Has it worked? The problems of measuring response

J.Buscombe

Lecture plan

- Why do we measure response
- Radiological response measurements
- Lymphoma response a special case
- PET response
- Functional volumes
- Surrogates
- Survival
- Soft measures

Introduction

- Why do we need to measure response
- Patient will need to know how their disease is progressing
- Clinician needs to know does their treatment, should it be continued or stopped
- How do we prevent bias

Radiological response

- Only possible since cross section imaging used
- Tends still to be CT based, though MRI often used as a substitute
- Need to determine standards for measurement
- Need to be objective and consistent

New language of response

- Disease progression-needs to have increase > 25 % in tumour volume (actually its normally area)
- Disease stability Increase <25%, decrease<50% or no change in size
- Partial response Decrease in size >50%
- Complete response-No evidence of any remaining cancer

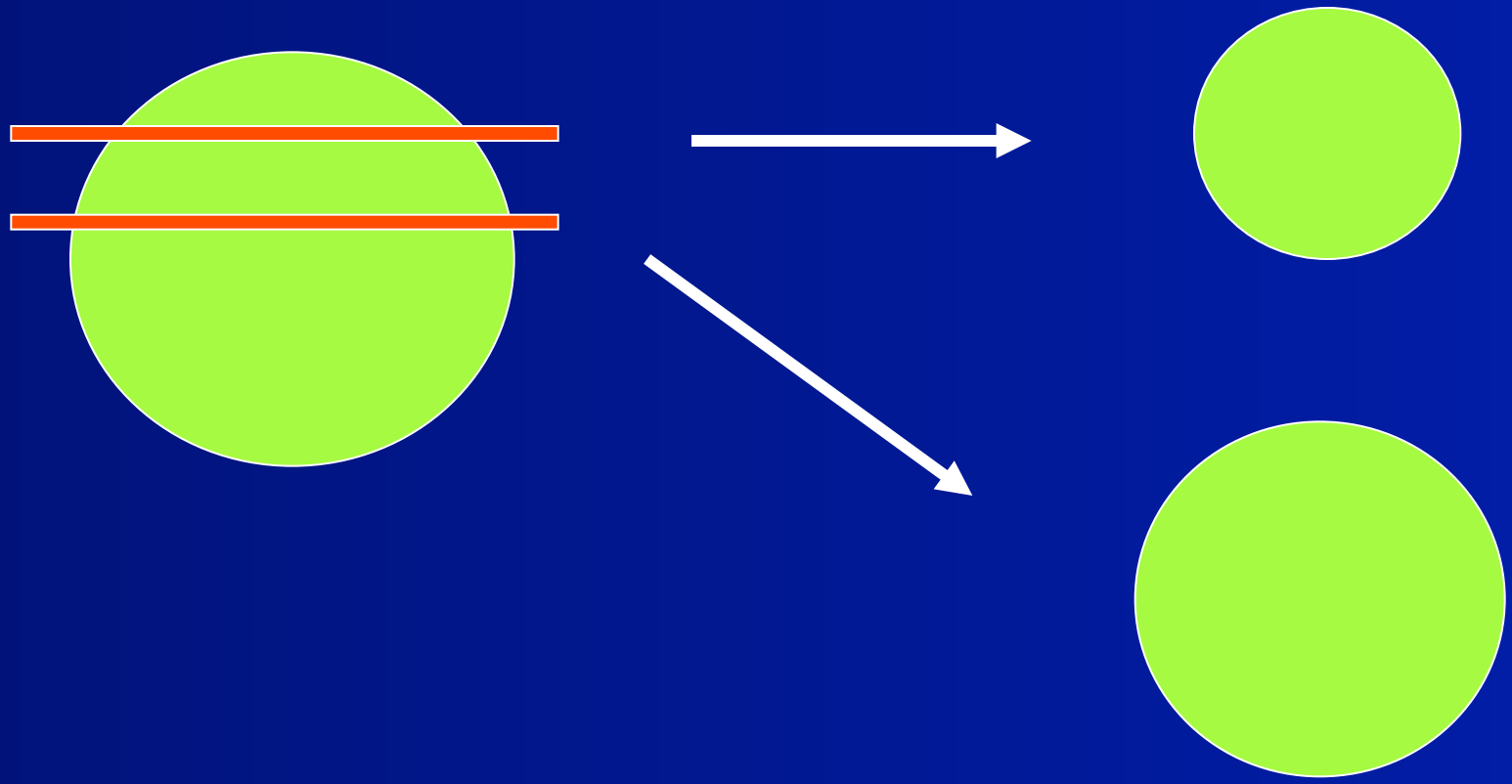
WHO criteria-1979

- Minimum measurement time 4 weeks-no maximum
- Uses single lesion-often the biggest-the index lesion
- Measure sum of 2 axes perpendicular to each other
- Look for changes as defined before

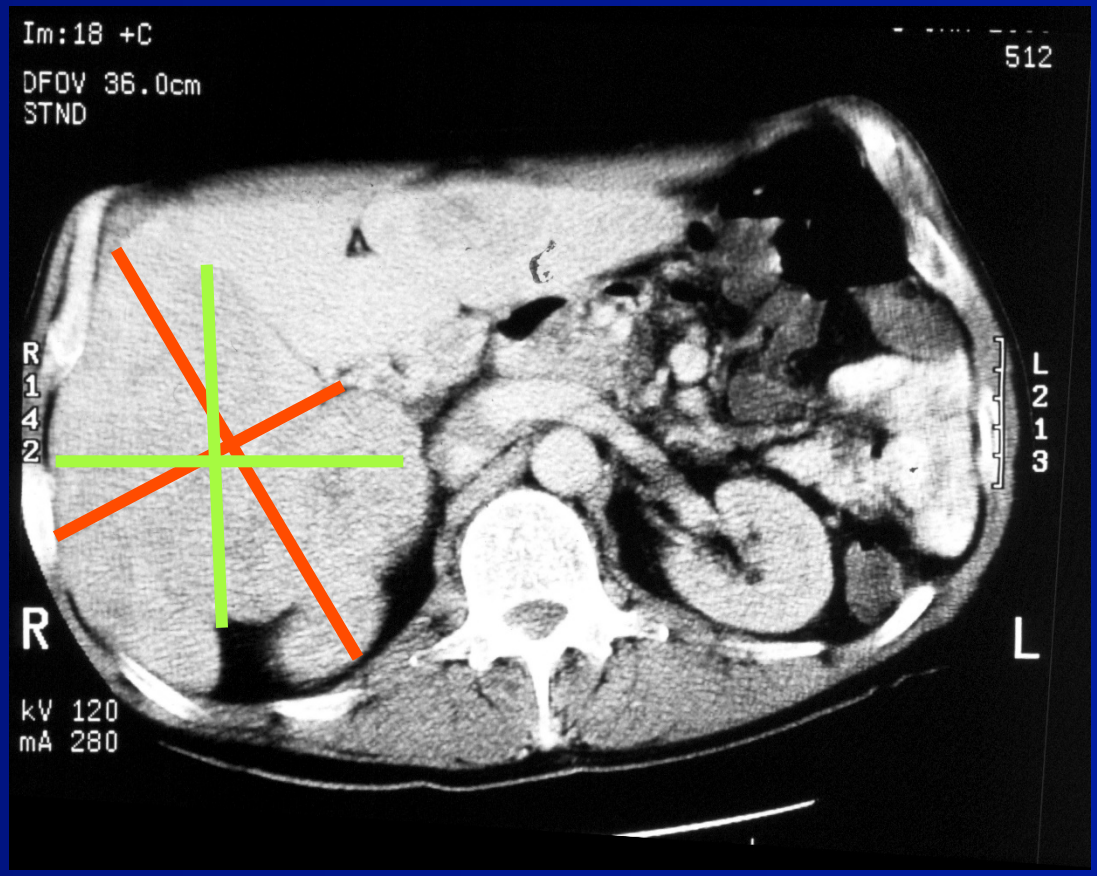
WHO problems

- Small lesions-partial volume
- Complex shapes what do you measure
- Is measurement consistent
- What happens if index lesion shrinks but new lesion grows elsewhere
- Tumours may not be homogeneous

Partial volume



Complex shape-which is correct?



