UNIVERSITY OF CALIFORNIA,
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Use of serum Prostate Specific Antigen doubling time kinetics to predict salvage surgery success 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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DEDICATION

To

my parents Henrik and Gayane, sister Ani, cousins, colleagues, and friends

to curiosity

"The important thing is not to not to stop questioning.
Curiosity has its own reason for existing.
I have no special talents.
I am only passionately curious."

Albert Einstein

and to following your dreams.

"In the time of your life, live – so that in that wondrous time you shall not add to the misery and sorry of the world, but shall smile to the infinite delight and mystery of it."

William Saroyan

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LIST OF ABBREVIATIONS

RP	: Radical prostatectomy
RARP	: Robot-assisted radical prostatectomy
BCR	: Biochemical recurrence
PSA	: Prostate-specific antigen
PSADT	: Prostate-specific antigen doubling time
PLND	: Pelvic lymph node dissection
PCSM	: Prostate cancer-specific mortality
NCCN	: National Comprehensive Cancer Network
LNI	: Lymph node invasion
AUA	: American Urological Association
ASTRO	: American Society for Radiation Oncology
NNT	: Number needed to treat
sPLND	: Salvage pelvic lymph node dissection
sPMR	: Salvage pelvic mass resection
RT	: Radiation therapy
HT	: Hormonal therapy
ADT	: Androgen deprivation therapy
EAU	: European Association of Urology
BMI	: Body mass index
p-stage	: Pathological stage
pGGG	: Pathological Gleason Grade Group

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To my dear cousins, Vartan, Vahan, Victoria, Stepan, Liana, and Lusine, your kinship has fortified a sense of belonging that remains unbroken. Each of you has touched my life in unique ways, filling it with laughter, love, and unforgettable memories. We share more than just blood – we share dreams and an unbreakable bond that transcends the confines of time and distance.

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served as a timely reminder of the crucial role research and translational medicine play in the evolving landscape of our world.

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ABSTRACT OF THE THESIS

Use of serum Prostate Specific Antigen doubling time kinetics to predict salvage surgery success following radical prostatectomy

by

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Master of Science of Biomedical and Translational Sciences

University of California, Irvine, 2023

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Importance: Prostate cancer remains as one of the most common malignancies in men in the United States. A substantial portion of men experience a biochemical recurrence (BCR) following radical prostatectomy (RP). Salvage surgeries, such as pelvic lymph node dissection (sPLND) and pelvic mass resection (sPMR) are utilized as potential interventions in eligible patients with BCR. However, the factors that predict success of salvage surgeries remain largely unknown.

Objectives: This study aims to investigate the utility of Prostate-specific Antigen doubling time (PSADT) kinetics in predicting salvage surgery success, defined as no need for further treatment post-salvage surgery. In patients who failed and required subsequent treatment, we aim to assess the utility of multiple dimensions of PSA kinetics in predicting the time to treatment post-salvage surgery.

Methods: A retrospective analysis of data from 32 patients with BCR post-RP who underwent salvage surgery was conducted. PSADT graphs were constructed for each patient to represent the pre- and post-salvage periods. A smoothing algorithm was applied to the data to refine PSADT calculation and analysis. The primary independent variable was the average PSADT rate of change over the one-year period pre-salvage surgery. The secondary variables included the instantaneous PSADT rate pre-salvage, pre-salvage PSADT, pre-salvage PSA, and post-salvage PSADT rate. The cohort was stratified into two groups: salvage surgery success (N=12) and salvage surgery failure (N=20). Two-tailed independent t-tests, chi-squared analyses, and linear regression analyses were utilized to compare and analyze our data.

Results: There were no statistically significant differences between the salvage surgery success and failure groups (Table 1-2). Additionally, none of the univariate or multivariate linear regression models were able to identify statistically significant predictors of salvage surgery success in our primary analysis. Subset analysis of the failure group also failed to identify any significant predictors of time to post-salvage surgery treatment.

Conclusion and Relevance: The study did not yield significant predictors of salvage surgery success or time to post-salvage surgery treatment, within the context of PSADT kinetics. This speaks to the complexity and challenges associated with using PSA kinetics alone in predicting salvage surgery outcomes. Additionally, this study highlights the need for studies with larger cohorts that integrate advanced analytical tools to create more

refined predictive models. Future studies exploring the general applicability of quantified PSADT rates in post-RP treatment decision-making are warranted.

I. INTRODUCTION

Prostate Cancer

Prostate cancer stands as the most prevalent non-cutaneous malignancy affecting men in the United States [1]. The disease predominantly impacts elderly males, and exhibits a unique pattern compared to other cancers due to its slow progression. Most patients with low-grade disease are unlikely to experience a prostate-specific mortality unless there is progression to metastasis, especially involving other organs and bones [2]. A common therapeutic modality for localized prostate cancer is radical prostatectomy (RP). Long-term studies indicate that men with clinically detected, localized prostate cancer who have a long life expectancy can benefit from radical prostatectomy, with an average gain of 2.9 years of life observed at 23 years post-RP. [3]. As such, RP, specifically, robot-assisted radical prostatectomy (RARP), has emerged as an effective intervention for localized prostate cancer due to its minimally invasive nature and potential for improved functional outcomes [4].

Despite its efficacy, roughly 20% of men suffer from a biochemical recurrence (BCR) post-RP, indicated by detectable levels of prostate-specific antigen (PSA) following surgery [5]. A PSA level of 0.2 ng/mL, confirmed by two consecutive measurements, is the most accepted criterion for a BCR [5,6]. Understanding the dynamics of PSA doubling time (PSADT) kinetics in these patients, particularly in the context of planning salvage therapies, may be crucial in determining treatment success and improving patient outcomes.

Pelvic Lymph Node Dissections at the Time of RP

Pelvic Lymph Node Dissection (PLND) at the time of surgery has long been a standard procedure performed during radical prostatectomy. PLND aims to improve therapeutic outcomes and more accurately assess the extent of tumor proliferation in prostate cancer patients. In recent times, the procedure has been subject to great controversy, as growing literature suggests that PLND may have no benefit for patients.

In patients diagnosed with prostate cancer, the presence of lymph node metastasis substantially increases the chance of unfavorable outcomes and overall prognosis. The long-term risk of prostate cancer-specific mortality (PCSM) is significantly higher in patients with lymph node metastasis [7]. Additionally, studies have shown that an increased number of lymph nodes in which the cancer has metastasized to is closely associated with poorer outcomes in prostate cancer patients [8,9]. The lack of accurate imaging tools to determine the presence of lymph node metastasis further complicates the issue. To account for such potential metastases, it was proposed that highly susceptible lymph nodes surrounding the pelvis should be excised during the removal of the prostate when performing the radical prostatectomy. Several retrospective studies linked the removal of lymph nodes via PLND at the time of RP to improved patient outcomes and prognosis [10,11]. In a study by Joslyn et al, PLND at the time of RP, where at least 4 node-positive or 10 node-negative lymph nodes were removed, was significantly associated with a lower risk of prostate cancer-specific mortality relative to cases where no PLND was performed [10]. These findings agree with those of Masterson et al, who found that an increased number of node-negative lymph nodes removed during PLND was significantly associated with an improved BCR-free rate in men without positive lymph node

involvement [11]. As BCR of prostate cancer is highly unfavorable, any intervention that can prevent or delay its onset is of great clinical importance. However, further analysis demonstrated that PLND did not significantly improve outcomes in men with positive lymph node involvement [11]. This finding runs counter to the therapeutic intentions of PLND and has opened the door for further studies questioning the efficacy of the procedure at time of RP.

