Clinical Utility of the Percentage of Positive Prostate Biopsies in Defining Biochemical Outcome After Radical Prostatectomy for Patients With Clinically Localized Prostate Cancer

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Purpose: To determine the clinical utility of the percentage of positive prostate biopsies in predicting prostate-specific antigen (PSA) outcome after radical prostatectomy (RP) for men with PSA-detected or clinically palpable prostate cancer.

Methods: A Cox regression multivariable analysis was used to determine whether the percentage of positive prostate biopsies provided clinically relevant information about PSA outcome after RP in 960 men while accounting for the previously established risk groups that are defined according to pretreatment PSA level, biopsy Gleason score, and the 1992 American Joint Committee on Cancer (AJCC) clinical T stage. The findings were then tested using an independent surgical database that included data for 823 men.

Results: Controlling for the known prognostic factors, the percentage of positive prostate biopsies added clinically significant information (P < .0001) regarding time to PSA failure after RP. Specifically, 80% of the patients in the intermediate-risk group (1992 AJCC T2b, or biopsy Gleason 7 or PSA > 10 ng/mL and ≤ 20 ng/mL) could be classified into either an 11% or 86% 4-year PSA control cohort using the preoperative prostate biopsy data. These findings were validated in the intermediate-risk patients using an independent surgical data set.

Conclusion: The validated stratification of PSA outcome after RP using the percentage of positive prostate biopsies in intermediate-risk patients is clinically significant. This information can be used to identify men with newly diagnosed and clinically localized prostate cancer who are at high risk for early (≤ 2 years) PSA failure and, therefore, may benefit from the use of adjuvant therapy.


The prostate-specific antigen (PSA) level, biopsy Gleason score, and the 1992 American Joint Committee on Cancer (AJCC) clinical T stage have been established as comprising the first step toward defining the probability of organ-confined prostate cancer in an individual patient before the delivery of definitive treatment. Yet, although finding organ-confined prostate cancer at the time of pathologic sectioning of the radical prostatectomy (RP) specimen is a favorable prognostic factor, it does not guarantee PSA control. PSA failure occurs despite pathologic evidence of organ-confined disease in some men.

PSA has been used for evaluating treatment success or failure. Whether PSA can be used as a surrogate end point for cause-specific survival after a radical retropubic prostatectomy awaits further follow-up. Nevertheless, treatment recommendations after primary treatment failure are often made on the basis of the PSA end point. The availability of PSA outcome data after RP would provide a useful tool for counseling patients about PSA outcome after RP and also for selecting patients who are unlikely to remain PSA failure–free after RP alone for inclusion in adjuvant therapy trials. The question remains, however, as to the most predictive and reproducible clinical variables on which to base the PSA outcome data.

Previously published studies confirm that the serum PSA level, 1992 AJCC clinical T stage, and biopsy Gleason score are independent predictors of PSA failure–free survival after either RP or external-beam radiation therapy (RT). Risk groups that are defined according to PSA level, biopsy Gleason score, and the 1992 AJCC clinical T stage and that identify the risk of PSA failure after RP or RT have been previously published. The fraction of prostate biopsies that are found to contain prostate cancer represents information that is readily available for all patients with PSA-detected or clinically palpable prostate cancer. Studies investigating the ability of the fraction of positive prostate biopsies × 100 to predict pathologic end points after RP suggest a role for this clinical factor in predicting tumor volume, extracapsular extension...
(ECE), seminal vesicle invasion (SVI), lymph node involvement, and the percentage of Gleason score 4 and 5 disease in the RP specimen. Yet whether the percentage of positive prostate biopsies provides information in addition to that which is already embodied in the known prognostic factors involved in predicting PSA control after RP has not been clearly elucidated.

This study had two goals. The first goal was to establish whether the percentage of positive prostate biopsies provided further clarity in predicting PSA outcome after RP after accounting for the previously published prognostic risk groups in men with PSA-detected or clinically palpable prostate cancer. The second goal was to test the results using a validation analysis that used a second independent surgical data set. Particular attention was given to the patients who were classified in the intermediate-risk group, for whom improvements in the prediction of PSA outcome are most needed.

