DOI:10.1093/jncimonographs/lgs029


# Temporal Changes in the Pathologic Assessment of Prostate Cancer

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Thirty years have witnessed dramatic changes in the manner in which we diagnose and manage prostate cancer. With prostate-specific antigen screening, there was a shift towards smaller, clinically localized tumors. Tumors are often multifocal and display phenotypic and molecular heterogeneity. Pathologic evaluation of tissue obtained by needle biopsy remains the gold standard for the diagnosis and risk assessment of prostate cancer. Years of experience with grading, along with changes in the amount of biopsy tissue obtained and diagnostic tools available, have produced shifts in grading practices among genitourinary pathologists. Trends in Gleason grading and advances in pathological risk assessment are reviewed with particular emphasis on recent Gleason grading modifications of the International Society of Urologic Pathology. Efforts to maximize the amount of information from pathological specimens, whether it be morphometric, histochemical, or molecular, may improve predictive accuracy of prostate biopsies. New diagnostic techniques are needed to optimize management decisions.

J Natl Cancer Inst Monogr 2012;45:157–161

The last 30 years have witnessed immense growth in our understanding of the biology of prostate cancer. Whereas the dependence on androgens for prostate cancer growth and development has been known since the pioneering work of Hudgins and Hodges (1), the mechanistic role of restored androgen receptor (AR) signaling driving progression in patients treated with androgen blockade has now been established (2). Ongoing molecular genetic investigations have revealed a number of key molecular alterations that occur with high frequency in prostate cancer, including loss of PTEN, amplification of cMYC, and TMPRSS2:ETS translocations amongst others (3). The role of chronic inflammation and oxidative stress in the development and progression of prostate cancer is a subject of increasing interest (4,5). All of these investigations are critically important for the development of new and improved prostate cancer therapies.

In parallel with these advances, over the last 30 years, there have been dramatic changes in the manner in which we diagnose and manage prostate cancer. The advent of the prostate-specific antigen (PSA) screening in the late 1980s, coupled with increased public awareness of the disease, has resulted in a marked shift in stage towards clinically localized disease (6–8). Pathologically, pre–PSA-era tumors tended to be large, occupying the majority of the glandular volume, and often had extensive extraprostatic extension. In contrast, tumors of today are typically smaller in volume, organ-confined, and associated with improved therapeutic outcomes (7,8). Indeed, it is now clear that more men die *with* prostate cancer than *of* prostate cancer. Concern arises that we are now detecting more clinically insignificant cancers, cancers that might be better managed expectantly (9). Recognition of these limited cancers pathologically becomes crucial in order to properly stratify patients for expectant management.

## The Pathology of Prostate Cancer and the Gleason Grading System

The volume or extent of a tumor combined with its biologic aggressiveness ultimately determines the outcome for a patient following treatment. In the mid-1990s, it was recognized that prostate cancer is a multifocal disease and that large tumors often result from the assimilation of multiple smaller tumors as they grow to confluence (10). Individual tumors may display marked differences in grade, molecular markers, and DNA ploidy from region to region even within a single tumor (11,12).Understanding the impact of specific molecular abnormalities on disease progression and therapeutic outcome is still unclear and an area of intensive study. Thus, the pathological evaluation of prostate cancer remains central to assessing the risk of progression. The Gleason grade of a tumor reflects its biologic aggressiveness and is currently the most important pathologic prognostic factor for prostate cancer that can be readily determined on biopsy or prostatectomy. The Gleason system is a five-tiered classification that categorizes tumors by their architectural pattern of growth rather than cytologic features. Since its first description by Donald Gleason in 1966 (13), the grading system has undergone a number of modifications over time by Gleason and others (14,15). Tumors often display more than one pattern of growth. This was originally addressed by the Gleason system by adding the two most prominent patterns, a primary pattern (majority of tumor) and a secondary pattern (second most extensive pattern), together to obtain a Gleason "score." If only one pattern was present, then the grade was doubled with the resulting sums between 2 (grade 1 + grade 1) and 10 (grade 5 + grade 5).

