Overview of prostate cancer imaging

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Disclosures

• Clovis Oncology: grant support
• Philips: grant support
• Novartis/AAA: trial participation
• ITM: consultant
• Curium: consultant
• RayzeBio: consultant
• Blue Earth Diagnostics: advisory board
• Ipsen: advisory board
1. Review of CT/MRI
2. Introduce PSMA PET
3. Review the impact of PSMA
1. Review of CT/MRI
2. Introduce PSMA PET
3. Review the impact of PSMA
1. "Conventional Imaging" (CT and MRI)

2. PET and conventional imaging
CT: computed tomography

- Is a measurement of density
- Intravenous contrast helps in evaluation of solid organs and soft tissues
- Also allows for imaging of bone and lung
CT: computed tomography

- Is a measurement of density
- Intravenous contrast helps in evaluation of solid organs and soft tissues
- Also allows for imaging of bone and lung

Bone windows
CT: computed tomography

- Is a measurement of density
- Intravenous contrast helps in evaluation of solid organs and soft tissues
- Also allows for imaging of bone and lung

Lung windows
MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous
MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous

*T1 post-contrast imaging*
MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous
MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous
Bone scintigraphy

• Study takes four hours
  – three hours of uptake after injection
• Can perform an associated SPECT/CT, but increases time and costs
• Limited by low sensitivity and specificity
### “Conventional Imaging”

<table>
<thead>
<tr>
<th>CT</th>
<th>MRI</th>
<th>Bone Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widely available</td>
<td>Usually limited to imaging the pelvis</td>
<td>Fast, easy</td>
</tr>
<tr>
<td>Fast, easy</td>
<td>Uncomfortable</td>
<td>Cheap, no issues with reimbursement</td>
</tr>
<tr>
<td>Full coverage</td>
<td>(endorectal coil, long, loud, claustrophobic)</td>
<td>In all existing guidelines and used in all trials</td>
</tr>
</tbody>
</table>
PET/CT

- Radiolabeled compound
  - typically 18F-FDG
  - also Ga68, C11, Cu64...
- Decays by releasing a positron
- Positron then travels a finite distance and decays into two photons
  - positron range of F18 is roughly 2 mm
**PET/CT: various radioisotopes**

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Emax</th>
<th>Rmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ga-68</td>
<td>1.9</td>
<td>8.2</td>
</tr>
<tr>
<td>O-15</td>
<td>1.7</td>
<td>7.3</td>
</tr>
<tr>
<td>N-13</td>
<td>1.2</td>
<td>5.1</td>
</tr>
<tr>
<td>C-11</td>
<td>0.97</td>
<td>4.1</td>
</tr>
<tr>
<td>F-18</td>
<td>0.64</td>
<td>2.4</td>
</tr>
</tbody>
</table>
NaF PET/CT

- Better spatial resolution
- High signal to background
- CT available for correlation
- Shorter time from injection to imaging
  - imaging is done 60 minutes after injection compared to three hours with bone scans
FDG PET/CT

• No value in detection
• Uptake is correlated with aggressiveness
• Infrequently used, and role is mainly in castrate resistant patients
1. Review of CT/MRI
2. Introduce PSMA PET
3. Review the impact of PSMA
Prostate Specific Membrane Antigen

Extracellular

Intracellular
68Ga-PSMA-11

chelator (HBED-CC) (binds to a radiometal)
68Ga-PSMA-11

targeting molecule
"urea motif"
68Ga-PSMA-11

Ga-68
69 year old man status post RP
PSA = 0.67

Disease site 1: right humerus

Disease site 2: left internal iliac node
UCSF/UCLA BCR clinical data

- 635 patients in total, split between UCSF and UCLA
- Median PSA of 2.1
- Three blinded readers — Actually 9 in total
- Composite endpoint:
  - 223 patients with composite validation
  - 93 with histologic validation
- PPV:
  - Composite endpoint: 0.92
  - Histopathology: 0.84

Inter-reader variability
- Prostate bed, $\kappa = 0.65 \ (0.61-0.70)$
- Pelvic nodes, $\kappa = 0.73 \ (0.69-0.78)$
- Extrapelvic soft tissue, $\kappa = 0.70 \ (0.65-0.74)$
- Bone, $\kappa = 0.78 \ (0.73-0.82)$

Fendler, JAMA Oncology (2019)
Ga 68 PSMA-11 Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

– with suspected metastasis who are candidates for initial definitive therapy.
– with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

Approved December 2020
Gallium-68

- 68 minute half-life
- Generator produced
  - Usually can only make 2-3 doses per synthesis
- PET emitter (91%)
  - 8 mm positron range
- Metal chemistry
  - Simple synthesis using modules
18F-DCFPyL

- Termed the “PyL” compound
- Much lower blood pool activity
- Completed Phase III trials awaiting NDA approval!

