Prostate Cancer: Turtles, rabbits and birds!

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Disclosures

- **Faculty/Speaker:** Jay Nayak, MD

- **Relationships with financial sponsors:** None
  - **Grants/Research Support:**
  - **Speakers Bureau/Honoraria:**
  - **Consulting Fees:**
  - **Other:**

Mitigating Potential Bias

- Not applicable

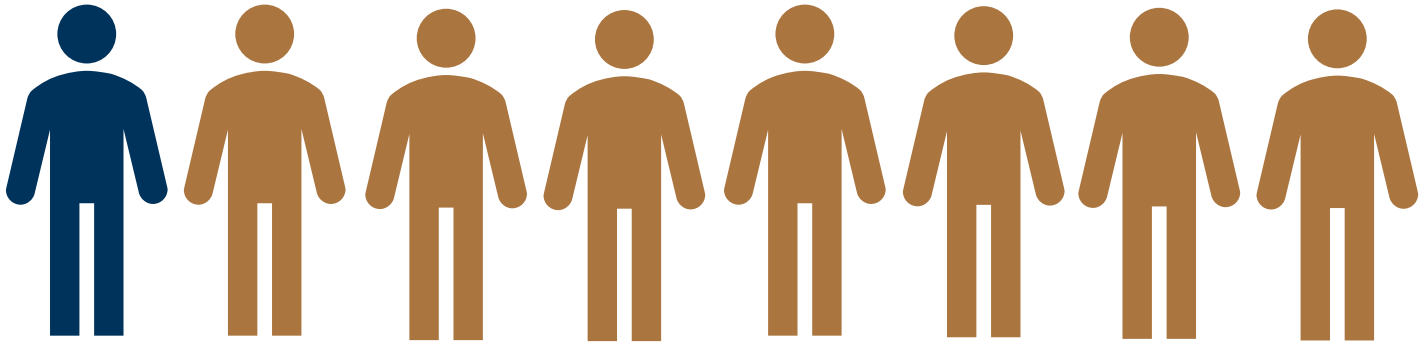
Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

Learning Objectives

1. Describe the basic epidemiology of prostate cancer
2. Describe the risk stratification of prostate cancer
3. Explain the different treatment options for localized prostate cancer
4. Understand the rationale for active surveillance of prostate cancer

How common is prostate cancer?



1 in 8 Canadian men will develop PCa

Canadian Cancer Statistics 2022

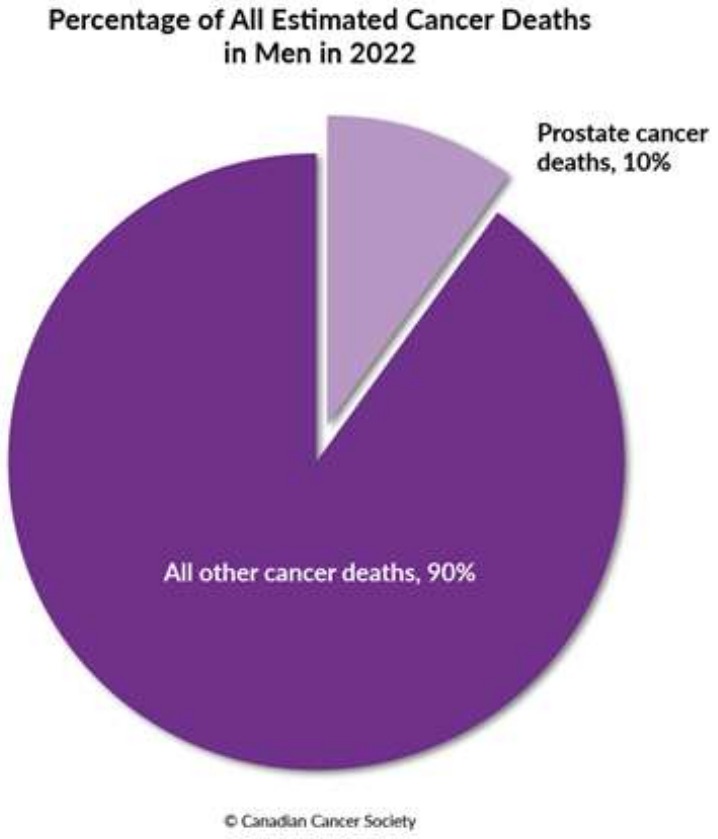
Prostate cancer epidemiology

Males
118,200
New cases

Prostate	20.3%
Lung and bronchus	12.5%
Colorectal	11.6%
Bladder	8.0%
Non-Hodgkin lymphoma	5.2%
Head and neck	4.6%
Kidney and renal pelvis	4.4%
Melanoma	4.0%
Leukemia	3.4%
Pancreas	3.1%
Stomach	2.2%
Liver	2.2%
Multiple myeloma	1.9%
Esophagus	1.6%
Brain/CNS	1.5%
Thyroid	1.5%
Testis	1.0%
Hodgkin lymphoma	0.5%
Breast	0.2%
All other cancers	10.3%

Females
110,900
New cases

Breast	25.0%
Lung and bronchus	13.3%
Colorectal	10.0%
Uterus (body, NOS)	7.2%
Non-Hodgkin lymphoma	4.5%
Thyroid	4.4%
Melanoma	3.6%
Bladder	2.7%
Pancreas	2.7%
Ovary	2.7%
Leukemia	2.4%
Kidney and renal pelvis	2.3%
Head and neck	1.8%
Multiple myeloma	1.4%
Cervix	1.3%
Stomach	1.3%
Brain/CNS	1.2%
Liver	0.7%
Esophagus	0.5%
Hodgkin lymphoma	0.4%
All other cancers	10.5%



