Prostate Cancer: new Diagnostic and Therapeutic Approaches with Molecular Imaging

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Topics

1. PET imaging for prostate cancer: Tracers

2. Choline-PET/CT imaging protocols & indications

3. Choline-PET/MR – outlook

4. Prostate cancer therapy
1. PET imaging for prostate cancer: Tracers
Alphabet-soup:

- $^{11}$C-Acetate
- $^{11}$C-Choline
- $^{18}$F-FCH
- $^{18}$F-FECH
- $^{18}$F-FDGT
- $^{18}$F-FB-$^{3}$Lys$^{3}$BBN
- $^{18}$F-Fluoride
- $^{18}$F-DCFPyL
- $^{64}$Cu-labeled mAb 3/A12
- $^{68}$Ga-PSMA
Targets:

Metabolism:
- $^{18}\text{F-FDG}$
- $^{11}\text{C-Acetate}$

Bone reaction:
- $^{18}\text{F-Fluoride}$

Androgen receptor:
- $^{18}\text{F-FDHT}$

GRP receptor:
- $^{18}\text{F-FB-[Lys}^3]\text{BBN}$

Membrane proliferation:
- $^{11}\text{C-Cholin}$
- $^{18}\text{F-FECH}$
- $^{18}\text{F-FCH}$

PSMA targeting:
- $^{64}\text{Cu-labeled mAb 3/A12}$
- $^{89}\text{Zr-J591}$
- $^{111}\text{IN-7E11}$
- $^{18}\text{F-DCFPyL}$
- $^{68}\text{Ga-PSMA}$
Overview:

PET Molecular Imaging of Prostate Cancer

Cell Metabolism
- Glucose ¹⁸F-FDG
- Choline / Acetate ¹⁸F-FCH
- Amino Acids
  - Leucine ¹⁸F-FACBC
  - Methionine ¹¹C-Methionine
  - Tryptophan ¹⁸F-FTryptophan
- Nucleosides ¹⁸F-FLT
- Androgen Receptor ¹⁸F-FDHT

Receptors and Membrane Proteins
- GRP-Receptor ⁶⁸Ga-Bombesin
- PSMA (Prostate Specific Membrane Antigen)

Bone Matrix ¹⁸F-NaF

Antibodies
- Intra-Cellular ¹¹¹In-7E11
- Extra-Cellular ⁸⁹Zr, ¹⁷⁷Lu-J591

Minibodies ⁸⁹Zr-DF-IAB2M

Small molecules ⁶⁸Ga-PSMA
Cell Metabolism: FDG: is limited!

Acetate participates in cytoplasmic lipid synthesis, which is believed to be increased in tumors.

Prostate cells undergo metabolic transformation from citrate producing cells to citrate-oxidizing malignant cells (1)

This leads to an increased acetate turnover in malignant cells (1)

Similar sensitivity to Cholin (2)

1) Costello et al. Urol 1997
2) Buchegger F. et al. EJNMMI, 2014 (41:68-78)
Amino acids: $^{18}$F-FACBC (Leucine)

- Leucine is essential for the mTOR pathway regulating cell growth (controlling mRNA translation)
- Membrane transporters of L-leucine are overexpressed in prostate cancer.

(A) MRI axial T2 weighted image showing indeterimined 5 mm lymphnode within the mesorectal fascie.  (B) FACBC PET/CT confirmed the suspicion for lymphnode metastasis with very high $^{18}$F-FACBC uptake.

(Images Courtesy: Dr. Frode Willoch, MD PhD, Aleris, Norway)
18\textsuperscript{F}-Fluoride – a better bone scan?

+ Very high sensitivity for bone metastasis
- Expensive & radiation (5-8 mSv)
- No lymphnode or local recurrence detection
### 18F-Fluoride – a better bone scan: YES

- **A)** Planar bone scan negative
- **C)** Degenerative change (Osteophyt)
- **B&D)** solitary bone metastasis

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>BS</td>
<td>39</td>
<td>79</td>
<td>52</td>
<td>64</td>
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<tr>
<td>SPECT</td>
<td>71</td>
<td>85</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>18F PET</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</table>

1) Even-Sapir et al. JNM 2006
Metastasis in the left acetabulum is Fluoride and Choline positive.

