Prostate Cancer: PSMA Imaging

Rathan Subramaniam
MD, PhD, MPH, FACNM, FRANZCR

Robert W. Parkey MD Distinguished Professor
Professor & Chief, Division of Nuclear Medicine
Medical Director, Cyclotron and Molecular Imaging Programs
Program Director, Nuclear Medicine Residency & PET/CT Fellowships
Disclosures

- Medical advisory board member and speaker, Blue Earth Diagnostics Ltd
- All PSMA PET radiotracers are investigational in the US
Objective

• To review the status of PSMA PET imaging in the management of patients with prostate cancer
PSMA Molecule

- Type II transmembrane glycoprotein
- Encoded by glutamate carboxypeptidase II gene (GCP II)
PSMA Molecule Expression

• Expressed in normal prostate tissue
• Over expressed in prostate cancer by several orders of magnitude (100 – 1000 folds)
• 5-10% of prostate cancers do not express PSMA or PSMA PET negative
• Expression progressively increased (prostate cancer)
  • Higher grade tumors
  • Under androgen deprivation
  • Hormone Refractory & Metastases
PSMA PET Radiotracers
<table>
<thead>
<tr>
<th>$^{68}$Ga-labeled PSMA-ligands</th>
<th>$^{18}$F-labeled PSMA-ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image of 68Ga-PSMA-11" /></td>
<td><img src="image2" alt="Image of 18F-DCFBC" /></td>
</tr>
<tr>
<td><img src="image3" alt="Image of 68Ga-PSMA-I&amp;T" /></td>
<td><img src="image4" alt="Image of 18F-DCFPyL" /></td>
</tr>
<tr>
<td><img src="image5" alt="Image of 18F-PSMA-1007" /></td>
<td><img src="image6" alt="Image of 18F-PSMA-1007" /></td>
</tr>
</tbody>
</table>
In 2013, Heidelberg group published the first human series

- Most commonly used PSMA radiotracer
- $^{68}$Ga is eluted from $^{68}$Ge/$^{68}$Ga generator - shelf half life 6 - 12 months
- $^{68}$Ga $t_{1/2}$ - 68 min
- Not approved by FDA and investigational in US; used clinically in Europe, Australia, Asia & other parts of the world
• Sympathetic ganglia uptake can be seen in upto 60% of patients
Clinical Indications

• High benefit or diagnostic utility:
  • Primary staging in high risk disease
  • Biochemical recurrence with low PSA value (0.2 – 10 ng/ml)

• Low benefit or diagnostic utility:
  • Primary staging in low to intermediate risk disease
Clinical Indications

• Potential applications with promising prelim data:
  • Biopsy targeting after previous negative biopsy but high suspicion for prostate cancer

• Potential applications with data lacking:
  • Therapy monitoring in metastatic castration resistant or sensitive prostate cancer
  • Therapy monitoring after $^{177}$Lu PSMA therapy
  • Active surveillance / Follow up
I - Primary Staging: High Risk Disease

• High Risk Disease: D’ Amico classification
  • PSA > 20
  • Gleason score > 8
  • Clinical stage T2c or T3a

• PSMA PET/CT can either
  • (a) upstage – identifying occult metastases
  • (b) down stage
Primary Staging: High Risk Disease

- Newly diagnosed Gleason 4 + 5
- Conventional CT/MRI of pelvis and bone scan showed no metastatic disease
- PSMA PET identified small right obturator LN and metastasis in the rib

Primary Staging: High Risk Disease
# Primary Staging: High Risk Disease

<table>
<thead>
<tr>
<th></th>
<th>PSMA PET</th>
<th>Conventional Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>66%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>99%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Most lymph nodes missed in $^{68}$Ga PSMA PET/CT were <5 mm

*J Urol 2016; 195:1436-1443*
Primary Staging: High Risk Disease

$^{68}$Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review

- Sensitivity: 33 – 99%
- Specificity: >90%

World Journal of Urology 2018; 36:519-527
Primary Staging: High Risk Disease

MRI and Bone SPECT

PSMA PET/CT

Patient underwent radical prostatectomy

Primary Staging: High Risk Disease

• Real value:
  • Nodal staging and metastatic staging
    • Locoregional nodes – within true pelvis
    • M1a – nodes outside true pelvis
    • M1b – skeletal metastases
    • M1c – organ metastases
Primary Staging: High Risk Disease
Primary Staging: High Risk Disease
Primary Staging: High Risk Disease
Primary Staging: High Risk Disease

• Issues:
  • Lack of high quality clinical trial data to establish the quantitative value of the improved accuracy for staging compared to conventional imaging
  