Therefore to make it simpler-

- Idea of single measurement across tumour mass
- Can look at up to 5 lesions
- The maximal dimension can be added together
- If nominated lesions decrease but new proven disease then always DP

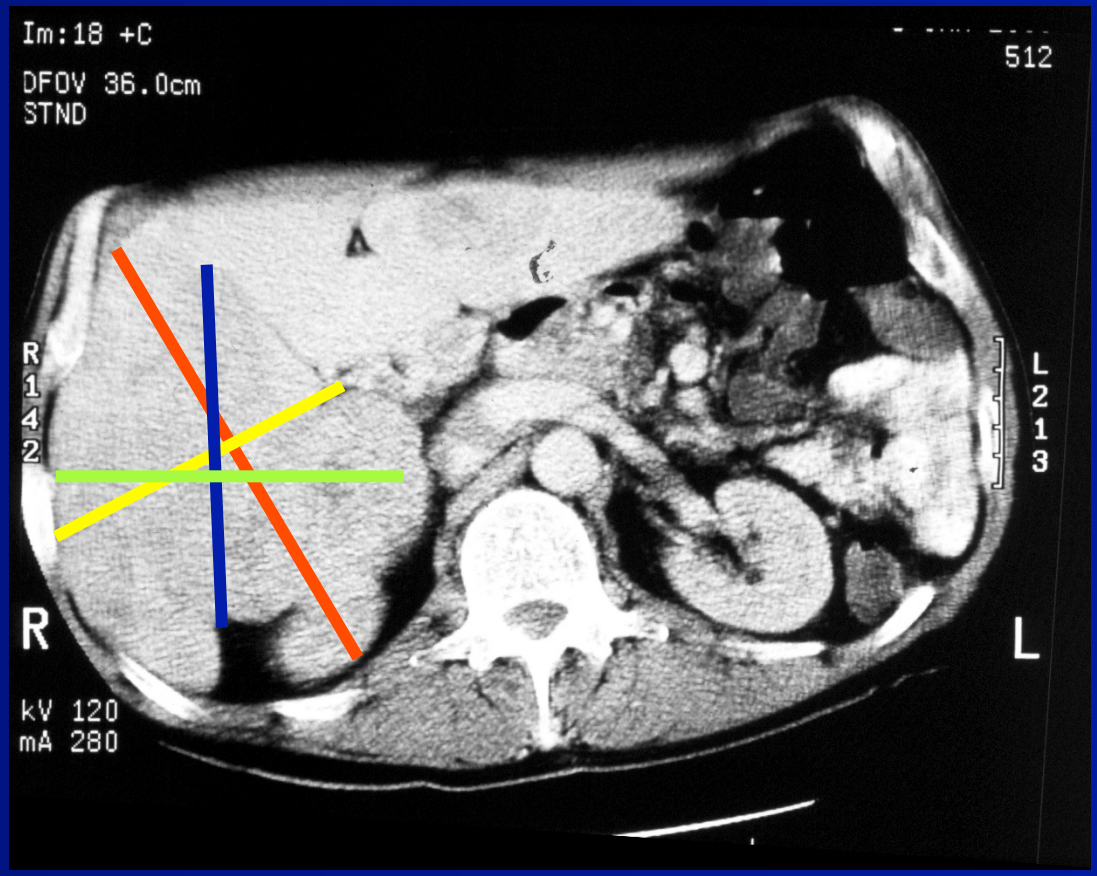
New language of response-RECIST

- Disease progression-needs to have increase > 20 % in tumour volume (actually its normally area)
- Disease stability Increase <20%, decrease<30% or no change in size
- Partial response Decrease in size >30%
- Complete response-No evidence of any remaining cancer again taken at 4 weeks minimum

Why the difference

Response	RESIST (r)	WHO (r^2)	Volume (r^3)
PR	-30%	-50%	-65%
	-50%	-75%	-78%
DP	+12%	+25%	+40%
	+20%	+44%	+73%
	+25%	+56%	+95%
	+30%	+69%	+120%

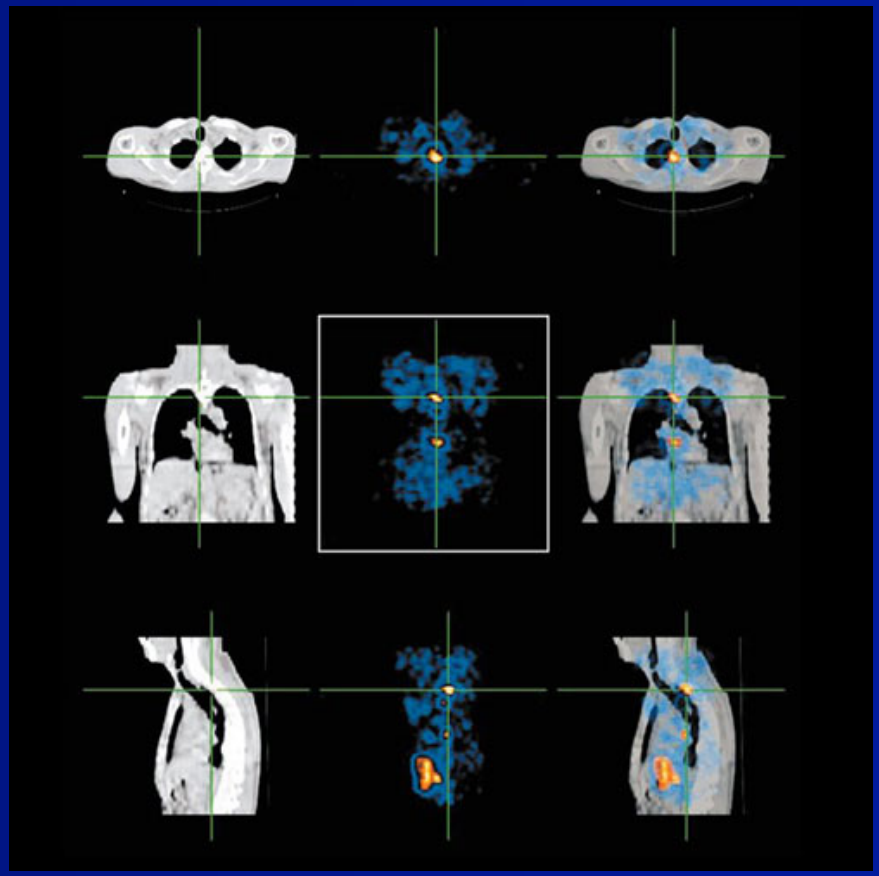
Complex shape-which is correct? RECIST



We are now agreed

- EORTC, NIH, CCB
- All use RECIST (now RECIST 1.1 uses less target lesions and PET allowed)
- How does the patient we illustrated stay alive and have DP
- What happens if tumour is hypoxic and so some just fibrosis
- What about residual masses

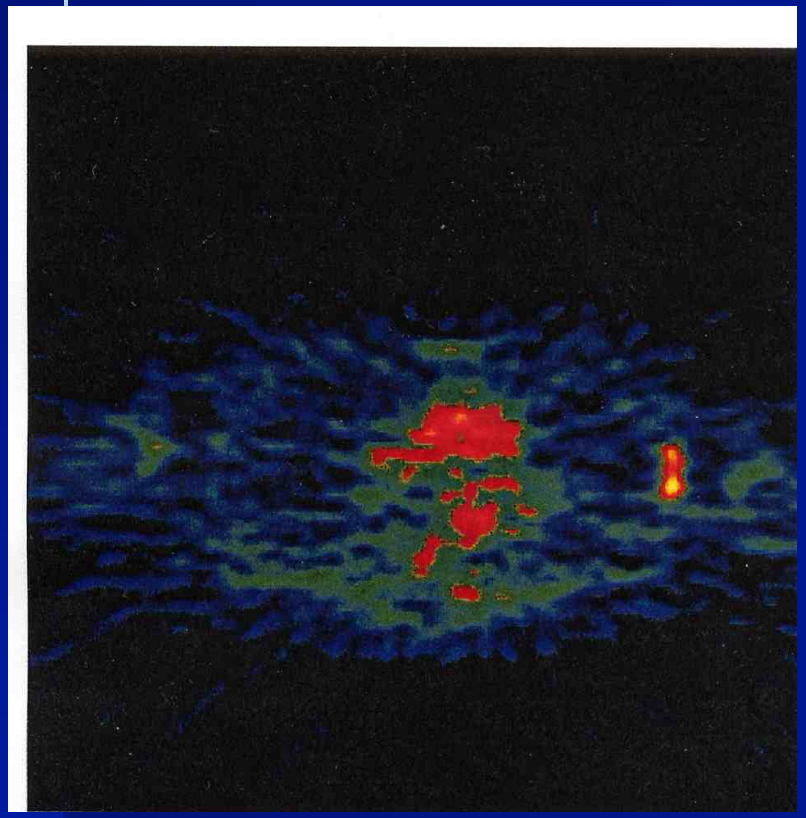
Looking at the residual mass in lymophoma



