PET/CT imaging and RIT of prostate cancer

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Rigshospitalet, Copenhagen
Denmark
Prostate cancer

- Prostate cancer is the most common malignancy in men

- Imaging modalities are important
  - Staging and restaging
  - Guiding treatment
  - Evaluation of therapy response

- No effective treatment of advanced prostate cancer
  - New treatment strategies are urgently needed
PET/CT and prostate cancer
$^{18}$F-FDG & prostate cancer

- Not useful for diagnosis and primary staging
- Low metabolism in prostate cancer cells – low FDG uptake
- However, $^{18}$F-FDG may be useful in advanced prostate cancer
## TABLE I: Clinical Trials of $^{18}$F-FDG PET in Prostate Cancer

<table>
<thead>
<tr>
<th>Tracer</th>
<th>No. of Patients</th>
<th>Objective</th>
<th>Results (%)</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG</td>
<td>48</td>
<td>Staging</td>
<td>Sensitivity, 81</td>
<td>1996</td>
<td>Effert et al. [36]</td>
</tr>
<tr>
<td>FDG</td>
<td>14</td>
<td>Staging</td>
<td>Sensitivity, 17</td>
<td>1996</td>
<td>Haseman et al. [37]</td>
</tr>
<tr>
<td>FDG</td>
<td>13</td>
<td>Staging</td>
<td>NA</td>
<td>1996</td>
<td>Yeh et al. [38]</td>
</tr>
<tr>
<td>FDG</td>
<td>34</td>
<td>Staging</td>
<td>Sensitivity, 65</td>
<td>1996</td>
<td>Shreve et al. [39]</td>
</tr>
<tr>
<td>FDG</td>
<td>13</td>
<td>Restaging</td>
<td>NA</td>
<td>1999</td>
<td>Hofer et al. [40]</td>
</tr>
<tr>
<td>FDG</td>
<td>24</td>
<td>Staging</td>
<td>Sensitivity, 4</td>
<td>2001</td>
<td>Liu et al. [41]</td>
</tr>
<tr>
<td>FDG</td>
<td>10</td>
<td>Treatment follow-up</td>
<td>Sensitivity, 80</td>
<td>2001</td>
<td>Oyama et al. [42]</td>
</tr>
<tr>
<td>FDG</td>
<td>17</td>
<td>Staging</td>
<td>NA</td>
<td>2002</td>
<td>Morris et al. [43]</td>
</tr>
<tr>
<td>FDG</td>
<td>24</td>
<td>Staging</td>
<td>Sensitivity, 75; specificity, 100</td>
<td>2003</td>
<td>Chang et al. [44]</td>
</tr>
<tr>
<td>FDG</td>
<td>91</td>
<td>Restaging</td>
<td>Sensitivity, 31</td>
<td>2005</td>
<td>Schoder et al. [45]</td>
</tr>
<tr>
<td>$^{11}$C-acetate, FDG</td>
<td>22 and 18</td>
<td>Staging</td>
<td>Sensitivity, 100 and 83</td>
<td>2002</td>
<td>Oyama et al. [46]</td>
</tr>
<tr>
<td>$^{11}$C-acetate, FDG</td>
<td>46</td>
<td>Restaging</td>
<td>NA</td>
<td>2003</td>
<td>Oyama et al. [47]</td>
</tr>
<tr>
<td>$^{18}$F-FDHT, FDG</td>
<td>7</td>
<td>Staging</td>
<td>Sensitivity, 78 and 97</td>
<td>2004</td>
<td>Larson et al. [48]</td>
</tr>
<tr>
<td>$^{11}$C-methionine, FDG</td>
<td>12</td>
<td>Staging</td>
<td>Sensitivity, 72.1 and 48</td>
<td>2002</td>
<td>Nuñez et al. [49]</td>
</tr>
</tbody>
</table>

Note: NA indicates not applicable, $^{18}$F-FDHT = 16β-$^{18}$F-fluoro-5α-dihydrotestosterone.

