Medical Therapy to Keep Men on Active Surveillance

Michael Schweizer, MD

Associate Professor
University of Washington &
Fred Hutchinson Cancer Research Center

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Outline

- Prostate cancer biology
- Background
- Local Management
- Medical therapy in active surveillance

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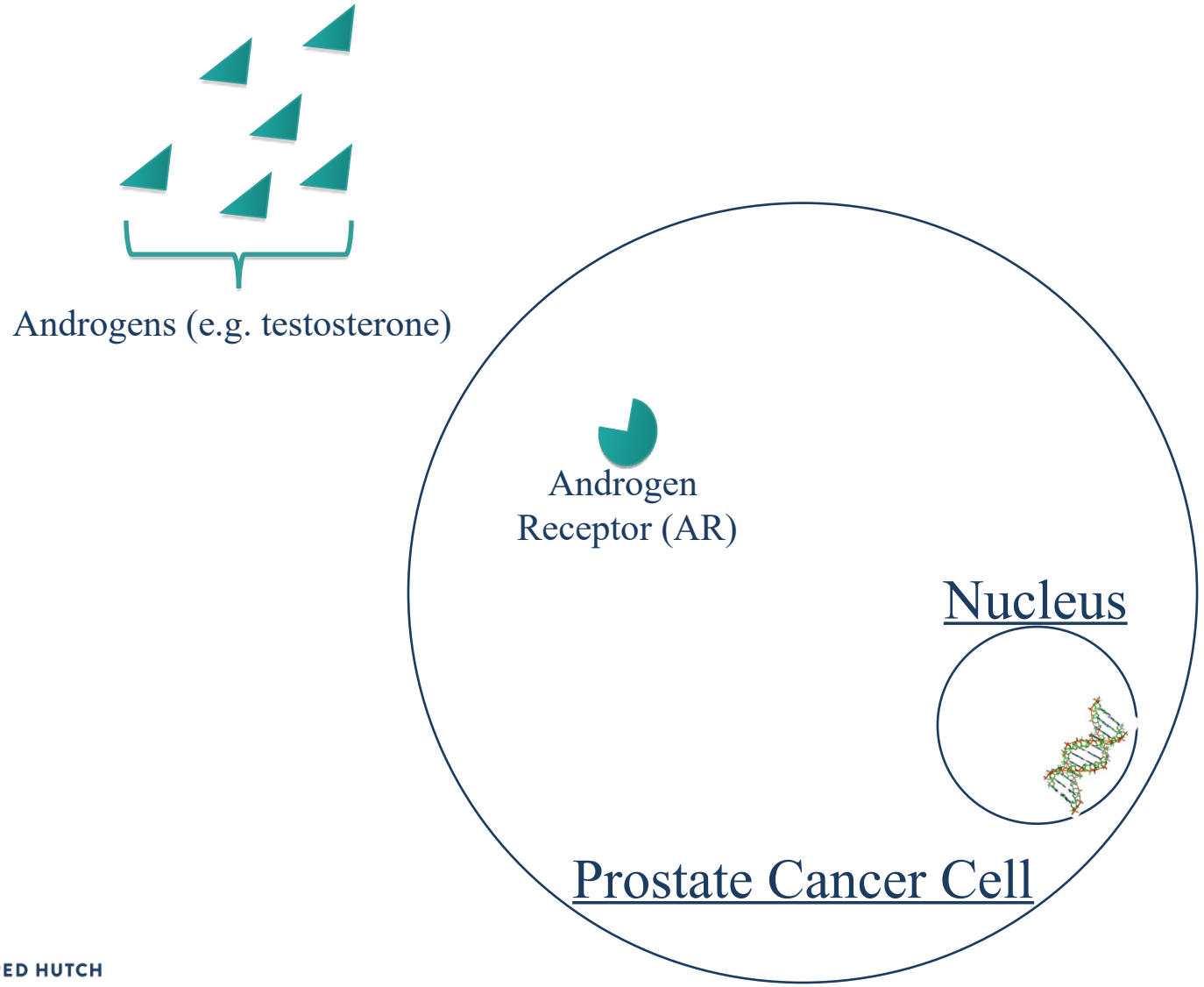
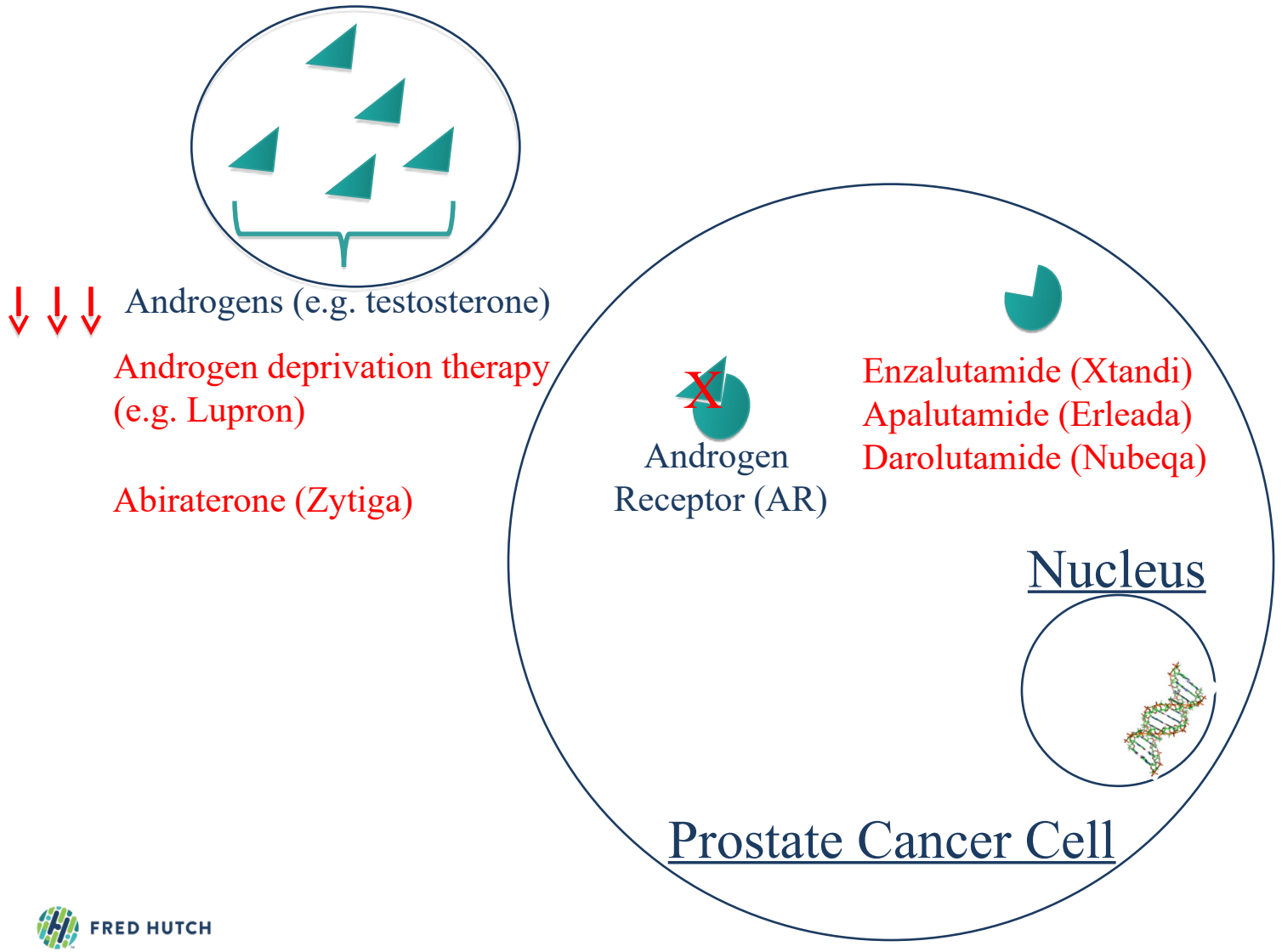
Almost all prostate cancers are addicted to testosterone and other male sex hormones...

