Novel Imaging in Advanced Prostate Cancer

Robert J. Hamilton, MD MPH FRCSC
Princess Margaret Cancer Centre

ICUC Saturday January 21, 2017
<table>
<thead>
<tr>
<th>Faculty/Presenter Disclosures</th>
<th>Company/Organization</th>
<th>Details</th>
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<tbody>
<tr>
<td>I am a member of an <strong>Advisory Board or equivalent</strong> with a commercial organization.</td>
<td>Bayer, Janssen, Abbvie, Astellas</td>
<td>Ad-board</td>
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<td>I am a member of a <strong>Speakers bureau</strong>.</td>
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<td>I have <strong>received payment from a commercial organization</strong> (including gifts or other</td>
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<td>consideration or ‘in kind’ compensation).</td>
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<td>I am currently participating in or have participated in a <strong>clinical trial</strong> within the past two years.</td>
<td>SPARTAN (Janssen), Astellas/Janssen (Barrier-P), ARASENS (Bayer)</td>
<td>Site-PI</td>
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Overview

• Where could novel imaging help us?
• Rationale for novel imaging
• CT and Bone scans
• Whole body MRI
• PET scans
  – What is a PET scan?
  – Different types of PET scans
    • Choline, PSMA, NaF
• Reality check: how to get a PET scan
Continuum of Prostate Cancer

- **Symptomatic**
  - Androgen Deprivation
  - Death
  - Tumor Volume & Activity

- **Hormone-Sensitive Castrate-Resistant**
  - Surgery and Radiation
  - Androgen Deprivation
  - Therapies After LHRH Agonists and Antiandrogens
  - Immunotherapy

- **Asymptomatic**
  - Premetastatic
  - Radiographically Metastatic
  - Chemotherapy
  - Hormonal therapies
  - Oligometastases

7-15 years

3-5 years

Monitoring Treatment Response
Better imaging needed:

- Volume and distribution of mets influences prognosis
- Volume and distribution of mets influences therapy choice
- Thus early detection may lead to improved outcomes
- Early characterization of mets phenotype may lead to better treatment selection
- Time to progression of mets is important in next treatment selection
- Emerging field of oligoprogression
Problems with bone scans

- It’s detecting reactive bone not tumor
- Delays in detecting progression/resistance
  - PCWG criteria mandates 14 weeks delay in utilizing bone scan
- Can’t detect progression in individual lesions
- Can’t detect new lesions in “super scan”
- Reductions in lesion activity do not equate to response necessarily
- May take patients off for flare phenomenon
  - COU-302: 20% flare $\rightarrow$ not confirmed on subsequent scans

1. Morris et al., JCO 2015
Problems with CT Scans

- Insensitive for low volume mets
- Anatomic but not functional
- Typically only positive at higher PSA levels

<table>
<thead>
<tr>
<th>TABLE I. Post-treatment PSA and PSA velocity by bone scan and CT scan result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone scan result</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
</tr>
<tr>
<td>CT scan result</td>
</tr>
</tbody>
</table>

Kane et al., Urology 2003
Whole-Body MRI (+DWI)

- More sensitive than CT & bone scan
- Strength: response to treatment
- More widely available than PET
- MET-RADS-P (Padhani et al., Eur Urol 2016)
- Intense sequencing

<table>
<thead>
<tr>
<th>Sequence description</th>
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</thead>
<tbody>
<tr>
<td>1. Whole spine-sagittal, T1 W, TSE, 4–5 mm slice thickness</td>
</tr>
<tr>
<td>2. Whole spine-sagittal, STIR (preferred) or fat suppressed T2 W, 4–5 mm slice thickness</td>
</tr>
<tr>
<td>3. Whole body (vertex to mid thighs)-T1 W, GRE Dixon technique. Fat image reconstructions are mandatory</td>
</tr>
<tr>
<td>- A 3D FSE T1 W sequence offering multiplanar capability may be performed as an alternative to replace sequences 1 and 3</td>
</tr>
<tr>
<td>4. Whole body (skull base to mid-thighs)-axial, diffusion weighted, STIR fat suppression, 5–7 mm contiguous slicing, multiple stations</td>
</tr>
<tr>
<td>- ADC calculations with mono-exponential data fitting</td>
</tr>
<tr>
<td>- Coronal b800–1000 multiplanar reconstructions</td>
</tr>
<tr>
<td>- 3D-MIP reconstructions of highest b-value images</td>
</tr>
<tr>
<td>5. Whole body (vertex to mid thighs)-axial, T2 W, TSE without fat-suppression, 5 mm contiguous slicing, multiple stations, preferably matching the diffusion weighted images</td>
</tr>
<tr>
<td>6. Regional assessments including dedicated prostate, small field of view spine, brain studies, and contrast enhancement</td>
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</table>
Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) vs choline-positron emission tomography-computed tomography (choline-PET/CT) for selecting treatments in recurrent prostate cancer

