UNIVERSITY OF CALIFORNIA,
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Use of serum Prostate Specific Antigen doubling time and change to determine need for secondary treatment for prostate cancer following radical prostatectomy

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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Thesis Committee:
Professor Dr. Thomas Ahlering, Chair
Assistant Professor Dr. Robert Wilson
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DEDICATION

To

my parents, George and Elle Huang, colleagues, and friends

to dreams

Dream,
May all your creations be with you until the end of times.
Wherever you are in life, may it be generous.
May your trials end in full bloom.
Though your beginnings might be humble, may the end be prosperous.

Agust D
So Far Away

and to everything that has built them.

The only time you should ever look back is to see how far you have come.

BTS
Butterfly

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LIST OF ABBREVIATIONS

ADT	: Androgen Deprivation Therapy
ARO	: (German) Applied Radiation Oncology (group)
ART/RT	: Adjuvant Radiation Therapy/Radiation Therapy
AUA	: American Urological Association
BCR	: Biochemical Recurrence
CRPC	: Castrate-Resistant Prostate Cancer
EAU	: European Association of Urology
EORTC	: European Organization for Research and Treatment of Cancer
pGGG	: pathological Gleason Grade Group
OBS	: Observation (cohort)
OM/OS	: Overall Mortality/Overall Survival
p-stage	: Pathologic Stage
PCSM/PCSS	: Prostate Cancer Specific Mortality/Prostate Cancer Specific Survival
PSA	: Prostate-Specific Antigen
PSAdt/DT	: Prostate-Specific Antigen Doubling Time/Doubling Time
RP	: Radical Prostatectomy
RCT	: Randomized Control Trial
SWOG	: South Western Oncology Group

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ABSTRACT OF THE THESIS

by
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Importance: Biochemical recurrence (BCR) following radical prostatectomy (RP) is an unreliable predictor of distant metastatic progression or prostate cancer death, consequently resulting in overtreatment. Following BCR, guidelines recommend that patients are treated with radiation therapy. However, little has been published about observation without secondary treatment management recommendations.

Objectives: Establish that a cohort of patients can be managed with observation without secondary intervention, and establish a process to safely manage men with BCR using observation versus therapeutic secondary intervention following RP using kinetics of PSA doubling time (PSAdt).

Methods: In a retrospective cohort analysis of 1865 patients following RP from June 2002 and September 2019 at a tertiary referral center, 407 patients experienced BCR as defined as two PSA levels >0.2ng/ml. 137 were managed with observation compared to 270 treated with secondary intervention. Using PSAdt graphs, patient doubling times (DT) kinetics were (re)calculated with each new date and PSA level and categorized as Increasing or Decreasing. Kaplan-Meier analysis and multivariate logistic regression were used to model PCSM and no need for treatment, respectively.

Results: Table 1 describes the patient Demographics between the Observation and Treatment groups. Significant univariate differences include preoperative PSA, pathologic

stage (p-stage), pathological Gleason Grade Group (pGGG), and DT change. The median follow-up was 7.3 years (IQR 3.9-10.7). 10-year Kaplan-Meier analysis demonstrated no PCSM in the observation group compared to 7.1% PCSM in the treated group (p=0.001).

In adjusted logistic regression analysis, PSAdt > 12 months and increasing DT were significant predictors for continued observation without treatment (p<0.001), while pGGG was p=0.06. In ROC analysis, the model including these three variables were an excellent predictor of no need for treatment (AUC = 0.84), similar to the model including only PSAdt and pGGG (AUC = 0.82). In adjusted logistic regression analysis in patients with PSAdt < 12 months, PSAdt group 6-12 months and increasing DT were significant predictors of no treatment. Of interest, pGGG was not predictive of treatment.

Conclusions and Relevance: There exists a group of patients (137/407, 33%) who can be observed without secondary treatment following BCR after RP, with 0% PCSM. No patients with PSAdt > 12 months experienced PCSM. PSAdt > 12 months, increasing DT, and a low pGGG (1-2) were excellent predictors of no need for treatment. Further studies of DT kinetics in cohorts of patients with PSAdt < 12 months in subset analysis may help direct more tailored processes for timing and intensity of treatment.

I. INTRODUCTION

Prostate Cancer and Radical Prostatectomy

Prostate cancer is the most common cancer, after non-melanoma skin cancer, to affect men in the United States [1]. Typically affecting older men, prostate cancer is unique to other cancers in that it is slow-growing, and most patients with low-grade disease will not experience prostate-specific mortality unless the cancer metastasizes beyond the prostate to the lymph nodes and bones [2]. One common and effective treatment for localized prostate cancer is radical prostatectomy (RP). In long-term follow-up studies, those with pathologically most aggressive prostate cancers have a 60 to 86% survival rate at 10-years following radical prostatectomy [3]. In another more recent trial, prostate-cancer specific survival (PCSS) was 50% at 23 years post-RP for men with the highest risk groups (Gleason 4-5) [4]. RP is an efficacious primary treatment option for prostate cancer patients with localized cancer. However, approximately 20% of men still experience a biochemical recurrence (BCR) after RP, as defined by detectable prostate-specific antigen (PSA) levels following surgery. While BCR has been defined by different cutoffs in literature, the most commonly used PSA level to indicate BCR has been two levels with a PSA of 0.2 ng/mL [5].

Current treatment practices following radical prostatectomy

Does Radiation Therapy improve survival?

In the past thirty years, a combination of secondary treatments such as radiotherapy with and without hormonal therapy have been recommended for men after radical prostatectomy. According to the American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) and European Association of Urology (EAU) recommendations, adjuvant (immediate) radiotherapy after radical prostatectomy is recommended for patients with seminal vesicle invasion, positive surgical margins, and extraprostatic extension [6,7]. To date, there are three randomized control trials (RCT) comparing adjuvant radiotherapy and wait-and-see treatments after radical prostatectomy conducted by: the European Organization for Research and Treatment of Cancer (EORTC) by Bolla and colleagues, the German Applied Radiation Oncology (ARO) by Wiegel and colleagues, and the American South Western Oncology Group (SWOG) by Thompson and colleagues [8–10]. All three trials demonstrated an approximate 50% decrease in BCR after RP at 10 years. However, even though all 3 demonstrate significant improvement of the PSA metric, the outcomes in metastasis free survival (MFS), prostate cancer specific survival (PCSS), and overall survival (OS) were remarkably ambiguous.

Of concern, the SWOG 9874 trial is the only trial to see a difference in aggressiveness of disease between RT and the control populations which appears to have been overlooked [9]. The RT population had higher proportions of men with high grade disease compared to the wait-and-see group ($p = 0.081$). While there is dispute on whether baseline characteristics should be tested for differences in randomized control trials, this

considerable discrepancy in disease aggressiveness is not noted at all in the discussion of the paper. Remarkably, only the SWOG (8794) trial demonstrated MFS and OS benefit. [9].

In the EORTC trial preliminary report, the primary endpoint was changed from prostate cancer progression-free survival to biochemical-progression free survival a few years into the trial [11]. This change in primary endpoint is a remarkable deviance from protocol and not explained. The question the trials were trying to answer was "although we know postoperative RT consistently reduces PSA recurrence, improvement in prostate cancer progression had not been proven". Remarkably the EORTC Kaplan-Meier curves of BCR compared to progression-free survival is stark. So while all three studies demonstrate improved BCR rates, only the SWOG trial showed PC specific benefit whereas the EORTC and ARO trials (neither with demographic issues) saw nearly identical MFS, PCSS and OS over 18 years of follow-up. It seems evident that the BCR metric and the more important endpoint, prostate cancer progression-free survival, are not uniform and interchangeable outcomes.

