Prostate Cancer Supportive Care

RECOGNITION AND MANAGEMENT OF TREATMENT RELATED SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY(ADT)

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RESEARCH TREATMENT

VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence

Department of UROLOGIC SCIENCES UBC

PROSTATE CANCER SUPPORTIVE CARE (PCSC) PROGRAM

The program is currently comprised of eight modules:

1. Introduction to Prostate Cancer & Primary Treatment Options
2. Managing the Impact of Prostate Cancer Treatments on Sexual Function and Intimacy
3. Exercise for Prostate Cancer Patients
4. **Recognition & Management of Treatment Related Side Effects of Androgen Deprivation Therapy (ADT)**
5. Pelvic Floor Physiotherapy for Bladder and Bowel Concerns
6. Counselling Services
7. Metastatic Disease Management
8. Nutrition Advice for Prostate Cancer Patients

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INTRODUCTION TO ANDROGEN DEPRIVATION THERAPY (ADT)

- Prostate Cancer Overview
- Androgen Deprivation Therapy
- Treatment Options
- Side Effects and Management

PROSTATE CANCER OVERVIEW

- It is the most common cancer for Canadian men
  - 1in 9 men will be affected
- Often slow growing and treatable
- Advances in screening, testing, and treatment options have improved prostate cancer outcomes
- 20% of men present with De Novo metastatic disease and about 20% of men will relapse post primary treatment

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CERTAIN FACTORS ARE ASSOCIATED WITH INCREASED RISK OF DEVELOPING PROSTATE CANCER

Age and race/ethnicity

≥65
Unc
com
≥65

Afric
Com
men
highe
prost
diagr
dying

Diet and cigarette smoking

Hereditary and genetic factors

Median survival for those with *BRCA1/2* or *ATM* gene mutations was half than that of adults without mutations

ly history of prostate cancer
ate cancer risk is higher in
nts with relatives who have been
osed with the disease[2]

her who has/had a
gnosis of breast cancer
state cancer risk is 19%-24%
er in these men*[1]

mline HRRm
luding BRCA)[5]
se mutations have been associated with increased prostate cancer risk[5]

HRRm=homologous recombination repair.
*Results from observational cohort studies

1. Wein AJ, et al. Campbell-Walsh Urology. 11th ed, international ed. China: Elsevier; 2016; 2. Am Cancer Soc. Prostate cancer risk factors. Available at https://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html (Accessed June 2021); 3. Irizarry-Ramirez M, et al. *Prostate.* 2017;77:1118-1127; 4. Prashanth R. *World J Oncol*. 2019 Apr; 10(2): 63–89; 5. Nicolosi P, et al. *JAMA Oncol*. 2019 Apr; 5(4): 523–528.

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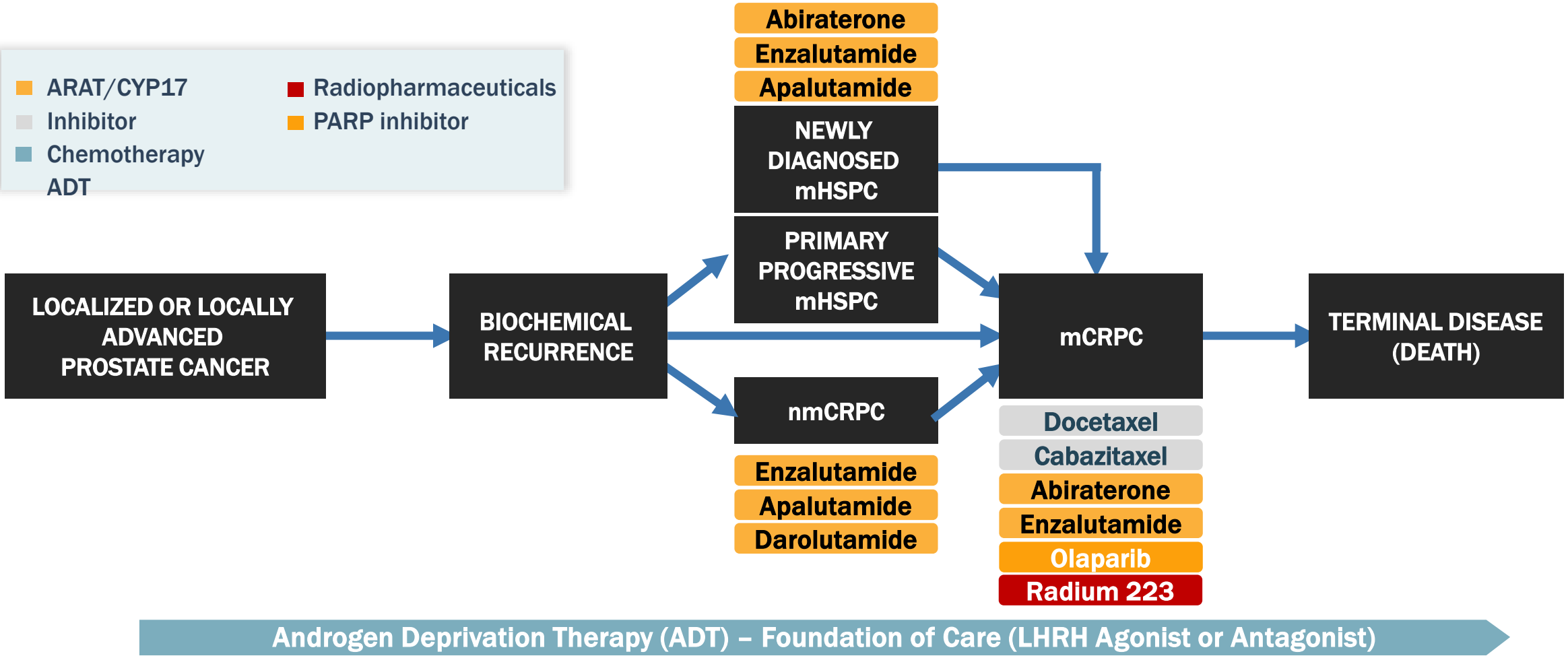
THE PROSTATE CANCER LANDSCAPE



