Principles of nuclear metabolic imaging

Prof. Dr. Alex Maes

AZ Groeninge Kortrijk and KULeuven
Belgium

I. Molecular imaging probes

A. Introduction

- Chemical disturbances will precede anatomical abnormalities in disease. For example, genetic mutations will precede clinical symptoms of cancer by many years.

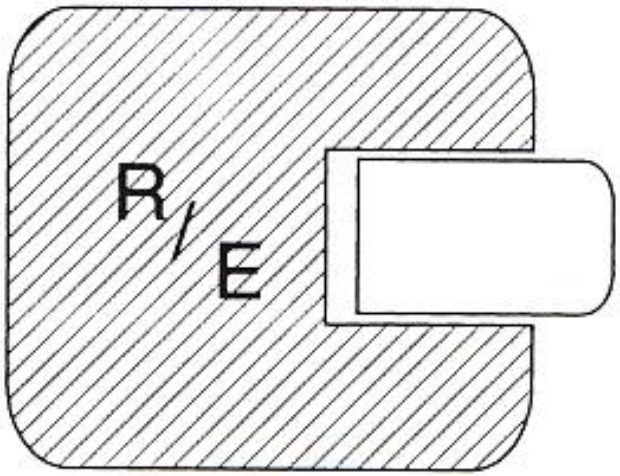
- Diagnostic procedures using imaging probes which detect biochemical abnormalities will permit earlier detection of disease.

- Imaging probes and drugs share common concepts in structural design and principle of action because they target the same enzymes, receptors and neurotransmitter systems.

- Drugs block or inhibit their targets and thus restore chemical imbalances resulting in control or remove clinical symptoms.

-Molecular imaging probes probe the same targets assessing their functional status.

-Thus, drugs and molecular imaging probes will be structural analogs of each other.



Drugs

In high concentrations

Molecular Imaging Probes

At tracer levels

Michael E. Phelps - PET Molecular Imaging and Its Biological Applications - Springer - 2004

B. Molecular probe design: general principles

- Investigation of living organisms must be performed with a minimum of interference with the system under investigation.

- The introduction of radioactive molecules produces only minimal disturbances due to the extremely low mass of the probe.

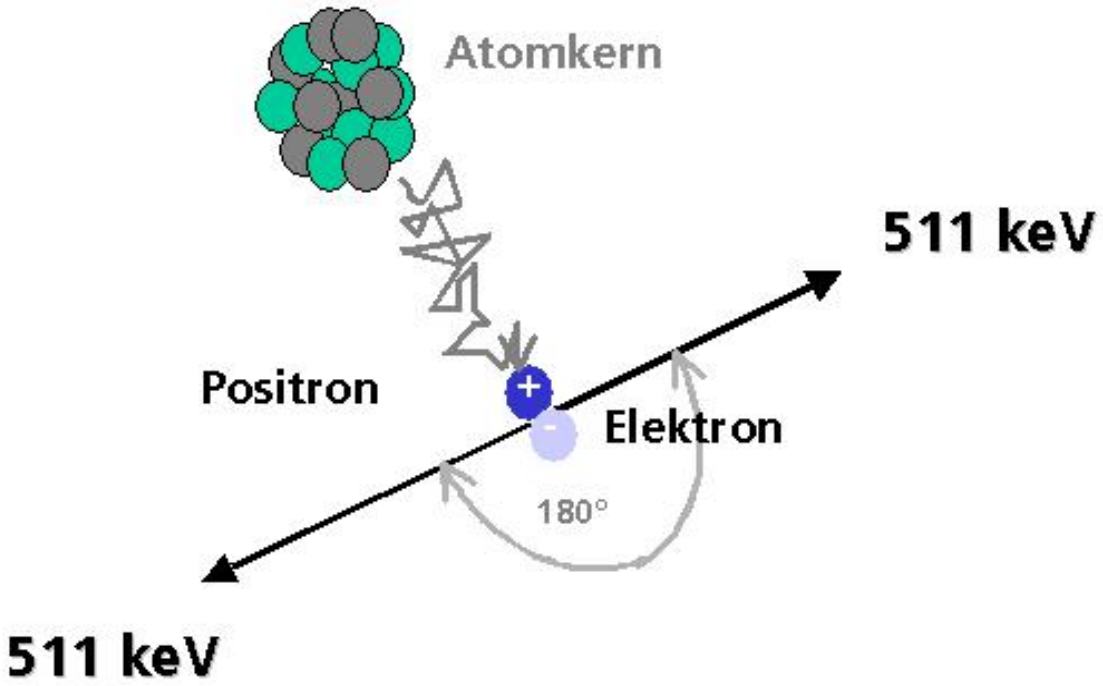
Criteria for selecting and using molecular imaging probes

1. Target specificity
2. High membrane permeability to reach target areas
3. Use of molecules specific to one biochemical pathway
4. High affinity of the molecular probe for its tissue target
5. Rapid blood pool clearance
6. No or slow peripheral metabolism of the probe
7. High specific activity to trace the process without exerting mass effects on the target molecule.
8. Low non specific binding

Probes used in positron emission tomography:

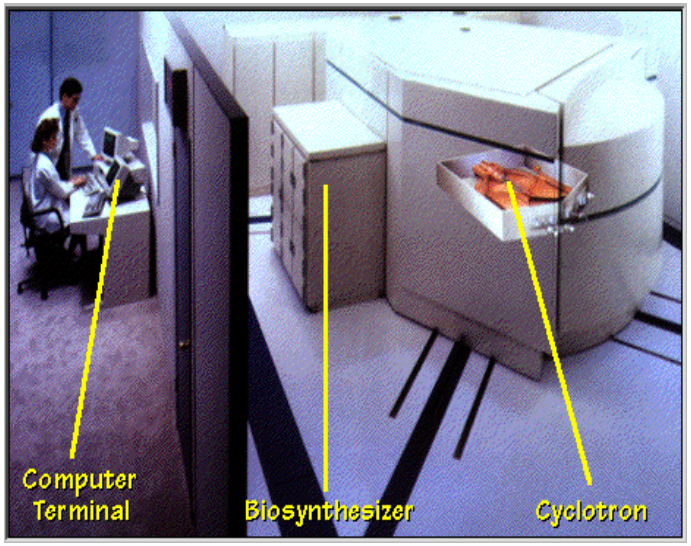
Positron emittors

^{18}F, ^{15}O, ^{13}N, ^{11}C

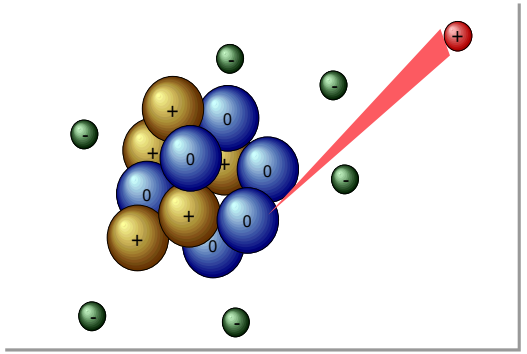


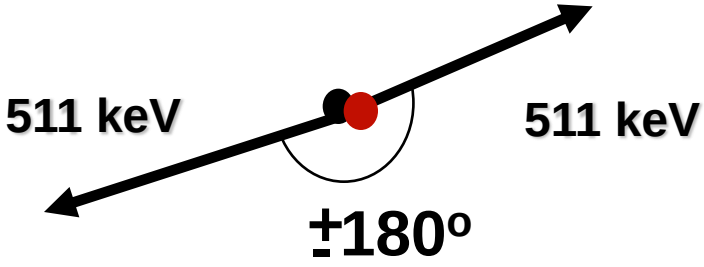
Cyclotron

CYCLOTRON & RADIOCHEMISTRY



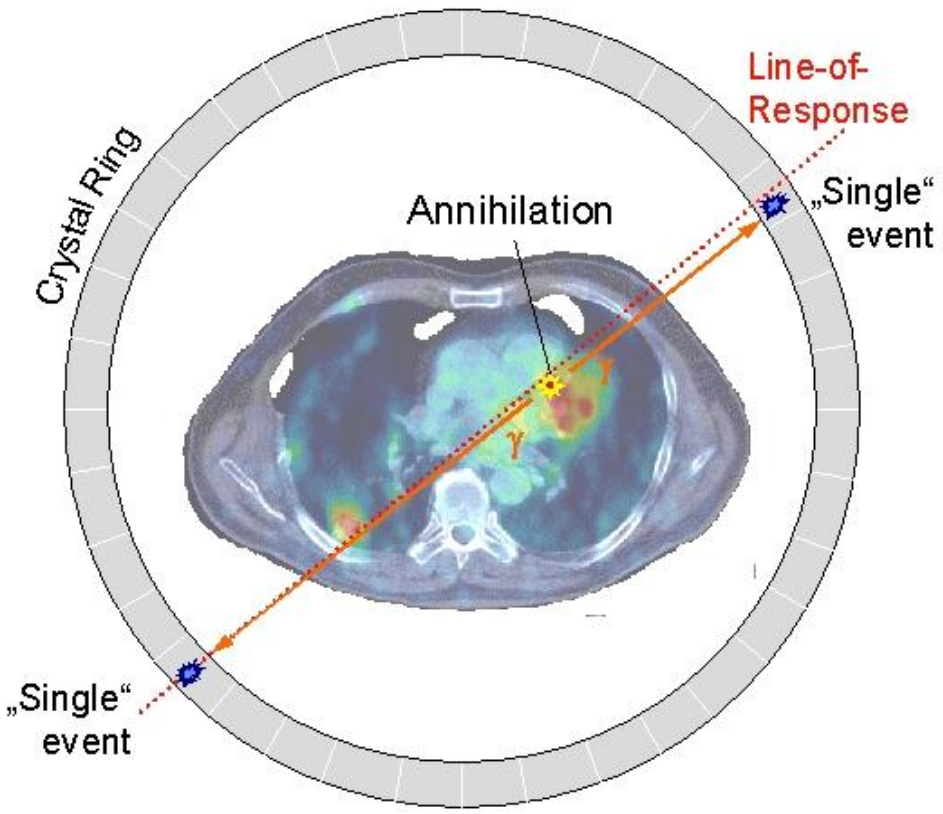
(β + emissie)
^{11}C, ^{18}F, ^{13}N, ^{15}O

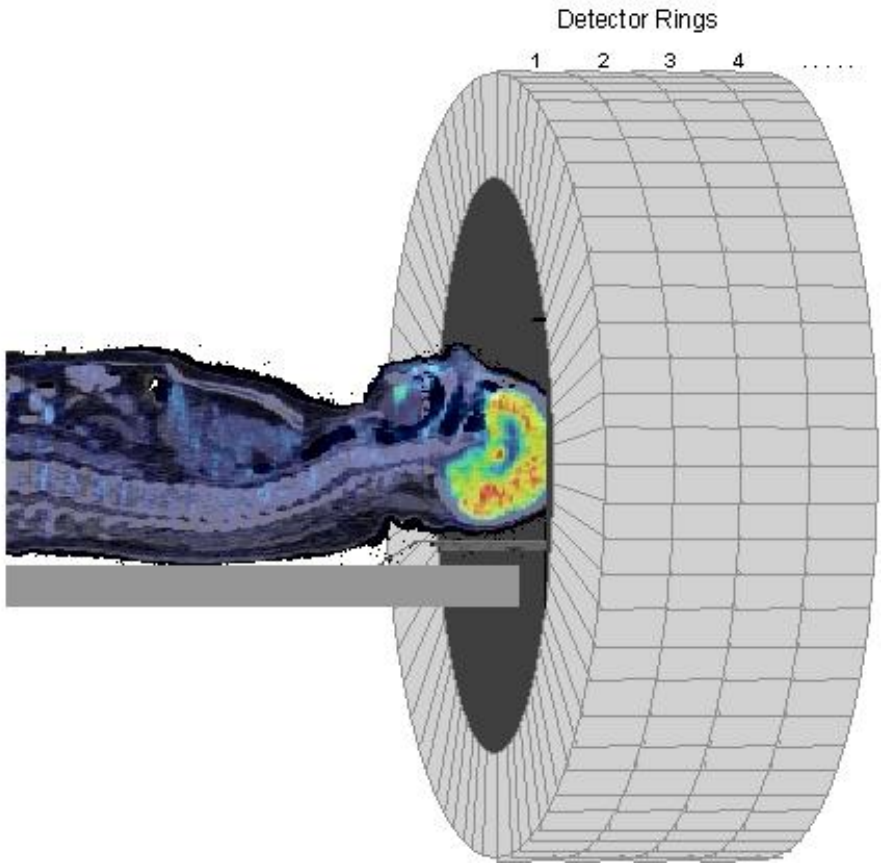




Annihilation Radiation

Detection in Positron emission tomography (PET): Localization of positron annihilation



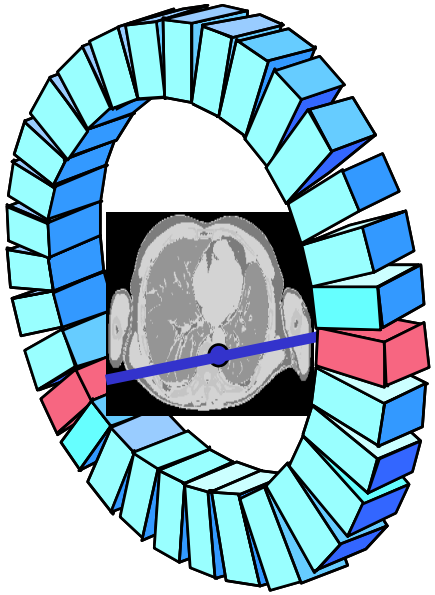


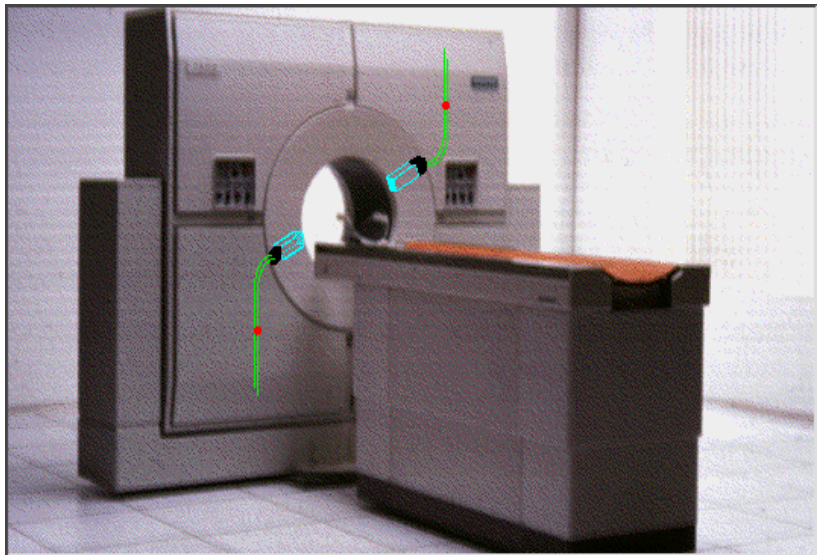
The Multidisciplinary Art of PET

PET SCANNER → IMAGE

coincidence detection

3D-biodistribution (whole-body)





C. Types of molecular imaging probes

1. Probes for determination of perfusion

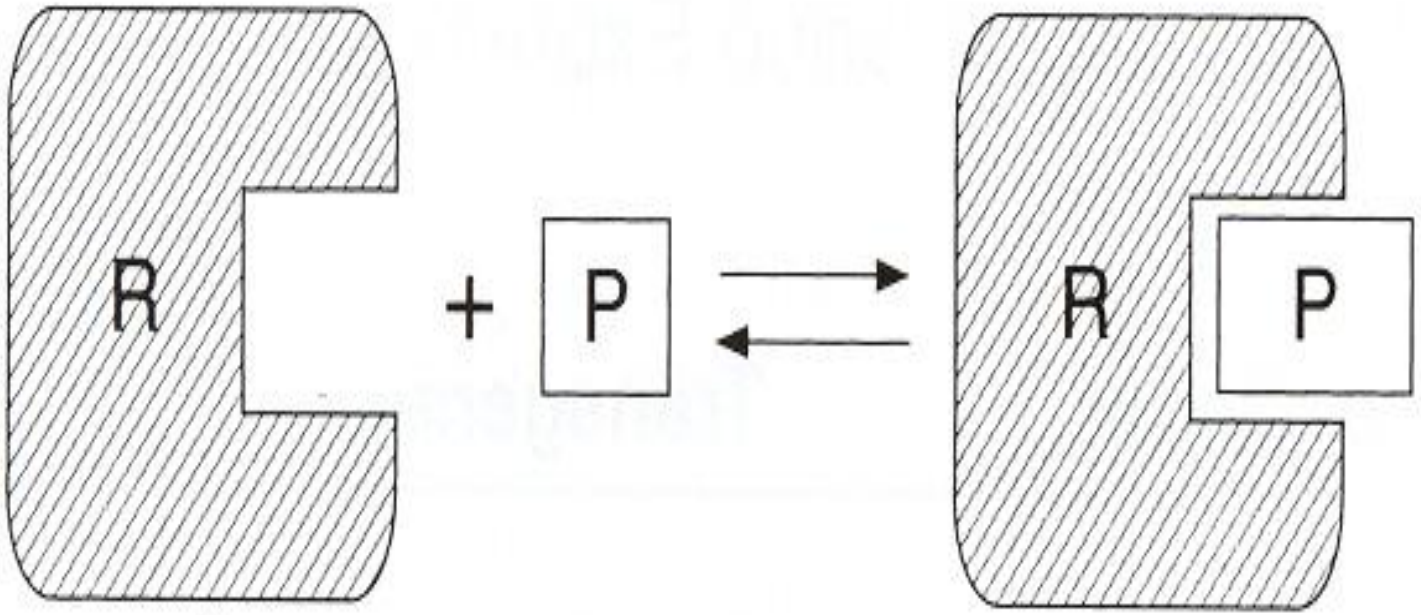
These probes have no specific structural requirements, except for high vascular membrane permeability without specific macromolecular targets in tissue.

2. Probes based on stoichiometric binding interactions

These imaging probes are radiolabeled drug derivatives or analogs binding with a high degree of specificity to receptor systems, neurotransmitter presynaptic reuptake carriers or enzymes.

The probes do not experience chemical modifications as a result of the interaction.

Trapping of receptor mediated probes is the result of stoichiometric binding to the target site.



