The Critical Role of the Pathologist in Determining Eligibility for Active Surveillance as a Management Option in Patients With Prostate Cancer

Consensus Statement With Recommendations Supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation

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• ***Context.***—**Prostate cancer remains a significant public health problem. Recent publications of randomized trials and the US Preventive Services Task Force recommendations have drawn attention to overtreatment of localized, low-risk prostate cancer. Active surveillance, in which patients undergo regular visits with serum prostate-specific antigen tests and repeat prostate biopsies, rather than aggressive treatment with curative intent, may address overtreatment of low-risk prostate cancer. It is apparent that a greater awareness of the critical role of pathologists in determining eligibility for active surveillance is needed.**

Objectives.—**To review the state of current knowledge about the role of active surveillance in the management of prostate cancer and to provide a multidisciplinary report focusing on pathologic parameters important to the successful identification of patients likely to succeed with active surveillance, to determine the role of molecular tests in increasing the safety of active surveillance, and to provide future directions.**

Design.—**Systematic review of literature on active surveillance for low-risk prostate cancer, pathologic parameters important for appropriate stratification, and issues regarding interobserver reproducibility. Expert panels were created to delineate the fundamental questions confronting the clinical and pathologic aspects of management of men on active surveillance.**

Results.—**Expert panelists identified pathologic parameters important for management and the related diagnostic and reporting issues. Consensus recommendations were generated where appropriate.**

Conclusions.—**Active surveillance is an important management option for men with low-risk prostate cancer. Vital to this process is the critical role pathologic parameters have in identifying appropriate candidates for active surveillance. These findings need to be reproducible and consistently reported by surgical pathologists with accurate pathology reporting.**

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In December 2011, the National Institutes of Health conducted a state-of-the-science conference with a summary statement on the role of active surveillance in the management of men with localized prostate cancer.[1] In the conference, there were concerns expressed about the accuracy and consistency of pathologic information in prostatic needle biopsies and how that affected patient eligibility, patient management, and the success of the entire modality of active surveillance (AS). The concerns were largely related to the lack of widespread understanding by clinicians and pathologists of the important role of needle biopsy findings in determining their eligibility for AS as a management option for men diagnosed with prostate cancer.

Discussions were initiated by the College of American Pathologists, which had become aware of the controversy through its pathologist members. The discussions included other relevant pathology organizations—the International Society of Urological Pathology (ISUP) and the Association of Directors of Anatomic and Surgical Pathology—with the goal of creating a consensus publication that would outline, with recommendations, the critical role of the pathologist in helping to determine the appropriate candidates among patients with prostate cancer who would benefit from AS as a management option. The National Institutes of Health/National Cancer Institute, organizers of the state-of-the-science conference, were informed that members of the pathology community would work on creating such a resource that could be circulated within the pathology and urology communities, which was one of the needs identified at the conference.

Leadership from the College of American Pathologists, ISUP, and the Association of Directors of Anatomic and Surgical Pathology identified 3 key issues and a group of individuals who would help in formulating a resource document to address: (1) clinical perspective on AS; (2) pathologic parameters critical to stratifying patients in AS protocols; and (3) the role of ancillary molecular diagnostic tests to increase the safety of AS. Project leaders Mahul Amin, MD, and Elizabeth Hammond, MD, identified 4 teams: team 1, clinical perspective on active surveillance (Daniel Lin, MD; and John Gore, MD, MS [team leads]; John Nacey, MD; Ballentine Carter, MD; Laurence Klotz, MD; Howard Sandler, MD; Anthony Zietman, MD; and Stuart Holden, MD); team 2, tumor quantification and other pathologic parameters (John Srigley, MD; and Hema Samaratunga, MBBS [team leads]; Rodolfo Montironi, MD; Peter Humphrey, MD, PhD; and Andrew Evans, MD); team 3, Gleason grading of prostate cancer (Lars Egevad, MD [team lead]; Jonathan Epstein, MD; Brett Delahunt, MD; Mahul Amin, MD; Jesse McKenney, MD; Dan Berney, MD; and Thomas Wheeler, MD); and team 4, ancillary molecular diagnostic tests (Mark Rubin, MD [team lead]; Arul Chinnaiyan, MD, PhD; Lawrence True, MD; and Beatrice Knudsen, MD, PhD).

There were 2 face-to-face meetings at the 101st and 102nd Annual Meeting of the United States and Canadian Academy of Pathology in Vancouver, British Columbia, Canada, and Baltimore, Maryland, in March 2012 and 2013. Numerous conference calls and e-mail communications between team leads and members within respective teams occurred in the ensuing 24 months, with each team lead preparing a consensus document for their respective teams. A Web-based, shared electronic folder was made available for each team to insert relevant documents of interest. The College of American Pathologists provided operational, logistic, and administrative support for the face-to-face and virtual meetings. This manuscript reflects the combined product of those deliberations.

CLINICAL PERSPECTIVE ON ACTIVE SURVEILLANCE (TEAM 1)

Epidemiology of Prostate Cancer

Prostate cancer is an important public health burden and remains the most common cancer among men in the United States, and it accounts for more cancer-specific deaths in men than any cancer, other than lung cancer.[2] Most men newly diagnosed with prostate cancer will opt for primary curative therapy, either with surgery to remove the prostate (radical prostatectomy) or radiation to eradicate the cancer.[3] Most prostate cancers, however, are indolent,[4,5] and the number of newly diagnosed prostate cancers far outnumbers the number of lethal cases. The magnitude of this so-called overdiagnosis, where cancers are identified that would never progress or cause harm to the patient if left untreated (not to be confused with a false-positive cancer diagnosis), ranges anywhere from 15% to 84% of new prostate cancer cases.[6–8] Most new prostate cancers are diagnosed based on abnormal screening results with the prostate-specific antigen (PSA) test. Although PSA screening may partially account for the 49% decline in prostate cancer deaths since the early 1990s,[9] large, randomized trials of PSA screening of men for prostate cancer on mortality have yielded mixed results.[10,11] Those studies have been confounded by high contamination, prescreening in the control population, and limited follow-up time, yet they clearly confirm substantial overdiagnoses. Despite that, PSA screening practices changed minimally after publication of those trials.[12]

The PSA testing practices may change, however, following publication of formal recommendations of the US Preventive Services Task Force against PSA screening for prostate cancer[13] and the results of the Prostate Cancer Intervention Versus Observation Trial.[14] The US Preventive Services Task Force D recommendation against PSA screening was largely based on the United States and European screening trials and the determination that the harms of screening outweighed any demonstrated benefit to patients. Patients in the Prostate Cancer Intervention Versus Observation Trial undergoing prostatectomy had similar survival rates to observed patients 12 years after enrollment, although the study suffered from accrual limitations, extensive crossover between treatment groups, and poor generalizability of the participant population. Despite those highly publicized studies, screening and treatment of prostate cancer will likely remain prevalent. Patients continue to drive prostate cancer screening,[15,16] and some guidelines continue to promote informed decision-making between physician and patient about PSA screening.[17]

Overdiagnosis is problematic for several reasons. Patients are exposed to the risk of overtreatment. Even if overtreatment is avoided, overdiagnosis induces anxiety associated with the new cancer diagnosis, often results in further tests and expenses, and confers on the patient a *survivor* label he carries for the rest of his life. Male offspring may worry about familial inheritance and increased risk of the disease.

Table 1. Participant Characteristics and Inclusion Criteria for Several Large Active Surveillance Cohorts

Source, y	Patients, No.	Age, y	Nonwhite, %	Inclusion Criteria: Clinical Stage	PSA, ng/mL	Gleason Score	Prostate Biopsy,[a]	Other Criteria
Lin et al,[152] 2013	351	63.8[b]	9	≤T2	≤10	≤7 (3 + 4)	≤33A	
Cooperberg et al,[31] 2011; and Glass et al,[52] 2012	640	62[c]	18	≤T2	≤10	≤6	≤33B, ≤50C	
Klotz et al,[33] 2010	453	70[c]	NR		≤15	≤7 (3 + 4)		
Selvadurai et al,[172] 2013	471	66[c]	NR	≤T2a	≤15	≤7 (3 + 4)	≤50B	
Adamy et al,[173] 2011	238	64[c]	NR	≤T2	≤10	≤6	≤3D, ≤50C	
Bul et al,[174] 2013	2494	65.8[c]	NR	≤T2	≤10	≤6	≤2D	PSAD ≤ 0.20
Patel et al,[175] 2014	870	66[c]	10	T1c		≤6	≤2D, ≤50C	PSAD ≤ 0.15

Abbreviations: NR, not reported; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.

[a] Biopsy code: A, percentage of positive cores; B, percentage of cores; C, percentage of any core; D, No. of cores.
[b] Mean.
[c] Median.

Overtreatment is a common consequence of overdiagnosis. In the United States, most men diagnosed with low-risk prostate cancers still undergo primary curative therapy.[5,18,19] Reasons that may drive this overtreatment include physician and patient uncertainty about the precision of their clinical knowledge of the cancer's extent and growth rate.[19] Similarly, both physicians and patients may be concerned that current monitoring tools are neither sensitive nor specific enough to ascertain disease progression without compromising the curability of the treatment. Physicians have a tendency to underestimate the morbidity of their own treatments; thus, many men are subject to the side effects of prostate cancer treatment—including urinary dysfunction, impotence, and bowel problems—without substantial survival benefit.