Several studies exploring efficacy of PLND at time of RP in men with low-grade prostate cancer found no significant differences in BCR rates between groups where PLND was performed or omitted [12,13]. A study by Bhatta-Dhar et al demonstrated that PLND exclusion did not negatively affect biochemical recurrence rates 6 years post-RP in patients with low-risk prostate cancer [12]. These findings are further supported by Weight et al, whose study demonstrated that BCR rates remain insignificantly different between PLND and no-PLND groups at 10 years post-RP [13]. Both studies emphasize the need to consider cost and potential complications of PLND when performed at time of RP. Supporters of PLND argued that these findings may only be relevant in low-risk patients, and applicability of such findings may diminish in higher-grade cancers. In response, a study by Berglund et al demonstrated that in a large cohort, there remains no significant differences in BCR rates 5 years post-RP in low, intermediate, and high risk prostate cancer [14].

Pelvic Lymph Node Dissections for Staging

Currently, PLNDs are recommended in most surgical guidelines reported by leading organizations in Urology and Oncology. In light of studies questioning the proposed clinical benefits of the procedure, such organizations began to advocate for PLNDs at time of RP as a staging procedure, rather than for direct therapeutic benefit. Theoretically, by analyzing the excised lymph nodes for the presence of cancer, physicians could gain a more comprehensive understanding of the cancer's proliferation. This enhanced insight would allow for more accurate staging, which in turn could facilitate the design of an appropriately tailored treatment regimen, potentially leading to improved patient outcomes. The National Comprehensive Cancer Network (NCCN) recommends extensive PLND in patients with a 2% or greater risk of lymph node invasion (LNI), based on the predictive nomogram described by Cagiannos et al [15,16]. The American Urological Association (AUA) and the American Society for Radiation Oncology (ASTRO) recommend PLND at time of RP for more accurate staging in patients with unfavorable intermediate-risk or high-risk disease, however it is noted that therapeutic benefits have not been consistently observed [17]. Nonetheless, PLND, even strictly for staging purposes, is a highly limited procedure that has minimal effect on the accuracy of staging. A study by Mattei et al shows that even with the most extensive excisions, the “super-extended” PLND, 25% or more primary lymph nodes are missed [18]. Additionally, with the guideline-recommended extensive PLND, up to 37% of primary lymph nodes are missed [18]. Subsequent studies have shown that this accurate staging does not lead to any significant differences in patient outcomes between PLND and no-PLND groups, contrary to theoretical expectations [19–22]. Altok et al demonstrated that low to favorable

intermediate-risk patients without PLND who experienced upstaging had no significant differences in BCR rates in comparison to a similar cohort of PLND-receiving patients [20]. Perhaps one of the strongest studies demonstrating lack of clinical benefit from more accurate staging, a randomized clinical trial from Lestingi et al demonstrated that extended PLND results in more accurate pathological staging, however no differences in oncological outcomes were demonstrated regardless of the improvement [21]. These findings agree with the randomized clinical trial performed by Touijer et al, which similarly found no significant association between more accurate pathological staging and prostate cancer biochemical recurrence rates [22]. The expected therapeutic benefits from more accurate staging are not reflected in postoperative clinical outcomes.

Risks of Pelvic Lymph Node Dissections During RP

Several studies have demonstrated that more extensive PLNDs at time of RP are associated with significantly more complications in prostate cancer patients [23,24]. A study by Briganti et al observed a significant complication rate in extended PLNDs and limited PLNDs, with rates up to 19.8% and 8.2%, respectively [23]. Specifically, lymphocele rates in both groups were reported to be 10.3% and 4.6%, respectively [23]. Lymphoceles arise following damage to the lymphatic system, and can lead to serious consequences if left untreated. These findings agree with Stone et al, who demonstrated that increased number of nodes removed directly relates to complication rate [24].

It is important to note that the rate of lymph node invasion has been demonstrated to be particularly low in men with prostate cancer. According to a study by Kawakami et al, low, intermediate, and high-risk prostate cancer patients had lymph node invasion rates of 0.8%, 2.0%, and 7.1%, respectively [25]. Building upon the results of this study, a point/counterpoint article published by Abdollah et al connected these findings to the 10% biochemical-free survival reported by Masterson et al, [11] and determined the precise number of patients who need to undergo PLND at time of RP to experience the proposed beneficial effects of lymph node dissection [26]. Abdollah et al describes this as the "number needed to treat" (NNT), where they determined it must take 1250, 500 and 140 PLNDs at time of radical prostatectomy for low, intermediate, and high-risk patients, respectively, to improve outcomes for a single patient in each risk-category [26]. Reflecting on the findings of Briganti et al on complication rates [23], even with the most limited PLND, a complication rate of 8.2% is observed. Therefore, when taking this finding into consideration alongside the calculated NNT, it could be expected that complications will be

observed in 102/1250, 41/500, and 11/140 PLNDs at time of radical prostatectomy for low, intermediate, and high-risk patients, respectively.

Salvage Surgery following Radical Prostatectomy

With improvements in imaging technology, Gallium Ga-68 PSMA-PET/CT scans have demonstrated an ability to be effectively utilized as a tool in detecting pelvic lymph node metastases following biochemical recurrence of prostate cancer [27]. This has opened the door for a preferable alternative to performing PLNDs at time of RP for patients with excisable metastases: salvage PLND (sPLND) and pelvic mass resection (sPMR). Instead of performing the PLND on all patients at time of RP, salvage surgery provides the option to treat on an as-needed basis, where patients with prostate cancer BCR and a positive PSMA-PET/CT scan showing an excisable mass can undergo a second operation post-RP. Essentially, this avoids putting most patients at risk for complications from PLND. Instead, only candidates who have a viable chance of benefiting from such a procedure will undergo the operation post-RP when they have a biochemical recurrence. Several studies investigating salvage surgeries as a therapeutic option have demonstrated that patients may experience delays in BCR and subsequent treatment following the procedure [28,29]. Ploussard et al. conducted a systematic review that documented a growing body of evidence showing that sPLND is safe and can be effective in producing at least a temporary beneficial therapeutic response [29]. However, they emphasized that studies exploring salvage surgery outcomes over longer periods of time are needed.

PSA Doubling Time Kinetics as a Therapeutic Guideline

It is important to acknowledge the challenges associated with deciding on post-RP treatments. The slow-growing nature of prostate cancer, coupled with significant quality of life risks associated with secondary treatments such as radiation therapy (RT), hormonal therapy (HT), and androgen deprivation therapy (ADT), warrants a carefully considered approach in determining when secondary treatments are deemed necessary. This has led to the establishment of observation protocols, where patients undergo frequent PSA tests to monitor the PSADT and disease progression until treatment is required, if at all [30,31].

The applicability of PSADT as a prognostic tool has been underlined in several studies, highlighting it as a strong predictor of castration-resistant prostate cancer, PCSM, and overall mortality [32,33]. Current research emphasizes the potential of PSADT as an invaluable tool in decision-making for secondary intervention, with changes in PSADT potentially signifying shifts in the progression of prostate cancer recurrence [34–36].