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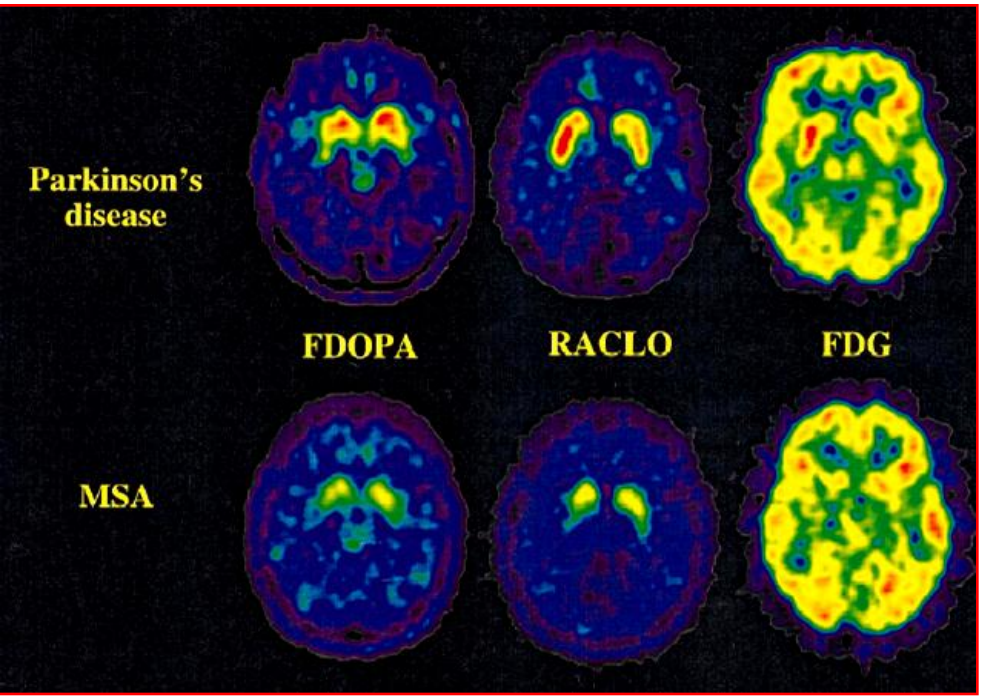
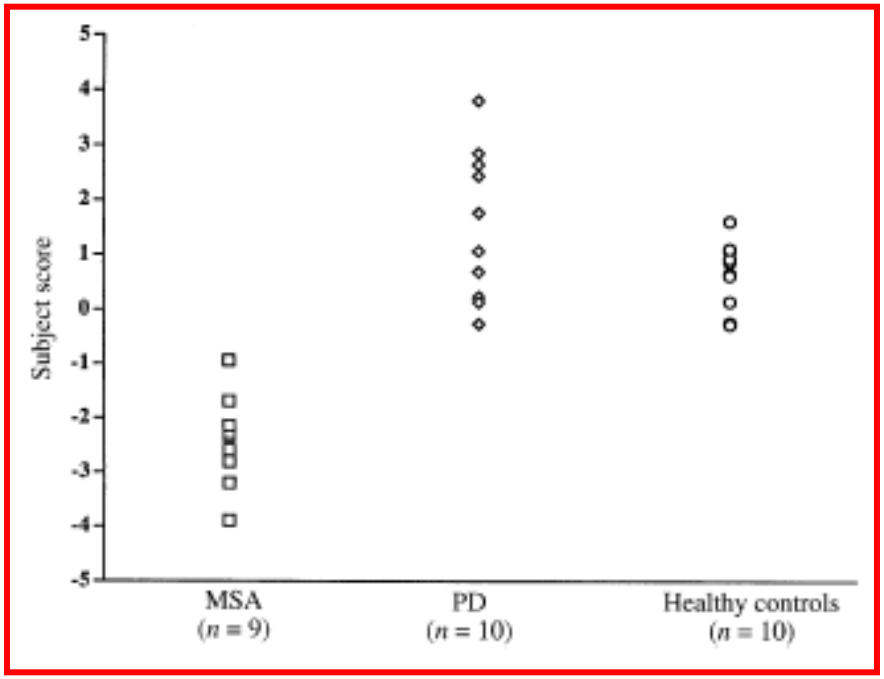
MSA vs IPD – postsynaptic PET measures





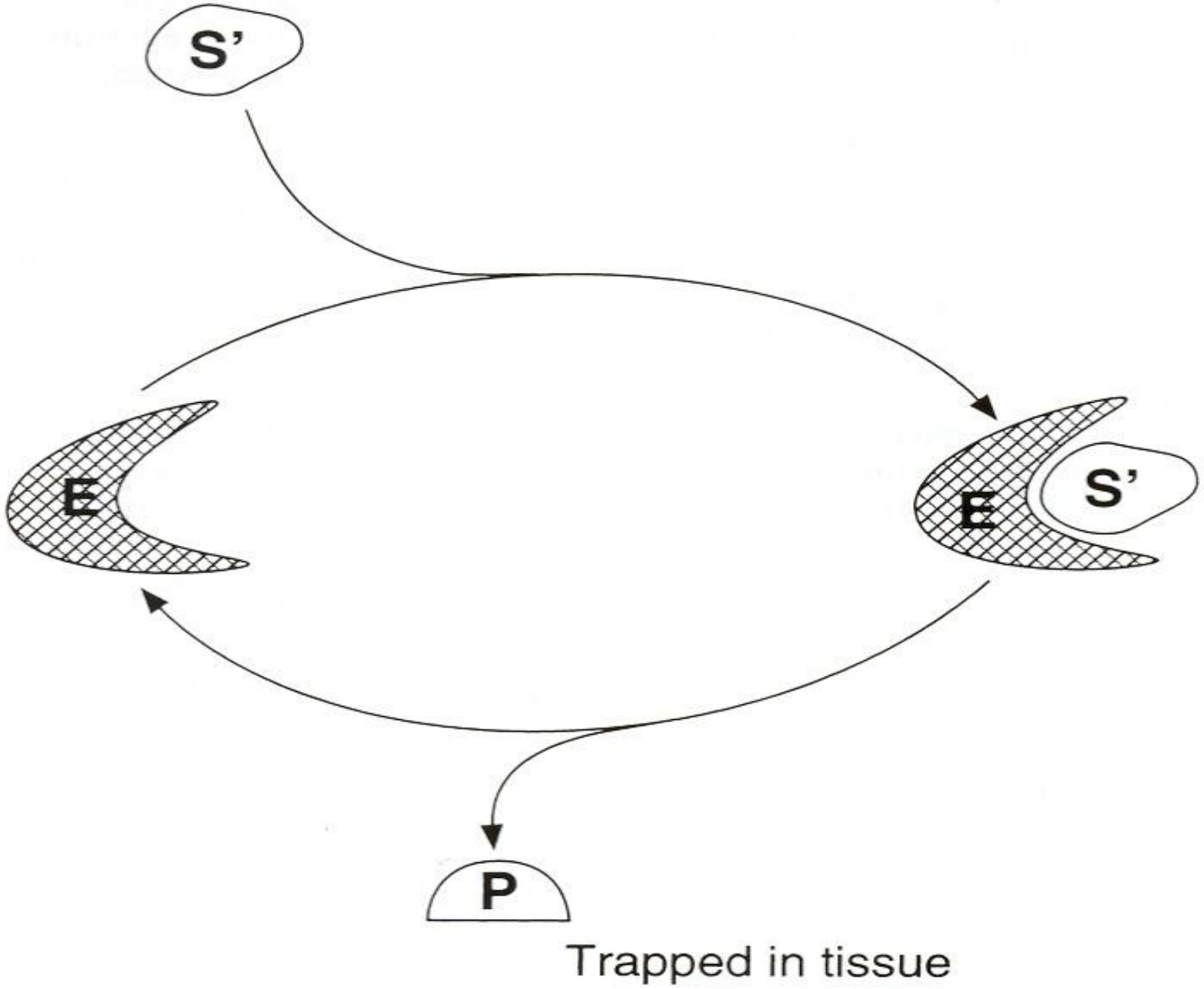
Antonini et al, Brain 1997

3. Probes based on enzyme-mediated transformations

- These probes are characterized by trapping in tissue the product of a specific interaction of the probe with an enzyme.

- The interaction will produce a chemical transformation of the original probe catalysed by the enzyme.

- The product of the enzyme-mediated transformation is impermeable to cell membranes and is retained in tissue in proportion to the rate of reaction of the enzyme-mediated process. This is called **metabolic trapping**.



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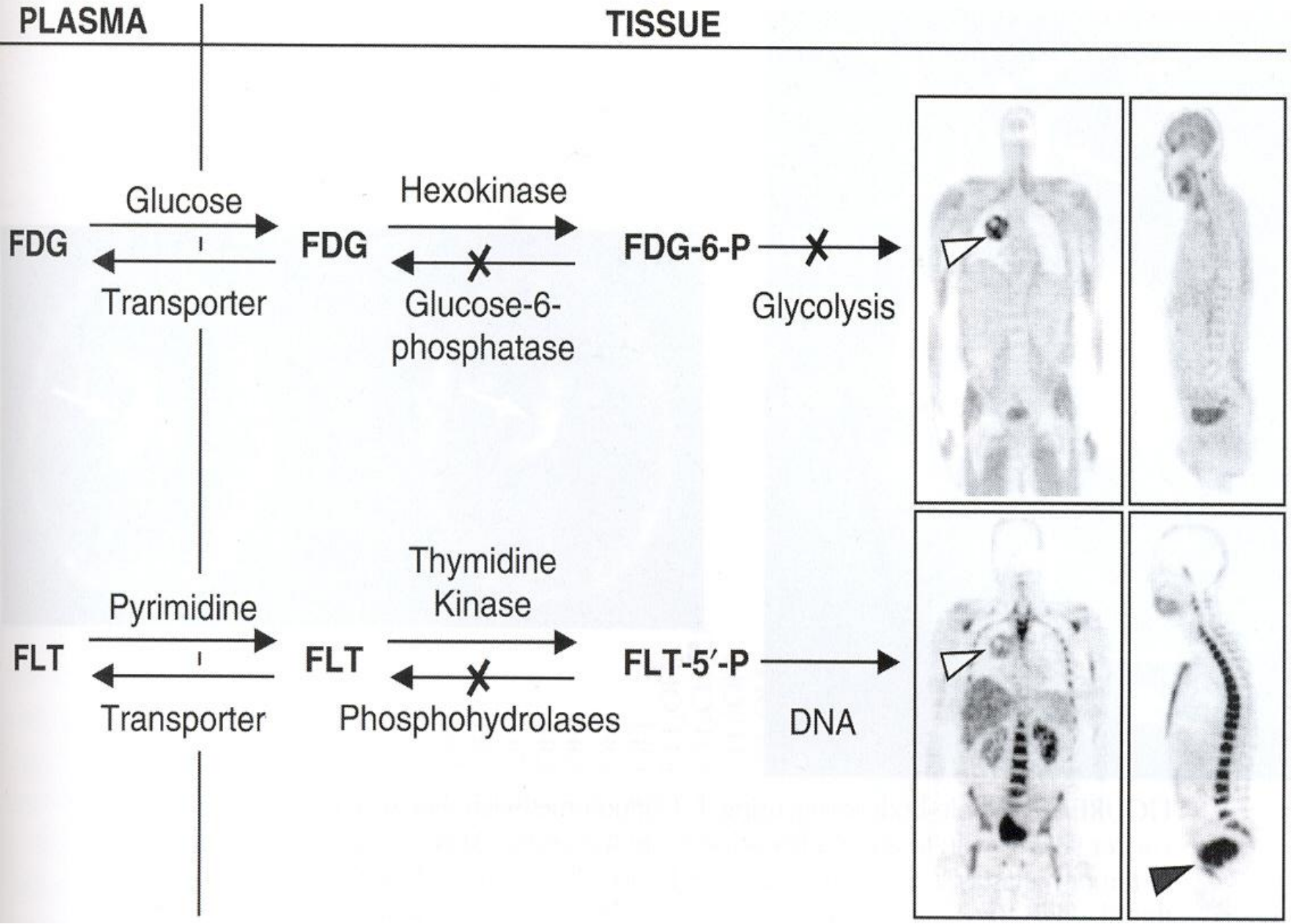
Examples of PET imaging probes acting through this mechanism:

- Hexokinase mediated trapping of FDG-6-phosphate after fluorodeoxyglucose (**FDG**) administration.



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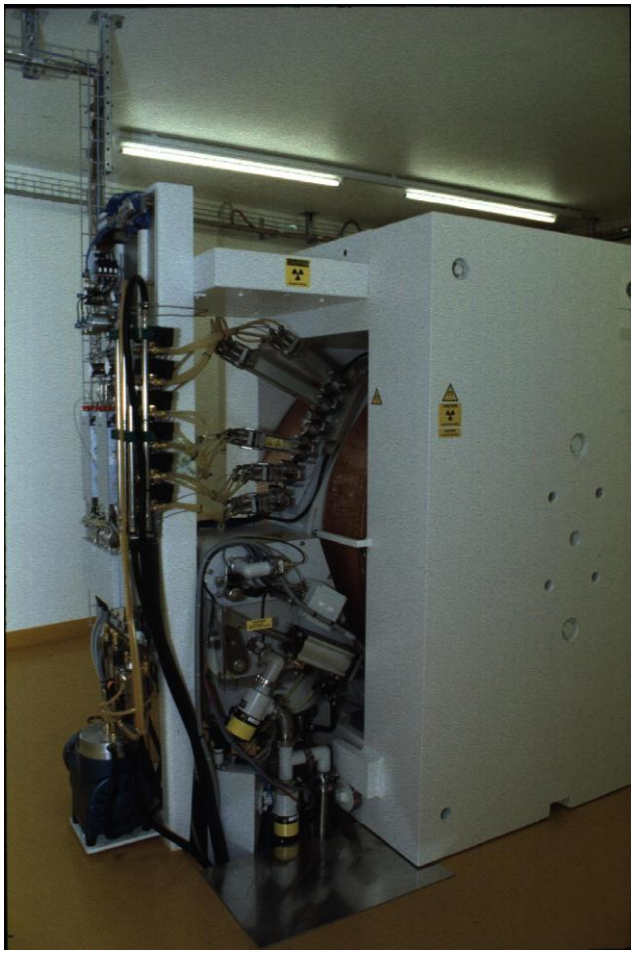
Most used PET tracer for clinical oncology

Fluor-18 – deoxyglucose = FDG

Half-life-time: 110 minutes, iv injection

Production of fluor-18 – deoxyglucose



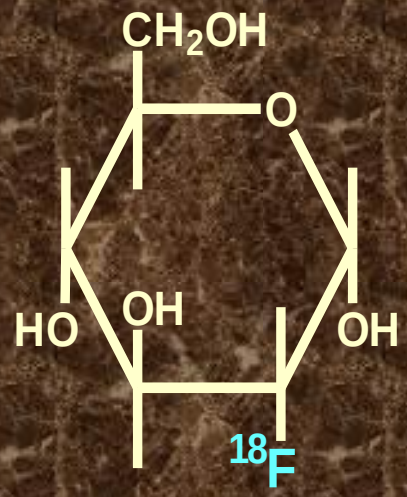
Cyclotron

METABOLISM

TRACERS

Glucose

^{18}F-FDG



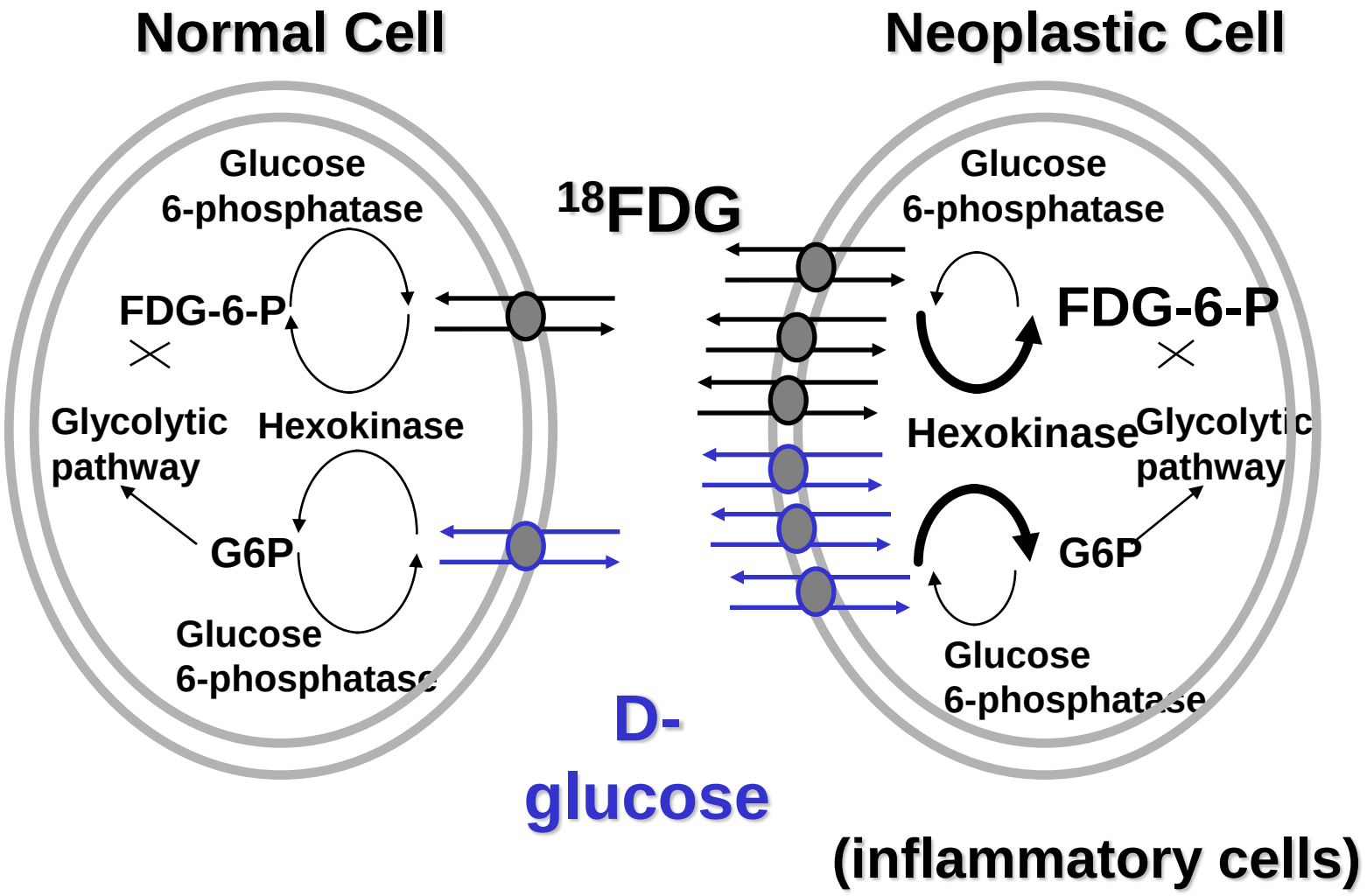
fluorine18-fluorodeoxyglucose

What is PET able to do with FDG ?