Degenerative lesion in the pubic bone only pos on Fluoride scan.

Metastasis in the thoracic spine only Choline positive.

1) Beheshti et al. EJNM 2008 35:1766-1774
But: $^{18}$F-Fluoride vs Choline

- Initial not sclerotic but Choline positive metastasis
- Under hormone therapy no FCH uptake is visible
- However an increase in bone density

1) Beheshti et al. EJNM 2008 35:1766-1774
\( ^{18} \text{F-FDHT} \)

- 16β-\(^{18}\text{F-fluoro-5 – dihydrotestosterone targeting the androgen receptor} \)
- Sensitivity of 78% (1)
- Usefull for multiparametric analysis (2)

1) Larson S et al. JNM 2004
2) Fox JJ et al. JNM 2011
Transmembranous protein with high specificity for prostate tissue

Intra- or extracellular domains targeted

Several antibodies or small antibodies have been tested

- High specificity but delayed washout for AB or small AB

- **small molecule inhibitors of the enzymatic domain: Ga-PSMA**

Improved biodistribution, faster BP clearance, less radiation
70 years old prostate cancer patient after def. RT 3 years ago. Now increase in PSA.

A) CT negative
B) FDG negative
C) Zr-89 J591 shows increased activity in T11 and L3 (black arrow)

Apart from the faint osseous reaction in L1 (arrow head) lesions have no CT correlation. No evidence of lymph node lesions or local residue.

Images Courtesy: Dr. H. Vargas, MSKCC, NY, USA
77 years old PCA, ED 01/2013, PSA to 4.14 ng/ml.
A) Ga-68 PSMA MIP image. With bone metastases in Th3, L1 and proximal femur (arrows). Apart from the faint osteoblastic reaction in L1 (arrow head) lesions have no CT correlation. No evidence of lymph node lesions or local residue.

Images Courtesy: Dr. Vikas Prasad, Charité, Berlin, Germany
PSMA – Antibody Tracers

PET images in the same patient:
(a) MIP $^{68}$Ga-labelled PSMA
(b) MIP $^{18}$Ffluoroethylcholine

The scan with the PSMA ligand shows significantly more lesions than the fluoroethylcholine
Gastrin-Releasing Peptide Receptor

- $^{18}$F-Bombesin – high uptake in Xenografts

In house experience:

Bombesin

Cholin
Gastrin-Releasing Peptide Receptor

- $^{68}$Ga-Bombesin – however:

Region based in 14 patients:
Sens / Spec / Acc of 89% / 81% / 83%


Nuclear Medicine, University Hospital Zurich, Switzerland
II. Choline-PET/CT imaging protocols & indications
# Choline Tracers

<table>
<thead>
<tr>
<th></th>
<th>$^{11}$C-choline</th>
<th>$^{18}$F-Fluoromethylcholine</th>
<th>$^{18}$F-Fluoroethylcholine</th>
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<tbody>
<tr>
<td>$^{11}$C-labeled</td>
<td>$^{18}$F-labeled</td>
<td>$^{18}$F-labeled</td>
<td></td>
</tr>
<tr>
<td>short half-life time</td>
<td>FCH</td>
<td>FECH</td>
<td></td>
</tr>
<tr>
<td>difficult to do dual-phase studies</td>
<td>Less lipophilic than FECH</td>
<td>More lipophilic than FCH</td>
<td></td>
</tr>
<tr>
<td>Little urinary secretion</td>
<td>probably slightly better tumor to background ratios compared to FECH</td>
<td>probably slightly lower tumor to background ratios compared to FCH</td>
<td></td>
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</tbody>
</table>

![Chemical structures](image1.png)
Fluorocholine PET: Mechanism of uptake

- **18F** Fluorocholine
  - Upregulated in malignant tumors
- **18F** Phosphorylcholine
- **18F** Phosphatidylcholine

