UK-NCRI Interim PET study

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Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphoma

Short title: PET after 2 cycles

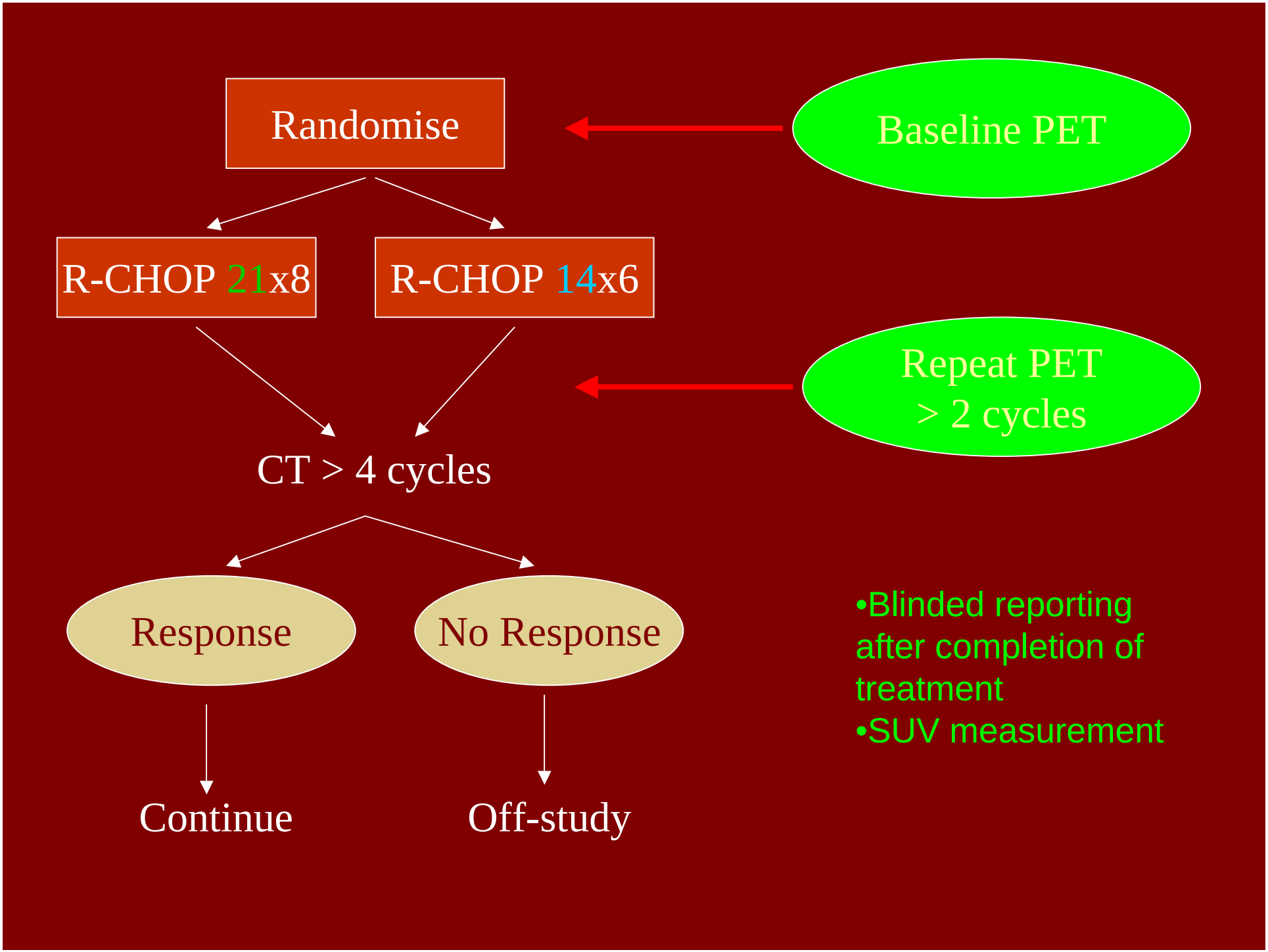
A sub-study of the R-CHOP-21 v R-CHOP-14 trial

Chief Investigator: George Mikhaeel

To use PET to change treatment (in a future RCT)

We need data on exact prognosis from:

- Homogenous patient group stratified by IPI
- Same Histology e.g. DLBCL
- Same treatment
- Rituximab
- Same criteria for response assessment and change of treatment
- No change of treatment on the basis of PET
- QA in PET centres + Central review of PET


Randomise
Baseline PET
R-CHOP 21x8
R-CHOP 14x6
Repeat PET
> 2 cycles
CT > 4 cycles
Response
No Response
•Blinded reporting after completion of treatment
•SUV measurement
Continue
Off-study

Inclusion criteria

- Age ≥ 18 years.
- Histologically proven DLBCL (central review)
- Bulky stage IA (>10cm) IB, II, III & IV.
- WHO PS: 0-2. Life expectancy >3 months.
- Adequate marrow, kidney, liver and cardiac function.
- Written informed consent
- +ve Baseline PET

Study Design

- Scanning:

All patients have 2 FDG-PET scans:

  - pre-treatment
  - >2 cycles

Blinding:

- Post cycle 2 scans are archived centrally & treating clinicians are blinded to the scans' findings
- Nuclear Medicine physicians are blinded to the outcome of treatment

Study Design

Treatment:

- All patients are treated with R-CHOP according to protocol.
- Response is assessed with a CT scan >4 cycles according to IWC criteria

Reporting & Analysis:

- The PET scans are reported in batches after completion of treatment.
- Final Analysis will be performed after completion of recruitment

PET scanning

- QC completed and passed by reference centre
- Reliability of SUV measurement after transfer
- Standard scanning protocol
- Week before 3rd cycle
- 90 min
- Anonymisation
- Central reporting

End Points

Primary Outcome Measure:

- Failure free survival at 2 years

Secondary Outcome Measures:

- Complete response rate
- Overall survival

Statistics

- Assuming that about 50% of patients will have a negative PET scan after 2 cycles and to detect **25%** in FFS at 2-years between PET negative & positive groups, with 5% type I error and 90% power, **200 patients** will be required

Details of Calculation for 25% difference:

- 2y FFS for PET -/+ of 80%/55%: events needed=47, patients needed=191
- 2y FFS for PET -/+ of 75%/50%: events needed=60, patients needed=209

Recruitment

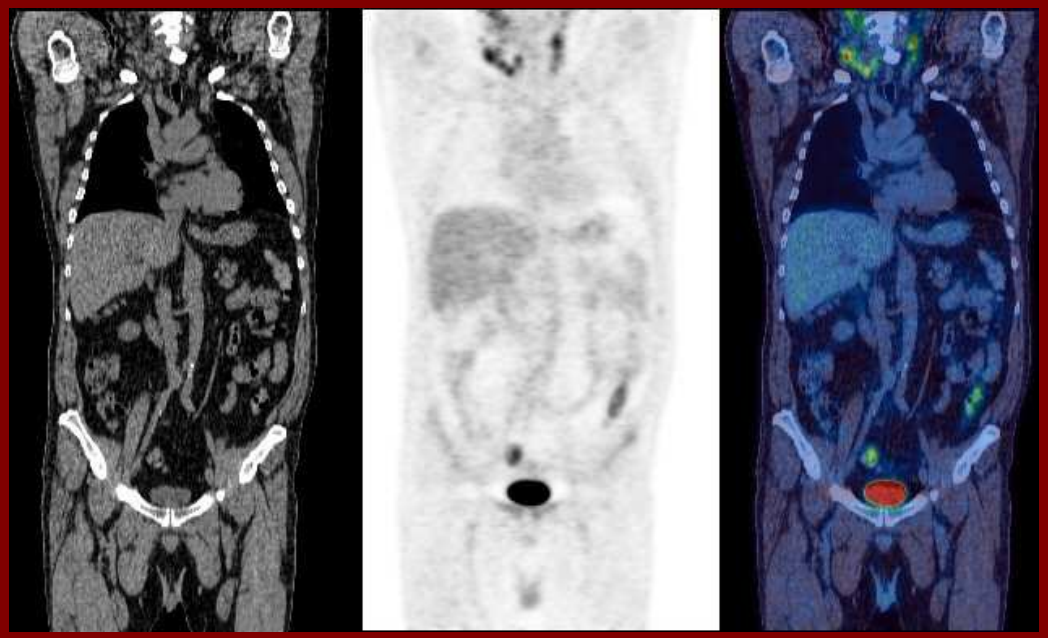
- Target: 200 patients
- March 2010: 142 pts (21 excluded) =121
- Expected completion: Early 2011