A. J. Conde-Moreno¹ • G. Herrando-Parreño¹ • R. Muelas-Soria¹ • J. Ferrer-Rebolleda² • R. Broseta-Torres³ • M. P. Cozar-Santiago² • F. García-Piñón⁴ • C. Ferrer-Albiach¹

Clin Transl Oncol October 2016

Table 3  Sensitivity, specificity, PPV and NPV

<table>
<thead>
<tr>
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<th>CHOLINE-PET/CT</th>
<th>WB-DW-MRI</th>
<th>Bone scintigraphy</th>
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<tr>
<td></td>
<td>Value (%)</td>
<td>CI 95%</td>
<td>Value (%)</td>
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<tr>
<td>Sensitivity</td>
<td>97.10</td>
<td>92.42–100.00</td>
<td>44.93</td>
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<tr>
<td>Specificity</td>
<td>58.33</td>
<td>26.27–90.39</td>
<td>64.29</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>93.06</td>
<td>86.49–99.62</td>
<td>86.11</td>
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<tr>
<td>Negative predictive value</td>
<td>77.78</td>
<td>45.06–100.00</td>
<td>19.15</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>36.67</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>47.06</td>
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<td></td>
<td></td>
<td></td>
<td>70.97</td>
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<td></td>
<td></td>
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<td>17.39</td>
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PET Scans
Why care about PET scans?

- Increasingly in the press
- Patients will ask you about it
- Look at MRI... it may actually help patients
  - If you believe in oligomets...
  - You better believe in PET scans
- It’s coming
What is a PET Scan

- Positron Emission Tomography
- “Functional imaging”
- Nuclear medicine
What is a PET Scan

- Radionuclide paired with biologically active molecule: e.g. Glucose
- 3-D image of tracer concentration
- Images fused with CT or MRI
- Tracer nomenclature

$^{18}$F-Choline

Radionuclide  Bioactive Compound
What is a PET Scan

• Common radionuclides
  – $^{18}$Fluorine: $T^{1/2}$ 110 min
  – $^{11}$Carbon: $T^{1/2}$ 20 min
  – $^{68}$Gallium: $T^{1/2}$ 67 min
  – $^{89}$Zirconium: $T^{1/2}$ 78.4 hrs

• Common tracers
  – FDG (90% of PET)
  – Choline
  – Acetate
  – PSMA
  – FDHT
  – FACBC (leucine)
  – NaF
Different types of PET scans

- **FDG:**
  - Limited utility
  - Prostate cancer has low glucose uptake
  - Excreted in urine so bladder artifact++
    - Thus limited utility to evaluate prostate or pelvic nodes
  - Maybe some utility in mCRPC setting when metabolism deranged
Different types of PET scans

• Choline
  – Component of phospholipids (cell membrane)
  – Thus requirement of actively dividing cells
  – Avid to cancer and BPH
    • Limited utility when prostate intact (e.g. local staging or post-radiotherapy)
  – Potential role for biochemical recurrence
    • Detection directly proportional to PSA and PSADT
  – Only FDA approved tracer other than FDG for clinical use
  – Subject of Movember GAP2
Choline Weaknesses

- Insensitive for liver mets (background)
- Insensitive near urinary tract
  - Local failure post RP
  - Local failure post EBRT
- Limited when PSA <1
- Ability to assess response to treatment has not been well evaluated
The Role of Choline Positron Emission Tomography/Computed Tomography in the Management of Patients with Prostate-Specific Antigen Progression After Radical Treatment of Prostate Cancer

Maria Picchio\textsuperscript{a,*}, Alberto Briganti\textsuperscript{b}, Stefano Fanti\textsuperscript{c}, Axel Heidenreich\textsuperscript{a}, Bernd J. Krause\textsuperscript{e}, Cristina Messa\textsuperscript{f}, Francesco Montorsi\textsuperscript{b}, Sven N. Reske\textsuperscript{g}, George N. Thalmann\textsuperscript{h}

