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Cancer Center

# Updates in Imaging of Advanced Prostate Cancer

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New York, 16 July 2015





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**Nothing to disclose**

# Outline

- MRI, PET/CT → what is the difference?
- Which PET tracers?
- Basis for uptake in Prostate Cancer (PCa)?
- Potential clinical uses
  - Beyond cancer detection and staging
  - Focus on non-invasive assessment of tumor biology



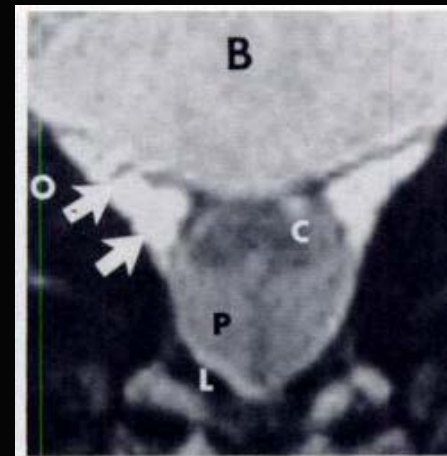
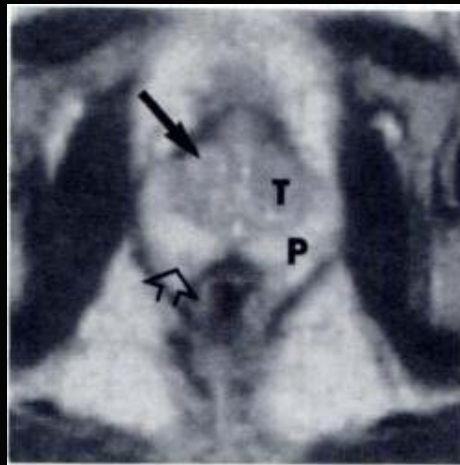
# Prostate MRI: the beginning

- Initial focus on zonal anatomy

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## MR Imaging of the Prostate Gland: Normal Anatomy

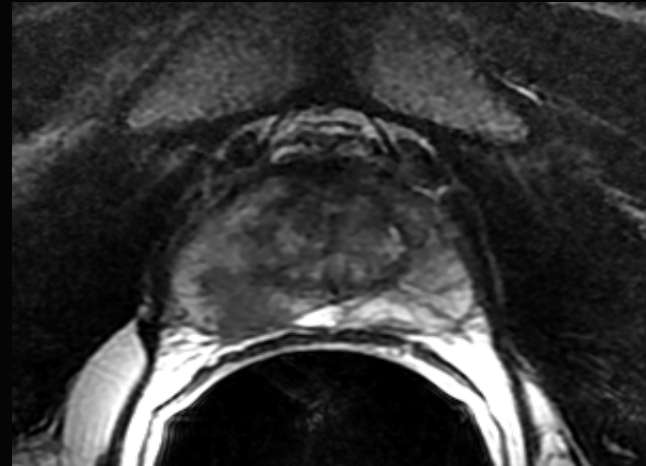
AJR 148:51-58, January 1987  
0361-803X/87/1481-0051  
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# Prostate MRI in 2015: The role of MRI has evolved!

- Zonal Anatomy is still immensely important



# Prostate MRI in 2015: The role of MRI has evolved!

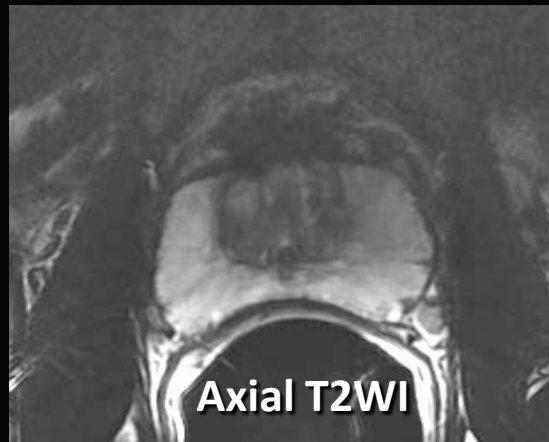
- Prostate MRI ≠ staging only
- It's about providing meaningful information relevant to patient management in specific clinical contexts
- Move away from the “one size fits all” approach to prostate MRI and towards a “wearing the right hat for the right outfit” approach



# Clinically Low-risk Prostate Cancer

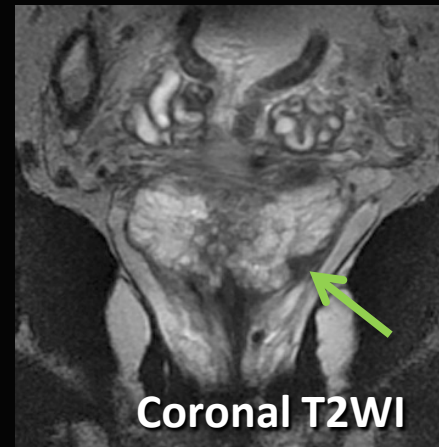
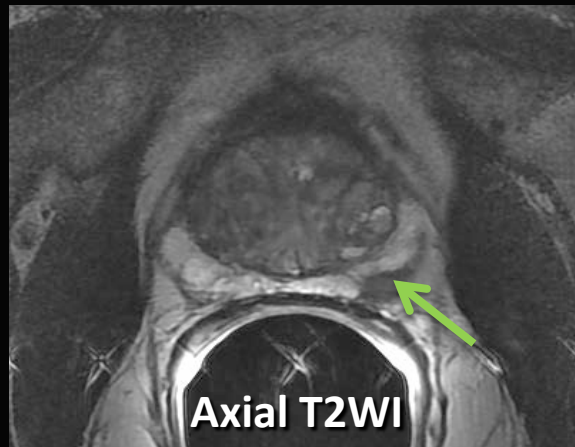
**The critical question:** does the MR fit with the biopsy result?

