Systemic treatment options in patients with advanced prostate cancer

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Presenter Disclosure

- **Faculty/Speaker: Joel Gingerich**

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  - **Other:** None.

Mitigating Potential Bias

- Not Applicable

Equity Commitment

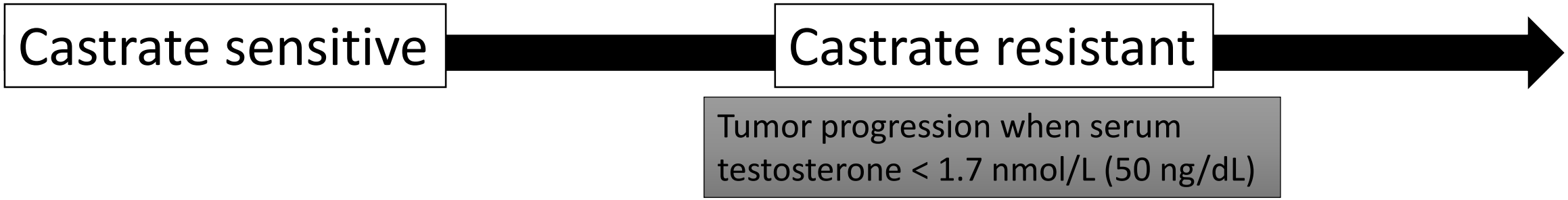
- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Learning Objectives

- List and/or describe systemic treatment options available for patients with advanced prostate cancer
- Describe the common side effects associated with treatment
- Recognize when to consider dose modifications in patients with treatment related side effects

Advanced prostate cancer



Goal = control the cancer, prolong survival and improve symptoms

Initial treatment for advanced prostate cancer

1) Gonadotrophin releasing hormone (GnRH)
   *agonist or antagonist preparations available
2) Orchiectomy (remove testicles)

Both options are equivalent:
   >90% respond
   Average response = 18 - 24 months
   10-15% will respond for > 10 years

Often called Androgen Deprivation Therapy (ADT)

Benefit identified in the 1940's

Seidenfeld J, et al: Ann Intern Med. 132:566-577, 2000
Robson M, Dawson N. Hematol Oncol Clin North Am. 10(3):727-47, 1996.
Eisenberger MA et al: N Engl J Med. 339(15):1036-42, 1998.
Chang A et al: J Clin Oncol. 14(8):2250-7, 1996.

Common Toxicity associated with ADT

- ↓ libido/sexual dysfunction (95%)
- Decreased genital size (93%)
- Gynecomastia (30-90%)
- Hot flashes (80%)
- Weight gain (70%)
- Depression (41% ↑)
- Metabolic syndrome (>50%)
- Insulin resistance (44x)
- Bone loss (5% loss in 1st year)
- Fatigue (14+%)
- Cognitive changes (50%)*
- Cardiovascular disease (16% ↑) *

* Studies have shown contradictory results

Nguyen PL, et al: Eur Urol. 2015;67(5):825-36
Rhee H, et al: BJU Int. 2015;115 Suppl 5:3-13
Kokorovic A, et al: Can Urol Assoc J. 2021 15(6):E307-E322

Management of ADT toxicity

- Monitor for hyperlipidemia, insulin resistance, metabolic syndrome
  - Treat as per best practice guidelines
- Metabolic assessment q6-12 months throughout treatment
- BP management
  - <130/80
- Encourage lifestyle modifications
  - Smoking cessation
  - Exercise
  - Diet (Canadian food guide)

Kokorovic A, et al: Can Urol Assoc J. 2021 15(6):E307-E322

Management of ADT toxicity: Bone health

- Supplements:
  - Calcium (1000-1200 mg od) + Vitamin D (800-2000 IU od)
- Exercise:
  - ASCO guidelines for cancer survivor
    - 150 min/week of exercise with 2+ strength training sessions
- Lifestyle modifications:
  - Smoking cessation
  - Moderating alcohol

Nguyen PL, et al: Eur Urol. 2015;67(5):825-36
Rhee H, et al: BJU Int.. 2015;115 Suppl 5:3-13
NCCN guidelines. Version 4.2019, 9/5/19. www.nccn.org
Kokorovic A, et al: Can Urol Assoc J. 2021 15(6):E307-E322

