Higher Free Testosterone as an Independent Predictor of Post-Radical Prostatectomy Recurrence

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1. Introduction

The relationship between testosterone and prostate cancer has long been a controversial topic. Literature supports a protective role of high free testosterone (FT) in preventing cardiovascular disease, diabetes mellitus, and other metabolic morbidity. Even further, recent data suggests high FT to be significantly associated with lower grade prostate cancers.

We seek to examine the relationship between FT and biochemical recurrence (BCR) in radical prostatectomy patients.

2. Materials and Methods

From December 2009 to June 2018, 687 patients underwent robot-assisted radical prostatectomy (RP) for primary treatment of prostate cancer, with prospectively collected total and free testosterone, sex hormone binding globulin (SHBG), prostate specific antigen (PSA), pathologic grade (GGG) and stage.

- **Primary outcome**: biochemical recurrence (2 consecutive PSA > 0.2 ng/dl), within 3 years of post-RP
- **Secondary outcome**: Kaplan-Meier time to recurrence; median follow-up of 3.2 years

Table 1. Baseline Characteristics, Stratified by 3-year Recurrence Status

	No BCR within 3 years		BCR within 3 years		
	543		144		p
Preoperative Demographics	**Mean**	**SD**	**Mean**	**SD**	
Adjusted PSA (ng/mL)	6.8	4.2	13.6	11.7	**<0.001**
Age (years)	62.2	7.5	65.2	7.4	**<0.001**
Prostate Volume (mL)	54.1	20.3	56.3	20.3	0.226
Body Mass Index (Kg/m^2)	27.2	3.6	27.4	3.8	0.550
Androgen Levels	**Mean**	**SD**	**Mean**	**SD**	
Preoperative TT (ng/dL)	361.0	160.0	342.0	175.4	0.208
Preoperative SHBG (nmol/L)	45.4	21.3	49.5	24.2	**0.041**
Preoperative FT (ng/dL)	6.1	3.1	5.4	2.4	**0.007**
3M TT (ng/dL)	401.7	192.3	367.4	189.6	0.083
3M SHBG (nmol/L)	43.4	19.9	48.3	20.7	**0.021**
3M FT (ng/dL)	7.1	3.8	6.0	2.9	**0.003**
Oncologic Metrics	**N**	**%**	**N**	**%**	
Pathologic Grade					**<0.001**
1	161	23.6	2	1.4	
2	316	46.3	16	11.2	
3	139	20.4	46	32.2	
4	32	4.7	14	9.8	
5	34	5	65	45.5	
Pathologic Stage					**<0.001**
pT2	514	74.9	38	26.4	
pT3	172	25.1	106	38.1	

Table 2: Logistic Regression of Factors Predicting BCR Status at 3-years post-RP

At median follow-up of 3.2 years, 144/687 (21.0%) experienced BCR.

Primary outcome: After adjusting for covariates, preoperative FT was significantly protective against BCR, such that each unit increase in FT resulted in a 0.638 times reduced likelihood of recurrence.

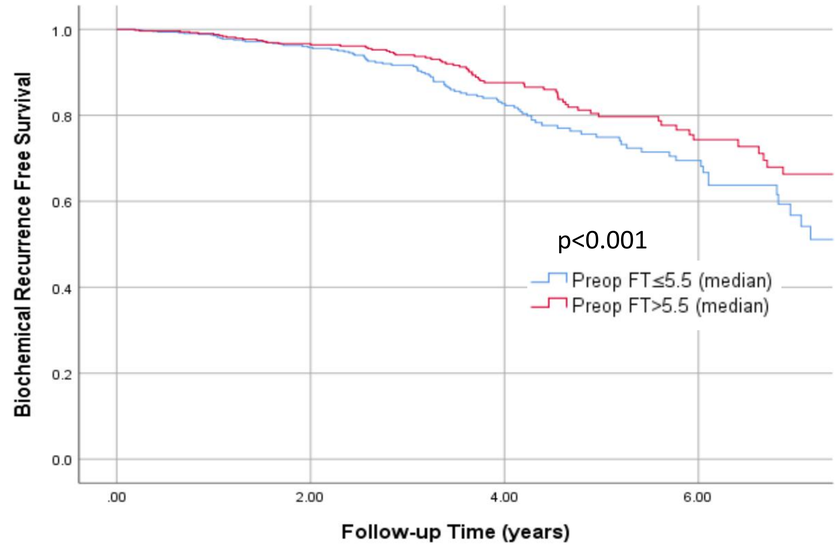
	B	S.E.	Wald	Sig.	OR	95% C.I.	
						Low	High
Age, cont.	0.02	0.016	1.534	0.216	1.02	0.989	1.052
Preoperative PSA, cont.	0.101	0.018	31.526	**<0.001**	**1.106**	1.068	1.146
pGS [<4+5 (ref) vs. 9-10]	1.734	0.244	50.583	**<0.001**	**5.661**	3.511	9.128
p-stage [pT2 (ref) vs. pT3/T4]	1.531	0.237	41.655	**<0.001**	**4.625**	2.905	7.364
FT, cont.	-0.449	0.235	3.639	**0.046**	**0.638**	0.402	0.999
Constant	-4.734	1.059	20	0	0.009		

Figure 1: Cox Regression of BCRFS at Mean of Covariates

	B	S.E.	Wald	Sig.	OR	95% C.I.	
						Low	High
Preoperative PSA, cont.	0.028	0.008	11.976	**0.001**	**1.028**	1.012	1.044
pGS [<4+5 (ref) vs. 9-10]	1.188	0.176	45.766	**<0.001**	**3.281**	2.326	4.629
p-stage [pT2 (ref) vs. pT3/T4]	1.201	0.174	47.631	**<0.001**	**3.24**	2.363	4.675

Secondary outcome: After adjusting for significant predictors of time to recurrence, patients with a preoperative FT ≤ 5.5 were less likely to recur, compared to those with preoperative FT > 5.5.

Both absolute BCR rate and time to recurrence had similar (although, smaller) correlations when repeated with 3-month values.



4. Conclusions

Low FT may hasten time to biochemical recurrence post-RARP. Men with biochemically low TT and FT may benefit oncologically with normalization of these values via testosterone replacement therapy. These results argue against previous notions that testosterone furthers progression of prostate cancer.

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