Patient 1:  
Gleason 6,  
PSA 5,  
cT2a



Repeat bx:  
Gleason 6,  
1 core +,  
5% tumor

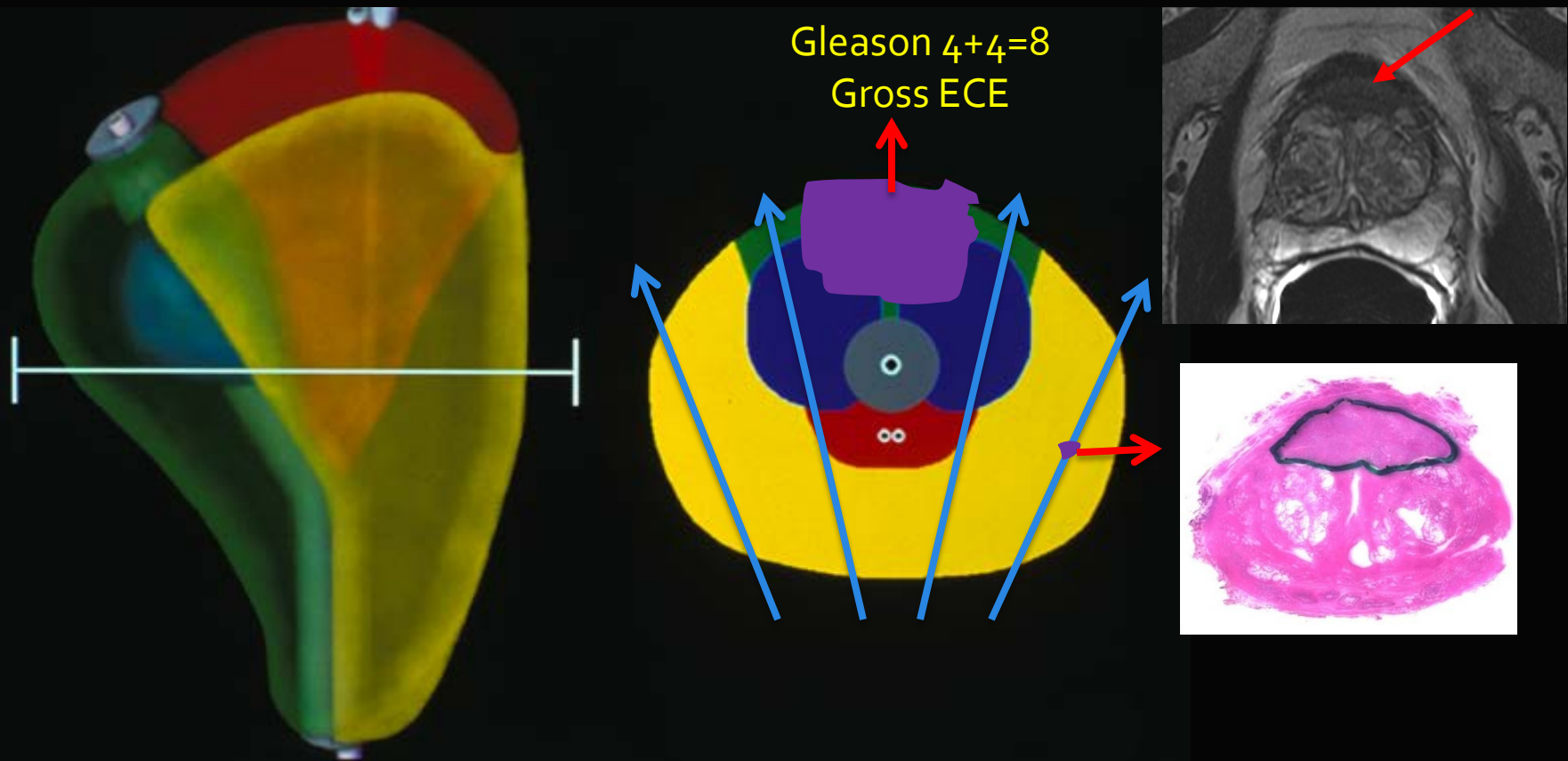
Patient 2:  
Gleason 6,  
PSA 5,  
cT2a



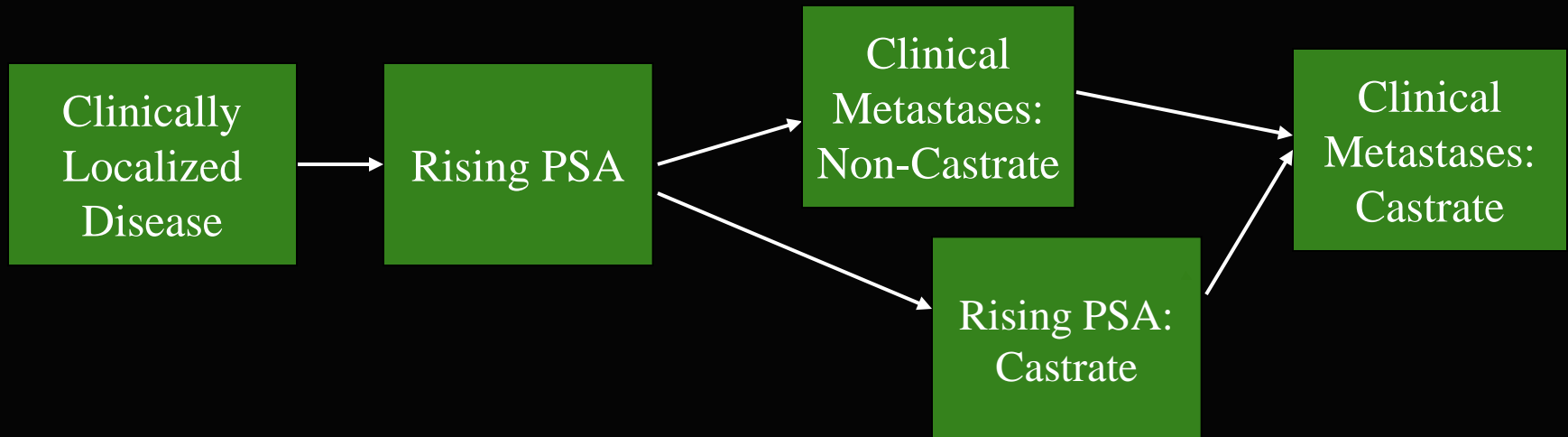
Repeat bx:  
Gleason 4+3  
4 cores +  
50-70% tumor

# Clinically Low-risk Prostate Cancer

What is the problem with random prostate biopsies?



# Prostate Cancer Clinical States

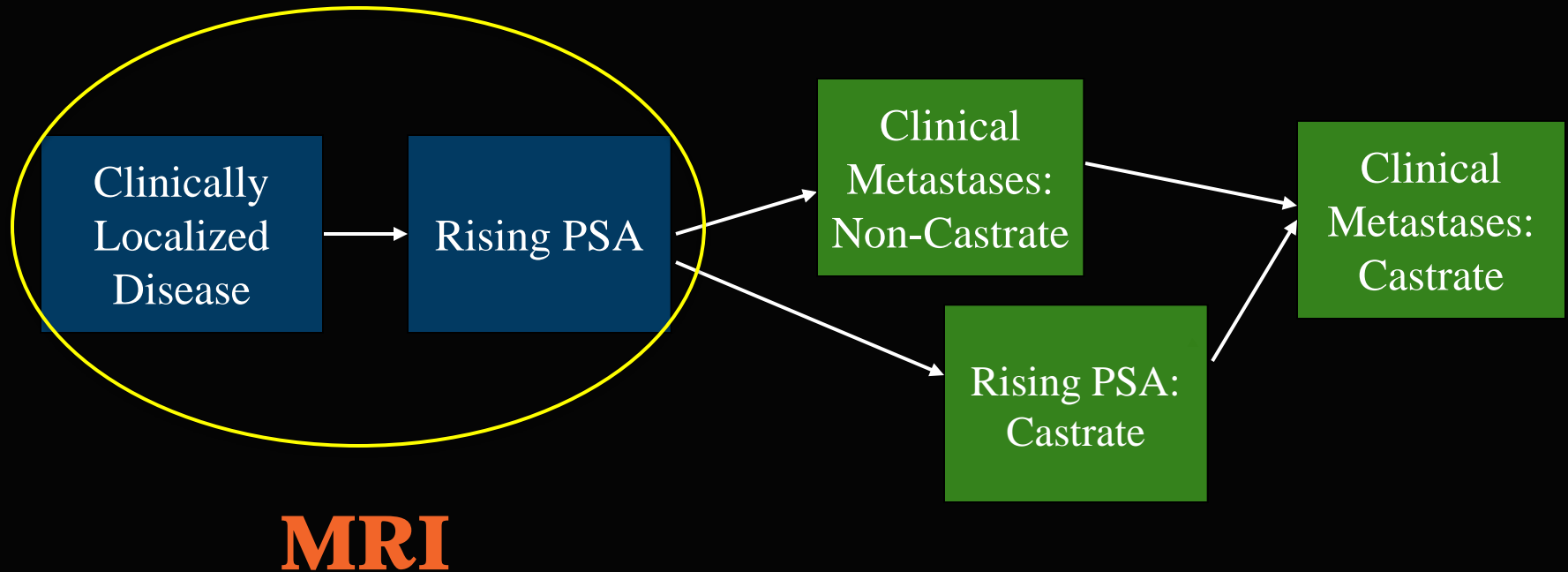


Scher HI et al. Urology 2000



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# Prostate Cancer Clinical States

