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Treatment of classical Hodgkin lymphoma in young adults aged 18–30 years with a modified paediatric Hodgkin lymphoma protocol. Results of a multicentre phase II clinical trial (CRUK/08/012)

William Townsend,[1,2] Sarah Leong,[1] Peter Hoskin,[3] Patricia Diez,[4] Pip Patrick,[2] David Linch,[1,2] Wai-Lup Wong,[5] Irfan Kayani,[6] Bal Sanghera,[5] Andre Lopes,[2] Stephen Daw,[7] Graham Collins,[8] Laura Clifton-Hadley[2] and Kirit Ardeshna[1,2]

[1]Department of Haematology, University College London Hospitals NHS Foundation trust, [2]Cancer Research UK and University College London Cancer Trials Centre, London, [3]Marie Curie Research Wing, Mount Vernon Cancer Centre, [4]National Radiotherapy Trials Quality Assurance Group, Mount Vernon Cancer Centre, [5]Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, [6]Department of Nuclear Medicine, University College Hospitals NHS Foundation Trust, [7]Department of Paediatric Oncology, University College Hospitals NHS Foundation Trust, London and [8]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK

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Correspondence: William Townsend, Department of Haematology, University College London Hospitals NHS Foundation trust, London, UK.
E-mail: william.townsend@nhs.net

Summary

This phase II trial was designed to determine the safety and efficacy of a modified paediatric risk-stratified protocol in young adults (18–30 years) with classical Hodgkin Lymphoma. The primary end-point was neurotoxicity rate. The incidence of grade 3 neurotoxicity was 11% (80% CI, 5–19%); a true rate of neuropathy of >15% cannot be excluded. Neuropathy and associated deterioration in quality of life was largely reversible. The overall response rate was 100% with 40% complete remission (CR) rate. Twelve months disease-free survival (DFS) was 91%. We demonstrate that a risk-stratified paediatric combined modality treatment approach can be delivered to young adults without significant irreversible neuropathy.

Keywords: Hodgkin lymphoma, paediatric, neuropathy.

Although there have been no randomised comparisons, children with classical Hodgkin lymphoma (cHL) treated with paediatric protocols appear to have better outcomes than adults with equivalent stage disease treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). It is not known whether this is a function of age, due to differences in the biology of the disease, or because paediatric regimens are more effective.

The current standard of care for adults with cHL is ABVD or EscalatedBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) with the number of cycles and addition of radiotherapy dependent on stage and positron-emission tomography (PET)-guided response assessment (Radford *et al.*, 2015; Johnson *et al.*, 2016; Borchmann *et al.*, 2017).

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In the paediatric setting, combined modality treatment is used in a risk-stratified approach with patients allocated to treatment groups (TGs) according to stage (Rühl *et al.*, 2001; Mauz-Körholz *et al.*, 2010; Dörffel *et al.*, 2013). The chemotherapy regimens used in paediatric studies include OEPA (vincristine, etoposide, prednisolone and doxorubicin) and COPP (cyclophosphamide, vincristine, procarbazine and prednisolone) or variations of these regimens. The chemotherapy protocols, radiotherapy fields and doses have been refined in a series of trials detailed in the supplementary files (Mauz-Körholz *et al.*, 2010; Dörffel *et al.*, 2013).

There are significant differences between paediatric regimens and ABVD. Most pertinent to this trial is the greater intensity and cumulative dose of vinca alkaloids in paediatric regimens with a maximum of 14 doses of vincristine (1.5 mg/m^2) in the paediatric protocol compared to 12 doses of vinblastine (6 mg/m^2) with six cycles of ABVD. Other differences are presented in the supplementary files.

Paediatric regimens have never previously been assessed prospectively in adult patients with cHL. The aim of this trial was to investigate whether a modified version of the paediatric protocol as used in the Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)-HD95 trial could be delivered to young adults without inducing excessive neurotoxicity (Dörffel *et al*, 2013).

