NHS
Manchester University
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Clinical protocols : cardiac imaging

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IPEM Introduction to PET : 24th – 25th May 2021

Cardiac applications

- Myocardial Perfusion Imaging
- Myocardial Viability

MPI : SPECT and PET

	SPECT	PET
Equipment	Gamma Camera (usually with CT) £350k to £500k	PET-CT £1.2M to £2.5M
Scan time	10-15 minutes	5-15 minutes depending on tracer
Imaging	Post-stress	Peak stress
Stressing	Pharmacological Exercise (and combination)	Pharmacological only
Tracers	Tl-201 (old) Tc-99m sestamibi Tc-99m tetrofosmin	Rb-82 N-13 ammonia (NH_3) O-15 water
Tracer production	Standard generator	Generator (Rb-82) Cyclotron (N-13 & O-15)
Imaging protocol	One-day or two-day	Single session

Positron-emitting radionuclides for cardiac imaging

Radionuclide	Half-life (min)	Production	Mean β^+ energy (keV)	Max β^+ energy (keV)	Mean range (mm)	Max range (mm)	Tracer
Nitrogen-13	10	Cyclotron	492	1190	1.5	5.1	Ammonia
Oxygen-15	2	Cyclotron	735	1720	2.5	8.0	Water
Fluorine-18	109	Cyclotron	250	635	0.6	2.4	FDG
Rubidium-82*	1.3	Generator	1535	3350	5.9	14.1	RbCl

*Also 776 keV single “prompt” gamma-ray

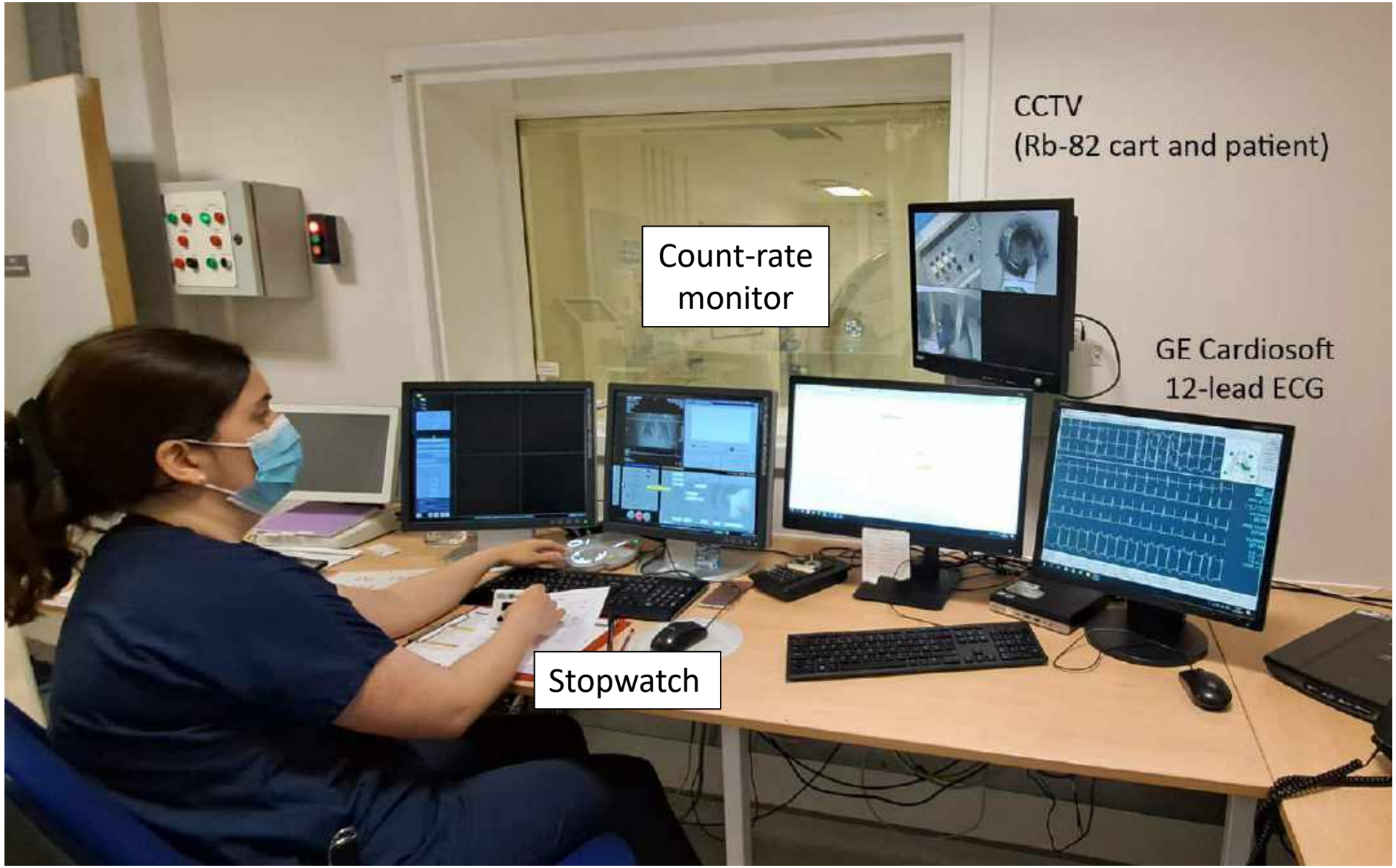
MPI PET : patient requirements and preparation

- Must be suitable for pharmacological stressing
  - Can use incremental adenosine protocol for controlled asthma
- Lie flat with arms up
- Caffeine free for 12 hours

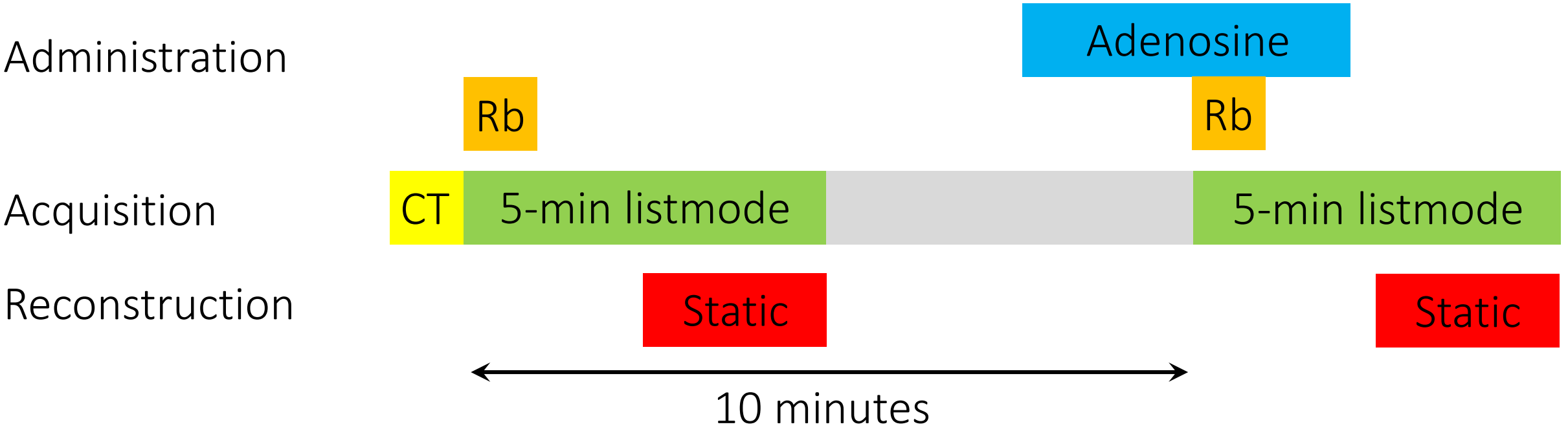
MPI PET : Rb-82 protocol

- CT first to plan scan (no persistence on PET)
- Rest-Stress or Stress-Rest
  - Stress first in severely claustrophobic
- Only adenosine or regadenoson used as the stress agent
- 740–1100 MBq (20–30 mCi) administered for each part
  - Biograph mCT : 1100 MBq
  - Biograph Vision : 740 MBq
- Start image acquisition as tracer is infused
- Generator can only be eluted once every 10 minutes

MPI PET : mission control

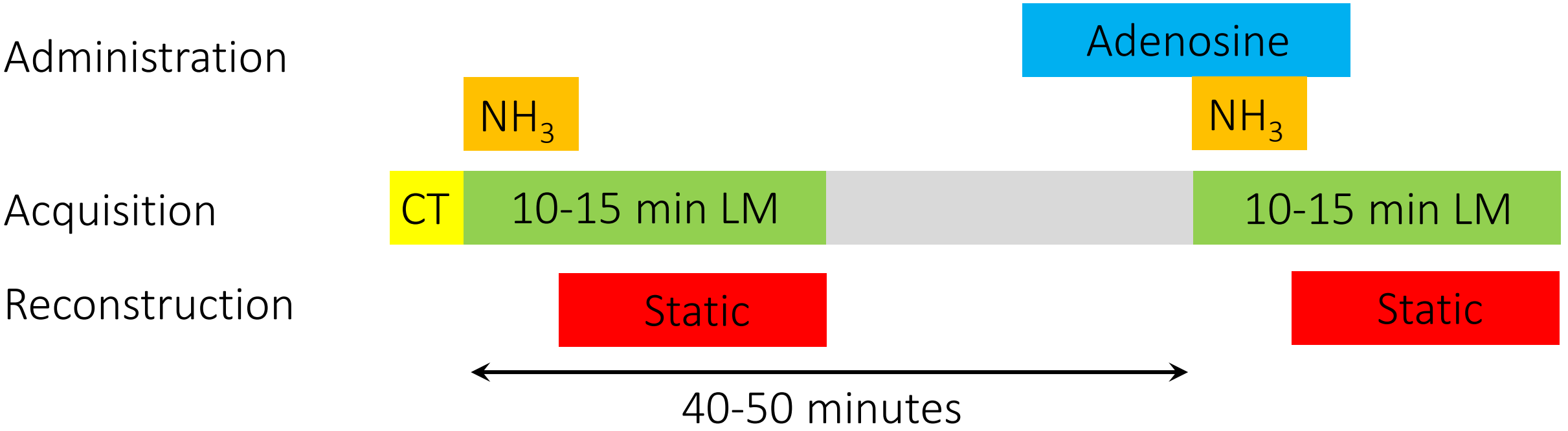


Rb-82 MPI acquisition protocol



- 740–1100 MBq (20–30 mCi) for each administration
- Static & gated reconstruction : 150 second delay and so 150 second image

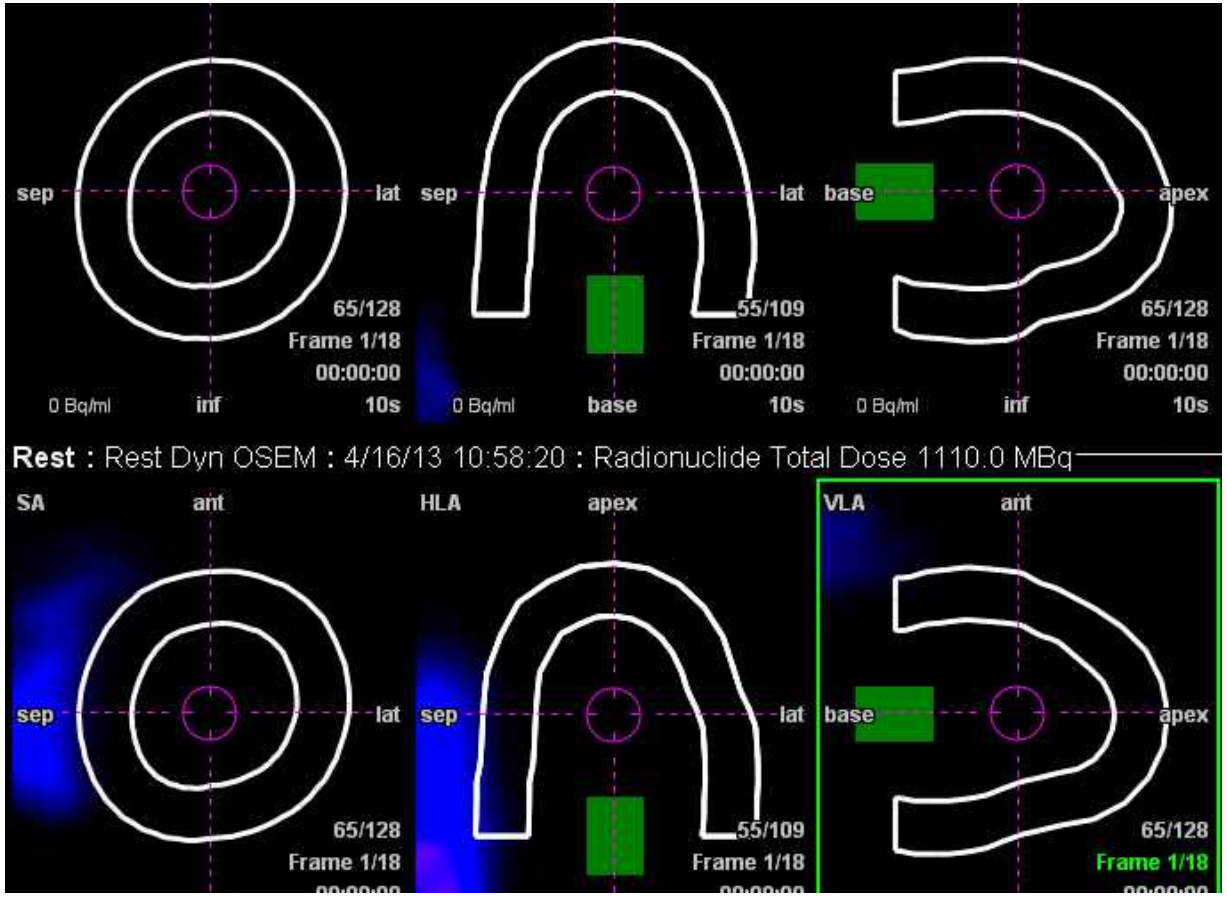
N-13 ammonia MPI acquisition protocol

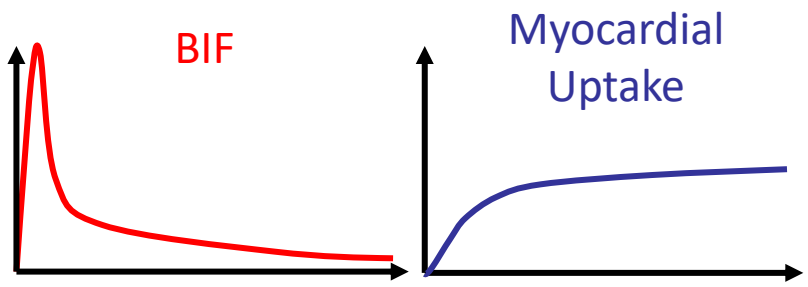


- 370–740 MBq (10–20 mCi) for each administration
- Static & gated reconstruction : 150 second delay and so 150 second image

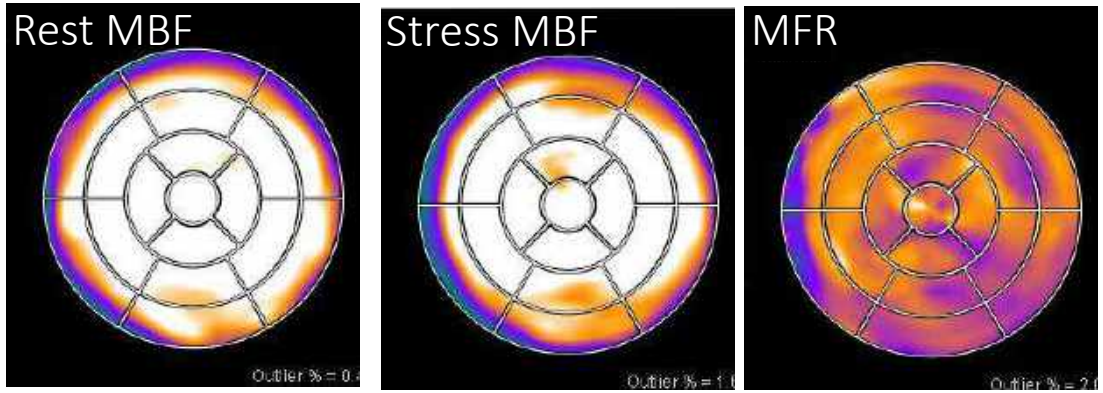
Myocardial Blood Flow

- Dynamic acquisition from tracer injection
- Segmented VOI for myocardium
- VOI for Blood Input Function (BIF)
- Generate time activity curves
- Feed in kinetic model of MBF
- MFR = stress MBF / rest MBF





Myocardial Blood Flow

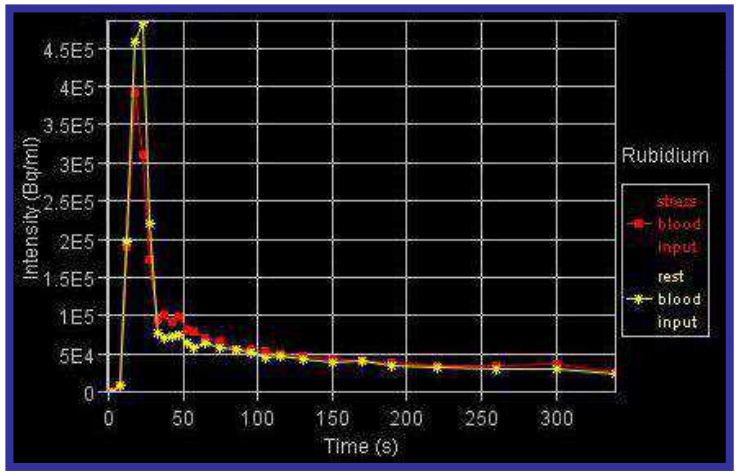


Myocardial Flow Reserve (MFR)
=
Stress MBF / Rest MBF

"Normal" Ranges
Rest MBF: 0.6 – 1.3 ml/g/min
Stress MBF: 1.2 – 3.3 ml/g/min

"Adequate" MFR: > 2.0
"Equivocal" MFR: 1.5 – 2.0
"Abnormal" MFR: < 1.5

	QMP (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev	mean	std dev	mean	std dev
LAD	2.47	0.61	0.93	0.17	2.67	0.63
LCX	2.42	0.58	0.90	0.23	2.72	0.33
RCA	2.81	0.70	0.93	0.26	3.10	0.64
Global	2.53	0.64	0.92	0.21	2.79	0.57



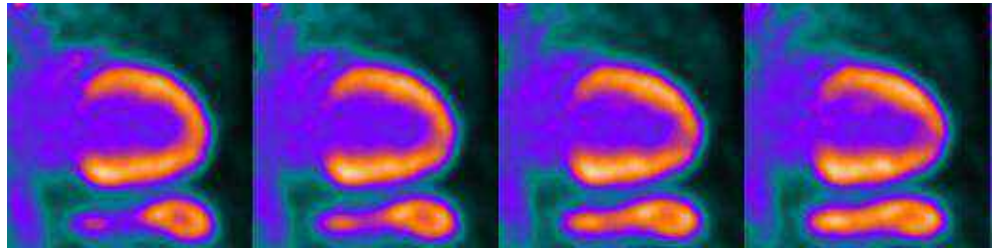
MPI PET : image reconstruction

- Unlike SPECT, corrected images may only available once the scan has been completed
  - May be able to perform “on-line” reconstruction during portion of scan on some systems
- Multiple datasets can be produced from the scan
  - Static: shows regional perfusion
  - Gated: shows wall motion
  - Dynamic: can perform kinetic analysis to derive myocardial blood flow

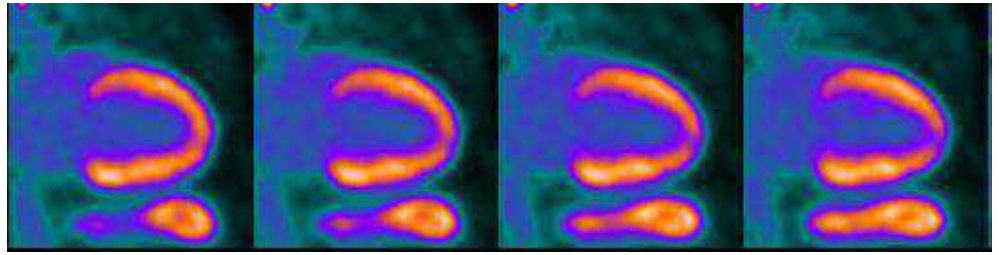
Listmode re-binning

- Cannot reconstruct listmode data directly
- They are binned into sinograms according to the time range specified
- Increased delay can reduce blood-pool activity
- Trade-off is fewer total counts and hence images are noisier

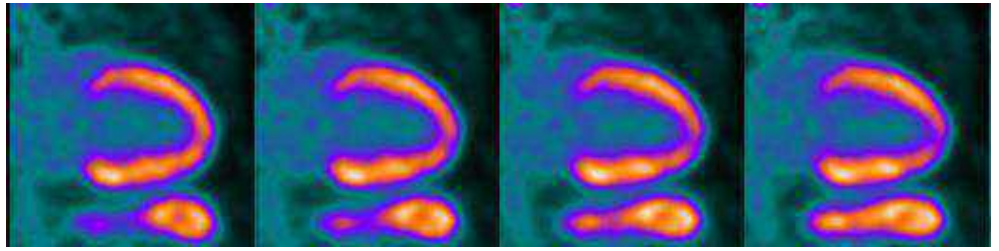
90–300 sec



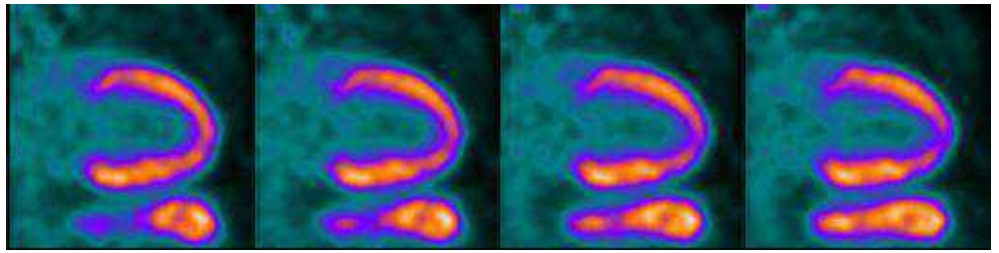
120–300 sec



150–300 sec



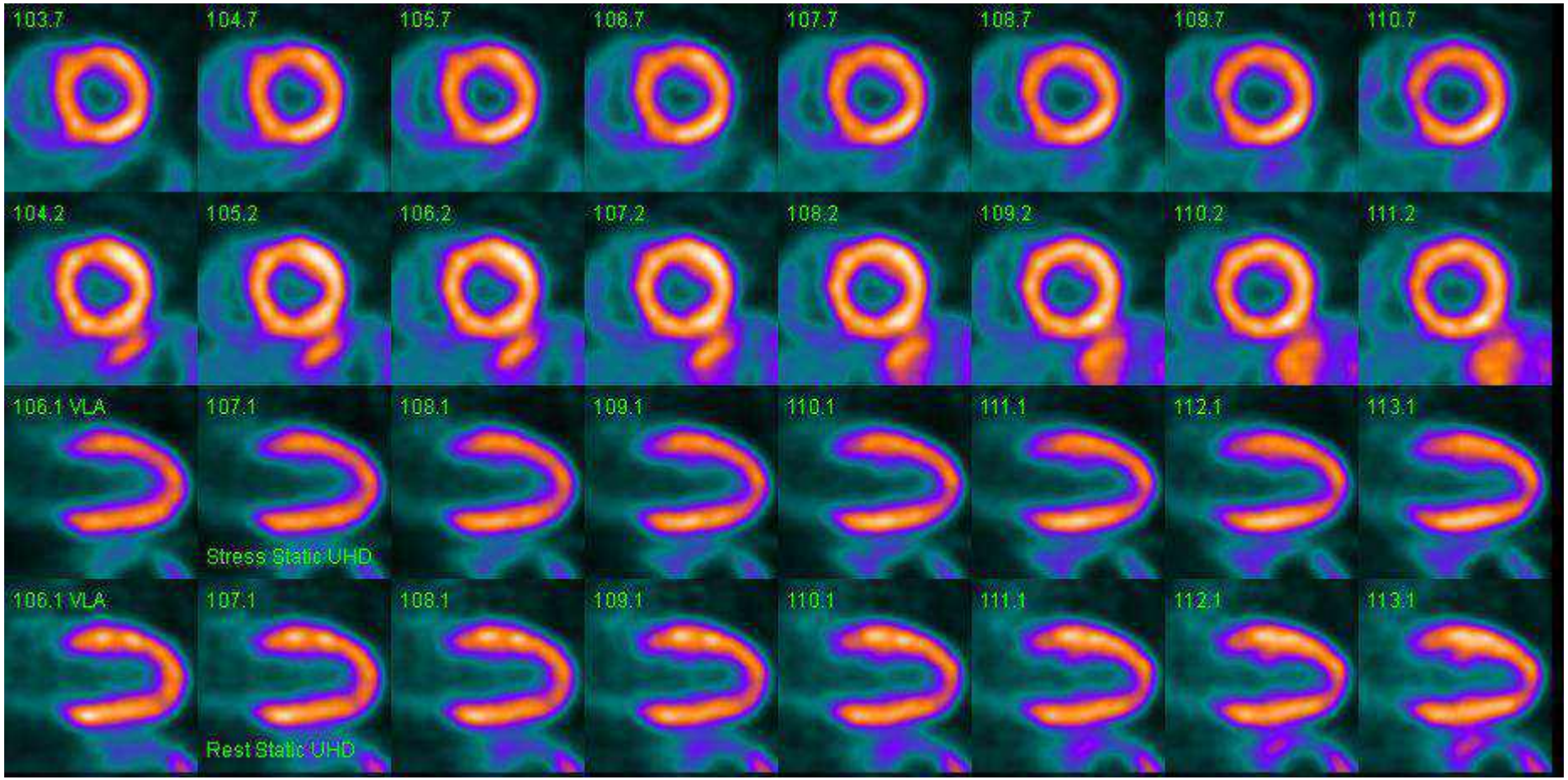
180–300 sec



MPI PET : image QC

- This is mainly based around registration of PET and CT images
- Can not easily tell if patient has moved from initial images (no projection view as in SPECT)
  - No way to correct for motion in static and gated
- Rarely need to repeat scan
- If there is large misregistration between PET and CT images a second CT scan post stress may be needed
- The only way to ensure no movement is to explain the importance of staying still to the patient