**Sensitivity**: 4 - 81 %

**Specificity**: NA

Turkbey et al 2009
$^{18}\text{F-FDG}$ in advanced prostate cancer

Bouchelouche and Oehr 2008
# Choline

## TABLE 3: Clinical Trials of PET with Choline Compounds for Prostate Cancer

<table>
<thead>
<tr>
<th>Tracer</th>
<th>No. of Patients</th>
<th>Objective</th>
<th>Results (%)</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C-acetate, $^{11}$C-choline</td>
<td>10</td>
<td>Staging</td>
<td>Sensitivity, 70</td>
<td>2003</td>
<td>Kotzerke et al. [57]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>10</td>
<td>Staging</td>
<td>NA</td>
<td>1998</td>
<td>Harris et al. [58]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>10</td>
<td>Staging</td>
<td>Sensitivity, 92; specificity, 90</td>
<td>2000</td>
<td>Kotzerke et al. [59]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>30</td>
<td>Staging</td>
<td>Sensitivity, 100</td>
<td>2002</td>
<td>de Jong et al. [60]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>87</td>
<td>Staging</td>
<td>Sensitivity, 80; specificity, 96</td>
<td>2003</td>
<td>de Jong et al. [61]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>36</td>
<td>Treatment follow-up</td>
<td>Sensitivity, 38</td>
<td>2003</td>
<td>de Jong et al. [62]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>19</td>
<td>Staging</td>
<td>NA</td>
<td>2004</td>
<td>Sutinen et al. [63]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>41</td>
<td>Staging</td>
<td>Sensitivity, 66; specificity, 81</td>
<td>2005</td>
<td>Farag et al. [64]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>20</td>
<td>Staging</td>
<td>Sensitivity, 100</td>
<td>2005</td>
<td>Yamaguchi et al. [65]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>13</td>
<td>Staging</td>
<td>Sensitivity, 56.3; specificity, 12.5</td>
<td>2005</td>
<td>Yoshida et al. [66]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>43</td>
<td>Staging</td>
<td>Sensitivity, 66; specificity, 84</td>
<td>2006</td>
<td>Marroquen et al. [67]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>26</td>
<td>Staging</td>
<td>Sensitivity, 81; specificity, 87</td>
<td>2006</td>
<td>Resko et al. [68]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>50</td>
<td>Restaging</td>
<td>Sensitivity, 91; specificity, 50</td>
<td>2007</td>
<td>Rinnab et al. [69]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>58</td>
<td>Diagnosis and staging</td>
<td>Sensitivity, 86.5; specificity, 62</td>
<td>2007</td>
<td>Scher et al. [70]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>25</td>
<td>Staging</td>
<td>Sensitivity, 55; specificity, 86</td>
<td>2007</td>
<td>Testa et al. [71]</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>57</td>
<td>Staging</td>
<td>Sensitivity, 60; specificity, 97.6</td>
<td>2008</td>
<td>Schiavina et al. [72]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>17</td>
<td>Staging</td>
<td>Sensitivity, 93; specificity, 48</td>
<td>2005</td>
<td>Kwee et al. [73]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>19</td>
<td>Restaging</td>
<td>Sensitivity, 100</td>
<td>2005</td>
<td>Schmid et al. [74]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>28</td>
<td>Staging</td>
<td>Sensitivity, 60; specificity, 90</td>
<td>2006</td>
<td>Kwee et al. [75]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>100</td>
<td>Restaging</td>
<td>Sensitivity, 98; specificity, 100</td>
<td>2006</td>
<td>Cimini et al. [76]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>20</td>
<td>Staging</td>
<td>Sensitivity, 10; specificity, 80</td>
<td>2006</td>
<td>Hacker et al. [77]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>34</td>
<td>Restaging</td>
<td>NA</td>
<td>2006</td>
<td>Heinisch et al. [78]</td>
</tr>
<tr>
<td>$^{18}$F-FCH</td>
<td>111</td>
<td>Staging, restaging</td>
<td>Sensitivity, 94.7 and 86</td>
<td>2008</td>
<td>Husarik et al. [79]</td>
</tr>
</tbody>
</table>

Note—NA indicates not applicable, $^{18}$F-FCH = $^{18}$F-fluorocholine.
$^{18}$F-choline and prostate cancer

Bouchelouche et al 2010
$^{18}$F-choline and prostate cancer

Bouchelouche et al 2010
$^{11}$C-choline and prostate cancer

- 58 patients with clinical suspicion of prostate cancer
- $^{11}$C-choline PET/CT
- 64% (37/58) with prostate cancer (histology)
- Sensitivity 87% (32/37)
- Specificity 62% (13/21)
- False positive may be due to BPH and prostatitis

Scher et al 2007
$^{18}$F-choline & preoperative N-staging

- Prospective study of 130 prostate cancer patients
- Intermediate or high risk of extracapsular disease (Gleason $\geq 7$ and/or PSA $>10$ ng/mL)
- 912 LN sampled overall
- 85 LN malignant overall in 40/130 pts
- A per-patient analysis

