Unparalleled Contributions of 18F-FDG-PET Imaging to Medicine Over the Past Four Decades

Abass Alavi, M.D.
M.D. (Hon), Ph.D. (Hon), D.Sc. (Hon)
Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
How did this journey begin and where is it heading?
14C-deoxyglucose autoradiography
14C-deoxyglucose autoradiography
Concept of Fluorodeoxyglucose (FDG)

Alavi, Kuhl, Reivich
(University of Pennsylvania)

Wolf, Ido, Fowler
(Brookhaven National Laboratory)

December 1973
[\textsuperscript{18}F] FDG – the Molecule of the Century
Uptake and Metabolism
The First Brain FDG Image
1976
The first whole body human FDG scan was performed by Abass Alavi in August 1976 at University of Pennsylvania by employing a conventional rectilinear machine as the only option at the time.
### Relative Sensitivity of Molecular Imaging Modalities

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Modality</th>
<th>Agents</th>
<th>H</th>
<th>R</th>
<th>Primary uses</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>pM</td>
<td>FMT</td>
<td>fluorescent proteins</td>
<td>X</td>
<td></td>
<td>gene expression, tagging superficial structures</td>
<td>GFP, RFP, NIRF probes</td>
</tr>
<tr>
<td>nM</td>
<td>BLI</td>
<td>luciferin</td>
<td>X</td>
<td></td>
<td>gene expression, therapeutic monitoring</td>
<td>fLuc rLuc</td>
</tr>
<tr>
<td>μM</td>
<td>SPECT</td>
<td>$^{99m}$Tc, $^{123/51}$I, $^{111}$In</td>
<td>X</td>
<td>X</td>
<td>site-selectivity, protein labeling</td>
<td>$^{99m}$Tc-annex in V, $^{123}$I-A85380</td>
</tr>
<tr>
<td></td>
<td>PET</td>
<td>$^{11}$C, $^{18}$F, $^{124}$I, $^{64/62/60}$Cu</td>
<td>X</td>
<td>X</td>
<td>site-selectivity, gene expression, drug development</td>
<td>$^{11}$C-RAC, $^{124}$I-FIAU, $^{64}$Cu-ATSM</td>
</tr>
<tr>
<td></td>
<td>spectroscopy</td>
<td>endogenous metabolites</td>
<td>X</td>
<td>X</td>
<td>CNS, prostate, heart, breast</td>
<td>NAA, Cr, Cho, Glx, ml, $^{31}$P</td>
</tr>
<tr>
<td></td>
<td>contrast agents</td>
<td>Gd, Mn, FeO</td>
<td>X</td>
<td></td>
<td>cell trafficking, enzymatic activation</td>
<td>poly-L-lysine, dendrimers, MION</td>
</tr>
<tr>
<td></td>
<td>contrast agents</td>
<td>perfluorinated microbubbles</td>
<td>X</td>
<td></td>
<td>drug-delivery, gene transfection</td>
<td>human albumin (Optison)</td>
</tr>
</tbody>
</table>
Integrated PET-CT Systems

- Siemens
- GE
- Philips
Current and Potential Indications for FDG-PET Imaging

- CNS Disorders (AD, Seizures disorders)
- Cancer
- Infection
- Inflammation
- Myocardial Viability
- Atherosclerosis
- Muscle Dysfunction
- Clot detection
Normal Variation and Effects of Aging on Organ Function and Structure as Demonstrated by Modern Imaging Modalities

Abass Alavi, M.D.
M.D.(Hon), Ph.D.(Hon), D.Sc.(Hon)
University of Pennsylvania School of Medicine
Correlation between age and whole brain metabolic rate (age range: 18–85 years).
CANCER DIAGNOSIS
58 yrs old female with Palpable mass in Right Breast
CANCER SATAGING
Staging widespread melanoma
ASSESSING RESPONSE TO THERAPY
Early Assessment for Response
CT

2-3 months

Therapy “A”

Therapy “B”

Therapy “B”
PET BASED PRACTICE
PET/CT

24 - 48 hours

Therapy “A”

Therapy “A”

Therapy “B”

Therapy “B”

6 months
DETECTION OF RECURRENCE
<table>
<thead>
<tr>
<th>MRI T1Gd</th>
<th>90 min</th>
<th>473 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="MRI Image" /></td>
<td><img src="image2.png" alt="90 min Image" /></td>
<td><img src="image3.png" alt="473 min Image" /></td>
</tr>
</tbody>
</table>
The Role of PET-CT/MRI Co-registration in Radiation Therapy
FDG-PET for the Diagnosis of Infections and inflammation
Chronic Osteomyelitis

Sinus Track Connecting Soft-Tissue Abscess With Bone

Sagittal FDG-PET

Precontrast SPGR

Postcontrast SPGR

SPGR = spoiled gradient.
FDG-PET/CT in Diabetic Foot
FDG-PET Image - vasculitis is confirmed.

