Diagnostic Nuclear Oncology

John Buscombe

Introduction

- It is important to know what your aim is in nuclear imaging
- Functional imaging different form anatomical imaging so should do different things
- Used to do those things other radiology not so good or effieicient doing

What is our aim

- Diagnosis
- Staging
- Re-staging post therapy
- Looking at predicting response
- Deciding on functional therapy

Diagnosis

- Not commonly done with nuclear medicine
- Has been shown to be of use in breast cancer especially in the younger or dense breast
- PET techniques may useful in finding cause of raised tumour markers
- Characterising a defect seen on other imaging eg SPN

Scintimammography

- Method uses a radiopharmacauetical Tc-99m MIBI/TF
- This had preferential uptake for tissues with higher metabolic rate
- Includes many cancers such as breast
- Imaging techniques optimised (by Diggles & Khalkhali) – use of early prone lateral images

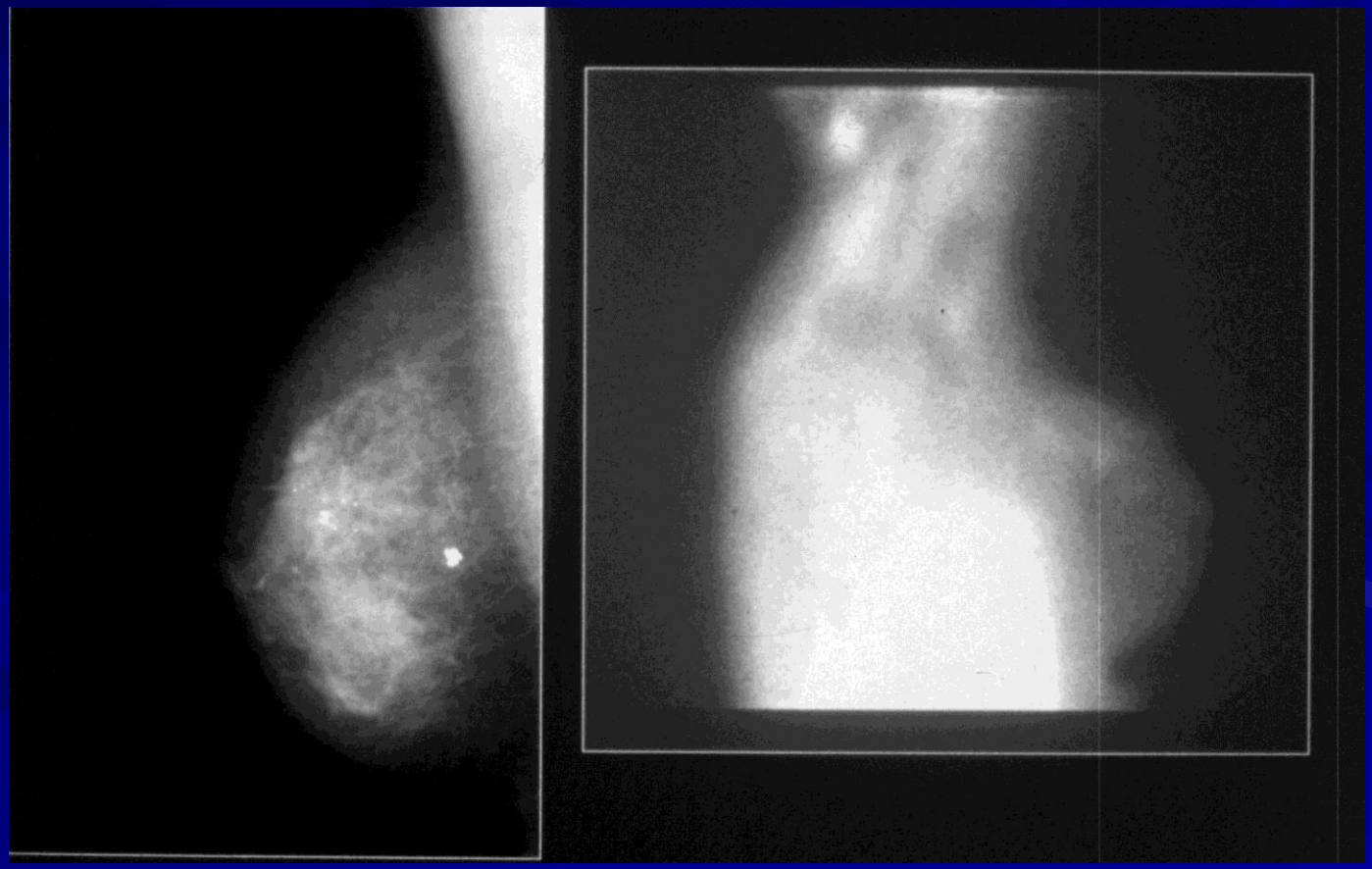
Setting up image

- Image side of suspicious lesion first
- Use special mattress to perform prone lateral image
- Do not crush or pinch breast
- Image for 10 minutes
- Start imaging at 5 mins p.i.

Scintimammography

- Technique found to deliver high sensitivity in many centres (normally >90%)
- Specificity varies from 60-90%
- PPV therefore 60-95%
- Also shown to perform well in blind read multicentre trials
- Consistency in inter-observer reads (>90%)

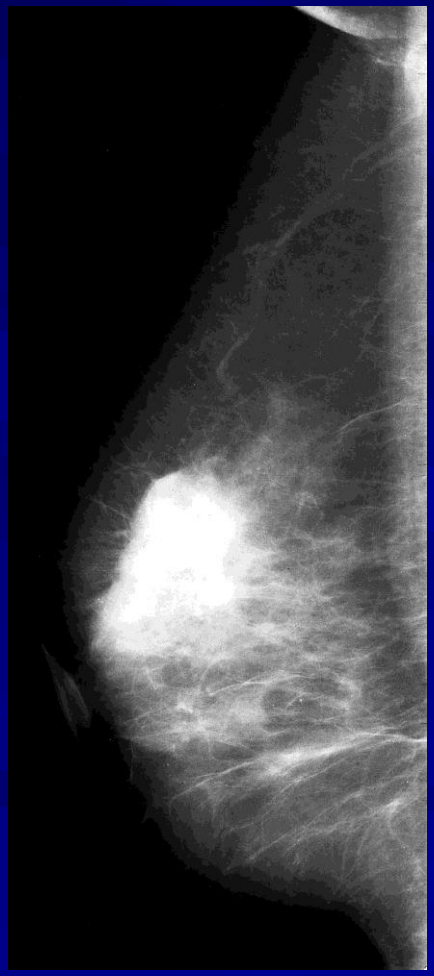
Which test finds the cancer?

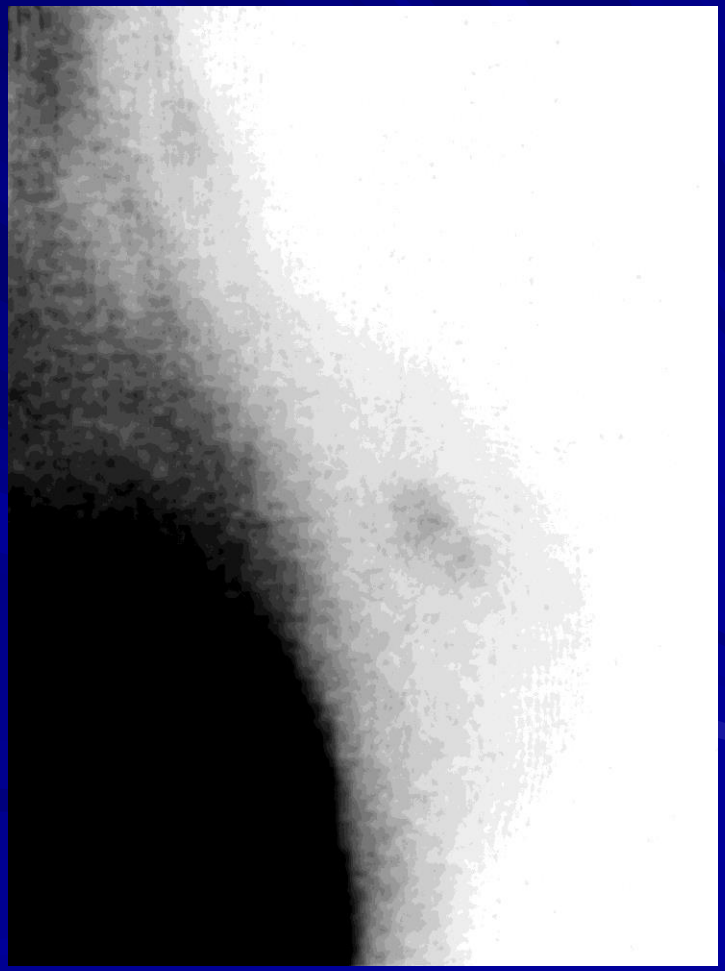


scintimammography

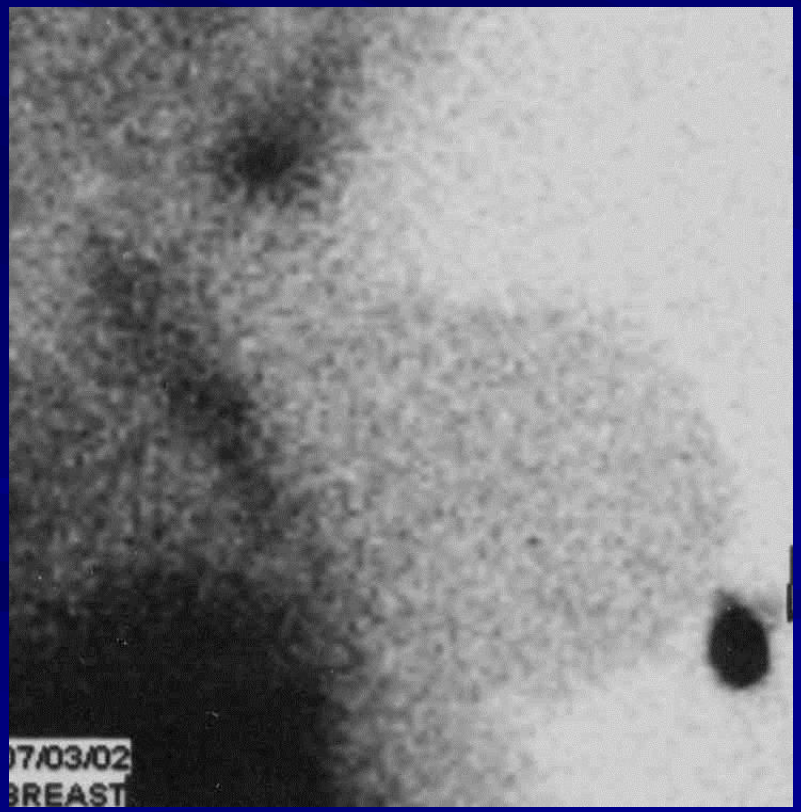
45 year old woman with dense breast tissue

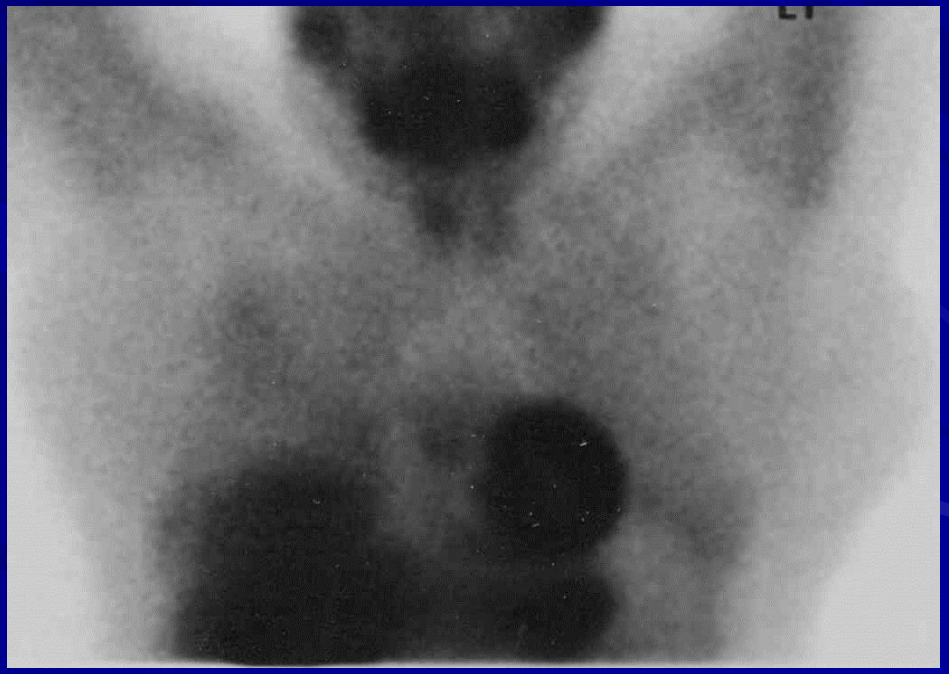
Scinti-mammography shows cancer at top of density



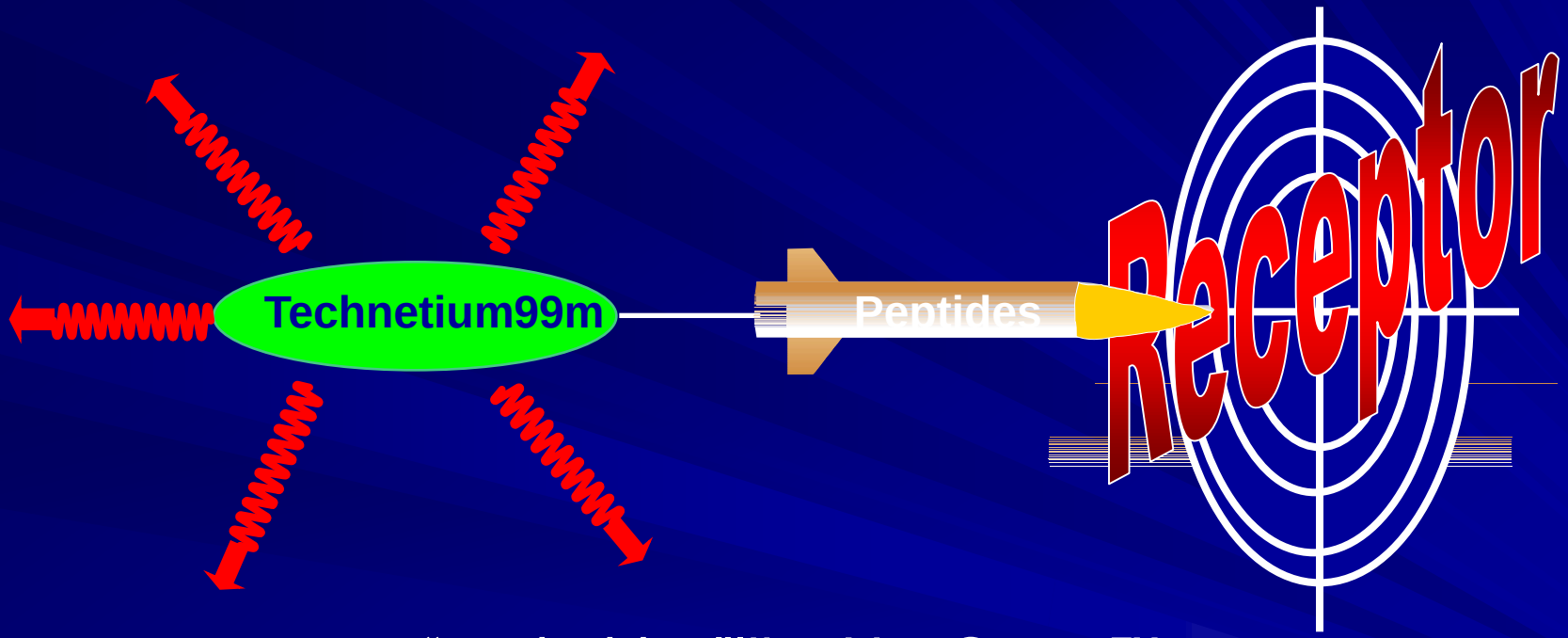


61 year old physician with T1 tumour 5 years previously Tx, WLE, now mammogram suggests breast recurrence





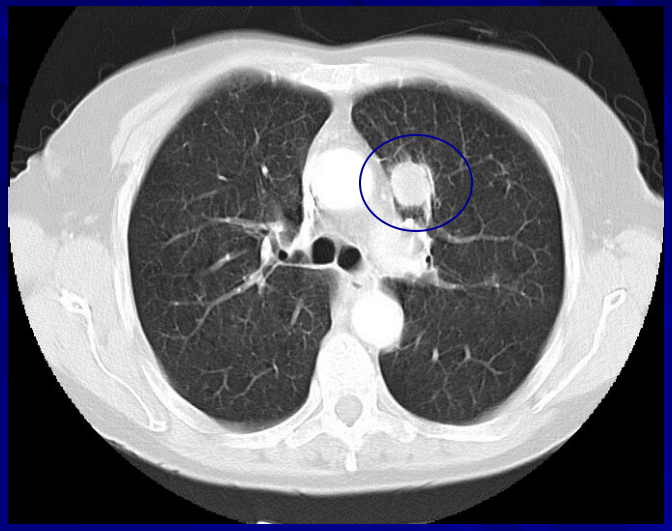
Molecular targeting with Nuclear Medicine

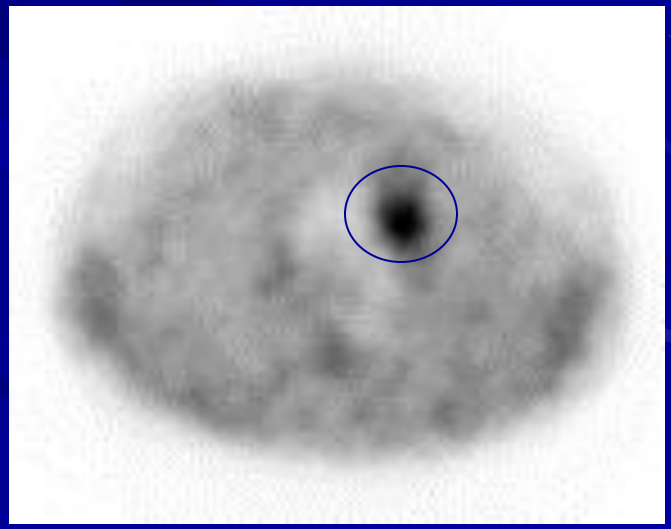


"TechTides"like NeoSpect™ are
"Smart Drugs for Imaging"
They transport Tc99m to a specific receptor

45 year old female smoker

- Remote 30 year history of smoking
- Chest CT showing SPN in left upper lobe
- CT not typical of Ca-no nodes (prob 75%)
- Positive Tc-99m Depreotide
- 23mm T1 well diff AdenoCa removed-no nodes



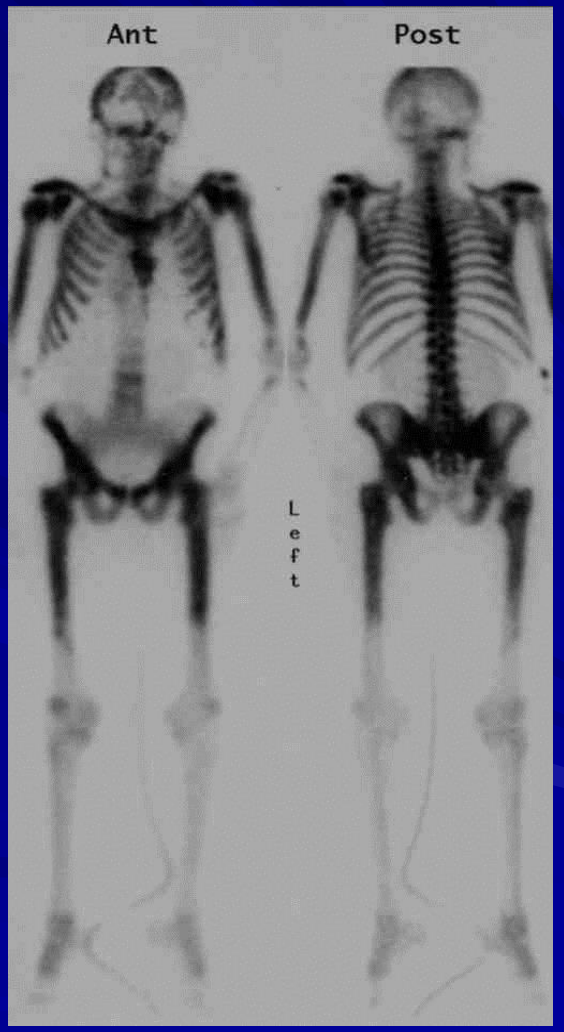


Staging

- This may be the largest role for nuclear medicine in oncology
- Simple bone scan often best way to stage a bone seeking tumour
- Sentinel node studies in breast, melanoma, penile and vulval cancers
- PET esp Ca lung pre-surgery

