Integrating MRI and PSMA PET Imaging in Prostate Cancer

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Natural History of Prostate Cancer

- Local Therapy
- Castration
- Castration Resistance
- Metastatic
- Localized
- Biochemical recurrence
- Castration Sensitive
- Castration Resistant Metastases
- Non-Metastatic
- Metastatic
- Castration Sensitive
- Castration Resistant

Time

Death
How can PET imaging help?

- **For localized disease:** Staging
  - Is there disease in nodes or bones?
  - Is there disease in seminal vesicles?

- **For Recurrent disease:** Restaging
  - Is there residual tumor in prostate bed?
  - Is there nodal or bony disease?

- **For Metastatic disease:**
  - What is extent of disease?
  - Is it progressing or responding to therapy?
The Development of Prostate Imaging and Image Guided Biopsy 2000-2016

- Multiparametric MRI 2000’s
- In gantry biopsy 2003-6
- MRI-TRUS-GPS-2006
- Clinic MR-TRUS Fusion 2008
- Commercial MR-TRUS fusion Devices 2013
- World wide- Image Guided Bx (IGB) 2016
Prostate Specific Membrane Antigen (PSMA)

- PSMA (prostate specific membrane antigen) is a transmembrane protein, which is highly expressed in many prostate cancers, particularly high grade cancers.
- Urea-based compounds have high affinity for the enzymatic domain of PSMA and are used for PET imaging.
Lutje et al Theranostics 2016
PSMA PET Imaging

• Available PSMA targeting PET tracers:
  • $^{68}$Ga Labelled:
    • $^{68}$Ga-PSMA-11 ($^{68}$Ga-PSMA-HBED-CC)
  • $^{18}$F Labelled:
    • $^{18}$F-DCFBC
    • $^{18}$F-DCFPyL
Comparison of $^{68}\text{Ga}$ and $^{18}\text{F}$

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<tr>
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<th>$^{68}\text{Ga}$</th>
<th>$^{18}\text{F}$</th>
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<tbody>
<tr>
<td>68</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>generator production</td>
<td>cyclotron</td>
<td></td>
</tr>
<tr>
<td>1899</td>
<td>Positron energy (keV)</td>
<td>633</td>
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<tr>
<td>89%</td>
<td>Positron yield</td>
<td>96%</td>
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**$^{68}$Ga PSMA-11 PET**

- Small ligand, imaged 60 minutes after injection

- 319 PC pts Afshar-Oromieh et al 2015
  - Lesion-based analysis: Sens, Spec, NPV, PPV: 76.6%, 100%, 91.4% and 100%
  - Patient-based analysis: sensitivity 88.1%
  - 416 histological lesions: 30 false negative on $^{68}$Ga

- BCR in 248 pts after RP Eiber et al 2015

- PET/MR more accurate than PET/CT Afshar-Oromieh et al 2014

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<th>Tumor detection rate (%)</th>
<th>PSA (ng/ml)</th>
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<tr>
<td>58</td>
<td>0.2-0.5</td>
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<tr>
<td>73</td>
<td>0.5-1</td>
</tr>
<tr>
<td>93</td>
<td>1-2</td>
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<tr>
<td>97</td>
<td>≥2</td>
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$^{68}$Ga-PSMA PET/CT demonstrating a patient representative for disseminated lymph node and bone metastases of prostate cancer.
71-year old man with PSA=4ng/ml after radical prostatectomy.

Courtesy of Dr. Frederik Giesel from University of Heidelberg, Germany
18F-DCFBC PET

- 18F- N-[N-[N-(S)-1,3-dicarboxypropyl] carbamoyl]-4-[18F]fluorobenzyl-l-cysteine
- Low molecular weight PSMA inhibitor
- 5 pts with PCa metastases Cho et al 2012
  - Biodistribution, dosimetry
  - 32 PET positive lesions
    - 21 concordant with conventional imaging
    - 11 only with DCFBC, most in bone
T2W MRI