Years of experience with Gleason grading in relation to disease outcomes, along with changes in the amount of tissue

**Table 1.** Comparison of the classical and International Society of Urological Pathology modified Gleason grading system

| Classical Gleason system (14) | 2005 ISUP modified Gleason system (15) |
|---|---|
| *Pattern 1:* Well-differentiated small, uniform, and closely packed glands in tight circumscribed masses | *Pattern 1:* Circumscribed nodule of closely packed, separate, uniform round-oval, medium-sized glands (generally larger than pattern 3) |
| *Pattern 2:* Similar to pattern 1, with moderate variation in size and shape of glands and some cellular atypia; glands more loosely packed but still relatively circumscribed | *Pattern 2:* Similar to pattern 1, but more loosely packed glands with minimal infiltration at edges of tumor nodule and mild glandular irregularity |
| *Pattern 3:* Very small infiltrating glands with marked irregularity of size and shape but generally retaining individual glandular differentiation; individual cells invading stroma away from circumscribed glandular masses; papillary and cribriform arrangements ranging from small to large but maintaining smooth rounded edges | *Pattern 3:* Small discrete glandular acini (generally smaller than patterns 1 and 2) with marked variation in size and shape and that typically infiltrate amongst nonneoplastic prostatic acini; smoothly circumscribed small cribriform glandular units |
| *Pattern 4:* Raggedly infiltrating fused glands that coalesce and branch and are no longer single and separate; glands with large clear cells resembling hypernephroma | *Pattern 4:* Fused microacinar glands and ill-defined glands with poorly formed glandular lumina; large cribriform glandular units or cribriform glands with irregular borders; hypernephromatoid, ductal tumors |
| *Pattern 5:* Infiltrative, very poorly differentiated cells arranged in solid or diffuse masses or individual cells with essentially no glandular differentiation; includes signet ring cell morphology and comedocarcinoma | *Pattern 5:* Tumor cells with essentially no glandular differentiation arranged in solid sheets, cords, or single cells; comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid cell masses |
| *Gleason scoring* | |
| Gleason score obtained by adding together the most prominent pattern (primary) with the second most prominent pattern (secondary) | Similar to classical, with following exceptions: Gleason scores 2–4 should rarely (if ever) be assigned to tumors on biopsies |
| Same scoring method used for prostatectomy and biopsy | On biopsies, the Gleason score should be obtained by adding together the most prominent pattern (primary) with the highest remaining grade pattern (even if tertiary or <5%) |

obtained at biopsy and the diagnostic tools available such as immunohistochemistry for basal cell–specific markers (high molecular weight cytokeratins, p63) and alpha methylacyl Co-A racemase, have produced shifts in diagnostic and grading practices among academic genitourinary pathologists. In 2005, eighty genitourinary pathologists of the International Society of Urologic Pathology (ISUP) participated in a practice survey and consensus conference to document and address trends in and refine the guidelines for Gleason grading (15). Most notable of the changes to the classic Gleason grading system included 1) restrictions as to the assignment of very low grades (patterns 1 and 2) to biopsy specimens, 2) refinement of the separation of pattern 3 from pattern 4, 3) guidelines for assigning grade to cribriform patterns, 4) Gleason grading of variant carcinomas, and 5) Gleason scoring of biopsies when minor amounts of high-grade tumor or tertiary-grade patterns are present. A comparison of the classic Gleason system as refined by Gleason in 1977 (14) and the 2005 modifications is presented in Table 1.

### The 2005 ISUP Consensus Conference on Gleason Grading Modifications

The first recommendation by the ISUP was that Gleason grade patterns 1 and 2 should be rarely applied to tumors on needle biopsy because most such tumors are upgraded on subsequent prostatectomy. Most cases that would have been graded as 1 + 1 (score = 2) years ago would today be diagnosed as benign adenosis with the use of basal cell markers. This trend is not new. In a study looking at temporal trends in Gleason scoring, Gleason scores of 2–4 fell from 21% of tumors in 1983–84 to 11% in 1992–93 (16). By 2001, the proportion had dwindled to less than 5% (17). Data from a recent European study suggest that abandoning Gleason scores below 6 on prostatectomy specimens may not be prudent because tumors that were graded with Gleason scores of 2–4 had better prognosis than those graded as Gleason score 5–6 on prostatectomy (18). However, whereas Gleason score 2–4 tumors represented 16.4% of tumors diagnosed on biopsy in this study, they only accounted for 4.6% of the tumors at prostatectomy, again demonstrating that most tumors have higher grade foci at prostatectomy.