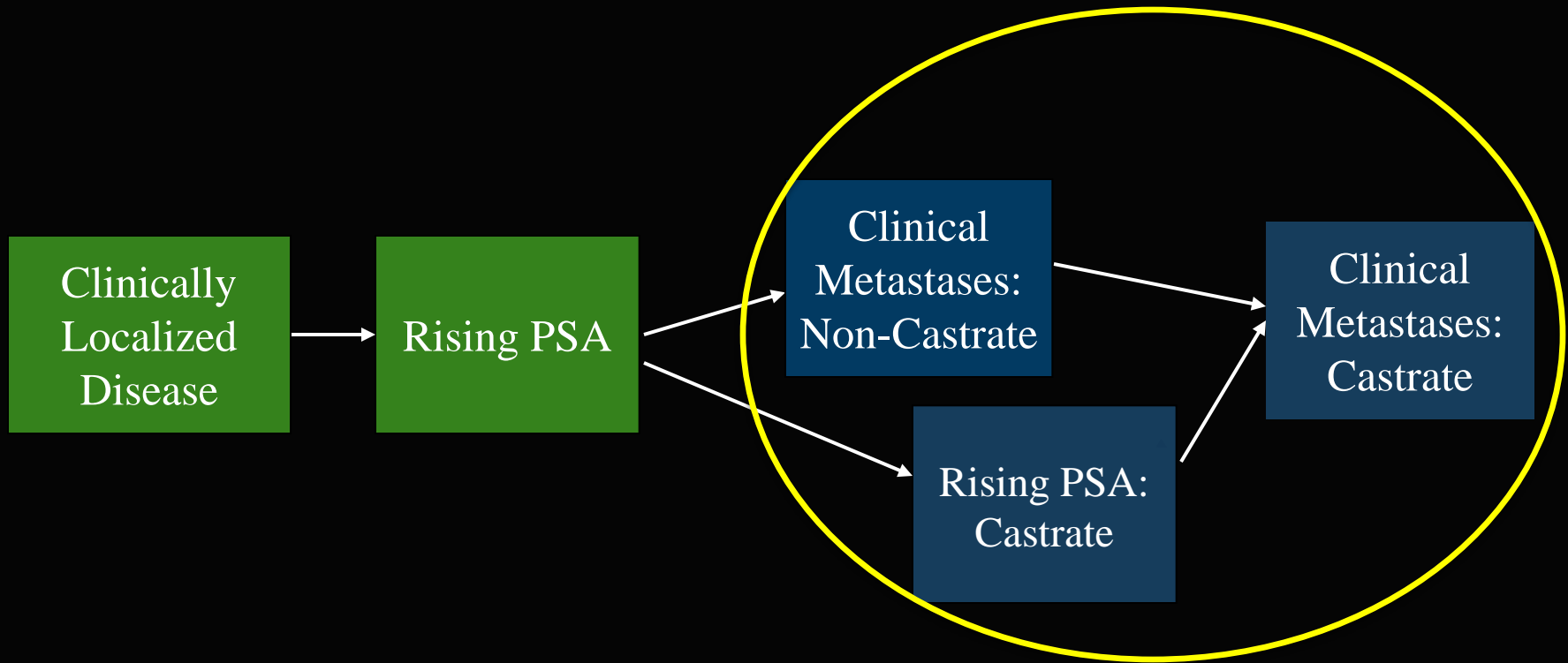


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# Prostate Cancer Clinical States



**PET**

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# PET Radiotracers

Isotope → Pharmaceutical compound

F18

Fluorodeoxyglucose (FDG)

C11

Choline

N13

Aminoacids

O15

Sodium Fluoride

Zr89

Receptors: FDHT, PSMA,

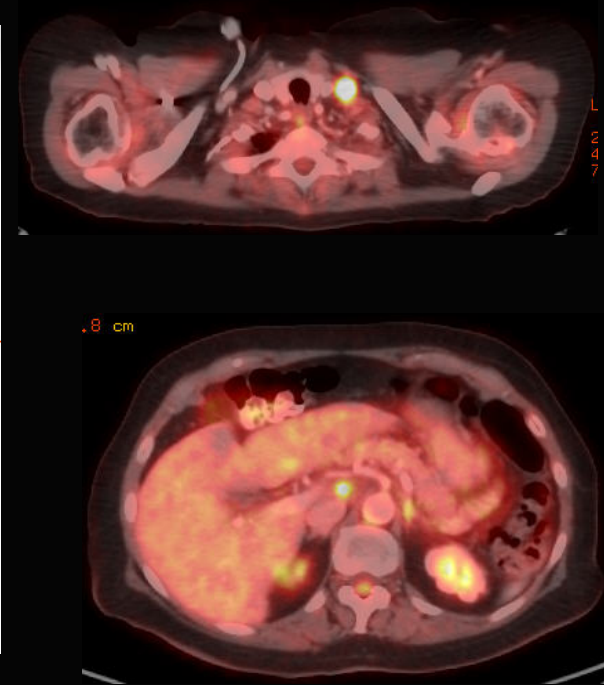
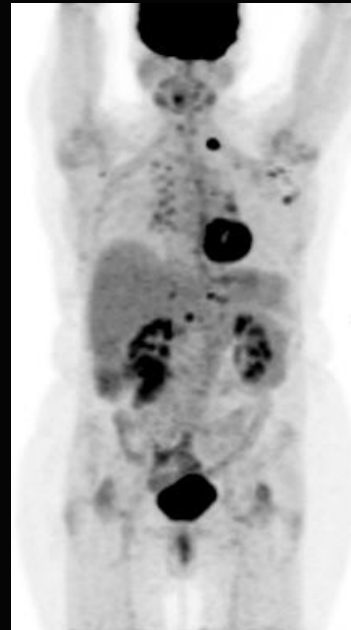
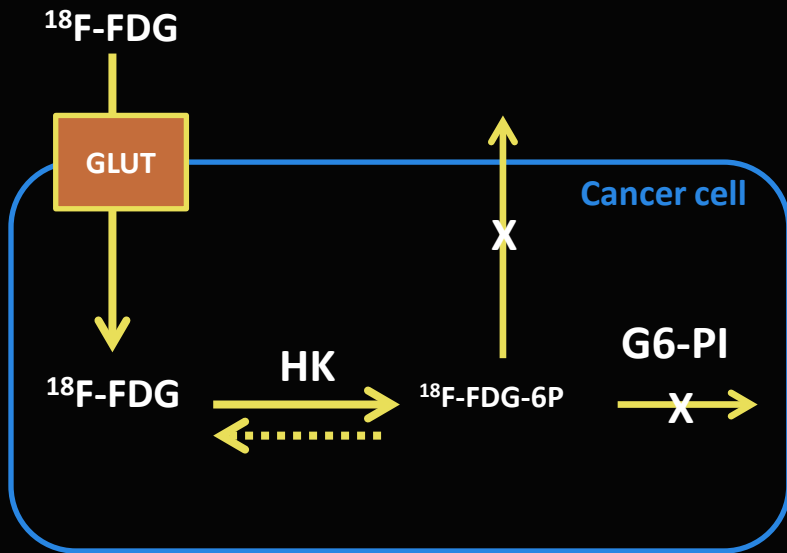
Ga68

Bombesin



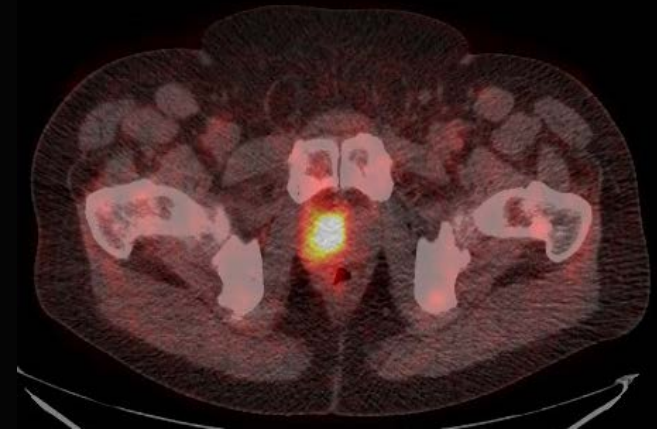
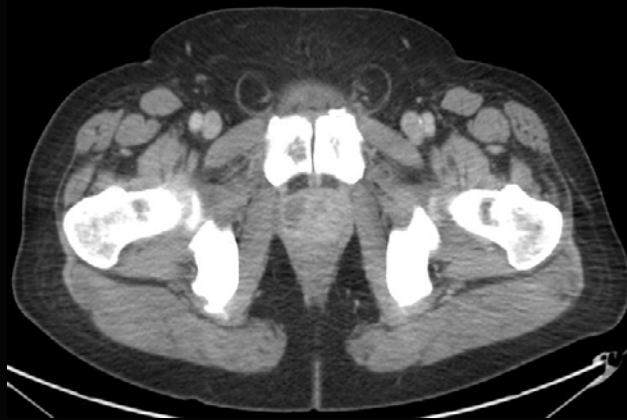
# PET has revolutionized cancer imaging!

## Fluorodeoxyglucose



# FDG and Prostate Cancer

- For the initial diagnosis and staging of prostate cancer, FDG PET is considered limited
- Patterns of GLUT expression in PCa is variable →
  - Affected by dedifferentiation, aggressiveness, androgen sensitivity, hypoxia
  - Overlap in tracer uptake in normal and abnormal prostate tissue (including inflammation!)



