The role of $^{68}$Ga-PSMA PET/CT in prostate cancer

Dr. Cristina Mitea, MD, PhD
Dept. of Radiology and Nuclear Medicine
Maastricht University Medical Centre
$^{68}$Ga-PSMA PET/CT
Which radioactive material?

- $^{68}$Ga: gallium, positron emitter
- obtained from a $^{68}$Ge/$^{68}$Ga generator
- half-life of 67.63 min
What is PSMA?

**PSMA** (prostate-specific membrane antigen)
- glutamate carboxypeptidase II
- present in all prostatic tissues

- increased expression in **prostate cancer**:
  - de-differentiated
  - metastatic
  - hormone-refractory disease
PSMA
potential prostate cancer target

• Tracer uptake identifies tumor foci

• Uptake correlates with the PSMA-expression on PCa cells and increases with higher grade and metastasis

Rowe et al, JNM 2015
Is PSMA specific for prostate cancer?

- Also present in:
  - normal tissues: salivary glands, colon, duodenum
  - other malignancies: colon, kidney, thyroid, lung
PSMA expression in non-prostate tumors
Thyroid carcinoma

Verburg et al, EJNM 2015
PSMA expression in non-prostate tumors
Lung carcinoma

Histology: prostate cancer metastasis

Histologically proven primary LC with LNM

Pyka et al, JNM 2015
More types of $^{68}$Ga-PSMA?

- $^{68}$Ga-PSMA-11
- $^{68}$Ga-PSMA-617
- $^{68}$Ga-PSMA-I&T
- $^{18}$F-PSMA
## Patient preparation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Protocol example for $^{68}$Ga-PSMA PET/CT image acquisition and reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient preparation</strong></td>
<td>Hydration with e.g. oral intake of 500 mL of water 2 h prior to acquisition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
<th>1.8–2.2 MBq $^{68}$Ga-PSMA per kilogram bodyweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>i.v., Flushing with at least the same volume of saline</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>Furosemide (20 mg i.v.)</td>
</tr>
<tr>
<td>Uptake time</td>
<td>60 min (acceptable range: 50 to 100 min)</td>
</tr>
<tr>
<td>Patient position</td>
<td>Arms elevated above the head</td>
</tr>
<tr>
<td>CT Protocol</td>
<td>FOV: base of the skull base to mid-thigh; Phase: portal venous (80 s after contrast agent, 1.5 mL per kilogram bodyweight)</td>
</tr>
<tr>
<td>PET Protocol</td>
<td>FOV and acquisition: from mid-thigh to base of the skull base; 3–4 min per bed position</td>
</tr>
<tr>
<td>PET Reconstruction</td>
<td>Ordered subsets expectation maximization; attenuation correction from CT data</td>
</tr>
</tbody>
</table>
Patient preparation

• No need to fast
• Medication can be continued
Normal PSMA distribution
PSMA expression in non-prostate lesions celiac ganglia

89.4% (76/85) of patients celiac ganglia PSMA PET positive

Krohn et al, EJNMMI 2015
$^{68}$Ga-PSMA PET/CT in prostate cancer
When can we use it?

- Biochemical recurrence
- Primary staging in high-risk disease
PSMA PET/CT: Diagnostic Sensitivity

248 patients

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>87 (35.1)</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td></td>
</tr>
<tr>
<td>Abdominopelvic</td>
<td>130 (52.4)</td>
</tr>
<tr>
<td>Supradiaphragmatic</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>89 (35.9)</td>
</tr>
<tr>
<td>Other (e.g., lung, liver) metastases</td>
<td>13 (5.2)</td>
</tr>
</tbody>
</table>

Data in parentheses are percentages.

Eiber et al, JNM 2015
PSMA PET/CT: Diagnostic Sensitivity

248 patients

Eiber et al, JNM 2015
Positive PSMA PET-CT
PSA cut-off value?

319 patients

Afshar-Oromieh et al, EJNMMI 2015
Positive PSMA PET-CT correlation with Gleason score?

319 patients

Afshar-Oromieh et al, EJNMMI 2015
Sensitivity of $^{68}$Ga-PSMA PET/CT in biochemical recurrence

Systematic review and meta-analysis: 16 studies, 1309 patients

**PSA level:**
- 42% for PSA <0.2 ng/ml,
- 58% for PSA 0.2–0.99 ng/ml
- 76% for PSA 1.00- 1.99 ng/ml
- 95% for PSA > 2.00 ng/ml

**PSA dt:**
- 64% for PSAdt >6mo
- 92% for PSAdt <6 mo

Perera et al, Eur Urol 2016
How big do the lymph nodes metastasis need to be?

