

Southwestern Chapter, SNMMI: Clinical Perspective on Prostate Cancer

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Educational Objectives

- Imaging with isotopes to stage prostate cancer (prostatic adenocarcinoma)
- Management of localized and metastatic prostate cancer
- Isotope therapy for castration-resistant prostate cancer (CRPC) – approved and experimental agents
- Assessing treatment response and progression using Tc99m MDP bone scintigraphy in patients with castration resistant prostate cancer (CRPC)
- Considerations for future use of isotope imaging to assess response to treatment in patients with prostate cancer

Prostate Cancer: Incidence and Mortality

American Cancer Society US estimates

2018

- 164,690 new cases - #1 for men
- 29,430 deaths - # 2 for men

2012

- 241,740 new cases - #1 for men
- 28,170 deaths - # 2 for men

Lifetime probability: 1 in 8

Focus of presentation:

prostatic adenocarcinoma

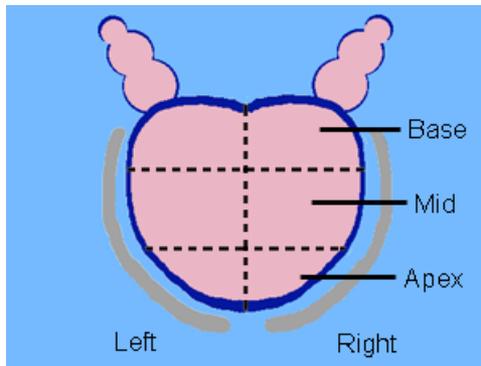
Siegel RL, et al. "Cancer Statistics, 2012." CA CANCER J CLIN 2012;62:10-29

Siegel RL, et al. "Cancer Statistics, 2018." CA CANCER J CLIN 2018, 68:7-30.

American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017

Prostate cancer pathology: Gleason grading

- Gleason score 2-4 essentially a thing of the past



- ≥ 12 Cores

Epstein JI, J Urol, 2010.

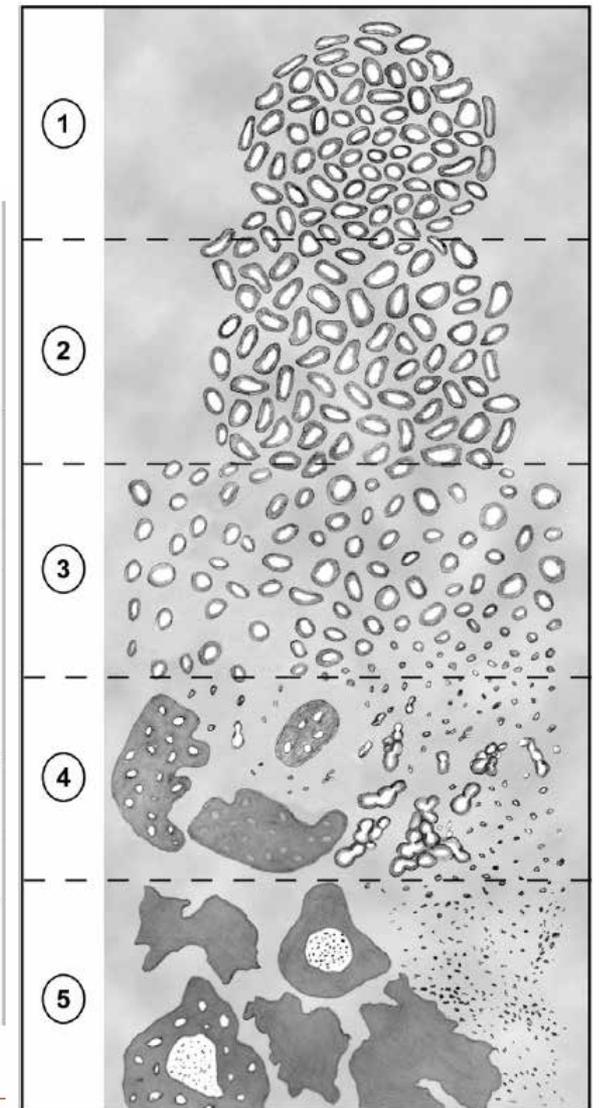
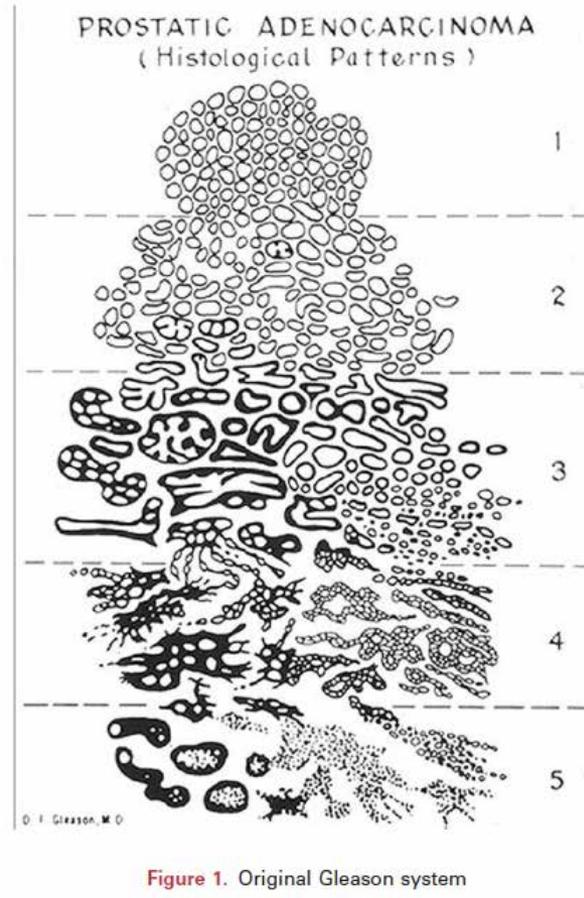


Figure 2. Modified Gleason system. Note cribriform glands are only seen in patterns 4 and 5. Poorly formed glands are also component of pattern 4.

Prostate cancer risk stratification for metastasis and recurrence (D'Amico classification)

	VERY LOW	LOW	INTERMEDIATE	HIGH	VERY HIGH
PSA	< 10 ng/mL	< 10	10 -20	> 20	
Gleason score	and ≤ 6	≤ 6	7	8 to 10	
Clinical T stage	and ≤ T1c and < 3 + cores and ≤ 50% cancer / core and PSA density < 0.15 ng/mL/g	T1-T2a	T2b-T2c	T3a	T3b-T4

Prostate cancer staging work up

- If life expectancy \leq 5 years and asymptomatic, reasonable to wait until symptoms develop prior to treating unless high-risk disease where risk of complications such as hydronephrosis or metastasis are expected within 5 years
- If life expectancy $>$ 5 years or symptomatic, stage and risk stratify
 - Pelvic CT or MRI if T3, T4 or T1-T2 and probability of LN involvement $>$ 10% by nomogram
 - Prostatic adenocarcinoma is bone tropic with stereotypically sclerotic lesions
 - **Technetium 99m-methylene diphosphonate (Tc99m-MDP) bone scan** if T1 and PSA $>$ 20 ng/mL or T2 and PSA $>$ 10 or Gleason \geq 8 or T3, T4 or symptomatic
 - Sites of increased uptake indicate accelerated bone turnover

Potential role for PET in prostate cancer staging

- Limitations of standard imaging:
 - Tc99m-MDP bone scan: rarely positive if asymptomatic and PSA < 10 ng/mL
 - CT/MRI: “pathologic” lymph node: > 1 cm short axis
- Can functional imaging improve prostate cancer staging with increased sensitivity and specificity to detect target lesions?
 - Primary staging in high-risk disease
 - Biochemical recurrence with low PSA values (0.2 to 10 ng/mL)
- How to act on PET scan results when all phase III trials to date have used progression criteria with RECIST and Tc99m-MDP bone scans?