Patients and methods

This phase II, non-randomised, open label, multicentre trial (ClinicalTrials.gov: NCT00666484) was designed to determine the safety and efficacy of a modified, risk-stratified, combined modality paediatric regimen in young adults aged 18–30 years with a diagnosis of cHL. Full inclusion and exclusion criteria are listed in the supplementary files. The primary outcome measure was neurotoxicity, secondary outcome measures included response rate, DFS and quality of life (QoL).

The trial was managed by the Cancer Research UK and University College London Cancer Trials Centre. The protocol was approved by the national research ethics committee. Informed consent was obtained from all patients and the trial was conducted in accordance with the Declaration of Helsinki.

Staging was performed according to the methods described in the supplementary data and patients were allocated into one of three treatment groups according to centrally reviewed staging scans (Fig 1).

Response was assessed 10–14 days after the last dose of chemotherapy according to the GPOH-HD definitions in use at the time and the 2007 International Harmonisation Project Response criteria (Cheson *et al*, 2007), which predates and differs from the Lugano criteria currently used (Table SIV, and Data S1) (Mauz-Körholz *et al.*, 2010; Cheson *et al*, 2014; Cheson *et al.*, 2016). All fluorodeoxyglucose (FDG)-PET scans were performed in accredited centres according to a standardised protocol.

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, radiotherapy toxicities were assessed according to Radiation Therapy Oncology Group criteria. The impact of neuropathy on QoL was assessed using the EORTC QLQ-C30 QOL and Chemotherapy Induced Peripheral Neuropathy supplementary questionnaires (QLQ-CIPN20).

Treatment in TG1 comprised two cycles of OEPA with no radiotherapy in patients who achieved CR. Treatment in TG2 comprised two cycles of OEPA and two cycles of COPP followed by radiotherapy. Patients in TG3 received two cycles of OEPA and four cycles of COPP followed by radiotherapy (Fig 1). See Data S1 for full dosing information.

Patients developing grade 3 peripheral neuropathy were switched to vinblastine (6 mg/m^2) and vinca alkaloids were stopped if neurotoxicity further progressed.

Radiotherapy was commenced within four weeks of day 28 of the final cycle of chemotherapy for all patients except those in TG1 who achieved CR after chemotherapy.

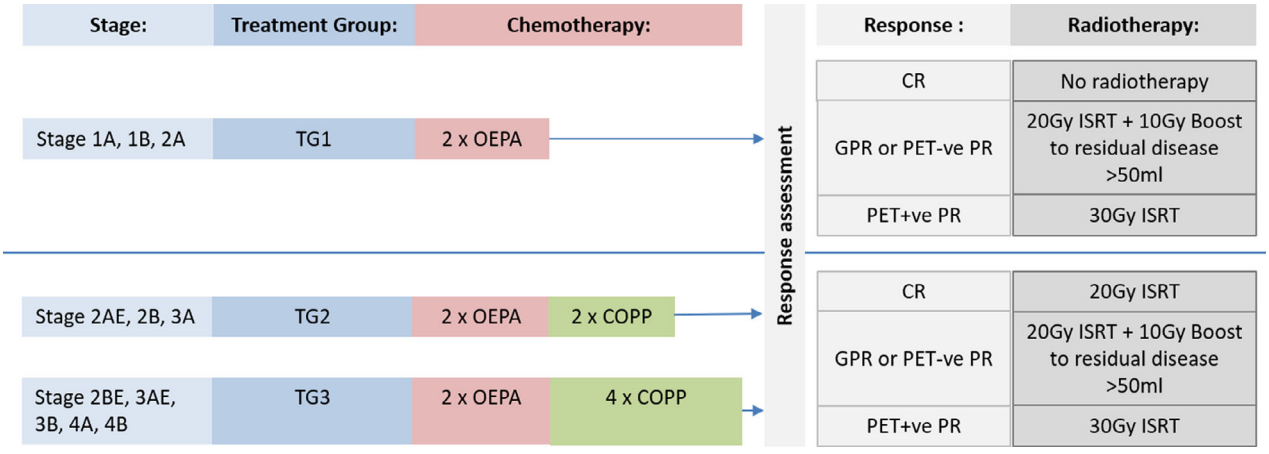

Fig 1. Trial schema. [Colour figure can be viewed at wileyonlinelibrary.com]

Radiotherapy volumes were determined by central review of baseline and end-of-chemotherapy scans;, full details of radiotherapy planning and delivery are provided in Data S1.