62Male carcinoma of the prostate, pain in many sites, Hb 10g/dl

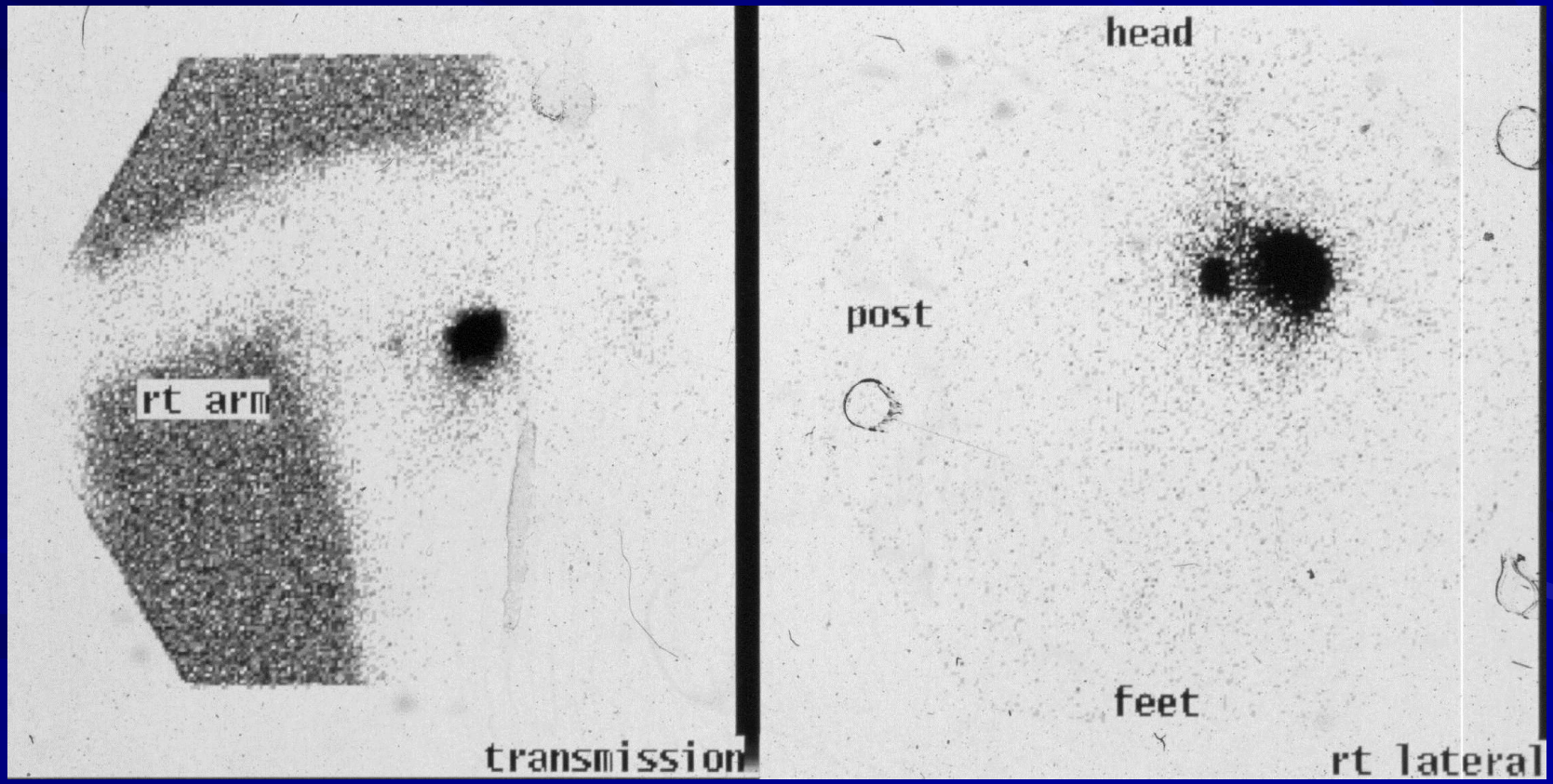
Clearly most of the axial skeleton and proximal long bones are involved This is actually a Superscan



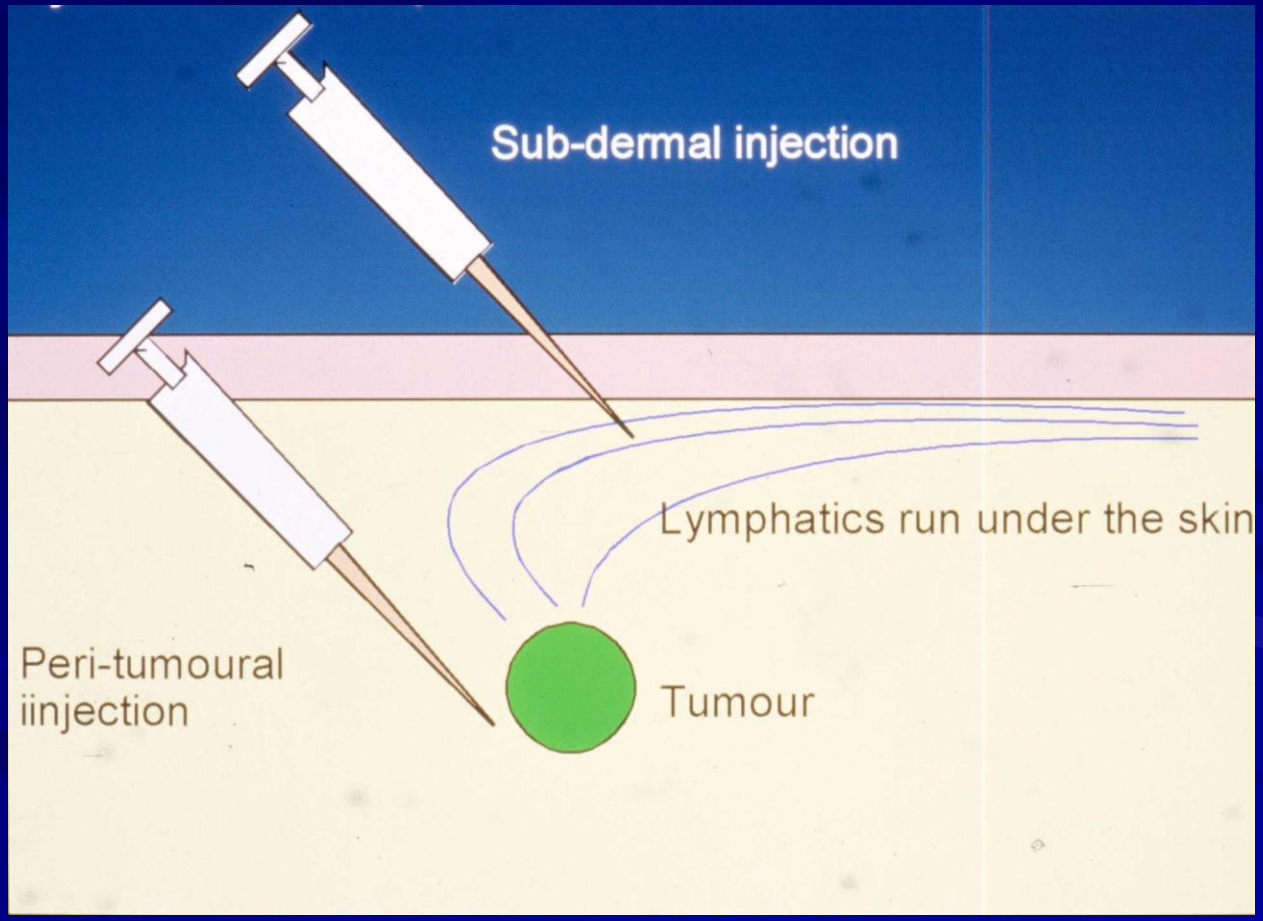
Sentinel Nodes

- Uses the Morton principle of logical lymph drainage from a tumour
- Methods use include blue dye and radiotracers
- Combination of 2 may be best
- Pioneers in breast
  - Morton/Krag/Guilianno USA
  - (EIO, Italy and AMC, Netherlands)
- May replace high morbidity axillary clearance

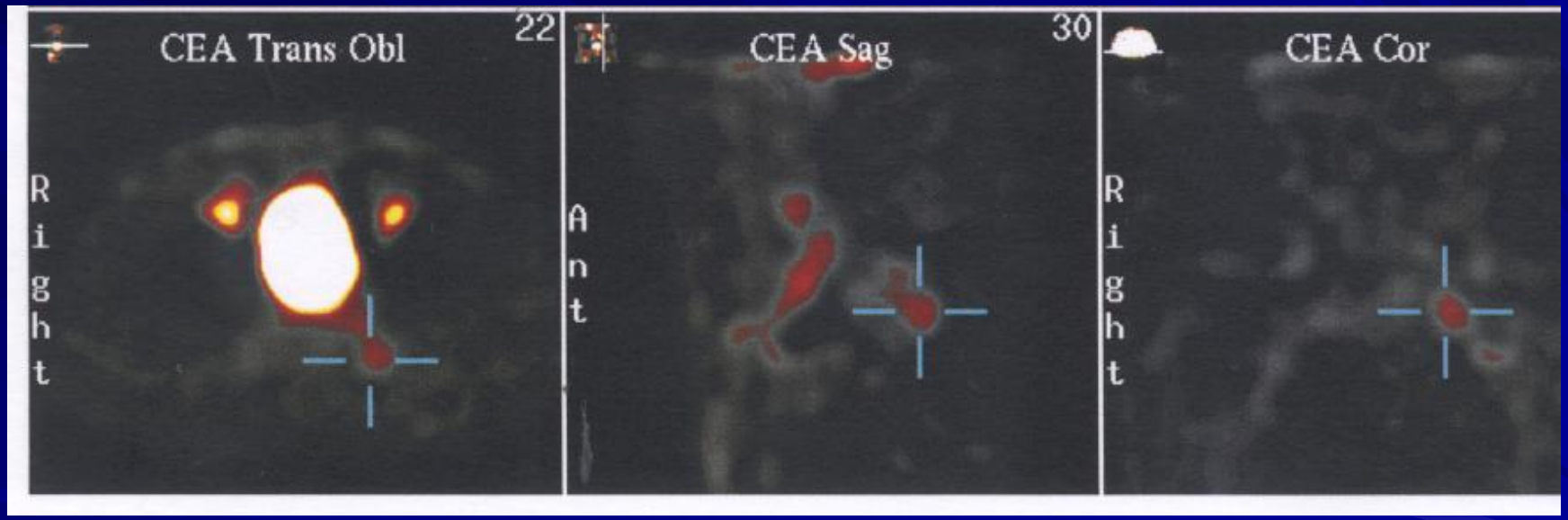
Sentinel nodes



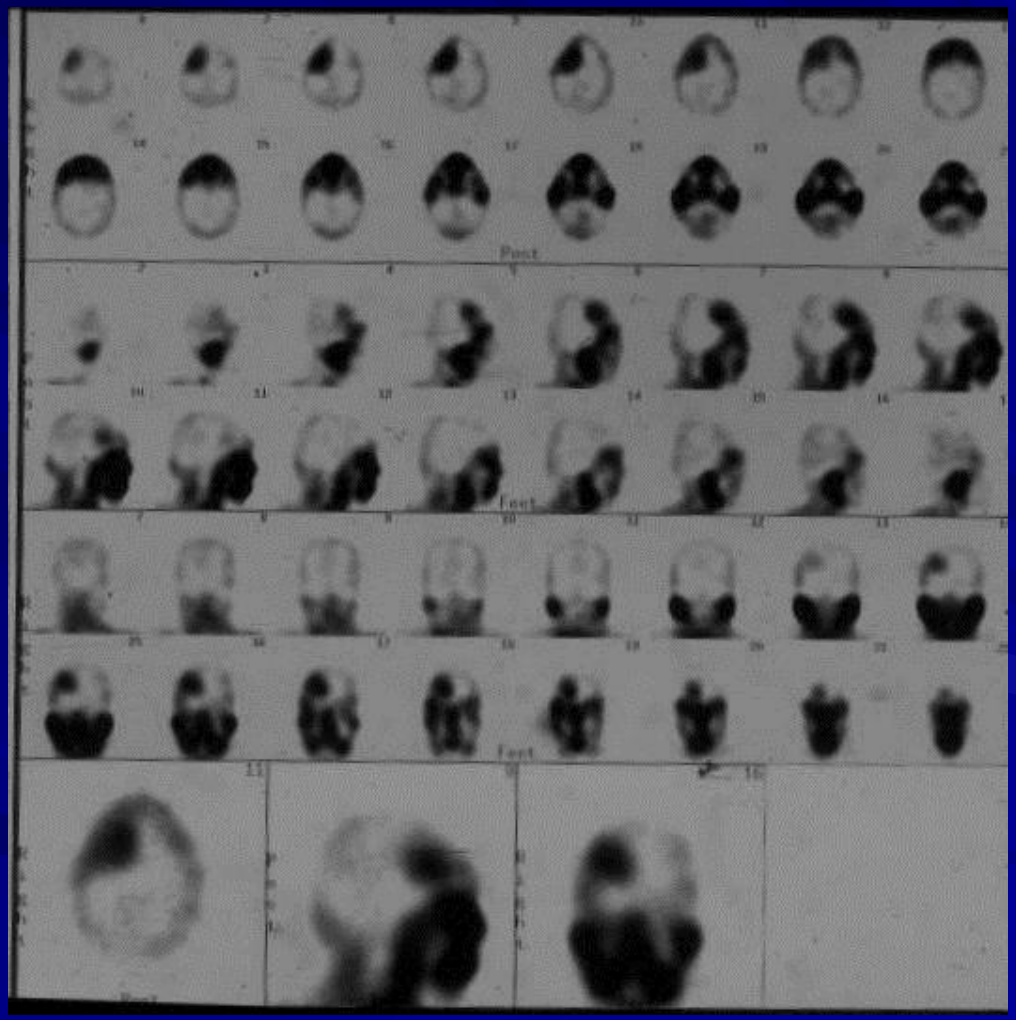
Where to inject?



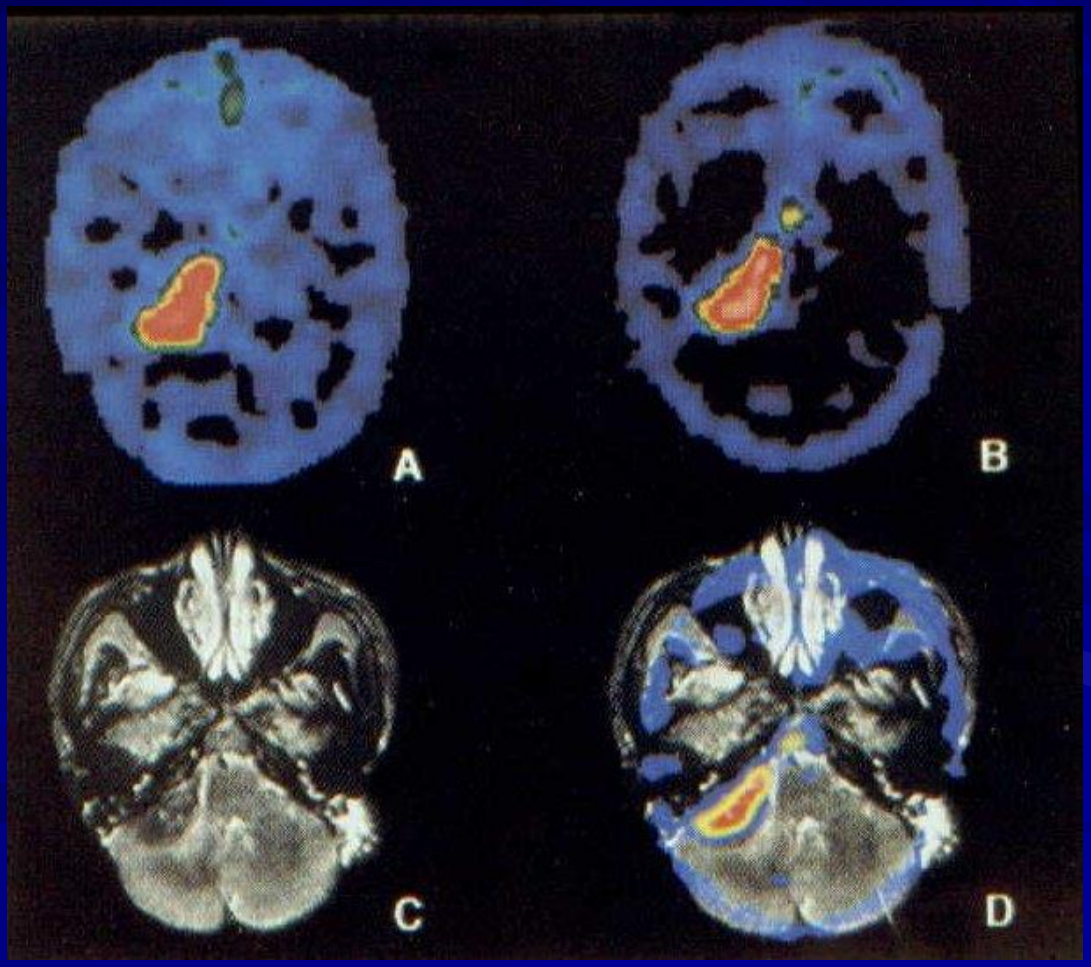
Tc-99m CEAscan in rising CEA post surgery