Imaging isotopes for staging prostatic adenocarcinoma

- Approved
 - Technetium 99m-methylene diphosphonate: bone reaction
 - 18F-NaF: bone reaction
 - 18F-FDG: soft tissue and bones
 - 11C-choline: soft tissue and bones
 - 18F-FACBC (Axumin): soft tissue and bones
- Experimental
 - 11C-acetate: soft tissue and bones
 - 18F-FDHT: soft tissue and bones
 - 68Ga-PSMA: soft tissue and bones
 - 18F-DCFBC: soft tissue and bones
 - 18F-DCFpyL: soft tissue and bones

PET radioligands for prostate cancer imaging

Table. Mechanism and Diagnostic Efficacy of Positron Emission Tomographic (PET) Radioligands for Prostate Cancer Imaging

Radiotracer	Mechanism of Action	%		Advantages	Disadvantages
		Sensitivity	Specificity		
[¹¹ C]choline	Cell membrane synthesis	38-98	50-100	Minimal bladder excretion; available in the United States	Variable sensitivity and specificity for BCR, especially at lower PSA levels; requires on-site cyclotron (short half-life)
¹⁸ F-choline	Cell membrane synthesis	47-92	33-99	Longer half-life than [¹¹ C]; can be produced off-site	Variable sensitivity and specificity for BCR, especially at lower PSA levels; limited availability in the United States
[¹¹ C]acetate	Lipid synthesis	42-90	64-96	Minimal bladder excretion	Short half-life requiring an on-site cyclotron; only few centers in the United States are producing it
¹⁸ F-FACBC	Amino acid transport	89-100	67	More sensitive at lower PSA levels than choline and acetate; slow urinary excretion improving signal	Moderate specificity; only moderate performance at lower PSA levels; larger study validation needed
¹⁸ F-FDHT	Androgen receptor	63	NA	Uses AR, which plays an important role in prostate growth	Used mainly in specific drug development; needs validation in BCR and metastatic prostate cancer
¹⁸ F-NaF	Chemisorption in bone matrix	87-89	80-91	Well-validated. Better sensitivity compared with conventional ^{99m} Tc-bone scan. Rapid bone specific uptake; lack of blood pool; good axial skeleton visualization. More rapid acquisition than conventional bone scan	Lower specificity with a high false-positive rate detection; approved but not yet reimbursed
⁶⁸ Ga-PSMA	PSMA analog	63-86	95-100	High sensitivity and specificity even at low PSA levels	Relatively newer radiotracer, still under investigation; requires considerable up-front expenditure and a radiopharmacy
¹⁸ F-DCFBC	PSMA inhibitor and/or antibodies	92	88	F 18 is a superior positron emitter compared with ⁶⁸ Ga with longer half-life	Significant blood pool activity; still under investigation with need for further validation in larger studies
¹⁸ F-DCFpyL	PSMA inhibitor and/or antibodies	NA	NA	Higher tumor to background ratios owing to high affinity; may be more sensitive than ⁶⁸ Ga in detecting BCR	Newer radiotracer that needs further validation in larger studies

Abbreviations: AR, androgen receptor; PET, positron emission tomography; PSMA, prostate specific membrane antigen.

C-11 choline PET/CT

- Cell membrane phospholipid biosynthesis
- Indicated for PET imaging of suspected recurrence based on elevated PSA and non-informative bone scintigraphy, CT, or MRI following prior treatment
- Poor performance with PSA < 2 ng/mL
- Concomitant androgen deprivation therapy (ADT) or colchicine may interfere
- Mayo Clinic

18F-FACBC (Axumin) PET

- 18F-Fluciclovine (18F) = anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (FACBC)
- L-leucine analog
- Indicated for men with suspected prostate cancer recurrence with rising PSA following treatment
- Comparable or superior sensitivity to 11C-choline

PROSTATE CANCER TREATMENT

Management options for prostate cancer without distant metastases

- Observation (elderly, significant co-morbidities)
- Active surveillance
- Radical prostatectomy (RP) – “open” retropubic vs robotic-assisted laparoscopic RP
- Cryotherapy (insufficient longitudinal data for my taste)
- HIFU (FDA approved for organ ablation)
- Radiation Therapy (RT)
 - Brachytherapy (seeds): 125-Iodine, 103-Palladium
 - External beam – photons
 - External beam – protons
 - Stereotactic radiotherapy (clinical trials)
- Androgen deprivation therapy (ADT)
- Multimodality therapy (eg: RT + ADT +/- chemotherapy)

Endocrine Axis in Prostate Cancer

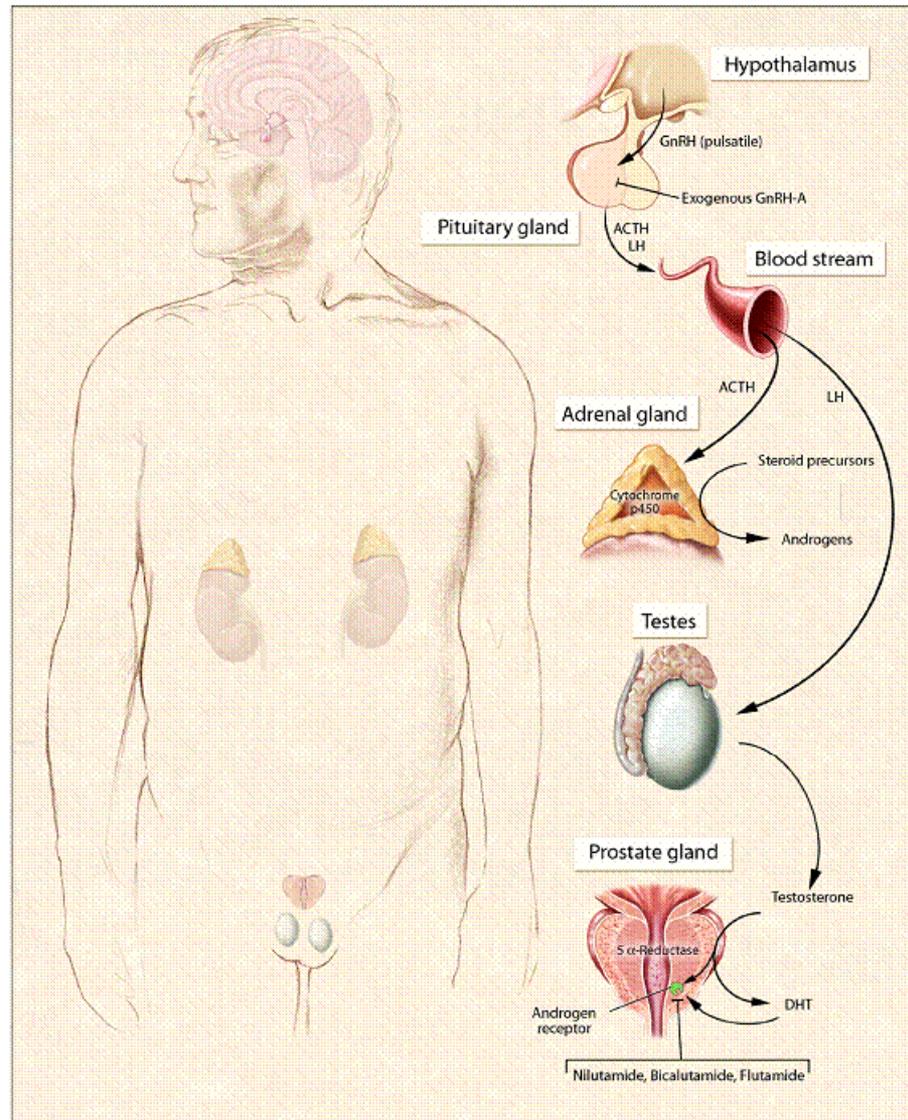
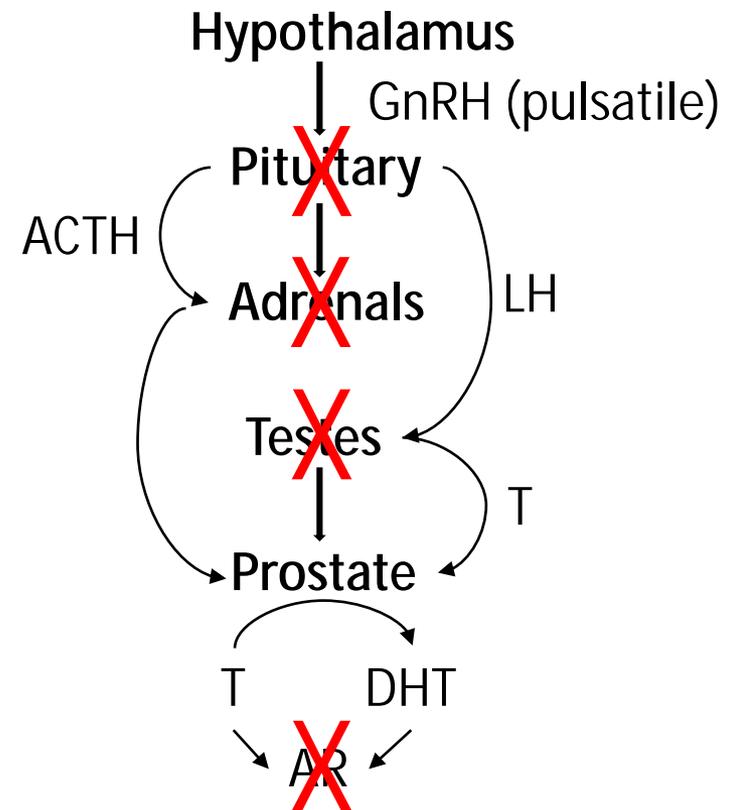