Statistical considerations and methods are provided in full in the supplementary data.

Results

Fourty-seven patients were recruited from eight UK centres between 2008 and 2011. The median follow-up (censoring at death) was 3·3 years. One patient withdrew consent before starting chemotherapy, 46 patients received trial treatment, one patient was withdrawn on day 1 of cycle 1 due to a grade 3 reaction to etoposide (Figure S1).

The median age was 23 years (IQR 20–26); patient characteristics are presented in Table SI. The number of patients in TG1, TG2 and TG3 were 16 (36%), 11 (24%) and 18 (40%) respectively; the two patients who withdrew from the trial were not allocated a final TG.

With the exception of the two patients who withdrew from the trial, all patients received the full number of cycles of chemotherapy specified in the protocol. Treatment delivered is detailed in Table SII.

Of the 45 patients completing chemotherapy, four patients in TG1 achieved CR and accordingly did not receive radiotherapy. The remaining 41 patients received radiotherapy. Compliance with the radiotherapy protocol was centrally assessed prospectively in 23 cases with five minor and four major variations from protocol identified (Table SIV). All variations were corrected before patients proceeded to treatment.

The incidence of grade 3 neurotoxicity in the 46 patients who started treatment was 11% (two-sided exact 80% CI, 5–19%). Five patients had one or more episodes of grade 3 neurotoxicity and there were no cases of grade 4 or 5 neurotoxicity (Table SVI). Severe neuropathy was not limited to patients in any particular TG, it occurred in three patients in TG2 and one patient in each of TGs 1 and 3; onset was during cycle 1 of OEPA in two patients, cycle 2 of OEPA in two patients and cycle 2 of COPP in one patient.

All cases of grade 3 neuropathy reverted to grade 0 with a median time to resolution of 91 days [interquartile range (IQR) 12–100 days]. In addition to the severe neuropathy, there were 32 episodes where the maximum recorded neurotoxicity was grade 1/2 in 19 patients (41%), this resolved to grade 0 in all except for one patient who reported persistent grade 2 neuropathy. The median time to resolution of grade 1/2 neuropathy was 74 days (IQR 18–240 days).

Haematological toxicities were the commonest severe toxicity with grade 3/4 neutropenia reported in 38 patients (83%) (Table SVII).

Three patients developed osteonecrosis of the hips or knees, grade 3/4 in two patients (4%) and grade 2 in one patient with grade 3 pain. The affected patients were 19, 20 and 29 years at trial entry and all were male. Osteonecrosis occurred in one patient in TG1 and two patients in TG3, the diagnosis was made >1 year after completion of chemotherapy in two of the patients. One patient required bilateral decompression of the femoral heads and hip replacement surgery.

Radiotherapy toxicities were reported in 56% of patients receiving radiotherapy (Table SVIII).

There was a significant deterioration in the sensory and motor neuropathy QoL scales between pretreatment and immediately after chemotherapy, mean difference in QoL 9·5 (99% CI 2·5–16·5, $P < 0·001$) and 10 (99% CI 2·9–17·0, $P < 0·001$) respectively, with no significant difference in autonomic neuropathy scale ($P = 0·26$). At 12 months after treatment, the sensory scale had improved and was no longer significantly worse than at baseline. The motor scale had improved but remained 2·6 points worse than pretreatment, which is not considered clinically important (99% CI 0·4–4·8, $P = 0·003$) (Figure S3).

