Blinded evaluation of the prognostic value of FDG-PET/CT after 2 cycles of RCHOP in DLBCL – UK-NCRI study

N.George Mikhaeel[1], Jessica Brady[1], David Cunningham[2], Andrew McMillan[3], John Radford[4], Kirit Ardeshna[5], Nicholas Counsell[6], Anthony Lowry[6], Paul Smith[6], Michael O'Doherty[7], Sally F Barrington[7].

[1]Department of Clinical Oncology, Guy's & St Thomas' NHS Trust, London, UK, [2]The Royal Marsden Hospital, London, UK, [3]Department of Haematology, Nottingham University Hospital, Nottingham, UK, [4]Department of Medical Oncology, The Christie Hospital and Manchester University, Manchester, UK, [5]Mount Centre Cancer Centre, Northwood, Middlesex, UK, [6]Cancer Research UK and UCL Clinical Trials Centre, London, UK, [7]KCL PET imaging centre at St Thomas' hospital, London, UK

OBJECTIVES

- The prognostic value of early PET scanning in Diffuse Large B cell Lymphoma (DLBCL) has not been established.
- The UK-NCRI initiated a prospective blinded study (UKCRN-ID 1760) to evaluate the prognostic value of FDG-PET/CT after 2 cycles of RCHOP in a subset of patients treated in the prospective NCRI study comparing RCHOP-21 and RCHOP-14.
- The objective of the study was to answer the following questions:
1. Does FDG-PET/CT after 2 cycles of chemotherapy predict the remission status after treatment?
2. Does early response predict long-term prognosis?
3. What is the magnitude of difference in Progression-free Survival (PFS) between PET positive and negative patients?
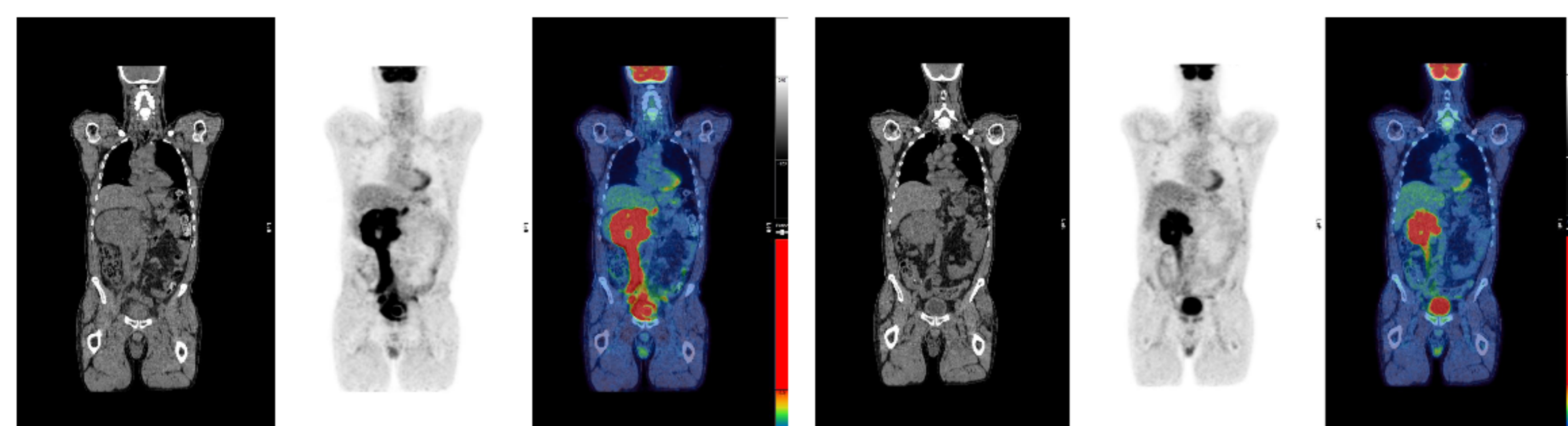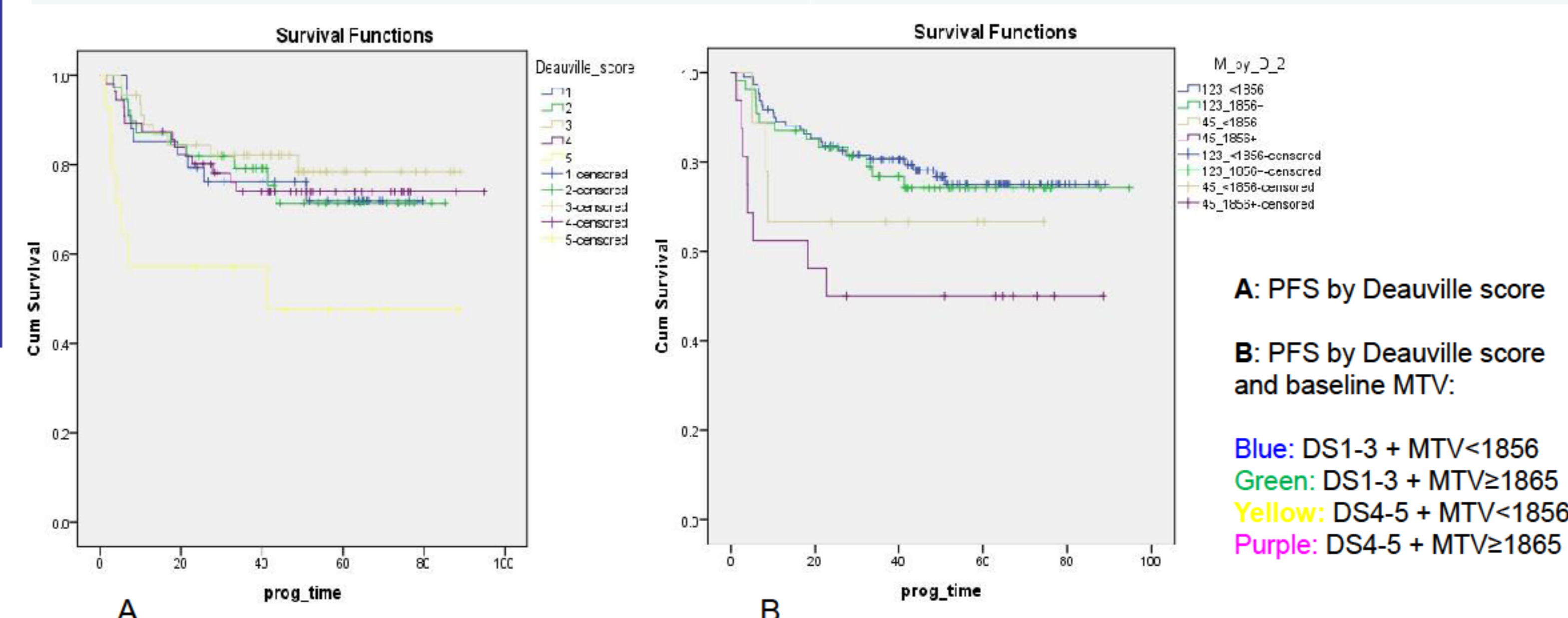4. What is the value of quantitative assessment of response?