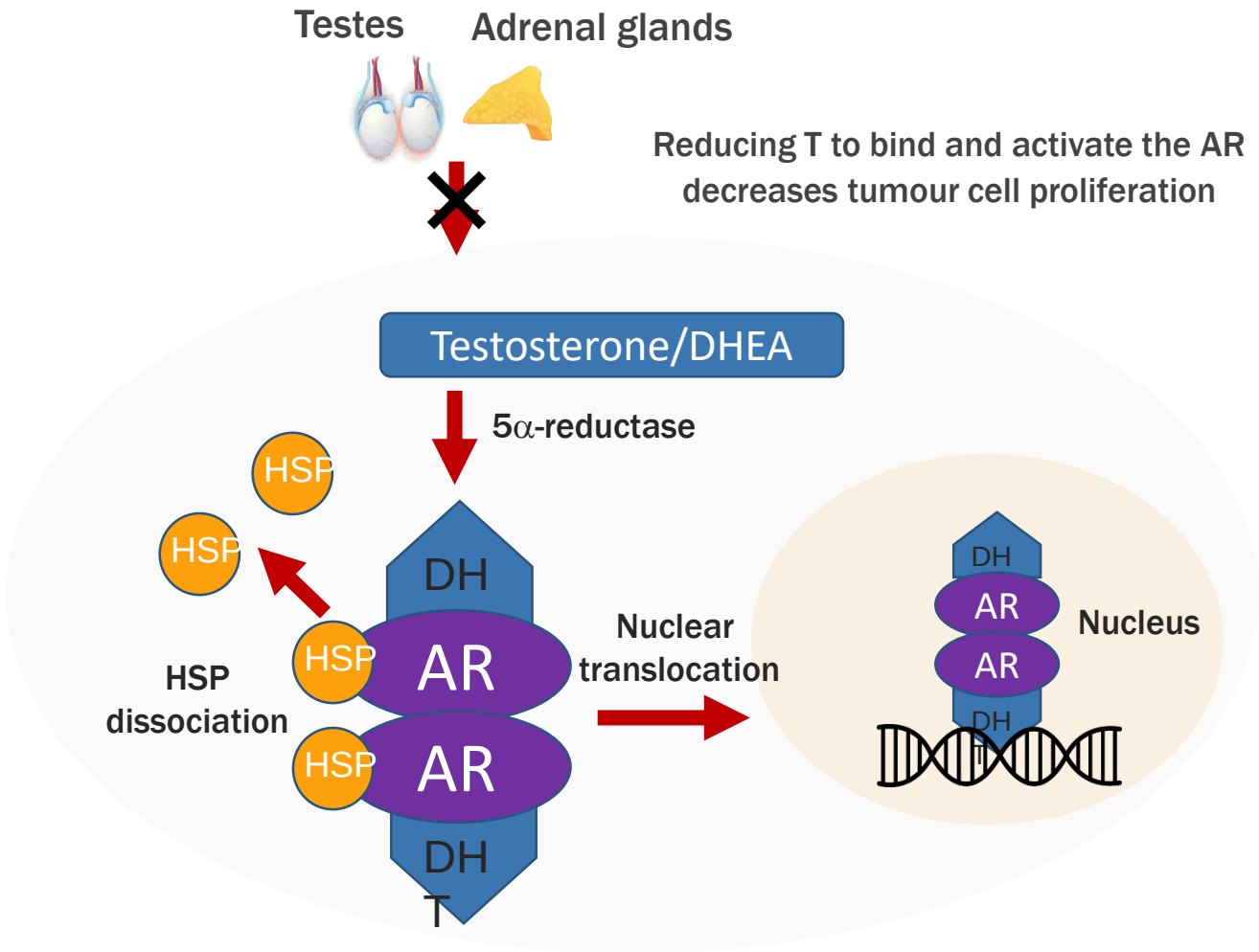
ARAT Androgen-receptor axis-targeted agents **LHRH** Luteinizing hormone-releasing hormone
mHSPC Metastatic hormone sensitive prostate cancer
nmCRPC Non-metastatic castration resistant prostate cancer **mCRPC** Metastatic CRPC

ANDROGEN RECEPTOR (AR) SIGNALLING PATHWAY

Androgens (T) are produced at 3 sites

- Testes
- Adrenal glands
- Prostate tumour cells (occasionally)

In the eugonadal state, 95% of androgens are produced by the testis



AR Androgen receptor **DHT** Dihydrotestosterone
HSP Heat shock protein **T** Testosterone

Figure adapted from ©Bandyopadhyay M, Muthuirulan P. J Drug Des Devel 2017;1:1-10

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GOALS OF ADT

- Achieve and maintain an environment of low T activity
  - Suppress T to “castrate levels” and/or
  - Effectively block AR
- Rapid onset of T suppression
- Block effect of T surge if relevant
- Reduce T to < 0.7 nmol/L (< 20 ng/dL)
- Consistent T suppression
  - No escapes or microsurges while on treatment
- Achieve and maintain low nadir T
- Personalize
  - Tailor to patients’ lifestyles and schedules
- Minimize side effects
- Consider cost
- Improve patient outcomes
  - Reduce morbidity
  - Extend survival

GUIDELINES: TESTOSTERONE TARGETS DURING ADT

There are different definitions of castrate testosterone:

Bethesda (US) Consensus 2012[1]
T < 20 ng/dL (0.7 nmol/L)

EAU Guidelines 2021[2]
T < 20 ng/dL (0.7 nmol/L)

Canadian Consensus 2018[3]
T ≤ 20 ng/dL (0.7 nmol/L)

NCCN Guidelines 2021[4]
T < 50 ng/dL (1.7 nmol/L)

AUA Guidelines 2018[5]
T < 50 ng/dL (1.7 nmol/L)

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OPTIONS TO CONTROL TESTOSTERONE LEVELS

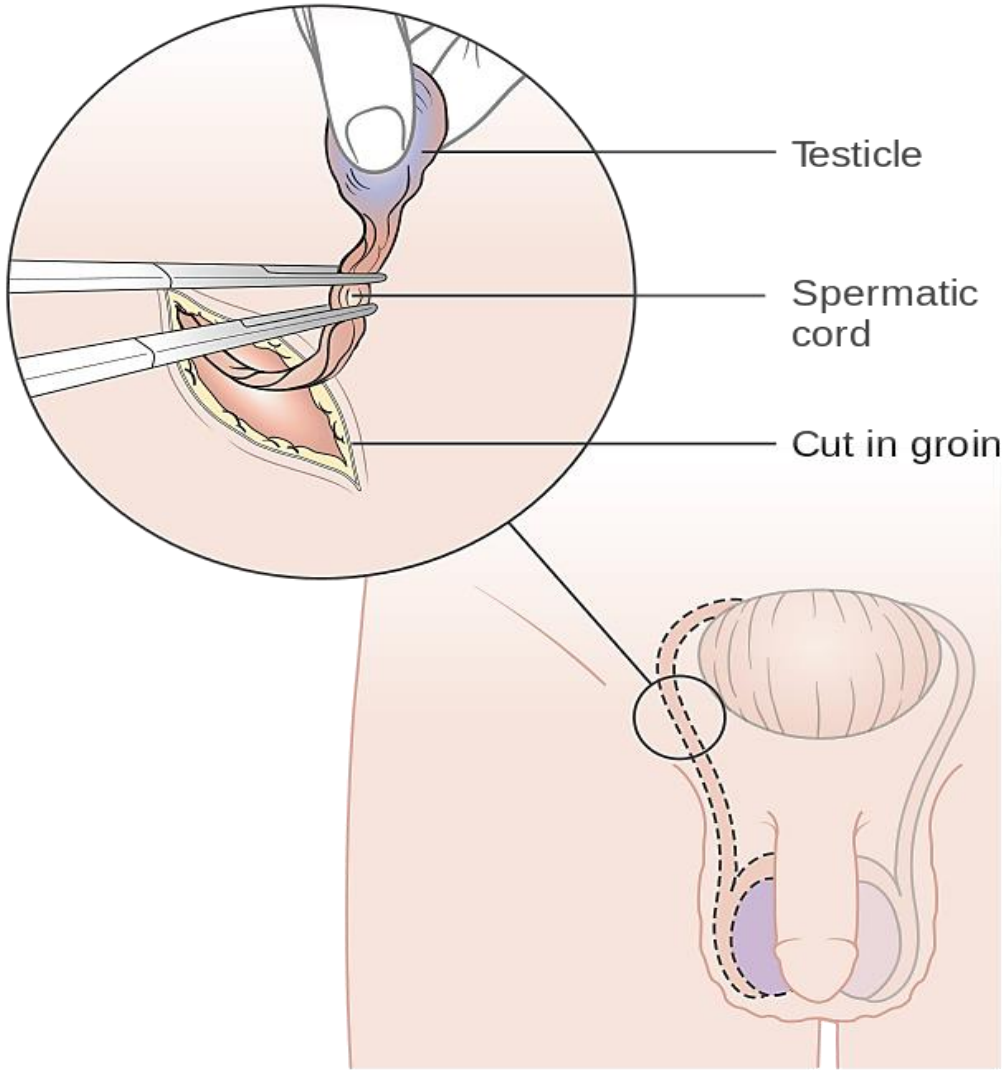
- **Surgery**
  - Orchiectomy

- **Human Luteinizing Hormone-Releasing Hormone (LHRH) Agonist**
  - Goserelin Acetate (Zoladex)
  - Leuprolide Acetate (Lupron or Eligard)
- **Human Luteinizing Hormone-Releasing Hormone (LHRH) Antagonist**
  - Degarelix (Firmagon)
- **First Generation Non-Steroidal Anti-androgens**
  - Bicalutamide (Casodex)
  - Nilutamide (Nilandron)
  - Flutamide (Euflex)

OPTIONS TO CONTROL TESTOSTERONE LEVELS

Orchiectomy

1. The surgeon will make a cut (incision) near the groin.
2. The testes are removed through the incision.
3. The incision is closed with stitches and covered with a dressing.