The overall response rate (ORR) at end of chemotherapy was 100% (2-sided exact 80% CI 95–100%) with 40% achieving CR according to local response assessment. The CR rates prior to radiotherapy in TG1, TG2 and TG3 were 25%, 55% and 44% respectively (Table I). Male and female patients had similar CR rates of 41% and 39% respectively ($P = 0·90$). Central review of end-of-chemotherapy PET

Table I. Response to treatment (response at restaging after chemotherapy and before radiotherapy).

	All patients ($n = 45$)*		TG1 ($n = 16$)		TG2 ($n = 11$)		TG3 ($n = 18$)	
Response	*N*	%	*N*	%	*N*	%	*N*	%
Complete remission	18	40	4	25	6	55	8	44
Good partial remission	18	40	7	44	2	18	9	50
Partial remission	9	20	5	31	3	27	1	6
Overall response (CR + GPR + PR)	45	100	16	100	11	100	18	100
PET negative†	28	72	9	64	8	89	11	69

*Two patients withdrew from the trial, only 45 completed treatment.

†PET response by central review: 39 patients had central review of PET at end of chemotherapy, central review was not completed in six patients (two in TG1, two in TG2 and two in TG3). Percentages are based on the total number of patients with available central review assessment.

scans was performed for 39/45 patients who received at least one cycle of treatment and was negative in 28/39 patients reviewed (72%), corresponding to metabolic remission by International Harmonization Project (IHP) 2007 and Lugano 2014 criteria.

Four patients have relapsed of whom one patient has died due to cHL; no patients achieving CR (n = 18) with a negative PET have relapsed. The 12-month DFS rate is 91% (95% CI 78–97) (Figure S2).

Discussion

In this trial we investigated whether delivering a paediatric-style, risk-stratified, combined modality regimen to young adults is feasible without inducing excessive neurotoxicity due to the intensive use of vinca alkaloids. We found that 11% of patients treated with this protocol developed grade 3 neuropathy, which was reversible in all cases, with a median time to resolution of 91 days. One patient with G1/2 neuropathy had persisting toxicity at last follow-up. The upper limit of the 80% CI was higher than the predetermined unacceptable rate stated in the trial protocol of >15%; therefore we cannot exclude the possibility that the true rate of grade 3 neurotoxicity was >15%. Although an initial deterioration in neuropathy-related QoL was recorded, this had improved 12 months after treatment. Overall, we conclude that the vinca alkaloid dosing used in this protocol in this age group is tolerable and associated neuropathy is reversible in most cases.

It is difficult to make direct comparisons with the neurotoxicity rate in other trials due to variations in reporting; however, it is similar to that reported in the paediatric GPOH-HD-2002 trial (Mauz-Körholz *et al.*, 2010). Whilst it is higher than reported in adults after ABVD (Diehl, Franklin *et al.*, 2003), it may be comparable to the rate experienced after EscalatedBEACOPP, where 12·7% of adults treated with eight cycles reported grade 3/4 'nervous system' adverse events (Engert *et al.*, 2012).

Of concern, three patients (6·5%) in this trial developed avascular necrosis. This is likely to be due to the high dose of corticosteroids in this regimen. It is known from studies of childhood acute lymphoblastic leukaemia (Mattano, Sather *et al.*, 2000) that avascular necrosis is more common in older children and with higher doses of steroids, which may indicate why we identified a high rate in this trial of young adults treated with high doses of corticosteroids. In a retrospective review of adult cHL patients treated in German Hodgkin Study Group trials, the cumulative incidence of osteonecrosis was 0·93% and was more frequent in male patients. Osteonecrosis was not specifically assessed in these studies and the true rate may be higher as indicated by a small series reporting a rate of 21% (Fosså *et al.*, 2011, Borchmann *et al.*, 2016). Osteonecrosis has not been specifically reported in the GPOH paediatric trials.