# PET tracers used in Prostate Cancer

Cell  
Metabolism

Bone Matrix

Receptors  
and  
Membrane  
Proteins



# PET tracers used in Prostate Cancer

## Cell Metabolism

Glucose

$^{18}\text{F}$ -FDG

Choline

$^{11}\text{C}$ -choline  
 $^{18}\text{F}$ -choline

Acetate

$^{11}\text{C}$ -acetate  
 $^{18}\text{F}$ -acetate

Amino Acids

$^{18}\text{F}$ -FACBC



# Choline

- Precursor for phospholipid synthesis
  - Major components of the cellular membrane
- Enters the cell through choline transporters
- Can be labeled with  $^{11}\text{C}$  or  $^{18}\text{F}$
- FDA approval → evaluation of recurrence



# Choline

- Pooled sensitivity and specificity of 86% and 93% for detecting PCa
- Performance correlated to PSA levels
- Recent study compared Choline PET and MRI:
  - Choline better for lymph nodes
  - MRI better for prostate bed
  - Both good for bone metastases



# PET tracers used in Prostate Cancer

## Cell Metabolism

Glucose

~~$^{18}\text{F}$ -FDG~~

Choline

~~$^{11}\text{C}$ -choline  
 $^{18}\text{F}$ -choline~~

Acetate

$^{11}\text{C}$ -acetate  
 $^{18}\text{F}$ -acetate

Amino Acids

$^{18}\text{F}$ -FACBC



# Acetate

- Major sources of acetate consumption:
  - Krebs cycle
  - Production of phospholipids in cellular membranes
- Upregulation of fatty acid synthetase → basis of PCa uptake



# Acetate PET

- Uptake appears unaffected by androgens (in contrast to FDG and choline)
- Study comparing  $^{11}\text{C}$ -Acetate PET and MRI
  - Sensitivity/specificity (tumors >5 mm):
    - 62%/80% for PET/CT and 82%/95% for MRI
  - >9 mm, comparable accuracy for PET and MRI

# PET tracers used in Prostate Cancer

## Cell Metabolism

Glucose

~~$^{18}\text{F}$ -FDG~~

Choline

~~$^{11}\text{C}$ -choline  
 $^{18}\text{F}$ -choline~~

Acetate

~~$^{11}\text{C}$ -acetate  
 $^{18}\text{F}$ -acetate~~

Amino Acids

$^{18}\text{F}$ -FACBC



# Aminoacids (AA): Leucine

- Basis for uptake in Pca:  $\uparrow$  AA transport +  $\uparrow$  protein synthesis
- $^{18}\text{F}$ -FACBC tumor uptake comparable to FDG; but bladder excretion  $\downarrow$  20-fold;  $\uparrow$  cancer/inflammation uptake ratios
- SUVmax  $\uparrow$  tumor than in normal prostate
- Sensitivity/specificity for tumor detection slightly  $\uparrow$  for MRI (73/79%) than FACBC (67/66%)
- Recurrence: Sensitivity/specificity 90/40% for prostatic fossa vs 55/97% in distant disease (n=93)

# PET tracers used in Prostate Cancer

Bone Matrix

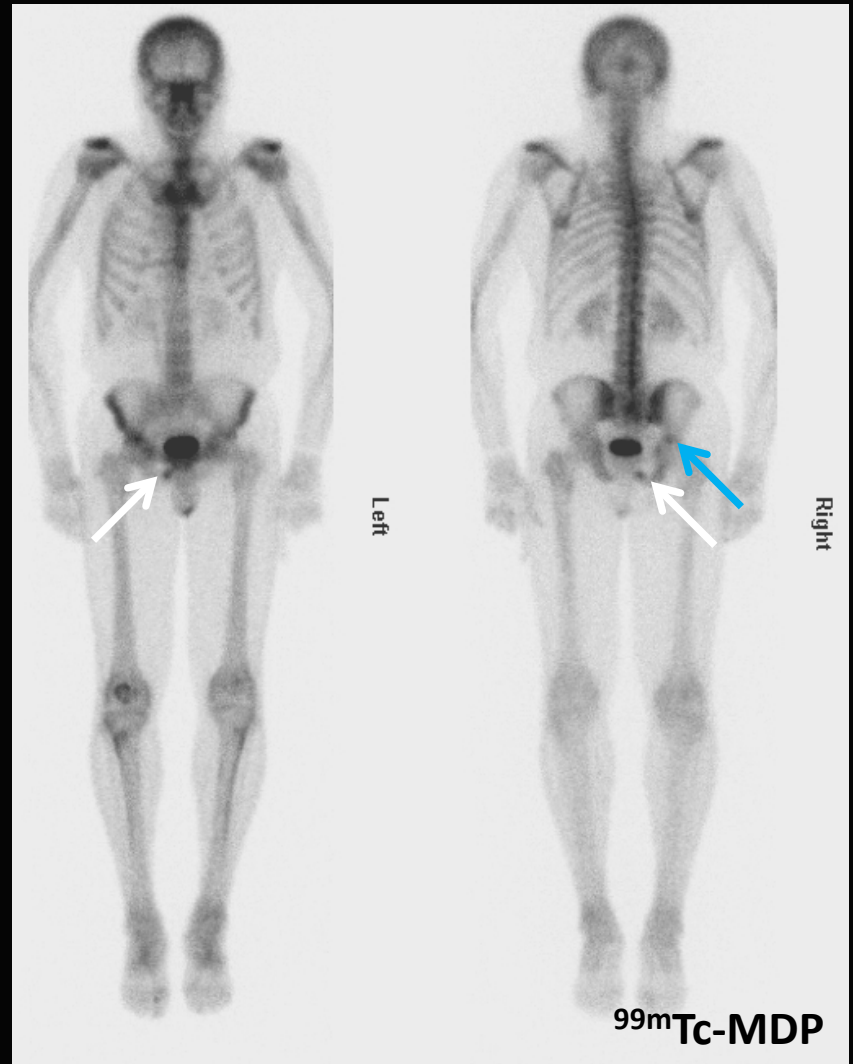
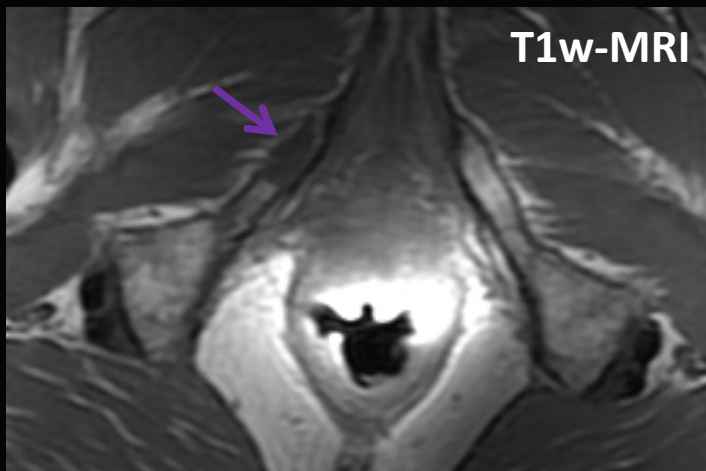
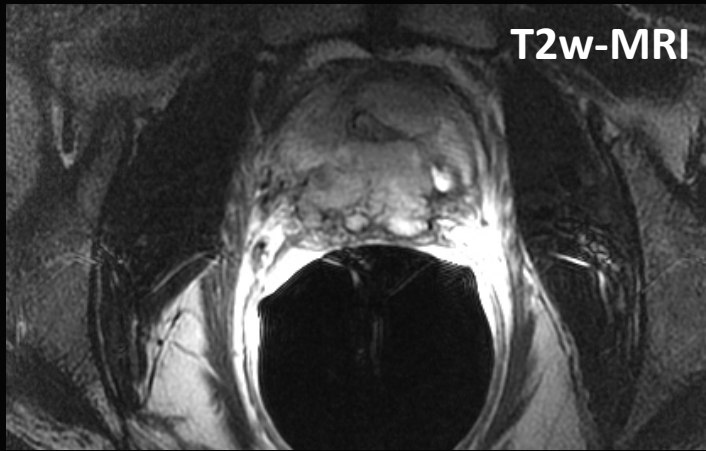
$^{18}\text{F}$ -NaF



# Sodium Fluoride (NaF)

- Developed in 1962; FDA approved 1972
- Uptake mechanism similar to “bone scan”
  - ↑ blood clearance, ↑ bone/background ratio, ↓ interval from administration to imaging
- Similar pitfalls to bone scan
  - accumulates in bone matrix; not cancer cells → no uptake in non-bone metastases
  - Uptake in degenerative bone disease
  - Flare phenomenon

