Prostate-specific Membrane Antigen (PSMA) and PET

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Adana 05.04.2015
Prostate Cancer Incidence Worldwide

Turkey: 41/100 000 people
Prostate Cancer: Hybrid PET imaging

- High patient throughput
- established PET-technique
- workflow/reading straightforward

- high contrast in soft-tissue and bone
- combination anatomy, functional MR, molecular information
“Molecular targets” for hybrid PET-imaging in PCa

- GRPr-Antagonists ($^{68}$Ga, $^{64}$Cu)
- Aminoacids (FACBC, GE148)
- $^{11}$C/$^{18}$F-AcOH
- PSMA-antibodies ($^{89}$Zr-J591, $^{89}$Zr-7E11)
- PSMA-inhibitors ($^{68}$Ga-PSMA-HBED-CC, $^{68}$Ga-PSMA I&I-T, $^{18}$F-DCFBC)
- $^{11}$C/$^{18}$F-Choline
- $^{18}$F-hormones
- $^{18}$F-FDG
- Angiogenesis ($^{18}$F-Galacto-RGD, ...)

Department of Nuclear Medicine, Technische Universität München
Choline based radiotracers for prostate cancer

- Increased choline metabolism in prostate cancer
- Elevated phosphatidylcholine turnover in cell membrane
- Increased expression of cholin transporter and transport rate

courtesy: Krause B
### Choline based radiotracers in biochemical recurrence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tracer</th>
<th>Pop.</th>
<th>N</th>
<th>PSA range</th>
<th>Detection rate</th>
<th>PSAvel</th>
<th>PSAdbt</th>
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<tbody>
<tr>
<td>Castelluci 2009</td>
<td>11C-Choline</td>
<td>RP</td>
<td>190</td>
<td>4.2 (0.2-25.2)</td>
<td>38.9%</td>
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<tr>
<td>Giovacchini 2010</td>
<td>11C-Choline</td>
<td>RP</td>
<td>109</td>
<td>0.81 (0.22 – 16.8)</td>
<td>11%</td>
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<tr>
<td>Giovacchini 2010</td>
<td>11C-Choline</td>
<td>RP</td>
<td>358</td>
<td>3.77 (0.23 – 45.2)</td>
<td>45%</td>
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<td>Krause 2008</td>
<td>11C-Choline</td>
<td>RP/RT</td>
<td>63</td>
<td>5.9 (0.2 - .39)</td>
<td>56%</td>
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<tr>
<td>Soyka 2012</td>
<td>18F-Choline</td>
<td>RP/RT</td>
<td>123</td>
<td>3.3 (0.2-25.5)</td>
<td>79%</td>
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<tr>
<td>Graute 2011</td>
<td>18F-Choline</td>
<td>RP</td>
<td>82</td>
<td>4.4 (0.03-36)</td>
<td>62%</td>
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</table>

- Considerable advantage compared to morphological imaging
- Increasing detection rate dependent on PSA-level

Adopted from EUA guideline: Prostate cancer
Histopathology versus $[^{11}\text{C}]$Cholin PET/CT

**Conclusion:** “…PCa tissue could not be distinguished from benign pathologies in the prostate” Souvatzoglou et al, Clin Cancer Res 2011
$^{11}$C-Choline PET/MR in rec. PCa: accumulating evidence
$^{11}$C-Choline PET/MR in rec. PCa: accumulating evidence
Comparison of $^{11}$C-Choline PET/CT and PET/MR

- 39 patients with recurrent prostate cancer
- Single injection / dual imaging
- Local recurrence: significant higher detection rates
- Bone metastases: questionable advantageous
- Lymph node metastases: similar performance

<table>
<thead>
<tr>
<th></th>
<th>no. lesions</th>
<th>no. patients</th>
<th>mean rating</th>
<th>p</th>
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<tbody>
<tr>
<td>local recurrence</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PET/CT</td>
<td>12</td>
<td>8</td>
<td>1.485</td>
<td>0.028</td>
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<td>PET/MR</td>
<td>19</td>
<td>13</td>
<td>1.215</td>
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<td>lymph node metastases</td>
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<tr>
<td>PET/CT</td>
<td>52</td>
<td>9</td>
<td>1.180</td>
<td>0.251</td>
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<tr>
<td>PET/MR</td>
<td>50</td>
<td>9</td>
<td>1.337</td>
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<td>bone metastases</td>
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<tr>
<td>PET/CT</td>
<td>14</td>
<td>4</td>
<td>1.183</td>
<td>0.124</td>
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<tr>
<td>PET/MR</td>
<td>17</td>
<td>5</td>
<td>1.045</td>
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One patient presented with non-sclerotic, PET-negative bone metastases

- 71 y/o: slow PSA-increase from 0.07 ng/ml (nadir) to 0.31 ng/ml within 5 years after RRP

Eiber M et al, SNM 2013
PSMA

- Prostate-specific membran antigen
- [syn. Glutamate carboxypeptidase II (GCP-II)]
- cell surface protein with overexpression in prostate cancer (750 AS, 84 kDa)
- PSMA expression increases progressively in:
  - Higher grade tumors
  - Metastastic disease
  - Hormone-refractory Prostate cancer
  - also in tumor neovasculature
- promising target for prostate cancer specific imaging and therapy
- variety of tracers for PET/SPECT-imaging

