

Beyond Ultrasound and MRI: Imaging Prostate Cancer

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Imaging Modalities Used for the Evaluation of Prostate Cancer

- Plain X-Ray
- Ultrasound
- CT scan
- ^{99}Tc Bone scan
- MRI
- PET: scans exploit various aspects of cancer metabolism

Prostate Cancer Characteristic To Capitalize Upon	Clinical Imaging Modality
Low water content	T2 weighted MRI
Restricted water diffusion	Diffusion weighted images MRI
Increased vascularity	Dynamic contrast enhanced MRI Doppler US Contrast enhanced Ultrasound
Increased glucose metabolism	FDG PET
Increased cellular proliferation, cell membrane synthesis	Choline, Acetate PET
Amino-acid transport	Fluciclovine-PET
PSMA expression	PSMA PET
AR expression	FDHT PET
Proclivity for bone metastases	NaF PET, Tc99 bone scan

Selected PET Imaging Methods in PC

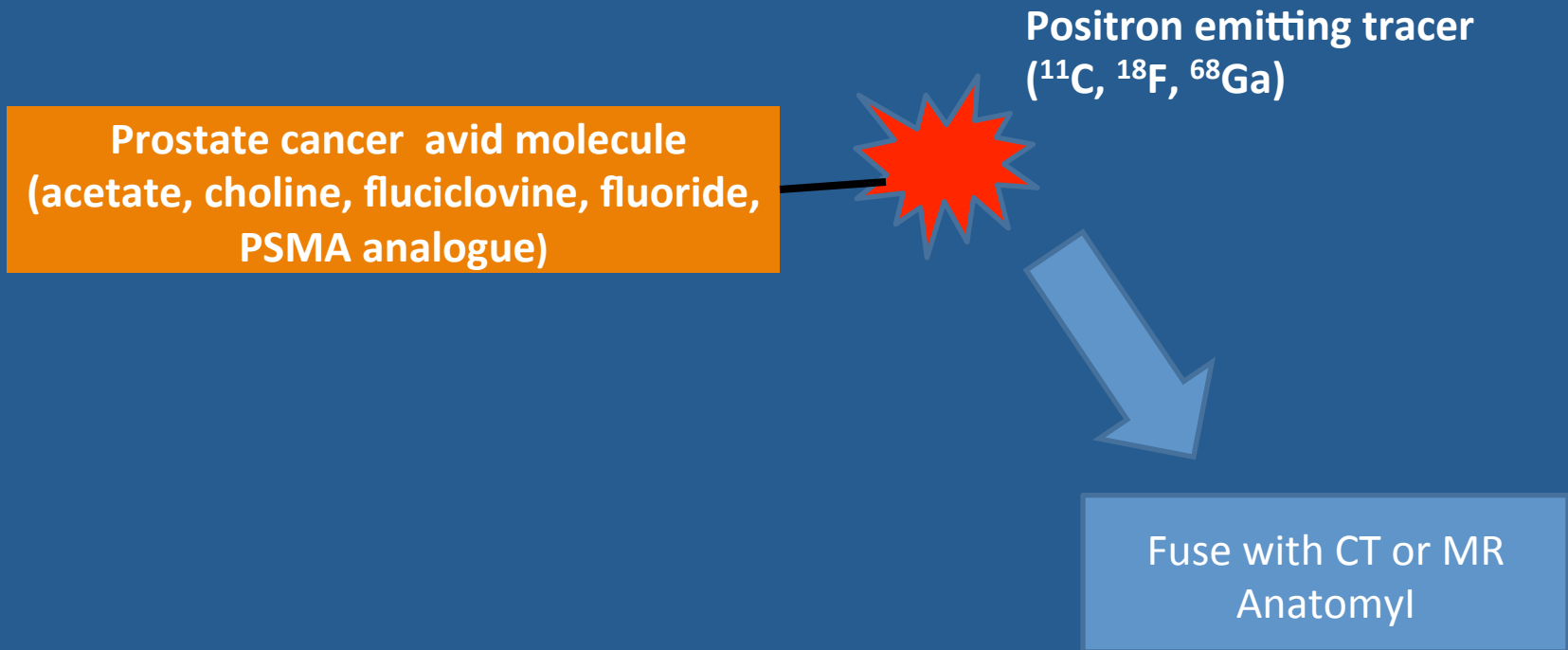
Technique	Description
<u>¹¹¹In ProstaScint</u>	Radiolabeled murine monoclonal antibody against intracellular epitope of PSMA
<u>¹⁸F-FDG</u>	Positron-emitting radiopharmaceutical transported by glucose proteins
<u>¹⁸F-NaF</u>	Chemisorption occurs with exchange of ¹⁸ F-ion for OH-ion to form fluoroapatite, which migrates into crystal matrix of bone for recognition via PET scan
<u>¹¹C-Na acetate</u>	Uses carbon and acetate to recognize fatty acid synthase upregulated in PC
<u>¹¹C-Choline</u>	Recognizes choline kinase overexpressed from cell proliferation in PC
<u>¹⁸F Fluciclovine</u>	AA based detects upregulated amino acid transport in tumors (Axumin)
<u>^{99m}Tc MIP-1404</u>	Radiolabeled to target PSMA extracellular domain
<u>⁶⁸Ga-HBED-CC PSMA</u>	
<u>¹⁸F CTT1057 PSMA inhibitor</u>	Irreversible binding affinity to PSMA and robust internalization (ASCO 2017)
<u>⁶⁴Cu-TP3805</u>	Targets VPAC-1 receptor

Tracer	Radionuclide	Synthesis	Mechanism / Target	Number of not yet recruiting, recruiting, active, invited, or completed clinical trials using the tracer for PCa on clinicaltrials.gov (as of 07/17)
PSMA				
DCFPyL	18F	Cyclotron	PSMA	17
HBED-CC-PSMA (PSMA-11)	68Ga	Generator	PSMA	15
J591	89Zr	Cyclotron	PSMA (ImmunoPET)	4
IAB2M	89Zr	Cyclotron	PSMA (immunoPET)	2
P16-093	68Ga	Generator	PSMA	1
Lipid metabolism				
Choline, Fluorocholine, Ethylcholine, Fluoroethylcholine	18F/11C	Cyclotron	Membrane turnover	35
Acetate	11C	Cyclotron	Lipid synthesis	9
Nutrient Transport				
FDG	18F	Cyclotron	Glucose transport	25
Fluciclovine (FACBC, axumin)	18F	Cyclotron	Amino Acid Transport	13
MeAIB	11C	Cyclotron	Amino Acid Transport	1
Methionine	11C	Cyclotron	Amino Acid Transport	1
Sarcosine	11C	Cyclotron	Amino Acid Transport	1
GRPR Targeting				
RM2	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	4
MJ9	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
RM26	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
MATBBN	18F	Cyclotron	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
BBN-RGD	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) and avB3 integrin	1
Hypoxia				
FMISO	18F	Cyclotron	Hypoxia	1
HX4	18F	Cyclotron	Hypoxia	1
FAZA	18F	Cyclotron	Hypoxia	1
Bone Targeting				
NaF	18F	Cyclotron	Osteoblast activity	14
P15-041	68Ga	Generator	Bone	1
DNA Synthesis				
FMAU	18F	Cyclotron	DNA synthesis	3
FLT	18F	Cyclotron	DNA synthesis	4
Miscellaneous				
FDHT, FMDHT	18F	Cyclotron	Androgen Receptor	4
AE105	68Ga/64Cu	Generator/Cyclotron	Urokinase Plasminogen Activator Receptor (uPAR)	3
TP3805	64Cu	Cyclotron	VPAC1	2
Gallium citrate	68Ga	Generator	Multiple mechanisms	1
MSTP2109A	89Zr	Cyclotron	STEAP1 (immunoPET)	1

Non-US Novel Imaging Methods in PC

Technique	Description
<u>¹¹¹In ProstaScint</u>	Radiolabeled murine monoclonal antibody against intracellular epitope of PSMA
<u>¹⁸F-FDG PET</u>	Positron-emitting radiopharmaceutical transported by glucose proteins
RSI MRI	Detects images based upon the motion of water molecules between tissues
Multiparametric MRI	Combines T2-weighted MRI plus dynamic contrast-enhanced MRI plus magnetic resonance spectroscopy
MRI SPIO	IV lymphotropic ultrasmall SPIO particles to differentiate benign/malignant nodes
<u>¹⁸F-NaF</u>	Chemisorption occurs with exchange of ¹⁸ F-ion for OH-ion to form fluoroapatite, which then migrates into crystal matrix of bone for recognition via PET scan
<u>¹¹C-Na acetate PET</u>	Uses carbon and acetate to recognize fatty acid synthase upregulated in PC
<u>¹¹C-Choline PET</u>	Recognizes choline kinase overexpressed from cell proliferation in PC
<u>AA based PET (fluciclovine)</u>	Detects upregulated amino acid transport in tumors (Axumin)
<u>^{99m}Tc MIP-1404</u>	Radiolabeled to target PSMA extracellular domain; urea based
<u>Ga-68 labeled HBED-CC PSMA PET</u>	
<u>¹⁸F CTT1057 PSMA inhibitor</u>	irreversible binding affinity to PSMA and robust internalization (ASCO 2017)

PET Scan Principle



PET Scan Molecules Applicable in Prostate Cancer

- FDG (Fludeoxyglucose)- FDA approved in cancer (F-18 general PET)
 - Sodium Fluoride (NaF) - FDA approved
 - Choline: C-11 PET - FDA approved
 - Fluciclovine/FACBC (Axumin)- FDA approved
-
- Acetate - not FDA approved
 - PSMA Ligand - PSMA-HBED-CC - not FDA approved
 - DHT/AR - not FDA approved

PET- SCAN RADIO TRACERS

¹¹Carbon vs ¹⁸Fluorine vs ⁶⁸Gallium

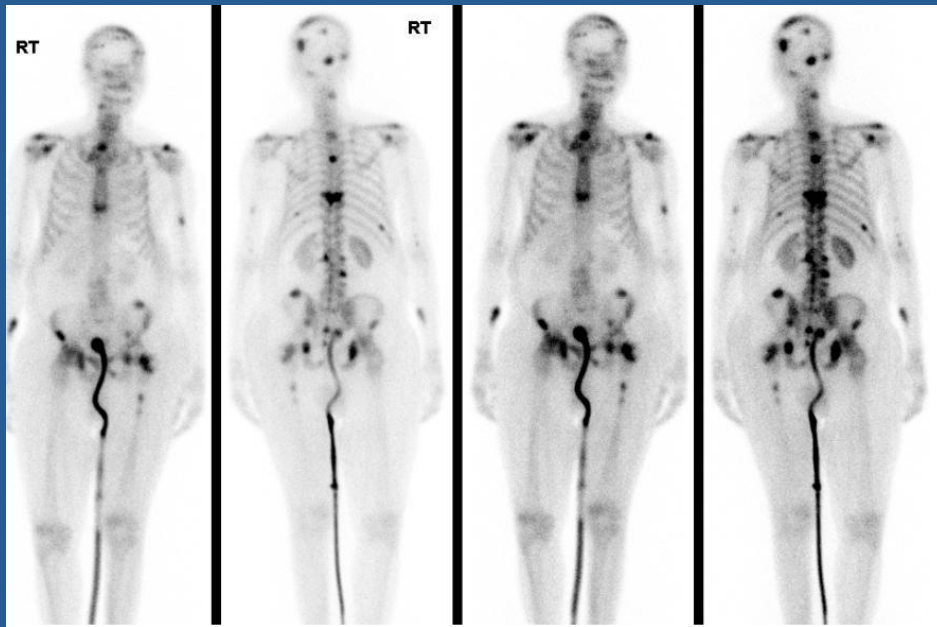
	¹¹ C	¹⁸ F	⁶⁸ Ga
Half-life	20 min	110 min	68 min
Excretion	Hepatobiliary	Urinary	Urinary
Decay Energy	> 99% Positrons	97 % Positrons	>95% Positrons
Source	Cyclotron	Cyclotron	Generator

^{18}F -FDG PET

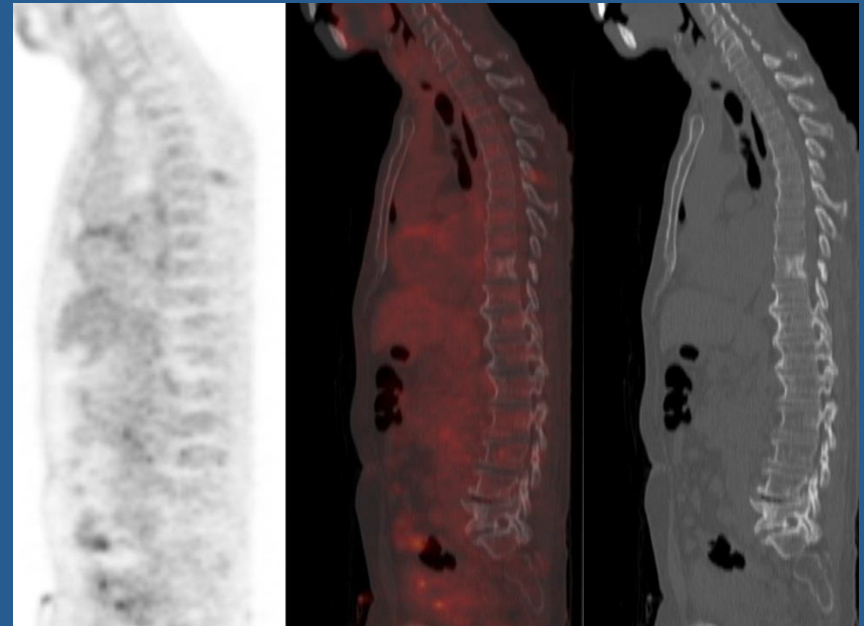
(fluorodeoxyglucose-“Every day PET”)

Limited utility; relatively low glucose metabolism of most hormone sensitive prostate cancers.

