Personalized Prediction of Tumor Response and Cancer Progression on Prostate Needle Biopsy

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Purpose: To our knowledge in patients with prostate cancer there are no available tests except clinical variables to determine the likelihood of disease progression. We developed a patient specific, biology driven tool to predict outcome at diagnosis. We also investigated whether biopsy androgen receptor levels predict a durable response to therapy after secondary treatment.

Materials and Methods: We evaluated paraffin embedded prostate needle biopsy tissue from 1,027 patients with cT1c-T3 prostate cancer treated with surgery and followed a median of 8 years. Machine learning was done to integrate clinical data with biopsy quantitative biometric features. Multivariate models were constructed to predict disease progression with the C index to estimate performance.

Results: In a training set of 686 patients (total of 87 progression events) 3 clinical and 3 biopsy tissue characteristics were identified to predict clinical progression within 8 years after prostatectomy with 78% sensitivity, 69% specificity, a C index of 0.74 and a HR of 5.12. Validation in an independent cohort of 341 patients (total of 44 progression events) yielded 76% sensitivity, 64% specificity, a C index of 0.73 and a HR of 3.47. Increased androgen receptor in tumor cells in the biopsy highly significantly predicted resistance to therapy, ie androgen ablation with or without salvage radiotherapy, and clinical failure ($p < 0.0001$).

Conclusions: Morphometry reliably classifies Gleason pattern 3 tumors. When combined with biomarker data, it adds to the hematoxylin and eosin analysis, and prostate specific antigen values currently used to assess outcome at diagnosis. Biopsy androgen receptor levels predict the likelihood of a response to therapy after recurrence and may guide future treatment decisions.

Key Words: prostate; prostatic neoplasms; biopsy; receptors, androgen; biological markers

Abbreviations and Acronyms

AMACR = α-methyl-acyl-coenzyme A racemase
AR = androgen receptor
bGG = dominant biopsy Gleason grade
bGS = biopsy Gleason sum
CF = clinical failure
CK18 = cytokeratin 18
FP = favorable pathology
MST = minimal spanning tree
pAKT = phosphorylated
SVRc = censored data support vector regression

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Study received Durham Veterans Affairs Medical Center, Mayo Clinic, University of Connecticut Health Science Center, University of Graz and University Hospital at Uppsala institutional review board approval.

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Supplementary material for this article can be obtained at jason.alter@aureon.com.

For another article on a related topic see page 317.

PROSTATE cancer remains the most commonly diagnosed nonskin cancer in American men and it causes approximately 29,000 deaths each year.[1] Treatment options are radical prostatectomy, radiotherapy and watchful waiting with

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no apparent consensus on how to maximize disease control and survival, especially in men with intermediate risk prostate cancer (PSA 10 to 20 ng/ml, clinical stage T2b-c and Gleason score 7). The only randomized clinical study to compare observation vs surgery showed a lower overall rate of death in men with T1 or T2 disease treated with radical prostatectomy, although results must be weighed against quality of life issues and comorbidity.[2,3] Furthermore, PSA screening has challenged traditional prognostic models due to the over diagnosis of indolent tumors, lead time bias, grade inflation and longer life expectancy.[4–8]

Several groups have developed methods to predict prostate cancer outcomes based on information at diagnosis. The updated Partin tables predict the risk of pathological stage (extracapsular extension, and seminal vesicle and lymph node invasion),[9] while the 10-year preoperative nomogram[10] provides the probability of freedom from biochemical recurrence within 10 years after radical prostatectomy. A recognized limitation is that these tools rely on clinical data and predict a biochemical recurrence outcome that does not invariably relate to systemic disease, suggesting that additional end points are required for optimal patient specific risk stratification.[11]

We previously used systems pathology to identify quantitative features associated with prostate cancer progression.[12,13] Our prostatectomy CF model used a complex end point comparable to that in the biopsy study, including castrate PSA increase, bone metastasis and prostate cancer specific death with the androgen resistance PSA end point denoting early progression as a surrogate for systemic metastasis.[13] Incorporating the castrate PSA increase end point in the biopsy model maximized the number of patients at high risk and more importantly optimized our ability to identify men with rapidly progressive disease for potential early intervention. We now report a biopsy tool developed in a multi-institutional cohort followed a median of 8 years postoperatively.

METHODS

Patients and Samples

This study was approved by the Durham Veterans Affairs Medical Center, Mayo Clinic, University of Connecticut Health Science Center, University of Graz and University Hospital at Uppsala institutional review boards. Information was compiled on 1,487 patients treated with radical prostatectomy between 1989 and 2003 for localized or locally advanced prostate cancer (cT1c-T3) for which formalin fixed, paraffin embedded tissue samples were available. We excluded from study patients treated with neoadjuvant therapy. Researchers elsewhere who were not involved in the study randomized and split the cohort between the training and validation sets (67% vs 33%) with a similar proportion of CF events and demographic balance.

CF was prespecified as any of 3 events, including 1) unequivocal radiographic or pathological evidence of metastasis, castrate or noncastrate (including skeletal or soft tissue disease in lymph nodes or solid organs), 2) increasing PSA in a castrate state, ie androgen ablation with or without salvage radiotherapy, or 3) death from prostate cancer, as documented by a review of the medical record and death certificate. Time to CF was defined as from prostatectomy to the first of these events. If a patient did not experience CF as of the last visit or the outcome at the most recent visit was unknown, the outcome was censored. Hormonal therapy or salvage radiotherapy was done at treating physician discretion. The castrate PSA increase was the first PSA increase in a trajectory regardless of treatment dose, type and duration. Gleason score and bGG were obtained after reevaluating the primary diagnostic biopsy at each institution. Clinical stage was assessed by chart review.

Only patients with complete clinicopathological, morphometric and molecular data, including outcome information, were further studied for a total of 686 for training and 341 for validation (table 1). Characteristics in these 1,027 patients were similar to those in the original 1,487 (data not shown). Patients were excluded from analysis primarily due to poor biopsy specimen quality (crush or artifact), poor antigen quality due to over fixation and/or auto-fluorescence, too little usable tumor content (6 or fewer glands) and/or incomplete clinical data. Exclusion parameters were evenly distributed among the different cohorts. Up to 7 unstained slides and/or paraffin blocks

Table 1. *Characteristics of patients in training and validation sets*

Characteristics	No. Training (%)	No. Validation (%)
Overall	686	341
Mean age	63.6	64
Preop PSA (ng/ml):		
10 or Less	460 (67.1)	231 (67.7)
Greater than 10	226 (32.9)	110 (32.3)
bGG:		
2	25 (3.6)	8 (2.3)
3	524 (76.4)	246 (72.1)
4	130 (19.0)	85 (24.9)
5	7 (1.0)	2 (0.6)
Gleason score:		
4	5 (0.7)	4 (1.2)
5	31 (4.5)	7 (2.1)
6	294 (42.9)	159 (46.6)
7	287 (41.8)	137 (40.2)
8	46 (6.7)	25 (7.3)
9	17 (2.5)	8 (2.3)
10	6 (0.9)	1 (0.3)
Clinical stage:		
T1a	6 (0.9)	3 (0.9)
T1c	263 (38.3)	116 (34.0)
T2	374 (54.5)	198 (58.1)
T3	27 (3.9)	15 (4.4)
Missing	16 (2.3)	9 (2.6)
CF events:	87 (12.7)	44 (12.9)
Castrate PSA increase	77 (11.2)	40 (11.7)
Pos bone scan	9 (1.3)	4 (1.2)
Death from prostate Ca	1 (0.1)	0