Inflammatory Bowel Disease
FDG PET CT – Inflammation in Aorta

Blomberg, 2012
61-year-old caucasian male

- Adipose, recent pneumonia and gout, bedridden for weeks
- 2 day history of swelling and tenderness of right lower extremity
- D-dimer 19 mg/L (ref. < 0.5 mg/L), Wells’ score 4

- CUS: RLE DVT (mid-femoral to distal calf)
- PET/CT: Positive for RLE DVT, otherwise normal
Differential dynamics of FDG between malignant and inflammatory cells
[\textsuperscript{18}F] FDG – the Molecule of the Century
Uptake and Metabolism

\begin{itemize}
  \item Blood
  \item Glucose Transporter Polypeptides
  \item GLUT 1 - 4
  \item \( K_1 \)
  \item \( K_2 \)
  \item Hexokinase
  \item Glycogen
  \item \( \textsuperscript{18}FDG-1-P \)
  \item \( \textsuperscript{18}FDG-6P \)
  \item Glucose-6-Phosphatase
  \item \( \textsuperscript{18}F-fru-6-P \)
  \item Glycolysis
  \item \( \textsuperscript{18}FDG-6-	ext{phospho-glucono-lactone} \)
  \item HMP shunt
\end{itemize}
Retention Index: SUVmean

Hodgkin Lymphoma

Non-Hodgkin Lymphoma

R.I. = 100 \times \frac{\text{SUVmean2 - SUVmean1}}{\text{SUVmean1}}

P-Value = 0.004
Lung Ca, additional pleural and Lymph nodes mets
FIRST TIME POINT (Early)

SECOND TIME POINT (Delay)

DUAL TIME IMAGING IN MESOTHELIOMA

Early Image Max SUV = 3.5

Delayed Image Max SUV = 4.8
### RESULTS

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Avg. SUVmax 1</th>
<th>Avg. SUVmax 2</th>
<th>Avg. Percent SUV Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant Mesothelioma (n = 28)</strong></td>
<td>4.6 ±2.5</td>
<td>5.3 ±2.8</td>
<td>14.0 ±12.4</td>
</tr>
<tr>
<td><strong>Benign Pleural Disease (n = 4)</strong></td>
<td>1.5 ±0.2</td>
<td>1.3±0.2</td>
<td>-10.5 ±21.6</td>
</tr>
</tbody>
</table>

Table

\( P < 0.002 \)
Temporal profile of FDG uptake in Lung Cancer

Basu S et al, QJNM 2008
Assessing Tumor Biology and Forecasting Prognosis
## Assessment of Tumor Biology in Breast Cancer Based on Time Course of FDG in the Primary Site

<table>
<thead>
<tr>
<th>SUVmax1</th>
<th>SUVmax2</th>
<th>%ΔSUVmax</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Breast lesions in patients without Axillary or Distant Metastasis</td>
<td>2.9 ± 2.7</td>
<td>3.4 ± 2.4</td>
<td>4.5 ± 4.2%</td>
</tr>
<tr>
<td>Primary Breast lesions in patients with Axillary Metastasis</td>
<td>4.8 ± 3.9</td>
<td>5.3 ± 4.5</td>
<td>9.4 ± 12.8%</td>
</tr>
<tr>
<td>Primary Breast lesions in Patients with Distant Metastasis</td>
<td>7.7 ± 6.2</td>
<td>8.9 ± 7.1</td>
<td>15.7 ± 10.8%</td>
</tr>
</tbody>
</table>

