Positron Emission Tomography (PET) in the liver

- (brief reminder of how PET works)
- How liver works (physiology)
- Detecting Liver Tumors
  - Why it works better for some tumors than others
- Monitoring Tumors after rad/chem therapy
- (Measuring liver function)

Basis of PET

- Liver (& all other organs) function by a series of biochemical reactions
- To use PET
  - Determine which biochemical process you want to study?
- Attach a radioactive element to that biochemical
  - Called "labeling" the biochemical
- Administer labeled biochemical (radiopharmaceutical) to patient
- Use a PET scanner to image and "trace" the fate of this biochemical

For Example

- If you want to know where marijuana goes in the brain
  - Label the biochemical that is the active component of marijuana with a radioactive element
    - For ex. Replace a C atom with a radioactive C
  - Administer *very* small quantities of the "labeled" marijuana
  - Use PET scanner to make images of the brain to see where the labeled biochemical goes

PET

- Trace fate of biochemical compounds
  - Static image of their distribution in organ(s)
  - Images over time
    - Uptake by organ/tissue
    - Metabolism
    - Clearance
- Can make absolute measurements
- *Can measure actual ngm/ cc of biochemical*

PET (unlike CT and MRI)

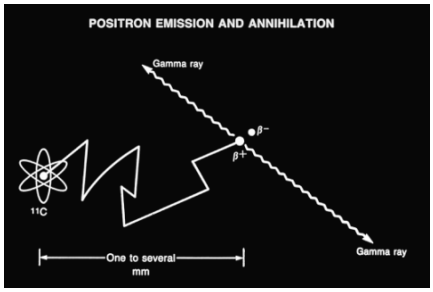
- Positron Emission Tomography):
  - Image of *physiology*
  - Images of Biochemical Function
  - Not *necessarily* of anatomic size/shape
    - If part of liver or tumor not functioning
      - That part may not appear in image
    - If part of liver is HYPER active
      - That part of liver may appear very bright

What is a positron?

- Its given off (at high speed) by the nucleus of the PET radioisotope
- Its just like an electron but + charged
- It's the ANTI-matter of an electron

What does positron do in body?

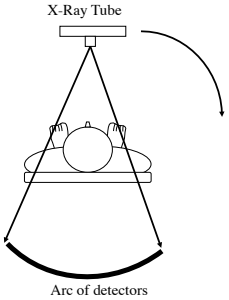
- Just like an electron, bounces around off other atoms
- Travels a fraction of a mm or up to a few mm as it slows down
- Slows down and eventually spends too much time near its anti-matter sister, the electron
- The two particles annihilate each other
  - Produce a burst of energy
  - Two photons travelling in opposite directions



- Two 511 KeV photons are created
- Travelling in opposite directions
- These photons produce the image

How do we make images?

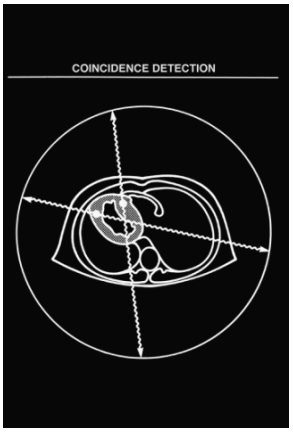
Just as in a CT scanner



- If you know WHERE photons came from
- Along line between detector and Xray Tube
- Can make image

In a PET scanner

- Surround patient with detectors
- Look for 2 photons hitting opposite detectors
- Know where photons came from
- Can make an image



Modern PET scanners

- In-plane resolution ~ 4mm
- Slice thickness about 2-3mm
- Axial field of view ~15cm (so ~60+ slices)
- Nearly always combined with a CT scanner
  - New: combined with MRI
- Sensitivity ~many 1000's x greater than MR

PET Radioisotopes (positron emitters)

- Biochemically Important Atoms

^{11}C (20 min.)	- cyclotron
^{13}N (10 min.)	-cyclotron
^{15}O (2 min.)	-cyclotron
^{18}F (2 hours)	-nearby (few 100 Km) cyclotron
^{82}Rb (1.3 min)	-generator - no cyclotron

PET

For Example:

- replace a Carbon atom with *radioactive* Carbon atoms
  - Labeled biochemical behaves IDENTICALLY to original
- Inject biochemical into blood
- PET "traces" the biochemical as it is used by the body.
- PET makes images of the biochemical within the body
  - At one time point
  - As a function of time.

PET is so sensitive

- You can detect sub-nano grams of labeled biochemical
- Therefore: Biochemical you inject does NOT alter patient's physiology
  - Such a small amount is needed:
    - could safely inject arsenic, CO, or most anything else.
    - That's why its called a "tracer"

First Step in Using PET in the liver

- Know the physiology of the liver (or liver tumor) i.e. how it works
- Figure out which biochemical reactions you want to study
- Label and image those biochemicals
- PROBLEM
  - We only partially understand how the liver works
  - (same holds true for most other organs as well)

Liver is VERY complicated

- Performs over 500 important jobs
  - Main metabolic/energy production engine of body
  - Production of bile
  - Storage of iron, vitamins, trace elements…
  - Detoxification
  - Makes urea and converts other waste products for excretion by kidneys
  - Many more…..