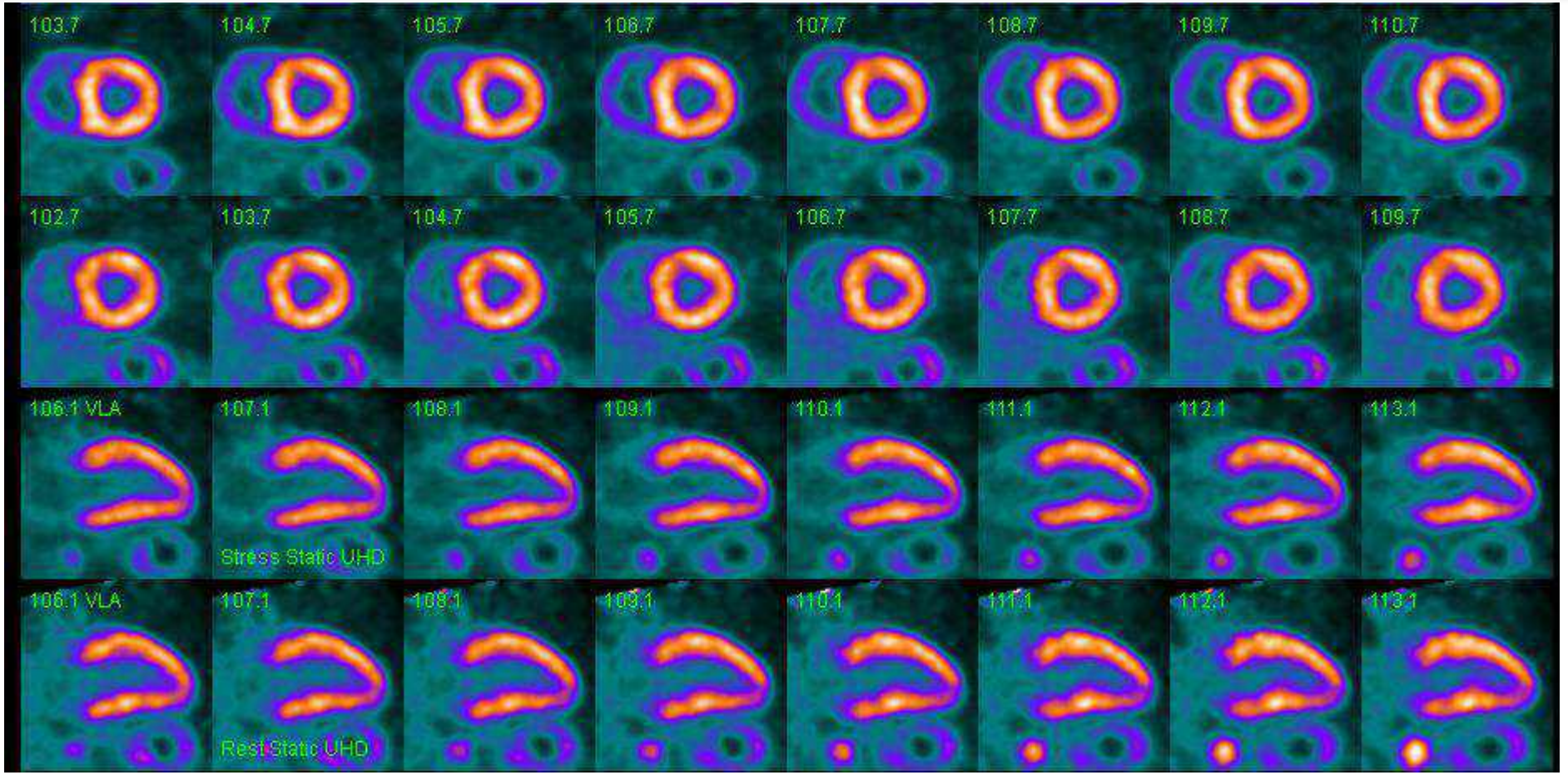
Rubidium cardiac scans



Female 83 kg 34.5 kg/m^2

2 × 20 mCi (740 MBq) rubidium 150 second static image

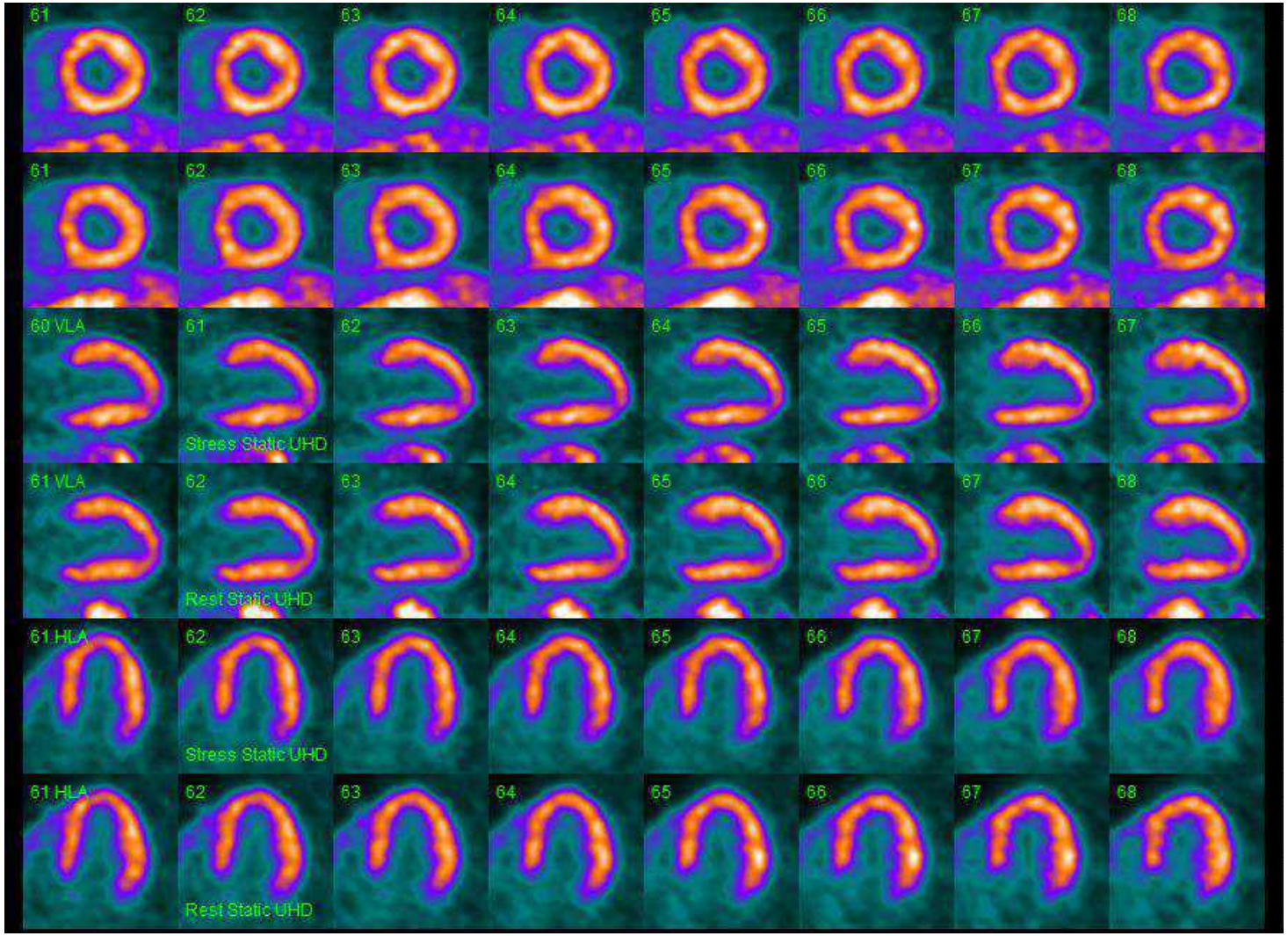
Rubidium cardiac scans



Male 90 kg 31 kg/m^2

2 × 20 mCi (740 MBq) rubidium 150 second static image

Rubidium cardiac scans



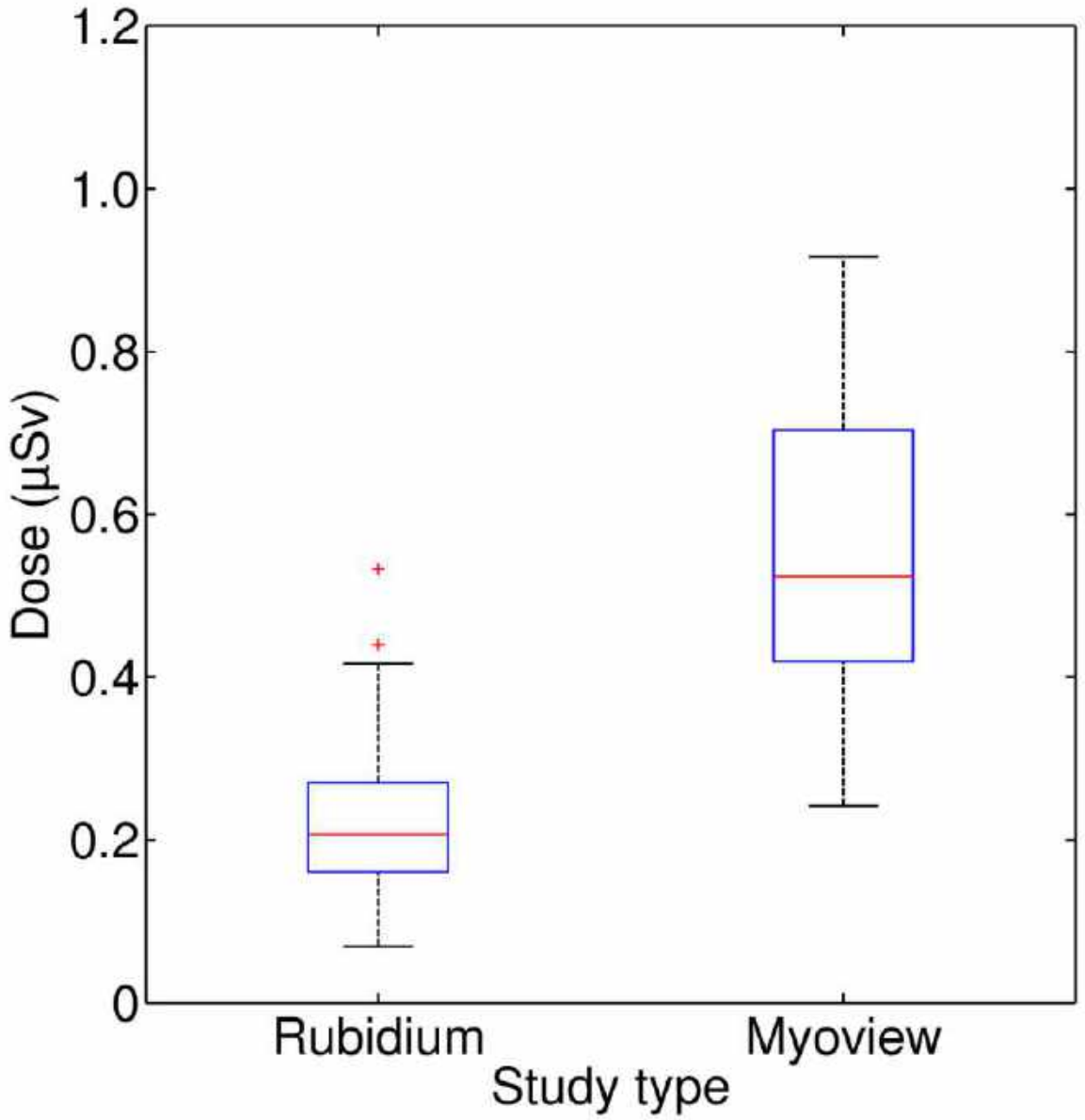
Male 160 kg, BMI 70.2 kg/m^2

2 × 20 mCi (740 MBq) rubidium 150 second static image

MPI : SPECT and Rb-82 PET patient dosimetry

	Activity	Radiation dose	With AC CT dose
Tc-99m sestamibi	800 – 1600 MBq	8 – 16 mSv	8.3 – 16.8 mSv
Tc-99m tetrofosmin (Myoview)	800 – 1600 MBq	6 – 12 mSv	8.3 – 16.8 mSv
Rb-82	1480 – 2220 MBq	1.8 – 2.4 mSv	2.2 – 2.9 mSv

MPI: SPECT and PET staff dosimetry



Myocardial viability

- In areas of reduced / lack of perfusion in resting state MPI images can also perform a viability study
- Determines whether the cardiomyocytes area still “alive” and hence viable to revascularisation

Myocardial viability : preparation

- Patient will have had rest rubidium perfusion scan
- Carefully managed blood sugar prior to scan
  - Aiming to inject FDG at 5.5-7.7 mmol/l
  - Baseline : 4.0 – 13.9 mmol/l
  - Give glucojuice
  - Measure BM one hour after glucojuice then insulin as required

Viability : FDG protocol

- CT first to plan scan
- Fixed 280 MBq FDG administered at optimum BM range
- Image at 90 minutes
- 10 minute listmode

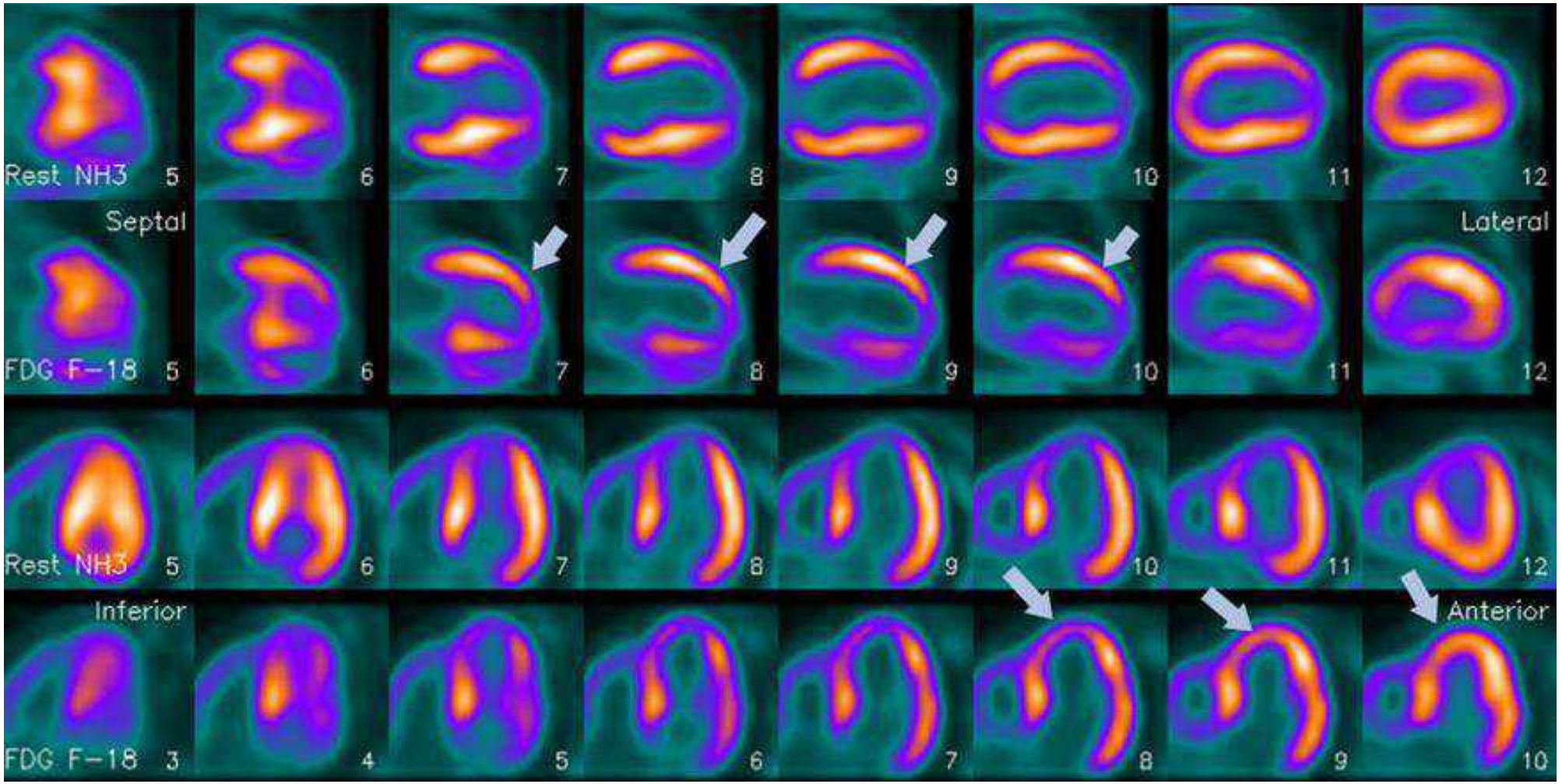
Myocardial viability

Perfusion (NH_3)

Metabolism (FDG)

Perfusion (NH_3)

Metabolism (FDG)



Garcia MJ et al. *Circ: Cardiovasc Imaging* 2020; 13:e53

Viability : highlighting positron range

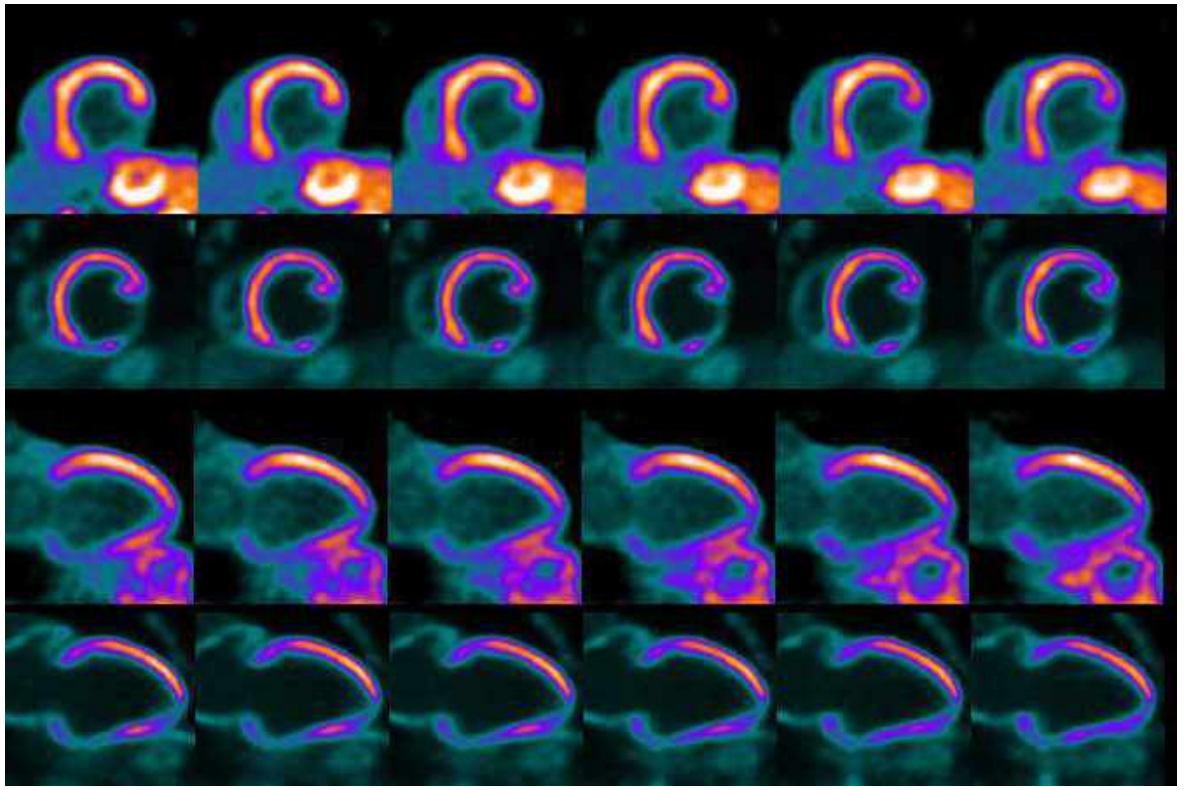
- Fundamental limit of spatial resolution
- Rb-82 has mean range of 5.9 mm in soft tissue
- F-18 has mean range of 0.6 mm in soft tissue

Rb-82

F-18

Rb-82

F-18

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Clinical Imaging Protocols: Oncology

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Clinical imaging

Oncology
- F-18-FDG [Fluorodeoxyglucose]
- Ga-68-DOTA [DOTA-TATE, DOTA-NOC, DOTA-TOC]
- F-18-fluoride
- Ga-68-PSMA (F-18-PSMA) [Prostate Specific Membrane Antigen]
- Others …

2

Clinical imaging

- Oncology

–F-18-FDG [Fluorodeoxyglucose]

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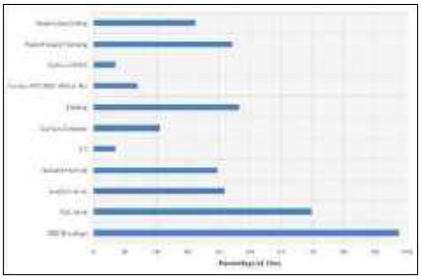
3

PET-CT scan types in the UK

Survey of practice in 2015/16. Responses from 43/56 sites across the UK performing PET-CT.



