F18 PSMA imaging
A viable option
Dr Rob Ware
Disclosure

• Clinical affiliation Peter MacCallum Cancer Centre
• I am a shareholder and Director of several CYCLOTEK companies whose principal business is the commercial production of PET Radiopharmaceuticals in Australia and New Zealand
F18 PSMA imaging-a viable option

BACKGROUND

• Nuclear medicine long a main stay of prostate cancer management - bone scanning (WBBS)

• Status quo was shaken by advent of PSA screening

• Early detection raised hopes of cure, but exposed the inadequacies of ceCT and WBBS for staging/restaging and disease characteristion
F18 PSMA imaging—a viable option

BACKGROUND

• Problem of applying right treatment, to the right patient at the time persists
• Imaging remains crucial to the decision making process
F18 PSMA imaging—a viable option

BACKGROUND

• MRI improved primary assessment
• Advances have occurred in molecular imaging
  – F18 Bone scan
  – FDG can help identify “bad players” non invasively
  – Choline PET/CT
  – PSMA PET/CT
F18 PSMA imaging-a viable option
CHOLINE PET/CT evidence

- Systematic review indicates very good diagnostic performance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood ratio</th>
<th>Negative Likelihood Ratio</th>
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<tbody>
<tr>
<td>Staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient (N=637)</td>
<td>84%</td>
<td>79%</td>
<td>4</td>
<td>.2</td>
</tr>
<tr>
<td>Lesion (N=5117)</td>
<td>66%</td>
<td>92%</td>
<td>8.3</td>
<td>.4</td>
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<tr>
<td>Re-staging</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patient (N=1005)</td>
<td>85%</td>
<td>88%</td>
<td>7</td>
<td>.2</td>
</tr>
</tbody>
</table>

Umbehrr et al. European Association of Urology. 2013

- Peter Mac RCT evaluating independent and incremental value of FCHOL compared to CT/WBBS analysis awaited
F18 PSMA imaging—a viable option

CHOLINE PET/CT evidence

• Sensitivity limited, especially in patients with PSA< 2ng/ml. Surgically controlled studies have indicated per lesional sensitivity as low as 39%.

• Poor guide to grade of prostatic carcinoma

• False positives—inflammation
F18 PSMA imaging-a viable option

**PSMA Biology**

- Integral membrane carboxypeptidase II
- Expressed on 90-100% prostate cancers
- Function in tumour biology uncertain
- Increased expression higher grade, metastatic and castrate resistant tumours
- 100-1000 fold lower expression on normal cells except small intestine, renal tubular cells and salivary glands
- High expression also in renal cell carcinoma and tumour neovasculature
F18 PSMA imaging—a viable option

PSMA Biology

- Large number of agents developed
  - Monoclonal antibodies
    - In111-capromab recognised intracellular epitope and has limited sensitivity
    - In111-J591 targets extracellular epitopes, accurately detects bone and soft tissue metastases
    - Lu177-J591 has been used safely for therapy
F18 PSMA imaging—a viable option

PSMA Biology

- Large number of agents developed
  - Monoclonal antibodies
  - Small molecule inhibitors of catalytic site
    - Tc
    - I123/I124/I131
    - C11
    - Ga68
    - F18
F18 PSMA imaging-a viable option
Glutamate-Urea-Lysine based PSMA Ligands

• Pomper’s JHU group have been leaders in
  the field of radiolabeled urea based PSMA
  inhibitors-first to report C11, I125, Ga68,
  and F18 labeled ligands based on GLU-urea-
  LYS

• Greater stability of HBED-CC (Eder et al) has
  led to Ga68 PSMA PET/CT ligand being
  introduced into many clinical imaging
  facilities worldwide particularly Germany
  and Australia following early clinical reports
  in 2012
F18 PSMA imaging—a viable option
Ga68 HBED PSMA imaging

- PMCC performed over 700 studies since late 2014
- Fast elimination of tracer from background tissues
- Highly sensitive and specific

Ga68 PSMA-rising PSA after EBRT
F18 PSMA imaging-a viable option
Ga68 HBED PSMA imaging

<table>
<thead>
<tr>
<th>Site</th>
<th>Analysed</th>
<th>T/B mean</th>
<th>T/B range</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>26</td>
<td>41</td>
<td>10-166</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>55</td>
<td>50</td>
<td>10-290</td>
</tr>
<tr>
<td>Bone</td>
<td>36</td>
<td>49</td>
<td>5-242</td>
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</table>

Ga68 PSMA-increasing PSA on ADT post RP
F18 PSMA imaging-a viable option
Ga68 HBED PSMA imaging
F18 PSMA imaging-a viable option
Ga68 HBED PSMA imaging

- Afshar-Oromieh et al. retrospectively investigated the diagnostic value of 68 Ga-HBED-PSMA-PET/CT in 319 patients with recurrent prostatic carcinoma

  - PET/CT at 1 h p.i. detected PCa in 83% of the patients (264 of 319 patients)

  - No false positive examinations

Afshar-Oromieh et al. EJNMMI 2015
F18 PSMA imaging—a viable option

Ga68 HBED PSMA imaging

Eiber et al. JNM 2015
F18 PSMA imaging—a viable option
Ga68 HBED PSMA vs FCHOL imaging

Emmett et al. JNM 2016
F18 PSMA imaging-a viable option
Ga68 HBED PSMA vs FCHOL imaging

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>PSA &gt; 2ng/ml</th>
<th>PSA .5- 2ng/ml</th>
<th>PSA &lt; .5ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMA</td>
<td>88%</td>
<td>71%</td>
<td>50%</td>
</tr>
<tr>
<td>FCHOL</td>
<td>63%</td>
<td>36%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- Total management impact 24/38.
- Major management impact in 13/38 patients due to Ga68 PSMA alone
- No additional management impact due to accurate discordant FCHOL findings
F18 PSMA imaging—a viable option
Ga68 HBED PSMA imaging

• Undoubtedly an excellent tracer for staging and restaging prostate cancer!
• Guide for planning and monitoring PSMA based radionuclide therapy
• On-site on demand production from a Ge/Ga generator

Who could wish for more?
F18 PSMA imaging - a viable option
Ga68 HBED PSMA - some limitations?

