Prostate Cancer 101
GU Oncology Nursing Education

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Part 3

Treatment of Advanced Prostate Cancer, Management of Side Effects

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Objectives

- Identify different treatment options for advanced prostate cancer.
- Define strategies for managing treatment side effects with consideration for advanced disease process.

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Advanced Prostate Cancer

Recurrent prostate cancer following definitive therapy, locally recurrent disease, systemic recurrence, clinical (symptomatic) recurrence; newly diagnosed distant disease

- Biochemical: PSA recurrence (most common)
- Local: Cancer identified within the prostate (e.g., after XRT)
- Distant: Cancer identified in distant organs (e.g., bone mets)
- Clinical: Local or distant w/ symptoms (e.g., LUTS, pain)

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Advanced Prostate Cancer

Other important highlights

- Adjuvant therapy: Given after primary therapy to lower the risk that the cancer will recur
- Salvage therapy: Given after cancer has not responded to primary therapy
- Androgen deprivation therapy (ADT) and “hormone therapy” often used interchangeably
- PSA recurrence and biochemical recurrence are used interchangeably

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Considerations for additional treatment

- Performance status & Co-morbidities
- Side effects from definitive treatment
- Life expectancy
- Patient preference
- PSA doubling time
  - PSADT > 15 mos. Associated w/ low risk of death from prostate cancer over 10 yrs.
  - PSADT > 9 mos. Associated w/ higher probability of long-term, mets free, and OS

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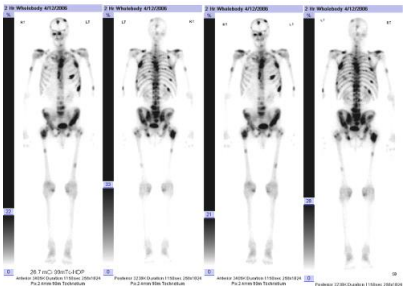
Diagnostics

- CT AP
  - Lymph nodes
    - Pelvic, retroperitoneal
  - Visceral
- Bone scan
  - Eval for lesions of axial skeleton
  - Follow distribution of adult red bone marrow
    - Skull, thorax, pelvis, spine, proximal long bones
  - Bone scans should reveal osteoblastic appearance due to *increased* bone density in the areas of bone mets
- Bone density
- Prostate MRI



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Diagnostics

PET imaging with novel tracers

- Prostate-Specific Membrane Antigen (PSMA)
  - Targets PSMA, which is a protein expressed by prostate cancer cells
    - Piflufolastat F 18
    - Gallium 68 PSMA-11
  - Indications: Risk stratification for very high risk localized; patients w/ BCR s/p definitive therapy; work up for progression; before PSMA-targeted radioligand therapy
- F18-Naf
  - Rarely used
- FDG scan not used

Lisney AR, at al. The Role of PSMA PET/CT in the Primary Diagnosis and Follow-Up of Prostate Cancer-A Practical Clinical Review. Cancers (Basel). 2022 Jul 26;14(15):3638

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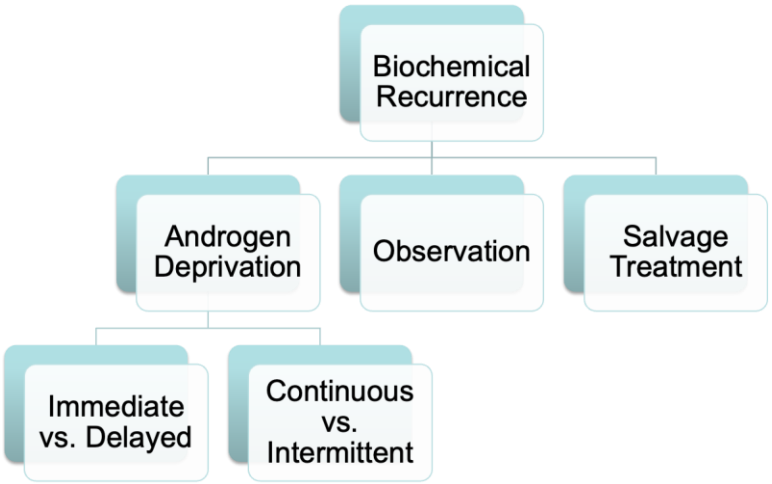
Advanced Prostate Cancer



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Advanced Prostate Cancer

- Biochemical recurrence (BCR)
  - Post-radical prostatectomy (RP)
    - PSA > 0.2 ng/mL x 2 (AUA)
    - Detectable PSA x 2 (NCCN)
    - 20-40% of pts s/p RP will have BCR within 10 years
  - Post-radiation (XRT)
    - PSA rise of ≥ 2ng/mL above nadir PSA (Phoenix)
    - Mid-point between nadir PSA + 1st of 3 consecutive rises (ASTRO)
    - 30-50% of pts s/p XRT will have BCR within 10 years

-Roehl KA, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol* 2004; 172:910–914
-Lowrance W., et al. Updates to advanced prostate cancer: AUA/SUO guideline (2023). J Urol. 2023;209(6):1082-1090.
-Mack Roach et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference, International Journal of Radiation Oncology*Biology*Physics, Volume 65, Issue 4,2006, Pages 965-974