Management of ADT toxicity: Bone health

- Baseline bone density testing
  - Then q1-3 years
- High risk for fractures:
  - T score -2.5 (Dual-energy x-ray absorptiometry)
  - Hip fracture ≥ 3% (FRAX score)
  - Any fracture ≥ 20% (FRAX score)

- Treatment in patients at higher risk for fracture:
  - Zoledronic acid 5 mg IV annually
  - Denosumab 60 mg sq q6 months
  - Alendronate 10 mg po daily, or 70 mg po weekly
  - Risedronate 5mg po daily, or 35 mg po weekly, 150 po mg monthly

Kokorovic A, et al: Can Urol Assoc J. 2021 15(6):E307-E322

Management of ADT toxicity continued

- Gynecomastia:
  - Reassurance > tamoxifen, XRT

- Hot flashes:
  - Venlafaxine 75 mg od or SSRI
  - Medroxyprogesterone 20 mg od
  - Cyproterone 100 mg od
  - Gabapentin 900 mg od
  - Acupuncture

Nguyen PL, et al: Eur Urol. 2015;67(5):825-36
Rhee H, et al: BJU Int.. 2015;115 Suppl 5:3-13
NCCN guidelines. Version 4.2019, 9/5/19. www.nccn.org
Kokorovic A, et al: Can Urol Assoc J. 2021 15(6):E307-E322

Metastatic castrate-sensitive prostate cancer (mCSPC)

- ADT

- ADT plus:
  - Abiraterone/prednisone
  - Enzalutamide
  - Apalutamide

  } Androgen Receptor Antagonist Therapy (ARAT)