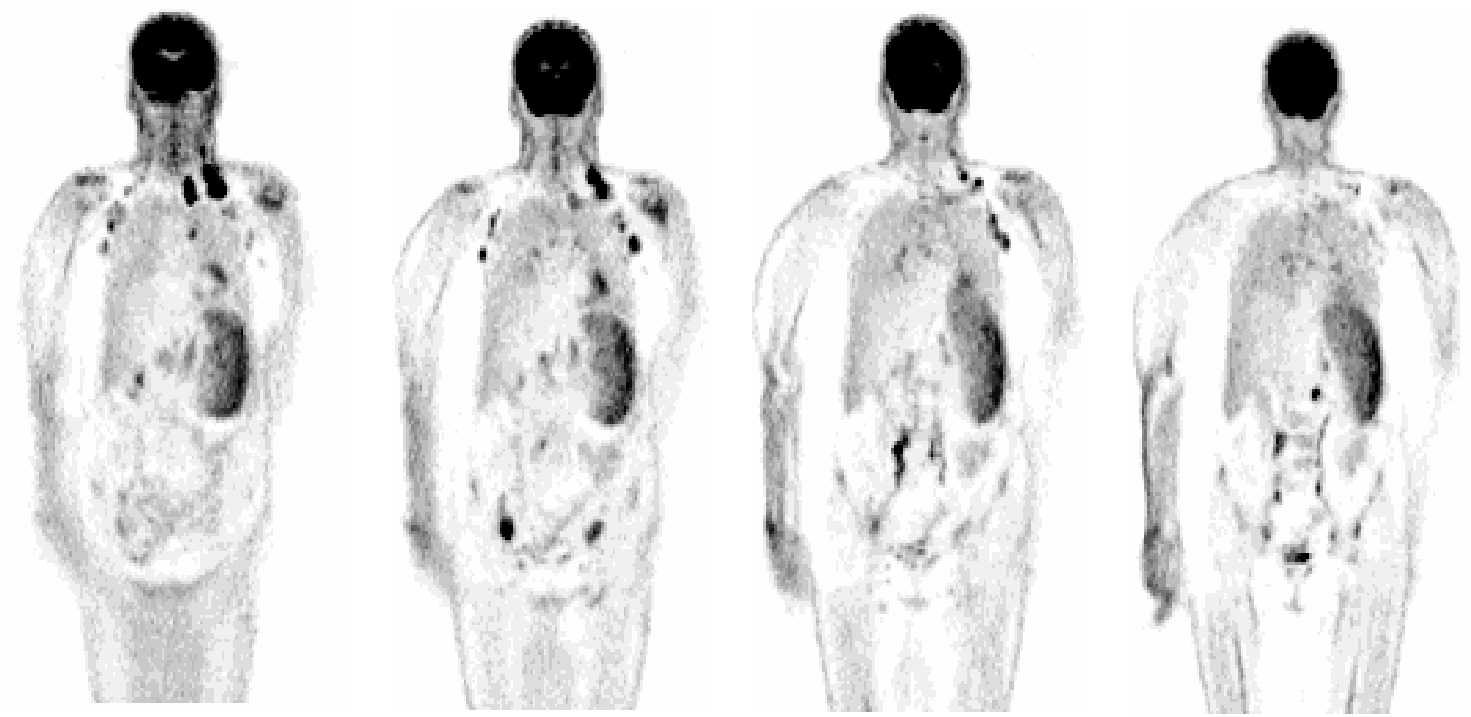
- Imaging and measurement of glucose uptake
- Into normal tissue
  - **Brain, heart, liver and other organs**

- In cancer tissue
  - **Brochial, skin, colon, liver, lymph node, esophagus, larynx-cancer**

- in inflammation

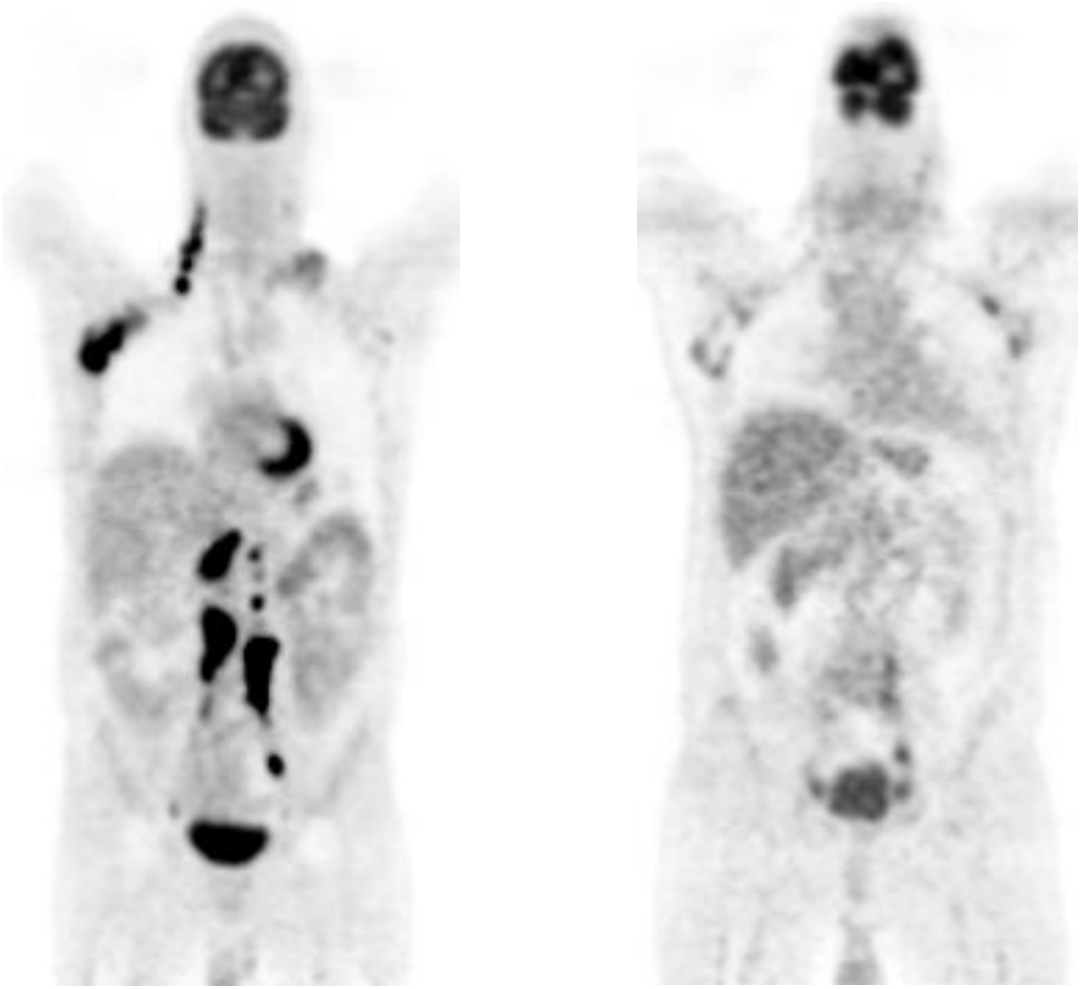

Normal Cell
Neoplastic Cell
Glucose
6-phosphatase
FDG-6-P
Glycolytic
pathway
Hexokinase
G6P
Glucose
6-phosphatase
18FDG
Glucose
6-phosphatase
FDG-6-P
Hexokinase
Glycolytic
pathway
G6P
Glucose
6-phosphatase
D-
glucose
(inflammatory cells)

Whole body FDG PET
lymphoma



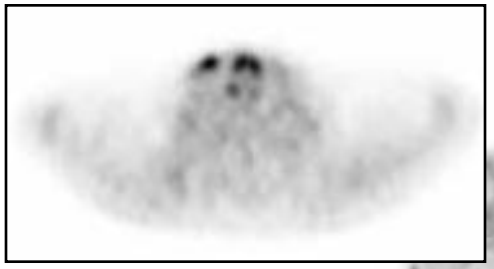
FDG avidity

Variability within same histological subtype: example DLBCL

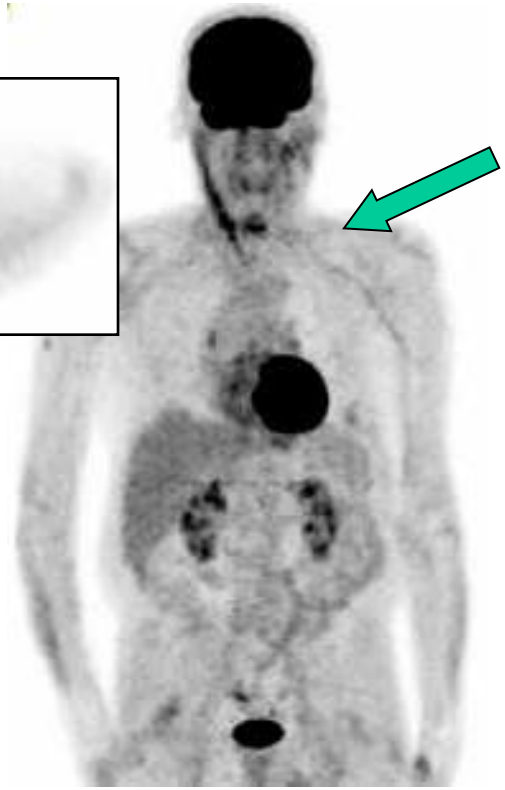


Vocal cords

speaking

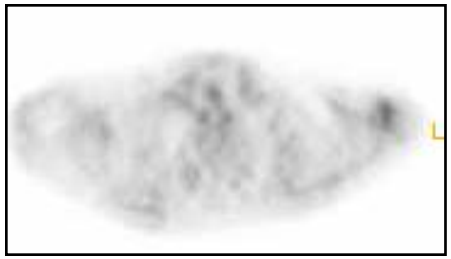


axial

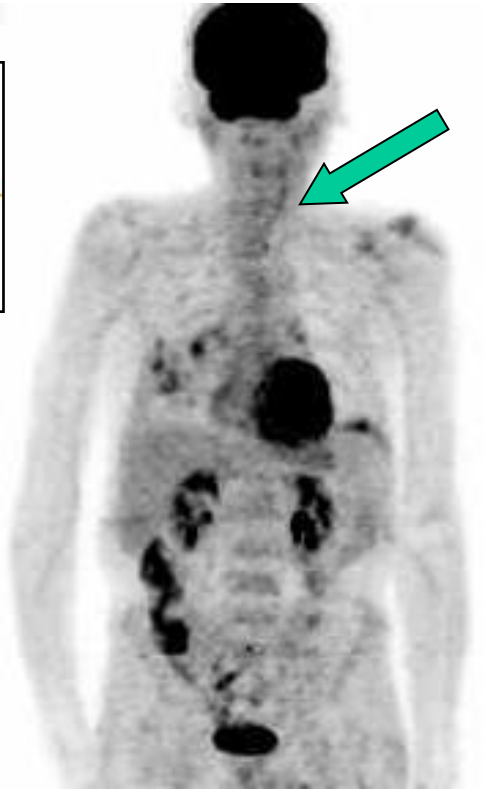


coronal

silence



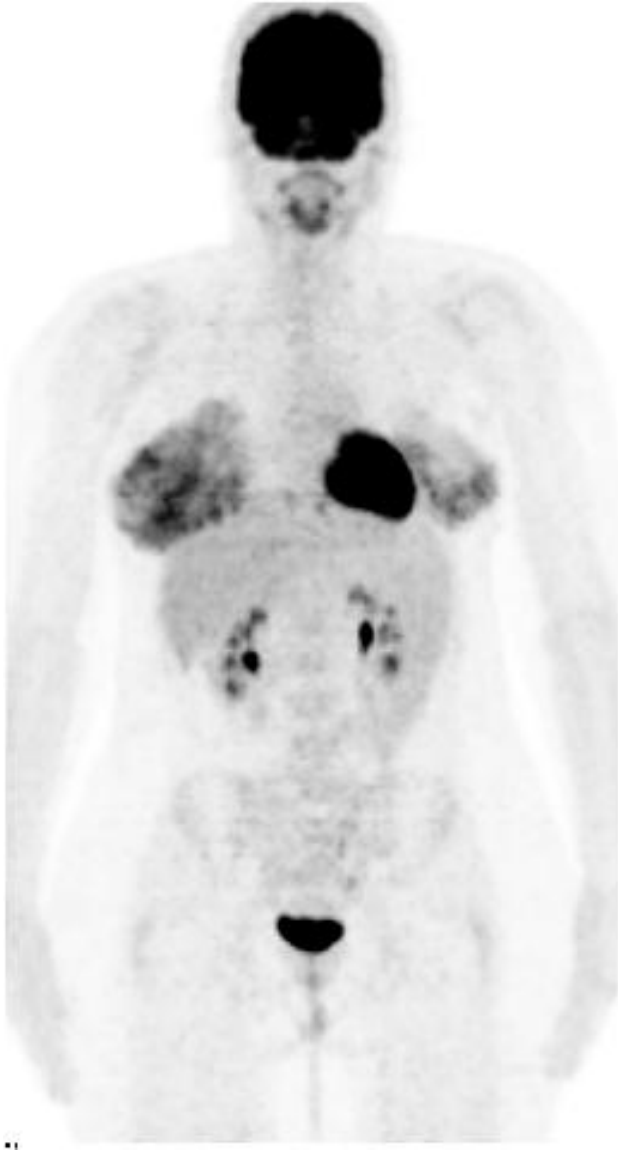
axial



coronal

Breast feading

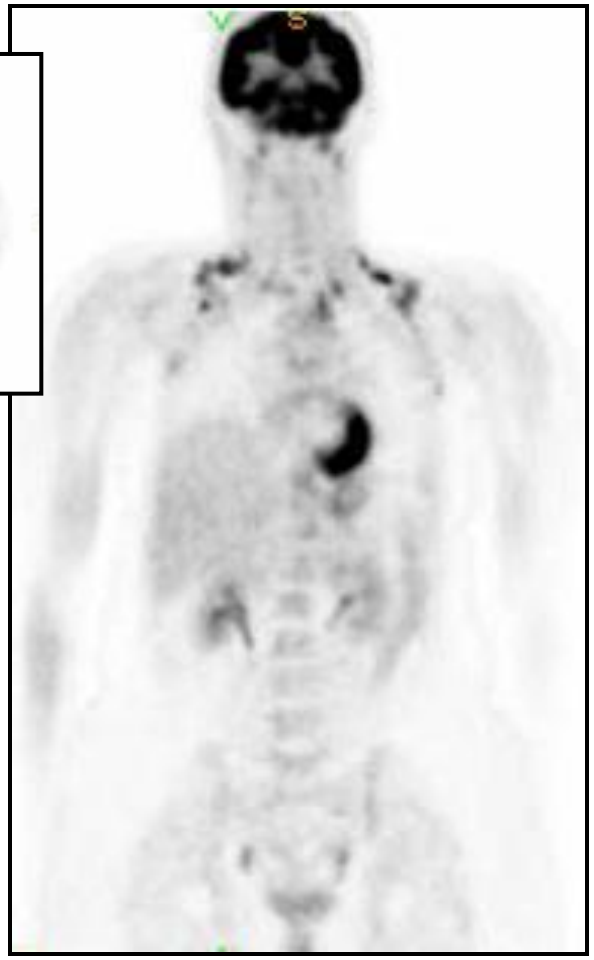
axial



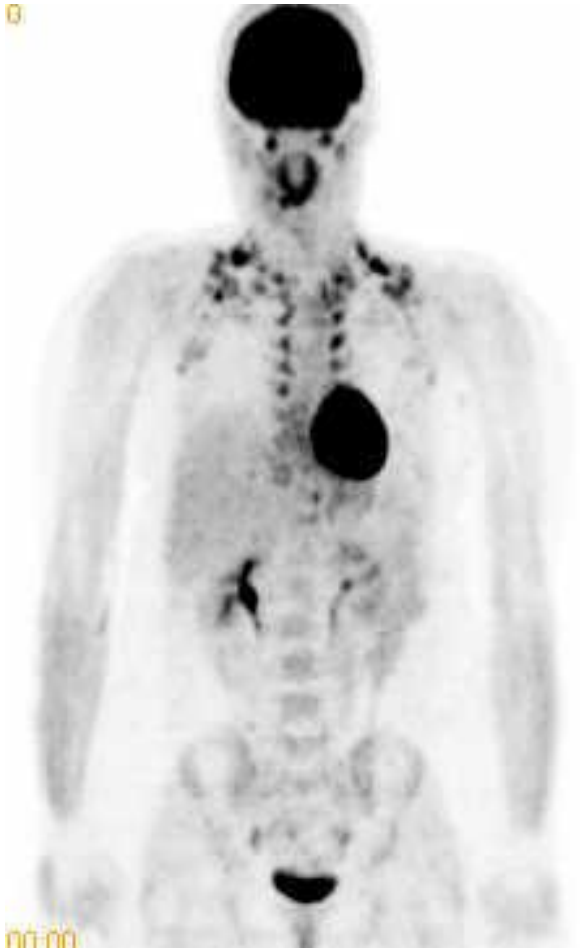
Mip

brown fat

axial

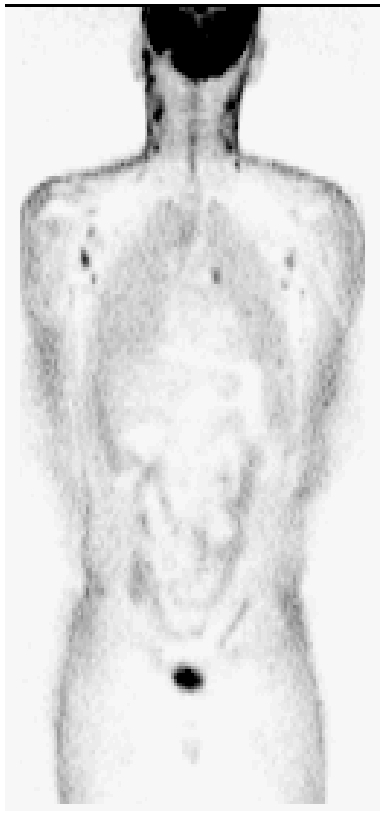


coronal

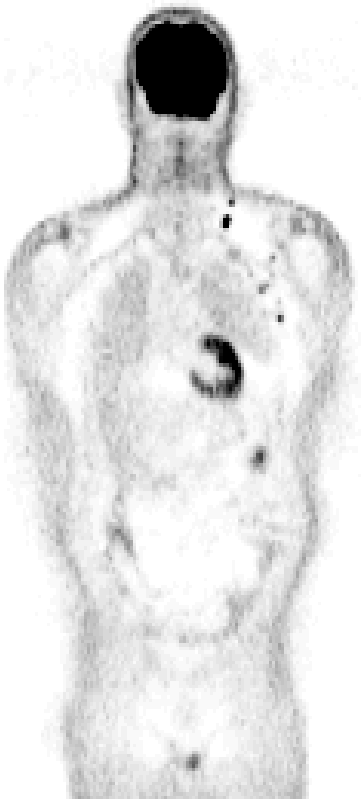


mip

Infections



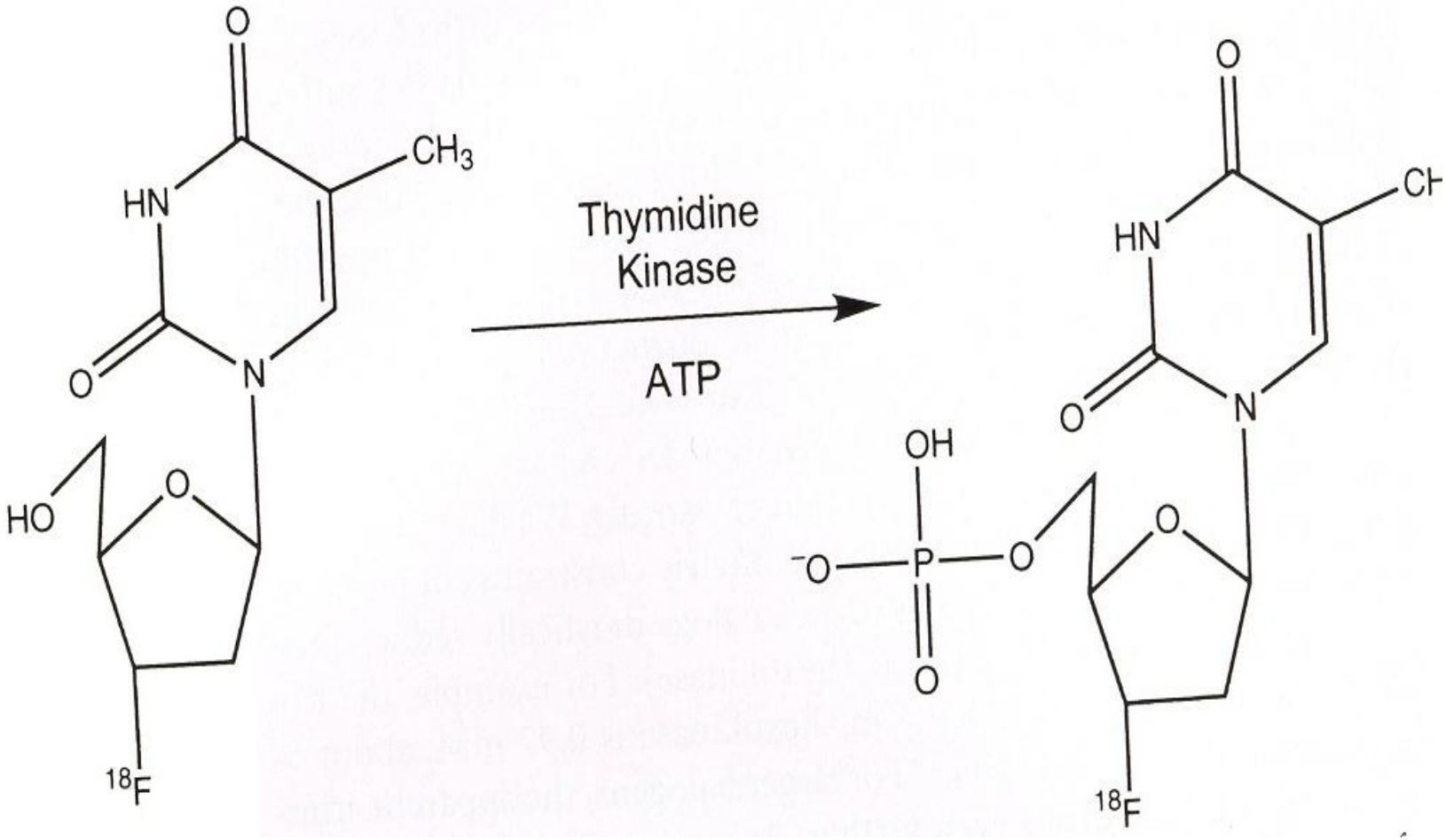
toxoplasma



NHL

Examples of PET imaging probes acting through this mechanism:

- **Fluorodeoxythymidine (FLT)** used in the assessment of DNA replication based on the thymidine kinase-mediated phosphorylation to its 5’ phosphate. -
- At the time of PET imaging (<2 h), this monophosphate is metabolically trapped in tissue. With longer exposure times, the monophosphate would be phosphorylated by cellular kinases to the di- and tri-phosphate, and the latter incorporated into DNA.