METHODS

- 189 eligible patients had baseline (PET-0) and post-cycle 2 (PET2) according to study protocol in centres which satisfied QA requirements.
- The PET-2 scan was not reported but archived for central reporting at least 3 months later. The primary endpoint was 2-year progression-free survival (PFS).
- Response was assessed using *visual* [NCRI criteria (see box below) and Deauville score (DS)] and *quantitative* methods [reduction in maximum standardised uptake value (SUVmax)].
- Baseline metabolic tumour volume (MTV) was also measured (defined as volume with SUV≥2.5).
- Cox regression and Kaplan Meier curves were used to examine the relationship between PFS and the study variables; receiver operator characteristic (ROC) analysis was used to determine the optimal cut-off for continuous variables.

RESULTS

- After a median *follow-up* of 53.8 months, the 2-year PFS was 79.8% (95% CI: 74.1-85.5) and 2-year overall survival (OS) was 85.6% (95% CI: 80.5-90.7).
- *Univariate* Cox regression analysis showed the following parameters to be associated with worse PFS:
  - NCRI score 2c-2d (HR=8.2, 95% CI: 2.6-26.7, p<0.001)
  - DS-5 (HR=3.0, 95% CI: 1.3-6.7, p=0.007)
  - International Prognostic Index (IPI) score 4-5 (HR=2.7, 95% CI: 1.4-5.2, p=0.003)
  - baseline MTV ≥1856cc as defined by ROC (HR=2.5, 95% CI: 1.3-4.8, p=0.009)
  - SUVmax reduction <66% (HR=2.2, 95% CI: 1.1-4.5, p=0.035).
- The number of patients in the worse prognostic group for each variable was relatively small (4, 14, 26, 25, and 21 respectively).
- *Multivariable* analysis showed the following variables to be independent predictors of worse PFS:
  - NCRI score 2c-2d (HR=7.2, 95%CI: 1.7-31.0, p=0.008)
  - DS-5 (HR=3.3, 95%CI: 1.2-9.2, p=0.022)
  - IPI score 4-5 (HR=2.7, 95%CI: 1.3-5.3, p=0.005)

Prognostic group	2-year PFS % (95% CI)
NCRI score:	
1 – 2b (n=185)	81.0 (75.3 – 86.7)
2c – 2d (n=4)	25.0 (0 – 67.5)
Deauville score:	
1 – 4 (n=175)	81.6 (75.9 – 87.3)
5 (n=14)	57.1 (31.2 – 83.0)
SUVmax reduction:	
≥66% (n=168)	81.5 (75.6 – 87.4)
<66% (n=21)	66.7 (46.5 – 86.9)
Baseline MTV:	
<1856cc (n=164)	83.5 (77.8 – 89.2)
≥1856cc (n=25)	56.0 (36.6 – 75.4)
IPI:	
1 – 3 (n=161)	82.6 (76.7 – 88.5)
4 – 5 (n=26)	61.0 (42.0 – 80.0)

A: PFS by Deauville score

B: PFS by Deauville score and baseline MTV:

Blue: DS1-3 + MTV<1856
Green: DS1-3 + MTV≥1865
Yellow: DS4-5 + MTV<1856
Purple: DS4-5 + MTV≥1865

NCRI Score
Score 1: complete disappearence of abnormal uptake
Score 2:
  a: **Minimal Residual Uptake (MRU):** Residual uptake just above background
  b: **Partial Response:** Reduction of uptake but significant residual uptake
  c: **Stable:** No significant change
  d: **Progression:** increase in baseline abnormal uptake &/or appearence of new sites

Example: PET 0 (left) & PET 2 (right) scans of patient with DS 5 post 2 R-CHOP with residual high grade uptake in right renal mass & retroperitoneal nodes

CONCLUSIONS

- FDG-PET/CT after 2 cycles of RCHOP identifies a small group of patients who have worse PFS. However most of the relapses occur in the group of patients with complete metabolic response.
- After 2 cycles of RCHOP, only DS 5 was predictive of worse prognosis.
- Baseline characteristics have independent prognostic value from early PET-2 response.
- Improving prognostic value of PET-2 may be possible by combining baseline characteristics with PET-2 response.