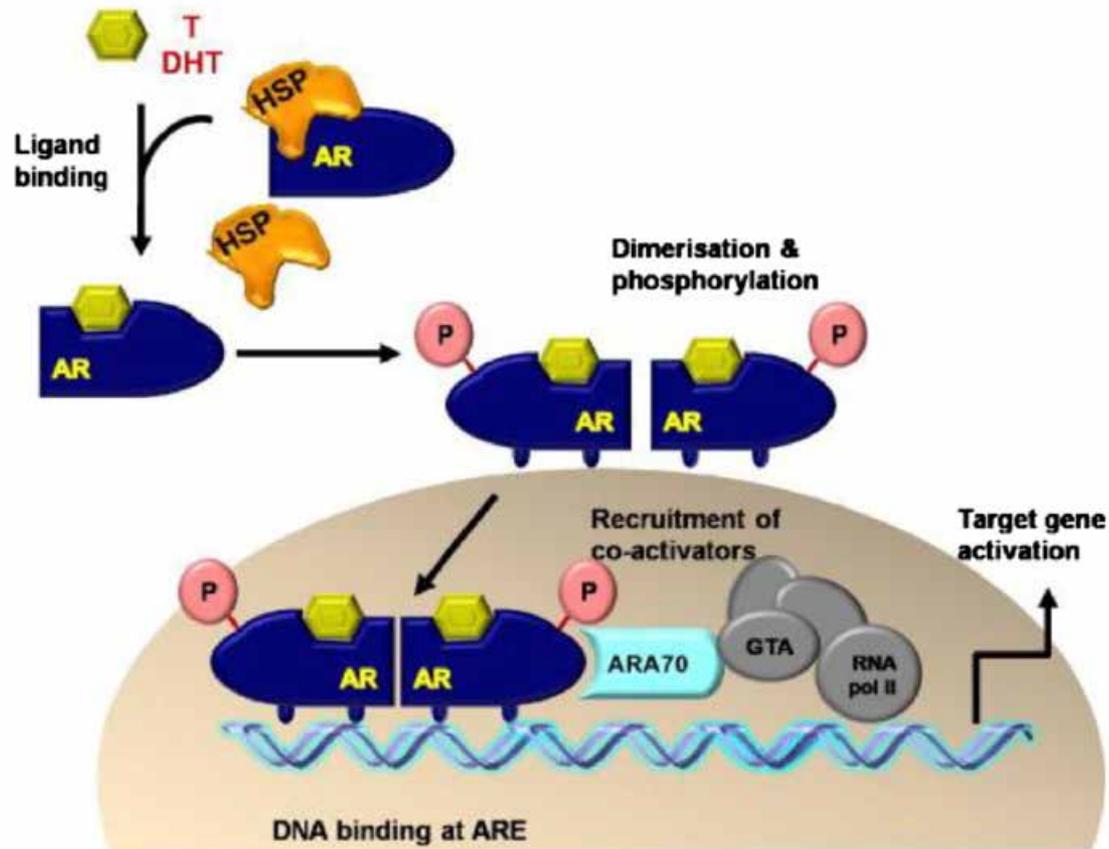
Image courtesy of N. Sharifi. Modified from Sharifi N, Gulley JL, and Dahut WL. (2005) JAMA; 294:238-44.

Methods of androgen deprivation therapy (ADT) to treat prostate cancer

- Orchiectomy (surgical castration)
- GnRH agonist / antagonist (eg: leuprolide / degarelix)
- Antiandrogen (block androgen receptor)
- CYP17 inhibition in the adrenal gland (eg: abiraterone, ketoconazole)



Androgen receptor signaling



The presence of testosterone (T) or dihydrotestosterone (DHT) causes dissociation of HSP, dimerization, and phosphorylation (P) of the AR and translocation to the nucleus where the AR binds to an ARE, causing recruitment of DNA transcriptional machinery and gene transcription. (Adapted from Li J, Al-Azzawi F. Mechanism of androgen receptor action. *Maturitas* 2009;63:142–8; with permission.)

Inhibition of CYP17 (17 α -hydroxylase / 17,20-lyase) to impair androgen synthesis: abiraterone acetate

Acquired *de novo* androgen synthesis by the testis and extra-gonadal sources in mCRPC