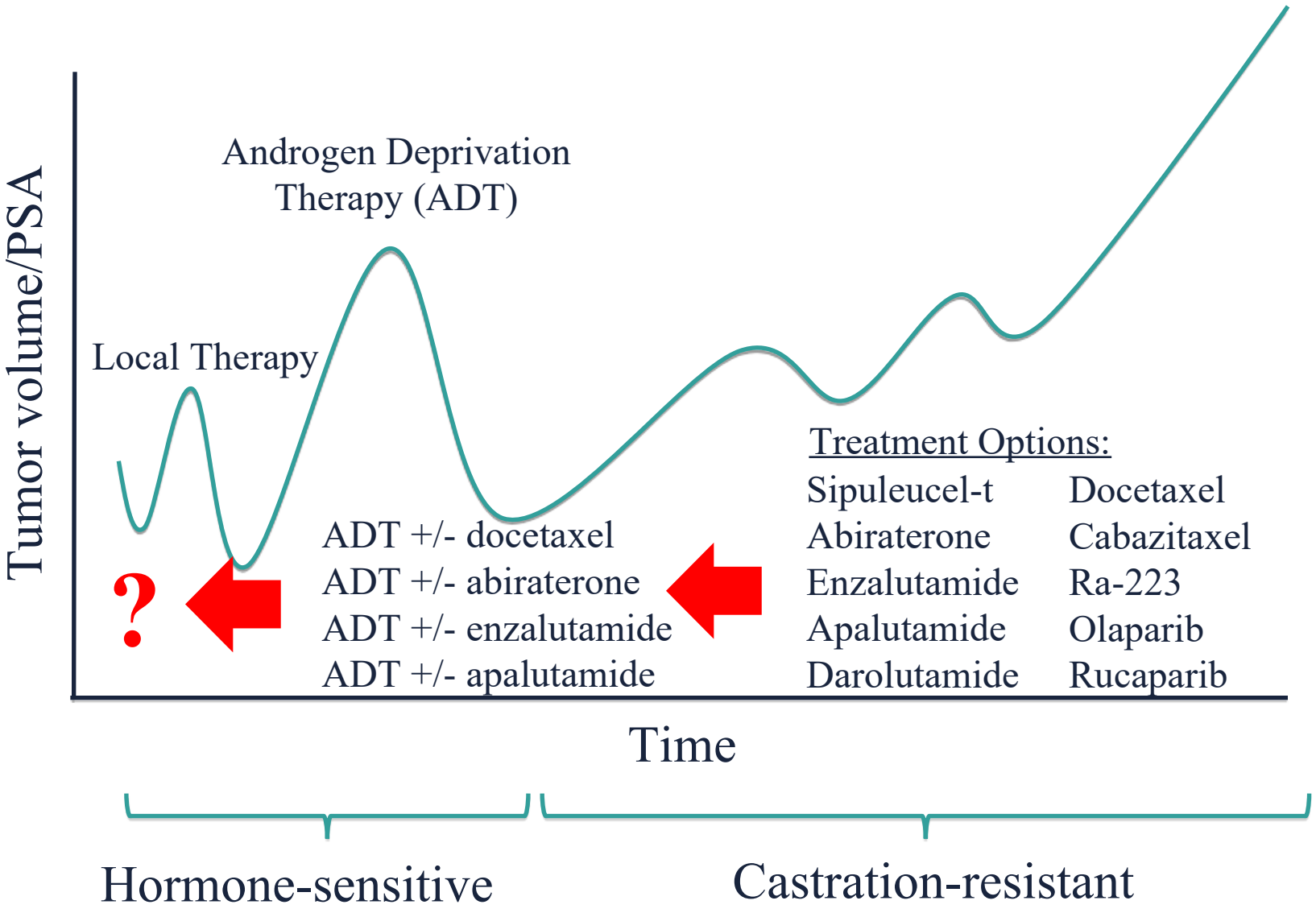
Prostate Cancer Biology



Prostate Cancer Biology



Prostate Cancer Disease Continuum



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Epidemiology

Estimated New Cases

Prostate	248,530	26%
Lung & bronchus	119,100	12%
Colon & rectum	79,520	8%
Urinary bladder	64,280	7%
Melanoma of the skin	62,260	6%
Kidney & renal pelvis	48,780	5%
Non-Hodgkin lymphoma	45,630	5%
Oral cavity & pharynx	38,800	4%
Leukemia	35,530	4%
Pancreas	31,950	3%
All Sites	**970,250**	**100%**

Estimated Deaths

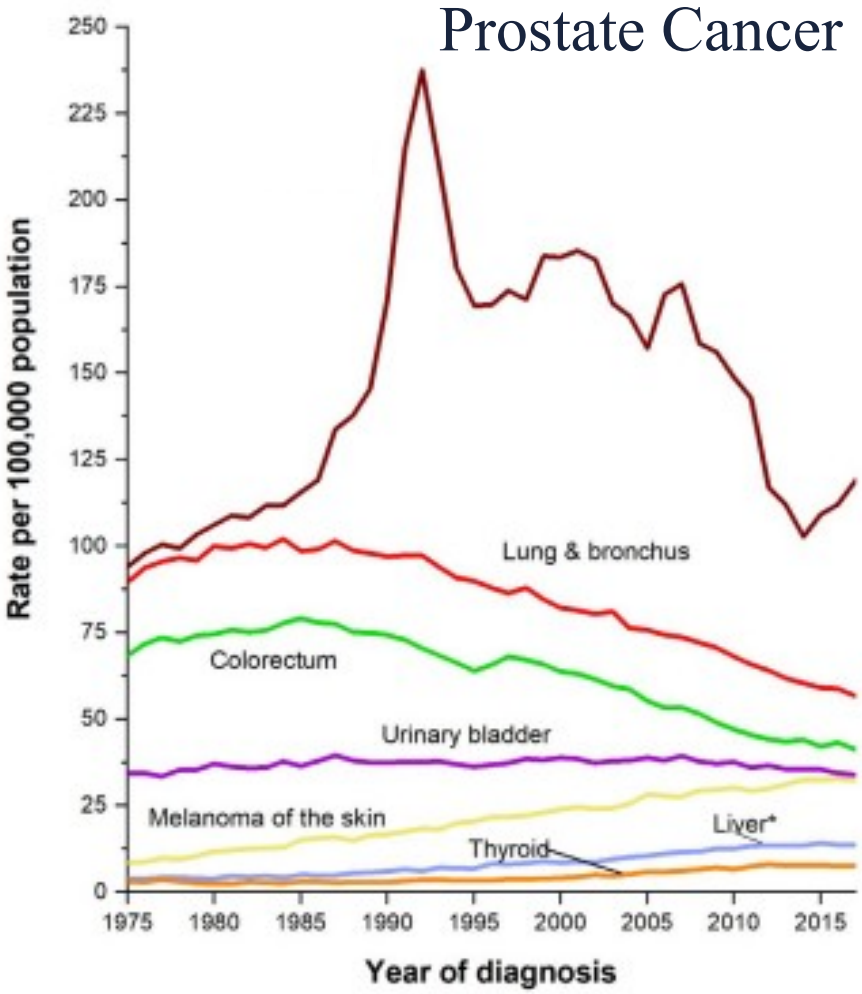
Males

Lung & bronchus	69,410	22%
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All Sites	**319,420**	**100%**