<table>
<thead>
<tr>
<th>LN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 5.0$ mm</td>
<td>$66$</td>
<td>$96$</td>
<td>$82$</td>
<td>$92$</td>
</tr>
<tr>
<td>Overall</td>
<td>$45$</td>
<td>$96$</td>
<td>$82$</td>
<td>$83$</td>
</tr>
</tbody>
</table>

Beheshti et al 2010
$^{18}$F-choline PET/CT & N-staging of PC
Preliminary results of a large prospective study

- 25 patients with newly diagnosed PC
- Gleason score > 6 and/or PSA > 10 µg/l and/or T3
- $^{18}$F-choline PET/CT prior to lymphadenectomy
- PET/CT compared to histology of lymph nodes
- Dual scans (15 min and 60 min)

Poulsen et al 2010
18F-choline PET/CT & N-staging of PC
Preliminary results of a large prospective study

Sensitivity 100%
Specificity 95%
PPV 75%
NPV 100%

Poulsen et al 2010
\textsuperscript{18}F-choline PET/CT & N-staging of PC

Poulsen et al 2010
$^{18}$F-choline and PSA

- 100 prostate cancer patients

- Persistent increase in serum PSA (>0.1 ng/ml) after:
  - radical prostatectomy (N=58)
  - radiotherapy (N=21) or
  - hormonal therapy alone (N=21)

Fig. 4. Relationship between FCH PET/CT results and post-treatment serum PSA levels and G score
18F-choline – early and delayed imaging

- 48 prostate cancer patients
- Dual imaging (<15 min & 60 min)
- Persistent increase in serum PSA (>0.1 ng/ml) after therapy

Cimitan et al 2006
190 patients with prostate cancer
radical prostatectomy
$^{11}$C-choline PET/CT due to PSA increase
retrospective study
In 106 patients PSA velocity and PSA doubling time were available
$^{11}$C-choline and trigger PSA

Castellucci et al. 2009
\(^{11}\)C-choline and PSA kinetics

Castellucci et al. 2009
# Acetate

## TABLE 2: Clinical Trials of $^{11}$C-Acetate ($^{11}$C AC) PET in Prostate Cancer

<table>
<thead>
<tr>
<th>Tracer</th>
<th>No. of Patients</th>
<th>Objective</th>
<th>Results (%)</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C AC</td>
<td>36 (30 BPH and 6 prostate cancer)</td>
<td>Staging</td>
<td>NA</td>
<td>2002</td>
<td>Kato et al. [51]</td>
</tr>
<tr>
<td>$^{11}$C AC, $^{18}$F-FDG</td>
<td>22 and 18</td>
<td>Staging</td>
<td>Sensitivity, 100 and 83</td>
<td>2002</td>
<td>Oyama et al. [46]</td>
</tr>
<tr>
<td>$^{11}$C AC, FDG</td>
<td>46</td>
<td>Restaging</td>
<td>NA</td>
<td>2003</td>
<td>Oyama et al. [47]</td>
</tr>
<tr>
<td>$^{11}$C AC</td>
<td>20</td>
<td>Restaging</td>
<td>Sensitivity, 75</td>
<td>2006</td>
<td>Sandblom et al. [52]</td>
</tr>
<tr>
<td>$^{11}$C AC</td>
<td>50</td>
<td>Staging</td>
<td>NA</td>
<td>2006</td>
<td>Wachter et al. [53]</td>
</tr>
<tr>
<td>$^{11}$C AC</td>
<td>32</td>
<td>Restaging</td>
<td>Sensitivity, 82</td>
<td>2007</td>
<td>Albrecht et al. [54]</td>
</tr>
<tr>
<td>$^{11}$C AC</td>
<td>32</td>
<td>Staging</td>
<td>Sensitivity, 83</td>
<td>2002</td>
<td>Kotzerke et al. [55]</td>
</tr>
<tr>
<td>$^{11}$C AC</td>
<td>24</td>
<td>Staging</td>
<td>Sensitivity, 83</td>
<td>2003</td>
<td>Fricke et al. [56]</td>
</tr>
<tr>
<td>$^{11}$C AC, $^{11}$C-choline</td>
<td>10</td>
<td>Staging</td>
<td>Sensitivity, 70</td>
<td>2003</td>
<td>Kotzerke et al. [57]</td>
</tr>
</tbody>
</table>

Note—BPH = benign prostatic hyperplasia, NA indicates not available.