Performs better in CRPC



^{99}Tc Bone scan

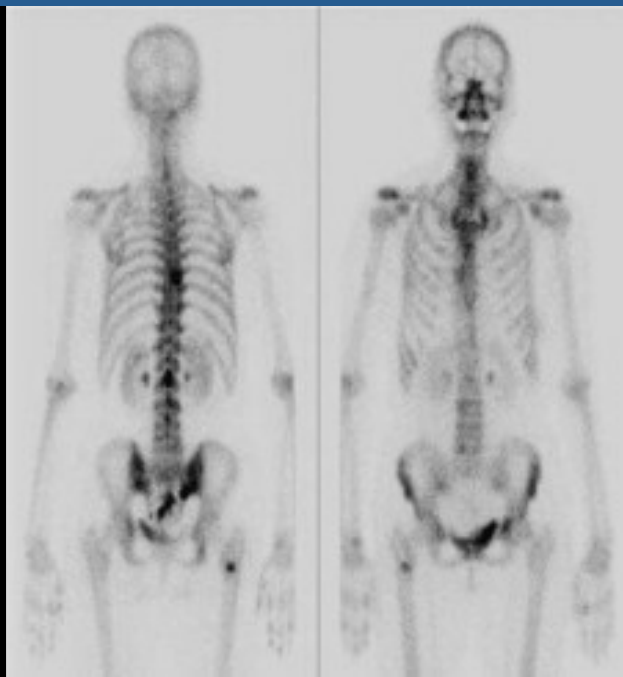


^{18}F FDG PET

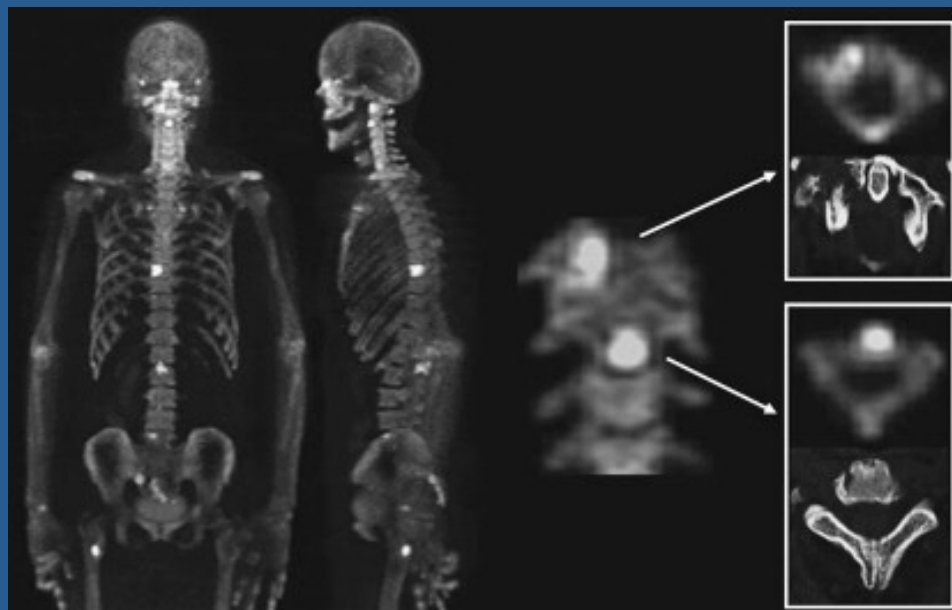
Sodium Fluoride (^{18}F -NaF PET/CT)

- Fluoride tracer uptake is a biomarker for bone metabolism.
- ^{18}F -NaF has been evaluated in men with biochemical relapse of PC after prior local therapy.
- The positive detection rate by ^{18}F -NaF of bone metastases not seen on CT and BS was 16.2%
- Drawback is low specificity with false positives

Tc-99
bone scan



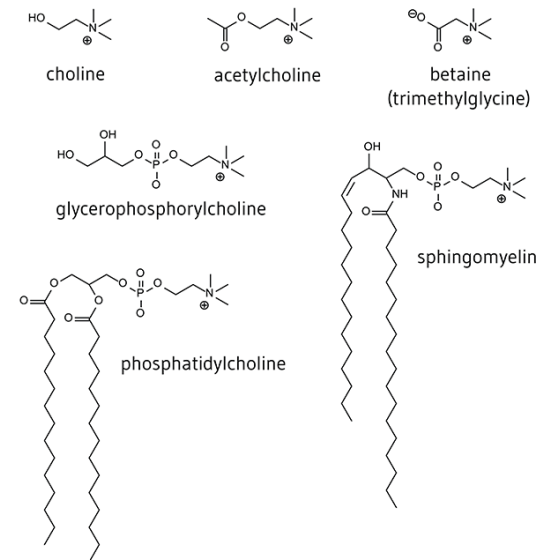
F-18 NaF scan in
the same patient



Choline and Acetate Tracers

- Choline kinase is over expressed in prostate cancer cells
- Choline is used to synthesize phosphatidylcholine – integral component of cell membranes
- Acetate also membrane associated

Figure 1. Chemical Structures of Choline and Derivatives



¹¹C-choline PET/CT (Carbon 11)

Detection rate for recurrent PC*:

- PSA <1 - 36%
- PSA 1-2 - 43%
- PSA 2-3 - 62%
- PSA >3 - 73%

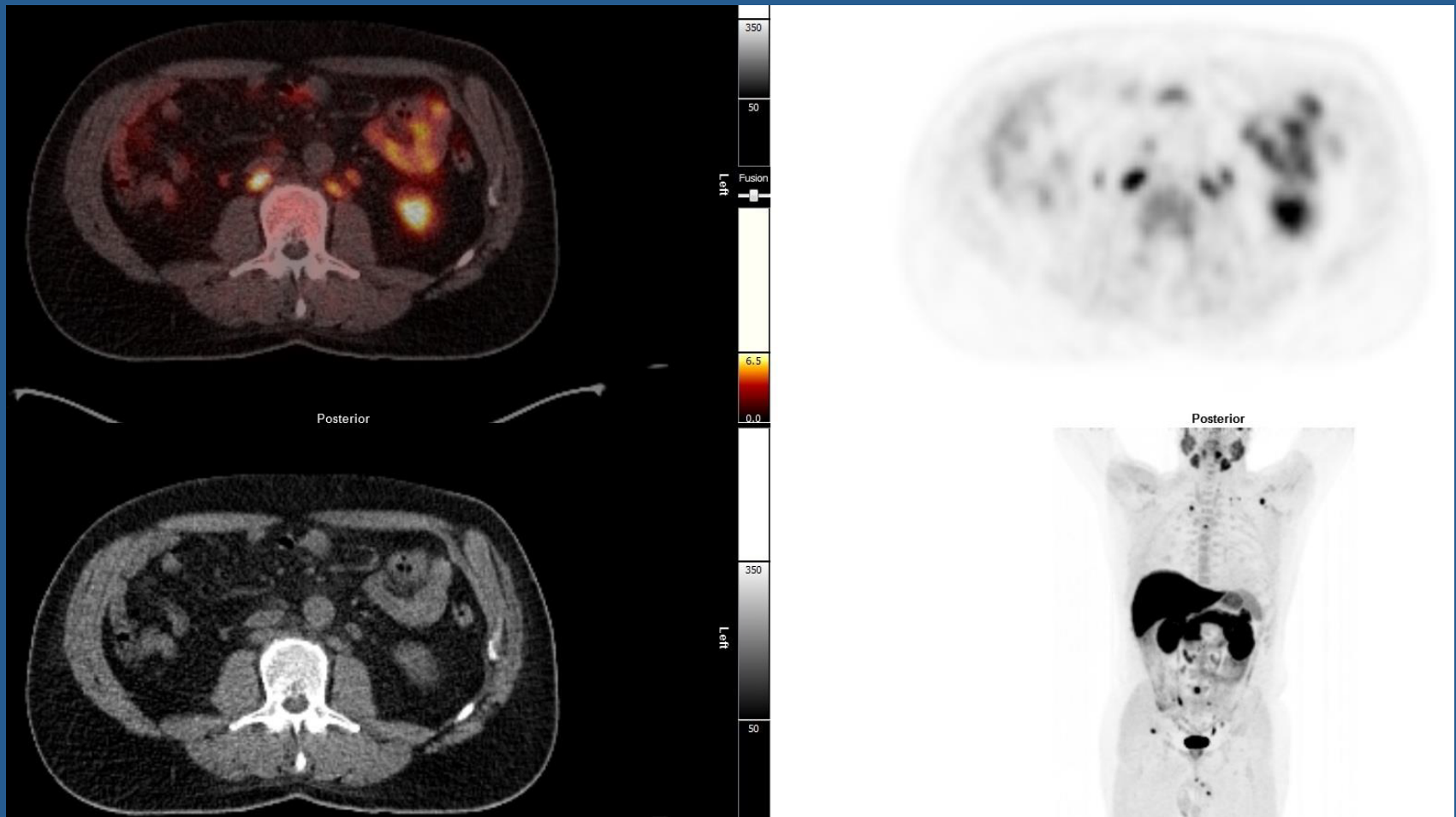
Limitations:

- Performance at clinically relevant PSA levels for salvage RT is modest
- Appears slightly inferior in detection of bone mets than MRI
- Very limited access because of 20 min half-life of C¹¹

*Krause et al. The detection rate of [¹¹C]Choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Jan;35(1):18-23.

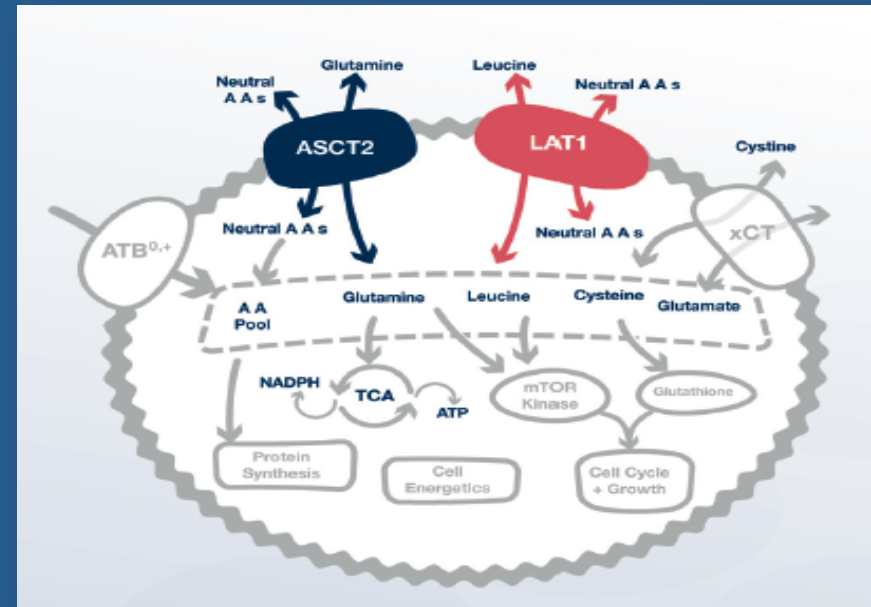
^{11}C -choline PET/CT

Detection of Retroperitoneal LN in a Patient with PSA Recurrent PC



¹⁸F Fluciclovine (FACBC) (Axumin)

- ¹⁸F-Fluciclovine is an artificial amino acid PET imaging agent labelled with ¹⁸F.
- Recognized and taken up by amino acid transporters¹ that are upregulated in many cancer cells, including prostate cancer.

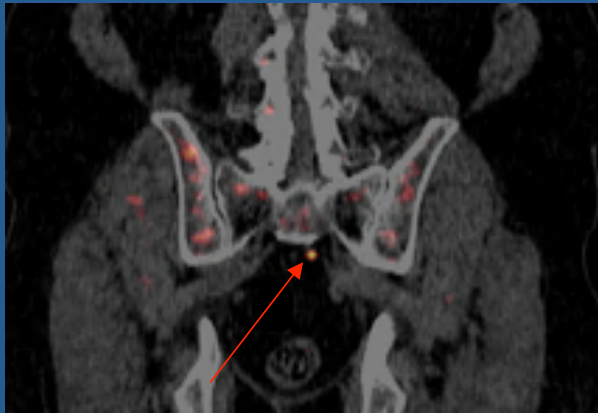


¹ Fuchs and Bode. Semin Cancer Biol. 2005;15(4):254.