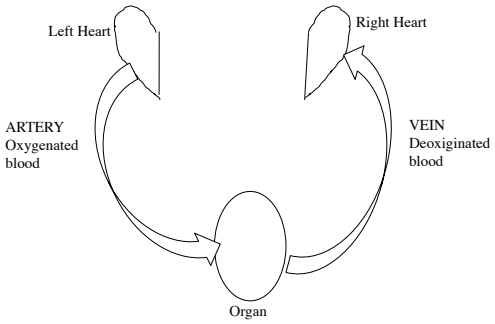
Liver is special

- As you heard earlier
  - Liver has unusual blood supply
  - The "portal" circulation

In all organs EXCEPT liver

- Left Heart pumps oxygenated blood to organ
  - Thru an artery
- Organ extracts oxygen and nutrients
- Blood (Unoxygenated) goes back to right heart
  - Thru a vein
- ONLY supply of blood is directly from left heart (i.e. from an artery)

All organs Except Liver



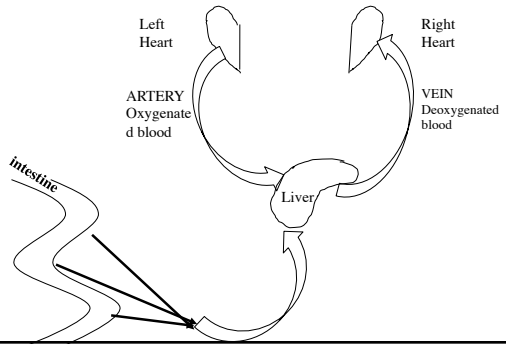
Liver

- Same as all other organs

PLUS – "Portal Circulation"

- Special blood supply going directly *from* Intestines (and spleen & pancreas) *to* Liver
- ALL substances absorbed by gut -> directly to liver
- Liver processes ALL material from gut
  - Glucose, proteins, vitamins, bacteria … *ever*ything
  - Tries to metabolize/process bad stuff so it doesn't reach other organs (e.g. brain)

Liver: same as all other organs PLUS: Portal Circulation



Main metabolic engine of body

- Takes in all nutrients (and bad stuff) from intestines
- Regulates glucose in blood
  - Stores it as glycogen when not needed
  - Releases it to blood when it is needed
- Regulates cholesterol
  - Synthesizes it
  - Converts it to bile salts and excretes it
- Stores iron, vitamins, trace elements
- Metabolizes proteins (amino acids)
- Produces clotting factors

More Liver Functions

- Body can't store protein
  - Eat too much, it must get broken down
    - When broken down, it produces ammonia ion - very toxic
    - Liver converts this into harmless Urea, which is returned to blood and excreted by kidney
- Red blood cells only last ~120 days
  - Liver and spleen break them down
  - Kupfer cells in liver gobbles dead RBC hemoglobin and breaks it down, recovering iron
  - Breakdown product is bilirubin (yellow substance)
    - Liver excretes this as bile into intestines

Liver as "defender"

- Kupfer cells (like phagocytes)
  - Harmful bacterial products from gut metabolized or converted to something harmless
  - See in next talk -they can trap many small particles
- Harmful substances ingested:
  - Toxins (amanita? Spoiled food? Etc.)
    - IF it can, metabolizes into less harmful, if not…
    - Metabolites may themselves be toxic to liver and rest of body
  - Alcohol
    - Metabolites and intermediate metabolites can damage liver (hepatitis)

Hepatitis

- Toxins, diseases, etc. of liver -> inflammation
- "Hepatitis"
  - ¾ billion people
  - Impairs function of liver (including clotting)
  - Predisposes you to primary liver cancer
  - Can be caused by *many* different things
    - Viruses (most common cause)
      - Hepatitis A, B and C viruses
      - Hep B (biggest group) most common in Asians (born/1st gen.)
        - » One of top causes of death amongst asian americans

Hepatitis

- NOT just caused by virus
  - Alcohol use
  - Other toxic chemicals ingested (or breathed or injected)
    - Drugs, Mushrooms, poisons, etc
  - Blockage of bile duct system
  - Autoimmune reactions
    - Similar to Lupus, but in the liver

Hepatitis (from any cause)

- Main presenting symptom
  - fatigue, malaise, often extreme
  - Despite the fact that so many people have hepatitis
    - No idea what produces this debilitating symptom
- Yellow skin/eye
  - RBCs die -> bilirubin
  - Liver cells not converting bilirubin (yellow) into bile salts and excreting into gallbladder
  - Bilirubin builds up in blood (hence color)
- Elevated AST and ALT in blood
  - These enzymes present inside hepatocytes
  - Inflamation can injure/destroy cell membrane
  - Enzymes leak out and are returned to blood

Chronic hepatitis

- Ultimately -> fibrosis and scarring
  - Increased chance of primary liver tumor (HCC)
- Useful to monitor amount of fibrotic tissue in liver over time (need transplant? Therapy or lifestyle changes working?)
  - "gold" (copper?) standard is biopsy
  - No good way: CT/MR/US cant really image it
  - Elastography by US (or US+ MR), has been shown to be useful
  - PET glucose metabolism quantitatively? See not fibrosis but number of functioning liver cells. Combine with CT/MR for total volume.

Now that we know some of biochem Rx liver is involved in:

- Can figure out what kind of PET biochemical tracers might be important

PET tracers in Liver & tumors

- Tracers for glucose metabolism
- ^{11}C-Choline
  - Needed for cell membranes
  - Elevated in malignant cells
  - Is an ^{18}F version available in Europe
  - Good for prostate and primary Liver tumors (HCC)
- Hypoxia tracers (F-MISO and Cu-ATSM)
- Protein Synthesis - 11C-methionine
- Cell proliferation (F-Thymidine or FLT).
- Tumor blood flow (pre/post anti vegf)
- Many others

Despite all these possiblities

- Most important physiologic process for Tumors:
  - **Glucose metabolism**
- Why?
  - Primary molecule Tumors burn to produce energy.
    - To divide rapidly -> need lots of Energy
  - Something special about tumor cells that makes them need LOTS more glucose

Why tumor cells use so much more glucose than normal cells

- NOT just because they are rapidly dividing
  - Altho that certainly is important
- Due to fundamental way tumors grow
  - When they grow or metastasize
  - Don't start out with their own capillary bed
  - Don't necessarily have a good supply of oxygen
  - Over the millenia, adapted to survive with low O_2

Glucose Metabolism

- Normal Cells
  - Oxidative metabolism
  - Glucose -> pyruvate -> CO2 and Water
  - Get about 30 ATP's for every glucose metabolised
  - First steps (called "glycolysis") need no oxygen
    - Produced very little Energy (ATP)
  - Pyruvate on -> needs LOTS of oxygen
    - Produce LOTs of Energy (ATP)