Linked with fatty acids – part of the cell membrane
Fluorocholine (FCH)-PET vs FDG-PET
FCH-PET/CT Imaging Protocol

- Patient positioning on the PET/CT scanner
- CT acquisition
- i.v.-injection of FCH (aprox. 200 MBq)
- PET-imaging
  - wait for 3 minutes after injection
  - always start at the pelvic floor
  - 1.5 – 3 minutes per cradle position
  - early and late phase imaging recommended
FCH: Typical Time Activity Curves

Nuclear Medicine, University Hospital Zurich, Switzerland
Imaging goals

- Initial staging
  - (Primary tumor?)
  - Lymph node metastasis?
  - Distant metastasis?

- Recurrent disease
  - Local recurrence?
  - Lymph node metastasis?
  - Distant metastasis?
19 patients:
- 10 newly diagnosed PC
- 9 suspected recurrence

Results: Differentiation of benign hyperplasia from PC is not possible. In recurrent prostate cancer, FCH PET/CT promising imaging modality for local recurrence and lymph node metastases.
Tumor related Fluorocholine Uptake

Schmid DT et al; Radiology 2005.
FCH: Benign Prostate Hyperplasia

10 patients:
1 FCH = extent of tumor
9 FCH = regions with BPH

* Schmid DT et al; Radiology 2005.
Staging: 59y, GS 9, (PSA 24): high risk

$^{18}$F-Fluorocholine-PET/CT  $^{99m}$Tc-DPD
Staging: 63y, cT3, (PSA 20): high risk

Histology:

Cytokeratin stain
FCH-PET/CT Indications: PC Recurrence

- Biochemical recurrence with a PSA > 2.0 ng/ml or with a high PSA velocity (PSAdt < 7.2 months)
  - Local recurrence only?
  - Lymph node metastases?

- PSA elevation during anti-hormonal treatment
  - Documentation and localization of tumor progression
FCH-PET/CT: biochemical PC Recurrence

Biochemical recurrence detection correlates well with the PSA values:

N = 2124 patients

N = 63 patients

Giampiero et al, EJNM 2010

Krause et al, EJNM 2008
FCH-PET/CT: biochemical PC Recurrence

- But also PSA velocity has an impact on the detection rate of PC recurrence:

  - PSA\(_{dt}\)
  - Cut off: 7.2 m

![Box plot showing the distributions of PSA\(_{dt}\) values in the two groups of PET-negative (n=73, left) patients and PET-positive (n=29, right) patients.](image1)

![ROC analysis of PSA\(_{dt}\) values in 102 patients; the optimal cutoff point was 7.25 months, AUC 0.85, 95% CI 0.77–0.91, sensitivity=93%, specificity=74%, PPV=60%, NPV=96%.](image2)

N = 102 patients, PSA < 1.5

Castellucci et al, EJNM 2010
FCH-PET/CT: recurrence (PSA 13,1)

Initial tumor stage: pT3a cN0 cM0, Gleason 6
Clinical impact of $^{18}$F-choline PET/CT in patients with recurrent prostate cancer

- 156 questionnaires answered after Choline PET/CT in recurrent PC:

**Conclusion:** CH-PET/CT has an important impact on the therapeutic strategy in patients with rPCA and can help to determine an appropriate treatment.

**Table 2** Treatments with CH-PET/CT and hypothetical treatments without CH-PET/CT as indicated by the referring physicians

<table>
<thead>
<tr>
<th>Therapy with CH-PET/CT</th>
<th>Watchful waiting (no therapy)</th>
<th>Antihormonal treatment</th>
<th>Radiation therapy</th>
<th>Surgery</th>
<th>High-intensity focused ultrasound</th>
<th>Chemotherapy</th>
<th>Antihormonal and radiation therapy</th>
<th>Surgery and radiation therapy</th>
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</thead>
<tbody>
<tr>
<td>Therapy with CH-PET/CT</td>
<td>19</td>
<td>37</td>
<td>59</td>
<td>11</td>
<td>6</td>
<td>1</td>
<td>22</td>
<td>1</td>
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<tr>
<td>Hypothetical therapy</td>
<td>22</td>
<td>54</td>
<td>60</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>14</td>
<td>0</td>
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</tbody>
</table>