Yet, determining the precise criteria for treatment initiation post-RP remains complex, with various studies proposing different nomograms based on different start points, endpoints, and predictive oncologic characteristics [37–40]. Furthermore, it's worth noting that a subset of patients with BCR may exhibit long-term survival even without secondary treatment post-RP, suggesting the existence of 'low-risk BCR' patients that might not need immediate intervention.

Specific Aims

Factors leading to the success of salvage surgery after RARP are largely unknown. This study is premised on recent evidence suggesting the potential utility of PSADT patterns in guiding treatment decisions following radical prostatectomy. The success of salvage surgeries is operationally defined as the lack of need for additional treatment (in the form of ADT, HT, or RT) post-surgery. Using retrospective data, this study will focus on the following specific aims:

Primary Aim: Investigate the predictive power of the average PSADT rate of change across the year leading up to salvage surgery in determining the necessity of subsequent treatments. We hypothesize that specific trends in PSADT rates could potentially indicate the success of salvage surgery, thereby informing further treatment decisions.

Secondary Aim: Examine the capacity of three dimensions of PSA kinetics, specifically, PSA value immediately pre-salvage, PSADT immediately pre-salvage, and PSADT rate of change immediately pre-salvage, in conjunction with the PSADT rate of change immediately post-salvage, to predict the need for further treatment.

Secondary Outcome (Subset Analysis): Among patients who required additional treatment post-salvage surgery, determine whether any of the primary or secondary variables can predict the time to treatment post-salvage.

By exploring the potential of PSADT kinetics to predict the success of salvage surgeries, this research aims to contribute to a more nuanced understanding of treatment decisions in the context of biochemically recurrent prostate cancer. The ultimate goal is to optimize patient outcomes while minimizing unnecessary interventions and their associated risks and costs.

II. METHODS

Patient Population, Data Collection, and Follow-Up

Our methodology employed a retrospective analysis of data extracted from a patient database, specifically those who underwent salvage surgery in the form of a sPLND or sPMR after RP. These patients, who received the salvage procedures consecutively from April 2017 to August 2022, were all managed by a single surgeon affiliated with the University of California, Irvine.

The database securely and anonymously recorded patient information, encompassing preoperative patient demographics, oncological data, and follow-up information. This data acquisition process was conducted in accordance with the approved institutional review board protocol at the University of California, Irvine (HS#1998-84). To ensure a consistent dataset for statistical analysis, the database was sealed for data collection on May 1st, 2023. All data gathering procedures conformed to the Health Insurance Portability and Accountability Act, and all federal guidelines regarding informed consent were observed.

Upon identification of BCR post-RARP, patients were appropriately counseled about their treatment alternatives, including ADT, HT, RT, or salvage surgery per the European Association of Urology (EAU) guidelines. Additionally, all patients were recommended to undergo a 68Ga-PSMA-PET/CT scan. This diagnostic tool was employed to precisely determine the location of recurrence following RARP. Patients with an observable and excisable recurrence in the lymph nodes or pelvic region were potential candidates for salvage surgery.

124 patients who experienced BCR and subsequently underwent 68Ga-PSMA-PET/CT imaging were initially identified. Of these patients, 95 presented with positive findings

from their PSMA-PET/CT scans. An expert surgeon meticulously reviewed the charts of these 95 patients to determine which individuals would be suitable candidates for salvage surgery. A total of 34 patients ultimately underwent salvage procedures. Following the exclusion of patients with less than six months of follow-up after the salvage operation (N=2), our final analysis included 32 patients. This selection process ensured that our sample accurately represented the patient population of interest (Figure 1).

To ensure the inclusion of the most recent data, a follow-up protocol was implemented for all patients. This protocol entailed periodic contact with each patient for a minimum of six months following the salvage surgery. This communication was conducted through multiple methods, including phone calls, emails, scheduled appointments, and mail correspondences. This comprehensive follow-up strategy ensured we maintained an accurate and current understanding of each patient's postoperative status.

Two distinct PSADT graphs were constructed for each of the 32 patients who underwent salvage surgery: one representing the pre-salvage period and the other, the post-salvage period. These graphs were initially developed using all available post-RARP PSA values. However, to refine our analysis, a smoothing algorithm was applied to the dataset. Consequently, only PSA values that exhibited an increase relative to the preceding PSA results were incorporated into the final PSADT calculations.

Initially, a median of 11 (ranging from 4 to 26) PSA values were integrated into the pre-salvage PSADT graphs. Following the application of the smoothing algorithm, an average of 21.88% (SD: 19.47%) of the PSA values were deemed non-contributory and subsequently removed from each PSADT graph. This refined approach yielded a median of 9 (ranging from 4 to 19) PSA values that were ultimately included in our final models.

PSADT was calculated for each respective PSA entry using the validated growth function: $^{\ln (2)}/_{x}$, where x refers to the slope of the relationship between two PSA values and time of measurement ($^{\ln(PSA_n) - \ln (PSA_1)}/_{t_{PSA_n} - t_{PSA_1}}$) , t refers to time of PSA test, and n refers to a measurement greater than 1 (Figure 2) [41].

For the period spanning one year prior to the salvage operation, PSADT values were visualized using a scatter plot against their respective times of measurement. Subsequently, a linear equation was fitted to these data points to produce a simple graphical representation (Figure 3). The slope of this fitted line served as a reliable indicator of the average rate of PSADT over this one-year period. Furthermore, the instantaneous PSADT rate was derived from the final two PSADT measurements obtained before the salvage surgery. The post-salvage PSADT rate was determined by using the PSADT measurements from the point immediately following the salvage procedure up until either the initiation of subsequent treatment or the most recent follow-up, as applicable.

The success of salvage surgeries is operationally defined as the lack of need for additional treatment (ADT, HT, or RT) post-surgery. Hence, two groups will be compared: salvage surgery success (N=12) and salvage surgery failure (N=20).

Statistical Methods and Analysis

The initial assessment of patient demographic variations between the salvage surgery success and failure groups involved two-tailed independent t-tests for continuous variables. Categorical variables were analyzed using chi-squared tests to discern proportions.

Following this, we evaluated the predictive utility of PSA kinetics for successful salvage surgery (no need for post-salvage treatment). Univariate and multivariate linear regression analyses were utilized to identify potential predictors of post-salvage treatment. Our primary exposure variable was the average PSADT rate of change over the one-year period preceding the salvage operation. Concurrently, we also assessed several secondary variables: the instantaneous PSADT rate of change pre-salvage, pre-salvage PSADT, pre-salvage PSA, and the PSADT rate of change post-salvage. These variables were selected to represent multiple dimensions of PSA kinetics based on their significance as indicated in literature and expert opinion, with each measured as a continuous variable.

Ad hoc subset analysis was conducted to assess the predictive power of these variables for the duration of time to subsequent treatment post-salvage within the salvage failure group. The time to treatment was quantified as a continuous variable.

Given our study cohort comprises 32 patients - 12 who experienced success following salvage surgery and 20 who did not - we conducted a modified power analysis utilizing the comparison of means formula for independent samples. This method was utilized to determine the necessary mean difference in the average rate of change in PSADT over the year preceding the salvage procedure to achieve statistical significance, defined as $p<0.05$,

with an 80% power. Our findings indicate that a mean difference of 0.261 would meet the threshold for statistical significance.

All statistical tests and figures were performed and created using SPSS Statistics (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL).

