Molecular Imaging in Prostate Cancer

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Introduction

3 different stages of the disease

- Localized prostate cancer
- Recurrent/progression
- Castrate-resistant disease

Local treatment with curative intent
Introduction

3 different stages of the disease

- Localized prostate cancer
- Recurrent/castrate-sensitive disease
- Castrate-resistant disease
- Advanced systemic therapy

Low PSA levels
Biochemical failure / relapse

• **Definition BCR:**
  - Two consecutive increases of PSA > 0.2 ng/ml

• **Staging:**
  * Conventional imaging studies (BS, CT)
    - Not sensitive **enough** for low PSA levels
    - Positive findings in <10%
  - Only recommended if:
    • PSA > 10 ng/ml
    • PSA_{dt} < 6 months.

Beresford et al. Clin Oncol. 2010
• **Treatment:**
  - Salvage Radiotherapy after RP
    • If we treat with PSA<0.5ng/ml, 60-70% patients will respond with PFS at 5y of 80%.
    • But treatment failure (PSA keep increasing) in about 30% (target failed!)

Need better staging

Low PSA levels

Local OligoM1 MultiM1

?  Define therapeutic strategy

EAU Guidelines
Imaging PCa

• Coventional imaging
  – Ultrasound
  – CT
  – Bone scintigraphy

  \{ \text{Limitations} \}
  \begin{itemize}
    \item Not sensitive enough for low PSA levels
    \item Positive findings in \textless 10\%
  \end{itemize}

• PET/CT? (molecular targets)
  – FDG
  – Fluoride
  – Choline
  – Acetate
  – PSMA
  – FDHT
  – …
Which tracer??
Molecular imaging

Osteotropic

Bone

- $^{99m}$Tc-HDP
- $^{18}$F-Fluoride

Oncotropic

Tumor cells

- $^{18}$F-Choline
- $^{18}$F-FACBC
- $^{68}$Ga-PSMA
Bone M+: $^{99m}\text{Tc}$ vs $^{18}\text{F}$-Fluoride

- Better spatial resolution
- Same limitations

*Only bone lesions
*Bone healing persistent activity (No response assessment)
*Progression based on (PCWG2) 2+2

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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</thead>
<tbody>
<tr>
<td>Planar BS</td>
<td>57 (35)</td>
<td>57 (95)</td>
<td>59 (89)</td>
<td>55 (44)</td>
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<tr>
<td>Planar + SPECT†</td>
<td>78 (39)</td>
<td>67 (86)</td>
<td>72 (75)</td>
<td>74 (31)</td>
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<tr>
<td>$^{18}\text{F}$-Fluoride PET</td>
<td>100 (48)</td>
<td>62 (95)</td>
<td>74 (92)</td>
<td>100 (63)</td>
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<td>$^{18}\text{F}$-Fluoride PET/CT</td>
<td>100 (87)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (87)</td>
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</table>

Even-Sapir et al JNM 2006
Molecular imaging

**Osteotropic**
- Bone
- $^{99m}$Tc-HDP
- $^{18}$F-Fluoride

**Oncotropic**
- Tumor cells
- $^{18}$F-FDG
- $^{18}$F-Choline
- $^{68}$Ga-PSMA
$^{18}$F-FDG PET/CT
Biochemical recurrence

- FDG: only 8.1% detection rate at PSA<2ng/ml
GLUT1 expression:

- **lower** in the well-differentiated; hormone-sensitive LNCaP cell line.
- **higher** in poorly differentiated; hormone-resistant cell lines DU145 and PC3

GLUT 1 expression increases with progression of malignancy grade.

Prognostic value to be explored (like NET, HCC, ...)

Effert, et al. Anticancer research, 2004
Prognostic value
SUVmax correlated with survival

Low SUVmax <6
Sx 32.8 m

High SUVmax >6
Sx 14.4 m

mCRPC response assessment

Meirelles, et al. 2010
Teaching Points:

*FDG PET for diagnosis / staging / recurrence detection is NOT indicated

*FDG PET/CT may be most useful in:
- detection of aggressive disease (prognostic value)
- evaluation of treatment response in mCRPC
Choline PET
Biodistribution Choline

