Classification and Regression Tree Analysis for the Prediction of Aggressive Prostate Cancer on Biopsy

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Purpose: Prostate cancer screening allows early cancer detection but not all patients benefit from subsequent therapy. Thus, identifying patients who are likely to harbor aggressive cancer could significantly decrease the number of prostate biopsies performed.

Materials and Methods: Data were collected on 1,563 consecutive referred men with serum PSA 10 ng/ml or less who underwent an initial prostate biopsy. Predictors of aggressive cancer (Gleason sum 7 or greater) were identified using CART analysis. Model building was done in a randomly selected training set (70% of the data) and validation was completed using the remaining data.

Results: Cancer was detected in 406 men (26.1%). Gleason 7 or greater cancer was found in 130 men (8.3%). CART created a decision tree that identified certain groups at risk for aggressive cancer, namely 1) PSAD greater than 0.165 ng/ml/cc, and 2) PSAD greater than 0.058 to 0.165 ng/ml/cc or less, age greater than 57.5 years and prostate volume greater than 22.7 cc. The incidence of aggressive prostate cancer was 1.1% when PSAD was 0.058 ng/ml/cc or less in the validation set. The sensitivity and specificity of CART for identifying men with aggressive cancer were 100% and 31.8% for model building data, and 91.5% and 33.5% for the validation data set, respectively.

Conclusions: CART identified groups at risk for aggressive prostate cancer. Application of this CART could decrease unnecessary biopsies by 33.5% when only a diagnosis of high grade prostate cancer would lead to subsequent therapy.

Key Words: prostate, prostatic neoplasms, prostate-specific antigen, risk, biopsy

It is estimated that more than 230,000 cases of prostate cancer were diagnosed in 2004, during which time almost 30,000 deaths occurred due to prostate cancer.[1] In a longitudinal study of patients with prostate cancer treated conservatively the lifetime risk of prostate cancer mortality was 16%.[2] Thus, a substantial majority of men diagnosed with prostate cancer do not die of this disease. Therefore, the identification of those at greatest risk for poor prostate cancer outcomes is an important priority.

Inadequate specificity of currently used noninvasive tests necessitates a large number of unnecessary biopsies to detect prostate cancer. The pre-biopsy stratification of patients at greatest risk for death from disease could allow clinicians to optimize the decision process regarding prostate biopsy. By defining risk groups for aggressive cancer clinicians could avoid biopsies in men who would only be treated if aggressive prostate cancer were detected. This is particularly important in patients with limited life expectancy or competing comorbidities in whom local treatment might only be considered if they harbored aggressive prostate cancer. Several pre-biopsy risk factors have been associated with biochemical recurrence after definitive local therapy, although to our knowledge many of these covariates have yet to be linked to prostate cancer mortality. In contrast, biopsy grade remains the most accurate predictor of prostate cancer progression and mortality in cases managed conservatively by observation.[2,3] Furthermore, Gleason grade has been the only perioperative factor that could be used to predict subsequent disease specific mortality after radical prostatectomy.[4]

Recently the usefulness of traditional factors such as PSA and DRE for the prediction of cancer regardless of histological grade has come into question.[5–7] To improve the accuracy of prostate cancer detection several pre-biopsy models using various statistical methods have been developed to predict prostate cancer on needle biopsy.[8–10] However, to our knowledge models that accurately predict high grade prostate cancer have yet to be developed. Novel methods that identify patients with aggressive prostate cancer are needed to decrease the rates of negative biopsies and prostate cancer over diagnosis.

Recently we reported the use of CART analysis to improve the detection of cancer on prostate biopsy.[11] In the current study we used this method to detect high grade prostate cancer. The CART technique uses a binary recur-

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TABLE 1. *Patient characteristics*

No. pts	1,563
Median age (range)	66.0 (41–85)
% Race:	
White	93.3
Black	4.1
Other	2.6
% Family history*	17.1
% Vasectomy	34.0
PSA (ng/ml):	
Mean	4.8
Median (range)	5.0 (0.04–10)
% DRE findings:†	
Normal	50.3
Asymmetrical only	5.0
Suspicious	40.9
Ca likely	3.9

* Not available in 11 patients.
† Not available in 6 patients.

sive partitioning method to classify subjects into high and low risk groups, and it presents the resulting classification rule as a decision tree, which is easily interpretable.[12] CART has been shown to be competitive with other traditional statistical techniques, eg logistic regression.[13] However, unlike other methods it does not require specification of the risk function and it can detect complex interactions among risk factors.