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OPTIONS TO CONTROL TESTOSTERONE LEVELS

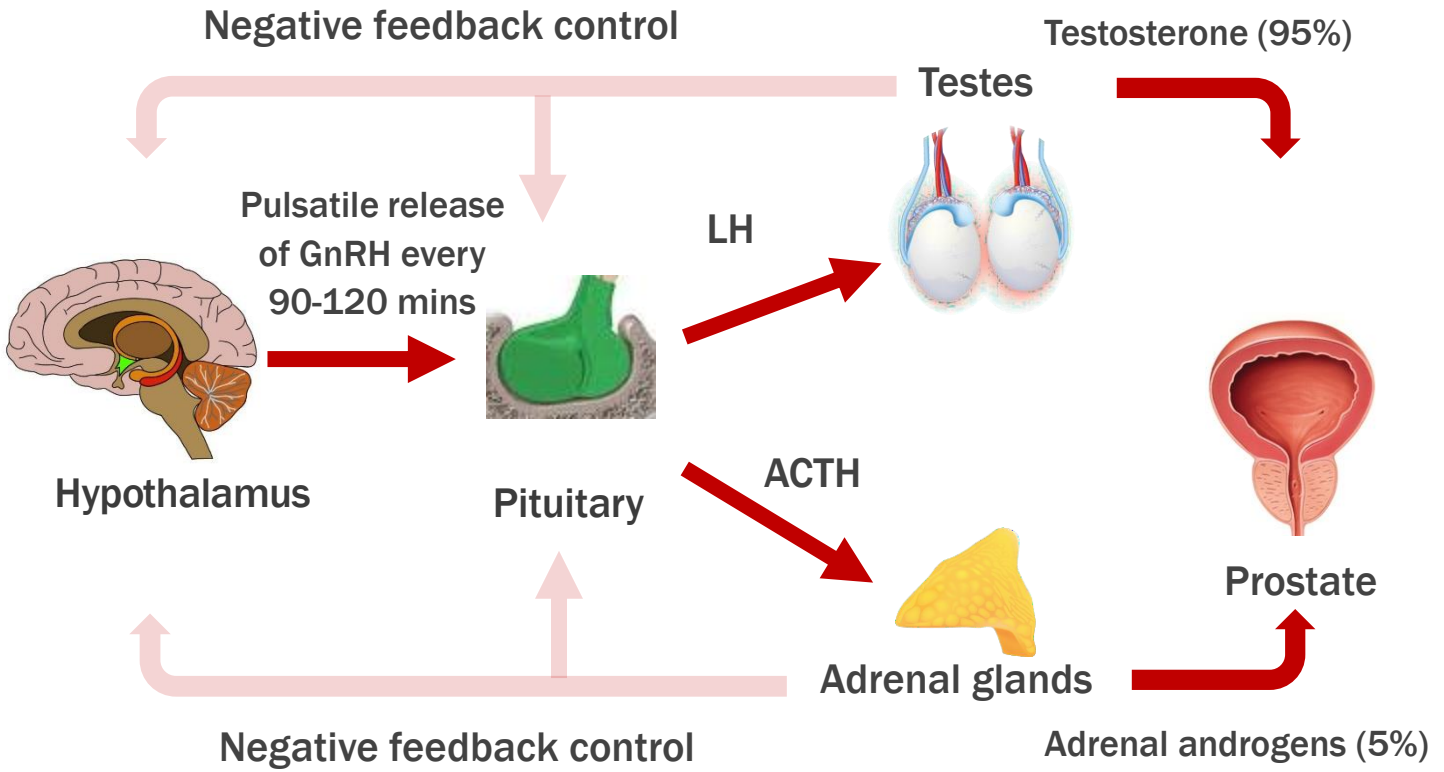
Androgen Deprivation Therapy

LHRH agonists

- Overstimulate the pituitary gland and over-ride the pulsatile control of LH release by natural LHRH
- Result: downregulation of LHRH receptors and desensitization of the gland

LHRH antagonists

- Directly bind to the pituitary
- Prevent release of LH + FSH
- Result: Removes stimulus to the testes to produce T



- **ACTH** Adrenocorticotropic hormone **FSH** Follicle-stimulating hormone
  GnRH Gonadotropin-releasing hormone **LH** Luteinizing hormone **T** Testosterone

Drudge-Coates L. Int J Urological Nursing 2010;3:85-92

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LHRH THERAPY OPTIONS

Attributes	leuprolide SC[1]	leuprolide IM[2,3]	goserelin[5,6]	degarelix†[6,7]
Needle Gauges	20 (7.5, 22.5, 30 mg) 18 (45 mg)	23 (all doses)	16 (3.6 mg) 14 (10.8 mg)	27
Route of administration	Subcutaneous	Intramuscular	Subcutaneous Implant	Subcutaneous
Dosing Intervals (months)	1 ✓ 3 ✓ 4 ✓ 6 ✓	1 ✓ 3 ✓ 4 ✓ 6	1 ✓ 3 ✓ 4 6	1 ✓ 3 4 6
Injection Volume per Dose (mL)	0.25 0.37 0.50 0.375	1.0 1.5 1.5	0.01 0.03	2x3.0

† LHRH antagonist
* Initial dose of 240mg (2 x 3 mL), followed by monthly maintenance doses of 80 mg (4 mL)
IM Intramuscular **SC** Subcutaneous

1. Eligard Product Monograph, December 2018 **2.** Lupron Product Monograph (Canada), November 2020
3. Lupron Product Monograph (US), June 2016) **4.** Trelstar Product Monograph, January 2021
5. Zoladex Product Monograph, December 2017 **6.** TerSera Therapeutics Inc., Data on file
7. Firmagon Product Monograph, March 2016

HOW DO THEY COMPARE?

Items	Surgical Castration	Medical Castration	
Procedure	Orchiectomy	LHRH Agonists	LHRH Antagonist
Castration	Irreversible	Reversible	Reversible
Castrate of level of testosterone	3-4 days	3-4 weeks	3-4 days
Testosterone flare	No	Yes	No
Prior Anti-Androgens	No	Yes	No
Local reaction	N/A	1%	40%
Administration	Once	3, 4, and 6 months	monthly
Cardiovascular complications	Similar?		
Psychologic preference	22%	78%	
Costs	Hundreds	Thousands	

CHOOSING AN ADT REGIMEN

There are many choices of ADT, which are often influenced by coverage, physician preference, or other factors:

Frequency of administration influenced by:

- Mobility issues
- Living in remote locations
- Compliance
- Lifestyle
- Availability of home injection program