Canadian Cancer Statistics 2022

PSA screening

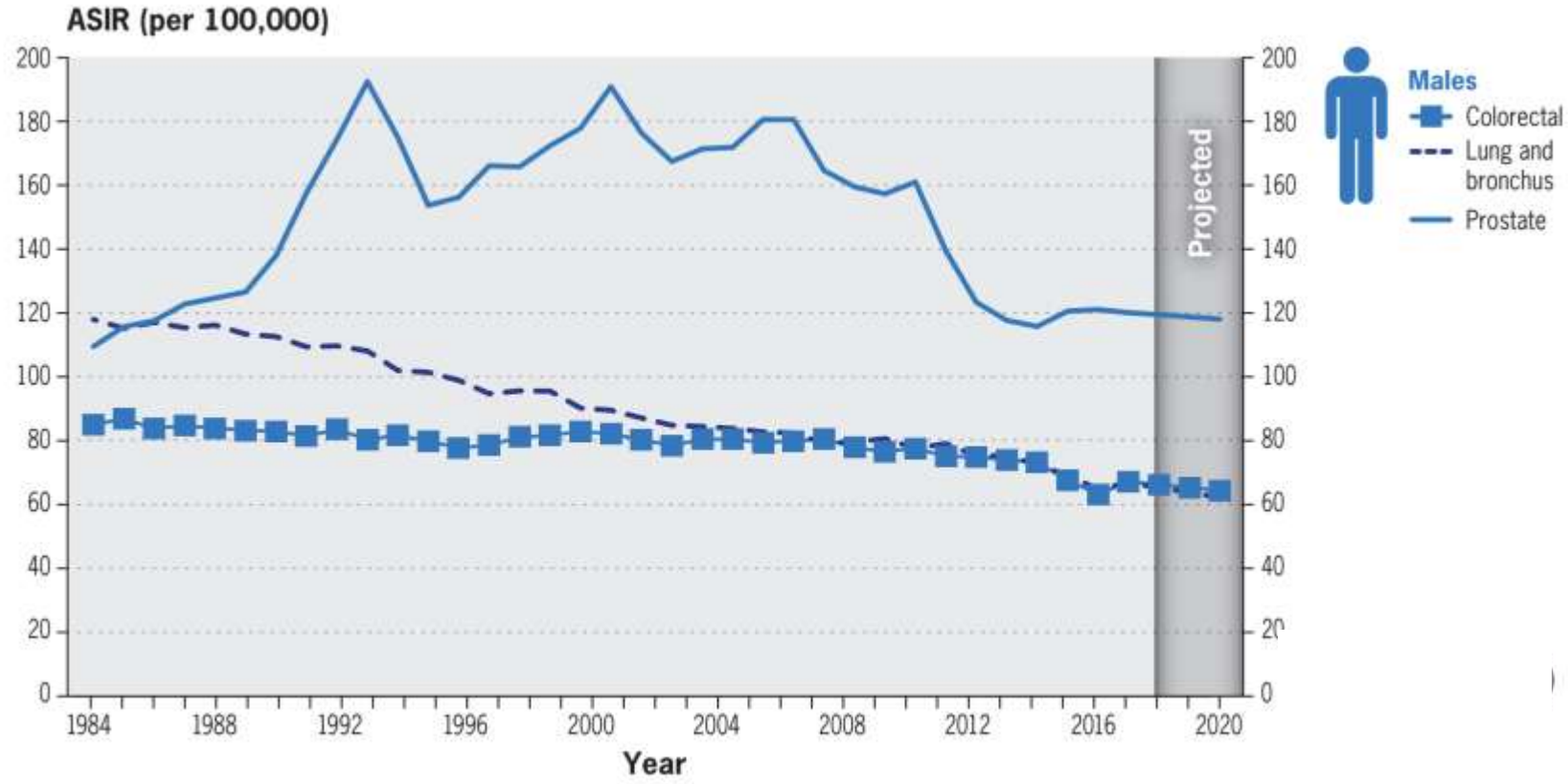


Table 1. Most recent results from three randomized, controlled trials investigating PSA screening

	PLCO (2017 update)[15]	ERSPC (2014 update)[16]	Goteborg (2014 update)[17]
n	76 683	162 243	20 000
Age	55–74	55–69	50–64
Site	10 US centres	8 European countries	1 city (Goteborg, Sweden)
Intervention	PSA annually x 6 years Annual DRE x 4 years	PSA q4 years (in most centres) Some centres offered DRE	PSA q2 years
Current median followup	15 years	13 years	18 years
Definition of positive test	PSA >4 ng/ml Abnormal DRE	PSA>3 ng/ml (most centres)	PSA >2.5 ng/ml (from 2005 on) PSA >2.9 ng/ml (from 1999–2004) PSA>3.4 ng/ml (from 1995–98)
Prostate cancer deaths	Control: 244 Screened: 255	Control: 545 Screened: 355	Control: 122 Screened: 79
Rate ratio for CSS (95% CI)	1.04 (0.87–1.24)	0.79 (0.69–0.91) 21% relative risk reduction in favour of screening	0.58 (0.46–0.72) 42% relative risk reduction in favour of screening
NNS	N/A	1:781	1:139
NND	N/A	1:27	1:13

PSA screening RCT trials

2/3 screening trials suggested relative risk reduction in PCa deaths

1/3 was a negative study (US study) but had high levels of contamination (placebo group received testing)

Rendon R et al CUAJ 2017

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

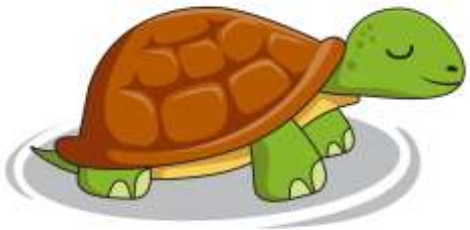
Reconsidering the Trade-offs of Prostate Cancer Screening

Jonathan E. Shoag, M.D., Yaw A. Nyame, M.D., M.B.A., Roman Gulati, M.S., Ruth Etzioni, Ph.D., and Jim C. Hu, M.D., M.P.H.

- 16 years of follow-up from randomization may not provide a sufficient time horizon to examine the mortality benefit from screening

- Benefits of screening cannot be measured only in mortality reduction – should also reflect diminished morbidity from avoidance of advanced disease

Turtles, rabbits and birds!