Rowe JNM (2015)
### DCFPyL: OSPREY and CONDOR trials

<table>
<thead>
<tr>
<th>OSPREY</th>
<th>CONDOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cohort A: initial staging (n=252)</td>
<td>• Biochemical recurrence only</td>
</tr>
<tr>
<td>• Specificity 98%, sensitivity 40%</td>
<td>• n=208</td>
</tr>
<tr>
<td>• Cohort B: biochemical recurrence (n=93)</td>
<td>• Did not require biopsiable lesions</td>
</tr>
<tr>
<td>• Inclusion criteria required disease on conventional imaging</td>
<td>• Baseline PSA of 0.8</td>
</tr>
<tr>
<td>• Sensitivity 96% and PPV 82%</td>
<td>• Correct localization rate: 85-87%</td>
</tr>
<tr>
<td>• Median PSA of 11.3</td>
<td>• CLR: % of patients with a one-to-one correspondence between 18F-DCFPyL by the central readers and the composite SOT</td>
</tr>
<tr>
<td></td>
<td>• Detection rate 59-66%</td>
</tr>
</tbody>
</table>

Pienta J Urol 2021  
Morris Clin Cancer Res 2021
• PYLARIFY Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
  – with suspected metastasis who are candidates for initial definitive therapy.
  – with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

Approved May 2021
DCFPyL
PSMA-1007
NCT04742361

FDA approved
PSMA-11
NCT04186845
NCT04186819
rh-PSMA-7

FDA approved
VISION trial
PSMA-617
ILLUCCIX, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

– with suspected metastasis who are candidates for initial definitive therapy.
– with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.
Variations in biodistribution...
NCCN guidelines: *updated 9/10/2021*

- Initial staging (PROS-2)
  - Indicated in unfavorable intermediate, high and very high risk patients
- Biochemical recurrence (PROS-9, PROS-10 and PROS-11)
  - No PSA cutoff provided
- Progression for CSPC systemic therapy (PROS-12)
  - Includes patients with castration resistant disease
- Progression with M0CRPC (PROS-13)
• Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging.
• Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
• Studies suggest that F-18 piflufolastat PSMA or Ga-68 PSMA-11 PET imaging have a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels.
• Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.
CMS coverage

• The following diagnoses are applicable to piflufolastat F 18 (PYLARIFY®) injections when billed with 78811, 78812, 78813, 78814, 78815 or 78816. Use A9597 to bill for this service effective 5/26/2021. Use the PS modifier.
  –NOTE: Whenever a personal history diagnosis code (Z85.XXX) is on a claim, the claim must also contain a diagnosis code from the list of covered C, D, or R diagnosis codes.

• Effective 09/10/2021, the NCCN Guidelines have been updated to allow PMSA-PET/CT or PMSA-PET/MRI with F 18 piflufolastat PSMA to be considered effective for initial bone imaging with the use of the ‘PI’ modifier.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>R97.21</td>
<td>Rising PSA following treatment for malignant neoplasm of prostate</td>
</tr>
<tr>
<td>Z85.46</td>
<td>Personal history of malignant neoplasm of prostate</td>
</tr>
</tbody>
</table>
PSMA vs Fluciclovine

Inter-reader variability (k)

<table>
<thead>
<tr>
<th></th>
<th>PSMA</th>
<th>Fluciclovine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.67</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

Calais, Lancet Oncology (2019)
False positive interpretations

- Benign lesions
  - Rib lesions
  - Pre-sacral ganglia
  - Dorsal root ganglia
  - Hemangiomas
  - Paget’s disease

- Other tumors
  - HCC
  - Thyroid cancer
  - Lung cancer
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TP disease!
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Fibrous dysplasia
False positive interpretations

- Benign lesions
  - Rib lesions
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  - Paget’s disease
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Prostate cancer

Primary treatment:
- Radical prostatectomy
- Radiation therapy

PSA recurrence:
"Biochemical recurrence"

Initiation of ADT:
(androgen deprivation therapy)

Development of castration resistant prostate cancer

Frank metastases

2nd and 3rd line therapies:
- abiraterone / enzalutamide
- docetaxel / cabazitaxel
- Ra-223
- PARPi
- Immunotherapy

Death
72 year old man with Gleason 4+4
72 year old man with Gleason 4+4
Role in initial staging: PSMA PET versus pathology at time of prostatectomy (n=277)

<table>
<thead>
<tr>
<th></th>
<th>+ LN on path</th>
<th>- LN on path</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ LN on PSMA</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>- LN on PSMA</td>
<td>45</td>
<td>192</td>
</tr>
</tbody>
</table>

75 patients were positive on pathology (27%)

- Sensitivity ➡ 40%
- Specificity ➡ 95%
PSA of 23.7, Gleason 4+3
Recurrence after radiation therapy
Effect of PSMA PET on RT planning

- 45 patients with high risk at staging
  - 12 received boost to nodes
  - 6 had RT to bone metastases
  - 8 had nodes outside of consensus CTV