Tl-201 in glioma

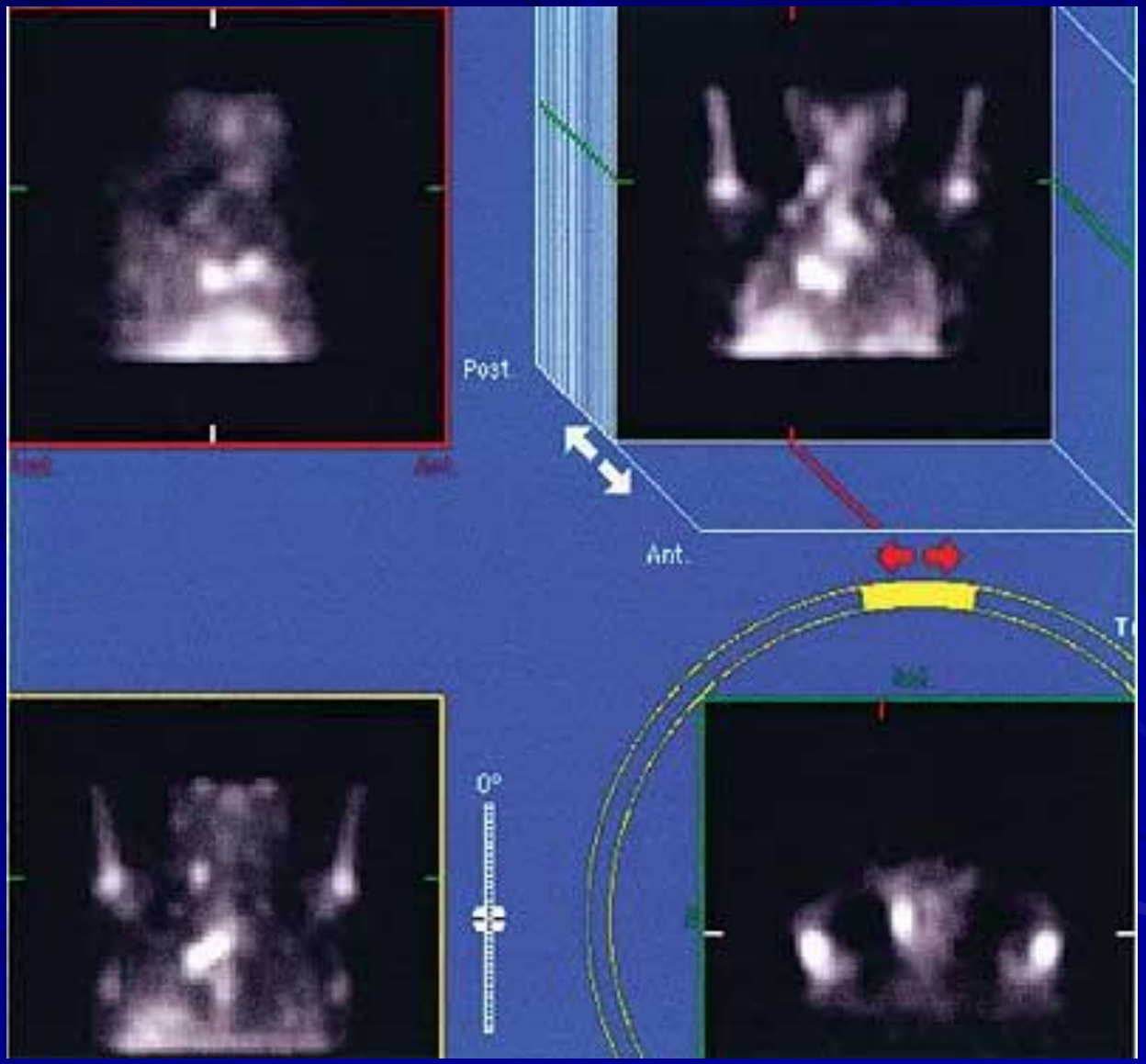


Tl-201/MRI registration

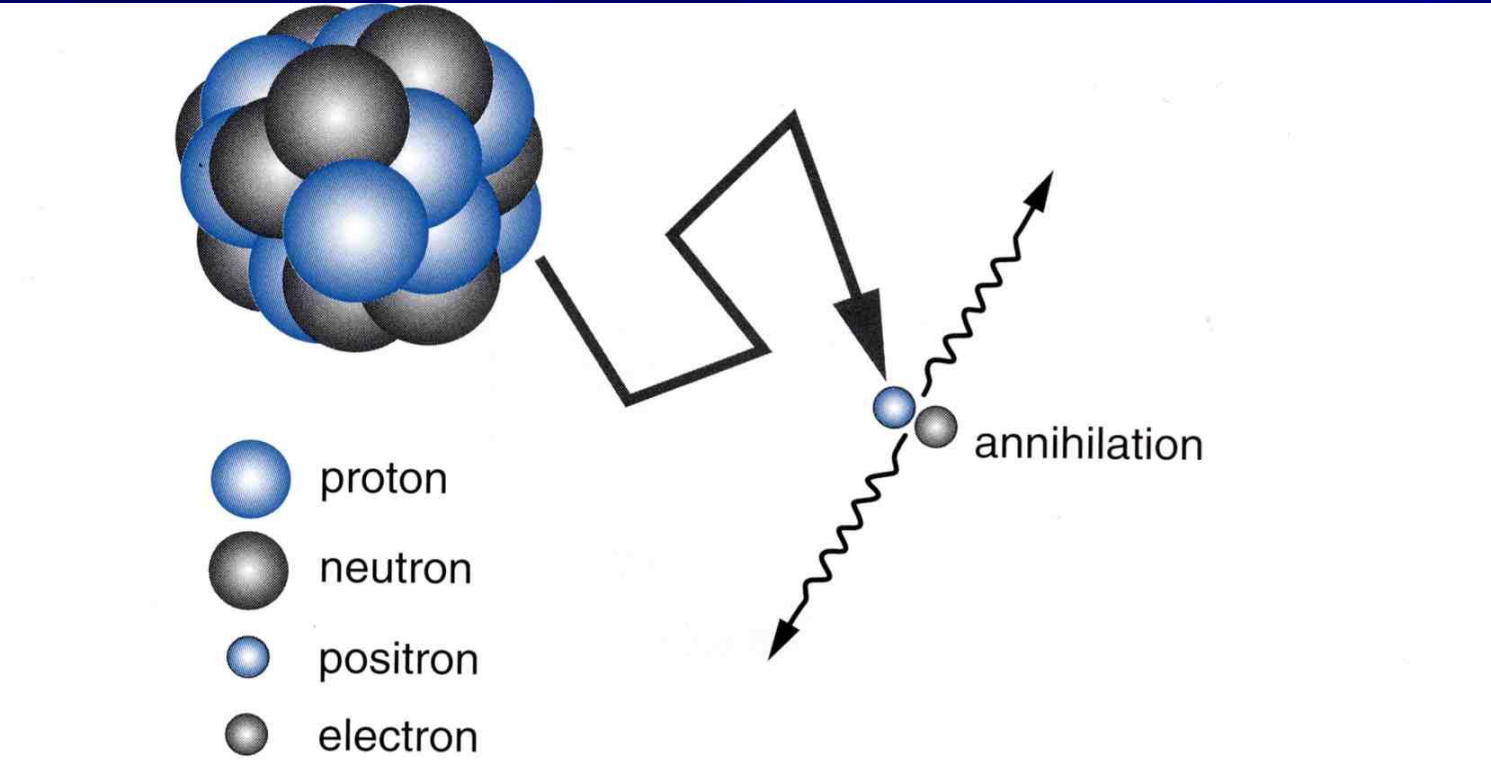


Ga-67 SPECT of the chest showing intense uptake in thoracic residual mass

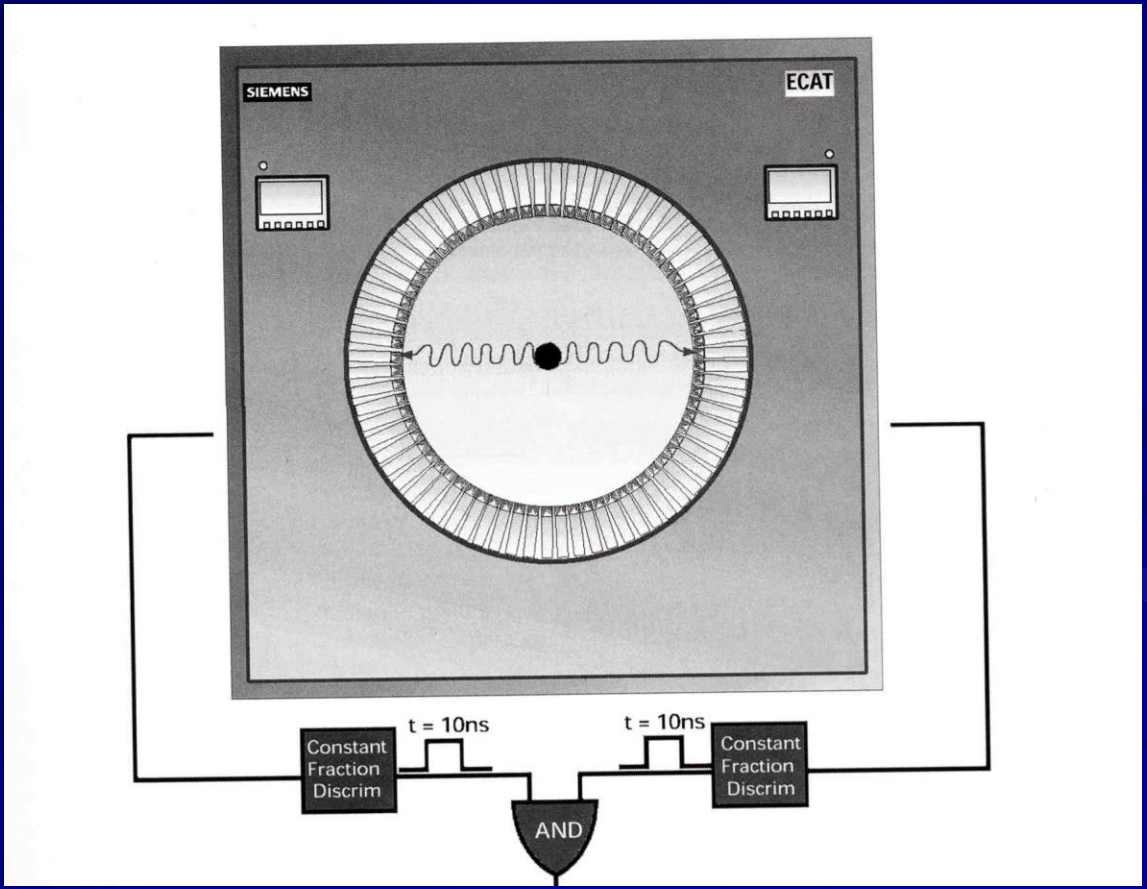
(Janiceck et al New York)



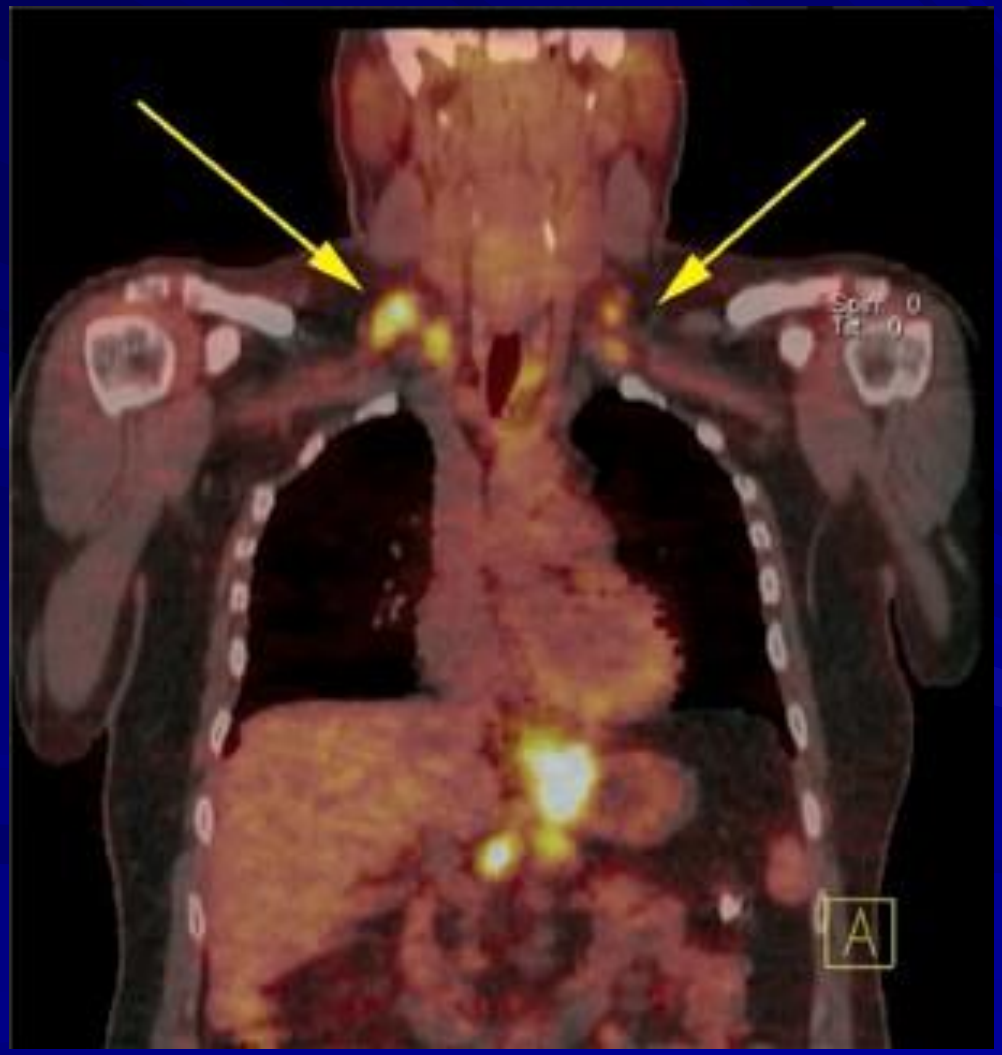
Positron annihilation



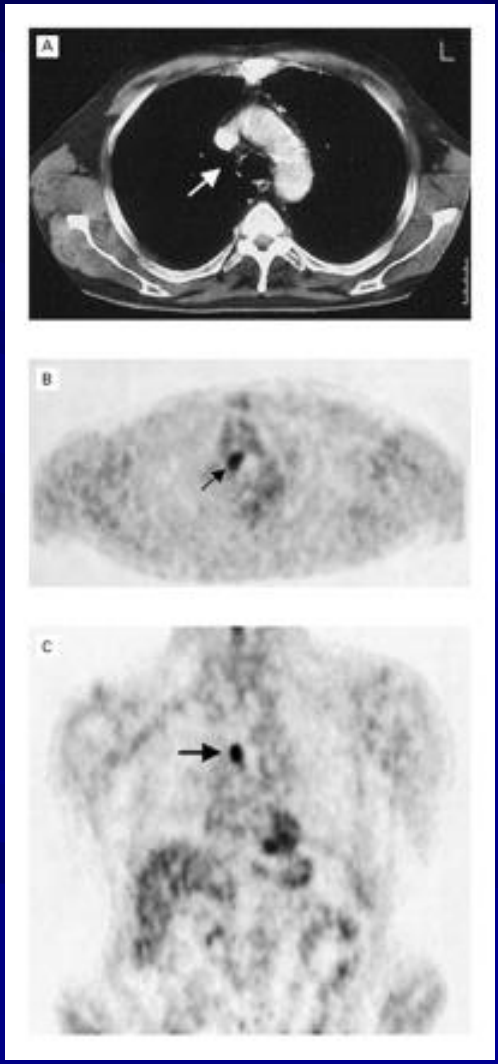
PET detection

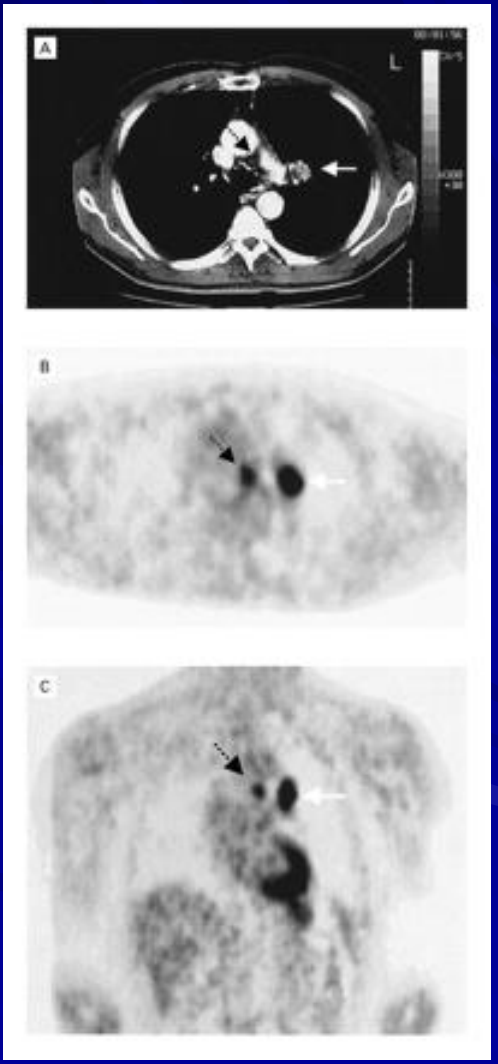


Use of PET in staging FDG in Ca oesophagus

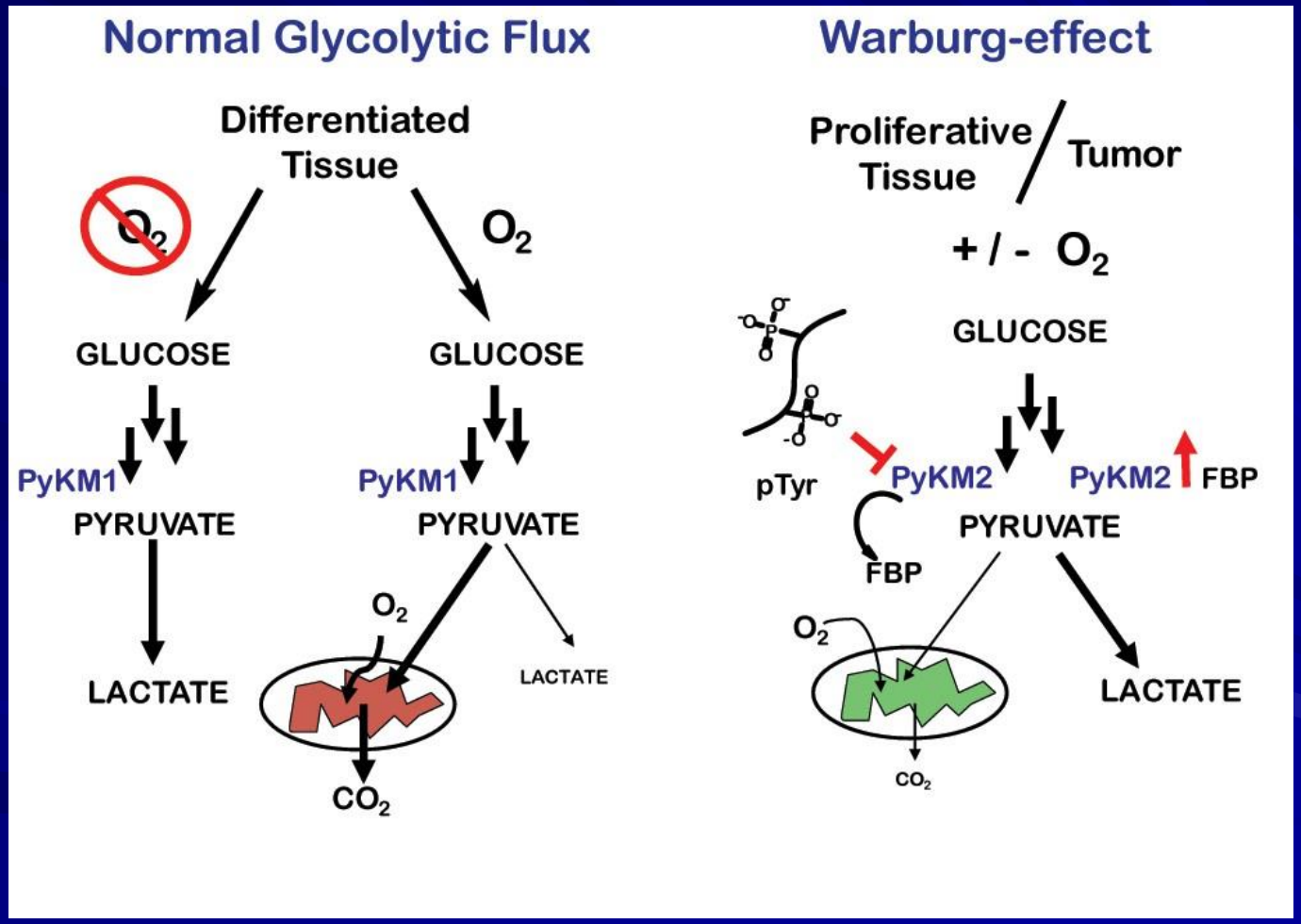


Examples of PET staging





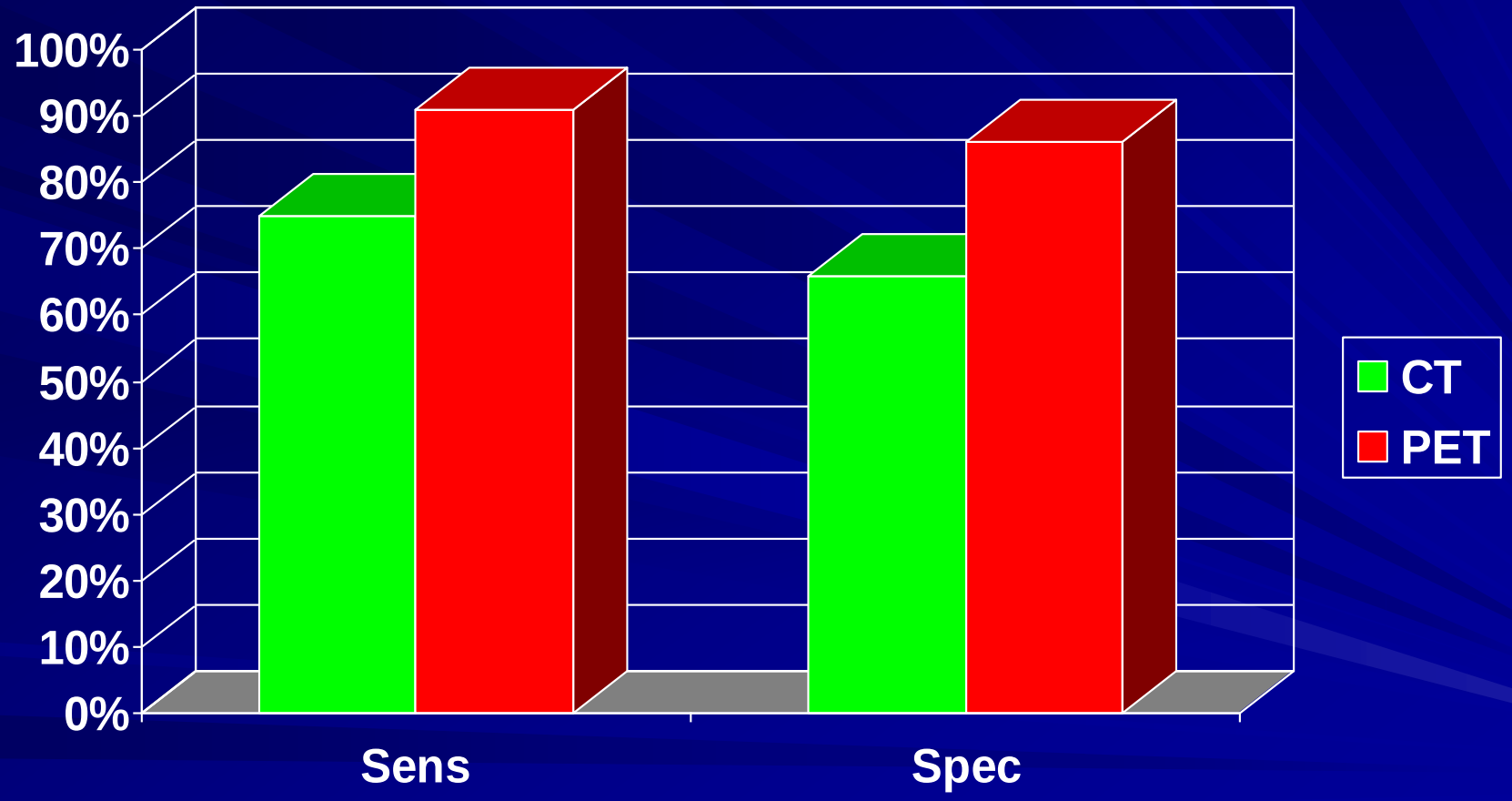
Glucose uptake into tumours



PET in Pre-operative staging

- Pieterman et al NEJM 2000
- Prospective comparison of PET and CT in staging NSCLC correctly
- Results of imaging compared with histology found at operation
- PET found to be significantly better than CT

CT vs PET (Pieterman et al)



PET imaging in centres without PET service in the management of NSCLC.Is it cost effective?