**Sensitivity** 70-100 %  
**Specificity** NA  

Turkbey et al 2009
$^{11}$C-acetate and prostate cancer

Bouchelouche et al 2010
Other tracers

<table>
<thead>
<tr>
<th>Tracer</th>
<th>No. of Patients</th>
<th>Objective</th>
<th>Results (%)</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-FDHT, $^{18}$F-FDG</td>
<td>7</td>
<td>Staging</td>
<td>Sensitivity, 78, 97</td>
<td>2004</td>
<td>Larson et al. [48]</td>
</tr>
<tr>
<td>$^{18}$F-FDHT</td>
<td>20</td>
<td>Staging</td>
<td>Sensitivity, 63</td>
<td>2005</td>
<td>Dehdashti et al. [83]</td>
</tr>
<tr>
<td>Anti-$^{18}$F-FACBC</td>
<td>15</td>
<td>Staging, restaging</td>
<td>NA</td>
<td>2007</td>
<td>Schuster et al. [82]</td>
</tr>
<tr>
<td>$^{11}$C-methionine, FDG</td>
<td>10</td>
<td>Staging</td>
<td>NA</td>
<td>1999</td>
<td>Macapinlac et al. [80]</td>
</tr>
<tr>
<td>$^{11}$C-methionine, FDG</td>
<td>12</td>
<td>Staging</td>
<td>Sensitivity, 72.1, 48</td>
<td>2002</td>
<td>Nuñez et al. [49]</td>
</tr>
</tbody>
</table>

Note—$^{18}$F-FDHT = 16$^{18}$F-fluoro-5α-dihydrotestosterone, anti-$^{18}$F-FACBC = anti-1-amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid, NA indicates not applicable.
Bone metastases

The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: $^{99m}$Tc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT

Einat Even-Sapir, MD, PhD$^{1,2}$; Ur Metser, MD$^{1,2}$; Eyal Mishani, PhD$^3$; Gennady Lievshitz, MD$^1$; Hedva Lerman, MD$^1$; and Ilan Leibovitch, MD$^{2,4}$

$^{18}$F-fluoride and bone metastases (PC)

Even-Sapir et al 2006
**18F-fluoride and bone metastases (PC)**

**TABLE 2**
Assessment of Skeletal Metastatic Spread by Planar $^{99m}$Tc-MDP BS, Planar and SPECT BS, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT: Patient-Based Analysis in 44 Patients with High-Risk Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Spread of metastases (n = 23)</th>
<th>No metastases (n = 11)</th>
<th>Final diagnosis</th>
<th>Interpretation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>E</td>
<td>B/N</td>
<td>M</td>
</tr>
<tr>
<td>Planar BS</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Planar + SPECT†</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>$^{18}$F-Fluoride PET</td>
<td>11</td>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$^{18}$F-Fluoride PET/CT</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Even-Sapir et al 2006
Detection of bone metastases in patients with prostate cancer by $^{18}$F fluorocholine and $^{18}$F fluoride PET–CT: a comparative study

Mohsen Beheshti • Reza Vali • Peter Waldenberger • Friedrich Fitz • Michael Nader • Wolfgang Loidl • Gabriele Broüger • Franz Stoiber • Ignac Foglman • Werner Langsteger
• 38 patients with prostate cancer

• Both imaging modalities within a maximum interval of 2 weeks

• 321 lesions were evaluated

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-Fluoride PET/CT</td>
<td>81%</td>
<td>93%</td>
<td>86%</td>
</tr>
<tr>
<td>$^{18}$F-choline PET/CT</td>
<td>74%</td>
<td>99%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Beheshti et al. 2008
PSMA – prostate specific membrane antigen

• Transmembrane glycoprotein

• Absent or moderately expressed in benign or hyperplastic prostatic tissue

• Highly expressed by virtually all prostate cancers

• Expression increases with:
  • tumor aggressiveness
  • androgen-independence
  • metastatic disease
  • disease recurrence
PET Imaging of Prostate Cancer Xenografts with a Highly Specific Antibody against the Prostate-Specific Membrane Antigen

Ursula Elsässer-Beile¹, Gerald Reischl², Stefan Wiehr³, Patrick Bühler¹, Philipp Wolf¹, Karen Alt¹,⁴, John Shively⁵, Martin S. Judenhofer³, Hans-Jürgen Machulla², and Bernd J. Pichler³