Aerobic vs anaerobic glucose metabolism

Glycolysis

Needs a little ATP

Glucose -----> Glucose 6P -------> Pyruvate

NO OXYGEN NEEDED

(Lactate)

Gives off net 2 ATP

Pyruvate ----> CO2 + Water + **Lots** of ATP (~34)

OXYGEN NEEDED

Note: Just "Bacharach's version" of biochemistry - don't trust details

Glucose Metabolism (cont'd)

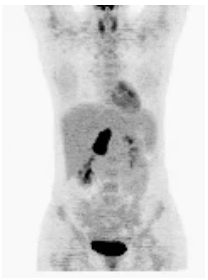
- Tumor cells
  - Have adapted to grow in an anaerobic environment
  - Even if they are NOT in anaerobic environment, Warburg (1930's) discovered that tumors often undergo anaerobic metabolism
  - Glucose -> lactate + 2ATP's
- So tumor cells produce ~15 times less ATP per glucose than normal cells
- Therefore tumors need ~15 times more glucose than normal cells!! (for same energy consumption)

(factors are approximate - I think I forgot atp needed)

Malignant lesions have elevated glycolysis (Warburg, 1930)

- Energy Production
  - Normal cells: E from oxidative metabolism
  - Rapidly growing Tumor: E from glycolysis (no O_2 req'd)
- Tumors -> Often over-expressed GLUT's
- Increased activity of hexokinase
  - Enzyme needed in glycolysis (the "no-O2" process)

What a glucose metabolic image looks like



Glucose metab & agressivemess

- Differentiated vs. un-differentiated cancer cells
  - Well diff. Colon cancer cell
    - Looks a lot like a regular colon cell
    - Has adapted to to grow and survive in the colon
    - Doesn't do well if transplanted elsewhere
    - So metastases are difficult – not very aggressive
  - Poorly differentiated colon cancer cell
    - Not yet developed into a real colon cell
    - A bit like a stem cell
    - Can grow anywhere
    - Can move to brain, liver,etc and adapt to its new surroundings
    - VERY aggressive
- Un-Diff cells: ↑glycolytic capacity
- Well Diff. cells: ↓ glycolytic capacity
- Aggressive (poorly diff) tumors use MORE glucose than less aggressive (highly diff)

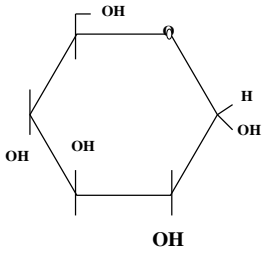
Glucose and agressiveness

- High glucose metabolism
  - Aggressive tumor
- Low glucose metabolism
  - Less aggressive tumor

How to measure glucose consumption with PET?

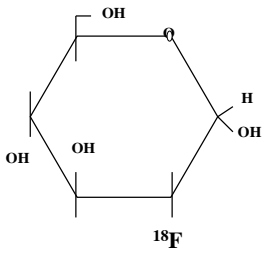
- Label glucose (e.g. with ^{11}C)
  - Bad idea
  - The $^{11}C0_2$ or lactate goes all over the place
- 2deoxy-D-glucose
  - form that traps the glucose in the cell

Glucose



$C_6H_{12}O_6$

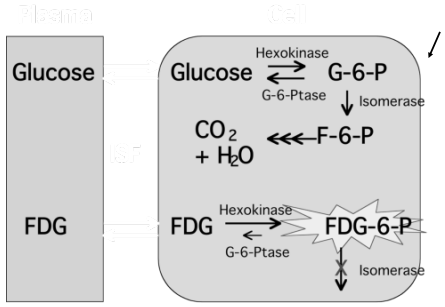
^{18}F-Fluoro-Deoxy-Glucose (FDG)



'Molecule of the Century'
- Henry Wagner

Patient injected activity: 10 mCi ~ 1 nano-gram
($6.4*10^{-12}$ moles = $3.8*10^{12}$ molecules)

How Cells "burn" Glucose and F-DeoxyGlucose

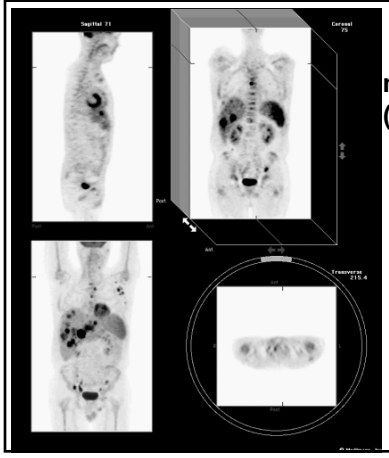


Glucose Metabolism by F-18 FDG PET

- Both FDG and Glucose enter the cell in same way
- Both FDG and Glucose get phosphorylated (1st step in E-production process)
- An enzyme converts the phosphorylated Glucose to the next step of the process.
- This enzyme doesn't work on Deoxy-Glucose
- FDG is trapped in cell

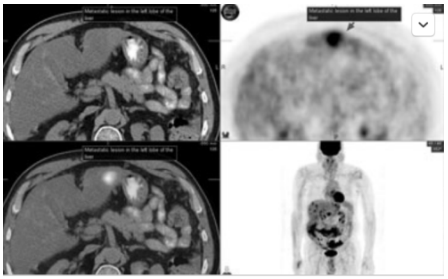
For Oncology

- Fast subject overnight
  - Reduces FA levels and competing glucose levels
  - More importantly…..
- Do NOT Generate insulin response
  - Don't want insulin response
  - Don't want high muscle uptake
  - NO Oral glucose
- Inject 18FDG
  - Wait about 45' - 1 hour



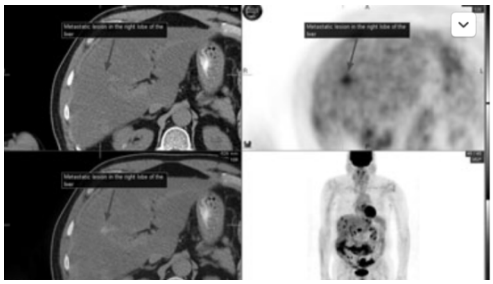
Glucose metabolic images (whole body PET)

FDG PET + CT



From: HemOnc Today, September 10, 2009
Liana Makarian, MD; Munir Ghesani, MD

FDG PET + CT (no contrast)



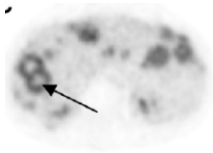
From: HemOnc Today, September 10, 2009
Liana Makarian, MD; Munir Ghesani, MD

Which part of tumor is still alive?

