Prognostic Factors in Prostate Cancer

College of American Pathologists Consensus Statement 1999

David G. Bostwick, MD; David J. Grignon, MD; M. Elizabeth H. Hammond, MD; Mahul B. Amin, MD; Michael Cohen, MD; David Crawford, MD; Mary Gospadarowicz, MD; Richard S. Kaplan, MD, PhD; Daniel S. Miller, MD, MPH; Rodolfo Montironi, MD, PhD; Thomas F. Pajak, PhD; Alan Pollack, MD, PhD; John R. Srigley, MD; John W. Yarbro, MD

● Background.—Under the auspices of the College of American Pathologists, a multidisciplinary group of clinicians, pathologists, and statisticians considered prognostic and predictive factors in prostate cancer and stratified them into categories reflecting the strength of published evidence and taking into account the expert opinions of the Prostate Working Group members.

Materials and Methods.—Factors were ranked according to the previous College of American Pathologists categorical rankings: category I, factors proven to be of prognostic importance and useful in clinical patient management; category II, factors that have been extensively studied biologically and clinically but whose importance remains to be validated in statistically robust studies; and category III, all other factors not sufficiently studied to demonstrate their prognostic value. Factors in categories I and II were considered with respect to variations in methods of analysis, interpretation of findings, reporting of data, and statistical evaluation. For each factor, detailed recommendations for improvement were made. Recommendations were based on the following aims: (1) increasing uniformity and completeness of pathologic evaluation of tumor specimens, (2) enhancing the quality of data collected pertaining to existing prognostic factors, and (3) improving patient care.

Results and Conclusions.—Factors ranked in category I included preoperative serum prostate-specific antigen level, TNM stage grouping, histologic grade as Gleason score, and surgical margin status. Category II factors included tumor volume, histologic type, and DNA ploidy. Factors in category III included perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, prostate-specific antigen derivatives, and other factors (oncogenes, tumor suppressor genes, apoptosis genes, etc).

(Arch Pathol Lab Med. 2000;124:995–1000)

CATEGORY I

Prostate-Specific Antigen1–6

Method Variation Issues

● Multiple methods are available (>30 different assays). Hybritech and Abbott AXSYM are most common. Digi-
**Recommendations.**—Follow 1997 American Joint Committee on Cancer (AJCC)/TNM system for local staging. Fresh versus fixed processing is at the pathologist’s preference. Partial sampling is acceptable if a logical approach is followed. Whole-mount sections are optional. Surgical margin status is not included in this staging system (see below).

**Interpretation Variation Issues**
- Definition of extraprostatic extension (pT3 disease).
- Definition of seminal vesicle invasion.
- Definition of pT4 in the radical prostatectomy specimen.

**Recommendation.**—Clarification of terminology and definitions of the T categories in 1997 AJCC/TNM is recommended.

**Reporting Variation**
- Variability in terminology.

**Recommendation.**—Clarification of terminology and definitions of the T categories in 1997 AJCC/TNM is recommended.

**Statistical Issues**
- Variation in definition of pathologic stage used in prognostic marker studies.

**Recommendations.**—In prognostic marker studies, stage should be reported using a minimum of 3 categories, namely, pT2, pT3a, and pT3b. Amount and location of extraprostatic extension should be reported.

**Other**
- Obtaining fresh tissue for research while maintaining integrity of surgical pathology evaluation.
- Reports have indicated that some form of quantification of volume and extent of tumor outside the gland in pT3a tumors is of prognostic significance.

**Recommendation.**—There are insufficient data at the present time to make this a mandatory reporting variable. We would recommend it nonetheless, according to the recommendations of the Mayo consensus conference.

**Histologic Grade by Gleason Score**
Gleason scoring (a composite number composed of 2 patterns recognized by their architectural arrangement) has been shown to be an important predictor of outcome. It is also an important predictor of biochemical failure as a measure of disease recurrence. Nomograms have been developed to predict disease outcome using the clinical stage, serum PSA level, and biopsy Gleason score.5,14,30-32

**Method Variation Issues**
- Multiple grading systems have been used during the past several decades. Two systems continue to be applied, namely, the Gleason system and the World Health Organization system. The Gleason system is recommended as the standard for grading prostate cancer.
- Variation has existed as to whether the second pattern reported should be on the basis of the second most frequent pattern or, alternatively, the highest-grade pattern.