With kind permission, Dr John Dickson. IPEM survey of the current status of PET/CT imaging. SCOPE September 2016. NMSIG on behalf of IPEM.

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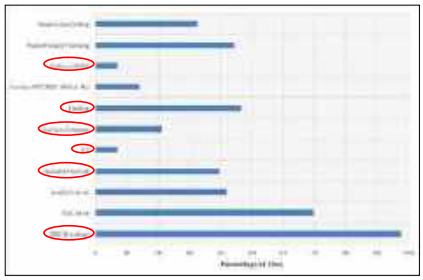

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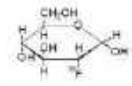
F-18-flourodeoxyglucose (FDG)

- It is by far the most common PET-CT imaging tracer used in >90% of PET-CT investigations in UK
- F-18 is a cyclotron produced radio-isotope, which decays via positron emission with $t_{½}$ = 109.8 min.
- FDG is an analogue of glucose which is metabolised by cells and then trapped. Uptake is proportional to the glucose utilisation, which is increased in many cancers. (Increased expression of glucose transporters is common.)
- F-18-FDG is delivered ready to inject twice-daily in a multi-dose vial in a shielded transport container from the cyclotron. Shipped prior to completion of radiopharmaceutical QC.
(QC result is subsequently passed to the customer and the product is "released".)



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F-18-FDG Oncology

- Procedure guidelines published by EANM (2015).
- Indications for use, published by the RCR (2016).

7

F-18-FDG Administered activity

1. For systems that apply a PET bed overlap of ≤30 %, the minimum recommended administered activity is calculated as follows: FDG (MBq)=14 (MBq·min·bed^{-1} ·kg^{-1}) × patient weight (kg)/emission acquisition duration per bed position (min·bed^{-1}).
2. For systems that apply a PET bed overlap of >30 %, the minimum FDG administered activity is calculated as follows: FDG (MBq)=7 (MBq·min·bed^{-1} ·kg^{-1}) × patient weight (kg)/emission acquisition duration per bed position (min·bed^{-1}).

EANM Eur J Nucl Med Mol Imaging (2015) 42:328–354

Typical activity	3 to 4 MBq/kg ±10%, up to 400MBq, dependent on scanner. [ARSAC DRL is 400 MBq, 4.5 MBq/kg] Where the patient weight ≥ 120 kg, consider increasing the scan time per bed where possible. For Brain scans a fixed administered activity of 200 MBq is typically used for an adult, irrespective of the patient weight. [ARSAC DRL is 250 MBq]
Reduced activity	If target activity is not achievable with the available activity, reduced activity may be considered as long as the patient can be imaged for commensurately longer and with agreement of the ARSAC holder.
Minimum activity	A minimum activity should be applied e.g. 75-100MBq.
Paediatric patients	Guidance from EANM (2008). Adjustment scheme presented is approximately linear from 14MBq at 3kg, to 200MBq at 70kg. Locally determined optimisation is encouraged.

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9

F-18-FDG Patient preparation

Fasting time	6 hours (Water only. No caffeine, alcohol, sugar-free drinks etc…) Ensure well hydrated at time of administration. Diabetic patients will require careful management of their blood glucose. Discuss requirements with the patient.
Blood Glucose	>3.0 mmol/L and <12.5 mmol/L (EANM: ≥ 4mmol/L and ≤ 11 mmol/L) If lower, consider giving the patient a snack/drink and discuss with ARSAC holder. (very cautious about injecting FDG soon after drink/snack) If higher, investigate circumstances & re-book.
Uptake time (from administration to start of PET scan)	55 – 75 mins. (As close to 60min as practical.) The patient should not be moved from a warm, quiet uptake area until >50min post-administration.
Patient set-up	The patient should be asked to void their bladder immediately prior to moving into the scanner room. Positioned supine , with all metal objects (zips, buttons, jewellery etc…) out of the scan range. (May need to change into gown/scrubs.) Arms raised unless; - interested in the head/neck region, or - patient unable to hold the position for the period of the scan. Ensure that the patient is centred vertically in the scanner bore. Scan length of patient as required according to the referral. Scan direction from Inferior to Superior (to minimise bladder activity in FoV) unless interested in the Head-Neck region.

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Crunchy Nut Cornflakes…

Slide from P Julyan

11

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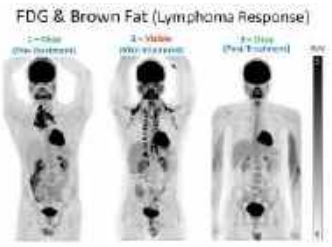
Brown fat uptake

- Brown fat is vascular adipose tissue (more so than white fat).
- Increased FDG uptake is seen in approx. 5% of patients, is more common in women than men, and is often associated with low ambient temperature.



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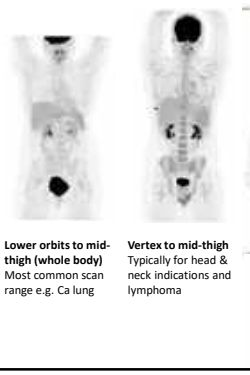
F-18-FDG - scan range



Lower orbits to mid-thigh (whole body)
Most common scan range e.g. Ca lung

Vertex to mid-thigh
Typically for head & neck indications and lymphoma

Total body
May need to be scanned in two parts on some scanners due to limited range of couch movement. (The patient is rotated after completion of the upper body.)
Some scanners may require a different couch top.

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F-18-FDG Acquisition & reconstruction

Time-per-bed position	2-3 mins Dependent on administered activity, FoV overlap and scan range. Consider extending acquisition time for large patients e.g. > 120 kgs.
% overlap for axial FoV	50%, or as appropriate to match the sensitivity profile of the FoV to ensure uniform sensitivity over the scan range. [Some debate over this with manufacturer recommending alternate practice. More FoVs = more data, longer reconstruction times etc.] Not relevant for scanners using continuous bed motion.
Reconstruction algorithm	Options will be manufacturer specific… Reconstruction should be iterative based. Where time of flight (ToF) information is available this should be incorporated into the reconstruction. Where resolution recovery options are provided these should be investigated in conjunction with the ARSAC holder & reporter to confirm acceptability of image quality and particularly the impact on calculated SUVs. Multiple reconstructions will be required, potentially including; - non- attenuation corrected (NAC) data, - iterative reconstruction for consistency in SUV calculation - "enhanced" dataset making use of manufacturer specific reconstructions tools. Reconstructed data set labelled indicating which reconstruction algorithm was used.

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% overlap for axial FoV

Example of artefacts caused by insufficient slice overlap. Patient scanned with 5 slice overlap on system with 47 axial slices

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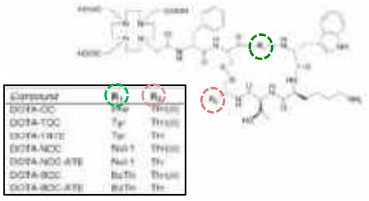
Ga-68-DOTA [TATE, NOC, TOC]

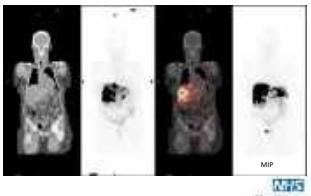
- Ga-68-DOTA binds to somatostatin receptors (much like In-111-pentetreotide).
- The variations TATE, TOC, NOC have different affinity for different somatostatin receptor subtypes. The choice is usually based on commercial restrictions or availability. (Use of Ga-68-DOTA-NOC at The Christie.)
- Normal physiologic uptake seen in spleen, adrenals, kidneys and pituitary.



19

Ga-68-DOTA [TATE, NOC, TOC]

- Ga-68 eluted from a Germanium-68/Gallium-68 generator. Ge-68 t½ = 271 days. Ga-68 t½ = 68 mins. Generator lasts 9-12 months (limited elutions). 1-3 pt doses per elution.
- Decays with a higher positron energy than F-18 (max e+ range Ga-68 is 9 mm, F-18 is 2.5 mm) therefore resolution is reduced.
- Not commercially available as a labelled product in the UK. Manufactured in house using a synthesis unit and multiple reagents. (More involved than Tc-99m processes, requiring more QC and inherent waste of $^{68}Ga^{3+}$.)
- Logistical problems with introduction as a new manufacturing process into an existing radiopharmacy (time, space and money) therefore few centres currently doing this.
- [A kit using Ge-68/Ga-68 generator eluate has had early trials but is not commercially available.]



20

Ga-68-DOTA

Procedure guidelines
- Bozkurt et. al. Euro J Nucl Med Mol Imaging 2017

Pre-Administration
- The patient well hydrated in encourage renal clearance.
- No need to fast.
- Many authors recommend interrupting Sandostatin (Octreotide) treatment.
  - Sandostatin stopped 3 days in advance if possible. Minimum 12 hours.
  - Patients on long acting – monthly – actreotide (Sandostatin LAR) should have the study 4 weeks after last injection – i.e. book just prior to injection or delay injection by a few days where possible.

Administration
- Bolus IV administration via indwelling catheter
- Administered activities **100-200 MBq** often independent of patient weight.
  - ARSAC DRL is 250MBq
  - Adjustment for weight should be considered

Post-Administration
- Patients remain seated in a quiet environment during the uptake.
- The suspected tumour area to be imaged ≥ 60 min post-injection.
- Patients should empty their bladder immediately prior to imaging.

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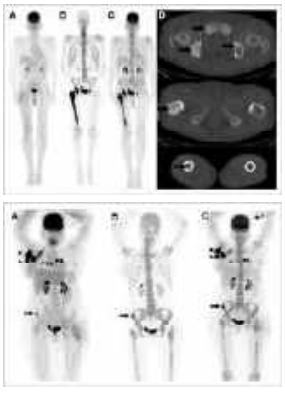
F-18-Fluoride

- F-18-Flouride is trapped in the bone complex by the action of the osteoblasts forming new bone matrix
- RCR guidelines recommend use for assessment of benign and malignant diseases of bone in selected patients, and that it has been shown "to be more sensitive and specific than Tc-99m-MDP".
- ARSAC DRL = 250 MBq (effective dose 4.3 mSv)
- Ensure the patient is well hydrated (no need to fast or stop medication)
- Start imaging 30-60 minutes after the injection
- As with all PET-CT imaging, patients should be encouraged to empty their bladder prior to imaging the lumbar spine & pelvis
- Some increased use of this isotope in the UK during Tc-99m shortages (2008-12 and onwards) although requires significant PET-CT capacity to be able to replace Tc-99m bone scanning. Commercially available in the UK.

http://www.isotopia.co.il

22



A 74-y-old man with metastatic prostate cancer.
A) F-18-FDG scan
B) F-18-Fluoride scan
C) Combined FDG-Fluoride scan

A 45-y-old woman with metastatic breast cancer.
A) F-18-FDG scan
B) F-18-Fluoride scan
C) Combined FDG-Fluoride scan

Andrei Iagaru et al. J Nucl Med 2012;54:176-183

23

Prostate specific membrane antigen (PSMA)

- PSMA ligand binds to antigen on the membrane-bound enzyme
- Normal physiologic uptake in the lacrimal and salivary glands, spleen, kidneys and small bowel.
- Different PSMA ligands have been produced [e.g. Ga-68-PSMA HBED-CC, Ga-68 PSMA I&T, F-18 PSMA-1007] with similar uptake but differing production & labelling processes
- PSMA initially labelled with Ga-68 and more recently F-18.
- F-18 PSMA is commercially available in UK. Currently only from PETNET (Siemens - Healthineers).
- There is considerable interest in this area, driven by high incidence of prostate cancer. (FDG is not taken up by most prostate cancers.)

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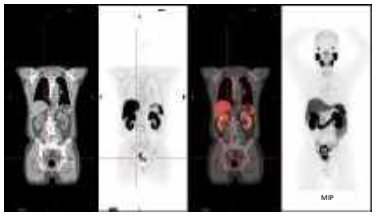
Prostate specific membrane antigen (PSMA)

- ARSAC DRL F-18-PSMA = 280 MBq (4MBq/kg). Typically use ≈ 3 MBq/kg.
- No need to fast. 60 min to 180 min uptake time has been proposed.
- Acquisition parameters are similar as for FDG imaging.
- Some sites recommend use of diuresis to minimise activity in the urinary system.
- EANM guidelines. Wolfgang et. al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. 2017



25

Development of Theragnostics. The same ligand is labelled with a diagnostic PET tracer (Ga-68 or F-18) and (separately) a therapy isotope (e.g. Lu-177). There is considerable research being done in this area.

Fig. 1. Serial Ga-68-PSMA scans performed along with Lu-177-PSMA-I&T therapy (4 treatments over 8 weeks).

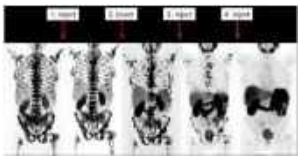


Figure 1. Heck MM, J Urol. 2016 [19 pts, 4 completed 4 cycles. Fifth line treatment for patient shown.]

Fig. 2. Case report. Diffuse bone metastases on Ga-68-PSMA PET-CT (B) in a patient with prostate cancer and normal bone scan (A). [Imaging within 1 month.] Lavalaye et al, EJNMMI July 2016

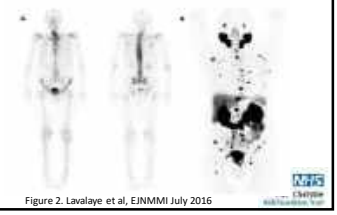


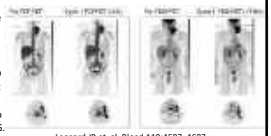
Figure 2. Lavalaye et al, EJNMMI July 2016

26

Others …

F-18-FLT

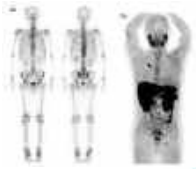
- F-18-FLT (Fluorothymidine) is a substrate for thymidine kinase 1 (TK1) and moves into cells by active transport, and phosphorylated. The concentration of FLT is proportional to TK1 activity and therefore, in theory, to cellular proliferation.
- Once widely regarded as a potential rival for FDG but failed to develop specific applications. Ongoing research for treatment response and staging of various less common tumours.
- 200 – 400 MBq. Some use of dynamic and focused view. 60 to 90 min uptake time. Typical acquisition parameters as for FDG.



Leonard JP et. al. Blood 119:4597–4607

C-11-Choline/F-18-Choline

- Choline is a precursor, and is taken up by choline transporters which are overexpressed in many tumours, e.g. prostate and hepatocellular carcinoma.
- Initially developed as C-11 labelled tracer but F-18 labelling developed to make it a more practical imaging tool. (Different excretion patterns mean C-11 preferred if available.)
- F-18-choline available commercially in the UK but PSMA is likely to be the nail in the coffin for choline. (RCR states PSMA has "superior diagnostic accuracy".)
- For F-18; 3-4MBq-per-kg. Most acquisition protocols recommend early (immediately post injection) pelvic imaging and delayed (55-65min) WB imaging.



Tc-99m bone scan (2a) performed <2 wks before C-11-Choline PET-CT (2b).
Nagoya J Med Sci. 2017 Aug; 79(3): 387–399.

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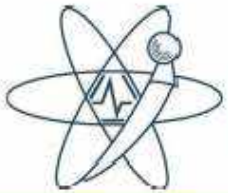
Thank you

28



IPEM conferences

An Introduction to PET Physics

24th and 25th May 2021, Online

Image Artefacts / Interesting Cases

Compiled by **Peter Julyan**

Christie Medical Physics & Engineering

The Christie NHS FT, Manchester, UK

The Christie NHS
NHS Foundation Trust

IPEM conferences

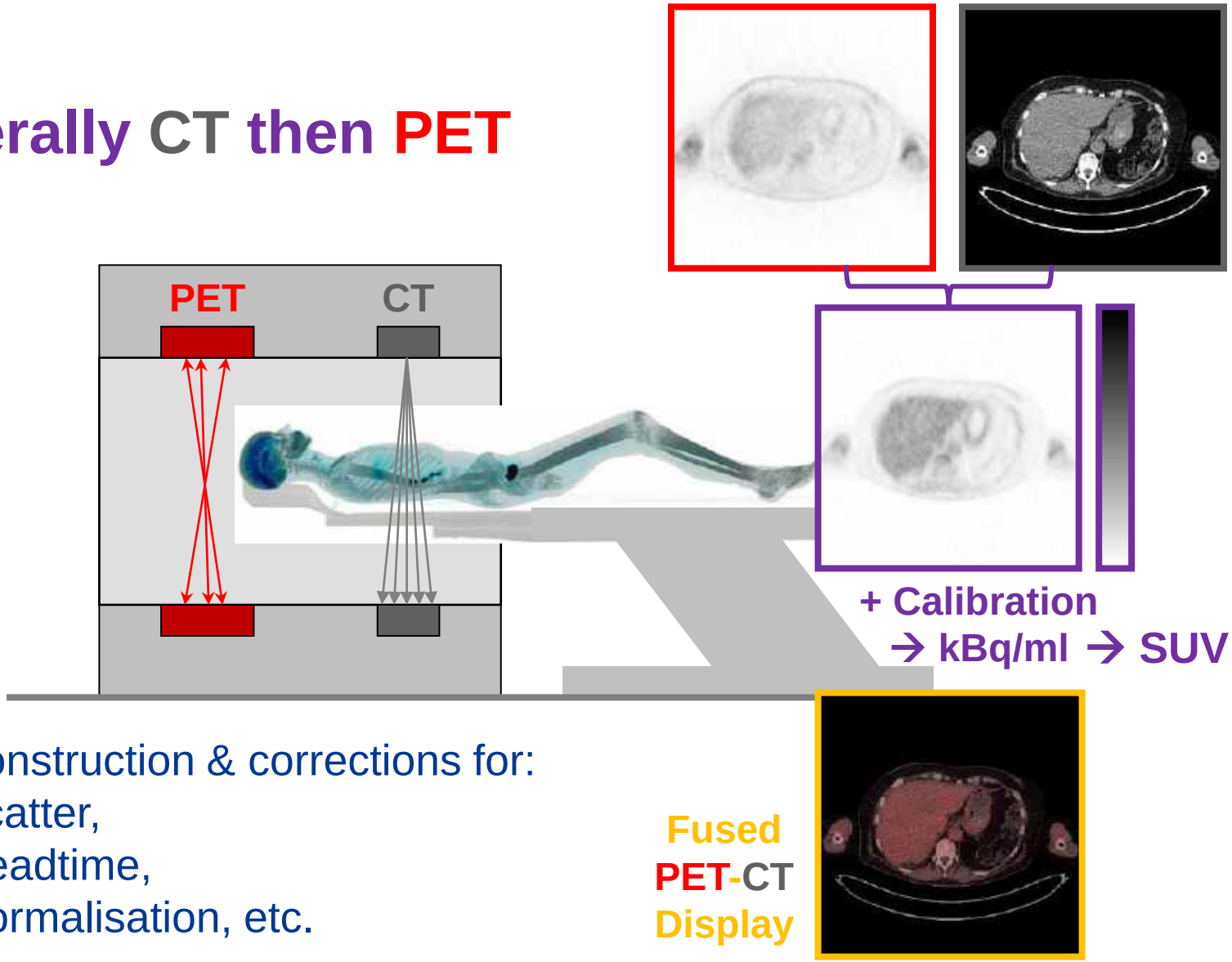
An Introduction to PET Physics

24th and 25th May 2021, Online

	DAY TWO
13.30 – 14.00	**Clinical imaging protocols: Oncology** Andy Harris, The Christie NHS Foundation Trust
14.00 – 14.25	**Clinical imaging protocols: Infection and Inflammation** Matt Memmott, Manchester University NHS Foundation Trust
14.25 – 14.50	**Clinical imaging protocols: Cardiac Imaging** Ian Armstrong, Manchester University NHS Foundation Trust
14.50 – 15.15	**Clinical imaging protocols: Neuroimaging** Matt Memmott, Manchester University NHS Foundation Trust
15.15 – 15.25	**Break**
15.25 – 15.55	**PET in the context of multi-centre trials** Lucy Pike, Kings College London
15.55 – 16.25	**Image Artefacts / Interesting Cases** All speakers – compiled by Dr Peter Julyan
16:25– 16:45	**Questions/discussion/close**

Quantitative PET-CT

Generally CT then PET



Reconstruction & corrections for:

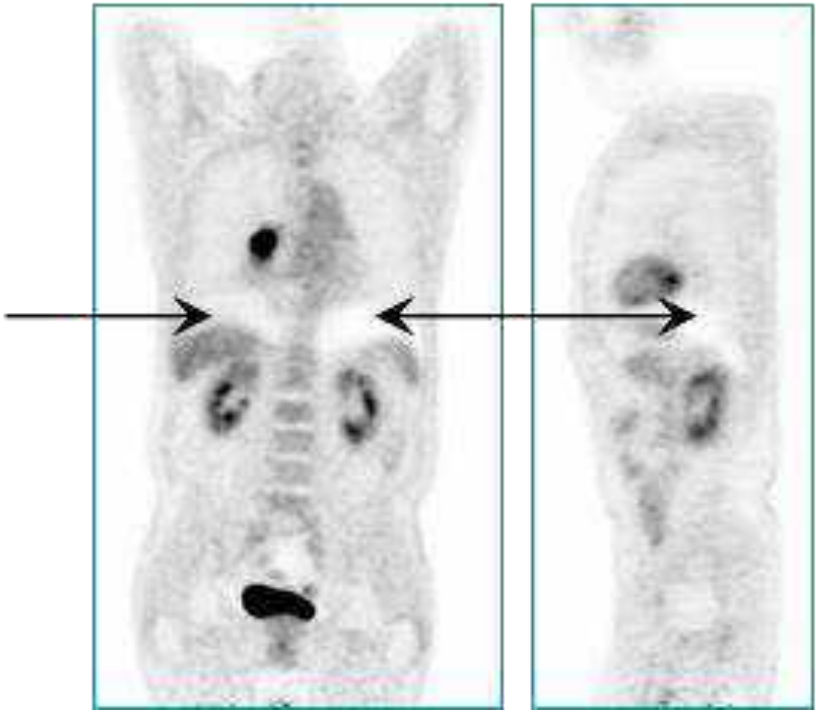
- Scatter,
- Deadtime,
- Normalisation, etc.

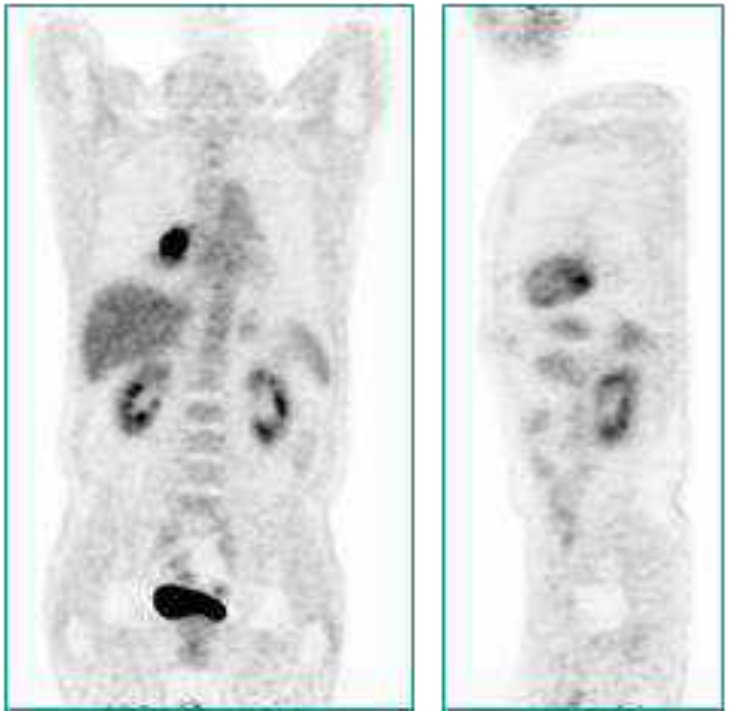
PET-CT Artefact – Respiration Mismatch

"Banana" Artefact

Initial PET reconstruction showing typical curved "banana" artefact due to misregistration with the CT.