Detection rate of 50% for lymph nodes of 3.7 mm (tumor of 2.3 mm) of 90% for lymph nodes of 6.0 mm (tumor of 4.5 mm)

Jilg et al, Theranostics 2017
PSMA vs CT
detection of lymph node metastasis

Giesel et al, EJNMMI 2015
PSMA is better than CT in detection of lymph node metastasis

$^{68}$Ga –PSMA PET-CT detects metastasis in “not pathological” lymph nodes

Giesel et al, EJNMMI 2015
PSMA vs CT
detection of metastasis

<table>
<thead>
<tr>
<th>Region/combo. of regions</th>
<th>No. of patients with positive</th>
<th>No. of patients with additional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>findings exclusively</td>
<td>involved regions exclusively</td>
</tr>
<tr>
<td></td>
<td>demonstrated in 68Ga-PSMA PET</td>
<td>demonstrated in 68Ga-PSMA PET</td>
</tr>
<tr>
<td>LR only</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>LN metastases only</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Bone metastases only</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>LR + LN metastases</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>LR + bone metastases</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>LN + bone metastases</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>LR + LN + bone metastases</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other (e.g., lung, liver metastases)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>81 (32.7%)</td>
<td>61 (24.6%)</td>
</tr>
</tbody>
</table>

Eiber et al, JNM 2015
PSMA vs Bonescintigrafie
for bone metastasis

- 213 patients with Pca

PSMA PET
- sensitivity 98.7–100 %
- specificity 88.2–100 %

Bonescintigrafie
- sensitivity 86.7–89.3 %
- specificity 60.8–96.1 %

Pyka et al, EJNMMI 2016
Guidelines

Oncoline

Een choline PET-scan kan van waarde zijn indien het PSA hoger is dan 5 ng/mL, of indien het PSA hoger is dan 1 ng/mL met daarbij PSA_{dt} < 3 maanden of Gleason score ≥8.
Choline vs PSMA

Choline PET

PSMA PET
<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>
Choline vs PSMA

PSMA has:
- Higher tumor uptake
- High tumor-to-background uptake
- Higher detection rate:
  - Overall sensitivity:
    - Choline vs PSMA: 66% vs. 88.5%
  - Sensitivity at PSA <2 ng/ml:
    - Choline vs PSMA: 31% vs 72%

Afshar-Oromieh et al, EJNMMI 2015


$^{68}$Ga-PSMA PET/CT in prostate cancer

When can we use it?

- Biochemical recurrence
- Primary staging in high-risk disease
PSMA and MRI good correlation for primary prostate lesion

Eiber et al, JNM 2015
Lymph nodes staging in initial diagnosis of prostate cancer

- 130 patients
- Comparison of PSMA with morphological imaging (CT and MRI)

*Maurer et al, Nat Rev Urol 2016*
PSMA vs multiparameter MRI

- 36 patients
- Primary staging

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison between $^{68}$Ga-PSMA PET/CT and MRI (patient-wise)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{68}$Ga-PSMA PET/CT</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>36</td>
</tr>
<tr>
<td>Number of patients with localization of the primary prostatic lesion</td>
<td>36</td>
</tr>
<tr>
<td>Number of patients with involvement of the seminal vesicle</td>
<td>23</td>
</tr>
<tr>
<td>Number of patients with regional lymph nodes</td>
<td>29</td>
</tr>
<tr>
<td>Number of patients with nonregional lymph nodes</td>
<td>15</td>
</tr>
<tr>
<td>Number of patients with skeletal metastases</td>
<td>20</td>
</tr>
</tbody>
</table>

Tulsyan et al, Nucl Med Commun 2017
Perspectives
PSMA PET-MR

Courtesy of Dr. Eiber
Theranostics

• The same target for diagnostics as for therapy:
  – PSMA is highly expressed on prostate cancer tumor cells

• Use of „heavier“ radionuclides coupled with tracer
  – Lutetium, Yttrium, Indium
Therapeutic response and side effects of repeated radioligand therapy with $^{177}$Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer

Hojjat Ahmadzadehfar$^1$, Elisabeth Eppard$^1$, Stefan Kürpig$^1$, Rolf Fimmers$^2$, Anna Yordanova$^1$, Carl Diedrich Schlenkhoff$^1$, Florian Gärtner$^1$, Sebastian Rogenhofer$^3$, Markus Essler$^1$

Therapie-Regime:
24 Pat. 6 GBq
Anti-PSMA ligand therapy
Results (UMC Aachen)
Anti-PSMA ligand therapy
Results (UMC Aachen)