Rationale for AS

With increasing prevalence of PSA screening in the United States, the proportion of men presenting with metastatic prostate cancer has declined dramatically,[20] and most new diagnoses today are categorized as being at low risk for progression.[5] Risk stratification schemes use pretreatment clinical information to prognosticate a patient's probability of suffering a recurrence of their prostate cancer after primary curative therapy. The risk stratification adopted by the National Comprehensive Cancer Network combines pretreatment PSA, Gleason score, and clinical stage based on digital rectal examination (DRE). Low-risk patients have PSA results of less than 10 ng/mL; Gleason scores of, at most, 6; and clinical stages of T2a or less (on examination, a nodule that occupies less than one-half of one side of the prostate).[21,22]

Given the indolent course of many prostate cancers detected by PSA screening,[23] AS has emerged as an initial management alternative for prostate cancer.[24–26] Active surveillance has been incorporated into national guidelines.[22] On AS, men avoid the side effects of prostate cancer treatment. Under most AS strategies, patients undergo careful monitoring of the cancer, most often with PSA kinetics and serial biopsies. Selective intervention under AS is usually based on those parameters and that any progression of the cancer while patients are monitored appears unlikely to threaten their quality or length of life.[27,28] Selection for AS focuses on the low- and very low-risk patients. Importantly, AS is distinguished from *watchful waiting*, in which treatment for localized disease is withheld and treatment for palliation of systemic disease is initiated. Watchful waiting is usually for older patients or for those with significant comorbidity, where life expectancy is unlikely to be affected by the prostate cancer.[29]

Selection, Surveillance, and Treatment of Men on AS

Table 1 describes the largest AS cohorts with inclusion criteria for consideration for AS. In general, men who are candidates for AS have low-grade, low-volume prostate cancers. Specific inclusion criteria for AS vary across institutions that have reported on their AS cohorts.[27] Other than cancer-specific clinical data comprising risk stratification, patients are further selected for AS based on their age, PSA density (PSA/prostate volume), percentage of positive biopsy cores, the extent of prostate cancer in any core, and measures of PSA kinetics, such as PSA velocity.[27] Many of those cohorts include patients with intermediate-risk clinical parameters, most commonly by allowing for inclusion of patients with a PSA result at diagnosis greater than 10 ng/mL or by including select men with Gleason 3 + 4 = 7 prostate cancer. Those studies often select men older than 70 years or those with significant comorbidities. Single institution reports have documented that extending AS inclusion criteria to selected higher-risk patients can be done safely without compromising cancer-specific outcomes; although that remains controversial and is reserved only for exceptional clinical circumstances.[30,31]

Surveillance schedules for AS vary across institutions (Table 2) and may even vary within a single institution. Most experts in prostate cancer agree that surveillance should include a combination of serial PSA and rectal examinations as well as repeat prostate biopsies.[22] However, there is little consensus regarding the frequency with which those tests should be performed. Some advocate for an annual prostate biopsy,[32] whereas others offer less-frequent biopsies.[33] Emerging technologies may be of some assistance on this issue because, in recent years, there has been a growing interest by urologists and radiologists in the use of multiparametric magnetic resonance imaging (MRI) to perform targeted prostate biopsies.[34,35] This modality has the potential to refine both the selection and the monitoring of patients on AS protocols.

A proportion of men on AS experience prostate cancer biopsy grade reclassification (Table 3). Definitions of progression include various measures of PSA change (eg, PSA doubling time), changes in clinical staging or imaging results, and findings on repeat biopsy that are indicative of a larger or higher-grade cancer (ie, increased Gleason score,

Table 2. Surveillance Schedules for Several Large Active Surveillance Cohorts			
Source, y	Patients, No.	PSA and DRE	Repeat Prostate Biopsy, mo After Diagnosis
Newcomb et al,[176] 2010	351	PSA, every 3 mo; DRE, every 6 mo	6–12 then 24 then every 2 y
Dall'Era et al,[55] 2008	640	Every 3 mo	Every 12–24
Tosoian et al,[177] 2011	870	Every 6 mo	Every 12
Klotz et al,[33] 2010	453	Every 3 mo for 2 y then every 6 mo	6–12, then every 3–4 y
Royal Marsden, London, UK[172]	471	Every month for a year, then every 3 mo for a year, then every 6 mo	18–24, then every 2 y
Memorial Sloan-Kettering Cancer Center, New York, NY[173]	238	Every 6 mo	12–18, then every 2–3 y
PRIAS[174]	2494	Every 3 mo for 2 y, then every 6 mo	1, 4, 7, and 10 y

Abbreviations: DRE, digital rectal examination; PSA, prostate-specific antigen.

increased number of cores with cancer, or an increase in the percentage of involved cores).[27,36–38] The value of serial PSA examinations has been questioned. Following a prostate cancer diagnosis under an AS protocol and in the setting of serial prostate biopsies, PSA kinetics may be less informative than prediagnosis PSA level in determining the need for prostate biopsy and posttreatment for cancer follow-up.[39] Although PSA result changes over time certainly provide some insight into prostate cancer tumor biology, the precise definition of PSA progression on AS is controversial.[40–42] Some groups do not use PSA kinetics to define reclassification on AS.[27] Depending on the specific definition of PSA failure, PSA progression could occur in anywhere from 0% to 49% of cases.[43,44] At this time, although PSA levels and PSA kinetics are gathered, they are not used to define progression on AS. Biopsy-grade reclassification has emerged as a more meaningful endpoint for men on AS. Higher-grade tumors (Gleason 7 and higher) clearly confer a higher likelihood of clinical progression. Currently, prostate biopsy remains the only method to ascertain prostate cancer grade. For that reason, a confirmatory biopsy within 1 year of initial diagnosis has been proposed to avoid misclassification.[45] Anterior-location tumors, particularly in African-American men, may lead to undetected cancer and misclassification and should be factored into initial sampling strategies.[46]

A finding of upgrading cancer on repeat biopsy commonly prompts treatment. Such an upgrading may represent undersampling at the time of initial diagnostic biopsy, where the preexisting, high-grade prostate cancer was missed. Typical biopsy templates have changed over time, transitioning from lesion-directed biopsies before the advent of transrectal ultrasound-guided prostate biopsy to systematic biopsy templates that initially sample 6 areas within the prostate.[47] Contemporary biopsy templates sample 12 to 16 areas within the prostate, but cancers can still be missed. The detection of high-grade prostate cancer may also represent true biologic-grade progression or the emergence of new foci of higher-grade cancer in a multifocal disease. Beyond grade, other biopsy parameters used to signify progression include an increase in the volume of prostate cancer based on the number of involved cores or the percentage of involvement within an individual biopsy core.

Treatment of men on AS is also used as a marker of progression, although a substantial proportion of men are treated without objective signs of progression based on PSA, Gleason score, or biopsy volume.[27] Treatment before clinical progression is often attributed to anxiety about cancer progression.[48] Men may also have preferences that make AS a poor fit, despite their low risk for cancer-specific adverse health outcomes. Misalignment between pretreatment preferences and quality-of-life detriments and subsequent treatment selection is common in prostate cancer.[49] Among men on AS, that misalignment would contribute to the occurrence of treatment without objective clinical progression. Provider barriers also limit maximal use of AS for low-risk prostate cancer. The fee-for-service structure of US health care incentivizes providers to treat men with newly diagnosed prostate cancer, although models have estimated that—long term—AS is associated with greater total clinician reimbursement than radical prostatectomy.[50] For many clinicians, the uncertainty around the accuracy of clinical prostate-cancer staging limits their confidence in recommending AS. In the United States, few men who are young and free of comorbid disease at the time of prostate cancer diagnosis undergo AS.[51] In Canada, where the incentives for intervention are more modest, AS has been widely adopted for low-risk disease, largely irrespective of age.

Table 3. Progression on Active Surveillance From Several Large Active Surveillance Cohorts						
		Definition of Progression		Rates of Progression		
Source, y	Patients, No.	PSA, ng/mL	Prostate Biopsy[a]	Median Follow-up, mo	Grade Progression, %	Treated, %
Tomlins et al,[152] 2013	351	>10	>33A	20	9	15
Cooperberg et al,[31] 2011; and Glass et al,[52] 2012	640	PSAV > 0.75	>6B	47	35	32
Tosoian et al,[177] 2011	870		>6B or >2C or >50D	36	18	33
Klotz et al,[30] 2010	453	PSADT < 3 y		82	9	30
Selvadurai et al,[172] 2013	471	PSAV > 1	Primary ≥4B or >50E	68	28	31
Adamy et al,[173] 2011	238	≤10	>6B or >3C or >50D	22	13	11
Bul et al,[174] 2013	2494	PSADT < 3 y	>6B or ≥3C	19	14	21

Abbreviations: PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSAV, prostate-specific antigen velocity.

[a] Biopsy code: A, percentage of positive cores; B, Gleason score; C, No. of cores; D, percentage of any core; E, percentage of cores.

Table 4. Essential Reporting Elements for Cancer-Bearing, Prostatic Needle Biopsies

- Histologic type
- Number of positive cores
- Location of positive cores
- Tumor quantitation
- Gleason grades and score
- Other (reported only if present)
  - Extraprostatic extension
  - Perineural invasion
- Other atypical acinar foci suspicious for carcinoma

Table 5. Tumor Extent Measurements

- Number of positive cores
- Fraction of positive cores
- Linear percentage × carcinoma in each site (core)
- Linear percentage carcinoma in core with the greatest amount of tumor
- Overall linear percentage of carcinoma across all sites (cores)
- Linear millimeters of carcinoma in each site (core)
- Linear millimeters of carcinoma in the core with greatest amount of tumor
- Total linear millimeters of carcinoma across all sites (cores)

Although biopsy or clinical reclassification occurs, the delay in intervention for those patients does not compromise cancer-specific outcomes. From the cohorts listed in Tables 1 through 3, overall survival for patients on AS ranges from 68% to 100%, with survival being highly dependent on the median follow-up for the cohort.[52] Cancer-specific survival ranges from 97% to 100%; thus, few men die from prostate cancer as a result of delays in primary curative treatment while on AS. Models have extrapolated the short-term results from AS cohorts and estimated that immediate treatment confers an average 1.8-month increase in life expectancy over AS for low-risk prostate cancer.[28] The 20-year risk of prostate cancer–specific mortality was 2.8% for men on AS, compared with 1.6% for men treated immediately.