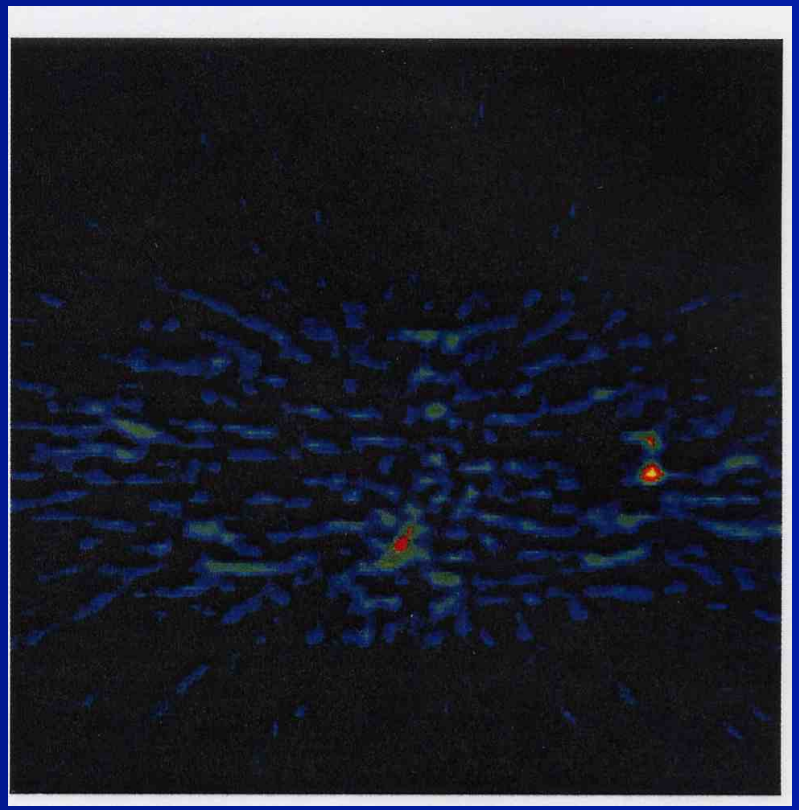
Can we use PET imaging

- Could be good but what in the criteria
- Activity not proportional to size
- eg a tumour with 50% less in size on PET may not be 50% smaller but 50% less active
- Especially small tumours
- EORTC working on this for 5 years
- What about SUV