Side Effects of Radiation

Studies have shown that men who undergo RT have significantly worse continence and sexual function compared to those who are in wait-and-see groups and salvage RT groups [12–14]. These results were further demonstrated in subsequent studies such as the RADICALS trial [15–17]. In addition to the decrease in quality of life due to impotence and incontinence, radiotherapy also increases a patient's risk of secondary cancers, such as rectal and bladder cancer. Several studies have shown that men are at higher risk of developing rectal cancer after radiation [18–20]. Additionally, studies have shown that men

undergoing radiotherapy for prostate cancer have a 5-6% greater risk of bladder cancer than those in observation groups [21]. Further, bladder cancers in men who have undergone radiotherapy have been shown to be more aggressive and lethal than in patients who did not have radiotherapy [20]. These risks are not insignificant – by radiating patients immediately without observing the actual prostate cancer risk, doctors could potentially give patients a much more life-threatening cancer. The wealth of evidence supporting the higher risk of complications and lower quality of life due to radiotherapy does not appear to be adequately taken into consideration especially with questionable survival benefit.

Considerations and Evidence for Observation Only Protocol

Men in wait-and-see arms with PT3 disease have a 13.3 year median time to overall death following RP [9], yet only have a 2% advantage in prostate cancer specific survival at 10 years compared to RT patients, and an insignificant difference in progression-free survival comparatively [8,9] – it is evident that it is not prostate cancer that is killing these patients. While biochemical progression-free survival is improved as seen in the earlier RCT's, physicians are not significantly lengthening a patient's life by recommending ART post-RP. Instead, physicians are subjugating patients to higher risk of complications, incontinence, impotency, and a larger medical debt due to potentially unnecessary treatment, since most of these men are not dying from prostate cancer, but rather other diseases. They are dying *with* prostate cancer (biochemical recurrence), not *from* prostate cancer. The most recent RADICALS trials disproves the necessity of treating patients post-surgery with ART, by citing no differences in BCR-free survival and significantly worse

urinary outcomes in ART groups, and recommend observation protocols with salvage therapy as the standard following RP to reduce the greater harm to patients by subjecting patients to unnecessary treatment [15]. In addition, an earlier retrospective study done by a group at Johns Hopkins, it is evident that certain groups of patients are capable of surviving for more than 15 years post-RP despite not having adjuvant therapy prior to biochemical recurrence after radical prostatectomy [22]. Hence, as biochemical recurrence is an evidently poor prognostic for prostate cancer specific death, physicians are greatly overtreating patients post-RP, where there is greater harm done to patients who receive adjuvant therapy at no benefit in BCR-free survival or PCSS.

PSA doubling time use in determining treatment

Partially responsible for overtreatment is the lack of consensus in determining the patient groups that can be safely observed without treatment after RP. In observation protocols, patients do not undergo second-line treatments such as RT and androgen deprivation therapy (ADT), but are instead closely monitored with frequent prostate-specific antigen (PSA) tests, observing PSA doubling time (PSAdt) and disease progression until secondary treatment is deemed necessary, if ever needed. Because prostate cancer is a slow-growing disease, with 50% of observation patients living for more than 20 years post-RP and most patients dying *with* prostate cancer and not *of* it, it is imperative for physicians to evaluate if and/or when patients should consider secondary treatments post-RP. Additionally, as mentioned, secondary treatments post-RP come with further quality of life risks, such as incontinence, impotency and risk of bladder or genitourinary cancers that are far more lethal than prostate cancer.

Current studies establishing nomograms for determining risk of progression post-RP are not uniform. Different start points (after RP, after BCR, after bone metastases) as well as endpoints (BCR, metastases, PCSM, OM) are used for determining the need for treatment. As mentioned previously, each of these measures are not interchangeable especially in the context of prostate cancer, due to the long course of this cancer. To further add to the discrepancy between all these measures, each nomogram has concluded varying combinations of oncologic characteristics that are the best predictors for each endpoint.

In 2011, Eggener and colleagues developed a nomogram evaluating 15-year PCSM for men post-RP. Significant factors affecting PCSM included primary and secondary Gleason grade 4-5, seminal vesical invasion, and surgery year [23]. In 2015, Brockman and colleagues validated a nomogram predicting 10-year PCSM for men with BCR following RP, including preoperative PSA, pathological Gleason score, extraprostatic extension, seminal vesicle invasion, time to prostate cancer BCR, PSA level at BCR, and PSAdt, with an internally validated concordance index of 0.774 [24]. Further, Abdollah and colleagues constructed a nomogram evaluating 10-year PCSS for patients with node-positive cancer (pN1) following RP, utilizing PSA value, pathologic Gleason score, pathologic tumor stage, surgical margin status, positive lymph nodes, and ART as significant predictors with a high discrimination accuracy (79.5-83.3%)[25]. This nomogram was then externally validated by Bianchi et al. in 2018, finding that it overpredicted patient's PCSS, and predictive accuracy was not as strong as the internal validation (65.8%)[26]. In men with bone-metastatic prostate cancer post-RP, Miyoshi and colleagues found that age, PSA levels, clinical T stage, disease extent in bone scan, and biopsy Gleason sum were independent predictors of overall survival at 1, 3, and 5 years [27].

However, when determining need for treatment, a straightforward study evaluating the best prognostic factors does not exist. The lack of uniformity and agreement in the literature exemplifies the need for further exploration of truly low risk patients. In current literature, prostate cancer patients with BCR who have not been treated with some form of secondary treatment have not been well-studied. However, multiple studies have demonstrated that there exists a group of patients with BCR who *can* live without treatment post-RP.

In 2005, Trock et al. published a retrospective observational study evaluating 10-year PCSS in post-RP BCR patients treated with observation only, RT, and RT and ADT. Despite older preoperative age, greater preoperative PSA, higher proportion of high-grade Gleason, greater proportion of patients with seminal vesicle invasion and lymph nodes metastases, and lower PSAdt in the observation only group compared to the other treatment groups, PCSM at an average of 9 years follow-up was 22% in the observation only group and 18% in the overall population. To adjust for the baseline demographic differences between all groups, the authors stratified by PSAdt ($\geq$ 6 months and $\leq$ 6 months) first, then surgical margins and Gleason when evaluating 10-year prostate-cancer specific survival (PCSS). Only the natural log of PSAdt and Gleason were significant predictors of PCSM in adjusted multivariate regression analysis. The authors concluded that salvage radiotherapy administered within 2 years of BCR was associated with significant increase in PCSS among those with PSAdt of <6 months, independent of p-stage or Gleason score when compared to those with higher PSAdt [28]. This suggests that a group of patients, perhaps with PSAdt >6 months, may *not* benefit from early salvage

radiotherapy, and may be observed without treatment and achieve survival beyond 9 years post-RP.