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Advanced Prostate Cancer

- Adjuvant XRT
  - Giving post-op radiation before PSA becomes detectable (+/- ADT)
  - Patients w/ high risk features (e.g. pT3+, + margin)
  - Trials
    - SWOG 8794→ lower mets recurrence rates/improves survival
    - EORTC 22911→ lower rates of biochemical failure
    - ARO 96-02→ same as EORTC
    - Improvement in biochemical recurrence free survival (bRFS) across all three trials
    - RADICALS-RT→ No difference in bPFS (adjuvant vs salvage)

-Thompson IM, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009 Mar;181(3):956-62
-Bolla M, et alEuropean Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012 Dec 8;380(9858):2018-27.
-Parker C et al. Timing of radiotherapy after radical prostatectomy (RADICALs-RT); a randomized, controlled phase 3 trial. Lancet.. 2020; 396(10260); 1413-1421

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Salvage Treatment

- Salvage therapy for BCR
  - Getting post-op XRT to the prostate bed when PSA is detectable
  - Effectiveness greatest when PSA lower, <0.5 (i.e., higher bRFS)
  - ADT:
    - Patients with PSA <0.6 had no OS benefit with addition of bicalutamide (RTOG 9601)
    - 2 years of ADT can be considered w/ persistent PSA elevation s/ p RP or for PSA > 1.0 (RTOG 9601)

Dose- 64-72 Gy

Shipley et al. Radiation with or without Antiandrogen therapy in recurrent prostate cancer. NEJM. 2017: 376(5). 417-428.

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Salvage Treatment

- Salvage therapy for BCR
  - Post-XRT
  - Life expectancy, imaging, biopsy
    - Salvage RP
      - Can result in long-term disease control
      - Considerations: PSA < 5-10ng/mL, < cT3a, (-) mets, minimal urinary dysfunction
      - Not common practice given high morbidity

Calleris G, et alSalvage Radical Prostatectomy for Recurrent Prostate Cancer Following First-line Nonsurgical Treatment: Validation of the European Association of Urology Criteria in a Large, Multicenter, Contemporary Cohort. Eur Urol Focus. 2023 Jul;9(4):645-649. doi: 10.1016/j.euf.2023.01.006. Epub 2023 Jan 20. PMID: 36682962.

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Salvage Treatment

- Salvage therapy for BCR
  - Salvage cryotherapy
  - Salvage brachytherapy
    - Assessment of oncologic efficacy is limited by lack of long-term outcome data and/or small numbers of patients in published series
- Negative biopsy poses clinical uncertainties

Wei Phin Tan et al,Oncological and Functional Outcomes for Men Undergoing Salvage Whole-gland Cryoablation for Radiation-resistant Prostate Cancer,European Urology Oncology,. 6(3)
2023, Pages 289-294
-Tisseverasinghe SA, Crook JM. The role of salvage brachytherapy for local relapse after external beam radiotherapy for prostate cancer. Transl Androl Urol. 2018 Jun;7(3):414-435

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Advanced Prostate Cancer

- Indications for androgen deprivation therapy (ADT)
  - Symptomatic metastatic disease
  - Asymptomatic metastatic disease
  - BCR only (immediate vs. delayed)
    - PSA > 20 for shorter PSADT
    - PSA > 50
    - Patient preference
    - Arbitrary
  - Continuous vs. intermittent

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Advanced Prostate Cancer

Intermittent ADT for non metastatic disease

-Cyclic admin of ADT→ induction→ temporary withdrawal→ PSA monitoring→ reinitiation

-Role is not well defined

- Pr.7: BCR s/p XRT, IAD vs CAD; OS w/ IAD met criteria for noninferiority
- ICELAND: locally advanced or BCR, IAD vs CAD; all clinical outcomes similar
- Meta-analysis of 6 RCTs of IAD vs CAD w/ locally advanced prostate cancer found no difference in mortality and progression

Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM. 2013: 368(14); 1314-1325
Bertrand Tombal, et alClinical Outcomes and Testosterone Levels Following Continuous Androgen Deprivation in Patients with Relapsing or Locally Advanced Prostate Cancer: A Post Hoc Analysis of the ICELAND Study, The Journal of Urology, 198(5). 2017,1054-1060

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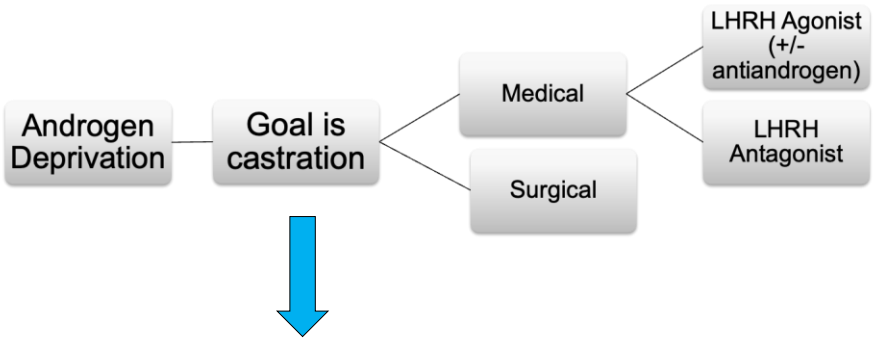
Androgen Deprivation Therapy



Testosterone ≤ 50

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Hormonal Regulation of the Prostate Gland

- Prostate growth depends on presence of androgens
  - Testes and adrenal glands major sources of circulating androgens
- Hormonal regulation of androgen synthesis is mediated through series of biochemical interactions between hypothalamus, pituitary, adrenals, testes
- LHRH from the hypothalamus stimulates release of LH & FSH from the pituitary
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, & FSH by a negative feedback loop operating at the hypothalamic and pituitary level.