Siegel, et al. CA Cancer J Clin. 2021

Epidemiology

- Approximately 1 in 6 men will be diagnosed with prostate cancer
- Incidence peaked in 1992 following introduction of PSA testing



Siegel, et al. CA Cancer J Clin. 2021
Farkas, et al. Urology 1998; 52:444

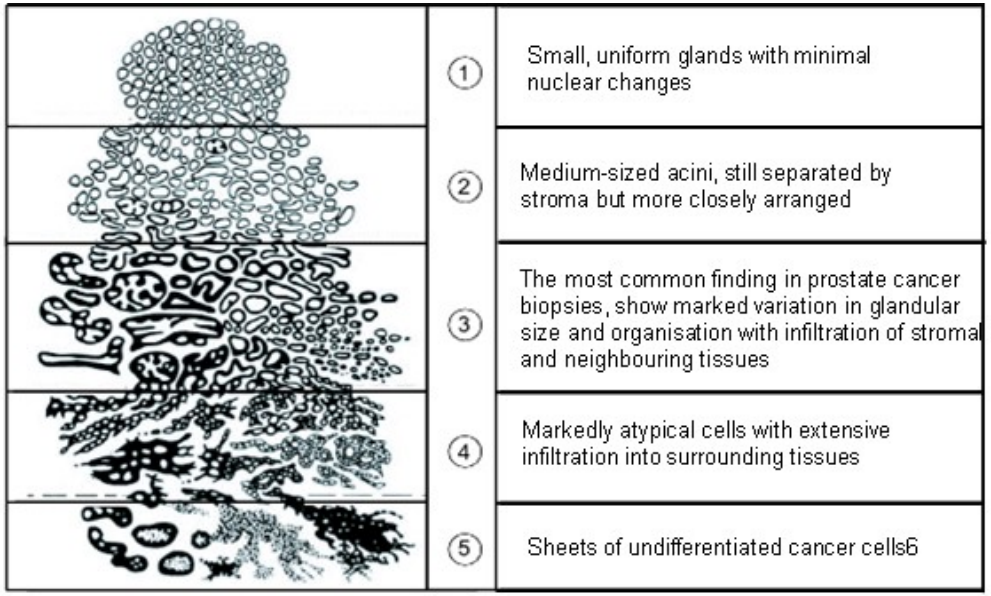
Workup

- Referral to urology for biopsy if:
  - Abnormal DRE
  - Elevated PSA
- Additional testing dependent on risk:
  - Bone scan: T1 and PSA>20, T2 and PSA>10, Gleason ≥8, T3-T4 or symptomatic
  - Pelvic CT or MRI: T3-T4, T1-T2 and >10% chance of lymph node involvement

Risk Group	Clinical Features
Very low	T1c Gleason score ≤6 PSA <10 <3 positive biopsy cores ≤50% cancer in each core PSA density <0.15
Low	T1-T2a Gleason ≤6 PSA <10
Intermediate	T2b-T2c or Gleason score 7 or PSA 10-20
High	T3a or Gleason score 8-10 or PSA >20
Very high	T3b-T4

Gleason Score

- Based on cancer appearance
  - Range from 1 (normal appearing) to 5 (very abnormal appearing)
- Correlates closely with clinical behavior
  - High score is worse
- Reported as a composite score:
  - Primary + Secondary = total Gleason score



Gleason Grade Group

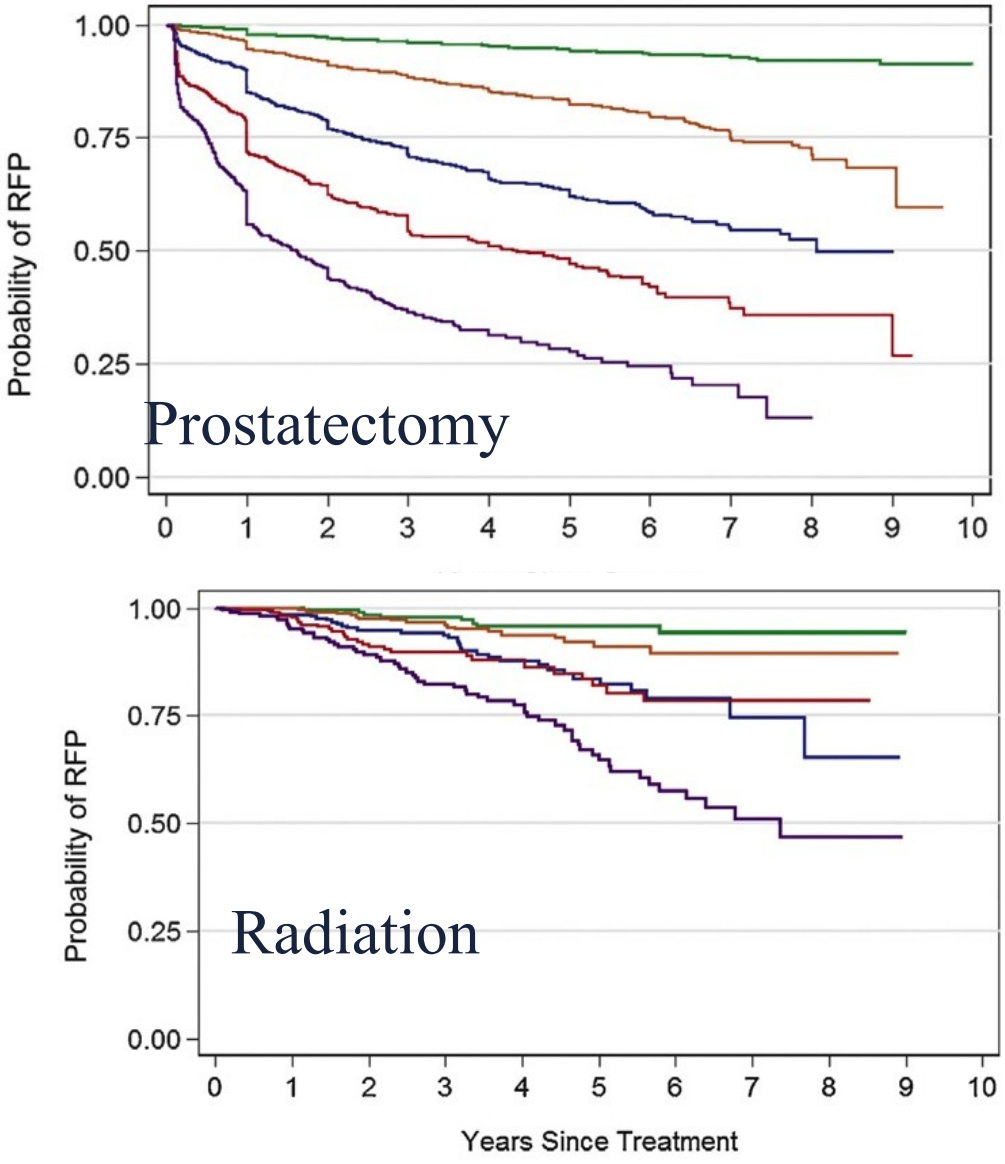
Grade Group reporting recommended by International Society of Urological Pathology and WHO

More accurate risk stratification than composite Gleason score

Grade Group	Gleason Pattern
Group 1	Gleason 3+3
Group 2	Gleason 3+4
Group 3	Gleason 4+3
Group 4	Gleason 4+4
Group 5	Gleason 4+5, 5+4 or 5+5

Epstein, et al. Eur Urol. 2016;69(3):428.