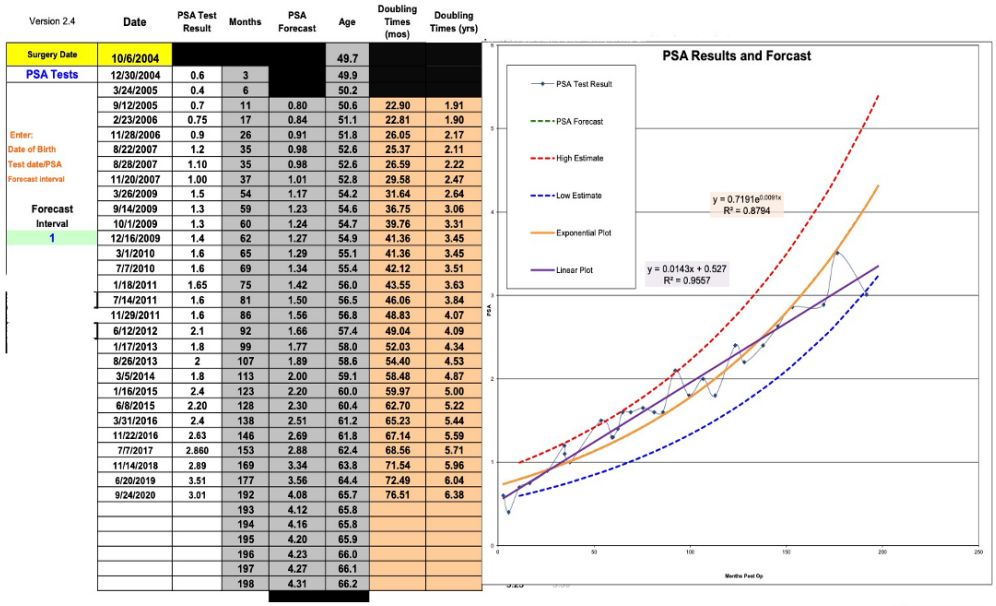
Similarly, a contemporary study by Matsumoto et al. evaluated stratified groups of patients, stratified by risk as defined by Gleason and PSAdt. In univariate analysis for castrate-resistant prostate cancer (CRPC)-free survival and PCSS in the intermediate/high risk patients (Gleason Grade 8-10 and/or PSAdt < 6 months), the authors found that there was no significant difference between delayed treatment when compared to early treatment, although this difference was significant between late/no treatment and early treatment. However, in the low-risk patients (Gleason Grade <8 and PSAdt > 6 months), CRPC-free survival saw no difference between all three groups. The authors conclude that observation after BCR without salvage therapy is viable option for low-risk patients with Gleason $\leq$ 7 and PSAdt $\geq$ 6 months. For other patients, early salvage therapy against BCR may be advantageous for CRPC free survival and CSS. The similar stratification by Gleason and PSAdt allowed the authors to account for the demographic differences between different levels of cancer-risk patients, while evaluating their risk of CRPC and cancer-specific death [29].

Hence, there is some evidence showing that patients have been observed without secondary treatment in some groups of patients, at no risk of PCSS. However, no study has evaluated this group of observation only patients, as all studies besides Matsumoto et al., have only peripherally touched on the existence of a group of patients that may not need treatment. Additionally, nomograms have not agreed on what combinations of demographic and oncologic characteristics best account for “low-risk BCR” following surgery, and hence, those who should be treated.

PSAdt, or the time in months it takes for PSA to double, has been widely used as a clinical tool in patients with BCR following primary treatments for prostate cancer, effectively aiding in risk analysis for patients considering treatment [30]. PSAdt is typically calculated based on a series of serum PSA values, graphed according to a growth function. PSAdt is established to be a strong predictor of CRPC, PCSM, and OM [22,31]. While it has not been directly clinically proven to correlate with cancer cell growth, shorter PSAdt seems to be associated with prostate cancer progression and tumor growth [32]. PSAdt has been used as a continuous variable in previous studies with varying cutoffs (6 months, 9 months, 12 months) to correlate with higher risk of CRPC, PCSM, and/or OM. However, PSAdt change is a novel indicator and has not been evaluated in literature. In this study, we hypothesize that an increasing PSAdt (indicating the time it takes for PSA to double is slowing) may correlate with positive clinical indications, such as a stable prostate cancer recurrence that does not need secondary intervention. On the other hand, decreasing PSAdt (indicating the time it takes for the PSA to double is quicker) logically suggests unstable DNA potentially resulting in uncontrolled growth and increased aggressiveness which should be studied for benefit as a metric of treatment need and PCSM.

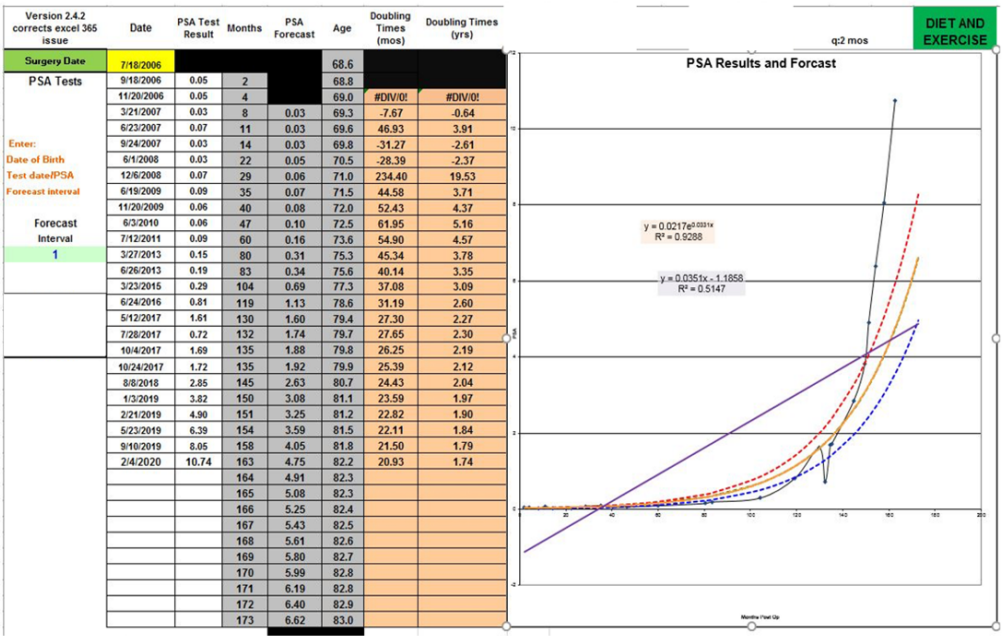
***Figure 1**: **a)** A patient's doubling time graph, demonstrating an* increasing *PSAdt following surgery. **b)** A patient's doubling time graph, demonstrating a* decreasing *PSAdt following surgery. Patient was treated when indicated.*

A)