¹Department of Urology, University of Freiburg, Freiburg, Germany; ²Radiopharmacy, Department of Radiology, University of Tübingen, Tübingen, Germany; ³Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation, Department of Radiology, University of Tübingen, Tübingen, Germany; ⁴Faculty of Biology, University of Freiburg, Freiburg, Germany; and ⁵Division of Immunology and Beckman Research Institute, City of Hope National Medical Center, Duarte, California


⁶⁴Cu-DOTA-3/A12 mAb

Ronnie C. Mease,¹ Crystal L. Dusich,¹ Catherine A. Foss,¹ Hayden T. Ravert,¹ Robert F. Dannals,¹ Jurgen Seidel,¹ Andrew Prideaux,¹ James J. Fox,¹ George Sgouros,¹ Alan P. Kozikowski,² and Martin G. Pomper¹

[\textsuperscript{18}F]FBEM-Z\textsubscript{HER2:342}—Affibody molecule—a new molecular tracer for in vivo monitoring of HER2 expression by positron emission tomography

Gabriela Kramer-Marek · Dale O. Kiesewetter · Lucia Martinova · Elaine Jagoda · Sang Bong Lee · Jacek Capala

Fig. 8. Scans of a mouse bearing 3 T4-HER2 tumor located on the left, dorsal side and dose-converted whole body PET images of the same animal attaining 1, 2, 3, and 4 hr after i.v. injection of [18F]FBEM-Z\textsubscript{HER2:342}-Affibody
RIT and prostate cancer
Endoradiotherapy

- Combines the favorable targeting properties of peptides and antibodies with the effect of radiation-induced cell death
- Smaller amounts of drugs
- Drugs can be labeled with both a diagnostic and a therapeutic nuclide
- Scintigraphy and dose estimation prior to treatment
- Do not need to be internalized into the cell to evolve a cytotoxic effect
- "bystander" or "crossfire effect" - damage of nearby tumor cells
"Crossfire effect"
<table>
<thead>
<tr>
<th></th>
<th>$^{131}\text{I}$</th>
<th>$^{90}\text{Y}$</th>
<th>$^{177}\text{Lu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical half-life, d</td>
<td>8.05</td>
<td>2.67</td>
<td>6.7</td>
</tr>
<tr>
<td>$\beta^-$ particles (MeV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>0.61</td>
<td>2.280</td>
<td>0.497</td>
</tr>
<tr>
<td>Average</td>
<td>0.20</td>
<td>0.935</td>
<td>0.149</td>
</tr>
<tr>
<td>Range in tissue, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>2.4</td>
<td>12.0</td>
<td>2.20</td>
</tr>
<tr>
<td>Average</td>
<td>0.4</td>
<td>2.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Gamma emission, MeV</td>
<td>0.364 (81%)</td>
<td>None</td>
<td>0.113 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.208 (11%)</td>
</tr>
<tr>
<td>Equilibrium dose constant, g·c Gy/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta^-$ radiation</td>
<td>0.389</td>
<td>1.9886</td>
<td>0.314</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.815</td>
<td>No</td>
<td>0.075</td>
</tr>
</tbody>
</table>

$^{131}\text{I}$ indicates $^{131}$Iodine; $^{90}\text{Y}$, $^{90}$Yttrium; $^{177}\text{Lu}$, $^{177}$Lutetium.

Tagawa et al 2010
Tumor targeting with antibodies

• Intact antibodies or antibody fragment

• High affinity and specificity to cell-surface antigens

• Do not need to be internalized to evolve their effect

• Intact antibodies
  • High molecular weight prevent a rapid renal excretion

• Engineered antibody fragments
  • Faster pharmokinetics
  • Improved tumor penetration
  • More homogenous tissue distribution
  • More favorable in treatment of several solid tumors
RIT attractive in prostate cancer

- Metastases especially in bone marrow and lymph nodes (good access to circulating mAbs)
- Metastases often small (good antibody penetration)
- Biomarker (PSA) – evaluation of therapeutic effect
Targets for RIT in prostate cancer

- Prostate specific membrane antigen (PSMA)
  - 7E11-C5 ($^{111}$In-CYT-356 (ProstaScint)
  - J591
    - a deimmunized mAb
    - binds with high affinity to the extracellular domain of PSMA
  - Other

- HER2/neu
  - Herceptin
  - Affibody

- Other antigens
  - TAG72, CA170, L6 antigen, E4 antigen etc
Phase I Trial of Yttrium-90–Labeled Anti–Prostate-Specific Membrane Antigen Monoclonal Antibody J591 for Androgen-Independent Prostate Cancer


- Patients with androgen-independent prostate cancer with progression received \(^{111}\text{In}} \text{J591} for pharmacokinetics and biodistribution determinations