  - Docetaxel x 6 cycles

  } Chemotherapy

  - Abiraterone/prednisone + Docetaxel
  - Darolutamide + Docetaxel

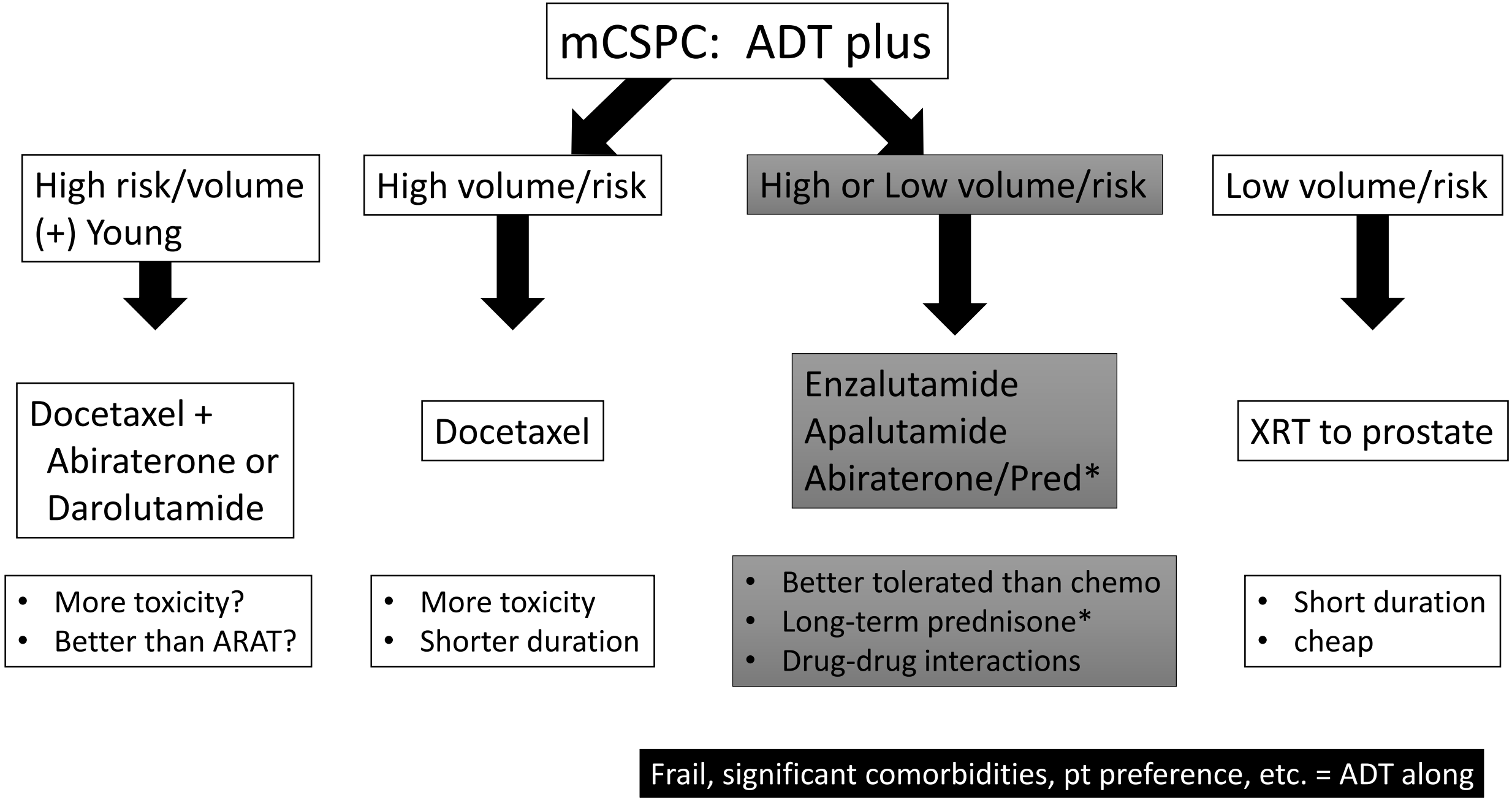
  } ARAT + Chemotherapy

  - Prostate XRT

Summary: mCSPC RCT's

Treatment (ADT plus)	Standard arm	Patient population	Outcome	Absolute OS benefit	HR (P value)
Abiraterone/Pred	ADT	"High risk"	51.2 vs. 34.4 mo	17 mo	0.66 (< 0.001)
Docetaxel	ADT	"High volume"	51.2 vs. 34.4 mo	16 mo	0.63 (<0.002)
Enzalutamide	ADT ADT	Any met dz Any met dz	3 year: 80 vs. 72% 4 year: 71 vs. 57%	8% at 3 years 14% at 4 years	0.67 (0.002) 0.66 (<0.0001)
Apalutamide	ADT	≥ 1 bone met	4 year: 65 vs. 51%	13% at 4 years	0.67 (0.005)
XRT	ADT	"low volume"	3 year: 73 vs. 81%	8% at 3 years	0.68 (0.007)
Abi/pred + Docetaxel	ADT + docetaxel	"De novo" met dz	4.43 y vs. NR		0.75 (0.017)
Darolutamide + Docetaxel	ADT + docetaxel	Met. dz	4-year: 63 vs 50%	12% at 4 years	0.68 (<0.001)

High risk: Gleason 8+, 3+ bone mets, visceral mets (2+ risk factors)
High volume: visceral mets or 4+ bone mets, 1 outside spine/pelvis


mCSPC: ADT plus
High risk/volume (+) Young
High volume/risk
High or Low volume/risk
Low volume/risk
Docetaxel + Abiraterone or Darolutamide
Docetaxel
Enzalutamide
Apalutamide
Abiraterone/Pred*
XRT to prostate
• More toxicity?
• Better than ARAT?
• More toxicity
• Shorter duration
• Better tolerated than chemo
• Long-term prednisone*
• Drug-drug interactions
• Short duration
• cheap
Frail, significant comorbidities, pt preference, etc. = ADT along

Summary: Selected Toxicity

Treatment	
Abiraterone/Pred	HTN, hypokalemia, LFT toxicity, edema, CV toxicity
Enzalutamide	Fatigue, falls, seizures, cognitive changes, HTN, IHD, QT prolongation
Apalutamide	Rash, falls, hypothyroidism, HTN, IHD, QT prolongation
Docetaxel	Fatigue, myelosuppression, N/V/D, hair loss, neuropathy, LFT toxicity
Abi/pred + Docetaxel	Combination of Docetaxel + Abiraterone
Darolutamide + Docetaxel	Similar to Docetaxel; ↑ HTN, transaminitis
XRT	Fatigue, rash, diarrhea, urinary symptoms