Schally AV, Comaru-Schally AM. Mode of Action of LHRH Analogs. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.

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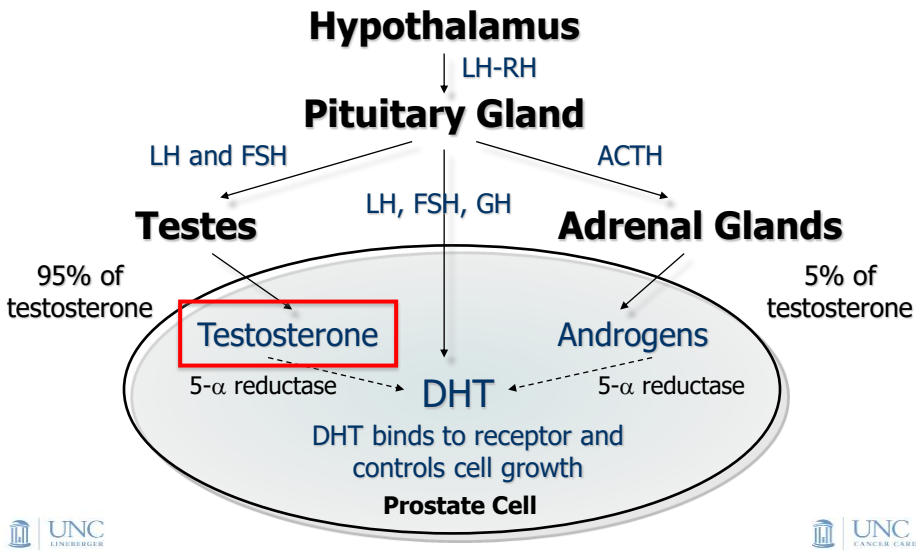
Hormonal Regulation of the Prostate Gland



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Androgen Deprivation Therapy

- Surgical castration (bilateral orchiectomy)
  - Castrate testosterone levels occur 2-12 hours post-op
  - Eliminates > 90% of androgens
  - Low cost, compliance not an issue
  - No testosterone flare
  - Irreversible

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Androgen Deprivation Therapy

- Medical Castration
  - LHRH Agonists:
    - Stimulation of LHRH receptors in pituitary producing initial increase in LH and FSH, causing initial increase in testosterone. Continued LHRH agonism suppresses LH and FSH secretion, causing decrease in testosterone
  - Castrate within 21 days
  - Leuprolide, Goserelin, Triptorelin
  - Flare: Initial increase in T can cause pain in patients with bone mets

Meani D, et al.Practical differences between luteinizing hormone-releasing hormone agonists in prostate cancer: perspectives across the spectrum of care. *Therapeutic Advances in Urology*. 2018;10(2):51-63

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Androgen Deprivation Therapy

- Medical Castration
  - LHRH Antagonists:
    - Block GnRH receptors in pituitary, which decrease LH, FSH, and testosterone
  - Castrate within 3 days
  - No flare (ideal for patients with bone mets)
  - Degarelix
    - Loading dose 240mg SC then 80 mg monthly
    - Loading dose 240mg SC then LHRH Agonist

Gittelman M,, et al: A 1-year, open-label, randomized phase II dose-finding study of degarelix, a novel gonadotropin-releasing hormone (GnRH) receptor blocker, in the treatment of prostate cancer in North America. J Urol 180:1986-1992, 2008

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Androgen Deprivation Therapy

- Medical Castration
  - LHRH Antagonists:
  - Relugolix 120 mg daily
    - HERO trial; phase 3 RCT vs leuprolide for 48 weeks
      - Sustained T suppression; 96.7% vs 88.8%
      - Mean T level at day 4: 38mg/dl vs 625 ng/dl
      - Mean T 90 days s/p d/c: 288.4 ng/dl (n=137) vs 58.6 ng/dl (n=47)
      - Eligible patients = BCR, newly dx mCSPC, or advanced localized disease unlikely to be cured by local treatment
      - Few cardiovascular SE

Shore N et al. Oral relugolix for androgen deprivation therapy in advanced prostate cancer. N Engl J Med 2020; 382:2187-2196

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Androgen Deprivation Therapy

- Medical Castration
  - Antiandrogens: Block cells ability to bind hormone
  - Monotherapy rarely used
  - Flutamide, **Bicalutamide,** Nilutamide
  - Combined Androgen Blockade
    - ~2% benefit in OS after 5 years of combined ADT must be balanced against SE and $
  - To avoid flare

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Advanced Prostate Cancer

Intermittent ADT in metastatic disease

- SWOG 9346
  - After 7 months of ADT, 1535 patients whose PSA dropped to 4 or below were randomized to IAD vs CAD
  - Median survival 5.1 yrs (IAD) and 5.8 yrs (CAD)
  - Survival results inconclusive
- Several other meta-analyses reported no survival difference between IAD and CAD

Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM. 2013: 368(14); 1314-1325

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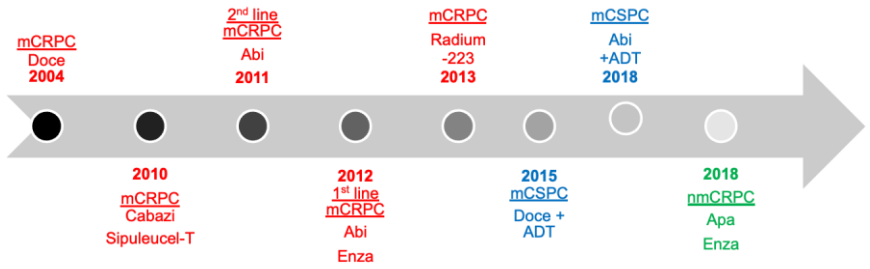
FDA approvals timeline for advanced prostate cancer



Abbreviations: metastatic castrate resistant prostate cancer (mCRPC), metastatic hormone sensitive prostate cancer (mHSPC), non-metastatic castrate resistant prostate cancer (nmCRPC)

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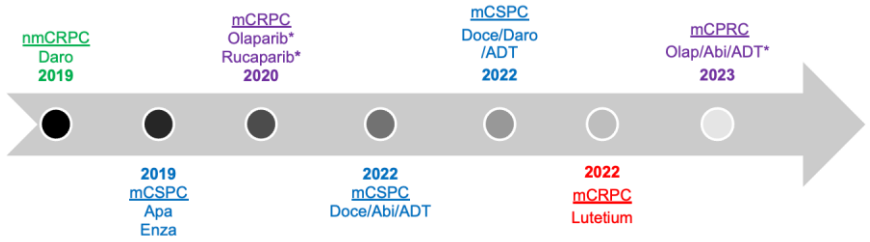
FDA approvals timeline for advanced prostate cancer



Abbreviations: metastatic castrate resistant prostate cancer (mCRPC), metastatic hormone sensitive prostate cancer (mHSPC), non-metastatic castrate resistant prostate cancer (nmCRPC)

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Systemic options

Cytotoxic chemotherapy
Docetaxel (Taxotere®)
Cabazitaxel (Jevtana®)

Antiandrogens
Abiraterone (Zytiga®)
Enzalutamide (Xtandi®)
Apalutamide (Erleada®)
Darolutamide (Nubeqa®)

PARP Inhibitors*
Olaparib (Lynparza®)
Rucaparib (Rubraca®)

Immunotherapy
Sipuleucel-T (Provenge®)
Pembrolizumb (Keytruda®)*

Radiotherapy
Radium-223 (Xofigo®)
Lutetium Lu 177 (Pluvicto®)

Androgen deprivation
Leuprolide (Lupron®, Eligard®)
Degarelix (Firmagon®)
Relugolix (Orgovyx®)

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Metastatic Castrate Sensitive Prostate Cancer (mCSPC)

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mCSPC

Docetaxel*

- CHAARTED trial (n= 790)
  - High volume (i.e. visceral mets and/or 4+ bone mets)
  - ADT naïve (or started <120 days)
  - Primary objective = mOS would be 33.3% longer w/ ADT + chemo
  - Increased survival by 13.6 months (from 44 to 57.6 months)
  - 6 cycles every 21 days
  - MOA: Microtubule inhibitor
  - SE: Fatigue, myelosuppression, rash, n/v, LE edema, neuropathy, alopecia, hypersensitivity

Almost unprecedented in oncology that addition of single chemo has this significant of an effect

Sweeney C et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. NEJM 2015; 373:737-746

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mCSPC

Abiraterone + prednisone

- LATITUDE (n = 1,200)
  - 2 of 3 risk factors: GG ≥ 8, at least 3 bone mets, or 3 visceral mets
  - ADT naïve
  - ADT + abiraterone 1,000mg vs ADT + placebo
  - Abi associated with 53% lower risk of radiographic POD (POD delayed by 18.2 months)
- STAMPEDE (n = 1,917)
  - 71% improvement in time to treatment failure
    - 37% diff in OS
- MOA: Inhibits CYP17, enzyme needed for androgen synthesis in the testes, adrenals, and tumor
- SE: Mineralocorticoid SE, fatigue, hot flashes, hepatotoxicity, edema, HTN

Fizazi K et al. Abiraterone plus prednisone in metastatic , castration sensitive prostate cancer. NEJM 2017; 377:352-360
James N et al. Abiraterone for prostate cancer not previously treated with hormone therapy. NEJM 2017; 377:338-351

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mCSPC

Apalutamide

- TITAN (n = 1,052)
  - Low and high volume disease, de novo, or prior local tx, or prior docetaxel
  - Apalutamide 240 mg + ADT vs placebo + ADT
  - 33% reduction in risk of death
  - MOA: androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR→ prevents AR translocation, DNA binding, and AR-mediated transcription
  - SE: arthralgia, rash, anorexia, fall, hypothyroidism, fracture, diarrhea

Chi K et al. Apalutamide for metastatic, castration-sensitive prostate cancer. NEJM 2019. 381: 13-24

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mCSPC

Enzalutamide

- ARCHES (n = 1,150)
  - mCSPC either de novo or after recurrence following local therapy. Prior ADT and and up to 6 cycles prior docetaxel allowed
  - Enzalutamide 160 mg + ADT vs placebo + ADT
  - Primary endpoint was radiographic progression-free survival
  - Reduced risk of radiographic POD or death by 61%
  - MOA: Inhibits androgen binding to AR and inhibits AR nuclear translocation and interaction with DNA
  - SE: Myalgia, arthralgia, fatigue, hot flash, HTN; seizure warning