FDG changes with chemotherapy



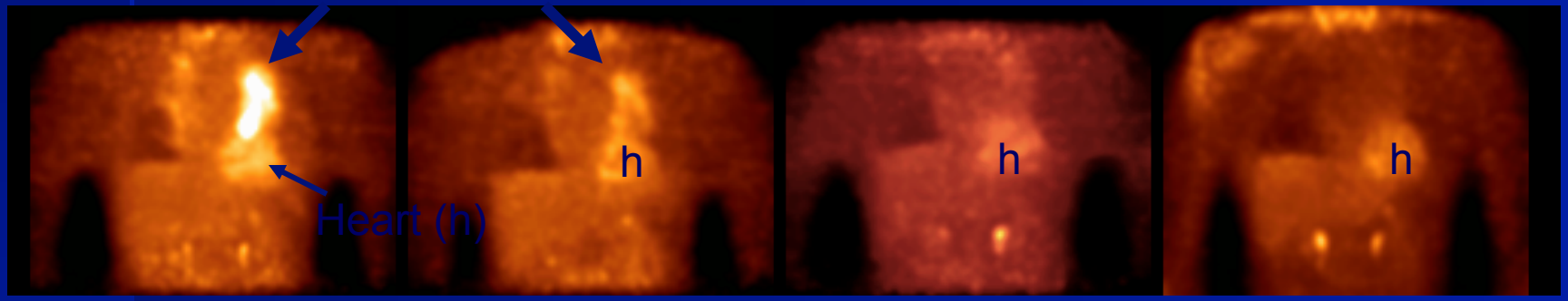
Pre chemotherapy



After 3 cycles

Response Assessment by ^{18}FDG-PET

Tumour uptake of FDG



17 April
Before 1st Treatment

10 May
before 2nd

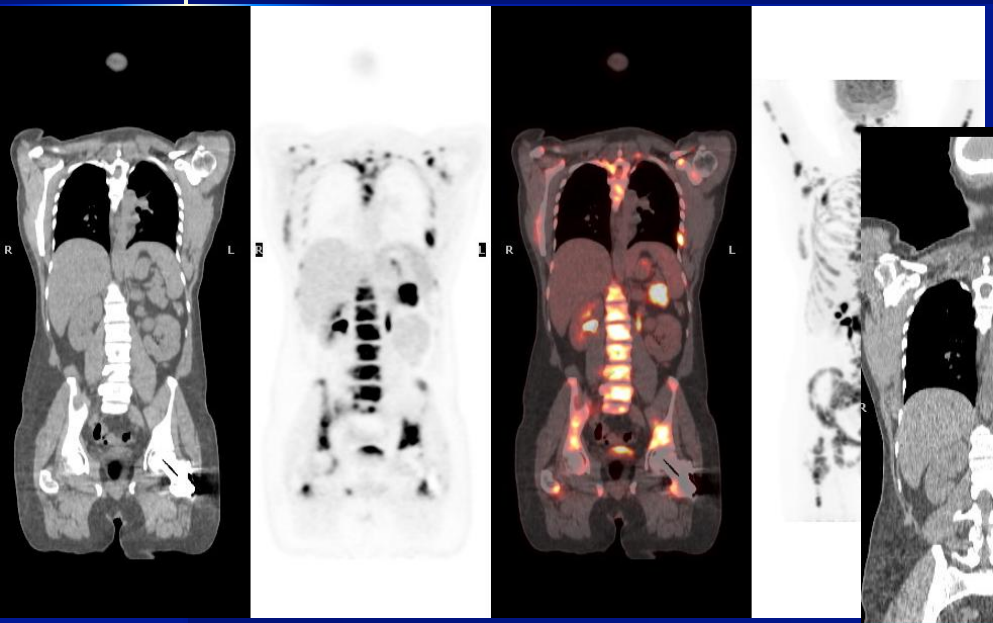
6 June
before 3rd

23 Aug
after 3rd

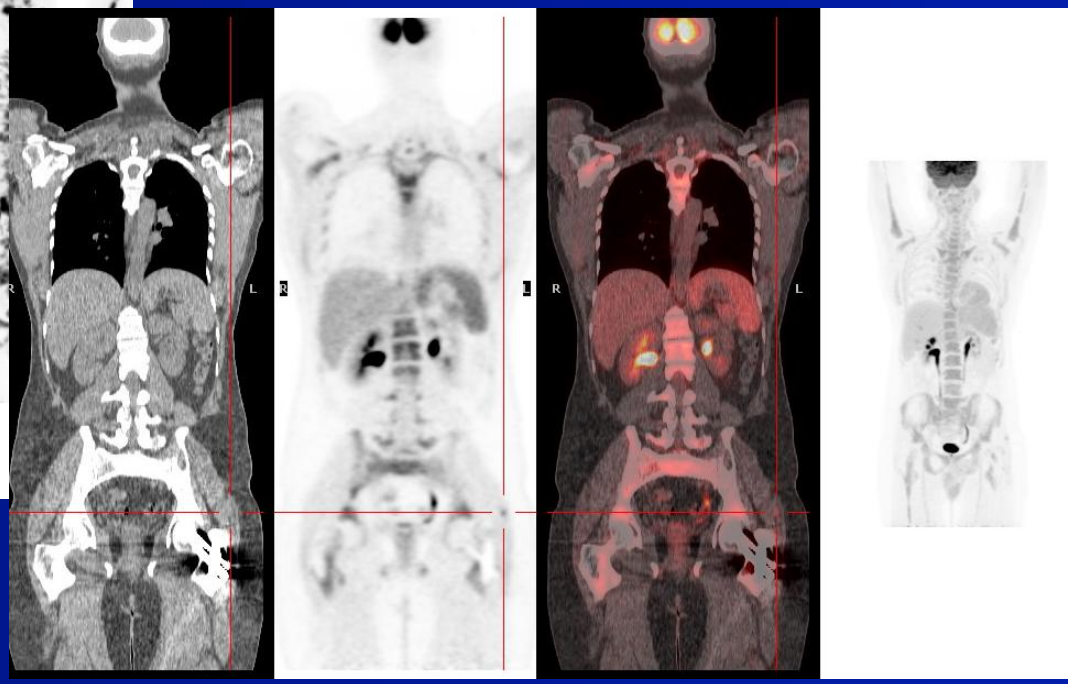
Using F-18 FDG in HD

- 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

Measuring response -25 yr male HD induction chemo

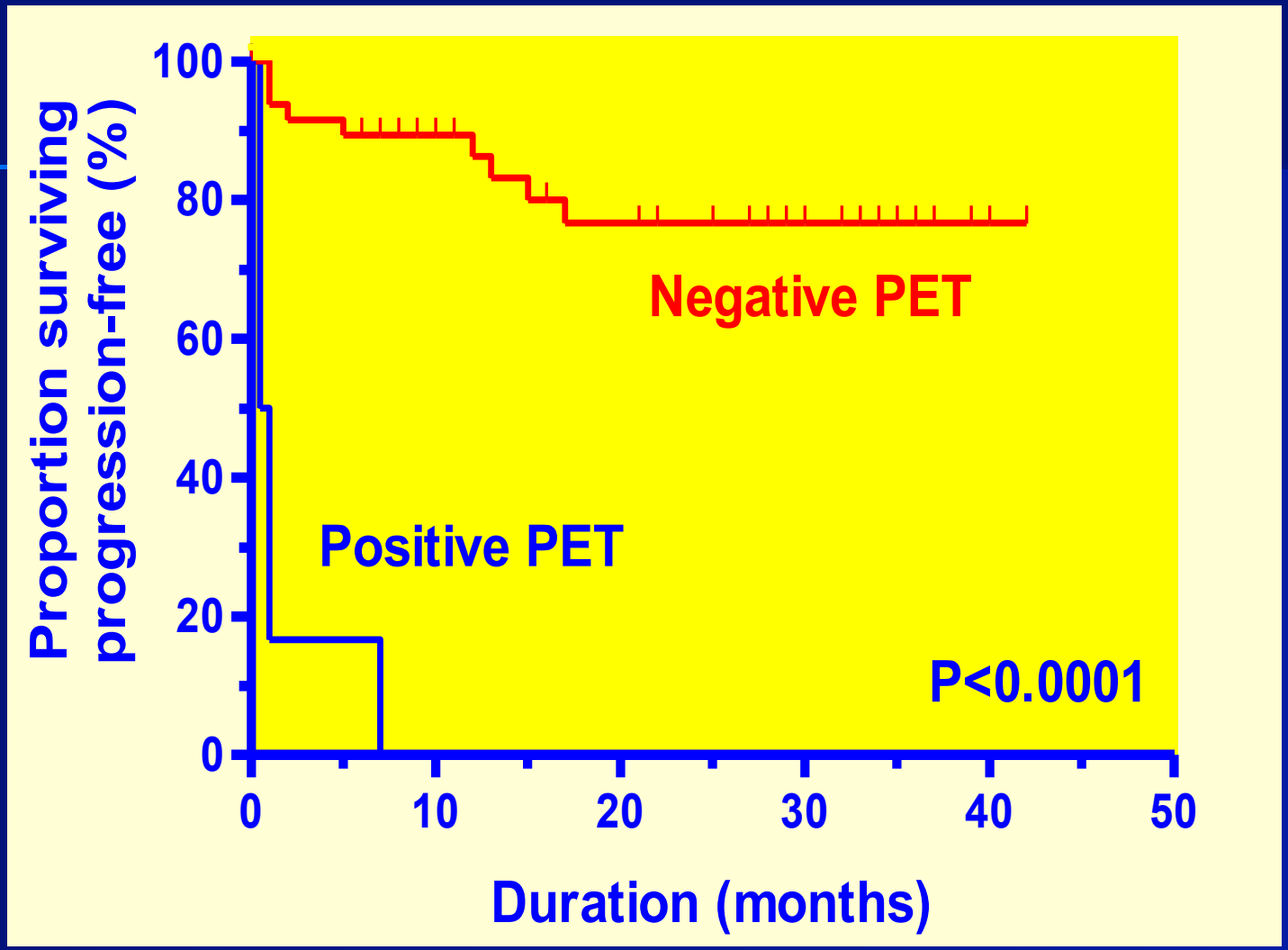


Pre treatment



After a single dose of chemotherapy

Progression free survival related to PET response

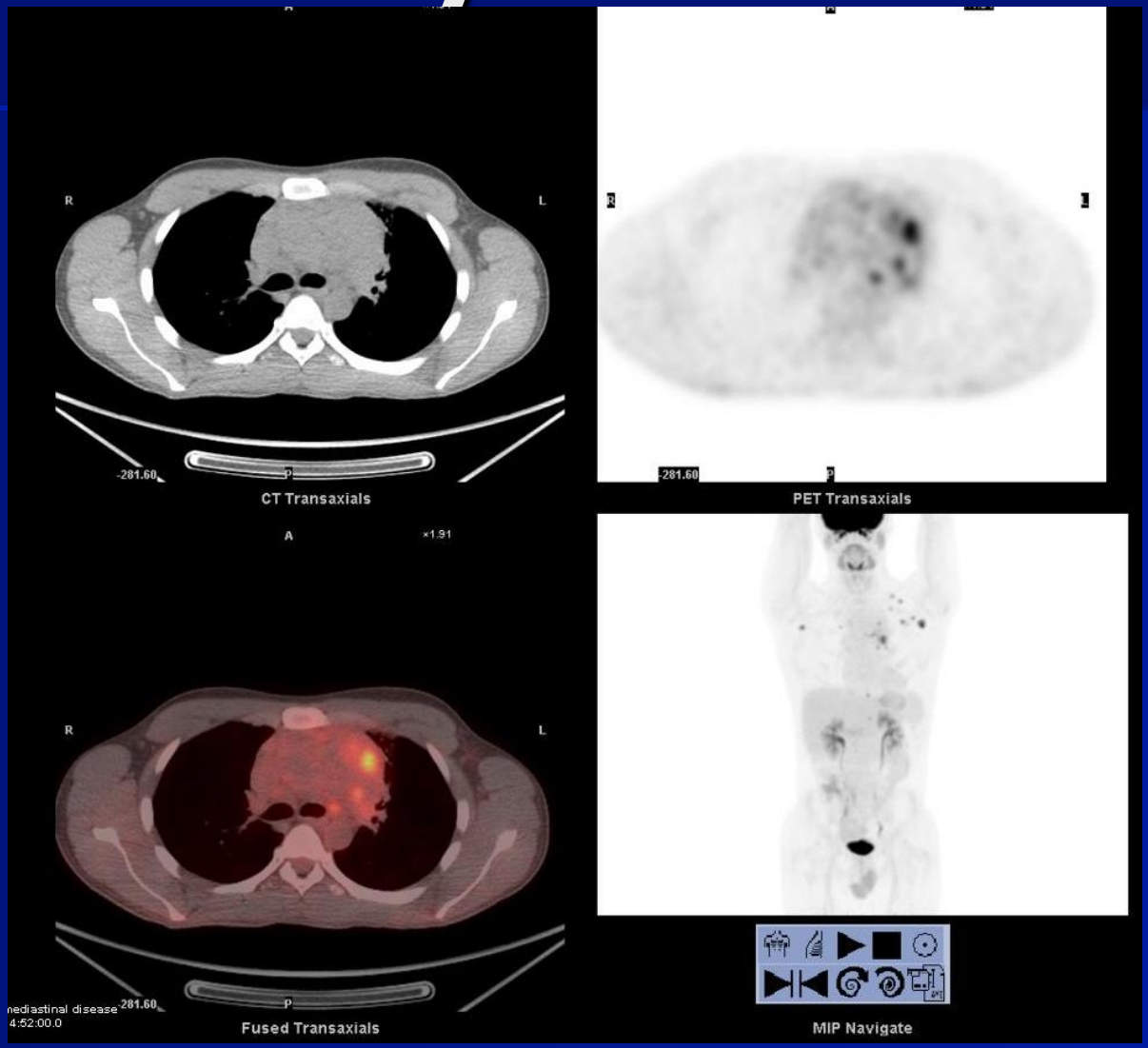


Deauville criteria

Score*	Characteristics Based on SUVmax in lesion, liver and mediastinum
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