THE INFLUENCE OF TUMOR EXTENT MEASUREMENTS AND OTHER PATHOLOGIC FINDINGS (EXCEPT GLEASON GRADING) IN ACTIVE SURVEILLANCE PROTOCOLS (TEAM 2)

Given that some patients with apparent low-risk cancer have underlying high-risk disease undetected at the time of diagnosis, appropriate patient selection for AS is of paramount importance. To that end, accurate histopathologic diagnosis is crucial. It is the pathologist's responsibility to provide the necessary information on needle biopsy histologic evaluation (Table 4). Considering the number of clinical and pathologic criteria used to determine whether a patient with prostate cancer is suitable for AS, Gleason score is one of the most significant. Issues around the Gleason system are covered in the team 3 section of this document. The other pathologic factors to be considered include tumor extent measurements, the histologic subtype of carcinoma, perineural invasion (PNI), and involvement of periprostatic fat. Clearly, patients with the latter finding should not be considered candidates for AS because the tumor is already extraprostatic. Herein, we examine evidence from the literature and suggest guidelines about the most appropriate methods to be followed.

Tumor Location

Understanding the extent and location of the cancer is important in patient selection for AS. Tumor location is reported by pathologists based on the site of the biopsy as designated during submission of the specimen. Pathologists can only report location based on information provided. It is, therefore, essential that site-specific, targeted biopsies include clearly specified locations and that biopsy cores be separated and submitted accordingly for appropriate reporting and documentation of positive/negative cores. Although the effect of tumor location at the time of the first diagnosis of cancer and site-specific targeting of positive biopsy locations for determination of subsequent detection/progression of cancer in patients on AS has not been studied, such information may be valuable during further follow-up of those patients.

Tumor Extent Measurements and Methodologies

Tumor extent measurements are used for patient selection in most AS protocols. Variation exists in the specific measurements used in various protocols, and there is no consensus on the best method or methods. Measurements include the number of positive cores, the fraction of positive cores, the linear percentage of carcinoma in each site (core), the linear percentage of carcinoma in the core with greatest amount of tumor, the overall linear percentage of carcinoma across all sites (cores), the linear millimeters of carcinoma in each site (cores), the linear millimeters of carcinoma in the core with greatest amount of tumor, and the total linear millimeters of carcinoma across all sites (cores) (Table 5).

Tumor measurements are usually performed as a visual estimate or with a ruler or an ocular micrometer on the side graticule. The knowledge of the diameter of the field at each magnification for the microscope used to measure tumor extent can also help maximize accuracy of a visual estimation of length. Occasionally, other morphometric measurements, such as computerized methods, are employed. Visual estimation of the percentage without morphometric measurements is commonly performed,[53] although many recent studies do not actually describe whether visual estimation or morphometric measurements were used.[32,45,54,55] Some clinicians use a regular ruler or the side graticule available on most microscopes for estimation of tumor length and percentage.

In general, and unless specifically stated otherwise, the visual estimate of carcinoma involves determining the percentage of the linear extent or the linear millimeters of tumor along the long axis of the core or cores and not the percentage of area occupied by the tumor or the actual area of the tumor in millimeters.[56]

In a recent abstract, Mahamud et al[57] found no overall difference between visual estimations and measurements when determining the percentage of involvement from prostate biopsies assessed only by whole-slide images. However, there was a significant difference between the 2 methods when they considered a subset of cores deemed to have 40% to 60% involvement by visual estimation. This observation is particularly germane to cases where more than 50% involvement of any core would exclude a patient from an AS protocol. It is unclear whether the accuracy of

Table 6. Recommendations for Reporting Carcinoma Extent in Prostate Needle Biopsy Tissue

College of American Pathologists[a]

- Number of cores positive/total number of cores
- Proportion (linear percentage) of prostatic tissue involved by tumor, and/or
- Total linear millimeters of carcinoma/length of core(s)

Association of Directors of Anatomic and Surgical Pathology[b]

- Absolute number of involved cores out of total number of cores and
- Linear extent of tumor (in millimeters) per core or total or
- Percentage of cancer in each involved core

World Health Organization[c]

- Number of cores involved (if possible, include percentage of cores involved)
- Amount of carcinoma in biopsy specimen (either of the 2 methods listed can be used)

Optional

1. Composite (global) percentage of carcinoma in all needle biopsy tissue
2. Percentage of carcinoma in most extensively involved core

[a] Data derived from Meng et al[36] and Srigley et al.[72]
[b] Data derived from Epstein et al.[73]
[c] Data derived from Amin et al.[74]

the visual estimation of an image can be compared with that of a tissue core on a glass slide on a microscope. Data are conflicting about whether morphometric measurements are superior to visual estimations and whether differences in the 2 methods would affect clinical management.[58] Computerized morphometric measurements are time-consuming and not practical for most pathologists. Measurements of core length given in gross descriptions are suboptimal because they may not always be accurate.

A few studies have assessed the value of the different methods of tumor extent measurement in prostate needle biopsies in predicting pathologic stage or prognosis.[58–65]

Quintal et al[59] found that the total percentage of carcinoma in all cores and the number and percentage (fraction) of cores with cancer were significantly stronger than other methods, such as greatest linear percentage of cancer or greatest millimeter length in a single core, in predicting biochemical recurrence. Total percentage of carcinoma in all cores had the strongest correlation, and, when combined with preoperative PSA and Gleason score, improved prediction of pT3 in multivariate analysis ($P < .05$), independent of the risk of biochemical recurrence. Bismar et al[60] found that, although many tumor measurements, such as greatest linear percentage of cancer, total tumor length in millimeters, the fraction of positive cores, and the total percentage of carcinoma, were significant in univariate analysis, only the fraction of positive cores was significant in multivariate analysis in predicting pT3 disease or positive margins ($P < .001$). In that study,[60] all the measures were highly related to one another in a formal correlation analysis.

Park et al[61] examined the significance of the number of cores positive for cancer, the percentage of positive biopsy cores, the total linear cancer length, the total percentage of carcinoma, and the maximum cancer core length and found that, when considering PSA and Gleason score, none were significant in predicting pT3 disease in multivariate analysis. In a study by Brimo et al,[62] the fraction of positive cores, the total percentage of carcinoma, and both the total and the greatest cancer core length were closely associated with pathologic stage and biochemical failure. The fraction of positive cores was found to be the factor most closely associated with pT3 disease in radical prostatectomy ($P < .001$).

Correlating needle biopsy cancer measurements with tumor volume in radical prostatectomy, Poulos et al[63] found that the highest percentage of carcinoma in any biopsy site ($P = .01$), the percentage of adenocarcinoma at the biopsy site with the highest Gleason score ($P = .02$), the number of positive biopsy sites ($P = .03$), and tumor bilaterality ($P = .008$) were significant as predictors, with the percentage of biopsy sites positive for disease ($P < .001$) being the most-significant predictor of tumor volume. Sebo et al[64,65] used the percentage of surface area in prostate needle-biopsy volume assessment. They found that the joint predictors of tumor volume at radical prostatectomy were the percentage of cores positive for carcinoma ($P < .001$), the percentage of surface area positive for carcinoma ($P < .001$), the serum PSA result ($P < .001$), and the number of S-phase nuclei ($P = .03$). Percentage of surface area was not found to be significant in predicting extraprostatic extension. In another study,[66] tumor volume was best predicted by a combination of the linear extent of the carcinoma and the number of positive cores.

In a survey sent to 93 genitourinary pathologists,[67] the extent of cancer on needle biopsies was quantified by all respondents, with 80% reporting the number of cores involved by cancer. Linear extent was estimated by almost all participants, either as a percentage (80%) or as millimeters of cancer length (41%) or as both (22%). In a survey among 266 European pathologists, extent was most often given in millimeters (53%) followed by the percentage in each core (40%). Few reported overall percentage (25%).[68]

Several authors have examined the tumor-quantification methods requested by urologists. In a 2005 study,[69] 95% of French and Belgian urologists requested the number of positive cores, compared with 53% who requested the length of the cancer. In a study by Rubin et al,[70] 67% of urologists requested the percentage of involvement of each core by cancer, 33% requested the number of cores with prostate cancer, and 29% requested the length of core involvement.

Considering several publications on tumor-volume estimation in needle biopsy, it appears that 2 of the most useful predictors of pathologic stage in radical prostatectomy are the number of positive cores and the percentage of positive cores.[58,60,62,63,71,72] Therefore, it is important to record the number of cores submitted and the number of positive cores, thereby giving the fraction of positive cores. In some cases, that assessment is difficult because of fragmentation of the cores. In those situations, a comment regarding fragmentation precluding accurate assessment of the number of core needle biopsies involved should be made. In those infrequent instances, it is the urologist who is in the best position to make a determination of the number of cores involved, based on the original number of cores obtained; if necessary, the comment will prompt clinicopathologic correlation.

Recommendations by the College of American Pathologists,[72] the Association of Directors of Anatomic and Surgical Pathology,[73] and the World Health Organization[74]

Table 7. Problems Associated With Tumor Quantification in Needle Biopsy

- Measuring discontinuous foci of cancer
- Tissue core and tumor fragmentation
- Inadequate sectioning
- Inadequate core length
- Whether total core length should include extraprostatic tissues

for reporting carcinoma extent have been summarized in Table 6.[75] Given those recommendations, the extent parameters currently in use in AS protocols,[76] and the evidence from the literature, we suggest reporting the absolute number of involved cores out of the total number of cores and the amount of carcinoma as the percentage of involvement of the single core with the greatest amount of tumor or the linear extent of carcinoma in the core with the greatest amount of tumor. Percentage of involvement by carcinoma and/or the linear extent of carcinoma in each core may also be provided. Other measurements are optional. An example of a report of tumor extent follows: *Prostate gland, right side, adenocarcinoma of prostate, Gleason score 3 + 3 = 6; tumor involves 2 of 6 cores and 15% of all the sampled tissue. In the core with the greatest amount of tumor, the cancer length measures 3 mm and involves 30% of the core.*