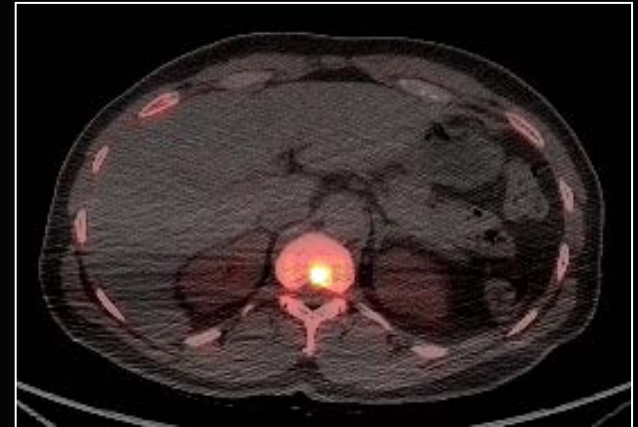
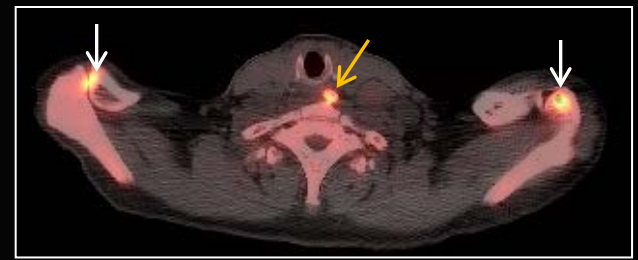
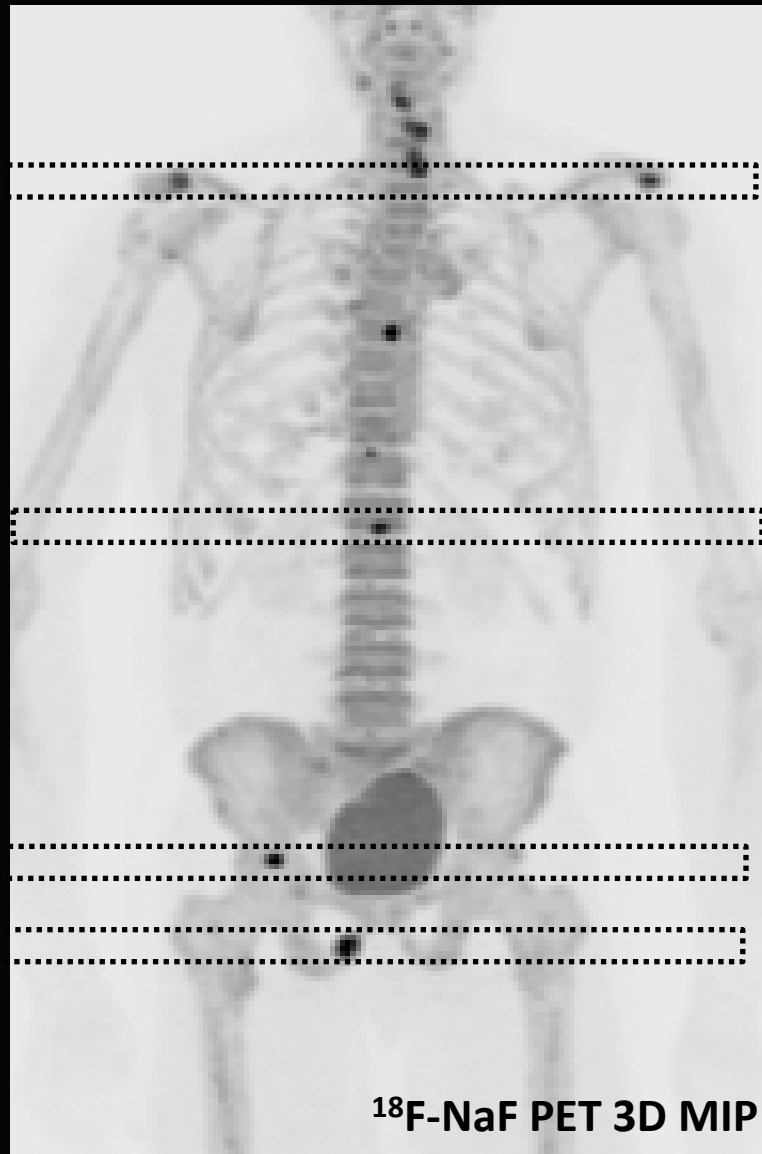




Gleason 8. PSA 22. Metastases?  
Anything outside of the pelvis?



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Anything outside the pelvis?

# PET tracers used in Prostate Cancer

## Receptors and Membrane Proteins

Androgen  
Receptor (AR)

$^{18}\text{F}$ -FDHT

Gastrin Releasing  
Peptide Receptor  
(GRP-R)

$^{18}\text{F}$ ,  $^{68}\text{Ga}$ ,  $^{64}\text{Cu}$ ,  
 $^{177}\text{Lu}$

Bombesin  
analogues

Prostate Specific Membrane Antigen (PSMA)

Antibodies

$^{111}\text{In}$ ,  $^{64}\text{Cu}$ ,  $^{89}\text{Zr}$ ,  
 $^{90}\text{Y}$ ,  $^{177}\text{Lu}$

7E11  
J591

Antibody  
Fragments  
"Minibodies"

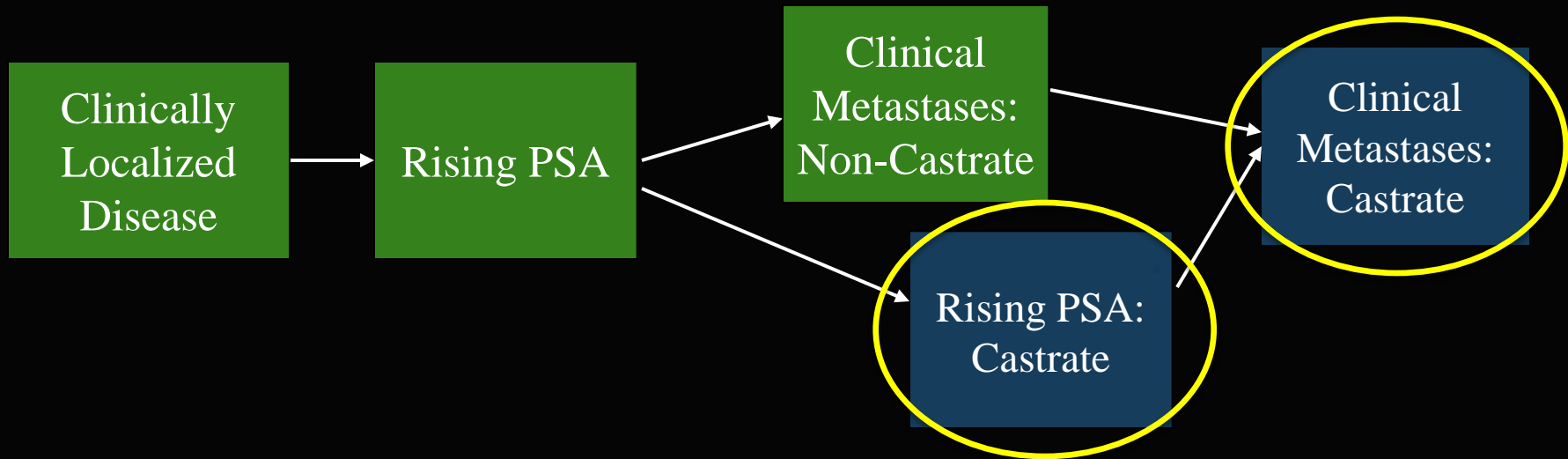
$^{89}\text{Zr}$ -Df-IAB<sub>2</sub>M

Small  
molecules

$^{18}\text{F}$ -DCFBC



# Prostate Cancer Clinical States



Androgen Receptor (AR) gene activation is a hallmark of castration-resistant prostate cancer



# The Androgen Receptor (AR)

- AR → ligand-dependent transcription activator involved in cellular proliferation and differentiation
- Almost all PCa patients initially respond to androgen deprivation, but eventually progress to a castration-resistant clinical state → bypassing or sensitizing the AR pathway
- Novel therapies targeting the AR have shown ↑ survival → recent FDA/EU approval



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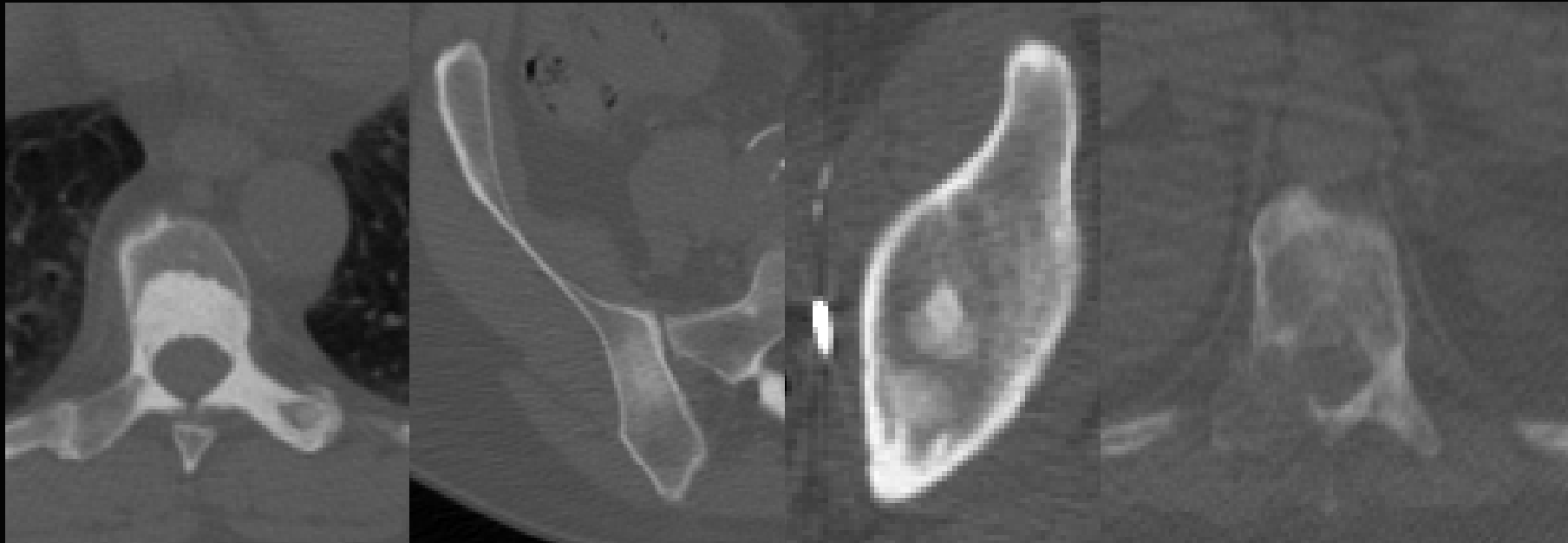
## Bone Metastases in Castration-Resistant Prostate Cancer:

Associations between Morphologic CT Patterns, Glycolytic Activity, and Androgen Receptor Expression on PET and Overall Survival<sup>1</sup>

Radiology

- 38 patients with castration resistant prostate cancer and discrete bone lesions
- All underwent CT, FDG PET and FDHT PET
- CT features (including Hounsfield Units), SUVmax from FDG and FDHT PET

# 1. Bone metastases demonstrate variable appearance on CT



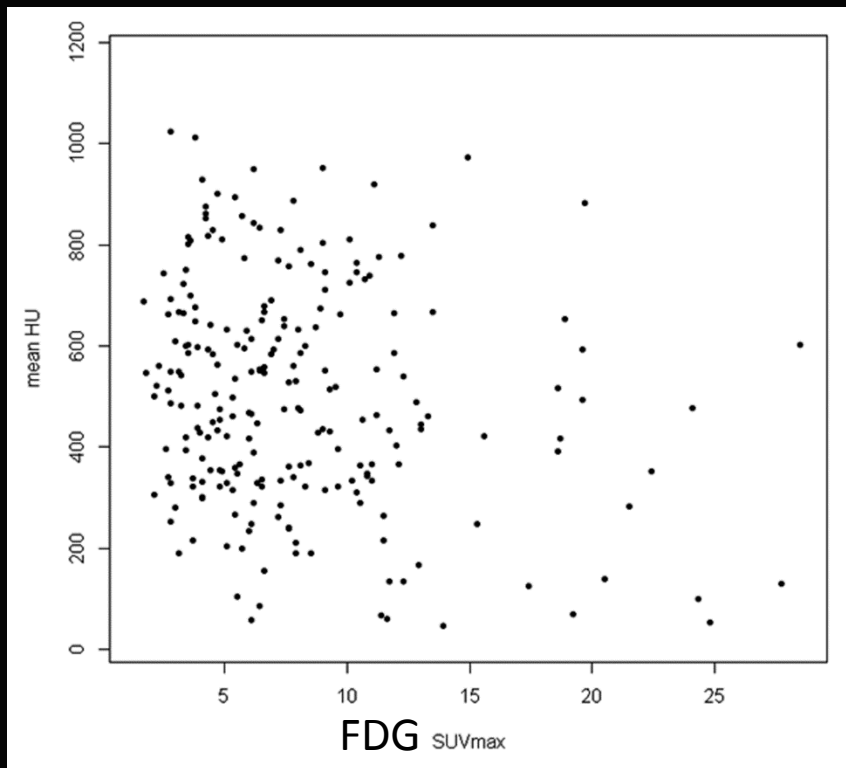
**Densely  
sclerotic**

**Groundglass**

**Mixed**

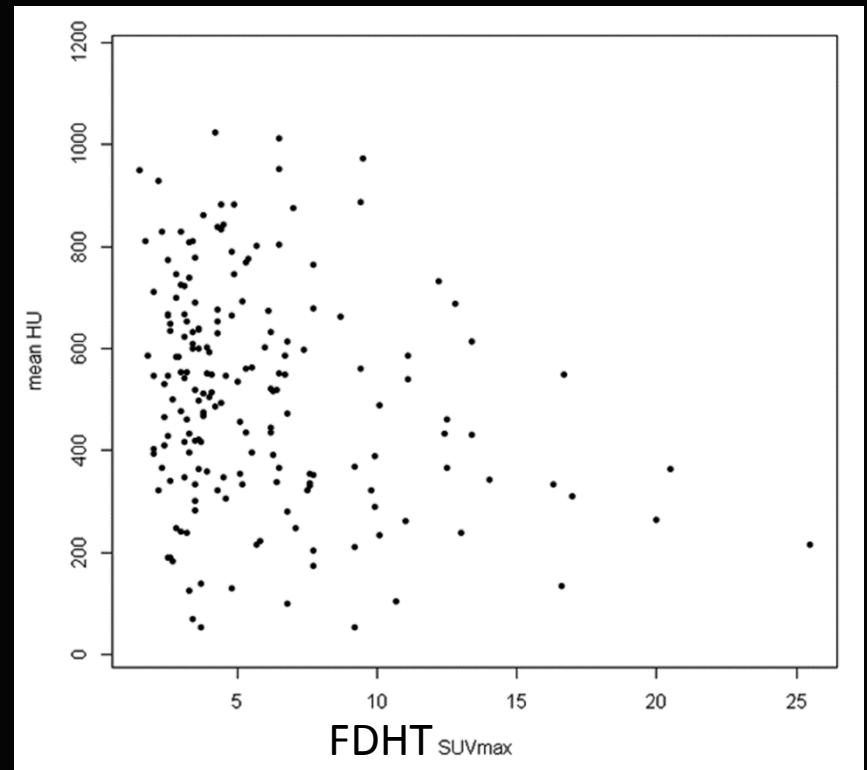
**Lytic**

## 2. CT density is inversely associated with FDG and FDHT PET uptake



Reader 1:  $r = -0.30$ ;  $P < .001$

Reader 2:  $r = -0.31$ ;  $P < .001$



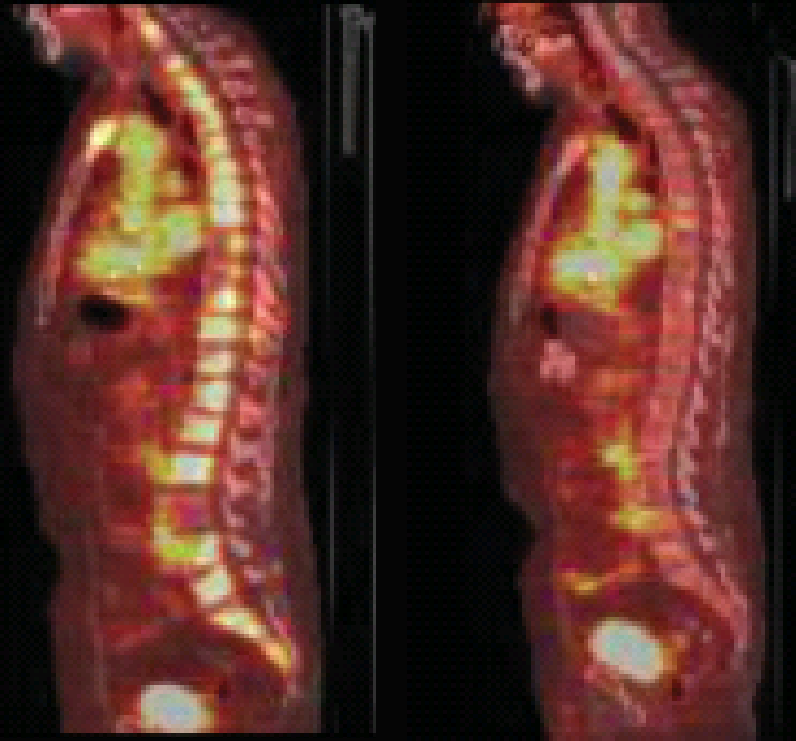
Reader 1:  $r = -0.27$ ;  $P = .001$

Reader 2:  $r = -0.37$ ;  $P < .001$

### 3. Preliminary associations with clinical outcomes

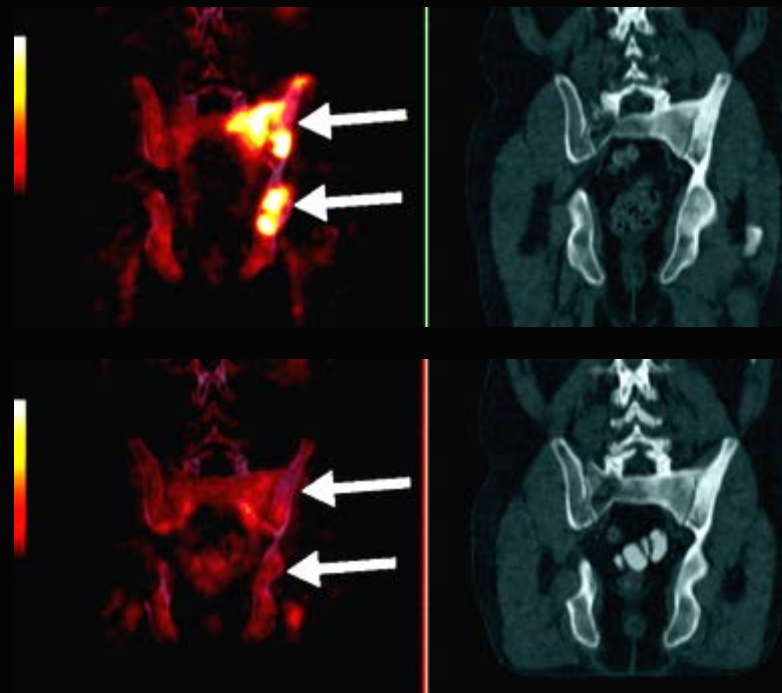
- # lesions on CT, FDG and FDHT PET associated with overall survival ( $p < 0.05$ )
- ↑ SUVmax on FDHT, shorter overall survival ( $P = 0.02$ )
- No association between SUVmax on FDG PET and survival ( $P = 0.38-0.65$ )

# FDHT for documenting pharmacologic targeting

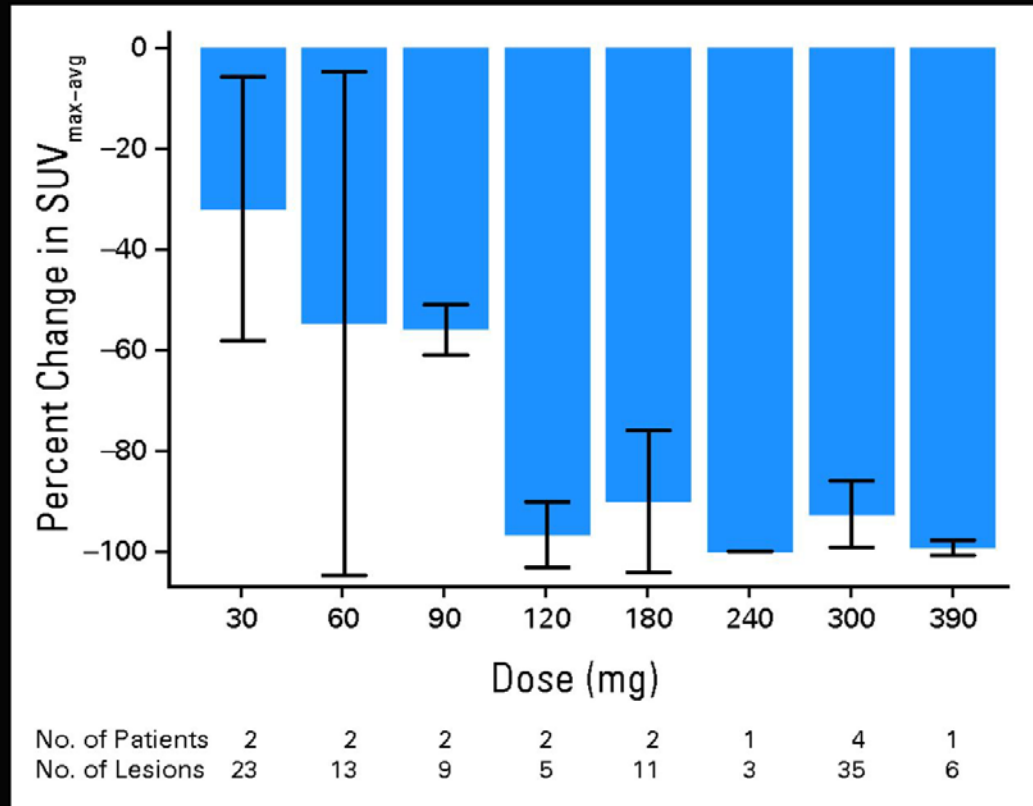


- FDHT PET pre- and 4 weeks post enzalutamide
- Uptake suppression: drug hits the pharmacologic target (AR)