Tumors that contain some proportion of pattern 4 or 5 (representing Gleason scores of 7–10) behave more aggressively than those graded with Gleason scores of 2–6 (19). Thus, the more important distinction lies in the separation of pattern 3 from pattern 4. In a departure from the original description of the Gleason system, it was recommended by the ISUP that single cells or ill-defined glands with poorly formed lumenae not be allowed within Gleason pattern 3. The latter should be within Gleason pattern 4. Pattern 3 should be reserved for tumors that have small discrete glands of variable size and well-defined lumenae separated by variable amounts of stroma. In addition, most cribriform cancers should be Gleason pattern 4. Consensus was that only small cribriform arrangements with smooth borders should warrant the designation of pattern 3. In practice, this distinction becomes somewhat arbitrary and subject to interobserver variability. In our experience, tumors with even small amounts of cribriform cancer regardless of the size of the cribriform glands behaved aggressively (20). Nevertheless, the above recommendations of the 2005 ISUP Consensus Conference may potentially have the effect of grade migration towards higher Gleason scores.

Finally, the 2005 ISUP Consensus Group recommended modifications to the assignment of individual grade patterns to the final Gleason score on biopsy. In the classic Gleason system, a grade pattern had to represent at least 5% of the tumor to be included in the Gleason score as a secondary pattern. In the 2005 modified system, higher grade patterns regardless of quantity were included in the score (98% pattern 3 and 2% pattern 4 is scored as 3 + 4 = 7). If more than two grades exist for a tumor on biopsy, then the most extensive pattern (the primary pattern) and the highest pattern of those remaining regardless of relative amount is included in the

score (eg, a tumor with 70% pattern 3, 25% pattern 4, and 5% pattern 5 is scored as 3 + 5 = 8). Theoretically, this could result in a trend towards higher Gleason scores on biopsy when these modifications to the Gleason grading system are applied. Conversely, these modifications could ultimately result in fewer prostate cancers being upgraded upon prostatectomy, a situation that occurs frequently when comparing biopsy grade with final tumor grade on prostatectomy (21). However, it should be noted that the refinements documented in the 2005 ISUP Consensus Conference report represent an attempt to standardize grading trends already practiced by leading genitourinary pathologists around the world rather than a new approach to Gleason grading. Thus, these modifications may have more impact on the general pathology community than the academic community. Nevertheless, it has been shown that application of the 2005 modifications had the effect of increasing average Gleason scores in population studies (22,23). Whether the modifications lead to improved correlation with clinical outcome remains to be seen.

## Diagnostic Trends for Prostate Cancer and the Identification of Indolent Tumors: Impact on Expectant Management

Despite the advances in molecular diagnostics, imaging modalities, and clinical chemistry, the pathologic evaluation of prostatic tissue obtained by needle biopsy remains the gold standard for the diagnosis and risk assessment of prostate cancer. Ultimately, the goal of pathologic examination of prostate biopsies is to 1) establish a diagnosis of cancer, and 2) help determine the aggressiveness (grade) and extent of the tumor to guide management decisions. Because most prostate tumors of today are not clinically palpable, prostate biopsies are taken systematically but randomly from the right and left sides of the prostate from base to apex. Although the caliber of the biopsy needles has become smaller, resulting in less tissue obtained per biopsy core, the number of cores obtained per biopsy session has increased. What began as sextant biopsies in the 1980s has been extended to 10, 12, or more biopsies concentrating on lateral portions of the gland in attempts to improve tumor detection. Yet, even extended biopsy schemes sample a limited portion of the prostate and frequently miss tumors (24). Consequently, many men undergo repeat biopsies that may or may not be necessary. Although repetition of the biopsy process itself does not interfere with pathological interpretation, each consecutive biopsy is still subject to the same sampling limitations as the original biopsy. Moreover, when cancer is sampled by needle biopsy, the Gleason score as determined on biopsy may not be the same as, and is often lower than, that determined on subsequent prostatectomy when the entire gland is examined (21). The main reason for this is that small foci of higher grade tumor can be missed by needle biopsy but readily seen when the whole prostatectomy is examined. However, grade discrepancies between biopsy and prostatectomy may also occur when different pathologists review the biopsy and prostatectomy specimens. Interobserver variation in Gleason scoring is well documented (25–27). Studies have demonstrated improved grade concordance between biopsy and subsequent prostatectomy when the biopsies are graded by experienced genitourinary pathologists (28,29). Therefore, it is our practice to have the pathology reviewed by inhouse genitourinary pathologists prior to making management decisions for all outside referral patients.