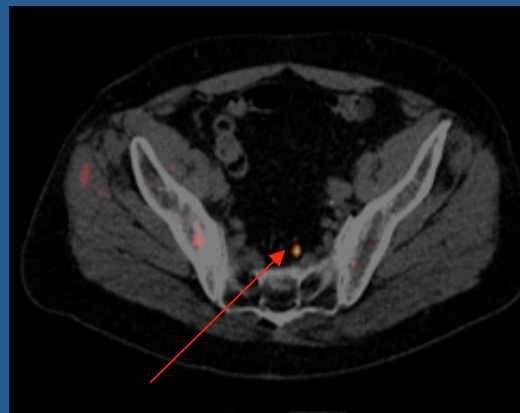
Fluciclovine (Axumin) Case Study

- Post-radical prostatectomy, negative lymphadenectomy
- Rising PSA to 0.73 ng/mL
- Negative MR for malignancy
- Negative skeletal screening
- **Imaging result:**
 - left pre-sacral node

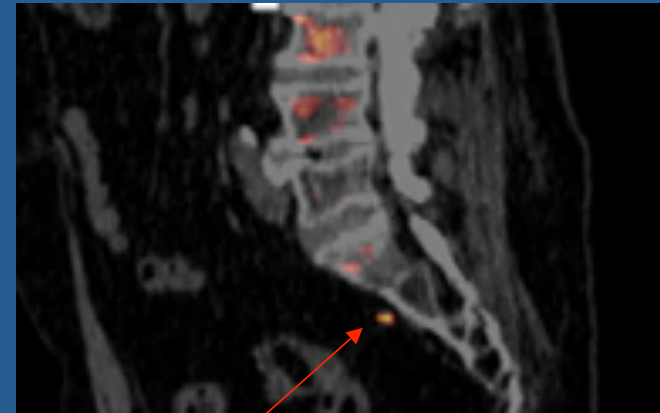
Axial



Coronal



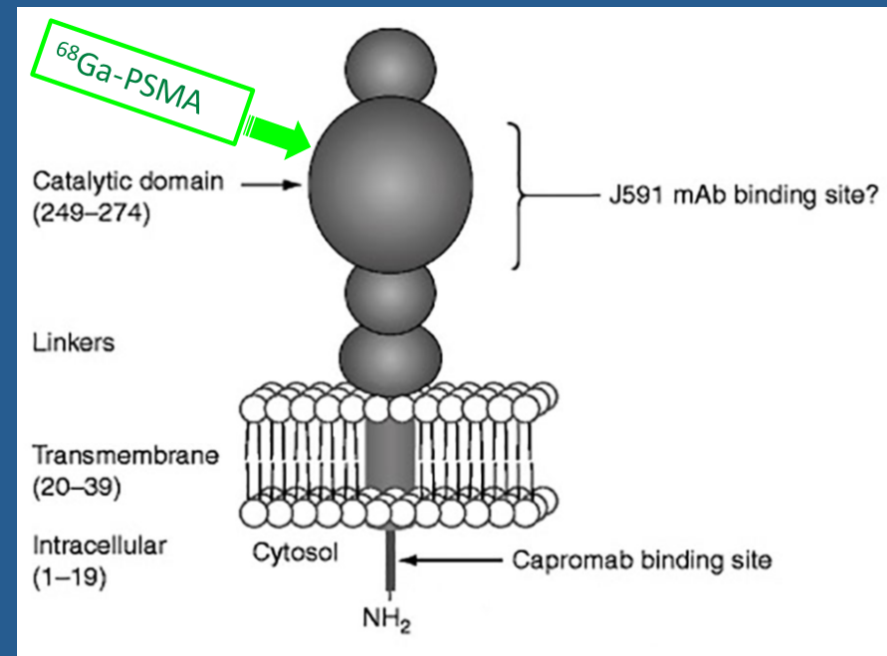
Sagittal



Images courtesy of Blue Earth Diagnostics, Ltd

Prostate Specific Membrane Antigen (PSMA)

- Transmembrane glycoprotein overexpressed on prostate cancer cells
 - This is **not** In-111 capromab pendetide (ProstaScint) which is specific for an epitope on the intracellular domain of PSMA and only accessible after membrane disruption in dead/dying cells
- High levels of PSMA expression correlate with:
 - Early biochemical recurrence
 - Tumor stage
 - Gleason grade
 - Postoperative PSA



⁶⁸Ga-PSMA-PET

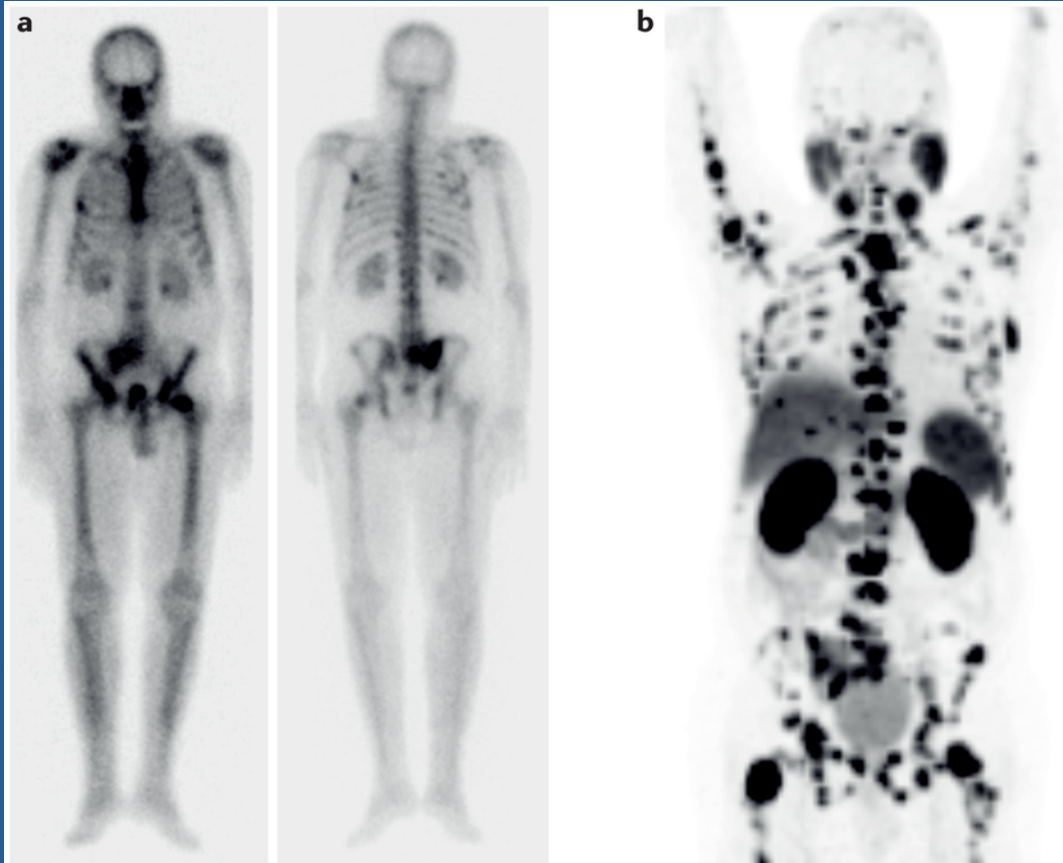
PSMA Ligand - NH-CO-NH-Lys(Ahx)-HBED-CC

- Extracellular PSMA (Prostasinct intracellular)
- Detection rate for recurrent PC* :
 - PSA <0.5 - 58% PSA 0.5-1 - 73%
 - PSA 1-2 - 93% PSA >2 - 97%
- Superior to choline scans
- Limitations: not globally available, in the US available only on clinical trials (UCSF, Houston)

* Elber M. J Nucl Med 56.668-674 (2015)

^{68}Ga -PSMA-PET vs ^{99}Tc Bone Scan

Prostate Cancer Bone Metastases



Nature Reviews | Urology

- Next development
- Lutetium-177 PSMA Therapy
 - Peptide Receptor Radionuclide Therapy (PRRT)
 - “Theranostic”

VPAC in GU Malignancy: Applications for PET Imaging

- VPAC receptors bind Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase Activating Peptide (PACAP)
- VPAC-1 receptors
 - exist on normal cells
 - 100% of prostate and bladder cancer overexpress VPAC1
 - high (10^4 /cell) receptor density on PCa cells
- Many tumors types overexpress VPAC-1
- Overexpression of VPAC-1 receptor an early event before histologic changes
- Activates various growth factors

Curr Pharm Des. 2007;13(11):1099-104



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Cu-64 TP3805 VPAC receptor ligand analog

- TP3805: peptide analog of VPAC receptor ligand
 - Can be conjugated to variety of radioisotopes
 - Possibly theranostic (with cytotoxic conjugates)
- Cu-64 is an emerging isotope in PET imaging
 - Positron emitter with relatively long half life (12.8 h)
 - Improved resolution than 99Tc spect scanning
- Can be shipped across country (do not need local generator)
- Comparatively low radiation dose to patient



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VPAC1 Targeted ^{64}Cu -TP3805 Positron Emission Tomography Imaging of Prostate Cancer: Preliminary Evaluation in Man

**Sushil Tripathi, Edouard J. Trabulsi, Leonard Gomella, Sung Kim, Peter McCue,
Charles Intenzo, Ruth Birbe, Ashish Gandhe, Pardeep Kumar, and Mathew Thakur**

UROLOGY 88: 111–118, 2016.

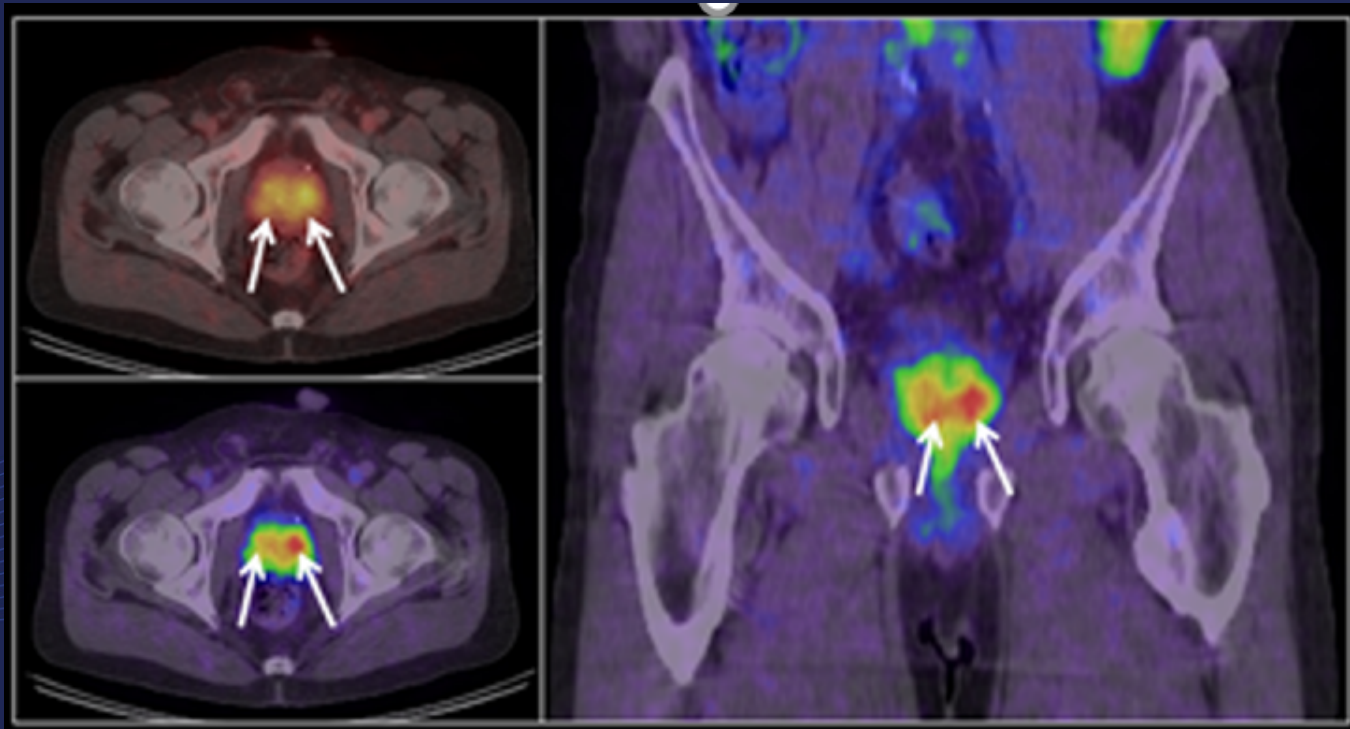
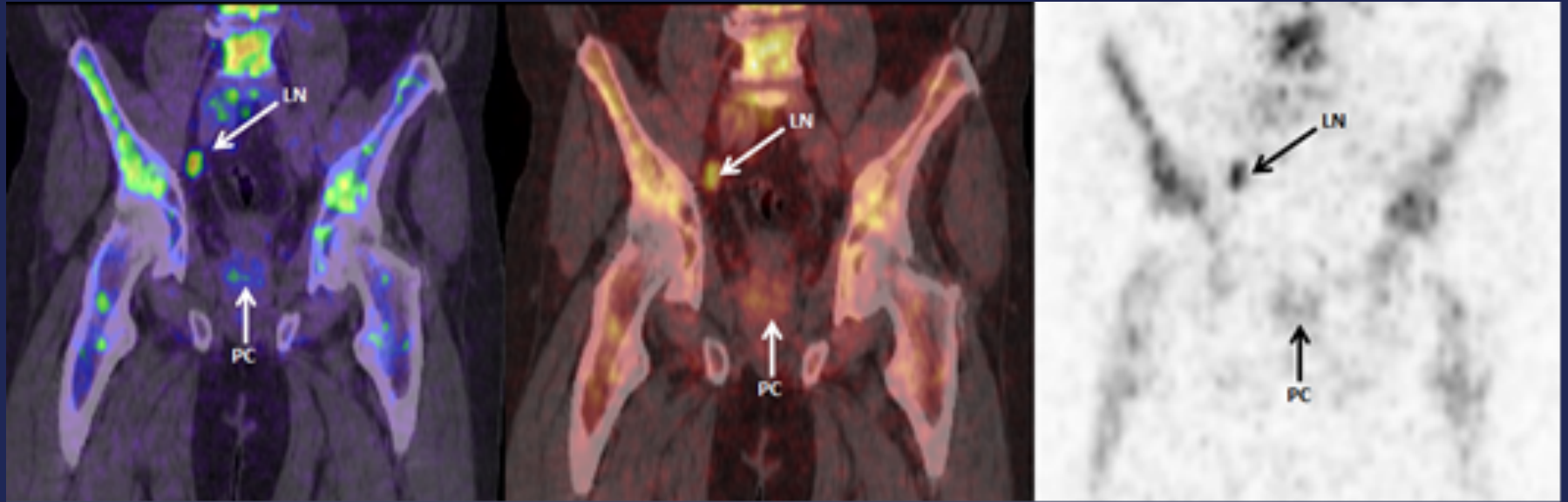
- 25 men going for RALP were imaged preoperatively
- PET/CT images compared with whole mount prostatectomy specimens
- Digital autoradiography performed on whole mount sections