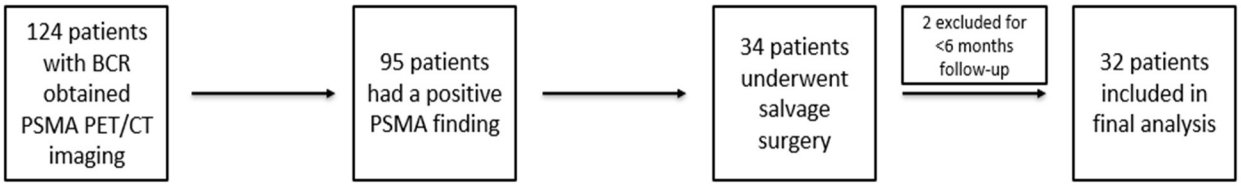


Figure 1*. Flowchart depicting patient selection process. Initial pool included 124 patients with biochemical recurrence (BCR) who underwent 68Ga-PSMA-PET/CT imaging. After excluding patients with less than six months of follow-up post-salvage operation, the final analysis included a cohort of 32 patients.*

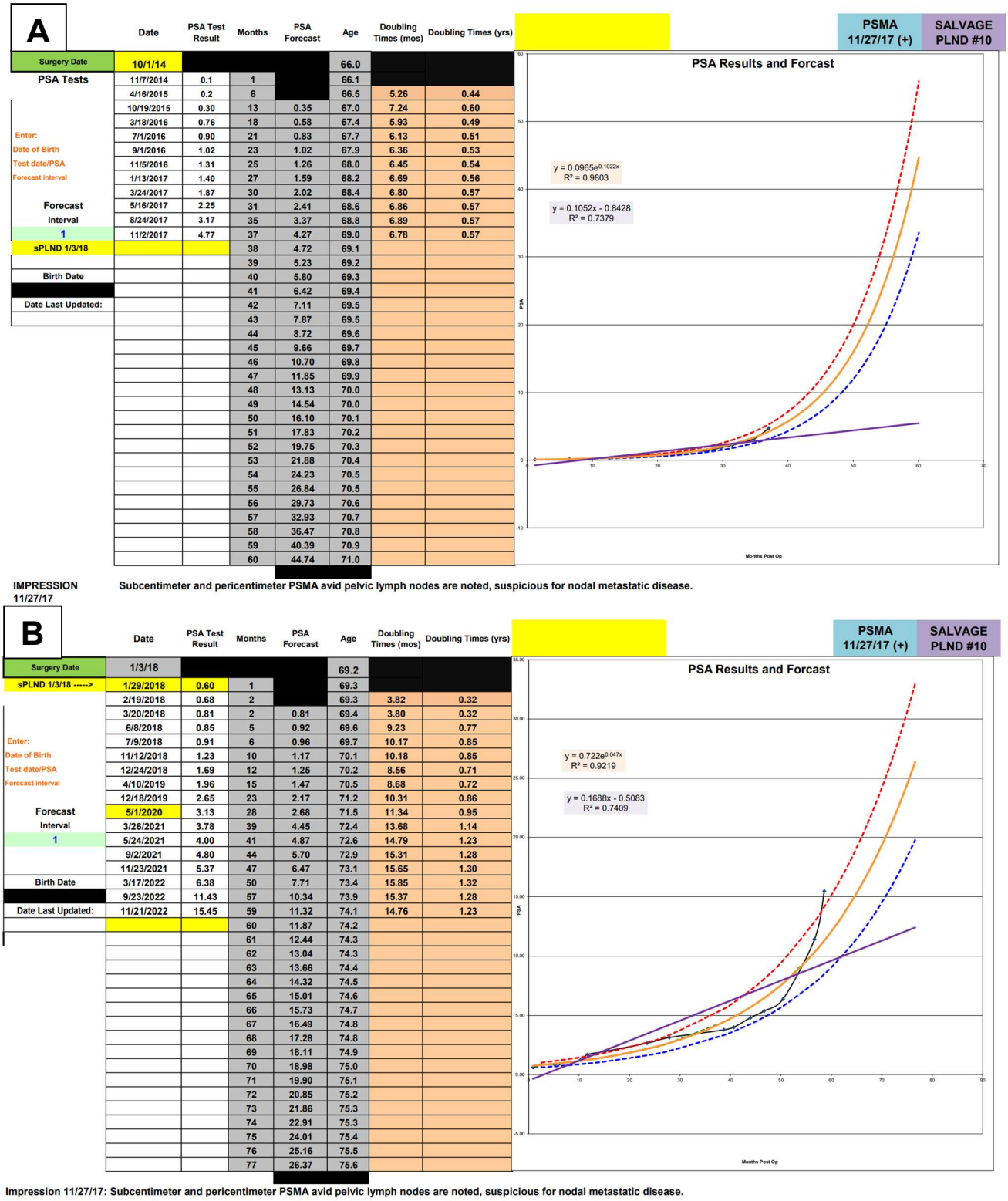
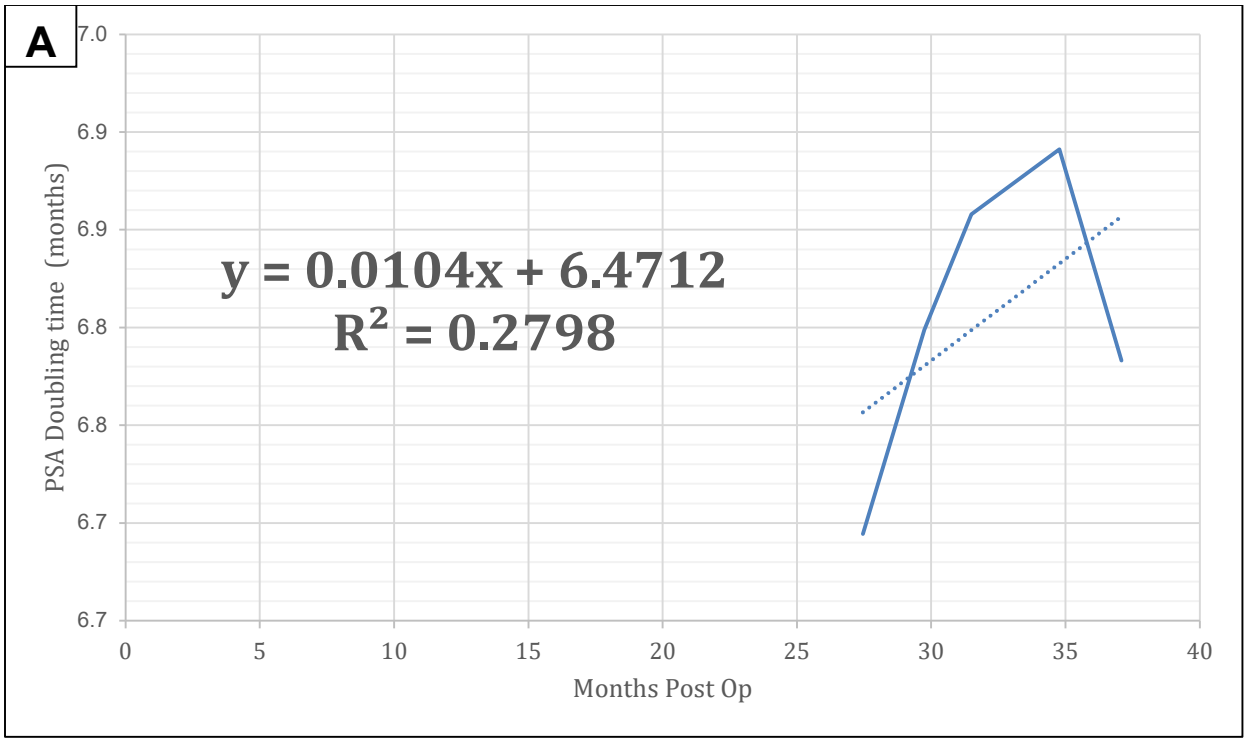