HD Clearly failed Tx



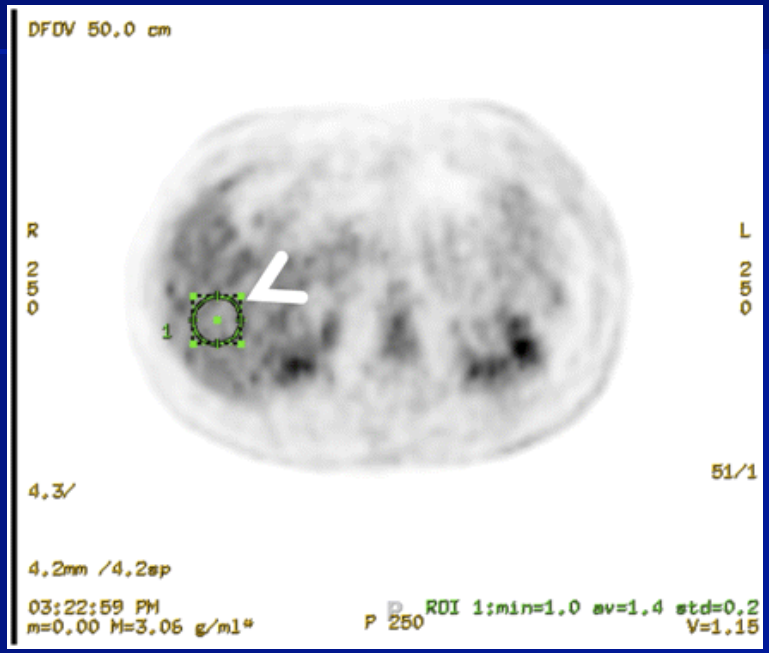
PERCIST

- PET Response Criteria in Solid Tumours
- Developed in USA
- Based at Johns Hospkins
- Based on higher sensitivity of PET
- Discussion of methods
  - SUVmax
  - SUVmean
  - Glycolytic volume

Basic methods

- SUVmax too variable
- SUVpeak may not include most active tumour
- PERCIST using a volumetric $1cm^3$ voxel
- Corrected for biodistrubtion and patient lean metabolism measured with $3.5cm^3$ voxel in normal liver the SUL

Liver voxel for correction

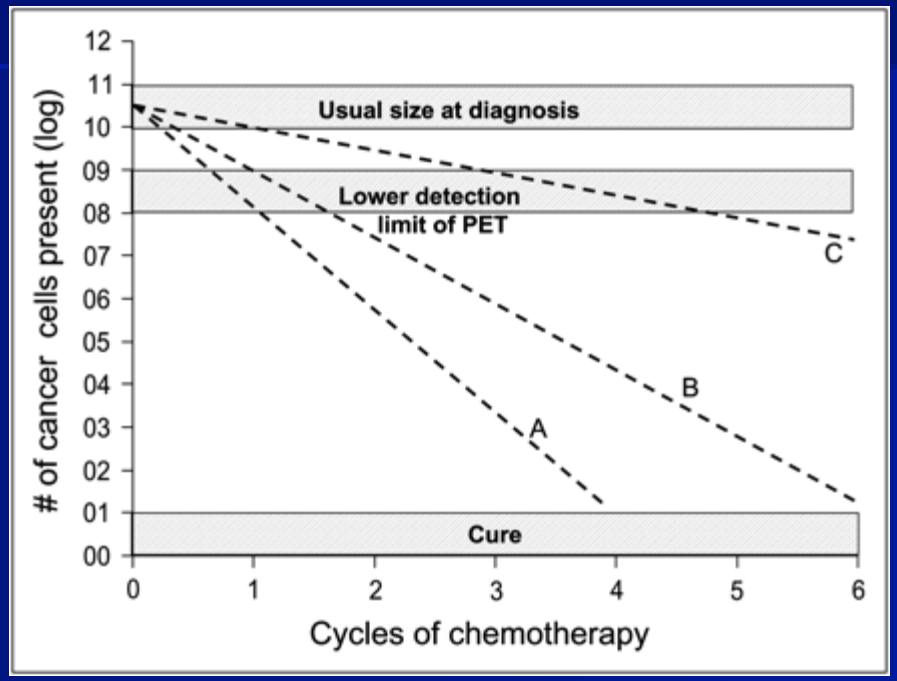


Example calculation of liver background for normalization of SUL. Images are displayed from Advantage Workstation (GE Healthcare). A 3-cm-diameter 3-dimensional ROI (ROI 1) is placed on normal inferior right lobe of liver (arrowhead). Average SUL and SD in ROI are displayed (arrows). Liver background is calculated as follows: (1.5 × average SUL liver) + (2 × SD average SUL liver). For this example, (1.5 × 1.4) + (2 × 0.2) = 2.5. Therefore, tumor SUL peak should be >2.5 in order to apply PERCIST criteria for this example

Criteria for PERCIST

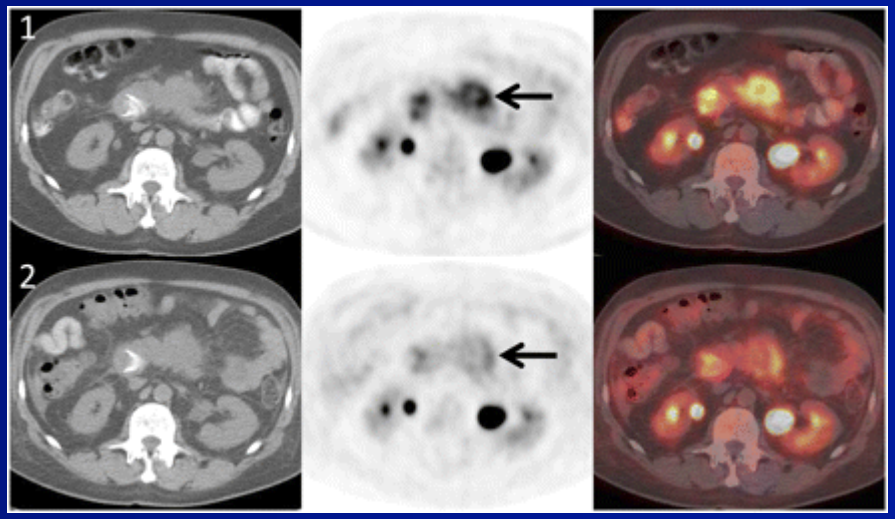
- Normally done after 3 cycles of chemo
- Compare with baseline (at baseline Tumour SUL>2.5)
- SUL liver between 2 sd of baseline
- 100% reduction CMR
- >30% reduction PMR
- >30% increase MPD
- Rest MSD

PET detects small lesions



Kinetics of tumor cell kill and relation to PET. Line A represents brisk tumor response that would produce cure after only 4 cycles ofchemotherapy. Line B represents minimum rate of tumor cell kill that will lead to cure in 6 cycles of treatment. Both lines would be associated with negative PET scan after 2 cycles of chemotherapy. In contrast, line C represents rate of tumor cell kill that would be associated with negative PET scan after 4–6 cycles but would not produce cure. Importantly, PET scan for line C would likely be positive after 3 cycles