**Interpretation Variation Issues**33-38
- Gleason score is based on an architectural pattern that is a continuum, resulting in significant interobserver and intraobserver variation. Interpretive errors in 23% of cases have been documented, with discordance between institutional pathologists and central reviewing pathologists, the majority of which represented undergrading of infiltrating well-formed glands (pattern 3) as pattern 1 or 2, and failure to recognize glandular fusion as pattern 4.
- Variability is related to several factors:
  - Lack of understanding of and experience with Gleason system
  - Uncertainty regarding which grade category certain histologic patterns should be placed in
  - Limited tumor often present in thin (18-gauge) needle biopsy specimens
  - Variation of handling of multifocality and wide range of patterns in radical prostatectomy specimens
  - Occasional poor correlation between needle biopsy Gleason score and radical prostatectomy Gleason score.

**Recommendations.**—We recommend continuing educational activities, including Web-based programs. In radical prostatectomy specimens, Gleason score assignment should include highest-grade lesion. In needle biopsy specimens, the entire specimen (all needles) should be considered in assignment of score. A consensus meeting should be held to resolve issues and variation in interpreting and reporting Gleason scores on thin-needle biopsy specimens.

**Reporting Issues**
- Gleason scores are variably reported as one number (the score) or as the score and its component patterns (score = pattern 1 + pattern 2), leading to confusion for clinicians as to whether the score or one pattern is being reported. On needle biopsies, the score or pattern is reported on individual needles, on the entire sample, or on both. Confusion exists about handling of biopsies in which only one pattern is seen.

**Recommendation.**—Gleason score should be reported as the composite score and its component patterns, e.g., Gleason 7 = 3 + 4 or Gleason 7 (3 + 4). First reported pattern is the most frequent and second reported pattern is the second most frequent. The highest-grade pattern should also be reported, regardless of frequency. If the sample is a needle biopsy, the Gleason score of the entire sample should be reported as a composite score.

**Statistical Issues**
- Handling of the Gleason score varies among different studies. Often Gleason scores are compressed into groups, and different statisticians handle this compression differently.

**Recommendation.**—If Gleason scores must be compressed for evaluation or reporting purposes, the groups should be 2–5, 6, 7, and 8–10, or 2–6, 7, and 8–10.

**Surgical Margins**39-46

**Method Variation Issues**
- There is controversy about the best method of examination of margins.

**Interpretation Variation Issues**
- None, except the definition of a positive margin, which is variably defined. The group did not discuss this issue.
Reporting Issues
● Cases with positive margins are erroneously included in the pT3 category.

Statistical Issues
● None.

Other
● Importance of location of positive margin
  Involvement of apex alone has less negative impact than other locations
  Involvement at site of extraprostatic extension in pT3a cases vs elsewhere.
● Length of margin involvement may be important.

Recommendations.—Surgical margin status should be a category I variable. It is a standard part of reporting used in clinical decision making and has been found to be a significant prognostic indicator. Issues related to location and method to measure length of involvement remain open questions.

CATEGORY II
Volume of Cancer in Needle Biopsies\textsuperscript{47-57}
Method Variation Issues
● Multiple different approaches have been taken in reporting, including any or all of the following:
  Number of cores positive
  Percent of cores involved
  Total length (mm) of tumor in all cores
  Maximum single length (mm) of tumor in any core
  Overall percent of biopsies involved (surface area).

Interpretation Variation
● For counting cores, how to account for specimen fragmentation.
● For measuring length, how to handle 2 foci of cancer in the same needle (eg, should uninvolved tissue between the foci be included in the measurement).

Reporting Variation Issues
● Highly variable, just as methods are variable.

Statistical Issues
● Cutoff points.

Recommendations.—Most groups now recommend that this information be part of the routine surgical pathology report, although there are insufficient data to formally move this factor into category I. Use of overall percent of biopsy tissue involvement is the most practical and likely to be accepted approach.

Volume of Cancer in Radical Prostatectomy\textsuperscript{58,59}
Method Variation Issues
● No widely accepted method for quantitation.
● Partial sampling vs total embedding remains unresolved as a practice issue.