METHODS

Study population and biopsy procedure. Data were retrospectively reviewed on 1,563 consecutive referred men seen at Portland Veterans Administration Hospital from February 1993 to July 2002 who had serum PSA 10 ng/ml or less and underwent prostate biopsy with a minimum of 6 cores. All patients were referred for routine clinical care, not as participants in a population based screening trial. To be eligible patients could not have undergone prior prostate biopsy.

Evaluation of all patients included repeat serum PSA testing (Abbott Diagnostics, Abbot Park, Illinois) and DRE, which was classified as normal, asymmetrical, suspicious or cancer likely by a member of the urology team. Prior to biopsy all patients underwent screening urinalysis, and received a cleansing enema and systemic antibiotic prophylaxis. Patients with evidence of prostatitis or cystitis on screening urinalysis, as identified by urine dipstick, were excluded. Additional recorded demographic and historical variables were patient age at biopsy, race, family history of prostate cancer in a first-degree relative, history of vasectomy and the indication for referral.

Three-dimensional TRUS was performed in all patients using a Bruel and Kjær 3535 Model 8551, 7.5 MHz probe device (Bruel and Kjær, Marlboro, Massachusetts). By measuring prostate width, length and height prostate volume in cc could be estimated using a modification of the prolate ellipsoid formula, (0.52 × [length (cm) × width (cm) × height (cm)]). PSAD was calculated using the equation, PSAD = (serum PSA/calculated prostate volume). In all patients a minimum of 6 biopsy cores (range 6 to 11) were obtained. Additional biopsy cores were obtained when TRUS identified a lesion outside of the initially planned biopsy field.

This study was approved by the Portland Veterans Administration Institutional Review Board and Research and Development Committees. It was granted exempt status from the need for informed consent.

Statistical methods. The primary study end point was the detection of Gleason 7 or greater prostate cancer. Those without prostate cancer or those with Gleason less than 7 prostate cancer were grouped as Gleason less than 7 cancer cases. The data were divided randomly into a model building set (70%) and a validation set (30%). CART analysis was performed in the model building set using CART software (Salford Systems, San Diego, California). Unequal misclassification costs were specified, so that there was a 2.5 times higher cost associated with misclassifying a Gleason 7 or greater case as a Gleason less than 7 case. Overall sensitivity and specificity of the resulting decision rule were evaluated using the validation set.

RESULTS

Patient characteristics. Median age was 66.0 years (range 41 to 85). The majority of patients (93.3%) were white. A family history of prostate cancer was reported in 17.1% of patients and 33.9% had undergone vasectomy. Median PSA was 5.0 ng/ml (mean 4.8). The majority of patients studied had undergone 6 biopsies (median 6.0, mean 6.8). DRE was classified as normal in 780 patients (50.3%), suspicious in 635 (40.9%), asymmetrical only in 77 (5.0%) and cancer likely in 60 (3.9%) (table 1).

Ultrasound and biopsy data. Median PSAD was 0.12 ng/ml/cc (mean 0.14) and median prostate volume was 40.3 cc (mean 34.6). Of the sampled patients 406 (26.0%) were found to have a histological diagnosis of prostate cancer. A total of 276 patients (68.0%) had a Gleason score of 6 or less, while the remaining 130 (32%) had Gleason 7 or greater cancer (table 2).

CART analysis. The CART procedure was done in the model building set of 1,067 patients using certain potential predictors, including DRE findings, race, family history, va-

TABLE 2. *Biopsy and ultrasound results*

No. pts	1,563
PSAD (ng/ml/cc):	
Mean	0.139
Median	0.120
Prostate vol. (cc):	
Mean	40.28
Median	34.60
% TRUS findings:*	
Normal	50.3
Hypoechoic	44.1
Hyperechoic	3.5
Isoechoic	2.1
% Biopsies done:	
6	68.5
7	10.3
8	6.9
9–11	13.9
% Gleason grade:	
4–5	15.7
6	52.2
7	23.4
8 or Greater	8.7

* Not available in 15 patients.