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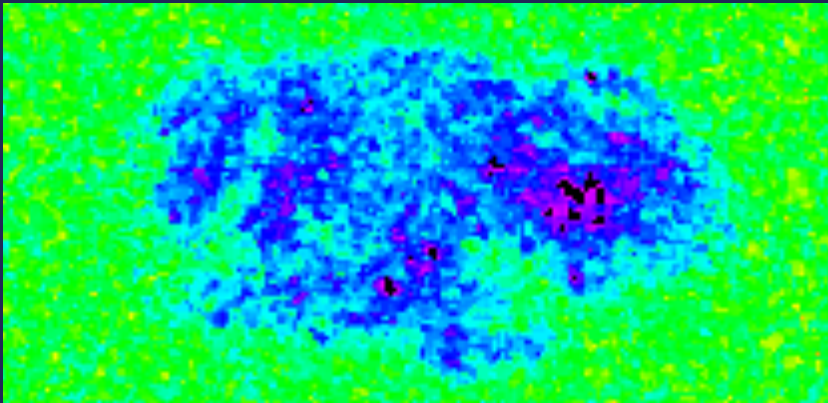
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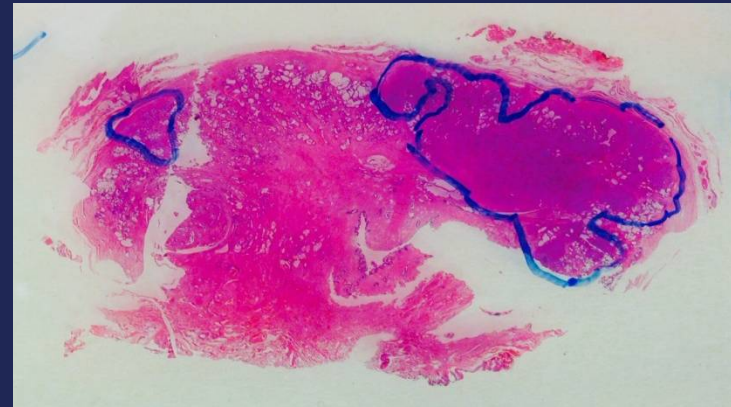


Autoradiography and optical imaging of prostate cancer tissue

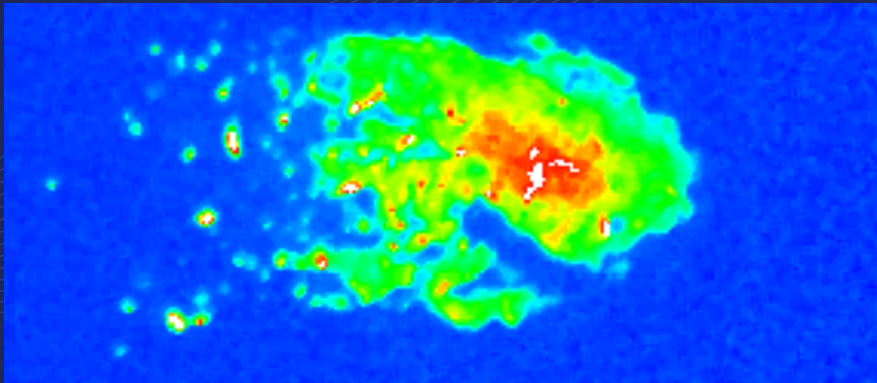
Digital Autoradiography (DAR)



Histology prostate cancer tissue



Optical image prostate cancer tissue



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Metastatic Prostate Cancer VPAC Imaging



70 year old male after Cu-64-TP3805 PET imaging. Images showed multiple bone lesions secondary to his PCa. Histological examination of the bone biopsy confirmed metastatic prostate cancer.



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SUMMARY

- New imaging modalities are more sensitive in visualizing PC (primary and recurrent) than CT and bone scan
 - Do any of these new scans improve clinical outcomes ?
 - Feed debate on early treatment of mCRPC
- FDA approval means the test can be performed reproducibly/safely , no verdict on clinical utility
- Which imaging modality is the most useful at this point ?
 - Practical point: ^{18}F -fluciclovine PET/CT (Axumin)
- PSMA-based PET promising but US access is limited.
- Clinical trials assessing outcomes of salvage therapy (efficacy, costs) based on guidance from new imaging techniques are needed

Pigeons, the next great cancer detector?



By **Jen Christensen**, CNN

🕒 Updated 10:12 AM ET, Fri November 20, 2015



Top stories



Facebook's Zuckerberg is a dad



'Homeless man' flies first class

BACK UP Slides

Fluciclovine F18:

Dosing, administration & image acquisition

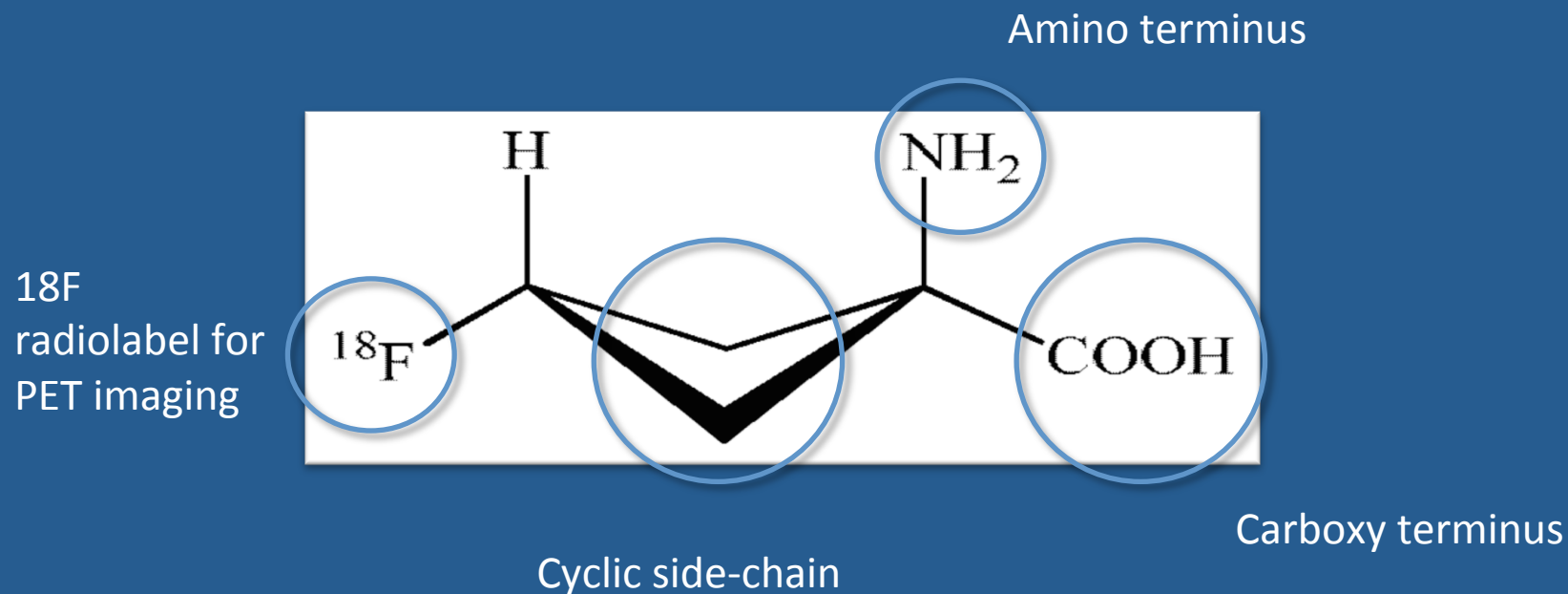
- Recommended dose is 370 MBq (10 mCi) administered as an intravenous (IV) bolus injection, followed by IV saline flush
- Avoid any significant exercise for at least one day prior to PET imaging.
- Fasting for at least 4 hours prior to administration.
- Inject on PET scanner table
- Position the patient supine with arms above the head.
- Begin PET scanning 3 to 5 minutes after completion of injection.
- Start acquisition at mid-thigh and proceed to the base of the skull.
- Typical total scan time is between 20 to 30 minutes.

SUMMARY OF MAIN PET IMAGING TECHNIQUES UTILIZED IN PROSTATE CANCER

Tracer	Half-life	Cyclotron	Mechanism of action	Excretion	Sensitivity*	Specificity*	Advantages	Disadvantages
¹¹ C-choline	20	On-site	Cell membrane synthesis	Hepatic	38-98	50-100	Low urine excretion	Short half-life
¹¹ C-acetate	20	On-site	Lipid synthesis	Hepatic	42-90	64-96	Low urinary excretion	Moderate specificity Not FDA approved
¹⁸ F-Fluciclovine	110	Regional	Amino acid transport	Renal	89-100	67	Availability	Moderate specificity
¹⁸ F-NaF	110	Regional	Adsorption within bone matrix	Hepatic	87-89	80-91	Sensitivity	Only for bones, not specific
⁶⁸ Ga-PSMA	68	Generator (no cyclotrone)	PSMA analog	Renal	63-86	95-100	Not dependent on cyclotrone	Moderately short half-life Not FDA approved
¹⁸ F-FDHT	110	Regional	AR	GI and renal	63	N/A	AR - specific	not effective in castrate sensitive setting, not FDA approved

* Interpret with caution, few studies used biopsy / surgery as gold standard

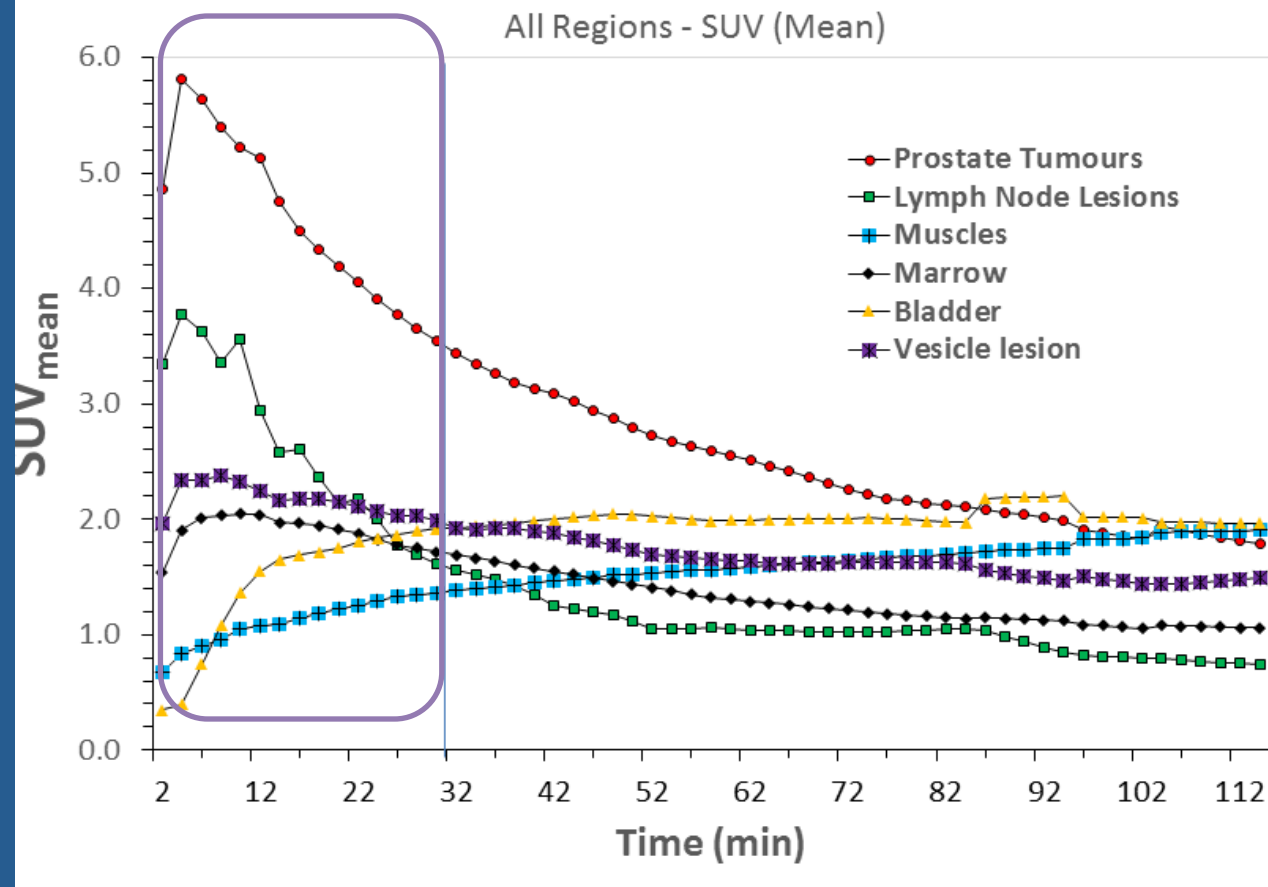
Fluciclovine Tracer (also known as FACBC)



*anti*1-amino-3-18F-fluorocyclobutane-1-carboxylic acid

Fluciclovine F18: Pharmacodynamics

Imaging: begin with in 3-5 minutes;
complete within 20 – 30 minutes.