An example Wahl et al

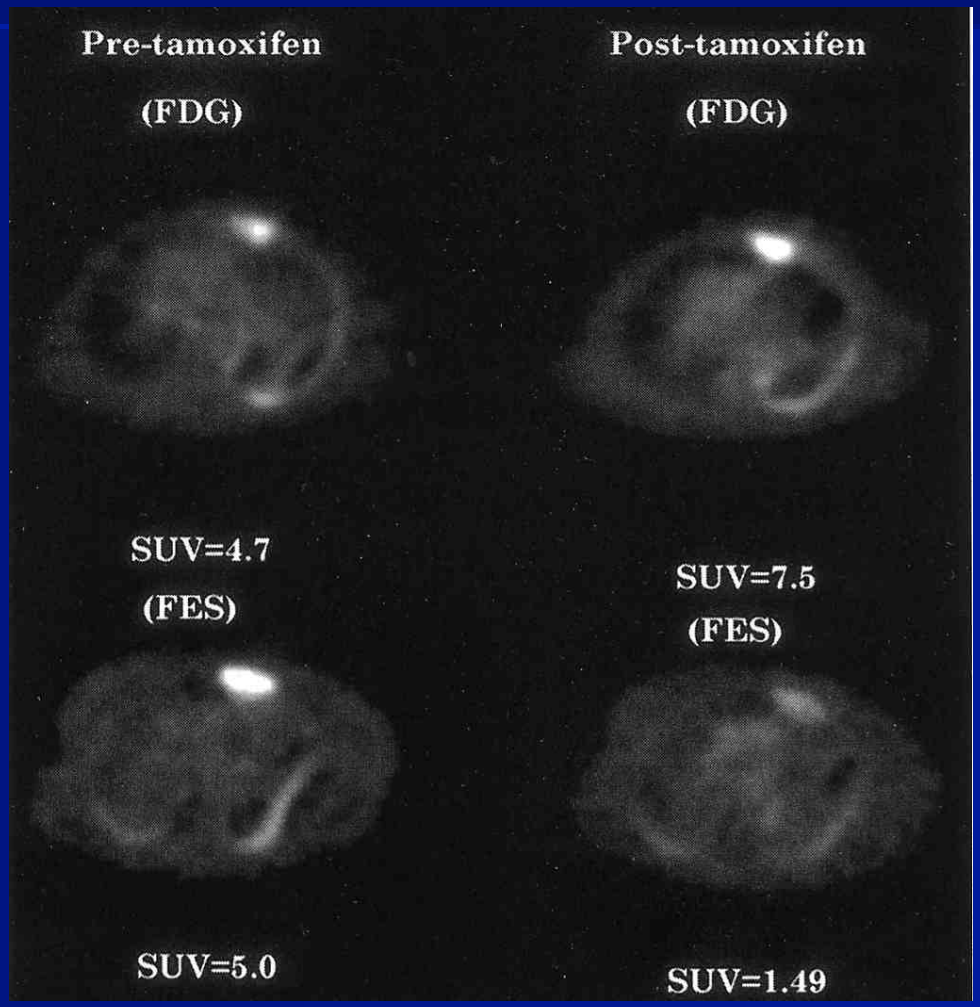


PET/CT images obtained before (1) and after (2) treatment ofpancreatic carcinoma with experimental therapy targeting mammalian target of rapamycin. Note profound decline in SUL (~41%) despite stable pancreatic mass anatomically (arrows). This decline represents metabolic partial response by PERCIST (41% decline in marker lesion at 2 wk after therapy). Not all metabolic PMRs are clinically relevant; relevance will depend on the specific treatment.

Problems with PERCIST

- Complex and time consuming
- Needs special software
- Still needs good verification
- Will it be done as well in all centres
- Will clinicians believe PERCIST or RESIST
- Is FDG the right tracer anyway

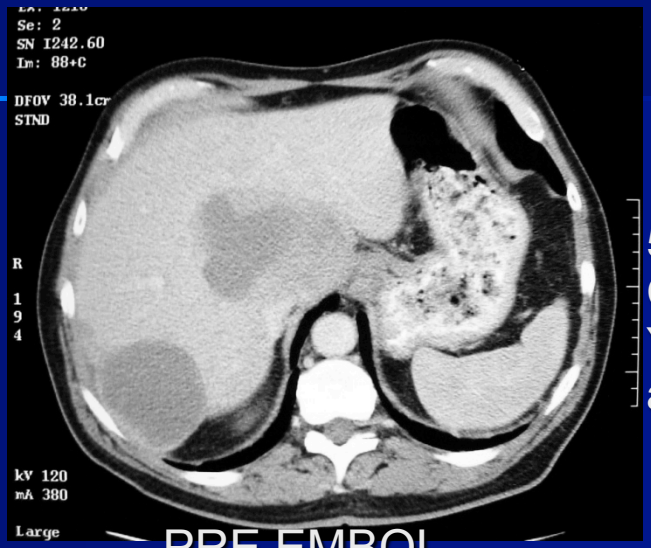
F-18 FDG vs F-18 FES



No PET scanner?

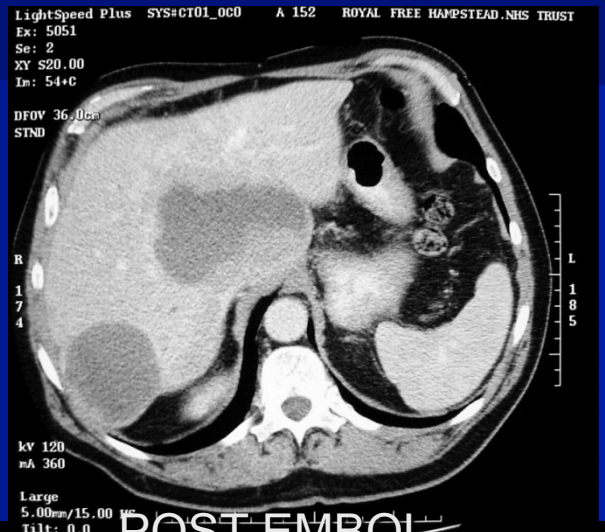
- Problem if no access to PET
- Also if tumour not well seen with PET
- Can we use SPECT
- Problem not quantifiable – or less so
- Looking at functional volumes
- Gopinath et al NMC 2004 - RFH

Imaging Discrepancy

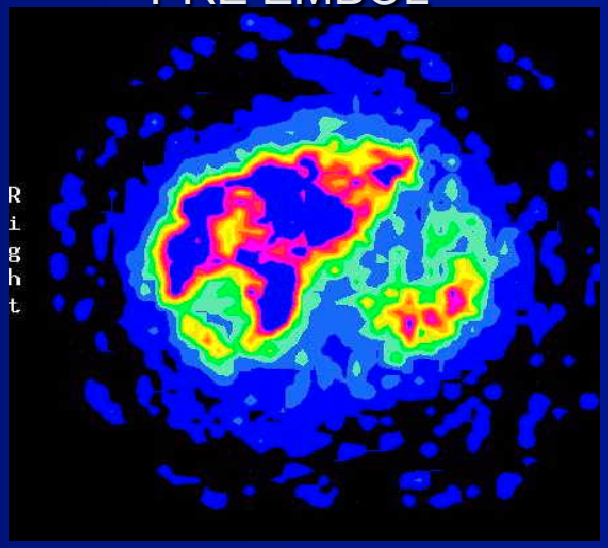


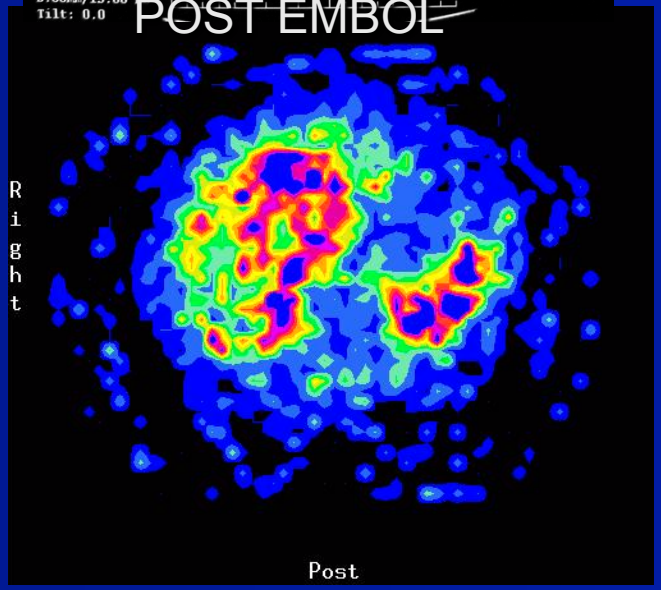
PRE EMBOL

51yrs MidGut
Carcinoid
Y90
and particles



POST EMBOL





Can we use both?

- May be best combination
- However which do we believe
- Nuclear Medics-Functional
- Radiologists-Anatomical
- What happens if you cannot see the tumour
- Need surrogate marker

However still problems

- Maybe not able to measure size
- Blood/urine levels may be affected by co-drugs such as sandostatin in carcinoid
- Need to look at other measures
- Do patients live longer-objective
- Do they feel better-subjective