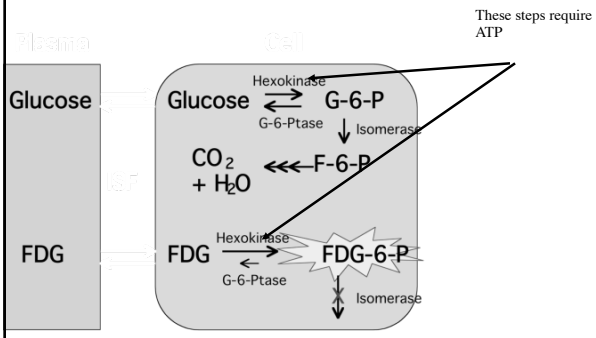
- Dead cells don't produce ATP
  - ATP needed to start the process of glucose (and FDG) metabolism
- No glucose uptake -> No living cells
  - So even if tumor still there on regular CT or MR
  - If biochemistry is not working, it will NOT show up on PET

Necrotic center of tumor (colon metastases)

- Center of tumor no longer can get good blood supply



FDG uptake -> viability



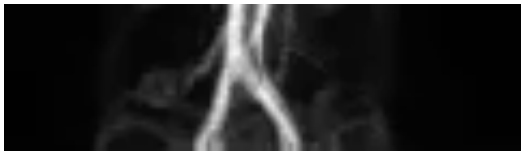
Two types of liver tumor

- Metastatic liver tumor (colon, breast, prostate,…..)
  - PET with FDG is *very* good at detecting
  - Good contrast
    - Normal Liver cells have LOTS of G6p-tase (more than other cells)
    - Normal Liver cells clear out FDG over time
    - tumor cell NOT a liver cell so stays bright
- Primary liver tumor (HCC) - not common
  - PET poorer at detecting
  - Is really a kind of liver cell
  - Not a colon cell, breast cell, etc
  - It ALSO has elevated G-6Ptase, so tumor clears out FDG too
  - Contrast isnt as good

Other interesting PET biochemical compounds

- Blood volume - using ^{11}CO
  - CO is a "poison"
  - It binds to the hemoglobin of RBCs preventing Oxygen from binding there
  - Amount CO =k*(#RBCs)
  - Patient breaths 10 or 20 mCi of CO
  - Wait 5 minutes to mix and image

^{11}CO blood volume



•Not nearly as good resolution as angiography (CT or X-ray)
•BUT: Can compute absolute volumes: brightness =K*absolute volume of blood

PET Tumor Blood flow

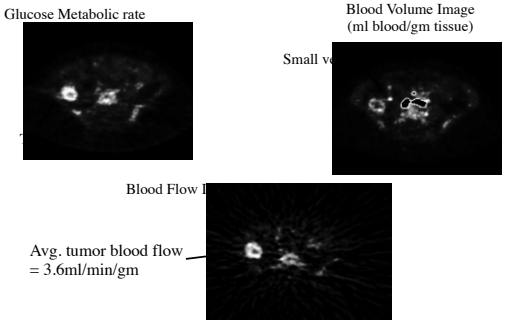
- Important for Rad therapy to see if tumor is well oxygenated
- Just like with cardiac (from last year)
  - NH_3, ^{15}O –water, etc
  - Can measure absolute blood flow to tumor

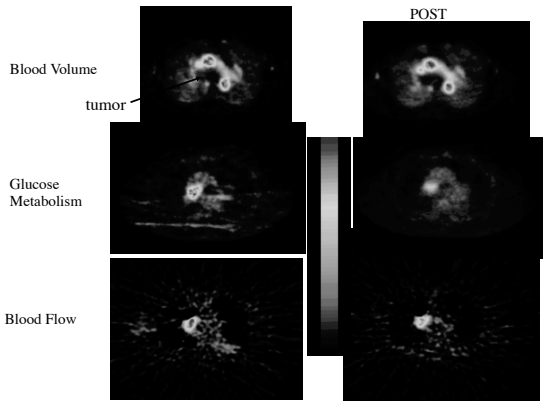
PET: Monitor Therapy

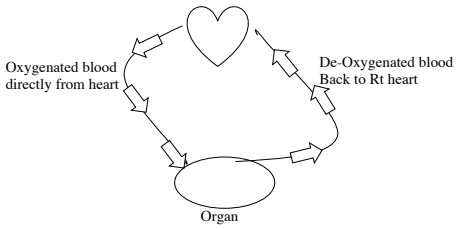
- Metabolic activity of tumor decreases as soon as cell is damaged by chemo or Rad.
  - Can see immediate drop in FDG metabolic rate
  - Can quantify this drop
  - If it does NOT drop, can quickly alter therapy
    - New chemo agent
    - Before old useless one damages patient
- Anatomic size of tumor may take weeks to significantly change
  - May be too late to alter chemo
  - Ineffective chemo has already taken its toll