$^{11}$C-Choline

$^{18}$F-Choline
Detection PCa recurrence

PET/CT with $^{11}$C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Detection rate</th>
<th>SE</th>
<th>Screen detected</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Detection rate IV, Random, 95% CI</th>
<th>Detection rate IV, Random, 95% CI</th>
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<tr>
<td>Castellucci 2011</td>
<td>0.28</td>
<td>0.045</td>
<td>29</td>
<td>102</td>
<td>5.7%</td>
<td>0.28 [0.19, 0.37]</td>
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<tr>
<td>Castellucci 2009</td>
<td>0.39</td>
<td>0.035</td>
<td>74</td>
<td>190</td>
<td>5.8%</td>
<td>0.39 [0.32, 0.46]</td>
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<tr>
<td>Giovacchini 2010a</td>
<td>0.44</td>
<td>0.038</td>
<td>75</td>
<td>170</td>
<td>5.8%</td>
<td>0.44 [0.37, 0.51]</td>
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<tr>
<td>Giovacchini 2010b</td>
<td>0.44</td>
<td>0.026</td>
<td>159</td>
<td>358</td>
<td>5.0%</td>
<td>0.44 [0.39, 0.49]</td>
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<td>Namede 2013</td>
<td>0.46</td>
<td>0.059</td>
<td>33</td>
<td>71</td>
<td>5.5%</td>
<td>0.46 [0.34, 0.56]</td>
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<tr>
<td>Picchio 2003</td>
<td>0.47</td>
<td>0.05</td>
<td>47</td>
<td>100</td>
<td>5.6%</td>
<td>0.47 [0.37, 0.57]</td>
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<tr>
<td>De Jong 2003</td>
<td>0.55</td>
<td>0.106</td>
<td>12</td>
<td>22</td>
<td>4.6%</td>
<td>0.55 [0.34, 0.76]</td>
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<tr>
<td>Krause 2008</td>
<td>0.56</td>
<td>0.063</td>
<td>35</td>
<td>63</td>
<td>5.4%</td>
<td>0.56 [0.44, 0.68]</td>
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<td>Richter 2010</td>
<td>0.59</td>
<td>0.058</td>
<td>43</td>
<td>73</td>
<td>5.5%</td>
<td>0.59 [0.48, 0.70]</td>
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<tr>
<td>Ceci 2013</td>
<td>0.66</td>
<td>0.038</td>
<td>104</td>
<td>157</td>
<td>5.8%</td>
<td>0.66 [0.59, 0.73]</td>
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<tr>
<td>Rybalov 2013</td>
<td>0.67</td>
<td>0.035</td>
<td>132</td>
<td>185</td>
<td>5.6%</td>
<td>0.67 [0.60, 0.74]</td>
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<tr>
<td>Ceci 2014a</td>
<td>0.73</td>
<td>0.036</td>
<td>109</td>
<td>150</td>
<td>5.6%</td>
<td>0.73 [0.66, 0.80]</td>
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<td>Mitchell 2011</td>
<td>0.75</td>
<td>0.033</td>
<td>132</td>
<td>176</td>
<td>5.6%</td>
<td>0.75 [0.69, 0.81]</td>
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<tr>
<td>Yoshida 2005</td>
<td>0.75</td>
<td>0.129</td>
<td>6</td>
<td>8</td>
<td>4.1%</td>
<td>0.75 [0.50, 1.00]</td>
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<td>Breekwesma 2010</td>
<td>0.81</td>
<td>0.046</td>
<td>57</td>
<td>70</td>
<td>5.7%</td>
<td>0.81 [0.72, 0.90]</td>
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<tr>
<td>Rinnab 2007</td>
<td>0.88</td>
<td>0.046</td>
<td>44</td>
<td>50</td>
<td>5.7%</td>
<td>0.88 [0.79, 0.97]</td>
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<tr>
<td>Rinnab 2009</td>
<td>0.88</td>
<td>0.051</td>
<td>36</td>
<td>41</td>
<td>5.6%</td>
<td>0.88 [0.78, 0.98]</td>
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<tr>
<td>Ceci 2014b</td>
<td>0.88</td>
<td>0.028</td>
<td>123</td>
<td>140</td>
<td>5.9%</td>
<td>0.88 [0.83, 0.93]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1242</strong></td>
<td><strong>2126</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.62 [0.53, 0.71]</strong></td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.04, Ch² = 378.86, df = 17 (P = 0.00001), P = 96%
Test for overall effect: Z = 13.22 (P < 0.00001)

*Fig. 2 Detection rates for any relapse

*Heterogeneity of patient population in terms of PSA levels

Fanti et al. EJNM 2016
Detection PCa recurrence

The graph shows PET detection rates for different PSA doubling time (PSAdt) intervals. The y-axis represents the PET detection rate (%) and the x-axis represents PSAdt in months (mo).

