Molecular Imaging of Prostate Cancer: Beyond the Bone Scan

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Emory University
Disclaimers

• Dr. Schuster: No specific COI
  – Participate in Emory University commercial grants including FACBC

• Emory University and Dr. Mark Goodman
  – Eligible for royalties for FACBC
  – GE provides FACBC cassettes for research

• Non-FDA approved imaging will be discussed

Support: National Institutes of Health (5R01CA129356) and (P50 CA 128301), SNMMI REF, with additional support from the Georgia Cancer Coalition.
Talk can be found at radiology.emory.edu
Emory Department of Radiology and Imaging Sciences

Mission Statement

Emory Department of Radiology and Imaging Sciences serves the community through advanced innovation, translational research and clinical application of imaging sciences. The department is committed to excellence in scholarship and to the training of the next generation of radiologists, technologists, and imaging scientists. The department’s goal is to provide the highest quality patient care with predictive, diagnostic and therapeutic imaging-based approaches.

Chair from the Chair

Recent Accomplishments

3 Distinguished Investigator Award

Baowei Fei was one of 43 researchers that were selected as recipients of the Academy of Radiology Research (ARR) 2013 Distinguished Investigator Award. The Distinguished Investigator Award recognizes individuals for their accomplishments in the field of imaging research and significant contributions to the record of scientific progress and innovation. The ARR held an induction ceremony for members of its Council of Distinguished Investigators on Monday, December 2 at RSNA 2013.
Clinical Divisions - Nuclear Medicine & Molecular Imaging

The faculty of the Emory Division of Nuclear Medicine & Molecular Imaging offers the highest quality patient care, incorporating the latest knowledge, innovation and equipment. Nuclear Medicine not only uses the most advanced methods, but also helps set the bar for the field. All of our physicians are board certified in nuclear medicine, and some are double-boarded in other fields, particularly Radiology; many have national and international reputations in their fields.

Equipment includes PET/CT and SPECT/CT scanners at Emory University Hospital (Clifton campus) and Emory University Hospital Midtown. We offer a wide variety of specialized nuclear medicine therapies including that for thyroid cancer, bone cancer pain palliation, lymphoma, neuroendocrine tumors and Y-90 liver therapy in cooperation with Interventional Radiology. Research devices at our disposal include a high-resolution brain PET scanner, micro-PET/CT for animal research, and a research cyclotron. A full range of nuclear medicine and PET/CT services are also provided at Grady Memorial Hospital, Emory Johns Creek Hospital, and the Atlanta VA Medical Center. The Division is integrally involved in research as well as close collaboration with colleagues in Radiology, Cardiology and the Emory Winship Cancer Institute. Our faculty are principal investigators and co-investigators on many research grants including those sponsored by the NIH.

- David M. Schuster, MD
  Associate Professor of Radiology and Imaging Sciences
  Director, Division of Nuclear Medicine and Molecular Imaging

Recent Conferences

Lecture: Current Status of Imaging in Prostate Cancer
Lecturer: David Schuster, MD
SNMMI Midwinter Meeting 2014
Palm Springs

Lecture: Robert Lull Memorial Lecture: Growing into Mentorship
Lecturer: David Schuster, MD
Society of Nuclear Medicine 2013 Annual Meeting June 8-12th
Vancouver, Canada
TWO CASES....
PSA 4.9 post-EBRT/HT/brachytherapy

- Negative bone scan
- Negative MP-MR and CT for Extraprostatic. “Unchanged from priors.”
- Molecular imaging with FACBC: uptake 7mm aortocaval LN fatty hilum

Malignant on laparoscopic biopsy
Post brachytherapy with local recurrence. PSA 8.9 ng/dl. Enlarged aortocaval and retrocaval nodes with restricted diffusion MP-MR (B Value 800)

If not on trial, likely placed on ADT

Negative on FACBC so biopsy performed

Reactive lymphoid tissue: Gets shot at local therapy
How Can Molecular Imaging Help?