Version 2.4	Date	PSA Test Result	Months	PSA Forecast	Age	Doubling Times (mos)	Doubling Times (yrs)
Surgery Date	10/6/2004				49.7		
PSA Tests	12/30/2004	0.6	3		49.9		
	3/24/2005	0.4	6		50.2		
	9/12/2005	0.7	11	0.80	50.6	22.90	1.91
	2/23/2006	0.75	17	0.84	51.1	22.81	1.90
Enter:	11/28/2006	0.9	26	0.91	51.8	26.05	2.17
Date of Birth	8/22/2007	1.2	35	0.98	52.6	25.37	2.11
Test date/PSA	8/28/2007	1.10	35	0.98	52.6	26.59	2.22
Forecast interval	11/20/2007	1.00	37	1.01	52.8	29.58	2.47
	3/26/2009	1.5	54	1.17	54.2	31.64	2.64
Forecast	9/14/2009	1.3	59	1.23	54.6	36.75	3.06
Interval	10/1/2009	1.3	60	1.24	54.7	39.76	3.31
1	12/16/2009	1.4	62	1.27	54.9	41.36	3.45
	3/1/2010	1.6	65	1.29	55.1	41.36	3.45
	7/7/2010	1.6	69	1.34	55.4	42.12	3.51
	1/18/2011	1.65	75	1.42	56.0	43.55	3.63
	7/14/2011	1.6	81	1.50	56.5	46.06	3.84
	11/29/2011	1.6	86	1.56	56.8	48.83	4.07
	6/12/2012	2.1	92	1.66	57.4	49.04	4.09
	1/17/2013	1.8	99	1.77	58.0	52.03	4.34
	8/26/2013	2	107	1.89	58.6	54.40	4.53
	3/5/2014	1.8	113	2.00	59.1	58.48	4.87
	1/16/2015	2.4	123	2.20	60.0	59.97	5.00
	6/8/2015	2.20	128	2.30	60.4	62.70	5.22
	3/31/2016	2.4	138	2.51	61.2	65.23	5.44
	11/22/2016	2.63	146	2.69	61.8	67.14	5.59
	7/7/2017	2.860	153	2.88	62.4	68.56	5.71
	11/14/2018	2.89	169	3.34	63.8	71.54	5.96
	6/20/2019	3.51	177	3.56	64.4	72.49	6.04
	9/24/2020	3.01	192	4.08	65.7	76.51	6.38
			193	4.12	65.8		
			194	4.16	65.8		
			195	4.20	65.9		
			196	4.23	66.0		
			197	4.27	66.1		
			198	4.31	66.2		

B)



Version 2.4.2 corrects excel 365 issue	Date	PSA Test Result	Months	PSA Forecast	Age	Doubling Times (mos)	Doubling Times (yrs)
Surgery Date	7/18/2006				68.6		
PSA Tests	9/18/2006	0.05	2		68.8		
	11/20/2006	0.05	4		69.0	#DIV/0!	#DIV/0!
	3/21/2007	0.03	8	0.03	69.3	-7.67	-0.64
	6/23/2007	0.07	11	0.03	69.6	46.93	3.91
Enter:	9/24/2007	0.03	14	0.03	69.8	-31.27	-2.61
Date of Birth	6/1/2008	0.03	22	0.05	70.5	-28.39	-2.37
Test date/PSA	12/6/2008	0.07	29	0.06	71.0	234.40	19.53
Forecast interval	6/19/2009	0.09	35	0.07	71.5	44.58	3.71
	11/20/2009	0.06	40	0.08	72.0	52.43	4.37
Forecast	6/3/2010	0.06	47	0.10	72.5	61.95	5.16
Interval	7/12/2011	0.09	60	0.16	73.6	54.90	4.57
1	3/27/2013	0.15	80	0.31	75.3	45.34	3.78
	6/26/2013	0.19	83	0.34	75.6	40.14	3.35
	3/23/2015	0.29	104	0.69	77.3	37.08	3.09
	6/24/2016	0.81	119	1.13	78.6	31.19	2.60
	5/12/2017	1.61	130	1.60	79.4	27.30	2.27
	7/28/2017	0.72	132	1.74	79.7	27.65	2.30
	10/4/2017	1.69	135	1.88	79.8	26.25	2.19
	10/24/2017	1.72	135	1.92	79.9	25.39	2.12
	8/8/2018	2.85	145	2.63	80.7	24.43	2.04
	1/3/2019	3.82	150	3.08	81.1	23.59	1.97
	2/21/2019	4.90	151	3.25	81.2	22.82	1.90
	5/23/2019	6.39	154	3.59	81.5	22.11	1.84
	9/10/2019	8.05	158	4.05	81.8	21.50	1.79
	2/4/2020	10.74	163	4.75	82.2	20.93	1.74
			164	4.91	82.3		
			165	5.08	82.3		
			166	5.25	82.4		
			167	5.43	82.5		
			168	5.61	82.6		
			169	5.80	82.7		
			170	5.99	82.8		
			171	6.19	82.8		
			172	6.40	82.9		
			173	6.62	83.0		

Specific Aims

It is evident that overtreatment of patients with BCR following RP with RT and/or ADT leads to unnecessary complications and other risks, as well as decreased quality of life. In addition, the literature has indirectly shown that not all patients need to be treated following BCR. First, this retrospective analysis of prospectively collected data seeks to demonstrate that a group of BCR patients with PSAdt >12 months can be observed without treatment assessed via 10-year prostate cancer-specific mortality. Second, I will evaluate the additional value of PSAdt change (increasing or decreasing DT) as a novel predictor of continued observation or need to treat. We hypothesize that increasing DT is a predictor of patients who can continue to be observed, while decreasing DT is a predictor of those who need treatment. Last, PSAdt in conjunction with PSAdt change will be assessed for optimal predictive value in conjunction with other known predictors of progression risk: age, preoperative PSA, pathological Gleason Grade Group (pGGG), pathological stage (p-stage).

II. METHODS

Patient Population and Follow-Up

A retrospective review of prospectively collected data of consecutive patients undergoing robot-assisted radical prostatectomy (RARP) between June 2002 and September 2019 by a single surgeon at the University of California, Irvine. Preoperative demographics, oncologic information, and long-term follow-up were prospectively recorded in an anonymized, electronic database, under approved institutional review board protocol at the University of California, Irvine (HS#1998-84). The database was frozen for the statistical analysis based on follow-up through March 29, 2021. All data collection was conducted in compliance with the Health Insurance Portability and Accountability Act and federal guidelines for informed consent were followed.

Active PSA observation began at serial elevation of the PSA >0.1. Patients were counseled about treatment interventions, such as RT or ADT, when PSA > 0.1 and observed according to European Association of Urology (EAU) guidelines. Treatment interventions were guided by previous studies indicating that patients with PSAdt < 12 months and high pGGG and stage are at higher risk for cancer progression. In similar fashion patients classified as EAU low-risk (PSAdt > 12 months, pGG < 7) were counselled about the option of observation [30].

1865 patients were identified after excluding for patients undergoing cytoreductive (n = 3) or simple prostatectomy (n = 9), and patients with neuroendocrine/small cell adenocarcinoma (n = 3). Of these patients, 407 patients were identified to have experienced BCR, defined as two consecutive PSA values 0.2 ng/mL (n=364) or adjuvant intervention due to advanced pathologic grade and/or stage disease (n = 43). Among these

407 patients, careful chart review of patients by an expert (TA) was undertaken to ensure patients were assigned to the correct treatment group. Patients were followed-up over the course of 6 months (May 2020 – October 2020) via phone call (3x), email, patient appointment, and/or mail to ensure most up-to-date information was included.

In summary, among the 407 patients who have experienced BCR, 270 patients were included in the treatment group, 91 of which underwent concurrent RT+ADT, 156 ADT alone, and 23 RT only. Chemotherapy patients (n=4) were excluded from the total treatment group in this study as they indicated more aggressive disease, typically bone metastases. Finally, 137 patients did not undergo any secondary treatment and remain in the observation group.

PSAdt graphs of all 407 patients included all PSA's drawn after patient's RP. PSAdt was calculated using a growth function, taking into account all PSA's after BCR (0.2 ng/ml) [33]. PSAdt's were calculated for each PSA entry (Figure 1). To determine DT change, or whether PSAdt is increasing or decreasing, the PSAdt's calculated for at least the last three PSA tests for observation group and at least the last three tests prior to treatment intervention for the treatment group was used. Current PSAdt reported in this study was the PSAdt calculated with the patient's most recent PSA test for the observation group. In the treatment group, current PSAdt was calculated at the final PSA test prior to secondary intervention. Patients undergoing adjuvant therapy and/or without sufficient follow-up with insufficient points (less than three recorded PSA tests) to calculate PSAdt were not included in the PSAdt change analysis (n=64).