Problems Associated With Tumor Quantification in Needle Biopsy

Although prostate cancer is multifocal and, hence, may be seen as discontinuous foci in needle biopsies, there is no consensus as to reporting those discontinuous foci (Table 7).[53,62,77] Karram et al[53] advocate treating discontinuous foci as a single focus. For example, if a 2-cm-long biopsy had 2, 1-mm foci at 2 ends of the biopsy, the entire biopsy would be considered to be involved and would be reported as 100% of the needle core involved. That method appears counterintuitive because, by linear extent, two, 1-mm foci involving a 2-cm biopsy would mean involvement of 10% of the biopsy, not 100%. Karram et al[53] showed that measurement of discontinuous foci better correlated with stage and margins, compared with collapsing the tumor and ignoring intervening benign tissue in the measurement. This method of measuring discontinuous foci of cancer was supported in a more recent study by Schultz et al.[78] In the future, this issue may not have as much relevance because more-recent data show bilateral cancer is a better predictor of significant cancer at radical prostatectomy than the maximum percentage of cancer per core and is a more objective measurement.[79]

Brimo et al[62] have advocated that if 2 discontinuous foci are within 5 mm of each other, they should be considered one focus, based on their outcome correlations. Therefore, in the example provided above, with 2 foci at the ends of a biopsy reported as 100% involvement by the Hopkins criteria[53] would still be 10% by the Brimo criteria. It is, therefore, vital that pathologists and clinicians within an institution be in close communication with each another; they need to understand that variability exists in criteria for reporting discontinuous foci, to understand the AS protocols used for clinical decision making, and to report findings accordingly. Because few studies have been published on this methodology, additional data from many patients are needed, with clinical endpoints. An example of a report with discontinuous foci would include the following: *Adenocarcinoma of prostate, Gleason score 3 + 3, involving 1 of 6 cores, with 2 discontinuous foci measuring 2 mm in aggregate, involving 10% of the core, and spanning 70% of the length of the core.*

If more than one core is submitted in the same container, and tumor fragmentation has occurred, it may not be possible to give the accurate number of cores submitted, the number of cores positive for cancer, or tumor extent for each core. In such a situation, it may only be possible to record the extent of cancer for the entire specimen. There is evidence in the literature that there is a greater tendency to core fragmentation when more than one core is submitted in a container.[80] Although submission of more than one core is suboptimal, if multiple cores are submitted, we recommend that no more than 2 cores per cassette be submitted because foci of adenocarcinoma of prostate may be very small. If more than one core is submitted in a block, not all tissue may be represented on a slide because of loss of alignment of all tissue in one plane during the process of embedding[81] (Figure 1). Needle biopsies collected onto gauze or paper are more likely to fragment; therefore, it is best that the needle biopsy be placed directly into formalin. Pathologists should not place the contents of more than one specimen container in a cassette for embedding because similar problems can occur.

Inadequate sectioning may lead to an erroneous impression of the extent of tumor. For example, more tumor can appear in deeper sections compared with the initial levels. To make an accurate assessment of all tumor present in the needle biopsy, adequate levels of the cores need to be examined.

Currently, there is no definition for adequate or minimum acceptable core length. Based on the needles used in most prostate biopsy needle guns, tissue cores should be 15 to 20 mm long. The percentage of cancer in a short core (eg, <5–10 mm) versus that in a sufficiently long core mean entirely different tumor lengths, which has implications for interpretation of the percentage of core involvement in the setting of AS. It is our experience that the average length of a prostate needle biopsy core is approximately 15 mm. When the core is less than, for example, 6 mm, the percentage of the core involved by cancer may be misleading. For example, a 3-mm cancer in a 15-mm core translates to approximately 20% of the core being involved. If 3 mm of a 6-mm core is involved, then the percentage of core involved is 50%. Although no prospective data have analyzed the implications of our recommendations for AS eligibility, we recommend that, in addition to reporting the percentage of core involved, when the core is less than 6 mm, the core-length information be provided.

Because percentage of core involvement is based only on total length of prostatic parenchyma, nonprostatic elements should not be included in total core-length assessment.

Histologic Subtype of Carcinoma

Most prostatic adenocarcinomas are acinar types (conventional, not otherwise specified). Less than 1% of these tumors are in other categories. In the World Health Organization classification,[82] the other specific types of nonacinar carcinoma include ductal adenocarcinoma, sarcomatoid carcinoma, and small cell carcinoma. Other carcinomas involving the prostate include squamous carcinoma, adenosquamous carcinoma, urothelial carcinoma, and basal cell carcinoma. Patients with these nonacinar and

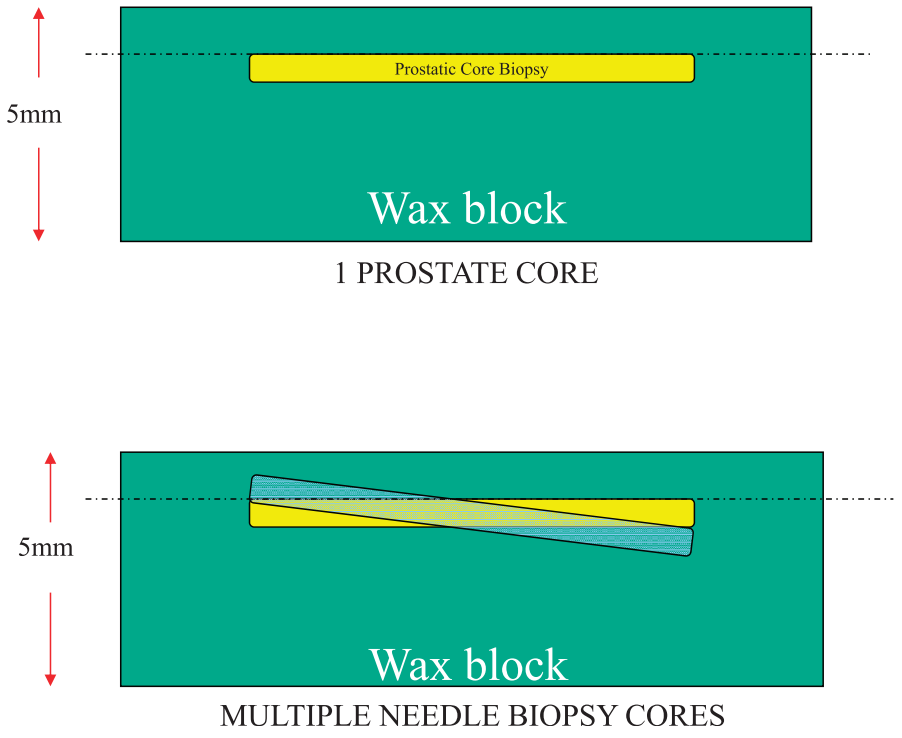

Figure 1. *Multiple cores embedded in a paraffin block often result in uneven levels among cores and result in the loss of tissue when cutting for histology.*

other tumor types are not candidates for AS. Patients with variants of acinar adenocarcinoma, including atrophic, pseudohyperplastic, and foamy gland variants, can be candidates for AS if the carcinoma is of appropriate Gleason grade and extent in needle core tissue.

Perineural Invasion

The role of prostate needle biopsy PNI in treatment planning has been a source of considerable debate. Whether PNI that is sufficiently extensive to be sampled on needle biopsy signals an increased risk of extraprostatic extension of cancer is controversial. Studies assessing the significance of PNI have had varied results. Some studies have shown PNI on needle biopsy not to be predictive of extraprostatic extension, whereas others have shown that PNI significantly predicts extraprostatic extension. In some studies, significance was found only on univariate analysis but not in multivariate analysis.[60,70,83–85]

There is only one study, to our knowledge, dealing with the significance of PNI on needle biopsy in patients who are otherwise candidates for AS.[85] Cases with PNI had significantly greater likelihood of having more than 2 positive cores, compared with cases without PNI (56.9% versus 39.7%, respectively; $P = .02$). Despite the greater extent of cancer on biopsy, cases with and without PNI on biopsy showed no significant difference in surgical margin involvement (6% and 7.3%, respectively) or organ-confined disease (84.3% and 91.6%, respectively). These results suggest that patients with PNI who otherwise meet criteria for AS should not be excluded from that option.

Atypical Small Acinar Proliferation in Patients Eligible for AS

Atypical small acinar proliferations or atypical foci are defined as atypical glands with features suspicious for carcinoma but that lack sufficient architectural or cytologic atypia for a definitive diagnosis of carcinoma.[86–88] A lesion labeled *atypical* could be a focus of cancer which, for various reasons, cannot be identified as cancer; tangentially cut outpouchings of high-grade prostatic intraepithelial neoplasia; or a benign mimic of prostate cancer. In larger studies,[89] the incidence has been found to be 2.4% to 9%, with a median incidence of about 5%. The diagnosis of atypical small acinar proliferations in prostate needle biopsy carries the risk of finding cancer in subsequent biopsy in 40% to 50% of cases.[90]

Use of immunohistochemical stains can help resolve an atypical diagnosis in some cases. Absence of basal cells confirms the diagnosis of carcinoma in some cases that have sufficient atypical features. The 2 most commonly used basal cell markers are high–molecular-weight cytokeratins, detected by antibodies 34βE12 and p63, separately or as a cocktail.[91] Currently, a cocktail of antibodies reactive with α-methylacyl coenzyme-A racemase, high–molecular-weight cytokeratins, and/or p63 is commonly used.[88,89]

In cases with atypical glands in one or more cores with cancer detected in other cores, is it necessary to perform immunostains to investigate the atypical foci? Those atypical foci need to be investigated with immunostains only if they mean that a cancer diagnosis in the atypical foci would convert treatment from AS to definitive radical treatment in the short term. In general, if there is Gleason pattern 4 in one or more cores, no workup of atypical foci is necessary. If there is a Gleason score $3 + 3 = 6$ in less than one-third of cores involving less than 50% of any single core and a finding of other foci of cancer that would significantly change management, then the workup of atypical foci is necessary.

Other Considerations

Many cancer attributes can predict aggressive clinical phenotypes. Some of those situations are rare and, although not formally evaluated, should likely exclude a patient from

Table 8. Rare Pathologic Situations That Should Likely, Automatically, Exclude a Patient From Active Surveillance and Focal Therapy Protocols

- Histologic types: prostatic adenocarcinoma with predominant ductal carcinoma histology, sarcomatoid carcinoma, small cell carcinoma
- Intraductal carcinoma without invasive carcinoma
- Extraprostatic extension in needle biopsy
- Vascular-lymphatic invasion in needle biopsy

AS protocols. Those cancer attributes have been summarized in Table 8.

