FLUCICLOVINE:
1ST FDA APPROVED F-18 PET IMAGING AGENT FOR RECURRENT PROSTATE CANCER

KEVIN P BANKS, MD
SAN ANTONIO MILITARY MEDICAL CENTER
ASSISTANT PROFESSOR OF RADIOLOGY, USU
I HAVE NO FINANCIAL DISCLOSURES.
GOALS AND OBJECTIVES

1. Review characteristics and clinical pharmacology of Fluciclovine F-18.
2. Discuss role of Fluciclovine F-18 in management of prostate cancer and research supporting its efficacy.
3. Contrast administration & image acquisition of Fluciclovine F-18 to commonly utilized FDG.
Anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid (FACBC)

- L-Leucine Amino Acid Analogue

- LEUCINE: essential amino acid for protein synthesis and cell growth
- Taken up via LAT & ASCT systems
- LAT & ASCT systems up regulated in many carcinomas
  - LAT1 and ASCT2 associated with more aggressive disease
- FACBC does not undergo metabolism
- Uptake in prostate-specific membrane antigen (PSMA) expressing and non-expressing tumor cells
PERFORMANCE OF F-18 FACBC

• Efficacy initially evaluated by Emory University

• 105 F18-FACBC PET/CT scans compared to histopathology

• Interpreted by 3 blinded independent readers

• Detection rate 60% PSA <1.78
• Detection rate 80% PSA >1.78

• <10% extra-prostatic FP rate

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>READER 1</th>
<th>READER 2</th>
<th>READER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=104</td>
<td>N=105</td>
<td>N=99</td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td>75</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>FP</td>
<td>24</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>TN</td>
<td>5</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>FN</td>
<td>0</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>PROSTATE BED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td>58</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>FP</td>
<td>29</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>TN</td>
<td>10</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>FN</td>
<td>1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>EXTRAPROSTATIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td>25</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>FP</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TN</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FN</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
PERFORMANCE OF F-18 FACBC

- Efficacy initially evaluated by Emory University
- 105 F18-FACBC PET/CT scans compared to histopathology
- Interpreted by 3 blinded independent readers
- Detection rate 60% PSA <1.78
- Detection rate 80% PSA >1.78
- <10% extra-prostatic FP rate

<table>
<thead>
<tr>
<th></th>
<th>PATIENT</th>
<th>PROSTATE/BED</th>
<th>EXRAPROSTATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95%</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>Specificity</td>
<td>31%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>PPV</td>
<td>78%</td>
<td>70%</td>
<td>92%</td>
</tr>
<tr>
<td>NPV</td>
<td>71%</td>
<td>77%</td>
<td>0%</td>
</tr>
</tbody>
</table>
18F-FLUCICLOVINE PET-CT VS IN-111 CAPROMAB PENDETIDE SPECT-CT

Patients and methods:
• 93 patients with suspected recurrent prostate carcinoma
• Underwent 18F-Fluciclovine PET-CT & 111In-capromab pendetide (Prostascint) SPECT-CT
• Both exams completed in 90 days
• Reference standards applied by multidisciplinary board

Results:

<table>
<thead>
<tr>
<th>PROSTATE/BED</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACBC</td>
<td>55</td>
<td>12</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Capromab pendetide</td>
<td>41</td>
<td>17</td>
<td>13</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROSTATE/BED</th>
<th>SENS</th>
<th>SPEC</th>
<th>ACC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACBC</td>
<td>90%</td>
<td>40%</td>
<td>74%</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>Capromab pendetide</td>
<td>67%</td>
<td>57%</td>
<td>64%</td>
<td>76%</td>
<td>46%</td>
</tr>
</tbody>
</table>

✓ FACBC identified 14 more positive prostate bed recurrences (55 vs 41)

Schuster, J Urol, 2014
18F-FLUCICLOVINE PET-CT VS IN-111 CAPROMAB PENDETIDE SPECT-CT

Patients and methods:
• 93 patients with suspected recurrent prostate carcinoma
• Underwent 18F-Fluciclovine PET-CT & 111In-capromab pendetide (Prostascint) SPECT-CT
• Both exams completed in 90 days
• Reference standards applied by multidisciplinary board

Results:

<table>
<thead>
<tr>
<th>EXTRAPROSTATIC</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACBC</td>
<td>22</td>
<td>29</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Capromab pendetide</td>
<td>4</td>
<td>26</td>
<td>4</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXTRAPROSTATIC</th>
<th>SENS</th>
<th>SPEC</th>
<th>ACC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACBC</td>
<td>55%</td>
<td>97%</td>
<td>73%</td>
<td>96%</td>
<td>62%</td>
</tr>
<tr>
<td>Capromab pendetide</td>
<td>10%</td>
<td>87%</td>
<td>43%</td>
<td>50%</td>
<td>42%</td>
</tr>
</tbody>
</table>

✓ FACBC identified 18 more patients with extraprostatic involvement (22 vs 4)
✓ Correctly up-staged 18 of 70 cases (26%)
✓ Radiation exposure of FACBC was ~1/3 of Prostascint

Schuster, J Urol, 2014
18F-FLUCICLOVINE VS 11C-CHOLINE PET/CT

Choline: Marker of lipogenesis; enters cell and catalyzed by choline kinase (up-regulated in PCa) to phosphorylcholine then phosphatidylcholine in cell membrane.

Patients and methods:
• Fifteen patients radically treated for prostate cancer
• Presented with rising PSA levels, median PSA 1.44 ng/mL
• Underwent (11)C-choline PET/CT & (18)F-fluciclovine PET/CT within 1 week

Results:
• (18)F-fluciclovine significantly superior to (11)C-choline
  • Patient-based analysis AND
  • Lesion-based analysis; lymph nodes, bone, & local relapse
✓ Superior performance of FACBC at low, intermediate, and high PSA levels

C11-CHOLINE
POS 3/15 PTs → 20%

F18-FACBC
POS 6/14 PTs → 40%

C11-CHOLINE DETECTED 6 LESIONS
4 BONE, 1 LN, 1 LOCAL

F18-FACBC DETECTED 11 LESIONS
5 BONE, 5 LN, 1 LOCAL TO INCLUDE ALL 6 SEEN ON C11

BIODISTRIBUTION

• **PANCREAS** > **LIVER** most intense uptake

• Moderate salivary & pituitary uptake

• Variable mild to moderate bowel activity

• Moderate red marrow & mild **MUSCLE** activity present early (<15 min)
  • Marrow activity ↓ while **MUSCLE** activity ↑ with time

• Lungs have little to no uptake

• **In contrast to FDG:**
  • Minimal to no brain uptake
  • Little **RENAL** excretion
  • Mild activity may accumulate in **BLADDER**, but not to degree that interferes with interpretation
PHARMACOKINETICS

→ In contrast to FDG:
FACBC uptake in prostate cancer & lymph node mets peaks early @ 4-10 min
VERSUS
FDG peaks @ 90+ min most tumors

❖ 61% ↓ uptake of FACBC by prostate cancer lesions @ 90 min

GIVEN THIS, imaging begins
3-5 min post injection FACBC
VERSUS
45-90 min for FDG

Time activity curves data from 6 subject, GE148-001 and adapted from Axumin Imaging & Interpretation Manual. Blue Earth Diagnostics Ltd.
FACBC (Fluciclovine)

- Withhold voiding x30 min prior
- Perform injection with patient on PET-CT scanner bed in supine position
- Immediately reposition arms above head
- 1-2 min after injection, initiate CT
- Begin PET scan 3-5 min after injection
  - Tumor-to-normal tissue contrast is highest 4-10 min after injection
  - 61% $\downarrow$ tumor uptake by 90 min

*If acquisition started too early, increased blood pool may be encountered*
*If acquisition started too late, increased muscle uptake typically present*
INTERPRETATION CRITERIA

PROSTATE BED AND PROSTATE GLAND

Avidity of pathologic FACBC uptake assessed visually

Prior Prostatectomy
• Focal avidity ≥ bone marrow is suspicious for cancer.
  o BUT if focus of avidity small (<1cm), suspicious if >> blood pool.