Statistical Methods and Analysis

To evaluate demographic differences of observation and treatment groups, Student t-test were conducted for continuous variables and test of proportions or ANOVA for categorical variables. 10-year Kaplan-Meier survival analysis (OS and PCSS) between observation and treatment groups were conducted to evaluate survival. Patients were censored at death, or last follow-up.

To determine oncologic predictors of patients who do not need treatment following RP, univariate and multivariate logistic regressions were conducted to evaluate predictors of treatment, including PSAdt change as the primary exposure variable, and preoperative PSA, pGGG, age, current PSAdt, and p-stage as secondary variables. Variables were selected based on univariate models, literature, and expert opinion. Preoperative PSA and age were measured as continuous variables, and PSAdt change (increasing or decreasing DT), pGGG (grade groups 1-3 or 4-5) and p-stage (pT2 or pT3/pT4) were measured as categorical variables. PSAdt was measured as both a categorical variable (PSAdt 0-12 and >12 months). A backwards logistic regression model was performed to reach the final multivariate model. To compare the addition of PSAdt change into the model, a backwards regression analysis with all other variables except PSAdt change was also performed. ROC analysis was conducted to evaluate each model's predictive value.

Ad hoc stratification analysis between patients with PSAdt < 12 months was also conducted. Adjusted regression analysis was similarly conducted as above, but with PSAdt as categorical variable between PSAdt 0-6 months, 6-12months instead.

All statistical tests and figures were conducted and produced in R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

III. RESULTS

Patient Characteristics and Survival Outcomes

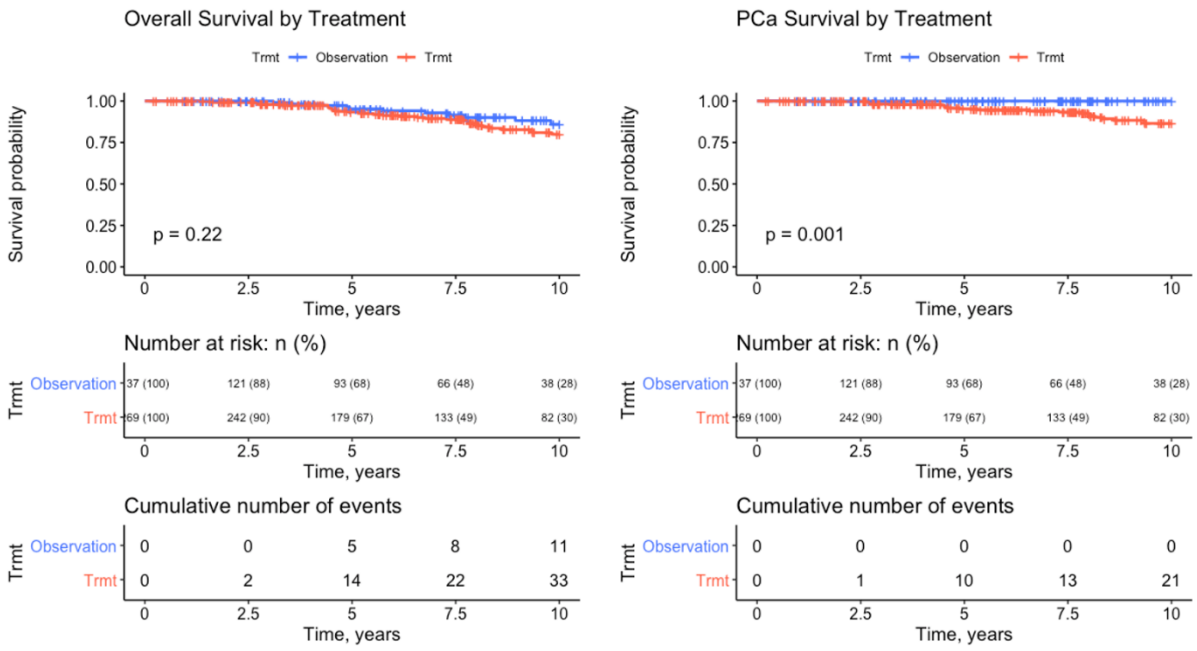
Of the 1865 patients who underwent RARP between February 2002 and September 2012, 407 patients with BCR were included in this study, with 137 undergoing no secondary treatment (observation) and 270 undergoing RT and/or ADT (treatment). Patients included in the observation group were required to be at least 3 years post RP. Demographics of the two groups under study (Group 1 observation and Group 2 Treatment) are listed in Table 1. Patients were of similar age, with similar average follow-up times of 7.5 and 7.6 years following RARP, respectively. Oncologically, preoperative PSA, both continuous and categorical current PSAdt, positive margins, pathological stage (p-stage), Gleason Grade Group (pGGG) and PSAdt change were significant (Table 1).

OS is 92% in the observation group and 81% in the treatment group ($p<0.001$). Similarly, PCSS is 100% in the observation group, and 89% in the treatment group ($p<0.001$) (Table 1). Figure 1 demonstrates 10-year survival Kaplan-Meier curves for PCSS ($p=0.001$) and OS ($p=0.22$).

Table 1. *Demographics of observation (n=137) and treatment (n=270) groups.*

Treatment	**Observation**	**Treatment**	**Total**	
	Count (%)	**Count (%)**	**Count (%)**	
N, all patients	137 (33.7%)	270 (66.3%)	407 (100%)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**p value**
Age, years	63.5 (7.3)	63.8 (7.2)	63.7 (7.3)	0.703
Pre-PSA, ng/mL	8.3 (5.7)	12.7 (16.9)	11.2 (14.3)	0.004
Follow Up, years	7.5 (4.1)	7.6 (4.4)	7.6 (4.3)	0.835
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)	
PSAdt, months	26.1 (19.9)	8.3 (8.9)	15.6 (16.9)	< 0.001
Margins	37 (27.0%)	108 (40.0%)	145 (35.6%)	0.01
p-stage				< 0.001
pT2	67 (48.9%)	69 (25.7%)	136 (33.5%)	
pT3/T4	70 (51.1%)	200 (74.3%)	270 (66.5%)	
Gleason Grade Group				< 0.001
1	17 (12.4%)	4 (1.5%)	21 (5.2%)	
2	49 (35.8%)	51 (18.9%)	100 (24.6%)	
3	43 (31.4%)	79 (29.3%)	122 (30.0%)	
4	17 (12.4%)	22 (8.1%)	39 (9.6%)	
5	11 (8.0%)	114 (42.2%)	125 (30.7%)	
PSAdt Group, months				< 0.001
>12	108 (80.0%)	42 (21.8%)	150 (45.7%)	
6 to 12	23 (17.0%)	45 (23.3%)	68 (20.7%)	
<6	4 (3.0%)	106 (54.9%)	110 (33.5%)	
DT Change				< 0.001
Increasing	93 (67.9%)	49 (18.1%)	142 (34.9%)	
Decreasing	35 (25.5%)	101 (37.4%)	136 (33.4%)	
NA	9 (6.6%)	120 (44.4%)	129 (31.7%)	
PCSM	0 (0.0%)	29 (10.7%)	29 (7.1%)	< 0.001
Overall Mortality	13 (9.5%)	50 (18.5%)	63 (15.5%)	0.017