Gleason Grade Group



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Local Management

Radical prostatectomy

Radiation therapy

- External beam
- Brachytherapy
- External beam + brachytherapy

Active surveillance

- Typically, no more than low-intermediate risk prostate cancer

Radical Prostatectomy: SPCG4

Radical prostatectomy (RP) vs. observation

T1 or T2 prostate cancer

Number of patients = 695

- Average PSA = 13
- 12% non-palpable tumors (T1c)
- 64% intermediate/high-risk

23.6 years median follow up

- Death (RP vs. Observation): 72% vs 84%
- Mean years of life gained in RP group: 2.9 years
- Distant metastases: 27% vs 43%
- Benefits most pronounced in those <65 years and with intermediate risk disease

Bill-Axelson, et al. N Engl J Med. 2014 Mar 6;370(10):932-42
Bill-Axelson, et al. N Engl J Med. 2018 Dec 13;379(24):2319-2329.

Radical Prostatectomy: PIVOT

Prostatectomy vs. Observation

T1-T2 prostate cancer

731 men

- Median PSA=7.8
- 50% with non-palpable tumors (T1c)
- 66% with intermediate/high risk

10-year median follow up:

- Death (RP vs. Observation): 47% vs. 49.9%
  - Significant improvement in survival in men with if PSA >10 and near-significant in intermediate/high-risk group
- Bone mets: 4.7% vs. 10.6%

Wilt, et al. N Engl J Med. 2012 Jul 19;367(3):203-13

Prostatectomy or Radiation: ProtecT

Prostatectomy vs. Radiation vs. Observation

T1 or T2 prostate cancer

1643 men enrolled

- Median PSA = 4.6
- 76% with non-palpable disease (T1c)
- 77% Gleason 6

10-years median follow up

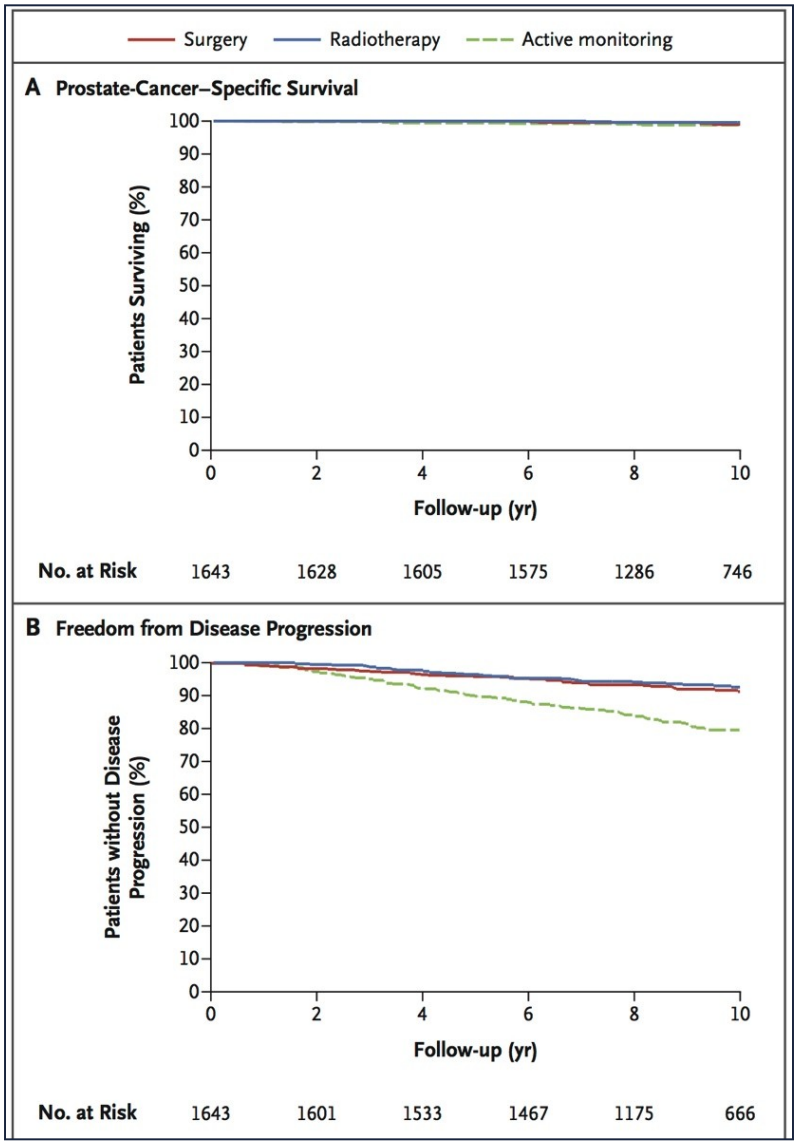
- Few patients died on study → no significant differences between groups
- 55% of observation patients received local therapy

Hamdy, et al. N Engl J Med. 2016 Sep 14

Prostatectomy or Radiation: ProtecT

Lower rates of metastatic disease with prostatectomy or radiation (P=0.004)

- Radiation: 3 per 1000 person-yrs
- Prostatectomy: 2.4 per 1000 person-yrs
- Observation: 6.3 per 1000 person-yrs



Hamdy, et al. N Engl J Med. 2016 Sep 14

Active Surveillance

Goal is to not sacrifice cure-rate

Active surveillance program differs by institution

- Eligible patients typically have low to intermediate risk prostate cancer
- PSA monitoring every 3-6 months
- Repeat biopsies every 1-4 years
- Most require pathologic reclassification to trigger intervention

>40% of low-risk cancer are managed with AS in the US

Soloway MS, et al. European urology 2010;58:831-5.
Cooperberg MR, et al. JCO 2011;29:228-34.
Adamy A, et al. The Journal of urology 2011;185:477-82.
Tosoian, et al. Nat Rev Urol. 2016 Apr;13(4):205-15.
Tosoian JJ, et al. JCO 2011;29:2185-90.
Klotz L, et al. JCO 2015;33:272-7.

Prostate Cancer Active Surveillance

Well recognized management strategy for men with lower risk prostate cancer

Aim to decrease overtreatment while maintaining cure rates

ASCO/AUA/ASTRO/SUO Active Surveillance Guidelines:

- Very low-risk : best option
- Low-risk: preferred option
- Favorable intermediate risk: offer to select patients; inform risk of metastases is higher

Bekelman, et al. J Clin Oncol. 2018 Nov 10;36(32):3251-3258.

Prostate Cancer Active Surveillance

Safe and effective strategy to mitigate overtreatment of lower risk prostate cancers

~3/4 of men undergo local treatment due to changes in biopsy findings

Center	Toronto[1,2,3]	Johns Hopkins[4,5,6,7]	UCSF[8]	UCSF (newer cohort)[9]	Canary PASS[10]
No. patients	993	1298	321	810	905
Median follow-up (mos)	77	60	43	60	28
Cancer-specific survival	98% (10-y)	99.9% (10-y)	100% (5-y)	-	-
Conversion to treatment	36.5% (10-y)	50% (10-y)	24% (3-y)	40% (5-y)	19% (28-mos)

Adapted from Prostate Cancer NCCN Guidelines v2.2020

1. Klotz, et al. J Clin Oncol. 2015 Jan 20;33(3):272-7.
2. Klotz, et al. J Clin Oncol. 2010 Jan 1;28(1):126-31.
3. Yamamoto, et al. J Urol. 2016 May;195(5):1409-1414.
4. Tosoian, et al. J Clin Oncol. 2015 Oct 20;33(30):3379-85.
5. Carter, et al. J Urol. 2007 Dec;178(6):2359-64
6. Sheridan, et al. J Urol. 2008 Mar;179(3):901-4
7. Tosoian, et al. J Clin Oncol. 2011 Jun 1;29(16):2185-90.
8. Dall'era, et al. Cancer. 2008 Jun 15;112(12):2664-70.
9. Welty, et al. J Urol. 2015 Mar;193(3):807-11.
10. Newcomb, et al. J Urol. 2016 Feb;195(2):313-20.

