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Avoiding Overtreatment in Prostate Cancer Recurrence Post-Radical Prostatectomy with PSA Doubling Time:

A 10-Year Follow-Up of Outcomes

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Financial Disclosure

I do not have any relationships to report with ACGME defined ineligible companies.

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals.

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Background:

- Following RARP, GUIDELINES, sometimes suggest immediate treatment intervention (Adjuvant) based on pathologic findings or following PSA recurrence (Salvage)
- BCR = PSA ≥0.2ng/ml twice
- **BCR is a limited predictor** of prostate cancer progression and mortality. (Remmers et al.)

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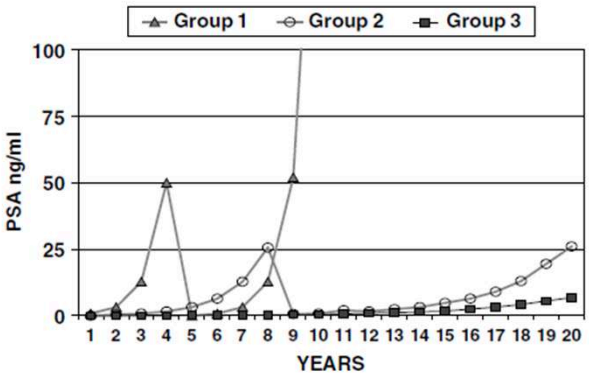
Introduction

- **PSA doubling time (PSADT)** has been widely used to predict tumor progression after a BCR
- Aids the counseling of secondary treatment and assessing risk of metastasis or cancer mortality. (D'Amico et al, 1993)
- More men will die WITH prostate cancer and NOT of it"



Ahlering and Skarecky, 2005
Prostate Cancer and Prostatic Diseases, (Nature)

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Previous Publication:

- (Cancers Journal, 2022) – Looking at the impact of PSADT in determining need for secondary treatment.
  - 1 out of 3 men with BCRs are either benign or have minimal prostate cancer mortality risk.
    - ADT/RT initiation was best based on PSADT kinetics over surgical pathology

Simple Summary

This observational study on 407 patients experiencing biochemical recurrence (BCR) following radical prostatectomy (RP) reveals that 33% of men were managed with active observation without risk of prostate-related death (0%), at an average of 7.5 years follow-up. These findings support that a significant portion of men following RP develop a benign recurrence that does not require treatment intervention.

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Study Objective:

- Retrospective study, extending follow-up time to 9-21 years of cancer progression
- Investigate RARP BCR patients who did not undergo castrating ADT/RT compared to those that had treatment

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Database Utilized

Our database is an approved institutional review board protocol at the **University of California. Irvine USA (HS#1998-84).** Data collection and storage was conducted properly in accordance with the Health Insurance Portability and Accountability Act with informed consent given to patients.

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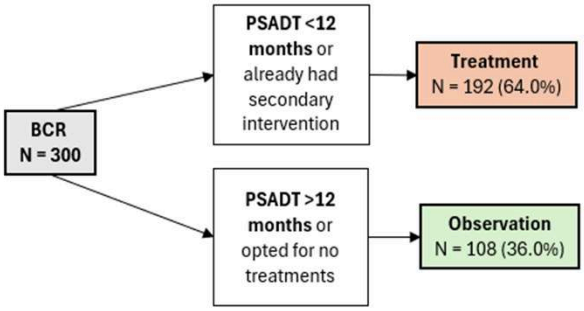
Patients & Methods

- 1455 patients underwent a RARP (2002 through 2015) under a single surgeon
  - 300 had a BCR.
- Separated into two groups based on their initial PSADT at time of BCR.



