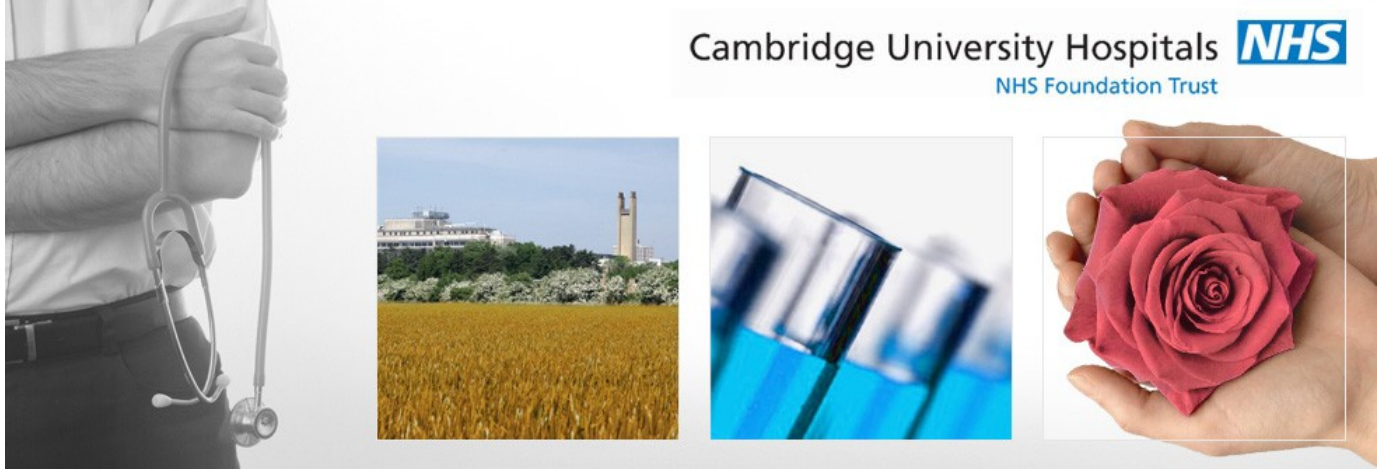

Molecular imaging of the cancer cell

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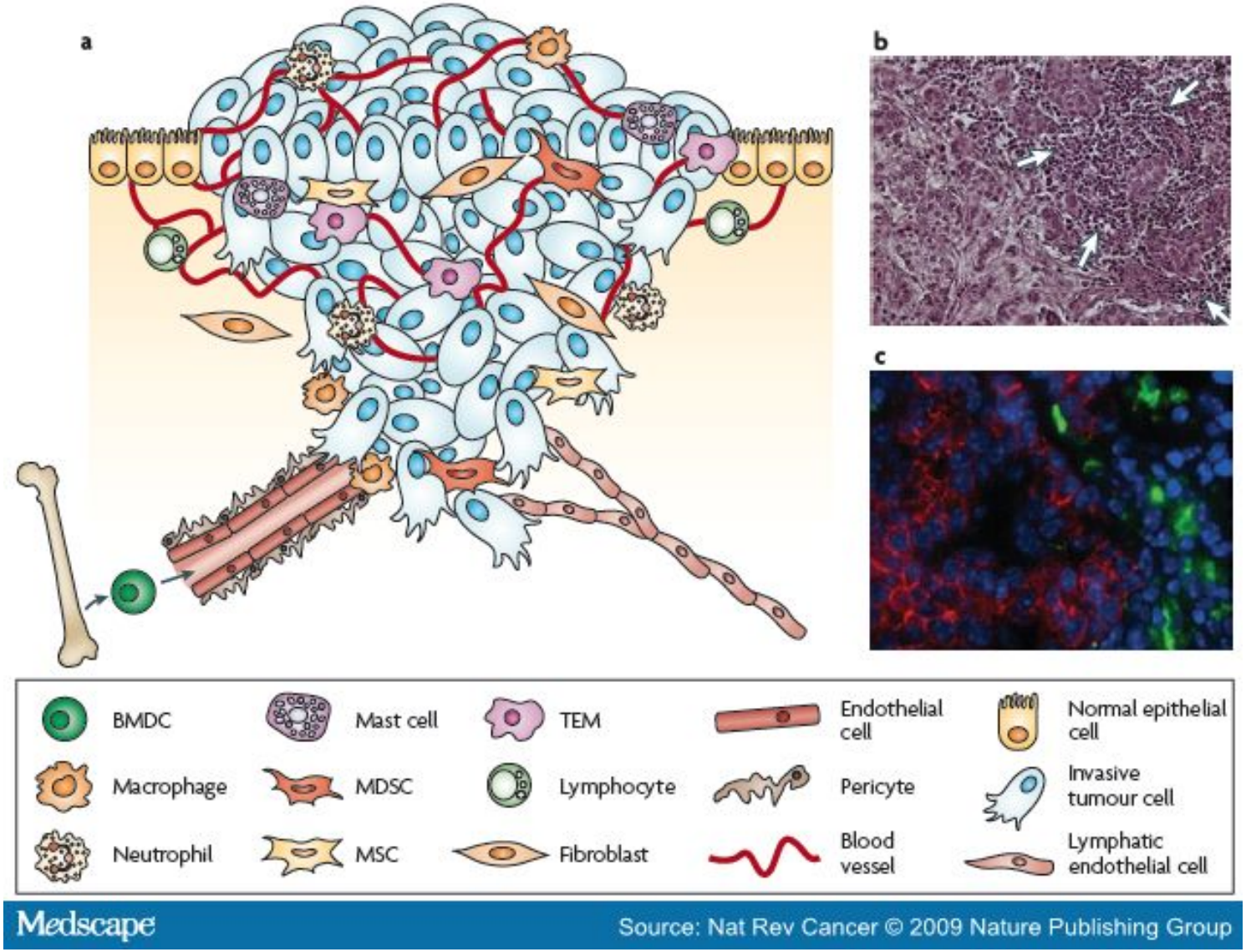
Introduction

- We are learning more about tumour cells
- Many Nobel prizes over past 20 years concern the tumour cell and how it functions
- Understanding tumours do not live in isolation but interaction with host is vital for their survival and growth
- Often animal models inadequate
- So need to see processes in-vivo
- One tool is PET