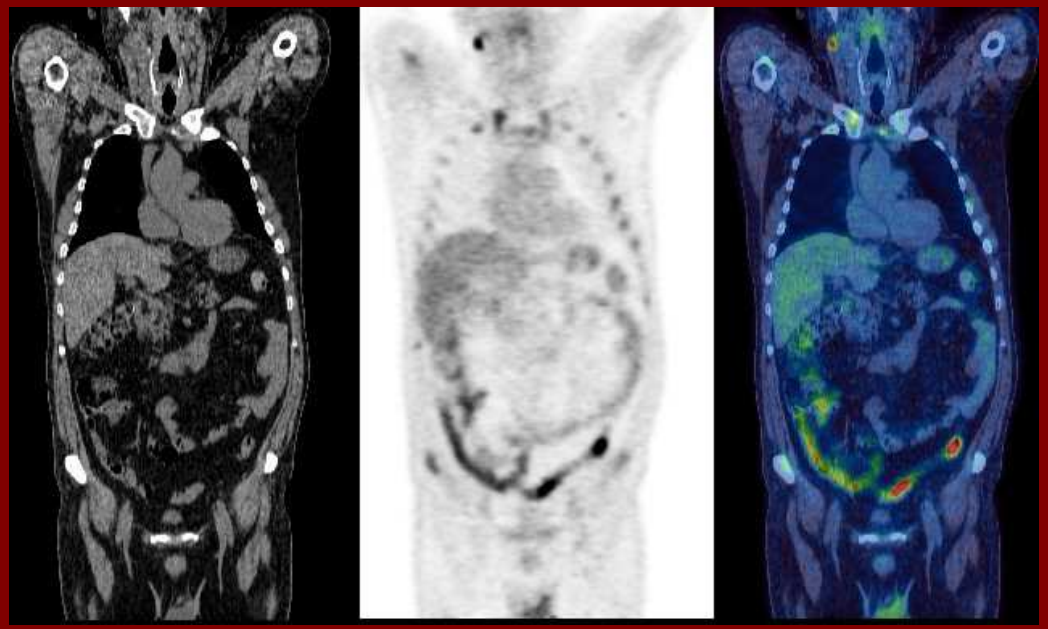
Results

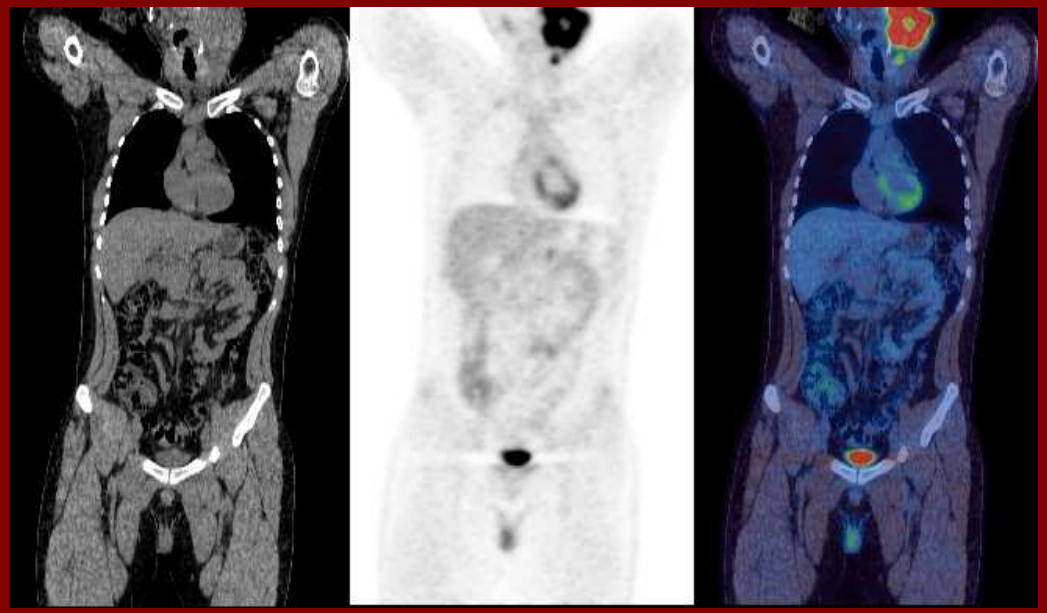
- 97 patients who completed all treatments were analysed
- No outcome analysis
- Comparison of different scoring systems