Recommendations

1. Always report the number of cores submitted and the number of positive cores, thereby giving the fraction of positive cores. The linear percentage of involvement by carcinoma in the single core with the greatest amount of tumor should also be provided.
2. Ensure pathologists and clinicians within an institution are in close communication with each another; both need to understand the variability in criteria for reporting discontinuous foci, to understand the AS protocols used for clinical decision making, and to report results accordingly.
3. Investigate atypical foci in a patient who already has cancer with immunostains, such as α-methylacyl coenzyme-A racemase and basal cell markers, only if it means that a cancer diagnosis in the atypical foci would convert the patient from AS to definitive treatment.

THE ROLE OF GLEASON GRADING IN ACTIVE SURVEILLANCE (TEAM 3)

Background

The past decade has seen considerable change in practice relating to Gleason grading of prostatic carcinoma, and in 2005, the ISUP undertook a major revision of the Gleason grading system to reflect current practice and to incorporate recently gained knowledge on the biology of prostate cancer.[92] The ISUP 2005 modification of the Gleason grading system has resulted in changes to the definitions of Gleason-pattern 3 and 4 tumors, which is of particular importance for those patients in which deferred treatment is being contemplated because grade is central to the criteria used for identifying patients suitable for inclusion in AS programs.

Summary of Evidence That Gleason Score Is Useful in Defining Candidates for AS

Definition of Insignificant Prostate Cancer.—The most commonly used criteria for defining insignificant prostate cancer at radical prostatectomy includes 3 well-established prognostic factors, as described by Epstein et al[93] and Ohori et al[94]: (1) radical prostatectomy with a tumor Gleason score of 6 or less and without a Gleason pattern 4 or 5; (2) organ-confined disease (no extraprostatic extension, seminal vesicle invasion, or lymph node involvement); and (3) a tumor volume of less than 0.5 cm. The Gleason score of the tumor is based on separate tumor nodules. Studies have shown that 25% to 29% of radical prostatectomy specimens undertaken for PSA-detected prostate cancer have insignificant cancer using these criteria.[93,95] Many of the PSA-detected prostate cancers currently diagnosed are associated with a low risk of aggressive behavior, and many men with such disease will die of other causes, as opposed to death from their prostate cancer.[95] With the modification of the Gleason grading system, leading to an expansion of the criteria for Gleason pattern 4 cancer, it remains undetermined whether a small amount of secondary Gleason pattern 4 in a small, organ-confined tumor should still be considered "insignificant." A recent study has shown that pure Gleason score 6 adenocarcinoma does not have the ability to metastasize to lymph nodes[96] and as a consequence, one could potentially expand the definition of "insignificant" cancer to organ confined Gleason score 6 cancers that are larger than the original cut-off of 0.5 cm^3.

Active surveillance is increasingly recommended as an option for the appropriate patient who does not opt for definitive therapy with its associated morbidity. Two of the most critical aspects of AS are the selection criteria and the determination of when a patient has developed a more substantial disease requiring definitive therapy. The Gleason score of the tumor is central to both of those decisions.

Intervention Criteria.—Criteria for recommending definitive therapy for men previously on AS vary between institutions. In part, that variation reflects differences in repeat biopsy strategy between programs, which facilitate identification of potential changes in Gleason score and cancer extent. Rebiopsy interval for men on AS ranges from annually at Johns Hopkins Medical Institute (Baltimore, Maryland), to a single biopsy at 1 year following entry in the Japanese multi-institutional study.

Most current programs use an increase in Gleason score to 7 or more as one of the criteria to recommend interventional therapy for men on AS. In the John Hopkins data, upgrading to Gleason 7 or greater on repeat biopsy has been shown to be present in about 50% of men who receive a recommendation to switch to definitive therapy.

Grade Inflation

The past decade has seen a considerable trend toward reporting of higher Gleason scores.[97] This development has partly been driven by a better understanding of the biologic significance of certain morphologic patterns of adenocarcinoma, whereas other changes have been driven by a shift in reporting criteria. Most studies[98–103] have shown that the modified Gleason system results in overall higher Gleason scores, compared with the original Gleason system. Representative data regarding the effect of the modified system on the distribution of needle biopsy Gleason scores comes from the study by Helpap and Egevad,[100] wherein Gleason scores 2 to 5 almost disappeared, and the prevalence of Gleason score 6 decreased markedly, whereas Gleason score 7 increased. A recent population-based registry study[104] from Sweden showed an increase in biopsy Gleason scores 7 to 10 in low-risk tumors (stage T1c and S-PSA 4–10 ng/mL) from 16% of cancers in 1998 to 40% in 2011. After standardization for clinical T stage and S-PSA of 1998 Gleason score 7 to 10 tumors increased from 59% during 1998–2004 to 72% in 2006–2011. The use of Gleason scores 2 to 5 decreased sharply after 2005. The upward shift in grades reflects some of the histologic features of Gleason pattern 3 in the original Gleason system, which were classified as Gleason pattern 4 in the modified Gleason system. For example, poorly formed glands and some cribriform glands were considered Gleason pattern 3 in the original system but were upgraded to Gleason pattern 4 in the modified system. Furthermore, the decision to always

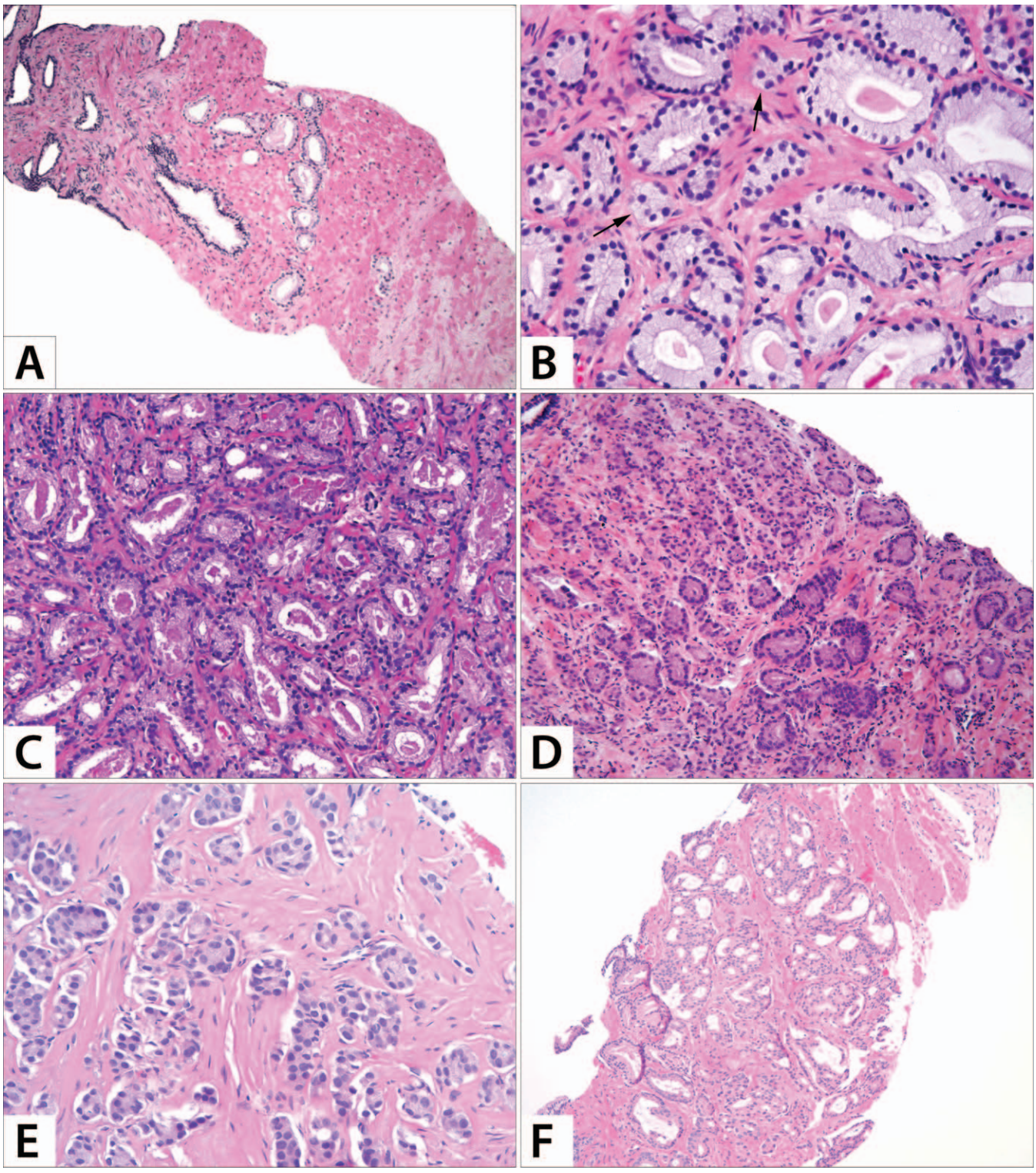

Figure 2. *Examples of Gleason grades in prostate cancer. A, Gleason score 3 + 3 = 6. Classic Gleason pattern 3 prostatic adenocarcinoma is characterized by discrete cancer glands with luminal formation. B, Gleason score 3 + 3 = 6. In most cases of Gleason pattern 3 prostatic adenocarcinoma, occasional, small, cellular aggregates without lumina can be identified (arrows) because of tangential sectioning through the wall of a gland. For active surveillance management, it is important not to overinterpret these foci as poorly formed glands (ie, Gleason pattern 4) because that could lead to a clinical classification as surveillance "failure." C, Gleason score 3 + 3 = 6. More crowded foci of Gleason pattern 3 carcinoma are much more likely to have tangential sectioning that leads to small, cellular aggregates without lumina. Again, this should not be overinterpreted as a focal-admixed component of Gleason pattern 4. D, Gleason score 3 + 4 = 7. In this case, the upper left of the figure shows carcinoma without luminal formation (ie, poorly formed glands of Gleason pattern 4). These aggregates of carcinoma cells are too irregular and too evenly distributed across the field to represent tangential sectioning. E, Gleason pattern 4 (poorly formed glands). On high-power magnification, these small, irregular aggregates of epithelium span the entire field without intervening well-formed glands. We would regard these to be "poorly formed glands" and classify them as*

include the highest Gleason grade in the Gleason score has contributed to this trend. For those institutions where the overall score was recorded, selecting the Gleason score of the core with the highest grade would also lead to overall increased grade.[101]

Sampling Errors

When low-grade prostate cancer is diagnosed on needle biopsy, there is a risk of undergrading because of sampling error, which occurs when a higher-grade component in the prostate gland is not sampled during the biopsy process, which is highlighted in studies that correlate agreement between biopsy grade and subsequent final grade in the paired radical prostatectomy specimen. For purposes of AS, it is most relevant to look at the incidence of upgrading from biopsy Gleason score 6 to a radical prostatectomy score of 7 or higher because a score 6 is the grading most commonly required for enrollment in AS. The importance of this has been shown in a meta-analysis[105] of 23 studies (with 100 cases or more) in which 35% (4614 of 13 163) of all cases were found to have a higher grade at radical prostatectomy (mean, 36%; median, 35.5%; range, 14%–51%).

