BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

FDG-PET/CT after 2 cycles of RCHOP in DLBCL predicts complete remission but has limited value in identifying patients with poor outcome - Final result of UK-NCRI prospective study

Journal:	*British Journal of Haematology*
Manuscript ID	BJH-2020-00733.R1
Manuscript Type:	Ordinary Papers
Date Submitted by the Author:	n/a
Complete List of Authors:	Mikhaeel, N; Guy's and Saint Thomas' NHS Foundation Trust, Department of Clinical Oncology Cunningham, David; Royal Marsden Hospital, Haematology Counsell, Nicholas; University College London, CRUK UCL Cancer Trials Centre McMillan, Andrew; Nottingham University Hospitals, Centre for Clinical Haematology; Radford, John; The Christie NHS Foundation Trust and The University of Manchester, Hematology Ardeshna, Kirit; UCLH, Haematology Lawrie, Anthony; Cancer Research UK and UCL Cancer Trials Centre, CTC Smith, Paul; University College London, Cancer Research UK and UCL Cancer Trials Centre Clifton-Hadley, Laura; University College London, CRUK and UCL Cancer Trials Centre O'doherty, Michael; King's College London, Faculty of Medicine and Pharmaceutical sciences Barrington, Sally; Division of Imaging and Biomedical Engineering, King's College London, PET Imaging Centre
Key Words:	LYMPHOMAS, diffuse large b-cell lymphoma, PET, RCHOP

FDG-PET/CT after 2 cycles of RCHOP in DLBCL predicts complete remission but has limited value in identifying patients with poor outcome - Final result of UK-NCRI prospective study

N George Mikhaeel[1], David Cunningham[2], Nicholas Counsell[3], Andrew McMillan[4], John A Radford[5], Kirit M Ardeshna[6], Anthony Lawrie[3], Paul Smith[3], Laura Clifton-Hadley[3], Michael J O'Doherty[7], Sally F Barrington[7]

[1] Guy's Cancer Centre, Guy's & St Thomas' Hospital NHS Trust and School of Cancer and Pharmaceutical sciences, King's College London University, London, UK.

[2] The Royal Marsden NHS Trust, London and Surrey, UK

[3] Cancer Research UK and UCL Cancer Trials Centre, London, UK

[4] Nottingham University Hospital NHS Trust, Nottingham, UK

[5] University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[6] University College London Hospital NHS Trust, London, UK

[7] King's College London and Guy's and St Thomas' PET Centre, School of Biomedical Engineering and Imaging Sciences, King's College London, King's Health Partners, London, UK

Corresponding author:

N George Mikhaeel

Guy's Cancer Centre

Guy's & St Thomas' NHS Foundation Trust

Great Maze Pond

SE1 9RT

London, United Kingdom

Email: george.mikhaeel@gstt.nhs.uk

Tel: +44 207 188 4225

ORCID : 0000 0003 0359 0328

Acknowledgments:

National Health Service provided funding for PET scans through excess treatment cost subvention fund. CRUK provided funding for technical support to PET centre core lab at St Thomas' Hospital.

DC acknowledges financial support from NIHR Biomedical Research Centre at the Royal Marsden NHS trust. KMA is supported by the UCL/UCLH Biomedical Research Centre. SFB acknowledges financial support from the National Institute for Health Research and Social Care (NIHR) [RP-2-16-07-001] and also through NIHR comprehensive Biomedical Research Centre awards to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and the King's College

London and University College London Comprehensive Cancer Imaging Centre funded by the CRUK and EPSRC in association with the MRC and DoH (England). This work was also supported by the Wellcome/EPSRC Centre for Medical Engineering at King's College London [WT 203148/Z/16/Z]. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The R-CHOP study was managed by the Cancer Research UK and University College London Cancer Trials Centre.

ABSTRACT

PURPOSE

The UK-NCRI initiated a prospective study (UKCRN-ID 1760) to assess the prognostic value of early FDG-PET/CT in Diffuse Large B-Cell Lymphoma (DLBCL).

METHODS

189 DLBCL patients treated with RCHOP had baseline and post-cycle-2 PET (PET2) within a quality assurance framework. Treatment decisions were based on CT; PET2 was archived for central blinded reporting after treatment completion. The association of PET2 response with end-of-treatment CT, progression-free (PFS) and overall survival (OS) was explored.

RESULTS

The end-of-treatment complete response rate on CT was 83.9%, 75.0%, 70.5%, 40.4% and 36.4% for Deauville score (DS) 1 (n=34), 2 (n=39), 3 (n=46), 4 (n=56) and 5 (n=14) ($p<0.001$), and 64.1% and 50.0% for ΔSUVmax≥66% (n=168) and <66% (n=21) respectively ($p=0.25$). After 5.4 years median follow-up, 5-year PFS was 69.4%, 72.8%, 76.7%, 71.2% and 47.6% by DS 1-5 ($p=0.01$), and 72.6% and 57.1% by ΔSUVmax≥66% and <66% ($p=0.03$) respectively. The association with DS remained in multivariable analyses, and was consistent for OS.

CONCLUSIONS

Early complete metabolic response (DS 1-3) at interim PET/CT after 2 cycles of RCHOP in DLBCL is associated with higher end-of-treatment complete and overall response rates; however, only DS-5 patients had inferior PFS and OS.

Keywords: Lymphoma, Large B-Cell, Diffuse (DLBCL); positron emission tomography (PET); R-CHOP chemotherapy.

INTRODUCTION

The cure rate of diffuse large B-cell lymphoma (DLBCL) has improved over the last two decades with the addition of rituximab (R) to cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy and improvements in supportive care that have enabled more patients to tolerate full-dose chemotherapy [1,2]. However, a significant proportion of patients are not cured with R-CHOP. In clinical trials this ranges from 20-30% and 30-40% in population-based studies [3]. Salvage treatments after R-CHOP are less effective than after CHOP [4]. Improving the outcome of DLBCL requires identification of patients who are unlikely to be cured by R-CHOP and the availability of alternative, more effective treatments. Efforts to classify DLBCL according to molecular profile and to target specific pathways are ongoing but have not resulted in a change in therapeutic options yet [5]. Therefore, early identification of patients unlikely to be cured with R-CHOP remains an important step towards testing alternative approaches to improve their chance of cure.

PET-CT shows metabolic response earlier than anatomical response on CT and early response assessment may predict final remission and prognosis. Studies have shown that interim PET (iPET) is a strong prognostic indicator in Hodgkin lymphoma (HL) and several clinical studies testing response-adapted treatment algorithms in HL have been performed [6,7]. In DLBCL, while early data favoured iPET [8,10], more recent data have suggested iPET is less predictive for prognosis with immunochemotherapy and end-treatment PET is a better predictor [11-13].

Response criteria have also evolved which affect the utility of iPET in response assessment. The Deauville criteria, a 5-point scale, has been adopted worldwide as the visual assessment method of choice and is recommended by international guidelines replacing older criteria [14,15]. Semi-quantitative response assessment (e.g. reduction in the maximum standardised uptake value, ΔSUVmax) has also been studied in DLBCL with some success [16].

The UK National Cancer Research Institute (NCRI) initiated a prospective blinded study (UKCRN-ID 1760) to evaluate the prognostic value of 18F-fluorodeoxyglucose (FDG) PET/CT after 2 cycles of R-CHOP in a subset of patients treated in the phase III randomised controlled trial of RCHOP-21 versus RCHOP-14 [17]. The study protocol allowed response assessment by CT only, and iPET performed after 2 cycles was not used for response assessment nor treatment decisions.

The study aims were to: (1) evaluate the prognostic value of FDG-PET-CT response after 2 cycles of R-CHOP chemotherapy for newly diagnosed DLBCL, in terms of final remission status after treatment and long-term outcomes, and (2) evaluate if a quantitative method of response assessment (ΔSUVmax) improved the prognostic value of visual assessment.

PATIENTS AND METHODS

Study design and population:

Eligibility criteria included: a) newly diagnosed adult patients with histologically proven DLBCL confirmed by a specialist histopathologist, b) entry into UK-NCRI phase III randomised study (ISRCTN 16017947) comparing RCHOP-21 to RCHOP-14, c) written informed consent, and d) a baseline FDG-PET/CT showing uptake in sites of disease. Exclusion criteria were: a) negative pre-treatment FDG-PET/CT, and b) PET/CT performed more than 2 weeks before commencing treatment. Patients were treated with R-CHOP given as either a 14-day cycle x6 + 2 cycles of rituximab or as a 21-day cycle x8 as published previously [17]. Following the completion of randomisation in the phase III study, the PET substudy was extended as a single arm with RCHOP-21 treatment (the main trial results showed that R-CHOP-14 was not superior to R-CHOP-21, so the 21-day cycle x8 remained standard of care).

Patient registration and trial management were performed by the Cancer Research UK and University College London Cancer Trials Centre. The trial was overseen by a trial steering

committee and an independent data monitoring committee. The protocol was approved by the UK Medicines and Healthcare products Regulatory Agency and the Hull and East Riding Research Ethics Committee, and carried out in accordance with the Declaration of Helsinki and the European Union Clinical Trials Directive 2001/20/EC. Patients provided written informed consent.