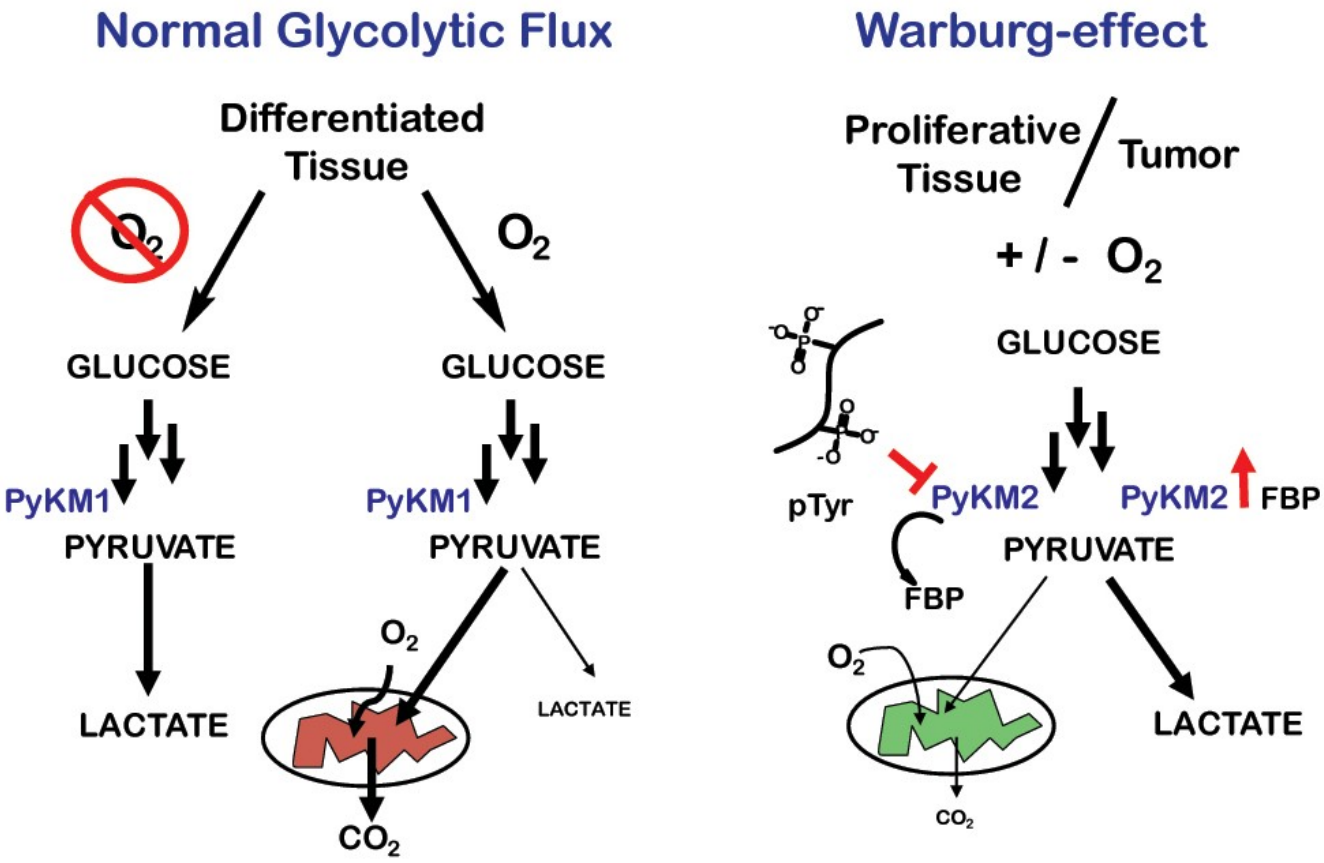
What is in a tumour



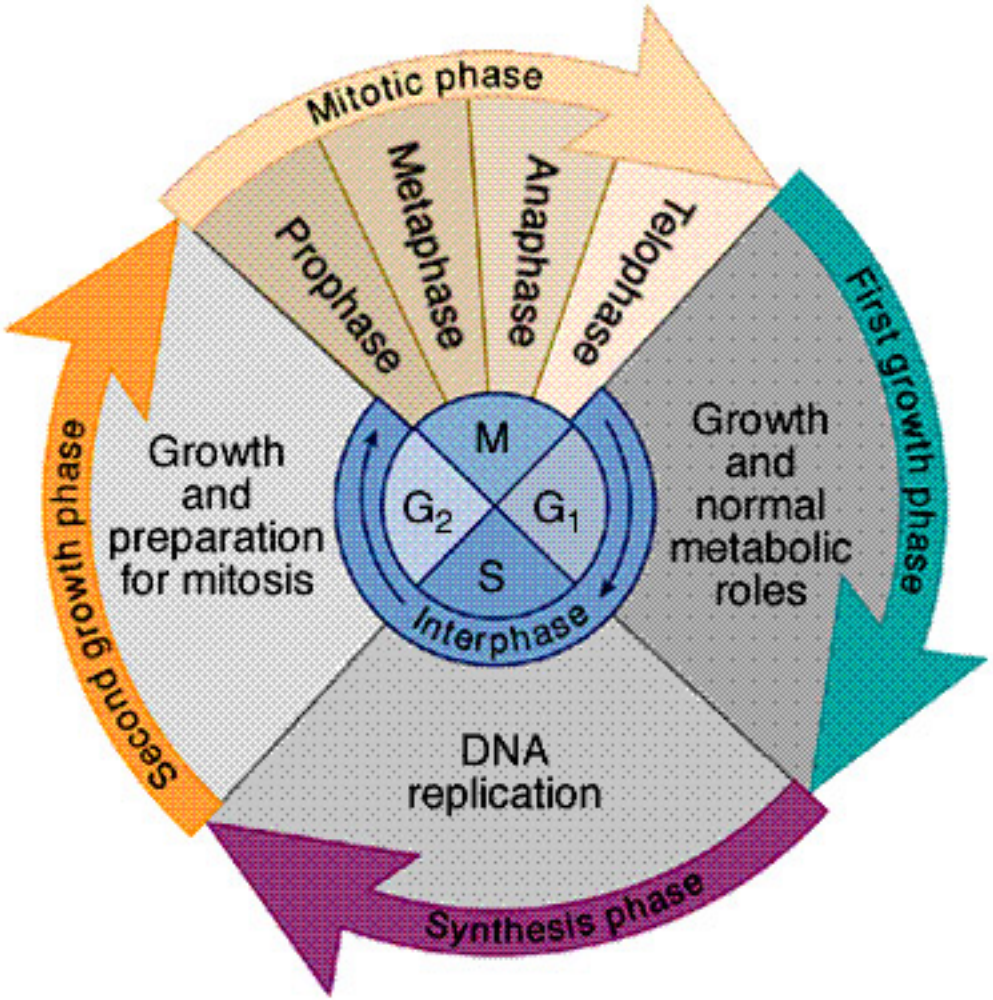
What factors can we image

- Tumour metabolism
- Tumour cell turnover
- Tumour cell hypoxia
- Tumour related angiogenesis
- Apoptosis
- Receptor status

