PSMA imaging of high risk and recurrent disease

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Imaging in Prostate Cancer By Clinical Stage

- Visualize disease during treatment (e.g. surgery or focal therapy)
- Extent
  - Prognosticate
  - Treatment Response
  - Biological profile
  - Determine pharmacodynamics of treatment

Adapted from Scher et al.
Molecular Imaging Modalities

- Established
  - Bone scintigraphy
  - $^{18}$F-FDG PET/CT
  - Prostascint
- Available in North America
  - NaF PET/CT
  - C11-acetate PET/CT
  - C11-choline PET/CT
  - $^{18}$F DHT PET/CT

- Europe/Australia
  - $^{68}$Ga-PSMA PET/CT
  - $^{18}$F Choline and Acetate
- Future
  - IAB2M PSMA PET/CT
  - $[^{18}]$DCFPyL PSMA
  - Optical Imaging Probes
  - Immune Imaging Probes
  - And MUCH MORE!!
Prostate Specific Membrane Antigen

- PSMA is a multifunctional zinc protease expressed in most prostate cancer cells and is negatively regulated by AR.
Rationale for PSMA targeted imaging

- Clinical staging with cross-sectional CT-scans, MRI imaging, and/or other PET radiotracers marred by both low sensitivity and specificity.
- PSMA PET provides a prostate/prostate cancer specific target that may provide better sensitivity and should provide high specificity (ie low rate of false positives)
PSMA Targeted Imaging Modalities

- **Scintigraphy:**
  - Prostascint® (intracellular)
  - Anti-J591 Antibodies (extra-cellular)

- **PET/CT Imaging:**
  - $^{68}$Ga-PSMA
  - $^{[18}F]$DCFPyL PSMA
  - IAB2M PSMA PET/CT
  - Euk-Subkff-$^{68}$Ga-DOTAGA
PSMA in High-Risk Prostate Cancer

• Budäus, et al 2016:
  – *Goal*: Determine the accuracy of lymph node staging in high-risk patients prior to radical prostatectomy.
  – *Results*: Per-patient Se, Sp, PPV, NPV, and accuracy were 33.3%, 100%, 100%, 69.2%, and 73.3%, respectively, for initial PCa nodal staging by $^{68}$Ga-PSMA PET/CT.
  – *Conclusion*: $^{68}$Ga-PSMA PET/CT was limited in its ability to detect smaller lymph node metastases.
## PSMA in High-Risk Prostate Cancer

<table>
<thead>
<tr>
<th></th>
<th>No LN metastases (n = 18)</th>
<th>LN metastases (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSMA negative (n = 18)</td>
<td>PSMA positive (n = 0)</td>
</tr>
<tr>
<td>LNs removed, no. (%)</td>
<td>393 (64.6)</td>
<td>–</td>
</tr>
<tr>
<td>LNMs removed, no. (%)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Intranodal LNM size, mm *, mean, median (range)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Overall LNM size, mm *, mean, median (range)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

LN = lymph node; LNMs = lymph node metastasis; NA = not applicable; PSMA = prostate-specific membrane antigen.

* Largest/index lymph node per patient is presented.

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<th>No LN metastases (n = 18)</th>
<th>LN metastases (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMA positive (n = 4), n (%)</td>
<td>0 (0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>PSMA negative (n = 26), n (%)</td>
<td>18 (100)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Specificity 100%</td>
<td>Sensitivity 33.3%</td>
<td>Accuracy 73.3%</td>
</tr>
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</table>

LN = lymph node; NPV = negative predictive value; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.
PSMA in Recurrent Prostate Cancer

• Morigi, et al 2015:
  – Goal: Prospectively compare $^{11}$C-Choline or $^{18}$F- Fluoromethylcholine (FMC) to $^{68}$Ga-PSMA PET/CT in recurrent PC following curative intent therapy.
  – Conclusions: In patients with rising PSA following curative intent therapy, $^{68}$Ga-PSMA has a higher detection rate of recurrent disease when compared to $^{18}$FMC, which has potential to impact management decisions.
PSMA in Recurrent Prostate Cancer

“A higher percentage of lesions were identified loco-regionally, in lymph nodes and in bone on PSMA”

“PSMA identified a higher number of lesions at every PSA cohort when compared to FMC”
PSMA in Recurrent Prostate Cancer

A) 62M, GS7, s/p RP and salvage XRT. Presents with rising PSA.

B) 70M, GS7, s/p RP. Presents with rising PSA.

Detection rates of FMC and PSMA at different PSA intervals

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>$^{18}$F-fluoromethylcholine</th>
<th>$^{68}$Ga-PSMA</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>12.5% (2/16)</td>
<td>50% (8/16)</td>
<td>0.03</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>36% (5/14)</td>
<td>71% (10/14)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>63% (5/8)</td>
<td>88% (7/8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total</td>
<td>32% (12/38)</td>
<td>66% (25/38)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Morigi et al J Nuclear Medicine 2015
Future Directions: $^{89}$Zr-Df-IAB2M Imaging

- **J591 antibody limitations**
  - Prolonged blood circulation
  - Increased background activity
  - Increased radiation dose to organs

- **Engineered antibody advances**
  - Faster clearance rate
  - Improved tumor to blood ratios
  - Approximately half the atomic mass of traditional antibodies
89Zr-Df-IAB2M Imaging

Comparison with Bone scan and FDG PET
(PSA 40.5, GS 9, Multiple bone lesions and nodal lesions)
Imaging lymphatic progression in PCa patients with no radiographic evidence of disease by conventional means

89Zr-Df-IAB2M Imaging

Able to resolve **regional lymph node chain**

Imaging lymphatic progression in PCa patients with no radiographic evidence of disease by conventional means
89Zr-Df-IAB2M Imaging

• Analysis of first 6 patients:
  – 11/48 (22.9%) nodes pathologically positive for prostate cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>89Zr-Df-IAB2M</th>
<th>111In–Capromab Pendetide</th>
<th>Conventional Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>54.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>(TP/TP+FN)</td>
<td>(6/11)</td>
<td>(0/11)</td>
<td>(0/11)</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.3%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(TN/TN+FP)</td>
<td>(36/37)</td>
<td>(37/37)</td>
<td>(37/37)</td>
</tr>
</tbody>
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Table 5-9: Preliminary Analysis of initial 48 total nodal basins examined from 6 subjects in 2014-2M-03 study.
\textsuperscript{89}Zr-Df-IAB2M Imaging

\textsuperscript{89}Zr-Df-IAB2M shows uptake in the location of tumor, confirmed by pathology

\textsuperscript{111}In Capromab Pendetide  \hspace{1cm} T2W FS +Gad MRI  \hspace{1cm} \textsuperscript{89}Zr-Df-IAB2M PET CT

PSA 7.0 ng/mL, Gleason 4+4
Pathology confirmed 89Zr-Df-IAB2M signal uptake in left internal obturator node was cancer.

PSA 31.8 ng/mL, Gleason 3+4
Conclusions

- Current cross sectional and early generation PET probes have relatively low sensitivity and poor specificity.
- Most proven indication for PSMA-PET imaging lies within the state of recurrent disease.
  - Sensitivity, however, still low for lesions <0.5 cm and low PSA.
- Further optimization of PSMA-PET imaging will likely detect recurrent lesions with very high accuracy, which will guide more effective adjuvant and salvage therapies.
- Molecular imaging remains an unmet need but ongoing and novel agents are very promising.