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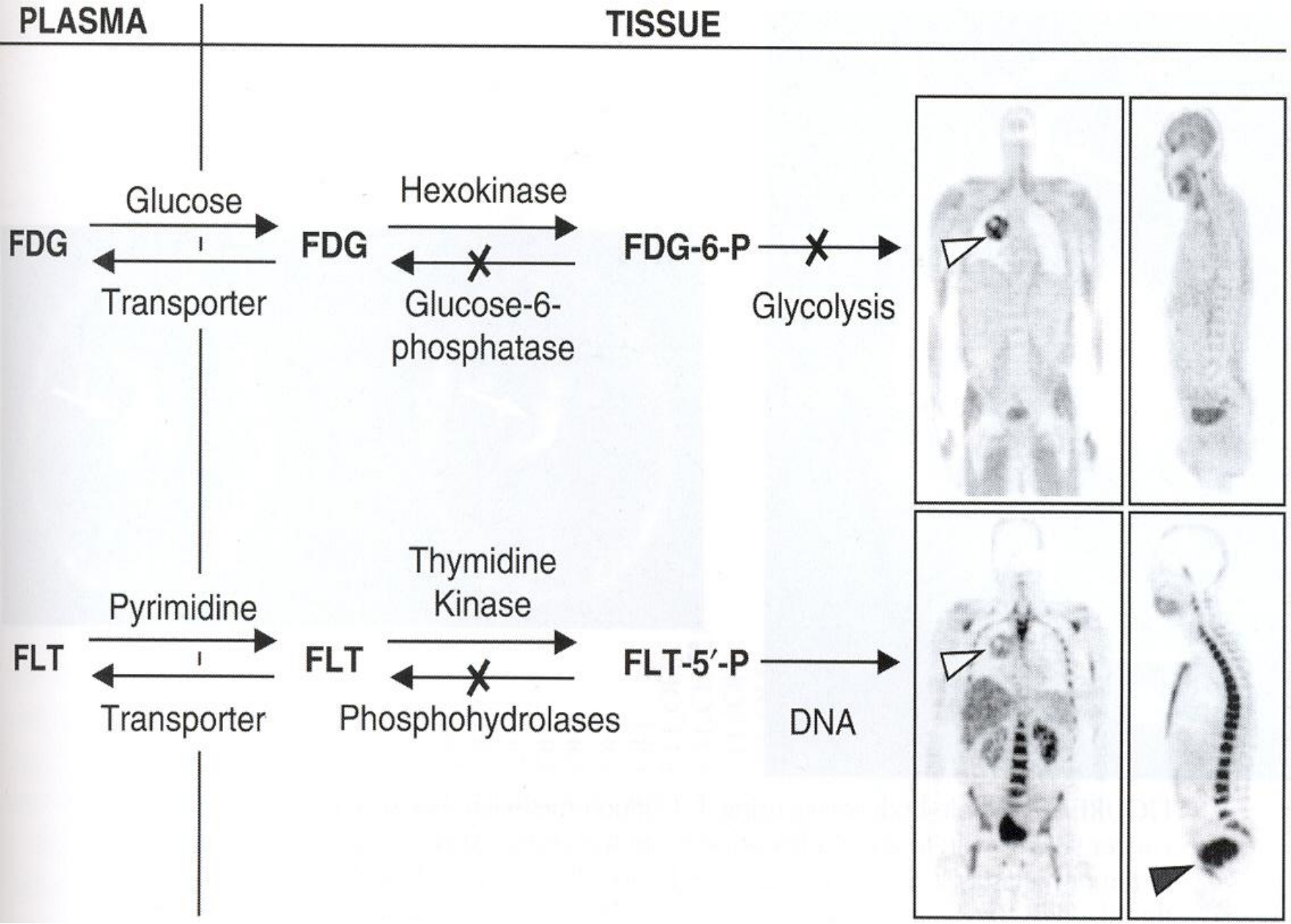

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II. Instrumentation for molecular imaging

Structural Imaging

Radiology

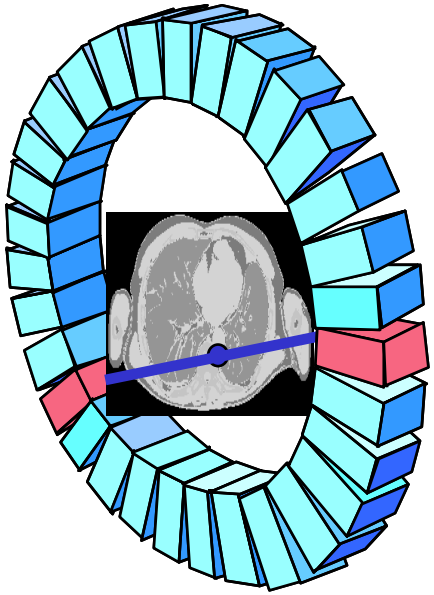
- **planare X-Ray**
- **CT**
- **echography**
- **Magnetic Resonance Imaging**

Metabolic Imaging

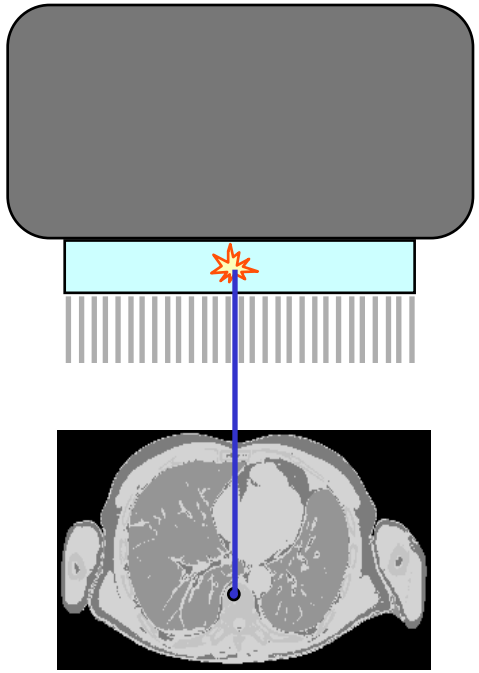
Nuclear Medicine

- **planar scintigraphy**
- **SPECT**
- **PET**

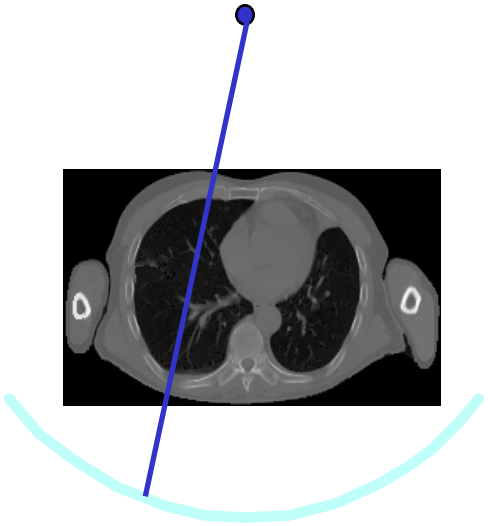
MRI



PET

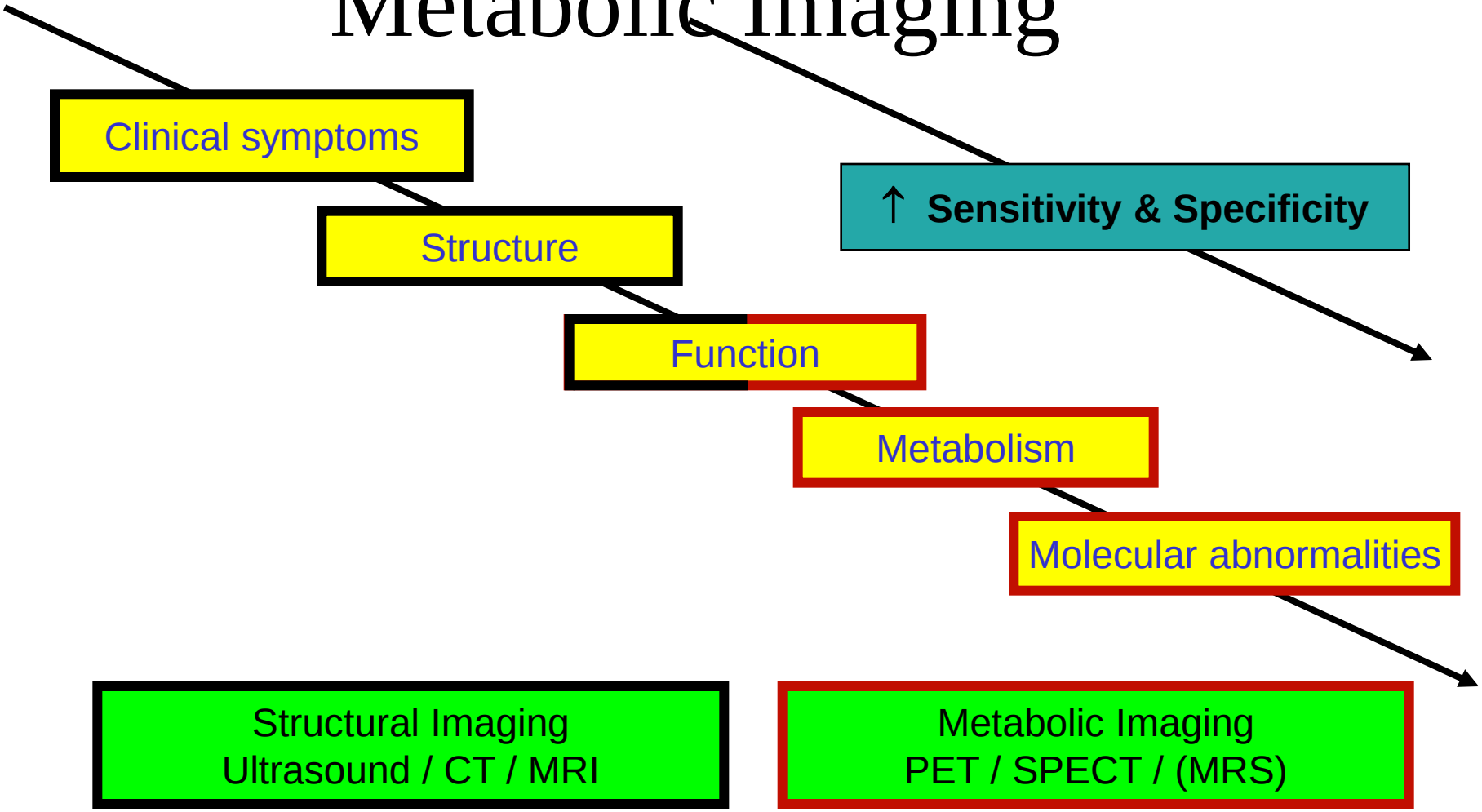


SPECT

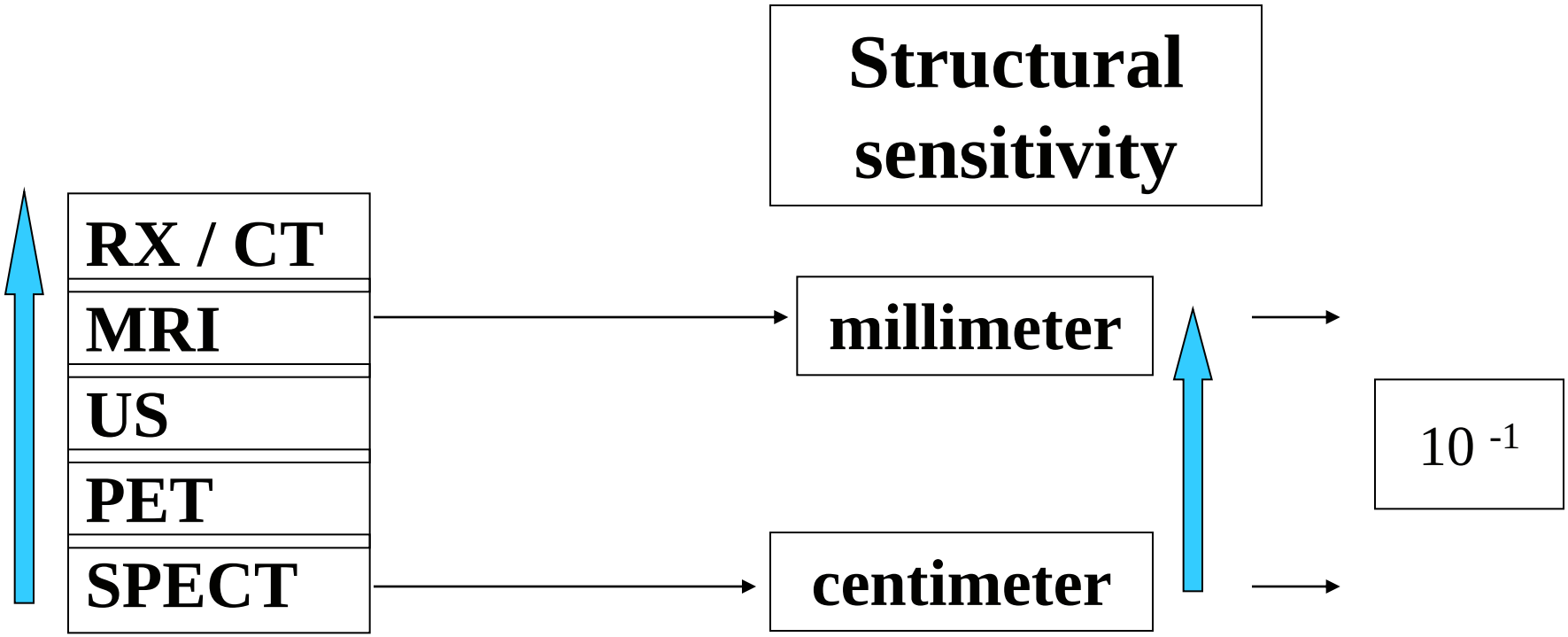


CT

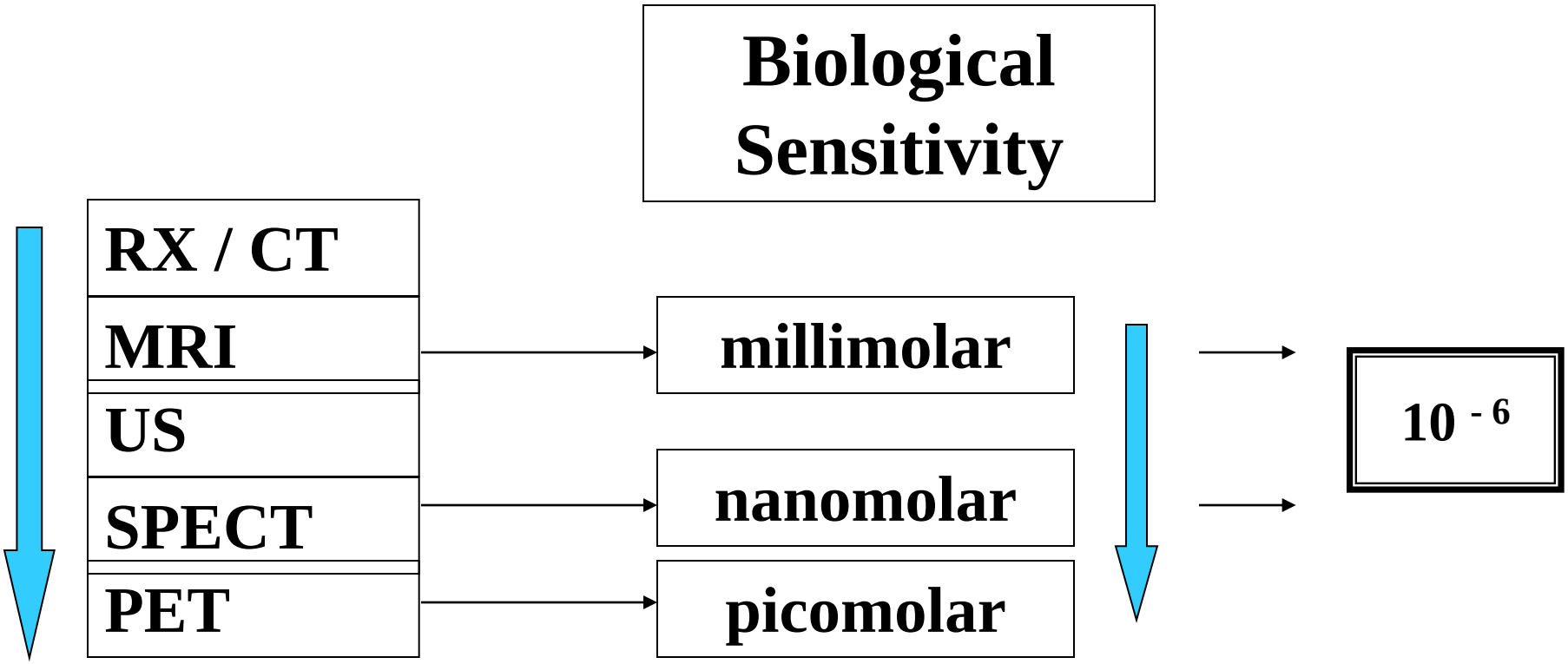
Metabolic Imaging



Sensitivity of imaging modalities

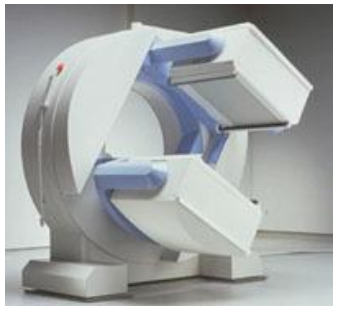


Sensitivity of imaging modalities



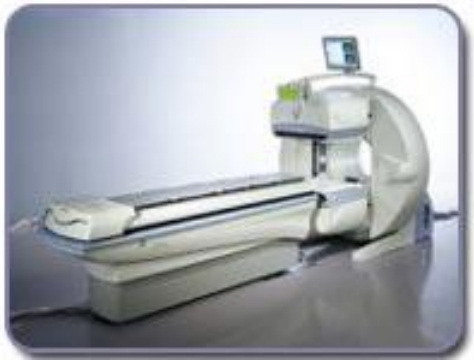
modalities available for molecular imaging in humans