Whilst the sample size is too small to draw conclusions about the efficacy of this protocol in adults, the 100% response rate, high proportion of patients with a negative PET and high DFS in this trial are promising.

The use of radiotherapy in this trial reflects standard practice in paediatric trials at the time of protocol development. Subsequent work published in abstract form has demonstrated that radiotherapy can be omitted in children with a negative interim PET scan regardless of TG without impairing event-free survival and much less radiotherapy is being used in current trials (Landman-Parker *et al.*, 2016).

It is acknowledged that since this protocol was developed, standsardised PET reporting has been developed which differs from the PET scoring system used in this trial (Cheson *et al.*, 2016).

This trial demonstrates that a risk-stratified approach using paediatric-style treatment can be delivered to young adults aged 18–30 years without inducing unacceptable levels of severe irreversible peripheral neurotoxicity, and without impairing the ORR compared to historical cohorts. Results justify further testing of paediatric-style treatment in adults and this trial has informed the design of an on-going international trial using risk-stratified treatment in children and young adults up to the age of 25 (EuroNet-PHL-C2 trial, NCT02684708).

Acknowledgements

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplementary methods.

Table SI. Baseline patient characteristics.

Table SII. Number of patients who received less than 90% of the intended dose for each of the drugs in each cycle, by treatment group.

Table SIII. Schedule of investigations and follow-up.

Table SIV. Radiotherapy outlining protocol variations (one major variation patient displayed two types of variation).

Table SV. FDG-PET response categories.

Table SVI. Worst grade of neurotoxicity during the trial.

Table SVII. Non-neuropathy toxicities: worst toxicity grade at any point in time of the trial (excluding neurotoxicity).

Table SVIII. Worst grade of radiotherapy toxicity reported six months after completing radiotherapy.

Fig S1. Consort diagram.

Fig S2. Disease-free survival.

Fig S3. Sensory and motor quality-of-life scales. There was a significant deterioration in both scales between pretreatment and postchemotherapy. At 12 months post-treatment, sensory scale was not significantly different to baseline but motor scale remained 2.6 points worse than at baseline.

References

Borchmann, S.M., Haverkamp, H., Baues, H., Markova, C., Huttman, J., Glunz, A., Fuchs, A. & Engert, M. (2016) Osteonecrosis as a treatment complication in Hodgkin lymphoma patients: an analysis of the German Hodgkin study group (GHSG) Congress of the European Hematology Association Copenhagen, Denmark, June 9–12, 2016. *Haematologica*, **101**, 1–881.

Borchmann, P., Goergen, H., Kobe, C., Lohri, A., Greil, R., Eichenauer, D.A., Zijlstra, J.M., Markova, J., Meissner, J., Feuring-Buske, M., Hüttmann, A., Dierlamm, J., Soekler, M., Beck, H.-J., Willenbacher, W., Ludwig, W.-D., Pabst, T., Topp, M.S., Hitz, F., Bentz, M., Keller, U.B., Kühnhardt, D., Ostermann, H., Schmitz, N., Hertenstein, B., Aulitzky, W., Maschmeyer, G., Vieler, T., Eich, H., Baues, C., Stein, H., Fuchs, M., Kuhnert, G., Diehl, V., Dietlein, M. & Engert, A. (2017) PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *The Lancet*, **390**, 2790–2802.

Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stroobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V. (2007) Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*, **25**, 579–586.

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E. & Lister, T.A. (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology*, **32**, 3059–3067.

Cheson, B.D., Ansell, S., Schwartz, L., Gordon, L.I., Advani, R., Jacene, H.A., Hoos, A., Barrington, S.F. & Armand, P. (2016) Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy. *Blood*, **128**, 2489–2496.

Diehl, V., Franklin, J., Pfreundschuh, M., Lathan, B., Paulus, U., Hasenclever, D., Tesch, H., Herrmann, R., Dörken, B., Müller-Hermelink, H.-K., Dühmke, E. & Loeffler, M. (2003) Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *New England Journal of Medicine*, **348**, 2386–2395.

