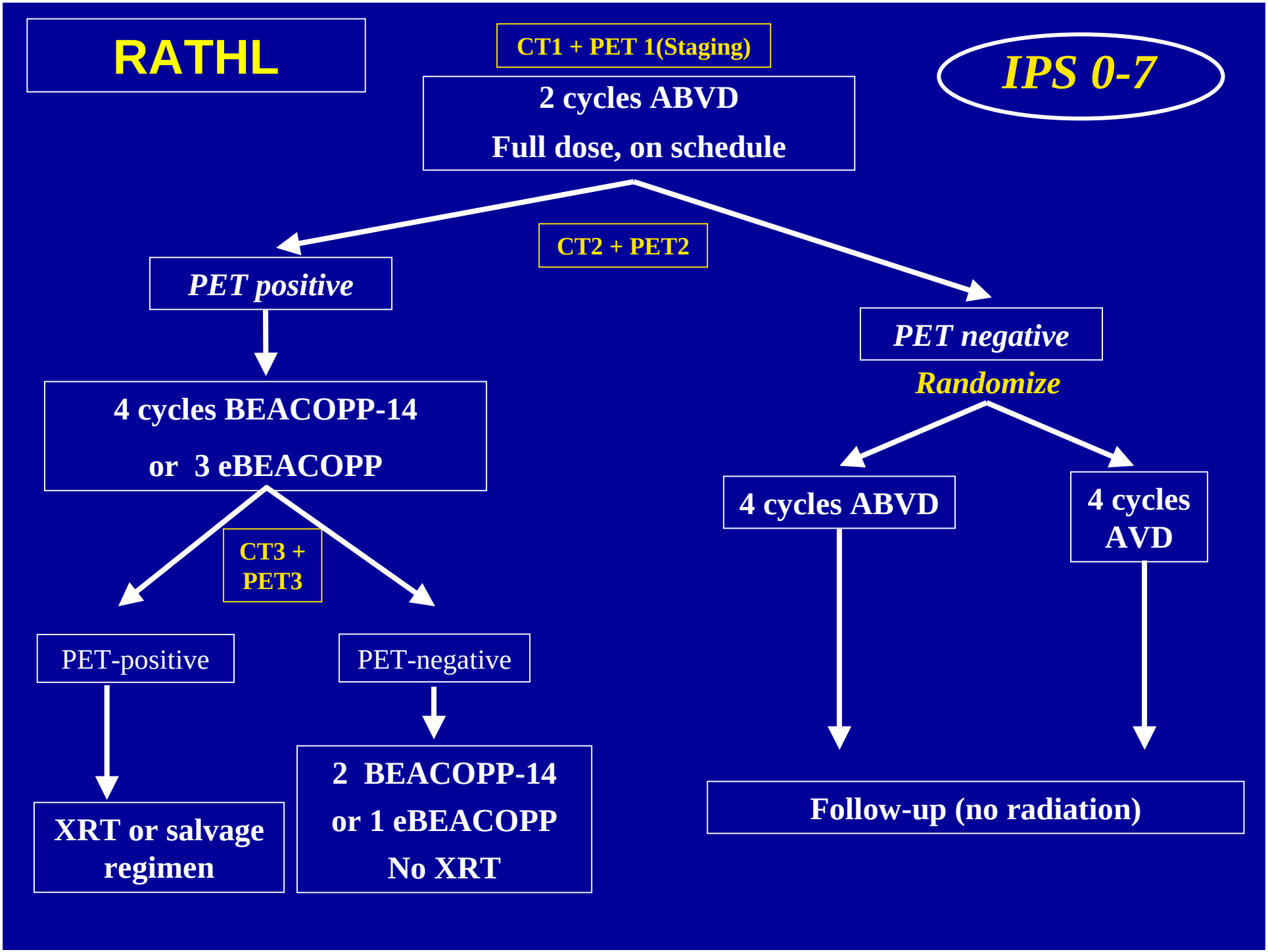
Response-adjusted therapy for Hodgkin Lymphoma (RATHL)