Glucose uptake into tumours

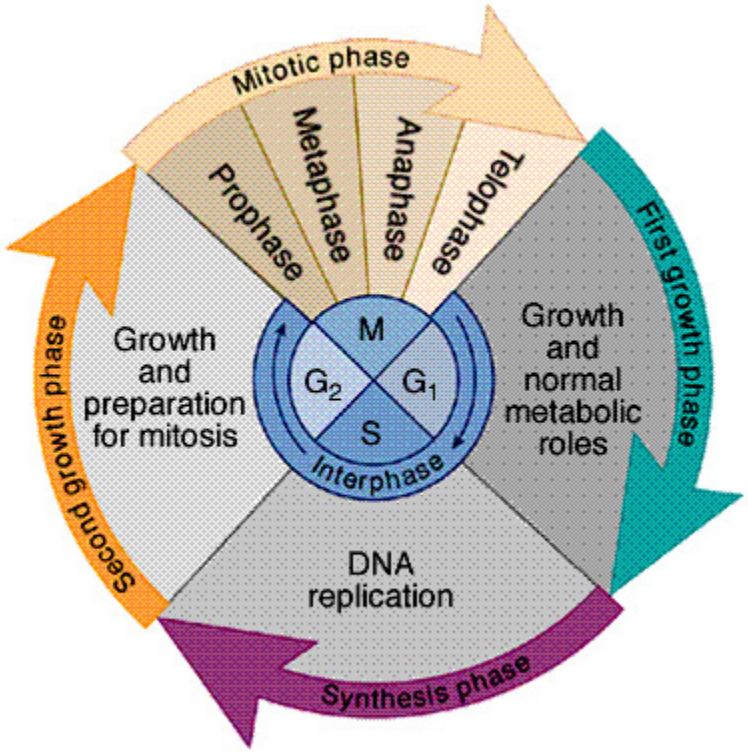


The cancer cell cycle



PET tracers and the cell cycle

C-11 meth
C-11 chol
F-18 chol



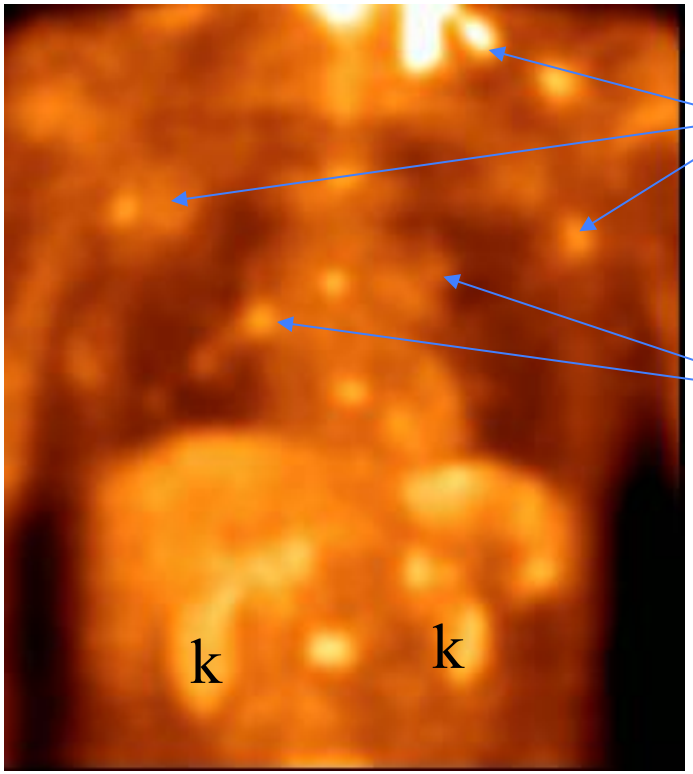
F-18 FDG
C-11 acetate
C-11 meth

F-18 FET
F-18 FLT

Tumour metabolism

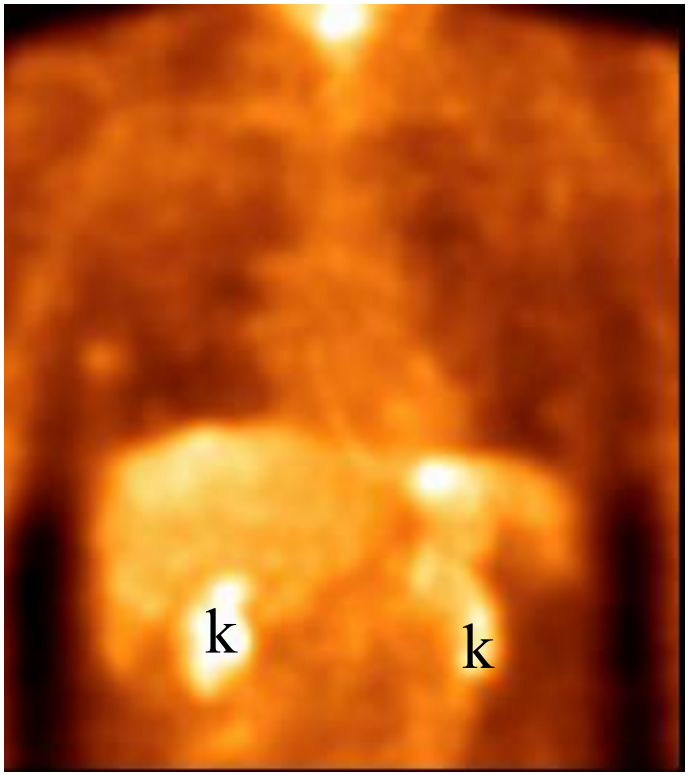
- Most commonly used is F-18 FDG
- Non-specific uptake in inflammation especially difficult in immediate assessment of tumour response to treatment may need 6 weeks after last treatment before assessment-longer for surgery
- Uptake may be related to hypoxia
- Other metabolic agents such as C-11 acetate could be used but not widely applied