- Followed 1 week later by \(^{90}\text{Y}} \text{J591} at five dose levels: 5, 10, 15, 17.5 and 20 mCi/m^2

- Up to three re-treatments if platelet and neutrophil recovery were satisfactory
• 29 patients received $^{90}$Y-J591, and 4 of these were retreated

• Dose limiting toxicity (DLT) was seen at 20 mCi/m$^2$

• MTD was determined to be 17.5 mCi/m$^2$

• Nonhematologic toxicity was not dose limiting

• Targeting of known sites of bone and soft tissue metastases was seen in the majority of patients

• No HAMA was seen

• Antitumor activity was seen
  • 2 patients: PSA decline
  • 6 patients (21%): PSA stabilization

Bander et al 2004
Fig 1. Anterior and posterior (B) views of bone scan flanked by the respective indium-111 ($^{111}$In)-J591 images (A, C). Sites of technetium-99m and $^{111}$In-J591 uptake are seen in both shoulders, manubrium, ribs, spine, sacrum, pelvis, and femoral heads.

Milowsky et al 2004
Phase I Trial of $^{177}$Lutetium-Labeled J591, a Monoclonal Antibody to Prostate-Specific Membrane Antigen, in Patients With Androgen-Independent Prostate Cancer


• 35 patients with progressive prostate cancer received $^{177}$Lu-J591

• All patients underwent $^{177}$Lu imaging, phamacokinetics, and biodistribution determinations.

• Patients were eligible for up to three treatments
• 16 (16/35) received up to three doses.

• Myelosuppression was dose limiting at 75 mCi/m²

• Single MTD was determined to 70 mCi/m²

• Up to three doses of 30 mCi/m² could be administered safely

• Nonhematologic toxicity was not dose limiting

• Targeting of all known bone and soft tissue metastases was seen

• No HAMA was observed

• Antitumor effect was seen:
  • 4 patients: > 50% PSA decline up to 8 months
  • 16 patients (46%): PSA stabilization for median 60 days
Fig 1. Anterior and posterior images of bone scan and $^{177}$Lu-Lutetium-labeled J591 ($^{177}$Lu-J591) scan done 10 days apart. The latter reveals significantly more areas of increased uptake than the former. Area of prior radiation to lumbar spine shows no increase in isotope uptake with either technique. Prostate-specific antigen at the time was 51.0 ng/mL.
Phase 2 trial of $^{177}$Lu-J591

- Progressive metastatic prostate cancer
- 1 dose of $^{177}$Lu-J591 in 2 cohorts
  - Cohort 1: 15 patients 65 mCi/m$^2$
  - Cohort 2: 17 patients 70 mCi/m$^2$
- $^{177}$Lu imaging was performed to confirm tumor targeting
- All patients underwent planar $^{177}$Lu-J591 scans after treatment

Tagawa et al 2010
Phase 2 trial of $^{177}$Lu-J591

- Excellent targeting of known metastases was observed in 30 of 32 (94%) patients

- Thrombocytopenia was the most commonly seen hematologic toxicity

- No nonhematologic toxicity occurred

- PSA declines were observed in more patients receiving the dose of 70 mCi/m$^2$ (71%) compared with 65 mCi/m$^2$ (46%)
J591 RIT

- Radiolabeled J591 is well tolerated and non-immunogenic.
- J591 RIT effectively targets prostate cancer metastases and produces PSA declines.
- Both $^{177}$Lu-J591 and $^{90}$Y-J591 are dose limited by myelosuppression with little nonhematologic toxicity.
- Anti-PSMA RIT is tolerated either before or after chemotherapy.
- No long-term effects on bone marrow function have been seen.

Tagawa et al 2010
J591 RIT – future directions

- Improving patient selection
- Dose fractionation
- Chemoradiotherapy
- Salvage RIT
Conclusions (1) - PET/CT in prostate cancer

• $^{18}$F-choline, $^{11}$C-choline and $^{11}$C-acetate are useful in PC

• However, large prospective trials are needed to establish the role in the clinical management of PC

• $^{18}$F-fluoride is useful for bone metastases

• Other promising tracers are currently being investigated
Conclusions (2) – RIT and prostate cancer

• RIT in advanced prostate cancer warrants further investigation

• J591 RIT is showing promising results

• J591 RIT is well-tolerated and demonstrates antitumor activity

• Clinical RIT studies with J591 are ongoing to improve efficacy and patient selection
Thank you!