PSMA-inhibitors

- **$^{18}$F-DCFBC**
  - Cho S et al, JNM 2012

- **$^{68}$Ga-PSMA HBED-CC**
  - Afshar-Oromieh A al., EJNMMI 2013

- **$^{68}$Ga-PSMA I&T**
  - TUM
**$^{68}$Ga-PSMA HBED-CC**

- "Heidelberg Compound"
- Glu-NH-CO-NH-Lys-(Ahx)-[$^{68}$Ga(HBED-CC)]
- preliminary studies: high detection rate\(^1\) and high lesion-to-background ratio\(^2\)

\(^1\) Afshar-Oromieh A et al. EJNMMI 2013
\(^2\) Afshar-Oromieh A et al. EJNMMI 2014
Example: local recurrence

81y patient, s/p prostatectomy (18 years ago), PSA-value 5.5 ng/ml

$^{11}$C-Cholin

$^{68}$Ga-PSMA
Example: single LN metastasis

72y patient, s/p prostatecomy 2000, s/p RTx 2006, PSA-value 2.8 ng/ml

- operative LN picking: LN metastasis
- drop of PSA-value to 0.07 ng/ml!
Examples: Local recurrence

46y patient; prostatectomy 8/11, radiotherapy 11/11, PSA 03/14 1.2 ng/ml

63y patient; prostatectomy 2003 pT2c, pN1, Gleason 7, radiotherapy 2009, PSA 02/14 0.9 ng/ml
\textbf{\textsuperscript{68}Ga-PSMA-PET for staging in mCRPC}

75j Patient, s/p RPE 2003, castration resistant, PSA-value 48 ng/ml

\begin{itemize}
  \item \textbf{skeletal scintigraphy}
  \item \textbf{\textsuperscript{68}Ga-PSMA-PET}
\end{itemize}
Recurrent prostate cancer: detection efficacy

- 332 patients: 256 PET/CT, 76 PET/MR using $^{68}$Ga-PSMA
- PSA: median 1.9 ng/ml (range: 0.2 – 45 ng/ml)
- in 85.2% (283/332) of patients at least 1 suspicious lesion

Eiber M et al, JNM 2015

Siemens Biograph mMR
First fully integrated whole body PET/MR scanner

Advantages:
- Multiparametric Imaging (DCE, DWI, perfusion)
- High soft tissue and bone marrow contrast
Workflow Issues – integrated PET/MR

- fully diagnostic vs. reasonable time frame
- dedicated regional MR vs. whole body coverage
- primary vs. recurrent PCa vs. biopsy targeting

Advantages high soft tissue contrast

- Local staging: Exact lesion definition (preop. planning)
- Pre-Biopsy
68Ga-PSMA PET/MR after primary negative biopsy

65y, 2x negative Bx (11/10, 09/11), cont. PSA-increase (17ng/ml at imaging)

⇒ Gleason 6 (3+3) at biopsy, single lesion (1.5 cm left side) on operation
The beauty of multiparametric imaging........
Advantages Multiparametric Imaging

58y Patient, PC, ED 2013, RPE 4/13, PSA 09/13 0,65 ng/ml

- PET: no pathological signal
- Perfusion: Hyperperfusion adjacent to vessel wall
Local recurrence: Comparison of PET/CT and PET/MR

- no statistical significant difference in detection rate between PET/CT and PET/MR (each \( p > 0.05 \))
- in PSA<1 ng/ml: increase in definite lesion detection from 32.0% to 42.1% for PET/MR vs. PET/CT
Local recurrence in $^{68}$Ga-PSMA PET/MR

74y/o, s/p prostatectomy 2005 pT3b, pN1, R0, PSA 0.74 ng/ml

66y/o, s/p prostatectomy 2001 pT2b, pN0, G2, R0, PSA 0.42 ng/ml
$^{68}$Ga-PSMA PET for preoperative LN staging

73j Patient, iPSA 120 ng/ml, Gleason 8

- pN+: AIC re (2/2+) AIE re (2/6+), Obt re (11/17+)
PSMA-PET negative primary tumor: LN metastases
73 y/o patient, newly diagnosed Gleason 8 PC, iPSA 24 ng/ml
PSMA-PET **negative** primary tumor: LN metastases

73 y/o patient, newly diagnosed Gleason 8 PC, iPSA 24 ng/ml

=> Histopathology: Gleason 8, pT3a, pN1 (3/24 in EIA field)
Challenges in $^{68}$Ga PSMA PET/MR

- Anatomical delineation of small LN often superior in CT
- Limited detection of lung nodules
- Attenuation correction (metal implants, e.g. hip prosthesis)
- Long examination time (60min) – Space for protocol optimisation
Conclusion

• recurrent PCa:
  – substantial improvements in detection rate by $^{68}$Ga-PSMA-ligand
  – treatment decisions (low PSA-values <-> advanced disease)
  – limited role of PET/MR (higher diagnostic certainty)

• primary PCa – role of PET/MR
  – „image guided“- targeted biopsy („future“ of prostate bx !)
  – multiparametric analysis of tumor biology (dominant intraprostatic lesion, active surveillance, …)
  – complementary information PET and MR ?

• However: prospective multicenter trials on performance still missing!
• Clinical benefit of better imaging yet unclear (disease free survival, OS)
**Acknowledgements**

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**Teşekkürler**