FDG-PET response in Hodgkin's disease following 5000 MBq I-131 CHT 25

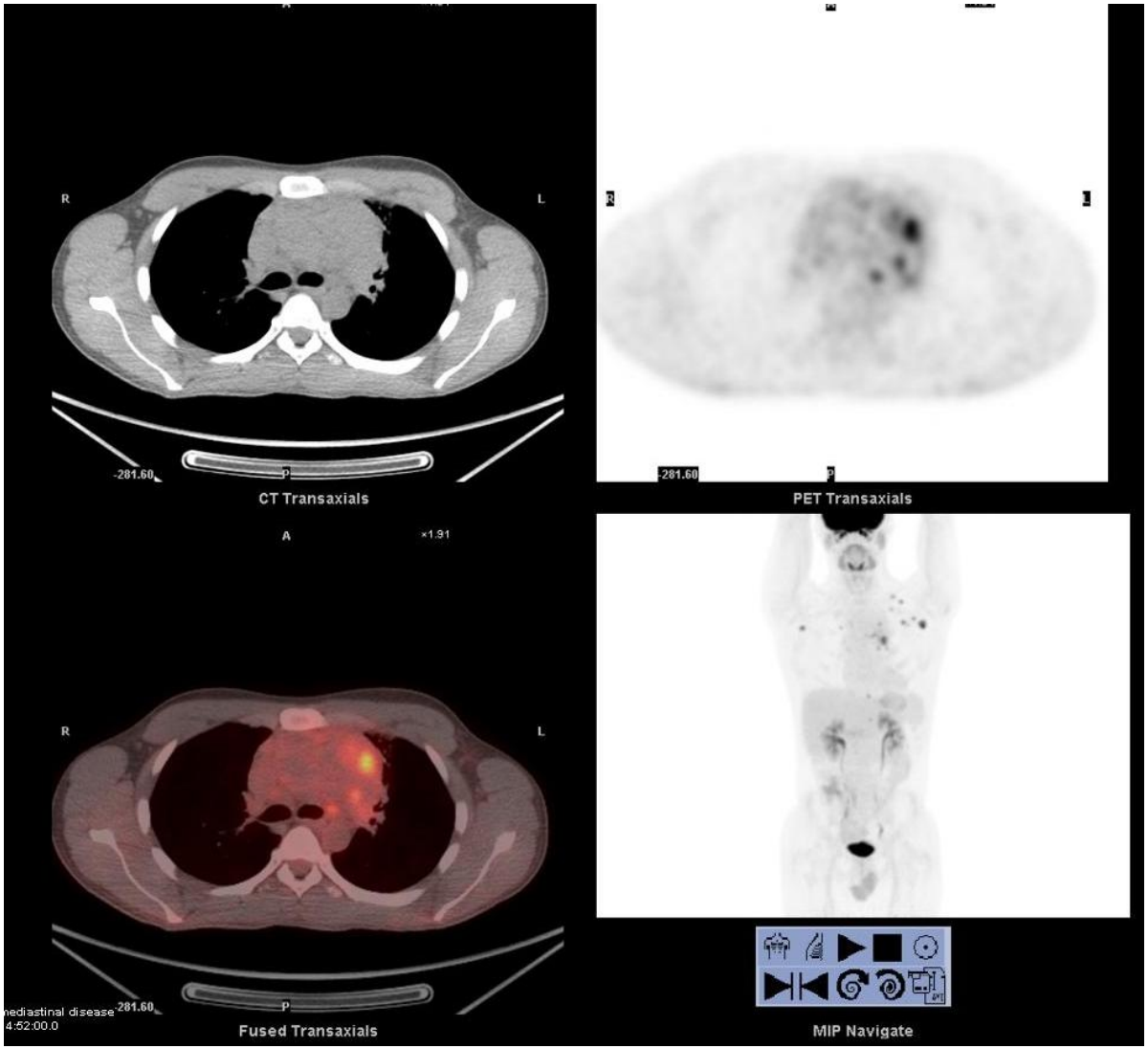


Axillary and cervical LN

Mediastinal LN



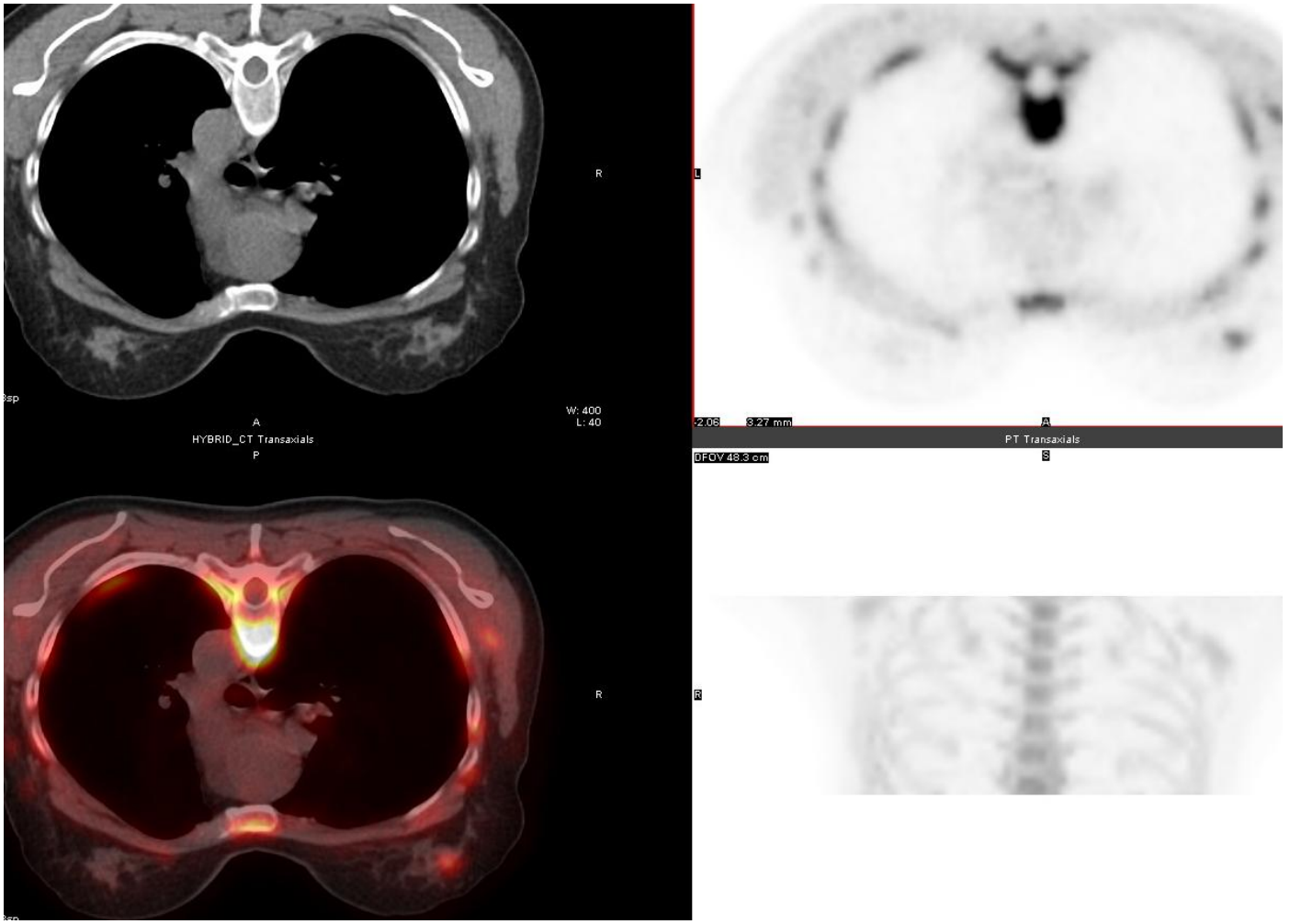
HD Clearly failed Tx



Cell turnover

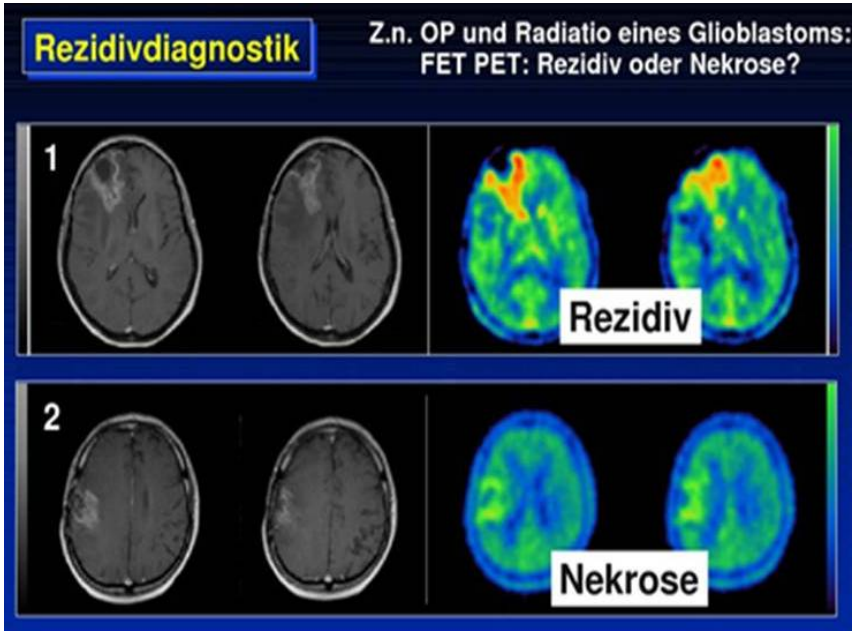
- Imaging cell turnover thought to be more cancer specific
- Still needs context
- Most based on amino acid uptake/DNA precursors
- This tends to be normal in inflammation
- Maybe high in bone marrow due to tumour turnover-proliferation
- Agents F-18 FLT, F-18 FET, C-11 methionine

FLT imaging in breast cancer



F-18 FET

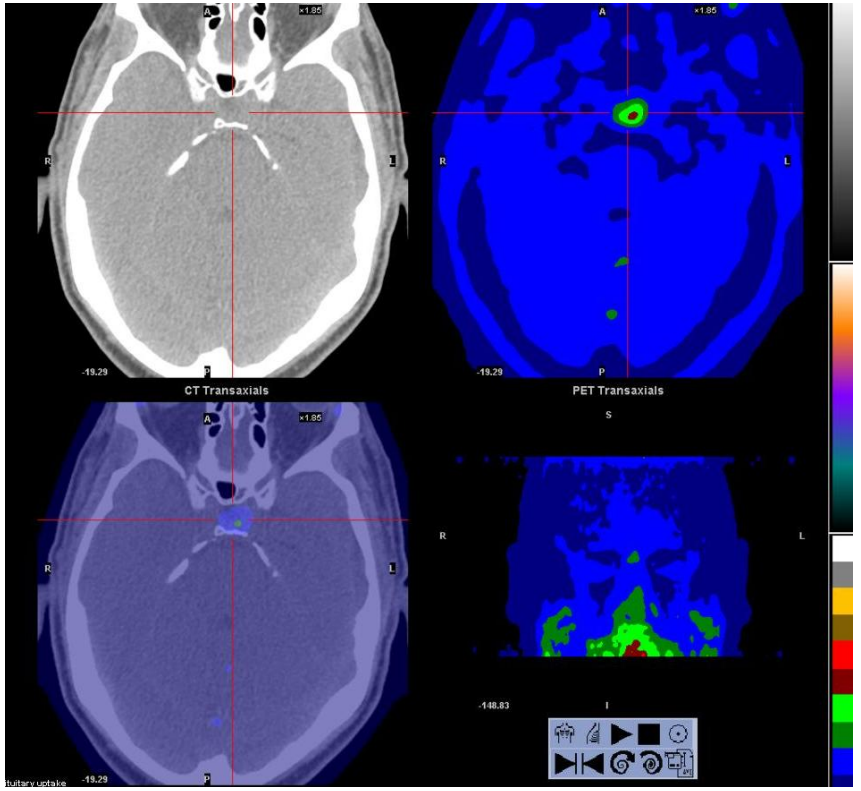
- Fluoroethyl tyrosine
- Pauliet at al Nuc Med Biol 2009
- 52 patients low grade glioma
- Imaged with F-18 FDG and F-18 FET
- FDG positive in 35%
- FET positive in 89%



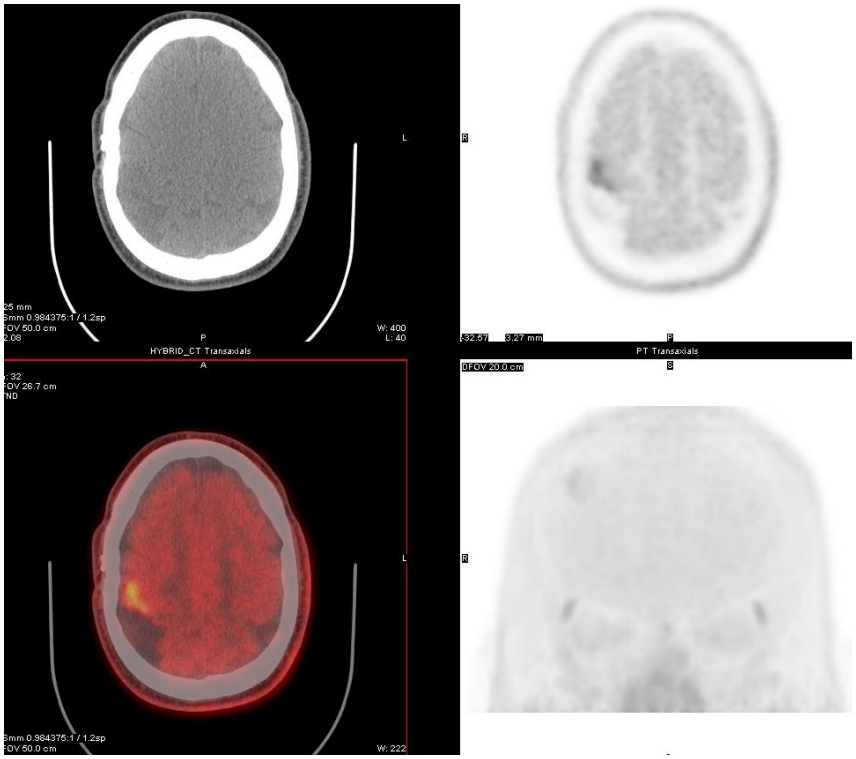
Astrid Marquart Akademie Esslingen

C-11 methionine

- C-11 12 minutes half life
- Very tumour specific
- Good for tumours with where there is high physiological FDG activity
  - Brain
  - Liver (?)