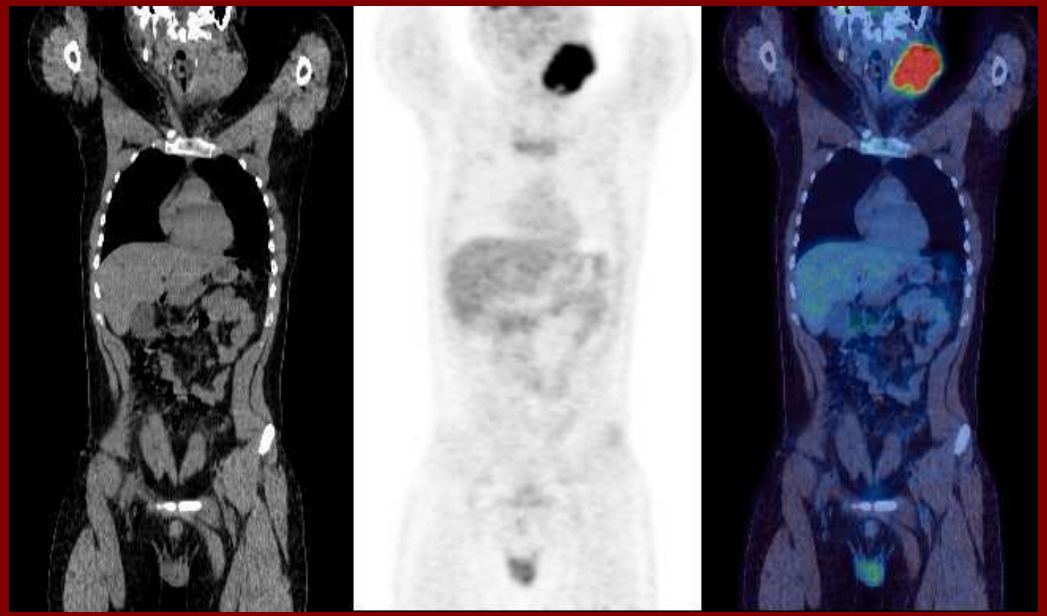
PET scoring

Score			Description
Negative	1		complete disappearance of all abnormal uptake
Positive	2a	MRU	Disappearance of most abnormal uptake, but residual low-grade uptake in sites of previous disease, just above the background activity
	2b	Partial response	Reduction in the abnormal uptake, but significant residual activity
	2c	Stable	No significant change
	2d	Progression	Increase in abnormal uptake &/or appearance of new sites









Deauville 5 point Scoring System

- Score 1 (CR): no uptake

- Score 2 : uptake ≤ mediastinum
- Score 3 : uptake > mediastinum but ≤ liver

- Score 4 : uptake > liver
- Score 5 : markedly increased uptake
  AND
  new lesion(s) likely to be lymphoma

Comparison of Deauville and R-CHOP substudy scores

NCRI Study Score		Deauville Score	
Score	No of Patients	Score	No of Patients
1	24	1	24
2a	21	2	21
2b	49	3	18
2c	3	4	34
2d	0	5	0
TOTAL	97		97