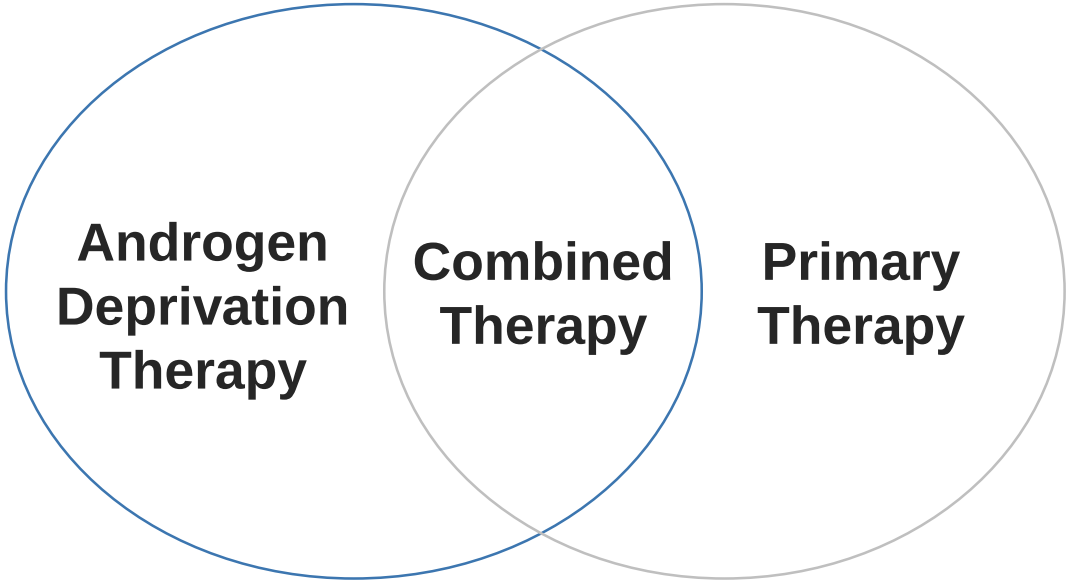
Intermittent therapy considered for:

- nmCSPC with good initial response to ADT
- Low burden mCSPS and complete response to ADT

PRIMARY THERAPY AND ADT SIDE EFFECTS

Androgen Deprivation Therapy

- Weight gain
- Loss muscle mass
- Gynecomastia
- Testicular atrophy
- Loss of body hair
- Hot flashes
- Fatigue
- Mood disturbances



Primary Therapy

- Urinary incontinence
- Climacturia
- Altered or painful orgasm
- Dry ejaculation

Combined Therapy

- Erectile dysfunction
- Penile shortening
- Low/no libido
- Depression
- Altered couple relationship
- Partner distress

SIDE EFFECTS OF ADT

What physicians commonly tell patients

Loss of libido

(sex drive)

Erectile dysfunction

Hot flashes

Modified from Higano C Hematol Oncol Clin North Am. 2006 20(4):909-923.

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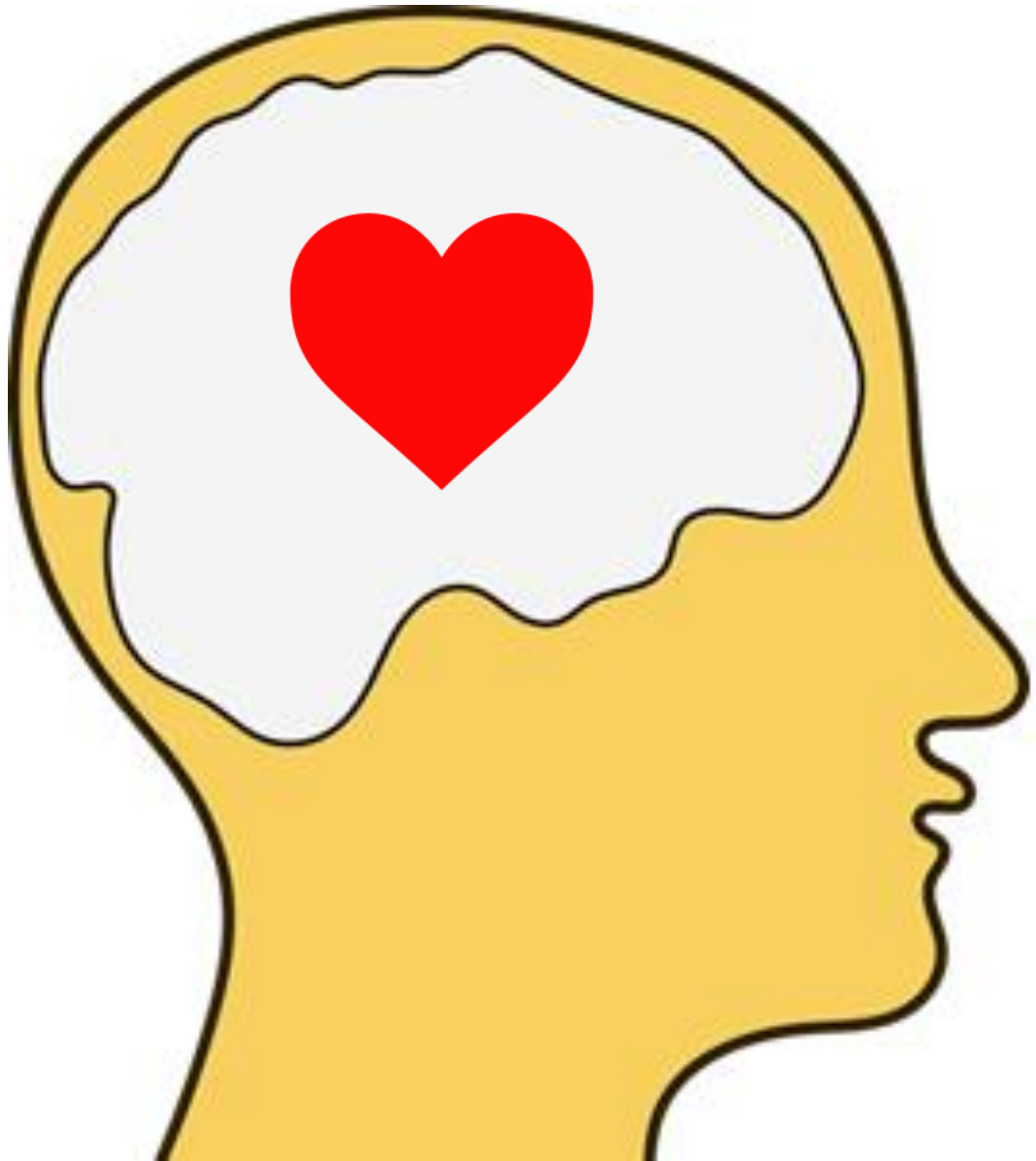
LOSS OR LOWERING OF LIBIDO (SEX DRIVE)

- No magic pill to improve libido
- Lower libido is age related

How to enhance your libido?				
Exercise	**Enhance Intimacy**	**Mindfulness**	**Sensate Focus**	**Simmering**

Module 2: Managing the Impact of Prostate Cancer Treatments on Sexual Function and Intimacy



ERECTILE DYSFUNCTION (ED)

ADT can lower your sex drive and cause ED

Erectile Dysfunction Treatments:

- Oral medications (e.g. Viagra or Cialis)
- Vacuum pump erection devices
- Penile injections

Incorporate couple-based coping and education
Psychological and/or relationship counseling

Note! It is still possible to orgasm without an erection

ERECTION=ERECTION, ORGASM=ORGASM, ERECTION≠ORGASM

HOT FLASHES

Commonly occur after the first 2 months of starting ADT

What worsens hot flashes?

- Diet: avoid alcohol, spicy food, and caffeine (coffee, tea, colas, chocolate…etc.)
- Heat: stay cool and hydrated
- Stress: try to relieve stress

What can help with my hot flashes?

- Wear sweat wicking material
- Sleep with layers that can be removed and use a fan
- Massage and acupuncture
- Follow a regular exercise program
- Relaxation and Cognitive Behavioral Therapy (CBT)

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HOT FLASHES

Other things people try:

- Soy foods
- Flaxseed
- Vitamin E
- Black Cohosh
- Garlic
- Ginseng

Note! Always ask your doctor before trying a new supplement!