- PSA dt ≤ 2: High PET detection rate
- 2 < PSA dt ≤ 4: Moderate PET detection rate
- 4 < PSA dt ≤ 6: Lower PET detection rate
- PSA dt > 6: Low PET detection rate

Castelluci JNM 2011
* Indication for a Choline PET in biochemical recurrence
  • PSA > 1.5 ng/ml
  • PSA\(_{dt}\) < 6 months

* Similar results for \(^{11}\text{C}\)-Chol and \(^{18}\text{F}\)-Chol
Prostate-specific membrane antigen (PSMA)
Prostate-Specific Membrane Antigen (PSMA)

- Prostate-specific membrane antigen (PSMA) is a cell surface glycoprotein with a large extracellular domain.
  - significantly increased expression in prostate cancer cells.

- PSMA function not clear

- Upon ligand binding, PSMA is internalized via endocytosis.

- NOT only in Prostate Cancer:
  - PSMA overexpression in endothelial cells of tumor neovasculature of non-prostatic solid tumors and benign lesions:
    - colon, gastric, breast, thyroid, ovary; Paget Disease.
    - probably stimulated by secreted angiogenic factors
Prostate-Specific Membrane Antigen (PSMA)

- Development of small molecules of **PSMA ligands or inhibitors** binding to active site of PSMA
  - High specificity for receptors
  - higher permeability in solid tumors
  - improve pharmacokinetics in normal tissues
  - enhanced target to background ratios
  - Easy to produce, easy labelling
  - No host-inmune response

- **PSMA tracers (why so many?)**
  - Different inhibitors used
    - N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4
    - Lysine-glutamate **urea based**
    - EuK-Sub-KFF
  - can be labelled with different isotopes
    - $^{68}\text{Ga}$, $^{18}\text{F}$, $^{99m}\text{Tc}$, $^{123/124}\text{I}$, $^{111}\text{In}$ (gamma = imaging)
    - $^{177}\text{Lu}$, $^{131}\text{I}$, $^{90}\text{Y}$ (beta=therapy)
  - using different chelators
    - DOTA, HBED-CC
Most widely used agent is $^{68}$Ga-PSMA-HBED-CC

- **PSMA ligand**
  Dimer Urea-based ligand: Glu-NH-CO-NH-Lys(Ahx)

+ **Chelator**
  HBED-CC

+ **Isotope**
  $^{68}$Ga

Eder et al, Bioc Chem, 2012
$^{68}$Ge/$^{68}$Ga Generator

$^{68}$Ga-PSMA synthesis: IN-HOUSE
Cold kit based PSMA DKFZ-11

Gallium-68 Generator + Lyophilized PSMA-ligand Cold kit = $^{68}$Ga-PSMA-ligand PET/CT
• Normal biodistribution

– Intense uptake in
  • Kidneys
  • Salivary glands

– Moderate uptake
  • Lacrimal glands
  • Liver
  • Spleen
  • Small and large bowel
• **PSMA vs Choline PET**
  
  – Better detection rate compared to $^{18}$F-Choline PET
    • 86% vs 70%

  – More lesions detected with PSA<2ng/ml
    • 68% vs 43%

  – Higher SUVmax (in 80% lesions)

  – Higher tumour to background (in 95% lesions)
    • LN metastases (even infracentimetric LN)
    • Bone marrow and Liver metastases

Ashfar-Oromieh et al, EJNM, September 2013
$^{68}$Ga-PSMA

- PSMA vs Choline PET

Ashfar-Oromieh et al, EJNM, Sept 2013
Recurrence detection

N = 248

Eiber et al, JNM, 2015
Clinical impact of PSMA-PET

- 38 patients after curative treatment
  - mean PSA 1.74ng/ml
  - Considered for targeted treatment
  - PSMA & Choline PET

- In biochemical recurrence with low PSA
- PSMA PET shows
  - Higher detection rate
  - Higher clinical management impact
    - 63% PSMA vs 28% Choline

Morigi et al, JNM, 2015
68Ga-PSMA PET/CT in PCa

• Take home messages

Can results change your attitude?

– Indication for Recurrence detection
  • Increasing PSA > 0.5ng/ml
  • Fast kinetics (PSAvel > 1ng/ml/y)

– Initial staging
  • High Risk patients (to exclude M1)
  • Guided biopsies?

