

The RAPID trial in patients with clinical stages IA/IIA Hodgkin lymphoma and a “negative” PET scan after 3 cycles ABVD

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on behalf of the UK NCRI Lymphoma Clinical Studies
Group

Objectives in early stage HL

To maximise the number of cures and minimise late toxicity by restricting RT to those who require it for the elimination of residual disease after chemotherapy

Question addressed by RAPID

Is a “negative” FDG-PET scan after 3 cycles ABVD a sufficiently sensitive/specific biomarker of disease elimination that RT can be avoided in these patients without unacceptable reduction in disease control?

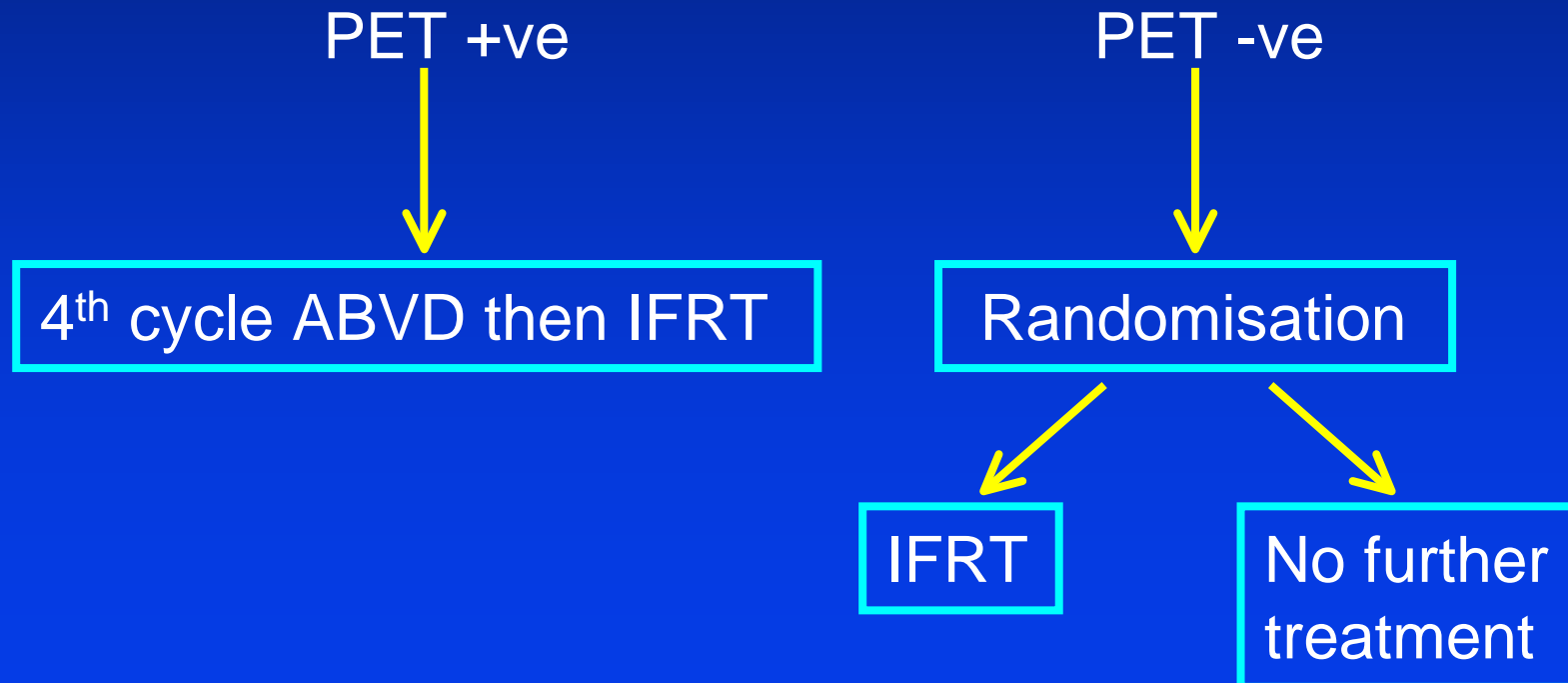
RAPID - eligibility

- Histologically confirmed HL
- Males and females ≥ 18 years
- Clinical stages IA/IIA with no mediastinal bulk
- No previous treatment
- Able to conform to requirements of protocol