Check CCMB website for Regimen Reference Orders (RRO's)

Metastatic castrate resistant prostate cancer (mCRPC)

- Docetaxel

Tumor progression + serum testosterone < 1.7 nmol/L (50 ng/dL)

- Abiraterone/prednisone
- Enzalutamide

- Cabazitaxel
- Radium 223

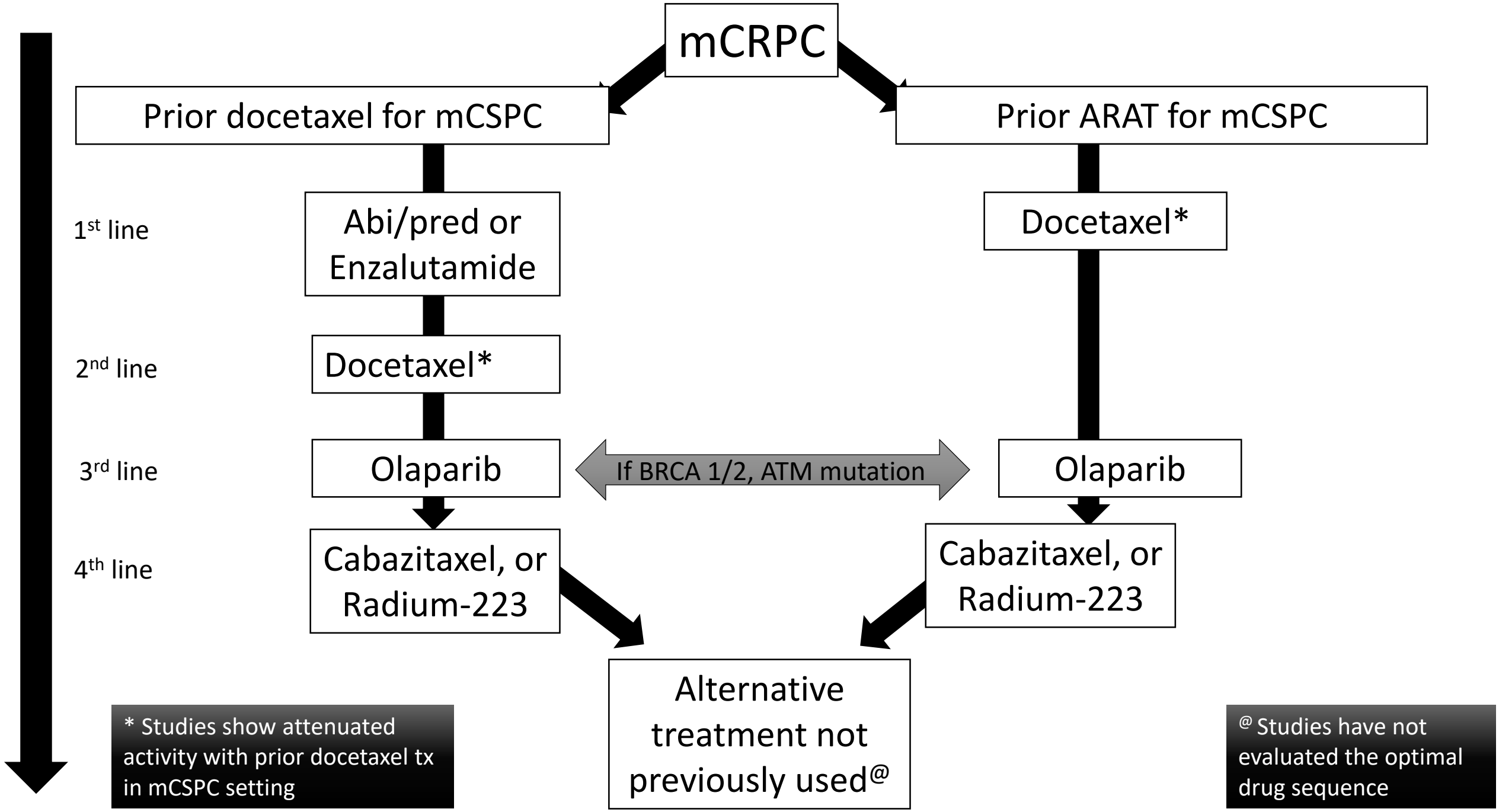
All treatments require ongoing ADT or orchiectomy