Progression vs pseudoprogression

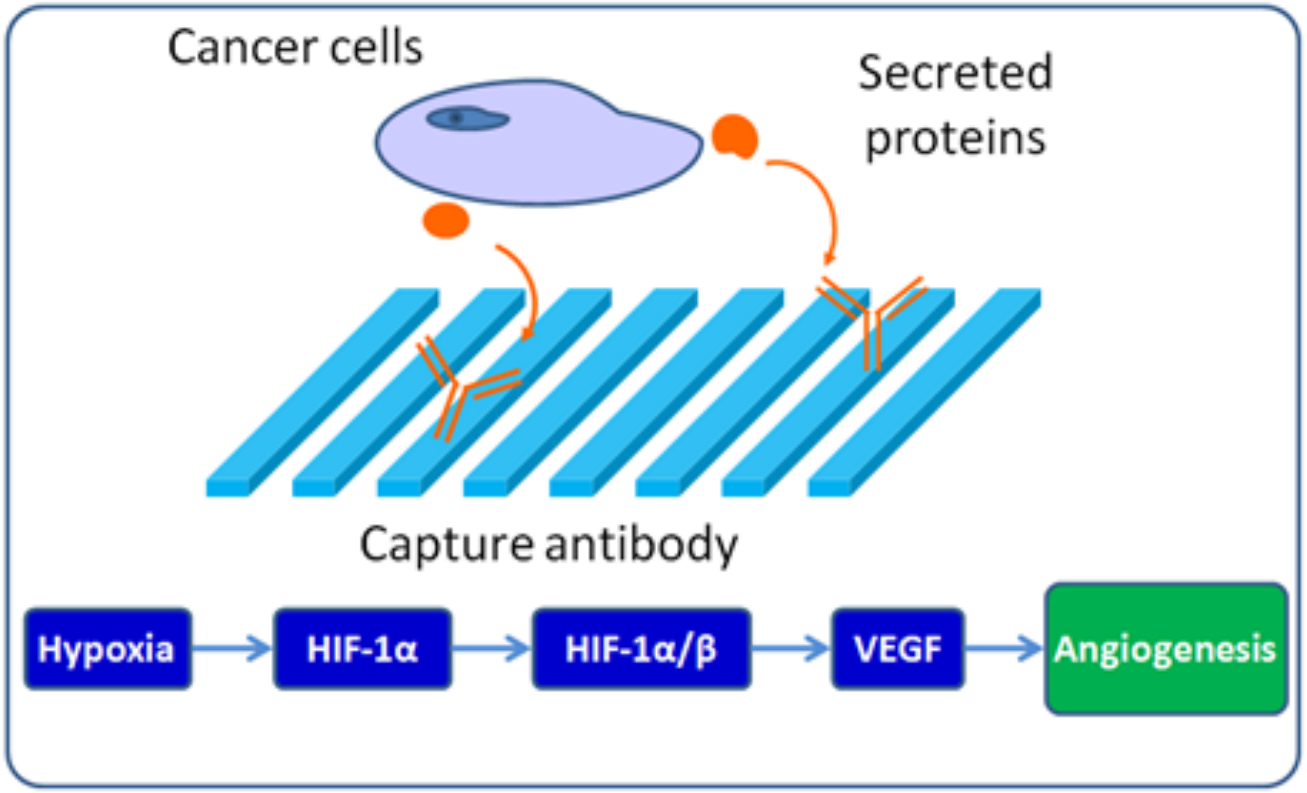


- Tsuyunguchi et al Ann Nuc Med 2004
- 11 patients treated with stereotactic surgery and RT
- Sens of C-11 meth for recurrent disease = 100% same as MRI
- Spec of C-11 meth 82% c/w 60% MRI

Tumour cell hypoxia

- Tumours grow fast
- Outgrow their own blood supply
- Become hypoxic
- Release HIP and EGF to induce angiogenesis
- Increases uptake of FDG
- Increases resistance to chemotherapy and radiotherapy

Hypoxia and angiogenesis

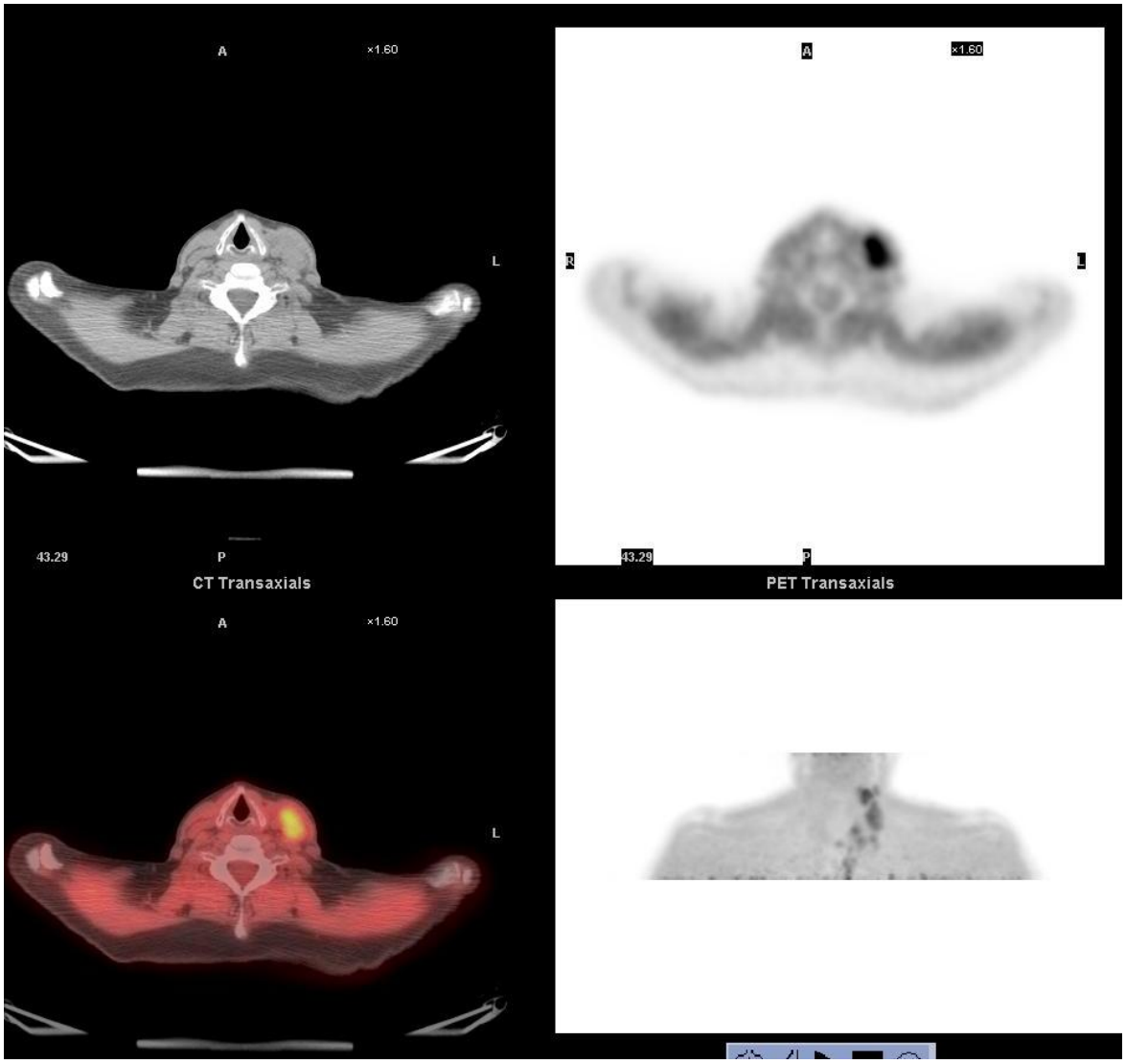


Caltech 2009

Hypoxia and angiogenesis

- Hypoxia imaging
  - F-18 FDG too non specific
  - F-18 FMISO diamazole ester in presence of oxygen splits and product expelled from cell
  - If hypoxic is retained needs dynamic imaging, limited to 1 bed position imaging up to 1 hour
  - C-64 ATSM