Medications:

- Androcur (cyproterone acetate)
- Depo-Provera (medroxyprogesterone)
- Megace (megestrol acetate)
- Gabapentin 300 mg at bedtime or 100 mg every 8 hours and titrate
- Venlafaxine (Effexor XR) 37.5mg – helps hot flashes *and* depressive symptoms

SIDE EFFECTS OF ADT

What physicians commonly tell patients	What patients see
Loss of libido (sex drive)	Weight gain
Erectile dysfunction	Gynecomastia (increased breast tissue)
Hot flashes	Loss of muscle mass and strength
	Shrinkage of penis and testicles
	Hair changes

Modified from Higano C Hematol Oncol Clin North Am. 2006 20(4):909-923.

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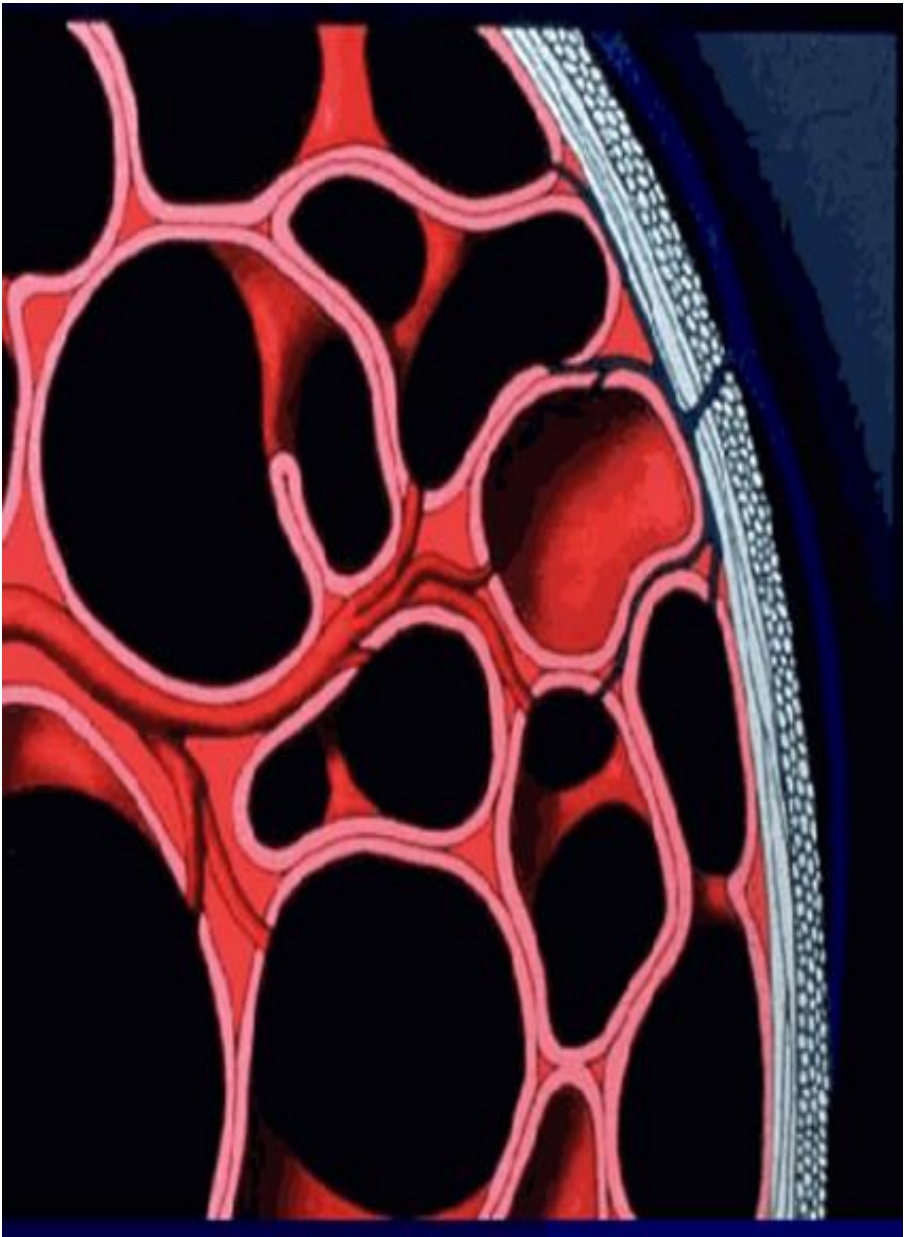
WEIGHT GAIN AND ASSOCIATED CHANGES

- More than 40% of men are overweight at diagnosis
- Common to gain up to 10 kg over 6-9 months due to increased appetite
- Increase in body fat especially at waist, hips, thighs
- Loss of muscle mass and strength
- Weight is difficult to lose even if ADT is stopped!

- Need to be physically active-aerobic and resistance exercise
- Engage in healthy lifestyle habits
- **Module 3 and Module 8 : Exercise and Nutrition**

SHRINKAGE OF PENIS AND TESTICLES



- Genital shrinkage: penis length, girth and testicular volume
- Apoptosis (cell death) of trabecular smooth muscle
- Impaired veno-occlusive mechanism
- Fibrotic changes
- Usually stops 12-18 months after starting ADT

Work with PCSC Sexual Health Clinician on penile rehabilitation strategies

(Module 2)

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HAIR CHANGES

- Thinning or loss of body hair on trunk, arms, legs
- Beard softer
- May or may not be bothersome
- Not a health issue although it can be distressing if not informed

- **Reversible if ADT is stopped!**

SIDE EFFECTS OF ADT

What physicians commonly tell you	What you see	What patients don't see
Loss of libido (sex drive)	Weight gain	Loss of bone density
Erectile dysfunction	Gynecomastia (increased breast tissue)	Diabetes and cardiovascular disease
Hot flashes	Loss of muscle mass and strength	Metabolic syndrome
	Shrinkage of penis and testicles	
	Hair changes	

Modified from Higano C Hematol Oncol Clin North Am. 2006 20(4):909-923.

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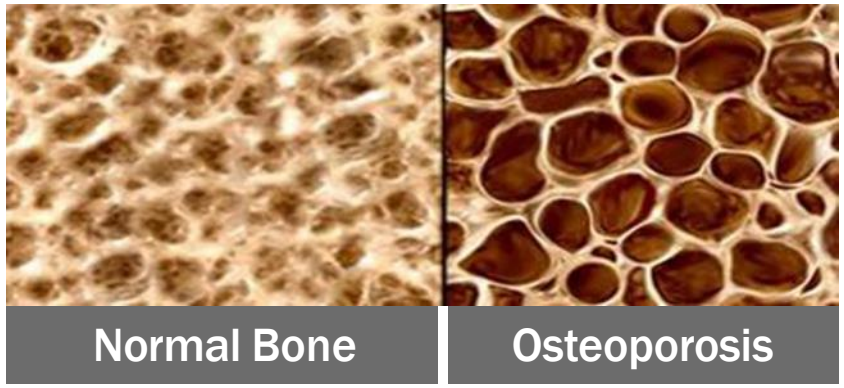
LOSS OF BONE DENSITY

Hypogonadal bone loss

- Among the leading causes of osteoporosis in men in the US[1]
- Incidence increases with age
- ADT causes hypogonadal bone loss[2,3]
  - Increased skeletal response to PTH
  - Low estrogen alters balance of osteoclast/osteoblast activity



NCCN Guidelines 2021:[4]

- Supplemental calcium and vitamin D3
- Additional treatment for men ≥ 50 yrs with low bone mass and:
  - 10-year probability of hip fracture ≥ 3%, or
  - 10-year probability of major osteoporosis-related fracture ≥ 20%
- Baseline BMD test, re-test after 1 year of treatment
- Consider anti-resorptive drugs