Recommendations.—Intraprostatic extent of cancer should be evaluated by some standard method so that percent of cancer in the sample can be reported.

Reporting Variation Issues
● No widely accepted method of reporting.

Recommendation.—Cancer volume should be reported as the percentage of cancer in the entire specimen.

Histologic Subtypes of Cancer\textsuperscript{60,61}

Variation Issues
● Specific histologic subtypes (eg, small cell, ductal [endometrioid], mucinous) may have significant prognostic or therapeutic implications.

Recommendation.—These subtypes should be specified in the pathology report if they are noted histologically.

DNA Ploidy\textsuperscript{62-67}

Numerous studies suggest that ploidy analysis adds clinically useful predictive information in some patients. The data in aggregate, however, are not compelling enough at this time to warrant routine use, because standardized methods have not achieved consensus, and the small tumor size of many tumors precludes use of the only standardized method (flow cytometry). Well-designed studies, such as those in the cooperative group setting, with comparable assays are needed. It is likely that if DNA ploidy is to achieve clinical utility, standardized image analysis methods must achieve consensus recommendation.

CATEGORY III
Perineural Invasion\textsuperscript{68-74}
Method Variation Issues
● Reporting of any perineural involvement versus only “large” nerve involvement.
● Reporting based on number of nerve fibers involved.

Interpretation Issues
● None known due to lack of research on this issue.

Reporting Issues
● None, except that perineural invasion is inconsistently mentioned.

Statistical Issues
● Cutoff points.

Recommendation.—This factor requires further study. Many reports will emerge in next 1 to 2 years that will likely make this a category II variable.

Lymph Node Micrometastases\textsuperscript{75,76}

Method Variation Issues
● There are substantial differences in assay methods (other than routine histology) that are being used to evaluate lymph node metastases, including immunohistochemistry and molecular methods.

Interpretation Variation Issues
● There is no agreement on the definition of micrometastases in prostate cancer.
● The clinical significance of minute foci of cancer in lymph nodes is uncertain.

Recommendations.—Conference recommendations regarding micrometastases should apply also to prostate
cancer. A histologically confirmed metastasis less than or equal to 2 mm in greatest dimension is regarded as a micrometastasis. The clinical utility of newer diagnostic modalities needs to be proven.

**Neuroendocrine Differentiation**

**Method Variation Issues**
- Light microscopy, identification of neuroendocrine cells in routine hematoxylin-eosin-stained sections (Paneth-like cells).
- Histochemical stains, argentafin and argyrophil reactions.
- Immunohistochemical methods
  - Chromogranin A
  - Chromogranin B
  - Neuron-specific enolase
  - Synaptophysin
  - Specific peptides.

**Interpretation Variation Issues**
- Definition of significant neuroendocrine differentiation, eg, any positive cells detected by immunohistochemistry or some specific number of cells (eg, >1 per high-power field).

**Reporting Variation Issues**
- As for interpretation issues.

**Statistical Issues**
- Cutoff point determination.

**Recommendation.**—Neuroendocrine differentiation should stay in category III. We see little data to suggest that it will move up.

**Microvessel Density**

Several studies have reported that assessment of microvessel density is very useful. In other studies, however, the opposite conclusion has been drawn. The conflicting results are likely the result of the variation in methods used to measure microvessel density and the significant interobserver variation that exists in interpretation of the number of positive vessels and the optimal way in which fields are selected (hot spot vs general counting of vessels).

**Recommendation.**—Given the importance of angiogenesis in tumor biology and conflicting results reported in evaluation of angiogenesis, additional well-designed studies are needed that will establish best assay method and interpretation criteria.

**Nuclear Roundness, Chromatin Texture**

**Interpretation Variation Issues**
- Conflicting data have been published, and there has been a lack of uniformity in calculating nuclear roundness. We do not recommend this factor for routine use at this time.
- Recent literature shows that the evaluation of chromatin texture is valuable as a prognostic factor.

**Recommendation.**—More data need to be collected.

**References**

15. Epstein JI, Carmichael MJ, Pizov G, Walsh PC. Influence of capsular pen-
42. Kupelian PA, Katcher J, Levin HS, Klein EA. Stage T1±2 prostate cancer: a protocol 8531. Mod Pathol. 1997;10:77A.