METHODS

Patient Population

Nine hundred sixty men treated with an RP and bilateral pelvic lymph node dissection at the Hospital of the University of Pennsylvania (PENN; Philadelphia, PA) between 1989 and 1998 who had PSA-detected or clinically palpable prostate cancer comprised the study population. Patients who received neoadjuvant androgen-suppression therapy or adjuvant RT and/or androgen-suppression therapy were excluded. Eight hundred twenty-three men treated with an RP and bilateral pelvic lymph node dissection at the Brigham and Women's Hospital (B&W) between 1989 and 1998 who had PSA-detected or clinically palpable prostate cancer comprised the validation cohort. Table 1 lists the preoperative clinical and postoperative pathologic characteristics for the 960 study patients and the 823-member validation cohort.

Preoperative Staging

In all cases, staging evaluation consisted of a history and physical examination, including a digital rectal examination (DRE), serum PSA, computed tomography of the pelvis or an endorectal and pelvic coil magnetic resonance imaging scan of the prostate and pelvis, bone scan, and a transrectal ultrasound-guided needle biopsy of the prostate with Gleason score histologic grading. The prostate biopsy was performed using an 18-gauge Tru-Cut needle (Travenol Laboratories, Deerfield, IL) via a transrectal approach. Sextant biopsies were obtained in the majority of RP-managed patients at PENN (56%) and B&W (75%). The remaining 44% of patients managed with RP at PENN had fewer than six (18% of patients) or more than six biopsies (26% of patients) as listed in Table 2. Also listed in Table 2 are the numbers of biopsies obtained, stratified according to the ultrasound-determined prostate gland volume. The clinical stage was determined from the DRE findings using the current 1992 AJCC staging system. Radiologic and biopsy information were not used to determine clinical stage. The PSA level was obtained on an ambulatory basis before radiologic studies and biopsy. All PSA measurements were made using the Hybritech (Beckman Coulter Inc, Fullerton, CA), Tosoh (Tosoh Inc, San Francisco, CA), or Abbot (Abbott Laboratories, Abbott Park, IL) assays.

Treatment

A referee genitourinary pathologist reviewed the diagnostic biopsy specimens for all patients undergoing surgery at the PENN (J.E.T.) or B&W (A.A.R.). Surgical treatment consisted of a radical retropubic prostatectomy and bilateral pelvic lymph node sampling. If the intraoperative frozen sections of any sampled lymph node were positive for carcinoma, then the RP was aborted. Focal and established ECE were recorded and defined as per Epstein et al for the PENN patients. Evidence of seminal vesicle invasion was also noted and recorded.

Follow-Up

The median durations of follow-up for the 960 and 823 surgically managed patients at PENN and B&W were 46 months (range, 8 to 100 months) and 52 months (range, 8 to 118 months), respectively. The patients were examined 1 month postoperatively and then at 3-month intervals for 2 years, every 6 months for 5 years, and annually thereafter. At each follow-up appointment, the serum PSA level was measured before the DRE was performed. All pretreatment PSA values were obtained within 1 month of the date of surgery. No patients were lost to follow-up.

Statistical Analyses

A Cox regression time-to-PSA-failure analysis that evaluated the ability of the percentage of positive biopsies to predict time to PSA failure was performed for all study patients. The assumptions of the Cox model were tested and met. The percentage of positive biopsies and the preoperative PSA level were treated as both continuous and categorical variables in separate analyses. The biopsy Gleason score was evaluated twice: first as a continuous variable that could take on integer values of 2 through 10 and second as a categorical variable that was grouped as 2 to 4, 5 to 6, 7, and 8 to 10 in the second analysis. The 1992 AJCC clinical T stage was evaluated first as a continuous and second as a categorical variable that could take on values of T1c, T2a, T2b, or T2c. Baseline groups for the categorical variables were biopsy Gleason score of 2 to 4 and 1992 AJCC stage T1c. When PSA was treated as a categorical variable, values were grouped in a standard fashion (0 to 4, > 4 to 10, > 10 to 20, and > 20 to 50 ng/mL) to allow comparison with results of other published series. The percentages of positive prostate biopsies were grouped as less than 34%, 34% to 50%, and greater than 50%. Baseline groups for PSA and the percentage of positive prostate biopsies were 0 to 4 ng/mL and less than 34%, respectively. Patients with 1992 AJCC clinical stage T1a or T1b disease were excluded because the diagnosis of prostate cancer in these cases was made on the basis of a transurethral resection sample of the prostate and not through the use of multiple needle-biopsy specimens.

Race was not included in the multivariable analysis because most patients were of the same race; therefore, the power to detect any difference according to race was low.