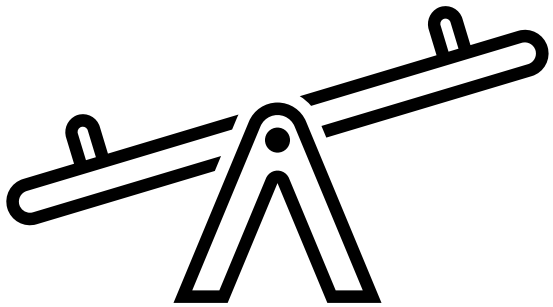
PSA screening

Benefits

Lower stage and grade of cancer at diagnosis

Significant reduction in prostate cancer specific mortality rates

Decrease the risk of metastatic disease



Harms

Psychological and physical side effects

Biopsy side effects

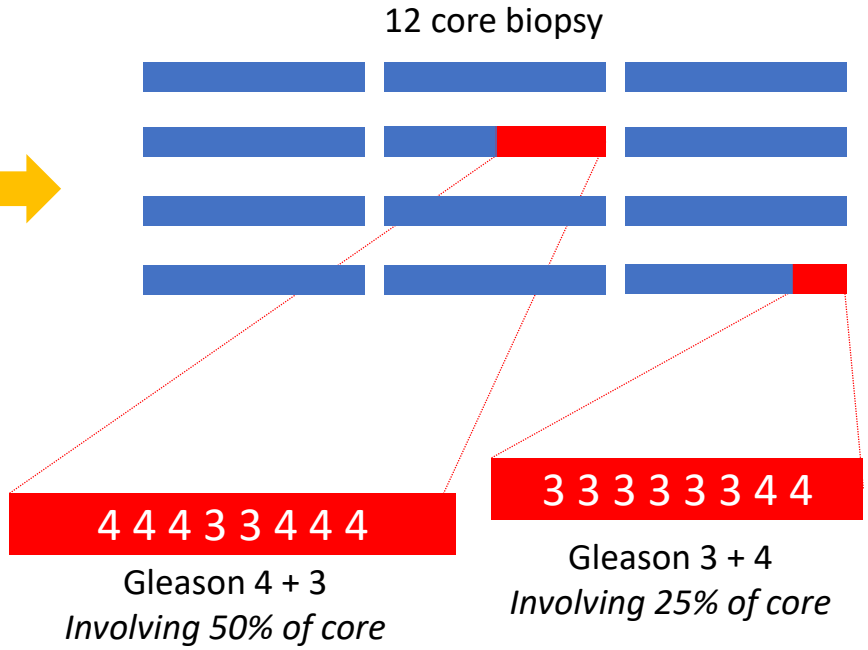
Risk of overtreatment of indolent disease

Rendon R et al CUAJ 2017

Prostate cancer diagnosis

PSA 9
T1 exam

Prostate biopsy

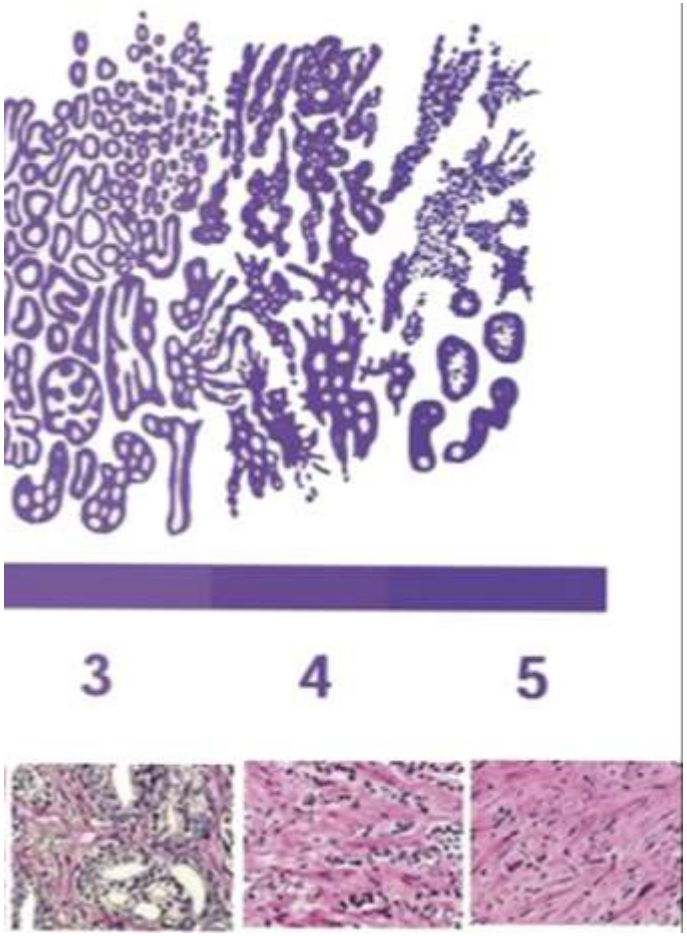


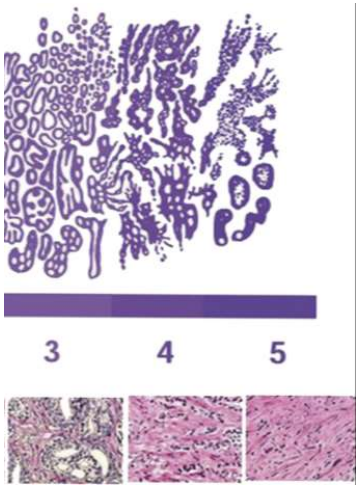
*"…Mr. Jones was diagnosed with a PSA 9, clinical T1 prostate adenocarcinoma with 2 of 12 cores positive for up to **Gleason 4+3** disease and core involvement ranging from 25-50%..."*

Gleason what?

- The Gleason Score is a histological grading system that pathologists use to “grade” a prostate cancer