• Primary diagnosis
  – Targeting elusive cancer
• Surveillance
  – Finding bad apple in bushel
• Staging and recurrence restaging
  – Prostate/bed vs extraprostatic
• Response to therapy
• *Not only practical clinical aspects but find niches in the armor of tumor biology*
  – Probe for weakness…
Beyond Bone Scan: $^{18}$F-NaF

- Originally FDA approved in 1972
- Migrates into crystal matrix of bone
  - Targets perfusion and bone turnover
  - Axial skeleton: 185 MBq (5 mCi)
    - Acquisition time 3 min/bed position starting 45 minutes after injection
18F-NaF

- CMS will pay under NOPR
  - Some third party
- Very sensitive
  - Beautiful images
- But there is a learning curve
- Important to window properly and PET-CT
**18F-NaF PET Bone Scan**

  - Prostate cancer:
    - Planar BS: 70% sens; 57% spec
    - SPECT: 92% sens; 82% spec
    - NaF PET-CT: 100% sens, spec

- Also prone to flare
  - *Wade AA et al. AJR 2006;186:1783*
Other Molecular Targets
$^{18}$F-FDG PET

- Glucose transport
- Limited utility overall
  - Lower sensitivity and specificity
    - Slow growing prostate cancer
      - Intense bladder activity
    - Detection rates in the range of 31-66%
- Less sensitive for bone lesions than $^{18}$F-NaF PET-CT
**18F-FDG PET**

- Utility with more aggressive disease, prognosis and treatment response

- Approved for “Subsequent Treatment Strategy” but not “Initial” Under CMS
FDG PET/CT in Met CAP: Treatment Response Evaluation

Baseline
CTHU=772     SUV=24.5     PSA=223.3

4 months
CTHU=837     SUV=21.7    PSA=284

8 months
CTHU=1084    SUV=16.8    PSA=119

12 months
CTHU=1121    SUV=8.1     PSA=52.5

Courtesy H. Jadvar – University of Southern California - NIH R01-CA111613
Amino Acid Based Imaging

• Amino acids
  – Utilized in protein synthesis
  – Precursors of bioactive molecules
  – Involved in energy metabolism

Ganapathy et al. Pharmacology & Therapeutics 2009;121:29
Amino Acid Based Imaging

• In tumors, amino acid transport is upregulated
  – LAT1, LAT3, ASCT2, xCT, ATB^{0,+}
    • Increased demand by tumors for protein and energy
    • Tumor cell signalling via mTOR pathway

• $^{11}$C-Methionine (naturally occurring)
  – Limited studies demonstrated
    • 72% sensitivity with metastatic prostate
    • 46.7% overall detection rate in primary
anti-1-amino-3-[\textsuperscript{18}F]fluorocyclobutane-1-carboxylic acid (FACBC) Unnatural Alicyclic Amino Acid Analogue

Unlike \textsuperscript{11}C-MET FACBC not metabolized
Little Urinary Excretion: First Studied in Renal Masses
Unexpected Metastatic Prostate Cancer
CT, Bone Scan, and ProstaScint negative. Negative TRUS and biopsy. Patient scheduled for salvage radiotherapy of prostate bed only.

*anti-3-[^{18}F]FACBC PET-CT*

Directed 5 mm left obturator node biopsy. Recurrent prostate carcinoma. Changed therapeutic approach.
PSA 13.8 Post-cryotherapy/EBRT
0.7cm Left Common Iliac LN
EBRT
PSA 44.6

Bone Scan
FACBC
PSA 7.24 Post-prostatectomy: BS Negative

CT at FACBC scan

CT 10 months post FACBC scan
115 Patient Clinical Trial of Suspected Recurrent Prostate Cancer

- 81.7% of FACBC PET scans positive on whole body basis
FACBC PET-CT performs better than ProstaScint (and CI). Correctly upstaged 25.7%