- **BMD** Bone mineral density
  PTH Parathyroid hormone

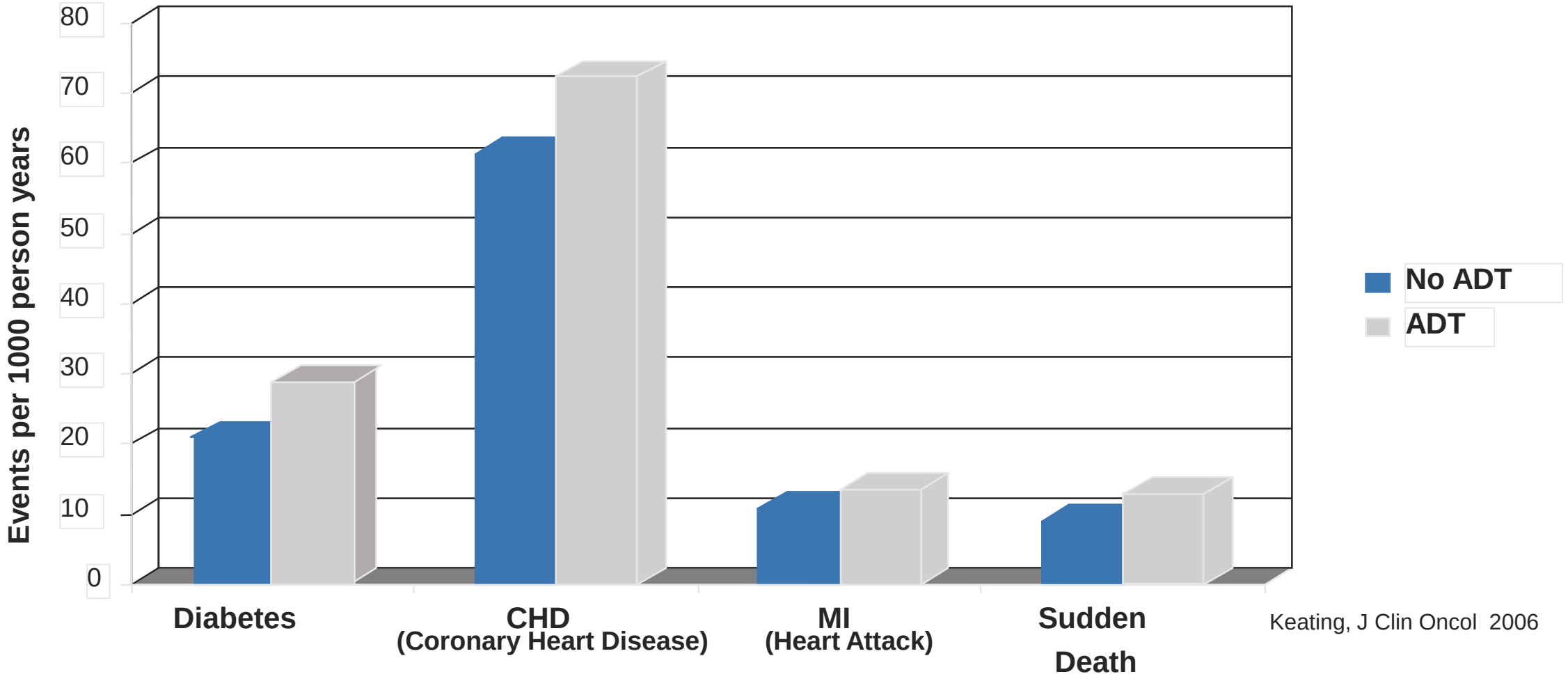
1. Bilezikian JP. J Clin Endocrinol Metab 1999;84:3431-4 **2.** Leder BZ, et al. J Clin Endocrinol Metab 2001;86:511-6 **3.** Falahati-Nini A, et al. J Clin Invest 2000;106:1553-60 **4.** NCCN. Prostate Cancer (Version 1.2021). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 3, 2021.

LOSS OF BONE DENSITY

- All patients on ADT need to ensure they are receiving adequate amounts of Calcium and Vitamin D
    - **1200 mg Calcium** (not to exceed 2000 mg/day)
    - **1000 IU Vitamin D** (not to exceed 4000 IU/day)

  *unless serum vitamin D levels are low and being followed by a physician
- Men with moderate to high risk of fracture at 10-years should be offered drug therapy
    - Denosumab (Prolia) 60mg SC every 6 months (Must have good dental hygiene!)
- Resistance exercises and high impact exercises help preserve BMD

Diabetes and Cardiovascular Disease During ADT: Observational Study of 73,196 Men



Keating, J Clin Oncol 2006

- Patients with pre-existing cardiovascular disease (e.g. heart attack and/or congestive heart failure) are at increased risk for cardiovascular events when treated with ADT

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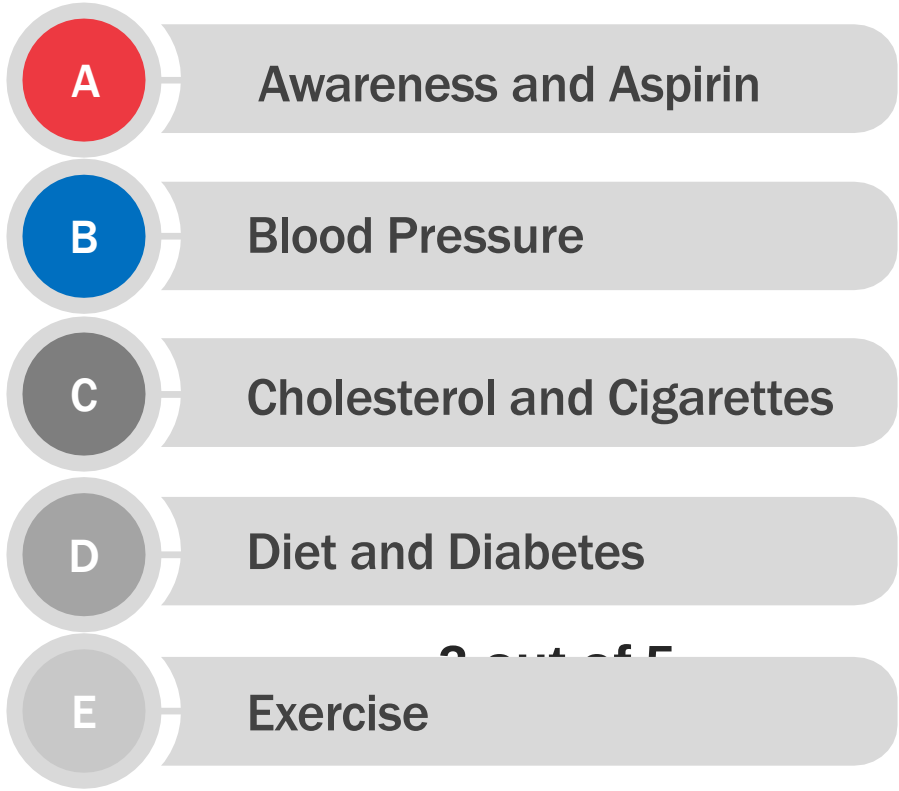
METABOLIC SYNDROME

- Fat mass inreases 10-20%
- Lean body mass decreases 2-3%
- Increased insulin levels within months
- Lipids increase in unpredictable ways
- Increases in blood pressure
- Increase in blood sugar levels
- Hemoglobin level could also decline on ADT on average to 125-130g/L (the mechanism is not clearly understood)

NCCN Guidelines:[1]

- Follow traditional assessments of risk factors for diabetes
- Team approach
  - Primary care
  - Nursing
  - Geriatrician
  - Endocrinologist

ABCD Paradigm:[2]



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SIDE EFFECTS OF ADT

What physicians commonly tell you	What you see	What you don't see	What you feel
Loss of libido (sex drive)	Weight gain	Loss of bone density	Muscle and Joint aches
Erectile dysfunction	Gynecomastia (increased breast tissue)	Diabetes and cardiovascular disease	Depression and emotional lability
Hot flashes	Loss of muscle mass and strength	Metabolic syndrome	Cognitive dysfunction
	Shrinkage of penis and testicles		Fatigue, lack of energy, lack of initiative
	Hair changes		

Modified from Higano C Hematol Oncol Clin North Am. 2006 20(4):909-923.