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Collection Methods:

- PSA observation began 8 weeks post-surgery.
- PSADT are obtained after 3-4 detectable PSAs are inputted onto a formula sheet

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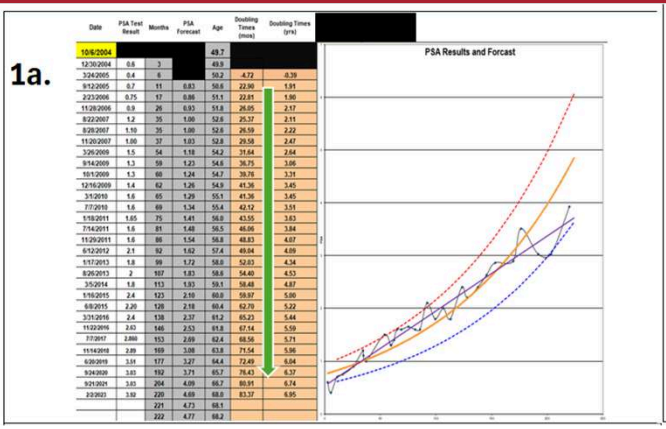
PSA Doubling Time:

1a.



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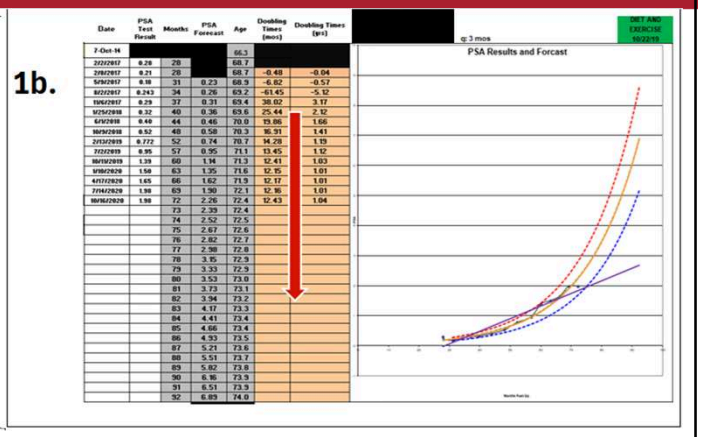

- **Increasing PSADT:** 22.9 to 83.4 mos
  - Slower growth, indolent disease
- **Decreasing PSADT:** 38.02 to 12.43 mos
  - Faster growth, more aggressive

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PSA Doubling Time:

	Date	PSA Test Result	Months	PSA Forecast	Age	Doubling Times (mos)	
Surgery Date	13-Jul-21				121.6		
PSA Tests	9/30/2021	0.05	3		121.8		
	4/6/2022	0.13	9		122.3	3.21	0.27
	8/12/2022	0.19	13	0.16	122.7	5.13	0.43
	10/7/2022	0.24	15	0.17	122.9	5.68	0.47
Enter:	11/23/2022	0.13	16	0.17	123.0	8.32	0.69
Date of Birth	2/16/2023	0.25	19	0.18	123.2	8.72	0.73
Test date/PSA	4/27/2023	0.24	21	0.18	123.4	9.81	0.82
Forecast interval	8/23/2023	0.24	25	0.19	123.7	11.91	0.99
	11/7/2023	0.26	28	0.20	123.9	13.63	1.14
Forecast	4/3/2024	0.17	33	0.22	124.4	20.82	1.74
Interval	7/3/2024	0.29	36	0.23	124.6	21.89	1.82
0	2/27/2025	0.230	44	0.25	125.2	29.02	2.42
	3/4/2026	0.20	56	0.30	126.3	47.23	3.94
			56	0.30	126.3		
Birth Date			56	0.30	126.3		
			56	0.31	126.3		
Date Last Updated:			56	0.31	126.3		
			56	0.31	126.3		
			56	0.31	126.3		
			56	0.31	126.3		
			56	0.31	126.3		
			57	0.31	126.3		
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			57	0.31	126.4		
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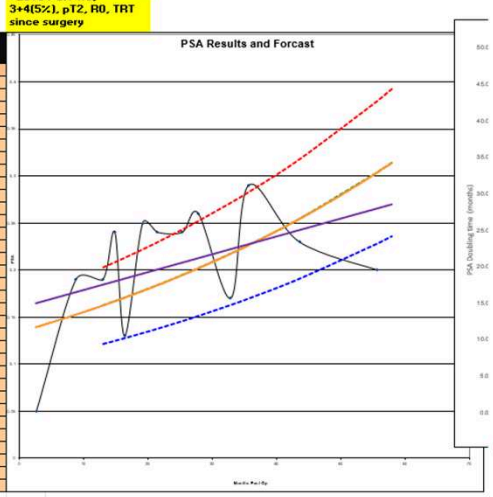
			57	0.31	126.4		
			57	0.31	126.4		
			58	0.31	126.4		
			58	0.31	126.4		
			58	0.31	126.4		
			58	0.31	126.4		
			58	0.31	126.4		