Blinding procedure:

The iPET scan was not reported but archived for central review at least 3 months later to allow completion of therapy. Treating clinicians were blinded to the scan findings and Nuclear Medicine physicians reporting the PET scans were blinded to the outcome of treatment. Response was assessed with a repeat CT scan after 4 cycles of chemotherapy and after completion of treatment according to the International Workshop Standardised Response Criteria [18]. Analysis of data was performed after completion of recruitment.

Response assessment on PET:

The study started before the 5-point scale (known as Deauville criteria) was introduced [19], however the protocol was later modified to allow response to be assessed by the Deauville score [DS]. Response was recorded primarily using visual assessment, although semi-quantitative measurements of SUVmax of lesion to liver were made to confirm visual assessment to minimise reporter error [12, 20-21]. Score 5 was assessed as a maximum SUV in tumour that was at least 3 times higher than the maximum SUV in a large region in the right lobe of an area of normal liver and/or the presence of new lesions attributable to lymphoma [16]. The percentage change in the maximum standardised uptake value between baseline and interim was measured, with response classified as a reduction in SUVmax of ≥ 66% [16].

PET scanning and Quality assurance

PET-CT scans were acquired at baseline, within two weeks prior to commencing treatment and at least 10 days after the second cycle of RCHOP. Scans were performed using commonly agreed methods for quality control, as previously reported [22]. Physicists from the Core Lab at St Thomas' Hospital, London visited each participating PET Centre to scan a standard phantom to check image quality and quantitative accuracy. Patients were asked to fast for 6 hours, prior to administration of 350-400 MBq of FDG with a recommended uptake period of 90 minutes. Half body scans were acquired using the site specific protocol with respect to 2D or 3D acquisition, time per bed position and image reconstruction, but OSEM reconstruction was specified. Baseline and response scans had to be performed on the same scanner. All scans were independently reported by two Nuclear Medicine Physicians (SFB, MJOD) each with > 20 years' experience, with any differences resolved by consensus.

Statistical considerations

The primary endpoint was progression-free survival (PFS) measured from the date of randomisation to the date of first appearance of disease progression, relapse or death from any cause, and censored at the date last seen. The secondary endpoints were overall survival (OS), measured from the date of randomisation to the date of death from any cause, and complete response (CR) rate assessed in accordance with the International Workshop Standardised Response Criteria for Non-Hodgkin's Lymphoma [18].

Previous studies showed that approximately 50% of patients have a negative PET scan after 2 cycles of chemotherapy [9,10]. Two hundred patients were required to detect a minimal clinically important difference in PFS at 2-years, of either 80% to 55% or 75% to 50%, between PET negative and positive groups respectively, with 90% power and 2-sided 5% significance level.

Hazard ratios with 95% confidence intervals (CIs) were calculated for PFS and OS using the Cox proportional hazards model, and survival curves presented using the Kaplan–Meier method. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for response rates using binary logistic regression. Protocol-defined analyses included exploring the associations between these outcome measures and Deauville criteria (scores 1-5) and SUV categories. Multivariable models were used to check robustness of findings after adjusting for potentially confounding baseline characteristics. The data analysis was generated using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA).

Role of the funding source:

The funding bodies played no role in the study design, data collection, analysis or writing of final report.

RESULTS

Between December 2006 and September 2012, 231 patients with histologically proven previously untreated DLBCL were recruited, of whom 189 had baseline (PET0) and post-cycle 2 PET (PET2) scans performed according to the study protocol and were eligible for analysis. PET/CT scans were performed in 13 UK PET centres which satisfied quality assurance requirements. Forty-two patients were excluded: 15 due to patient withdrawals or scan cancellations, 12 because the interim scan was not performed, 8 for imaging protocol violations and 7 for other reasons (Figure 1).

In total, 61 patients were included from the randomised phase (RCHOP-14, n=30; RCHOP-21, n=31) and 128 patients from the RCHOP-21 single arm extension. After a median follow-up of 5.4 years, the 2- and 5-year PFS rates were 79.9% (95% CI: 74.1-85.6) and 70.9% (95% CI: 64.1-77.6), and the 2- and 5-year OS rates were 85.7% (95% CI: 80.7-90.7) and 80.1% (95% CI: 74.1-86.1) respectively. There was no evidence of a difference between treatment arms (PFS, p=0.46; OS, p=0.63). The patient characteristics of the PET substudy cohort (Table 1) were generally similar to the characteristics of the randomised trial patients, however there was a lower proportion of patients with raised LDH, B symptoms and bulky disease and more patients with low risk IPI (0-1) in the substudy cohort.

End of treatment response:

Table 2 shows early metabolic response on interim PET in relation to final CT response which was available for 174 patients. At the completion of treatment, assessment of response based on CT imaging showed that 109 patients (62.6%) achieved CR/CRu, of whom, 84 (77.1%) achieved complete metabolic response (CMR) on interim PET after 2 cycles by Deauville criteria (DS 1-3), and 100 (91.7%) by quantitative criteria (ΔSUVmax≥66%).

The likelihood of achieving CR/CRu was associated with the depth of metabolic response on PET2; the CR/CRu rate was 83.9% (26/31), 75.0%, (27/36) 70.5% (31/44),

40.4% (21/52) and 36.4% (4/11) for DS 1, 2, 3, 4 and 5 respectively. There was strong evidence that CMR (i.e. DS 1-3) was associated with a higher CR/CRu rate compared to no-CMR (OR=4.73, 95% CI: 2.43-9.20, p<0.001), and a higher overall response rate (OR=2.80, 95% CI: 1.01-7.78, p=0.05). For ΔSUVmax the frequency of achieving CR/CRu was 64.1% (100/156) and 50.0% (9/18) for ≥66% and <66% respectively (OR=0.56, 95% CI: 0.21-1.49, p=0.25), and overall response rates were 91.7% (143/156) and 77.8% (14/18) respectively (OR=0.32, 95% CI: 0.09-1.11, p=0.07).

Progression-free & overall survival:

There was no strong evidence of a difference in PFS between the CMR **(DS 1-3)** and no-CMR **(DS 4-5)** groups (HR=1.37, 95% CI: 0.80-2.34, p=0.25), with 2-year PFS rates of 82.3% (95% CI: 75.4-89.2) and 75.7% (95% CI: 65.7-85.7) respectively. PFS by individual Deauville score is shown in Figure 2; there was no evidence of a difference between individual scores 1-4, however, DS 5 had significantly worse PFS than the DS 1-4 group (HR=2.68, 95% CI: 1.21-5.93, p=0.01), with 2-year PFS rates of 57.1% (95% CI: 31.2-83.0) and 81.7% (95% CI: 76.0-87.4) respectively**, using predefined criteria for score 5 of maximum SUV at least 3 times higher than the maximum SUV in liver and/or the presence of new lesions. A post-hoc analysis was also performed assigning score 5 to patients with uptake at least 2 times higher than normal liver and/or new lesions (suppl. Fig 1).** Patients with ΔSUVmax<66% had worse PFS than those with ΔSUVmax≥66% (HR=2.12, 95% CI: 1.07-4.21, p=0.03) (Figure 3)**; 11/14 (78.6%) of DS5 (3x liver) patients had ΔSUVmax<66% (suppl. Table 1).**

Investigating the impact of IPI on PFS (Figure 4), there was strong evidence that patients in the high-risk group (IPI score 4-5) had worse PFS than those with a score of 0-3 (HR=2.63, 95% CI: 1.41-4.92; p<0.01). ~~**For patients with CMR (DS 1-3), there was a significant difference in PFS between IPI 0-3 and IPI 4-5 (HR=3.16, 95% CI: 1.29-7.72, p=0.01), whereas a smaller effect was observed in those with no-CMR (HR=2.01, 95% CI: 0.83-4.90, p=0.12)(interaction p=0.57).**~~ Multivariable analysis demonstrated that both DS and IPI

were independently associated with PFS, but the association with ΔSUVmax did not remain (Table 3). **Similar results were observed in sensitivity analyses, both within RCHOP-21 patients only (n=169) and adjusting for trial arm, as well as when adjusting for other baseline characteristics. Findings were also consistent across analyses of OS.**

DISCUSSION

This is the largest prospective blinded observational study to assess the role of interim PET/CT in DLBCL treated homogenously with R-CHOP. PET/CT scans were performed after 2 cycles and not reported until the completion of treatment and all treatment decisions were made on the basis of CT. At the time of reporting, nuclear medicine physicians were blinded to treatment outcome on CT. Reporting was performed using the internationally recommended Deauville criteria and using the ΔSUVmax, recently adopted as a method for PET-guided response adaptation in some clinical trials [23,24].