***Figure 2**: PSADT graphs for a salvage surgery case. A. Pre-salvage surgery PSADT graph. B. Post-salvage surgery PSADT graph.*



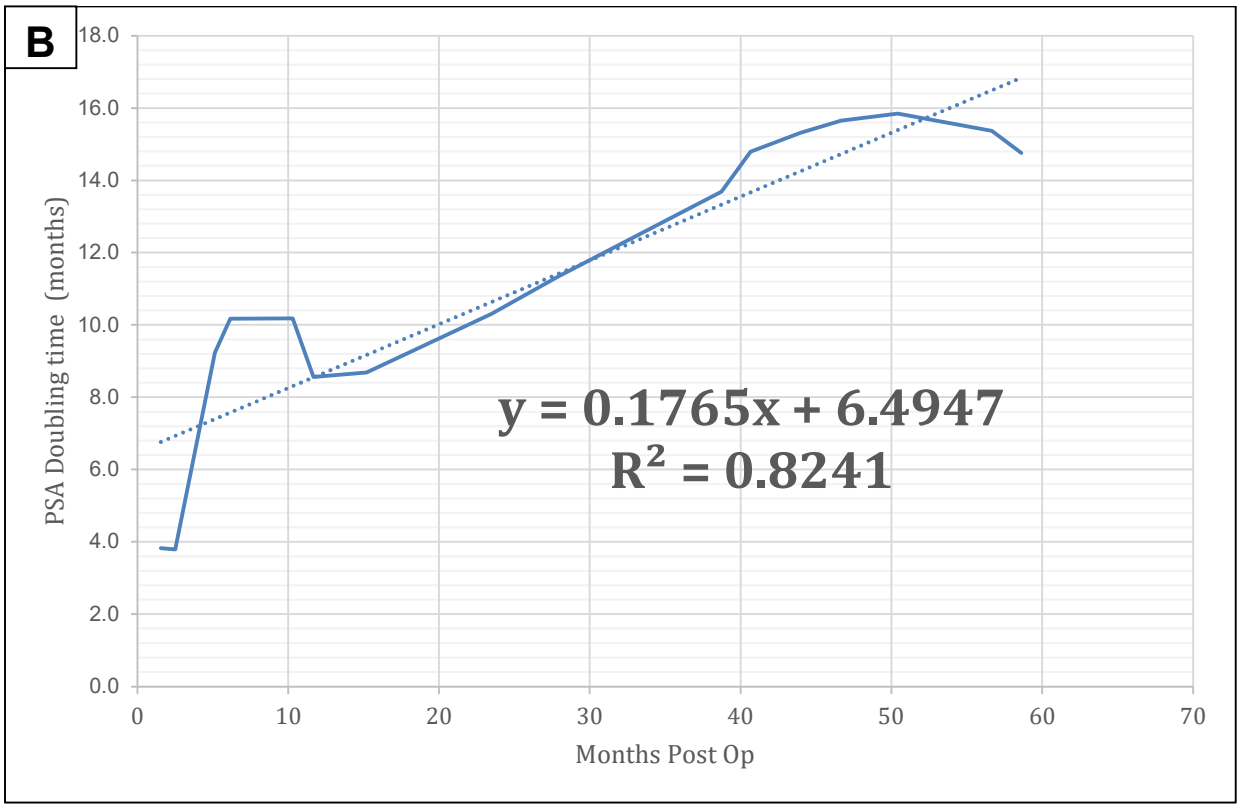


Figure 3*. PSA Doubling Times plotted over time to calculate PSADT rates. A. PSADT rate plot across one year pre-salvage surgery. B. PSADT rate plot post-salvage surgery.*

II. RESULTS

Patient Demographics and Comparison of Means

Out of 124 patients experiencing BCR post-RARP, a total of 32 patients were included in the final analysis. Group 1, salvage surgery success, consisted of 12 patients, while Group 2, salvage surgery failure, consisted of 20 patients who required further treatment post-salvage. Each patient was required to have a minimum of 6 months follow-up after their salvage surgery. Comparative demographics of both groups are detailed in Table 1. No statistically significant differences were found in variables including age, time to salvage surgery, follow-up times, pre-RP PSA, body mass index (BMI), surgical margins, pathological stage (p-stage), Gleason Grade Group (pGGG), or mortality rates between the salvage surgery success and failure groups. On average, patients had a follow-up of 38.76 months (SD: 19.46) following salvage surgery. Of note, a single mortality case was recorded in this cohort, occurring in the salvage surgery failure group due to complications from prostate cancer bone metastasis.

Additional analysis using independent comparison of means was performed to identify differences in the primary and secondary variables between the salvage surgery success and failure groups. The analysis demonstrated no statistically significant differences in these variables between the two groups, including the rate of PSADT over the year prior to the salvage operation ($p=0.433$), instantaneous pre-salvage PSADT rate ($p=0.667$), pre-salvage PSADT ($p=0.207$), pre-salvage PSA ($p=0.438$), and post-salvage PSADT ($p=0.961$; Table 2). Figure 4 presents a stacked histogram illustrating the distributions of the average PSADT rate over the one-year period prior to salvage surgery, stratified by treatment status.

Salvage Surgery		**Success**	**Failure**	
		Count (%)	**Count (%)**	
N, all patients		12 (37.5%)	20 (62.5%)	
		Mean (SD)	**Mean (SD)**	**p-value**
Age at RP, years		62.0 (4.5)	64.2 (5.1)	0.239
Age at Salvage, years		68.4 (4.0)	67.8 (5.9)	0.782
Time to Salvage, months		76.2 (52.6)	44.1 (46.2)	0.081
Follow Up post-RP, months		109.5 (64.9)	86.1 (53.3)	0.277
Follow Up post-Salvage, months		33.3 (22.1)	42.0 (17.4)	0.226
Pre-RP PSA, ng/mL		5.9 (2.8)	10.5 (7.9)	0.062
BMI		27.7 (3.2)	27.2 (4.1)	0.736
Margins		3 (25.0%)	5 (25.0%)	1.000
p-stage				
	pT2	4 (33.3%)	6 (30.0%)	0.844
	pT3/pT4	8 (66.7%)	14 (70.0%)	
Gleason Grade Group				0.271
	1	1 (8.3%)	0 (0.0%)	
	2	3 (25.0%)	2 (10.0%)	
	3	5 (41.7%)	9 (45.0%)	
	4	2 (16.7%)	2 (10.0%)	
	5	1 (8.3%)	7 (35.0%)	
PCSM		0 (0.0%)	1 (5.0%)	0.431
Overall Mortality		0 (0.0%)	1 (5.0%)	0.431

RP: radical prostatectomy; PSA: prostate-specific antigen; BMI: body mass index; p-stage: pathological stage; PCSM: prostate cancer-specific mortality.