Non-Prostatectomy
• Focal asymmetric ≥ bone marrow is suspicious for recurrence.
  o BUT if focus of uptake small (<1cm), suspicious if >> blood pool.
  ➔ Focal median lobe uptake has high likelihood of FP.
• Diffuse uptake >> bone marrow is moderately suspicious for recurrence

Manufacturer recommends review of PET only coronal images to aid interpretation.
PATHOLOGIC UPTAKE

PROSTATE BED, PROSTATECTOMY

66 YO S/P PROSTATECTOMY WITH BCR

- FOCAL UPTAKE
- ≥ 1 CM IN SIZE
- VISUALLY ≥ BONE MARROW
✓ SUSPICIOUS FOR CANCER RECURRENCE
PATHOLOGIC UPTAKE

NON-PROSTATECTOMY

62 YO S/P XRT WITH BIOCHEMICAL RECURRENCE (BCR)

▸ FOCAL ASYMMETRIC UPTAKE
▸ ≥ 1 CM IN SIZE
▸ VISUALLY ≥ BONE MARROW
✓ SUSPICIOUS FOR CANCER RECURRENCE
66 YO S/P XRT WITH BCR

- DIFFUSE UPTAKE
- VISUALLY >> BONE MARROW
✓ SUSPICIOUS FOR CANCER RECURRENCE
58 YO S/P XRT WITH BCR

- HETEROGENOUS UPTAKE
- VISUALLY ≥ BONE MARROW
- SUSPICIOUS FOR CANCER RECURRENCE

HETEROGENOUS OR MULTIFOCAL UPTAKE
NON-PROSTATECTOMY
18F-FLUCICLOVINE PET-CT FOR PRIMARY PROSTATE CANCER?

Schuster, AJNMMI 2013

• Correlated uptake of anti-3-[18F] FACBC with histology of prostatectomy specimens
• 10 patients
• Average SUVmax tumor 4.0 +/- 1.3
  • BUT nonmalignant 3.4 +/- 0.9

→ SIGNIFICANT OVERLAP OF AVIDITY FOR PCa VS NONMALIGNANT TISSUE

Turkbey, Radiology 2014

• Compared FACBC PET to MRI and Histology
• 21 patients with tumors > 0.5 cm
• Average SUVmax tumor 4.5 +/- 0.6
  • 2.8 +/- 0.5 normal prostate
  • BUT 4.3 +/- 0.7 BPH

→ NO DIFFERENCE PCa VS BPH

<table>
<thead>
<tr>
<th>T2-weighted MR</th>
<th>ADC maps of DW MR</th>
<th>18F FACBC PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity 73%</td>
<td>Sensitivity 73%</td>
<td>Sensitivity 67%</td>
</tr>
<tr>
<td>Specificity 79%</td>
<td>Specificity 80%</td>
<td>Specificity 66%</td>
</tr>
<tr>
<td>PPV 66%</td>
<td>PPV 68%</td>
<td>PPV 50%</td>
</tr>
<tr>
<td>NPV 87%</td>
<td>NPV 87%</td>
<td>NPV 78%</td>
</tr>
</tbody>
</table>
LYMPH NODES

Avidity of pathologic FACBC uptake assessed visually

Sites Typical for Prostate Cancer Recurrence
• Avidity ≥ bone marrow considered suspicious.
  o BUT if node is small (<1cm) and in site typical for recurrence, may still consider suspicious if >> than blood pool

Atypical Sites (inguinal, distal external iliac, hilar, and axillary nodes)
• Mild, symmetric uptake is typically physiologic
  o BUT if uptake present in context of other clear malignant disease, it may be considered suspicious for cancer recurrence.
SUSPICIOUS NODAL UPTAKE

ASYMMETRIC LYMPH NODE AVIDITY

69 YO WITH HISTORY OF PROSTATE CANCER

- NODES TYPICAL FOR PROSTATE CANCER SPREAD
- ≥ 1 CM IN SIZE
- VISUALLY ≥ BONE MARROW
- ☑ SUSPICIOUS FOR CANCER RECURRENCE
BENIGN NODAL UPTAKE

MILD LYMPH NODE AVIDITY

▸ NODES TYPICAL FOR PROSTATE CANCER SPREAD
▸ >= 1 CM IN SIZE
▸ VISUALLY < BONE MARROW
✘ NOT SUSPICIOUS FOR CANCER RECURRENCE