One major issue that complicates this definition of upgrading/sampling error is the varying threshold among observers for the distinction of small glands of Gleason pattern 3 from admixed poorly formed glands of pattern 4 (see next section). In any individual study, the authors' diagnostic threshold along that specific grading continuum could greatly influence the reported incidence of upgrading. This point is particularly relevant because emerging data suggest that some Gleason grade 4 architectural patterns may be more clinically prognostic than others (eg, cribriform glands versus poorly formed glands).[99,106–108]

Definitions and Detection Thresholds for Gleason Patterns 3, 4, and 5

Gleason Pattern 3.—Two features define Gleason pattern 3 glands: clearly infiltrating glands (in contrast to the overall nodular configuration of glands in patterns 1 and 2), and each gland being a single, discrete, individual glandular structure that is well formed (Figure 2, A through C). The ISUP modification of the Gleason grading system defined virtually all cribriform glands as Gleason pattern 4, although, in that classification, well-circumscribed, small, ovoid to round cribriform glands with regular bridging were included in Gleason pattern 3. More recently, it has been suggested[109] that as all cribriform glands appear to be associated with a less-favorable prognosis, these glands should be classified as pattern 4. Using these criteria, classification as Gleason pattern 3 should be confined to tumors consisting of well-formed, separate glands with lumina. They may show some variation in size. Poorly formed acini are classified as Gleason pattern 4; however, obliquely sectioned, Gleason pattern 3 glands may mimic poorly formed acini. Because of that, a few poorly formed acini are permissible in Gleason pattern 3 if each gland can be assumed to be "poorly formed" because of tangential sectioning. If there are several such foci that cannot be explained as a tangential sectioning artifact, the tumor should be classified as Gleason pattern 4.[110] It is also important to place those findings in the context of the overall company the carcinoma demonstrates, and when there is doubt, we recommend (1) defaulting to a lower grade, (2) considering a tangential sectioning artifact, (3) following the focus on multiple levels and sections, and (4) sharing such borderline cases with a colleague because the presence of a Gleason pattern 4 may preclude the patient from AS.

Studies have shown that Gleason score $3 + 3 = 6$ tumors identified using these criteria have a very favorable prognosis. Five-year biochemical recurrence-free survival following radical prostatectomy of 94.6% and 96.6% have been reported for patients with $3 + 3 = 6$ Gleason scores on needle biopsy and radical prostatectomy specimens, respectively.[111] Further evidence to support the indolent nature of Gleason $3 + 3 = 6$ adenocarcinoma comes from a study[96] of more than 14 000 radical prostatectomy specimens in which no tumor of Gleason score 6 was found to have metastasized to the lymph nodes.

Gleason Pattern 4.—Gleason pattern 4 is defined by gland fusion and the presence of ill-defined, poorly formed glandular structures (Figure 2, D through F). As mentioned above, all cribriform glands, as well as those with a hypernephroid pattern, should be included in Gleason pattern 4. That pattern should be diagnosed only after careful consideration of potential artifacts and, in particular, the exclusion of such compounding factors as problems relating to specimen processing and reactive changes within the prostate. As noted above, occasional, scattered glands that appear to be poorly formed or glands that appear fused may be the result of tangential cutting and should not be diagnosed as Gleason pattern 4. Crowded and tightly clustered glands of Gleason pattern 3 should not be mistaken for glandular fusion. Technical artifacts, such as crushing of tissue or overly thick sections, may also give a spurious impression of a higher grade. When artifacts are present, grading should be conservative, and the lowest probable grade be assigned.

Gleason Pattern 5.—The presence of Gleason pattern 5 excludes most patients from AS and should be diagnosed by strict criteria, including an unequivocal, sheetlike, and single-cell pattern not attributable to tangential sectioning. Other patterns include solid, comedo, single-file, and obvious, single-cell growth patterns. Occasionally, almost-solid and irregular cribriform formations do not have true lumina but, rather, an area of clearing within the cytoplasm mimicking rosettes. Such formations should be called Gleason pattern 5. Occasional cancer cells or tumor cells arranged in strands are insufficient criteria for a diagnosis of Gleason pattern 5. In a survey study[112] among 91 urologic pathologists, only 17% reported they would diagnose Gleason pattern 5 on needle biopsy when individual cells, strands, or nests were identifiable only at ×400 magnification, whereas 83% required clusters of such structures to be visible at magnifications lower than ×400.

Gleason Grading: Future Perspectives.—There is a need for standardization of the identification of cancer patterns that straddle between Gleason 3 and 4 cancer and

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Gleason pattern 4. F, Gleason pattern 4 (small–medium cribriform glands). These small- to medium-caliber cancer glands have intraluminal cribriform growth, which is regarded as Gleason pattern 4 (hematoxylin-eosin, original magnifications ×10 [A and F], ×40 [B and E], and ×20 [C and D]).

between Gleason 4 and 5 cancer—the cusp patterns. Better definitions and detection thresholds are needed. A more immediate, practical approach is the use of reference-image libraries, which could be made available to general pathologists for benchmarking of diagnostic features relating to grading.[113] A proposed mechanism for systematic standardization includes a panel of international experts who continuously upload cases to an image database, as proposed by Lars Egevad, MD. The same experts will independently grade the cases. Once a certain number of votes and a predefined consensus level have been achieved, the cases would be moved to a public database that can be accessed by general pathologists. Such a database could be hosted by the College of American Pathologists and should feature search functions. Images could also be tagged by grading difficulty and whether they are typical examples or borderline cases.

Recommendations

There is substantial evidence to support excluding all carcinomas showing a cribriform morphology from Gleason pattern 3. We recommend this guideline be adopted and enrollment in AS programs be confined to those individuals who are shown to have Gleason score $3 + 3 = 6$ tumor on needle biopsy. Cribriform glands and poorly formed glands not attributable to tangential sectioning should be classified as Gleason pattern 4.

TOWARD A PRECISION MEDICINE APPROACH FOR PROSTATE CANCER ACTIVE SURVEILLANCE: ANCILLARY MOLECULAR DIAGNOSTIC TESTS TO INCREASE THE SAFETY OF ACTIVE SURVEILLANCE (TEAM 4)

Background

Given the often-indolent course of screen-detected prostate cancer,[23] AS—or careful monitoring of the cancer with selected intervention based on specific parameters—is an emerging, initial management alternative for prostate cancer that appears unlikely to threaten quality or length of life.[27] A proportion of men on AS appear to either harbor tumor nodules with adverse pathology that are not sampled in the biopsies or display disease progression over time. Definitions of progression vary among published series and include various measures of PSA change (eg, PSA doubling time), increase in cancer grade on biopsy, increased number or percentage of core involvement, or changes in DRE and/or imaging.[27,36–38] Because of the uncertainty about the risk of progression, enrollment in AS is poor, and many men are treated unnecessarily. In addition, some men on AS require aggressive disease monitoring, whereas others can forego frequent biopsies. To increase the safety of AS and the confidence in an indolent disease course, markers that predict the risk of adverse pathology are needed. The development and qualification of AS-specific biomarkers require retrospective biopsy cohorts of cases that fulfill today's parameters for AS management. Such cohorts are amenable to prospective-retrospective biomarker studies, a design that has recently received recognition by the US Food and Drug Administration in the development of companion diagnostics.[114] However, the ultimate validation of biomarkers necessitates prospective multi-institutional clinical trials.