Principles for a trial in advanced Hodgkin Lymphoma

- ABVD will cure 70%
- eBEACOPP might cure more, but will probably make them sterile, and may risk MDS/AML
- Our retrospective data does not support the absolute need for maximum intensity at the start
- It is desirable to de-escalate treatment in the best responders to avoid late toxicity
- FDG-PET after 2 cycles appears highly predictive, particularly for treatment failure on ABVD

Inclusion criteria

- Classical Hodgkin Lymphoma by WHO
- Aged 18 or above
- Not previously treated
- Stages IIB - IV or stage IIA with adverse features (bulk, 3+ sites)
- All prognostic groups


RATHL
CT1 + PET 1(Staging)
2 cycles ABVD
Full dose, on schedule
IPS 0-7
CT2 + PET2
PET positive
PET negative
Randomize
4 cycles BEACOPP-14
or 3 eBEACOPP
4 cycles ABVD
4 cycles AVD
CT3 + PET3
PET-positive
PET-negative
XRT or salvage regimen
2 BEACOPP-14
or 1 eBEACOPP
No XRT
Follow-up (no radiation)

RATHL: statistics

- Assumptions:
  - 75% PET-negative after 2 ABVD
  - 3 year PFS 95% in PET-negative group
- 1200 patients and 3 years follow up:
  - 900 patients randomised in ABVD vs AVD
  - Primary end-point 3 year PFS
  - 90% power to exclude AVD being 3-4% worse than ABVD

PET Protocol

- 350 - 550 MBq ^{18}F-FDG for 2D acquisition
  150-350 MBq for 3D acquisition
- Emission scan at 60, or maximum 70, minutes after injection
- Response scans (day 9-13) performed at the same time after injection as the baseline scan $\pm$ 10 minutes
- Attenuation corrected 'half-body' PET-CT scan to cover the area from the base of the brain to mid-thigh using the CT of the PET - CT scanner
- Perform head and neck scan if required to cover sites of disease.
- Patients scanned with arms above the head for the body scan (if tolerated) and by the side for head and neck scan if acquired

Central PET review

Standardised protocol drawn up by expert panel:

- Only full-ring dedicated PET-CT scanners
- Documented daily quality control procedure
- Tested and secure method to transfer anonymised scan data, and agreed file naming convention.
- It must be demonstrated that image quality is comparable between centres and standard uptake values can be reliably determined from the PET/CT images

Scoring

1 no uptake
2 uptake ≤ mediastinum
3 uptake > mediastinum but ≤ liver

If mediastinal blood pool activity =/> liver:
lesion uptake less than liver = score 2
lesion uptake equal to liver = score 3

4 moderately increased uptake compared to liver
5 markedly increased uptake compared to liver

Testing the reading of PET scans

- 100 scans read at 4 centres
  - St Thomas's, Modena, Copenhagen, Lund
  - 50 baseline, 50 post cycle 2
- Agreement in 44/50 cases, 46/50 after discussion
- Kappa for neg vs pos 0.85

Current status of RATHL study

- Trial Opened August 2008
- Collaboration of Italian (GISL), Irish (ICORG), Australasian (ALLG) and Nordic groups
- Sites: UK 62, Italy 12, Norway 3 to date
- ALLG, Sweden, Denmark, Ireland with the lawyers
- 182 patients registered, 114 randomised
- 12/100 PET score 4/5
- 2 sub-studies:
  - Fertility/ ovarian cryopreservation: funded
  - Markers of bleomycin toxicity: under review

Patients not randomised

- Adverse events 2
- Patient choice 4
- Non-compliance 3
- Other 1

PET Centres: UK

Glasgow

Preston
Manchester

Birmingham
Coventry

Cheltenham
Oxford
Mount Vernon

Portsmouth

Aberdeen

Newcastle

Nottingham

Cambridge

Guy's/ St Thomas'
Royal Marsden
St Bartholomew's
UCL

Conclusions

- Central review system is working…
- …and can be replicated internationally
- Recruitment is accelerating
- Rate of PET+ lower than expected
- Number of withdrawals is low

CANCER RESEARCH UK