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Ideal medical therapy for men on AS

- Well tolerated
  - Goal is to avoid over treatment
- Effective
  - Unclear how to define this
  - Change in biopsy (pathology) may be an early indicator a drug is effective

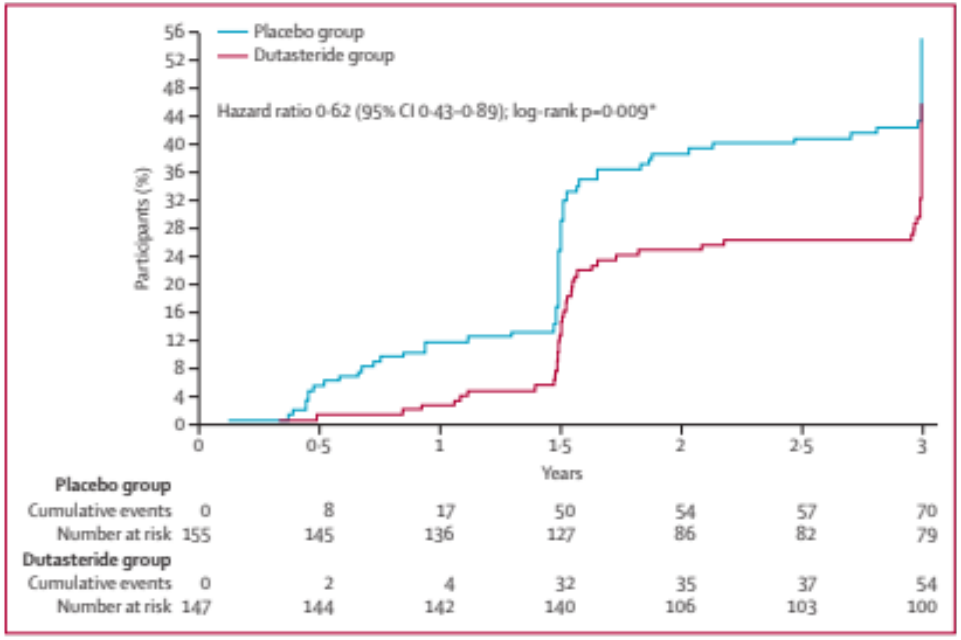
REDEEM

- Dutasteride 0.5 mg daily vs. placebo x 3 years
- Low-volume Gleason 5-6 prostate cancer
- Primary endpoint: time to prostate cancer progression (pathological or therapeutic)
- 302 patients enrolled

Fleshner, et al. Lancet 2012

REDEEM

No significant difference in pathologic progression between groups:
29% (dutasteride) vs. 33% (placebo)



	Dutasteride group	Placebo group
Pathological progression		
n	43	51
≥4 cores involved	19 (44%)	38 (75%)
≥50% of any one core involved	21 (49%)	23 (45%)
Gleason primary or secondary score ≥4	19 (44%)	21 (41%)
Therapeutic progression		
n	11	19
Surgical intervention	8 (73%)	11 (58%)
Prostatectomy	8 (73%)	8 (42%)
Other	0	3 (16%)
Non-surgical intervention	3 (27%)	8 (42%)
Drug therapy	1 (9%)	4 (21%)
External beam radiation	2 (18%)	3 (16%)
Other	0	1 (5%)

Data are n (%).

Progression at 3 years: 38% dutasteride vs. 48% placebo

Fleshner, et al. Lancet 2012

REDEEM

Higher negative biopsy rate with dutasteride vs. placebo: 36% vs. 23%

	Latest biopsy assessment on or before 18 months		Final biopsy assessment*	
	Dutasteride group (n=139)	Placebo group (n=136)	Dutasteride group (n=140)	Placebo group (n=136)
Gleason scores				
No cancer detected	39 (28%)	42 (31%)	50 (36%)	31 (23%)
5	0	1 (1%)	0	0
6	92 (66%)	77 (57%)	71 (51%)	83 (61%)
7–8	8 (6%)	16 (12%)	19 (14%)	22 (16%)
3+4	7 (5%)	10 (7%)	13 (9%)	15 (11%)
4+3	1 (1%)	4 (3%)	4 (3%)	4 (3%)
8	0	2 (1%)	2 (1%)	3 (2%)
Pathological characteristics†				
Mean percentage of cancer-positive cores	13·6% (12·41)	17·0% (17·43)	13·9% (13·51)	19·0% (17·23)
Mean cumulative length of tumours, mm	3·4 (5·76)	4·7 (6·49)	3·9 (5·75)	5·4 (6·83)

Data are n (%) or mean (SD). *Latest biopsy assessment for a participant, irrespective of when that assessment occurred. †Percentage of cancer-positive cores and tumour length were recorded as zero for biopsy assessments that did not detect cancer.

