Prostate Cancer: Epidemiology and Screening

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The challenge continues—to find better methods of screening for prostate cancer, of determining who should undergo needle biopsy, and of predicting who will fail initial therapy. Investigators are looking at the value of neural networks and an array of markers to provide improved screening and prognostic information.

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The wealth of information that can be gleaned from examination of prostate specimens obtained by needle biopsy and following radical prostatectomy underscores the importance of the urologist and the pathologist having an excellent working relationship. M. Scott Lucia, MD, stated that despite the dramatic increase in the ability to diagnose prostate cancer, in public awareness, and in the numbers of radical prostatectomies being performed, we are still severely limited in our ability to accurately predict in which patients this form of therapy will fail.[1]

Cancer Progression Prognosticators

The most important and established prognosticators for prostatic carcinoma include the Gleason grade, the extent of tumor or tumor volume, and the presence of capsular penetration or margin positivity at the time of prostatectomy. Unfortunately, of these, only the Gleason grade can be determined reliably by examination of the needle biopsy specimens. It is well recognized that high-grade cancer, most particularly the percent of Gleason grades 4 and 5, is associated with adverse pathologic findings and disease progression.[2] Other studies, however, have demonstrated that low-grade tumors can be biologically aggressive.[3-6] Of course, one is always mindful that the Gleason grade of the biopsy specimen may not reflect that of the radical prostatectomy specimen, with undergrading far more common than overgrading. Up to 50% of patients may be undergraded by examination of the needle biopsy specimens.[7,8]

Although tumor volume is difficult to ascertain based on preclinical parameters, it does remain an important prognostic variable.[3,4,9] Data in the literature have suggested a reasonable correlation between the extent of tumor in biopsy specimens, the number of biopsy cores involved, and tumor volume.[10-13] Larger tumors more often are associated with advanced grade and stage. Whether a tumor attaining a large size is the determinant of this biologic aggressiveness or whether tumors that are

intrinsically biologically aggressive become large is unknown. Miller and Cygan,[14] for example, have demonstrated that there is a range of Gleason scores (2 to 10) in men with tumor volumes less than 0.5 cc. This suggests tumors may originate as high-grade lesions.

Clinicians and patients alike are increasingly interested in excluding "insignificant" tumors—those with little likelihood of manifesting themselves during a patient's lifetime. Epstein and associates[10] and other researchers[11-13,15-17] defined insignificant tumors as those less than 0.2 cc, with no areas of Gleason grade 4 or 5. This is based on a review of 500 clinical T2 radical prostatectomy specimens in which none of the 21 patients with these criteria had either capsular penetration or disease progression during a 5-year follow-up. In selecting radical prostatectomy specimens from 157 patients with T1c disease, they found that 16% of tumors would be considered insignificant.[10] They were able to identify 73% of these men with insignificant tumors if the following criteria were used: stage T1c; prostate-specific antigen density (PSAD) less than 0.1 ng/mL per gram; no Gleason grade 4 or 5 on biopsy specimen; and cancer length less than 3 mm in only 1 biopsy core.[10] Unfortunately, 10 of 63 cancers considered clinically significant were mischaracterized using these parameters, and these men would have been denied curative therapy. Contrary findings have been reported by Elgamal and coworkers,[18] who found 25% of significant T1c tumors had less than 3 mm of cancer present, and Thorson and colleagues,[19] who noted that positive surgical margins were found in 22% of their patients who had less than 1 mm of tumor on biopsy.

Although theoretically useful, repeated biopsy in men who are considered to have insignificant cancer has not been shown to provide significant identification of men who need therapy.[20] This further underscores the major problem with needle biopsy, for both diagnosis and prediction of malignant potential: the profound effect of sampling error. Crawford and colleagues[21] carried out a computer-based simulation of random sextant core biopsies on 59 whole-mount radical prostatectomy specimens. Table 1 shows the major findings: 13% of insignificant tumors were detected, and 48% of significant tumors were missed.

Several groups have demonstrated that combining data on the number of positive biopsy results or amount of tumor on biopsy specimens with prostate-specific antigen (PSA) level, clinical stage, and Gleason grade can improve prediction of pathologically upstaged neoplasms.[11-13] A number of markers, including p53 and p21, have been investigated. Significant heterogeneity of expression of the mutated form of p53 lessens our ability to identify this marker reliably on biopsy specimens. Similar concerns are associated with DNA ploidy analysis.