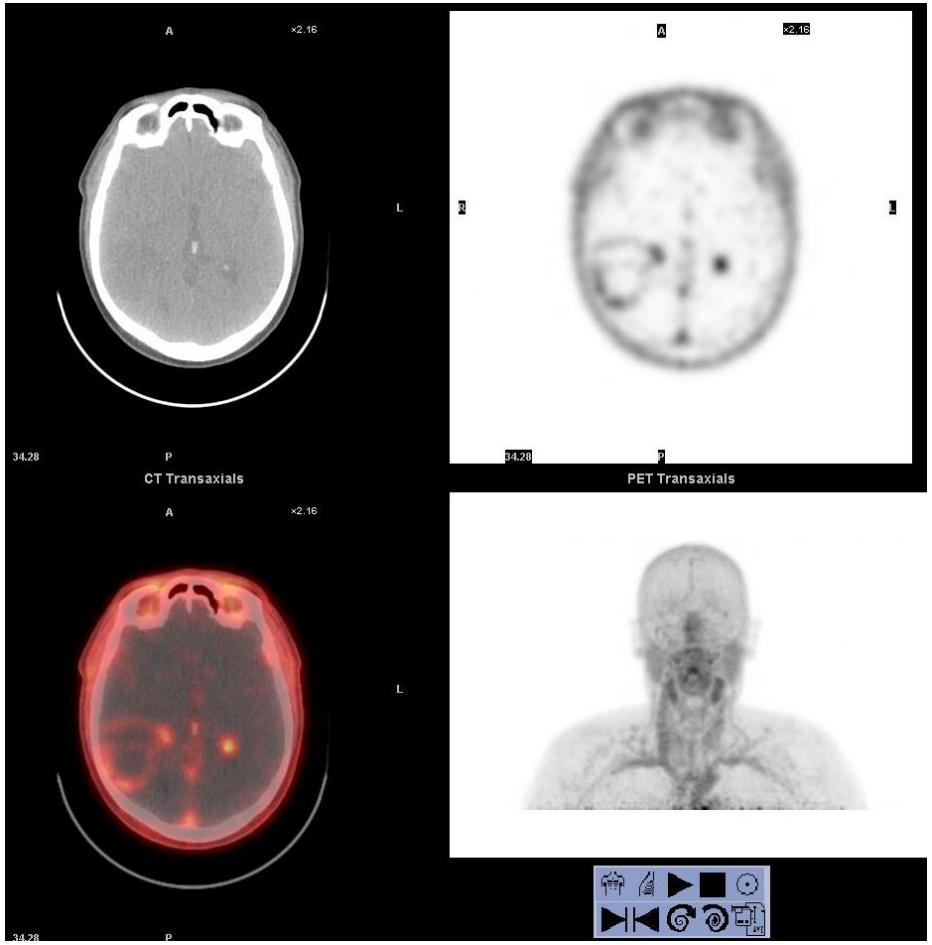
F-18 FMISO retention in Ca kidney met



The response to hypoxia

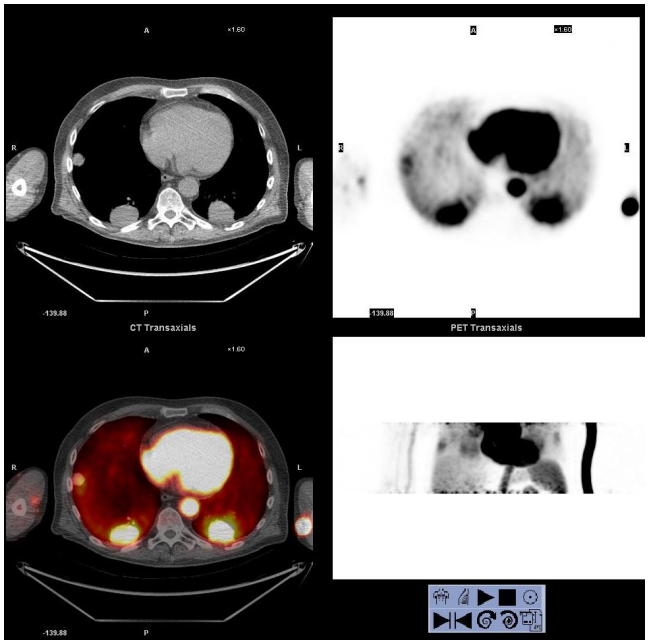
- The cell produces signal proteins such as vEGF
- These stimulate new blood vessels
- New vessels express vEGF receptors that can be targeted by RGD (arginine-glycine-aspartate) peptides
- Should result in increased blood flow
- Imaging may be useful to monitor effect of anti-angiogenic drugs such as Avastin

F-18 Fluciclatide (RGD)



Note uptake only on edge of tumour

Imaging blood flow



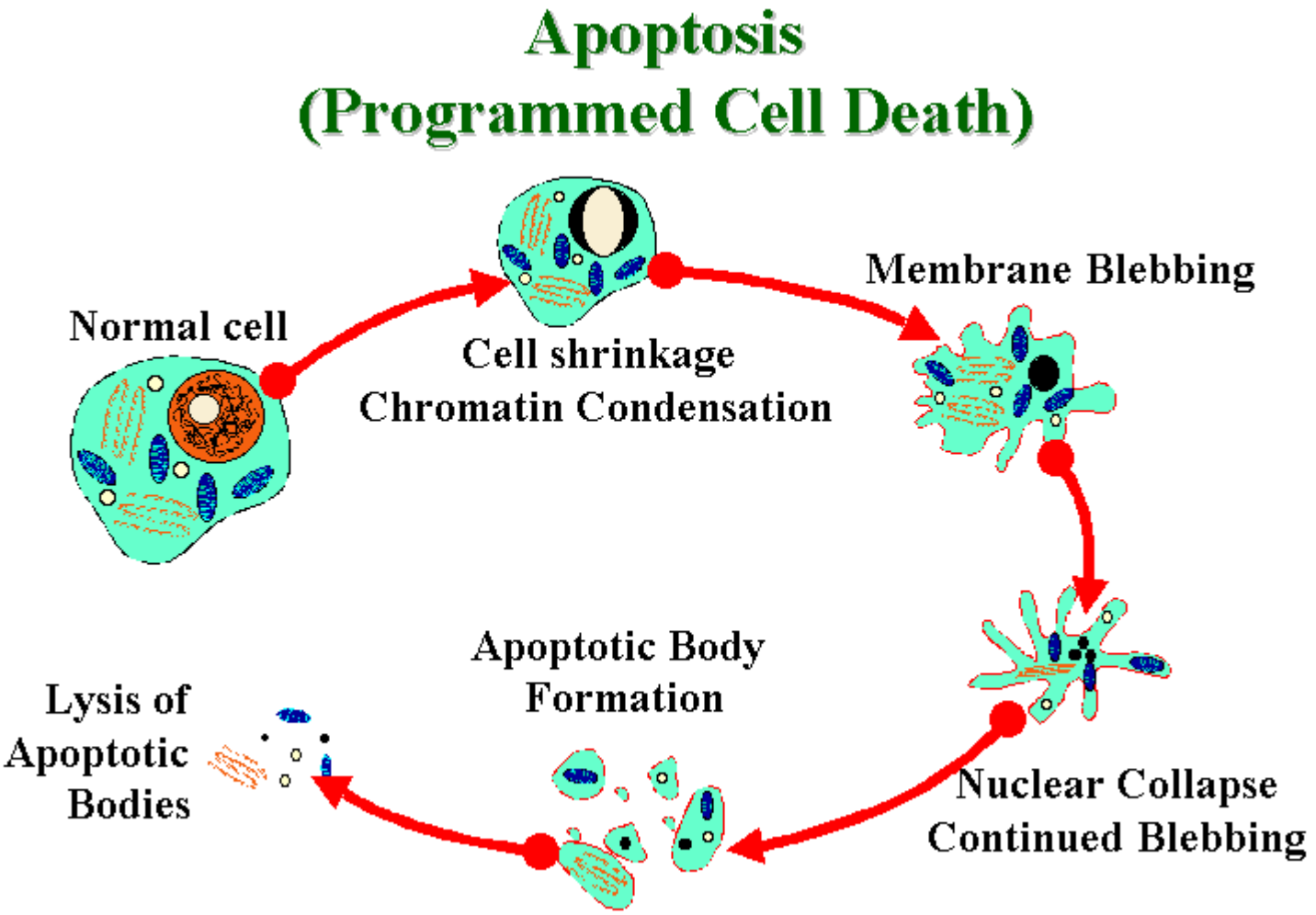
O-15 generator

O-15 water to look for tumour perfusion in renal cancer metastases

Imaging apoptosis

- Apoptosis is programmed cell death-normal process
- Response to cell damage
- Stopped by mutant p53-immortality
- Cell wall forms blebs
- Start to reverse inside/outside
- Intra-cellular proteins expossed
- Localisation of Annexin-V within 24 hours of effective treatment

Apoptosis

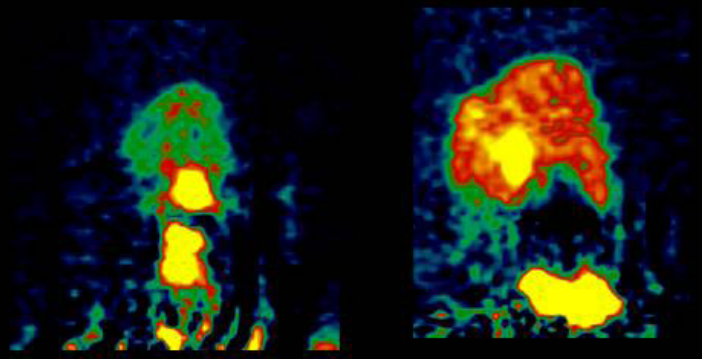

Apoptosis
(Programmed Cell Death)
Normal cell
Cell shrinkage
Chromatin Condensation
Membrane Blebbing
Nuclear Collapse
Continued Blebbing
Apoptotic Body
Formation
Lysis of
Apoptotic
Bodies