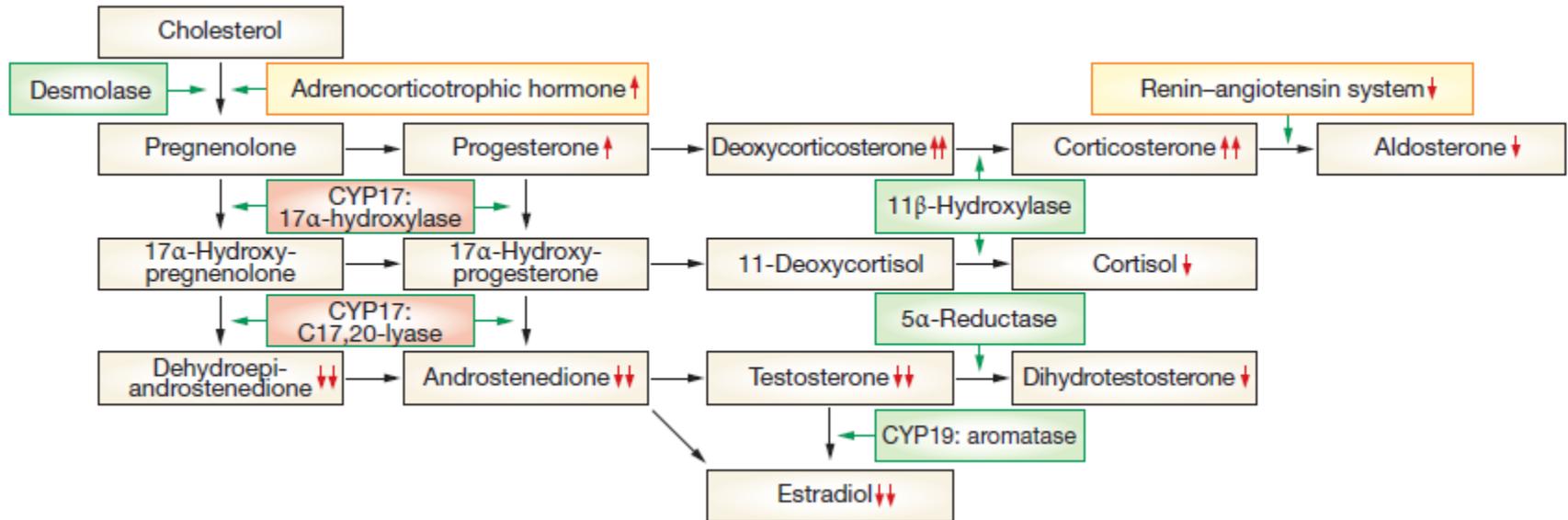
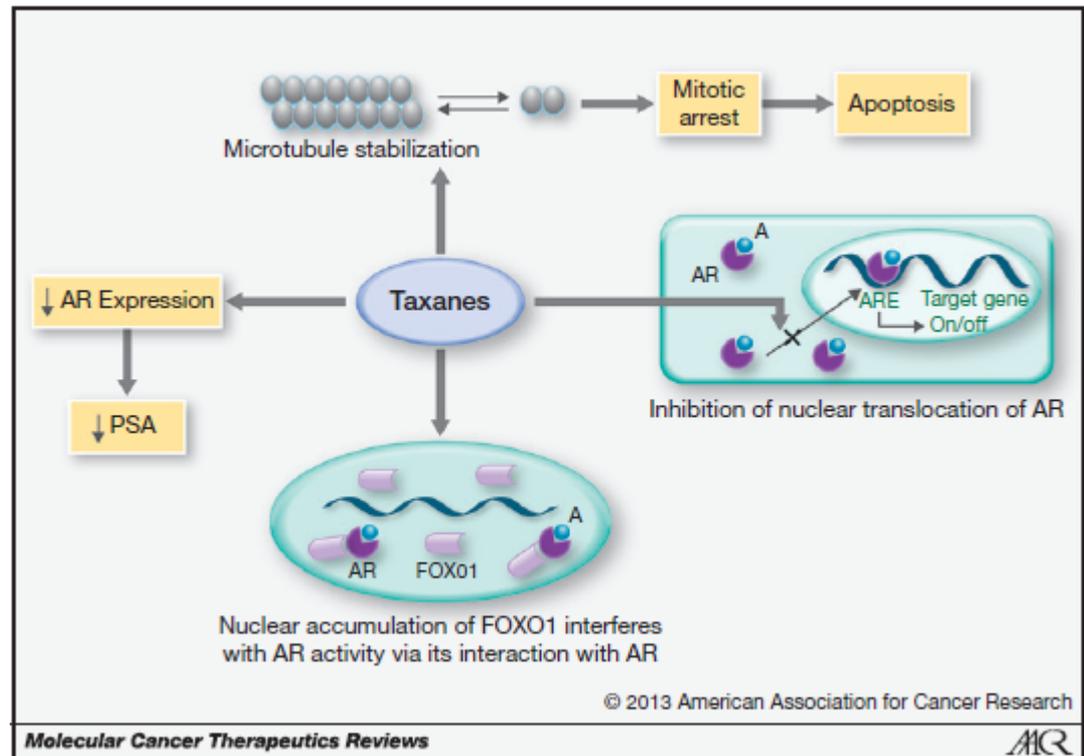


Figure from Reid AHM, et al. (2009) Nat Clin Pract Urol;5:610-20

- **Abiraterone acetate:** Irreversible inhibitor of CYP17 (17 α -hydroxylase / 17,20-lyase)
- Predominant toxicities from mineralocorticoid excess due to loss of negative feedback on ACTH: hypertension, hypokalemia, edema
- Prednisone is co-administered with abiraterone acetate to suppress symptoms of secondary hyperaldosteronism

Microtubule stabilization as a rational therapeutic target in prostate cancer: use of taxane chemotherapy

- Prostate cancer cells: long doubling times, low fraction of dividing cells – is chemotherapy relevant?
- Microtubules: dynamic polymers of α - and β -tubulin heterodimers
- Essential for regulation of chromosomal segregation
- Role in AR nuclear translocation? (seen at supra-clinical doses)
- Inhibition can increase nuclear accumulation of AR-suppressor FOXO1
- Inhibition by taxanes can decrease AR expression
- Docetaxel approved for metastatic prostate cancer in conjunction with ADT



Treatment of castration-sensitive metastatic prostate cancer

- GnRH agonist or GnRH antagonist or bilateral orchiectomy
- High-risk metastatic prostate cancer:
- Add 6 cycles of docetaxel chemotherapy **OR**
- Add abiraterone + prednisone

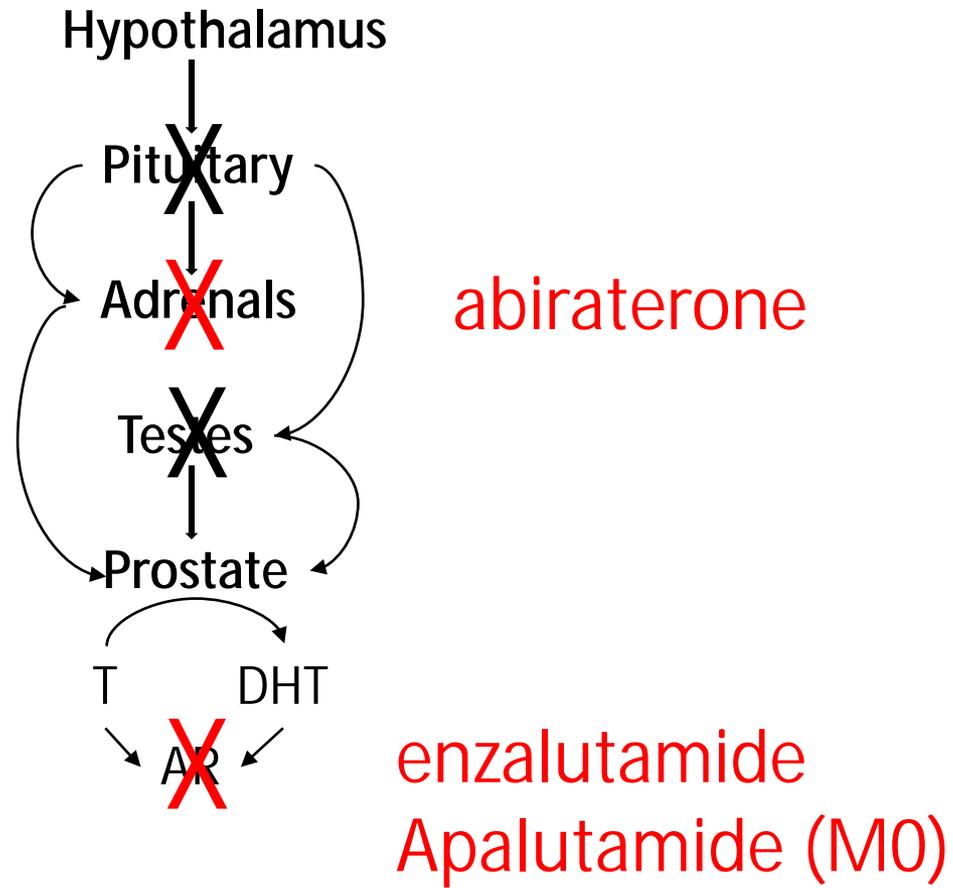
Castration-resistant prostate cancer (CRPC)