Table 1. *Demographics of salvage surgery success (N=12) and failure (N=20) groups.*

Salvage Surgery	Success	Failure	
	Count (%)	**Count (%)**	
N, all patients	12 (37.5%)	20 (62.5%)	
	Mean (SD)	**Mean (SD)**	**p-value**
1-year pre-Salvage PSADT Rate	-0.01 (0.22)	-0.12 (0.44)	0.433
Instantaneous pre-Salvage PSADT Rate	-0.13 (0.55)	-0.06 (0.37)	0.667
pre-Salvage PSADT	14.45 (12.80)	9.73 (8.02)	0.207
pre-Salvage PSA	2.02 (1.50)	2.60 (2.23)	0.438
post-Salvage PSADT Rate	-0.26 (5.92)	-0.18 (1.54)	0.961

PSADT: prostate-specific antigen doubling time

Table 2. *Primary and secondary variables compared between salvage surgery success (N=12) and failure (N=20) groups.*

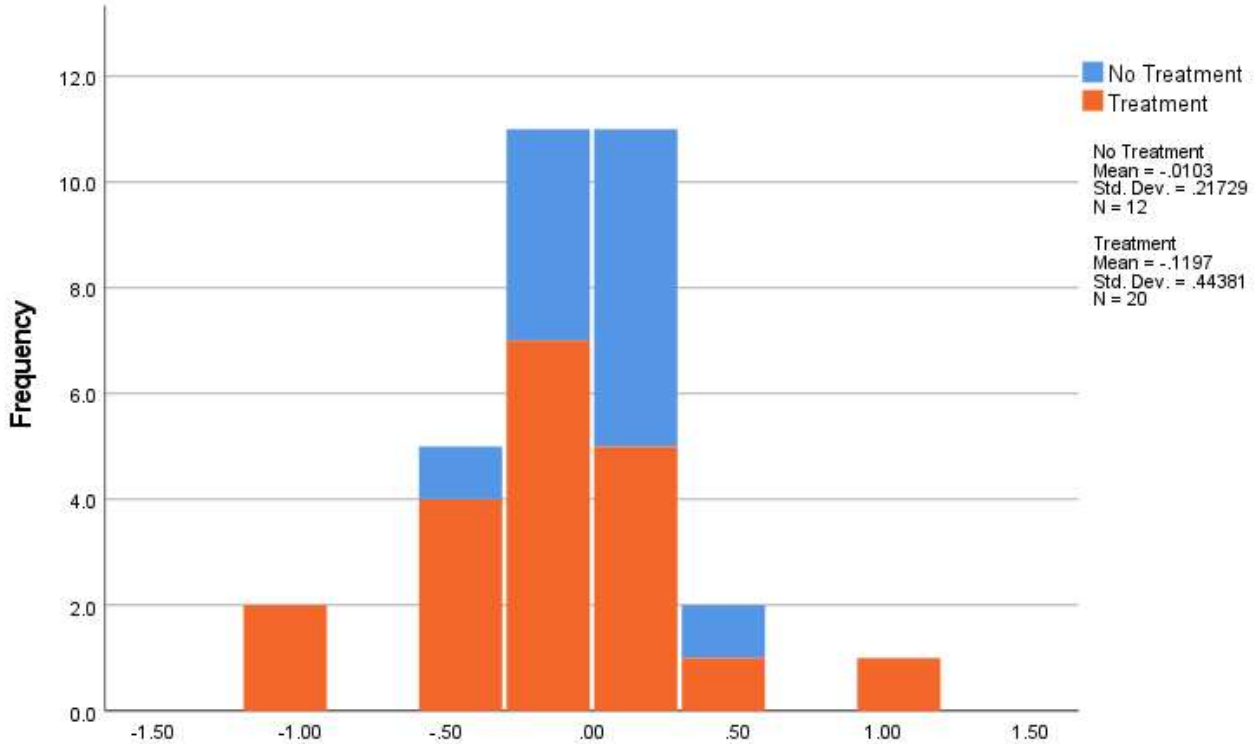


Figure 4*. Stacked histogram illustrating the distributions of the average PSADT rate in the year leading up to salvage surgery, stratified by treatment status.*

Predictors of Salvage Surgery Success

In order to identify the predictive factors for salvage surgery success, defined as no requirement for subsequent ADT, HT, or RT treatments, we assessed our primary and secondary variables which evaluate various aspects of PSA kinetics using univariate regression analyses. We also included multiple combinations of these variables in multivariate models, culminating in a comprehensive multivariate model that incorporated all variables.

None of the primary or secondary variables achieved statistical significance in predicting salvage surgery success following univariate linear regression analysis, including the rate of PSADT over the year prior to the salvage operation ($p=0.433$), instantaneous pre-salvage PSADT rate ($p=0.667$), pre-salvage PSADT ($p=0.207$), pre-salvage PSA ($p=0.438$), and post-salvage PSADT ($p=0.961$; Table 3).

Multivariate models were subsequently established, with Model 1 incorporating pre-salvage PSA and instantaneous pre-salvage PSADT rate, Model 2 including pre-salvage PSADT and instantaneous pre-salvage PSADT rate, Model 3 consisting of pre-salvage PSA and pre-salvage PSADT, and Model 4 including pre-salvage PSA, pre-salvage PSADT, and instantaneous pre-salvage PSADT rate. A comprehensive final model was developed, encompassing all secondary variables. Despite these combinations, none of the multivariate models emerged as significant predictors of successful salvage surgery. Detailed results of these models are presented in Table 4.

Model	Variable	R Square	p-value
Univariate Models	1-year pre-Salvage PSADT Rate	0.021	0.433
	Instantaneous pre-Salvage PSADT Rate	0.006	0.667
	pre-Salvage PSADT	0.052	0.207
	pre-Salvage PSA	0.020	0.438
	post-Salvage PSADT Rate	0.000	0.961

Table 3. *Univariate linear regression analyses of primary and secondary variables in predicting salvage surgery success.*

Model	Variable	R Square	p-value
Final Model	Instantaneous pre-Salvage PSADT Rate	0.052	0.866
	pre-Salvage PSADT		
	pre-Salvage PSA		
	post-Salvage PSADT Rate		
Model 1	pre-Salvage PSA	0.032	0.629
	Instantaneous pre-Salvage PSADT Rate		
Model 2	pre-Salvage PSADT	0.058	0.419
	Instantaneous pre-Salvage PSADT Rate		
Model 3	pre-Salvage PSA	0.068	0.359
	pre-Salvage PSADT		
Model 4	pre-Salvage PSA	0.078	0.509
	pre-Salvage PSADT		
	Instantaneous pre-Salvage PSADT Rate		

Table 4. *Multivariate linear regression models for predicting salvage surgery success.*

Predictors of Time to Treatment post-Salvage Surgery

A subset analysis was performed on patients who experienced unsuccessful salvage surgery and subsequently required further intervention in the form of ADT, HT, or RT (N=20). The objective of this analysis was to predict the time interval between the salvage surgery and the initiation of the next treatment phase. This was performed by using the same variable assignments in the univariate and multivariate linear regression models as those in the previous section. No statistically significant predictors of time to post-salvage treatment were identified in either the univariate (Table 5) or the multivariate (Table 6) analyses.