Correlation of Deauville and R-CHOP substudy scores

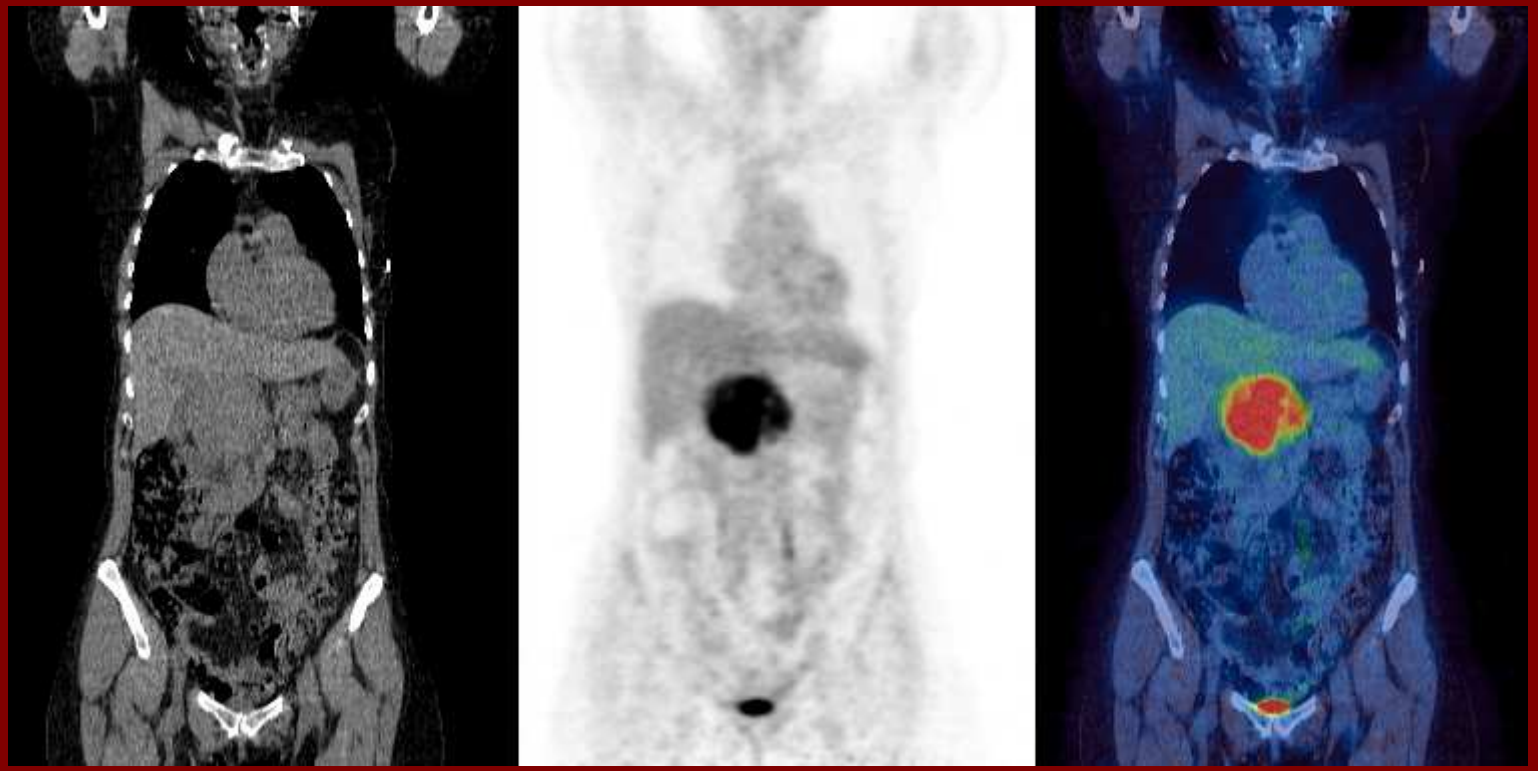
Deauville Score		Substudy score
Score	No of patients	
1	24	24 score 1
2	21	21 score 2a
3	18	18 score 2b
4	34	31 score 2b 3 score 2c
5	0	-
TOTAL	97	97