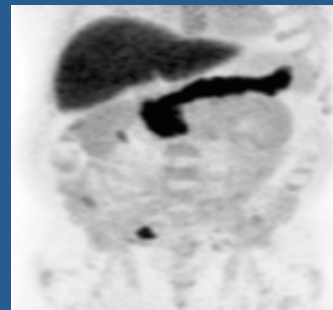
FDG and Acetate Tracers

- **FDG**- Analog of glucose; reflects the increased glycolytic activity of tumors (Warburg effect); FDG is trapped in cells via GLUT transport and irreversible HK phosphorylation – **poor performance in hormone sensitive prostate cancer**
- **Acetate**- Naturally occurring metabolite; converted to acetyl-CoA and incorporated into cholesterol and fatty acids ; fatty acid synthetase and acetyl-CoA carboxylase are oncogenic enzymes upregulated in prostate cancer – **not FDA approved**

Fluciclovine F18: Bio-distribution

- Amino acid (AA) transporters ubiquitous throughout body; upregulated in prostate cancer²
- Distribution after IV dosing²:
 - Liver: 14%*
 - Red bone marrow: 12%*
 - Lung: 7%*
 - Myocardium: 4%*
 - Pancreas: 3%*
- First 4 hrs. post-injection²:
 - 3% excreted in urine*

*% of administered radioactivity



5-16 min. post-injection¹



17-28 min. post-injection¹



29-40 min. post-injection¹

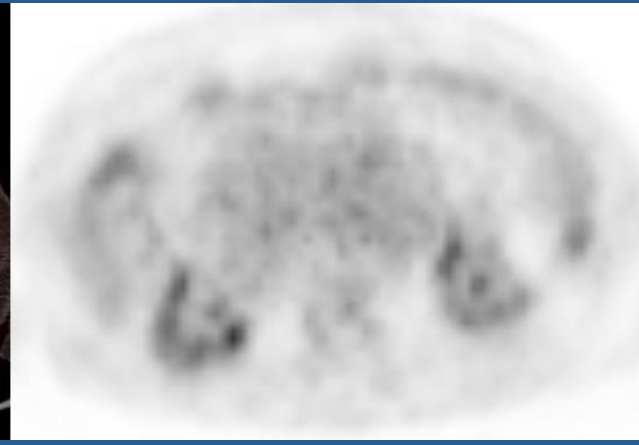
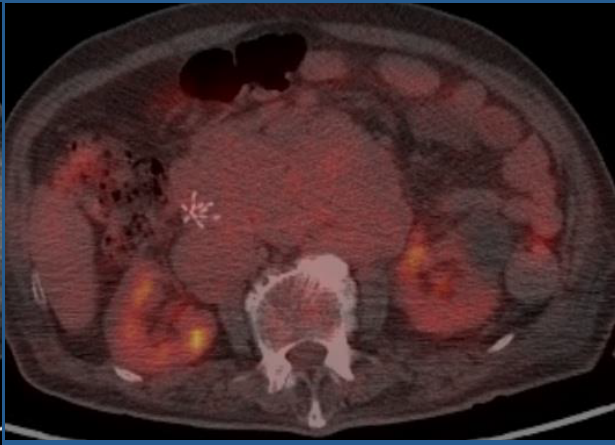
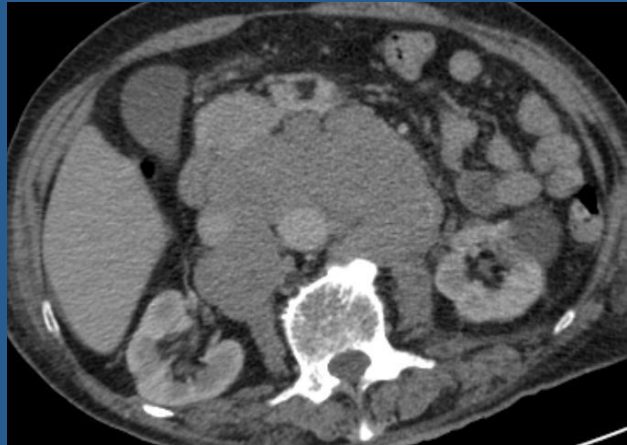


Early (5 mins.) post-injection¹

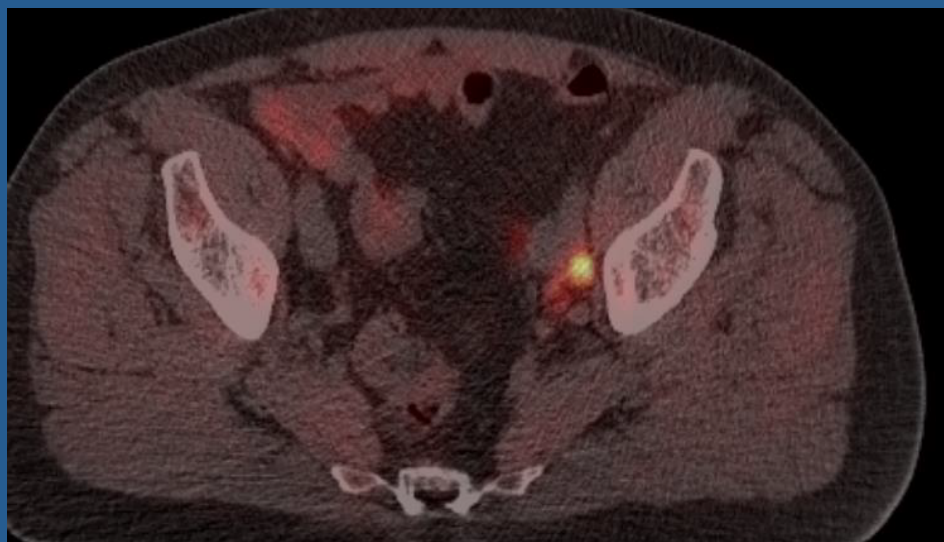
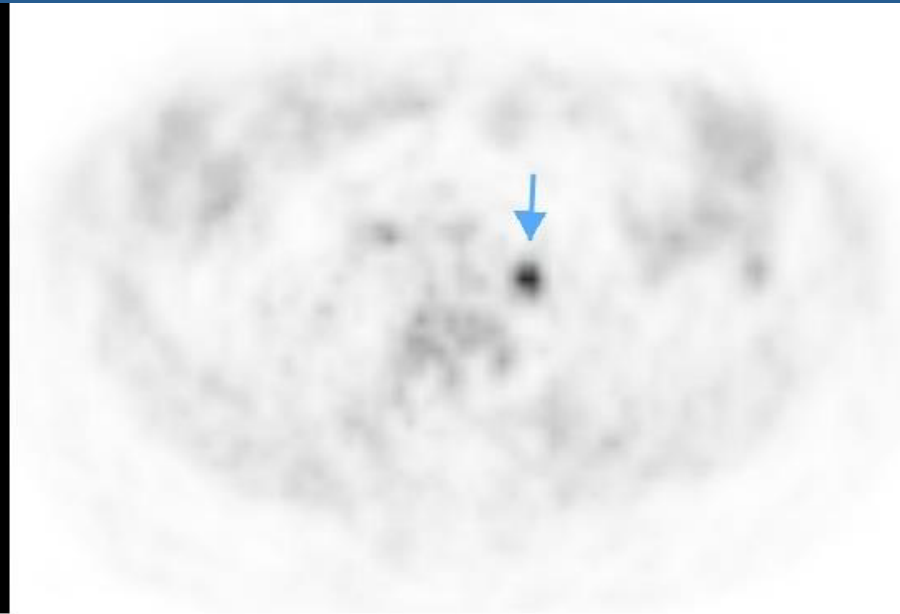
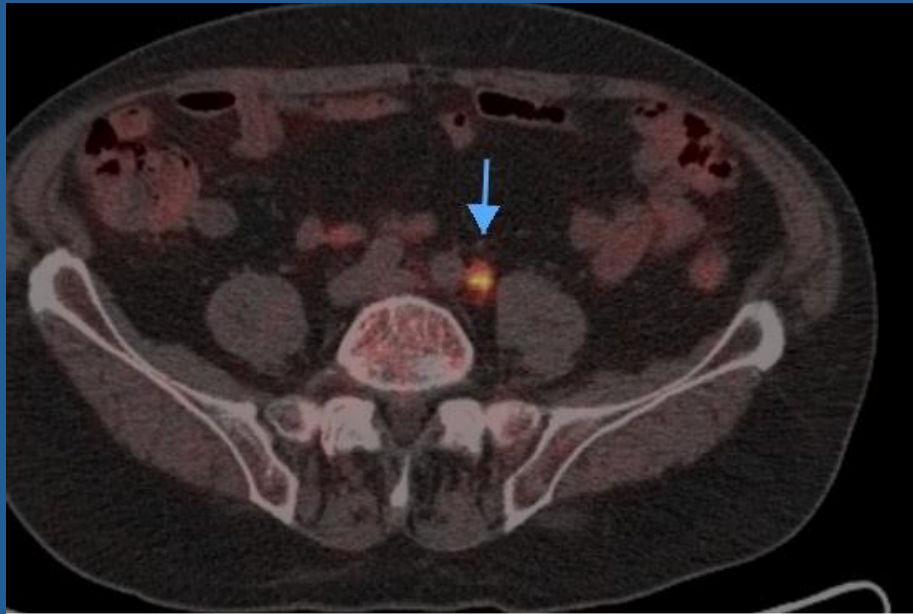
1. Schuster et al J Nucl Med 2014; 55:1986–1992

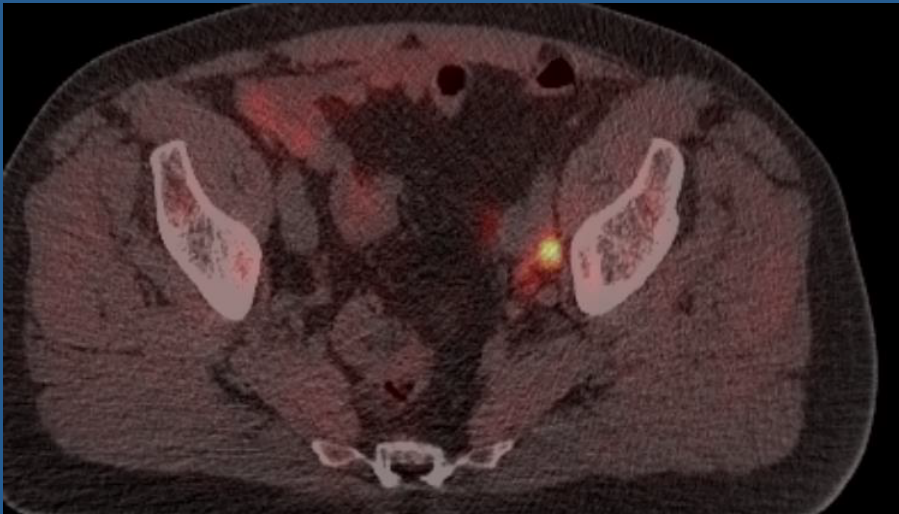
2. Fluciclovine F 18 Injection; US Prescribing Information, Blue Earth Diagnostics, Ltd; August 2016

FDG PET PC



77 yr old post RT , PSA recurrence





REVIEW ARTICLE

Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis

Guohua Shen • Houfu Deng • Shuang Hu • Zhiyun Jia

Role of ^{18}F -Choline PET/CT in Biochemically Relapsed Prostate Cancer After Radical Prostatectomy

Correlation With Trigger PSA, PSA Velocity, PSA Doubling Time, and Metastatic Distribution

Clinical Nuclear Medicine • Volume 38, Number 1, January 2013

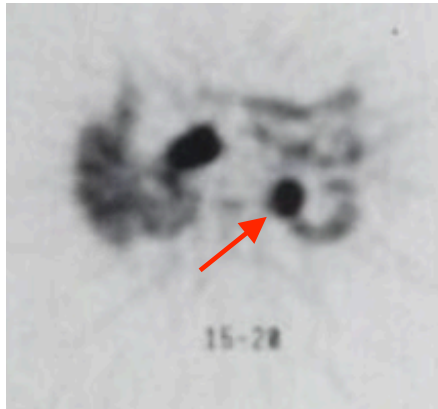
Maria Cristina Marzola, MD, Sotirios Chondrogiannis, MD,* Alice Ferretti, MD,† Gaia Grassetto, MD,* Lucia Rampin, MD,* Arianna Massaro, CNMT,* Paolo Castellucci, MD,‡ Maria Picchio, MD,§ Adil Al-Nahhas, MD, Patrick M. Colletti, MD,¶ Adriano Marcolongo, MD,# and Domenico Rubello, MD**

Quantitative Imaging of biologic processes

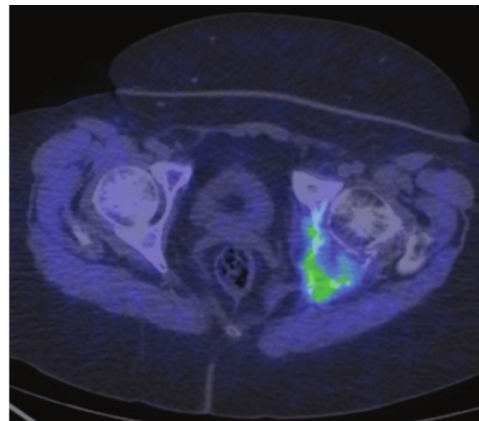
- **PET imaging inherently quantitative**
- **Metabolic**
 - **Warburg effect**
 - **Amino-acid metabolism**
- **Cell surface characteristics**
 - **PSMA**
 - **CA-IX**
 - **Varying ligands**
 - **Small molecules**
 - **Antigen-binding proteins**

Other PET tracers

- Tracers that reflect metabolism (Choline, Acetate)
Or
Hypoxia (F-MISO)
have not been utilized extensively.
- INCREMENTAL benefit to FDG may be minimal if any.