- Gleason Score vs. Gleason Sum vs. Gleason Grade Group





3	+	4	=	7
Most common pattern		*Second* most common pattern		**Gleason sum**

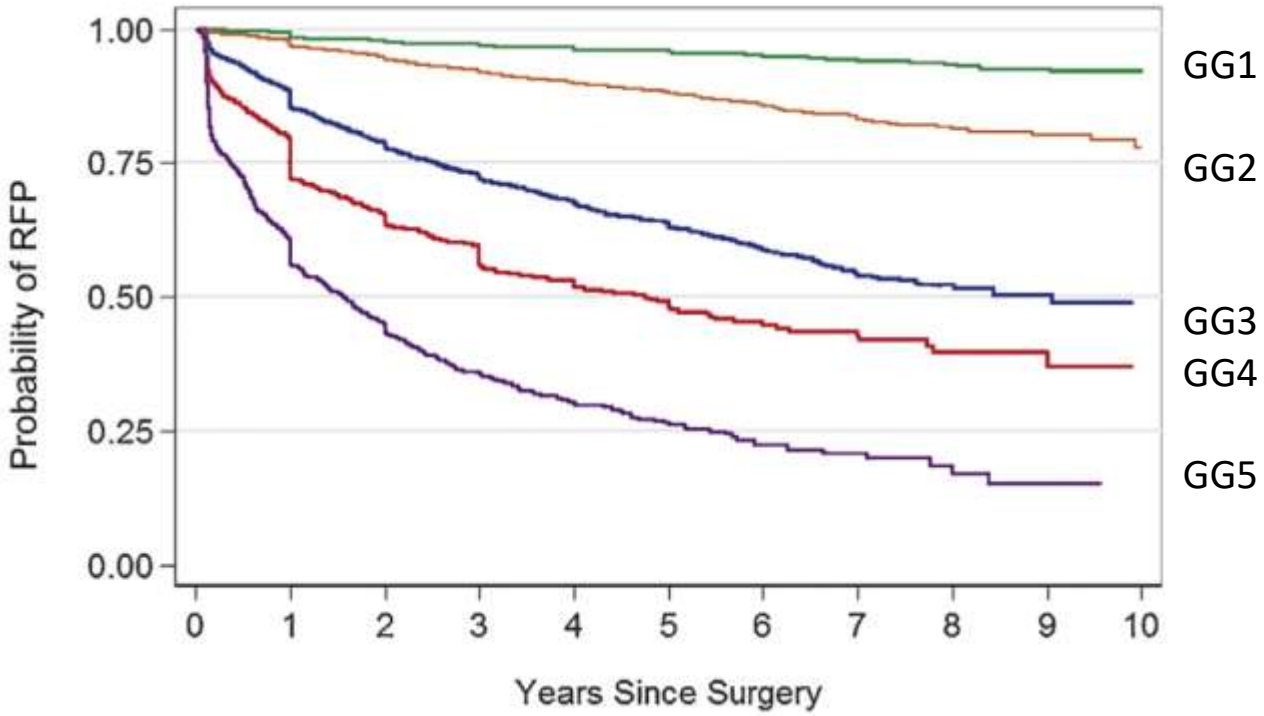
Gleason scores and risk stratification

Low risk	Intermediate risk	High risk
6	7	8+

Gleason Grade Groups (GG)

Gleason Score	Gleason Group
3+3	1
3+4	2
4+3	3
4+4	4
4+5, 5+4, 5+5	5

Gleason Grade group (GG) informs prognosis



Findings validated
Recurrence-Free probability

Epstein Jl et al. Eur Urol 2016
Leapman MS et al. Eur Urol 2016

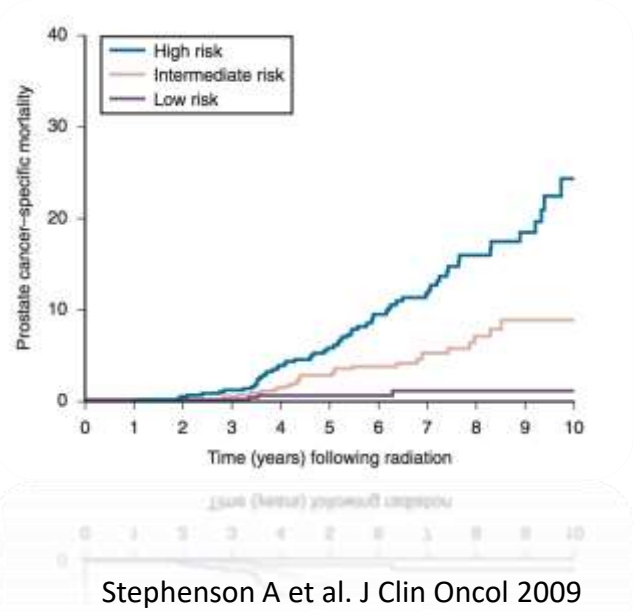
Based on a patients risk of recurrence, patients are stratified into risk groups, which may guide treatment recommendations

D'Amico risk classification

	LOW	INTERMEDIATE	HIGH
Gleason	≤ 6	7	≥ 8
PSA (ng/ml)	< 10	10-20	>20
Clinical stage	≤ T2a	T2b	≥ T2c

Favorable	Unfavorable
3+4	4+3
10-15	15-20

<u>15 year PCSM</u>
Low: 2%
Intermediate: 10%
High: 19%



Stephenson A et al. J Clin Oncol 2009

Risk groups

Risk Group	Clinical/Pathologic Features See Staging (ST-1)		
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g		
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[f]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

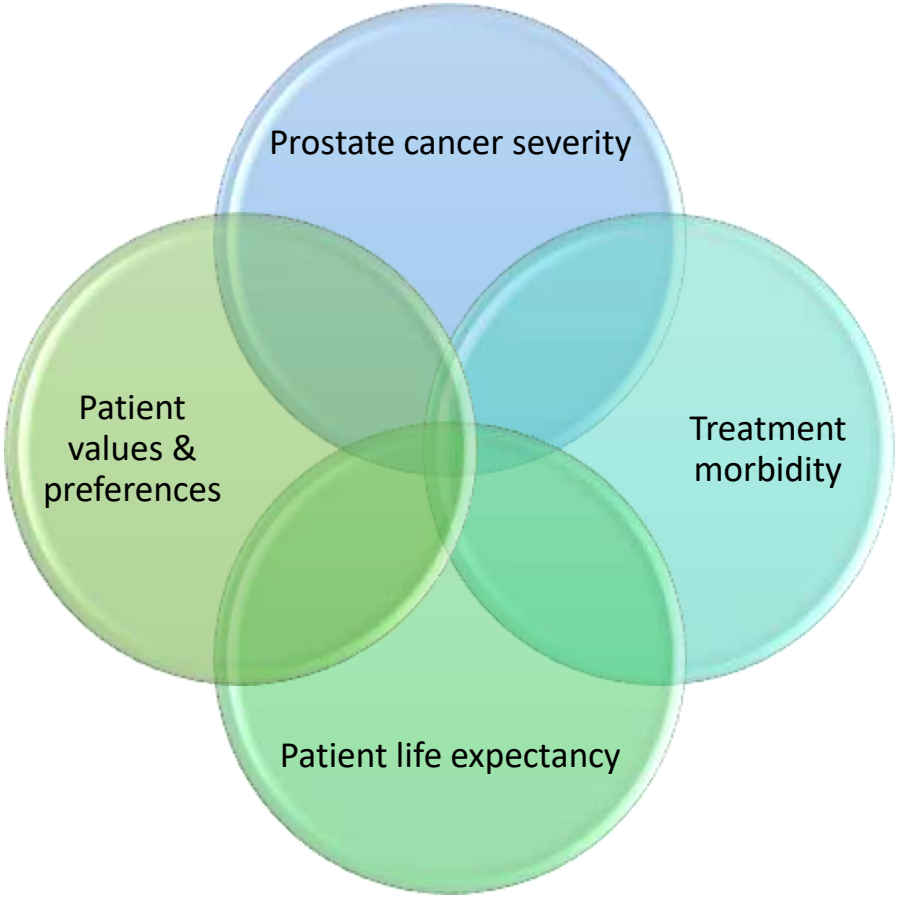
How do we treat prostate cancer?