- Olaparib

Summary: mCRPC RCT's

Treatment	Standard arm	Patient population	Outcome	Absolute OS benefit	HR (P value)
Docetaxel	mitoxantrone	(-)	19.2 vs. 16.3 mo	3 mo	0.76 (0.004)
Abiraterone/pred	Prednisone Prednisone	No prior docetaxel Prior docetaxel	34.7 vs. 30.3 mo 15.8 vs. 11.2 mo	4.4 mo 4.6 mo	0.81 (0.0033) 0.74 (<0.0001)
Enzalutamide	Placebo Placebo	No prior docetaxel Prior docetaxel	35.3 vs. 31.3 mo 18.4 vs. 13.6 mo	4 mo 4.8 mo	0.77 (0.0002) 0.63 (<0.001)
Cabazitaxel	Mitoxantrone	Prior docetaxel	15.1 vs. 12.7 mo	2.4 mo	0.70 (<0.0001)
Radium 223	Placebo	Prior docetaxel	14 vs. 11.2 mo	2.8 mo	0.70 (< 0.001)
Olaparib	Abi/pred or enzalutamide	BRCA 1/2, ATM mut. Prior ARAT	18.5 vs. 15.1 mo	3.4 mo	0.64 (0.02)

BRCA 1/2 mutation ~5 - 15% of patients

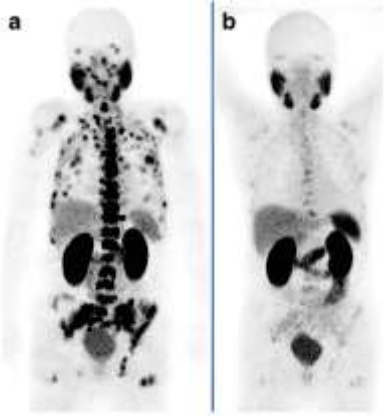

mCRPC
Prior docetaxel for mCSPC
Prior ARAT for mCSPC
1st line
Abi/pred or Enzalutamide
Docetaxel*
2nd line
Docetaxel*
3rd line
Olaparib
If BRCA 1/2, ATM mutation
Olaparib
4th line
Cabazitaxel, or Radium-223
Cabazitaxel, or Radium-223
Alternative treatment not previously used@
* Studies show attenuated activity with prior docetaxel tx in mCSPC setting
@ Studies have not evaluated the optimal drug sequence

Summary: Selected Toxicity

Treatment	
Cabazitaxel	Myelosuppression, diarrhea, fatigue, nausea, hematuria, peripheral neuropathy
Radium 223	Myelosuppression, pain, fatigue (no different than placebo)
Olaparib	Anemia, nausea, fatigue, decreased appetite, diarrhea, cough, SOB, pulmonary embolism

Cabazitaxel has less peripheral neuropathy, stomatitis, alopecia and nail disorders compared to Docetaxel

Check CCMB website for Regimen Reference Orders (RRO's)



Near future?

- Lutetium-177-PSMA-617
  - RCT of heavily pretreated prostate cancer pts
  - N = 831
  - OS = 15.3 mo vs 11.3 mo, HR = 0.62, p =<0.001

- Immunotherapy
  - Mismatch repair-deficient (dMMR)/ microsatellite instability (MSI-H)
    - 3-5% of prostate cancer patients
    - Small studies suggest benefit in some of these patients

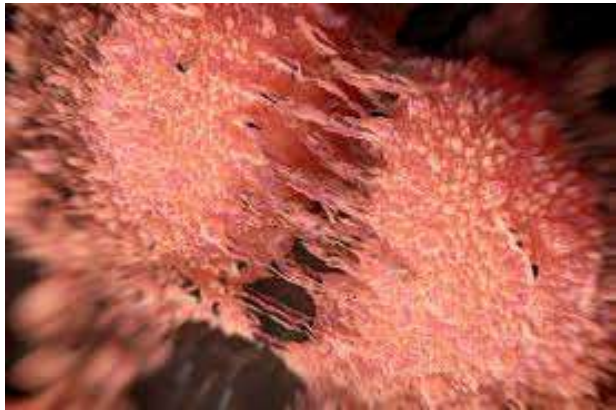
  - High Tumor Mutational Burdon (≥ 10 Mut/Mb)
    - Some, but not all retrospective studies suggest benefit