### anti-3-[¹⁸F]FACBC vs. ¹¹¹Indium-capromab-pendetide diagnostic performance in the prostate/bed (N=91/93)

<table>
<thead>
<tr>
<th></th>
<th>anti-3-[¹⁸F]FACBC</th>
<th>¹¹¹Indium-capromab-pendetide</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>55</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>True negative</td>
<td>12</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>18</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>6</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Sensitivity % (95% CI)</td>
<td>90.2 (79.8, 96.3)</td>
<td>67.2 (54.0, 78.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Specificity % (95% CI)</td>
<td>40.0 (22.7, 59.4)</td>
<td>56.7 (37.4, 74.5)</td>
<td>0.182</td>
</tr>
<tr>
<td>Accuracy % (95% CI)</td>
<td>73.6 (63.3, 82.3)</td>
<td>63.7 (53.0, 73.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPV % (95% CI)</td>
<td>75.3 (63.9, 84.7)</td>
<td>75.9 (62.4, 86.5)</td>
<td>0.530</td>
</tr>
<tr>
<td>NPV % (95% CI)</td>
<td>66.7 (41.0, 86.7)</td>
<td>45.9 (29.5, 63.1)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

### anti-3-[¹⁸F]FACBC vs. ¹¹¹Indium-capromab-pendetide diagnostic performance for extra-prostate disease (N=70/93)

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<tr>
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<th>¹¹¹Indium-capromab-pendetide</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>True positive</td>
<td>22</td>
<td>4</td>
<td></td>
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<tr>
<td>True negative</td>
<td>29</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>18</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Sensitivity % (95% CI)</td>
<td>55.0 (38.5, 70.7)</td>
<td>10.0 (2.8, 23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Specificity % (95% CI)</td>
<td>96.7 (82.8, 99.9)</td>
<td>86.7 (69.3, 96.2)</td>
<td>0.248</td>
</tr>
<tr>
<td>Accuracy % (95% CI)</td>
<td>72.9 (60.9, 82.8)</td>
<td>42.9 (31.1, 55.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>PPV % (95% CI)</td>
<td>95.7 (78.1, 99.9)</td>
<td>50.0 (15.7, 84.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>NPV % (95% CI)</td>
<td>61.7 (46.4, 75.5)</td>
<td>41.9 (29.5, 55.2)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Defaulted to biopsy for positive and biochemical control for negative truth

**Histologic confirmation?**
- 100% TP lesions in prostate/bed biopsy proven
- 89.3% TP extra-prostatic lesions biopsy proven
FACBC Primary Prostate Cancer

  - Suboptimal specificity
  - Correlation of uptake with Gleason Score but overlap
- *Turkbey et al. Radiology 2013 Nov [EPUB]*
  - 90% sensitivity patient based
  - Higher uptake than normal prostate (4.5 ± 0.5 vs 2.7 ± 0.5)
  - But not significantly different than BPH
Tumor Biology

- FACBC transported most like glutamine
  - Important substrate for tumor metabolism
  - System ASCT2 and LAT1
    - Mediate both influx and efflux
    - Little urinary excretion
- Unpublished data (Drs. Okudaira and Oka, NMP)
  - FACBC uptake stimulated by androgen in vitro
  - Greater uptake than glutamine, methionine, choline, and acetate

<table>
<thead>
<tr>
<th>Radiotracers</th>
<th>LNCaP cells</th>
<th>DU145 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^{14}\text{C}-\text{FACBC} )</td>
<td>105.9 ± 15.7</td>
<td>110.8 ± 14.5</td>
</tr>
<tr>
<td>( ^{14}\text{C}-\text{Gln} )</td>
<td>88.6 ± 14.9</td>
<td>59.0 ± 6.2</td>
</tr>
<tr>
<td>( ^{14}\text{C}-\text{Met} )</td>
<td>23.0 ± 1.6</td>
<td>56.7 ± 10.8</td>
</tr>
<tr>
<td>( ^{14}\text{C}-\text{Choline} )</td>
<td>45.8 ± 12.4</td>
<td>15.6 ± 2.8</td>
</tr>
<tr>
<td>( ^{14}\text{C}-\text{Acetate} )</td>
<td>14.1 ± 2.4</td>
<td>20.8 ± 3.8</td>
</tr>
</tbody>
</table>
Take Home Point: Literature Heterogenous. Best to Compare Directly in Same Patient