There is controversy as to whether microvessel density, a histologic marker of tumor angiogenesis, can offer significant enhancement of the ability to predict prognosis. It does seem to be an independent predictor of pathologic stage.[22,23] With regard to prognosis, Barth,[24] Rubin,[25] and Gettman[26,27] and their coworkers did not show independent prognostic information. Silberman and associates[28] determined that microvessel density provided useful stratifying information. Classic findings predicting progression based on biochemical disease-free survival, such as pelvic lymph node and seminal vesicle extension, remain important markers (Table 2). Their ability to offer unique, independent prognostic features, particularly when combined with the amount of Gleason grade 4 or 5 cancer, has been contested recently.[2] The fact that up to 15% of patients who have pathologic organ-confined disease that progresses[12,17,29] has been a confounding observation to students of this disease. Intraprostatic vessels may serve as a method of escape in this setting. For example, Bahnson and colleagues[30] demonstrated intravascular invasion associated with a 4-fold greater risk of progression. These findings have been corroborated by others.[31]

Table 1
Detection Rates of 6 Computer-Simulated, Random Sextant Core Biopsies by Alternative Classifications of Significance

	Number detected (%)	Number undetected (%)	Totals
Criterion A			
Significant (≥ 0.5 cc)	11 (58)	8 (42)	19
Insignificant (< 0.5 cc)	8 (20)	32 (80)	40
Criterion B			
Significant (≥ 0.25 cc)	15 (52)	14 (48)	29
Insignificant (< 0.25 cc)	4 (13)	26 (87)	30

Adapted from Crawford ED et al. *J Urol.* 1998.[21]

Screening Tests

Professor Fritz Schröeder believes that the value of screening for prostate cancer is unproven and will await the results of ongoing randomized studies in the United States and Europe.[32] He noted, however, that the recent decrease in US statistics of mortality from prostate cancer may suggest that aggressive early detection and treatment may be warranted. The best screening regimen, according to Dr Schröeder, is the method capable of detecting those cancers that constitute a significant risk to the patient, yet are still curable. The diagnostic tests leading to biopsy

should be associated with high specificity (thus decreasing the number of negative biopsy results) as well as high sensitivity (avoiding missing important neoplasms). By using standard indications for biopsy (abnormality on digital rectal examination [DRE] or PSA test), only about 20% to 25% of men subjected to biopsy will have carcinoma detected. Based on data from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer, the threshold for biopsy should be a PSA level higher than 3 ng/mL, and those men with a PSA lower than 1 ng/mL should be excluded from DRE.

Table 2
Prostate Cancer Risk of Progression at 5 Years

Pelvic lymph nodes	95%
Seminal vesicles	85%
Established capsular penetration	48%
Focal capsular penetration	33%
Organ-confined	9% - 13%

From Epstein JI et al. *J Urol.* 1993[17]; Stein A et al. *J Urol.* 1992.[29]

Racial Differences in PSA

Jackson Fowler, Jr, MD, has been one of the major investigators of the effects of race in men with prostate cancer. In his extensive experience at the Veterans Affairs Medical Center in Jackson, Miss (a setting that has a 40% black population), there is more variability in PSA levels in blacks.[33,34] Dr Fowler's work has demonstrated that the racial variability in serum PSA level is not related to prostate volume.[35] Dr Fowler's team has investigated the incidence of high-grade prostatic intraepithelial neoplasia (PIN) in black and white men. They compared 411 black and 639 white men and identified PIN in 55% and high-grade PIN in 8.9%. High-grade PIN was identified in 13% of the blacks and 6% of the whites ($P < .001$). The median PSA level was significantly higher in men with high-grade PIN.

The incidence of cancer on repeated prostate needle biopsies has been reported by numerous authorities to be quite high. Fowler and colleagues[36] studied 298 consecutive men undergoing 1 repeated biopsy and found cancer in 42 (32%) of 133 blacks, compared with 38 (23%) of 165 whites. These differences did not achieve statistical significance.