Shreve, J Nucl Med 1995

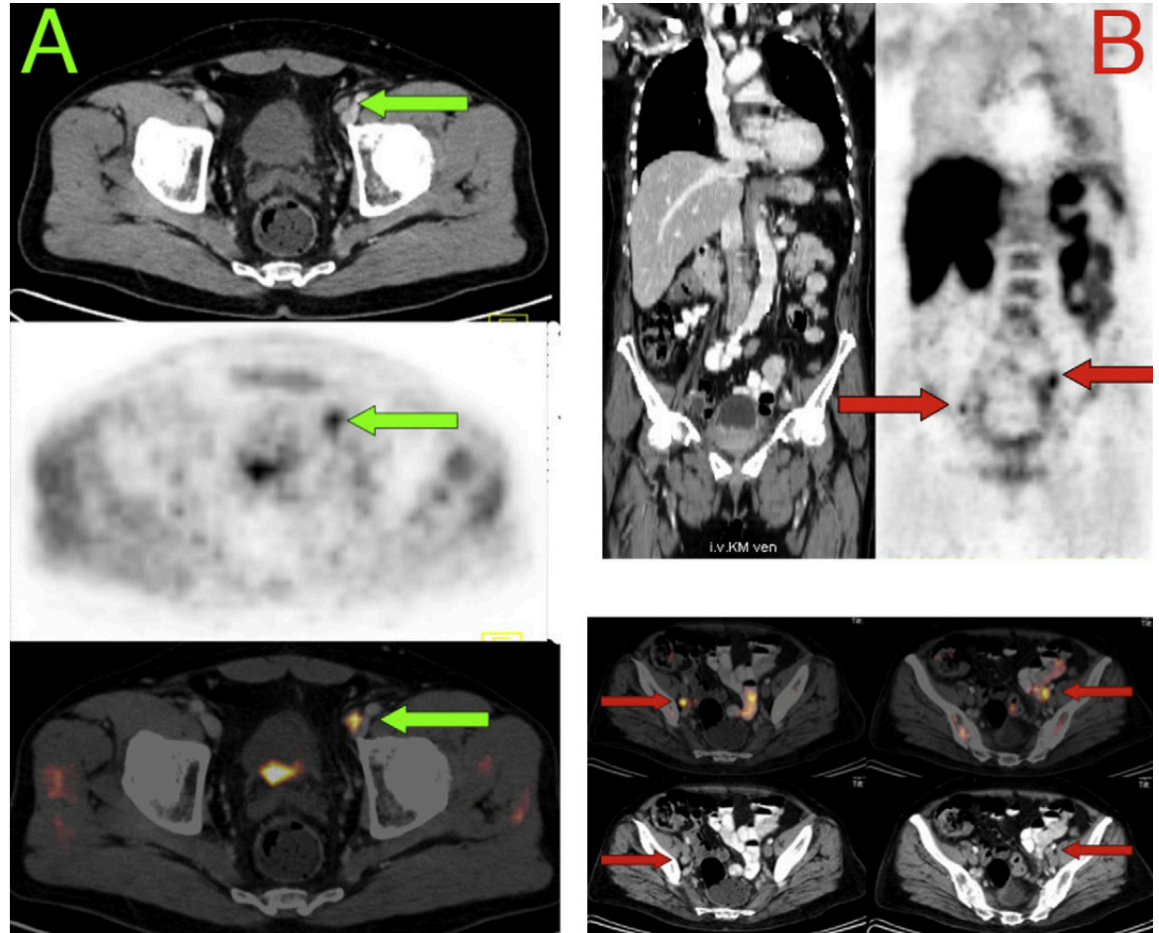


Grassi Am J Nucl Med Mol Imaging 2012.

Utility in staging may not be better than CT alone.

For all tracers excreted through the kidneys.

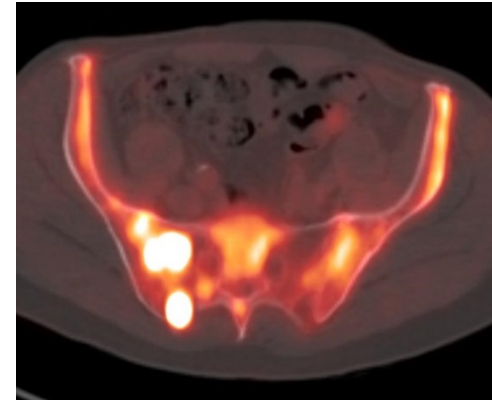
Maurer. Eur Urol 2012.



[11C]Choline

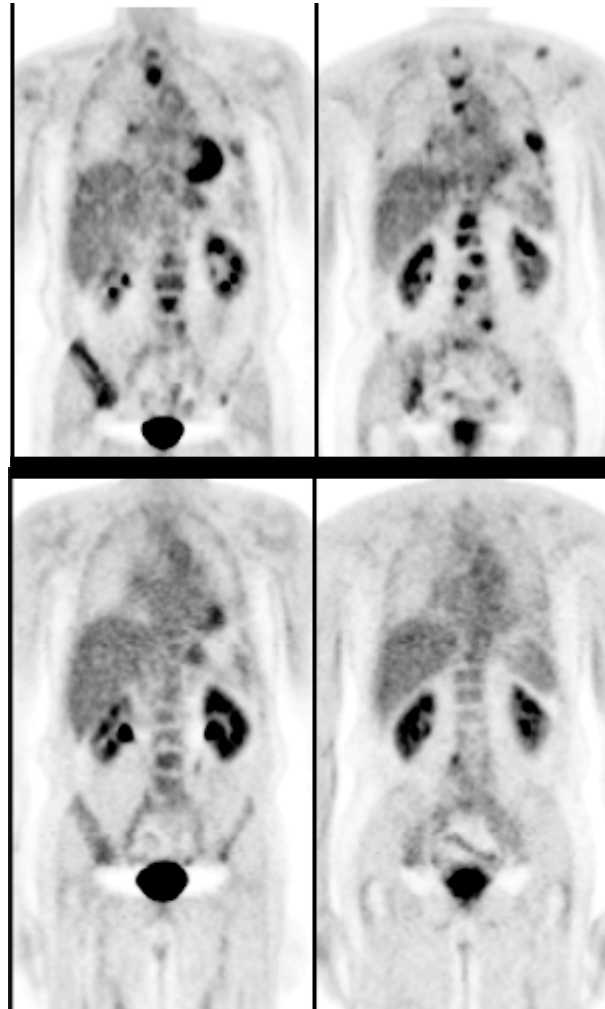
Imaging metastatic CaP

- PCWG2→3... imaging ill-defined
- Bone scans remain mainstay
 - NaF PET/CT greater accuracy (with ?higher FP)
 - Utility in f/u not clear
 - Flare
 - Non-specific



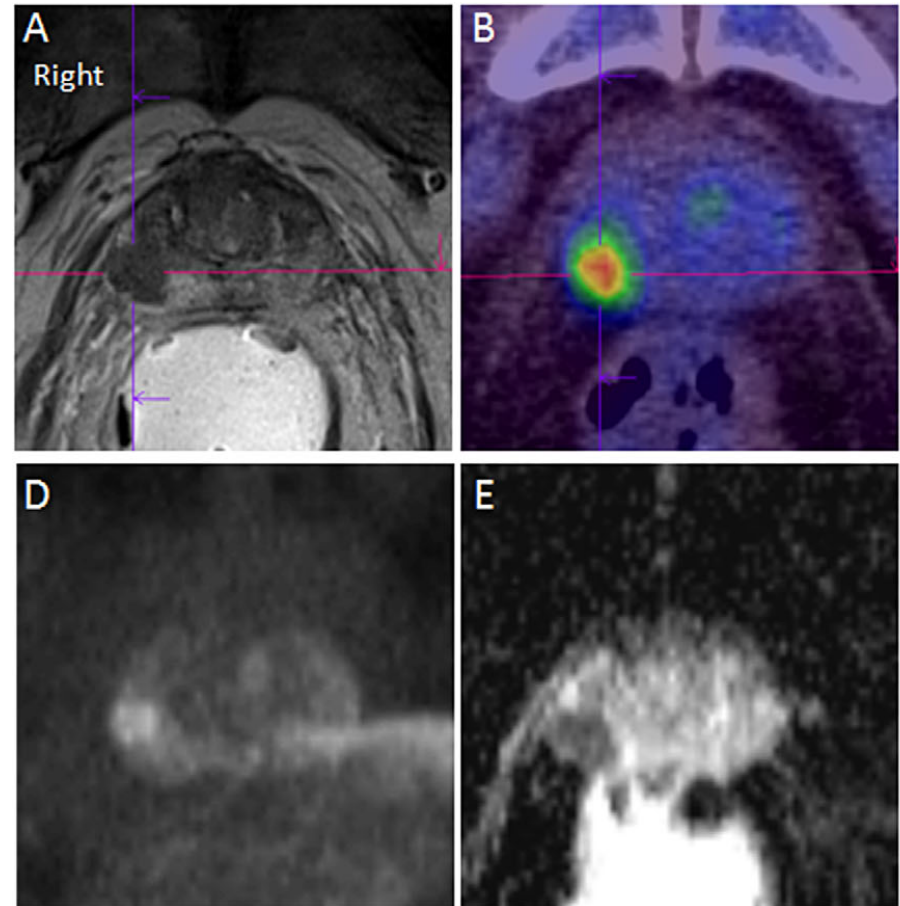
Prostate cancer PET imaging issues

- Castration-sensitive rarely glucose avid.
- Castration-resistant usually glucose avid.
- Other metabolic agents employed
 - Choline
 - *Fluciclovine*



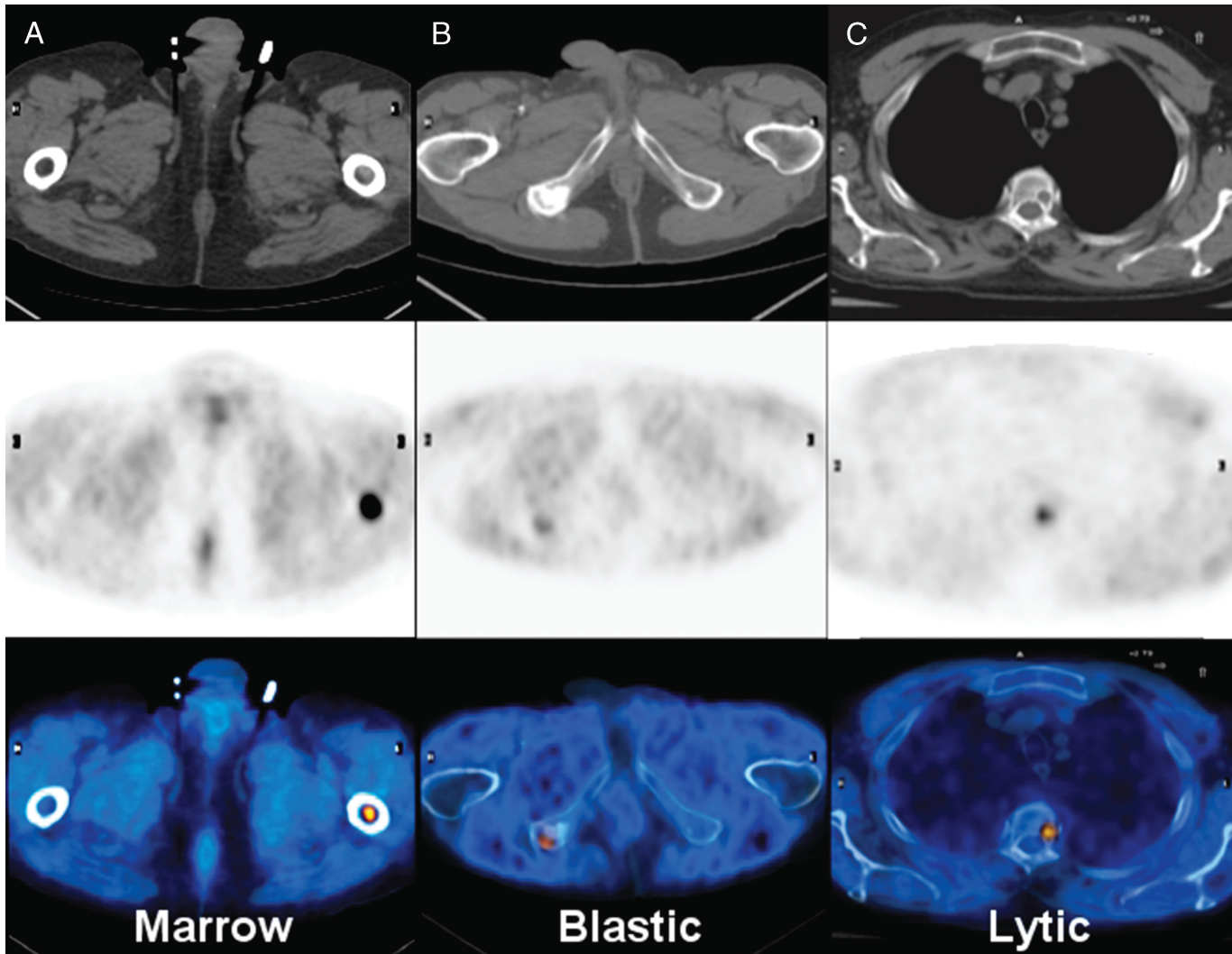
Radiocholine

- **[11C]-choline** has NDA approval
- **Increasing utilization in Europe**
 - **[18F]-choline**
- **NOT** incorporated as biomarker per EAU '13