Repeat PET reconstruction using aligned CT.



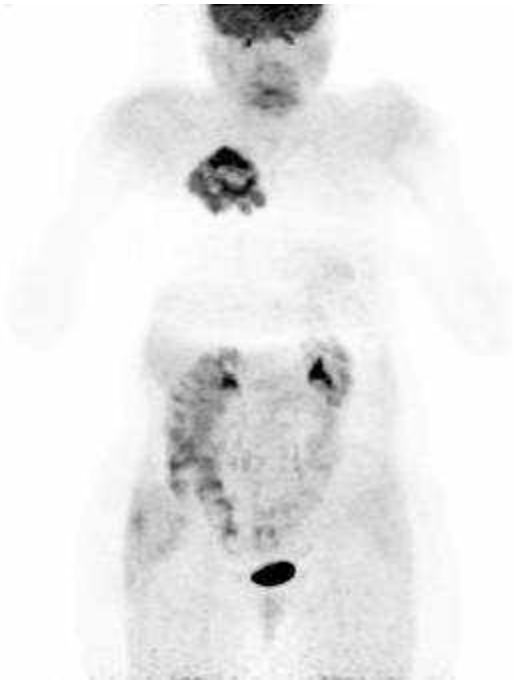


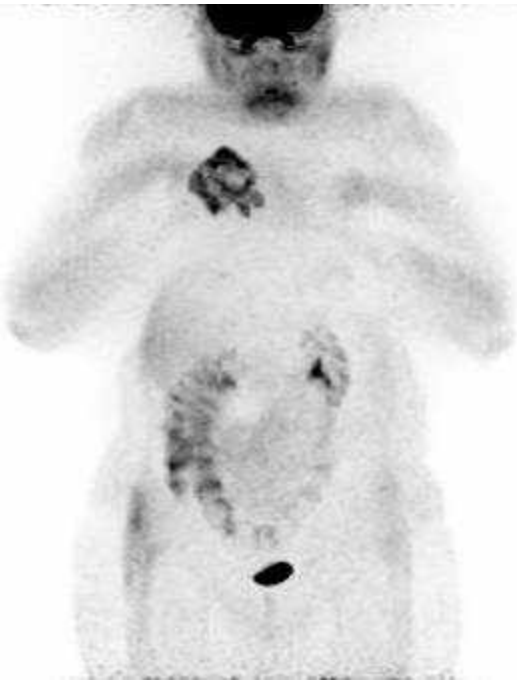
PET-CT Artefact – Movement

PET CTAC

PET noAC

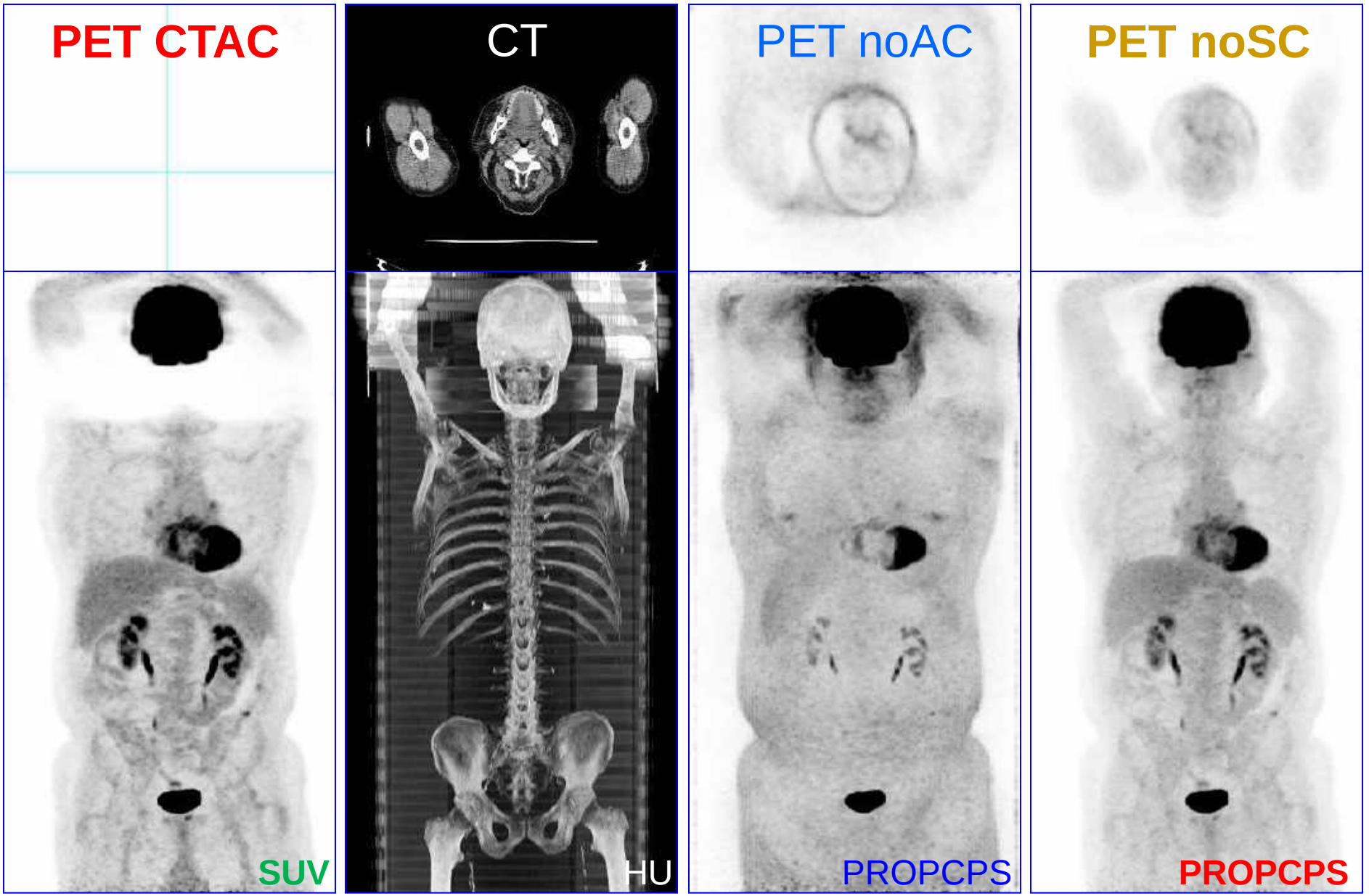
CT





Repeat Scan

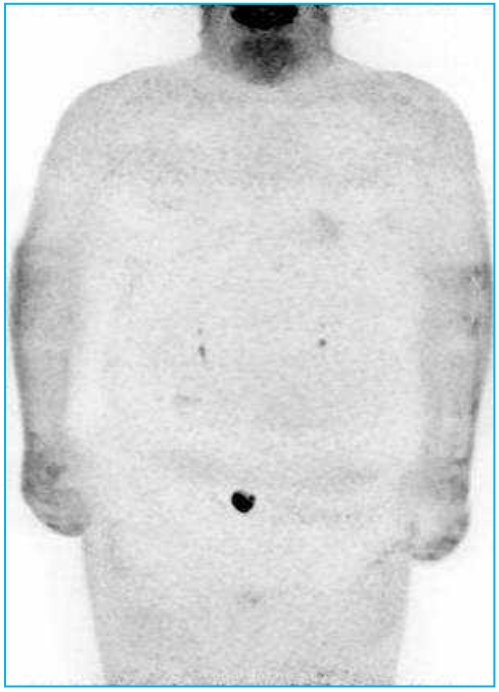
Movement → Attn & Scat Correction



Reconstruction Artefact (140 kg patient)

PET CTAC
“Q.Clear”

PET noAC

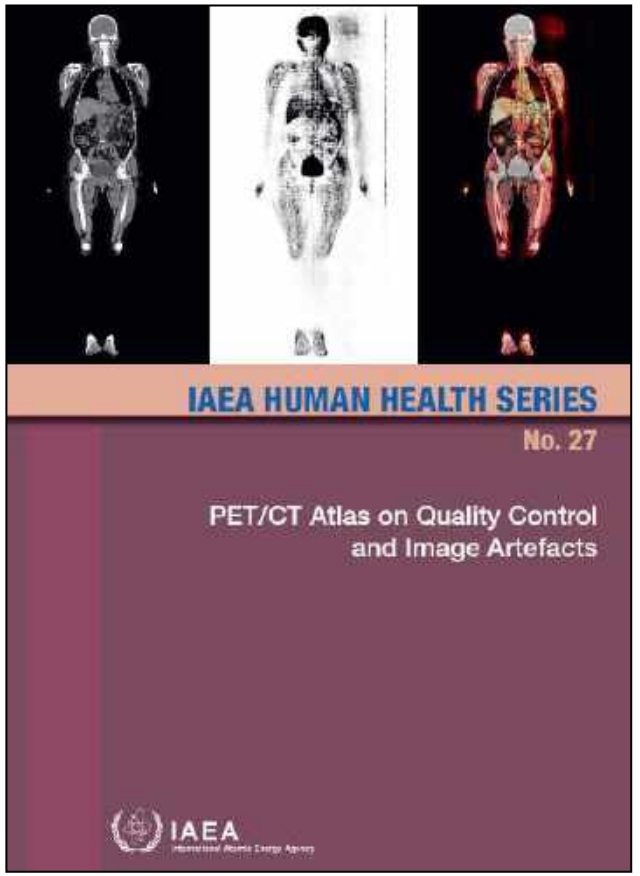


CT
50 cm
(70 cm not available)

PET CTAC
“VuePointHD”

Lessons – 1

- Become familiar with common artefacts
- Look at the **uncorrected PET**, the **CT** and their alignment
- What can I do?
  - Live with it
  - Re-scan patient
  - Re-process:
    - Turn off / alter scatter corr.
    - Different reconstruction



PET-CT Error

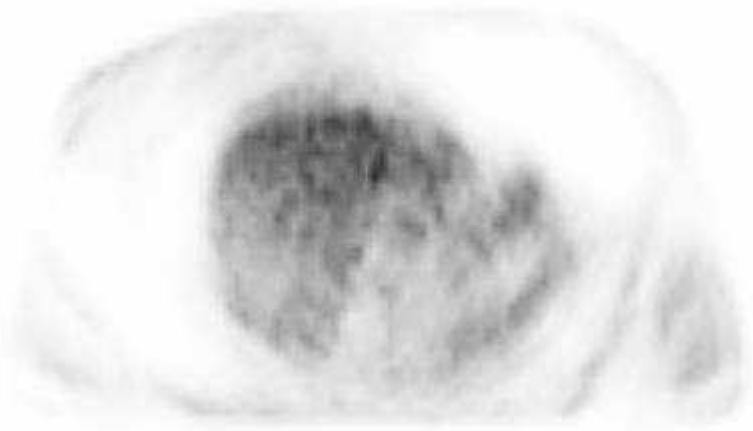
- WB FDG PET-CT

“Looks odd?”

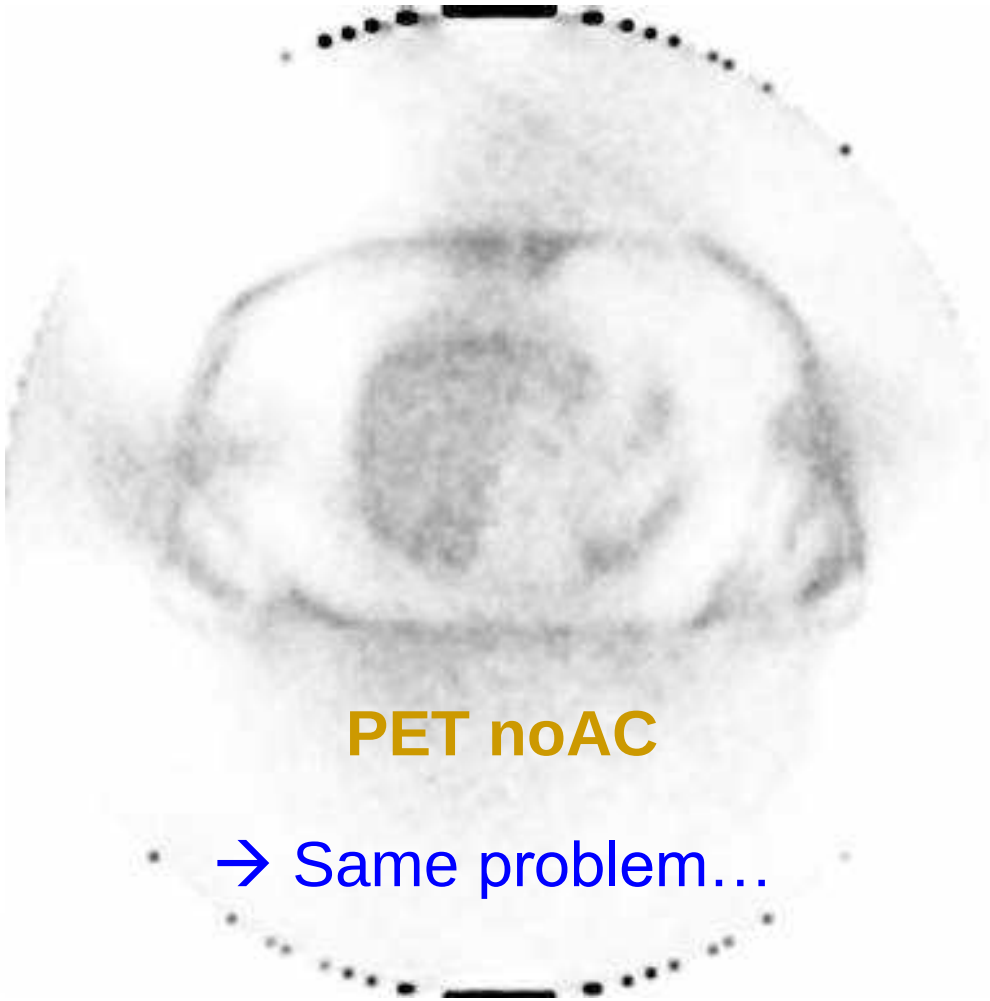
e.g. normal liver should be ~uniform

PET-CT Error

- Compare to noAC



PET CTAC

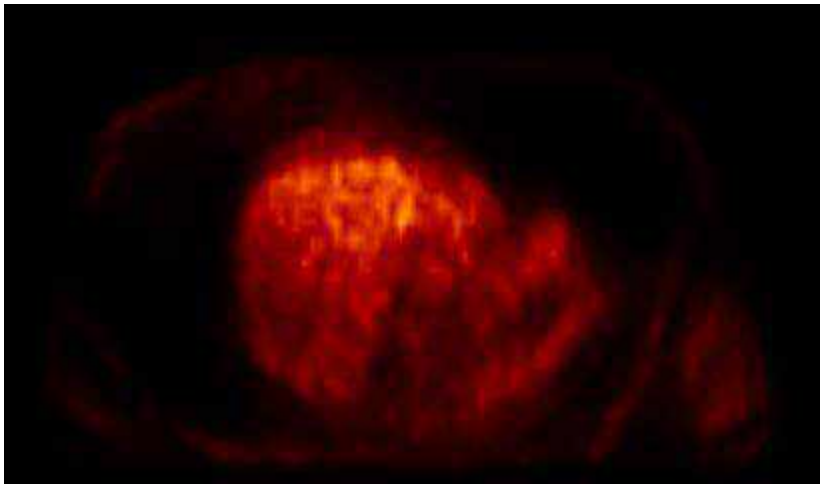


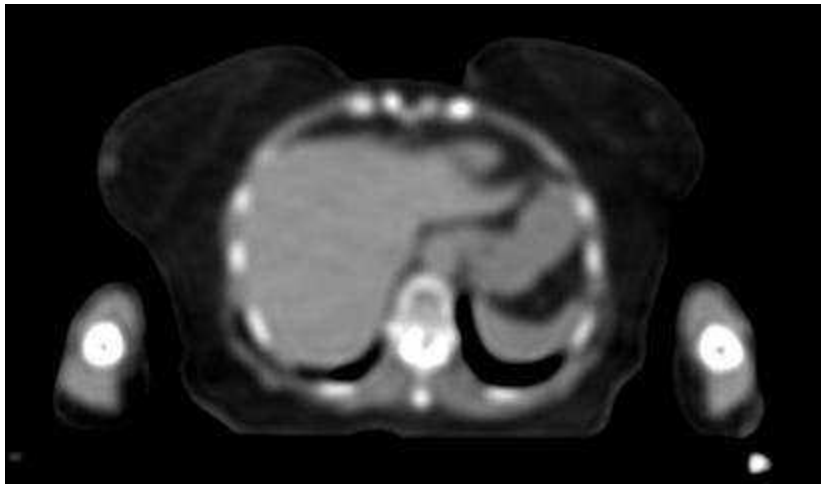
PET noAC

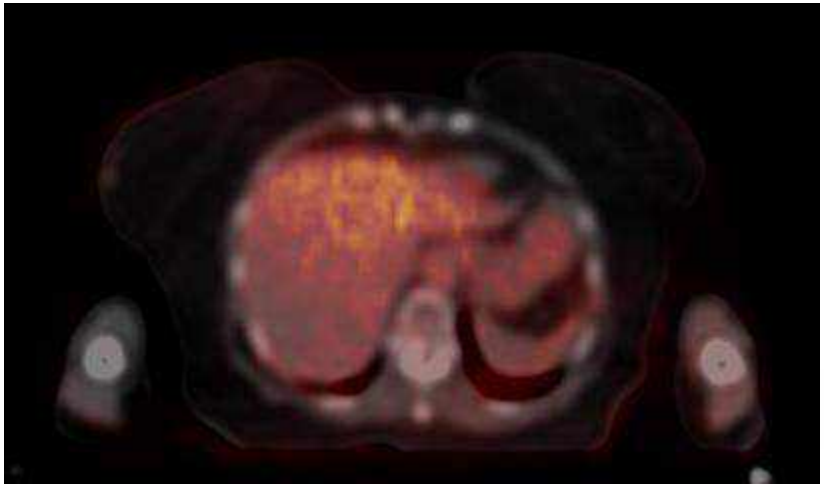
→ Same problem…

PET-CT Error

- Check alignment with CT





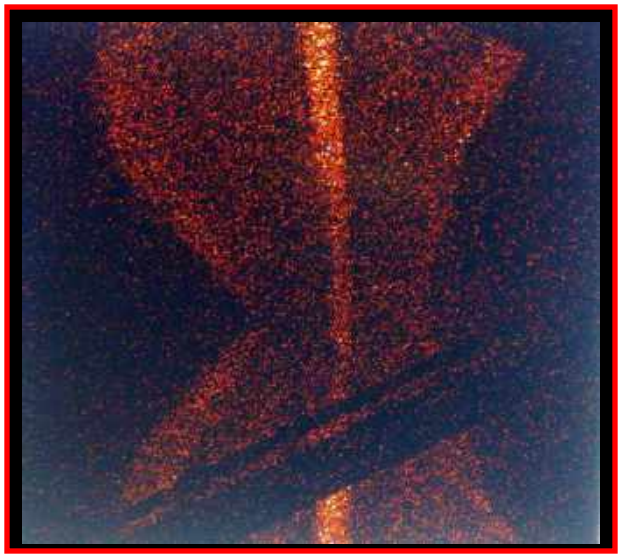


→ Okay…

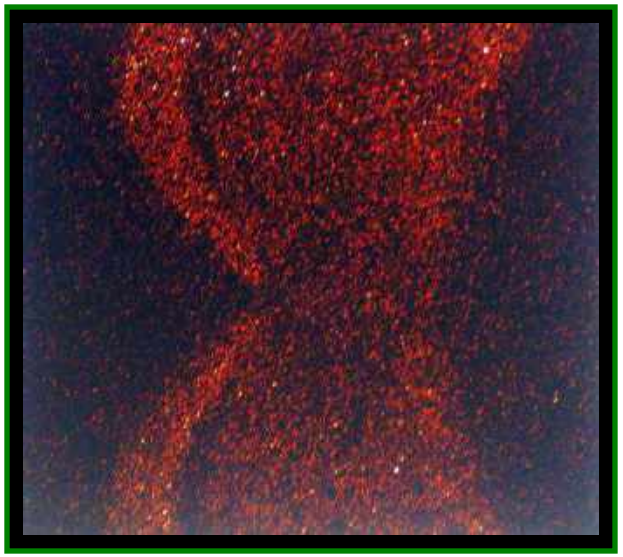
PET-CT Error

- Check raw (sinogram) data

Module Error

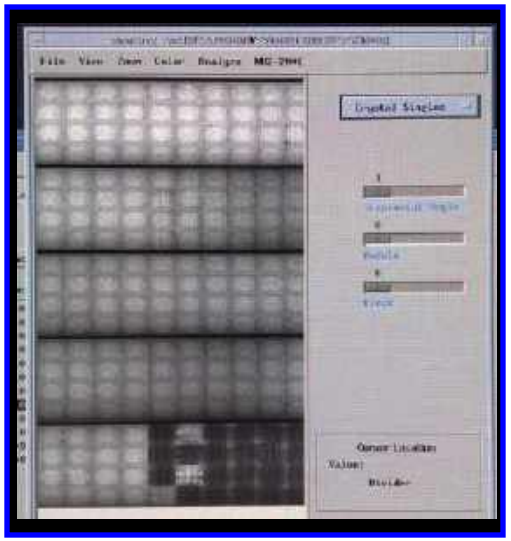


Normal



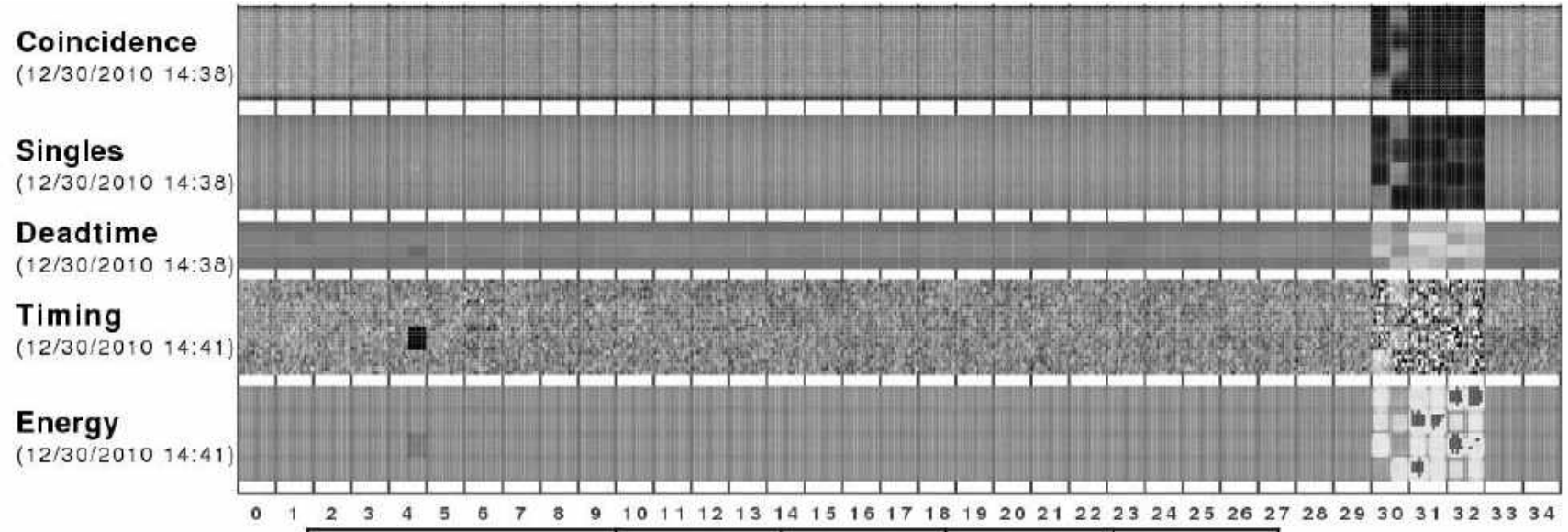
Crystal Singles

(**Fansums**)