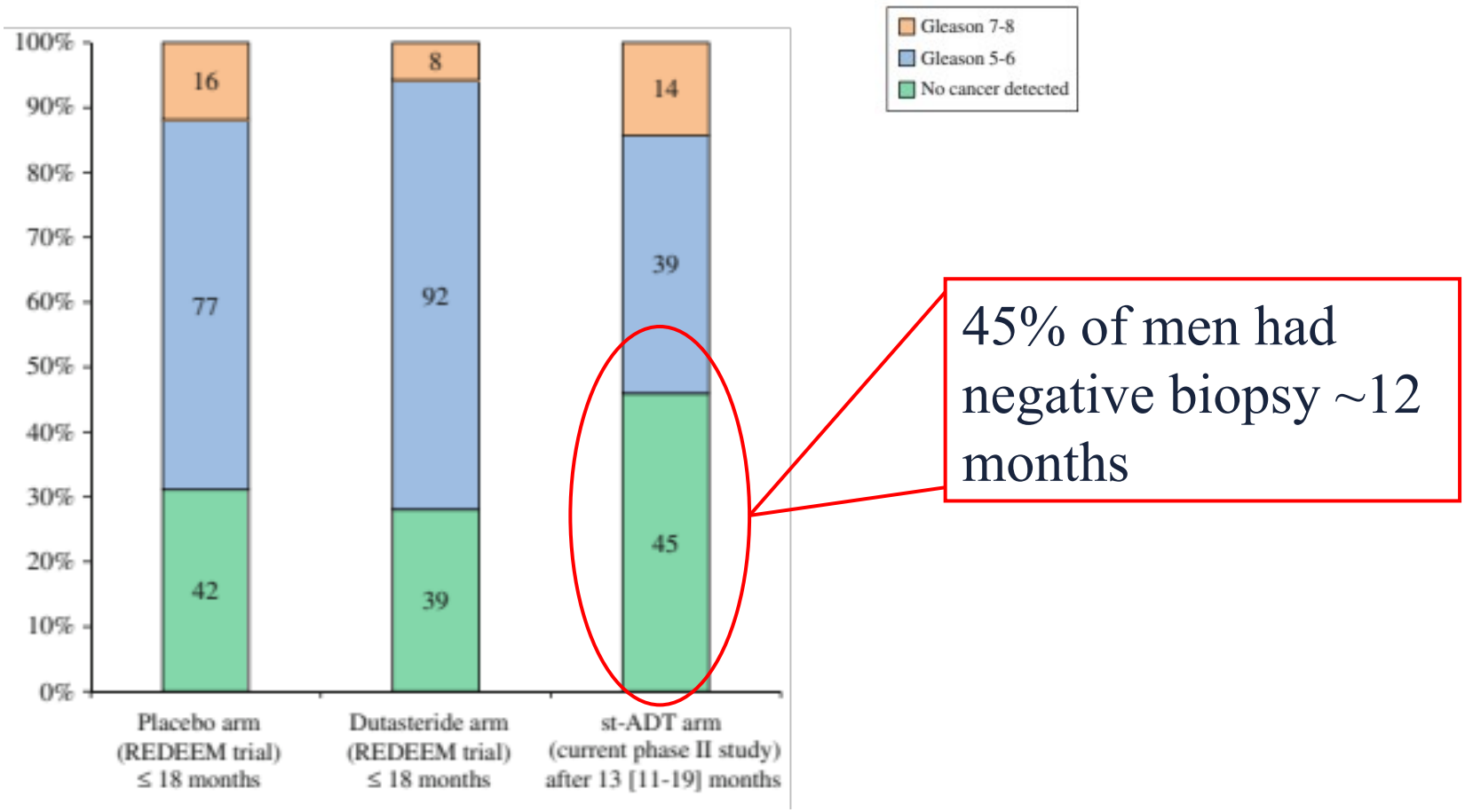
Fleshner, et al. Lancet 2012

Leuprolide + Bicalutamide AS Study

- Leuprolide 22.5 mg (3-month dose) x 1 plus bicalutamide 50 mg daily for 15 days
- Gleason 6 prostate cancer
- Primary endpoint: Presence of cancer on biopsy at 12 months
- 98 men enrolled

Cussenot, et al. World journal of urology 2014

Leuprolide + Bicalutamide AS Study



Cussenot, et al. World journal of urology 2014

Concerns with prior AS studies

- Dutasteride is not a very potent prostate cancer drug

- Leuprolide side effects will last well beyond 3 months

Apalutamide Active Surveillance Study

- Apalutamide is a potent oral hormonal agent
  - Blocks testosterone
- Approved in combination with leuprolide to treat:
  - Newly diagnosed metastatic prostate cancer or
  - Non-metastatic prostate cancer with a rising PSA on leuprolide
- Prior studies have shown testosterone goes *up* if used in the absence of leuprolide

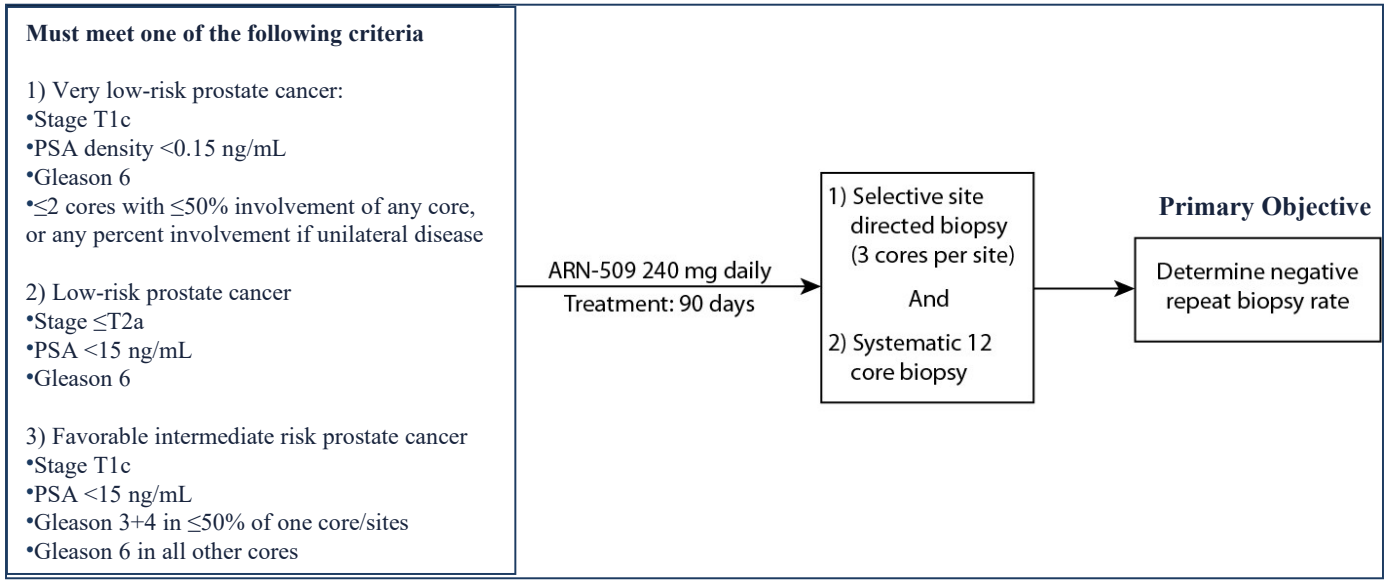
Schweizer, et al. SUO 2020

Apalutamide will lead to negative repeat biopsies in active surveillance patients...

...should be well tolerated and lead to decreased attrition from active surveillance.

Apalutamide Active Surveillance Study

Study Schematic



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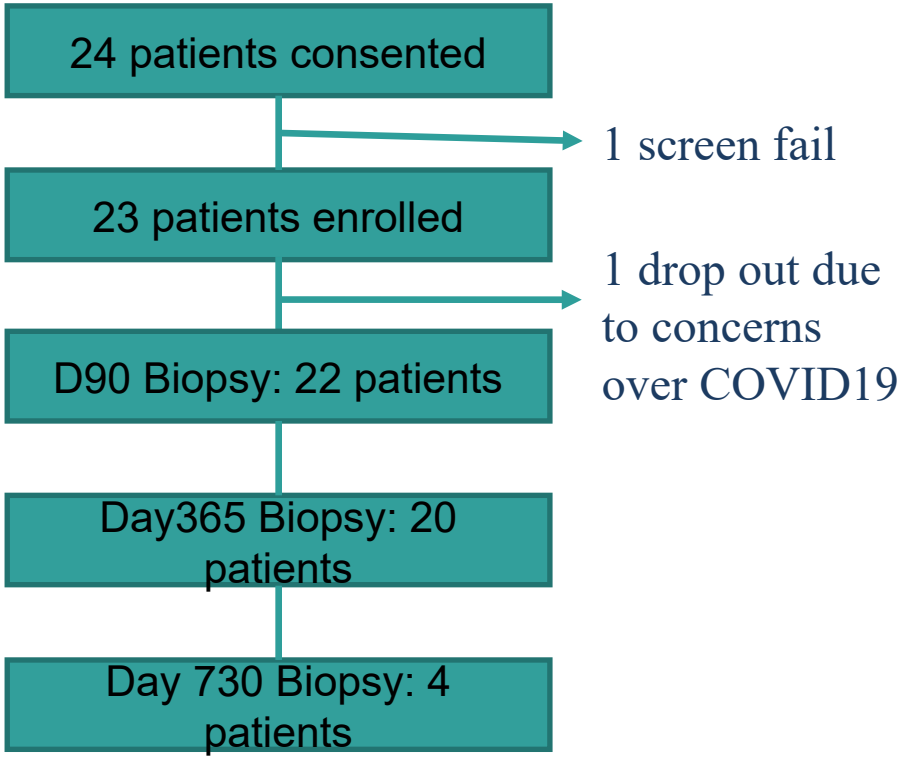
Schweizer, et al. SUO 2020