#2073 PSA 4.6, 3+4(5%), pT2, R0, TRT since surgery



- **Increasing PSADT:** 28 to 47.2 months
- Slower growth, indolent disease

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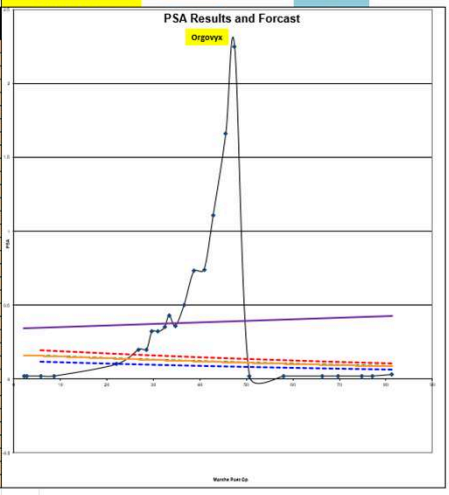
PSA Doubling Time:

Version 2.4.2 corrects excel 365 issue	Date	PSA Test Result	Months	PSA Forecast	Age	Doubling Times (mos)	Doubling Times (yrs)
Surgery Date	5/1/2019				63.2		
PSA Tests	7/8/2019	0.02	2		63.4		
	7/25/2019	0.02	3		63.4	#DIV/0!	#DIV/0!
	10/25/2019	0.02	6	0.16	63.7	#DIV/0!	#DIV/0!
	1/22/2020	0.02	9	0.15	63.9	#DIV/0!	#DIV/0!
Enter:	3/3/2021	0.1	22	0.14	65.0	9.25	0.69
Date of Birth	7/27/2021	0.2	27	0.13	65.4	7.23	0.60
Test date/PSA	9/15/2021	0.20	29	0.13	65.6	7.22	0.60
Forecast interval	10/20/2021	0.32	30	0.13	65.7	6.86	0.57
	11/30/2021	0.32	31	0.13	65.8	6.78	0.56
Forecast	1/11/2022	0.35	32	0.13	65.9	6.76	0.56
Interval	2/10/2022	0.43	33	0.12	66.0	6.69	0.56
0	3/22/2022	0.36	35	0.12	66.1	6.79	0.57
	5/18/2022	0.50	37	0.12	66.2	6.80	0.57
	7/21/2022	0.73	39	0.12	66.4	6.74	0.56
Birth Date	9/26/2022	0.74	41	0.12	66.6	6.78	0.57
3/12/1956	11/25/2022	1.11	43	0.12	66.8	6.74	0.56
Date Last Updated:	2/15/2023	1.66	46	0.11	67.0	6.65	0.55
10/15/2025 EH	4/14/2023	2.25	47	0.11	67.1	6.55	0.55
	7/20/2023	0.0199	51	0.11	67.4	9.61	0.72
	2/28/2024	0.0199	58	0.10	68.0	12.71	1.06
	11/7/2024	0.0199	66	0.10	68.7	22.15	1.85
	2/18/2025	0.0199	70	0.09	69.0	44.79	3.73
	7/25/2025	0.0199	75	0.09	69.4	175.45	14.62
	9/29/2025	0.0199	77	0.09	69.6	-179.78	-14.98
	2/4/2026	0.03	81	0.08	69.9	-85.05	-7.09
			81	0.08	69.9		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		
			81	0.08	70.0		

RB# 1849; Pre-PSA 5.1; pGG 4+5; pT3a; R0

PSMA 3/8/22 (-)