Although the number of cores positive for cancer in a given set of biopsies correlates with tumor volume, the finding of small amounts of tumor on a single biopsy does not always indicate a clinically inconsequential tumor (30). The most commonly used definition of "insignificant" tumor is a tumor confined to the prostate with a volume of less than 0.5 $cm^3$ and a Gleason score of 6 or less (no pattern 4 or 5) at prostatectomy (31). Epstein et al. define a tumor at biopsy as being "potentially insignificant" if the following criteria are met: 1) stage T1c, 2) PSA density less than 0.15 ng/mL/g, 3) Gleason score 6 or less (no pattern 4 or 5), and 4) tumor involving less than three cores with no core having more than 50% tumor involvement (32). However, attempts to predict clinical significance using biopsy criteria are imperfect with sensitivities ranging from 35% to 83% and specificities ranging from 68% to 98% (33). Furthermore, when such criteria were used to select patients for expectant management, 31.5% of the patients progressed within 2 years (34). Accurate identification of tumors that can be assured not to progress is therefore problematic. This is due in large part to the limited tumor sampling with current random systematic biopsy methods and because tumors within the anterior prostate, or those in large prostates, are often missed (35,36). To address this, more recent approaches using prostate mapping biopsy techniques employing large numbers of biopsies in a template-guided three-dimensional manner that more accurately "maps" the prostate for areas of cancer may be better able to distinguish those tumors that require immediate therapy from those that could be managed expectantly (37). This technique is labor-intensive, expensive, requires operating room time, and is currently used mainly as a staging procedure in men with prostate cancer opting for targeted focal therapy.

## Advances in Molecular and Systems Pathology

Compared with some other tumor sites such as colon (Kras) and breast (Her2/neu) where molecular diagnostics have become part of the standard of care, prostate cancer has lagged behind in identifying robust genetic or gene expression profiles that have an impact on patient care decisions. Although alterations of PTEN and the TMPRSS2:ETS gene fusions have been identified in large proportions of prostate cancer, their utility as prognostic or predictive biomarkers is still controversial. In the last decade, several DNA and RNA tests have been developed that have either failed to make it to the clinic or have not received wide implementation into clinical practice because of their added value and/or economics. For example, although promoter hypermethylation of GSTP1 has been identified in a large number of prostate cancers (3), GSTP1 protein loss by methylation is an early event in prostate carcinogenesis and has not been shown to contribute added value over classical pathology for treatment decisions. Hypermethylation of a number of other genes (eg, APC, RAR-beta2, CDH1, and others) has been identified in prostate cancers, and some of these have been shown to have potential prognostic value; however, well-designed validation studies are needed.

To better identify prostate cancers expected to behave aggressively, efforts have recently been focused on combining classical pathologic information with molecular or image analysis data derived from the biopsy specimen. For example, a commercially available assay (Myriad Genetics, Salt Lake City, UT) has been developed that determines a prostate cancer RNA expression signature derived from 31 cell cycle proliferation genes. In a recent study on RNA extracted from formalin-fixed paraffin-embedded tumor tissue obtained from prostatectomy and transurethral resection specimens, the cell cycle progression (CCP) score derived from these 31 cell cycle genes normalized to 15 housekeeping genes was found to be an independent prognostic indicator (38). The CCP score was predictive of outcome and showed additive value in a calculated risk score when combined with Gleason score. The performance of the assay on prostate biopsy tissue and its clinical utility is under investigation. A systems-based pathology approach combined classical pathological features (Gleason score, dominant Gleason grade) on biopsy with immunofluorescent analyses of tissue markers (AR, Ki-67) and various image analysis measurements to determine risk of progression and showed improvement over standard pathology (39). Unfortunately, most prostate cancers are extremely heterogeneous, not only in terms of tumor grade but also molecular expression patterns and genetic abnormalities (11,12). This has important ramifications when attempting to identify those features associated with an aggressive phenotype using biopsies that only sample a limited portion of a tumor.

## Conclusion

In an era when more conservative management options exist for prostate cancer including targeted focal therapy and expectant management, it becomes more crucial to be able to determine the aggressiveness and extent of tumors accurately. The pathologist's ability to do this is hampered by limitations in the amount of information obtainable from routine prostate biopsies. The tissue obtained on biopsy is a static view of a tumor at a particular point in the course of a dynamic process in which the tumor continues to evolve over time. Predicting the behavior of a tumor from a single biopsy is much like trying to define the slope of a curve from a single data point. Approaches that aim to maximize the amount of information from pathological specimens, whether it be morphometric, histochemical or molecular, may ultimately improve the predictive accuracy of prostate biopsies. The challenges are to provide this information in a cost effective manner within a timeframe that allows for proper clinical decision making. It is, therefore, critical that improved diagnostic techniques be developed to optimize management decisions.

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