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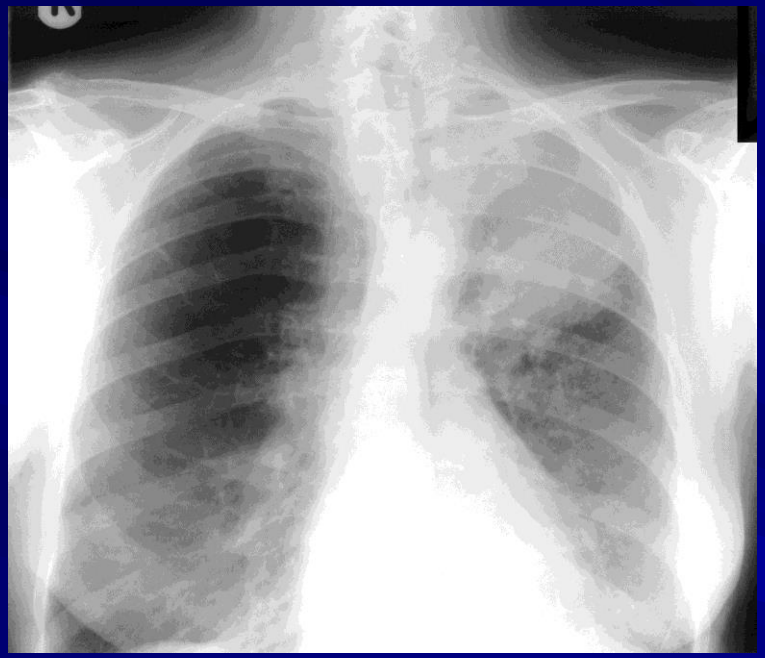
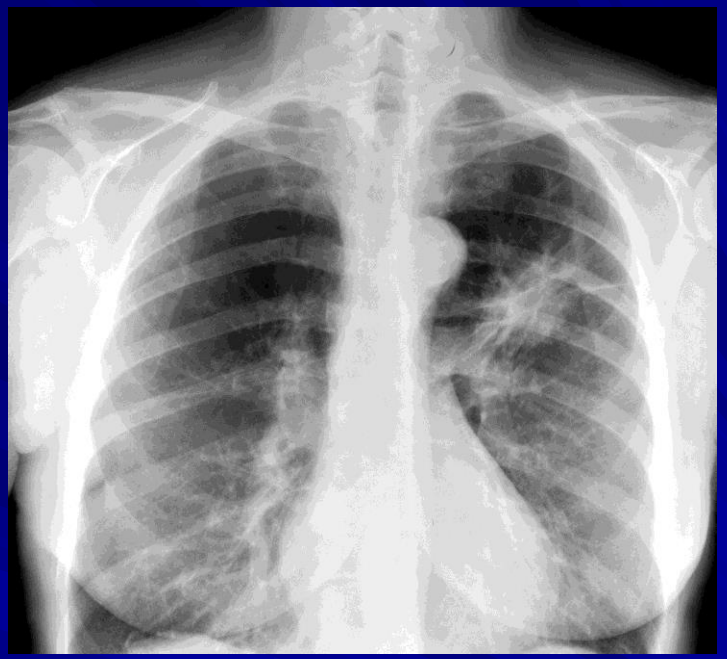
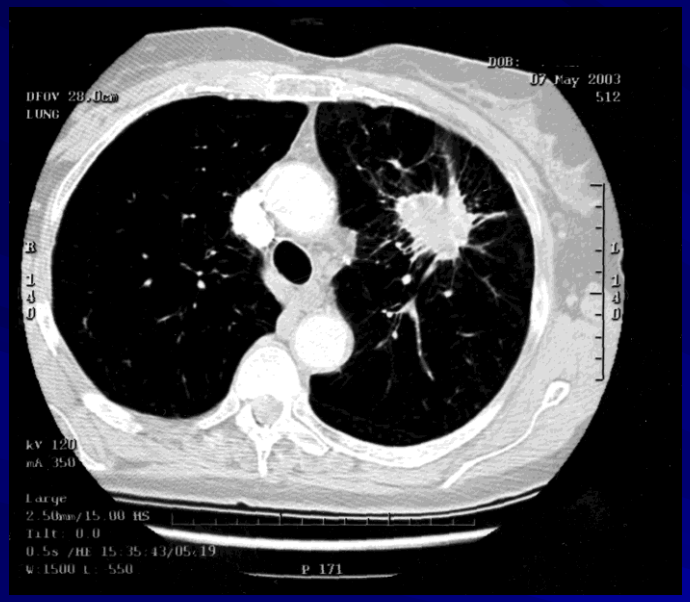
Example 1

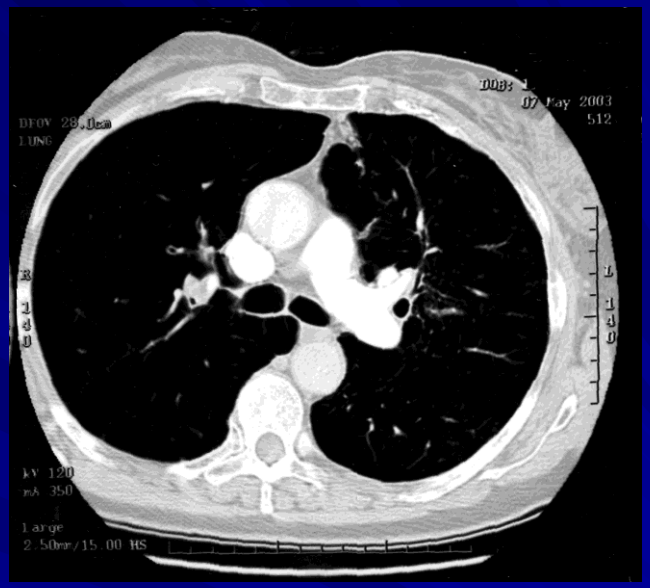




Initial film left upper lobe consolidation
Follow up film :Left upper lobe mass

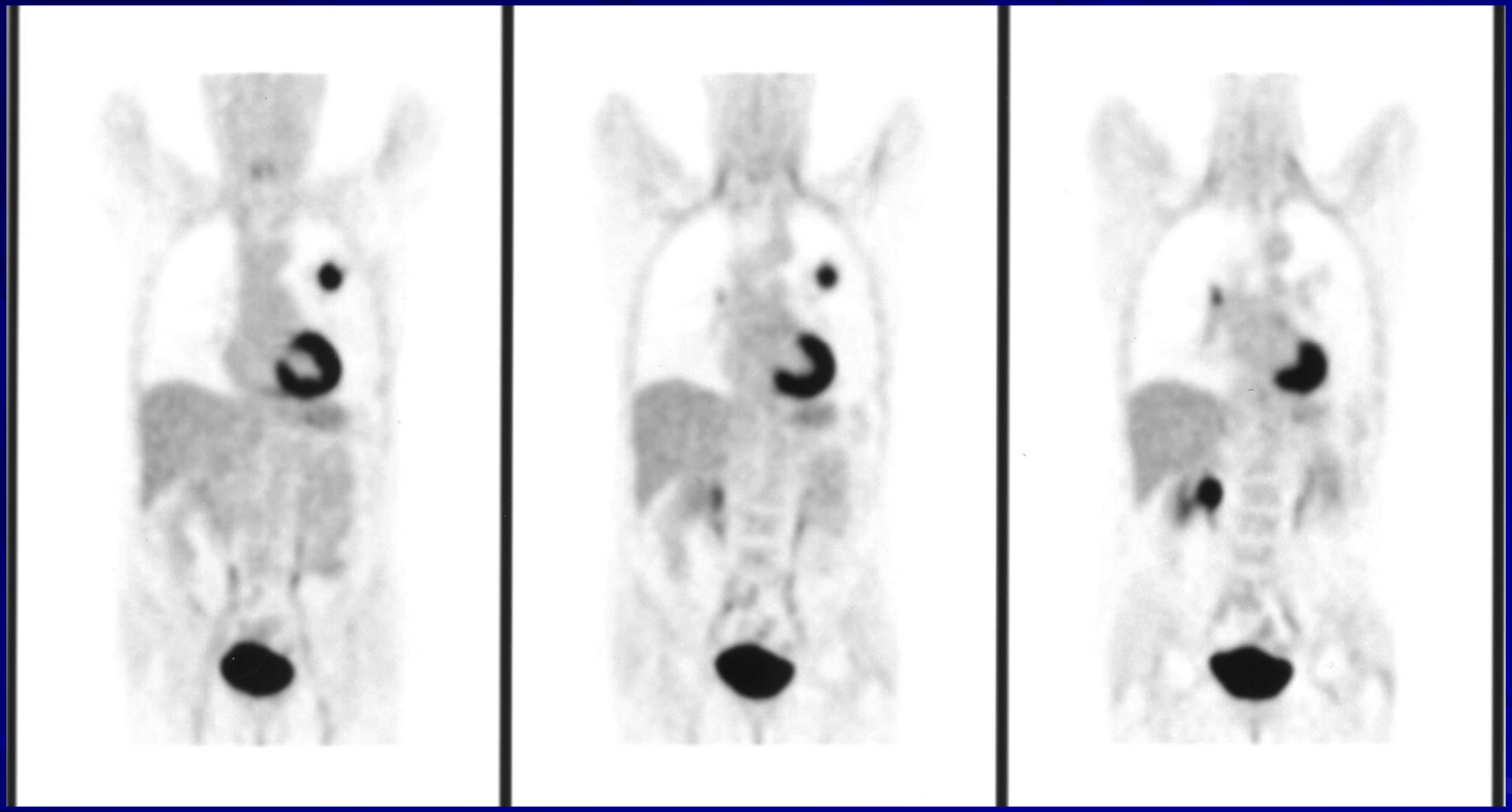
Example 1





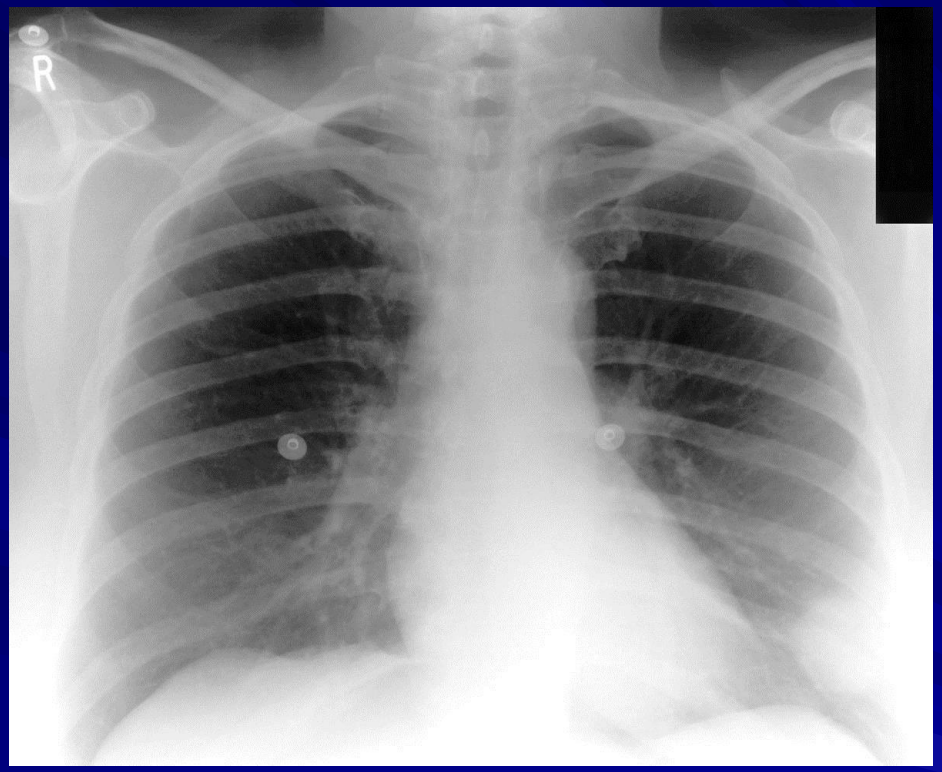
CT Spiculated mass left upper lobe.
No obvious mediastinal disease

Example 1



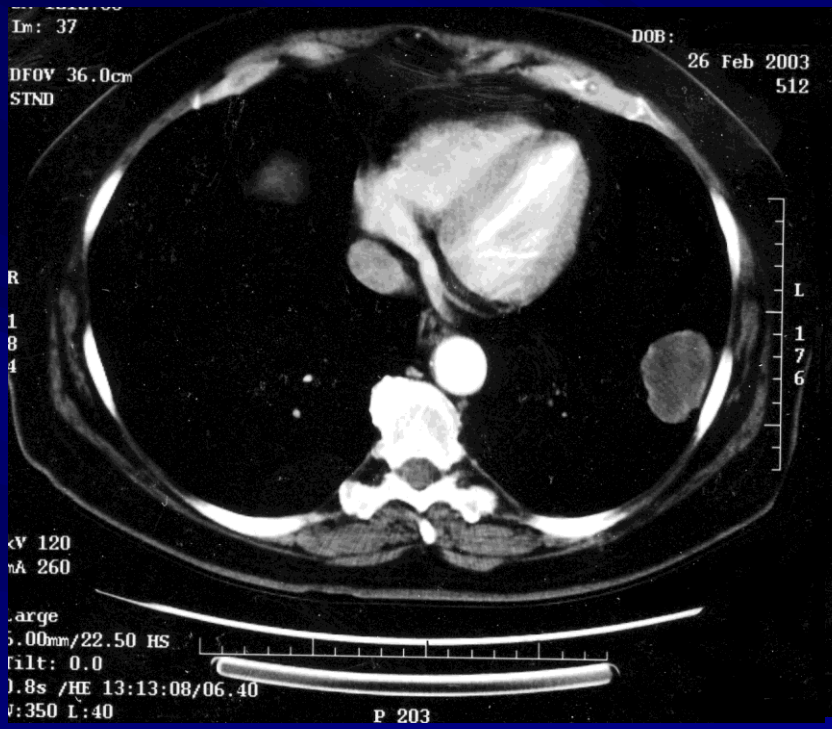
347 MBq F-18 FDG
FDG-avid lesion LUL; FDG-avid lesion right hilum
Lung cancer upstaged -> inoperable

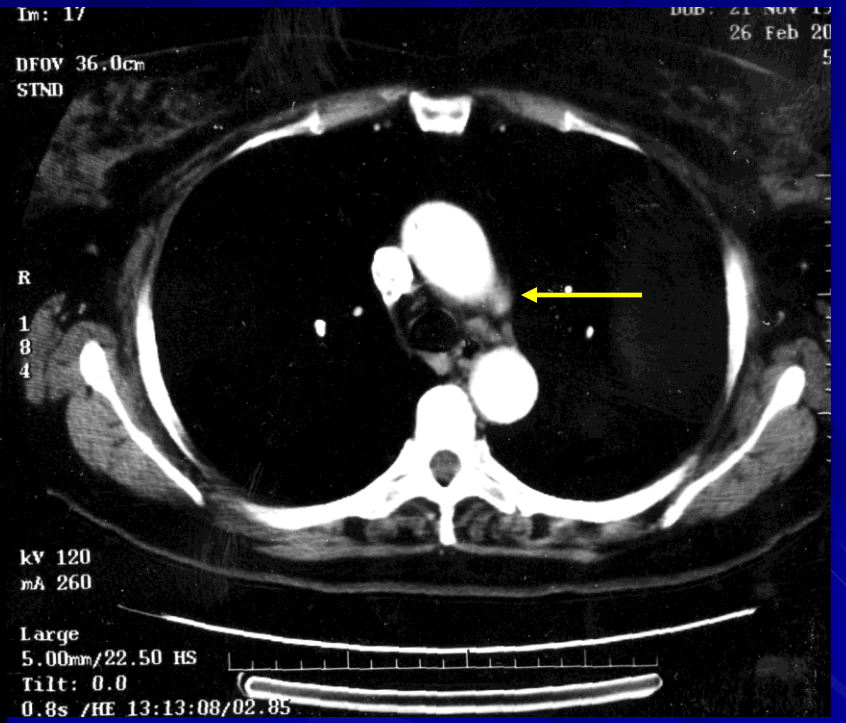
Example 2



Mass Left Base

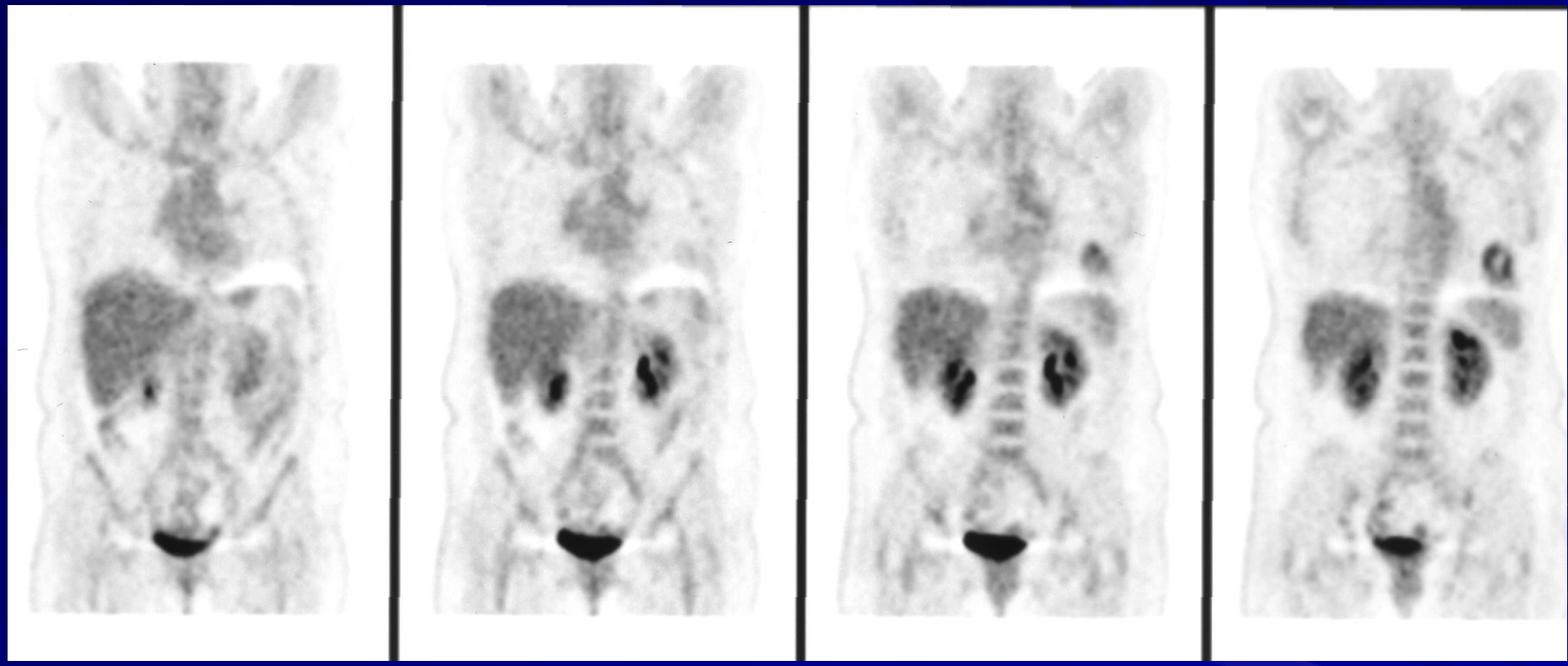
Example 2





Mass left lower lobe, enlarged nodes AP window

Example 2

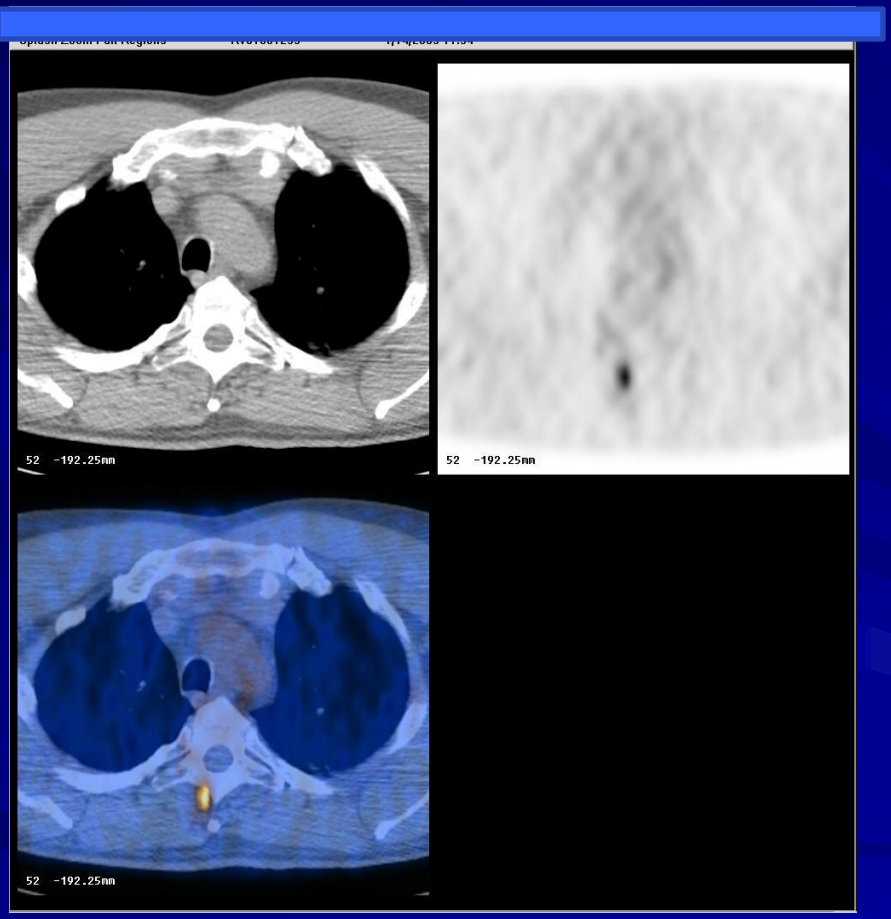


18 FDG PET 350 MBq
FDG avid mass left lower lobe
Mediastinum normal. Case downstaged

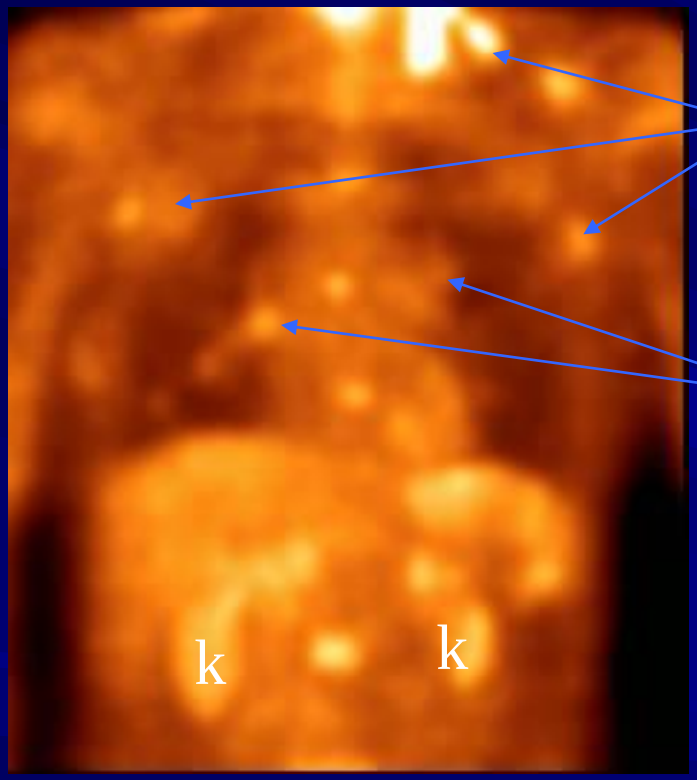
Re-staging after therapy

- Looking for residual disease especially were anatomy disturbed
- Gallium/Tc-99m MIBI/FDG in lymphoma
- Post surgery rise in CEA
- Thallium in brain tumours
- Recurrent residual disease in breast cancer