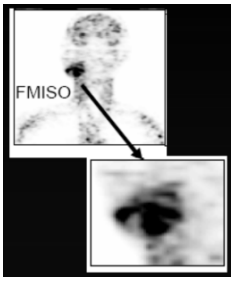
Physiologic Imaging with PET

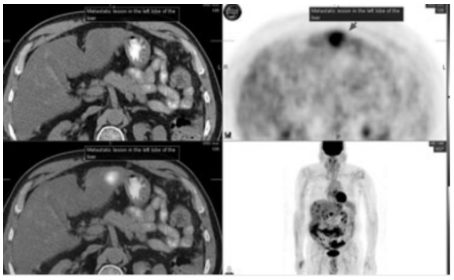
(1 Slice of 35)

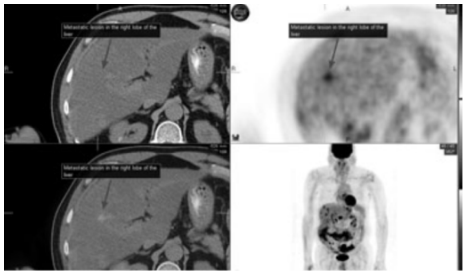




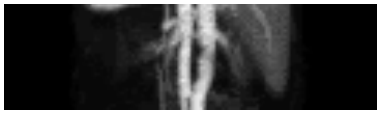








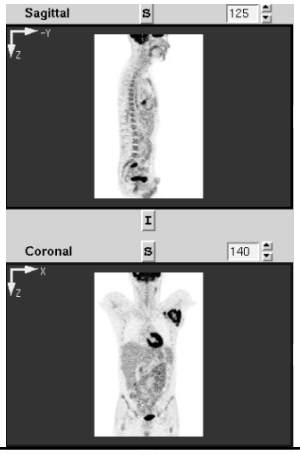
^{11}CO reprojections

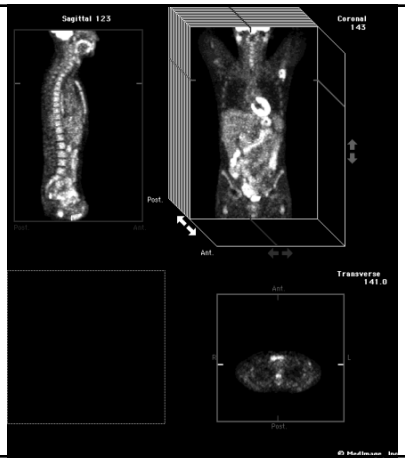


Other interesting PET biochemical compounds

- $H_2{}^{15}O$: a very good blood flow agent (we'll discuss it further later)
  - Has been used for both myocardium and tumors
- $^{13}NH_3$ - another flow agent (mostly for hearts)
- ^{82}Rb - a potassium analog
- A large number of labeled neuro-receptors
- ……(*lots* of others)

FDG:
One slice- coronal & sagittal (Lymphoma)





We have several oncology protocols to measure:

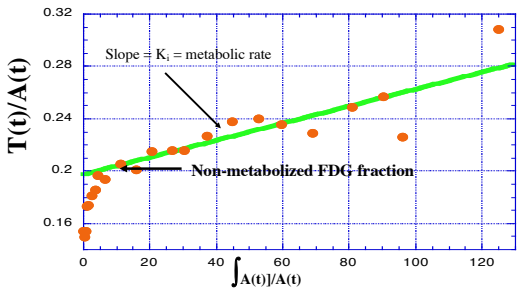
- Blood flow
  - Using O-15 water, getting ml/min/gm tissue perfused, with bolus injection
- Blood Volume (red blood cell volume)
  - Using 11CO (by inhalation)
- FDG metabolism
  - Dynamic acquisition
  - Patlak or full compartmental model
- Dynamic Enhanced MRI (DEMRI)

FDG Uptake or SUV

- Depends on amount available to tumor
  - Weight/LBM/BSA do NOT adequately correct for this
- Is *sum* of metabolized and un-metabolized FDG
  - Un-metabolized = in blood, intra/inter cellular space
- Depends on time you make image
  - Tumor FDG uptake may rise for 2 hours or more.

Patlak analysis : example

T(t) = tumor activity over time
A(t) = arterial [FDG] over time



Basis of Imaging (anti)-angiogenic therapeutic response:

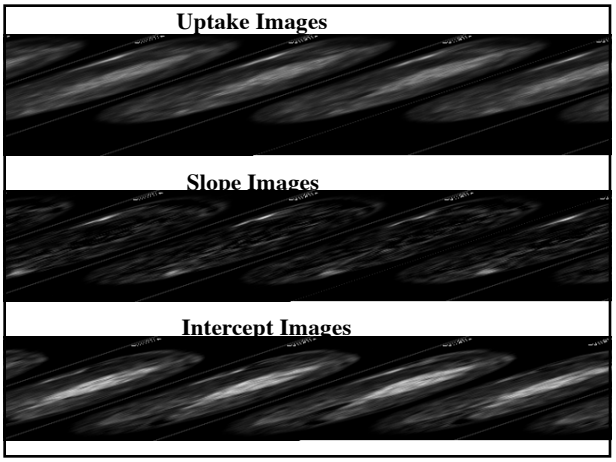
- Blood volume might increase
  - ^{11}CO PET: (Libutti et al.: Canc. J. Sci. Am., 1999)
- Blood flow might change(?)
  - $H_2{}^{15}O$ PET: (Libutti et al.: Canc. J. Sci. Am., 1999 and Lodge et al, JNM 2000)
- Permeability might increase
- Glucose metabolism might be altered (aerobic vs. anaerobic OR viable vs non-viable)