F-18 Caspase imaging Mach et al

MicroPET Imaging Study: [^{18}F]WC-II-89

Focus 120 Scanner

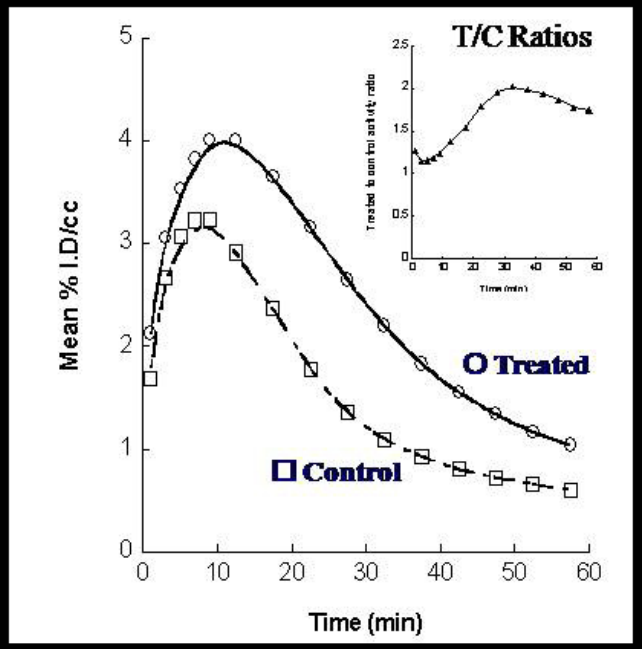
Focus 220 Scanner



Control

Cycloheximide

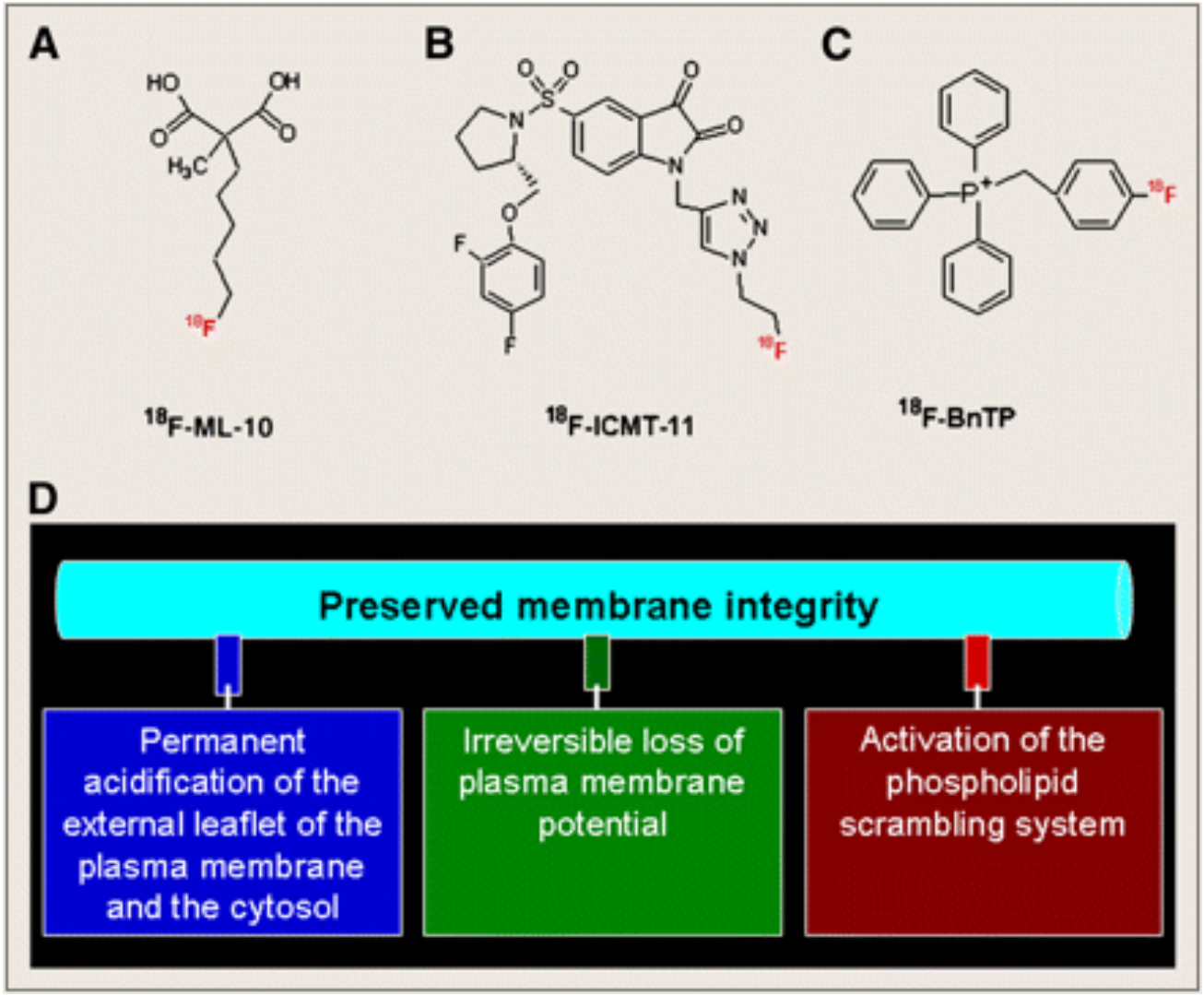
Sprague-Dawley Rats
Summed Images



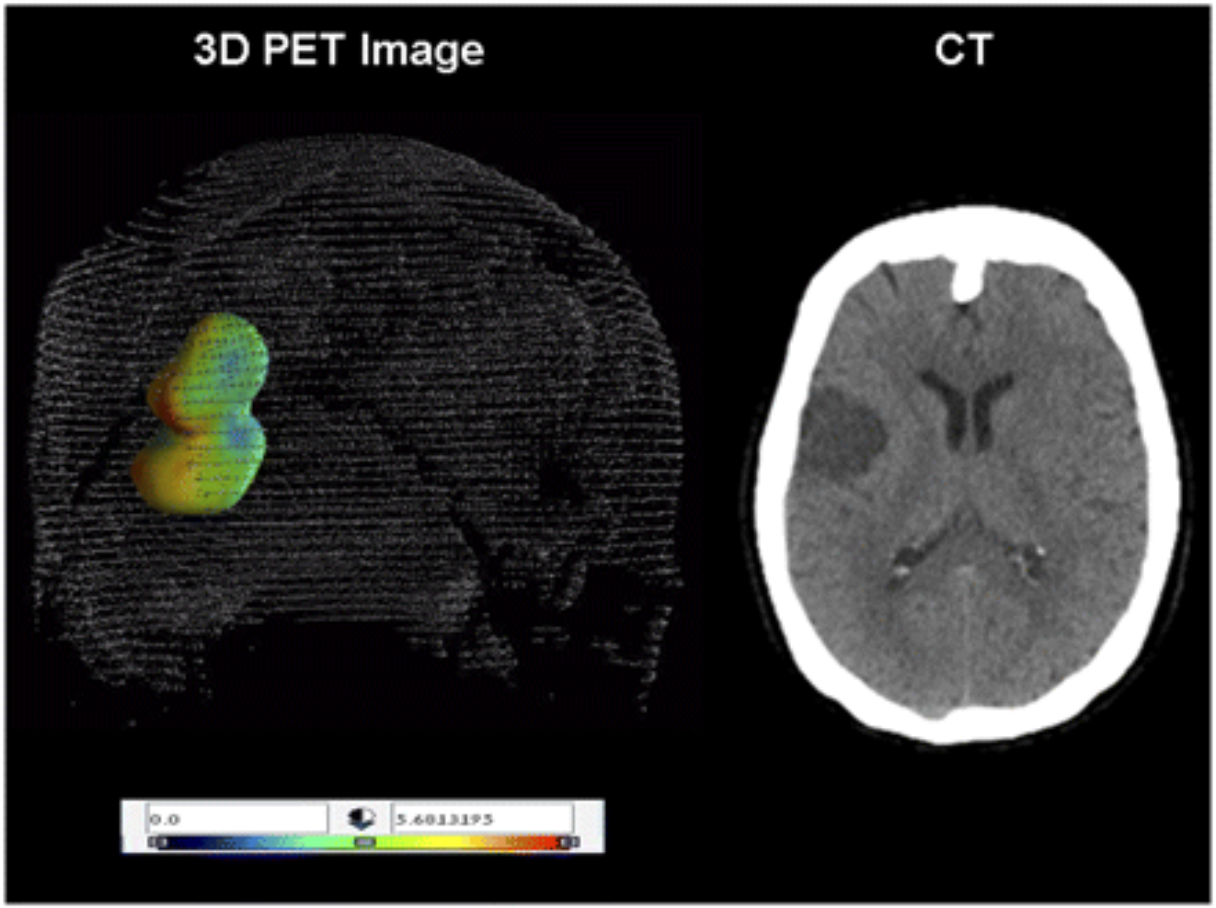
Time-Activity Curves

Bioorg. Med. Chem. Lett. 16: 5401; 2006

Small molecules for apoptosis
Reshav et al JNM 2010



Apoptosis imaging F-18 ML10 Reshav et al JNM – Aposense

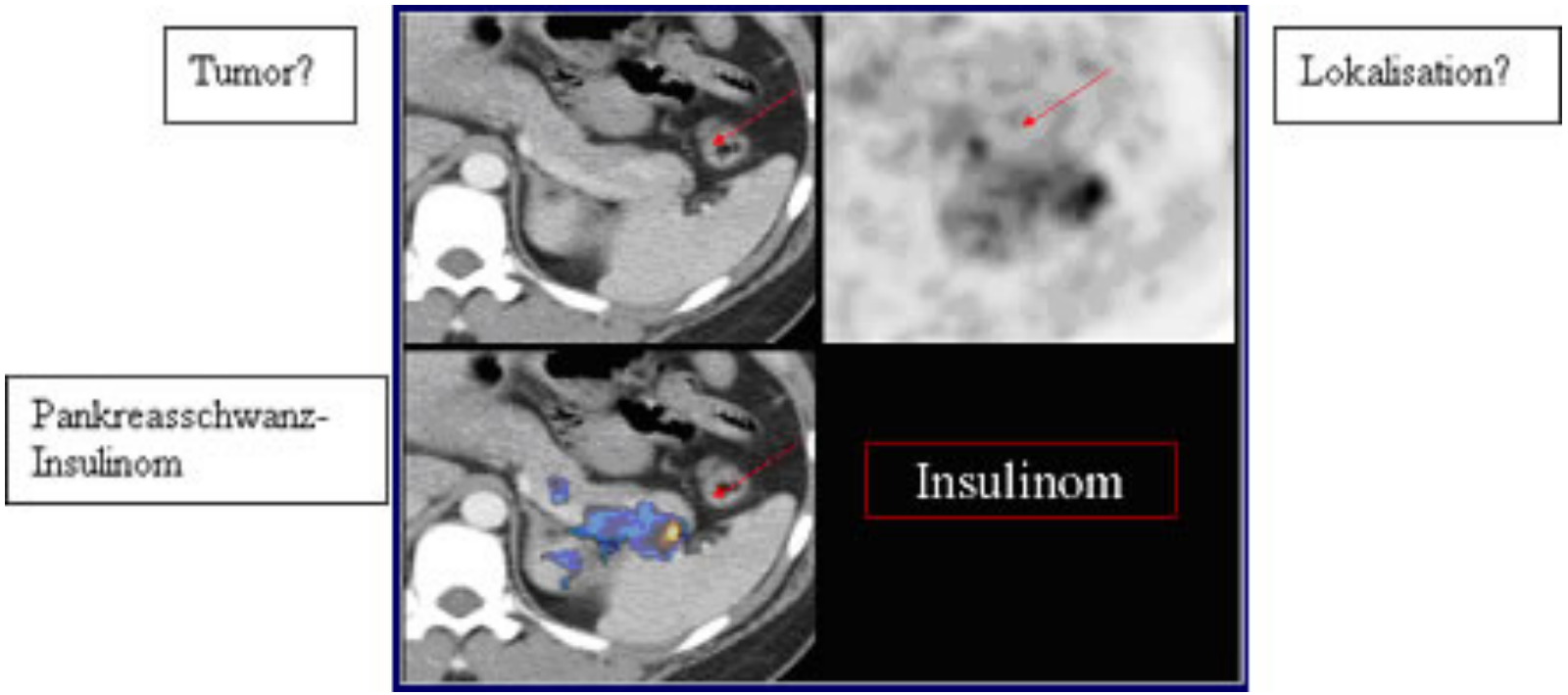


F-18 ML10 in CVA

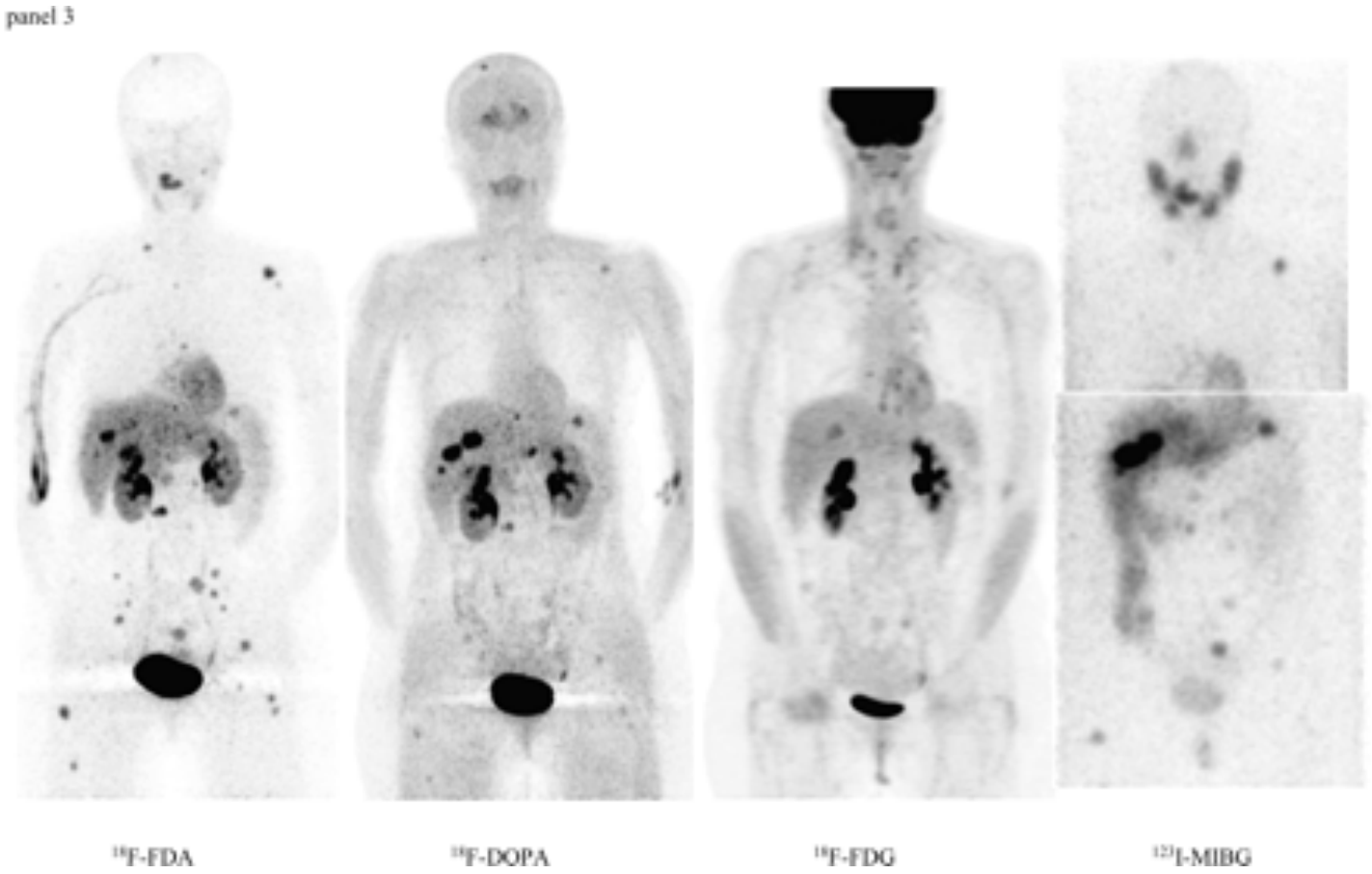
Dopamine system

- DOPA amine precursor of many bio-active molecules
- Labelling difficult
- Mostly done with F-18
- High failure rate so cost US$7500
- Used in some rare tumours
  - Insulinoma
  - Medullary cell thyroid cancer

F-18 F-DOPA in insulinoma-(from Zurich PET centre)



F-18 DOPA/F-18 Dopamine in Phaeo
Timmers et al J Clin End Met 2009



Conclusions

- PET expanding beyond FDG
- Newer agents expanding what we see
- Needs to be linked to what we learn from basic science – translational research
- Can enable us to look into those processes that will impact on tumour care
- Area of active development