Figure 2. *Kaplan-Meier analysis of Overall Survival and Prostate-Cancer Specific Survival between observation (n=137) and treatment groups (n=270). Patients were censored either at death or last follow-up.*



Predictors for No Treatment

To identify predictors of no treatment, significant oncological covariates of PSAdt change, preoperative PSA, pGGG, age, PSAdt, and p-stage in univariate analysis were included in the initial adjusted full model. Though everything but age was significant in the univariate model, in the full multivariate model, only PSAdt change (increasing or decreasing) and PSAdt group (greater or less than 12 months) were significant (p=0.0225 and p<0.001, respectively). Since pGGG was trending to be a significant predictor and is a commonly used factor determining treatment (p=0.0631), it was included in Model 1. Patients with an increasing doubling time are 4.94 times more likely to avoid being treated

following BCR after adjusting for PSAdt group and pGGG, while patients with pGGG 4-5 were twice as likely to need treatment after adjusting for PSAdt group and pGGG. The most significant predictor for no treatment was PSAdt > 12 months which was 7.74 times more likely to avoid treatment after adjustment for PSAdt change and pGGG (Table 2, $p<0.001$ for both).

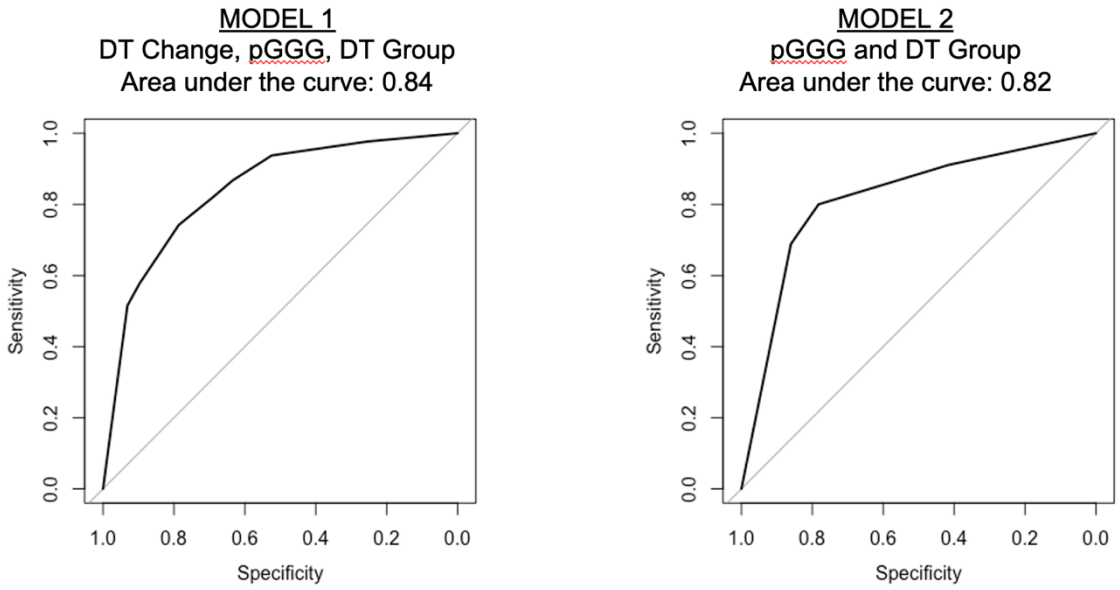
To evaluate whether DT change adds to currently useful clinical parameters of pGGG and PSAdt group, a separate regression model was conducted without DT change. In the final model (model 2), pGGG and PSAdt group were significant predictors of no need for treatment. Men with PSAdt > 12 months were 12 times more likely to not need treatment compared to men with < 12-month PSAdt, however men with pGGG 4-5 were twice as likely to need treatment compared to pGGG 1-3.

Table 2. *Multivariate logistic regression model of no treatment, after adjusting for demographic and oncologic covariates known to affect treatment.*

Model	Variable	Estimate OR (95% CI)	P-value
Full Model	DT Change (Decreasing [ref], Increasing)	4.91(2.71, 9.08)	<0.001 ***
	pGGG (pGGG1-3 [ref], pGGG4-5)	0.56 (0.28, 1.09)	0.0891
	Preoperative PSA [continuous]	0.98 (0.94, 1.01)	0.4487
	Age [continuous]	1.02 (0.98, 1.07)	0.3105
	PSAdt group (<12 months [ref], >12 months)	7.72 (4.19, 14.68)	<0.001 ***
	p-stage (pT2 [ref], pT3)	0.82 (0.44, 1.54)	0.5431
Model 1	DT Change (Decreasing [ref], Increasing)	4.94 (2.74, 9.12)	<0.001 ***
	pGGG (pGGG1-3 [ref], pGGG4-5)	0.54 (0.28, 1.03)	0.0631
	PSAdt group (<12 months [ref], >12 months)	7.74 (4.24, 14.55)	<0.001 ***
Model 2	PSAdt group (<12 months [ref], >12 months)	12.06 (7.01, 21.31)	<0.001 ***
	pGGG (GGG1-3 [ref], pGGG4-5)	0.45 (0.25, 0.82)	0.0094 **

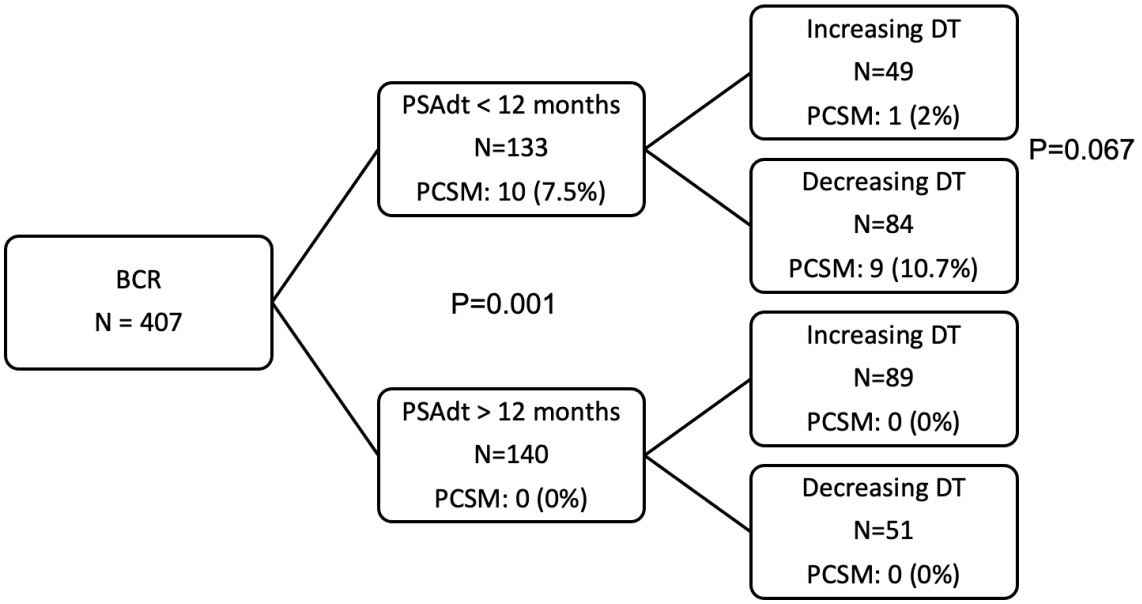
Model 1 had an AUC of 0.84, indicating that this model including pGGG, DT change, and PSAdt group is an excellent predictor of no need for treatment. The model had a sensitivity of 0.79, specificity of 0.74, positive predictive value of 0.78, and negative predictive value of 0.75. In regression model 2, excluding DT change and only including pGGG and PSAdt group, the AUC of 0.82 also similarly indicates its strength in predicting need for treatment. Model 2 also had sensitivity of 0.78, specificity of 0.80, positive predictive value of 0.84 and negative predictive value 0.72.