Armstrong A, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with Metastatic hormone-sensitive prostate cancer. JCO 2019. 37(32). 2974-2986

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mCSPC

Docetaxel + abiraterone

- PEACE-1 (n= 1,173)
  - De novo disease
  - 4 arms: SOC (ADT alone or + doce); SOC + XRT; SOC + abi/pred; SOC + XRT + abi/pred
  - Primary endpoints were rPFS and OS
  - Triplet therapy reduced risk of death by 25% and risk of rPFS by 50% vs docetaxel + ADT
  - Docetaxel 75 mg/m2 x 6 cycles, abiaraterone 1,00 mg Po daily + prednisone 5 mg BID + ADT
  - SE: HTN, fatigue, PN,

Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive Prostate cancer (PEACE-1); a multicentre, open-label, randomized, phase 3 study with a 2x2 factorial design. Lancet 2022.399(10336) 1695-1707

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mCSPC

Docetaxel + darolutamide

- ARASENS (n=1,306)
  - Doce+daro+ADT vs Doce+placebo+ADT
  - Primary endpoint overall survival
  - Triplet therapy reduced risk of death by 32.5% vs Doce+placebo+ADT
  - Docetaxel 75 mg/m2 x 6 cycles, + darolutamide 600 mg BID, +ADT
  - SE: Fatigue, alopecia, neutropenia

Smith M, et al. Darolutamide and survival in metastatic , hormonse-sensitive prostate cancer. NEJM 2022; 386: 1132-1142

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Comparing Metastatic Castrate Sensitive Treatment Options

Agent	Practical Considerations
Docetaxel	De novo high volume disease per CHAARTED Myelosuppression/neuropathy IV chemotherapy requiring frequent visits Limited therapy duration (6 x 21 day cycles) Cost $ Newer data supports use of either antiandrogen vs triplet therapy, not chemo alone
Abiraterone	De novo metastatic disease per LATITUDE and STAMPEDE mineralocorticoid excess syndrome and hepatotoxicity Continuous daily treatment until progression to mCRPC Cost $$$
Apalutamide	De novo metastatic disease or prior local tx per TITAN Rash and CNS effects (dizziness, fatigue, falls) Continuous daily treatment until progression to mCRPC Cost $$$
Enzalutamide	De novo metastatic disease or prior local tx per ARCHES Seizure warning Continuous daily treatment until progression to mCRPC Cost $$$
Doce + abi or daro	De novo metastatic disease per PEACE-1 and ARASENS Multiple therapies can lead to increase toxicity

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Advanced Prostate Cancer

Advanced prostate cancer responds to castration for an average of 2 years before the PSA begins to rise.

Then what?

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Castrate Resistant

- PSA rises and testosterone remains castrate
- Continue primary androgen treatment
- Obtain imaging studies prior to initiating additional treatment

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Nonmetastatic Castrate Resistant Prostate Cancer (nmCRPC)

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nmCRPC

Enzalutamide

- PROSPER (n = 1,401)
  - Enzalutamide 160 mg + ADT vs placebo + ADT
  - Primary endpoint = mets-free survival
    - 36.6 months vs. 14.7 months
  - Secondary endpoint = median time to subsequent CaP tx
    - 39.6 months vs. 17.7 months
  - MOA: Inhibits androgen binding to AR and inhibits AR nuclear translocation and interaction with DNA
  - SE: Myalgia, arthralgia, fatigue, hot flash, HTN; seizure warning

Sternberg C, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer
N Engl J Med 2020; 382:2197-2206

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nmCRPC

Apalutamide

- SPARTAN (n = 1,207)
  - Apalutamide 240 mg + ADT vs. placebo + ADT
  - Primary endpoint = mets-free survival
    - 40.5 months vs. 16.2 months
  - MOA: androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR→ prevents AR translocation, DNA binding, and AR-mediated transcription
  - SE: arthralgia, rash, anorexia, fall, hypothyroidism, fracture, diarrhea

Smith M et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378:1408-1418

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nmCRPC

Darolutamide

- ARAMIS (n = 1,509)
  - Darolutamide 600 mg BID + ADT vs. placebo + ADT
  - Primary endpoint = mets-free survival
    - 40.4 months vs. 18.4 months
  - MOA: Inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription
  - SE: Fatigue, rash, extremity pain

* Not associated with higher risk of falls, fractures, seizures, HTN compared with placebo

Fizazi K, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; 380:1235-1246

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Comparing Non-Metastatic Castrate Resistant Treatment Options

	Enzalutamide	Apalutamide	Darolutamide
Inclusion	PSA doubling time of < 10 months Baseline PSA ≥2 ng/mL	PSA doubling time of < 10 months Pelvic nodes <2 cm and below aortic bifurcation	PSA doubling time of < 10 months Baseline PSA ≥2 ng/mL, Pelvic nodes <2 cm and below aortic bifurcation
Dose	160 mg daily w/wo food	240 mg daily w/wo food	600 mg twice daily with food
ADEs	Fatigue, hypertension, dizziness, falls, fractures, headache	Fatigue, hypertension, rash, hypothyroidism, fracture	Fatigue, rash, pain in extremities, decrease in neutrophil count, increase in AST, Increase in bilirubin
Cost	$$$	$$$	$$$