International guidance suggests using DS 1-3 to assign CMR for patients receiving standard treatment. In this study, CMR after 2 cycles using this definition was associated with a higher chance of complete remission after treatment and the depth of early metabolic response (as measured by Deauville score 1 to 5) correlated with the likelihood of CR/CRu. However, achieving early CMR was not associated with a marked improvement in PFS or OS. Whilst there was some suggestion of a difference in outcomes the effect was not as large as anticipated (i.e. observed a 6.6 percentage-point difference in 2-year PFS compared to the target of 25 percentage-points); there was only strong evidence of a difference for patients with DS 5 (24.6% difference), patients with DS 4 had similar prognosis to those with DS 1-3, **using the UK NCRI definition of score 5 of uptake greater than 3 times liver uptake and/or new lesions attributable to lymphoma. A post-hoc analysis using uptake at least 2 times higher than normal liver and/or new lesions to define DS 5, which has been used by other research groups, increased the number of patients with score 5 but with reduced discriminative power. Similar findings were reported in a US-Nordic study of 112 patients with DLBCL scanned after one cycle of R-CHOP(like) chemotherapy, whereby only the small proportion of patients with DS-5 had inferior PFS and OS [25].** There is **also** evidence from other studies that inferior outcomes are seen in patients with DS 5 in Hodgkin lymphoma, primary mediastinal B cell lymphoma and DLBCL, although these studies used response adapted strategies or treatment was

consolidated with radiotherapy which could mitigate the adverse effect of a DS 4 result **[26-28].**

Quantitative response assessment using percentage reduction in SUVmax has been reported to improve response prediction compared with a purely visual assessment using the DS [21]. However, in our study with experienced readers using semi-quantitative assessment of lesion to liver uptake to confirm their visual impression, the Deauville criteria performed better in terms of identifying a group of patients with poor outcomes compared to ΔSUVmax using the previously reported cut-off of 66% [21]**, although it should be noted that the majority of DS5 patients had ΔSUVmax<66%**. We also studied the relationship between IPI and DS after 2 cycles; patients with high risk (IPI 4-5) had worse PFS than the remaining IPI categories (HR=2.63, p<0.01). A similar effect remained after adjusting for response after 2 cycles (HR=2.86, p<0.01), suggesting that the baseline prognosis and disease burden have an independent association with outcome even in patients showing evidence of early chemo-sensitivity **[29].**

There are a number of possible approaches going forwards to potentially improve the predictive value of PET-2 in DLBCL. The addition of baseline total metabolic tumour volume (MTV) to DS after 2 cycles has been shown to be strongly predictive, particularly for separating patients with DS4-5 or ΔSUVmax ≥66% into good and poor prognosis groups **[29,30].** The addition of gene expression profiling to response may also be helpful in improving the predictive value of PET-2 **[30,31].** Testing the combination of novel agents and R-CHOP may be a valid strategy in future studies using such a risk and response adapted approach.

A limitation of our study is the potential for selection bias, travel to a different hospital for the additional PET scan was sometimes required and this may have resulted in preferential accrual of motivated and fitter patients. This may explain the slightly better prognostic factors of the study population compared to the main randomised study (RCHOP 21 versus 14). Another limitation is the high dropout rate (18%, 42/231 patients), however, only 8 of these

were due to PET protocol violation. The majority of the dropouts were due to a lack of the second (PET2) scan, some of these patients may have missed the second scan because of disease progression which would have reduced the number of events in the study population.

The results of our study confirm reports that PET-2 is a good predictor of early response for patients with DLBCL treated with RCHOP [11, 24]. Nearly two-thirds (63.0%) of patients achieved CMR after 2 cycles and had a favourable PFS. Knowing this early has the advantage of reassuring patients and clinicians about the likely outcome of treatment as early as 4-6 weeks after starting therapy. The small proportion of patients (7.4%) with DS 5 should be monitored closely as they have a high chance of earlier progression or relapse. However, unlike Hodgkin lymphoma, treatment should not be changed on the basis of PET-2. The positive predictive value of PET2 is low, even for patients with DS 5, and there is currently no treatment alternative in DLBCL that has been shown to improve outcomes for patients compared to RCHOP **[32,33].** Several studies have examined treatment escalation for patients who do not achieve early CMR with RCHOP **[24,26,34,35].** None showed clear evidence of benefit for non-responders, although one study where patients received intensified treatment with stem cell transplantation had similar outcomes to patients achieving CMR. The only exception to this might be the very small group of patients where there is no response or even progression on treatment who might benefit from a change of treatment.

In conclusion, this blinded prospective study of interim PET/CT in DLBCL showed that PET-2 predicts complete remission early and identifies a small group of patients who have inferior PFS and OS. However, PET-2 alone should not be used to change treatment in clinical practice and efforts to improve response assessment by combining early PET results with baseline risk factors such as metabolic tumour volume and gene expression profiling are needed.

Author's contribution:

NGM, MJO, DC & SFB designed the study. NGM, DC, AM & JAR recruited patients. MJO & SFB reported PET scans. NC was the study statistician. PS, NC, AL & LCH were responsible for data collection and all aspects of study management in trials office. All contributed to data interpretation & manuscript writing. NGM had oversight of the study.

Compliance with Ethical Standards

Conflict of interest:

DC received research grants from Roche, Amgen, Sanofi -Aventis, Novartis, Astra-Zeneca, Merck KGA, and Celgene; participated on compensated advisory boards for Amgen, Roche, Merck, and Sanofi -Aventis, and uncompensated advisory boards for Roche (honoraria), Merck, and Sanofi-Aventis; and provided uncompensated expert testimony for Amgen. KMA has received research funding and honoraria from Roche. JAR has received research grants from Millennium, and provided expert testimony for Millennium Pharmaceuticals, Bayer-Schering, Roche, Napp Pharmaceuticals, Novartis, and GlaxoSmithKline. AM has received a research grant from Roche, and consultancy fees, honoraria, and travel expenses from Roche. The other authors declare that they have no conflicts of interest.

Role of Funding Source:

The trial sponsor (University College London) was responsible for data gathering, entry, and validation, monitoring procedures, liaison with investigators, statistical analysis, and production of the report. The NHS and CRUK had no role in interpretation of the data or production of final report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics Committee approval:

The protocol was approved by the Hull and East Riding Research Ethics Committee, and carried out in accordance with the 1964 Declaration of Helsinki and the European Union Clinical Trials Directive 2001/20/EC.

REFERENCES

1. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-42.
2. Pfreundschuh M, Kuhnt E, Trumper L, et al: CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013-22.
3. Sehn LH, Donaldson J, Chhanabhai M, et al: Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005;23:5027-33.
4. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in rituximab era. J Clin Oncol 2010;28(27):4184-4190.
5. Friedberg JW. Relapsed/Refractory Diffuse Large B-cell Lymphoma. Hematology 2011;2011:498-505
6. Andre MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35:1786-1794.
7. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374:2419-2429.
8. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al: 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk lymph 2000;39:543-53.
9. Mikhaeel NG, Hutchings M, Fields PA, et al: FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol 2005;16:1514-23.
10. Haioun C, Itti E, Rahmouni A, et al: F-18 fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005;106:1376-1381.
11. Mamot C, Klingbiel D, Hitz F, et al: Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). J Clin Oncol 2015;33:2523-9
12. Pregno P, Chiappella A, Bello M, et al: Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood 2012;119:2066-73.
13. Carr R, Fanti S, Paez D, et al: Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. J Nuc Med 2014;55:1936-44.
14. Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32:3048-58.
15. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
16. Lin C, Itti E, Haioun C, et al: Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. J Nucl Med 2007;48:1626-32.
17. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;25;381:1817-26.

18. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244
19. Meignan M, Gallamini A, Haioun C: Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk lymph 2009;50:1257-60.
20. Barrington, S.F. & Kluge, R. (2017) FDG PET for therapy monitoring in hodgkin and non-hodgkin lymphomas. European Journal of Nuclear Medicine and Molecular Imaging, 44, 97-110.
21. Itti, E., Juweid, M.E., Haioun, C., Yeddes, I., Hamza-Maaloul, F., El Bez, I., Evangelista, E., Lin, C., Dupuis, J. & Meignan, M. (2010) Improvement of early 18F-FDG PET interpretation in diffuse large B-cell lymphoma: Importance of the reference background. Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine, 51, 1857-1862.
22. SF Barrington, JE MacKewn, P Schleyer, et al. Establishment of a UK wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Ann Oncol 2011;22(3):739-45.
23. Casasnovas, R.O., Ysebaert, L., Thieblemont, C., Bachy, E., Feugier, P., Delmer, A., Tricot, S., Gabarre, J., Andre, M., Fruchart, C., Mounier, N., Delarue, R., Meignan, M., Berriolo-Riedinger, A., Bardet, S., Emile, J.F., Jais, J.P., Haioun, C., Tilly, H. & Morschhauser, F. (2017) A FDG-PET driven consolidation strategy in diffuse large B-cell lymphoma: Final results of a randomized phase II study. Blood, 130, 1315-1326.
24. Duhrsen, U., Muller, S., Hertenstein, B., et al. Positron emission tomography-guided therapy of aggressive non-hodgkin lymphomas (PETAL): A multicenter, randomized phase III trial. Journal of Clinical Oncology, 2018; 36, 2024-2034.
25. **Mylam KJ , Kostakoglu L , Martin Hutchings M, et al. 18 F-fluorodeoxyglucose-positron emission tomography/computed tomography after one cycle of chemotherapy in patients with diffuse large B-cell lymphoma: results of a Nordic/US intergroup study. Leukemia & Lymphoma, July 2015; 56(7): 2005–2012. http://dx.doi.org/10.3109/10428194.2014.975800**
26. Hertzberg M, Gandhi MK, Trotman J, et al. Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma and positive interim PET after 4 cycles of R-CHOP-14. Haematologica. 2017;102:356-363.
27. Ceriani L, Martelli M, Gospodarowicz MK, et al. Positron emission tomography/computed tomography assessment after immunochemotherapy and irradiation using the lugano classification criteria in the IELSG-26 study of primary mediastinal B-cell lymphoma. *Int J Radiat Oncol Biol Phys*. 2017;97(1):42-49.
28. Barrington, S.F., Phillips, E.H., Counsell, N., Hancock, B., Pettengell, R., Johnson, P., Townsend, W., Culligan, D., Popova, B., Clifton-Hadley, L., McMillan, A., Hoskin, P., O'Doherty, M.J., Illidge, T. & Radford, J. (2019) Positron emission tomography score has greater prognostic significance than pretreatment risk stratification in early-stage hodgkin lymphoma in the UK RAPID study. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 37, 1732-1741.
29. Mikhaeel NG, Smith D, Dunn JT et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. Eur J Nucl Med Mol Imaging 2016;43:1209.
30. Schmitz, C., Huttmann, A., Muller, S.P., Hanoun, M., Boellaard, R., Brinkmann, M., Jockel, K.H., Duhrsen, U. & Rekowski, J. (2020) Dynamic risk assessment based on positron emission tomography scanning in diffuse large B-cell lymphoma: Post-hoc analysis from the PETAL trial. European Journal of Cancer (Oxford, England : 1990), 124, 25-36.

31. Kasamon YL, Wahl RL, Ziessman HA, et al. Phase II study of risk adapted therapy of newly diagnosed aggressive non-Hodgkin lymphoma based on mid treatment FDG-PET scanning. Biol Blood Marrow Transplant 2009;15:242-8
32. Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2017 Nov 1;35(31):3529-3537. doi: 10.1200/JCO.2017.73.3402.
33. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet 2019; 20 (5): 649-662. https://doi.org/10.1016/S1470-2045(18)30935-5
34. Pardal E, Coronado M, Martin A, et al: Intensification treatment based on early FDG-PET in patients with high-risk diffuse large B-cell lymphoma: a phase II GELTAMO trial. Brit J Haem 2014;167:327-36.
35. Swinnen LJ, Li H, Quon A, et al: Response-adapted therapy for aggressive non-Hodgkin's lymphomas based on early [18F] FDG-PET scanning: ECOG-ACRIN Cancer Research Group study (E3404). British Journal of Haematology 170:56-65, 2015

TABLES

Table 1: Patient Characteristics

Patient characteristics		n=189 (%)
Sex	Female	75 (39.7)
	Male	114 (60.3)
Age	Range	21 – 80 years
	Median	61 years
	≥60 years	96 (50.8%)
Performance Status		
	0	101 (53.4%)
	1	66 (34.9%)
	2	22 (11.6%)
Raised LDH*		105 (55.6%)
>1 extranodal site (n=187)		47 (23.1%)
B symptoms		75 (39.7%)
Bulky disease (≥10cm)		78 (41.3%)
Stage	I	10 (5.3%)
	II	69 (36.5%)
	III	47 (24.9%)
	IV	63 (33.3%)
IPI** (n=187)	0/1	70 (37.4%)
	2	40 (21.4%)
	3	51 (27.3%)
	4/5	26 (13.9%)
RCHOP21		159 (84.1%)
RCHOP14		30 (15.9%)

*LDH = serum lactate dehydrogenase. **IPI = International Prognostic Index,

Table 2: Association between final CT response and interim PET response by (A) Deauville score and (B) ΔSUVmax

(A)

Final CT response	Interim PET response – Deauville score					Total
	1	2	3	4	5	
CR	24 (77.4)	23 (63.9)	26 (59.1)	15 (28.8)	2 (18.2)	**90 (51.7)**
CRu	2 (6.5)	4 (11.1)	5 (11.4)	6 (11.5)	2 (18.2)	**19 (10.9)**
PR	3 (9.7)	6 (16.7)	11 (25.0)	24 (46.2)	4 (36.4)	**48 (27.6)**
SD	1 (3.2)	3 (8.3)	2 (4.5)	2 (3.8)	1 (9.1)	**9 (5.2)**
PD	1 (3.2)	0 (0)	0 (0)	5 (9.6)	2 (18.2)	**8 (4.6)**
missing	*3*	*3*	*2*	*4*	*3*	***15***
Total	**34 (18.0)**	**39 (20.6)**	**46 (24.3)**	**56 (29.6)**	**14 (7.4)**	**189**

(B)

Final CT response	Interim PET response – ΔSUVmax		Total
	≥66%	<66%	
CR	83 (53.2)	7 (38.9)	**90 (51.7)**
Cru	17 (10.9)	2 (11.1)	**19 (10.9)**
PR	43 (27.6)	5 (27.8)	**48 (27.6)**
SD	8 (5.1)	1 (5.6)	**9 (5.2)**
PD	5 (3.2)	3 (16.7)	**8 (4.6)**
missing	*12*	*3*	***15***
Total	**168 (88.9)**	**21 (11.1)**	**189**

Table 3: Analysis of (A) progression-free survival and (B) overall survival by interim PET response and IPI group

(A) Progression-Free Survival

	Univariable HR (95% CI; p-value)	Multivariable HR (95% CI; p-value)
Deauville group 5 versus 1/2/3/4	2.68 (1.21-5.93; p=0.01)	2.80 (1.05-7.42; p=0.04)
SUV group <66% versus ≥66%	2.12 (1.07-4.21; p=0.03)	1.38 (0.60-3.19; p=0.45)
IPI group 4/5 versus 1/2/3	2.63 (1.41-4.92; p<0.01)	2.76 (1.45-5.24; p<0.01)

(B)Overall Survival

	Univariable HR (95% CI; p-value)	Multivariable HR (95% CI; p-value)
Deauville group 5 versus 1/2/3/4	3.10 (1.29-7.41; p=0.01)	3.02 (0.96-9.55; p=0.06)
SUV group <66% versus ≥66%	2.37 (1.08-5.17; p=0.03)	1.29 (0.46-3.62; p=0.63)
IPI group 4/5 versus 1/2/3	3.45 (1.70-7.01; p<0.01)	3.48 (1.68-7.17; p<0.01)

Supplementary table 1: Correlation of Deauville score and ΔSUVmax

Deauville score on PET2	ΔSUVmax <66%	ΔSUVmax ≥66%
1 (n=34)	0 (0%)	34 (100%)
2 (n=39)	0 (0%)	39 (100%)
3 (n=46)	4 (8.7%)	42 (91.3%)
4 (n=56)	6 (10.7%)	50 (89.3%)
5 (n=14)	11 (78.6%)	3 (21.4%)

FIGURES

Figure 1: CONSORT flow diagram

Figure 2: Kaplan-Meier progression-free survival curves for Deauville criteria

A: Deauville score (1, 2, 3, 4, 5)

B: Deauville group (1-3, 4-5)

C: Deauville group (1-4, 5)

Figure 3: Kaplan-Meier progression-free survival curves for ΔSUVmax

Figure 4: Kaplan-Meier progression-free survival curves for IPI

A: IPI score (0-1, 2, 3, 4-5)