Treating prostate cancer

- Many treatment options exist
- Is treatment necessary?
- What treatment is “best”?
- How do we balance morbidity of treatment with risk of cancer death?
- What side effects is the patient willing to accept?

Prostate cancer treatment decision making



Watchful waiting

Active surveillance

Radical prostatectomy

External beam radiotherapy

Brachytherapy

Watchful waiting

- For men with a short life expectancy
- A more “palliative” approach
  - Symptom guided treatment
  - Preserve QOL by avoiding side effects of curative-intent strategies
- “Wait” for the development of metastatic disease before starting therapy (i.e. androgen deprivation)

Active Surveillance

- Goal 1
  - Delay or avoid of treatment in men ***thought to have*** clinically indolent prostate cancer

- Goal 2
  - Avoid treatment associated adverse effects, without worse cancer outcomes

Who is eligible for AS?

- All low risk patients

- Some low volume, favourable intermediate risk patients (3+4=7, GG2, with <10% pattern 4)

Triggers for treatment while on AS

- Art of medicine
- May change in the MRI era
- Upgrading > PSA rise > cancer volume > anxiety

How do people do long term on AS?

Table 1. Protocols and Outcomes of Selected Active Surveillance Cohorts for Prostate Cancer[a]

	University of Toronto	University of California, San Francisco	Johns Hopkins University	Göteborg Screening Trial	ProtecT Active Monitoring Group
Source	Klotz et al,[37] 2015	Welty et al,[38] 2015	Tosoian et al,[39] 2015	Godtman et al,[40] 2016	Hamdy et al,[41] 2016
No. of participants	993	810	1298	474	545
Median follow-up, mo	77	60	60	96	120
Surveillance outcomes, No. (%)					
Definitive treatment	267 (27)	348 (43)	471 (36)	202 (43)	291 (53)
Metastasis	28 (2.82)	1 (0.12)	5 (0.40)	7 (1.48)	33 (6.06)
Prostate cancer mortality	15 (1.51)	0	2 (0.15)	6 (1.27)	8 (1.47)

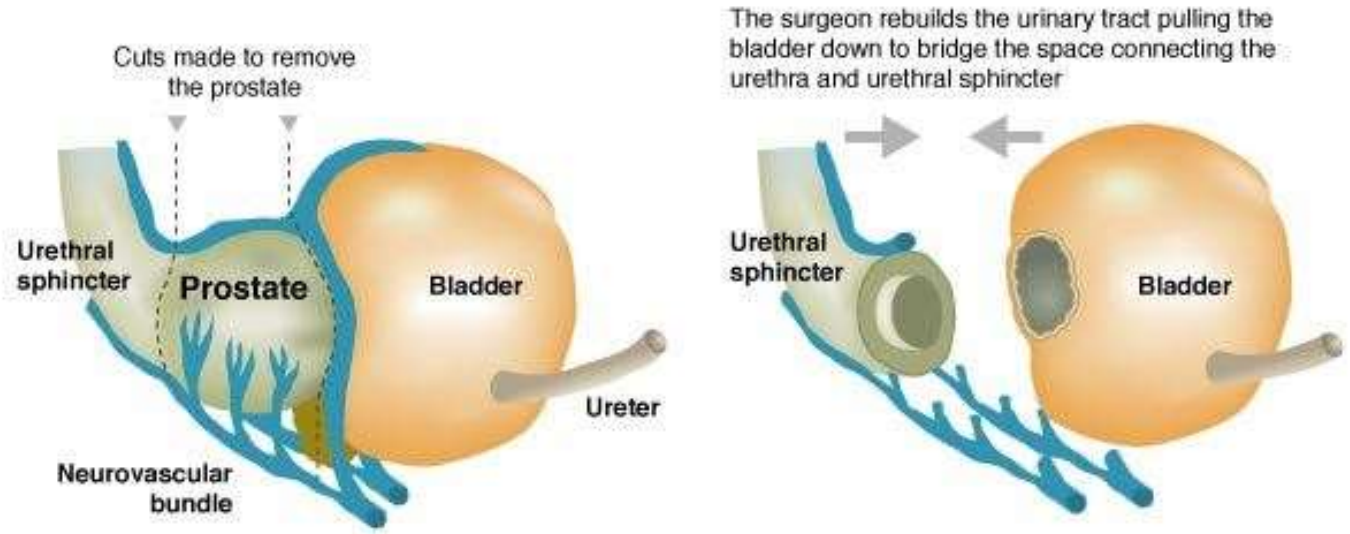
Abbreviations: CAPRA, Cancer of the Prostate Risk Assessment; ProtecT, Prostate Testing for Cancer and Treatment; PSA, prostate-specific antigen.

[a] Active surveillance is an expectant management approach that monitors for prostate cancer progression and triggers treatment with the intent to cure.

Risk of ultimately requiring treatment: 25-50%
Risk of developing metastatic disease: 0-6%
Risk of prostate cancer morality: 0-1.5%