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ADT-ASSOCIATED MUSCULOSKELETAL SYNDROME

- Muscle and joint aches and pains within 3 months of initiating ADT
- Could be associated with muscle wasting and tendons and ligaments thinning

Nonpharmacological

- Aerobic and resistance exercise
- Acupuncture x2 per week and then x6 weekly

Pharmacological

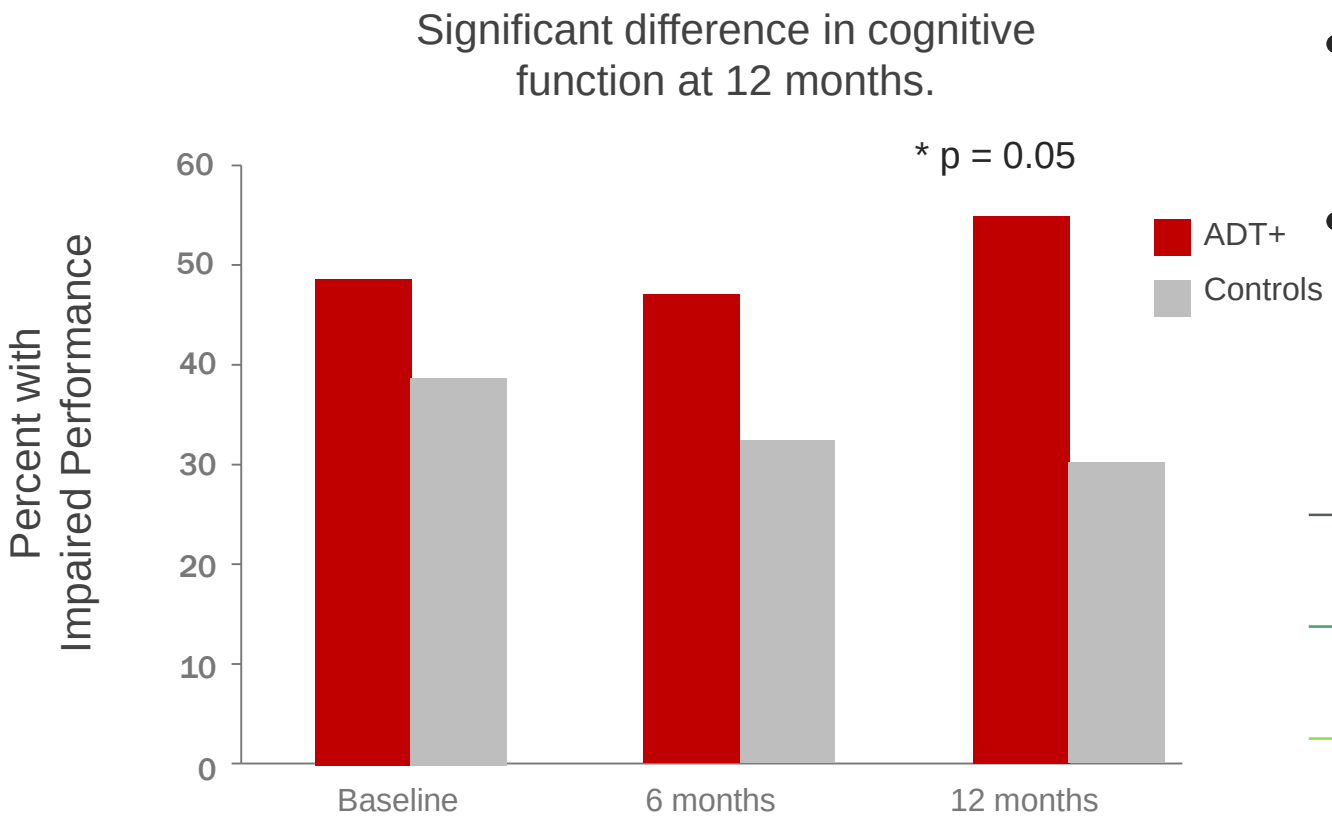
- NSAIDS 400 mg Advil x3 day for 5 days (if no contraindications) then 200-400 mg if needed
- Duloxetine (Cymbalta) 300 mg/day can increase to 60 mg/day if needed

DEPRESSION

- Some men report worsening mood on ADT
  - Many men describe feeling more emotional, greater irritability, crying more easily
- In a large US database study,[1] depressive disorders occurred
  6 – 60 mos following a cancer diagnosis in:
  - 9.5% of men **with PCa but no ADT**
  - 13.9% of men **with PCa on ADT**
    - **vs.** 9.6% of men **without cancer**
- Other studies have shown a similar increase in depressive symptoms in men with PCa, regardless of ADT[2]
- **Monitoring for mood changes is advisable for all patients with PCa**

Exercise impacts mood in a positive way

COGNITIVE FUNCTION



- Impact on a small number of patients
- Typically affects spatial memory (e.g. where did I park the car?)

Counselling services (Module 6)
Exercise! (Module 3)
Reduce clutter in living space
Reduce alcohol and other depressants

Gonzalez BD, et al.. J Clin Oncol 2015;33:2021-7

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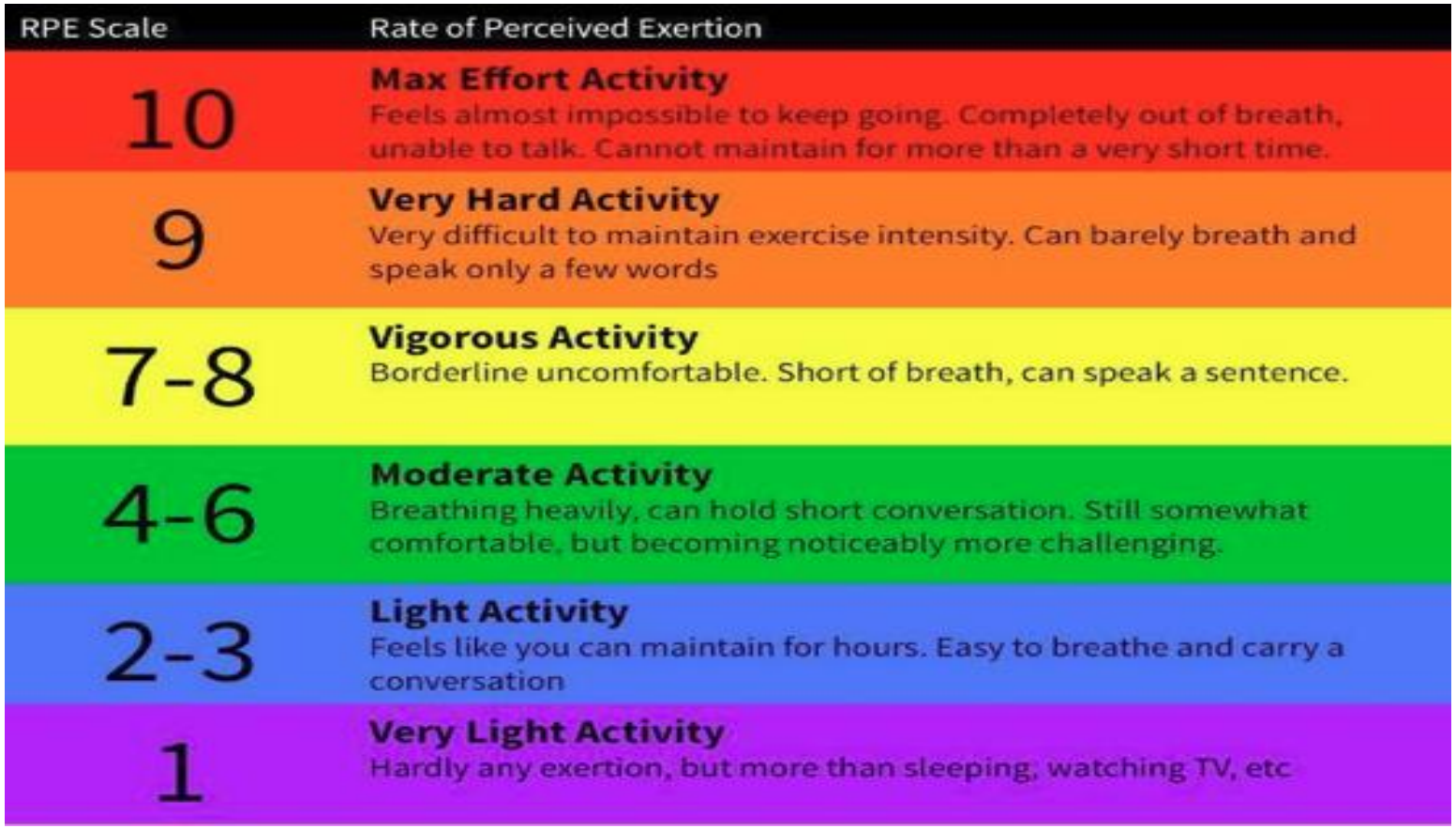
FATIGUE