Conclusion: Our results strengthen the current evidence of the usefulness of PET and PET/CT using 11C-choline or 18F-FCH as tracers in PCa work-up, whereby the diagnostic evidence is stronger in restaging than in staging settings. In general, proper patient selection, by considering predictive clinical parameters like PSA level, PSA doubling time, and initial tumor stage, is the key to avoiding FN results up front. The current evidence, although promising, has crucial limitations in terms of its applicability in common clinical scenarios.
III. Choline-PET/MR outlook
FCH-PET/MR Imaging Protocol

- Whole body MRI:
  - WB Dixon T1: dual-echo gradient echo pulse sequences decomposed into water-only and fat-only contrasts – for AC
  - Coronal T2 non fs
  - Optional diffusion weighted images (DWI)

- Pelvic MRI:
  - T2 fast spin echo sequences: in 3 planes with a small FOV
  - DWI and/or DCE / spectroscopy (not routinely)
FCH-PET/MR Imaging:

WB MR (15 min)  PET (21 min)  PET/MR image fusion
7 men with untreated Primary CAP
25 men with PSA Relapse after curative therapy

WB MRI: Sensitivity 78.4%, Specificity 94.1%
C-11 Ch: Sensitivity 96.6%, Specificity 76.5%

Complementary role of MRI and C-11 Choline PET-CT

Eschmann SM et al. Nuklearmedizin 2007
FCH-PET/MR: BPH versus tumor

Biopsy: Prostate Ca Gleason 9 (5+4)

BPH – nodules
Information about the exact location of FCH activity (peripheral vs central / transitional zone) can increase the specificity of FCH PET from 73 % to 92%

AUC for MRI(T2)/FCH > than multiparametric MRI

Perrot et al. EJNMMI 2014; 41:1744-1755
FCH/ADC: for T-staging?

Park et al. JNM 2012; 53:546-551
Parametric PET/MRI using $P_{\text{CHOL/ADC}}$ improves lesion-to-background contrast (TBRs) of Gleason $\geq 3 + 4$ disease, compared with $^{11}$C-choline PET/CT or diffusion-weighted MRI.

Park et al. JNM 2012; 53:546-551
Staging: 59y, GS 9, (PSA 24): high risk
Accurate local T-staging with PET/MRI

- Choline information might could replace DWI or DCE for local staging but this will need further investigation.
Staging Prostate Cancer: PET/CT-MRI

Pathology: pT3b, pN0(0/12)
One stop shop: Local tumor extent with N & M staging

- The additional MRI has to be performed as a dedicated MRI, high resolution T2 (pelvis), DWI and DCE.

- Pelvic MRI might increase specificity of Choline PET

- Choline/ADC might separate low risk from Gleason 7 disease

- Promising one step tool for patients with high risk prostate cancer:
  - Gleason score > 8 / PSA over 20 / extracapsular extension
IV. Prostate cancer therapy
Alpharadin ($^{223}$Radium-Chloride)

- Is now commercially available (Xofigo®)

Alpha-particles induce double-strand DNA breaks in adjacent tumour cells
  - Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue

Alpharadin (\(^{223}\)Radium-Chloride)

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

**Graph:**
- **Overall Survival**
- **Hazard ratio, 0.70 (95% CI, 0.58–0.83)**
- **P<0.001**
- **Radium-223**
  - Median overall survival: 14.9 mo
- **Placebo**
  - Median overall survival: 11.3 mo

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## Alpharadin (\(^{223}\text{Radium-Chloride}\))

### Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

<table>
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<tr>
<th>Adverse Event</th>
<th>Radium-223 (N = 600)</th>
<th>Placebo (N = 301)</th>
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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
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<tr>
<td>Hematologic</td>
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</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>9 (2)</td>
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<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>9 (2)</td>
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<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18)</td>
<td>10 (2)</td>
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<tr>
<td>Asthenia</td>
<td>35 (6)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>154 (26)</td>
<td>21 (4)</td>
</tr>
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</table>
Thank you!