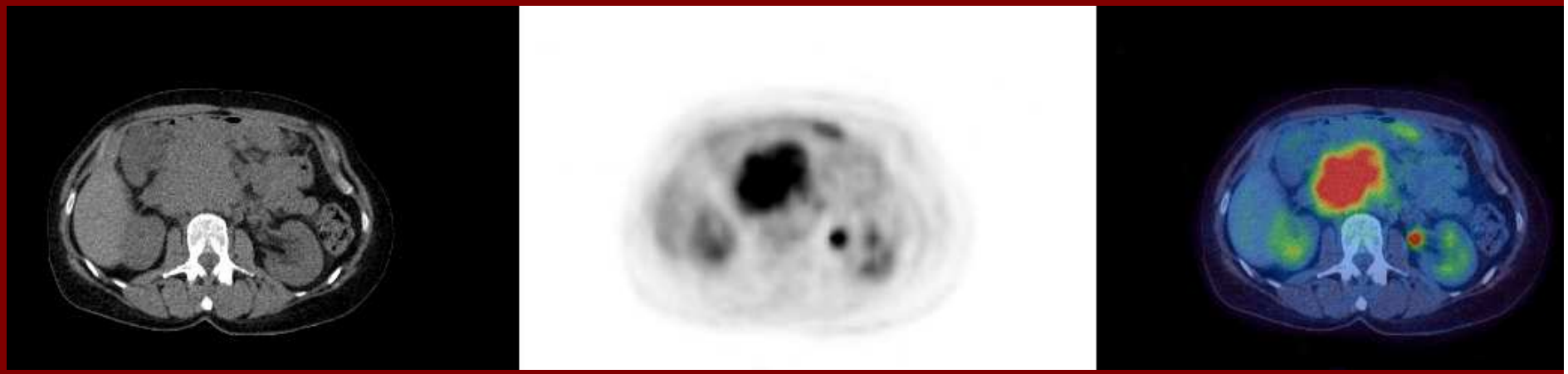
Comment

- Very few have stable disease (3/97)
- Deauville score may be better in separating significant residual uptake group

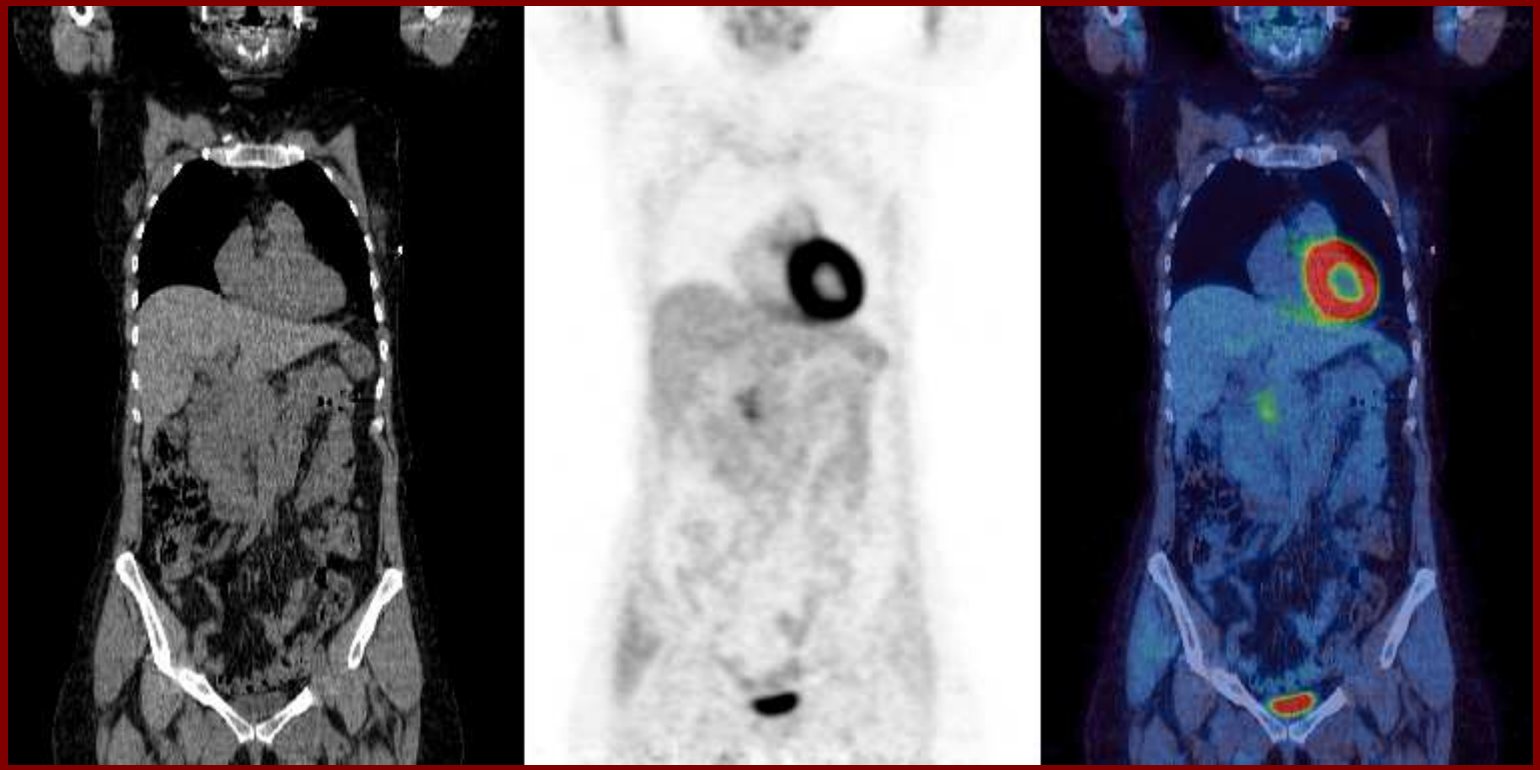
Comparison of Deauville score & Quantitative criteria