Predictive Instruments and Prostate Cancer Outcomes

Nomograms and other risk instruments integrate clinical variables, such as Gleason score, PSA, clinical stage, and biopsy data, to estimate risk of adverse outcomes.[115] Multivariable instruments have been developed to provide better prognostic information, mostly in the setting of presurgical or postsurgical assessment.[116–118] For example, the Partin et al[118] tables predict the likelihood of advanced-stage cancer at surgery, and the nomograms developed by Kattan et al[119] aim to predict multiple endpoints, although they are best validated and commonly used for predicting recurrence after prostatectomy. Other tools purport to predict the likelihood of "indolent" cancers that may be best suited for AS but, in fact, have been specifically developed to predict cancers based on pathologic criteria after prostatectomy.[120,121] Importantly, no instrument, to our knowledge, has been developed specifically to predict outcomes of men on AS. *The lack of accurate prediction tools of tumor behavior based on available clinical and pathologic data increases patient anxiety, hampering broad acceptance of AS.*

Need for a Precision Medicine Approach to AS

A critical need exists for biomarkers that can be assessed initially and serially to predict and monitor prostate cancer grade, stage, metastatic potential, and potential response to candidate drugs with better accuracy and less morbidity and cost than the currently available clinical metrics offer. Biomarkers for prostate cancer may be derived from multiple types of samples, including prostate tissue, serum, and urine. Although many candidates have been examined in recent years, including several that are highly associated with aggressive parameters, such as grade and stage, few candidates have prognostic power independent of the conventional parameters of tumor grade, serum PSA, and stage. Furthermore, those biomarkers were almost universally tested in the preoperative or postoperative setting and may not be applicable for AS. In this program, we selected promising, quantitative, molecular and genetic biomarkers to predict prostate cancer progression in an AS cohort with established infrastructure, track record of accrual, and high-quality biospecimens, responding to the call for multi-institutional studies in AS.[16]

Several groups have investigated the association of tumor-associated gene-expression signatures with relapse and progression, not only in prostate cancer but also in other solid tumors.[122–126] Indeed, the molecular classification of tumors is considered the standard of care in breast cancer, including the Oncotype DX breast cancer assay (Genomic Health Inc, Redwood City, California), which is incorporated into established treatment guidelines.[127–131] Data from 10 studies have shown that the recurrence score from the 21-gene signature has been associated with changes in treatment recommendations for 20% to 74% of patients with breast cancer,[132] resulting in a decrease in the usage of adjuvant chemotherapy.[133] Recently, 2 biopsy-based genomic assays have become available to assess the risk of occult adverse pathology. The Oncotype DX prostate cancer assay (Genomic Health) consists of 17 genes across 4 different pathways that are associated with androgen signaling, stromal response, proliferation, and cellular organization. The signature is most effective in identifying a "very low risk" patient population. Another commercial genomic test, Prolaris (Myriad Genetics Inc., Salt Lake City, Utah), serves as a risk-stratification tool for the danger of disease

progression. It was developed for the postprostatectomy setting; however, Prolaris can also be used in the AS population. The genes in this signature are associated with cell proliferation and the cell cycle. Confirmatory studies with both signatures are currently under way.[134–137]

Most prostate cancer molecular studies have focused on prediction of relapse after primary curative therapy, and very few studies have attempted to investigate the molecular or genomic factors associated with aggressive or lethal prostate cancer before attempted curative therapy. Although Gleason grade is one of the best prognostic biomarkers, only a few studies have associated genetic or molecular signatures with prostate cancer grade,[126,138] and to date, no specific gene or gene panel has been validated as a Gleason grade–associated biomarker. Whole-genome sequencing of primary prostate tumors has identified several mutations and rearrangements that may contribute to prostate cancer tumorogenesis,[139] and others have assessed the expression levels of genes associated with cell-cycle progression as markers prognostic of aggressive disease.[137,140] However, despite the extensive studies to date, prostate cancer lags behind other cancers in the identification of biomarkers or molecular signatures that alter clinical practice patterns.

The emergence of next-generation sequencing technologies has unveiled an increasingly complex biology underlying cellular function and cancer. Recent observations that abundant species of noncoding RNAs (ncRNAs) are transcribed have generated interest in those species as biologically important entities.[141] Whereas only approximately 2% of the genome represents protein-coding regions, a full 20% to 50% of the genome may be actively transcribed into ncRNAs.[142,143] Clinically, increasing interest in the diagnostic potential of ncRNAs has led researchers to evaluate their utility in a number of disease states from fragile X syndrome to Down syndrome.[144] In prostate cancer, the clinical importance of ncRNAs came to the forefront with the discovery that *PCA3*, a long ncRNA located on band 9q21, is a promising prostate cancer biomarker.[145,146] In numerous studies,[146–148] overexpression of *PCA3* was observed in 94% of prostate cancer tissues studied but not detected in any normal or benign prostatic hyperplasia. PCA3 is expressed in the urine and prostatic fluids of individuals with prostate cancer. *PCA3* has subsequently been observed as a biomarker in patient urine samples, and diagnostic tests (Progensa, Hologic Gen-Probe Inc, San Diego, California) have been introduced.[149] Assays used to detect PCA3 rely on urine produced following an attentive DRE, also know as *prostatic massage*, which improves the secretion of prostatic cells into the urethra.[150] Recently, sufficient peer-reviewed clinical evidence for a *PCA3* indication to eliminate unnecessary prostate biopsies has led to its US Food and Drug Administration approval. Importantly, novel, long ncRNAs, like PCA3, often display highly tissue-specific and cancer-specific expression patterns, thereby giving long ncRNAs an advantage as a clinical tool over many protein-coding genes and microRNAs, which are infrequently tissue specific overall.[151] Urinary PCA3 and TMPRSS2-ERGa were shown to correlate with the presence of more-aggressive cancers in the Canary Prostate Active Surveillance Study.[152]

Two of the most promising prognostic markers, when used in combination, are PCA3 (described above) and TMPRSS2:ERG.[153,154] Recent work using post-DRE urine from the Canary Prostate Active Surveillance Study cohort[152] demonstrated associations between urinary PCA3 and TMPRSS2-ERG status and Gleason grade and tumor volume as measured by percentage of core involvement. In 401 Canary Prostate Active Surveillance Study participants, the authors observed a significant correlation between PCA3 score and Gleason score from the most recent biopsy to study entry (Spearman $\rho = 0.14$; $P = .008$, Spearman rank correlation) and volume (Spearman $\rho = 0.2$; $P \leq .001$). They observed a similar positive association between the TMPRSS2:ERG score and biopsy Gleason score (Spearman $\rho = 0.19$; $P \leq .001$) and volume (Spearman $\rho = 0.29$; $P \leq .001$). These results suggest that both PCA3 and TMPRSS2-ERG appear to stratify risk of having aggressive cancer as defined by tumor volume or Gleason score and may have clinical applicability in selecting men with low-volume/low-grade disease for AS.

Next-generation sequencing has also revealed recurrent mutations in clinically localized prostate cancer that may emerge as useful biomarkers.[155] The most frequently mutated gene was *SPOP* (13%), which encodes the substrate-binding subunit of a cullin 3–based E3 ubiquitin ligase.[156,157] Other mutations include *FOXA1*, *MED12*, *THSD7B*, *SCN11A*, and *ZNF595*O.[139,158] However, as is the case for most biomarker discovery studies, the utility of the biomarkers has not been tested in patients on AS or other well-defined cohorts to determine the value added by the biomarker values in the clinical decision-making process.

Expectations are higher now that biomarker results should be reproducible.[159] Guidelines have been developed for what should ideally be included in publications of tissue-based biomarkers, with the expectation that adherence to those guidelines will increase the likelihood that an assay is reproducible.[160] Another quality that is expected of biomarkers is that there be evidence of their prognostic and predictive power. Levels of evidence have been developed for tissue-based biomarkers and applied most widely to predictive molecular biomarkers of breast carcinoma.[161]

SUMMARY AND FUTURE PERSPECTIVES

Given the overdiagnosis and overtreatment of low-risk prostate cancer, AS should be a ubiquitously adopted and formalized strategy. There are several issues and fundamental questions that arise from the combined clinicopathologic experience from formal and informal AS treatment management strategies that would be applicable to the management of prostate cancer patients outside of academic centers and clinical trials. These issues need to be resolved during the next few years to tighten criteria for selection of patients contemplating AS and their subsequent management. Table 9 is a high-level summary of the recommendations offered by this consensus statement document, and Table 10 is a synopsis of unresolved issues that need our collective attention going forward.

What Is the Appropriate Strategy for Sampling the Prostate?

Prostate cancer is rare among solid organ cancers in that the diagnosis is not based on a biopsy of a discrete lesion. Rather, a prostate biopsy is a systematic, anatomic sampling of the prostate. As a result, prostate biopsy is prone to misclassification. Multiple investigators have attempted to identify optimal templates for prostate biopsies that maximize detection of cancer. An optimal biopsy strategy

Table 9. Summary of Key Recommendations From the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, New Zealand Society of Pathologists, and the Prostate Cancer Foundation Consensus Statement Panelists

Overall, Including Sampling, Submission, and Processing Issues

- The Gleason score and tumor extent measurements are the most meaningful pathologic parameters in needle biopsies, determining eligibility for AS protocols.
- Sampling of the prostate gland, using contemporary biopsy templates that sample 12 to 16 areas within the prostate, including the midgland and lateral gland at the base, mid section, and apex of the prostate, is recommended; these may still miss detection of some prostate cancers.
- Samples for pathologic evaluation should ideally be separated and submitted according to biopsy sites targeted for appropriate reporting and documentation of the location and number of positive/negative cores.
- While submitting 1 core per container is optimal, if multiple cores are submitted in the same container, we recommend that no more than 2 cores be submitted per cassette.
- Although there is no definition for an optimal length of a prostatic needle core biopsy, the average length is 15 mm. When cancer involves a biopsy core less than 6 mm long, we recommend that the length of the core biopsy be specified, in addition to the extent of the needle core involvement.

Tumor Extent in Needle Biopsies

- Reporting should include in all cases:
  - Number of positive cores/total number of cores,
  - Linear percentage of prostatic tissue involved and/or total linear measurement of carcinoma and total core length,
  - Percentage of carcinoma in the most extensively involved core, and
  - Quantitation of these parameters should be based on the total amount of prostatic parenchyma; nonprostatic elements should not be included in the total core quantitation.
- Reporting biopsies with discontinuous foci:
  - Specify the presence of discontinuous foci, the linear extent in aggregate of the discontinuous foci, the percentage of involvement of the core (or the overall length of the core tissue), and the core length spanned by the discontinuous foci. An example of a report includes: Adenocarcinoma of prostate, Gleason score 3 + 3, involving 1 of 6 cores, with 2 discontinuous foci measuring 2 mm in aggregate, involving 10% of the core, and spanning 70% of the length of the core.
- Reporting biopsies with multiple cores in the same container:
  - Provide linear measurement (in millimeters) or linear extent (as a percentage) of prostatic tissue involved for the most-involved core and the overall linear percentage or measurement in millimeters of the tissue submitted from the site(s) with cancer.
- Reporting fragmented cores:
  - When assessment of the number of cores involved by carcinoma is difficult because of the extent of fragmentation and that determination is key for AS eligibility, a comment should be made suggesting that the urologist/physician obtaining the biopsy is in the best position to make the determination of the number of cores involved, based on the original submission of the number of cores; if necessary, undertake clinicopathologic correlation.
  - When an involved core is <6 mm long, reporting the percentage of the core involved by cancer and the core length information should be provided.