RAPID - trial design

Initial treatment: ABVD x 3

Re-assessment: if NR/PD, patient goes off study
if CR/PR, FDG-PET scan performed



RAPID - endpoints

- Primary
 - Progression-free survival
- Secondary
 - Incidence of FDG-PET +ve/-ve after 3 cycles ABVD
 - Overall survival
 - Incidence and type of 2nd cancers and cardiovascular events

RAPID - statistics

- With 320 PET -ve patients randomised, trial originally designed to exclude a $\geq 10\%$ difference in PFS with 90% power
- Number recruited to achieve this number is dependent on PET -ve/+ve rate after 3 cycles ABVD
- Planned annual interim analysis to exclude $\geq 15\%$ difference between trial arms in which case trial would be halted by IDMC

PET scanning - 1

- Fixed site scanners located at 21 regional PET Centres in the UK calibrated using standard phantoms and operated to trial SOP
- FDG-PET scan performed 10-12 days after day 15 of cycle 3 ABVD
- Data transmitted on-line to Clinical PET Centre at St Thomas' Hospital, London (Core Lab)

PET scanning - 2

- Central review performed by Mike O'Doherty and Sally Barrington at Core Lab
- Score of 1-5 assigned by these central reviewers
- For the purposes of this trial score 1 or 2 deemed “negative” and score 3,4 or 5 “positive”
- Duplicate report sent to Clinical Centre and Trials Office

PET scanning - 3

- Patient eligible for randomisation (RT vs no RT) if PET score of 1 or 2 at central review
- Clinical Centre requests randomisation for patient X
- Trials Office randomises if able to confirm score of 1 or 2 for patient X from duplicate central review report

Status at time of analysis - 1

- 369 patients registered; 190 male, 179 female, median age 34.5 years
- 331 had a PET scan after 3 cycles ABVD
 - Score 1, 203 (61%)
 - Score 2, 58 (18%)
 - Score 3, 35 (11%)
 - Score 4, 20 (6%)
 - Score 5, 15 (4%)
- Score 1,2 -ve (261, 79%); score 3,4,5 +ve (70, 21%)

Status at time of analysis - 2

- 257 of 261 PET -ve pts randomised
 - Involved field RT (n=125, 49%)
 - No further treatment (n=130, 51%)
 - Outcome of randomisation entered after database locked for analysis (n=2)
- 4 pts not randomised
 - Patient choice (n=2)
 - Clinician choice (n=1)
 - Error (n=1)

Status at time of analysis - 3

- Median follow-up of 13 mo from randomisation
 - 245 of 255 (96%) pts are alive and progression-free
 - 6 (2%) have progressed
 - 4 (1.5%) have died (HL 1, treatment related 1, other 2)

Summary

- Trials based on a quality controlled/assured PET scan results (calibrated fixed site scanners, central review at national core lab) are feasible
- Patients who are PET -ve after 3 x ABVD are willing to be randomised to receive either RT or no further treatment
- The observed PET +ve rate of 21% is at the upper end of the expected range
- The event rate after short follow-up is very low and the early stopping rule ($\geq 15\%$ difference between randomised arms) has not been met

Recruitment

- Delegate survey at 9th ISHL, Cologne 2007 suggested that *excluding a difference of $\leq 10\%$ required for RAPID to be practice changing*
- Recruitment continues with extended target of 600 (protocol amendment 3; *to deliver 400 PET negative pts for randomisation with aim of excluding $\geq 7\%$ difference between trial arms*)
- As of end March 2010, *565 registered and 382 PET negative patients randomised*



Effects of restricting RT to the PET +ve and those who subsequently relapse

- With CT and RT for all patients **100%** receive RT at baseline
- If only PET +ve irradiated and assuming PET +ve rate of 20%, then **20%** receive RT at baseline
 - If we also assume 10% of PET –ve patients relapse and receive RT at salvage, another **8%** (10% of 80%) receive RT at this point
 - So total receiving RT based on this policy is **20%+8% = 28%**

Sub-studies

- *Radiotherapy QA*; Tim Illidge and Peter Hoskin
- *Cardiac radiation dosimetry to individual cardiac structures*; David Cutter and Sarah Darby at University of Oxford
- *Cardiac function study*; for detailed evaluation of cardiac function in RT vs no RT RAPID population and correlation of these data with RT doses to myocardium, coronary vessels, conducting tissue and valves

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PET review

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Statistics

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