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Metastatic Castrate Resistant Prostate Cancer (mCRPC)

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Treating mCRPC

- Lots of factors to consider:
  - Prior treatment
  - Toxicities from prior treatment
  - Comorbidities
  - Goals of care
  - Drug interactions
  - Cost

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NCCN

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,sss]
• Preferred regimens ‣ Abiraterone[e,nnn] (category 1[ooo]) ‣ Docetaxel[fff,ppp] (category 1) ‣ Enzalutamide[u] (category 1) • Useful in certain circumstances ‣ Radium-223[rrr] for symptomatic bone metastases (category 1) ‣ Sipuleucel-T[fff,qqq] (category 1) • Other recommended regimens ‣ Other secondary hormone therapy[u]	• Preferred regimens ‣ Docetaxel (category 1)[fff] • Useful in certain circumstances ‣ Cabazitaxel/carboplatin[fff,jjj] ‣ Olaparib for HRRm (category 1)[ttt] ‣ Radium-223[rrr] for symptomatic bone metastases (category 1) ‣ Rucaparib for BRCA mutation[uuu] ‣ Sipuleucel-T[fff,qqq] • Other recommended regimens ‣ Abiraterone[u,nnn] ‣ Abiraterone + dexamethasone[nnn,vvv] ‣ Enzalutamide[u] ‣ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm]	**Prior docetaxel and prior novel hormone therapy[mmm,sss]**
• Preferred regimens ‣ Abiraterone[u,nnn] (category 1) ‣ Cabazitaxel[fff] ‣ Enzalutamide[u] (category 1) • Useful in certain circumstances ‣ Cabazitaxel/carboplatin[fff,jjj] ‣ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ‣ Radium-223[rrr] for symptomatic bone metastases (category 1) ‣ Sipuleucel-T[fff,qqq] • Other recommended regimens ‣ Other secondary hormone therapy[u]	• Useful in certain circumstances ‣ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[www] (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ‣ Cabazitaxel[fff] (category 1[ooo]) ‣ Docetaxel rechallenge[fff] • Useful in certain circumstances ‣ Cabazitaxel/carboplatin[fff,jjj] ‣ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ‣ Olaparib for HRRm (category 1[ooo])[ttt] ‣ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff] ‣ Radium-223[rrr] for symptomatic bone metastases (category 1[ooo]) ‣ Rucaparib for BRCA mutation[uuu] • Other recommended regimens ‣ Abiraterone[u,nnn] ‣ Enzalutamide[u] ‣ Other secondary hormone therapy[u]

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mCRPC: Chemotherapy

- Docetaxel
  - Approved in 2004 after showing survival advantage over mitoxantrone (3 months)
  - Microtubule inhibitor
  - Dose: 75mg/m^2 every 3 weeks with prednisone 5 mg BID x 10 cycles
  - SE: Hypersensitivity, myelosuppression, skin rash, alopecia, neuropathy, GI upset

Tannock IF, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502-12

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mCRPC: Chemotherapy

- Cabazitaxel
  - Approved in 2010 after showing survival advantage over mitoxantrone (2.4 months)
  - 2nd line use for men who have already been treated with Docetaxel
  - Microtubule inhibitor
  - Dose: 25mg/m^2 every 3 weeks with prednisone 5mg BID x 10 cycles
  - SE: GI upset, renal insufficiency, neutropenia, hypersensitivity, neuropathy

de Bono JS, et al. TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

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mCRPC: Chemotherapy

- Other SE: fatigue, asthenia, anorexia, taste change, arthralgia, alopecia, myelosuppression, electrolyte abnormalities
- Venous access

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mCRPC: Anti-Androgens

- Abiraterone
  - Approved in 2011 for mCRPC s/p Docetaxel after showing survival advantage vs. placebo (3.9 mos.)
  - Approved in 2012 for mCRPC pre-chemo after showing rPFS vs. placebo (8.2 mos.)
  - Oral biosynthesis inhibitor
    - Inhibits CYP17, enzyme needed for androgen synthesis in the testes, adrenals, and tumor
  - Dose: 1,000mg daily with prednisone 5mg BID
  - SE: Myalgia, edema, arthralgia, LUTS, hypokalemia, hepatotoxicity

de Bono JS, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005.

Ryan C et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-148

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mCRPC: Anti-Androgens

- Enzalutamide
  - Approved in 2012 for mCRPC s/p docetaxel after showing survival advantage vs. placebo (4.8 mos.)
  - Approved in 2014 for mCRPC pre-chemo after showing rPFS vs. placebo (65% rPFS vs. 14%)
  - Oral androgen receptor inhibitor
    - Inhibits androgen binding to AR and inhibit AR nuclear translocation and interaction with DNA
  - Dose: 160mg daily
  - SE: Myalgia, arthralgia, fatigue, hot flash; seizure warning

Scher HI, et al.; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97.