# FDHT for measuring dose related targeting efficacy



- FDHT PET pre- and 4 weeks post ARN-509
- Uptake suppression: dose dependent

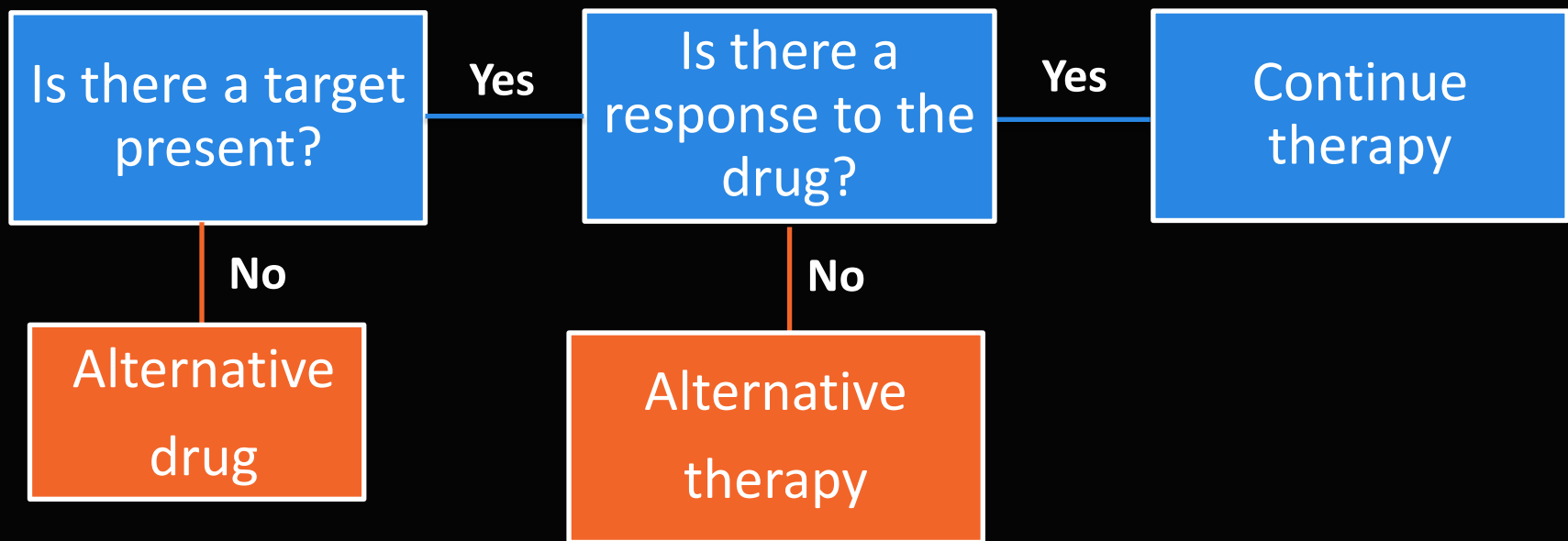


# Movember GAP 2 Imaging Project: FDHT

- Multi-institutional study, Co-PIs
  - MSKCC (lead site): Vargas, Morris
  - Royal Marsden London: Chua
  - VUMC Amsterdam: Hoekstra
  - Austin Health Australia: Scott
  
- Total funding: \$2.8 million



# FDHT PET for guiding AR-targeted therapy



# PET tracers used in Prostate Cancer

## Receptors and Membrane Proteins

~~Androgen  
Receptor (AR)~~

~~$^{18}\text{F}$ -FDHT~~

Gastrin Releasing  
Peptide Receptor  
(GRP-R)

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 $^{177}\text{Lu}$

**Bombesin  
analogues**

Prostate Specific Membrane Antigen (PSMA)

Antibodies

$^{111}\text{In}$ ,  $^{64}\text{Cu}$ ,  $^{89}\text{Zr}$ ,  
 $^{90}\text{Y}$ ,  $^{177}\text{Lu}$

**7E11  
J591**

Antibody  
Fragments  
"Minibodies"

$^{89}\text{Zr}$ -Df-IAB<sub>2</sub>M

Small  
molecules

$^{18}\text{F}$ -DCFBC



# Gastrin Releasing Peptide Receptor

- “Bombesin-like peptide family”
- Pca → GRP-R overexpression at the mRNA and protein levels (low to non-detectable in benign prostate)
- Can be labeled with  $^{68}\text{Ga}$  → generator produced