- Majority of patients with metastatic prostate cancer experience disease progression within 2-3 years despite surgical or chemical castration
- CRPC is principally responsible for prostate cancer mortality
- “Castration resistant”  “Androgen independent”

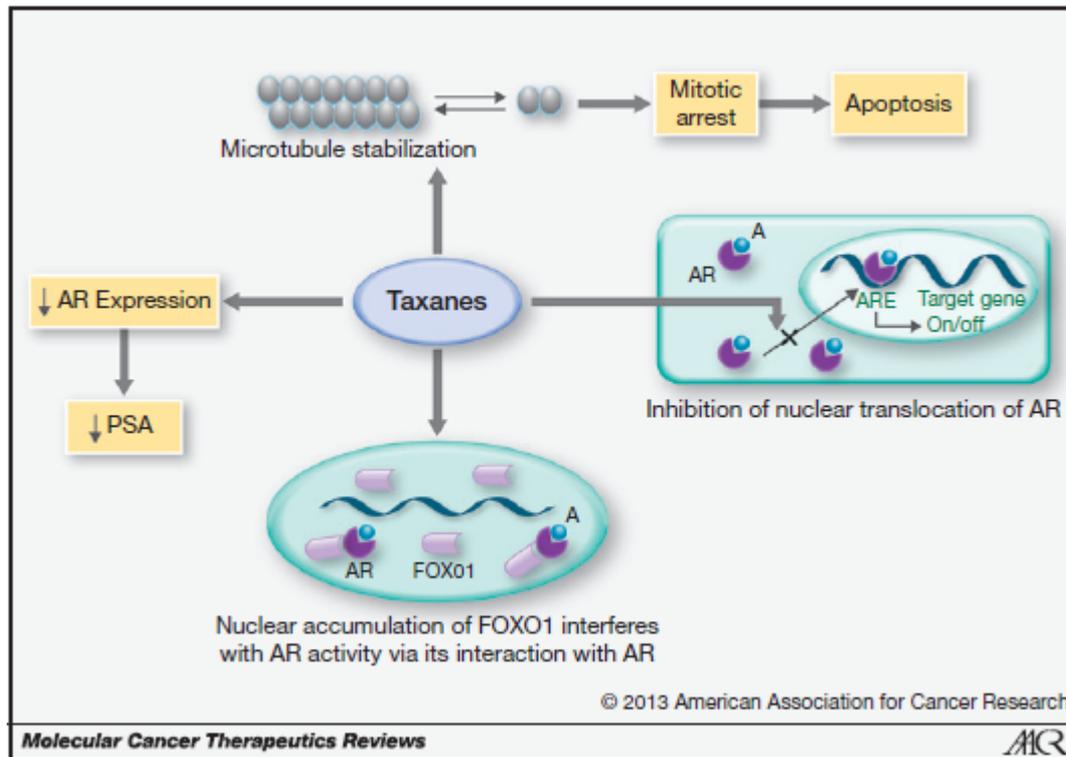
Mechanisms of prostate cancer progression and castration resistance: targets for therapy

- Persistent androgen signaling despite castration therapy
- Microtubule polymerization (taxanes)
- Immune escape
- Interactions with bone microenvironment

Inhibiting androgen signaling in CRPC: hormonal manipulation beyond castration

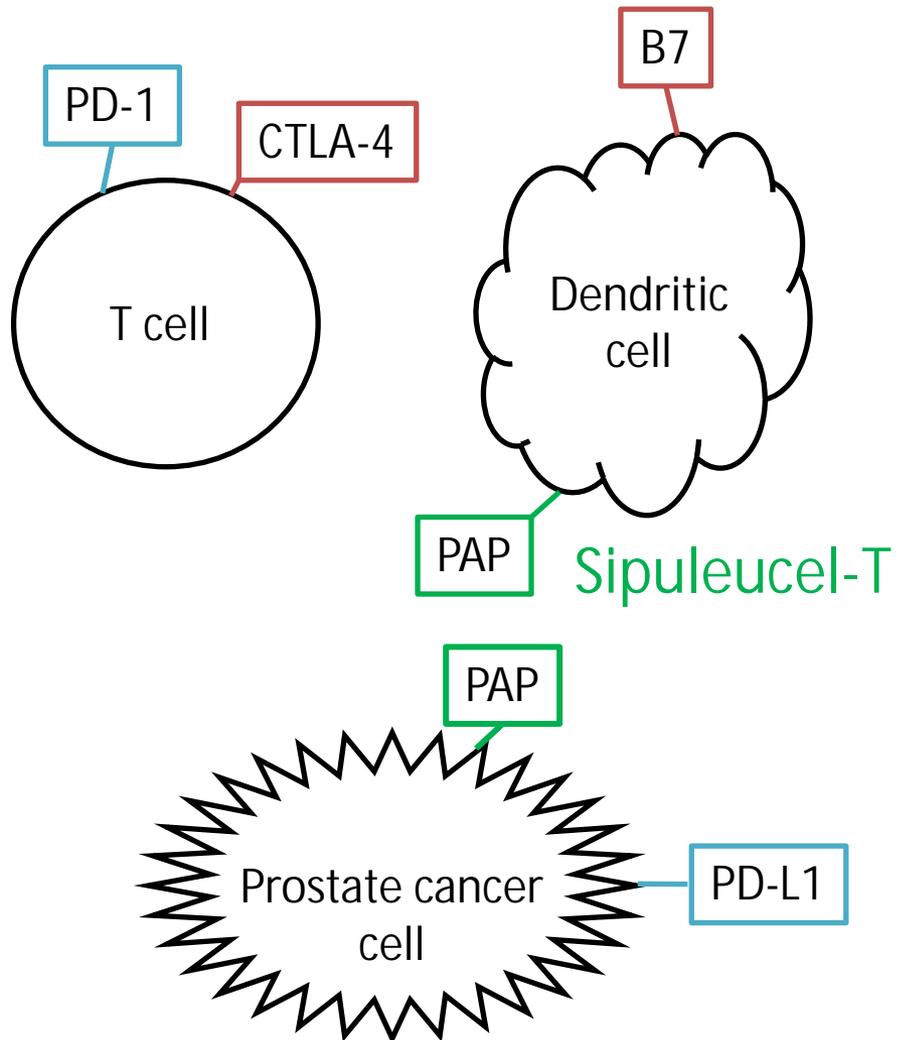


Microtubule stabilization with taxanes: docetaxel or cabazitaxel



Immunotherapy for CRPC

- Immune escape is a hallmark of cancer
- Increased activity of immunosuppressive T regulatory cells (Treg), myeloid-derived suppressor cells (MDSC)
- Upregulation of T-cell inhibitory checkpoint pathways (CTLA-4, PD-1)
- Impaired tumor antigen presentation by antigen presenting cells (APCs)
- Prostate-cancer specific antigens are non-essential: attractive therapeutic targets