PSA failure was considered to have occurred when two consecutive detectable PSA values were observed after an undetectable value. Time zero was defined as the date of surgery for all patients. If a PSA never became undetectable postoperatively, then PSA failure was considered to have occurred at time equal to zero. Patients who were found to have positive pelvic lymph nodes at the time of frozen section or at final pathologic section were started on androgen-suppression therapy and, therefore, were considered to have experienced treatment failure at time zero. The probability of 2-year PSA failure was calculated from the coefficients of the Cox model. The 95% confidence intervals for the 2-year PSA-failure probabilities were calculated using a bootstrapping procedure with 2,000 replications. The marginal proportion of vari-
ation explained (mPVE)\(^{20}\) for each of the significant clinical predictors of time to PSA failure were also calculated. The mPVE value defines the percentage of the variation in the PSA data that can be explained by the predictor and can range from 0% to 100%. The test for linear trend between pretreatment clinical predictors and pathologic outcomes was performed using a Cochran-Armitage test.\(^{21}\)

Three risk groups previously defined\(^7\) from a review of the literature\(^{22-33}\) that are based on the pretreatment PSA level, biopsy Gleason score, and 1992 AJCC T stage were used to illustrate the impact that the percentage of positive biopsy information had on the PSA failure–free (bNED) survival rates after RP. Low-risk patients had a preoperative PSA level of \(\leq 10\) ng/mL, a biopsy Gleason score of \(\leq 6\), or 1992 AJCC clinical stage T1c or T2a disease. Intermediate-risk patients had a PSA level of greater than \(10\) but \(\leq 20\) ng/mL, a biopsy Gleason score of \(7\), or \(1992\) AJCC clinical stage T2b disease. Finally, high-risk patients had a PSA level of greater than \(20\) ng/mL, a biopsy Gleason score of \(8\), or \(1992\) AJCC clinical stage T2c disease. Specifically, PSA failure–free survival (stratified by \(34\%\), \(34\%\) to \(50\%\), and \(> 50\%\) positive biopsies) was estimated using the actuarial method of Kaplan and Meier\(^{34}\) and graphically displayed. The cutoff points for the percentage of positive biopsy variables were selected to evaluate the clinical utility of this parameter and were defined before the statistical analysis was performed.

### Table 1. Clinical Pretreatment and Postoperative Pathologic Characteristics of the 960 Study and 823 Validation Patients

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<th>Pathologic ECE, established</th>
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Abbreviation: OC, organ-confined.

*Focal or established ECE.
A validation analysis of the ability of the percentage of positive biopsies to stratify PSA outcome after RP was performed using an independent surgical database that included data for 823 men with clinically localized prostate cancer who were managed at a separate institution during the same time period as the study cohort.

RESULTS

Pretreatment Clinical Characteristics and Pathologic Stage

The clinical characteristics and corresponding pathologic stages are listed in Table 1 for the 960 study patients. There was a statistically significant decrease in the pathologic organ-confinment rate, with an increasing value of the PSA \((P < .0001)\), 1992 AJCC clinical stage \((P < .0001)\), biopsy Gleason score \((P < .0001)\), and the percentage of positive biopsies \((P < .0001)\). Conversely, the finding of established ECE or SVI increased significantly as the preoperative PSA value (ECE, \(P < .0001\); SVI, \(P < .0001\)), 1992 AJCC clinical stage (ECE, \(P < .0001\); SVI, \(P < .0001\)), biopsy Gleason score (ECE, \(P < .0001\); SVI, \(P < .0001\)), or percentage of positive biopsies (ECE, \(P < .0001\); SVI, \(P < .0001\)) increased. No significant trend \((P > .38)\) was noted for the pathologic finding of focal ECE as a function of the pretreatment PSA level, biopsy Gleason score, 1992 AJCC clinical stage, or percentage of positive biopsies.

Time-to-PSA-Failure Analysis

As continuous variables, the pretreatment PSA level \((P < .0001)\), biopsy Gleason score \((P = .0003)\), 1992 AJCC clinical T stage \((P = .05)\), and percentage of positive biopsies \((P < .0001)\) were all independent significant predictors of time to PSA failure. PSA and the percentage of positive biopsies remained significant \((P < .0001)\) when the biopsy Gleason score and 1992 AJCC clinical T stage were evaluated as categorical variables. Table 3 lists all of the individual P values for the two Cox regression analyses in which the biopsy Gleason score and 1992 AJCC T stage were evaluated first as continuous and then as categorical variables.