ADC map

B=2000 DWI

DCE MRI permeability map

TRUS/MRI fusion guided biopsy Gleason 4+5 prostate cancer

18F-DCFBC PET study localizes the anterior TZ lesion
66-year old man, Gleason 4+5 PSA=216ng/ml
64-year old man, Gleason 5+4 PSA=39ng/ml with seminal vesicle and nodal metastases
69-year old man, S/P RP 6 years ago, PSA=0.25ng/ml
58-year old man, S/P radical prostatectomy, PSA=1.4ng/ml with recurrence at anastomosis
54-year old man, S/P radical prostatectomy, PSA=0.6ng/ml
54-year old man, S/P radical prostatectomy, PSA=0.9ng/ml with recurrence at right seminal vesicles
DCFBC 107 (JM) -
Arm 2: s/p RP + RT, PSA = 1.97 ng/ml (09/12/2016)

Focal abnormal DCFBC uptake fusing to a 1.6x1.9 cm left common iliac lymph node [SUV$_{\text{max}}$ 12.3]
Very subtle DCFBC uptake fusing to a small sclerotic bony lesion in the right ischium.

DCFBC 107 (JM) - Arm 2: s/p RP + RT, PSA = 1.97 ng/ml (09/12/2016)
68-year old man, S/P radical prostatectomy, PSA=9ng/ml
65-year old man on ADT, PSA=7.1ng/ml

18F-DCFBC PET
Paraaortic and iliac nodes

18F- NaF PET: negative for metastases
73-year old man on ADT, PSA<0.01ng/ml

R Ilium bone lesion: Positive on NaF, negative on DCFBC PET
72 year old man on ADT: PSA 1.2ng/ml NaF(+) DCFBC (±). Is this patient in transition to AR status?
$^{18}$F-DCFPyL PET

- 2-(3-{1-carboxy-5-[6-$^{18}$F]fluoro-pyridine-3-carbonyl]-amino]-penty]-ureido)-pentanedioic acid.
- Markedly reduced blood pool activity with corresponding overall higher uptake in prostate cancer.
- Superior to conventional imaging (8 patient pilot study by Rowe et al 2016).
- Commercial sponsor (now in phase 3 study).
\textsuperscript{18}F-DCFPyL PET images a patient with multiple bony and nodal metastases.

Image courtesy of Dr. Martin Pomper, JHU
Metastatic lymph nodes with variable sizes (4-6mm [arrows] and 20mm[arrowhead]) with selective uptake of $^{18}$F-DCFPyL in a prostate cancer patient.
A model of progressive reprogramming

**Androgen-dependent, AR⁺**
In castrate-resistant prostate cancer (luminal epithelial adenocarcinoma), cells express and depend upon androgen receptor (AR⁺) for growth.

**Androgen-indifferent, AR⁺⁻⁻**
After treatment with an AR antagonist, cells with altered RB1 and TP53 are selected. Factors including SOX2 and EZH2 contribute to dedifferentiation and plasticity.

**Androgen-independent, AR⁻⁻⁻**
Cells established are most often reprogrammed to the neuroendocrine lineage that is resistant to enzalutamide.
Neuroendocrine Prostate + GaDOTATATE study
Current and Recently Completed Prostate PET Clinical Trials by Tracer

Note: completed refers to trials completed in last 6 months

courtesy: Christine Lorenz Siemens
Current Prostate PET Clinical Trials

Locations for Top 5 Tracers in Evaluation

68Ga-PSMA
- USA, Canada, Austria, Belgium

18F-FACBC
- USA, Norway, UK

18F-NaF
- Switzerland, USA, Canada

18F-DCFPyl
- Canada, USA

11C-acetate
- USA

source: www.clinicaltrials.gov

courtesy: Christine Lorenz Siemens
Clinical Uses of PSMA PET

• Localized prostate cancer:
  • Lesion detection
  • TNM staging
• Biochemical recurrence after prostatectomy, xRT, brachytherapy
• Metastatic disease
  • Determining the tumor burden
  • Understand ADT response status?
Integrating MRI into PSMA PET

• MRI is very helpful in localizing PSMA uptake in primary tumors
  • Informs regarding EPE, SVI
  • Localization of local node and bone disease

• MRI is critical for localizing regional recurrence positive on PSMA
  • Localizing periurethral recurrence
  • Localizing residual SVI and node/bone disease

• MRI is helpful in verifying structural abnormalities in sites of PSMA uptake in metastatic diseased
Thank you...