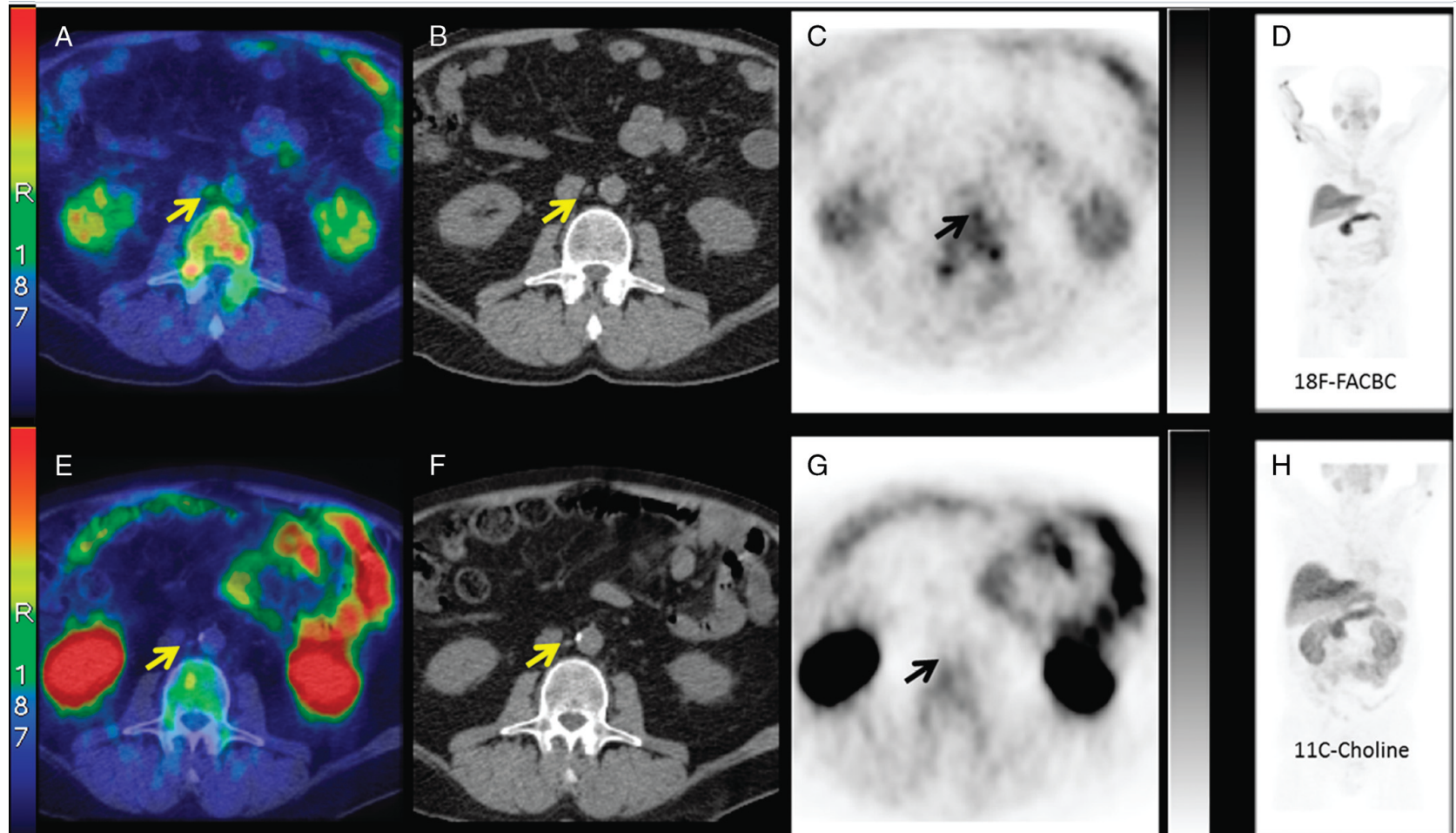
Hernandez-Argüello, Prostate, 2015

Radiocholeline for CRPC



Ceci, Clin Nucl Med 2015

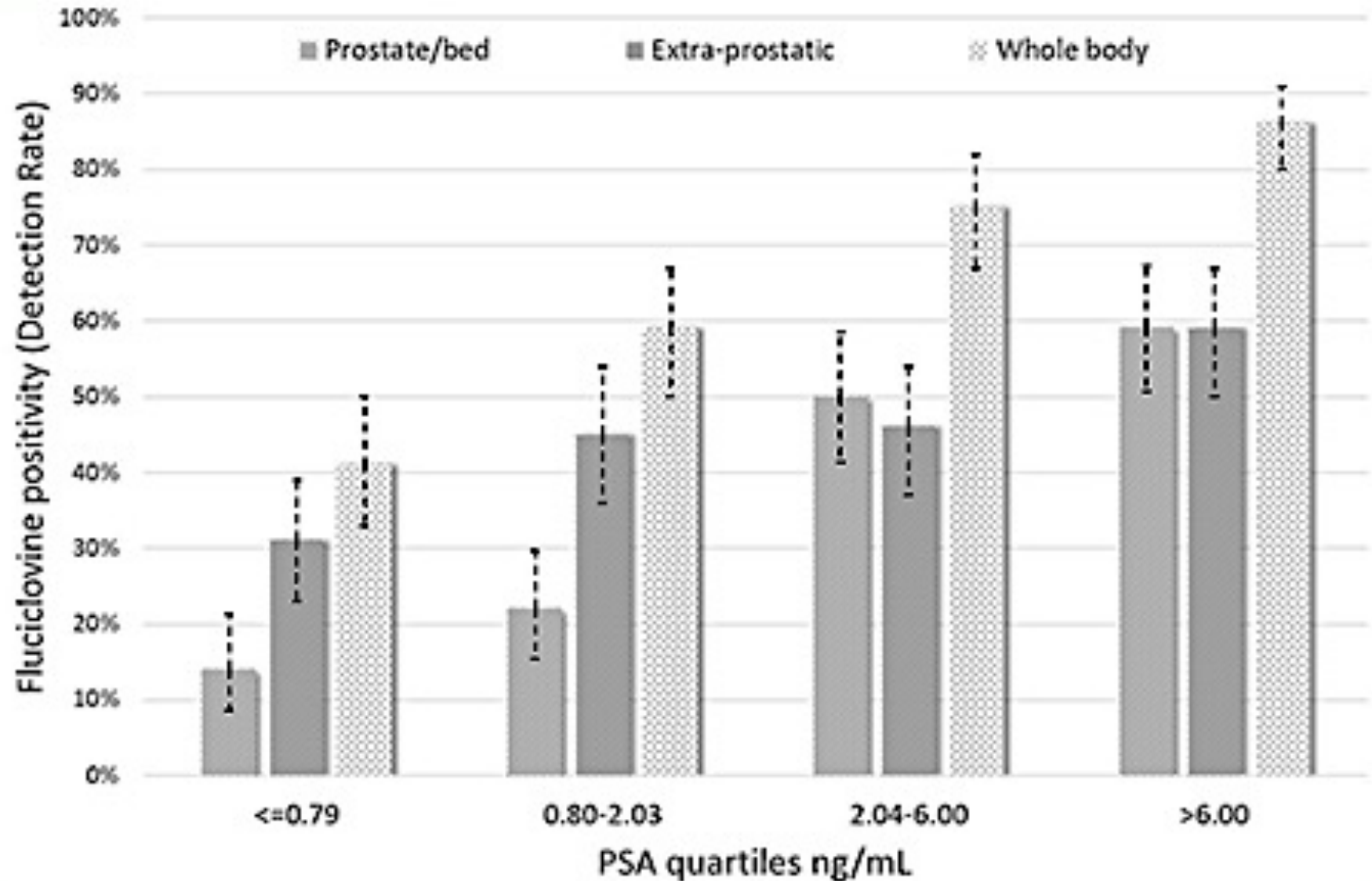
Metabolic tracers



Metabolic tracers

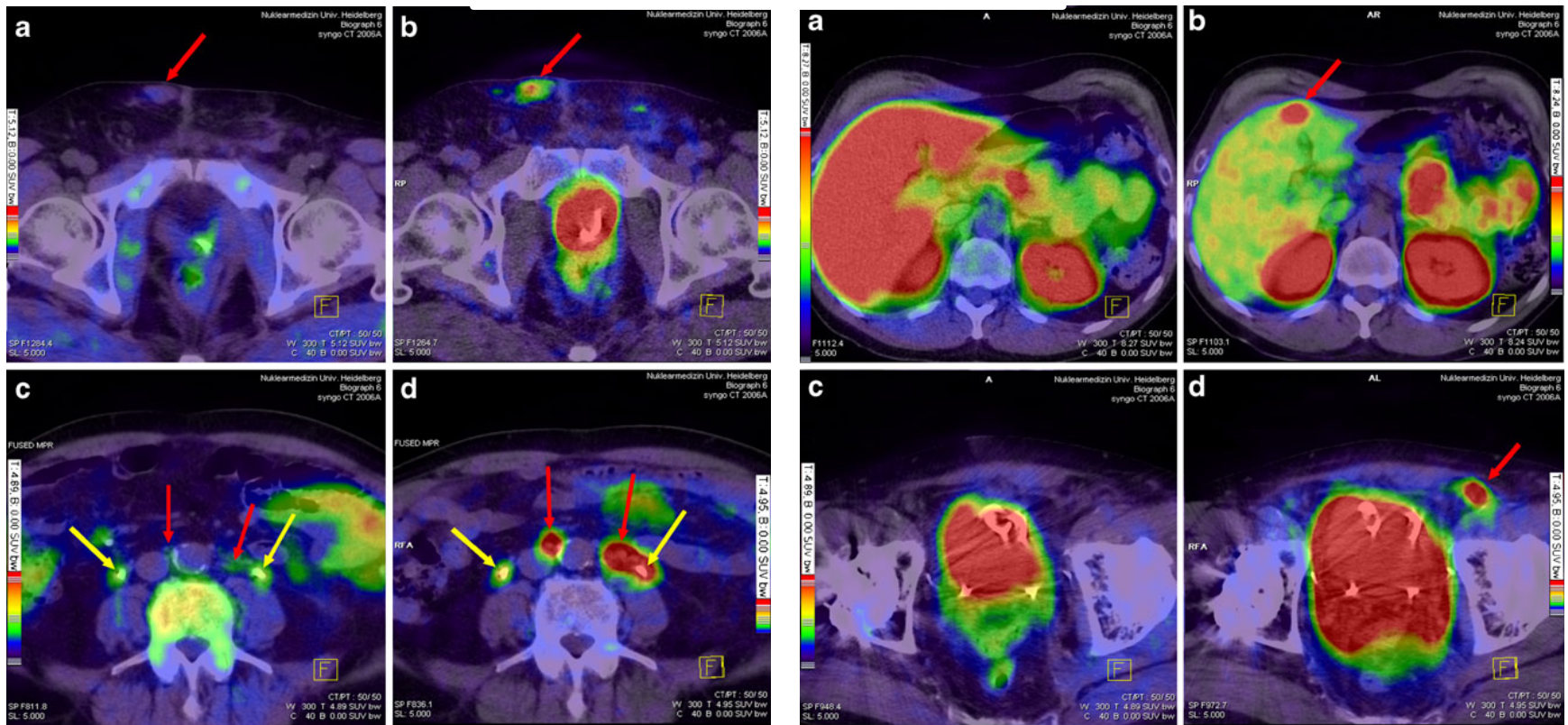
- Both amino acids and choline will likely have comparable biodistribution
- [11C]- half life limits centralized production
 - Addressed by FMC/FEC
- Dextro-amino acids may represent a metabolic paradigm akin to FDG
 - May provide better signal:noise (accumulation)
- Fluciclovine is [18F]-labeled
 - *FDA approved*

[18F]-Fluciclovine



Phenotype - PSMA

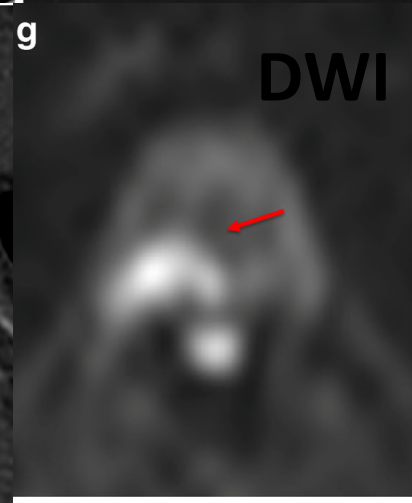
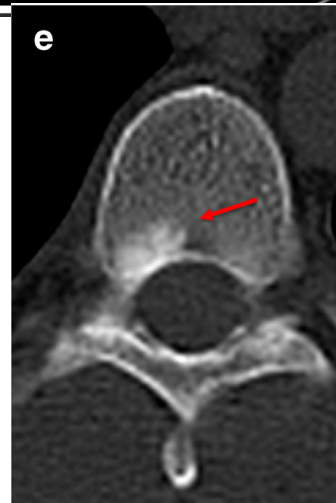
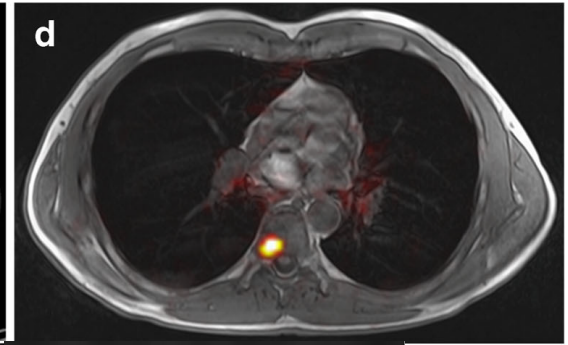
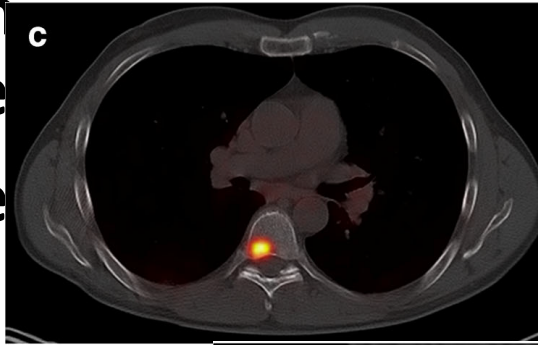
Choline v α PSMA