Beer T et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371:424-433

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Cross resistance

- 20-40% of pts. presents with primary resistance to abi and enza (i.e., no initial PSA response)
- Secondary resistance invariably develops
- Androgen receptor (AR) signaling axis very complex
- Many mechanisms alter the AR-axis signaling process, which leads to disease progression and/or treatment resistance
  - AR amplification, AR overexpression, AR somatic point mutations, AR splice variants, altered intratumoral androgen biosynthesis
  - One example of AR-V7

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mCRPC: Immunotherapy

- Sipuleucel-T
  - Approved in 2010 after showing survival advantage over placebo (4.1 mos.)
    - Asymptomatic or minimally symptomatic
  - Autologous cellular immunotherapy
    - Minimum of 50 million CD54+ cells
  - Dose: Pheresis, IV infusion every other week x 3 doses
  - SE: Chills, fever, fatigue, myalgia, infusion reaction
  - PSA changes will not be immediate

Kantoff P, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422

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mCRPC: Radiopharmaceutical

- Radium 223
  - Approved in 2013 after showing survival advantage vs. placebo (3.6 mos.)
    - Symptomatic bones mets and no visceral mets
  - Alpha particle-emitting radioactive agent
    - Isotope mimics calcium and forms complexes with bone mineral at areas of increased bone turnover
  - Dose: 50kBq/kg IV q 4 weeks x 6 doses
  - SE: Myelosuppression, nausea, diarrhea
  - PSA difficult to follow

Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369:213-223

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mCRPC: Radiopharmaceutical

- Lutetium Lu-177
  - Approved in 2022 after showing mOS of 15.3 months vs 11.3 months (best supportive care alone)
  - Radioligand; lutetium-177 is linked to a moiety that binds to PSMA and delivers radiation to PSMA-expressing cells
  - Had to have had at least one AR pathway inhibitor, and 1 or 2 prior chemos
  - Must have PSMA positive PET (at least 1 tumor with uptake greater than normal liver)
  - Dose: 7.4 GBq every 6 weeks for 6 doses
  - SE: fatigue, dry mouth, nausea, anemia

Sartor O et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385:1091-1103

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Mutations

- Sequencing of germline DNA from 692 mPC patients demonstrated 11.8% had mutation in DNA-repair gene
  - BRCA2- 5.3%
  - ATM- 1.6%
  - CHEK2- 1.9%
  - BRCA1- 0.9%
- Germline screening is recommended for all patients with metastatic prostate cancer and consider for high/very high risk localized. Consider also based on family history, histology, personal h/o other cancers
- Somatic testing


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin,

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mCRPC: Special circumstances

- Mutations in BRCA1, BRCA2, ATM, PALB2
  - Consider PARP Inhibitor
  - PROfound study: Olaparib in mCRPC w/ homologous recombination repair (HRR) deficiency s/p abi or enza
  - TRITON 2 study: Rucaparib for patients with BRCA-mutations (germline and/or somatic) s/p antiandrogen and chemo
  - PROpel study: Olaparib + abi/pred; no prior systemic tx for mCRPC
- Microsatellite instability (MSI- high of deficient mismatch repair (dMMR)
  - Consider pembrolizumab

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mCRPC

- When is treatment changed?
  - Progression of disease usually occurs at 3 different levels: PSA progression, radiographic progression, clinical progression
  - After chemo, monitor PSA and image PRN
  - On PO, when consistent rise in PSA w/ increased disease burden on scans and/or worsening clinical picture
  - Generally don't change treatment unless POD on scans
  - No consensus re: treatment sequencing

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Comparing Metastatic Castrate Resistant Treatment Options

Agent	Place in therapy
Sipuleucel-T	Asymptomatic minimally symptomatic, should be used early in therapy when disease burden is lower and immune system intact
Radium 223	Symptomatic bone metastasis only
Abiraterone	May be less effective after enzalutamide treatment
Enzalutamide	May be less effective after abiraterone treatment
Docetaxel	Visceral metastasis present, chemotherapy naïve
Cabazitaxel	Previously treated with docetaxel
Lutetium	Requires PSMA + PET and 2 lines of prior therapy
Pembrolizumab	Microsatellite instability (MSI) – high or deficient mismatch repair (dMMR), second and subsequent lines of therapy
PARP Inhibitors	Mutations in BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, second and subsequent lines of therapy

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The lineup

Agent	Category	BCR only	mCSPC	nmCRPC	mCRPC
Abiraterone	Antiandrogen		X		X
Enzalutamide	Antiandrogen		X	X	X
Apalutamide	Antiandrogen		X	X	
Darolutamide	Antiandrogen			X	
Docetaxel	Chemo		X (w/ abi or daro		X
Cabazitaxel	Chemo				X
Sipuleucel-T	Immuno				X
Radium-223	Radiopharm				X
Lutetium	Radiopharm				X
ADT	Hormone	X	X	X	X

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Supportive Care

- Bone health
  - All mCRPC with bone mets* & long-term ADT with osteoporosis (T score -2.5 or lower)**
    - Zoledronic Acid
      - IV bisphosphonate
      - Dose: 4 mg IV over 15 minutes
      - SE: Hypocalcemia, renal dysfunction, ONJ, flu-like sx
    - Denosumab
      - Monoclonal antibody that targets RANKL, a protein involved in cancer-related bone destruction
      - 120mg SC q 4-6 weeks/ 60 mg SC q 6 months
      - SE: Severe hypocalcemia, ONJ
    - Calcium (min 500 mg) & Vitamin D (400 IU)
    - Weight bearing exercise