NHL-post therapy residual disease

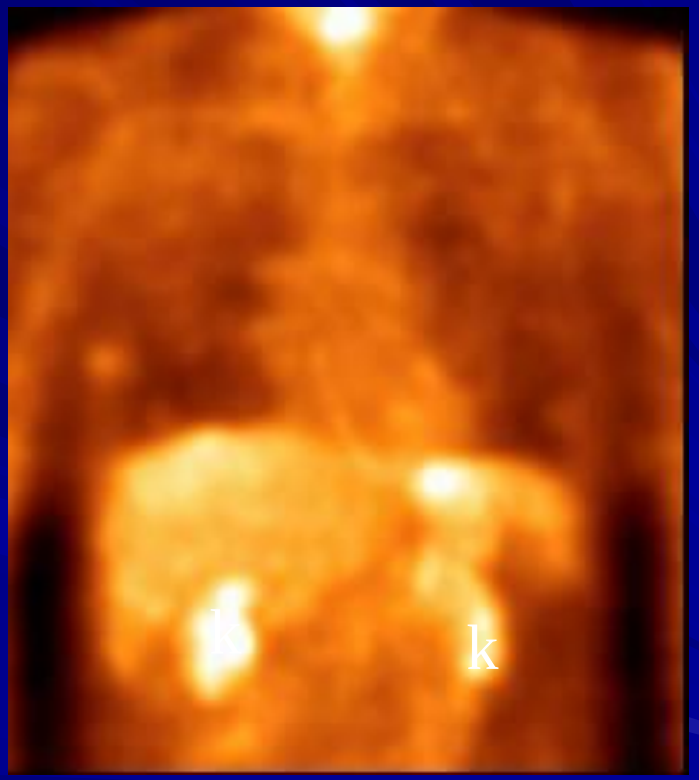


FDG-PET response in Hodgkin's disease following 5000 MBq I-131 CHT 25



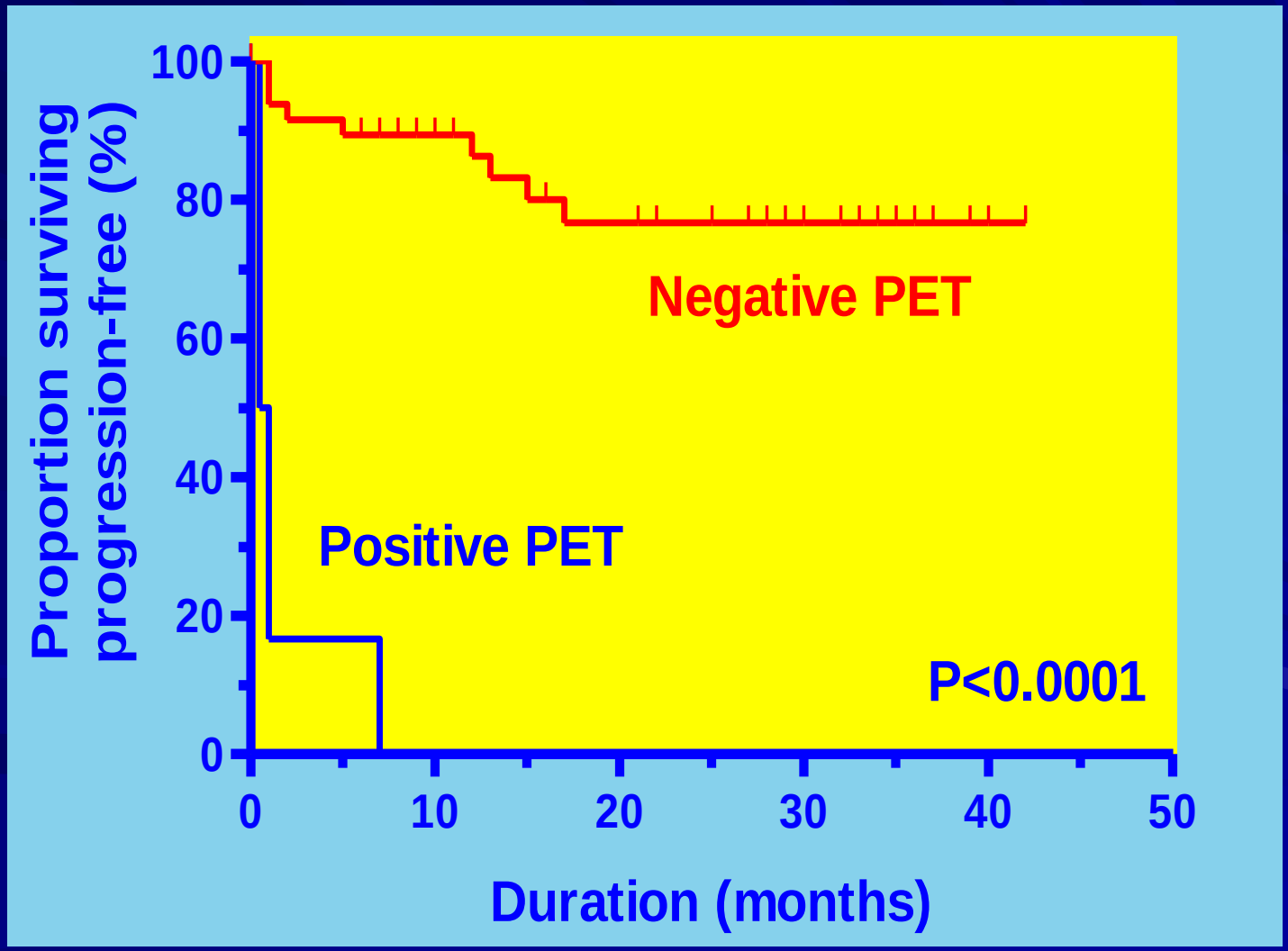
Axillary and cervical LN

Mediastinal LN



Progression free survival related to PET response

Jerulsalem et al 1999



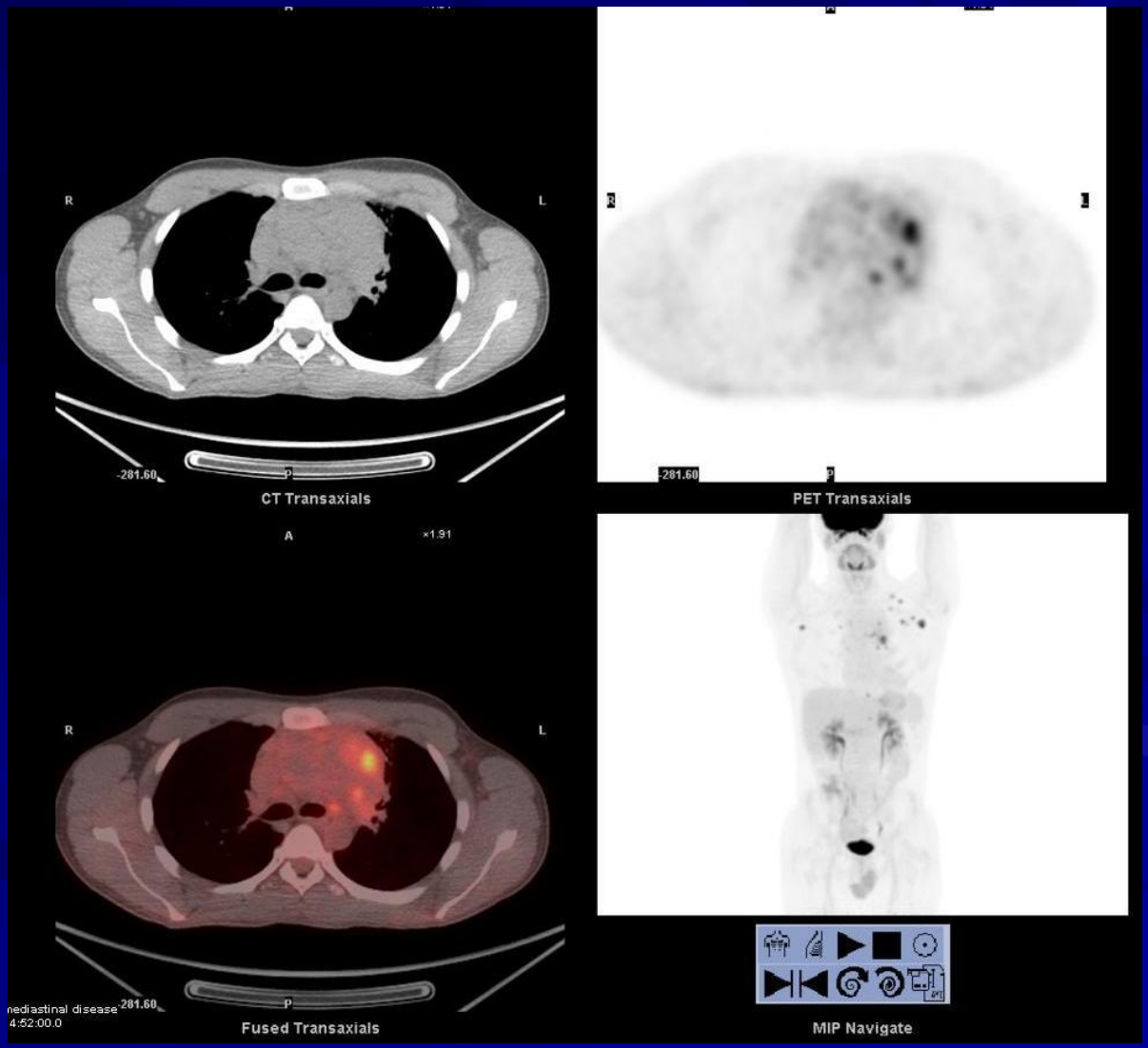
POST-TREATMENT EVALUATION

- **Jerusalem et al, Blood, 1999**
- **54 patients (NHL + HD)**
- **Median follow-up: 23 months**
- **Positive predictive value: 100%**
- **Negative predictive value: 83%**

Using F-18 FDG in HD

- HD a particular issue as tumour cells small percentage of tumour mass
- Therefore mass can remain without any tumour cells-the residual mass
- Consensus opinion based on the work of Sally Barrington – The Deauville criteria
- Uses a grading system to look for possibility of residual disease 6 weeks after end of therapy

HD Clearly failed Tx



Deauville criteria

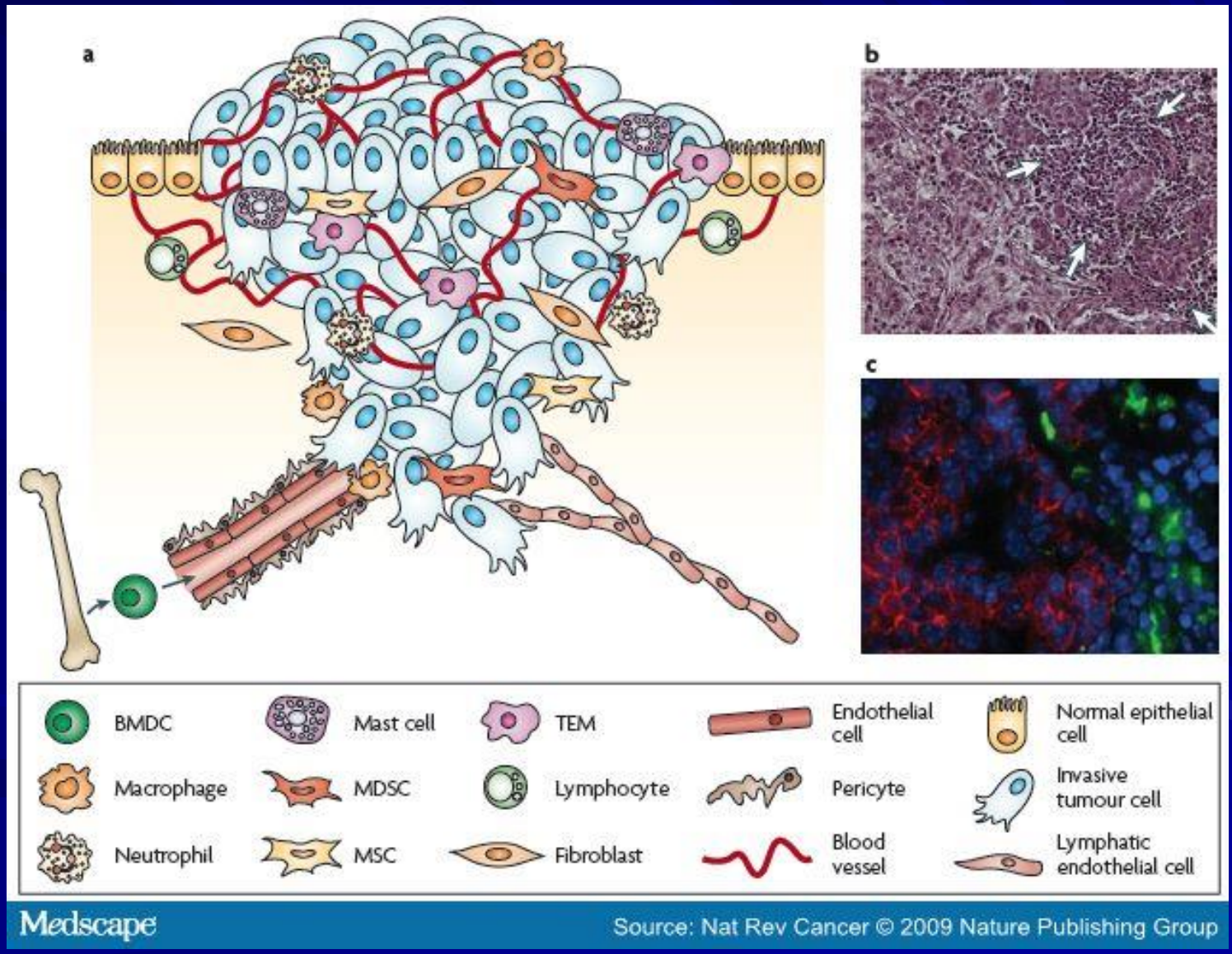
Score*	Characteristics
1	No uptake
2	Uptake < mediastinum
3	Uptake>mediastinum<liver
4	Uptake moderately more than the liver uptake, at any site
5	Markedly increased uptake at any site and new sites of disease.
X	New areas of uptake unlikely to be lymphoma

Grade 1 and 2 not tumour, 3 equivocal, 4-5 tumour still present

Imaging the tumour cell

- 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



Medscape

What factors can we image

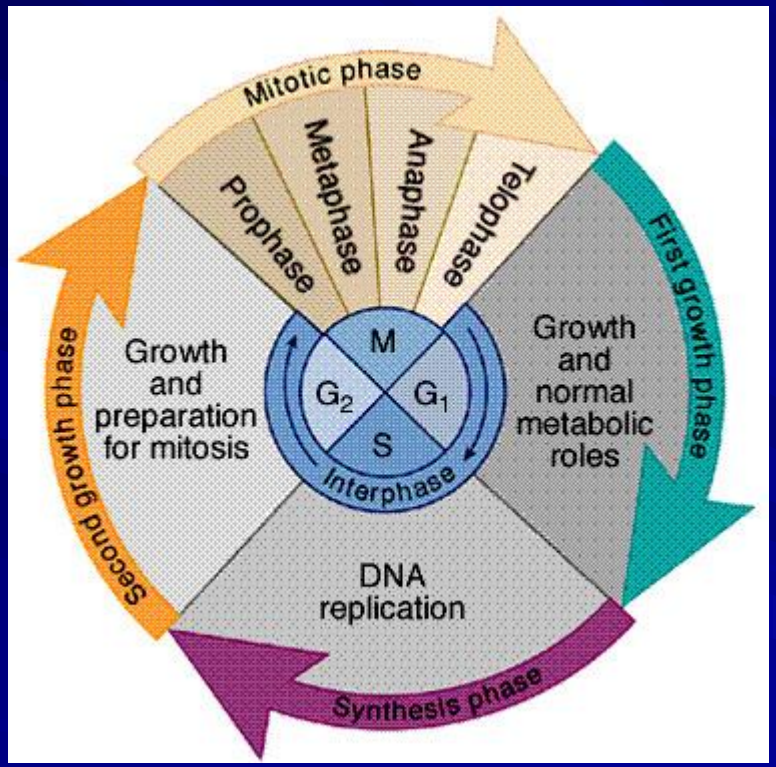
- Tumour metabolism
- Tumour cell turnover
- Tumour cell hypoxia
- Tumour related angiogenesis
- Apoptosis
- Receptor status

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

PET tracers and the cell cycle

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



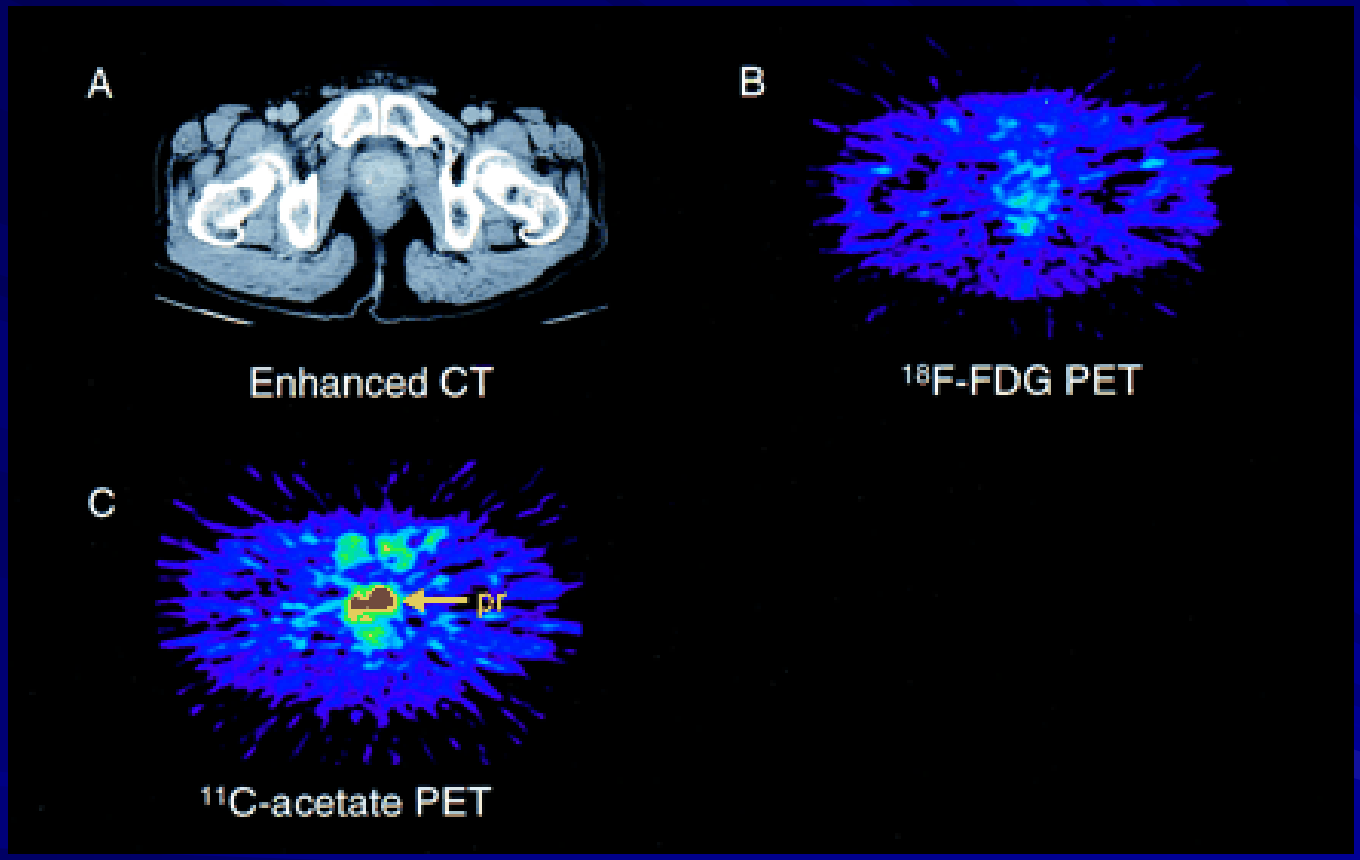
F-18 FDG
C-11 acetate
C-11 meth

F-18 FET
F-18 FLT

C-11 acetate

- Taken up by cells that use fatty acids
- Oyama et al JNM 2011 compare 20 minute uptake of C-11 acetate and 60 min F-18 FDG
- C-11 acetate found all primaries F-18 FDG just 15.
- Also more bone and lymph node mets found with C-11 acetate than F-18 FDG
- SUVmax of C-11 acetate 9.9 c/w 6.6 for FDG

