, it may provide marginal additional information and may play a role in deciding whether or not to sacrifice one or both neurovascular bundles during surgery.

Atypical Glands

Unfortunately, a significant minority ($\approx 5\%$) of prostate biopsies are neither definitively benign nor definitively diagnostic of carcinoma. The term often used in this situation is "atypical," sometimes in the phrase "atypical small acinar proliferation" (ASAP). The frequency of this occurrence is somewhat dependent on the experience of the pathologist interpreting the biopsies. Special studies (e.g., immunohistochemical staining) can occasionally lead to a more definitive diagnosis, but diagnosis usually hinges on tried and true ordinary techniques (i.e., H&E staining). The finding of atypical glands suspicious for carcinoma without other, definitively diagnostic areas warrants repeat biopsy.^{15,16} In fact, the chance of finding prostate cancer on subsequent re-biopsy (one or more sets) is approximately 50%. Should re-biopsy prove inconclusive, other factors, such as total PSA concentration, free/total PSA ratio, clinical findings, and patient desire, provide guidance in choosing a course for repeat re-biopsy or longer-term follow-up with measurement of PSA velocity.

It should be noted that it is important for each biopsy to be separately labeled to designate the area of the prostate from which it originated. One reason for this is that 90% of all cancers discovered following an initial atypical, non-definitively diagnostic biopsy are identified in the same region or an area adjacent to

the one from which the atypical biopsy originated. Thus, these areas are preferentially sampled on re-biopsy in order to maximize the sensitivity of the procedure in detecting tumor.

High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Other findings that may increase the suspicion of cancer in the absence of definitively diagnostic biopsy material include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN). Early studies indicated that the risk of unsampled carcinoma in the prostate gland associated with the isolated finding of HGPIN on needle biopsy was approximately 30%.^{16,17} At the time, re-biopsy was required. However, if no carcinoma was detected on two sets of re-biopsies, additional biopsies were unlikely to contain tumor. More recent data, especially in the case of more than six biopsies to a set, suggest that the increased risk associated with this circumstance may be less than originally estimated, and the significance of this finding is somewhat diminished.

Since HGPIN is thought by many to represent a precursor of prostate cancer, it is postulated that potential chemopreventive agents may help to prevent prostate cancer in men who have been diagnosed with isolated HGPIN.

Other Clues to Tumor Behavior

Needle biopsy may provide other clues to tumor behavior. For example, prostate cancer clearly identifiable within fat at one end of a core biopsy is indicative of extraprostatic tumor spread. Clearly such information must be factored into therapeutic decisions.

Biopsy Following Therapy

Biopsy following therapy for prostate cancer is useful in a limited set of circumstances and poses challenges for the pathologist interpreting the biopsy. Therapy often alters the microscopic appearance of the tumor, sometimes making recognition of the malignant prostate tissue difficult. It can also alter the appearance of the tumor in ways that abolish the correlation between microscopic pattern and biologic behavior, so that Gleason grading of tumor following therapy is not meaningful in some circumstances.

A rising PSA following therapy is indicative of growing tumor. However, it does not indicate whether the tumor is growing at the primary site (i.e., in the prostate or in the prostatic bed after prostatectomy) or at a metastatic site. Radiographic studies (e.g., x-ray studies or computerized tomography scans) can be used to detect metastases. In the absence of detectable metastatic disease, biopsy of the prostate or prostatic bed may be performed to assess for local tumor growth. As with initial biopsy, skill is required on the part of the pathologist to properly interpret the changes due to therapy and to give an accurate assessment of the presence of cancer and, sometimes, whether it shows effects of therapy.

Pathologic Assessment of Prostatectomy Specimens

Pathologic review of the prostate after it has been removed for cancer also provides important information regarding prognosis and whether further therapy (e.g., radiation therapy) might be of benefit. The main pathologic parameters evaluated are tumor grade, stage (extent of cancer), and whether there is cancer at the surface of the specimen, which might indicate that not all of the tumor was removed. Other parameters may also have prognostic impact.

Tumor Grade

As with prostate biopsy, the recently modified Gleason grading system is used to grade prostate cancer in the prostatectomy specimen. Tumor grade is a powerful predictor of outcome, including risk of recurrence and time to recurrence. Minor discrepancies between the grade assigned on biopsy and the grade obtained from the whole prostate specimen are common. This is typically due to the fact that prostate cancers are usually heterogeneous. Only about one thousandth of the prostate is sampled even with multiple thin-needle core biopsies, and the tissue obtained may not be perfectly representative of the entire tumor.

Lymphovascular Invasion

Careful microscopic examination of the prostatectomy specimen may reveal the presence of tumor within minute lymphatic or blood vessels. It is a significant factor indicative of a poorer prognosis. This finding is rarely discernable on biopsy.

Tumor Stage

Tumor stage is crucial in determining whether adjuvant therapy is likely to be of benefit. Staging is performed according to the American Joint Committee on Cancer (AJCC) guidelines.¹⁸ For example, invasion of the tumor into the adjacent fibroadipose tissue is designated stage T3a. Tumor invasion into either or both of the seminal vesicles is designated T3b, which supercedes T3a, and invasion into surrounding organs, such as the bladder, is designated T4. The absence or presence of metastatic spread into local lymph nodes (i.e., pelvic lymph nodes) is noted as N0 or N1, respectively, and the absence or presence of metastatic spread beyond this is designated M0 or M1. Thus, one might have a patient with staging "T3b N0 M1" if tumor has spread to the seminal vesicles and the spine, but is absent from the pelvic lymph nodes.