# PET tracers used in Prostate Cancer

## Receptors and Membrane Proteins

~~Androgen  
Receptor (AR)~~

~~$^{18}\text{F}$ -FDHT~~

~~Gastrin Releasing  
Peptide Receptor  
(GRP-R)~~

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 $^{177}\text{Lu}$~~

~~Bombesin  
analogues~~

Prostate Specific Membrane Antigen (PSMA)

Antibodies

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$^{89}\text{Zr}$ -Df-IAB<sub>2</sub>M

Small  
molecules

$^{18}\text{F}$ -DCFBC



# Prostate Specific Membrane Antigen (PSMA)

- Transmembrane protein normally expressed in prostate epithelium, bowel, renal tubular cells and salivary glands
- PSMA expression imaged with labeled:
  - Monoclonal antibodies (Mab)
    - 7E11: labeled with  $^{111}\text{In}$  (SPECT);  $^{89}\text{Zr}$  (PET)
    - J591
  - Antibody fragments: “Minibodies”
  - Small molecules



# 7E11: What happened to capromab pendetide- ProstaScint®?

- FDA approved in 1996; labeled with  $^{111}\text{In}$
- 7E11 binds to the intracellular domain of PSMA → only accessible if there is membrane disruption (e.g. dead or dying cells)
- The number of available targets for binding of the tracer is limited → low sensitivity for detecting viable tumor sites
- In contrast to PET, SPECT remains only semiquantitative in the clinical setting

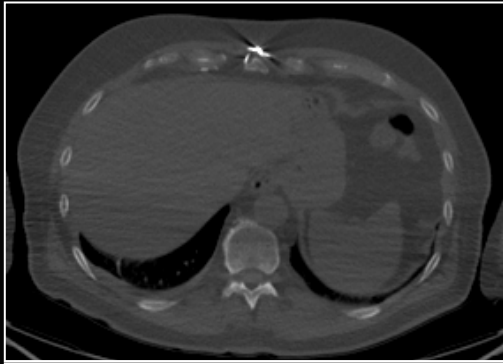


# Humanized monoclonal antibody J591

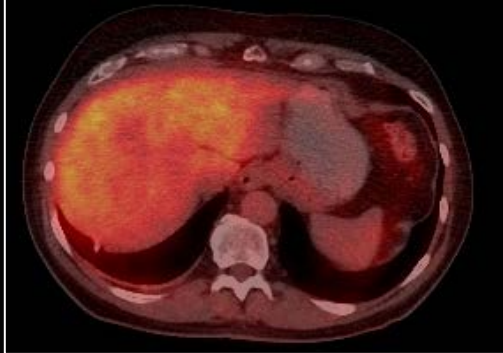
- Targets the extracellular domain of PSMA → accessible even if no membrane disruption
- The number of available targets for binding of the tracer better than 7E11 → higher sensitivity for detecting viable tumor sites
- Labeled with  $^{64}\text{Cu}$ ,  $^{89}\text{Zr}$  or  $^{90}\text{Y}$  and  $^{177}\text{Lu}$  for therapy
- Other mAb: 3/A12, 3/E7, 3/F11 and 3C6



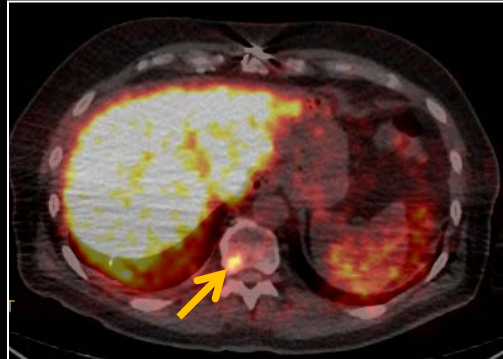
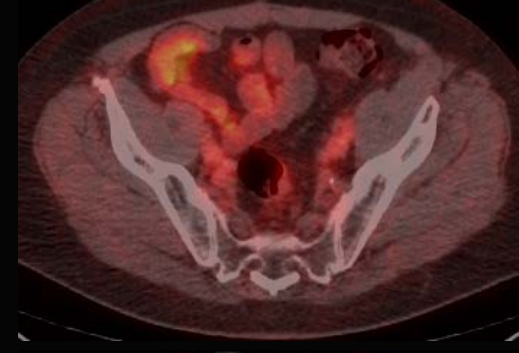
# Castration resistant PCA. ↑ PSA. Recurrence?



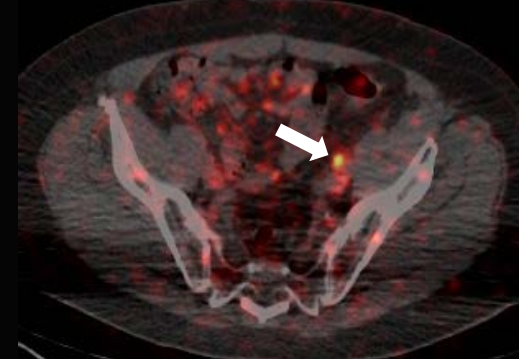
CT



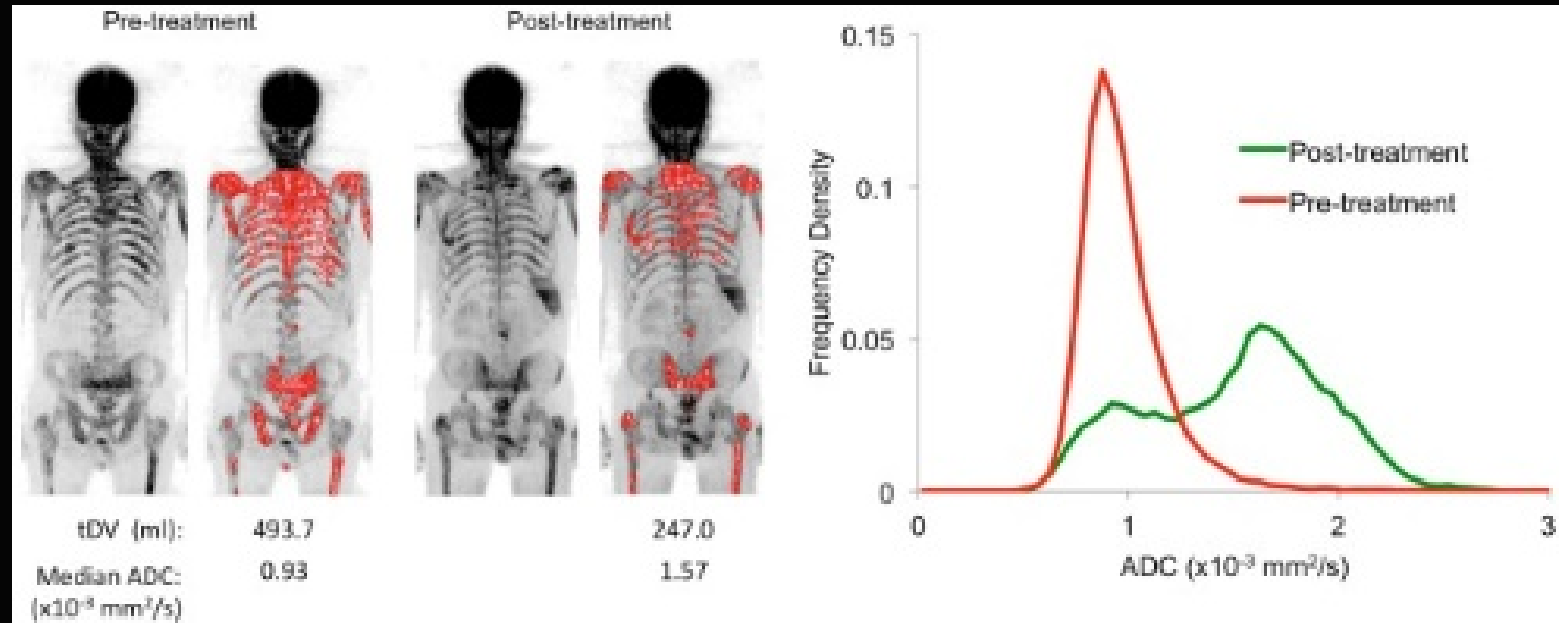
FDG



$^{89}\text{Zr}$ -  
J591



# Use of WB-MRI is increasing: beyond simple detection



# Summary

- PET is being increasingly used for the assessment of prostate cancer
- FDA approved tracers: FDG, Choline, NaF
- Tracers to watch:
  - Androgen receptor imaging (FDHT)
  - PSMA imaging
  - Bombesin
- Whole-body MRI may also have a role
- More research needed to determine which probe(s) should be used for each clinical scenario