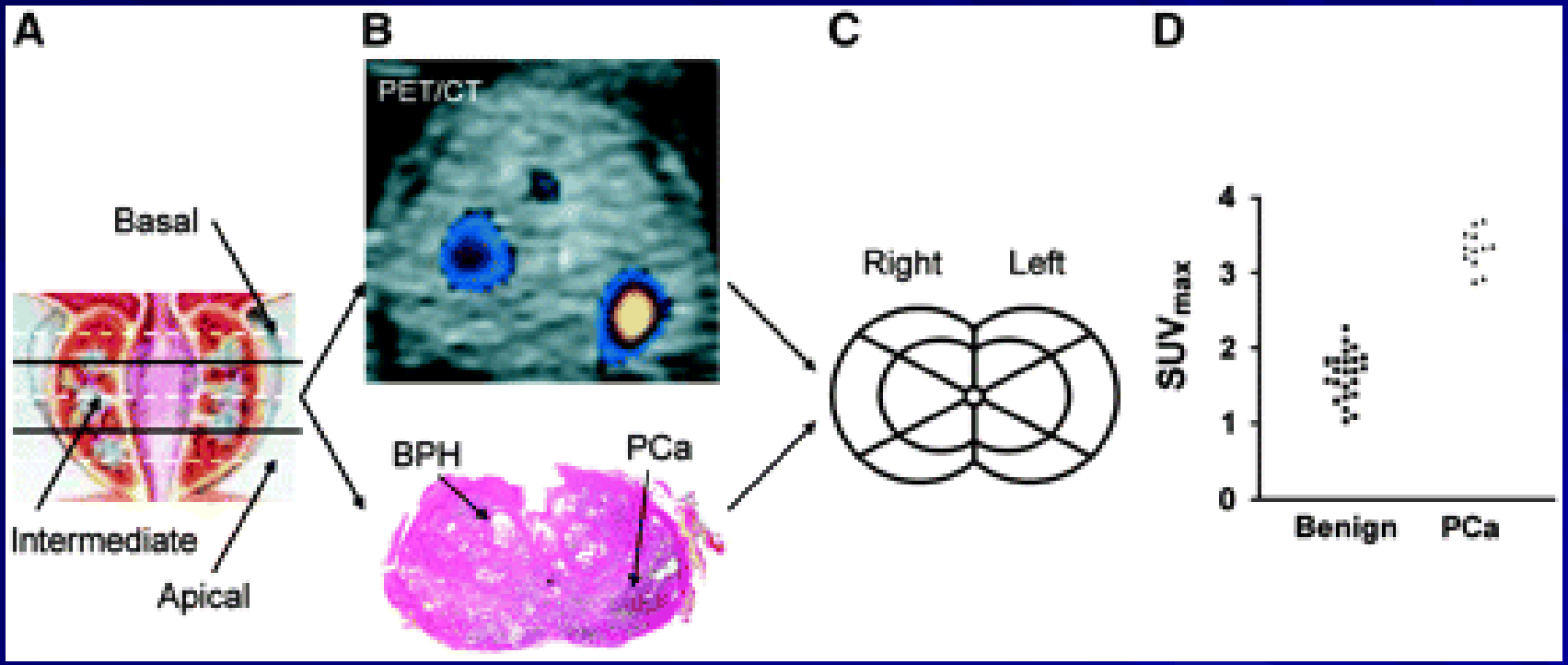
C-11 acetate in prostate



Choline imaging

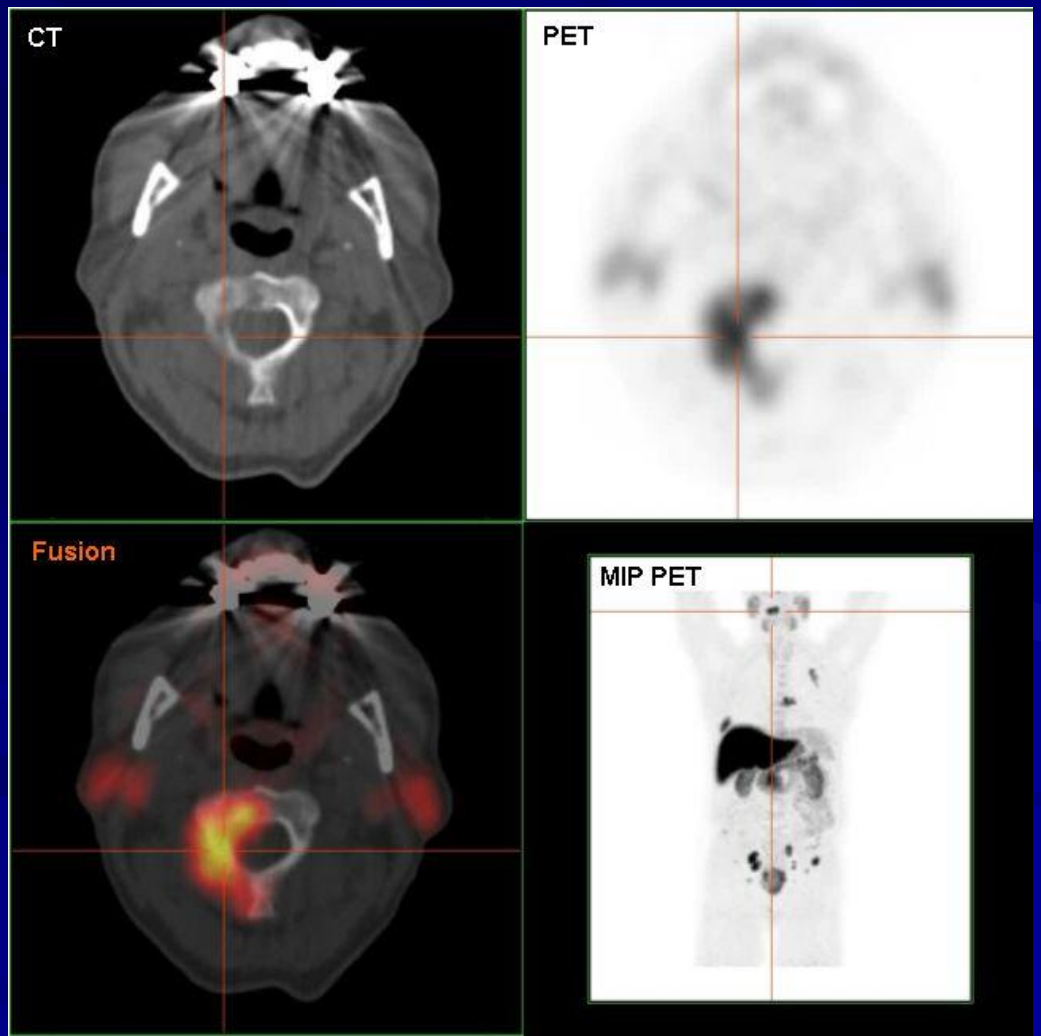
- Those cells that use fatty acid primarily have increased uptake of choline which is phophorilated before it enters the Kreb cycle
- C-11 Choline best looking at primary and pelvic mets as image before using activity high (Reske et al JNM 2006)
- F-18 choline allows more of the body to be imaged and better for metastases such as bone (Beshati et al Mol Imaging Biol 2009)

C-11 choline



(A–D) Image analysis of ^{11}C-choline PET/CT and histopathology. (A) Assessed cutting planes of prostate are indicated as dashed lines. (B) ^{11}C-Choline PET/CT slice from middle third of prostate: corresponding transversal whole-gland section (hematoxylin and eosin). (C) Segmental allocation. (D) Scatter plot of ^{11}C-choline maximal standardized uptake value (SUV_{max}) of all 36 segments of this patient. Tumor stage was pT2a;^{11}C-choline PET/CT localized PCa correctly to left lower peripheral segment (arrow in B). Scatter plot in D shows higher ^{11}C-choline SUV_{max} in segments with PCa than in those with benign histopathologic lesions

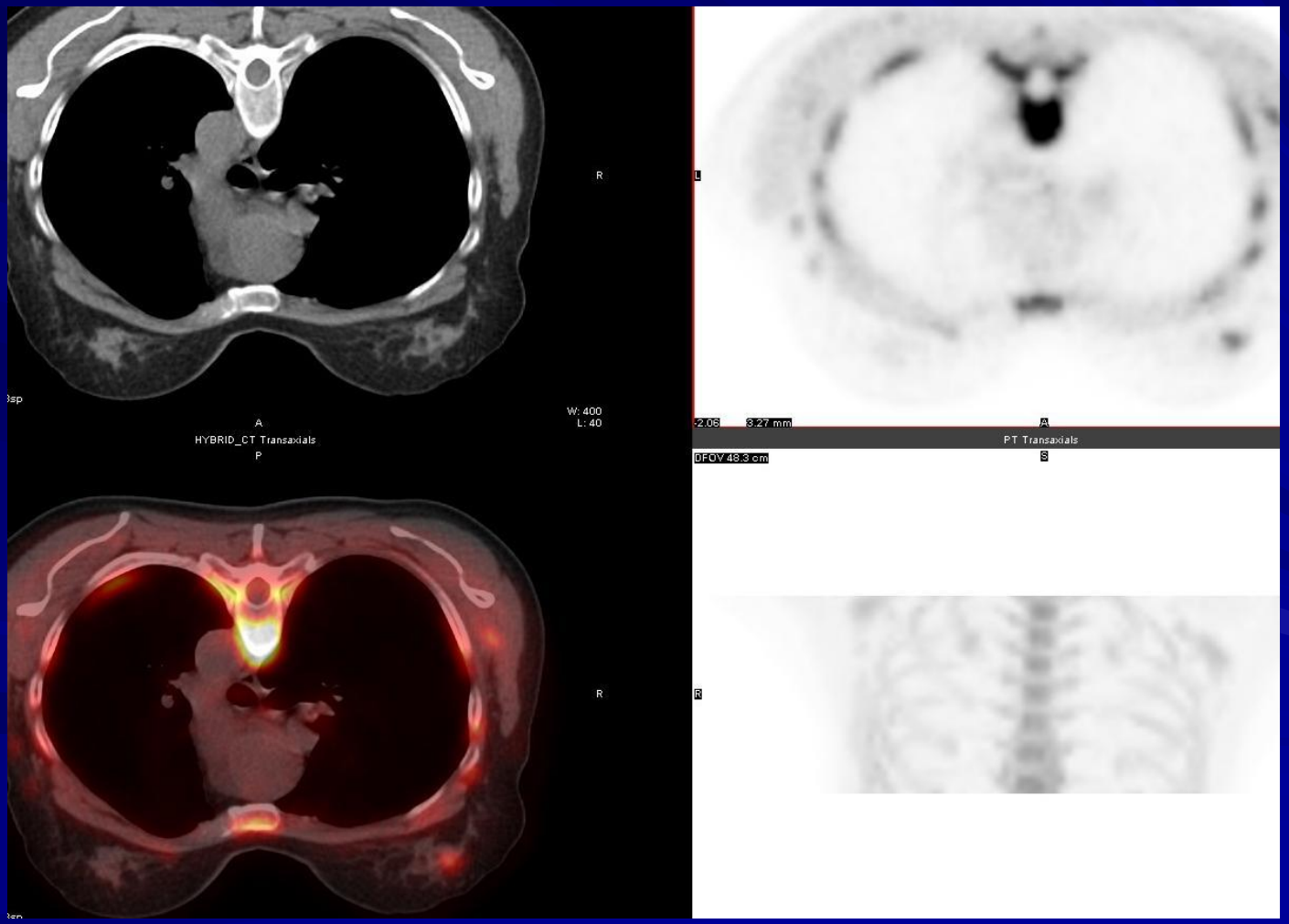
F-18 choline in bone (Uni Stutgart)



Cell turnover

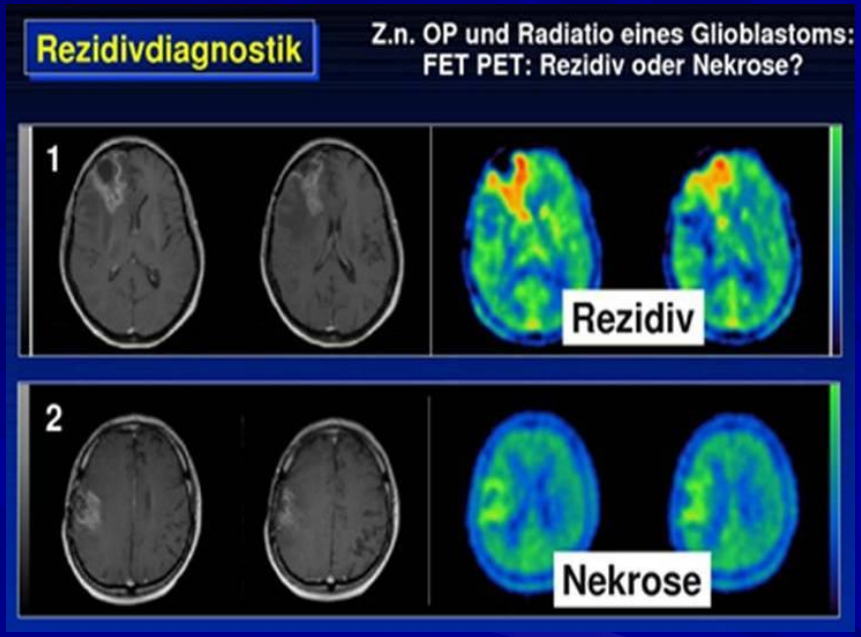
- Imaging cell turnover thought to be more cancer specific
- Still needs context
- Most based on amino acid uptake
- This tends to be normal in inflammation
- Maybe high in bone marrow due to tumour turnover
- Agents F-18 FLT, F-18 FET, C-11 methionine

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%

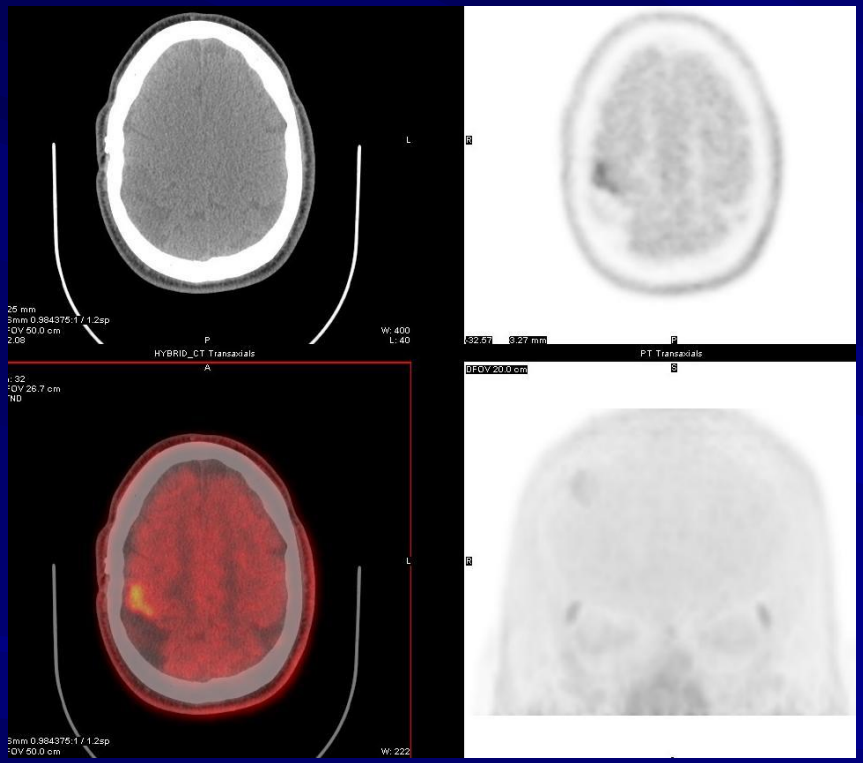


Astrid Marquart Akademie Esslingen

C-11 methionine

- Used to identify tumours
- Uptake related to cell growth
- In brain only malignant cells grow and divide
- So high TBR with normal brain c/w F-18 FDG
- Used to image brain tumours
- Developed use in post surgery recurrence
- Similar role in pituitary tumour

Progression vs pseudoprogression

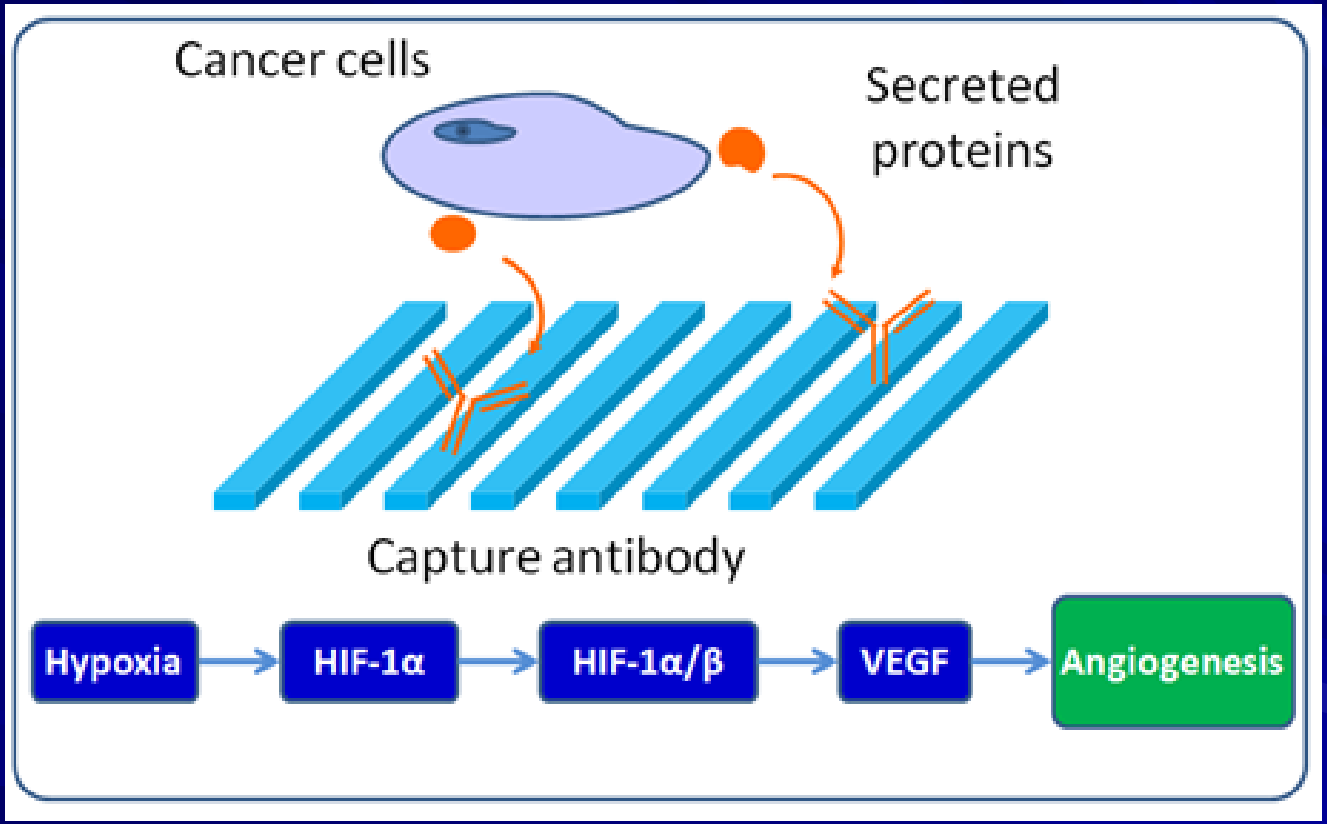


- Tsuyunguchi et al Ann Nuc Med 2004
- 11 patients treated with stereotactic surgery and RT
- Sens of C-11 meth for recurrent disease = 100% same as MRI
- Spec of C-11 meth 82% c/w 60% MRI