  - 28 patients BCF after prostatectomy
  - Mean PSA 2.9
  - $^{11}$C-choline positive 5/23
  - FACBC positive 10/23
  - 61.1% additional foci
  - TBR better with FACBC

Courtesy Cristina Nanni, MD and Stefano Fanti, MD
Ongoing Prostate FACBC Studies

- **R-01 outcomes**: FACBC to guide salvage radiotherapy
- **Trans-molecular Imaging**: FACBC and MP-MR for recurrent prostate cancer with genomic analyses
- **Other centers in Japan and Europe**
- **Multicenter multinational trial in planning stage**
  - SNMNI-CTN/Movember/ECOG-ACRIN
Androgen Receptor PET

- $^{18}$F-Fluorodihydrotestosterone (FDHT) most well studied
  - (ARN 509 Antiandrogen Therapy)

- Patterns: AR dominant, glycolysis (FDG) dominant, AR-glycolysis concordant

- Useful for AR antagonist therapy trials
  - e.g. saturation of AR and displacement by AR agonists

Courtesy Steve Larson, MD, MSKCC
PSMA: Beyond ProstaScint

- Urea-based PSMA inhibitor:
  - Extracellular domain responsible for enzymatic activity
- 32 positive sites in 5 patients, 11 not seen on CI

Courtesy Martin Pomper, MD PhD
$^{18}$F]DCFBC: First-in-Man Prostate Metastases

Courtesy Martin Pomper, MD PhD and Steve Cho, MD
PSMA: Beyond ProstaScint

• Gallium-labelled PSMA ligand ($^{68}$Ga-PSMA)
  – Targets extracellular domain PSMA

• 37 patients rising PSA detection rate of 60% at PSA $<$2.2 ng/ml and 100 % at PSA $>$2.2 ng/ml

High contrast even in small lymph nodal metastases.
PSMA: Beyond ProstaScint


Outperformed Fluoromethylcholine in number lesions detected and target to background.
Can We Tie the Strands Together?
FACBC with MP-MR

- **Turkbey et al. Radiology 2013 Nov [EPUB]**
  - Addition of FACBC to each sequence significantly improved PPV
  - Adding FACBC to MP-MR increased PPV from 75% to 82%
Taking to Next Level: Targeted Biopsy

Molecular Imaging with PET/CT or MRI/MRSI

PET/CT  MRI/MRSI  3D Visualization

Real-time 3D ultrasound-guided biopsy

Registration  Fusion  Visualization

3D Ultrasound

Segmentation  Planning  Biopsy

Courtesy Baowei Fei, PhD Emory University
3D Integrated MR-Molecular Biopsy

Suspected recurrence patient: Both studies concordant positive in base
FACBC positive - MR nonspecific in apex
Tumor in base and apex
In Conclusion

• Molecular Imaging can help with critical questions:

• NaF PET-CT
  – Advantages:
    • Available
    • Higher accuracy than MDP bone scan
    • FDA approved and generally reimbursed (NOPR)
  – Disadvantages:
    • Bone only, flare
    • Bang for buck versus MDP SPECT-CT?
    • Specificity
In Conclusion

- **FDG PET-CT**
  - Advantages:
    - Available
    - FDA approved and reimbursed for subsequent treatment strategy
    - Monitor therapy response
  - Disadvantages:
    - Lower sensitivity unless aggressive disease
    - Urinary excretion
    - Specificity
In Conclusion

- **FDHT PET-CT**
  - Advantages:
    - Therapy response for advanced disease
    - Highly targeted – specific
    - Drug discovery and optimization
  - Disadvantages:
    - Experimental
    - Probably not for staging/restaging
In Conclusion

- **FACBC PET-CT**
  - Advantages:
    - Encouraging early work
    - FastLab Cassettes (availability)
    - Little urinary excretion
  - Disadvantages:
    - Experimental
      - Less experience
    - Specificity
In Conclusion

• PSMA Ligands
  – Advantages:
    • Encouraging early work
    • Specificity
  – Disadvantages:
    • Experimental
      – Much less experience
    • Urinary excretion
    • Chemistry optimization for distribution