PSMA 9-8-22

1. No definite radiotracer avid disease.
2. Streak artifact from right hip arthroplasty as well as intense physiologic urinary bladder activity limits evaluation of prostatectomy surgical bed although no definite areas of increased focal activity are identified
3. Faint activity and sclerosis of the right anterior third rib is nonspecific and likely represents a benign lesion such as fibrous dysplasia. Note that the sclerosis was present on prior CT chest of 4/22/19

- **Decreasing PSADT:** 6 months
- Treated with ADT and PSA went down to undetectable level

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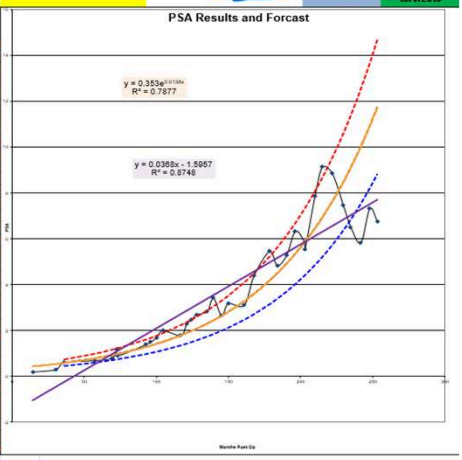
PSA Doubling Time:

Version 2.4.2 corrects excel 365 issue	Date	PSA Test Result	Months	PSA Forecast	Age	Doubling Times (mos)	Doubling Times (yrs)
Surgery Date	2/22/2005				60.1		
PSA Tests	5/10/2006	0.2	15		61.3		
	8/28/2007	0.3	30		62.6	26.69	2.22
	2/27/2008	0.6	36	0.58	63.1	15.13	1.26
	12/3/2009	0.7	57	0.78	64.9	22.89	1.91
Enter:	12/6/2010	0.8	69	0.92	65.9	27.68	2.31
Date of Birth	3/10/2011	1.2	73	0.96	66.2	25.85	2.15
Test date/PSA	3/23/2011	0.9	73	0.97	66.2	27.16	2.26
Forecast interval	11/20/2012	1.4	93	1.28	67.9	28.90	2.41
	2/21/2013	1.5	96	1.33	68.1	29.76	2.48
Forecast Interval	6/27/2013	1.7	100	1.41	68.5	30.10	2.51
0	11/5/2013	2.0	104	1.50	68.8	29.99	2.50
	11/19/2014	1.8	117	1.78	69.9	32.04	2.67
	3/24/2015	2.3	121	1.88	70.2	32.65	2.72
	7/1/2015	2.47	124	1.97	70.5	33.06	2.75
Birth Date	10/13/2015	2.690	128	2.07	70.8	33.30	2.77
1/26/1945	5/27/2016	2.840	135	2.29	71.4	33.88	2.82
Date Last Updated:	10/4/2016	3.420	139	2.43	71.7	33.97	2.83
4/1/26 JV	3/28/2017	2.650	145	2.63	72.2	35.35	2.95
	8/14/2017	3.180	150	2.81	72.6	36.16	3.01
	7/17/2018	3.11	161	3.27	73.5	37.75	3.15
	2/7/2019	4.39	168	3.59	74.1	38.25	3.19
	12/30/2019	5.45	178	4.16	75.0	38.60	3.22
	6/15/2020	4.84	184	4.49	75.4	39.59	3.30
	12/29/2020	5.30	190	4.92	76.0	40.48	3.37
	6/30/2021	6.340	196	5.34	76.5	40.96	3.41
	1/14/2022	5.83	203	5.85	77.0	41.93	3.49
	1/18/2022	5.550	203	5.86	77.0	42.84	3.57
	8/16/2022	7.860	210	6.44	77.6	42.99	3.58
	1/19/2023	9.130	215	6.92	78.0	42.95	3.58
	8/18/2023	8.840	222	7.62	78.6	43.26	3.60
	4/4/2024	7.470	229	8.46	79.2	44.22	3.68
	9/11/2024	6.500	235	9.09	79.7	45.58	3.80
	4/8/2025	5.830	242	10.00	80.2	47.33	3.94
	10/14/2025	7.330	248	10.90	80.8	48.58	4.05
	3/25/2026	6.740	253	11.73	81.2	50.08	4.17
PSMA (10/16/23):	PSMA avid changes in the right posterior pelvis concerning for neoplastic process						

RB#: #233 6.3, 3+3, pT2b, R0 [redacted]

PSMA 10/16/23 (-)

DIET AND EXERCISE 10/4/2016



Statistical Analysis:

- ANOVA and chi-squared for categorical variables and t-tests for continuous variables.