PET-CT Error

- Repeat Daily QC

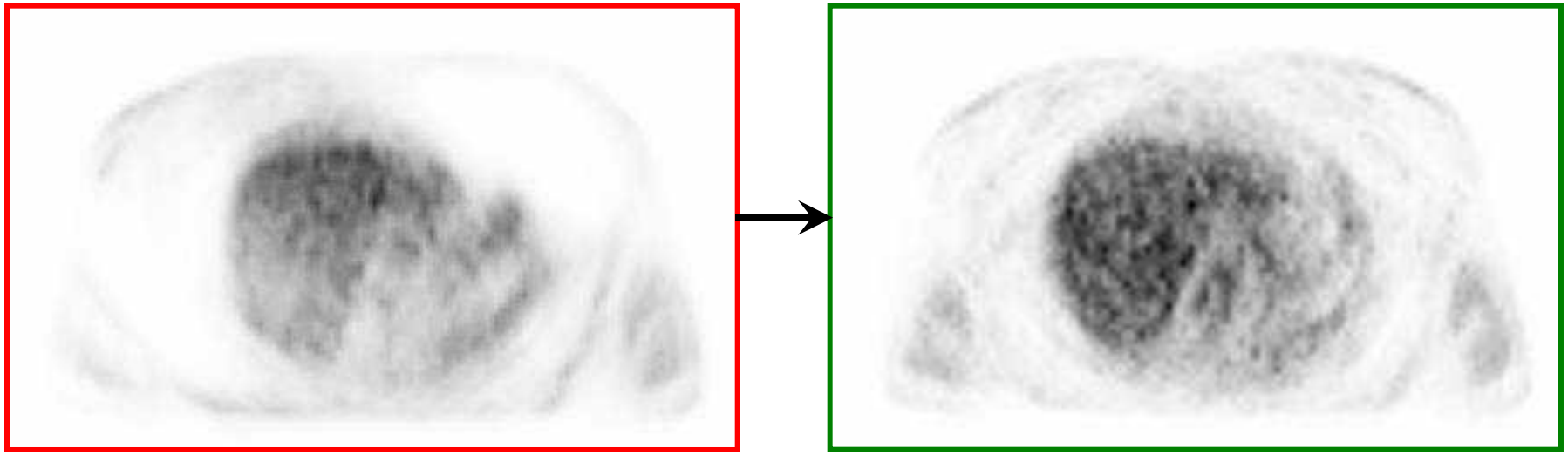


Item	Low Limit	High Limit	Previous Reading	R/Y/G
PET Coincidence Mean	246.20825	277.63907	219.47334	Red
PET Coincidence Variance	56.968906	64.24153	77.91989	Red
PET Singles Mean	4309.8394	4860.0312	4179.152	Yellow
PET Singles Variance	511.25095	576.51697	1084.9098	Red
PET Deadtime Mean	2.0E-5	0.033409998	0.00347	Green
PET Timing Mean	-0.06311	0.05589	-0.02028	Green
PET Energy Shift	-8.0	8.0	3.0455842	Green

Source Pin Count Rate Mean	Source Pin Count Rate Variance	Minimum Rate	Source Pin Life	Source Pin Status
5039.795	420.2123	4500.0	114 Days	Green

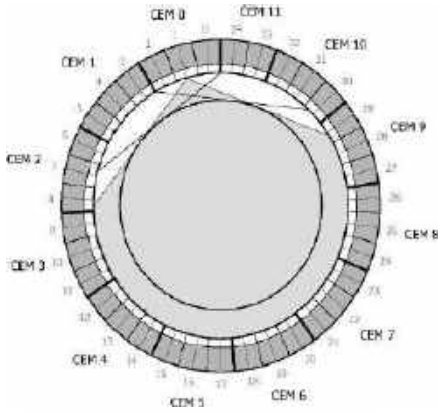
PET-CT Error

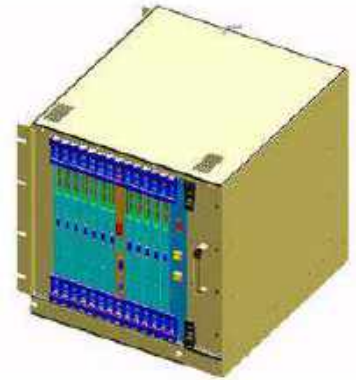
- → Re-scan (if transient error)
  (or scan on another system if possible!)



PET-CT Error

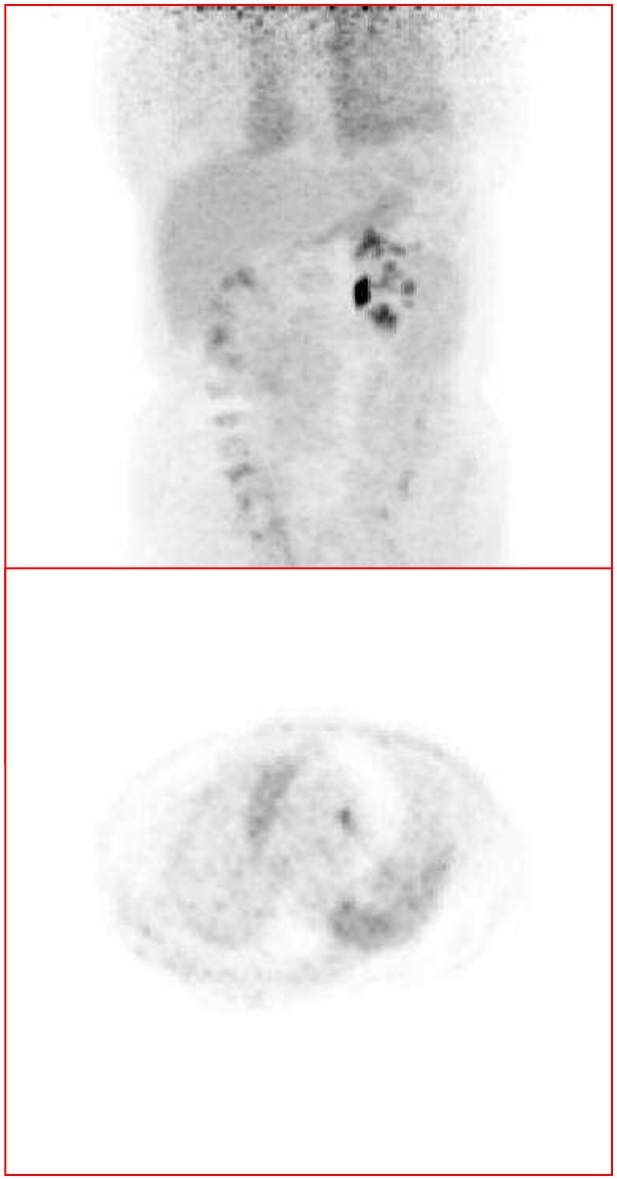
- → System down
- → Replace CEM board (& module)



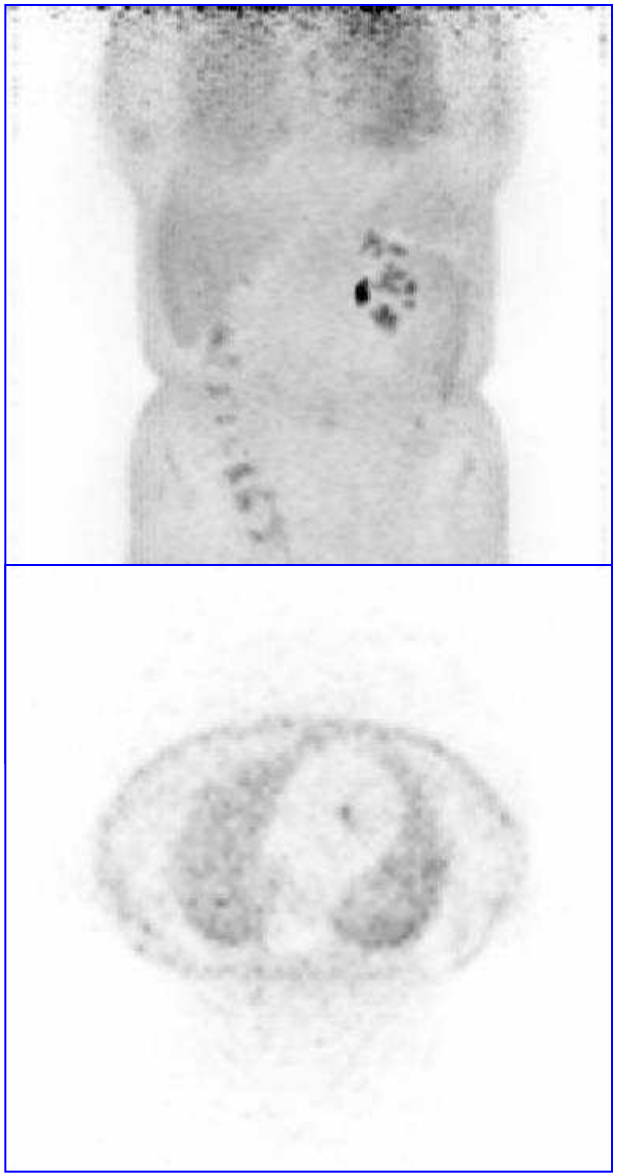


PET-CT Error → ???

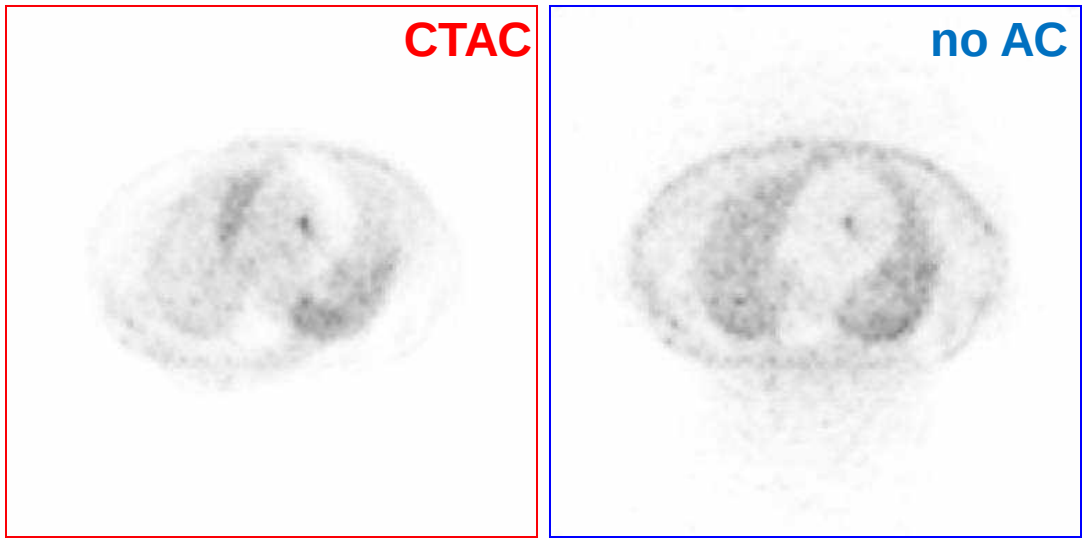
- MIP+Trans (CTAC)



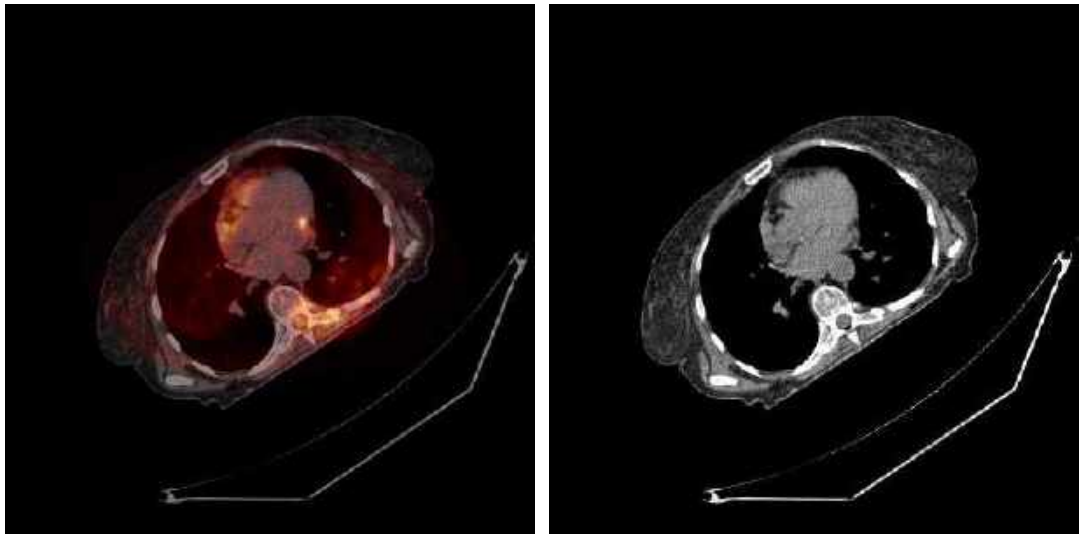
- MIP+Trans (no AC)



PET-CT Error → CT Encoder



- Compare to CT



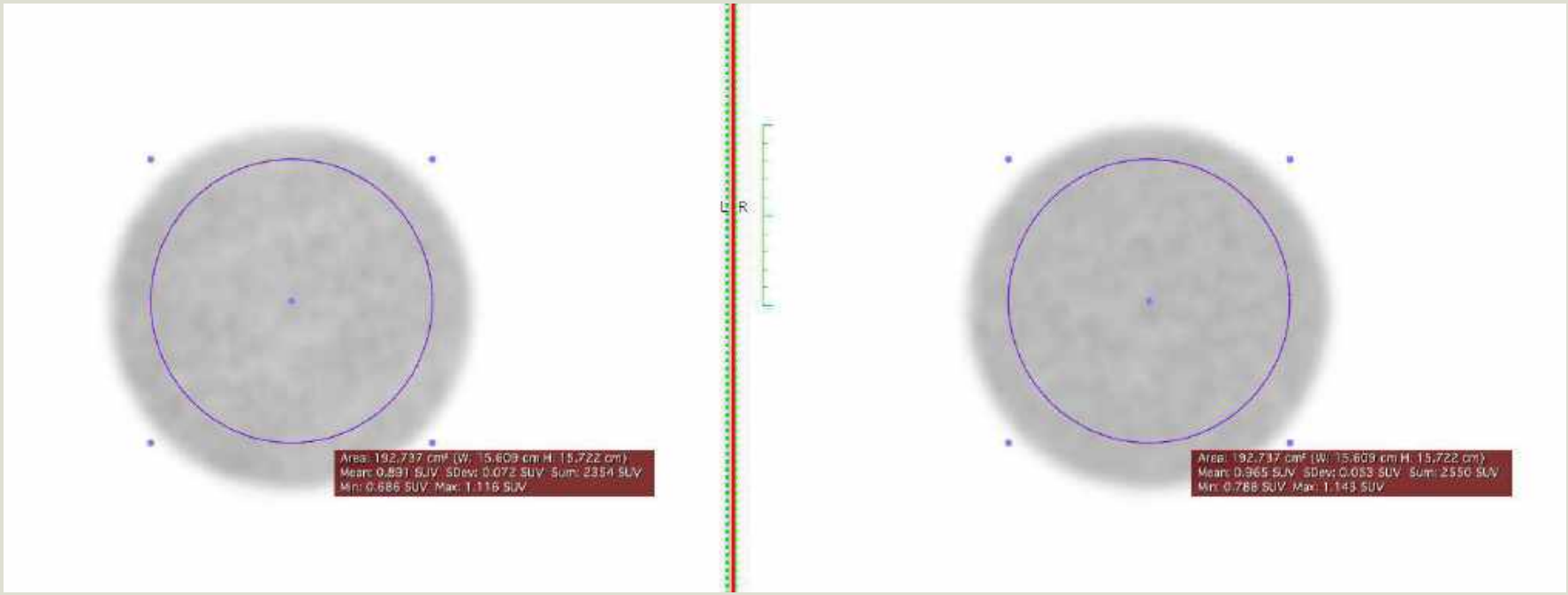
- **Scanner Broke → Mend & Re-scan Patient**

ToF Error

Lucy Pike,
King's, London

Issue identified on daily ^{68}Ge cylinder scan on DST04 (24/11/2014)

- GE daily QC passed
- SUV measured 0.90 (usually 1.02 every day)



