Validation of Prostate Specific Antigen Doubling Time Kinetics Following Radical Prostatectomy to Guide Active Observation and Intervention (MP20-03)

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1. Introduction

Biochemical recurrence (BCR) following radical prostatectomy (RP) has a limited ability to predict metastatic progression or prostate cancer specific mortality (PCSM).

- In our experience, a significant number of men (33.3%) with BCR have non-lethal BCR that can be safely observed based on PSA doubling time (DT) and subsequent DT change without radiation (RT) and/or androgen deprivation therapy (ADT).

The present study seeks to validate the use of DT kinetics to direct active observation (AO) and intervention.

2. Materials and Methods

A retrospective cohort analysis of 1864 men who underwent RP between June 2002 and September 2019 was conducted. 407 patients experienced BCR. Patients were assessed for treatment intervention (RT and/or ADT) versus AO with DT kinetics.

Our main outcome was the predictive value of multivariate regression models for no treatment via ROC analysis. Secondary outcomes were PCSM, analyzed via Kaplan-Meier survival analysis.

Students t-test, and chi-squared analysis were used to evaluate univariate p-values between no treatment (active observation) and treatment intervention groups.

Initial PSAdt was calculated using 3-4 PSA values after BCR (0.2 ng/ml, x2) and DT Pattern was determined based on current or most recent PSAdt progression prior to treatment intervention.

3a. Results, Patient Demographics

Table 1: Patient demographics stratified by no treatment (Active Observation) vs treatment.

Treatment	No Trmt	Trmt	Total	
	Count (%)	Count (%)	Count (%)	
N, all patients	136 (33.4%)	271 (66.6%)	407 (100%)	
	Mean (SD)	Mean (SD)	Mean (SD)	p value
Age, years	63.5 (7.3)	63.8 (7.2)	63.7 (7.3)	0.677
Adj Pre-PSA, ng/mL	8.4 (5.7)	12.6 (16.9)	11.2 (14.3)	0.005
SHIM score	19.8 (7.1)	17.9 (7.5)	18.6 (7.4)	0.023
Estimated blood loss, mL	102.2 (48.4)	96.2 (37.7)	98.2 (41.7)	0.171
Body mass index	27.0 (3.8)	27.3 (3.8)	27.2 (3.8)	0.467
Prostate Weight, grams	51.4 (21.3)	53.5 (19.4)	52.8 (20.1)	0.337
Follow Up, years	7.5 (4.0)	7.7 (4.4)	7.6 (4.3)	0.688
Time to Death, years	6.9 (2.7)	7.8 (4.0)	7.6 (3.8)	0.426
Time to Earliest Treatment	NA	3.0 (7.7)	3.0 (7.7)	
Current PSAdt, mos	26.0 (19.9)	8.5 (9.1)	15.6 (16.9)	< 0.001
Initial PSAdt after BCR, mos	39.4 (294.9)	12.6 (48.4)	23.6 (192.6)	0.272
	Count (%)	Count (%)	Count (%)	p value
Surgical margins	36 (26.5%)	109 (40.2%)	145 (35.6%)	0.006
p-stage				< 0.001
pT2	67 (49.3%)	69 (25.6%)	136 (33.5%)	
pT3/T4	69 (50.7%)	201 (74.4%)	270 (66.5%)	
Gleason Grade Group				< 0.001
1	17 (12.5%)	4 (1.5%)	21 (5.2%)	
2	48 (35.3%)	52 (19.2%)	100 (24.6%)	
3	43 (31.6%)	79 (29.2%)	122 (30.0%)	
4	17 (12.5%)	22 (8.1%)	39 (9.6%)	
5	11 (8.1%)	114 (42.1%)	125 (30.7%)	
Initial PSAdt Group, mos				< 0.001
>12	90 (73.8%)	37 (22.6%)	127 (44.4%)	
6 to 12	19 (15.6%)	48 (29.3%)	67 (23.4%)	
<6	13 (10.7%)	79 (48.2%)	92 (32.2%)	
NA	14 ***	107 **	121	
DT Pattern				< 0.001
Increasing	93 (71.5%)	49 (32.7%)	142 (50.7%)	
Decreasing	37 (28.5%)	101 (67.3%)	138 (49.3%)	
NA	6 *	121 **	127	
PCSM	0 (0.0%)	29 (10.7%)	29 (7.1%)	< 0.001
Dead	13 (9.6%)	50 (18.5%)	63 (15.5%)	0.019