• Logistical
  – Staff resources for synthesis and quality control
  – Variable generator synthesis yields
  – Occasional generator failure
  – Waste

• Low injected activity
  – Limited image statistics/image noise

• Short half-life
  – Late imaging difficult

• Cost
  – staff
  – Generator
  – Kits
  – Synthesis units
  – Microbiology/endotoxin
  – Compliant manufacturing environment

• Quality/Regulatory Milieu
  – Generators not ARTG registered
  – Complex synthesis - who is qualified to perform?
F18 PSMA imaging—a viable option

Ga68 PSMA alternatives

- Simpler synthesis
- Kit based formulation
- Ga68-THP-PSMA
- Phase 0/1 Trial PMCC
F18 PSMA imaging-a viable option
F18 PSMA development- F18 DCFBC

• 5 patients with prostate cancer studied (PSA 9-46)
  – No adverse effects
  – Radiation dose similar to FDG
  – Slow blood clearance
  – 21 known metastatic lesions visualised
  – 11 sites (bone>soft tissue) visualised, presumed metastases
  – Lesion contrast less than typically seen with Ga68HBED

Cho et al. JNM 2012
13 patients with primary prostate cancer studied

Compared PET/CT, MRI and surgical pathology on a dominant lesion basis

- Sensitivity PET .46 vs MRI .92
- All Gleason 8 and 9 score lesions >1cc volume detected by PET
- Low contrast apparent

*Cho et al. JNM 2015*
F18 PSMA imaging-a viable option

F18 PSMA development- F18 DCFPyL

• Phase O/1 Trial data
  – Safe
  – favorable biodistribution
  – favorable dosimetry
F18 PSMA imaging—a viable option

F18 PSMA development - F18 DCFPyL

• Phase O/1 Trial data
  – High uptake in prostate carcinoma lesions
  – More lesions apparent with time
  – Excellent image quality

Szabo et al. JNM 2015
F18 PSMA imaging—a viable option

F18 PSMA development- F18 DCFPyL

- Phase 0/1 Trial data
  - Different time course of uptake in primary, node and bone metastases
  - Possibility of greater sensitivity at later time points than feasible with Ga68 PSMA

Szabo et al. JNM 2015
Direct comparison F18DCFPyL and Ga68HBED
- 14 patients relapsed prostatic carcinoma (PSA 4-50 ng/ml)
- Administered activity of F18 at least 1.5 x Ga68

F18 PSMA imaging-a viable option
F18 DCFPyL vs Ga68HBED PET/CT

• SUV values higher for F18 DCFPyL
  -14.5 vs 12.2, p=.028
• T/B F18 DCFPyL
  – Higher kidney, spleen, parotid
  – Same liver, mediastinum

F18 PSMA imaging—a viable option
F18 DCFPyL vs Ga68HBED PET/CT

- All Ga68HBED lesions visualised on F18DFFPyL
- 3 patients additional lesions F18DCFPyL had potential management indications

F18 PSMA imaging - a viable option
F18 DCFPyL vs Ga68HBED PET/CT

- Both excellent tracers
- F18DCFPyL appears to provide
  - better image quality
    - Higher injected dose
    - Later imaging time
    - Less energetic positron emission
  - diagnostic performance appears non inferior

F18 DCFPyL synthesis
- High radiochemical purity (>95%)
- High specific activity (mean 72-158 GBq/micromole)
- Low yield (3–12 % non decay corrected)
- Complex two reactor synthesis
- Long synthesis of 90 minutes or more
- Synthesis characteristics make commercial distribution problematic
F18 PSMA imaging-a viable option
Recent improvements to F18 DCFPyL production

• Bouvet et al reported (SNM 2015) a simplified F18 DCFPyL synthesis
  – Radiochemical yield after HPLC of 27% decay corrected
  – 45 minute synthesis duration
  – Automated

• Similar results achieved at Johns Hopkins and by ABX

• Good basis for cost effective centralised production and distribution of F18PSMA ligand
F18 PSMA imaging—a viable option
CYCLOTEK development path

• Begin production validation for GMP compliance
• Do local non-inferiority trial and Peter Mac
• Facilitate multi-centre trials to establish improved clinical and economic outcomes
• Make available for individual patient use in Australia and New Zealand
F18 PSMA imaging—a viable option

CONCLUSION

• PSMA imaging with PET/CT is a huge advance for diagnostic assessment of patients with primary and recurrent prostatic cancer

• F18 PSMA imaging appears viable with DCFPyL, a GuL small molecule inhibitor developed at John’s Hopkins and which has been licensed to CYCLOTEK for clinical trial and clinical use in Australia and New Zealand

• Non inferior diagnostic performance to Ga68 HBED demonstrated

• Logistic improvements appear likely with development of improved and automated synthesis

• Cost efficiencies should be achievable

• GMP production will impact potential quality and regulatory issues associated with Ga68 HDEB, and may impact reimbursement potential
Register Early

The 4th Theranostics World Congress (4TWC)  
November 7 – 9, 2016  |
http://theranostics2016.org