Demographics & Patient Flow



Demographics	
Age, median (range)	67 (45-76)
Gleason Grade Group, N (%)	
1	15 (68%)
2	7 (32%)
3-5	0
NCCN Risk Category, N (%)	
Very low-risk	3 (14%)
Low-risk	11 (50%)
Favorable intermediate risk	8 (36%)
PSA, median (range)	4.57 (2.4-10.94)
Number of Cores involved, median (range)	2 (1-6)
Time on Active Surveillance (mos), median (range)	10.7 (0.9-102.7)

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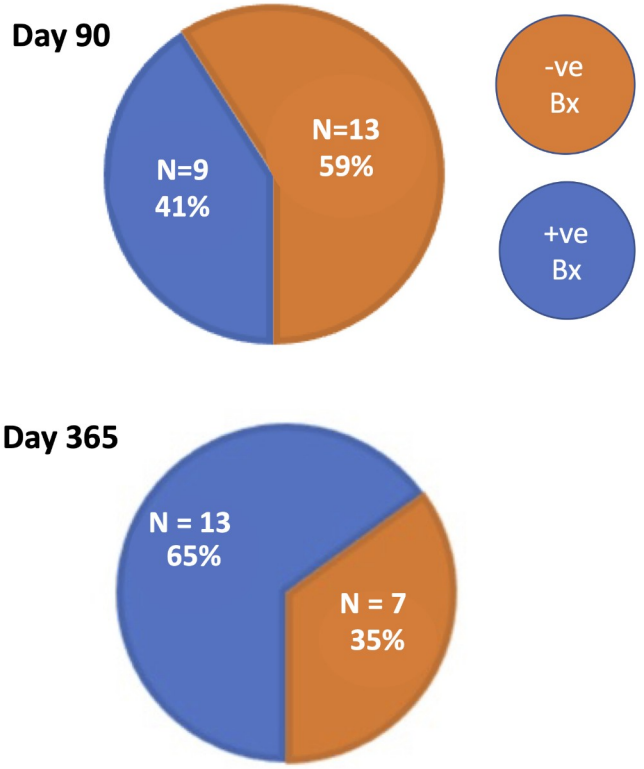
Schweizer, et al. SUO 2020

Pathologic Outcomes

	Day 90	Day 365	Day 730
Number	22	20	4
Negative biopsy, N (%)	13 (59%)	7 (35%)	0
Cores involved, median (range)	0 (0-7)	2 (0-5)	
Grade group, N (%)			
N/A	--	7	--
1	--	7	3
2	--	6	1
3-5	--	0	0



Schweizer, et al. SUO 2020

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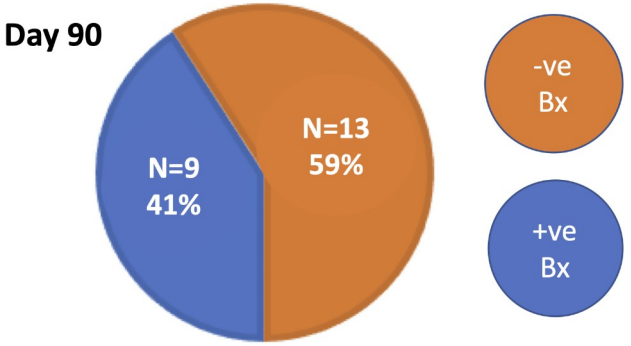