Model	Variable	R Square	p-value
Univariate Models	1-year pre-Salvage PSADT Rate	0.005	0.763
	Instantaneous pre-Salvage PSADT Rate	0.016	0.600
	pre-Salvage PSADT	0.045	0.849
	pre-Salvage PSA	0.012	0.646
	post-Salvage PSADT Rate	0.010	0.713

Table 5. *Univariate linear regression analyses of primary and secondary variables in predicting time to post-salvage treatment.*

Model	Variable	R Square	p-value
Final Model	Instantaneous pre-Salvage PSADT Rate pre-Salvage PSADT pre-Salvage PSA post-Salvage PSADT Rate	0.245	0.500
Model 1	pre-Salvage PSA Instantaneous pre-Salvage PSADT Rate	0.033	0.754
Model 2	pre-Salvage PSADT Instantaneous pre-Salvage PSADT Rate	0.016	0.875
Model 3	pre-Salvage PSA pre-Salvage PSADT	0.015	0.877
Model 4	pre-Salvage PSA pre-Salvage PSADT Instantaneous pre-Salvage PSADT Rate	0.033	0.908

Table 6. *Multivariate linear regression models for predicting time to post-salvage treatment.*

IV. DISCUSSION

PSA Kinetics and Salvage Surgery

This study investigated the potential utility of multiple aspects of PSA kinetics in the prediction of success of salvage surgeries post-RARP. PSA kinetics in the context of salvage surgeries has not been extensively studied in literature. Our cohort of 32 BCR patients underwent salvage surgery, in the form of a sPLND or sPMR, and were subsequently stratified into two categories: salvage surgery success (no need for subsequent treatments) and failure (need for further treatment). We initially hypothesized that significant correlations between PSA kinetics and successful salvage surgery outcomes would be identified, and ultimately serve as novel predictive biomarkers.

Comparing patient demographics between the two groups, we found there were no significant differences in any pre- and post-operative variables (Table 1). This suggests that there was a relatively uniform baseline between the two groups, thus minimizing potential confounding variables that could influence subsequent analyses. Initial comparison of our primary independent variable, the average PSADT rate across the one-year period pre-salvage surgery, and secondary variables, assessing multiple dimensions of PSA kinetics, between the success and failure groups yielded no statistically significant differences between the two groups (Table 2).

To determine the predictive power of PSA kinetics for successful salvage surgery, we utilized univariate and multivariate linear regression analyses with our primary and secondary independent variables. This included the average PSADT rate of change over the one-year period before salvage surgery, instantaneous PSADT rate of change pre-salvage, pre-salvage PSADT, pre-salvage PSA, and PSADT rate of change post-salvage. Each of these

variables were selected to represent multiple dimensions of PSA kinetics based on literature and expert opinion.

None of the univariate or the multivariate regression models demonstrated statistical significance in predicting salvage surgery success (Table3-4). Thus, our study failed to reject the null hypothesis. Subset analysis of patients in the failure group who required further intervention was conducted to determine the predictive ability of these regression models in regard to time to post-salvage ADT, HT, and/or RT. Once again, we found that our selected variables did not have the anticipated predictive power.

Limitations

A limitation of this study is the retrospective design. Despite the extensive criteria for patient selection, there is room for potential selection bias and information bias. As there were no random assignments to groups, decisions to receive treatment post-salvage surgery (the primary outcome used to determine success of salvage surgery) were primarily based on oncology guidelines and physician judgement.

Another limitation of this study regards our primary outcome of salvage surgery success or failure - the need for additional treatment post-salvage. Post-treatment PCSM and overall mortality rates are agreed to be better measures when assessing treatment success or failure. However, within the context of our study, there was only one mortality in our cohort, which would weaken the applicability of any subsequent regression analyses. Regardless, the need for subsequent treatment is important when determining the efficacy of a treatment modality. Given the relatively low PCSM rates within the first decade post-prostate cancer diagnosis, financial and patient quality of life outcomes become more

important. The need for further treatment can significantly interfere with patient quality of life and worsen associated financial burdens. Therefore, defining the success of salvage surgery based on the lack of need for additional treatment can be used as an indicator of favorable oncological and quality of life outcomes.

A critical limitation of this study is the small sample size of our study cohort. There were 12 patients in the salvage surgery success group, and 20 in the failure group. An independent sample means power analysis was conducted to determine the sample size needed to achieve adequate power. Given the observed mean difference of 0.109 between our two groups, 153 patients would be required in each arm (N=306) at a power of 80% to observe statistical significance. Therefore, our study is severely underpowered, with a total sample size of 32 patients.

Future Directions

Larger, prospective, multi-center studies would be needed to further investigate the role of PSA kinetics in predicting salvage surgery success. This would directly address the sample size limitation in the current study, as well as allow for more comprehensive analyses with a larger, more diverse dataset. Additionally, the present study opens the doors for future work that can incorporate advanced statistical and computational tools that integrate artificial intelligence and machine learning. Such tools can analyze large and complicated datasets, and build multidimensional models that can identify complex patterns that are not easily discernable with conventional statistical tools. Integration of such a tool would allow for patient-oriented modeling that could potentially provide

patient-specific predictions, which may greatly enhance treatment outcomes and decision-making.

Finally, in a recent study by Huang et al., PSADT kinetics were utilized to determine need for treatment following RARP, and identify a group of patients that could be safely observed without treatment [35,36]. Their study revealed that the direction of PSADT change (either increasing or decreasing) was a strong predictor for the necessity of treatment. Specifically, an increasing PSADT was identified as a strong indicator for no need for treatment. However, the specific threshold where a decreasing PSADT necessitates intervention remains unclear. Given this context, the quantification and application of PSADT rates of change, as performed in our current study, could be helpful in defining this threshold for patients with decreasing PSADTs. This approach could enhance our understanding of patient subsets that can be safely monitored without treatment post-RP and serve as a tool to aid treatment decision-making.

V. SUMMARY AND CONCLUSIONS

This study aimed to assess the predictive utility of PSADT kinetics for salvage surgery success following RP. Our cohort consisted of 32 patients who experienced a BCR post-RARP and underwent salvage surgery in the form of a sPLND or sPMR. Our univariate and multivariate regression models did not identify any statistically significant predictors of salvage surgery success or time to subsequent treatment post-salvage. Regardless, this study contributes to the ongoing discussion regarding the complexities and challenges of using PSA kinetics to predict therapeutic outcomes. Future studies with larger, more diverse cohorts that incorporate advanced analytical tools are warranted.

REFERENCES

1. Key Statistics for Prostate Cancer | Prostate Cancer Facts [Internet]. [cited 2023 Jul 3]. Available from: https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html

2. Pianou NK, Stavrou PZ, Vlontzou E, Rondogianni P, Exarhos DN, Datseris IE. More advantages in detecting bone and soft tissue metastases from prostate cancer using 18F-PSMA PET/CT. Hell J Nucl Med. 2019;22(1):6–9.

3. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med. 2018 Dec 13;379(24):2319–29.

4. Sooriakumaran P, Pini G, Nyberg T, Derogar M, Carlsson S, Stranne J, et al. Erectile Function and Oncologic Outcomes Following Open Retropubic and Robot-assisted Radical Prostatectomy: Results from the LAParoscopic Prostatectomy Robot Open Trial. Eur Urol. 2018 Apr;73(4):618–27.

5. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol. 2019 Jun;75(6):967–87.

6. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017 Apr;71(4):630–42.

7. Eggener SE, Scardino PT, Walsh PC, Han M, Partin AW, Trock BJ, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol. 2011 Mar;185(3):869–75.

8. von Bodman C, Godoy G, Chade DC, Cronin A, Tafe LJ, Fine SW, et al. Predicting biochemical recurrence-free survival for patients with positive pelvic lymph nodes at radical prostatectomy. J Urol. 2010 Jul;184(1):143–8.