IF < 1 CM IN SIZE
▸ NODES TYPICAL FOR PROSTATE CANCER SPREAD
▸ VISUALLY NOT >> BLOOD POOL & NOT APPROACHING BONE MARROW
✘ SUSPICIOUS FOR CANCER RECURRENCE
BENIGN NODAL UPTAKE

ATYPICAL SYMMETRIC LYMPH NODE AVIDITY

▸ ATYPICAL LN SITES FOR RECURRENCE
  INGUINAL
  DISTAL EXTERNAL ILIAC
  HILAR
  AXILLARY

▸ MILD TO MODERATE SYMMETRIC UPTAKE
✘ NOT SUSPICIOUS FOR CANCER RECURRENCE

MODERATE PHYSIOLOGIC FACBC ACTIVITY IN BLADDER IS ATYPICAL. OCCURS IN 10-15% OF PATIENTS. MAY THEORETICALLY BE REDUCED BY NOT HAVING PATIENT VOID WITHIN 30 MIN BEFORE ADMINISTERING RADIOTRACER.
SUSPICIOUS NODAL UPTAKE

ISOLATED ASYMMETRIC LYMPH NODE AVIDITY

65 YO WITH PRIOR PROSTATECTOMY AND BCR

- ATYPICAL NODAL SITE FOR RECURRENT: DISTAL EXTERNAL ILIAC
- ASYMMETRIC UPTAKE (INTENSITY DEPENDENT UPON SIZE)
- CAUSES OF FALSE POSITIVITY EXCLUDED: RECENT PROCEDURE OR IPSILATERAL HARDWARE/GRAFTS
- MODERATELY SUSPICIOUS FOR CANCER RECURRENT
BONE

Focal uptake CLEARLY visualized on Maximum Intensity Projection (MIP) or PET-only images, can be considered suspicious for cancer.

- Lytic metastases typically show intense FACBC avidity
- Mixed bony lesions most commonly show moderate uptake
- Dense sclerotic abnormality on CT without uptake does not exclude metastasis
  • Alternative imaging should be considered
BONE UPTAKE

SUSPICIOUS LESIONS

73 YO S/P PROSTATECOMY WITH BCR

- FOCAL UPTAKE CLEARLY VISUALIZED ON MIP OR PET-ONLY IMAGES SUSPICIOUS
- Lytic Lesions Most Intense
- Mixed Lesions Moderately Intense
- Dense Sclerotic Mets May Be Falsey Negative
INDETERMINATE SCLEROTIC BONE LESION

58 YO S/P PROSTATECOMY WITH BCR
• 9 MM SCLEROTIC LESION IN RIGHT FEMUR
• REMAINDER OF EXAM NEGATIVE
INDETERMINATE SCLEROTIC BONE LESION

- FOCAL UPTAKE CLEARLY VISUALIZED ON MIP OR PET-ONLY IMAGES SUSPICIOUS
- LYTIC LESIONS MOST INTENSE
- MIXED LESIONS MODERATELY INTENSE
- DENSE SCLEROTIC METS MAY BE FALSELY NEGATIVE
INDETERMINATE SCLEROTIC BONE LESION

- DENSE SCLEROTIC ABNORMALITY ON CT WITHOUT UPTAKE DOES NOT EXCLUDE METASTASIS
- ALTERNATIVE IMAGING SHOULD BE CONSIDERED

ADDITIONAL FOCI OF NAF AVIDITY SEEN ON MIP CORRESPONDED TO BENIGN DEGENERATIVE ACTIVITY.
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

POTENTIAL SOURCES OF FALSE POSITIVES

18F-FACBC has elevated uptake in numerous malignancies:
• Breast cancer
• Lung carcinoma
• Malignant and premalignant colonic neoplasia
• Squamous cell carcinoma of scalp
• Follicular lymphoma
• Multiple myeloma
• Primary and metastatic brain tumors

18F-FACBC also shows elevated uptake in benign tumors:
• Pituitary adenoma, meningioma, osteoid osteoma, and adrenal adenoma have been described.
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

POTENTIAL SOURCES OF FALSE POSITIVES

18F-FACBC also shows elevated uptake in inflammation:
• **Mild to moderate linear esophageal uptake in >50% of patients**
• Other acute and chronic inflammation and infection:
  • Hilar, axillary, and inguinal lymph nodes
  • Inflammatory skin lesions, ringworm infection, and muscle inflammation
  • Mild uptake in degenerative facet disease → intensity generally < than 18F-FDG.