$^{177}$Lu-anti-PSMA

PSMA PET-CT
before

first

second
Anti-PSMA ligand therapy
Results (UMC Aachen)

$^{177}$Lu-anti-PSMA

PSMA PET-CT before

first

second

PSMA PET-CT after
Ligand anti-PSMA therapy
Possible indications

• Palliative situation

• Visceral +/- bone metastases

• Progression / therapy resistant by conventional therapy

• Contraindications to Alpharadin (XOFIGO®)

→ Therapy with radioactively-labelled PSMA-ligand
PSMA PET/CT (PET/MRI)
Possible indications

1. Biochemical recurrence:
   - PET-CT guided biopsy and surgery
   - Radioterapy planning

2. Primary staging:
   - Guiding biopsy: path. PSA but negative „blind“ biopsy
   - Surgery planning in high-risk Pca patients

3. Staging:
   - Evaluation of therapeutic options (e.g. in case of visceral metastases)
   - Planning of radiolabelled therapy (Lu-PSMA therapy)
### Data from Aachen/Maastricht

<table>
<thead>
<tr>
<th></th>
<th>PSA &lt;1</th>
<th>PSA 1-2</th>
<th>PSA ≥2</th>
<th>PSA p-value</th>
<th>PSA &lt;6</th>
<th>PSA 6-12</th>
<th>PSA ≥12</th>
<th>PSA p-value</th>
<th>GSC &lt;8</th>
<th>GSC 8-10</th>
<th>GSC p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>27</td>
<td>19</td>
<td>121</td>
<td></td>
<td>26</td>
<td>16</td>
<td>12</td>
<td></td>
<td>61</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>No pathologic tracer accumulation</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Pathologic tracer accumulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No local tumour</td>
<td>23</td>
<td>16</td>
<td>74</td>
<td>0.014</td>
<td>22</td>
<td>13</td>
<td>6</td>
<td>0.057</td>
<td>48</td>
<td>32</td>
<td>0.037</td>
</tr>
<tr>
<td>Local tumour</td>
<td>4</td>
<td>3</td>
<td>47</td>
<td></td>
<td>4</td>
<td>3</td>
<td>6</td>
<td></td>
<td>13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No iliac LNM</td>
<td>17</td>
<td>12</td>
<td>67</td>
<td>0.67</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td>0.14</td>
<td>41</td>
<td>21</td>
<td>0.004</td>
</tr>
<tr>
<td>Iliac LNM</td>
<td>10</td>
<td>7</td>
<td>54</td>
<td></td>
<td>11</td>
<td>10</td>
<td>3</td>
<td></td>
<td>20</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>No inguinal LNM</td>
<td>27</td>
<td>19</td>
<td>118</td>
<td>0.56</td>
<td>26</td>
<td>16</td>
<td>12</td>
<td></td>
<td>61</td>
<td>49</td>
<td>0.057</td>
</tr>
<tr>
<td>Inguinal LNM</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No paraaortical LNM</td>
<td>23</td>
<td>13</td>
<td>79</td>
<td>0.13</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>0.028</td>
<td>44</td>
<td>32</td>
<td>0.23</td>
</tr>
<tr>
<td>Paraaortical LNM</td>
<td>4</td>
<td>6</td>
<td>42</td>
<td></td>
<td>13</td>
<td>4</td>
<td>1</td>
<td></td>
<td>17</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No supradiaphragmatic LNM</td>
<td>27</td>
<td>15</td>
<td>100</td>
<td>0.54</td>
<td>20</td>
<td>13</td>
<td>11</td>
<td>0.55</td>
<td>51</td>
<td>44</td>
<td>0.88</td>
</tr>
<tr>
<td>Supradiaphragmatic LNM</td>
<td>0</td>
<td>4</td>
<td>21</td>
<td></td>
<td>6</td>
<td>3</td>
<td>1</td>
<td></td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No bone metastases</td>
<td>23</td>
<td>16</td>
<td>77</td>
<td>0.030*</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>0.014*</td>
<td>47</td>
<td>38</td>
<td>0.63*</td>
</tr>
<tr>
<td>Solitary bone metastasis</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td></td>
<td>7</td>
<td>2</td>
<td>0</td>
<td></td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2-5 bone metastases</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;5 bone metastases</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td></td>
<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No organ metastases</td>
<td>26</td>
<td>18</td>
<td>108</td>
<td>0.43</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>0.026</td>
<td>56</td>
<td>48</td>
<td>0.92</td>
</tr>
<tr>
<td>Organ metastases</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td></td>
<td>6</td>
<td>0</td>
<td>0</td>
<td></td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

N=167

Verburg et al., EJNMMI 2016