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

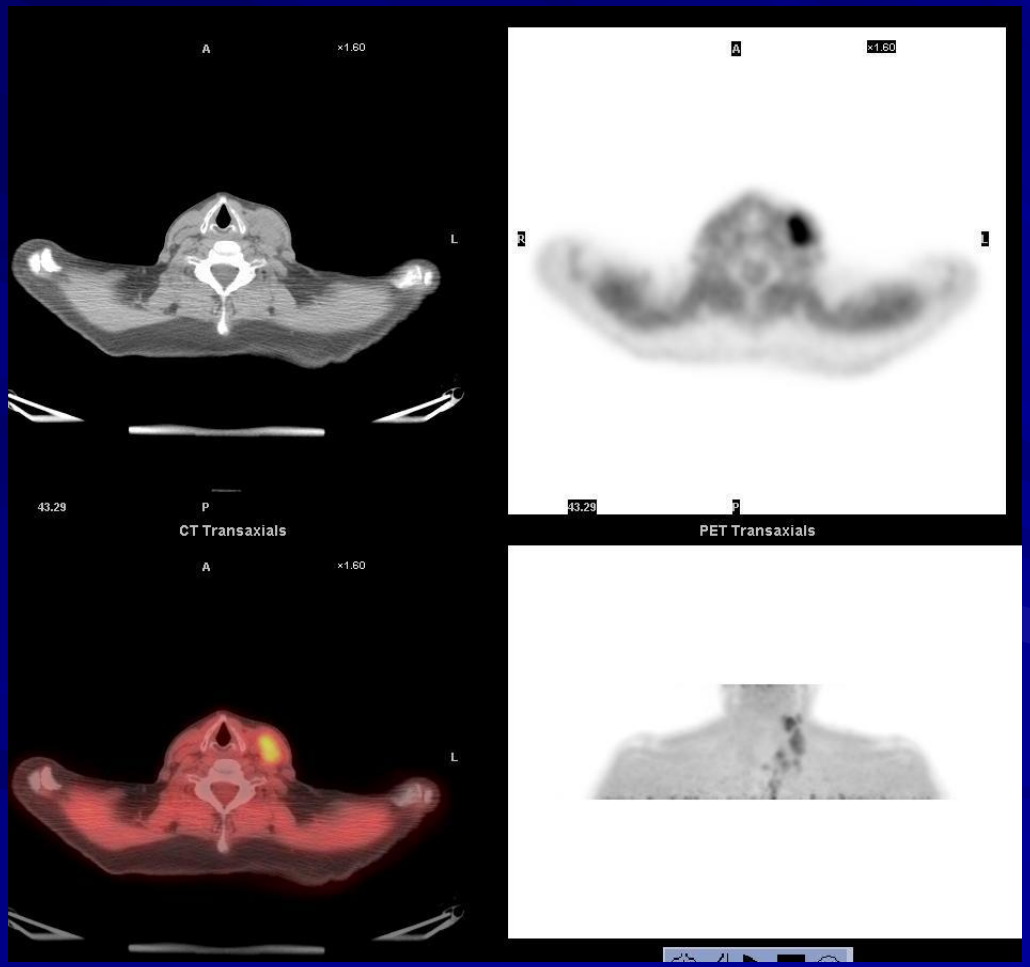


Caltech 2009

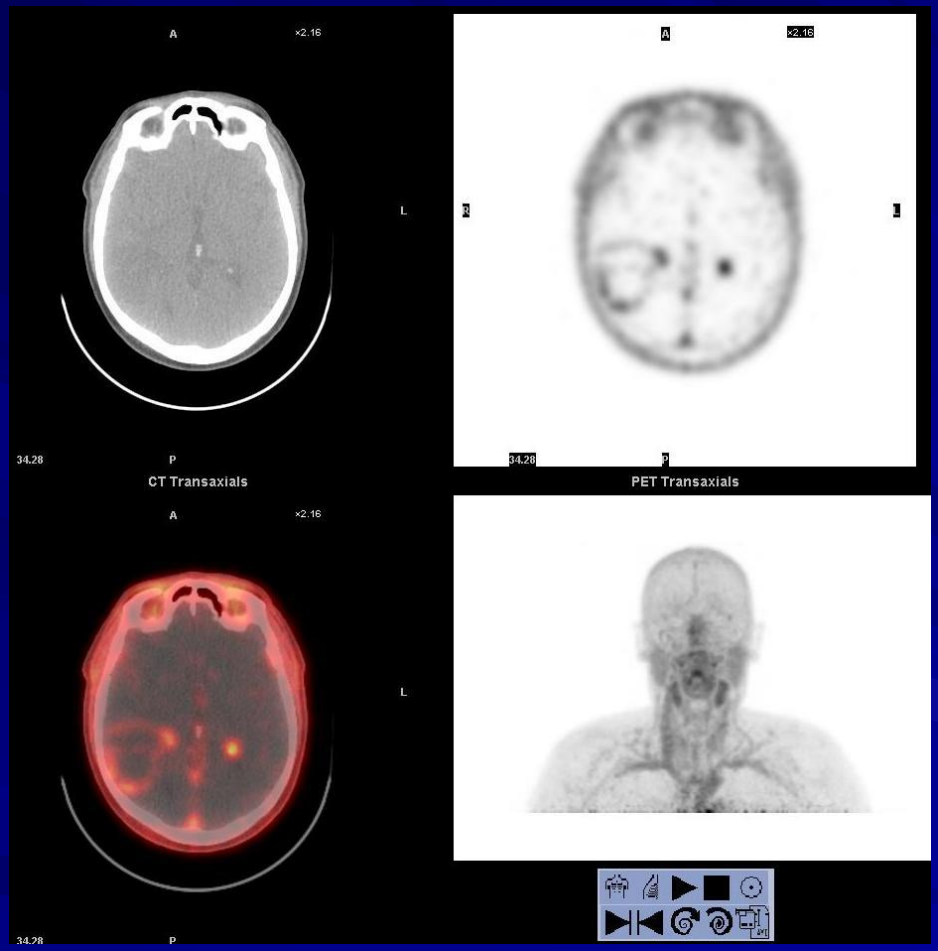
Hypoxia and angiogenesis

- 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
  - Cu-64 ATSM
- Angiogenesis
  - Imaging using RGD peptides which link to alpha/vbeta integrens

F-18 FMISO retention in Ca kidney met



F-18 Fluciclatide (RGD)

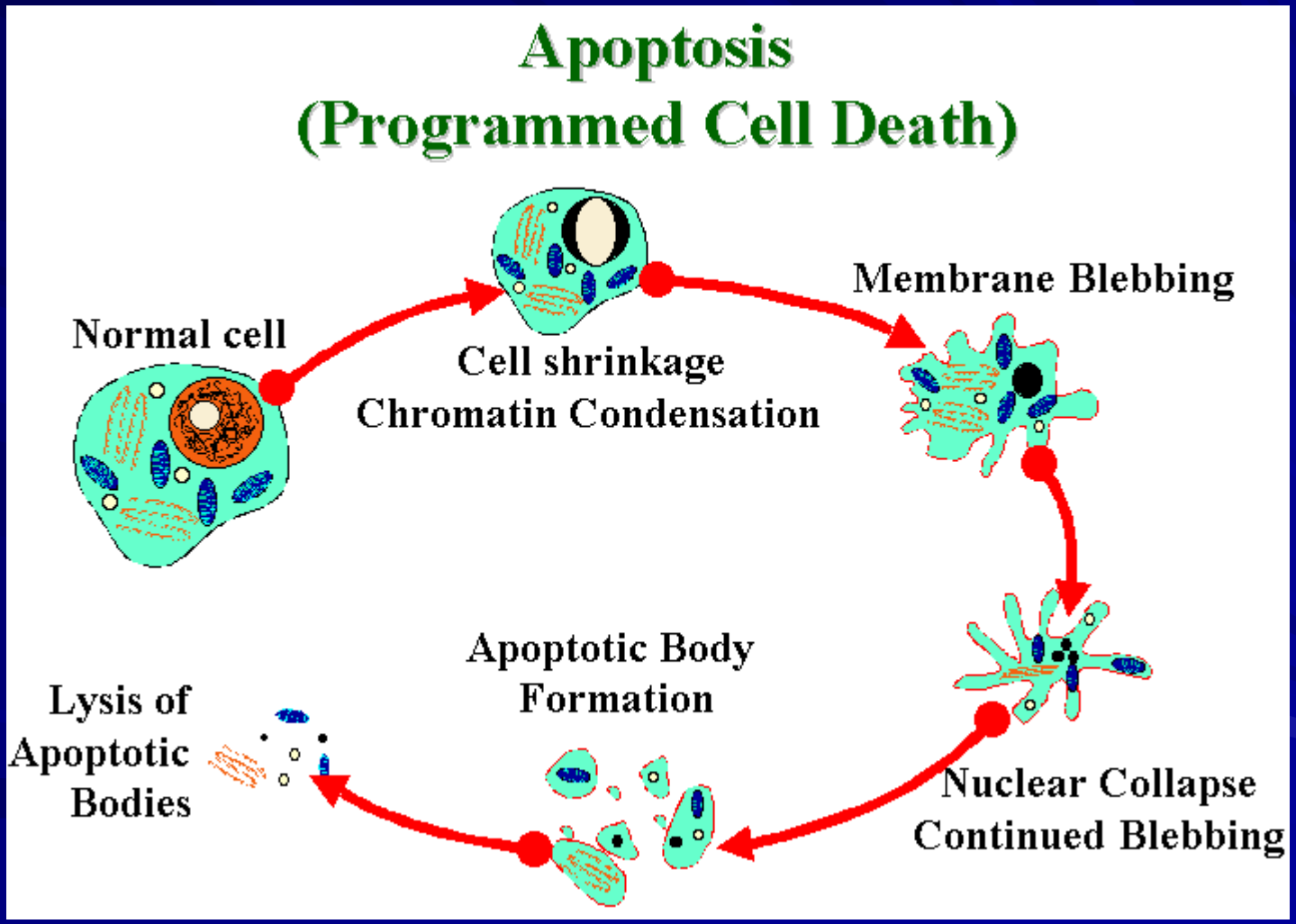


Note uptake only on edge of tumour

Imaging apoptosis

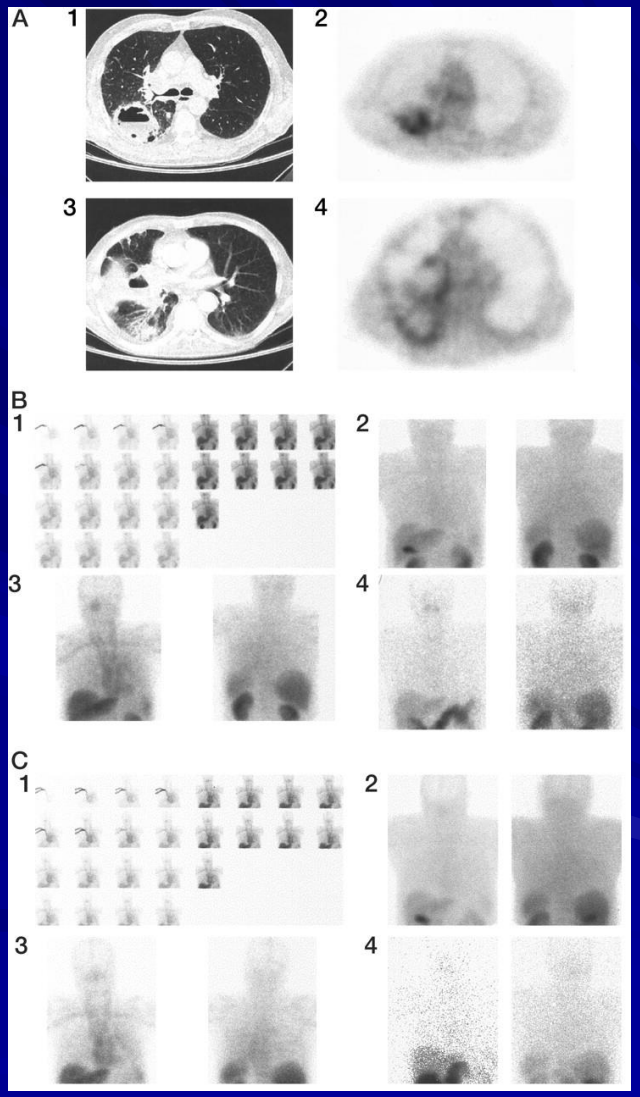
- Apoptosis is programmed cell death-normal process
- Response to cell damage
- Stopped by mutant p53-immortality
- Cell wall forms blebs
- Start to reverse inside/outside
- Intra-cellular proteins exposed
- Localisation of Annexin-V within 24 hours of effective treatment

Apoptosis

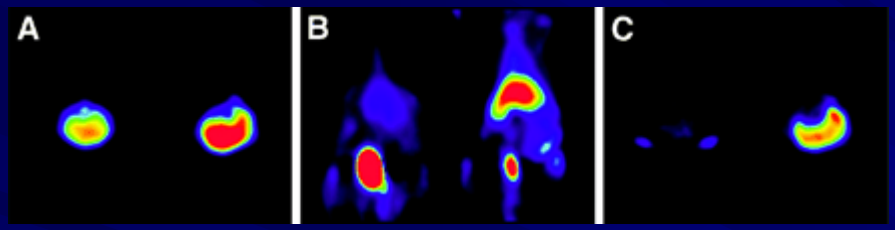

Apoptosis
(Programmed Cell Death)
Normal cell
Cell shrinkage
Chromatin Condensation
Membrane Blebbing
Nuclear Collapse
Continued Blebbing
Apoptotic Body
Formation
Lysis of
Apoptotic
Bodies

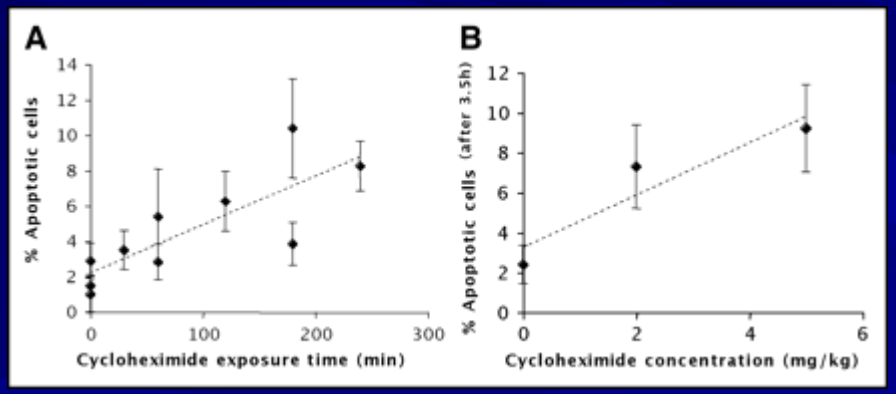
Annexin imaging

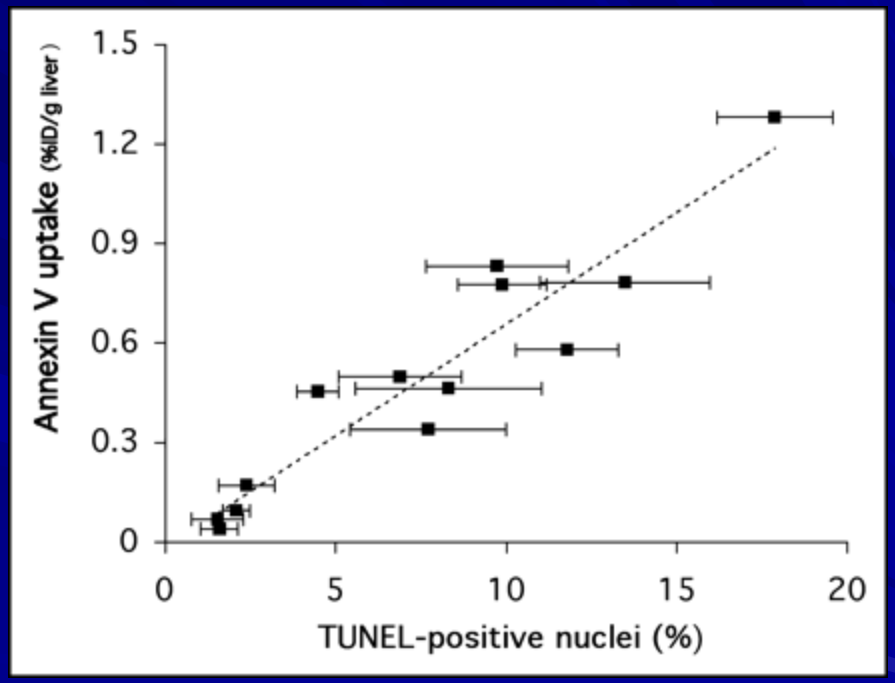
- Van de Weile et al
- Clin Cancer Res 2002
- Used Tc-99m Annexin-V
- Imaged lung cancer and HD 24 hours after treatment



F-18 annexin V Yagel et al 2005





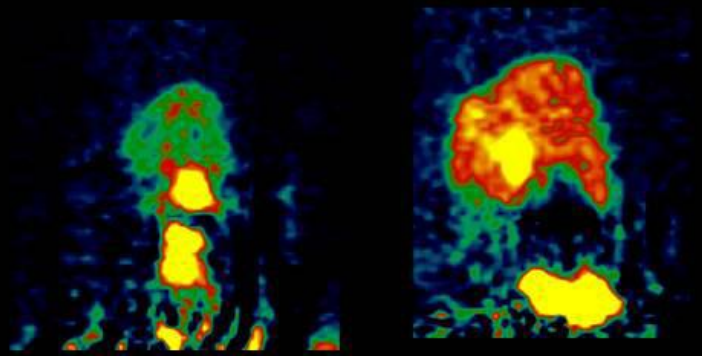


F-18 Caspase imaging Mach et al

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

Focus 120 Scanner

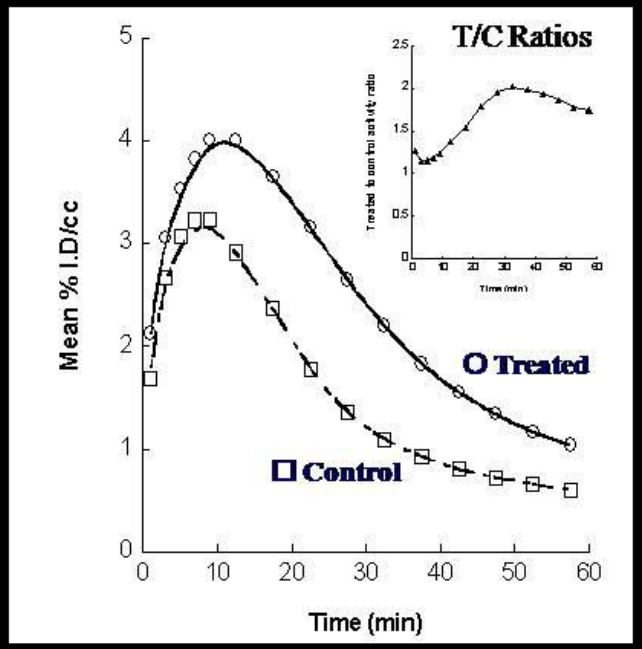
Focus 220 Scanner



Control

Cycloheximide

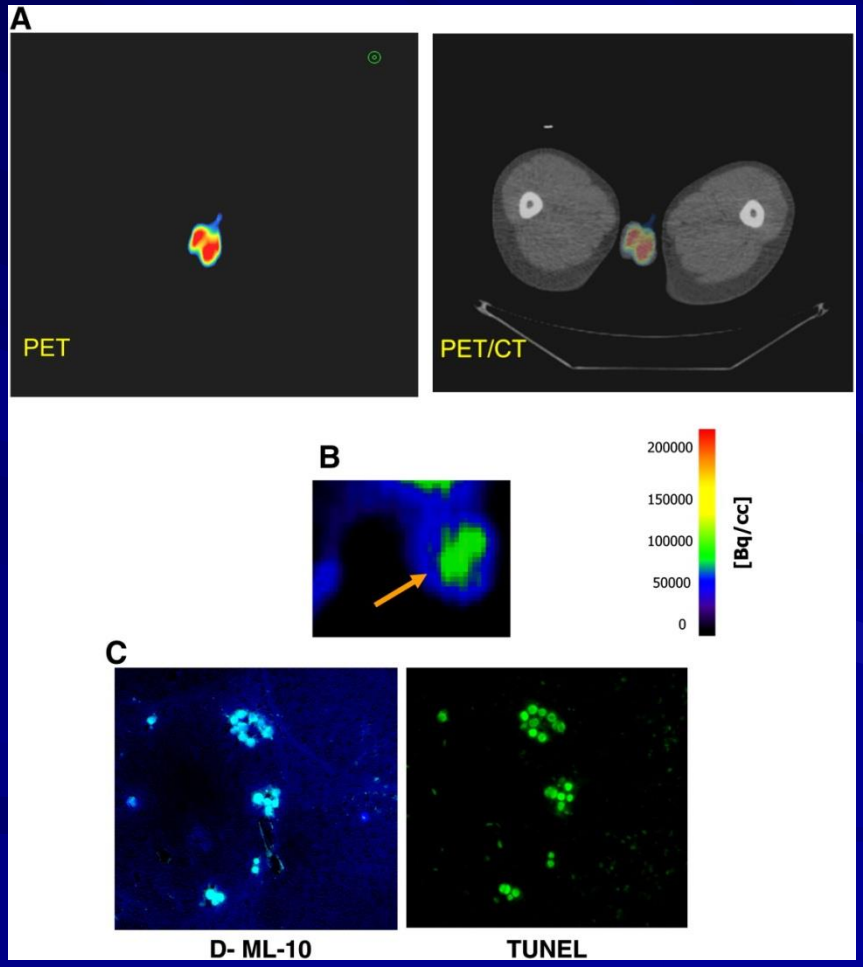
Sprague-Dawley Rats
Summed Images



Time-Activity Curves

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

F-18 ML10 in treated testicular cancer Hogland et al JNM 2011



Apoptosis imaging

- Looks as though there is increasing evidence that it is possible
- Good evidence there is a good correlation between uptake and degree of apoptosis
- Probably use agents targeting caspase 3
- However what is achievable is not always desirable

Peptide imaging

- Developed in 1980s in Rotterdam
- Based on somatostatin receptor system
- 5 receptor sub-types type 2 present on neuroendocrine tumours and some other tumour types eg lymphoma SCLC, NSCLC
- Various projects looking at nature of receptors in neuroendocrine tumours-in vivo
- Found not just variation between patients but between patients

Affinity different SSRs

5 receptor sub types identified

Different peptides have different affinities for range of receptors

SSR1 universally present

SSR2, 5 in low grade NETs

SSR3 in more malignant tumour types

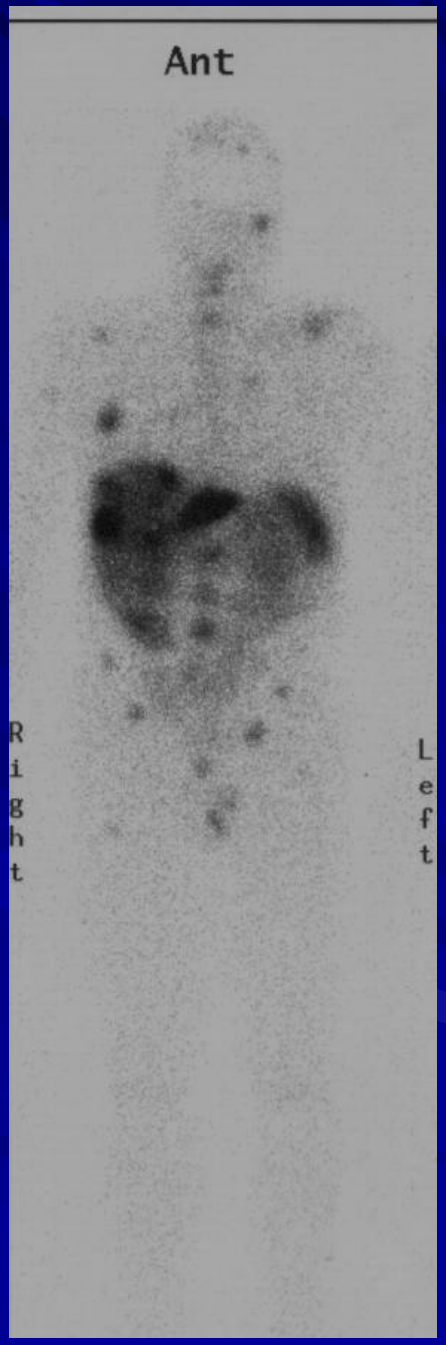
Radioligand	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
^{111}In-pentetreotide	>10 000	1.5	30	>1000	1.0
^{99m}Tc-depreotide	>1000	1.0	1.5	>1000	2
^{90}Y-DOTA-lanreotide	215	4.3	5.1	3.8	10
SOM230	9.3	1.0	1.5	>1000	0.16

Values are given in nmol·l^{-1} and indicate the binding affinity in terms of the inhibitory constant causing 50% inhibition of specific somatostatin receptor binding (IC50) [7,8].