Schuster, JNM, 2014
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

XRT CHANGES TO MARROW UPTAKE OF FACBC

59 YO S/P XRT FOR CAP WITH BCR
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

BENIGN INCREASED MUSCLE UPTAKE OF FACBC SECONDARY TO EXERCISE

59 YO S/P PROSTATECTOMY FOR CAP WITH BCR

- MILD DIFFUSE HOMOGENEOUS MUSCLE UPTAKE IS NORMAL & INCREASES WITH TIME AFTER INJECTION

- MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN SOFT TISSUE INFLAMMATION
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

FACBC UPTAKE SECONDARY TO SOFT TISSUE INFLAMMATION RELATED TO INSULIN INJECTIONS

55 YO S/P PROSTATECTOMY FOR CAP WITH BCR

- MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN SOFT TISSUE INFLAMMATION
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

FACBC UPTAKE SECONDARY TO PNEUMONIA

62 YO S/P PROSTATECTOMY FOR CAP WITH BCR

MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN INFLAMMATION
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

BENIGN INCREASED UPTAKE OF FACBC RELATED TO ADRENAL ADENOMA

62 YO S/P PROSTATECTOMY FOR CAP WITH BCR

- 18F-FACBC PET SHOWS SMALL FOCUS OF MILD INCREASED RADIOTRACER JUST POSTERIOR TO LIVER (ARROWHEAD).
- AXIAL CT IMAGE SHOWS AVIDITY LOCALIZES TO ADRENAL NODULE WITH ATTENUATION AND LONG TERM STABILITY CONSISTENT WITH BENIGN ADENOMA
- CONTRALATERAL NORMAL ADRENAL WITHOUT UPTAKE
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

INTENSE FACBC UPTAKE SECONDARY TO BENIGN BONE LESION

69 YO WITH PRIMARY CAP

- FOCAL UPTAKE CLEARLY VISUALIZED ON MIP OR PET-ONLY IMAGES SUSPICIOUS
- CT IMAGE SHOWS AVIDITY LOCALIZES TO SUBCHONDRAL GLENOID LESION

INCIDENTAL FOCUS OF UPTAKE ON AXIAL FUSED IMAGE (ARROWHEAD) RELATED TO ROTATOR CUFF INJURY RELATED INFLAMMATORY FACBC AVIDITY.
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

INTENSE FACBC UPTAKE SECONDARY TO BENIGN BONE LESION

- MDP BONE SCAN SHOWS OSTEOBLASTIC ACTIVITY AT SITE OF LESION IN ADDITION TO OTHER AREAS OF DEGENERATIVE UPTAKE
- NO FEATURES OF BONY METASTASES
- MILD FOCAL UPTAKE MAY BE SEEN IN DEGENERATIVE DISEASE, BUT USUALLY NOT TO SAME DEGREE AS WITH FDG.
NORMAL VARIANTS, ARTIFACTS, AND NONMALIGNANT PROCESSES

BENIGN FOCAL AVIDITY FROM NORMAL PITUITARY GLAND UPTAKE

59 YO S/P XRT FOR CAP WITH BCR

- MODERATE PITUITARY GLAND UPTAKE IS PART OF THE NORMAL FACBC BIODISTRIBUTION
FUTURE DIRECTIONS

STAGING PRIMARY DZ

59 YO S/P WITH HIGH GRADE PROSTATE CANCER ON MULTIPLE BIOPSY SPECIMENS
CONCLUSION

- In May of 2016, Fluciclovine F-18 was first FDA approved F-18 PET imaging agent for use in patients with suspected recurrent prostate cancer.
- Shows better accuracy than C-11 choline and In-111 Prostascint, only other radiotracers currently FDA approved for imaging recurrent prostate cancer.
- Detection rate increases with increasing PSA.
- Familiarization with novel imaging protocol and proper interpretation criteria key to success.
REFERENCES

Dr. Kevin P Banks
Department of Radiology and Nuclear Medicine
San Antonio Military Medical Center
Assistant Professor, Uniformed Services University
kevin.p.banks.civ@mail.mil