- **Kaplan Meiers** curves measured the time to BCR, overall survival, and PCSM.

Demographic Table

	Observation (AO) (N=107)		Treatment (N=192)		P-Value
	Mean	(SD)	Mean	(SD)	
Age at Surgery (yrs)	63.6	(7.4)	63.7	(7.4)	0.9109
Pre-Operative PSA (ng/ml)	7.9	(5.4)	11.4	(11.2)	**0.0026**
BMI (kg/m²)	27.6	(3.9)	27.5	(4.0)	0.8345
SHIM	20.2	(6.5)	18.1	(7.5)	**0.0156**
Prostate Weight (g)	51.7	(21.1)	53.7	(19.4)	0.4084
Total Time of Follow Up (yrs)*	11.3	(4.3)	10.9	(4.4)	0.4481
Time to BCR (yrs)	5.2	(3.4)	3.0	(3.2)	**< 0.001**
Initial PSADT (months)*	35.2	(29.6)	9.2	(9.6)	**< 0.001**
Time to Positive PSMA Scans from Surgery (yrs)	11.1	(3.3)	8.1	(3.7)	**< 0.001**
Time to Positive PSMA Scans from BCR (yrs)	4.8	(3.8)	3.5	(2.8)	**< 0.001**
Age at Death (yrs)	78.5	(6.8)	75.0	(9.4)	**< 0.001**
	N	(%)	N	(%)	
Testosterone Replacement Therapy	20	(18.7)	10	(5.2)	**< 0.001**
Diet & Exercise Regimen	31	(29.0)	19	(9.9)	**< 0.001**
Surgical Margins					**0.0243**
NSM	86	(80.4)	131	(68.2)	
PSM	21	(19.6)	61	(31.8)	
Gleason Grade Group					**< 0.001**
1	17	(15.9)	3	(1.6)	
2	38	(35.5)	45	(23.4)	
3	34	(31.8)	57	(29.7)	
4	6	(5.6)	16	(8.3)	
5	12	(11.2)	71	(37.0)	
Pathological Stage					**0.0217**
pT2	61	(57.0)	58	(30.2)	
pT3/4	46	(43.0)	134	(69.8)	
Mortality Rates					
Overall mortality (OM)	20	(18.7)	48	(25.0)	0.2130
Prostate Cancer Specific Mortality (PCSM)	2	(1.9)	24	(12.5)	**0.0018**

- Median follow-up was 10.7 years.
- **The treatment group had a higher risk of PCSM (12.5% vs 1.9%, p=0.0018).**

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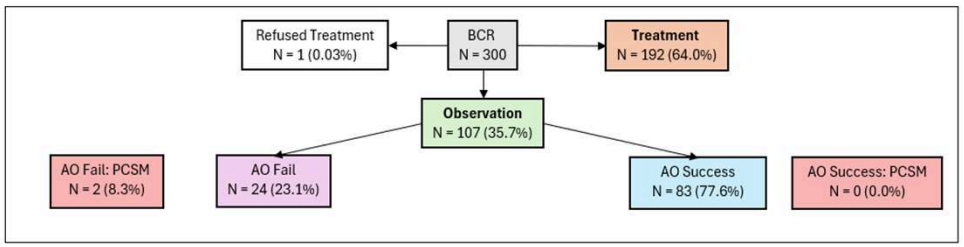
Patients Flow Chart



AO Success = continue through monitoring **without** undergoing definitive treatments

AO Fail = received treatment as **PSADT kinetics later worsened (less than 12 months).**

Demographics within Observation (AO):