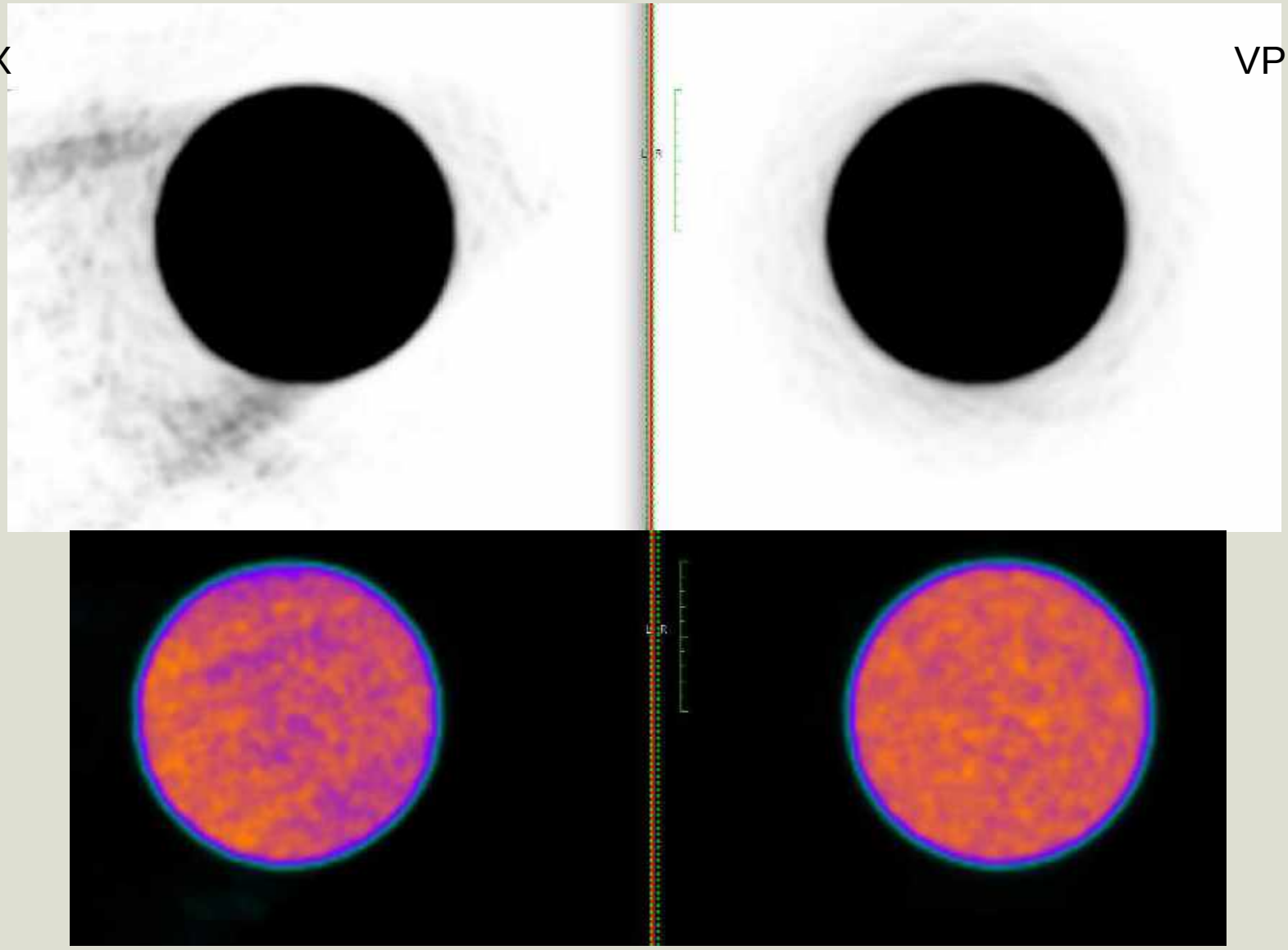
VPFX

VPHD

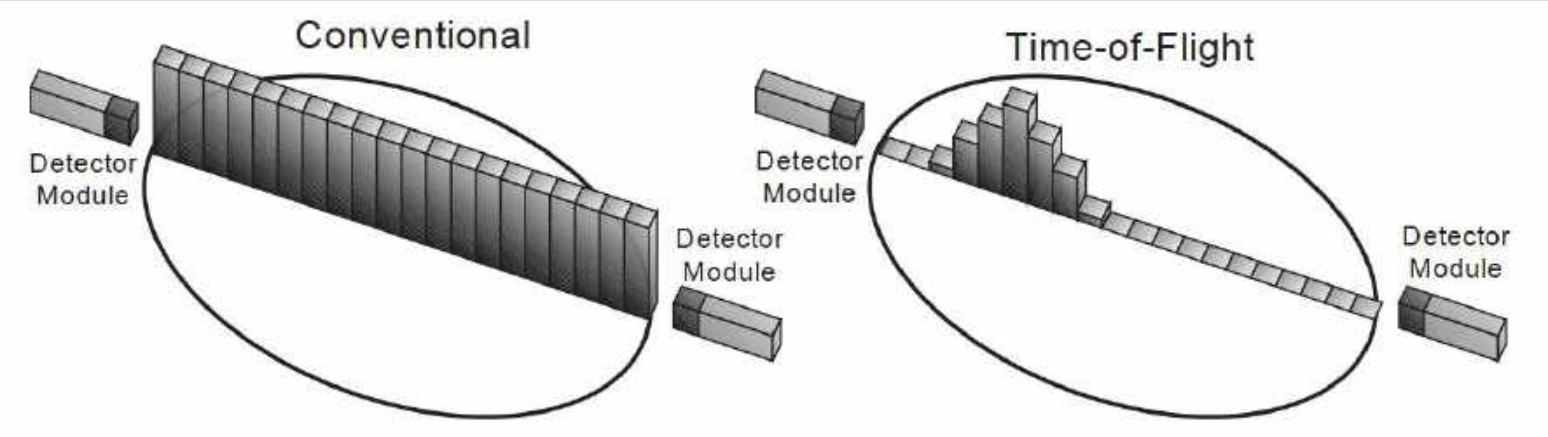
Phantom Visual Assessment

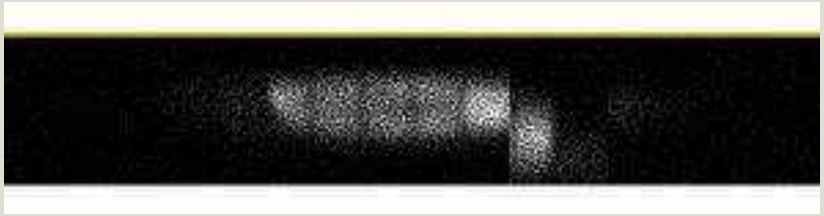
VPFX

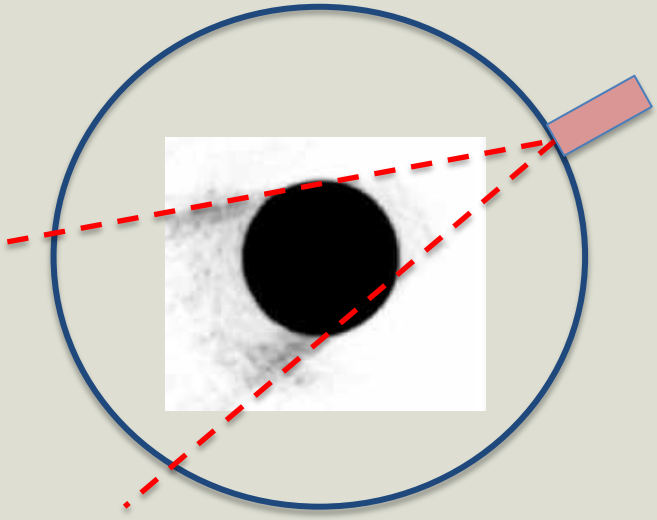
VPHD



Phantom Visual Assessment



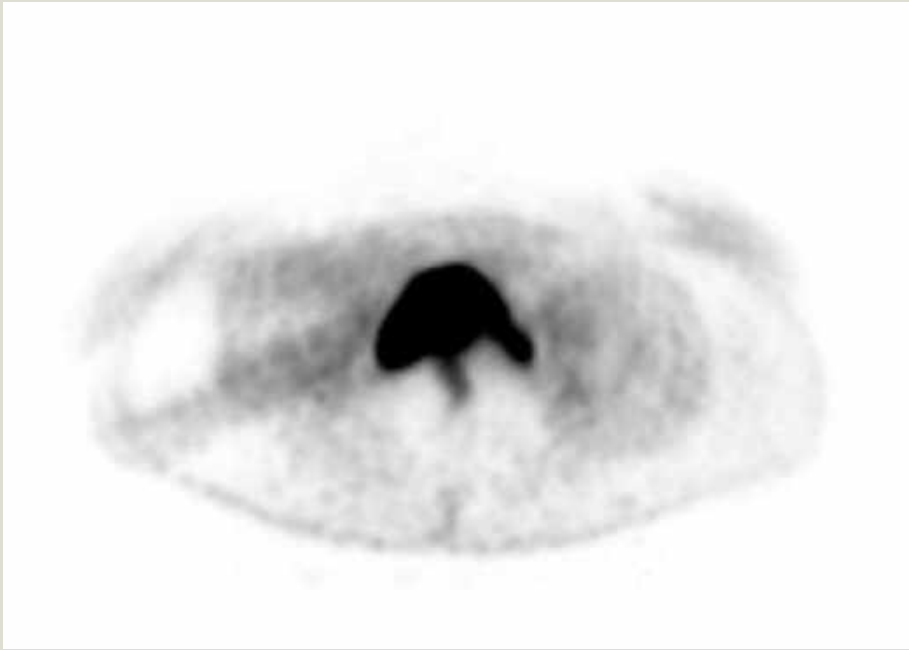


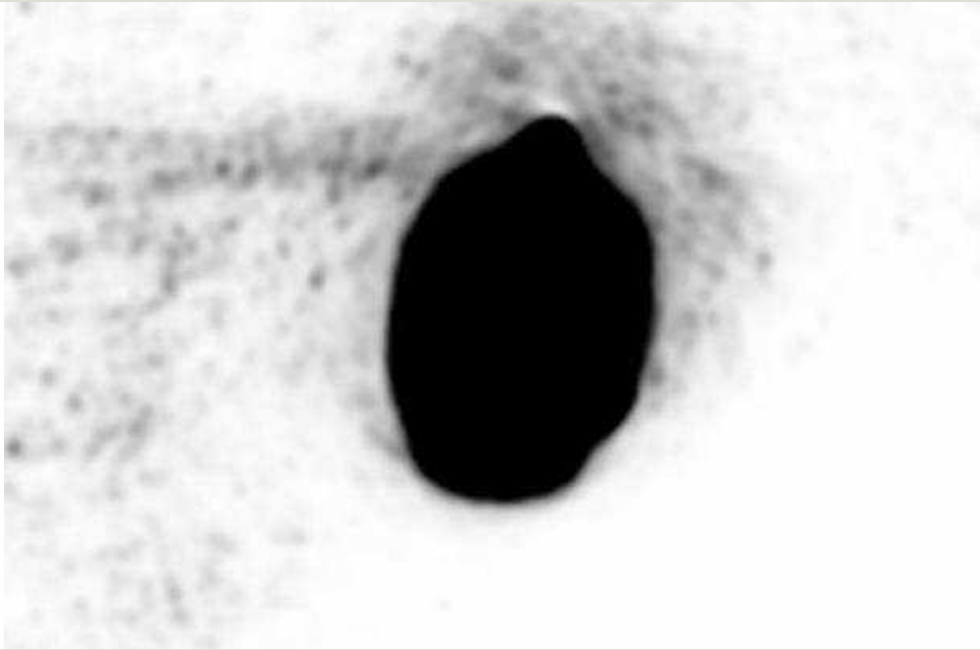


Clinical Visual Assessment

Review of clinical scans between 24/11/2014 and 21/01/2015

- 39 days / 9 weeks
- 373 scans
- Artefacts detected in TOF data for 10 scans (2.7%)
- 3 scans reviewed by clinician – no clinically relevant change
- 10 scans reviewed by physicist:

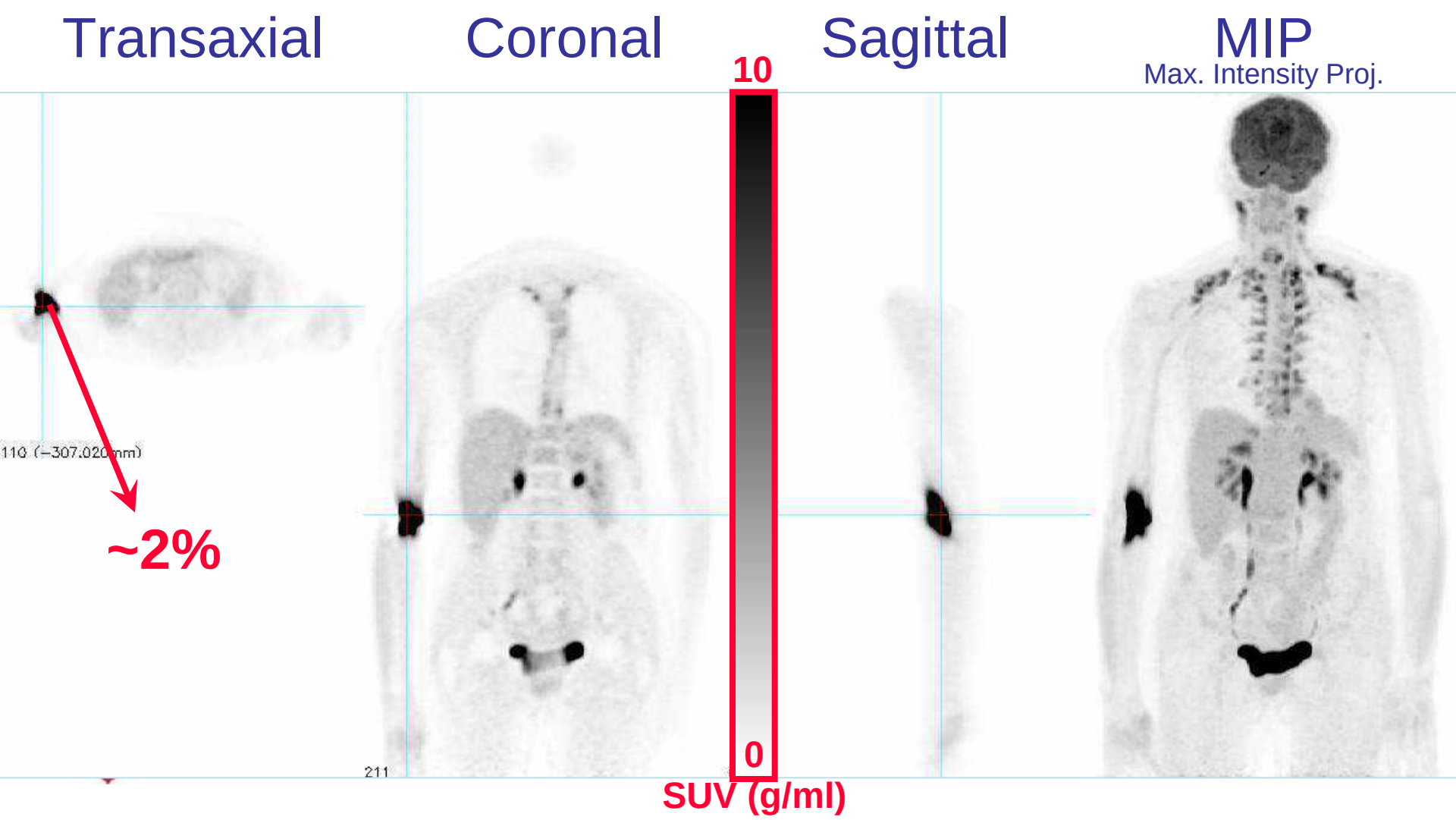




Lessons – 2

- Again, look at the **uncorrected PET** and **CT**
  →Cut the problem in half!
- **And non-ToF**
- Decisions to make:
  - Has the fault resolved?
    QC inc. ^{68}Ge cylinder is VERY useful
  - Is the scanner down?
  - Have I more patients injected…
  - Has the problem affected other scans?

FDG-PET → **Injection Site** & Brown Fat



Standardised Uptake Value

$$SUV\,(g/ml) = \frac{Uptake\,(kBq/ml)}{Inj.Act.(MBq) \,/\, Weight\,(kg)}$$

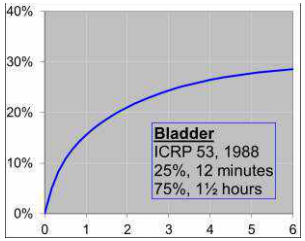
Decay Corrected

- Clocks:
  - GMT & BST (or even European time on mobile)
  - kBq/ml is decay corrected
- Patient demographics:
  - Errors
  - e.g. Swap 70 kg & 173 m (SUV→$x^{173}/_{70}$=2.5)
- Liver is, generally, a good reference tissue,
  - SUV_{liver}~2-3 g/ml

FDG-PET

- **Liver SUV ~2-3 g/ml?**

- **Should see 100% of the injected activity!**
- Minus:
  - Brain ~10%
  - Legs ~10%
  - Urine ~15%



- **½ Body Uptake ~60-70%?**

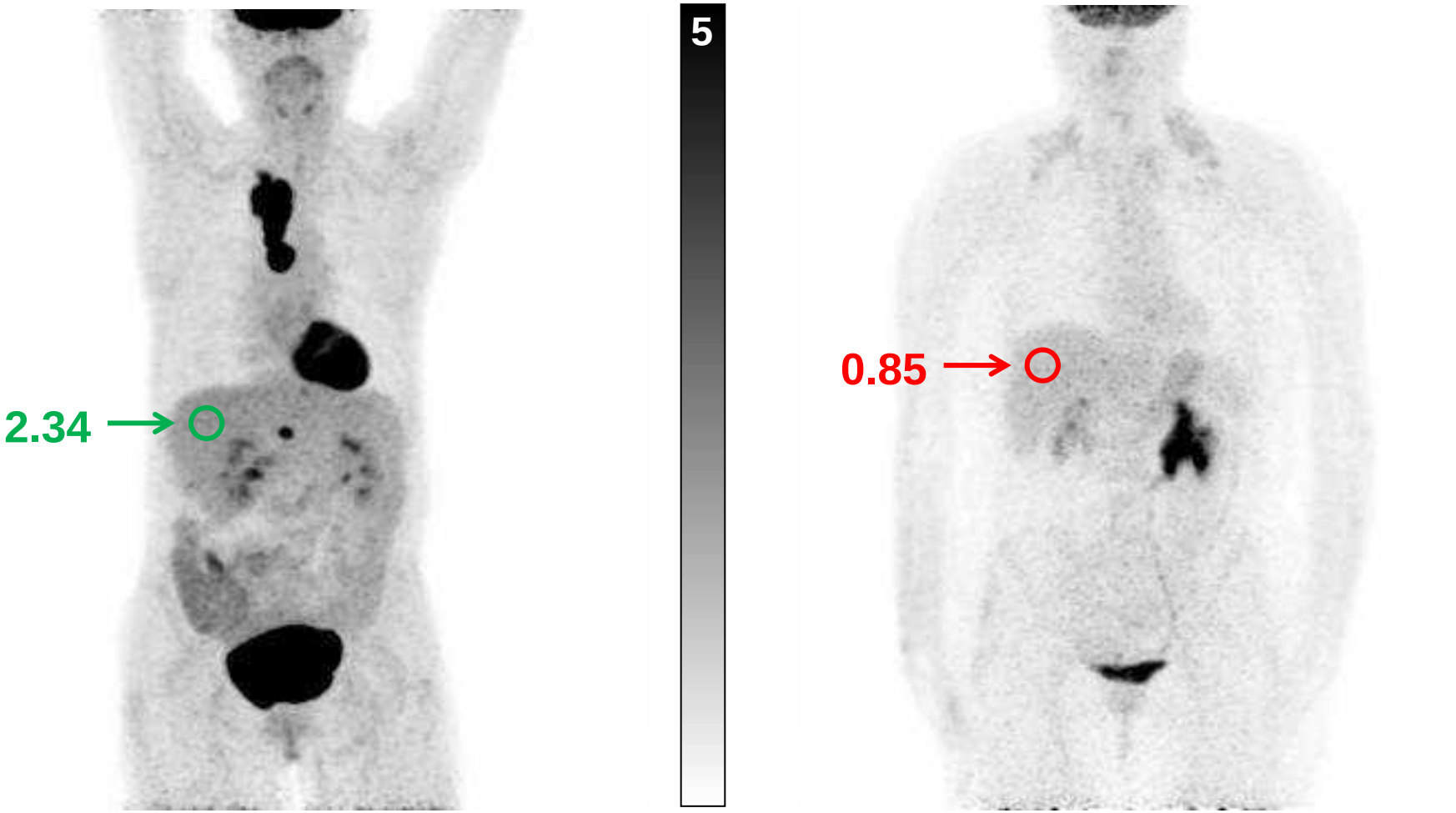
→ Are these useful for clinical data QC?

Julyan et al. NMC 2018 28(4) 337 (abs.)

Application – SUV

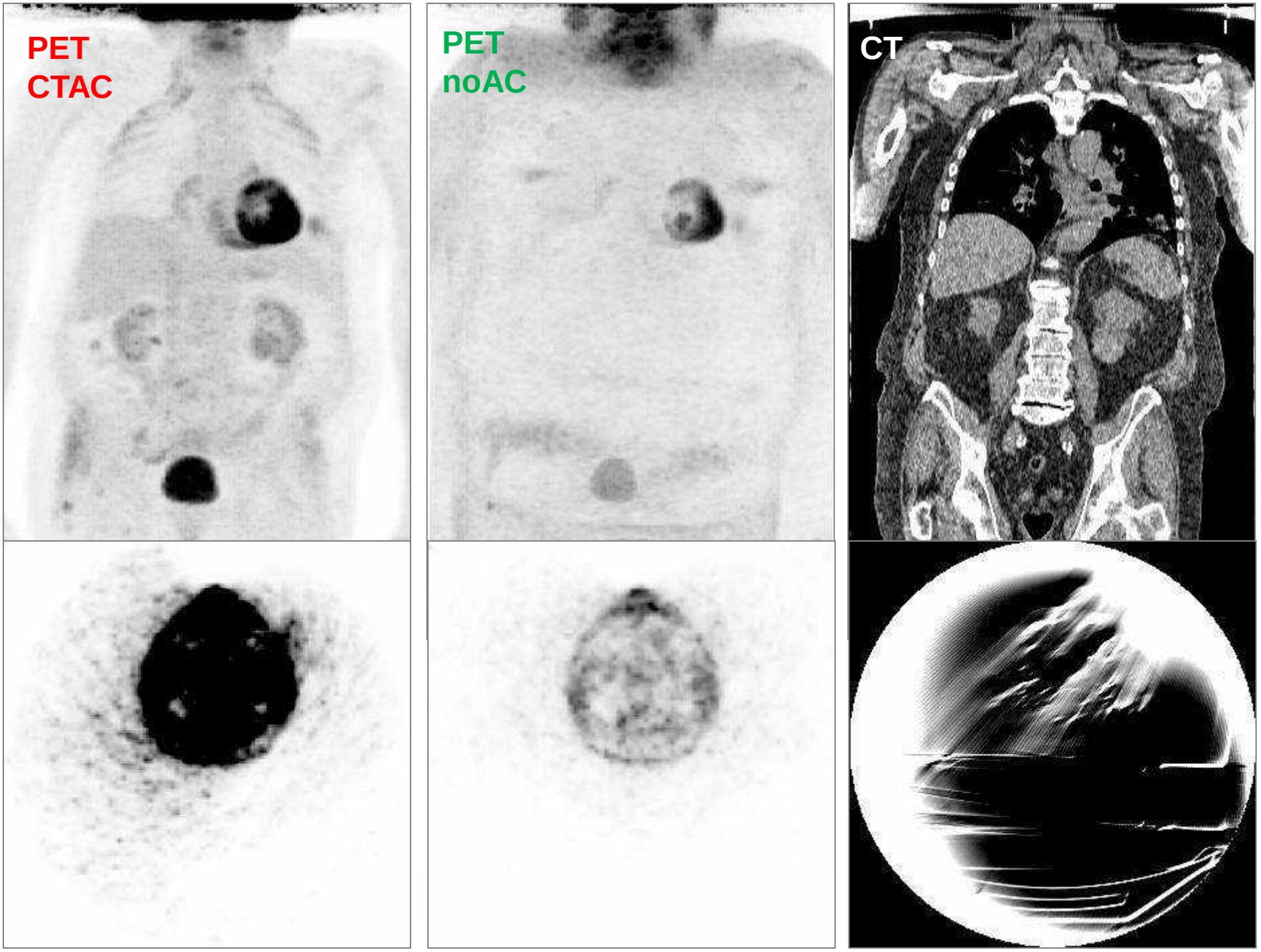
Incomplete injection

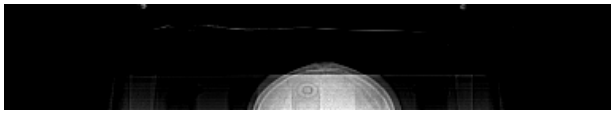
- Normal (2.24±0.39)
- ? Problem



Lessons – 3

- Patient preparation is critical
  – comfort/warmth, fasting, etc.
- Understand SUV – you're not in the dark
- Check for *"silly"* errors (height/weight, time)


PET
CTAC
PET
noAC
CT

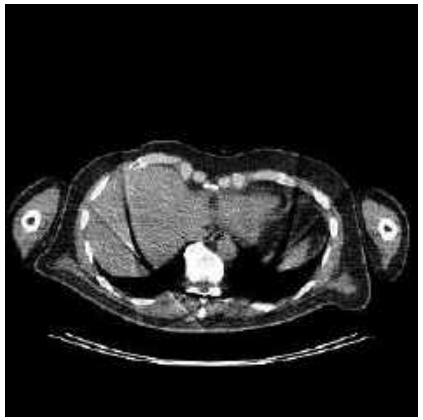


- CT problems that day:
  - CT QC
    - (Passed)
    - ? Dirt on Mylar window
  - Having to re-start scouts
  - Noisy!

→ New CT Tube

Included in service contract!

CT Artefact



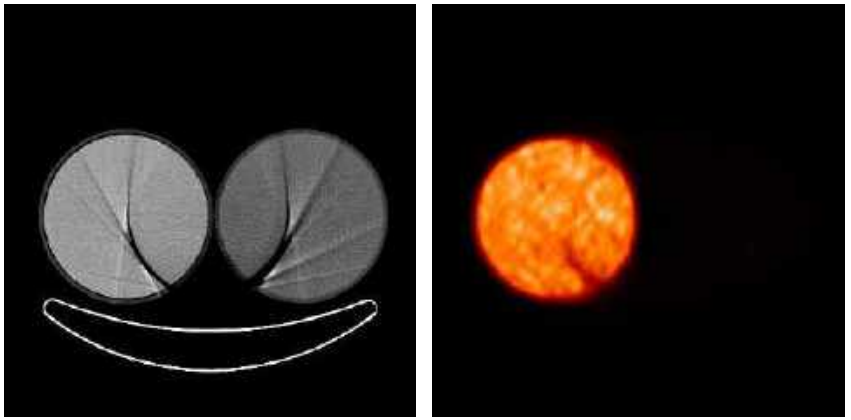
(Not FDG - *removed*)

CT Artefact – Investigation

- ^{68}Ge cylinder?

→ Subtle

- ^{68}Ge cyl. + water cyl.



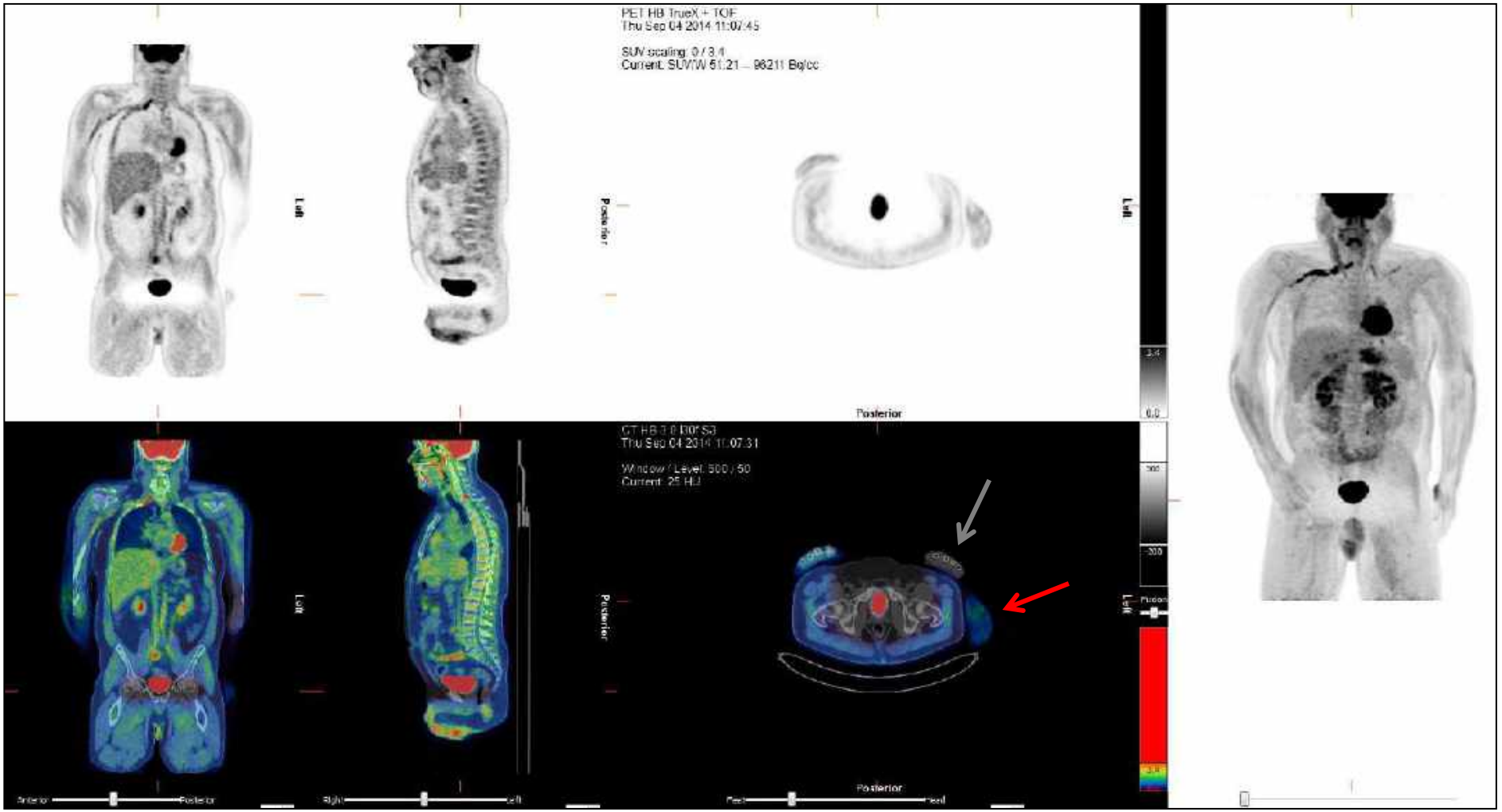
→ Easier to see

- Headrest in FoV during CT air calibration!
- Yes, there was a warning message!!!