Figure 3. *ROC curve of DT change as a predictor for treatment in multivariate regression models.*



When stratifying patients first based on PSAdt group (>12 months and 0-12 months) then DT change (increasing vs decreasing DT), patients with PSAdt < 12 months and decreasing DT see a higher rate of PCSM (10.7%) compared to patients with PSAdt < 12 months and increasing DT (2%, p=0.067). Despite the vast proportional difference in this population, the power for this stratified comparison was weak due to the small sample size, at 0.44. A total sample population of 194 patients (power=0.80) would be needed to see a difference between these two groups. On the other hand, all patients with PSAdt > 12 months and categorizable DT change saw no PCSM (0%) at an average follow-up of 7.5 years post-RP.

Figure 4*: Tree diagram for overall PCSM, with patients stratified first by PSAdt (<12 months, > 12 months), then increasing or decreasing PSAdt. P-values were calculated with chi-square statistics.*

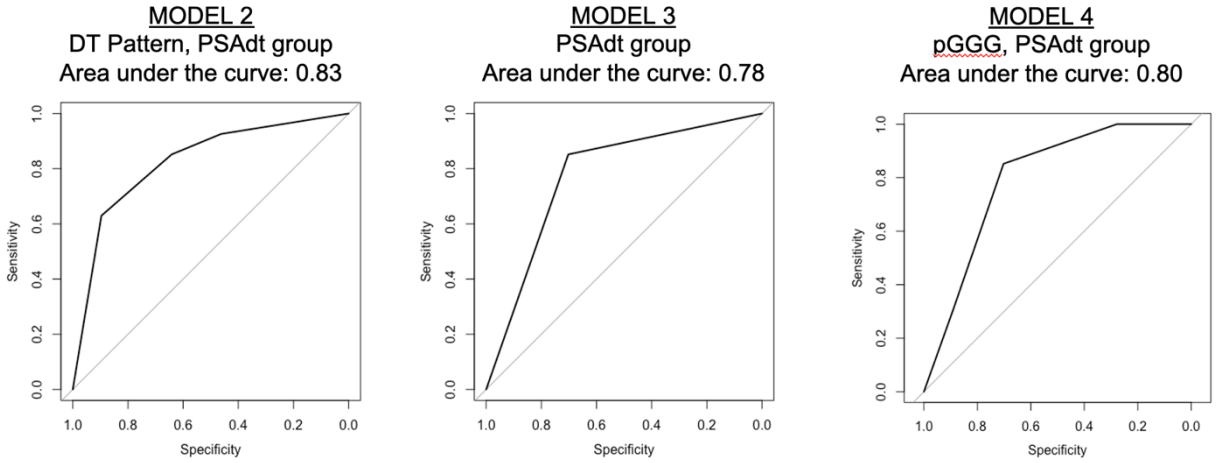


Because patients with PSAdt > 12 months evidently have no risk to prostate cancer specific survival, I conducted a similar multivariate regression model with only PSAdt < 12 months. In this model, pGGG is no longer a significant predictor of need for treatment, though PSAdt (0-6 months vs 6-12 months) and DT change remains significant (Table 3). The model including DT change and PSAdt has an AUC of 0.83, comparable to the previous models with the entire group (model 2, Figure 5), while the model with only PSAdt group included (0-6 months vs 6-12 months) had an AUC of 0.78. (model 3, Figure 5) Interestingly, when adding pGGG to the PSAdt model, though pGGG was not a significant predictor in the regression, the AUC improved to 0.80 (model 4, Figure 5).

Table 3. *Multivariate logistic regression model of no treatment for patients with PSAdt < 12 months, adjusting for demographic and oncologic covariates known to affect treatment.*

Model	Variable	Estimate OR, 95% CI	P-value
Full Model	DT Change (Decreasing [ref], Increasing)	5.37 (1.98, 15.8)	0.001 **
	pGGG (pGGG1-3 [ref], pGGG4-5)	1.73 (0.55, 5.71)	0.352
	Preoperative PSA [continuous]	0.99 (0.93, 1.00)	0.324
	Age [continuous]	0.97 (0.89, 1.05)	0.396
	p-stage (pT2 [ref], pT3)	1.17 (0.40, 3.62)	0.779
	PSAdt group (<6 months [ref], 6-12 months)	12.83 (3.87, 54.50)	<0.001 ***
Model 1	DT Change (Decreasing [ref], Increasing)	5.35 (2.01, 15.39)	0.001 **
	pGGG (pGGG1-3 [ref], pGGG4-5)	1.40 (0.49, 4.08)	0.53
	PSAdt group (<6 months [ref], 6-12 months)	10.65 (3.40, 42.08)	<0.001 ***
Model 2	DT Change (Decreasing [ref], Increasing)	5.50 (2.08, 15.77)	< 0.001 ***
	PSAdt group (<6 months [ref], 6-12 months)	9.55 (3.22, 35.70)	<0.001 ***
Model 3	PSAdt group (<6 months [ref], 6-12 months)	13.54 (4.88, 48.20)	<0.001 ***
Model 4	pGGG (pGGG1-3 [ref],p GGG4-5)	1.38 (0.54, 3.56)	0.502
	PSAdt group (<6 months [ref], 6-12 months)	14.86 (5.15, 54.66)	<0.001 ***

Figure 5. *ROC curve of DT change as a predictor for treatment in multivariate regression models, in patients with PSAdt < 12 months.*



IV. DISCUSSION

Observation without Secondary Treatment

Because observation without secondary treatment is not the current standard treatment pathway for patients with BCR following RP, this cohort of patients has not been studied exclusively in literature. It is evident here that following prostate cancer BCR, not all patients will need to seek secondary intervention. Among the 407 BCR patients in our cohort, 137 (33%) of patients were managed with observation only, with 0% PCSM at an average of 7.5 years follow-up (Table 1). Importantly, the observation group saw not only *no risk* to both OS and PCSS compared to the treatment group, but higher OS (p=0.22) and a significantly higher PCSS (p=0.001) at 10 years, further establishing that the observation cohort of patients does not need secondary treatment (Figure 2). This is a significant finding, indicating that at least one-third of patients who recur do not have mortal recurrences, despite PSA elevation. Thus, the current guidelines that recommend universal secondary treatment with radiotherapy and/or hormonal therapy for patients with PSA elevation following RP is grossly overtreating patients, subjecting patients to a decreased quality of life and greater risks of more lethal genitourinary cancers without conclusive evidence of survival benefit. Evidently, some BCR's can be established as "benign" recurrences. These patients thus can be observed without need for treatment at an average of 7.5 years following post-RP, calling for a review of current guidelines recommending secondary intervention immediately following BCR/PSA elevation.

Although 33% of patients did not need treatment, this cohort of patients has unique oncologic characteristics from the treated group. Notably, in univariate analysis, the untreated observation group had a lower preoperative PSA, rates of positive surgical

margins, pathological stage, disease Gleason grade and a higher current PSAdt. Further, the observation group had higher proportion of patients with an increasing PSAdt, indicating that the time it takes for PSA to double was lengthening. This characterization of PSAdt from a simple continuous variable to include PSAdt's dynamic nature may be a novel approach to help direct need for secondary treatment (Table 1).