Litwin M JAMA 2017

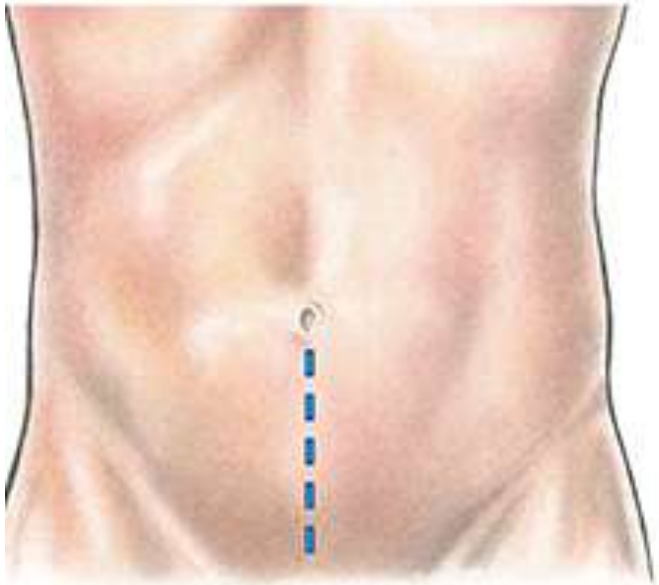
Radical prostatectomy



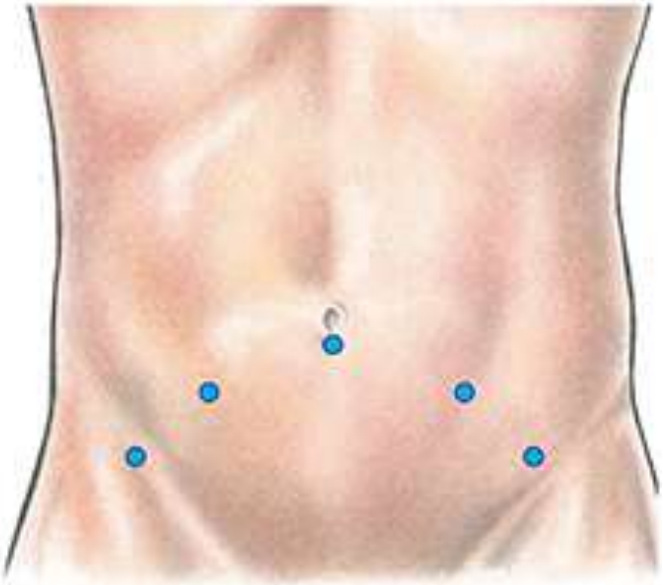
Source: Dr. Patrick Walsh's Guide to Surviving Prostate Cancer by Patrick C. Walsh, M.D. and Janet Farrar Worthington
Illustration by Dan Ion/The Wall Street Journal

Radical prostatectomy

Radical open prostatectomy incision (retropubic approach)



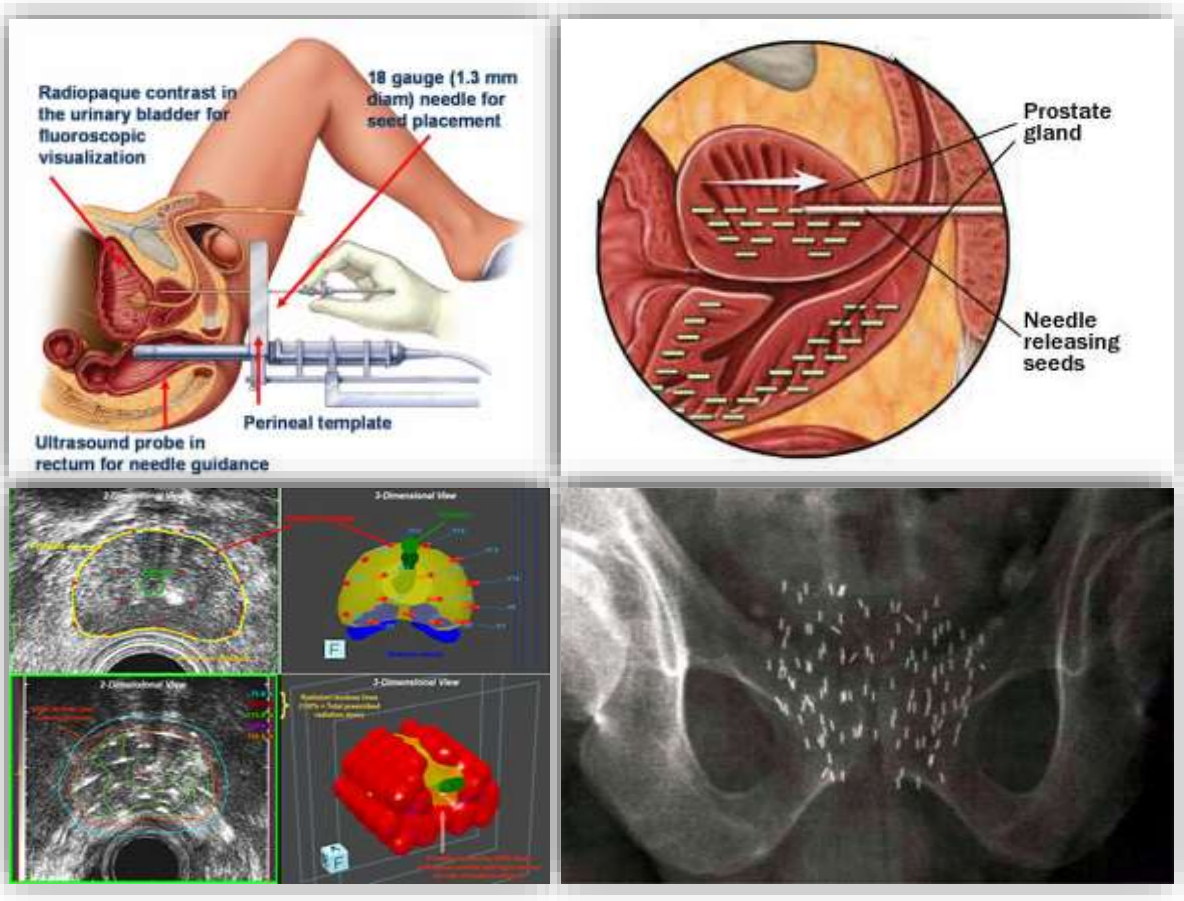
Robotic-assisted laparoscopic radical prostatectomy incisions



Minimally invasive surgery

External beam radiotherapy

Brachytherapy



ProTect Trial:
RCT for surgery vs XRT vs observation

Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

* P values were calculated with the use of a log-rank test of the null hypothesis of no difference in effectiveness across the three treatments. The planned adjusted analysis was not possible owing to the low number of events.
† Deaths due to prostate cancer were defined as deaths that were definitely or probably due to prostate cancer or its treatment, as determined by the independent cause-of-death evaluation committee.
‡ Disease progression was defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