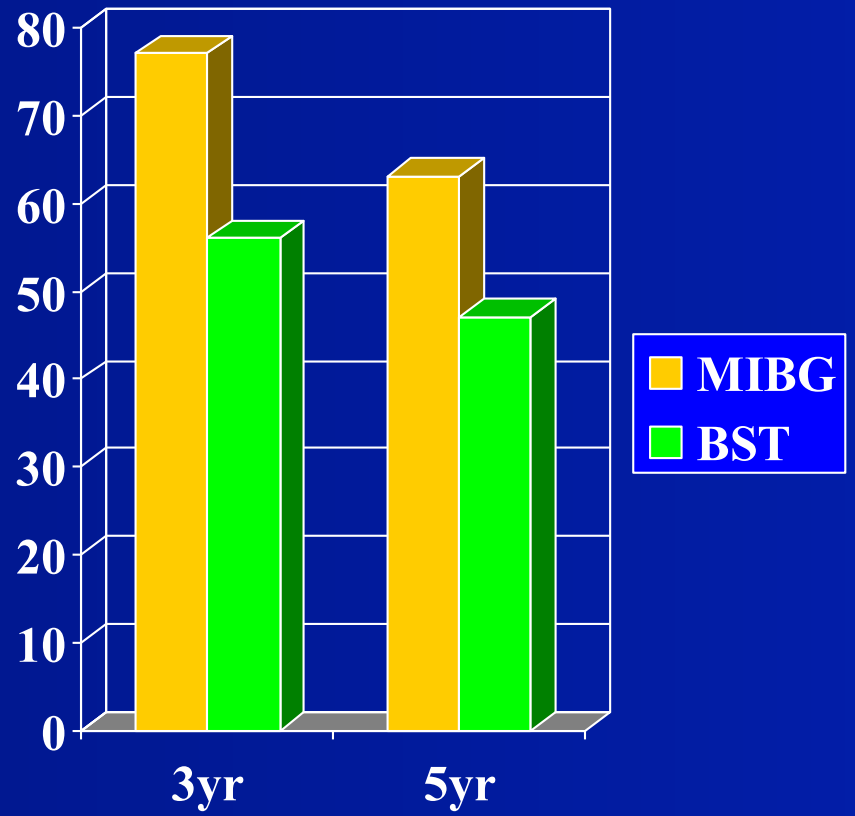
mIBG – carcinoid-EANM survey

N = 157 **96% Stage III/IV**

%	Tumour	Marker	Palliation
CR	0	17	10
PR	16	39	61
SD	65	36	27
PD	19	8	2

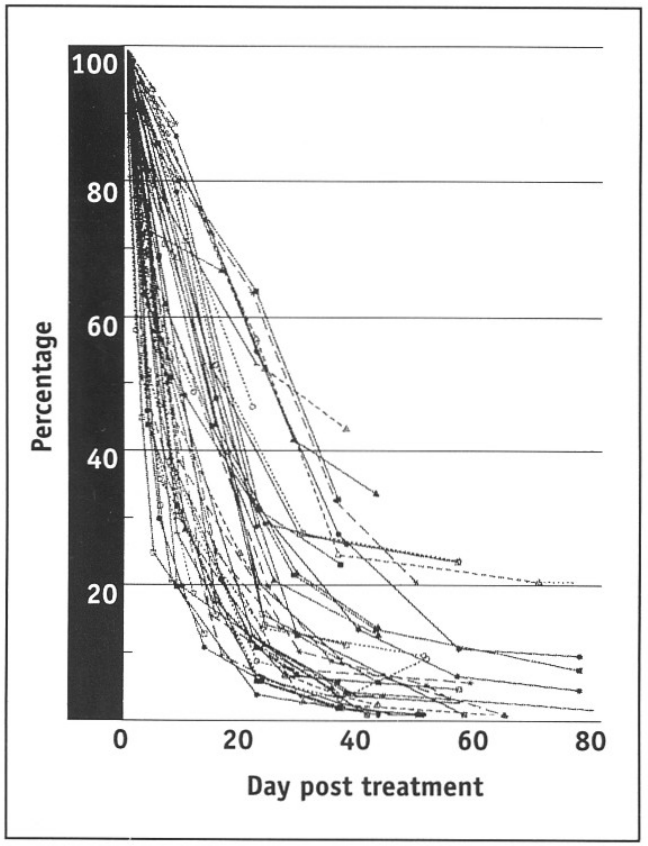
Survival with mIBG

- Syweck et al WJS 2004 compared 2 centres-58 patients at each
  - 1 MIBG
  - 1 without MIBG
- % Survival noted at
  - 3 yr
  - 5 yr



Y-90 SIR spheres in HCC

- Recorded drop in AFP before and for up to 8 weeks post therapy
- Leung et al Hong Kong

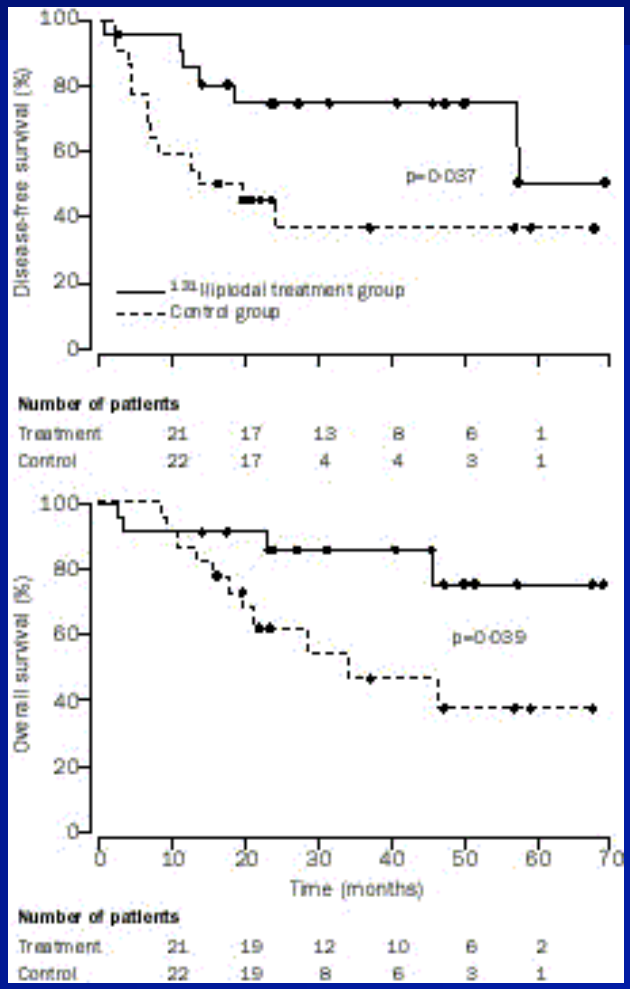


Survival

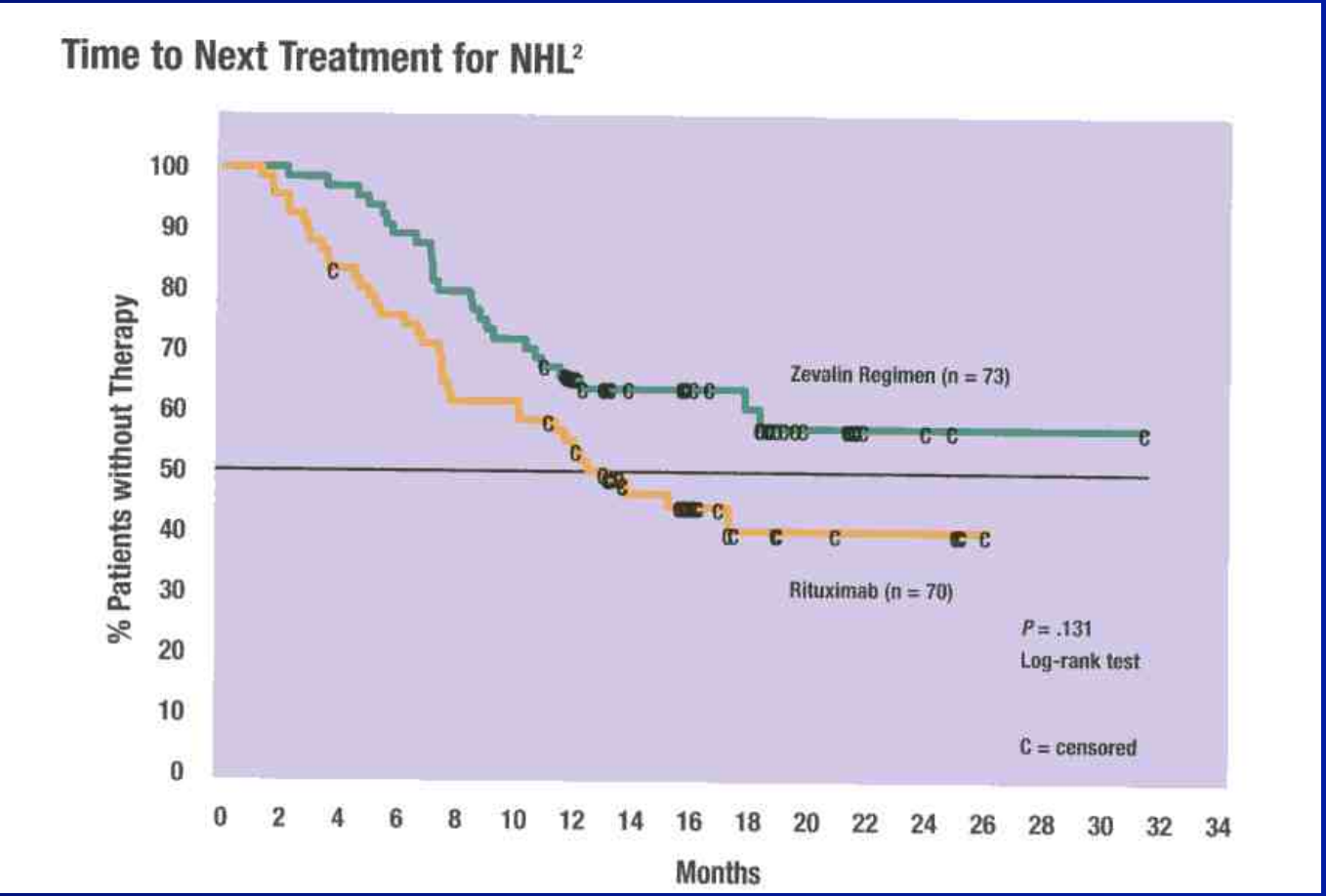
- Overall survival-till death
- Progression free survival – may not be important in advanced disease
- Time to next treatment-may be one of best measures
- Use of Kaplan-Meir graphs and statistics