– Response assessment
  • Not Validated
Clinical impact of PSMA-PET

- pT2bN0, Gleason 7
- Biochemical relapse (PSA 1,4)
  - after RP + ePLND and SRT
- Negative imaging:
  - BS
  - WB DW-MRI
  - Choline-PET
Clinical impact of PSMA-PET

• **What to do?**
  – Postpone HT
  – Targetted RT vs Surgery
    • Millimetric node
    • Patient with previous PLND
  – Future (guided surgery?)
    • $^{99m}$Tc-PSMA, $^{111}$In-PSMA

Vallabhajosula et al, JNM, 2014
Maurer et al, Eur Urol, 2015
OligoM1 treatment in PCa

- SBRT can delay 28mo ADT (>2y)

N=119

Median DPFS 24mo

OligoM1 patients based on Choline-PET

Better results with Ga-PSMA??

**Case example:**

- Radical Prostatectomy 2011 (Gleason 6, pT2cNxR0)
- BCR in 2014 → salvage RT prostatic bed (66Gy) but no PSA decline
- $^{68}$Ga-PSMA-11: pre-sacral LN → SBRT (30Gy)

**OligoM1 treatment in PCa**

**Fig 1: $^{68}$Ga-PSMA PET/CT Axial**

**Fig 2: T2 MRI Axial**

>1.5y of Biochemical Free Survival
PSMA outperformed BS:
- detection of more bone lesions in initial staging and BCR.
- PSMA: Se 99%, Sp 100%
- BS: Se 62%, Sp 97%

"These are probably tumour cells seeding in the bone marrow in an early metastatic stage, with no or very little osteoblastic reaction of the surrounding tissue."

Pyka et al. EJNM 2016
• Of a total of 235 bone lesions
  • 32 (13%) osteolytic
  • 64 (27%) osteoblastic
  • 163 (69%) showed no abnormality and were considered as bone marrow lesions.
Bone Scintigraphy

Ra$^{223}$ Response Assessment

PSA 1.29 ng/ml
AP 21 U/L

PSA 3.97 ng/ml
AP 16.5 U/L

PSA 8.5 ng/ml
AP 15.2 U/L
Ra\textsuperscript{223} Response Assessment

CT scan

SD? RECIST non-applicable No new lesions
**PSMA-PET**

**Ra$^{223}$ Response Assessment**

- **PSA 1,29 ng/ml**
  AP 21 U/L

- **PSA 3,97 ng/ml**
  AP 16,5 U/L

- **PSA 8,5 ng/ml**
  AP 15,2 U/L
Therapeutic strategy selection

M1 → M0

mCRPC with bone M1
- Treated with ADT + Xgeva
- PSA progression (PSAdt 3mo) = mCRPC

- Treatment?
  - Abiraterone/Enzalutamide
  - Radium-223 (Xofigo)
  - Other?

Bone Scan at PSA progression

68Ga-PSMA to exclude visceral M1
Therapeutic strategy selection

PSMA

No uptake in Osteoblastic lesions (lesion under response to ADT)

Bone Scan at PSA progression
Therapeutic strategy selection

PSMA

No uptake in Osteoblastic lesions
(lesion under response to ADT)
mCRPC with bone M1 (Bone scan)

- Treated with ADT + Xgeva
- PSA progression

- Treatment?
  - Abiraterone/Enzalutamide
  - Radium-223 (Xofigo)
  - Other?

Prostate RT

Save the bullet!
Bone lesions still not resistant to ADT
Therapeutic strategy selection

M0 $\rightarrow$ M1

CRPC (increased PSA under ADT)

Negative CT and BS (M0)

Multiple bone marrow metastases
+ Multiple juxta-centimetric lymph nodes

No possible inclusion to clinical trials. Which treatment?

$^{68}$Ga-PSMA
CONCLUSIONS

• Oncotropic PET tracers like $^{68}$Ga-PSMA can help in selecting the right therapeutic strategy for a single patient (tailored treatment):
  
  • Early detection metastatic disease
  • Exclude visceral metastases (Xofigo)
  • Detect progressive / active lesions
  • Assess PSMA expression before Radio Ligand Therapy (RLT) with Lu-PSMA / Ac-PSMA.


**177Lu-PSMA RLT**

- **177Lu-labelled PSMA ligand (177Lu-PSMA DKFZ-617)**
  - DOTA derivative of the Glu-urea-Lys motif.
  - Chelator improves tumour accumulation while reducing kidney uptake.

- mCRPC
- 7,4GBq 177Lu-DKFZ-617
- Complete PSMA response
- PSA decrease
  - 38ng/ml to 4,6ng/ml

Kratochwil et al, EJNM, 2015
Thank you