Lessons – 4

- Worry about the CT too…
- Use whatever it to hand to investigate
- Be warned by warning signs and messages!

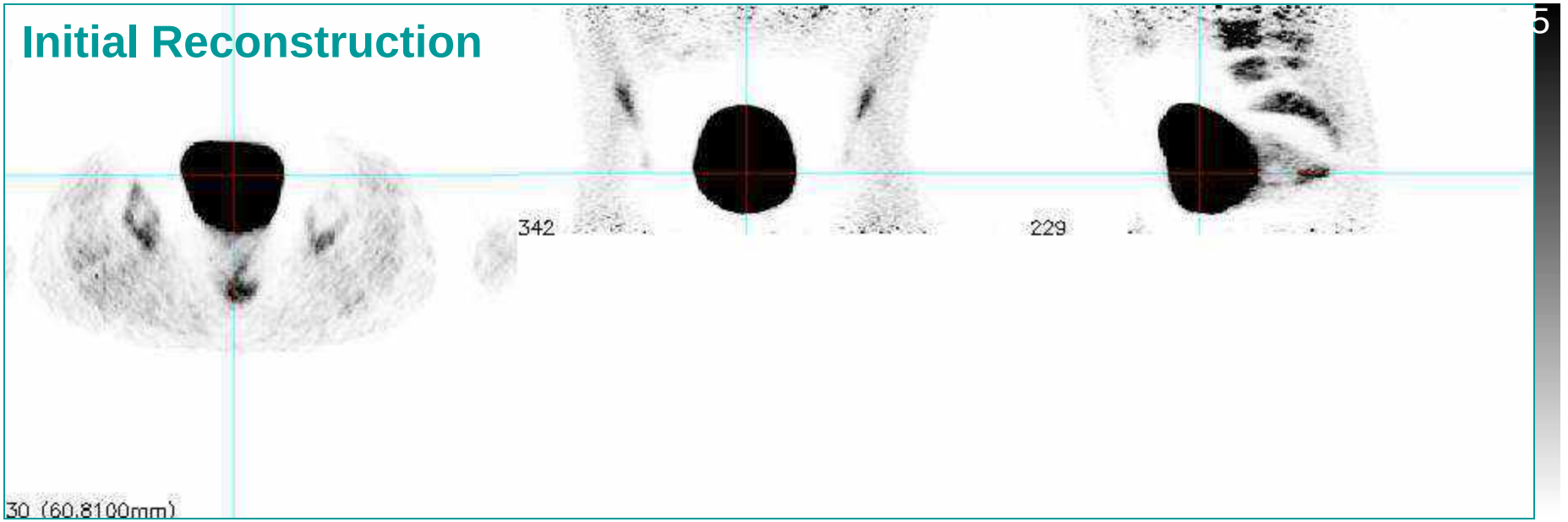
FDG – Hot Bladder

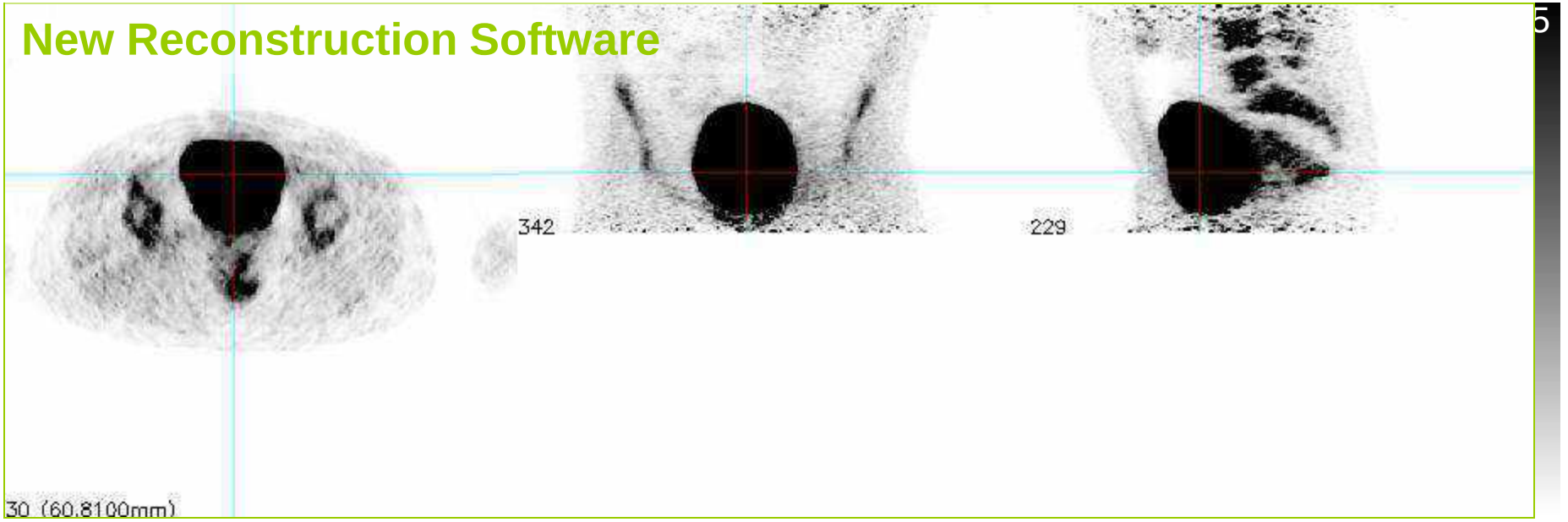


? Scatter correction

Maria Burniston
Royal Free, London

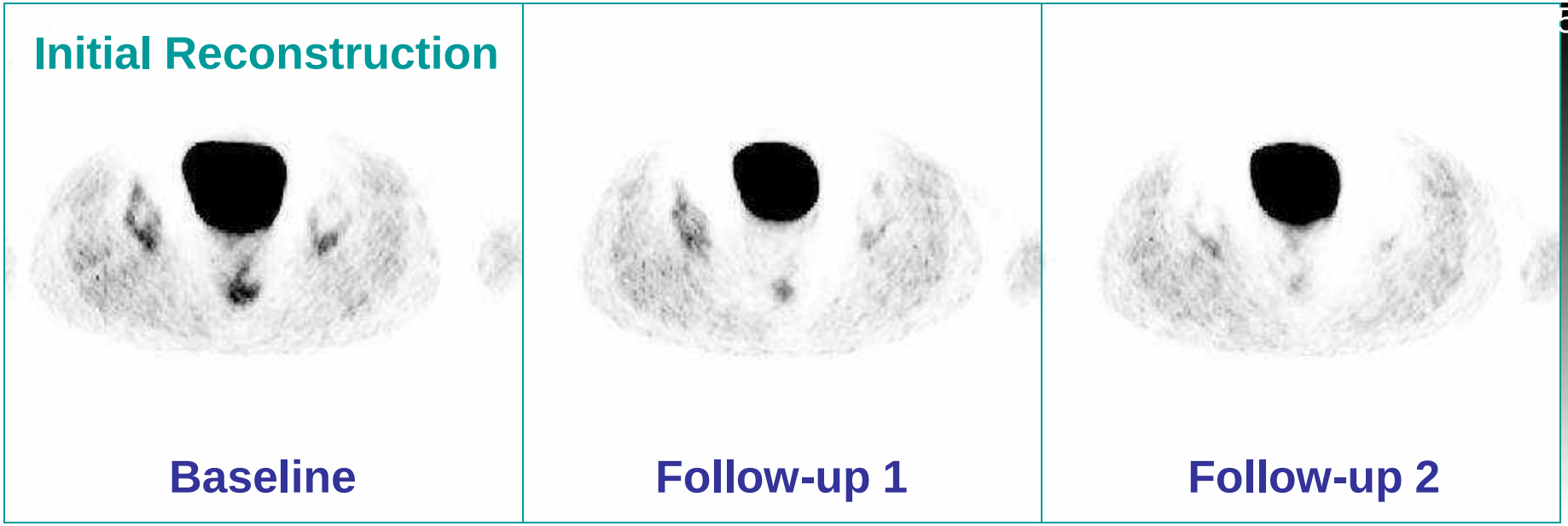
PET-CT Artefact → Hot Bladder & Scatter Corr.





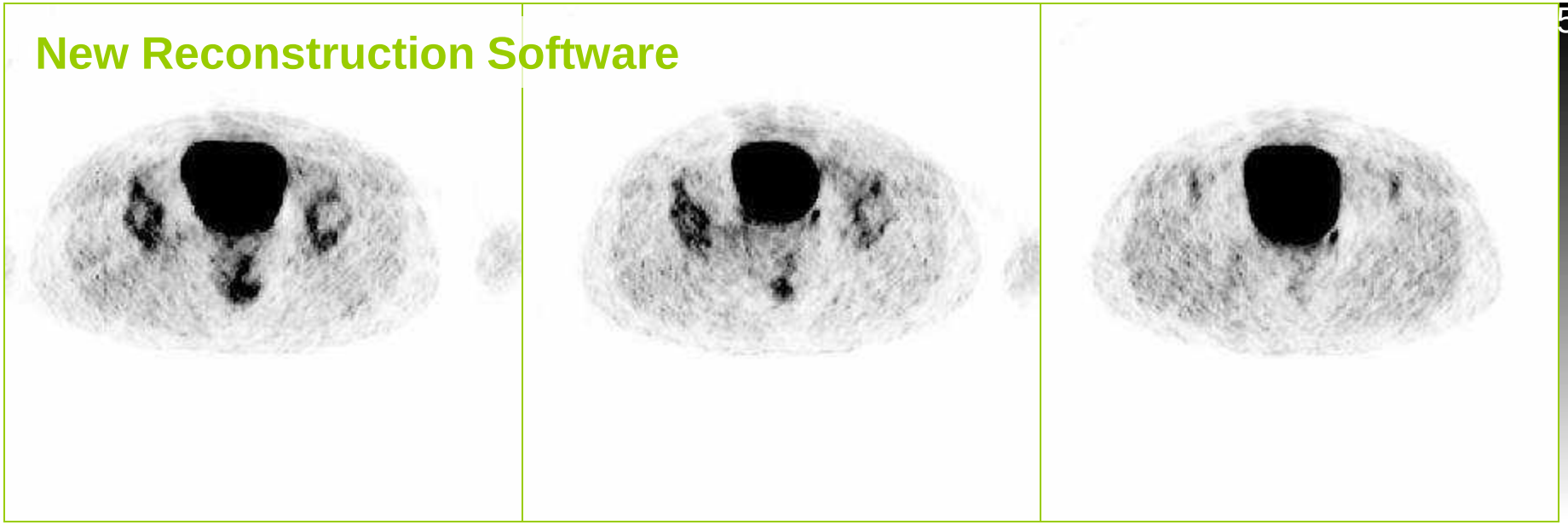
PET-CT Artefact → Reconstructions

Initial Reconstruction



Baseline | **Follow-up 1** | **Follow-up 2**

New Reconstruction Software



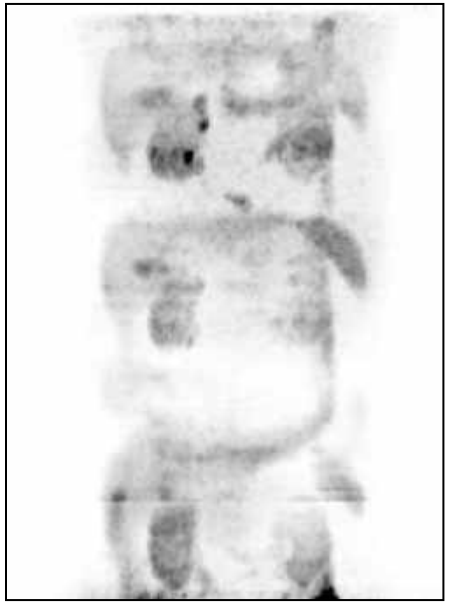
“Novel” Acquisition – CBM + LM

(Continuous Bed Motion & List-Mode, ^{18}F-PSMA)

- Static Scanner

SUV=20

Suspend and pull out bed…



- Repeat Static

- *Gating Offline, etc,… WIP…*

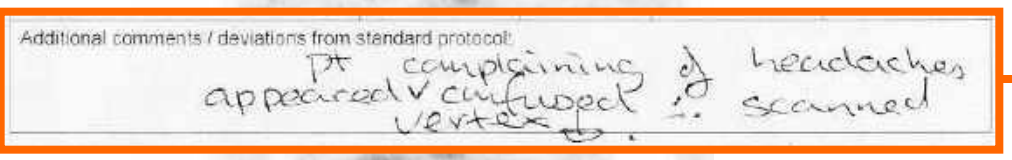
Lessons – 5

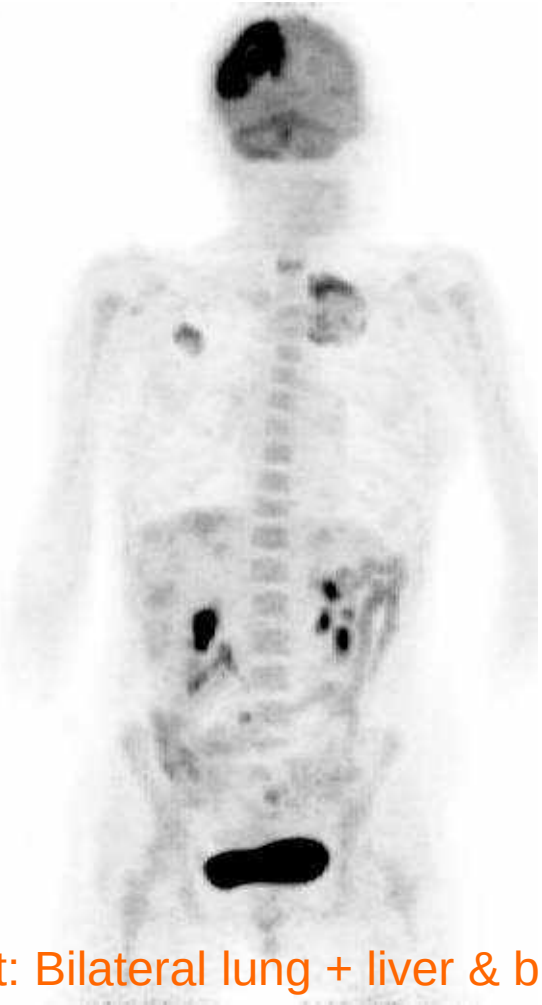
- The software ain’t perfect
- Check the system carefully after service visits
- Be careful with “up”grades
- Be careful with new things

The Good…

Lung

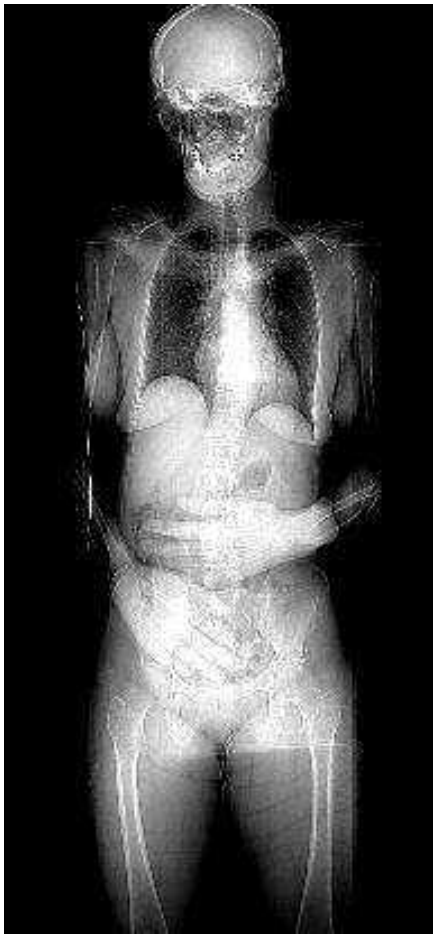
- Base-of-brain – Thigh (correct standard protocol)
- Vertex – Thigh

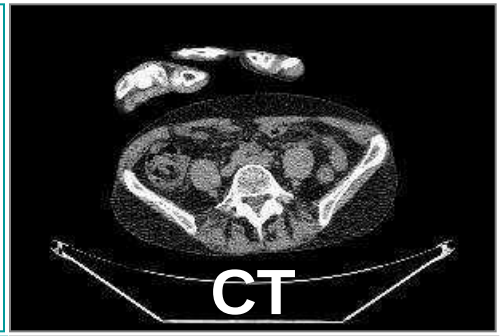


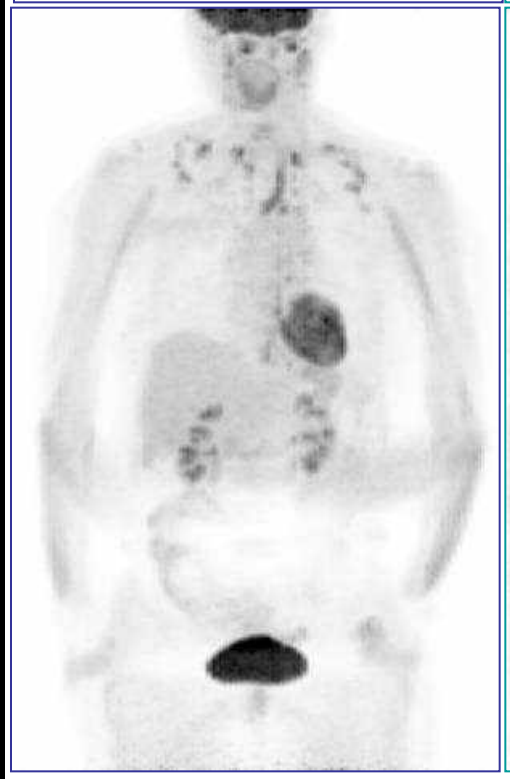


Report: Bilateral lung + liver & brain mets.

The Bad…





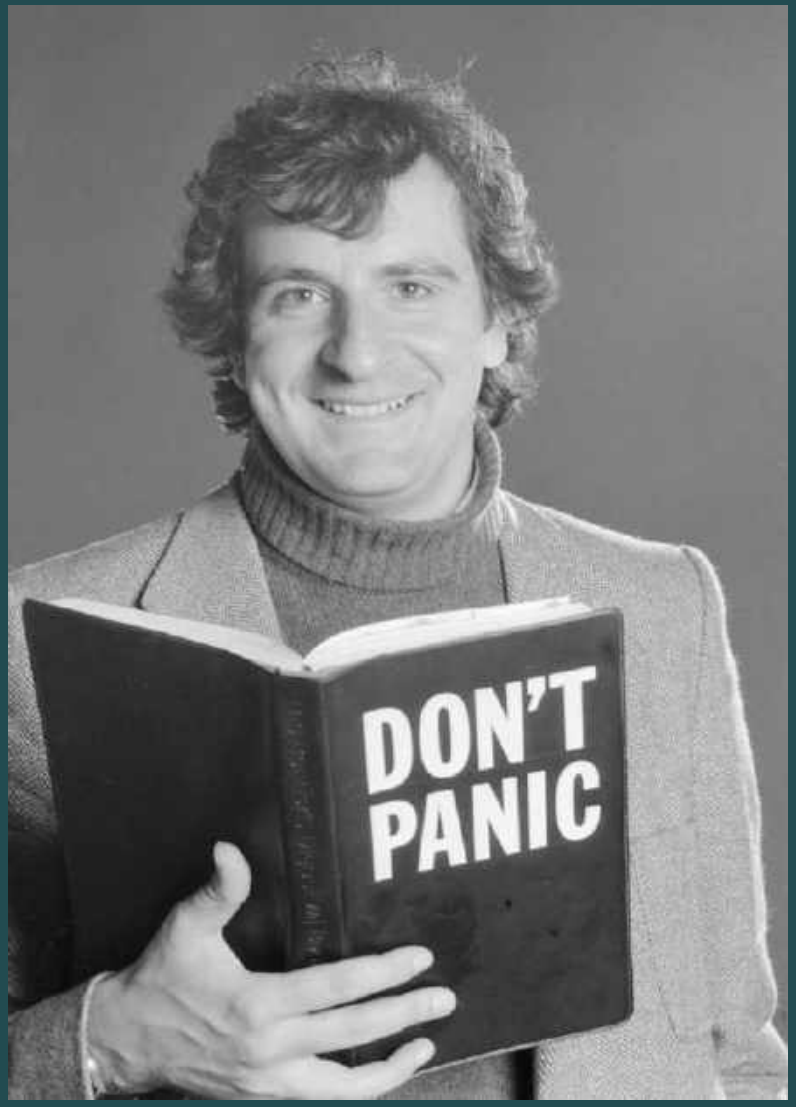


- **“Common” attn. corr. artefact: Mis-match between PET and CT**
- **BUT: Poor patient set-up, no re-scan, not communicated to reporter!**

Artefacts – Logical Approach

- Where's the problem?
  - Scanner, patient, operator…
  - "Cut the problem in half" (PET or CT)
- Check details for SUV are reasonable
  - Is liver SUV reasonable (~2-3 g/ml)
- Make sensible, rational, calm, evidence based decisions on what to do
  - ? Scanner down (what's the problem?)
  - ? Inject more patients
  - ? Re-scan, re-book patient(s)

And Finally…



"Technology is the name we give to stuff that doesn't work properly yet"

Douglas Adams

PET in the context of multi-centre trials

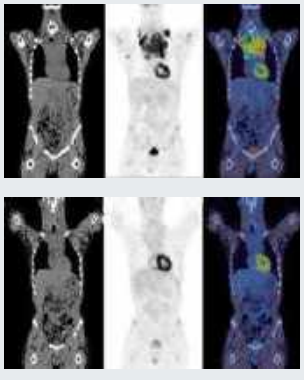
Lucy Pike
King's College London & Guy's and St Thomas' PET Centre
School of Biomedical Engineering & Imaging Sciences
King's College London

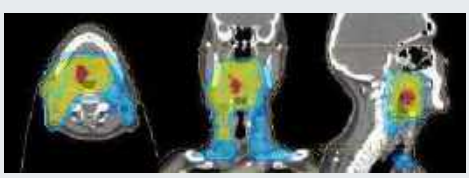
KING'S HEALTH PARTNERS

1

Use of PET in Oncology Multi-centre Trials

- **Initial diagnosis and staging**
  - Single PET/CT timepoint
  - Determine eligibility for a trial/treatment
- **Prognosis**
  - Single PET/CT timepoint
  - Does PET predict patient outcomes?
- **Therapy monitoring**
  - Multiple PET/CT scan timepoints
  - Evaluate response to treatment
- **Radiotherapy planning**
  - Single PET/CT timepoint
  - Delineation of biological tumour volumes

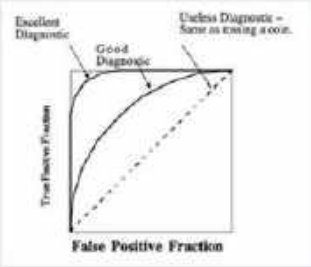




2

PET Metrics used in Oncology Multi-centre Trials

- **Visual Assessment**
  - Lesion detectability
    - primary tumour location, involved nodes, metastases
  - Comparison to normal tissue uptake
  - Subjective - observer dependent
  - Histology (benign or malignant)
  - Sensitivity & specificity - false negatives/positives