	AO Fail (N=24)		AO Success (N=84)		P-Value
	Mean	(SD)	Mean	(SD)	
Age at Surgery (years)	63.5	(8.5)	63.7	(7.1)	0.9076
Pre-Operative PSA (ng/ml)	8.6	(6.9)	7.9	(5.1)	0.5863
BMI (kg/m^2)	28.6	(3.4)	27.3	(4.1)	0.1589
SHIM	20.1	(5.9)	20.3	(6.8)	0.8963
Current PSADT (months) *	17.0	(9.3)	59.4	(94.0)	**0.0300**
Time to BCR (years)	5.1	(3.2)	5.2	(3.5)	0.9002
Time to Positive PSMA Scans from Surgery (yrs)	10.5	(3.9)	11.7	(2.9)	0.1021
Time to Positive PSMA Scans from BCR (yrs)	3.6	(2.9)	5.7	(4.3)	**0.0267**
	N	(%)	N	(%)	
Positive PSMA Scan	13	(54.2)	19	(22.6)	**0.0029**
Surgical Margins					0.3320
NSM	21	(87.5)	66	(78.6)	
PSM	3	(12.5)	18	(21.4)	
Gleason Grade Group					**0.0030**
1-2	6	(25.0)	50	(59.5)	
3-5	18	(75.0)	34	(40.5)	
Pathological Stage					**0.0016**
pT2	7	(29.2)	55	(65.5)	
pT3/4	17	(70.8)	29	(34.5)	
Doubling Time (DT) Kinetics					**0.0102**
Increasing/Stable	11	(45.8)	62	(73.8)	
Decreasing	13	(54.2)	22	(26.2)	
Mortality Rates					
Overall mortality (OM)	2	(8.3)	19	(22.6)	0.1201
Prostate Cancer Specific Mortality (PCSM)	2	(8.3)	1	(1.2)	0.0632

**SHIM = Sexual Health Inventory for Men (measures severity of ED)

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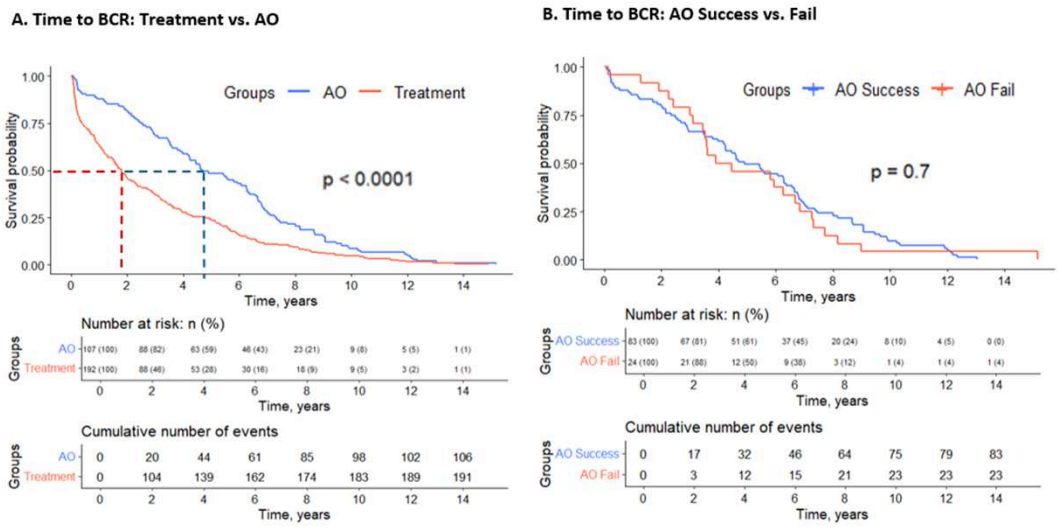
14-year Kaplan Meier of time to BCR



