Beyond Ultrasound and MRI: Imaging Prostate Cancer

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Director Sidney Kimmel Cancer Network
Sidney Kimmel Cancer Center
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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
<table>
<thead>
<tr>
<th>Prostate Cancer Characteristic To Capitalize Upon</th>
<th>Clinical Imaging Modality</th>
</tr>
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<tbody>
<tr>
<td>Low water content</td>
<td>T2 weighted MRI</td>
</tr>
<tr>
<td>Restricted water diffusion</td>
<td>Diffusion weighted images MRI</td>
</tr>
<tr>
<td>Increased vascularity</td>
<td>Dynamic contrast enhanced MRI, Doppler US, Contrast enhanced Ultrasound</td>
</tr>
<tr>
<td>Increased glucose metabolism</td>
<td>FDG PET</td>
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<tr>
<td>Increased cellular proliferation, cell membrane synthesis</td>
<td>Choline, Acetate PET</td>
</tr>
<tr>
<td>Amino-acid transport</td>
<td>Fluciclovine-PET</td>
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<td>PSMA expression</td>
<td>PSMA PET</td>
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<td>AR expression</td>
<td>FDHT PET</td>
</tr>
<tr>
<td>Proclivity for bone metastases</td>
<td>NaF PET, Tc99 bone scan</td>
</tr>
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## Selected PET Imaging Methods in PC

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<td><strong>68 Ga-HBED-CC PSMA</strong></td>
<td>Radiolabeled to target PSMA extracellular domain</td>
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<td>Irreversible binding affinity to PSMA and robust internalization (ASCO 2017)</td>
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<tr>
<td><strong>64 Cu-TP3805</strong></td>
<td>Targets VPAC-1 receptor</td>
</tr>
<tr>
<td>Tracer</td>
<td>Radionuclide</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>PSMA</td>
<td>18F</td>
</tr>
<tr>
<td>DCFPyL</td>
<td>68Ga</td>
</tr>
<tr>
<td>HBED-CC-PSMA (PSMA-11)</td>
<td>68Ga</td>
</tr>
<tr>
<td>J591</td>
<td>88Zr</td>
</tr>
<tr>
<td>IA82M</td>
<td>88Zr</td>
</tr>
<tr>
<td>P16-C93</td>
<td>68Ga</td>
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**Lipid metabolism**

| Choline, Fluorochocline, 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                                                                                                                             |
| MATBN                        | 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                                                                                                                             |
| HK4                          | 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**

| PMAU                         | 18F       | Cyclotron | DNA synthesis                       | 3                                                                                                                             |
| FLT                          | 18F       | Cyclotron | DNA synthesis                       | 4                                                                                                                             |

**Miscellaneous**

| FDHT, FMHDT                   | 18F       | Cyclotron | Androgen Receptor                   | 4                                                                                                                             |
| AE105                        | 68Ga/64Cu | Generator/Cyclotron | Urokinase Plasminogen Activator Receptor (UPAR) | 3                                                                                                                             |
| TPS805                       | 64Cu      | Cyclotron | VFA1                                | 2                                                                                                                             |
| Gallium citrate              | 68Ga      | Generator | Multiple mechanisms                 | 1                                                                                                                             |
| MSTP2108A                    | 88Zr      | Cyclotron | STEAP1 (ImmunopET)                  | 1                                                                                                                             |

*Joseph Ippolito, M.D., Ph.D., ver 07/24/2017*
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<td>RSI MRI</td>
<td>Detects images based upon the motion of water molecules between tissues</td>
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<td>Multiparametric MRI</td>
<td>Combines T2-weighted MRI plus dynamic contrast-enhanced MRI plus magnetic resonance spectroscopy</td>
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<td>MRI SPIO</td>
<td>IV lymphotropic ultrasmall SPIO particles to differentiate benign/malignant nodes</td>
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PET Scan Principle

Prostate cancer avid molecule (acetate, choline, fluciclovine, fluoride, PSMA analogue)

Positron emitting tracer ($^{11}\text{C}$, $^{18}\text{F}$, $^{68}\text{Ga}$)

Fuse with CT or MR Anatomyl
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

**11C Carbon vs 18F Fluorine vs 68Ga Gallium**

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<th></th>
<th>11C</th>
<th>18F</th>
<th>68Ga</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life</strong></td>
<td>20 min</td>
<td>110 min</td>
<td>68 min</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Hepatobiliary</td>
<td>Urinary</td>
<td>Urinary</td>
</tr>
<tr>
<td><strong>Decay Energy</strong></td>
<td>&gt; 99% Positrons</td>
<td>97 % Positrons</td>
<td>&gt;95% Positrons</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Cyclotron</td>
<td>Cyclotron</td>
<td>Generator</td>
</tr>
</tbody>
</table>
$^{18}$F-FDG PET

*(fluorodeoxyglucose-"Every day PET")*

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

Performs better in CRPC
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
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

$^{11}$C-choline PET/CT
Detection of Retroperitoneal LN in a Patient with PSA Recurrent PC
18 F-Fluciclovine (FACBC) (Axumin)

18F-Fluciclovine is an artificial amino acid PET imaging agent labelled with 18F.