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>DR at low PSA level, %</th>
<th>DR at intermediate PSA level, %</th>
<th>DR at high PSA level, %</th>
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</thead>
<tbody>
<tr>
<td>Rinnab et al. [4]</td>
<td>50</td>
<td>–</td>
<td>91 (&lt;2.5 ng/ml)</td>
<td>–</td>
</tr>
<tr>
<td>Krause et al. [24]</td>
<td>63</td>
<td>36 (&lt;1 ng/ml)</td>
<td>43 (1–2 ng/ml)</td>
<td>73 (&gt;3 ng/ml)</td>
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<tr>
<td>Castellucci et al. [39]</td>
<td>190</td>
<td>19 (&lt;1 ng/ml)</td>
<td>25 (1–2 ng/ml)</td>
<td>67 (&gt;5 ng/ml)</td>
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<tr>
<td>Giovacchini et al. [31]</td>
<td>358</td>
<td>19 (&lt;1 ng/ml)</td>
<td>46 (1–3 ng/ml)</td>
<td>82 (&gt;3 ng/ml)</td>
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<tr>
<td>Giovacchini et al. [30]</td>
<td>109</td>
<td>5 (&lt;1 ng/ml)</td>
<td>15 (1–2 ng/ml)</td>
<td>28 (&gt;2 ng/ml)</td>
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<tr>
<td>Pelosi et al. [10]</td>
<td>56</td>
<td>20 (&lt;1 ng/ml)</td>
<td>43 (1–5 ng/ml)</td>
<td>81 (&gt;5 ng/ml)</td>
</tr>
<tr>
<td>Husarik et al. [29]</td>
<td>111</td>
<td>71 (&lt;2 ng/ml)</td>
<td>–</td>
<td>87 (&gt;2 ng/ml)</td>
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</table>

- Not useful for:
  - Post EBRT local failure
  - Post RP local failure
  - Patients on ADT
  - Inflammatory tissue (e.g. IBD)

**Conclusions:** According to the current available data, choline PET/CT plays a role in the management of biochemical relapse. Its accuracy is correlated to PSA value, PSA DT, and other pathologic features. Choline PET/CT may be proposed as a guide for individualised treatment of recurrence.
PET/CT with $^{11}$C-choline and $^{18}$F-FDG in patients with elevated PSA after radical treatment of a prostate cancer

J.R. García a, M. Soler a, M.A. Blanch a, I. Ramírez b, E. Riera a, P. Lozano a, X. Pérez b, E. Delgado a, I. Carrio a and F. Lomeña a

- $n=38$ (20 post-prostatectomy, 18 post-rads)
- All had $^{11}$C-Choline and $^{18}$F-FDG PET
Choline PET in Assessing Response to Treatment
Prospектив evaluation of $^{11}$C-Choline PET/CT in therapy response assessment of standardized docetaxel first-line chemotherapy in patients with advanced castration refractory prostate cancer

Sarah M. Schwarzenböck$^{1,2}$ · Matthias Eiber$^1$ · Günther Kundt$^3$ · Margitta Retz$^4$ · Monique Sakretz$^2$ · Jens Kurth$^2$ · Uwe Treiber$^4$ · Roman Nawroth$^4$ · Ernst J. Rummeny$^5$ · Jürgen E. Gschwend$^4$ · Markus Schweiger$^1$ · Mark Thalgott$^4$ · Bernd J. Krause$^{1,2}$


- 32 patients with mCRPC starting docetaxel
- $^{11}$C-Choline PET before, after 1 cycle and after 10 cycles (or progression)
- No correlation between $^{11}$C-Choline uptake and response assessment using either clinical or RECIST criteria

Conclusion: Choline PET has limited use in therapy response assessment to first-line chemotherapy
Prediction of PSA Progression in Castration-Resistant Prostate Cancer Based on Treatment-Associated Change in Tumor Burden Quantified by $^{18}$F-Fluorocholine PET/CT

Joohee Lee$^{1,2}$, Miles M. Sato$^1$, Marc N. Coel$^3$, Kyung-Han Lee$^2$, and Sandi A. Kwee$^{3,4}$


- 42 patients with CRPC starting a new therapy
- Choline PET at baseline and 1-3 months after new treatment
- Metabolically Active Tumor Volume (MATV) was computed
- Change in MATV was prognostic of PSA progression

If MATV dropped >30%:
- 75% improvement in time to PSA progression
Prostate-Specific Membrane Antigen (PSMA)

- **PSMA**
  - Transmembrane protein
  - Actual function unknown
  - Significantly overexpressed in prostate Ca
  - ProstaScint®, generally poor sensitivity and specificity
    - Bound internal domain of PSMA
    - Newer antibodies bind external domain
    - Most promising of the tracers to date
Comparison of PET imaging with a $^{68}$Ga-labelled PSMA ligand and $^{18}$F-choline-based PET/CT for the diagnosis of recurrent prostate cancer


Ali Afshar-Oromieh · Christian M. Zechmann · Anna Malcher · Matthias Eder · Michael Eisenhut · Heinz G. Linhart · Tim Holland-Letz · Boris A. Hadaschik · Frederik L. Giesel · Jürgen Debus · Uwe Haberkorn