Mateo J, et al: N Engl J Med 2015;373:1697-708
Pomerantz MM, et al: Cancer 2017;123:3532-9.
Abida W, et al: JAMA Oncol. 2019;5(4):471-478
Sartor O, et al: N Engl J Med 2021;385:1091-103
Graf RP, et al: JAMA Netw Open. 2022;5(3):e225394

Neuroendocrine differentiation: Small cell and Aggressive-Variant Prostate Cancers (AVPC)

- Seen in < 2% of new cases
- Seen in 10-20% of prostate cancer patients treated with ADT
- Clinical factors:
  - Low PSA production
  - Liver metastases
  - Atypical clinical manifestations

- Treatment = carboplatin based



Skeletal related events in mCRPC

- Definition:
  - Pathologic bone fracture
  - Spinal cord compression
  - Surgery or radiotherapy to bone
  - Change in cancer tx because of bone pain

- 49% of mCRPC pts will develop a SRE within 2 years

Fizazi K, et al: Lancet 2011;377:813-22
Saad F et al. J Natl Cancer Inst 2004;96(11):879-882
Himelstein AL, et al: JAMA. 2017;317(1):48-58

RCT treatments that delay SRE's in mCRPC

Outcome	Placebo	Zoledronic acid	Denosumab	HR	P value
Median time to SRE	10.7 mo	16.3 mo	(-)	0.68	0.009
	(-)	17.1 mo	20.7 mo	0.82	0.008

Other agents shown to delay SRE's:
Radium-223, enzalutamide, abiraterone

The benefit in mCSPC has not been proven

Fizazi K, et al: Lancet 2011;377:813-22
Saad F et al. J Natl Cancer Inst 2004;96(11):879-882
Himelstein AL, et al: JAMA. 2017;317(1):48-58

Toxicity associated with treatment of SRE's

Toxicity	Zoledronic acid	Denosumab
Osteonecrosis of jaw	1%	2%
Hypocalcemia	6%	13%

The risk of ONJ increases with each year of use

Zoledronic acid (but not denosumab) is associated with nephrotoxicity

Fizazi K, et al: Lancet 2011;377:813-22
Saad F et al. J Natl Cancer Inst 2004;96(11):879-882
Himelstein AL, et al: JAMA. 2017;317(1):48-58

Managing bone resorptive agents toxicity

- Preventative:
  - Dental evaluation prior to starting tx
  - Hold treatment for major dental work
  - Ca/vit D supplements

↑ with tooth extractions, poor dental hygiene, dental appliances

- Monitor:
  - Renal function
  - Calcium
  - Osteonecrosis of the jaw

Take Home Messages

- ADT is the back-bone of advanced prostate cancer treatment
- Treatment options differ based on the tumor's sensitivity to castrate levels of testosterone
- Multiple treatment options are available that have defined toxicities
- CCMB Regimen Reference Orders can be used to determine when dose modifications are required

Biochemical recurrence after radical prostatectomy and or XRT (No metastatic disease on conventional imaging)

High Risk
Gleason 8+
PSA doubling time < 1 year (Prostatectomy)
PSA recurrence < 18 months (XRT)

↓

Intermittent ADT

Low risk
Gleason < 8
PSA doubling time > 1 year (Prostatectomy)
PSA recurrence > 18 months (XRT)

↓

Active surveillance

Virgo KS, et al: J Clin Oncol. 2021. 39:1274-1305

Prostate cancer statistics: 2021

Region	New cases (% total)	Rank	Deaths (% total)	Rank
Canada	24,000 (20 %)	1st	4,500 (10%)	3rd
Manitoba	710	1st	180	3rd

Lifetime probability of developing prostate cancer
11.9% (117.9/100,000)