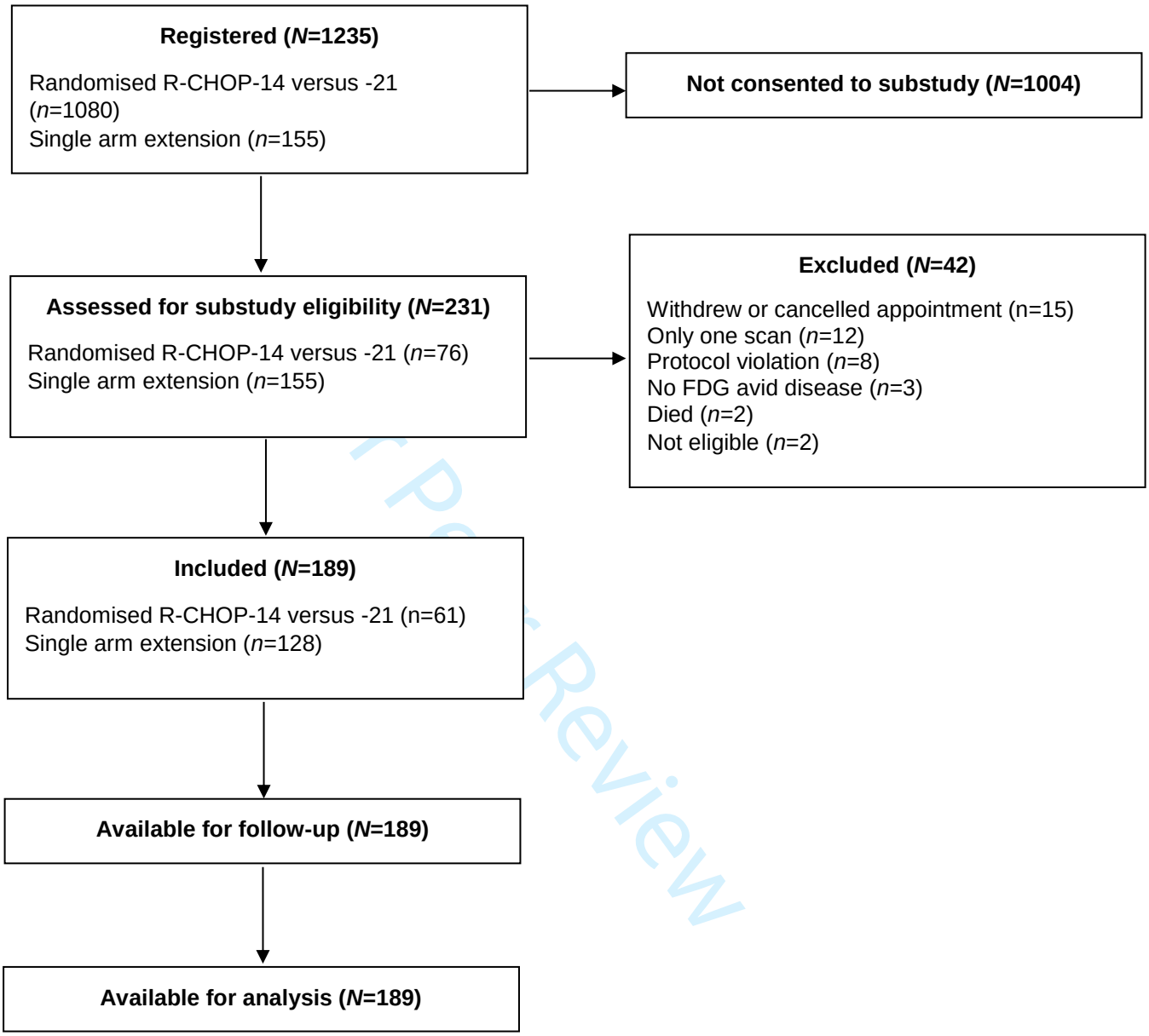
B: IPI risk group (0-3, 4-5)

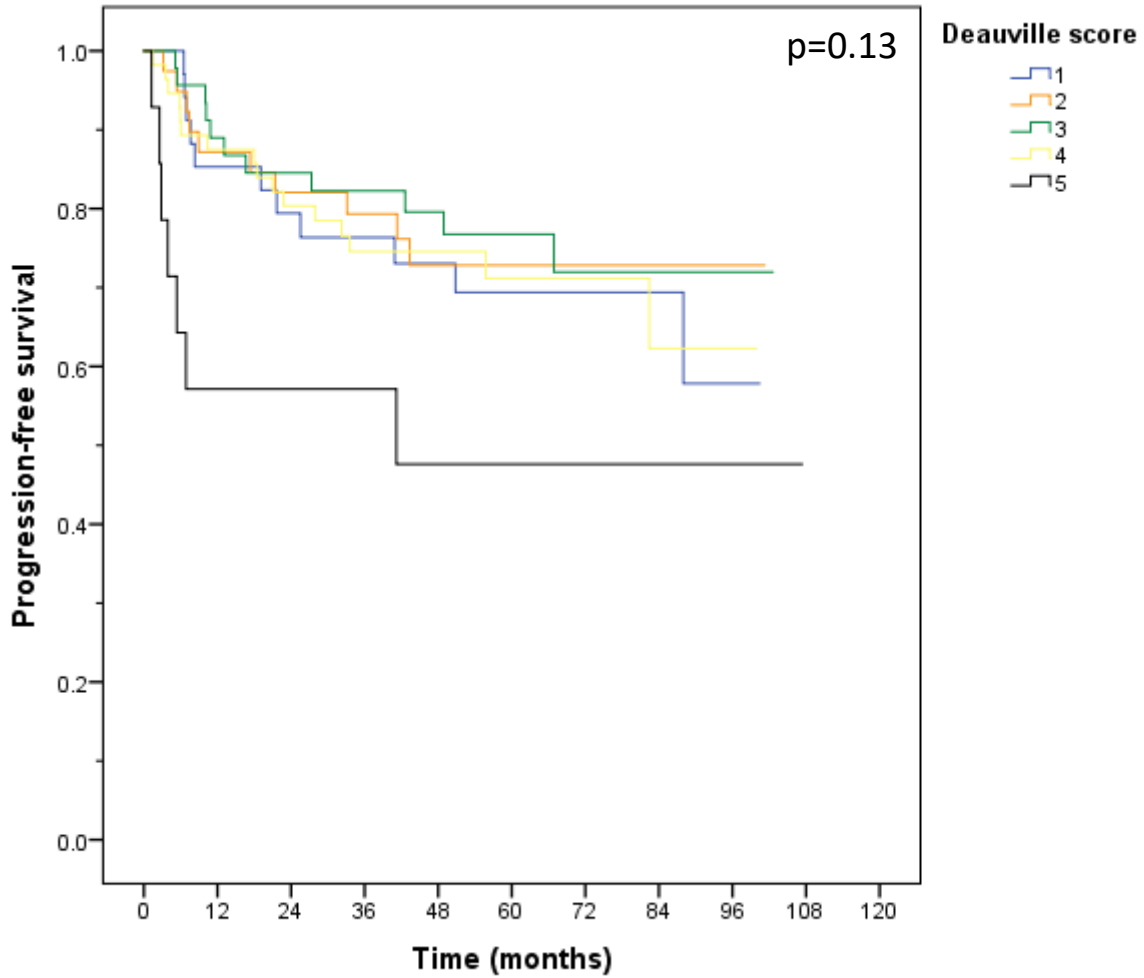
C: DS 1-3 divided by IPI 0-3 & 4-5

D: DS 4-5 divided by IPI 0-3 & 4-5

Supplementary Figure 1: Kaplan-Meier progression-free survival curves for Deauville score (1, 2, 3, 4, 5) with DS-5 defined as 2x liver