- 37 patients with BCR after primary treatment:
  - 28 had RP; 9 had XRT
  - Median PSA 4
- All underwent $^{18}$F-Choline and $^{68}$Ga-PSMA PET
- PSMA: 78 lesions in 32 patients found
- Choline: 56 lesions in 28 patients found
- ** All lesions seen by Choline were seen by PSMA
- Particularly more sensitive for LN mets
- PSADT not a factor; only factor is absolute PSA level
Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with $^{68}$Ga-PSMA-HBED-CC than with $^{18}$F-Fluoroethylcholine PET/CT

- N=38 with Choline; 28 with PSMA
- 90% had prior prostatectomy
- 66% had prior salvage rads
- Median PSA 2.5
- All patients went for pelvic +/- RPLND

<table>
<thead>
<tr>
<th></th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Choline</td>
<td>71.2</td>
<td>86.9</td>
<td>67.3</td>
<td>88.8</td>
<td>82.5</td>
</tr>
<tr>
<td>PSMA</td>
<td>86.9</td>
<td>93.1</td>
<td>75.7</td>
<td>96.6</td>
<td>91.9</td>
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</table>

Published online: 19 March 2016
$^{18}$F-NaF PET/CT

- Fluoride ion rapidly included into remodelling bone
- Not specific for cancer, but CT helps delineate
- Compared to bone scan:
  - Greater spatial resolution; better image quality
  - Much better Sn & Sp
- No utility for nodal, visceral disease
- Concern is False Positives; i.e. specificity
Meta-analysis of 11 studies

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<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Na-F</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>88%</td>
<td>80%</td>
</tr>
</tbody>
</table>

“We believe conventional bone scintigraphy will be replaced by $^{18}$F-NaF PET”

Langsteger et al., Nov 2016

Chen-Tian Shen, MD, Zhong-Ling Qiu, MD, Ting-Ting Han, MD, and Quan-Yong Luo, MD

Clinical Nuclear Medicine • Volume 40, Number 2, February 2015
Reality Check: How to get a PET

PET Scans Ontario uses an evidence-based approach to ensure appropriate access to PET scans in the province.

- **Insured Services**
  - OHIP covers PET scans for certain approved cancer and cardiac indications
  - Find out more

- **PET Registry**
  - Physicians can access PET scans for patients who do not meet the criteria for OHIP's insured indications
  - Find out more

- **PET Clinical Trials**
  - Eligible patients can participate in a clinical trial on the use of PET for diagnosis and treatment assessment
  - Find out more

- **PET Access Program**
  - Physicians can access PET scans for patients who do not qualify for a clinical trial or the PET Registry
  - Find out more

**Notices**
- New Paediatric Registry: May 1, 2014
- Three New Insured Indications are now available
- New Lymphoma Staging Registries available
- OCG PET Abstracts
- Request Insured PET Services online via eTool
Reality Check: How to get a PET

1. OHIP covered PET: NO
   - Only seminoma

2. PET Registry: NO
   - Panc, melanoma, lymphoma, peds

3. Clinical Trials: YES

4. PET Access Program: YES…but tough
   - 5 business days, 72% approval
PSMA Trials Available in Canada
PSMA Trials in Advanced Disease in Canada

• Quebec: OSPREY trial
  – 18-F-DCFPyL PET/CT locally recurrent or metastatic prostate cancer

• Hamilton (St. Joseph’s)
  – Comparison of PSMA PET/CT with conventional imaging for patients with CRPC
    • Outcomes:
      – Safety; Lesion counting; Progression Detection

• BC Cancer Agency
  – PSMA PET/CT to detect local recurrent

• Princess Margaret Cancer Centre (not open yet)
  – PSMA PET/MRI: Post-primary treatment, rising PSA – treated with SABR (Princess Margaret)
Ways to get PET scans off study

• **FDG PET**
  – Mississauga: 1250 CAD
  – Quebec: 2500 CAD

• **Choline PET**
  – Mayo Clinic: ≈$10,000 CAD
  – Several centres in Europe: ≈$4000 CAD

• **PSMA PET**
  – Heidelberg Germany: ≈$4000 CAD
Conclusions

- Bone scan & CT scan lack Sn & Sp
- If believe in oligometss.....believe in novel imaging
- PET scans are the future
  - FDG: sensitivity poor in prostate cancer
  - Choline: most data, but PSMA outperforms
  - PSMA: most promising thus far
- My take:
  - There is a role in select patients post-primary treatment
  - If willing to pay $2000 for Ontario FDG…
  - Might as well pay $4000 for PSMA and have a nice trip to Europe
  - Don’t spend $10,000 at Mayo