Margin Status

The final feature that must be assessed on the prostatectomy specimen is whether prostate cancer is present at the surface of the specimen. This is termed margin positivity and may, especially if it is present in more than a small area, be indicative of local tumor that could not be excised at the time of surgery. The pathologist should report the extent and location of tumor present at the margins. Like tumor stage, this information is needed to make decisions regarding subsequent adjuvant therapy.

Summary

In summary, the role of the pathologist has proven indispensable in diagnosing prostate cancer, planning initial therapy,

Table 2.
Utilities of Various Pathologic Parameters in Detecting Prostate Cancer and in Guiding Therapy.

	Determining need for biopsy/ re-biopsy	Planning initial therapy/ prognosis	Assessing likelihood of benefit from adjuvant therapy	Assessing for recurrence/ progression
PSA				
PSA Concentration	X	X	X	X
PSA Velocity	X			
PSA Density	X			
Free/Total PSA	X			
Biopsy				X
Tumor Grade		X	X	
Location/Extent of Tumor		X		
Perineural Invasion		X		
Atypical Glands	X			
HGPIN	X			
Prostatectomy				
Tumor Grade		X	X	
Stage		X	X	
Lymphovascular Invasion		X	X	
Margin Status		X	X	

assessing prognosis, estimating the likely benefit of adjuvant therapy following prostatectomy or radiation therapy, and in following patients for possible recurrent disease. Moreover, the work of pathologists has been pivotal in the research that has lead to our

present understanding of the natural history of prostate cancer and the present methods for estimating the likelihood of benefit from various therapies. Such work continues to be integral to scientific advancement in these areas. **NCMedJ**

REFERENCES

- 1 Horninger W, Berger A, Pelzer A, Klocker H, Oberaigner W, Schönitzer D, Severi G, Robertson C, Boyle P, Bartsch G. Screening for prostate cancer: Updated experience from the Tyrol study. *Can J Urol* 2005;12(suppl 1):7-13.
- 2 College of American Pathologists. Participant Summaries for Ligand (General) Proficiency Surveys K/KN-A, K/KN-B, K/KN-C, 2005.
- 3 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA. Prevalence of prostate cancer among men with a prostate-specific antigen level less than/equal to 4.0 ng per milliliter. *N Engl J Med* 2004;350(22):2239-2246.
- 4 Loeb S, Roehl KA, Antonor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology* 2006;67(2):316-206.
- 5 Froehner M, Hakenberg OW, Koch R, Schmidt U, Meye A, Wirth MP. Comparison of the clinical value of complexed PSA and total PSA in the discrimination between benign prostatic hyperplasia and prostate cancer. *Urologia Int* 2006;76:27-30.
- 6 Basso D, Fogar P, Piva MG, Navaglia F, Mazza S, Prayer-Galetti T, Castellucci E, Pagano F, Plebani M. Total PSA, free PSA/total PSA ratio, and molecular PSA detection in prostate cancer: Which is clinically effective and when? *Urology* 2000;55:710-715.
- 7 Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. *Urol Clin North Am* 1997;24:333-338.
- 8 Ray ME, Thames HD, Levy LB, Horowitz EM, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Shipley WU, Zelefsky MJ, Zietman AL, Kuban DA. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: A multi-institutional analysis. *Int J Radiat Oncol Biol Phys* 2006;64(4):1140-1150.
- 9 Siu W, Dunn RL, Shah RB, Wei JT. Use of extended pattern technique for initial prostate biopsy. *J Urol* 2005;174(2):505-509.
- 10 Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, ISUP Grading Committee: The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005;29(9):1228-1242.
- 11 Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI., Pearson JD. Prostate Cancer: The Partin Tables. Available at: <http://urology.jhu.edu/prostate/partintables.php>. Accessed March 27, 2006.
- 12 Rubin MA, Bassily N, Sanda M, Montie J, Strawderman MS, Wojno K. Relationship and significance of greatest percentage of tumor and perineural invasion on needle biopsy in prostatic adenocarcinoma. *Am J Surg Pathol* 2000;24(2):183-189.
- 13 D'Amico, AV. Combined-modality staging for localized adenocarcinoma of the prostate. *Oncology* 2001;15(8):1049-1059.
- 14 Cannon GM Jr, Pound CR, Landsittel DP, Bastacky SI, Dhir R, Becich MJ, Nelson JB. Perineural invasion in prostate cancer biopsies is not associated with higher rates of positive surgical margins. *Prostate* 2005;63(4):336-340.
- 15 Girasole CR, Cookson MS, Putzi MJ, Chang SS, Smith JA Jr, Wells N, Oppenheimer JR, Shappell SB. Significance of atypical and suspicious small acinar proliferations, and high grade prostatic intraepithelial neoplasia on prostate biopsy: implications for cancer detection and biopsy strategy. *J Urol* 2006;175(3):929-933.
- 16 Schlesinger C, Bostwick DG, Iczkowski KA. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. *Am J Surg Pathol* 2005;29(9):1201-1207.
- 17 Weinstein MH, Epstein JI. Significance of high-grade prostatic intraepithelial neoplasia on needle biopsy. *Hum Pathol* 1993;24(6):624-629.
- 18 American Joint Committee on Cancer. *AJCC Cancer Staging Manual*, 6th Ed, Springer-Verlag, New York, 2002.