Nuclear medicine

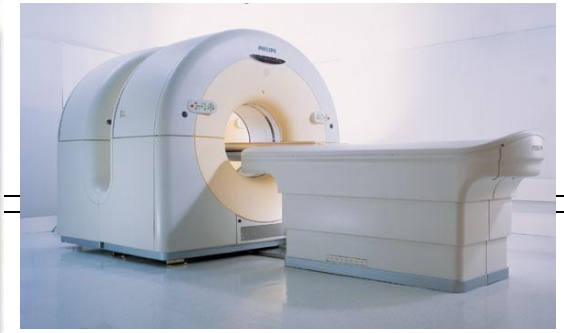


SPECT

SPECT-CT



PET-CT



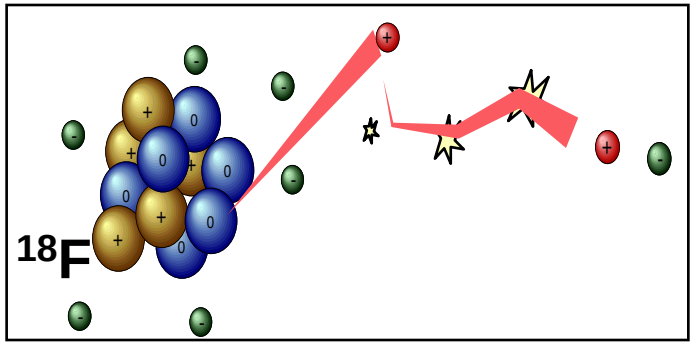
PET

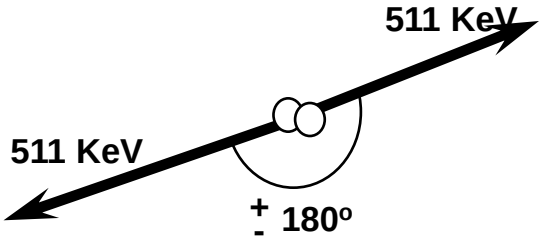
Radiology

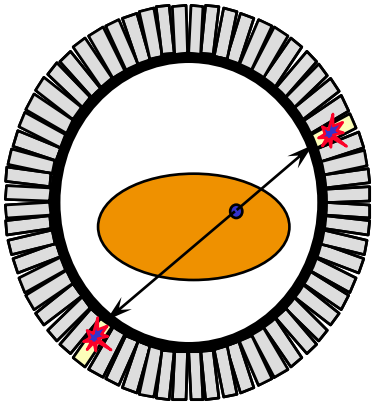
CT

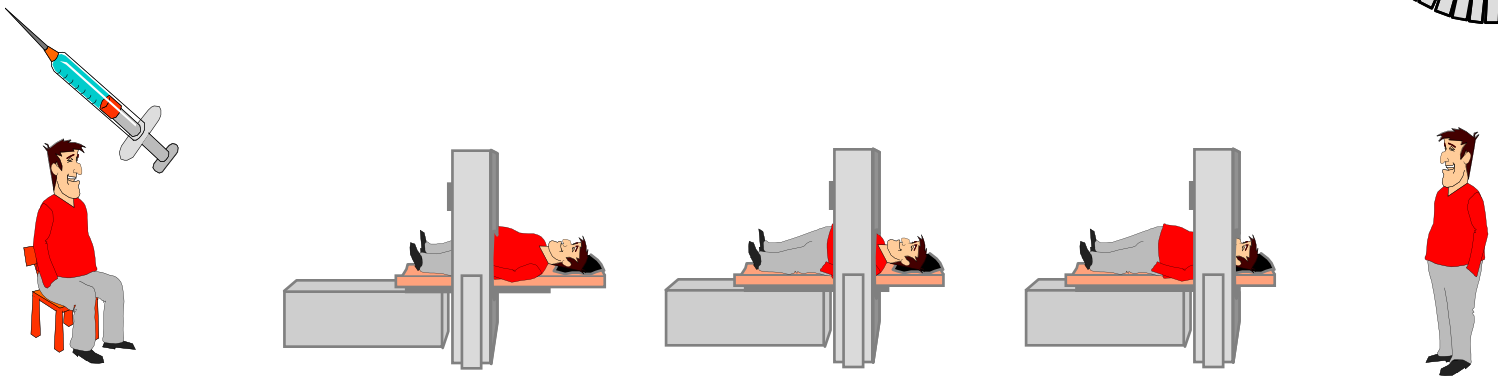
MRI/MRS/fMRI

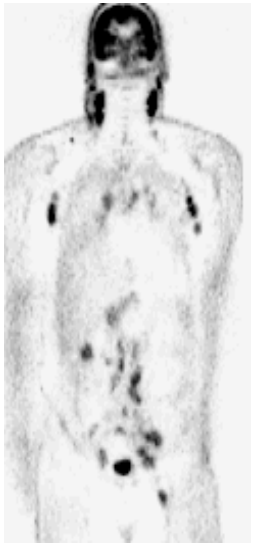
Whole-body 18-FDG PET











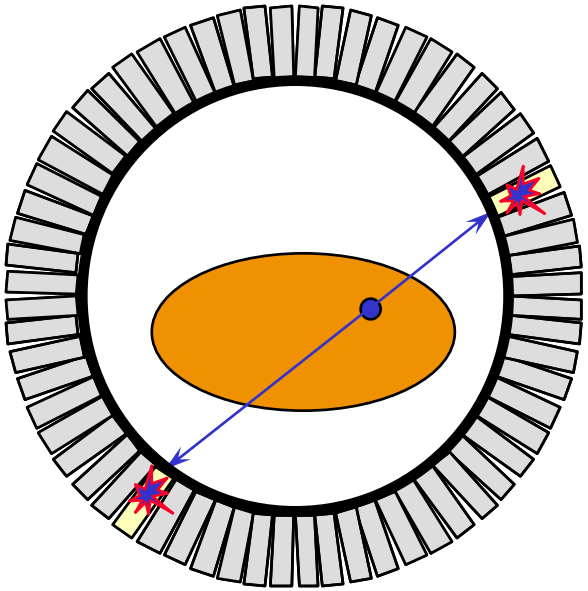
> 60 min

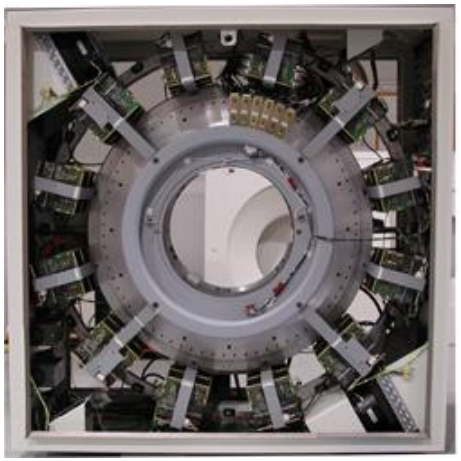
45 min

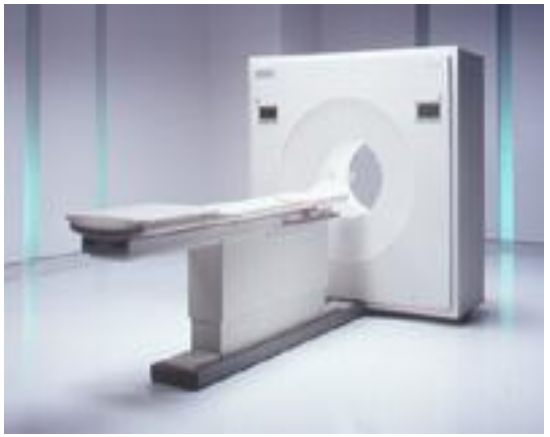
Injection of 6.5 MBq/kg FDG

start scan from pelvis up to head and down to toes

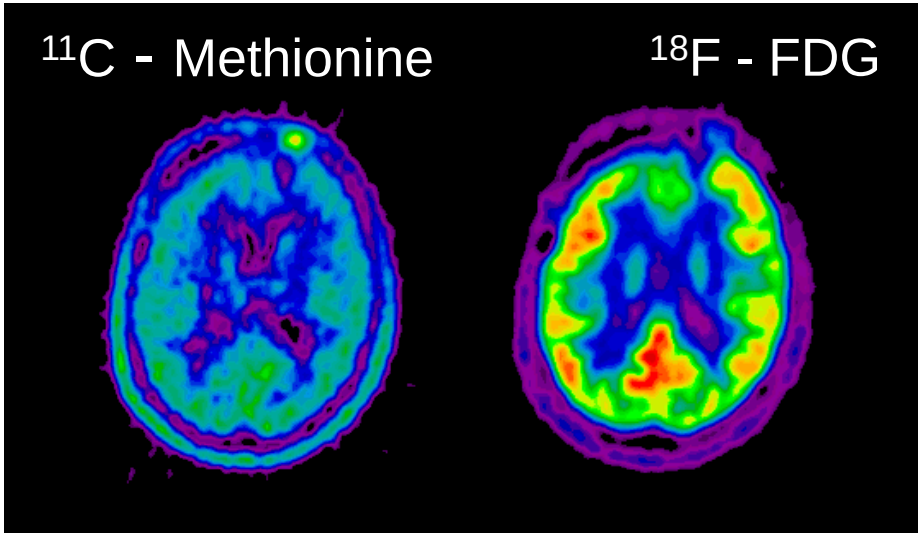
PET







- Advantages:
  - many tracers available
  - isotopes: ^{15}O, ^{13}N, ^{11}C, ^{18}F
  - very good sensitivity
  - quantification possible
- Disadvantages:
  - cyclotron needed
  - limited spatial resolution
  - positron range



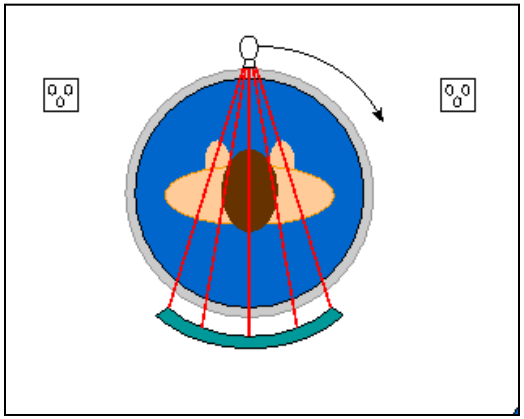
What is CT able to give us ?

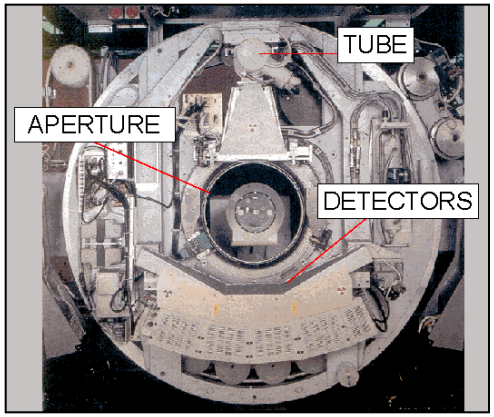
- Visualisation of normal tissue
- Vessels, intestine, bone, muscle

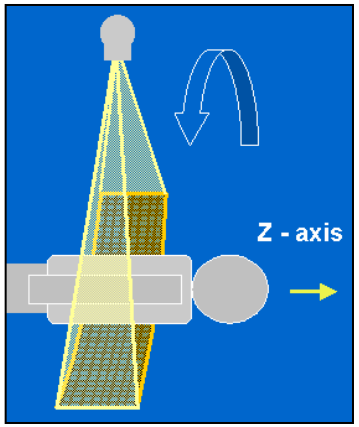
- Changes in morphology
- anatomic variants
- organ-enlargement
- pathological changes

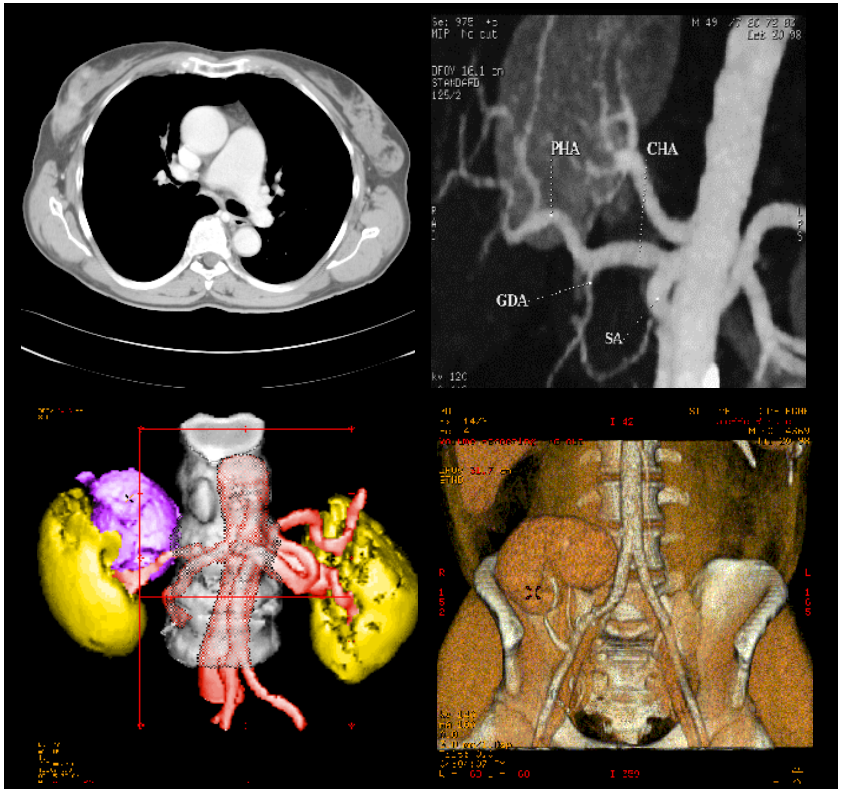
- BUT:
- Is not able to distinguish distinctly between malignant and benign changes

CT









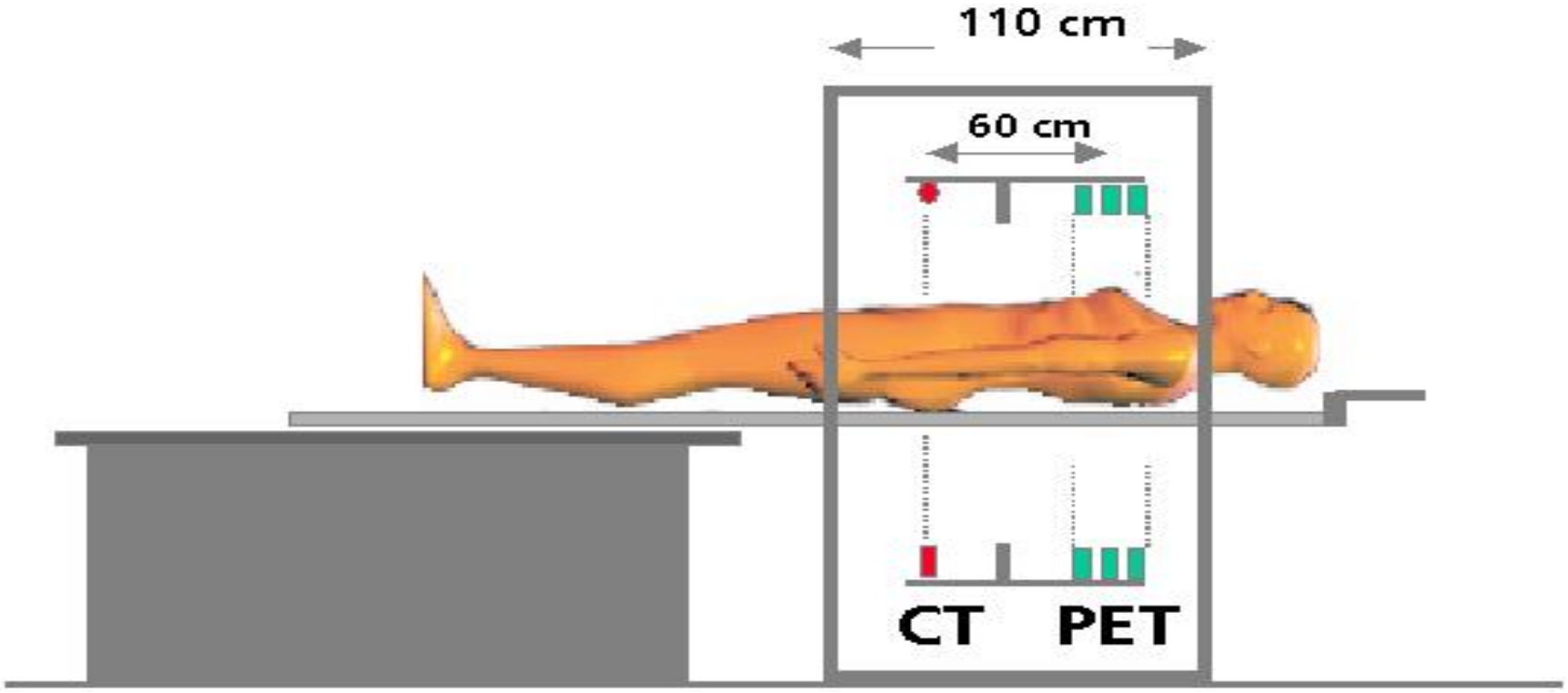
- Advantages:
  - Anatomical imaging
  - High spatial resolution
  - Fast
- Disadvantages:
  - Limited use for visualising soft tissue (eg WM vs GM)
  - Radiation exposure can be high
  - Contrast agents

PET/CT

- Combination of function
- PET – positron emission tomography

- and morphology
- CT – computed tomography

What is PET/CT ?