53% had change in RT plans

Wu, Urology (2019)
Prostate cancer

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Frank metastases

Death

DX

PSA Levels
# Biochemical Recurrence

<table>
<thead>
<tr>
<th>Post-RP</th>
<th>Post-Radiation</th>
</tr>
</thead>
</table>
| **AUA guidelines:**  
  - PSA > 0.2 ng/dL 6-12 weeks after prostatectomy  
  - Confirmed on repeated PSA | **ASTRO-Phoenix:**  
  - PSA rise over post-radiation nadir of at least 2.0 ng/dL |
Detection rate on PSMA PET directly related to the PSA at time of imaging

Please don’t “wait” for a higher PSA to get a positive PSMA PET
PSMA “negative” tumors

Outcomes in patients treated with SRT after PSMA PET (median PSA 0.26)

Freedom from Progression (FFP): PSA rise of 0.2 over nadir

Emmett JNM 2020
PSMA “negative” tumors

Remember, a negative PSMA PET does not mean that men should be observed…
Location of recurrence

- 125 patients with PSA < 2.0 after RP
- 53% with PSMA+ disease
- 30% had disease missed by standard RT

![Bar chart showing percent of patients with different PSA levels and their recurrence locations.](chart.png)
Management changes depend on location of disease

- Neg > surveillance
- Pelvic nodes > RT
- Mets > systemic

Fendler 2019 JNM
**Biochemical recurrence**

**Post RP: PSA increase from 0.5 to 0.9**

<table>
<thead>
<tr>
<th>Disease site 1: right pelvic side wall node 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image of disease site 1]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease site 2: right pelvic side wall node 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image of disease site 2]</td>
</tr>
</tbody>
</table>
EMPIRE-1: Fluciclovine vs CI

- Post-RP BCR patients
- Primary endpoint:
  - Event free survival (events defined as biochemical or clinical recurrence or progression, or initiation of systemic therapy)
- Biochemical free survival @ 4 years: 51.2% versus 75.5% (p<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>Conventional imaging-guided (n=82)</th>
<th>$^{18}$F-fluciclovine-PET/CT-guided (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA before radiotherapy, ng/mL</td>
<td>0.34 (0.82)</td>
<td>0.34 (0.92)</td>
</tr>
<tr>
<td>Androgen deprivation therapy—long-term use (18-24 months)</td>
<td>8 (10%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Androgen deprivation therapy—any use</td>
<td>28 (35%)</td>
<td>30 (38%)</td>
</tr>
</tbody>
</table>

Study group                           HR (95% CI)  
Conventional imaging group             1.84 (0.98:3.47) (reference)  
$^{18}$F-fluciclovine-PET/CT group      Log-rank p=0.0540  

Jani 2021 Lancet
Theranostics

- The use of a compound for both diagnostics and therapeutics

**Imaging**
- Ga-68

**Therapy**
- Lu-177
- Y-90

*PSMA I&T*  
Schottelius 2015, EJNNMME Research
VISION results: 177Lu-PSMA-617

Overall Survival

• HR: 0.62
• 15.3 vs 11.3 mths
• p<0.001

PFS

• HR: 0.40
• 8.7 vs 3.4 mths
• p<0.001
TheraP trial...

Hofman et al. Lancet 2021
## Pending PSMA trials

<table>
<thead>
<tr>
<th>Company sponsored</th>
<th>Academic trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMAAddition (AAA/Novartis); n=750+ 177Lu-PSMA-617+ADT/abi vs ADT/abi Metastatic CSPC</td>
<td>ENZA-P (ANZUP); n=160 177Lu-PSMA-617+enza vs enza First line mCRPC</td>
</tr>
<tr>
<td>PSMAfore (AAA/Novartis); n=495 177Lu-PSMA-I&amp;T vs second line abi/enza Pre-chemo mCRPC</td>
<td>LuPARP (Peter Mac); n=52 177Lu-PSMA-617 + olaparib Post-chemo mCRPC</td>
</tr>
<tr>
<td>SPLASH (POINT Biopharma); n=415 177Lu-PSMA-I&amp;T vs second line abi/enza Pre-chemo mCRPC</td>
<td>CCTG trial; n=200 177Lu-PSMA-617 vs docetaxel Pre-chemo mCRPC</td>
</tr>
<tr>
<td>AcTION (AAA/Novartis); n=30 225Ac-PSMA-617 Phase 1 Pre/post-chemo mCRPC</td>
<td>Bullseye (Radbound); n=58 177Lu-PSMA-617 in oligometastatic patients Pre-hormonal mCSPC</td>
</tr>
</tbody>
</table>
Targeted Ac225 Alpha Therapy is one of the most effective Treatments for Metastatic Prostate Cancer. For more information on the efficacy of Actinium 225 Therapy do call us at +91 98111 27080, or write to us at info@nuclearmedicinetherapy.in or visit nuclearmedicinetherapy.in
## Summary

1. Two PSMA PET radiotracers (PSMA-11 and 18F-piflufolostat) are FDA approved and covered by Medicare.

2. PSMA PET is superior to existing radiotracers for the detection of metastatic prostate cancer.

3. 177Lu-based PSMA-targeted radioligand therapy should be approved by the FDA in the coming months.
Thank you!

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