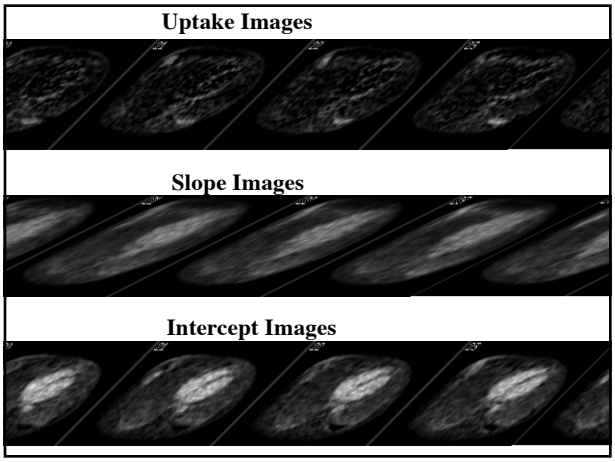
Patlak Images Revisited

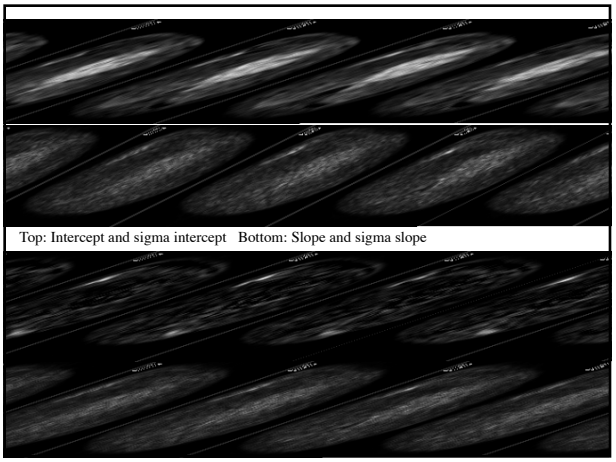
- SUV images:
  - Metabolized FDG plus un-metabolized FDG (blood, intracellular, intercellular)
  - Depend on time of acquisition
  - Depend on "available dose" (∫A(t))
- Pixel by pixel patlak images:
  - Separate metabolized and un-metabolized FDG
  - Remove time dependence
  - Built in compensation for "available dose"
  - (require dynamic scanning)

Patlak Functional Images

- Slope image (k_i)
- Intercept image (%un-metabolized FDG)
- Error images
  - Pixel by pixel Std. Dev. Images for slope and intercept

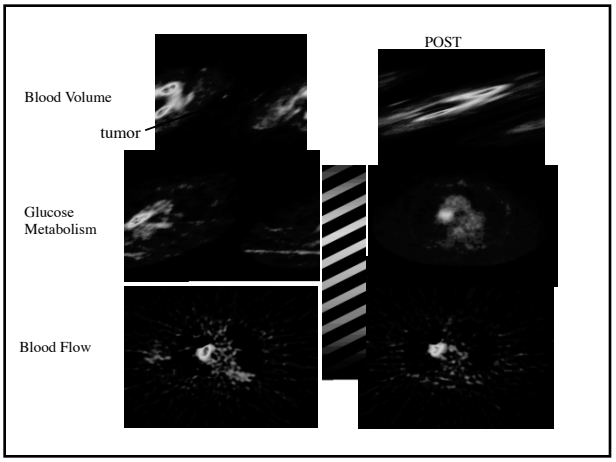






Implications for Monitoring Therapy

- Changes in SUV image do NOT necessarily reflect changes in metabolized FDG
- Inflamation, changes in vascularity can increase un-metabolized uptake
- Problem mostly at low SUV values (?)



Lets first re-examine Glucose Metabolism

- Why its important in oncology
- Why its important in cardiology
- How one images it
- Problems in quantifying

Metabolism of Glucose (one molecule)

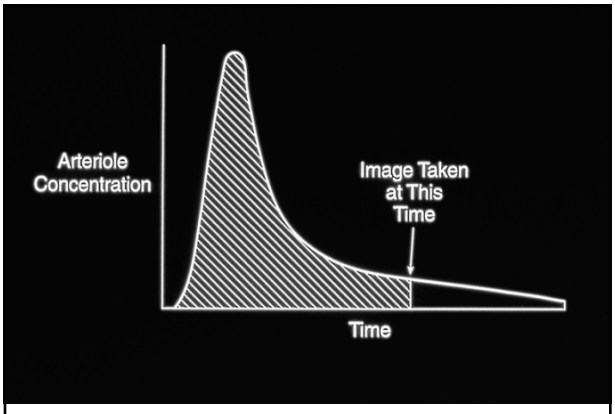
- 1st steps (called "glycolysis")
  - Don't require oxygen
  - Produce 2 ATP's of energy
- 2nd steps
  - DO require lots of oxygen
  - Produces 36 more ATP's of energy
- Therefore:
  - Very LITTLE energy w/o oxygen
  - LOTS of energy with oxygen

Malignant lesions have elevated glycolysis (Warburg, 1930)

- Energy Production
  - Normal cells: E from oxidative phosphorylation
  - Rapidly growing Tumor: E from glycolysis
  - (glycolytic capacity -> state of differentiation)
- Probably over-expressed GLUT's (many studies have found this in a variety of tumors)
- Increased activity of hexokinase

Cardiac Glucose Metabolism

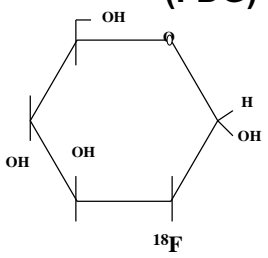
- Unlike brain (or tumors?), heart utilizes many substrates
- Of all oxygen consumption by heart:
  - ~30--40% from glucose metab.
  - ~60% from fatty acid metab.
- Hypoxia: ↑ Glucose metabolism
- Cardiac glucose metab. -> insulin



If you can't measure ∫A(t)

- Compute "Standardized Uptake Value" (SUV)
- SUV = (uptake) / { am't injected/body weight}
- SUV = (uptake)/ {am't injected/LeanBodyMass}

^{18}F-Fluoro-Deoxy-Glucose (FDG)



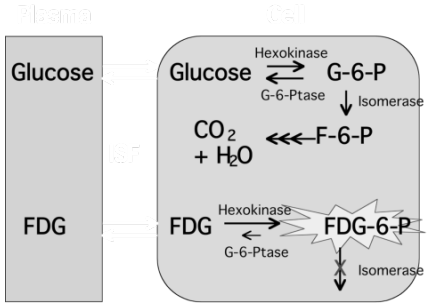
'Molecule of the Century' - Henry Wagner