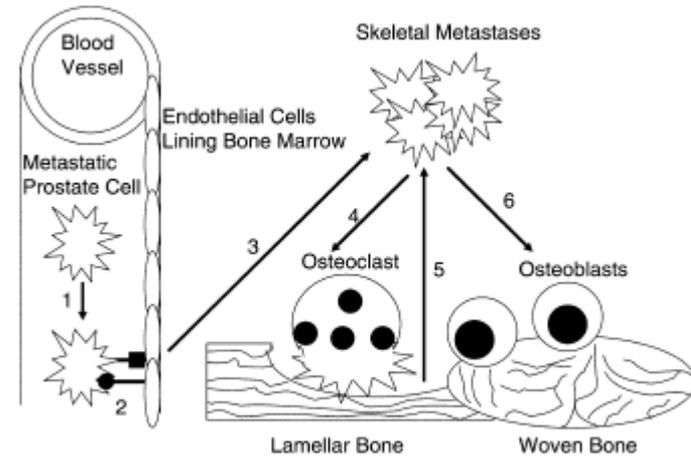


Sipuleucel-T for metastatic CRPC

- Active cellular immunotherapy approved for treatment of asymptomatic or minimally symptomatic men with mCRPC
- CD45+ APCs collected by leukapheresis and pulsed with fusion construct of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) called PA2024
- 3 leukapheresis procedures each separated by 2 weeks, with reinfusion of sipuleucel-T 3 days after each leukapheresis

Prostate cancer bone tropism and bone-targeted therapies

- ~ 90% of patients with metastatic prostate cancer develop bone metastases
- Zoledronic acid (bisphosphonate) and denosumab (RANKL inhibitor) approved in mCRPC to reduce SREs
- **Strontium-89 and samarium-153 lexidronam (beta-emitters) approved to provide palliation for painful bone metastases**
 - Single infusion
 - Myelosuppression risk



Model of cross-talk between prostate cancer and bone microenvironment: a “vicious cycle” where CaP cells stimulate osteoclasts to break down bone, releasing growth factors that support proliferation of CaP, which releases factors supporting osteoblast proliferation/survival.

Radium-223 dichloride preferentially targets osteoblastic metastases

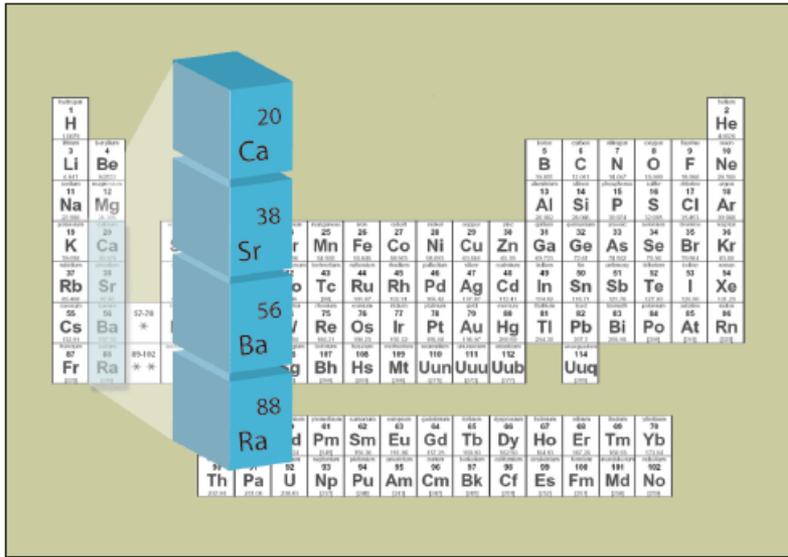
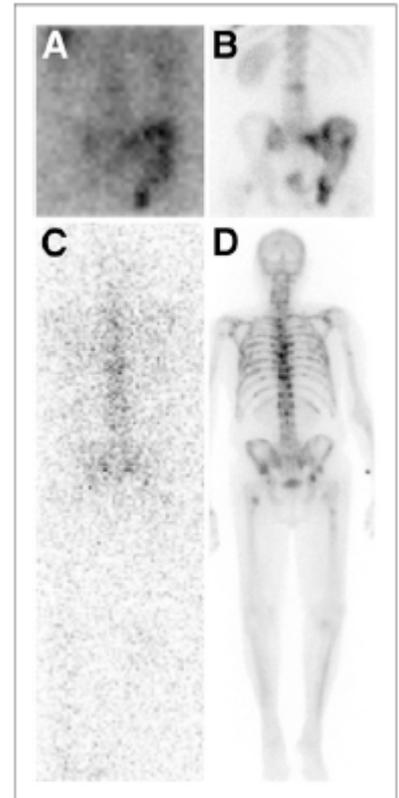
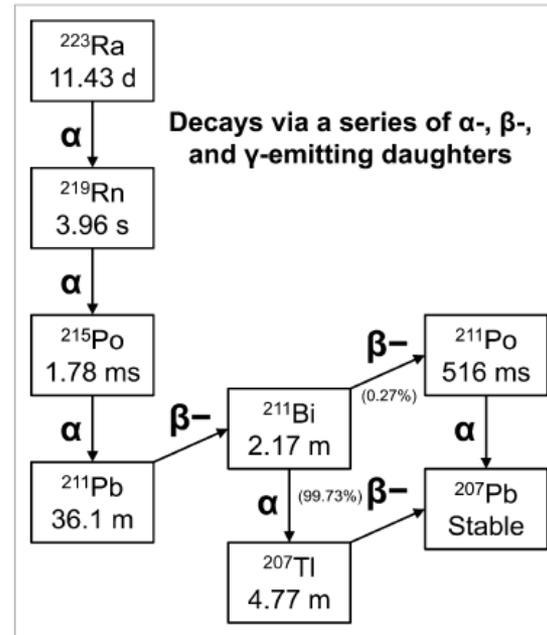


Figure 1: Radium-223 Physical Properties—Position of the alkaline earth metal, radium, in the periodic table. It has four natural isotopes of atomic weight: 228, 226, 224, and 223.



Imaging Radium-223

- Bone-targeted α -emitter
- Effective at inducing DNA double-strand breaks
- Emission over a short (microns) path-length vs. β -radiation (millimeters)
- Calcium mimic with preferential uptake in osteoblastic metastases vs. normal bone

Bone-targeted therapeutic isotope: radium-223 chloride

- **ALSYMPCA:**
- Randomized phase III study of patients with mCRPC previously treated with, unfit for, or refusing docetaxel
- **Symptomatic CRPC** with ≥ 2 bone lesions with **no visceral metastases or bulky (>3 cm) lymph nodes**
- 921 patients randomized 2:1 to Ra-223 vs placebo
- 6 injections 50 kBq/kg IV q 4 wks vs placebo
- **Median OS: 14.9 vs 11.3 mos**, HR 0.70, 95% CI 0.58-0.83, $P < 0.001$
- Prolonged time to 1st SRE: 15.6 vs 9.8 mos, HR 0.66, 95% CI 0.52-0.83, $P < 0.001$
- Improved or slower decline of QoL
- Low rates of Ra-223-associated myelosuppression (grade 3 to 4 neutropenia 3%, thrombocytopenia 6%, anemia 13%)
- Mild non-hematologic side effects: nausea, vomiting, diarrhea

Radium-223 chloride

- Prior to initial dose:
 - ANC $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 100 \times 10^9/L$
 - Hemoglobin ≥ 10 g/dL
- Prior to subsequent doses:
 - ANC $\geq 1.0 \times 10^9/L$
 - Platelet count $\geq 50 \times 10^9/L$
- Discontinue if counts do not recover with delay of 6-8 weeks

Radium-223 chloride

- Three-year safety follow up:
 - 98/600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs
 - No AML, MDS, or new primary bone cancer
 - One radium-223 patient had aplastic anemia 16 mo after the last injection.