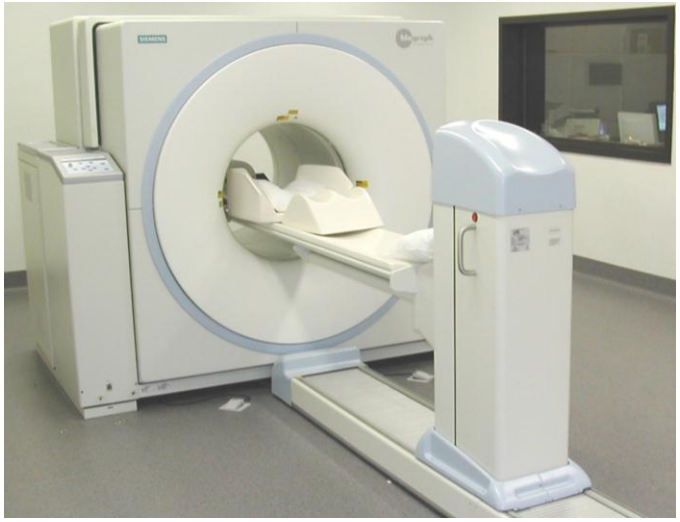


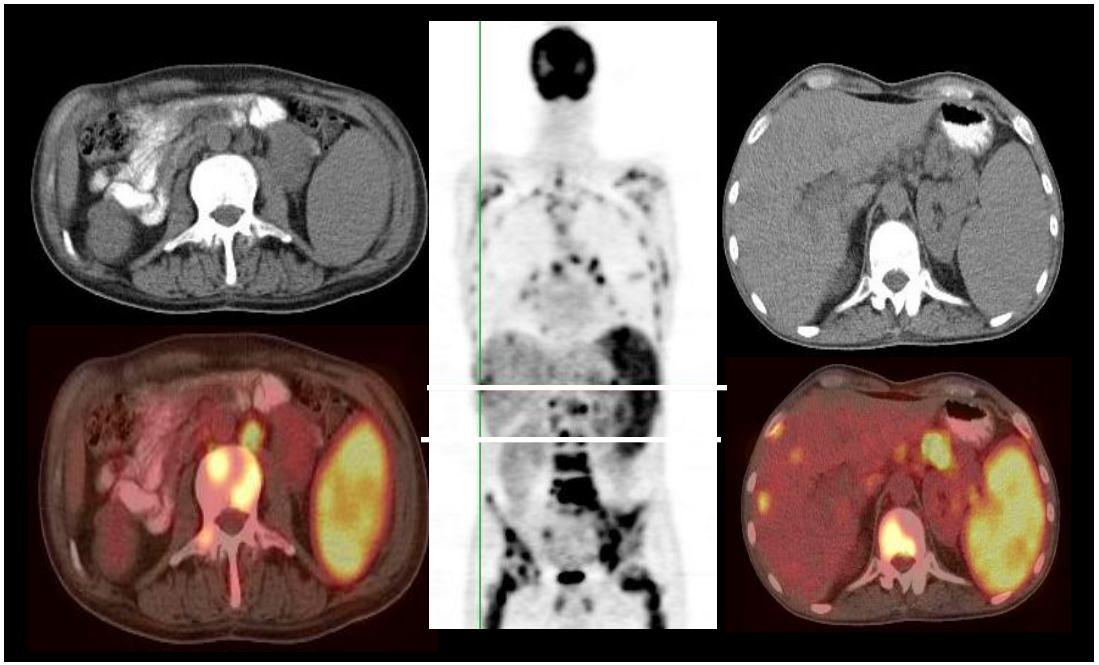
PET/CT: PET and CT in a single machine

- Combination:
  - Functional information from PET
  - morphological information from CT

- Time saving:
  - Reduced data acquisition time of PET/CT compared to PET alone
  - 45 minutes vs. 15-25 minutes

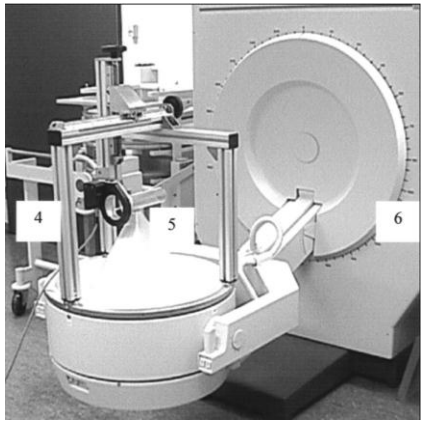
PET-CT



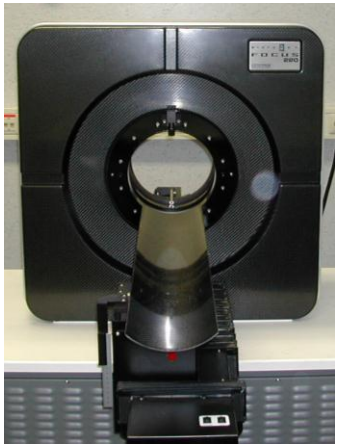


- Advantages:
  - Single examination
  - Easy registration
  - CT for attenuation correction
  - Combined reading
- Disadvantages:
  - High cost
  - Extra radiation
  - Contrast agents
  - Breathing artifacts possible

Modalities available for molecular imaging in small animals

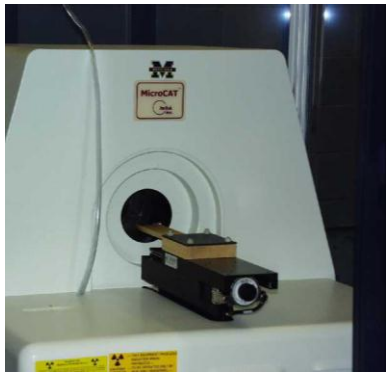


Pinhole SPECT

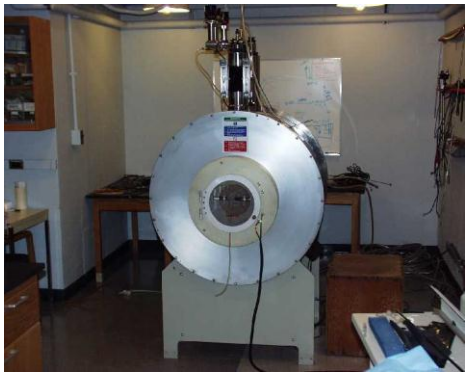


Small animal PET

Optical imaging



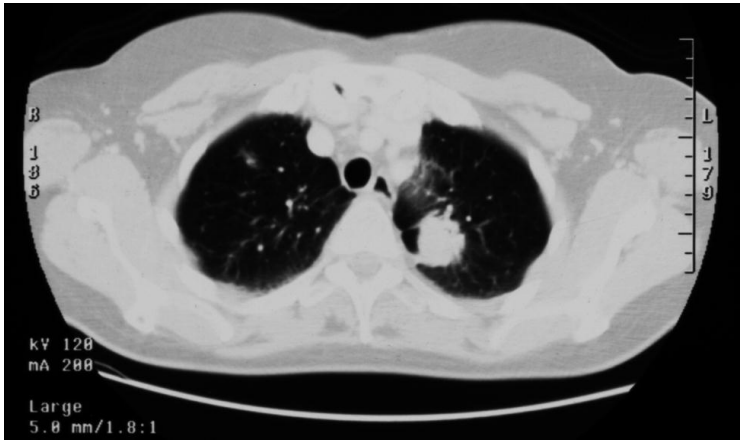
Micro CT

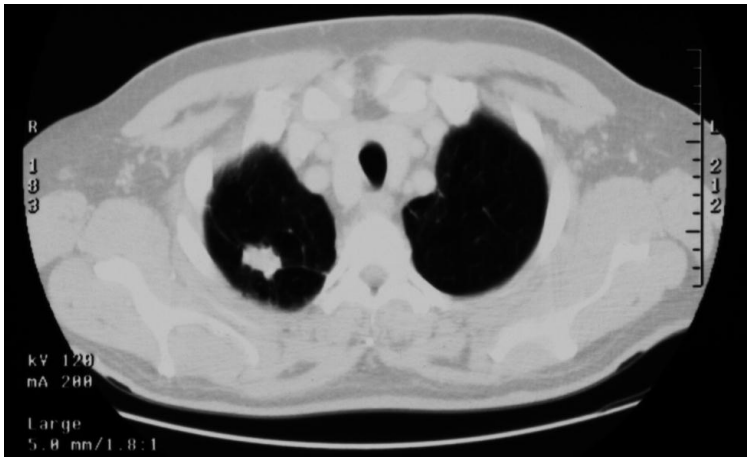


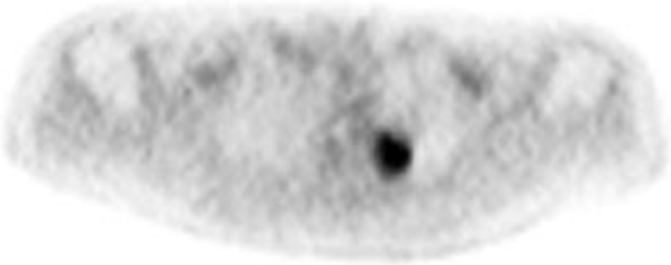
Micro MRI/MRS

FDG-PET in Oncology

Diagnosis	Staging	Prognosis	Therapy Monitoring
Metabolic characterization of structural lesions	**Whole-body screening**	**Correlation with response rate and survival**	**Responders versus Non-responders**