Patient injected activity: 10 mCi ~ 1 nano-gram
($6.4*10^{-12}$ moles = $3.8*10^{12}$ molecules)

Glucose Metabolism by F-18 FDG PET

- Both FDG and Glucose enter the cell in same way
- Both FDG and Glucose get phosphorylated (1st step in E-production process)
- An enzyme converts the phosphorylated Glucose to the next step of the process.
- This enzyme doesn't work on Deoxy-Glucose
- FDG is trapped in cell

How Cells "burn" Glucose and F-DeoxyGlucose



Using FDG uptake to monitor Tumor Therapy (or hearts)

- Is just looking at pre/post therapy FDG uptake images enough?
- Maybe - but can do *better*.

To use FDG to Monitor Therapy:

- Normal Physiologic variability of *tumor* must be small
  - Munich group: ~9% total variability on repeat studies
  - They controlled patient metabolic status
- Methodologic and physiologic variability of rest of body must be small
  - May *not* be true depending on how you do it

FDG Uptake in Tumor (over time, with therapy)

- Depends on physiology of tumor
  - *That's* what you are interested in
  - Changes in glycolytic rate in tumor
    - Changing energy needs
    - Glut transporter changes
    - Hexokinase changes/ ability to produce ATP
- Depends on how much FDG was available to tumor from the blood.
  - *Not* determined by blood flow

What *is* Amount Available to Tumor?

DEPENDS ON:

- [FDG] in blood perfusing tumor
  - A(t), the arterial concentration of FDG
- How high A(t) is and how long it stays that high

These in turn depend on:

- How much was injected
- Are other organs or tissues taking up glucose?
- How quickly is the FDG excreted
- *(Not* blood flow)

What does A(t) depend on?

- amount available to tumor (or other organ)
  - –amount injected
  - –amount taken up by other tissues
  - –amount eliminated from body

A(t) may be different pre and post therapy

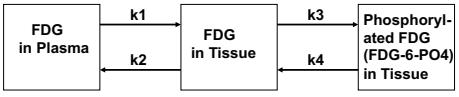
- To correct for this:
- Measure A(t)
- Divide measured uptake by area under A(t)

Corrected Uptake = (Uptake)/ ∫A(t)dt

SUV

- If FDG went to whole body uniformly
  - Dose/body weight gives SUV = 1
- But fat uses very little glucose
  - Therefore Dose/(Lean Body Mass) is better
  - Still assumes FDG goes uniformly to all non-fat tissue.
- Does *not* account for changes in metabolic status of body at different times
  - e.g. changes in liver, excretion, etc
  - Perhaps caused by the therapeutic agent

Model to Measure Regional Glucose Utilization



- **Measure arterial input function**
- **Measure tissue time-activity curve**
- **Fit model to measured arterial curve and tissue curve**
- **mRGU = (plasma glucose/ LC) * (k1* k3) / (k2 + k3)**

Patlak Analysis

- Avoid fitting the complicated model
- Still need arterial input function
- Much simpler and faster to do
- Fit (modified) data to straight line
  - –slope = mRGU

Why Tumor Blood Flow?

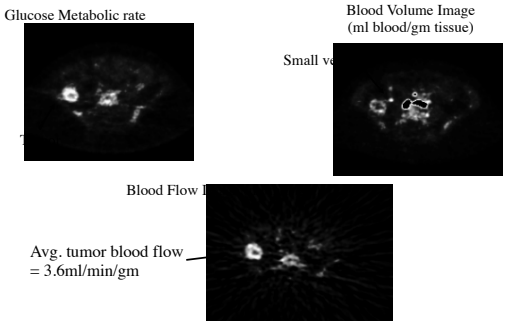
- Can affect metabolic activity
  - Relationship of metabolism to flow
- Assess delivery of therapeutic agents
- Monitor angiogenesis (?)

Tumor Blood Flow by $H_2{}^{15}O$

- Based on brain and heart models
- Are big differences between two
- Which is best for tumors?

Physiologic Imaging with PET

(1 Slice of 35)



To Compare Tracer Uptake from one study to next

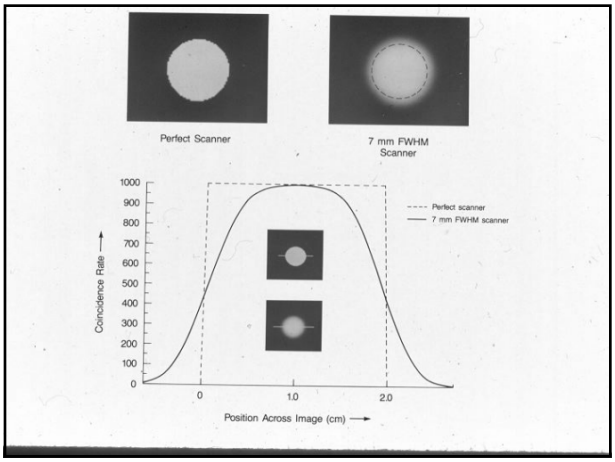
- Compute absolute metabolic rate or flow
- "Standardize" the uptake values

Low Variability of FDG uptake (for repeated studies)

- Keep blood glucose at same levels
- Keep insulin levels constant
  - even for insulin independent tumors
- Keep competing substrates constant
- Begin imaging at same time
  - Assumes tumor uptake curve the same

Partial Volume effect

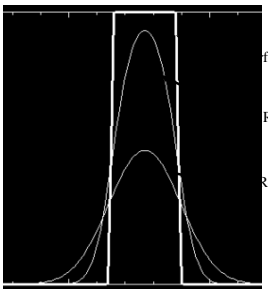
- A problem in all modalities when you image objects <2* resolution
  - CT or MR (in-plane or esp. with thick slices)
  - PET when lesions are <1 – 1.6 cm or so in any direction.