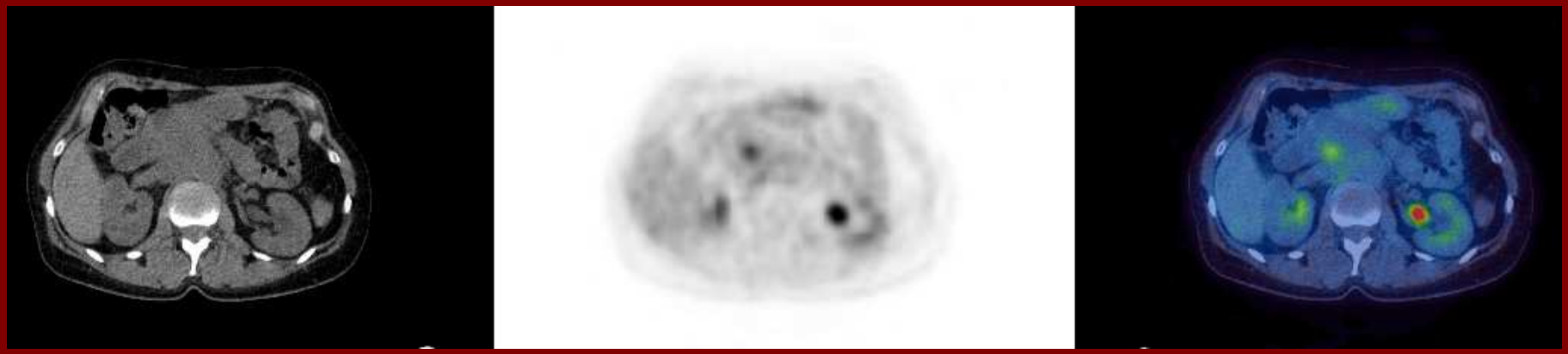
Deauville Score		SUV_{max} reduction	
Score	No of Patients	>66%	<66%
1	24	24	0
2	21	21	0
3	18	17	1
4	34	21 Range (67-92%)	13
5	0	0	0
	97	83	14





Baseline max SUV = 21.4





SUV after 2 x R-CHOP = 6.0
SUV reduction 72% BUT Deauville score 4

Comment

- Good Concordance for scores 1 & 2
- 17/18 of score 3 &
  21/34 (62%) of score 4
  would be responders with >66% SUV reduction
- What predicts response / FFS better:
  - % SUV reduction (regardless of residual uptake)
  - Residual uptake (regardless of initial uptake)
  - ?? Combination
- To improve PPV: cut-off within score 4?

Cut-offs

Deauville		Deauville		SUV reduction	
1+2	3+4+5	1+2+3	4+5	>66%	<66%
45 (46%)	52 (54%)	63 (65%)	34 (35%)	83 (86%)	14 (14%)
Substudy		Mikhaeel 41% -ve, 16% MRU, 43% +ve Haioun 60% -ve, 40% +ve			
1+2a	2b-2d				
45	52				

Conclusion

- Current cohort shows different separation of groups by Quantitative vs 5 point SS
- Final outcome analysis will aim to define cut-off:
  - Best separation of curves (highest accuracy)

  Or
  - Acceptable PPV to use in escalation studies
- Cut-off for interventional studies: may prove to be specific to : disease, treatment, scanning timing, QA / QC of PET

Guy's and St Thomas' NHS

NHS Foundation Trust

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