Radium-223 and concomitant therapies for mCRPC patients

- International, early access, open-label, single-arm phase 3b trial
- Symptomatic or asymptomatic
 - 50 kBq/kg (55 kBq/kg after implementation of National Institute of Standards and Technology update) every 4 weeks for up to six injections
 - 839 enrolled, 696 treated, 403 received 6 infusions
- Safe for asymptomatic patients
- Safe in combination with abiraterone* or enzalutamide (* now combined abiraterone contra-indicated)

Early unblinding of ERA-223 study: radium-223 should not be administered concomitantly with abiraterone

- ERA-223: randomized, double-blind trial for patients with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant mCRPC
- Patients randomized 1:1 ratio to radium-223 for 6 cycles with abiraterone acetate plus prednisone/prednisolone (n=401), or placebo for 6 cycles with abiraterone acetate plus prednisone/prednisolone and best supportive care (n=405)
- Independent Data Monitoring Committee recommended early unblinding: preliminary data show increased incidence of fractures (24% vs 7%) and deaths (27% vs 20%) in patients receiving radium-223 + abiraterone + prednisone/prednisolone

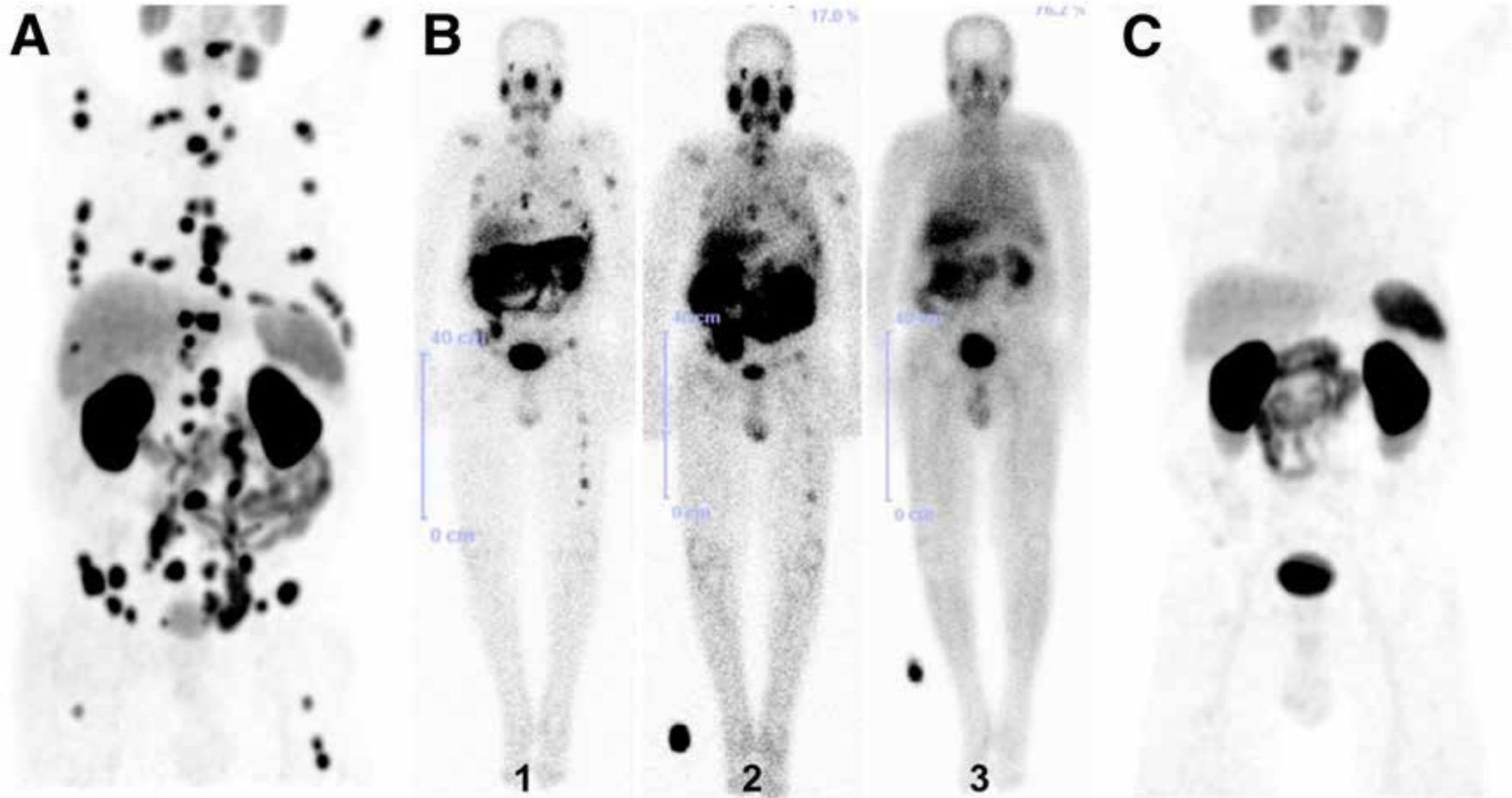
Currently approved therapies for metastatic CRPC

Agent	Action	Year	Primary Endpoint
Estramustine	Nitrogen mustard-estradiol conjugate	1981	Disease responses
Strontium-89	Radiopharmaceutical	1993	Pain palliation
Mitoxantrone + prednisone	Type II topoisomerase inhibitor	1996	Pain palliation
Samarium-153	Radiopharmaceutical	1997	Pain palliation
Zoledronic acid	Bisphosphonate	2002	Reduced SRE
Docetaxel + prednisone	Microtubule stabilizer	2004	Overall Survival
Sipuleucel-T	Cell-based immunotherapy	2010	Overall Survival
Cabazitaxel + prednisone	Microtubule stabilizer	2010	Overall Survival
Denosumab	mAb to RANKL	2010	Reduced SRE
Abiraterone + prednisone	CYP17 inhibitor	2011, 2012*	Overall Survival
Enzalutamide	AR antagonist	2012, 2014*	Overall Survival
Radium-223	Radiopharmaceutical	2013	Overall Survival

SRE, skeletal-related event; mAb, monoclonal antibody; RANKL, receptor of nuclear factor kappa-B ligand; * dates are for FDA approval for treatment of patients post- and pre-docetaxel, respectively

Modified from Pal SK, Lewis B, and Sartor O. Urol Clin N Am 2012; 39:583-591.

Experimental isotope therapy: ^{177}Lu -PSMA



^{68}Ga PSMA PET/CT
Baseline

SPECT During ^{177}Lu -
PSMA Therapy

^{68}Ga PSMA PET/CT
Post Therapy

Monitoring response to treatment in metastatic CRPC: Recommendations of the Prostate Cancer Clinical Trials Working Group (PCWG3)

- Symptom improvement
- PSA
- CTCs
- Soft tissue lesions (CT/MRI): RECIST criteria
- Bone lesions: Tc99m bone scan