Adjuvant I-131 Lipiodol after surgery Lau et al lancet 1998

- 21 patient treated with 1000 MBq I-131 Lipiodol vs no treatment
- Survival over next 6 months monitored
- Significant improvement in both OS and DFS

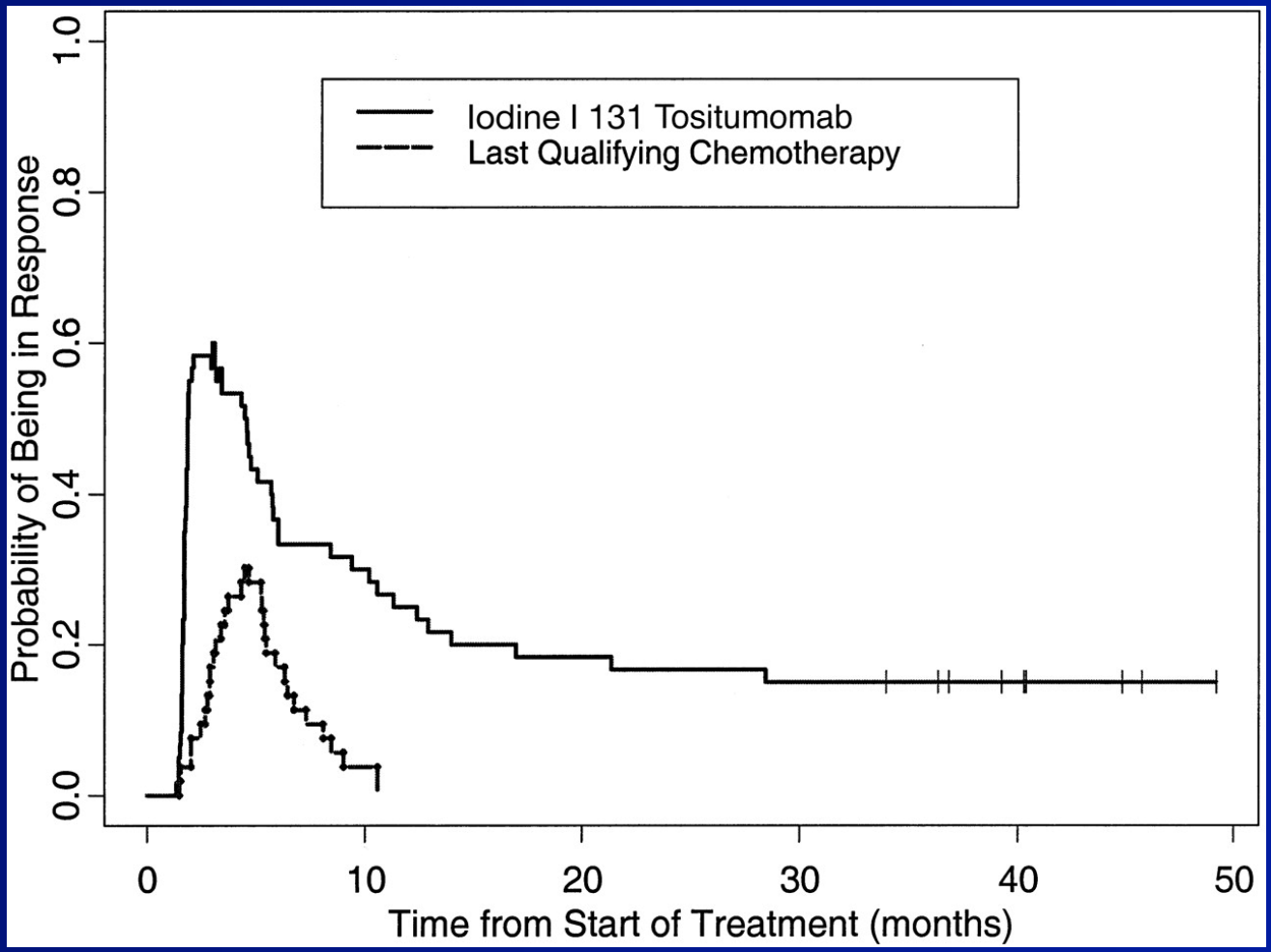


Time till relapse zevalin vs rituximab



Phase III multi-centre trial data

Bexxar vs chemotherapy –Kaminiski et al JCO 2001



Use of soft measures

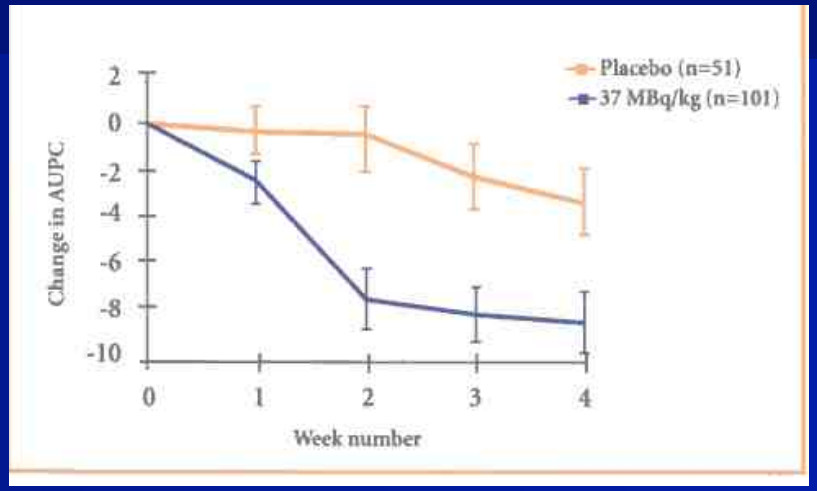
- How should these be done
- How can we measure these
- Hoe can we compare between treatments
- How can we compare between studies
- Use of VA scales and QOL questionnaires eg EORTC

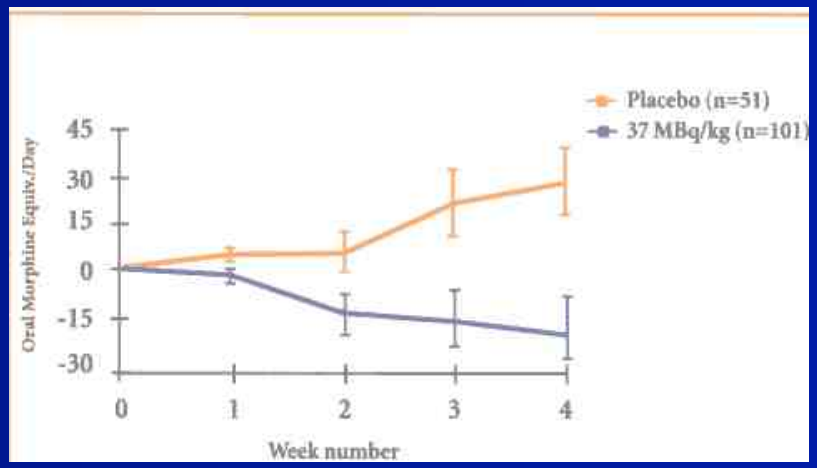
Visual Analogue scales

Please mark on the scale how you feel about this talk, marking 1 if you are so bored you want to chew your leg off and 10 if it so riveting you are having severe palpatations

Use of VA scales vs drug use

- Results of US/ European MCT for Merrill Pharm
- Phase III trail in prostate cancer
- Randomised to placebo lexidronam or Sm-153 product





Conclusions

- Size may not be everything
- May need to look at a combination of factors
- PET criteria still not fully accepted
- May need anatomical/functional volumes
- In addition QoL data and tumour markers