Mortality rates low:
99% PCSS at 10 years

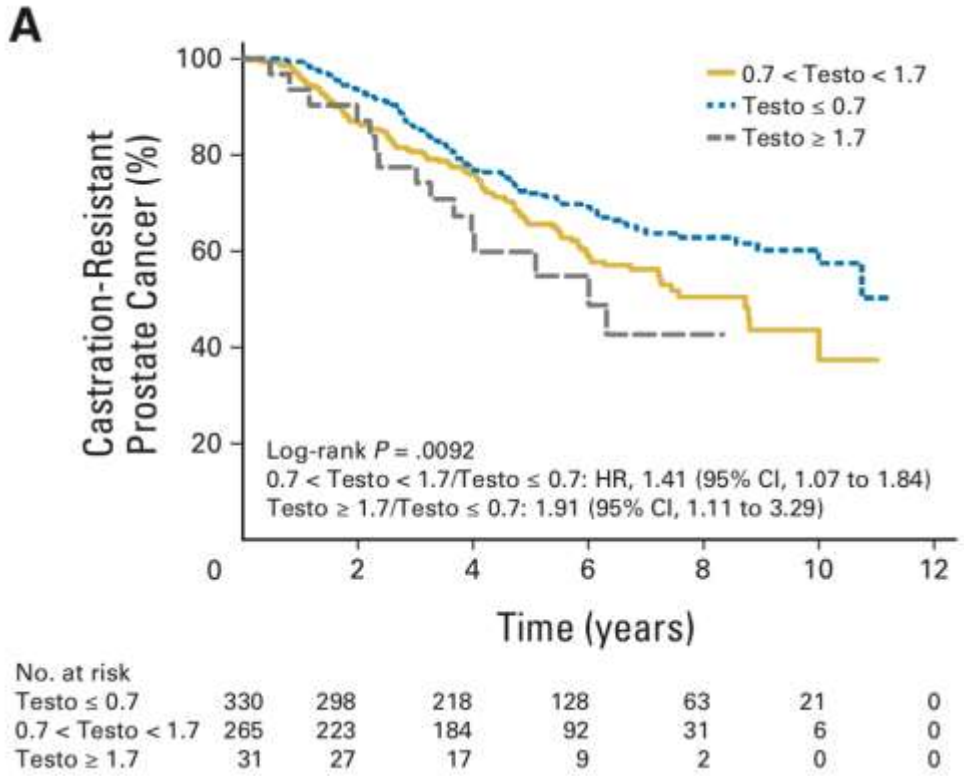
Surgery and radiation *both* reduced the rates of disease progression and metastatic disease, but with side effects

Hamdy FC et al NEJM 2016

Androgen deprivation therapy

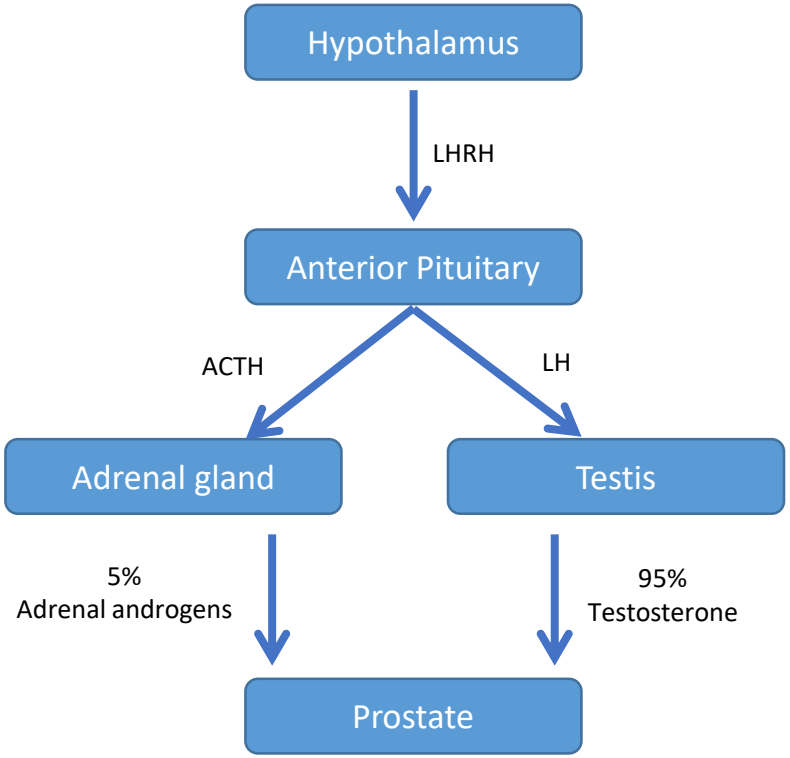
- Regularly used among patients treated with radiation therapy in localized disease
- A backbone of treatment for metastatic patients