9. Briganti A, Blute ML, Eastham JH, Graefen M, Heidenreich A, Karnes JR, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol. 2009 Jun;55(6):1251–65.

10. Joslyn SA, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. Urology. 2006 Jul;68(1):121–5.

11. Masterson TA, Bianco FJ, Vickers AJ, DiBlasio CJ, Fearn PA, Rabbani F, et al. The association between total and positive lymph node counts, and disease progression in clinically localized prostate cancer. J Urol. 2006 Apr;175(4):1320–4; discussion 1324-1325.

12. Bhatta-Dhar N, Reuther AM, Zippe C, Klein EA. No difference in six-year biochemical failure rates with or without pelvic lymph node dissection during radical prostatectomy in low-risk patients with localized prostate cancer. Urology. 2004 Mar;63(3):528–31.

13. Weight CJ, Reuther AM, Gunn PW, Zippe CR, Dhar NB, Klein EA. Limited pelvic lymph node dissection does not improve biochemical relapse-free survival at 10 years after radical prostatectomy in patients with low-risk prostate cancer. Urology. 2008 Jan;71(1):141–5.

14. Berglund RK, Sadetsky N, DuChane J, Carroll PR, Klein EA. Limited pelvic lymph node dissection at the time of radical prostatectomy does not affect 5-year failure rates for low, intermediate and high risk prostate cancer: results from CaPSURE. J Urol. 2007 Feb;177(2):526–9; discussion 529-530.

15. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. [cited 2023 Mar 10]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/Prostate.pdf

16. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol. 2003 Nov;170(5):1798–803.

17. Eastham JA, Boorjian SA, Kirkby E. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. J Urol. 2022 Sep;208(3):505–7.

18. Mattei A, Fuechsel FG, Bhatta Dhar N, Warncke SH, Thalmann GN, Krause T, et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol. 2008 Jan;53(1):118–25.

19. Badani KK, Reddy BN, Moskowitz EJ, Paulucci DJ, Beksac AT, Martini A, et al. Lymph node yield during radical prostatectomy does not impact rate of biochemical recurrence in patients with seminal vesicle invasion and node-negative disease. Urol Oncol. 2018 Jun;36(6):310.e1-310.e6.

20. Altok M, Chapin BF, Matin SF, Achim MF, Gregg JR, Davis JW. Therapeutic Consequences of Omitting a Pelvic Lymph Node Dissection at Radical Prostatectomy when Grade and/or Stage Increase. Urology. 2021 Sep;155:144–51.

21. Lestingi JFP, Guglielmetti GB, Trinh QD, Coelho RF, Pontes J, Bastos DA, et al. Extended Versus Limited Pelvic Lymph Node Dissection During Radical Prostatectomy for Intermediate- and High-risk Prostate Cancer: Early Oncological Outcomes from a Randomized Phase 3 Trial. Eur Urol. 2021 May;79(5):595–604.

22. Touijer KA, Sjoberg DD, Benfante N, Laudone VP, Ehdaie B, Eastham JA, et al. Limited versus Extended Pelvic Lymph Node Dissection for Prostate Cancer: A Randomized Clinical Trial. Eur Urol Oncol. 2021 Aug;4(4):532–9.

23. Briganti A, Chun FKH, Salonia A, Suardi N, Gallina A, Da Pozzo LF, et al. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol. 2006 Nov;50(5):1006–13.

24. Stone NN, Stock RG, Unger P. Laparoscopic pelvic lymph node dissection for prostate cancer: comparison of the extended and modified techniques. J Urol. 1997 Nov;158(5):1891–4.

25. Kawakami J, Meng MV, Sadetsky N, Latini DM, Duchane J, Carroll PR, et al. Changing patterns of pelvic lymphadenectomy for prostate cancer: results from CaPSURE. J Urol. 2006 Oct;176(4 Pt 1):1382–6.

26. Abdollah F, Sun M, Thuret R, Karakiewicz PI. Should all men having a radical prostatectomy have a pelvic lymph node dissection? No. Can Urol Assoc J. 2010 Dec;4(6):425–6.

27. Bolton D, Hong A, Papa N, Perera M, Kelly B, Duncan C, et al. Cribriform pattern disease over-represented in pelvic lymph node metastases identified on 68GA PSMA-PET/CT. BJUI Compass. 2022 Sep;3(5):371–6.

28. Tilki D, Mandel P, Seeliger F, Kretschmer A, Karl A, Ergün S, et al. Salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy. J Urol. 2015 Feb;193(2):484–90.

29. Ploussard G, Gandaglia G, Borgmann H, de Visschere P, Heidegger I, Kretschmer A, et al. Salvage Lymph Node Dissection for Nodal Recurrent Prostate Cancer: A Systematic Review. Eur Urol. 2019 Oct;76(4):493–504.

30. Matsumoto K, Niwa N, Hagiwara M, Kosaka T, Tanaka N, Takeda T, et al. Type of patients in whom biochemical recurrence after radical prostatectomy can be observed without salvage therapy. World J Urol. 2020 Jul;38(7):1749–56.

31. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA. 2008 Jun 18;299(23):2760–9.

32. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA. 2005 Jul 27;294(4):433–9.

33. Howard LE, Moreira D, De Hoedt A, Aronson WJ, Kane CJ, Amling CL, et al. Cut-points for PSA doubling time in men with non-metastatic castration-resistant prostate cancer. BJU Int. 2017 Nov;120(5B):E80–6.

34. Ahlering TE, Skarecky DW. Long-term outcome of detectable PSA levels after radical prostatectomy. Prostate Cancer Prostatic Dis. 2005;8(2):163–6.

35. Huang E, Huynh LM, Tran J, Gordon AM, Chandhoke R, Morales B, et al. Active Observation of Biochemical Recurrence without Treatment following Radical Prostatectomy: Long-Term Analysis of Outcomes. Cancers (Basel). 2022 Aug 23;14(17):4078.

36. Huang E, Tran J, Huynh LM, Skarecky D, Wilson RH, Ahlering T. Prostate-Specific Antigen Doubling Time Kinetics following Radical Prostatectomy to Guide Need for Treatment Intervention: Validation of Low-Risk Recurrences. Cancers (Basel). 2022 Aug 24;14(17):4087.

37. Brockman JA, Alanee S, Vickers AJ, Scardino PT, Wood DP, Kibel AS, et al. Nomogram Predicting Prostate Cancer-specific Mortality for Men with Biochemical Recurrence After Radical Prostatectomy. Eur Urol. 2015 Jun;67(6):1160–7.

38. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Predicting survival of patients with node-positive prostate cancer following multimodal treatment. Eur Urol. 2014 Mar;65(3):554–62.

39. Bianchi L, Schiavina R, Borghesi M, Bianchi FM, Briganti A, Carini M, et al. Evaluating the predictive accuracy and the clinical benefit of a nomogram aimed to predict survival in node-positive prostate cancer patients: External validation on a multi-institutional database. Int J Urol. 2018 Jun;25(6):574–81.

40. Miyoshi Y, Noguchi K, Yanagisawa M, Taguri M, Morita S, Ikeda I, et al. Nomogram for overall survival of Japanese patients with bone-metastatic prostate cancer. BMC Cancer. 2015 May 1;15:338.

41. Prostate Cancer Nomograms: PSA Doubling Time | Memorial Sloan Kettering Cancer Center [Internet]. [cited 2023 Jul 5]. Available from: https://www.mskcc.org/nomograms/prostate/psa_doubling_time