Using these P values and a bootstrapping procedure, estimates of 2-year PSA failure rates and 95% confidence intervals were derived and presented in nomogram format in Table 4. The values of the mPVE in the data regarding time to postoperative PSA failure for preoperative PSA level, biopsy Gleason score, 1992 AJCC clinical T stage, and percentage of positive biopsies were 17%, 6%, 8%, and 17%, respectively. These results are listed in Table 3 and suggest that other pretreatment clinical parameters are still needed to account for the remainder of the variation in the postoperative PSA data.
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<th>Positive Biopsies (%)</th>
<th>AJCC Stage</th>
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<th>95% CI</th>
<th>2a Failure Probability</th>
<th>95% CI</th>
<th>2b Failure Probability</th>
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Abbreviation: CI, confidence interval.
Risk Group–Based Analysis

Figure 1 illustrates the value of the previously described risk group system, in which assignment to risk group is based on the preoperative PSA level, biopsy Gleason score, and 1992 AJCC clinical T stage. All pair-wise comparisons are significant (P < .0001). Figures 2 through 4 illustrate the clinically relevant stratification provided by information regarding the percentage of positive biopsies in previously defined risk groups that were determined according to pretreatment PSA level, biopsy Gleason score, and 1992 AJCC clinical T stage. Specifically, patients in the intermediate- or high-risk subgroups who also had less than 34% positive biopsies improved their risk stratification for PSA outcome by one category. Conversely, patients with more than 50% positive biopsies had a poorer outcome than was expected. Of particular importance, however, is that the majority of patients (214 [80%] of 269 patients) in the intermediate-risk group could be classified into either an 11% or 86% 4-year PSA control cohort using the preoperative prostate biopsy.

Validation Analysis

Figure 5 illustrates the significant stratification (P < .0001) of the 823-member validation cohort using the previously described risk group system. Figure 6 shows that categorization of the percentage of positive biopsies (< 34%, 34% to 50%, and > 50%) successfully stratified the validation cohort in the intermediate-risk group in a statistically (all, pair-wise P ≤ .0001) and clinically significant manner. Specifically, 251 (78%) of the 322 intermediate-risk patients could be classified into either an 8% or 93% 5-year PSA control cohort using the preoperative prostate biopsy data. In addition, when the data in Table 4 were generated for the validation data set, the 95% confidence intervals for each category within the table were not statistically different.
DISCUSSION

The pretreatment PSA level, biopsy Gleason score, and 1992 AJCC clinical T stage remain the major clinical parameters on which recommendations for treatment of an individual patient with newly diagnosed and clinically localized prostate cancer are based. A nomogram for predicting PSA outcome at 5 years after RP based on the preoperative PSA level, biopsy Gleason score, and the 1992 AJCC clinical T stage has been previously published by Kattan et al.6 Five-year PSA failure–free survival rates stratified by treatment received (RP or RT) and matched for the pretreatment PSA level, biopsy Gleason score, and 1992 AJCC clinical T stage have also been published.7 Refinement of PSA outcome prediction data using new clinical, pathologic, and molecular tools has been explored.3,30,35-41 Although many of these methods are novel and promising, their generalizability awaits validation.

Prostate biopsy information is available for all patients with newly diagnosed prostate cancer, with the exception of the decreasing number of patients who are diagnosed today during a transurethral resection. Therefore, investigators have attempted to establish whether the number of biopsies that contain adenocarcinoma provides further information about PSA outcome after RP. In particular, Presti et al42 performed a Cox regression multivariate analysis to evaluate the clinical utility of the fraction of systematic biopsies (one to three vs four to six), pretreatment PSA level ($\leq 20$ ng/mL vs $> 20$ ng/mL), and biopsy Gleason score (2 to 6 vs 7 to 10) in predicting time to postoperative PSA failure. Their analysis included 109 patients and used two consecutive increases in PSA of more than 0.1 ng/mL as the definition of PSA failure. They found that both the biopsy Gleason score and the fraction of systematic biopsies were predictive of PSA outcome after RP.