Partial Volume Effects

- What do they do to our images?

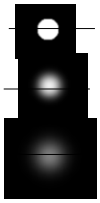
Tumor looks bigger and dimmer as resolution gets worse



fect scanner

Resolution =5 mm

Resolution =10 mm

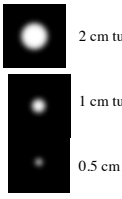


Same size tumors

(10mm diam)
Same uptake

Scanner w/ 5 mm resolution (but tumors of different sizes)

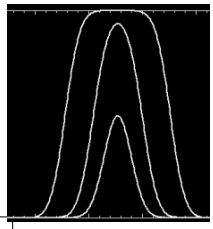
Should all have **same** max height



2 cm tumor

1 cm tumor

0.5 cm tumor



All tumors have SAME FDG uptake!

All should have SAME brightness!

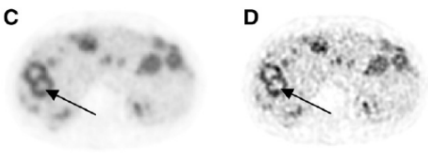
Partial volume effect: BIG problem

TUMORS	HEARTS
• You think small tumors are less aggressive than they are	• Thin myocardial walls may appear to be non-viable (or have reduced perfusion)
• If it shrinks during therapy you also THINK its metabolic rate has gone down (maybe wrong!)	• Changes in myocardial thickness cause you to THINK activity has changed (wrong!)
• If tumor grows, you erroneously think it got more metabolically active	

Partial Volume Correction

(see Soret, Buvat, et al JNM 2007)

Possible, but not yet clinically available



Ratio: (Hot "rind")/("necrotic" center)

Uncorrected (C): 1.7

Corrected (D): 5.3

Recovery coefficient

- Using phantoms, plot apparent activity versus actual activity
- Do it for different size tumors
- Apply the results to real tumor, using CT for estimating real size.

Instrumentation:
the first step in "getting it right"

Even if you get everything right

- Physiology

OR

- Physics
(or both)

Can mess you up

FDG Uptake in Tumor (over time, with therapy)

- Depends on physiology of tumor
  - *That's* what you are interested in
  - Changes in glycolytic rate in tumor
    - Changing energy needs
    - Glut transporter changes
    - Hexokinase changes/ ability to produce ATP
- Depends on how much FDG was available to tumor from the blood.
  - *Not* usually determined by blood flow
  - (explain why)

What *is* Amount Available to Tumor?

DEPENDS ON:

- [FDG] in blood perfusing tumor
  - A(t), the arterial concentration of FDG
  - Often called the "Input Function"
- How high A(t) is and how long it stays that high

This in turn depends on:

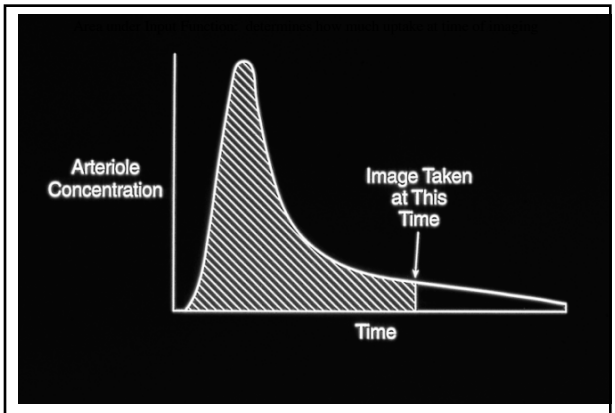
- How much was injected
- Are other organs or tissues taking up glucose?
- How quickly is the FDG excreted
- How long you waited before imaging
-
- *(Not* blood flow)

what factors does Arterial concentration depend on?

- Dose injected
- How much is taken up by all the various organs (and how fast is it taken up by these other organs, tumors, tissues)
- How much is excreted (and how fast).

Ideally:

- Measure arterial concentration as function of time A(t)
- Determine how much FDG was available to the tumor
- (this is the area under the A(t) curve how much [] and for how long)



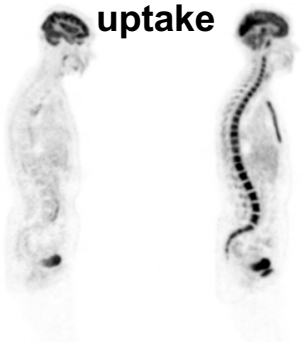
To normalize FDG uptake

- Measure uptake at time T
- Divide it by integral under A(t)
- Normalized Uptake = (measured uptake)/ $_0\int^T$ A(t)dt

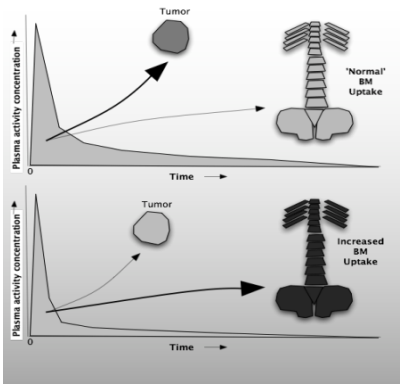
Area Under Curve: (and so the FDG available to the tumor) is affected by FDG uptake by other organs

- Chemo and rad therapy can affect metabolism of many body systems
- Example: often GCSF (a bone marrow stimulating factor) is given during or before therapy

Typical vs Increased BM uptake



BM "steals" FDG from the bloodpool, and therefore from the tumour



Tumor uptake affected by uptake of other organs

- We've used the example of BM uptake, but it could just as well be changes in liver uptake, kidney function, muscle uptake, etc.
- Uptake by other organs can be affected by drugs, rad therapy, diet, passage of time.

Can Correct for all of this

- Divide by the area under the curve

  (this could be made clinically practical)
  ("simplified" kinetic analyses, dual time point imaging)

  OR

- Do kinetic analysis (Patlak analysis)