• Intra-prostatic primary tumor staging
  • Limited accuracy – Better than Choline / Fluciclovine
  • Improved accuracy when combined with MRI
  • Role for PET/MRI
II - Biochemical Recurrence

• Definitions
  • After radical prostatectomy - PSA > 0.2 ng/ml
    • At least 2 consecutive measures 3 weeks apart
  • After external beam radiation, rise of > 2 ng/ml above the nadir PSA that occurs > 6 weeks after therapy completion
II - Biochemical Recurrence

• Detection rate (Meta Analysis)
  • 48% - PSA 0.2 ng/ml
  • 56% - PSA 0.5 ng/ml
  • 70% - PSA 1.0 ng/ml

• Comparison to $^{11}$C Choline PET/CT
  • Prospective study: PSMA PET detected 66% versus Choline PET 32%

Eur Urol 2016; 70: 926
Eur J Nucl Med Mol Imaging 2014; 41: 11
II - Biochemical Recurrence

PSA < 1 ng/ml

II - Biochemical Recurrence

II - Biochemical Recurrence

Detection rate PSA < 1 ng/ml

Choline
PSMA
II - Biochemical Recurrence

• High Impact on Management
  • Prospective study: 30% change in radiation therapy planning
  • Identification of Oligometastatic disease – SBRT option

• Issue
  • Lack of outcome data – not sure change in management leads to outcome benefit or harm to patients by lead time bias and over treatment?
II - Biochemical Recurrence

- Lead time bias
- No impact on outcome
III – Restaging of Metastatic Disease & Theragnosis
III - Restaging of Metastatic Disease & Theragnosis
III - Restaging of Metastatic Disease & Theragnosis

III – Restaging of Metastatic Disease & Theragnosis

III - Restaging of Metastatic Disease & Theragnosis

A

Survival function
Overall survival (%)

Time from start of treatment (mo)

B

Survival function
Radiographic progression-free survival (%)

Time from start of treatment (mo)

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>100%</td>
</tr>
<tr>
<td>0.24</td>
<td>98%</td>
</tr>
<tr>
<td>2.6</td>
<td>96%</td>
</tr>
<tr>
<td>3.2</td>
<td>95%</td>
</tr>
<tr>
<td>3.7</td>
<td>93%</td>
</tr>
<tr>
<td>6.6</td>
<td>91%</td>
</tr>
<tr>
<td>7.2</td>
<td>89%</td>
</tr>
<tr>
<td>7.5</td>
<td>86%</td>
</tr>
<tr>
<td>8.5</td>
<td>84%</td>
</tr>
<tr>
<td>9.7</td>
<td>81%</td>
</tr>
<tr>
<td>10.0</td>
<td>78%</td>
</tr>
<tr>
<td>13.6</td>
<td>71%</td>
</tr>
<tr>
<td>15.5</td>
<td>64%</td>
</tr>
</tbody>
</table>

J Nucl Med 2016; 57:1006-1013
IV – Pitfalls & Non Prostate Cancers

• ‘Flare’ phenomenon with androgen deprivation therapy
• PSMA negative prostate cancer
• Inflammatory Uptake
• Non prostate cancer
IV – Pitfalls & Non Prostate Cancers

‘Flare’ phenomenon with androgen deprivation therapy

Before

After

IV – Pitfalls & Non Prostate Cancers

PSMA negative prostate cancer

IV – Pitfalls & Non Prostate Cancers

PSMA & non prostate cancers

Adenoid Cystic Ca

FDG Gastric Cancer

PSMA
IV – Pitfalls & Non Prostate Cancers

PSMA & non prostate cancers

Triple negative breast ca

Metastatic clear cell RCC
IV – Pitfalls & Non Prostate Cancers

PSMA & non prostate cancers

Recurrent MTC
IV – Pitfalls & Non Prostate Cancers

PSMA & non prostate cancers

Recurrent GBM
Conclusions

• High benefit or diagnostic utility:
  • Primary staging in high risk disease
  • Biochemical recurrence with low PSA value

• Potential benefit or therapeutic utility:
  • Therapy monitoring in metastatic castration resistant or sensitive prostate cancer
  • Therapy monitoring after $^{177}$Lu PSMA therapy
Conclusions

- **Potential benefit - Diagnostic & therapeutic utility:**
  - Diagnosis and Therapy with $^{177}$Lu PSMA therapy in non prostate cancers

- **Pitfalls / Issues:**
  - Inflammatory/ infectious uptake: 10 – 15%
  - <10% PSMA negative prostate cancers
  - ‘Flare’ phenomenon after androgen deprivation therapy
  - Lack of outcome data: ‘Treating the scans’ than patients
  - FDA approval in US