Recognized and taken up by amino acid transporters\(^1\) that are upregulated in many cancer cells, including prostate cancer.

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

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

• Extacellular 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)

68Ga-PSMA-PET vs 99Tc Bone Scan
Prostate Cancer Bone Metastases

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*
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
• 25 men going for RALP were imaged preoperatively
• PET/CT images compared with whole mount prostatectomy specimens
• Digital autoradiography performed on whole mount sections
Autoradiography and optical imaging of prostate cancer tissue

Digital Autoradiography (DAR)

Histology prostate cancer tissue

Optical image prostate cancer tissue

Sidney Kimmel Cancer Center
at Thomas Jefferson University
NCI-designated
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.
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.
<table>
<thead>
<tr>
<th>Tracer</th>
<th>Half-life</th>
<th>Cyclotron</th>
<th>Mechanism of action</th>
<th>Excretion</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>$^{11}$C-choline</td>
<td>20</td>
<td>On-site</td>
<td>Cell membrane synthesis</td>
<td>Hepatic</td>
<td>38-98</td>
<td>50-100</td>
<td>Low urine excretion</td>
<td>Short half-life</td>
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<tr>
<td>$^{11}$C-acetate</td>
<td>20</td>
<td>On-site</td>
<td>Lipid synthesis</td>
<td>Hepatic</td>
<td>42-90</td>
<td>64-96</td>
<td>Low urinary excretion</td>
<td>Moderate specificity Not FDA approved</td>
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<tr>
<td>$^{18}$F-Fluciclovine</td>
<td>110</td>
<td>Regional</td>
<td>Amino acid transport</td>
<td>Renal</td>
<td>89-100</td>
<td>67</td>
<td>Availability</td>
<td>Moderate specificity</td>
</tr>
<tr>
<td>$^{18}$F-NaF</td>
<td>110</td>
<td>Regional</td>
<td>Adsorption within bone matrix</td>
<td>Hepatic</td>
<td>87-89</td>
<td>80-91</td>
<td>Sensitivity</td>
<td>Only for bones, not specific</td>
</tr>
<tr>
<td>$^{68}$Ga-PSMA</td>
<td>68</td>
<td>Generator (no cyclotron)</td>
<td>PSMA analog</td>
<td>Renal</td>
<td>63-86</td>
<td>95-100</td>
<td>Not dependent on cyclotron</td>
<td>Moderately short half-life Not FDA approved</td>
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<tr>
<td>$^{18}$F-FDHT</td>
<td>110</td>
<td>Regional</td>
<td>AR</td>
<td>GI and renal</td>
<td>63</td>
<td>N/A</td>
<td>AR - specific</td>
<td>not effective in castrate sensitive setting, not FDA approved</td>
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* Interpret with caution, few studies used biopsy / surgery as gold standard
Fluciclovine Tracer (also known as FACBC)

anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid

Amino terminus

Carboxy terminus

Cyclic side-chain

18F radiolabel for PET imaging
Fluciclovine F18: Pharmacodynamics

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

All Regions - SUV (Mean)

- Prostate Tumours
- Lymph Node Lesions
- Muscles
- Marrow
- Bladder
- Vesicle lesion
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 cancer

- Distribution after IV dosing:
  - Liver: 14%*
  - Red bone marrow: 12%*
  - Lung: 7%*
  - Myocardium: 4%*
  - Pancreas: 3%*

- First 4 hrs. post-injection:
  - 3% excreted in urine*

*% of administered radioactivity

2. Fuciclovine F 18 Injection; US Prescribing Information, Blue Earth Diagnostics, Ltd; August 2016
77 yr old post RT, PSA recurrence
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
Utility in staging may not be better than CT alone.

For all tracers excreted through the kidneys.


[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
Radiocholine for CRPC

Ceci, Clin Nucl Med 2015
Metabolic tracers

Nanni, Clin Nucl Med 2015
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

Fluciclovine positivity (Detection Rate)

- Prostate/bed
- Extra-prostatic
- Whole body

PSA quartiles ng/mL:
- \( \leq 0.79 \)
- 0.80-2.03
- 2.04-6.00
- > 6.00

T. Bach-Gansmo. 10.1016/j.juro.2016.09.117
Phenotype - PSMA

Choline v αPSMA

Afshar-Oromieh, EJNMMI 2014
[68]Ga-αPSMA

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

Freitag, EJNMMI 2015
Figure 5 | Imaging of 65-year-old patient with prostate cancer and diffuse
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)

Osborne, Urol Oncol 2013
[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 \((PSMA_\chi)\)
  • Small molecules (PSMA-11)
  • Antibody (J591) and antigen-binding proteins