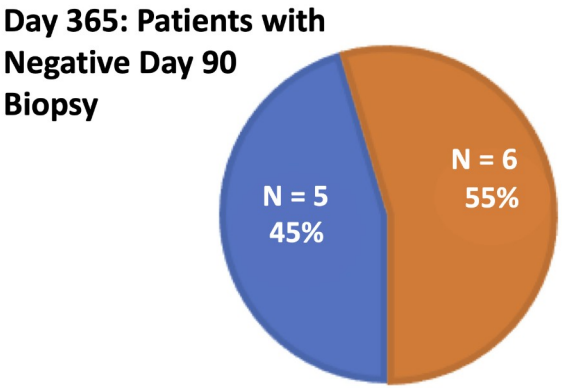

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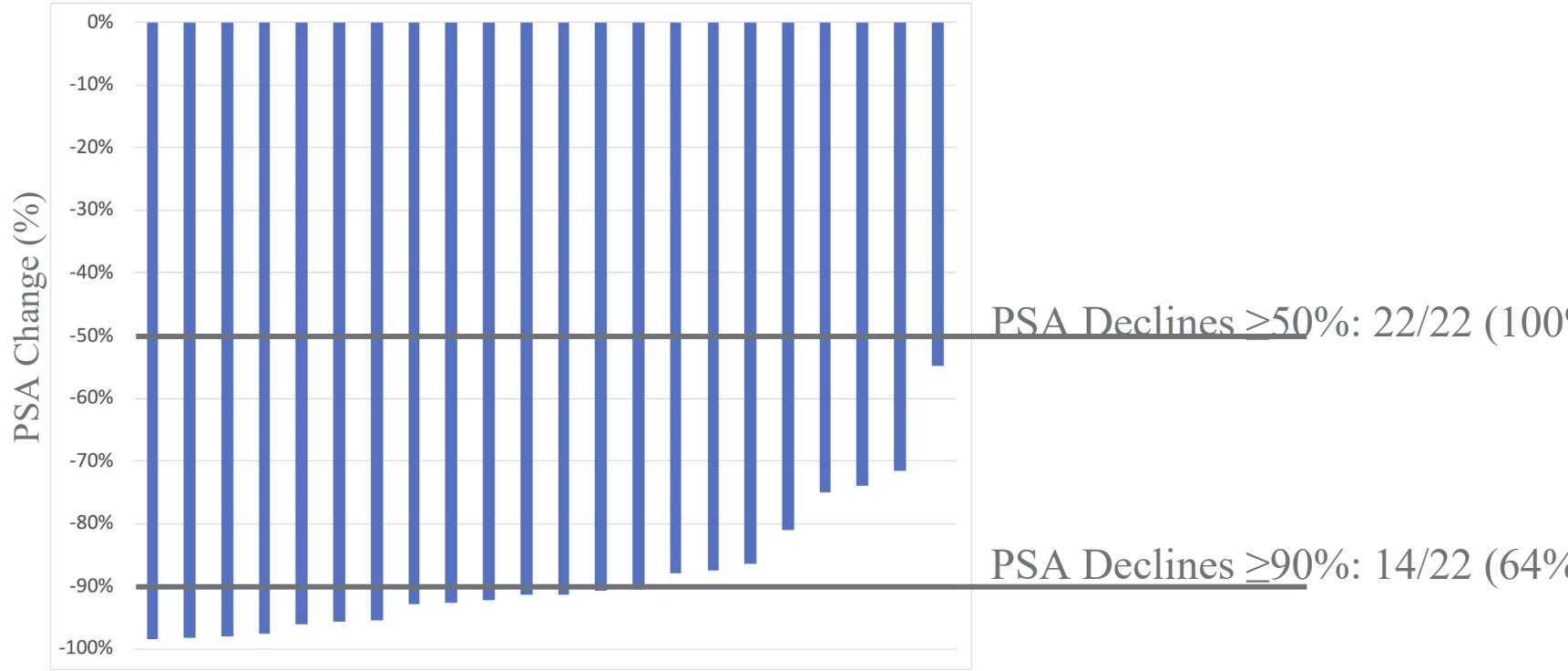
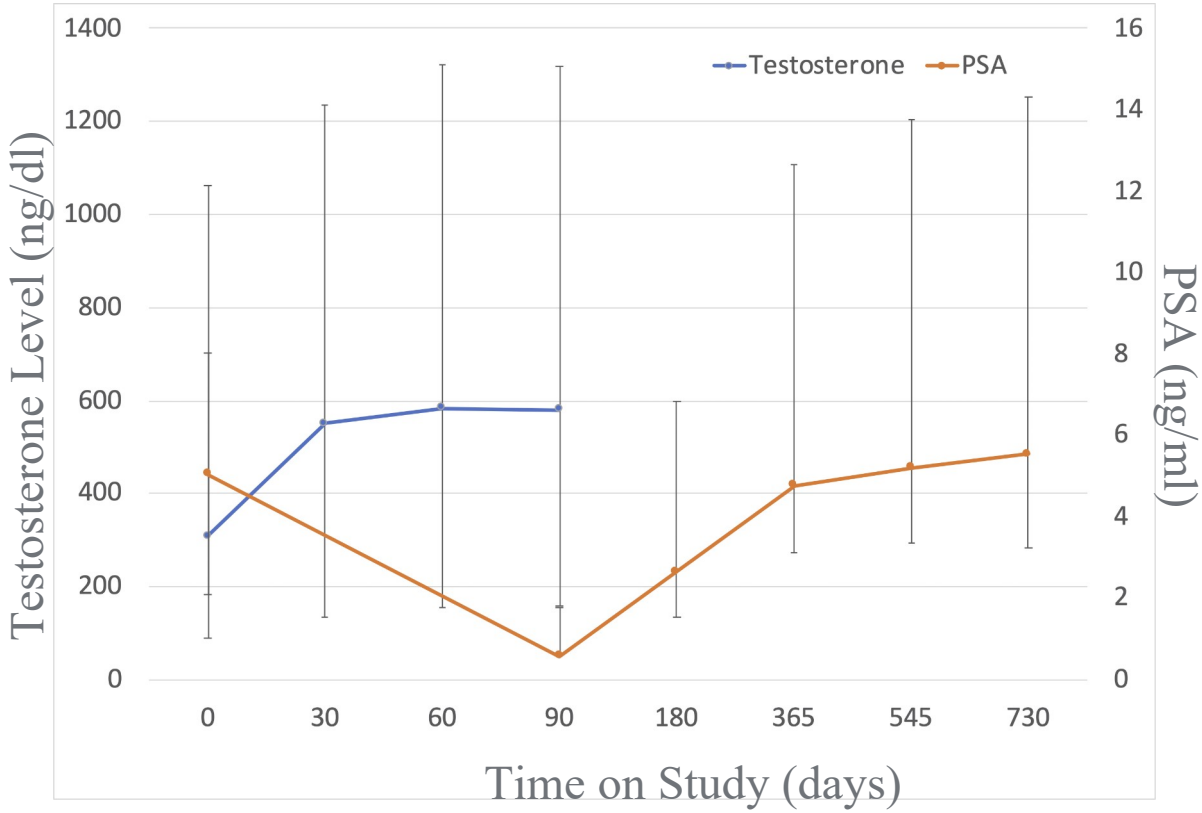
Schweizer, et al. SUO 2020

PSA Responses



Schweizer, et al. SUO 2020

PSA and Testosterone Changes



Data is presented as mean PSA/Testosterone +/- SD

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Schweizer, et al. SUO 2020

Adverse Events

- Treatment was generally well tolerated and AEs resolved after coming off study
- One patient had grade 3 hypertension, and another had grade 3 rash
  - Both remained on study following dose reductions

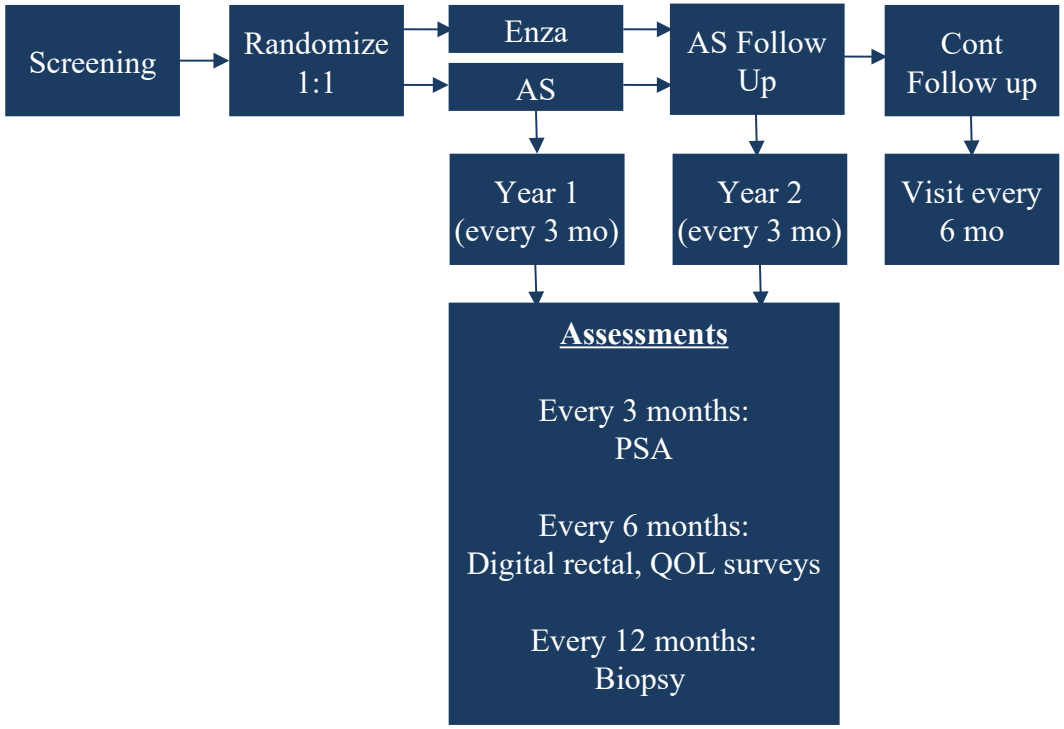
Treatment Related AEs in ≥5% of Subjects

Adverse Event	Grade 1	Grade 2
Fatigue	16 (70%)	2 (9%)
Gynecomastia	16 (70%)	
Arthralgia/myalgia	7 (30%)	
Dysgeusia	7 (30%)	
Rash	6 (26%)	
Cognitive impairment	5 (22%)	
Hot flashes	5 (22%)	
Elevated TSH	4 (17%)	
Anorexia	3 (13%)	
Dry skin	3 (13%)	
Libido decreased	3 (13%)	
Pruritus	3 (13%)	
Nausea	2 (9%)	
Weight loss	2 (9%)	

Schweizer, et al. SUO 2020

ENACT

- Enzalutamide x 1 year *vs.* active surveillance alone
- Low or intermediate risk prostate cancer
- <u>The primary end point:</u> time to prostate cancer progression (pathological or therapeutic).



Shore, et al. ASCO 2017

Summary

- Active surveillance is an effective way to mitigate overtreatment of low/intermediate risk prostate cancer
- 25%-50% of men on active surveillance still end up receiving local treatment (prostatectomy/radiation)
- Medical therapies have shown promise in decreasing rates of attrition from active surveillance

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