Gleason Score in Needle Biopsies

- Biopsy Gleason grade reclassification has emerged as one of the most meaningful intervention criteria for men on AS.
- Accurate distinction of Gleason pattern 3 from Gleason pattern 4 is critical for eligibility for most AS protocols. In cases with cusp histology between patterns 3 and 4:
  - Only poorly formed glands, not attributable to tangential sectioning and cribriform glands, should be classified as Gleason pattern 4,
  - Place these findings in the context of the overall company the carcinoma demonstrates (ie, predominantly Gleason pattern 3),
  - When there is doubt, default to the lower grade, follow the focus on the multiple levels and sections, and share such borderline cases with a colleague because the presence of Gleason pattern 4 may preclude the patient from AS.

Other Pathologic Considerations

- Pathologic findings in needle biopsies that would automatically exclude patients, irrespective of Gleason score, include prostatic adenocarcinoma with predominantly ductal features, intraductal carcinoma without invasive carcinoma, sarcomatoid, and small cell carcinoma, in addition to extraprostatic extension and vascular lymphatic invasion.
- Patients with prostate cancer with variant histology, such as atrophic, pseudohyperplastic, and foamy gland patterns, may be candidates for AS if the carcinoma is of an appropriate Gleason score and the extent in the needle biopsies with cancer is within guidelines.
- Perineural invasion in biopsies of patients who otherwise meet criteria for AS should not exclude patient for AS.
- Immunohistochemistry for atypical, small acinar proliferations in a patient with a cancer diagnosis should be performed only if the confirmation of cancer, or lack thereof, is important for AS or definitive treatment eligibility.

Precision Medicine Markers

- Currently, available data do not support a recommendation for any particular molecular tool or test for determining eligibility of patients into AS protocols. Several tests have recently been offered commercially and, although purported to be useful, need further clinical experience and prospective validation for consistent inclusion into clinical decision-making algorithms.

Abbreviation: AS, active surveillance.

that confers high accuracy for detection of high-grade cancers within the prostate would increase clinicians' confidence in their clinical staging. At minimum, patients enrolled in AS should have an initial prostate needle biopsy that samples the base, mid-gland, and apex in the mid section and lateral peripheral zones.

Should Men Considering AS Undergo Saturation Biopsy of the Prostate?

Some AS cohorts mandate saturation biopsy before enrollment.[162] Saturation biopsy, in which 18 or more biopsy cores are sampled from the prostate, often with a transperineal approach, may allow for greater accuracy in

Table 10. Issues Regarding Active Surveillance (AS) Eligibility and Reporting of Pathologic Parameters in Needle Biopsies That Are Unresolved or Need Further Study

- Inclusion criteria, surveillance schedules, and intervention/progression criteria for men on AS vary between institutions, within institutions, and between clinical trials. Standardization is encouraged.
- Sampling biopsy templates and protocols vary between institutions and trials.
- Studies vary in their approach to determining the extent of cancer when discontinuous foci are present. In addition, prospective studies are needed to determine how best to quantitate discontinuous foci.
- Additional resources and educational material regarding recognition of the cusp in Gleason patterns 3 and 4 are required to decrease interobserver variability.
- Criteria for minimum pattern 4, particularly with respect to poorly formed glands, need to be identified.
- There is need to develop an accurate predictive tool that includes biomarkers in a specifically, prospectively accrued data set to predict outcome of patients on AS.
- Unsampled, high-grade carcinoma remains an important factor in patients failing AS. More-sensitive imaging technologies and biomarkers for high-grade carcinoma, such as in the urine or blood, are required to complement AS eligibility criteria.
- Increased education efforts for urologists, primary care physicians, and pathologists are required to highlight their important respective roles in AS.

clinical staging and detection of high-grade cancers within the prostate. Transperineal biopsies may also provide better targeting of the anterior zone of the prostate, which may be difficult to access through a transrectal approach. However, it is unclear whether this more-intensive sampling strategy substantially affects eligibility for AS or risk of progression on AS, and most AS cohorts do not mandate repeat biopsies or saturation biopsies. At this time, we consider a saturation biopsy to be up to the discretion of the diagnosing urologist and the patient.

Can New Biomarkers or Genetic Tests Inform the Clinical Risk Stratification Currently Used to Identify Men Who Are Candidates for AS?

Anything that helps further discriminate risk of an adverse prostate cancer–specific outcome would aid clinicians struggling with the uncertainty in identifying good candidates for AS. The discovery of biomarkers associated with either the presence of undersampled, high-grade disease or the development of new high-grade disease with true biologic progression would be highly effective. Urinary PCA3 and TMPRSS2-ERGa were shown to correlate with the presence of more-aggressive cancers in the Canary Prostate Active Surveillance Study,[152] although those findings were not corroborated in other studies.[163–165] Integration of biomarker studies with AS cohorts could identify other tests that may increase the reliability of risk stratification at diagnosis.

For Men on AS, How Often Should They Have Their PSA Checked or Undergo Repeat Prostate Biopsies?

The protocols listed in Table 2 are based on expert opinion and clinical judgment as to what constitutes appropriate surveillance care for men on AS. Although PSA is a serum blood test with minimal risk, the PSA results may drive other testing, including off-protocol prostate biopsy and is not recommended. The PSA kinetics may not be the best marker of biologic progression on AS, and the frequency with which PSA should be monitored is unknown. Prostate biopsy carries more than minimal risk, with published rates of serious, infectious complications ranging from 0.5% to 3%.[166,167] Surveillance strategies should account for the heterogeneity of low-risk prostate cancer. Some men may require frequent biopsies for a higher risk of cancer progression on AS; others may require rare interval biopsies to confirm lack of progression. For example, men with very low-risk prostate cancer, whose first surveillance biopsy shows no cancer, may not need another biopsy for several years.

How Is Progression Defined for Men on AS?

The definition used for prostate cancer progression on AS varies substantially across institutions. Although PSA kinetics are a component of some protocols, all identified cohorts currently use cancer biopsy-grade reclassification to determine progression. That reclassification, "upgrading," may be due to undersampling of original disease or, in some instances, disease progression.

What Other Tests Aid in Decision-Making for Men on AS?

Emerging evidence suggests that MRIs may provide valuable information that is useful to patients considering AS or on an AS protocol. Endorectal MRI has been used to guide radical prostatectomy through identification of locally advanced cancers.[168,169] Similarly, endorectal MRI has demonstrated an association with clinically insignificant prostate cancers. An endorectal MRI of men undergoing confirmatory biopsy before AS with no identified tumor had high negative predictive value for upgrading.[170] Within identified tumors, the average diffusion coefficient of the lesion may suggest the grade of the cancer, further informing AS candidacy.[171]

What Is the Best Method for Reporting Discontinuous Foci of Prostate Cancer in a Needle Biopsy?

Discontinuous foci in a needle biopsy is an extremely common situation in patients diagnosed with prostate cancer, and very few studies have addressed this problem. Additional data from many patients are needed—studies with clinical endpoints. Therefore, there is no clear consensus based on the evidence at this time.

Gleason Grading—Future Perspectives

There is a need to standardize the identification of patterns at the cusp between Gleason patterns 3 and 4. Better definitions and detection thresholds for greater interobserver reproducibility are required. A more-immediate, practical approach is the use of reference image libraries, which could be made available to general pathologists for benchmarking of diagnostic features relating to grading.[113] In 2015, the International Society of Urologic Pathology will conduct a consultation among the experts to address these types of issues and will publish the consensus findings, similar to their efforts in 2005.[92]

Precision Medicine Approach—Future Perspectives

Work to develop clinically useful molecular biomarkers and signatures must include rigorous testing in the populations where the tests will be employed. We have observed that one of the greatest limitations in validating novel molecular biomarkers is obtaining support for the development and use of valuable clinical cohorts. Too often studies are limited to samples of convenience collected and analyzed in a single institution. The field of biomarker research for AS stratification would benefit greatly from (1) the qualification of existing biomarkers for use in AS stratification and prioritization for testing; (2) multi-institutional, "prospective-retrospective" clinical trials with archived tissue and DRE urine for new biomarker discovery; (3) prospective clinical trials for validation of biomarkers from retrospective biomarker studies; and (4) multi-institutional, prospective trials with tissue, blood, and DRE urine collections.

Generating biomarkers of clinical utility to guide AS decisions must await the establishment of those biomarker and clinical trial resources.

In summary, although several issues regarding AS require further study, an increasing number of patients are being managed with AS, and pathologists have a critical role in the selection and maintenance of patients on AS protocols. Herein, we aimed to promote awareness and to guide pathologists to be more effective in the reporting of prostate biopsy results and to enhance their role in clinical decision-making in low-risk prostate cancer.

Background on Sponsoring Organizations

The College of American Pathologists is the largest professional organization composed exclusively of pathologists in the United States and Canada and is known nationally and internationally for setting best practices and guidelines for pathologists and for proficiency testing and accreditation of hospital laboratories. The International Society of Urological Pathology is the international reference organization for urologic pathology. This society has been involved with important publications, such as the consensus classification on bladder tumors (1998); the update on Gleason grading, which was the first major update since the system was promulgated in 1966 (2004); the handling and reporting of radical prostatectomy specimens (2010); consensus on renal cell carcinoma (2012); and recommendations on the role of immunohistochemistry in urologic pathology (2013). The Association of Directors of Anatomic and Surgical Pathologists is the association of premier leaders in academic anatomic and surgical pathology. Its mission is to generate evidence-based solutions for common challenges in education, practice management, and professional development in surgical pathology through data collection and collaboration with cooperating societies. The New Zealand Society of Pathologists is the professional body for pathologists and the wider pathology profession in New Zealand. The Prostate Cancer Foundation is firmly committed to curing prostate cancer. It is the leading philanthropic organization funding and accelerating research globally. As a champion for increased government and private support, the Prostate Cancer Foundation has helped build a global research enterprise of nearly $10 billion and has funded more than 2000 programs at more than 200 research centers in 18 countries.[172–177]

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