Fowler's group has confirmed the findings of others[37-40] that PSA levels tend to be higher in black men than in white men with clinically localized (T1c-T2) prostate cancer (Table 3). Fowler's group has also clearly demonstrated that blacks have higher-grade carcinoma at diagnosis. They evaluated 222 black and 298 white men with clinically localized prostate cancer and PSA levels between 2.5 and 9.9 ng/mL.[41] Cancer was detected in 47% of blacks and 33% of whites; it was found in a higher percentage of blacks with each percent of free-to-total PSA. For example, of those men who had a percent-free PSA (%fPSA) less than 25, cancer was detected in 53% of blacks and 41% of whites. In those men who had a %fPSA higher than 25, 32% of blacks compared with 13% of whites had cancer. Both of these differences were statistically significant. There was no racial difference in age, prostate volume, total PSA, PSAD, or %fPSA in those without cancer. In those with cancer, only %fPSA was higher in blacks, providing a statistically significant difference. This suggests that racial differences and cancer detection in patients stratified by %fPSA are related to more of the free form in blacks. Dr Fowler concluded that while the PSA levels are higher in black men without evidence of cancer than in white men, there is no compelling rationale to use different reference ranges based on race.[42] He further noted cut points for %fPSA that are based on studies with predominantly white men may not be equally applicable to blacks.

Neural Networks

Recognition of the variable natural history of prostatic carcinoma coupled with the increasing number of variables being measured in hopes of providing prognostic information has often found traditional statistical methods lacking. Artificial neural networks have the potential advantage of identifying novel relationships between dif-

Table 3
Race and PSA Level in Men With Local Stage Prostate Cancer

	Black men	White men	*P* value
Number of patients	271	239	
Age (y)*	69.2 ± 7.7	68.1 ± 6.8	.08
PSA (ng/mL)†	8.9 (5.9 - 16.6)	6.6 (3.9 - 11)	< .0001
Prostate volume (mL)†	35 (25 - 48)	32 (24 - 44)	.06
Biopsy Gleason score ≥ 7	130 (48)	93 (39)	.04

PSA, prostate-specific antigen.
*Mean ± SD.
†Median, 25th to 75th percentile.

ferent types of data in ways distinct from conventional logistic regression approaches. E. David Crawford, MD, reported on several projects (funded by the Institute for Clinical Research in Washington, DC) dedicated to applying artificial intelligence methodology to prostatic carcinoma. These studies have used multivariate statistical modeling and nomograms. Established nomograms, including the one devised by Partin and associates,[43,44] provide useful information for groups. These nomograms present problems when dealing with the individual patient, however. Many markers, including imaging, reverse transcriptase–polymerase chain reaction assays, DNA ploidy, nuclear morphometry, p53 and other tumor suppressor genes, bcl-2, and angiogenesis of microvessel density, did not, in general, improve prognostic prediction for the individual patient.

The neural networks provide a potential alternative approach, because they can deduce patterns in data that other approaches cannot. Neural networks are complex mathematical models, based on the neuronal relationships within the brain. Multiple neural network units (processors) are connected with communication channels to carry numeric data. These units operate only with their local data and on inputs from other connections. Generally, studies incorporate a training set to establish the neural network methodology, followed by validation and test sets.

Crawford and colleagues evaluated 309 patients from their radical prostatectomy database. Of these, 85% had a pathologic stage of T3 or higher. The investigators used a training set of 50% of the database and a validation set of 40%. A test group (10%) was randomly selected from the database. Input variables included preoperative PSA levels; prior therapy; age; prostate volume determined by ultrasonography; clinical tumor, node, metastasis (TNM); number of positive biopsy results; and Gleason scores (both primary and sums).

With respect to prediction of pathologic stage, the artificial neural network achieved a sensitivity of 85% and a specificity of 57% for both the training and testing sets. Prediction of advanced and locally advanced disease shared an overall accuracy of 72%. Similar findings were observed with the validation cases, which demonstrated sensitivity and specificity of 79% and 81%, respectively, while accuracy for the validation set was 80%. In contrast, multivariate regression analysis for the validation cases demonstrated a sensitivity of 95% but a specificity of only 18%.

The variables, in order of importance in predicting pathologic stage, were clinical stage (TNM), prior new adjuvant therapy, prostate size, percentage of biopsy tissue that was positive, DRE, presurgery PSA level, primary biopsy Gleason score 8, age, and total Gleason score of the biopsy specimens.

With respect to prediction of biochemical failure, sensitivity and specificity for the neural networks were 43% and 92%, respectively, for the training and testing sets. The accuracy for detecting recurrence was 47%, while that for nonoccurrence was 91%. Accuracy in the training and testing cases was 85% for predicting recurrence. In contrast, multivariate regression analysis of the validation cases showed sensitivity and specificity of 0% and 97%, respectively. Dr Crawford concluded that the ability of artificial neural networks to use a variety of factors available in clinical use to ferret out relationships between parameters offers a useful adjuvant to our ability to ascertain the likely outcomes for patients with prostatic carcinoma. Advancement will occur with more variables and larger databases to establish these models. ■

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