- Feeling of weariness, tiredness, or lack of energy that does NOT always improve with rest
- May affect your ability to do daily activities
- No medication is known to effectively reduce fatigue
- Exercising improves fatigue, social functioning, and mental health

FATIGUE

150 minutes per week of moderate-to-vigorous physical activity (aerobic exercise) + 2-3 resistance training sessions



HEART RATE

Moderate Intensity
50 - 70%

Vigorous intensity
70 - 85%

ACSM Guidelines (2010), ACS Guidelines (2012), NCCN (2013)

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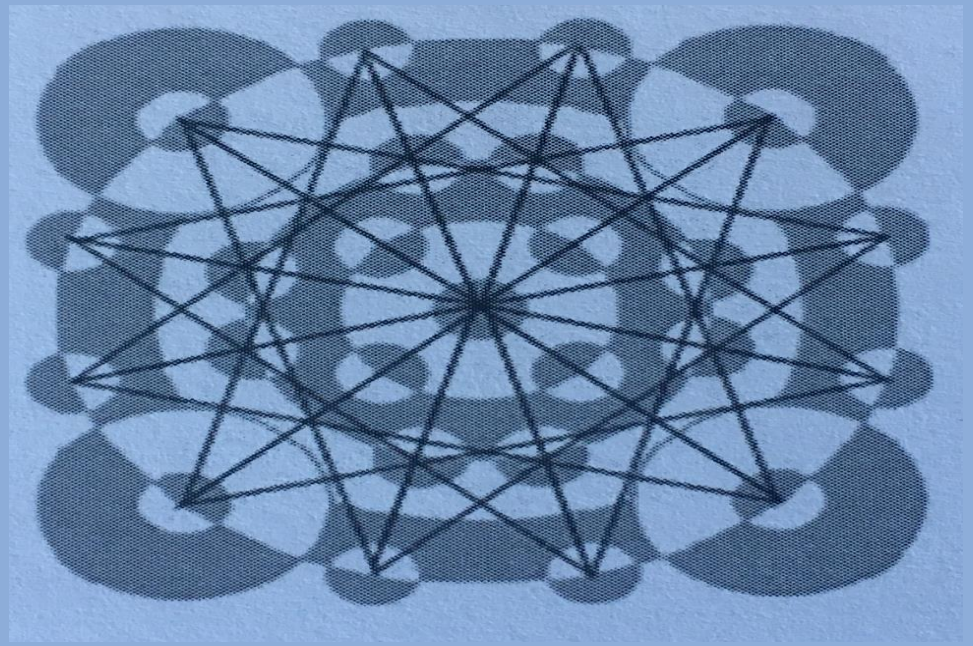
TAKE HOME MESSAGES

Multiple Domains of Wellbeing for Survivors

Physical
Fatigue
Sleep
Pain
Functional

Social
Family distress
Roles
Relationships
Work
Finances

Sexual



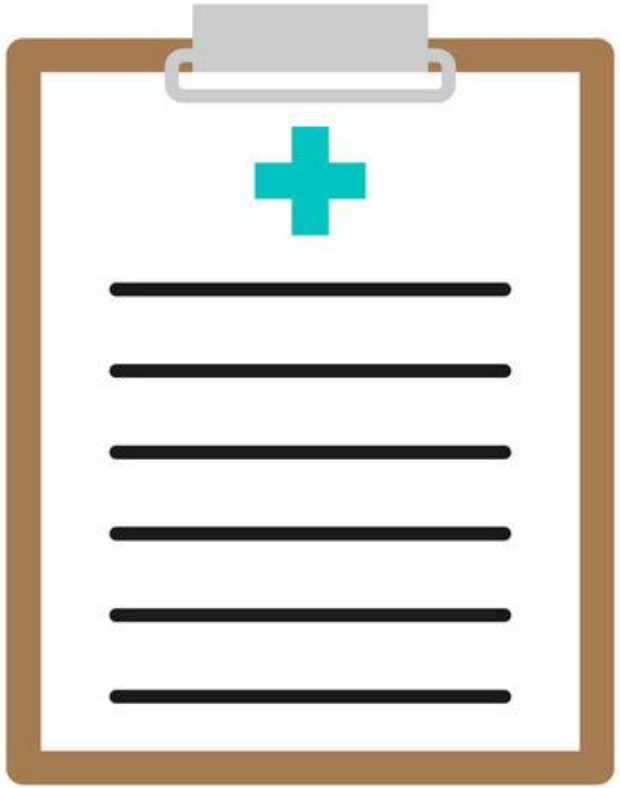
Psychological
Fear of recurrence
Loss of control
Anxiety
Depression
Cognition
Attention

Spiritual
Meaning
Hope
Inner strength
Transcendence

Adapted from Ferrell et al 1995, QOL in Long Term Cancer Survivors, Oncology Nursing Forum

MONITORING DURING ADT

- Confirm efficacy
  - Routinely measure PSA and T
- Monitor for Adverse Events
  - CV disease (e.g. lipids, blood pressure, weight, smok
  - Glucose
  - Bone mineral density
- Therapy compliance
  - Injection timing
- Compliance with calcium and vitamin D
- Caregiver feedback
- Shared care



Summary

- ADT remains a foundational treatment throughout the prostate cancer journey
- A variety of ADT options are available, and choice is based on a number of patient- and disease-related factors
- The goal of ADT is to lower and maintain testosterone to castrate levels and/or block activity at the androgen receptor
  - This results in a number of side effects that can impact a patient's QOL
- Patients undergoing ADT for prostate cancer should undergo continuous monitoring for:
  - Efficacy
  - Side effects
  - Compliance to treatment

TAKE HOME MESSAGES

- ADT can have many side effects
- Up to 20% of men DO NOT have any side effects ☺
- Dealing with side effects proactively is the best way to avoid long term problems with ADT
- Exercise and physical activity are the most effective treatments
- Patients must be active participants in prevention strategies
- The PCSC Program is here to help!