To provide clinical utility in this study, a specific categorization of the data for percentage of positive biopsies

Fig 4. PSA failure-free survival stratified by the percentage of positive biopsies for high-risk study patients managed using a radical retropubic prostatectomy. Pair-wise P values: less than 34% versus more than 34% to 50%, $P = .001$; more than 34% to 50% versus more than 50%, $P = .03$; less than 34% versus more than 50%, $P < .0001$.

Fig 5. PSA failure-free survival stratified by the risk group defined using the PSA value, biopsy Gleason score, and 1992 AJCC clinical T stage for validation patients managed using a radical retropubic prostatectomy. Pair-wise P values: low versus intermediate risk, $P < .0001$; intermediate versus high risk, $P < .0001$; low versus high risk, $P < .0001$.

Fig 6. PSA failure-free survival stratified by the percentage of positive biopsies for intermediate-risk validation patients managed using a radical retropubic prostatectomy. Pair-wise P values: less than 34% versus more than 34% to 50%, $P < .0001$; more than 34% to 50% versus more than 50%, $P = .0001$; less than 34% versus more than 50%, $P < .0001$. 

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was selected for evaluation before analysis, which corresponded to one to two (< 34%), three (34% to 50%), or four to six (> 50%) positive biopsies in the case of a standard sextant sampling. This selection was based on the presumption that more than one half of the cores being positive versus one third or fewer was a clinically meaningful difference. The percentage of positive biopsies, when analyzed in this manner, was found to be an independent predictor of time to PSA failure after RP after controlling for the previously defined risk stratification schema that was based on the known prognostic factors. The stratification of PSA outcome after RP provided by the percentage of positive biopsies was also clinically significant in that the vast majority (78% to 80%) of the intermediate-risk patients in the study and validation cohorts could be categorized into a high- or low-risk category for PSA outcome after RP. This result should translate into a marked improvement in the physician’s ability to counsel the patient regarding outcome after RP. Specifically, Table 4 lists the probability of PSA failure at 2 years and 95% confidence intervals stratified according to known prognostic factors and the categories of the percentage of positive biopsies that were selected for evaluation in this study. This information identifies patients who are at high risk for early PSA failure. Considering the recent data showing that a time to PSA failure of less than 2 years predicts for distant failure, patients who are at high risk for early PSA failure may be the ideal candidates to select for entry onto adjuvant therapy trials.

Several issues remain that need to be addressed. First, as in this study, some patients will have prostate biopsies obtained in practice that are not sextant. The results of this study depended on an accurate sampling of the prostate gland. That all patients in this study had at least four cores obtained may be relevant to the accomplishment of this end point. Therefore, these data may not be applicable in the case of patients for whom fewer than four cores were obtained. Next, 26% of the patients in this study from the PENN cohort had seven or more biopsies obtained. Specifically, 21%, 28%, and 44% of patients with a prostate gland volume of less than 30 cm³, 30 to 75 cm³, or more than 75 cm³, respectively, had at least seven cores obtained, as listed in Table 2. This trend suggested that a larger sample was generally performed in patients with larger prostate gland volumes, possibly in an effort to decrease sampling error. Therefore, the results of this study may not be applicable to patients with large gland volumes (> 75 cm³) who had fewer than seven cores obtained.

Another limitation of the study is that the results are based on PSA control and not patterns of failure or cause-specific survival data. However, a recent study has suggested that PSA failure may be a surrogate end point for death from prostate cancer for patients undergoing a radical perineal prostatectomy. Validation of this finding by others and for patients undergoing a radical retropubic prostatectomy is needed to establish PSA failure as a surrogate end point for death from prostate cancer.

Finally, the percentages of positive prostate biopsies of less than 34%, 34% to 50%, and more than 50% corresponded to positive surgical margin rates of 13%, 28%, and 35%, respectively, for the study cohort and 11%, 29%, and 37%, respectively, for the validation cohort. Therefore, it is conceivable that the use of adjuvant RT may benefit men with more than 50% positive prostate biopsies. A future study will address whether the factor of percentage of positive prostate biopsies retains its prognostic significance in a group of patients undergoing RP followed by adjuvant RT.

In conclusion, the percentage of positive prostate biopsies represents information that is routinely available for patients with newly diagnosed prostate cancer. This information has now been shown to provide a clinically significant improvement in predicting PSA outcome after RP for patients for whom it is most needed. Therefore, this information may be used to select men with clinically localized prostate cancer who are at very high risk of early PSA failure (< 2 years) for inclusion in adjuvant therapy trials.

REFERENCES