* Not enough PSA's prior to non-cancer specific death (n=2), not enough PSA's post-BCR to establish PSA (n=12)
** No PSAdt as treatment was initiated based on very rapid PSA progression
*** Not enough PSA's prior to non-cancer specific death (n=2), lost to follow-up (n=1), and after BCR (n=1).

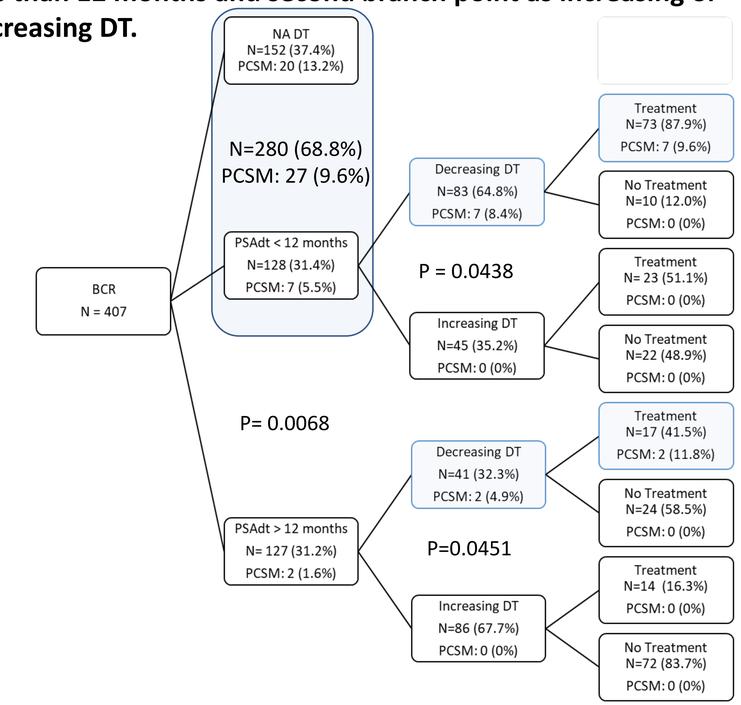
Table 2a: Univariate and Multivariate Models

Table 2: Univariate and Multivariate regression analysis in BCR patients for no treatment (n=407). AUC of multivariate model = 0.8348

Outcome: No treatment	Univariate		Multivariate	
Variable	OR (95% CI)	p	OR (95% CI)	p
Initial PSAdt binary (>12mos vs <12mos [ref])	8.79 (4.92,15.71)	< 0.001	8.93 (4.53,17.6)	< 0.001
DT Pattern (Increasing vs Decreasing [ref])	6.08 (3.48,10.62)	< 0.001	5.49 (2.81,10.71)	< 0.001
GGG (4-5 vs 1-3 [ref])	0.29 (0.17,0.52)	0.04		
Preoperative PSA (continuous)	0.95 (0.91,0.99)	0.204		
P-stage (pT3/4 vs pT2 [ref])	0.63 (0.38,1.05)	0.639		
Age (continuous)	0.987 (0.952,1.02)	0.985		

Figure 1: Tree Diagram

Figure 1: Tree Diagram, with first branch point as initial DT greater vs. less than 12 months and second branch point as increasing or decreasing DT.



4. Conclusions

- Significant predictors for directing "active observation" following BCR:
  - Initial DT > 12 months
  - DT increasing pattern
- In our experience, one third of BCR patients were observed without RT and/or ADT, with 0% PCSM at mean 7.6 years follow-up.
- We establish that PSA doubling time kinetics is a strong and independent predictor for guiding active observation and treatment intervention after surgery.