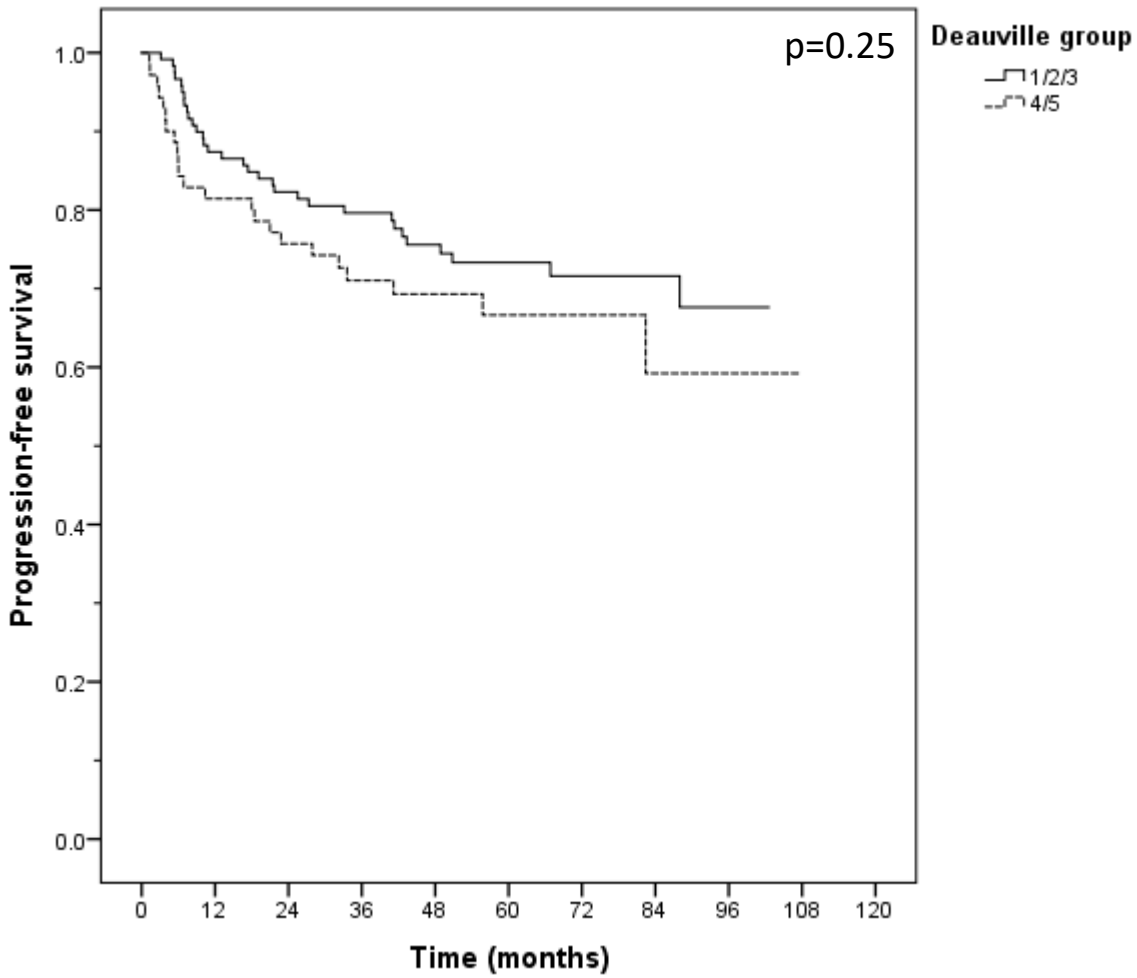
Figure 1. CONSORT flow diagram





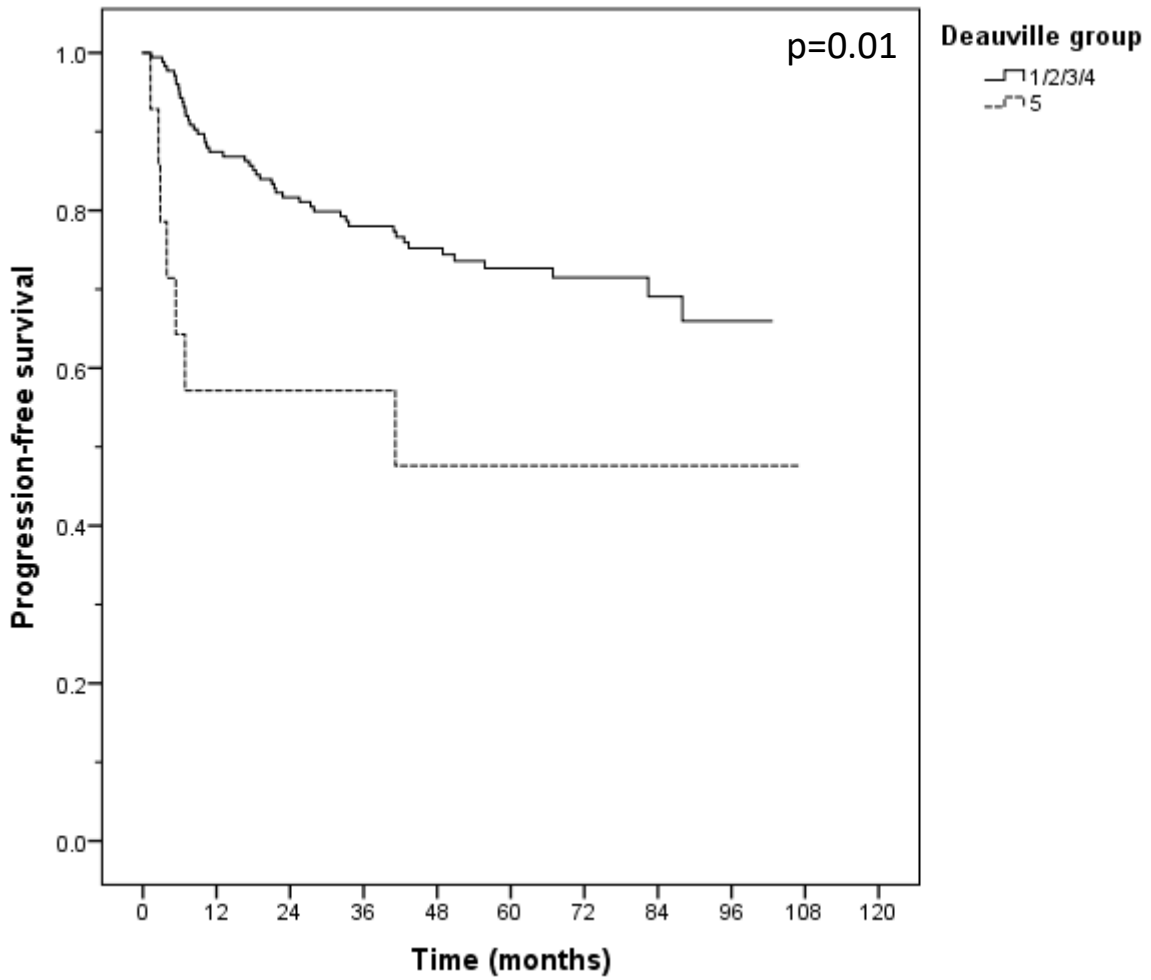
Number at risk:

1	34	29	26	24	20	18	12	7	2	0	0
2	39	34	32	28	21	19	9	4	2	0	0
3	46	40	37	34	28	18	14	11	4	0	0
4	56	49	44	38	29	21	17	6	2	0	0
5	14	8	8	6	5	3	1	1	1	0	0



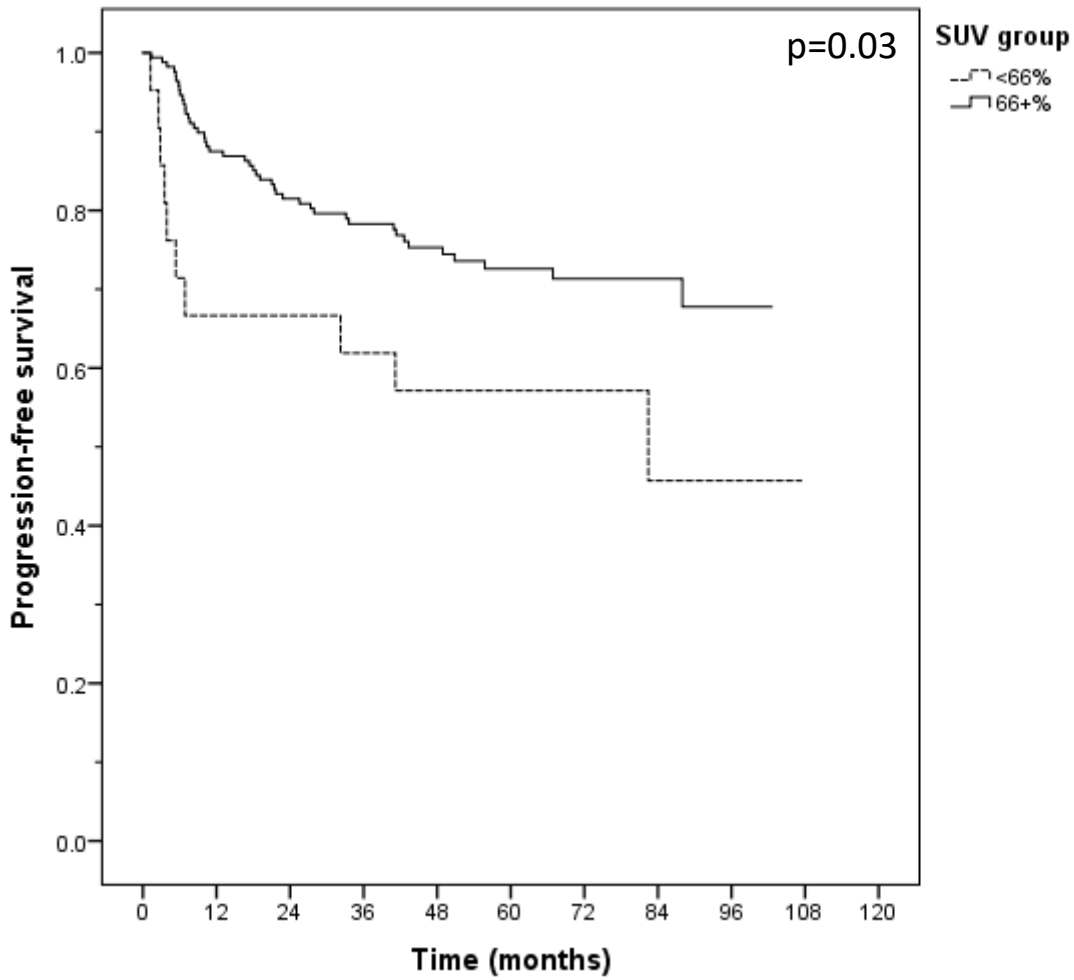
Number at risk:

1-3	119	103	95	86	69	55	35	22	8	0	0
4-5	70	57	52	44	34	24	18	7	3	0	0



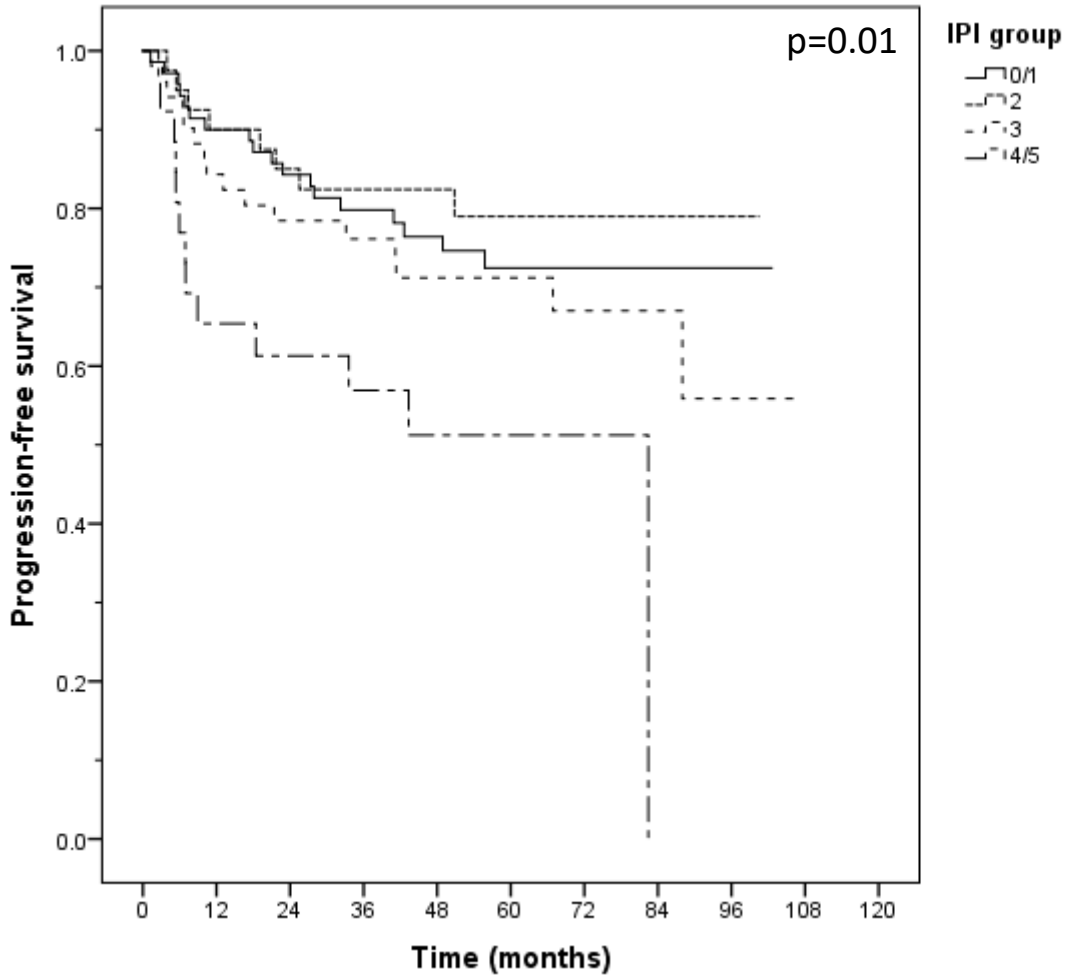
Number at risk:

1-4	175	152	139	124	98	76	52	28	10	0	0
5	14	8	8	6	5	3	1	1	1	0	0



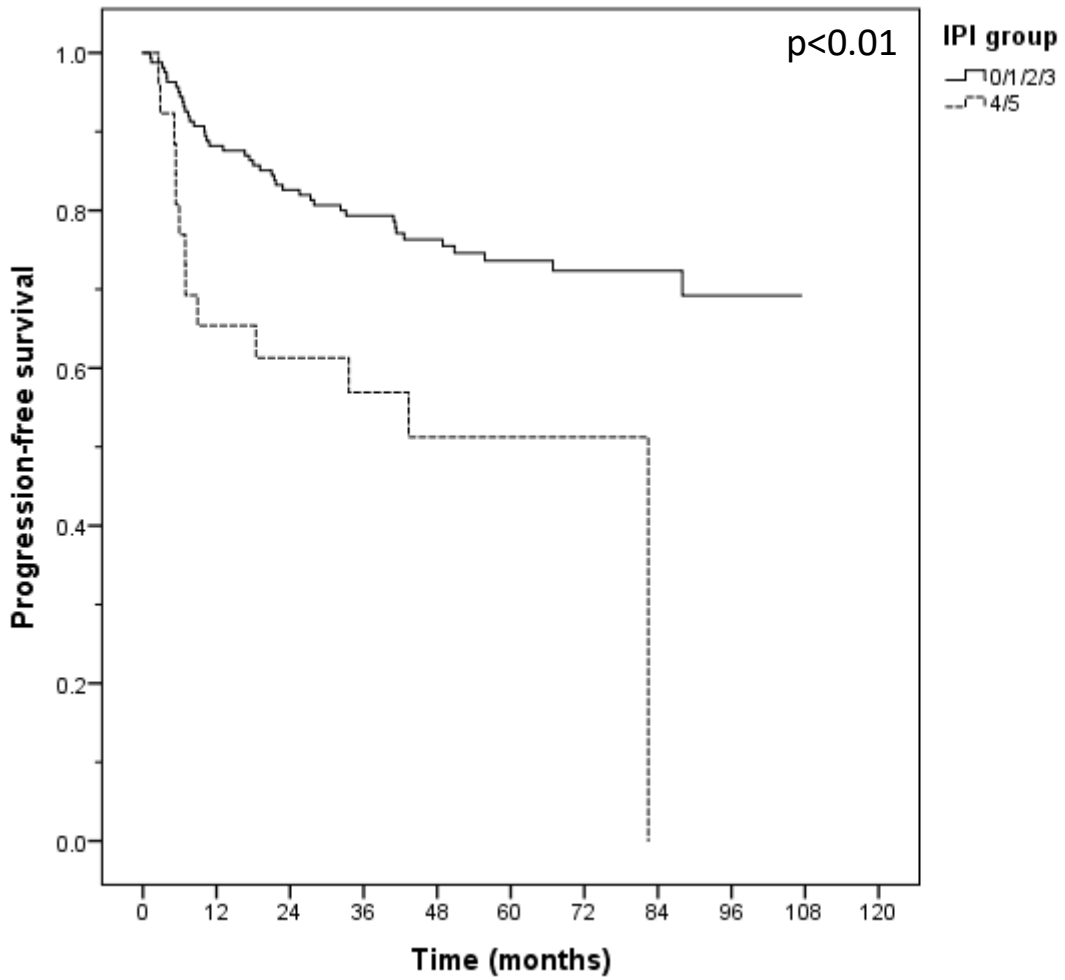
Number at risk:

<66%	21	14	14	13	11	7	6	4	2	0	0
≥66%	168	146	133	117	92	72	47	25	9	0	0



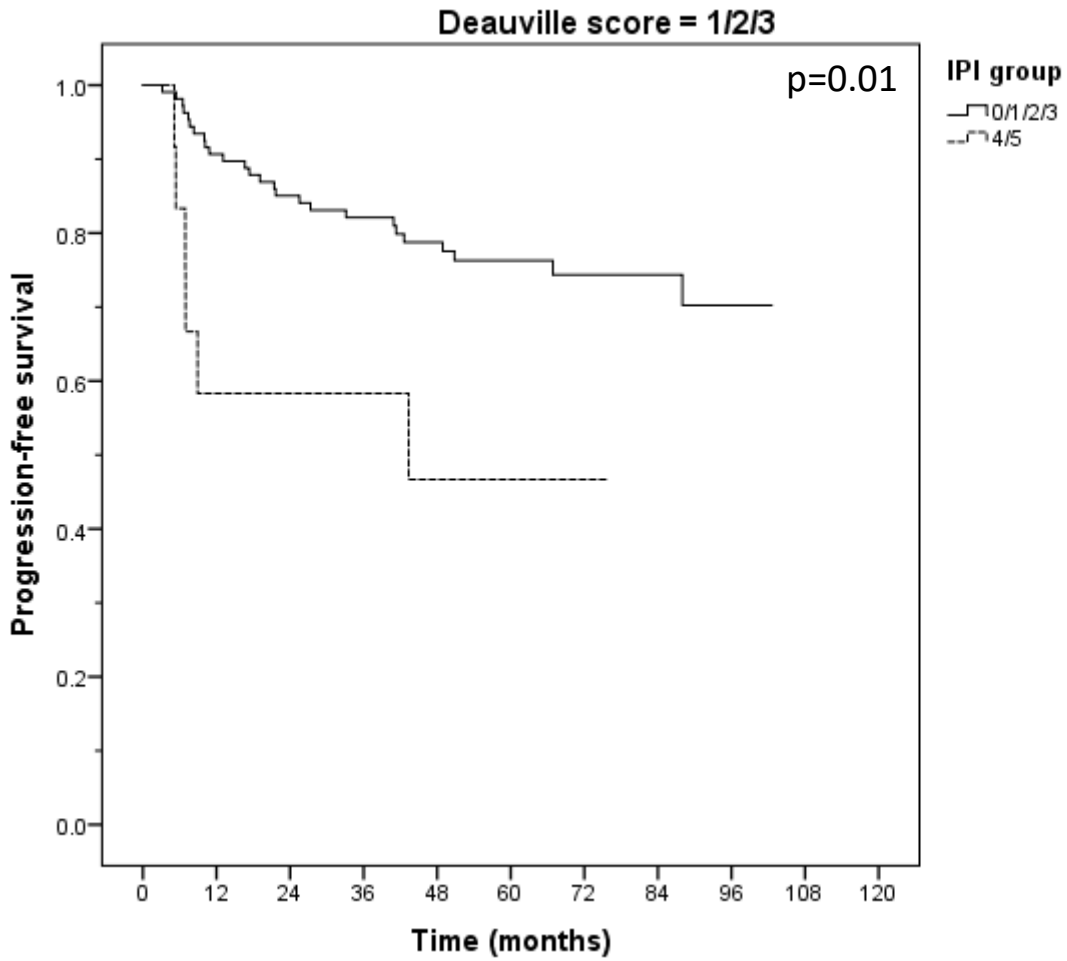
Number at risk:

0-1	70	63	58	52	43	32	23	15	4	0	0
2	40	36	34	31	26	21	12	6	4	0	0
3	51	43	39	32	24	19	13	8	3	0	0
4-5	26	16	14	13	8	6	4	0	0	0	0



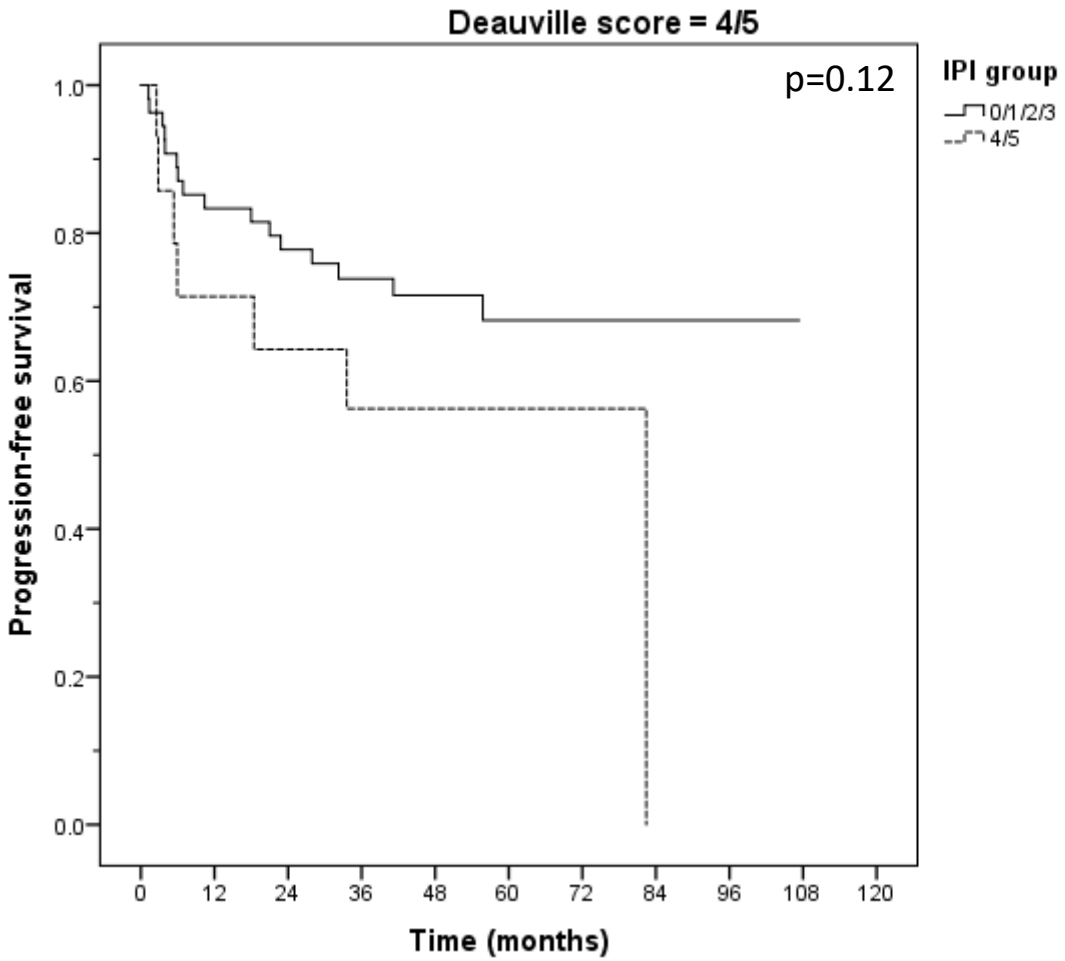
Number at risk:

0-3	161	142	131	115	93	72	48	29	11	0	0
4-5	26	16	14	13	8	6	4	0	0	0	0



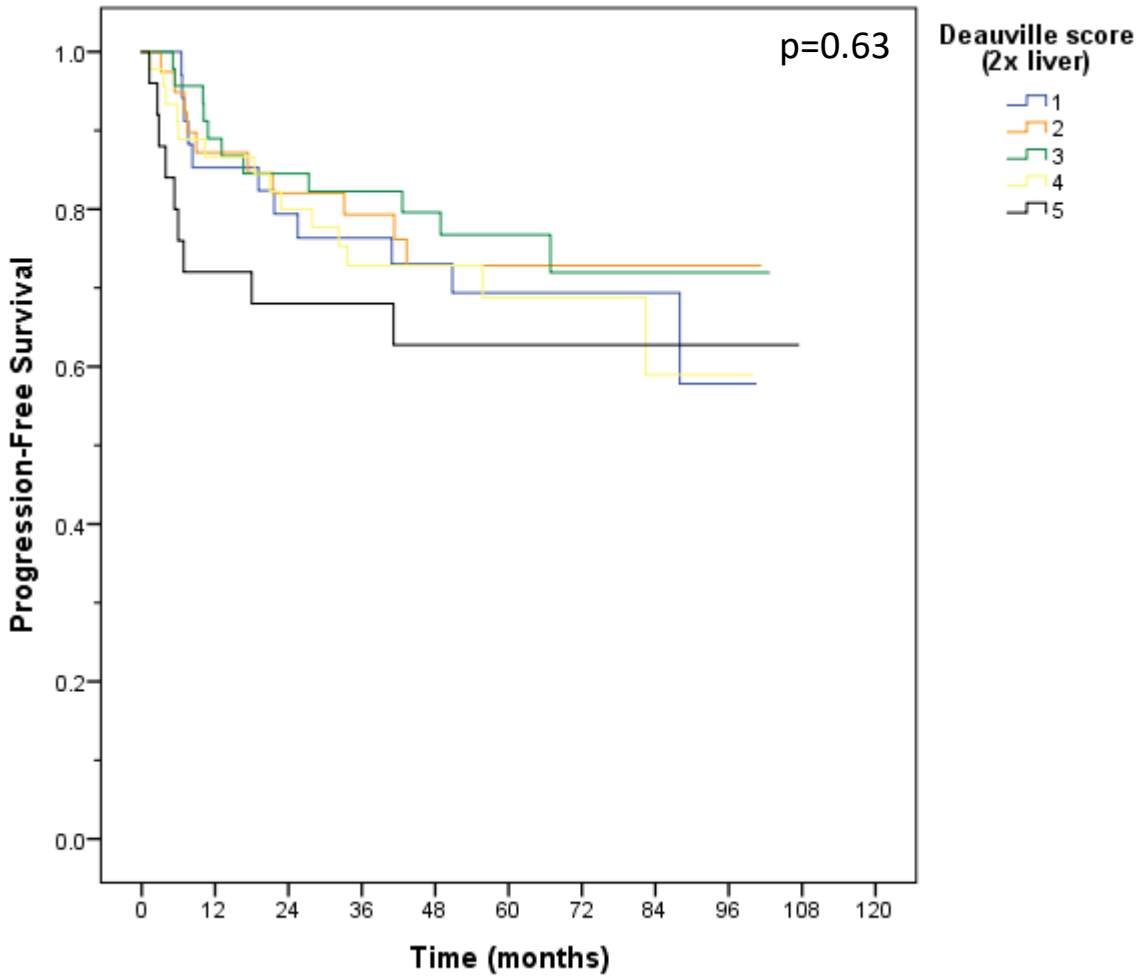
Number at risk:

0-3	107	97	89	80	66	52	33	22	8	0	0
4-5	12	6	6	6	3	3	2	0	0	0	0



Number at risk:

0-3	54	45	42	35	27	20	15	7	3	0	0
4-5	14	10	8	7	5	3	2	0	0	0	0



Number at risk:

1	34	29	26	24	20	18	12	7	2	0	0
2	39	34	32	28	21	19	9	4	2	0	0
3	46	40	37	34	28	18	14	11	4	0	0
4	45	39	35	30	24	17	13	5	2	0	0
5	25	18	17	14	10	7	5	2	1	0	0