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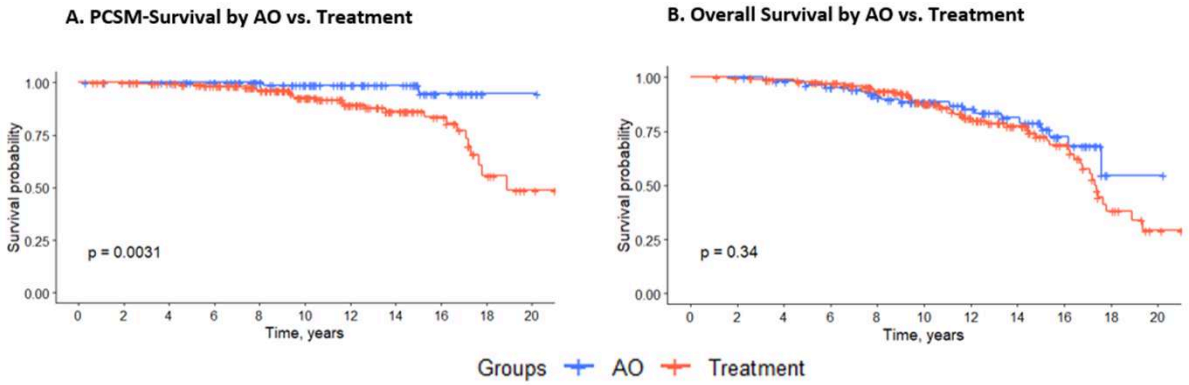
20-year Kaplan Meier of overall survival and PCSM-survival



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Brief Discussion:

- Stable or increasing PSADT in 71.1% of Observation Success patients
  - Suggest **slowed or non-biologically aggressive tumor disease.**
- PSADT <12 months indicates high risk for aggressive progression.

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Clinical Practice: Shared Decision Making

- **36.0% of men with BCR may safely avoid immediate ADT with active observation**
- **Delayed Treatment is reasonable**
- Support decisions to **delay ADT** in select patients

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Clinical Practice: Shared Decision Making

- Educate patients that although **overall PCa survival may differ long-term,** immediate treatment does not always improve early outcomes
- Escalate care (ART/ADT) when **Observation fails or PSA kinetics worsen**.
- Collaborate with urologists and medical oncologists to **trigger timely referral** when progression occurs

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Conclusion

- **36.0% of men with BCR can be managed with patterns of PSADT to guide providers on the need for secondary treatment or intervention**
- This risk-adapted approach will **mitigate RT/ADT overtreatment to preserve quality of life and reduce cost**

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Thank you for listening, any questions?

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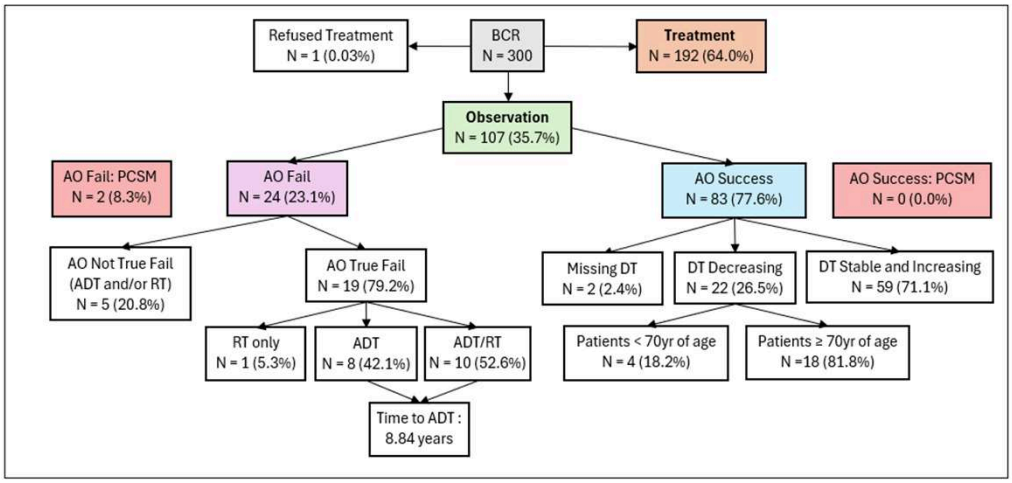
Patients Flow Chart



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