- **Semi-quantitative parameters**
  - Less user dependent
  - Tumour characterisation
  - Allows comparison between patients & sites –
    - PET parameters standardized so measured changes on PET are greater than statistical fluctuations
    - Need to understand bias and variation

before chemotherapy
SUV = 17.2

chemotherapy day 7
SUV = 3.9

3

PET Metrics used in Oncology Multi-centre Trials

- **First Order**
  - Simple – derived directly from PET images
  - Limited to small part of tumour
  - SUVmax, SUVpeak

- **Second Order**
  - Require segmentation
  - Whole tumour or wholebody tumour measurement
  - SUVmean
  - Measurements of tumour burden e.g.
    - Metabolic tumour volume (MTV)
    - Tumour lesion glycolysis (TLG)

- **Higher Order**
  - Require segmentation and image processing
  - Some textural analysis parameters

T. Carlier, (2015), Frontiers in Medicine, 2(March), pp. 1–12.

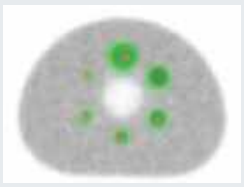
4

Factors Affecting SUV Quantification

- **Technical Factors**
  - Scanner calibration
  - Accurate activity measurement
  - Accurate timing
- **Biological Factors**
  - Blood glucose level (FDG)
  - Uptake period
  - Patient discomfort
  - inflammation
  - Motion/breathing
- **Physical Factors**
  - Scan acquisition parameters
  - Reconstruction parameters
  - ROI definition
  - Normalisation factor for SUV
  - Contrast agents







5

Factors Affecting SUV Quantification

- **Technical Factors**
  - Scanner calibration
  - Accurate activity measurement
  - Accurate timing
- **Biological Factors**
  - Blood glucose level (FDG)
  - Uptake period
  - Patient discomfort
  - inflammation
  - Motion/breathing
- **Physical Factors**
  - Scan acquisition parameters
  - Reconstruction parameters
  - ROI definition
  - Normalisation factor for SUV
  - Contrast agents

Quality Assurance system
- Standard operating procedures,
- Regular QC tests with tolerances (for all equipment)
- Processes for monitoring & corrective action

Clinical Trials Procedures
- Imaging manual
- Use of published evidence/guidance
- Define critical parameters to study outcomes

Image Quality / Quantification
- Harmonisation using phantoms
- Central analysis
- Generation of test datasets & standardized analysis procedures

6

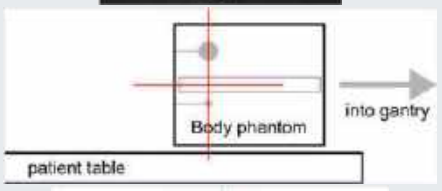
Harmonisation Methodology

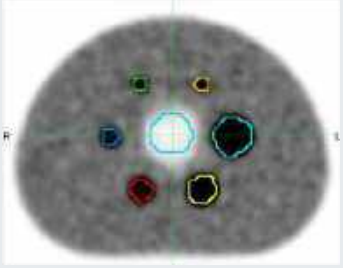
- **Developing specifications:**
  - Design phantom procedure
    - Choose suitable phantom for the task (brain, body, heart)
    - Define measures (lesion detection, quantitative measures)
    - Isotope dependent
  - Acquire phantom scans across sites (ideally single person visit sites)
  - Save list mode data
  - Start with clinical parameters – adjust scan time/speed, matrix size, iterations, post filter
  - GOAL: minimize variation and bias (lowest common denominator)
  - Exclude outliers if necessary (PET only, 2D PET)
  - Review of patient datasets by clinical experts

7

Harmonisation: Oncology

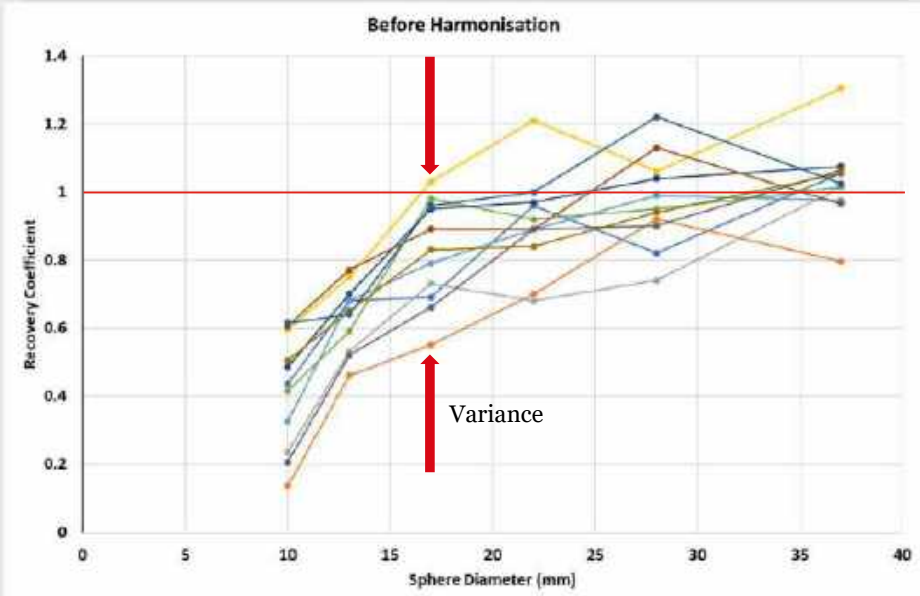
- **NEMA Image Quality Phantom**
  - Widely available (NEMA testing)
  - Thorax design with 'hot' objects
- **Procedure**
  - ^{18}F (^{68}Ga, ^{89}Zr)
  - Six 'hot' spheres
  - Spheres:background dependent on accreditation scheme (4:1 to 9.7:1)
  - Actual activity concentrations must be accurately known
- **Measurements**
  - 3D VOI based on 50% max voxel adapted for background
  - Recovery coefficients (measured:true activity concentration)
  - Noise - CoV (%) of background





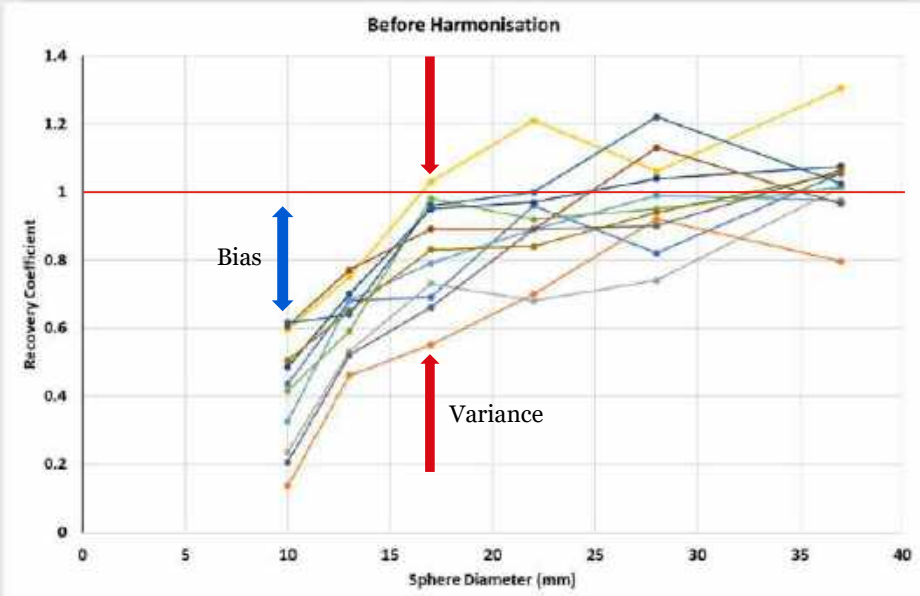
8

Harmonisation Methodology



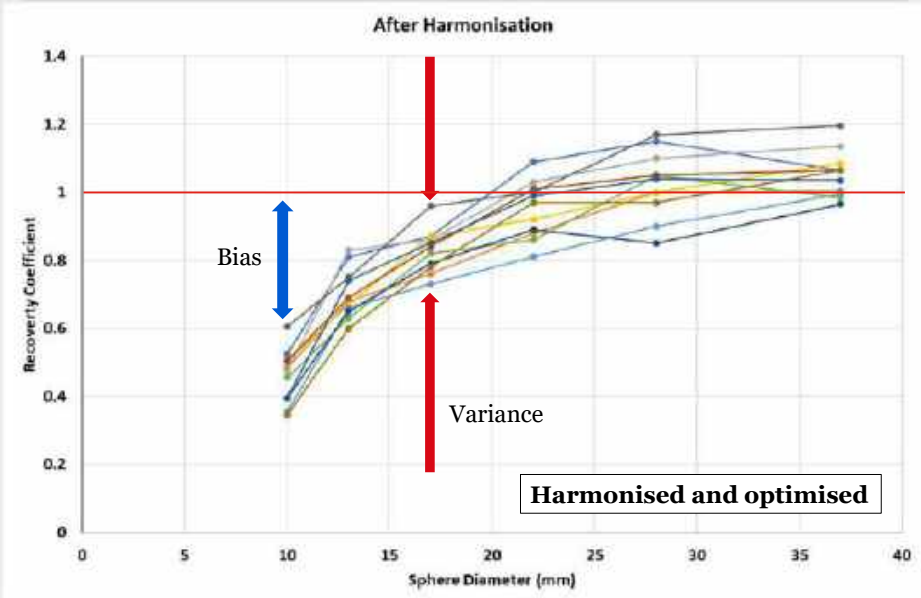
9

Harmonisation Methodology



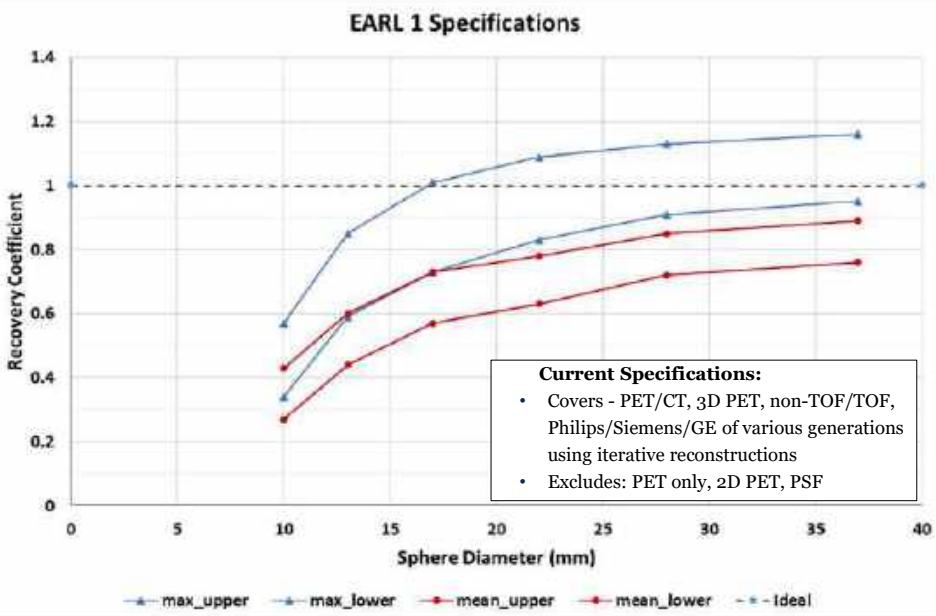
10

Harmonisation Methodology



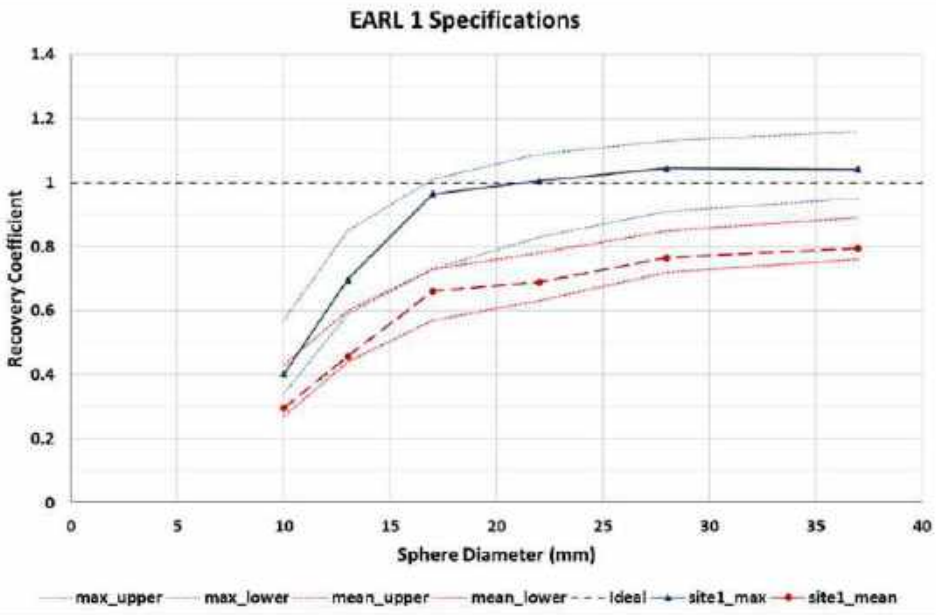
11

Specifications – EARL1



12

Specifications – EARL1



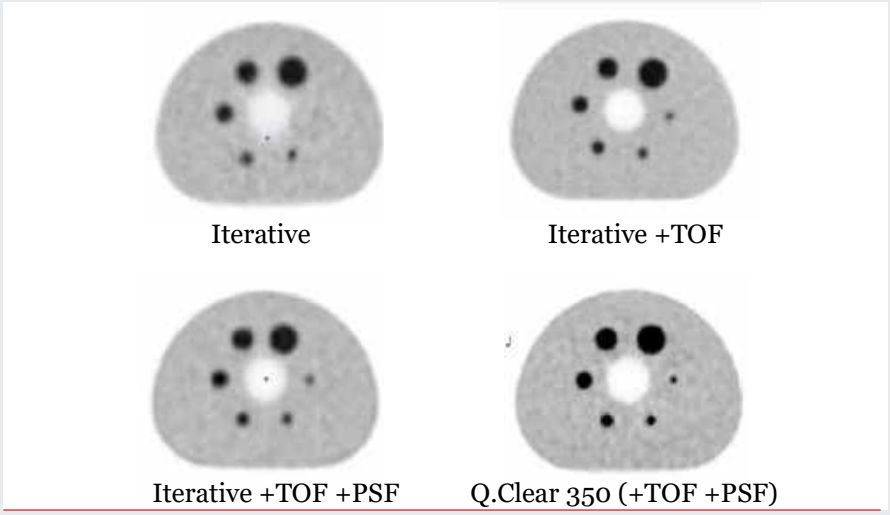
13

Harmonisation: Incorporation of 'new' Technology

- **Advanced Reconstructions**
  - Point spread function
  - Bayesian penalized likelihood
  - Smaller voxel sizes
- **SiPM detectors**
  - Improved time-of-flight
- **Larger Axial FOV**
  - Improved effective sensitivity
- **PET-MR**
  - Attenuation correction

14

Impact on Image Quality



Iterative

Iterative +TOF

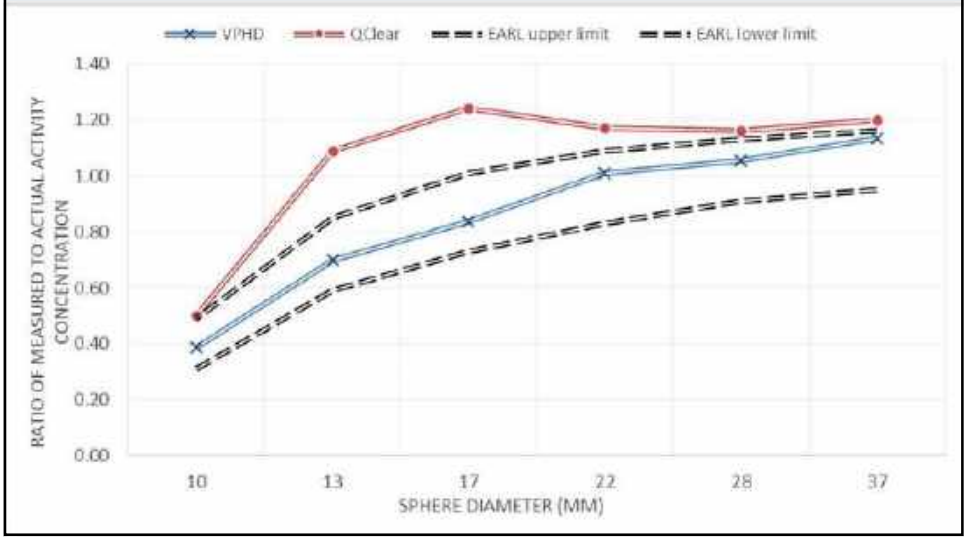
Iterative +TOF +PSF

Q.Clear 350 (+TOF +PSF)

15

Quantification – BPL

Recovery curves – max (single maximum voxel within each sphere)
QCLEAR = BPL + PSF + TOF
VPHD = OSEM



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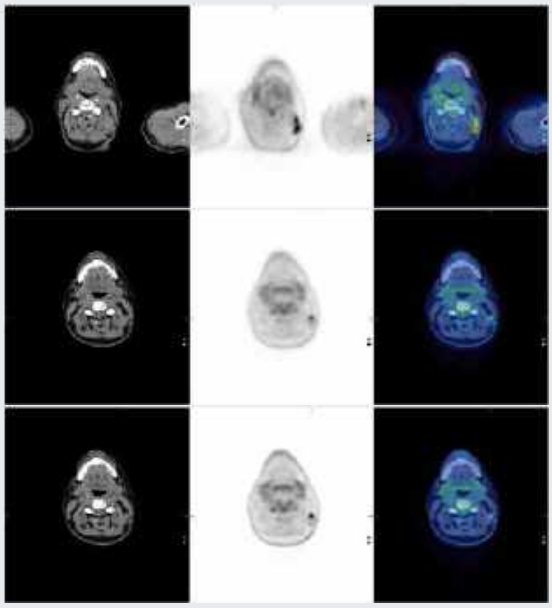
Harmonisation: Incorporation of 'new' Technology



Baseline

OSEM
Lesion SUV_{max} 3.0
Liver SUV_{max} 3.4
DS 3 responder

Q.CLEAR
Lesion SUV_{max} 6.8
Liver SUV_{max} 3.0
DS 4 non-responder

17

Scanners in the NCRI PET Research Network

Clinical protocols (fixed and mobile PET-CT)

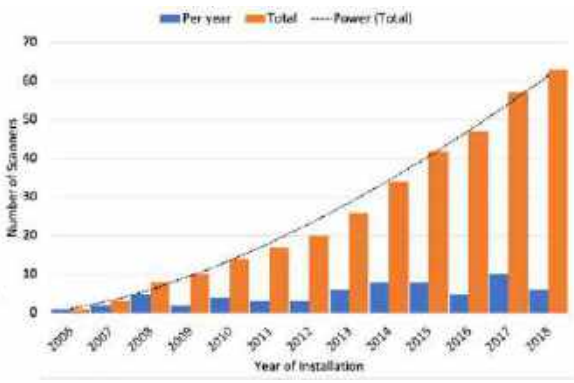
Siemens (n=25)

- 7 Siemens Biograph
- 1 Siemens Biograph Horizon
- 9 Siemens Biograph mCT
- 7 Siemens Biograph mCT Flow
- 1 Siemens Biograph Vision

GE (n=38)

- 2 GE Discovery VCT
- 7 GE Discovery 690
- 19 GE Discovery 710
- 9 GE Discovery MI DR
- 1 GE Discovery MI

Mobile / Fixed	10 / 53
TOF used routinely	54 (86%)
PSF used routinely	33 (52%)



King's College London & Guy's and St Thomas' PET Centre

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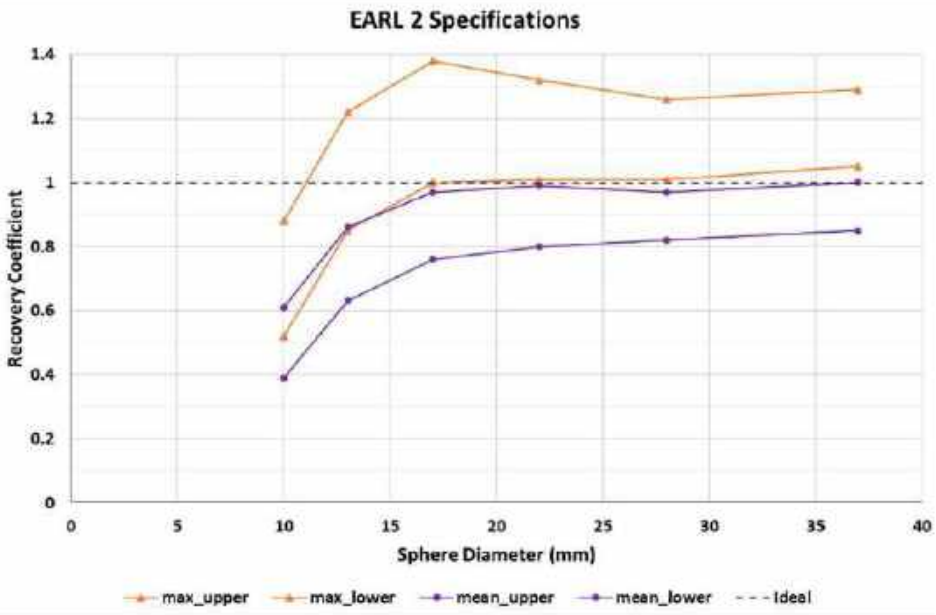
Specifications – EARL2



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Harmonisation – The Future

- **Move to new specifications**
  - Harmonized PET/CT system performance for multi-centre trials
  - Benefit from state-of-the-art PET/CT technology
  - Reflect clinical practice
  - Apply new quantitative metrics
- **Issues**
  - Images conforming to different specifications cannot be pooled due to differences in quantification
  - Visual interpretation of PET images may differ
  - Existing clinical trials – must still use 'old' specifications
  - New clinical trials - may exclude some centres which has implications for recruitment
  - Retrospective studies using large datasets from completed studies will still be based on 'old' specifications

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Retrospective Harmonisation Strategies

- **Adjustment of PSF data using filtering**
  - Post filter applied to image data
  - Requires accurate knowledge of PVE & calibration for each scanner
  - Can create greater errors if applied incorrectly
  - 1 vendor currently offers this as a commercial package

21

Retrospective Harmonisation Strategies

- **Statistical Correction of data using batch effect correction techniques**
  - Corrects for systematic differences in samples from different sites
  - Doesn't require any knowledge/phantom data from scanners
  - Requires sufficient cases from each scanner/site to apply (30+ cases)
  - May remove actual variation

22

Harmonisation Strategies

- **Storage of raw PET data for newer systems**
  - Comply with current specification
  - Retrospective studies to investigate impact of new technologies/specifications - visual and quantitative evaluation
  - Clinical follow up
- **Routine use of multiple reconstructions for different standards**
  - Use a local reconstruction for clinical review
  - Additional reconstruction matched for quantification
  - Takes up additional storage space
  - Can cause confusion for non-PET clinicians and external PET reviewers (need to be clear which reconstruction should be used for clinical management)

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Thank You

UK PET Core Lab
Quality Control for PET Clinical Trials

Further Information:
www.ncri-pet.org.uk
http://earl.eanm.org

Acknowledgements:
- Sally Barrington
- Paul Marsden
- Alyss Harman
- Sorcha Curry
- Georgios Krokos
- Malene Fischer
- Victoria Warbey

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