*for prevention of SRE **for osteoporosis

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Supportive Care

- Hot flashes (80%)
  - Data for pharmacologic management is lacking
  - Lifestyle modification
- Sexual dysfunction
  - ED
  - Decreased libido
  - Penile shrinkage
- Fatigue
  - Multifactorial
  - Exercise, sleep hygiene, mindfulness, treat the treatables
- Bone pain
  - XRT, opioids, non-opioids
- Emotional/psychological

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Supportive Care

- Urinary symptoms
  - Palliative prostate radiation
  - TURP
  - Suprapubic tube
  - External condom catheters
  - Urethral catheter
  - Stents
- Evidence-based Practice Resources for Supportive Care Management
  - Oncology Nursing Society
  - NCCN Guidelines

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Supportive Care

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Practical considerations

- Promoting adherence to PO therapies and treatment schedules
- Evaluating barriers to care
- Providing education about treatments (rationale, schedule, MOA, toxicities, etc.)
- Identifying resources at your institution and elsewhere
- Professional education to keep up with the growing landscape
- Partnering with other disciplines

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Advanced Prostate Cancer

- There is no cure for metastatic prostate cancer
- Shared decision making is important
- Clinical trials
- Always incorporate best supportive care
- Advanced Care Planning
- Caregivers
- Cancer care is complicated!
- Always let patients know that just because there are multiple treatment options does not mean that they have to exhaust them

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References

Lisney AR, at al. The Role of PSMA PET/CT in the Primary Diagnosis and Follow-Up of Prostate Cancer-A Practical Clinical Review. Cancers (Basel). 2022 Jul 26;14(15):3638

Roehl KA, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol* 2004; 172:910–914

Lowrance W,, et al. Updates to advanced prostate cancer: AUA/SUO guideline (2023). J Urol. 2023;209(6):1082-1090.

Mack Roach et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference, International Journal of Radiation Oncology*Biology*Physics, Volume 65, Issue 4,2006, Pages 965-974

Shipley et al. Radiation with or without Antiandrogen therapy in recurrent prostate cancer. NEJM. 2017: 376(5). 417-428.

Calleris G, et alSalvage Radical Prostatectomy for Recurrent Prostate Cancer Following First-line Nonsurgical Treatment: Validation of the European Association of Urology Criteria in a Large, Multicenter, Contemporary Cohort. Eur Urol Focus. 2023 Jul;9(4):645-649. doi: 10.1016/j.euf.2023.01.006. Epub 2023 Jan 20. PMID: 36682962.

Wei Phin Tan et al,Oncological and Functional Outcomes for Men Undergoing Salvage Whole-gland Cryoablation for Radiation-resistant Prostate Cancer,European Urology Oncology,. 6(3)
2023, Pages 289-294

Tisseverasinghe SA, Crook JM. The role of salvage brachytherapy for local relapse after external beam radiotherapy for prostate cancer. Transl Androl Urol. 2018 Jun;7(3):414-435

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References

Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM. 2013: 368(14); 1314-1325
Bertrand Tombal, et alClinical Outcomes and Testosterone Levels Following Continuous Androgen Deprivation in Patients with Relapsing or Locally Advanced Prostate Cancer: A Post Hoc Analysis of the ICELAND Study, The Journal of Urology, 198(5). 2017,1054-1060

Schally AV, Comaru-Schally AM. Mode of Action of LHRH Analogs. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.

Meani D, et al.Practical differences between luteinizing hormone-releasing hormone agonists in prostate cancer: perspectives across the spectrum of care. *Therapeutic Advances in Urology*. 2018;10(2):51-63

Gittelman M,, et al: A 1-year, open-label, randomized phase II dose-finding study of degarelix, a novel gonadotropin-releasing hormone (GnRH) receptor blocker, in the treatment of prostate cancer in North America. J Urol 180:1986-1992, 2008

Shore N et al. Oral relugolix for androgen deprivation therapy in advanced prostate cancer. N Engl J Med 2020; 382:2187-2196

Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM. 2013: 368(14); 1314-1325

Abbreviations: metastatic castrate resistant prostate cancer (mCRPC), metastatic hormone sensitive prostate cancer (mHSPC), non-metastatic castrate resistant prostate cancer (nmCRPC)

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Sweeney C et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. NEJM 2015; 373:737-746

68

References

Fizazi K et al. Abiraterone plus prednisone in metastatic , castration sensitive prostate cancer. NEJM 2017; 377:352-360

James N et al. Abiraterone for prostate cancer not previously treated with hormone therapy. NEJM 2017; 377:338-351

Chi K et al. Apalutamide for metastatic, castration-sensitive prostate cancer. NEJM 2019. 381: 13-24

Armstrong A, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with Metastatic hormone-sensitive prostate cancer. JCO 2019. 37(32). 2974-2986

Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive
Prostate cancer (PEACE-1); a multicentre, open-label, randomized, phase 3 study with a 2x2 factorial design. Lancet 2022.399(10336) 1695-1707

Smith M, et al. Darolutamide and survival in metastatic , hormonse-sensitive prostate cancer. NEJM 2022; 386: 1132-1142

Sternberg C, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer N Engl J Med 2020; 382:2197-2206

Smith M et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378:1408-1418

Fizazi K, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; 380:1235-1246

Tannock IF, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502-12

69

References

de Bono JS, et al. TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

de Bono JS, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005.

Ryan C et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-148

Scher HI, et al.; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97.

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Kantoff P, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422

Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369:213-223

Sartor O et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385:1091-1103

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