Use of DT Change in Directing No Need for Treatment

Largely responsible for the overtreatment of patients with BCR following RP is the lack of methodology in identifying patients who can be observed without secondary treatment. The fear of undertreatment has hindered the extensive study of patients without secondary intervention following BCR. Our study uniquely evaluates this group to determine the predictors of not needing treatment.

In multivariate (adjusted) modelling that included primary exposure DT change (increasing or decreasing) with covariates pGGG, preoperative PSA, age, PSAdt, and p-stage, only PSAdt and DT change were significant predictors of outcome no need for treatment after adjustment ($p<0.001$), although pGGG was very close to significance ($p=0.06$). This correlates with previously published literature indicating that patients with longer doubling time and lower pGGG disease can be observed without need for treatment, or are less likely to benefit from secondary intervention. A retrospective study by Ahlering and colleagues in 2005 observed that 40% of patients did not need secondary treatment with 0% PCSM at an average of 10 years follow-up. Significant predictors of PCSM include a low total and secondary Gleason score and a PSAdt of > 12 months [30]. Additionally, a more recent study by Matsumoto et al. in 2019 observed that patients with Gleason < 7 (pGGG 1-

2) and PSAdt > 6 months were candidates for observation without salvage therapy following BCR or delayed intervention [29].

When evaluating this in terms of those who would be more likely to benefit from treatment, our data similarly aligns with previously published literature, where Trock and colleagues state that patients with <6 months PSAdt (independent of p-stage and pGGG) would benefit from early salvage therapy [28]. Another study by D'Amico and colleagues state that patients older than 70 years of age, with PSAdt < 9 months and high D'Amico risk were more likely to benefit from treatment, while patients younger than 70 years of age with PSAdt > 9 months may benefit from delayed treatment [34].

While there is mounting evidence that patients with long PSAdt do not require treatment, the PSAdt cutoffs for those who need treatment (as opposed to no need of treatment) is not agreed upon, varying from 6, 9, to 12 months. Uniquely, we evaluated the dynamic nature of PSAdt in this study by assigning DT change to each patient with PSAdt. Though not as significant of a predictor as PSAdt cutoff of 12 months, PSAdt was still a strong predictor of no need for treatment after adjusting for PSAdt group and Gleason Grade ($p<0.001$). However, it did not add significantly to the model's strength in predicting no need for treatment, as when only currently used predictors of PSAdt group and pGGG were included in the model, the AUC did not differ much (Figure 3). Hence, while DT change (increasing/decreasing DT) is a strong predictor of no need for treatment, it does not add to current predictors of PSAdt and pGGG.

In stratification analysis by PSAdt group, it is evident that the patients with PSAdt > 12 months saw no PCSM (Figure 4), and it is in the group of patients with PSAdt < 12 months that predictors to determine no treatment may be more important. Interestingly, in

multivariate regression analysis for only patients with PSAdt < 12 months, pGGG was no longer a significant predictor for no need for treatment. The strongest predictor remains PSAdt (0-6 months, 6-12 months), but because all other oncological factors are no longer predictors, it may be useful for physicians to also use DT change as a measure for patients who may not need treatment. pGGG, though not a significant predictor for no treatment in patients < 12 months, when added to the predictive models including PSAdt, did improve the predictive value of the model modestly (Figure 5, model 4). While DT change also only improved the predictive model marginally, it did improve the model more than GGG (Figure 5, model 2). Especially because literature has not agreed between 6, 9, or 12 month cut-offs, DT change demonstrates a promising metric that can be used in conjunction to PSAdt to guide treatment.

Limitations

While the prospectively collected data is a strength in this study, the retrospective nature of this study inherently has its limitations. Most importantly, patients were not randomly assigned to treatment or no treatment, so currently present guidelines and physician bias is a concern. However, the first aim established that, indeed, the observation only group did not need treatment, with 0% PCSM despite having similar age and follow-up with the treated patients.

The second limitation is the use of no treatment as the primary outcome in the multivariate regression analysis, instead of a better measure of risk, such as PCSM or PCSS. The decision to use no treatment instead of PCSM was intentional as this group saw no PCSM, and was established by the first aim to be an ideal group of patients. Additionally,

there are more “no treatment” events then PCSM events, effectively increasing the strength of regression analysis. Future studies evaluating PCSM as the primary outcome would be beneficial to accurately evaluate the best predictors of PCSM risk.

Future Directions

Finally, there are evident steps that need to be taken before PSAdt and DT change can be integrated into clinical use. First, a uniform way to calculate PSAdt, and subsequently DT change, needs to be established. Currently, our model takes into account all PSA’s after BCR, while many external models in literature only take into consideration the last 3-4 PSA’s. In addition, we have preliminary evidence that PSAdt’s calculated prior to a detectable PSA (PSA < 0.1 ng/mL) is not as sensitive or accurate compared to the values post-BCR, which will need to be evaluated further.

Additionally, at this moment, is clinically difficult for all physicians to calculate PSAdt on all patients efficiently. Hence, while PSAdt has long been established as the best predictor for prostate cancer progression and mortality, it has not been included in any strong recommendation guidelines by the AUA/ASTRO or EAU. Establishing a tool that can help physicians efficiently visualize and monitor a patient’s PSAdt and DT change will be integral to PSAdt’s integration into treatment guidance.

Next, careful consideration of DT change’s role in determining need for treatment, especially in populations with < 12 month PSAdt following BCR is important. In this study, PCSM was only 2% in the increasing DT population, but 10% in the decreasing DT group. A study with better power evaluating PCSM risk in this group would be critical for physicians in guiding treatment following BCR.

However, of utmost importance is the close scrutiny and revision of current secondary treatment guidelines. Regardless of which indicators are the best predictors for determining no need for treatment, the 33% of patients who have not necessitated treatment post-BCR at an average 7.5 year follow-up with 100% PCSS in this study demonstrates that BCR and PSA elevation is not, and should not, be the indicator for treatment. Prostate cancer's unique long course demonstrate that many patients will live well beyond 10 years post-RP, and continued follow-up on this observation group is needed to ensure patients remain at no risk to PCSM. Due to prostate cancer's long nature, physicians should also be more inclined to observation protocols and less inclined to recommend immediate secondary treatment following BCR for patients with PSAdt > 12 months, pGGG 1-3, and increasing DT, who evidently have lower risk for PCSM. Observation following BCR in these cohorts may avoid subjugating patients to negative impacts on quality of life associated with RT and ADT unnecessarily.

V. SUMMARY AND CONCLUSIONS

In this study, I establish that there exists a group of patients that can be observed safely without risk to mortality following RP even after BCR. Current guidelines to immediately recommend secondary treatment to patients with BCR or PSA rise should be reevaluated, as in this study, 33% of BCR patients did not necessitate treatment with no risk to prostate cancer specific survival. Additionally, no patients with PSAdt > 12 months experienced prostate cancer specific mortality. Further, PSAdt > 12 months, low pGGG (1-3), and increasing DT, are indicators for no need for treatment. DT change, a novel indicator introduced in this study, does not add significantly to currently used models including PSAdt and pGGG. However, further evaluation of its use in patient cohorts with PSAdt < 12 months needs to be conducted, as it may provide additional information to guide patients who do not need treatment.

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