Goal of ADT:
Reduce testosterone to “castrate” levels

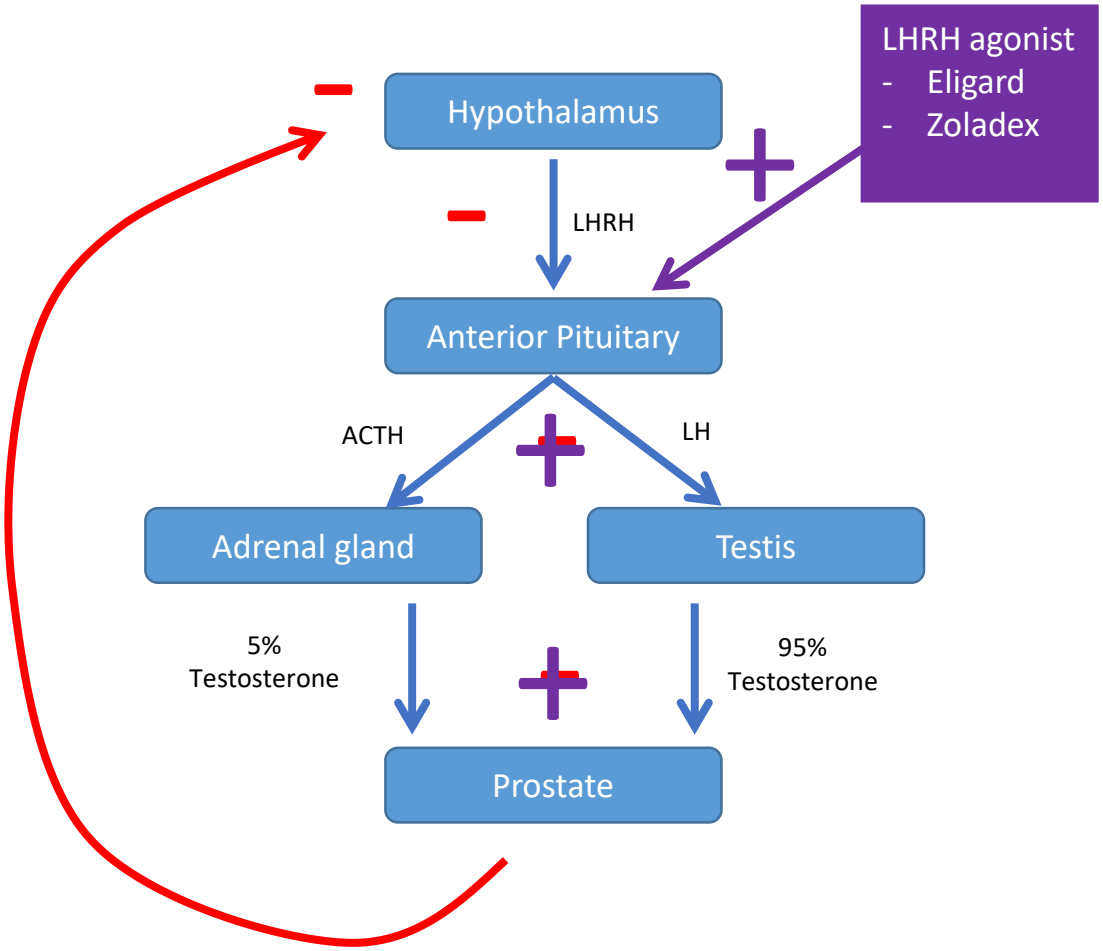


Klotz L et al. J Clin Oncol 2015

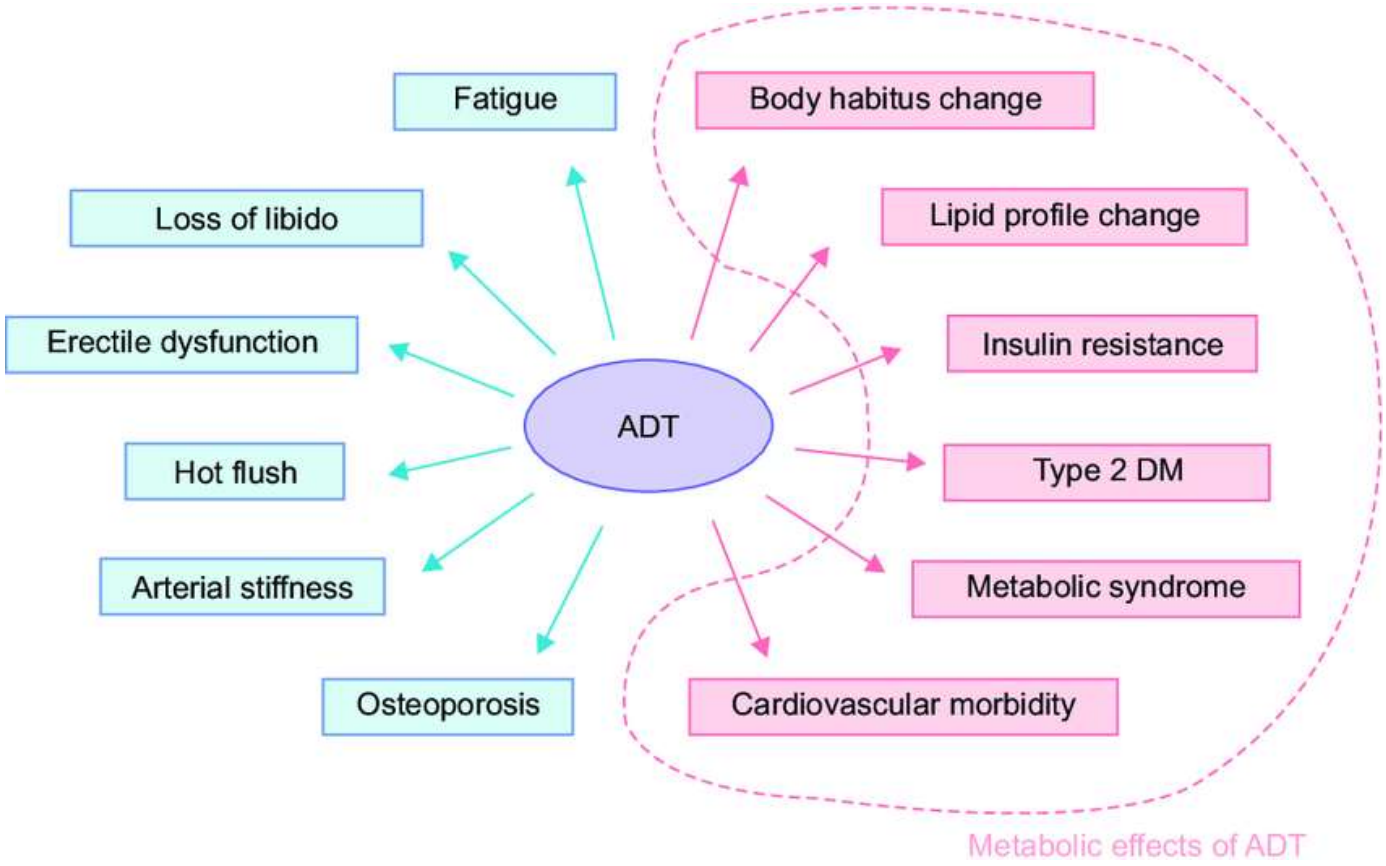
ADT: Mechanism of action



ADT: Mechanism of action



ADT has significant side effects



Managing side effects of ADT

CUA GUIDELINE

UPDATE – Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies

Andrea Kokorovic[1], Alan I. So[2], Hosam Serag[2], Christopher French[3], Robert J. Hamilton[4], Jason P. Izard[5], Jasmir G. Nayak[6], Frédéric Pouliot[7], Fred Saad[1], Bobby Shayegan[8], Armen Aprikian[9], Ricardo A. Rendon[10]

Take Home Messages

- Prostate cancer is very common
- Risk stratification guides treatment
- There are multiple treatment options for localized prostate cancer
- Treatment decisions must consider patient longevity, patient values and preferences
- Be aware of the side effects of ADT
- Always ask, is this a turtle, a rabbit or a bird?