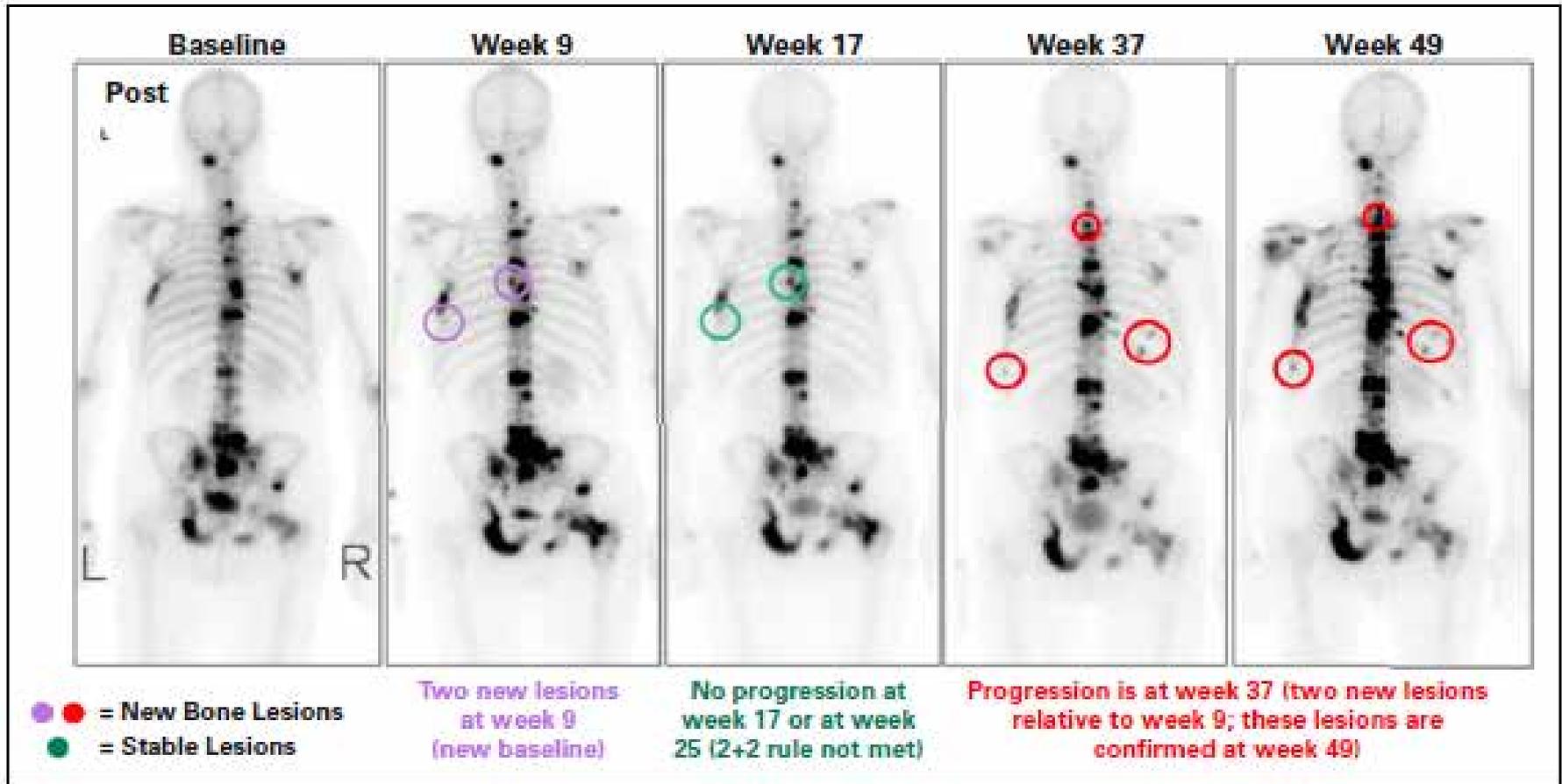
Tc99m-MDP bone scan: monitoring metastatic prostate cancer response to systemic therapy

- New lesions on initial post-treatment bone scan may represent progression or flare
- If no pain, falling PSA, and soft tissue disease response, new bone lesions may be flare / osteoblastic healing reaction
- Confirmatory bone scan at 8-12 weeks to distinguish true progression from flare reaction

Imaging Bone Lesions with Tc99m MDP bone scan: PCWG3 Recommendations

- Suggested frequency in prostate cancer clinical trials: every 8 to 9 weeks for first 24 weeks, then every 12 weeks
- Record outcome as new lesions, no new lesions, or resolved lesion
- First scheduled reassessment:
 - Resolved lesion: continue therapy
 - No new lesions: continue therapy
 - New lesions: perform a confirmatory scan to exclude pseudo-progression in the absence of symptoms or other signs of progression
 - Confirmatory scan:
 - Progression: 2+2 rule: at least 2 new lesions on first post-treatment scan and at least 2 additional new lesions on the next scan (date of progression is the first scan)
- Subsequent scheduled reassessments:
 - At least 2 new lesions vs the 1st post-treatment scan confirmed on a subsequent scan

Imaging Bone Lesions with Tc99m MDP bone scan: PCWG3 Recommendations 2+2 Rule



PCWG3 recommendations regarding PET imaging of bone

- “Because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.”

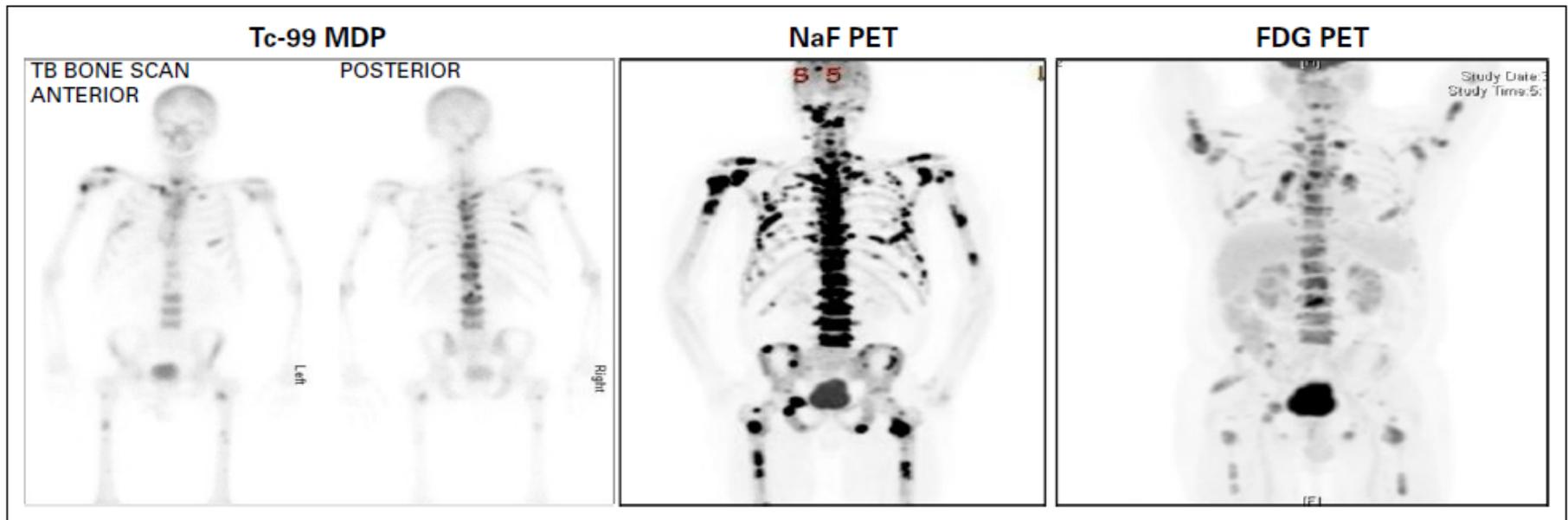


Fig A2. Radionuclide bone scan, sodium fluoride PET scan, and FDG PET scan of the same patient. Only FDG PET is tumor directed; Tc-99 MDP and NaF PET are bone directed. Note that neither the target of the tracer nor the clarity of the image necessarily implies a superior biomarker, and each modality must be validated analytically and clinically. ^{99m}Tc MDP, ^{99m}Tc methylene diphosphonate; NaF, sodium fluoride; FDG, fluorodeoxyglucose; PET, positron emission tomography.

PET evaluation for prostate cancer response to treatment

- Uptake and changes in uptake of fluciclovine, choline, PSMA, etc. may be appreciated in smaller lesions and non-pathologically enlarged lymph nodes in patients with CRPC
- This may distinguish utility of these isotopes in monitoring response to treatment in CRPC from FDG-PET in other tumor types

Parting thoughts

- The interface between urology, radiation oncology, medical oncology, and nuclear medicine physicians is critical to optimize staging, treatment, and monitoring of patients with prostate cancer
- Incorporation of more sensitive imaging methods for both bone and soft tissue lesions into clinical trials and clinical practice is a work in progress
- Novel isotope therapies and combination of isotope therapies with other agents targeting androgen signaling, microtubule stabilization, or other signaling pathways afford an exciting path of investigation to advance treatment of patients with prostate cancer