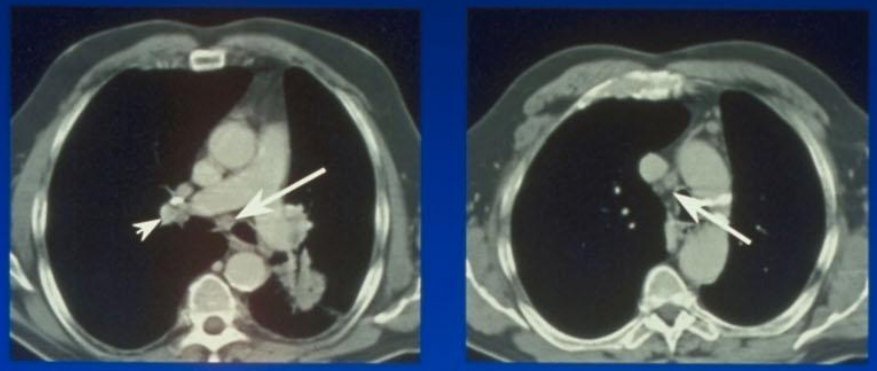

kV 120
mA 200
Large
5.0 mm/1.8:1


kV 120
mA 200
Large
5.0 mm/1.8:1

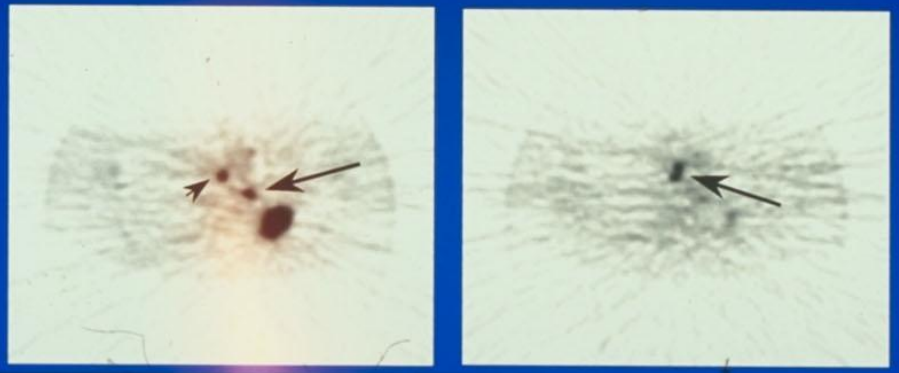


mediastinal staging in NSCLC

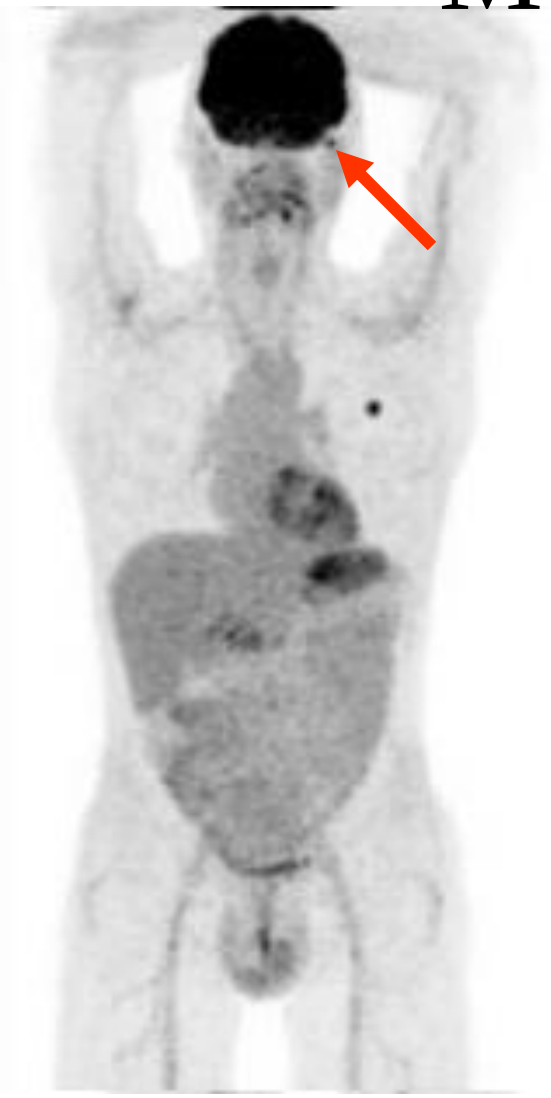
CT - N0

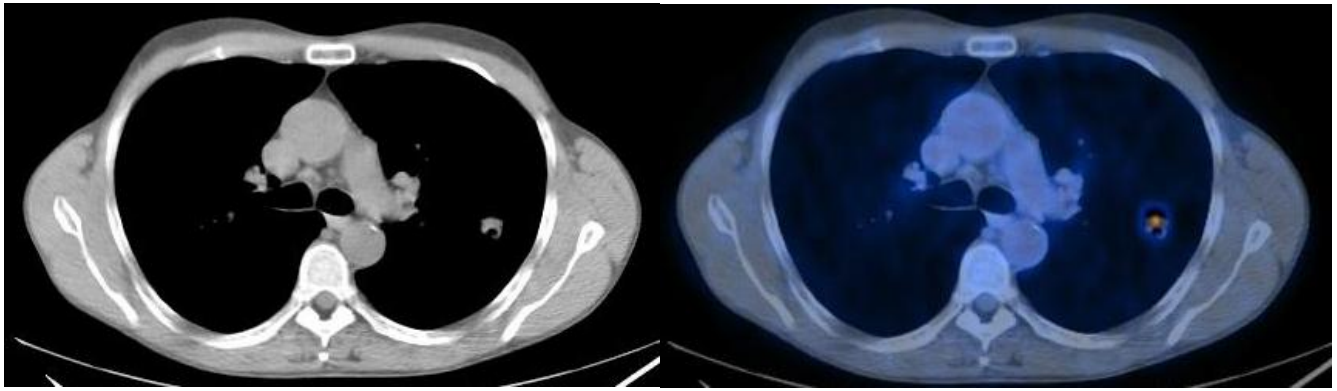


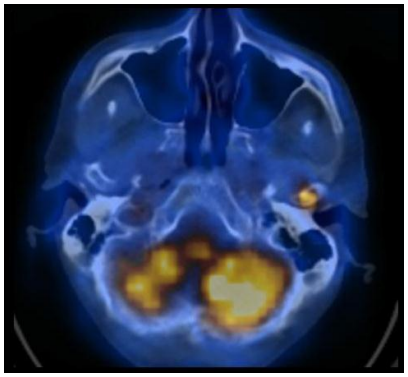
PET - N3



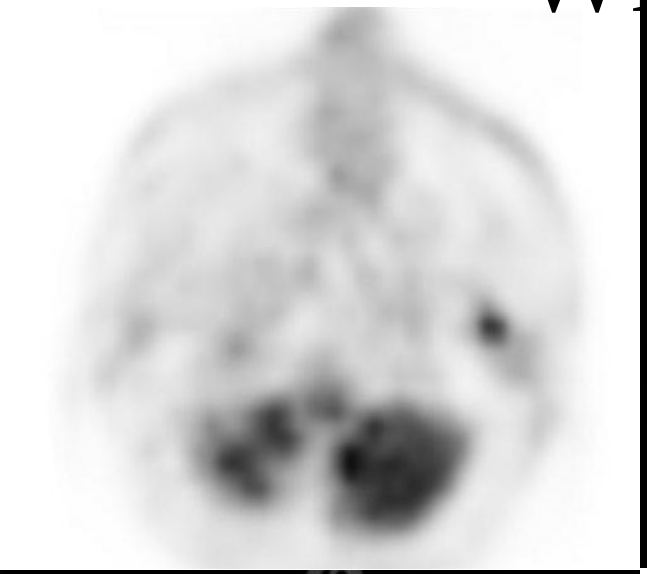
Metastases at distance

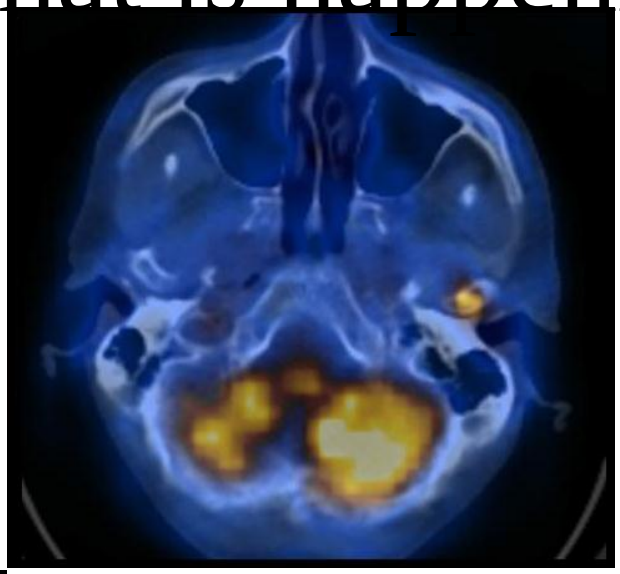


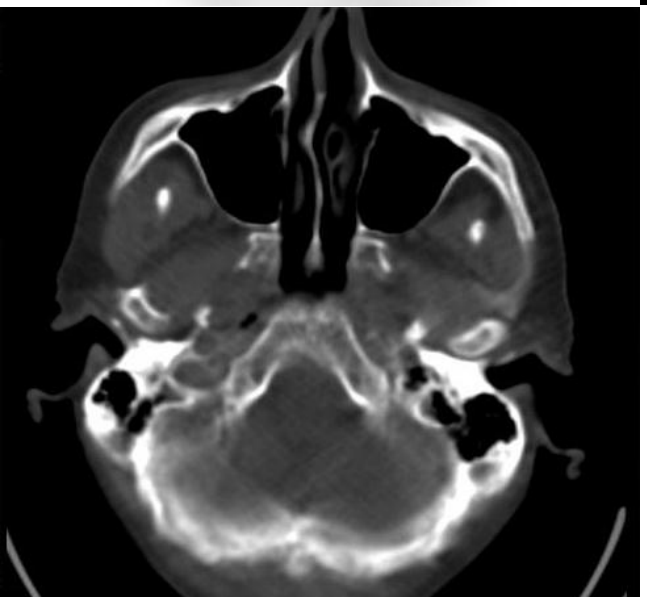




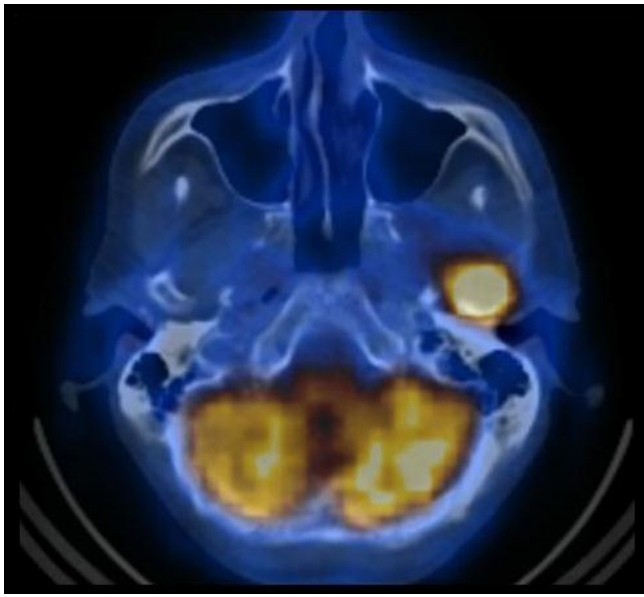
What is happening





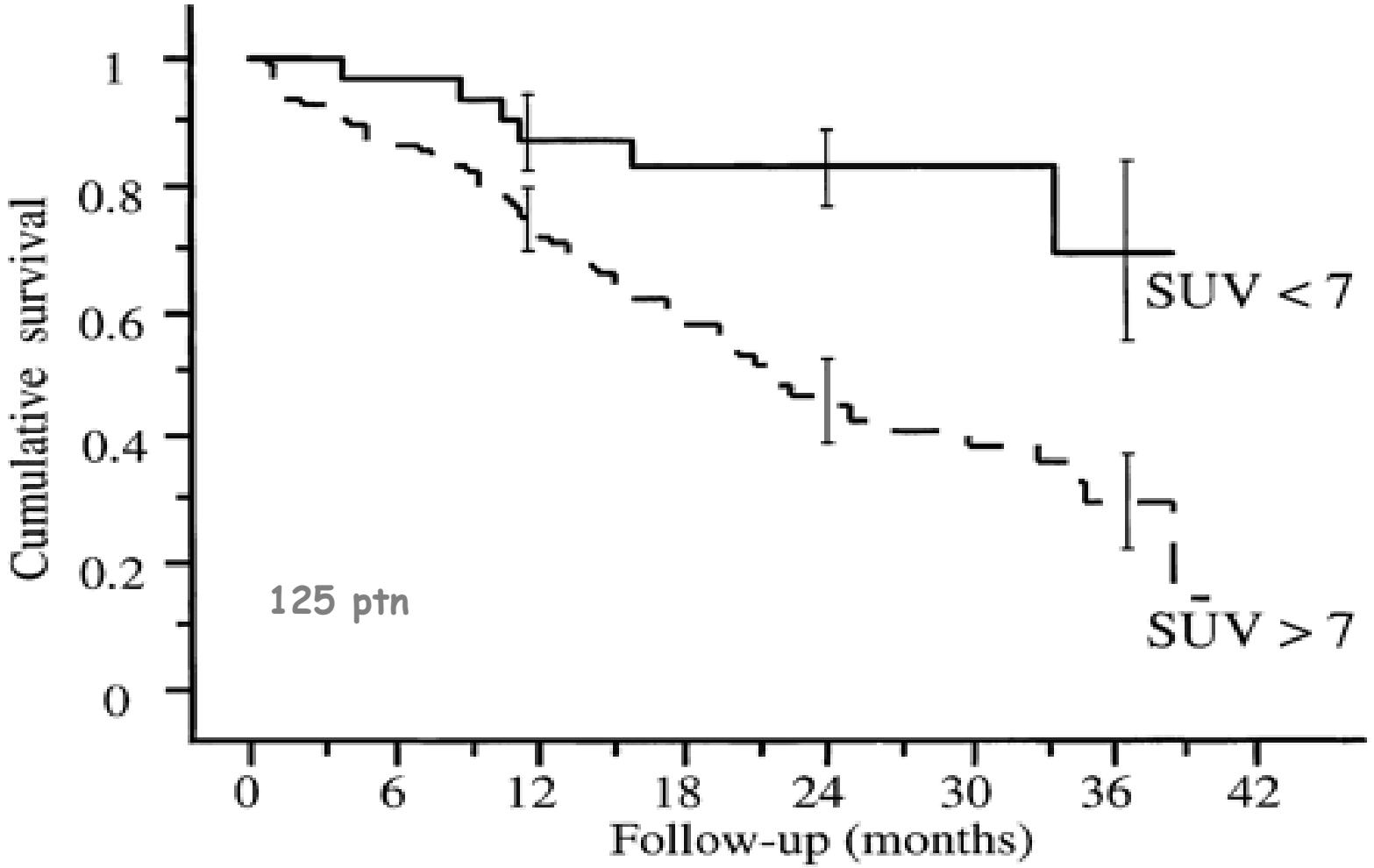


3 months later



FDG uptake as prognostic marker in lung Ca

Vansteenkiste et al, *JCO* 1999



Level of FDG uptake predicts risk for recurrence in melanoma patients presenting with lymph node metastases Bastiaannet et al, Ann Surg Oncol 2006 Jul;13(7): 919-26

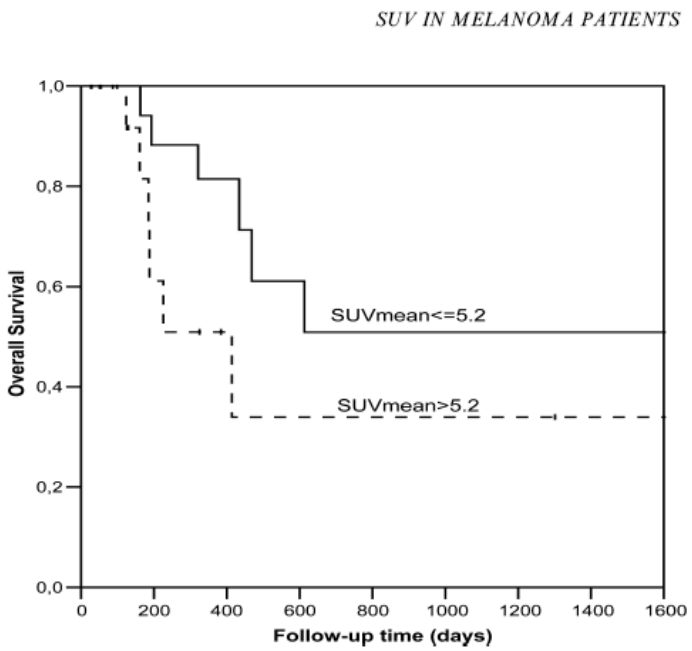


FIG. 1. Kaplan-Meier overall survival for patients with a high SUV_{mean} or low SUV_{mean} SUV, standard uptake value.

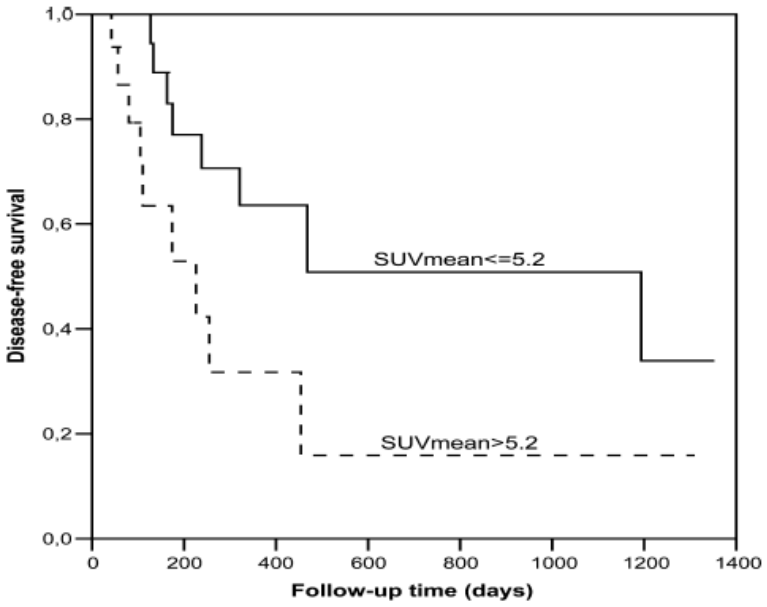
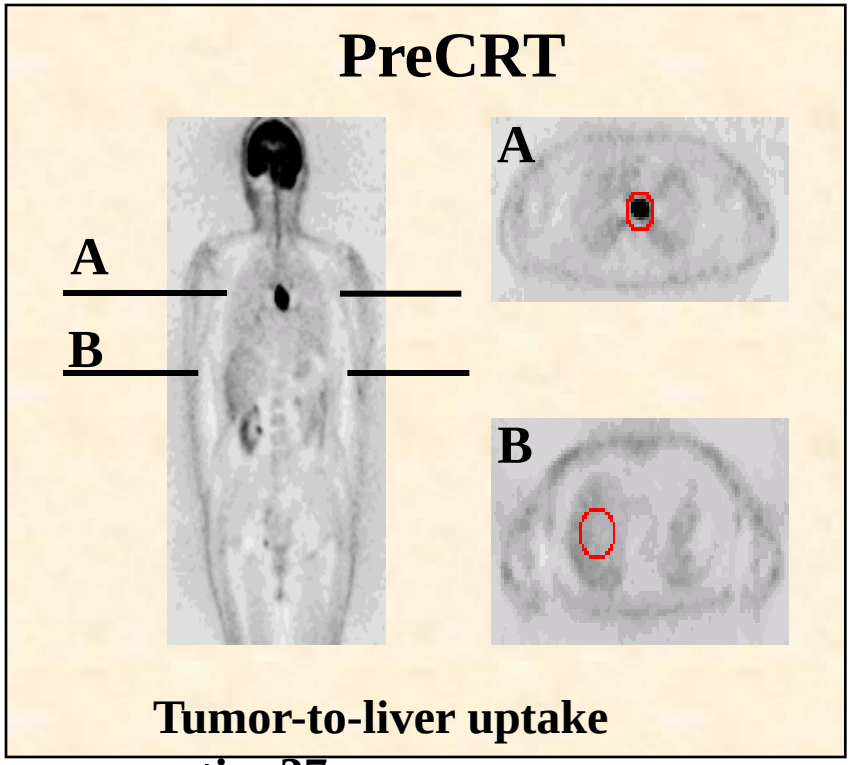
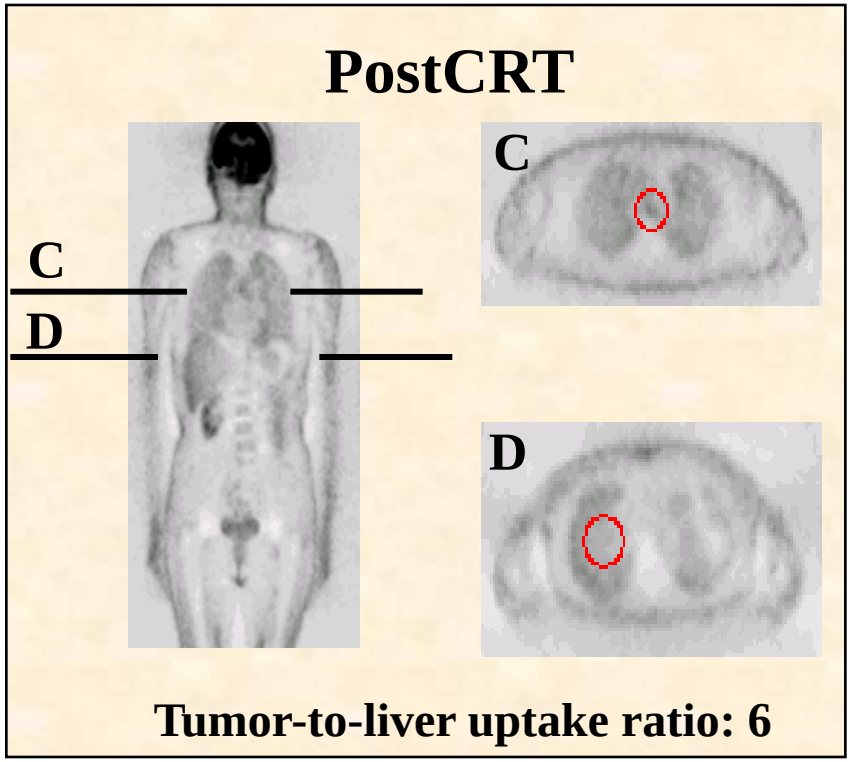


FIG. 2. Kaplan-Meier disease-free survival for patients with a high SUV_{mean} or low SUV_{mean}. SUV, standard uptake value.

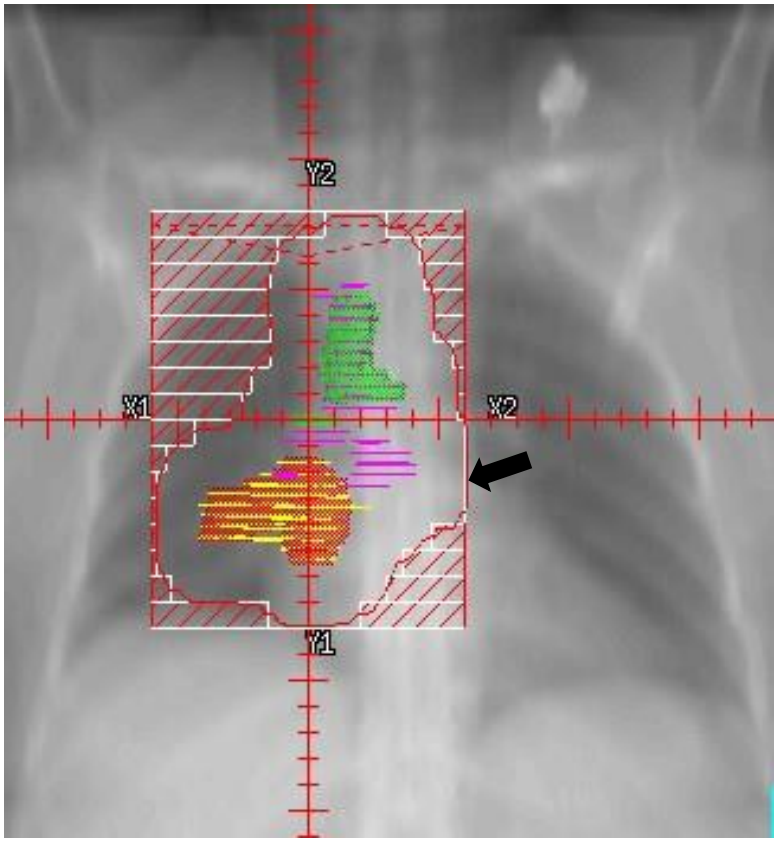
Therapy evaluation



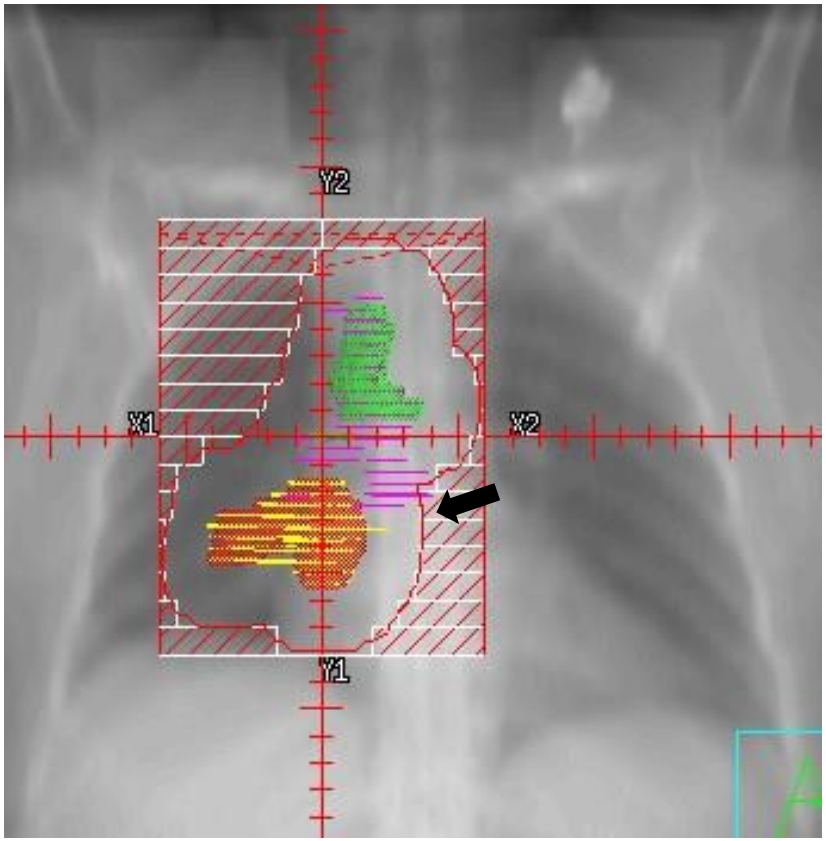


Primary Tumor: deltaTUR: 83%

Radiotherapy volume change



CT planning



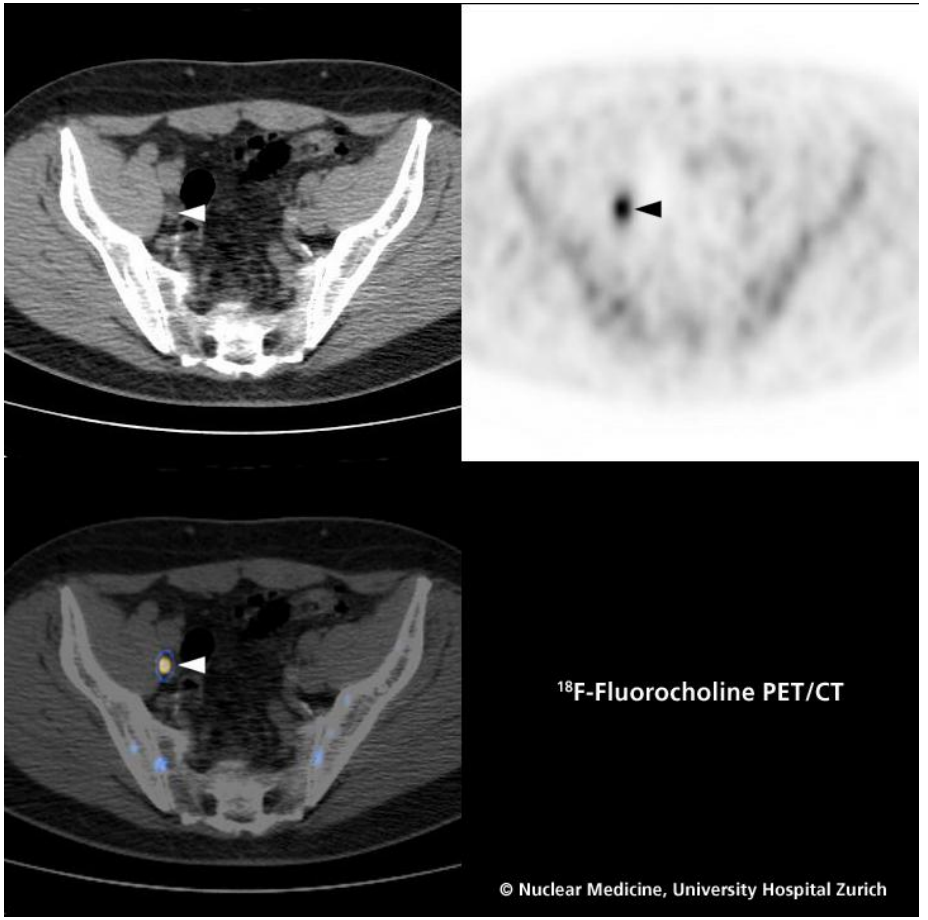
PET/CT planning

Biochemical recurrence of prostate cancer

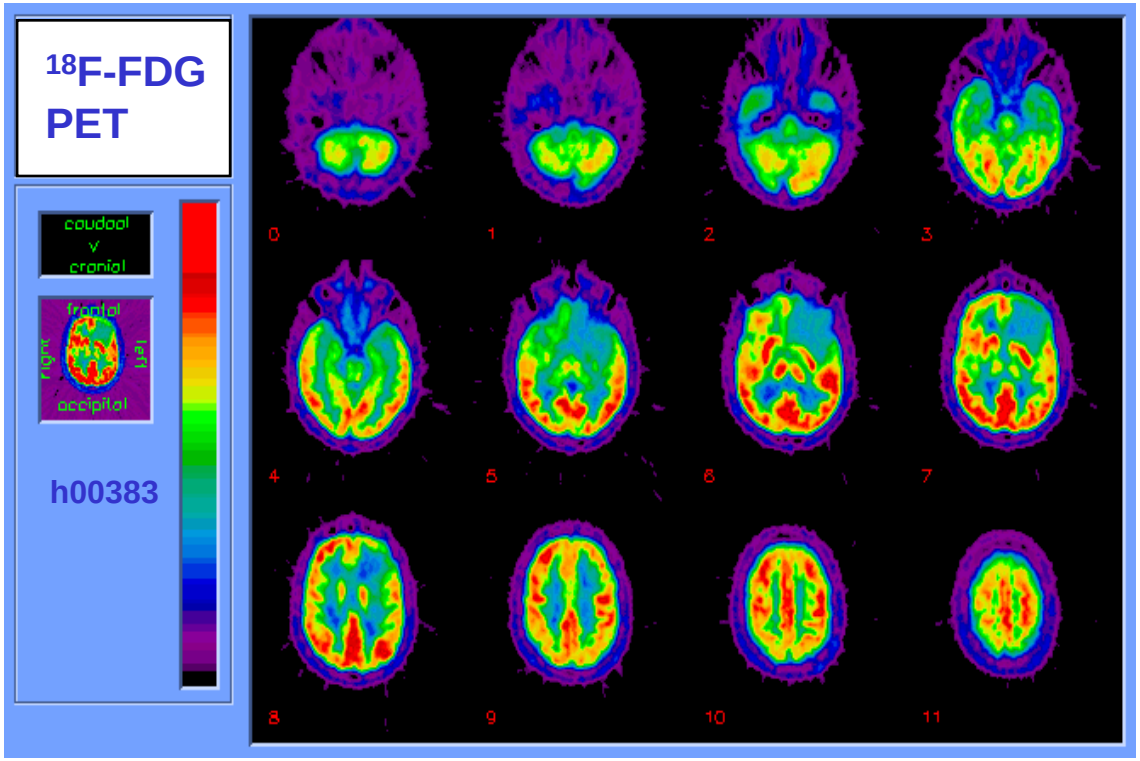
Schmid DT, Hany TF. (2005) Radiology. May;235(2):623-8.