Lifetime probability of dying from prostate cancer
3.5%

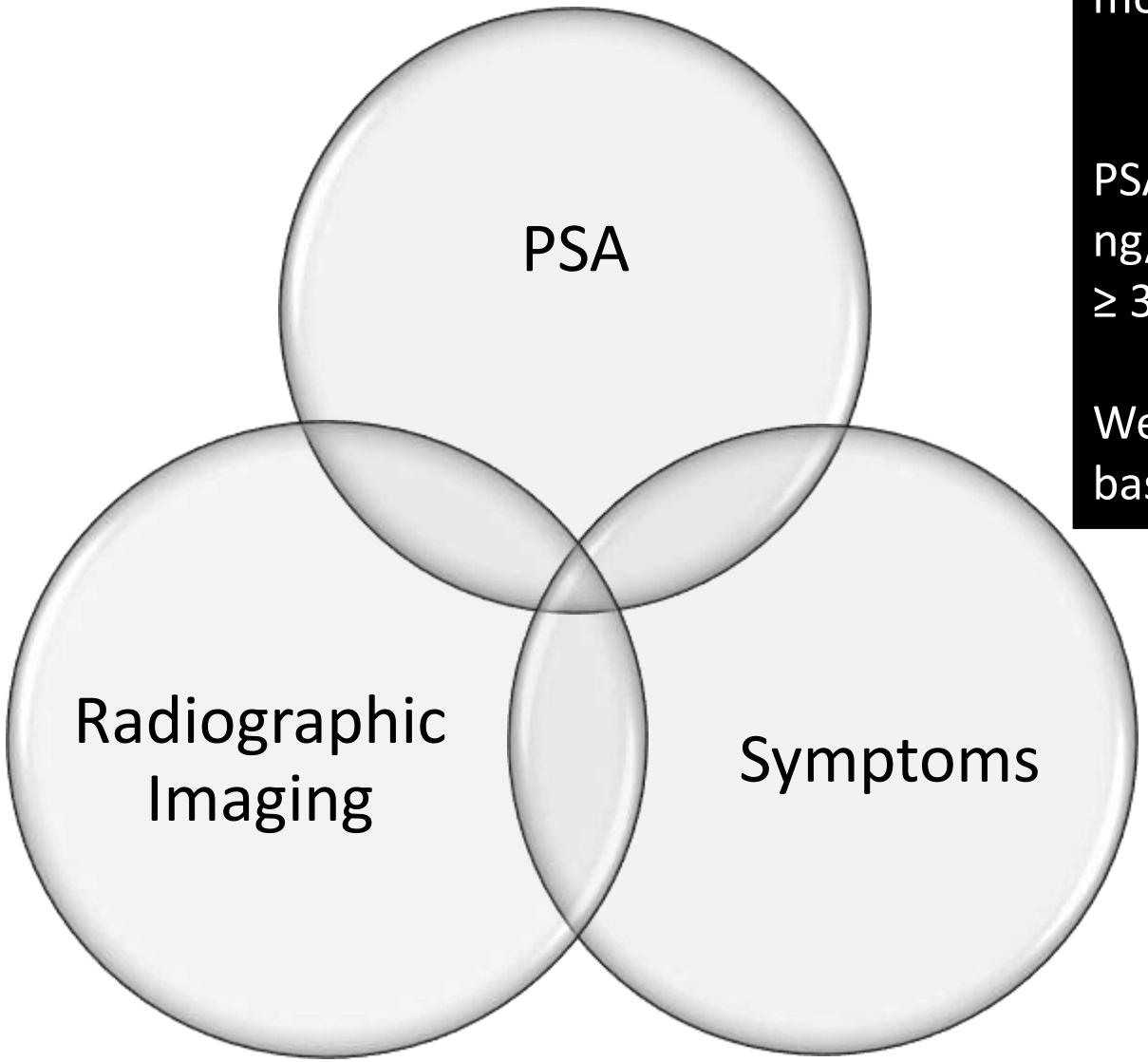
66 men in Canada are diagnosed with prostate cancer every day

Defining progression

Ignore ↑ PSA during 1st three months of treatment

PSA progression: ≥ 25% ↑ + 2 ng/mL above nadir, confirmed ≥ 3 weeks later

We don't make decisions based on PSA alone



Bone scan is the standard modality used to identify bone metastasis.

Progression = 2 + new lesions

Scher HI, et al: J Clin Oncol. 2016; 34:1402-1418