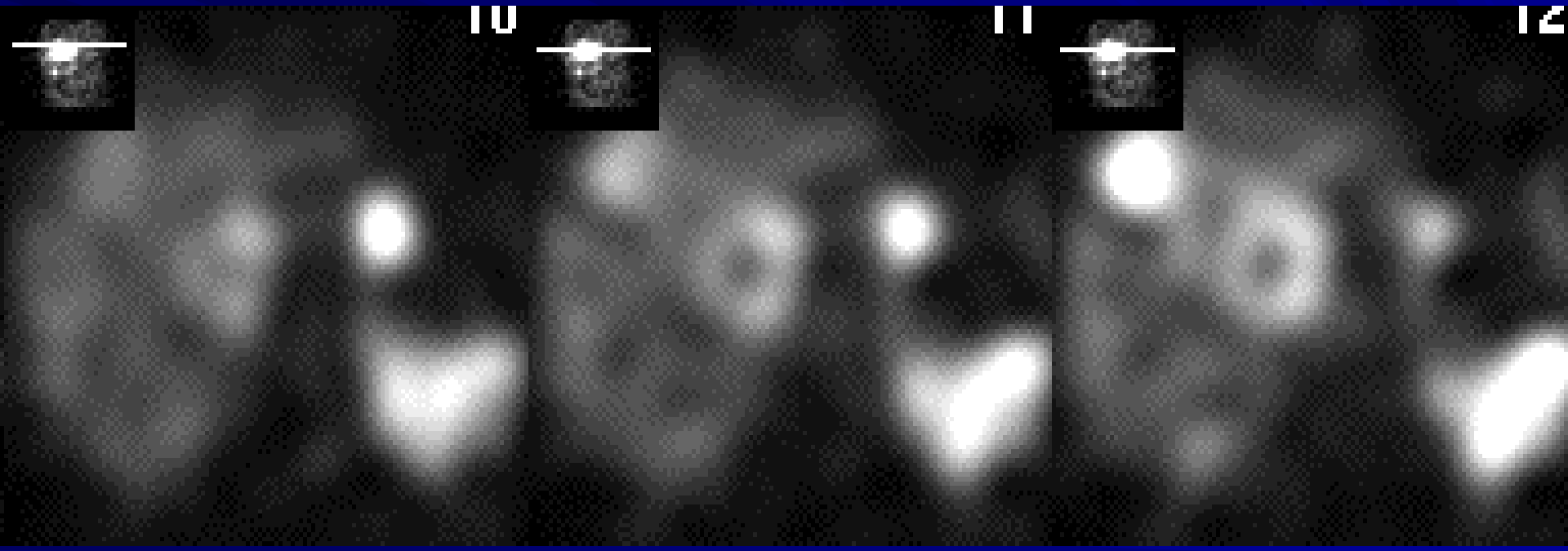
Imaging SSRs

- Method developed in 1988
- In-111 pentetreotide High affinity for SSR2 some for SSR5
- Developments to improve peptide octreoNOC and octreoTATE increased SSR2 affinity
- Depreotide pan receptor agent especially SSR3
- Isotopes Tc-99m cheaper more available, Ga-68 PET tracer

Whole body In-111 pentetreotide in mid gut carcinoid

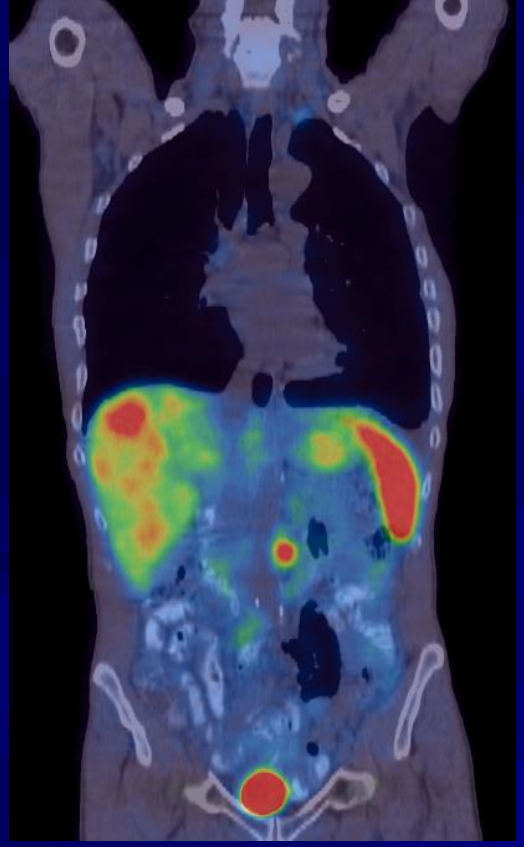


^{111}In-Octreotide necrotic mets



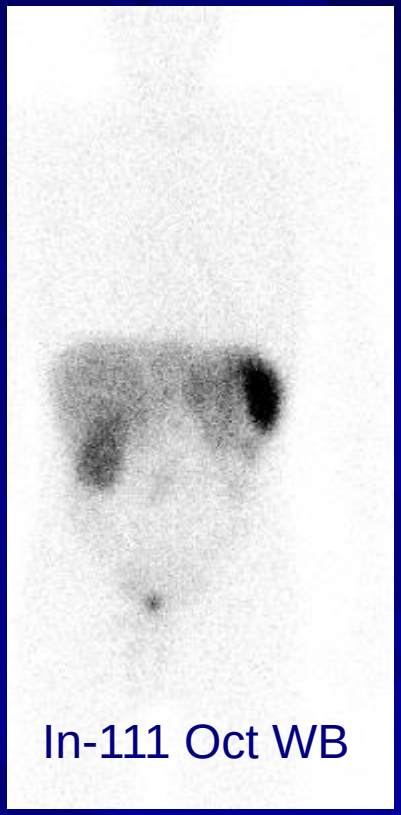
Ga-68 octreotate PET vs In-111 octreotide Quigley et al in preparation

SCAN APPEARANCE	N=44
both studies positive, Ga-68 more lesions	18
both studies positive, In-111 more lesions	1
both studies similar lesions	7
pos Ga-68, negative In-111	11
pos In-111, neg Ga-68	0
both studies negative	7

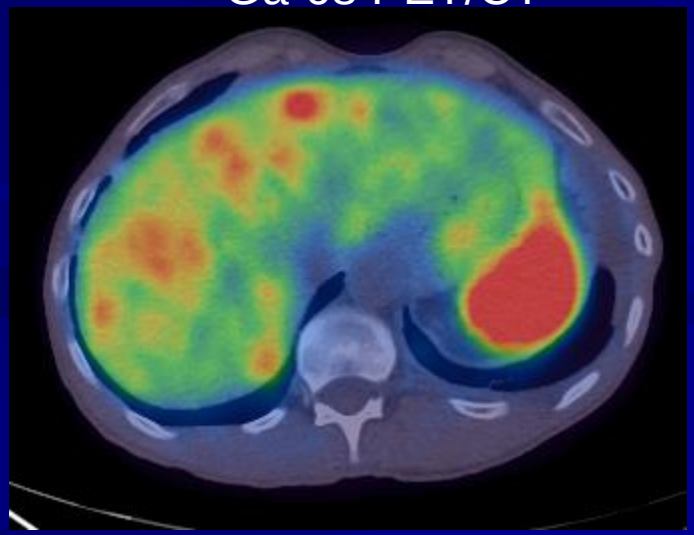


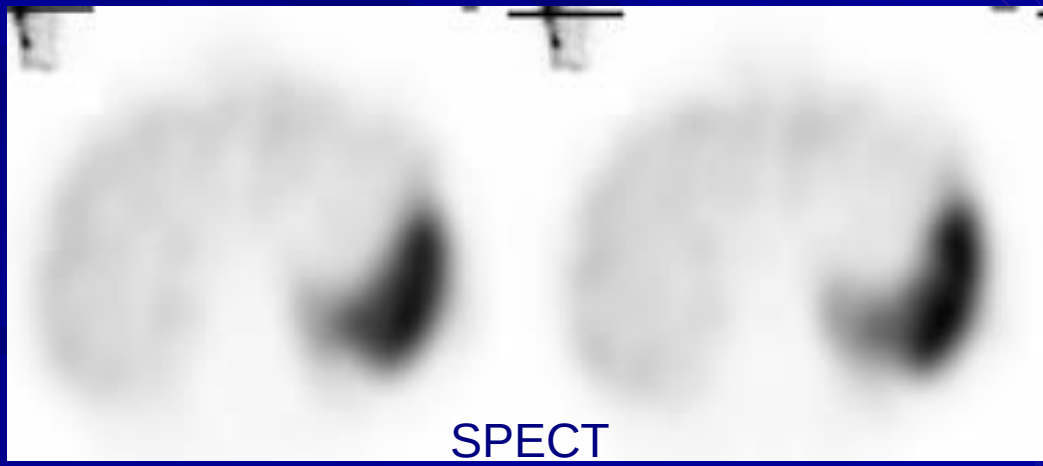
Ga-68 PET/CT

Ga-68 PET/CTfinds more lesions than In-111 Oct



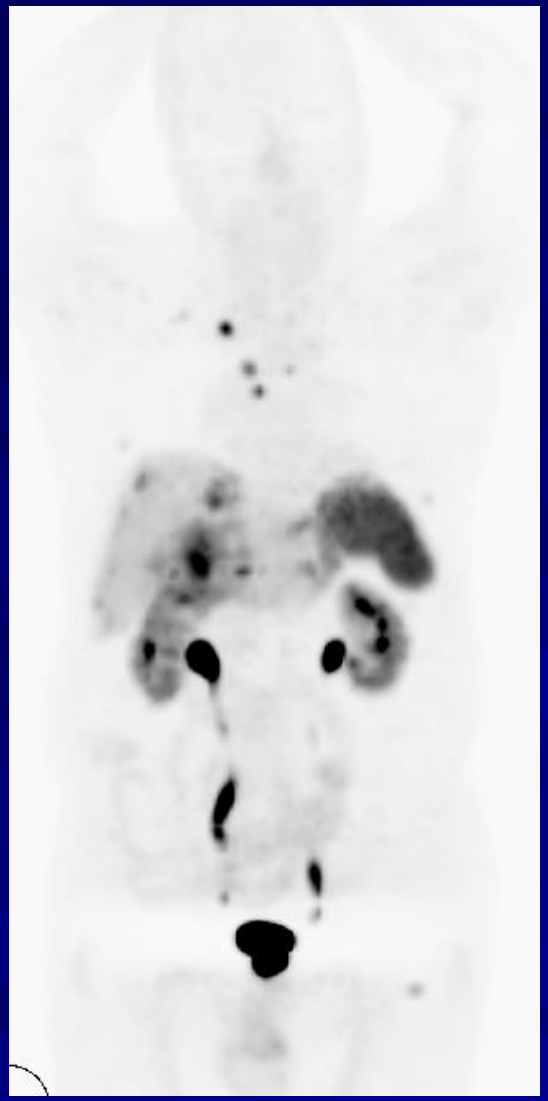
In-111 Oct WB



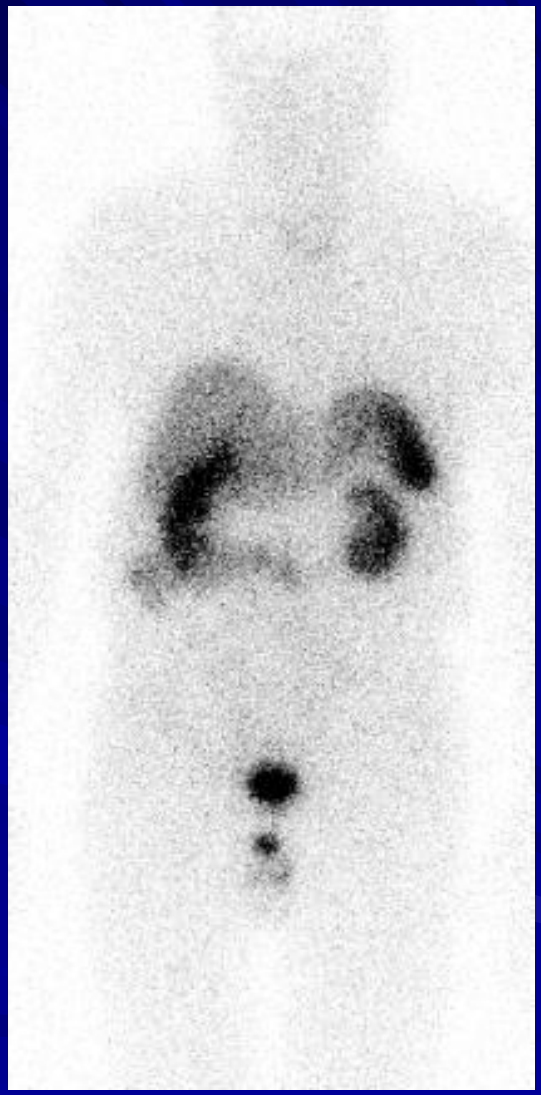


SPECT

Ga-68 PET/CT more lesions than In-111 Oct



Ga-68 PET (MIP)



In-111 Oct (WB)

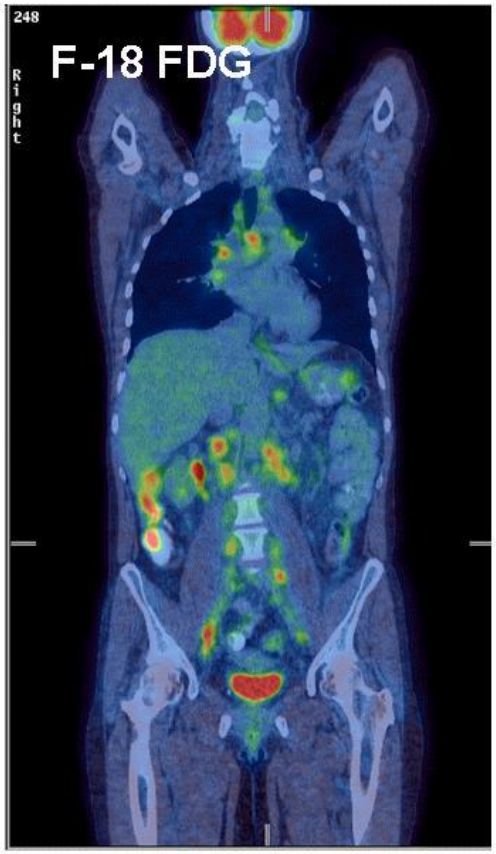
F-18 FDG measure metabolism and Ga-68 DOTATATE receptor activity

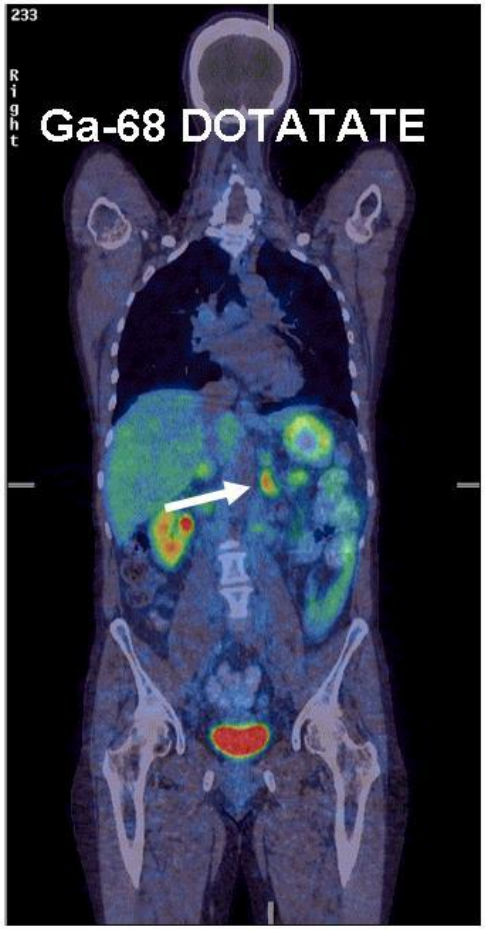
Same patient imaged with both tracers. NET unknown origin

Biopsy of F-18 FDG lesion shows Ki67 of >10%.

Biopsy of Ga-68 DOTATATE positive lesion Ki-67 1%

Patient responding to FCIST

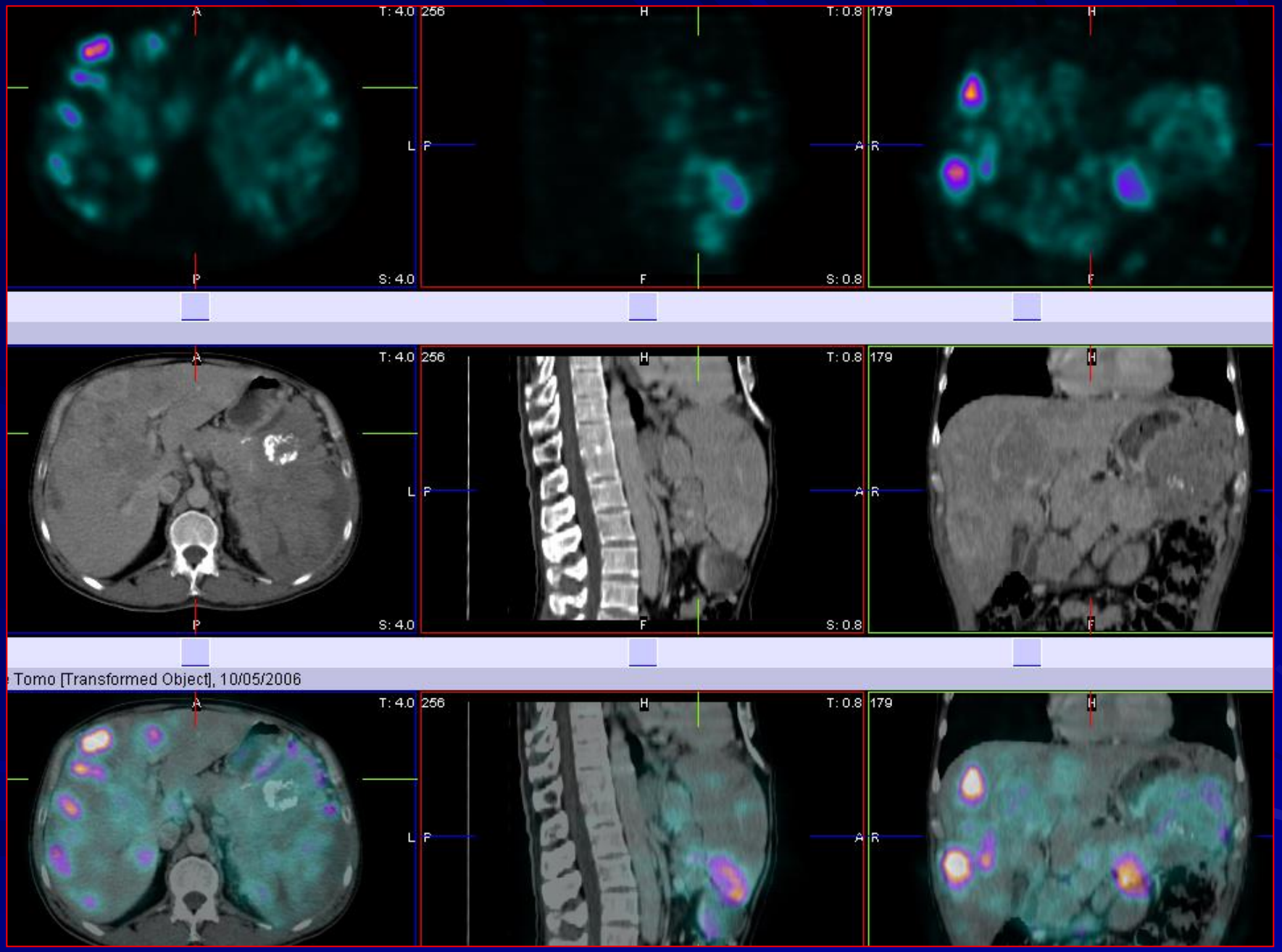




Buscombe et el in press Med Prin Meth

Tc-99m HYNIC TATE

- Based on octreotate
- Tc-99m linked via nicotinic acid linker
- Increased uptake in SSR2 positive tumours
- Much cheaper
- Lower radiation dose
- Development restricted by ECTD
- Available from Poland



Foregut, pancreas – non-secretor, NECLM (WHO 2)

In-111 GLP in 2 pancreatic tumours Christ et al JNM 2010