- PSA 2.1 ng/ml
- 10 d after surgery:

  0.12 ng/ml
- Actually after 1 year:
- 0.00ng/ml

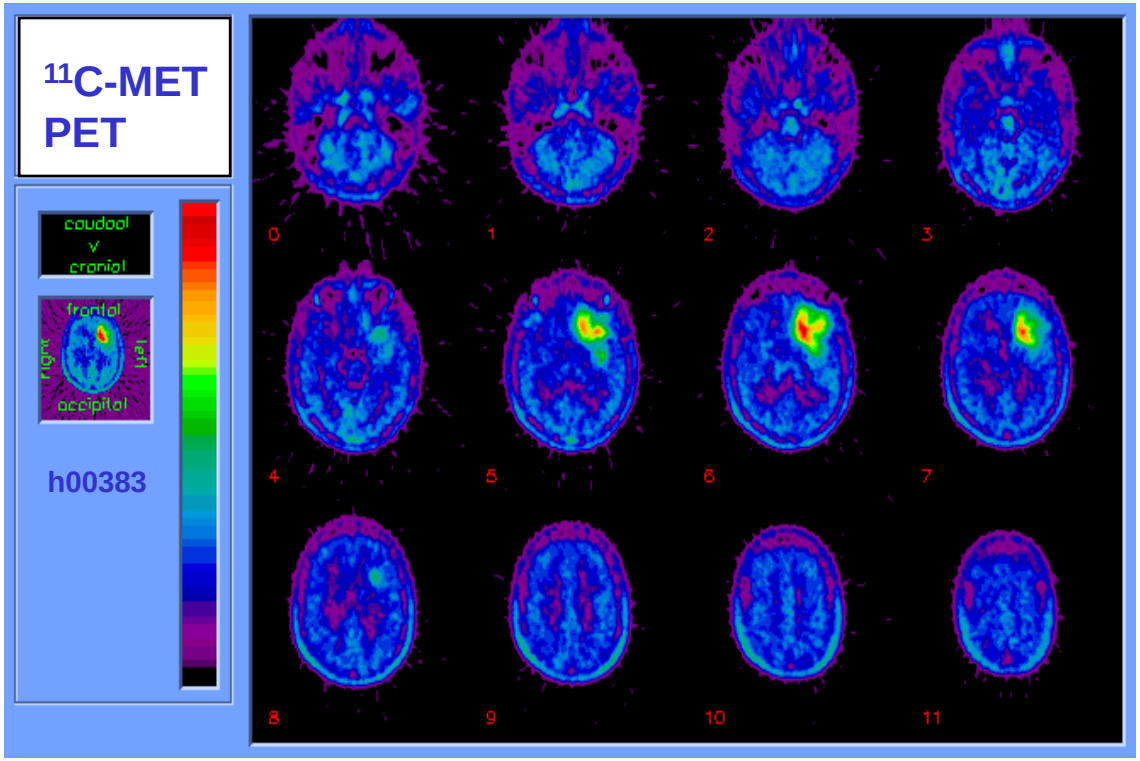


FDG PET



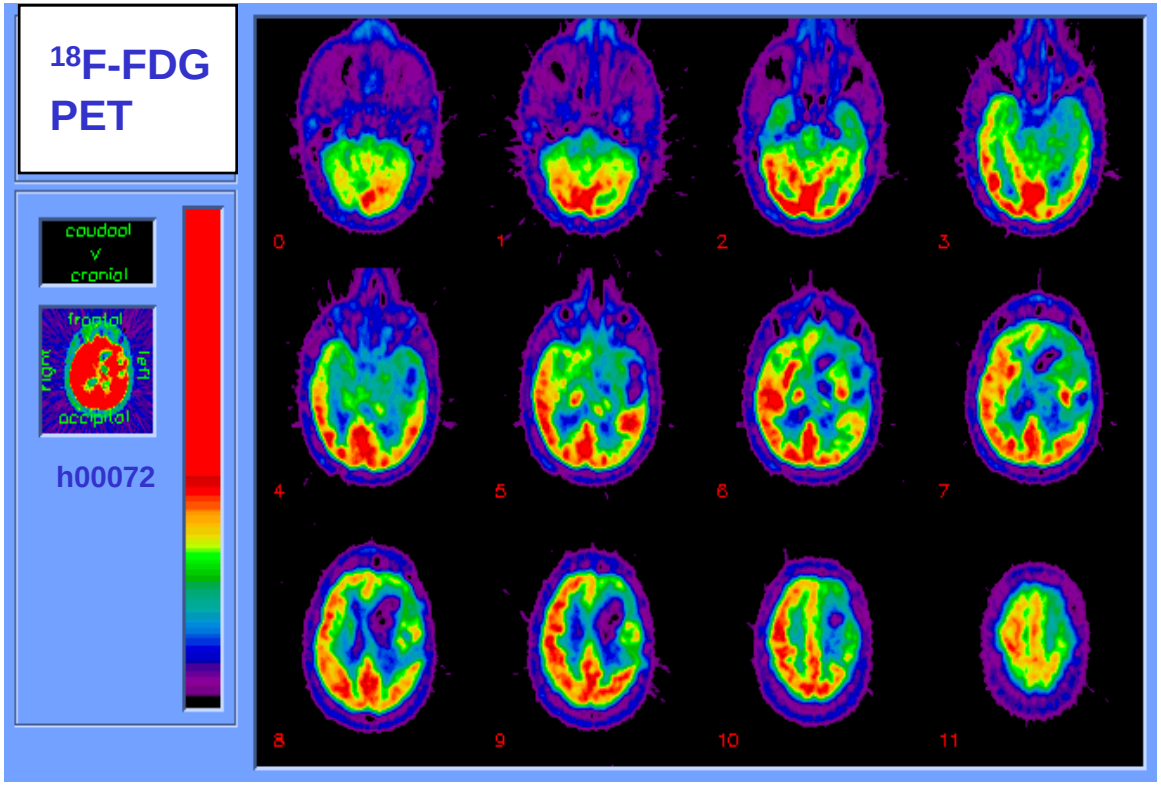
Follow up of low grade (II) glioma since 4 years, clinical suspicion of relapse; MRI: left frontotemporal lesion with focal zone of contrast captation

Methionine PET



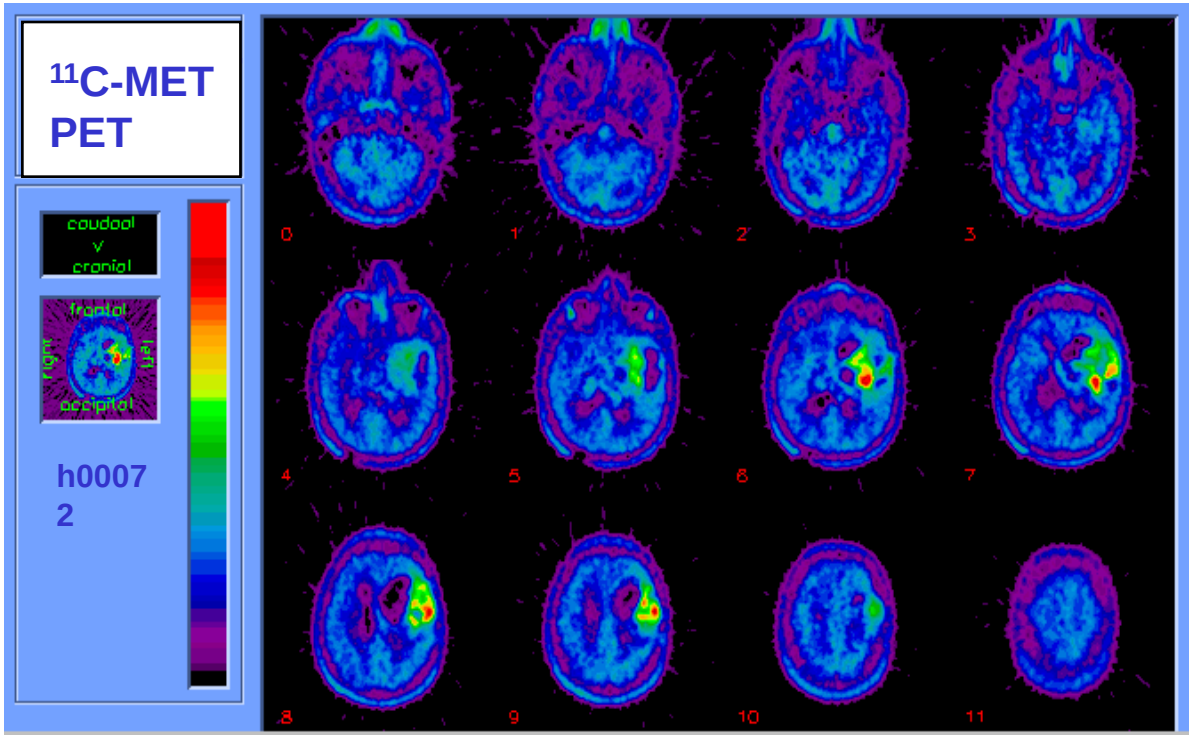
Histology : Glioma grade II

FDG PET



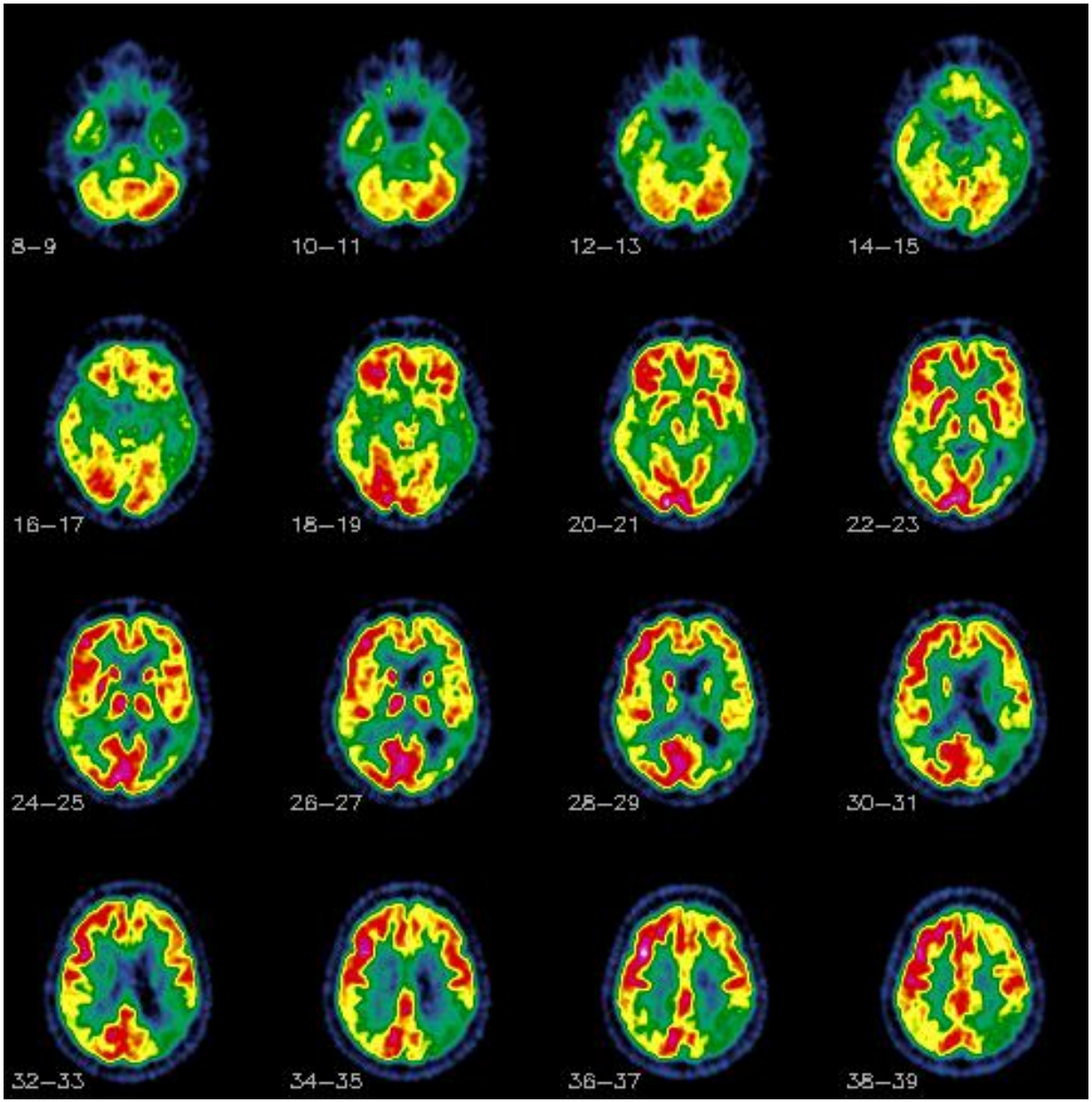
Glioma grade II status post resection and 60 Gy, clinical deterioration, MRI: frontotemporal tumor recurrence

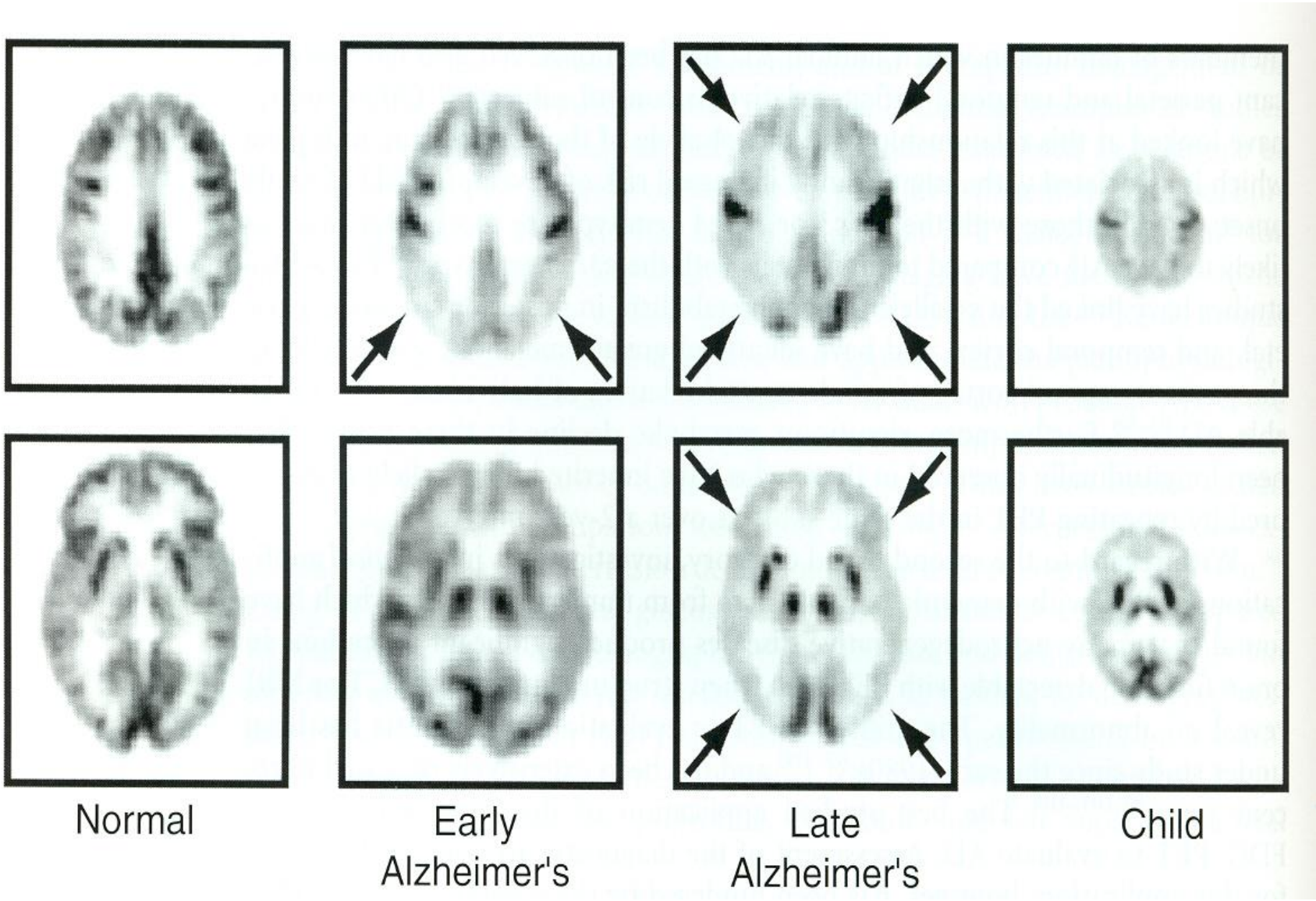
Methionine PET



Histology: glioma grade III

Alzheimer FDG PET

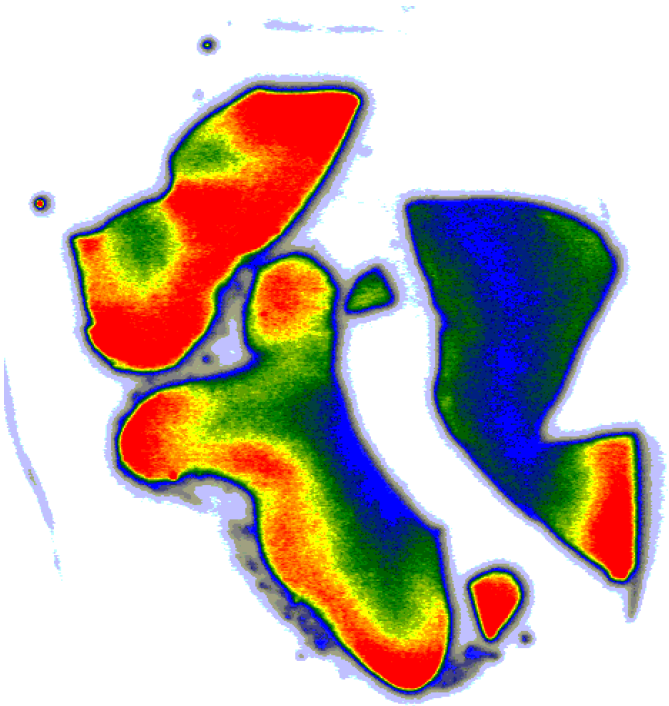




Michael E. Phelps - PET Molecular Imaging and Its Biological Applications - Springer - 2004

Imaging of amyloid plaques

βA4 immunohistochemic staining



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PET/CT ^{13}NH Perfusion