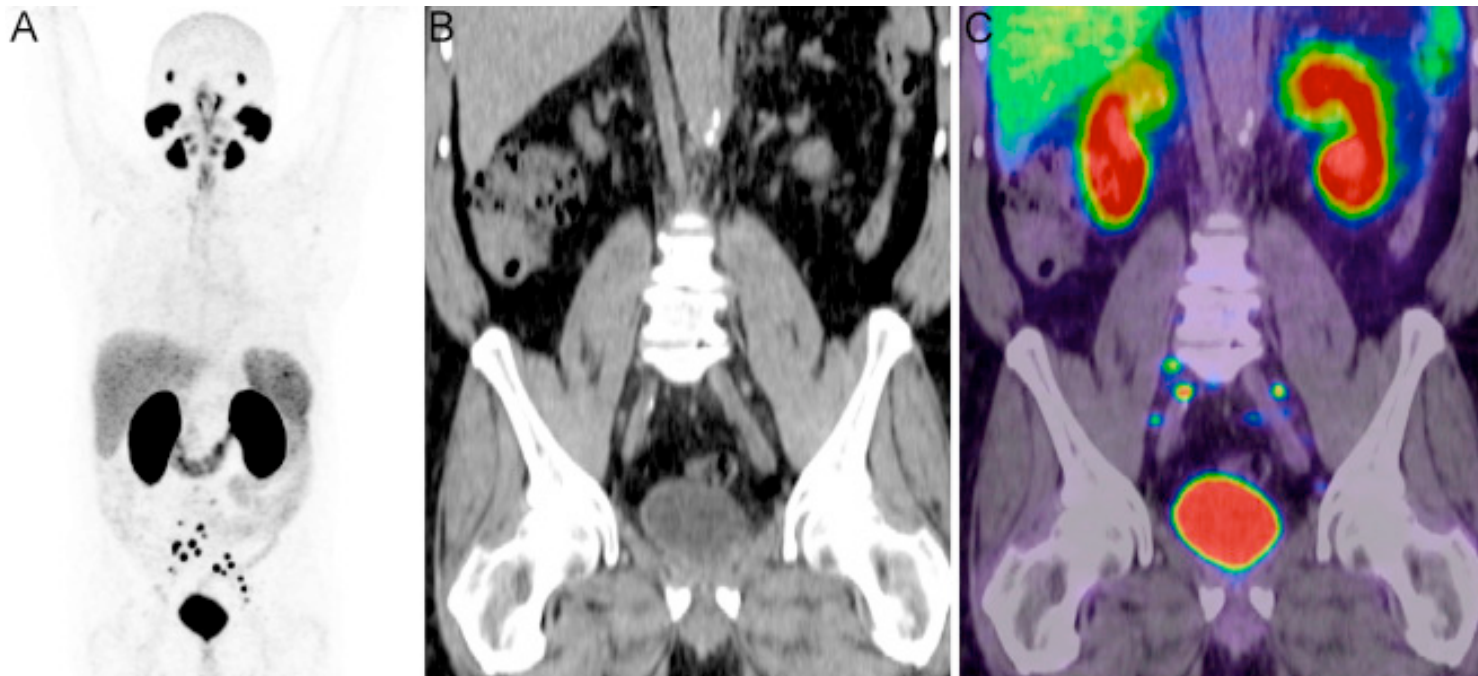


Afshar-Oromieh, EJNMMI 2014

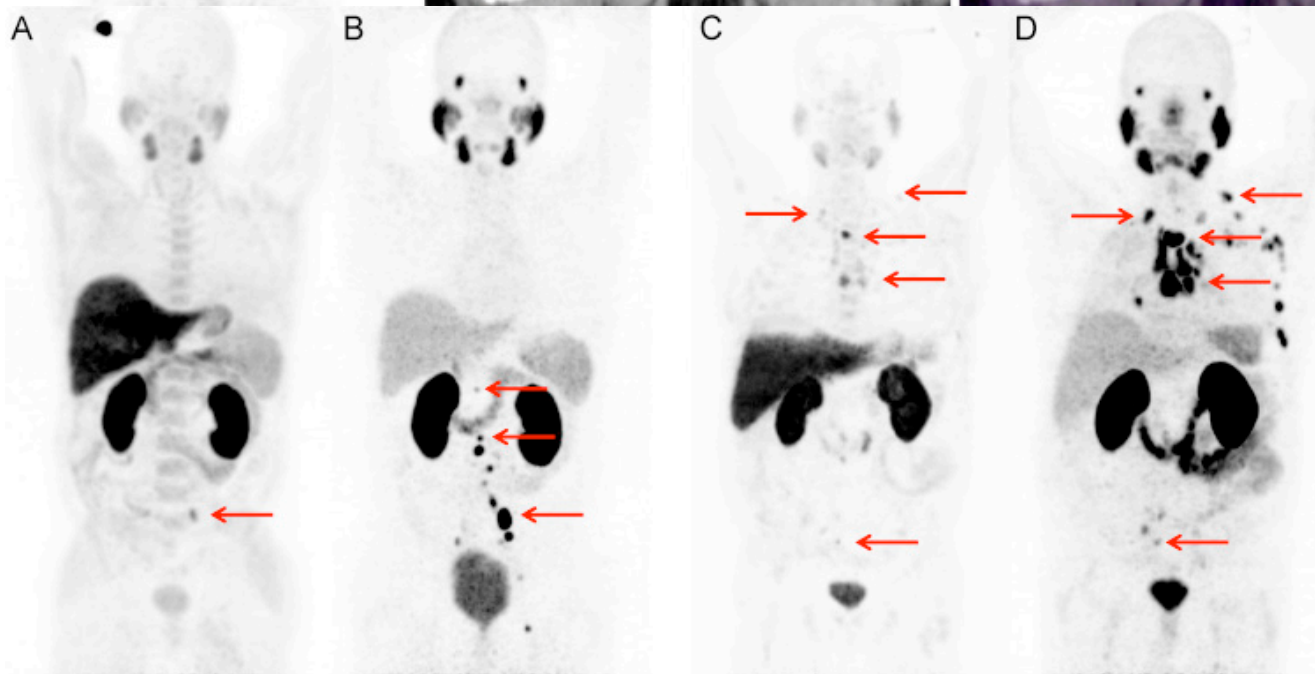
[68]Ga- α PSMA

- Small molecule with favorable clearance
- Ga-68 short half-life decreases patient radiation exposure
- Same day imaging
- Extra- and osseous disease





Kratochwil
Semin Nucl
Med 2016



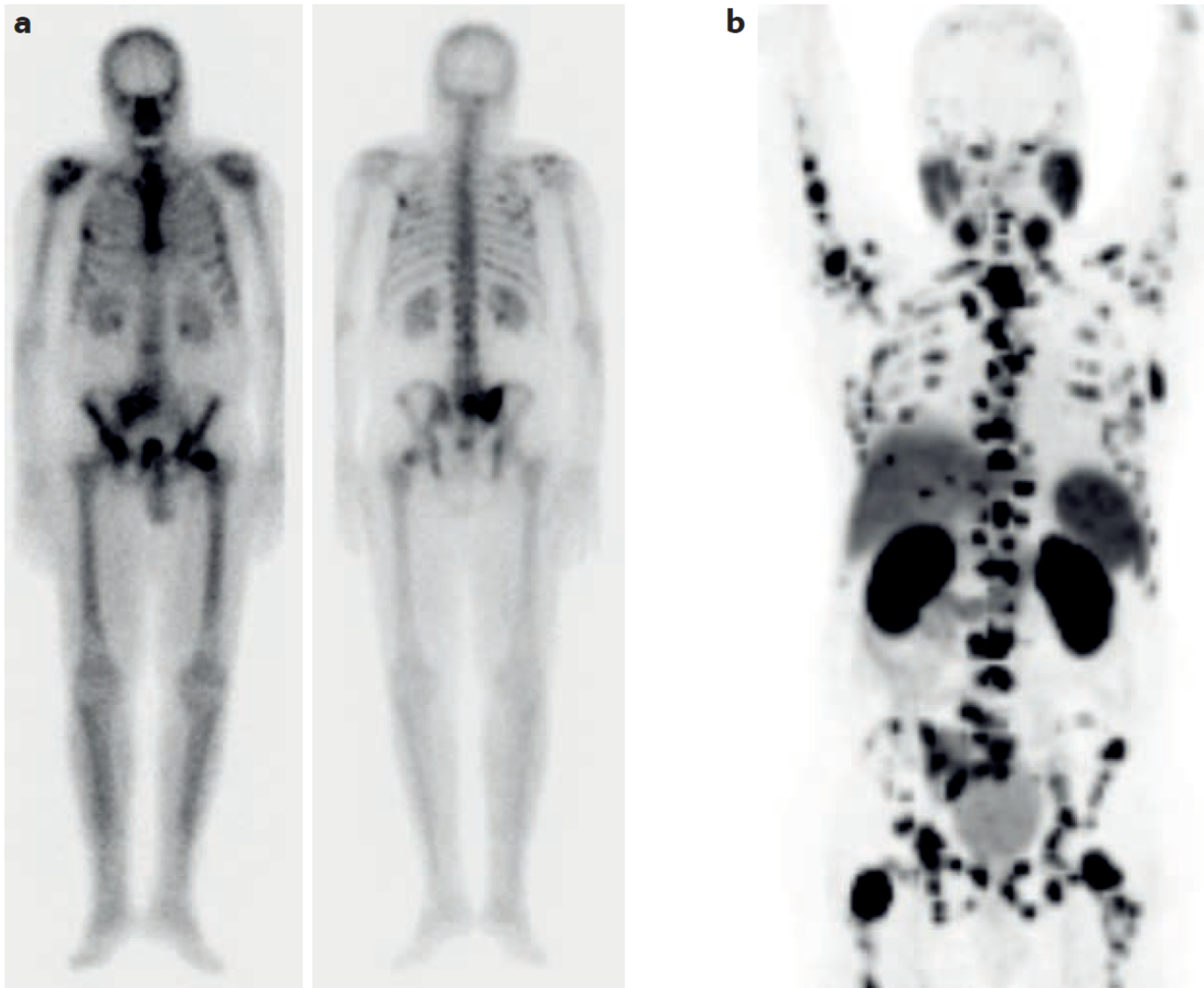
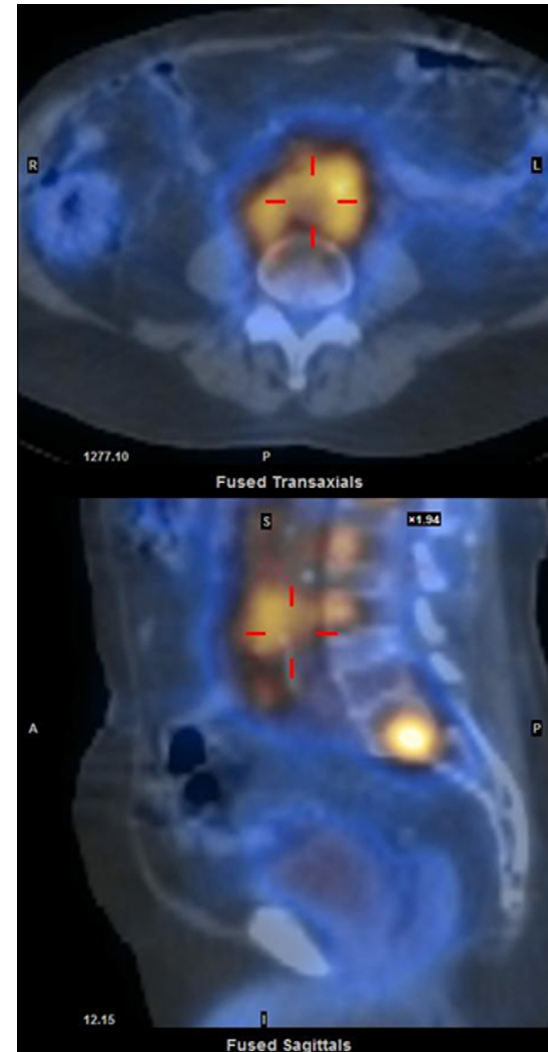


Figure 5 | **Imaging of 65-year-old patient with prostate cancer and diffuse**

Nature Reviews Urology April 2016

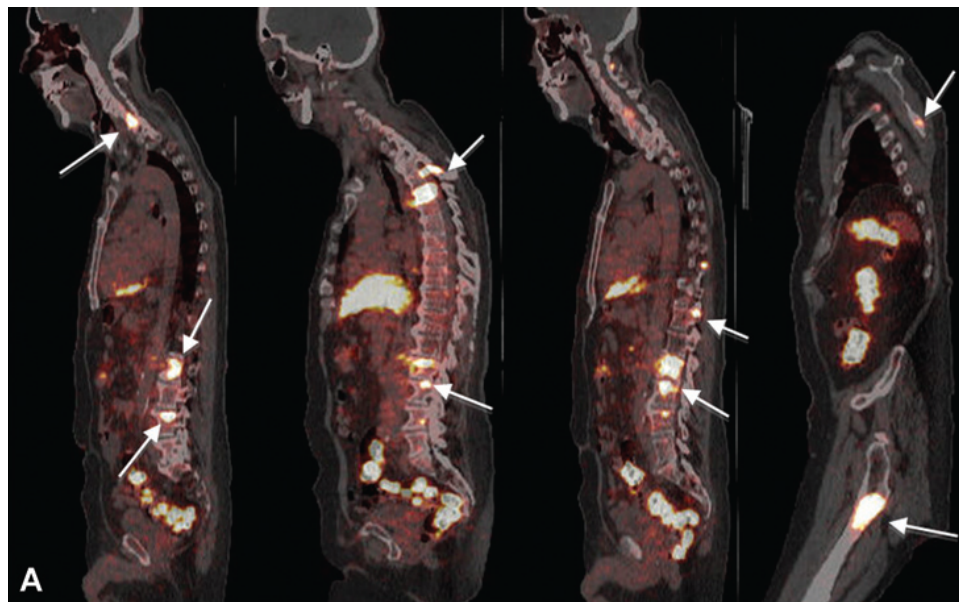
Imaging phenotype – PSMA - IgG

- Prostascint® with In-111 FDA-approved, not widely accepted
- HuJ591 against *external* domain of PSMA – greater potential
 - Long half-life
 - Theranostic (?Th-227)

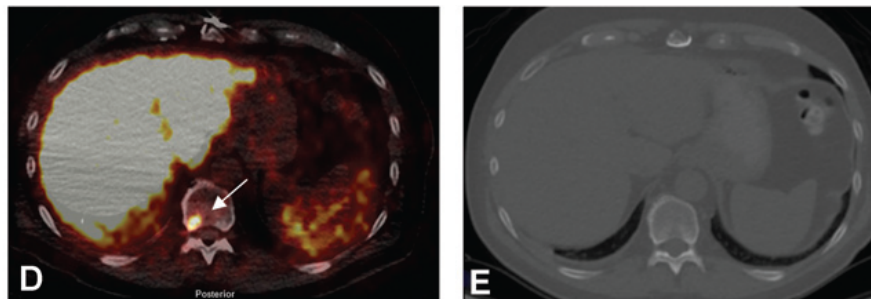


[⁸⁹Zr]-DFO-huJ591

- Slow clearance of intact IgG precludes same day imaging
- Current comparisons with sub-optimal imaging modalities (bone scans!!!)
- Theranostic potential



Pandit-Taskar, Clin Cancer Res 2015



PET in CaP

- **Metabolic agents:**
 - NaF sensitive, non-specific
 - FDG PET/CT may have utility in CRPC
 - [11C]-choline, FDA approved
 - [18F]-choline under development
 - [18F]-fluciclovine, FDA approved
- **Phenotype characterization (PSMA_x)**
 - Small molecules (PSMA-11)
 - Antibody (J591) and antigen-binding proteins