SUVs in the primary lesions were highest in Gp II (those with both axillary and distant metastases), followed by Gp I (those with only metastatic axillary adenopathy) and Gp III (patients without any metastasis).
Global metabolic activity (GMA)
DLBCL
V = 306.25 cc
MVP = 5175.79 SUV cc
cMVP = 9333.10 SUV cc
Δ MVP = 80.3%

Torigian DA et al, unpublished data

DLBCL
Life Beyond FDG

- FLT (DNA Synthesis)
- $^{60}$Cu-ATSM, $^{18}$F-EF5, $^{18}$F-FMISO
- (Assessment for hypoxia)
- FIAU, FHBG, FHPG (Gene therapy)
- $^{11}$C-Acetate (Slow growing tumors)
- $^{18}$F or $^{11}$C-labeled Choline
- (Slow growing tumors)
- $^{18}$F-Fuoride (Bone imaging)
Imaging of Non-small Cell Lung Cancer

AF Shields, JR Grierson, BM Dohmen, H-J Machulla et al.
90 Minutes

MRI Post-GAD Sequence

18F-EF5 PET

MR-PET Fusion

Evans, Koch 2005
Comparison of Average SUV$\text{mean-asc}$

- The mean±SD of SUV$\text{mean-arch}$ for healthy and non-healthy subjects were 0.83±0.20 and 1.02±0.29, respectively; and this difference was significant ($P$ value<0.001). The spearman CC of healthy and non-healthy subjects were 0.37 ($P=0.001$) and 0.67 ($P<0.001$), respectively. The trend-lines for both groups are shown below.
Global cardiac $^{18}$F-NaF uptake
The CT, PET, and PET/CT images shown above from two normal subjects, a 28 year-old male (A) and a 64 year-old female (B). The femoral neck activity is anatomically defined with the medial boundaries based on the epiphyseal line and lateral boundaries by the intertrochanteric ridge. Based on this delineation, quantitative metrics were generated in both subjects. Total calcium metabolism (TCM = SUVmean*metabolically active volume) in patient (A) was 6715.79 while TCM in patient (B) was 2587.44.
FIGURE 5. Heart uptake and DAR from control and apoE -/- mice. (A) Mean heart uptake obtained after intravenous administration of $^{125}$IIONPs into healthy and atherosclerotic mice ($n$=4). (B) Mean heart-to-blood ratios obtained after intravenous administration of $^{125}$IIONPs into healthy and atherosclerotic mice ($n$=4). (C) DAR obtained from heart of healthy and atherosclerotic mice, respectively, at 72 h post-injection of $^{125}$IIONPs (20 µCi, 0.8 mg Fe/kg).
Philips Ingenuity TF PET/MR

Sequential PET and MR imaging

CE Mark in Europe
FDA 510(k) clearance in US

http://multivu.prnewswire.com/mnr/phillips/48197/
Potential Future Applications

- Neurological Disorders and Diseases
- Cardiovascular Disorders and Diseases
- Musculoskeletal Disorders and Diseases
Fusion Imaging of PET and MRI
Metabolic Function in In-vivo Human Brainstem

Anatomy Obtained by 7.0T MRI

SUVR of Glucose Metabolism By Fusion PET-MRI
FDG PET/CT in Cardiac Sarcoidosis

Images in a 51-year-old man with history of cardiac dysrhythmias and sarcoidosis who underwent evaluation for cardiac involvement. Axial software-fused FDG PET/MR image of heart demonstrates heterogeneously increased FDG uptake (arrows) in left ventricular myocardium.

FDG-PET/CT in Diabetic Foot

Imaging Plaques and Tangles in Patients with Cognitive Impairment

Normal vs. Alzheimer’s Diseased Brain

Normal

Alzheimer’s

Neurofibrillary tangles

Amyloid plaques

Neuron
PiB
FDG
Imaging (PET)
Pathology
BRAAK AND BRAAK
CORTICAL DESTRUCTION IN ALZHEIMER’S DISEASE
Neurobiology of Aging, Vol. 18, No. 4, pp 351–357, 1997
Copyright © 1997 Elsevier Science Inc.
Printed in the USA. All rights reserved.
0197-4580/97 $17.00 + 00
FDG-PET-CT Imaging has had a substantial impact on research and on the day to day practice of medicine. This has resulted in minimizing pain and suffering for millions of patients with serious diseases/disorders and in reducing cost of health care worldwide.
Thank You
Thank you