Dörffel, W., Rühl, U., Lüders, H., Claviez, A., Albrecht, M., Bökkerink, J., Holte, H., Karlen, J., Mann, G., Marciniak, H., Niggli, F., Schmiegelow, K., Schwarze, E.-W., Pötter, R., Wickmann, L. & Schellong, G. (2013) Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. *Journal of Clinical Oncology*, **31**, 1562–1568.

Engert, A., Haverkamp, H., Kobe, C., Markova, J., Renner, C., Ho, A., Zijlstra, J., Král, Z., Fuchs, M., Hallek, M., Kanz, L., Döhner, H., Dörken, B., Engel, N., Topp, M., Klutmann, S., Amthauer, H., Bockisch, A., Kluge, R., Kratochwil, C., Schober, O., Greil, R., Andreesen, R., Kneba, M., Pfreundschuh, M., Stein, H., Eich, H.T., Müller, R.P., Dietlein, M., Borchmann, P. & Diehl, V.; German Hodgkin Study Group; Swiss Group for Clinical Cancer Research; Arbeitsgemeinschaft Medikamentöse Tumortherapie. (2012) Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *The Lancet*, **379**, 1791–1799.

Fosså, A., Fiskvik, I.H., Kolstad, A., Lauritzsen, G.F., Aurlien, E., Blystad, A.K., Hole, K.H., Ikonomou, I.M. & Holte, H. (2011) Two escalated followed by six standard BEACOPP in advanced-stage high-risk classical Hodgkin lymphoma: high cure rates but increased risk of aseptic osteonecrosis. *Annals of Oncology*, **23**, 1254–1259.

Johnson, P., Federico, M., Kirkwood, A., Fosså, A., Berkahn, L., Carella, A., d'Amore, F., Enblad, G., Franceschetto, A., Fulham, M., Luminari, S., O'Doherty, M., Patrick, P., Roberts, T., Sidra, G., Stevens, L., Smith, P., Trotman, J., Viney, Z., Radford, J. & Barrington, S. (2016) Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *New England Journal of Medicine*, **374**, 2419–2429.

Landman-Parker, J.W., Hasenclever, H., Balwierz, D., Karlen, W., Fossa, J., Daw, A. & Mauz-Korholz, S. (2016) First international inter-group study for classical hodgkin lymphoma in children and adolescents: EuroNet-PHL-C1. Report of the latest interim analysis. 10th International Symposium on Hodgkin Lymphoma, Cologne, October 22–25, 2016. Haematologica. *Haematologica*, **101**, 1–80.

Mattano, L.A., Sather, H.N., Trigg, M.E. & Nachman, J.B. (2000) Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *Journal of Clinical Oncology*, **18**, 3262–3272.

Mauz-Körholz, C., Hasenclever, D., Dörffel, W., Ruschke, K., Pelz, T., Voigt, A., Stiefel, M., Winkler, M., Vilser, C., Dieckmann, K., Karlén, J., Bergsträsser, E., Fosså, A., Mann, G., Hummel, M., Klapper, W., Stein, H., Vordermark, D., Kluge, R. & Körholz, D. (2010) Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin' lymphoma: the GPOH-HD-2002 study. *Journal of Clinical Oncology*, **28**, 3680–3686.

Radford, J., Illidge, T., Counsell, N., Hancock, B., Pettengell, R., Johnson, P., Wimperis, J., Culligan, D., Popova, B., Smith, P., McMillan, A., Brownell, A., Kruger, A., Lister, A., Hoskin, P., O'Doherty, M. & Barrington, S. (2015) Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *New England Journal of Medicine*, **372**, 1598–1607.

Rühl, U., Albrecht, M., Dieckmann, K., Lüders, H., Marciniak, H., Schellenberg, D., Wickmann, L. & Dörffel, W. (2001) Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: an interim report at 5 years of the German GPOH-HD 95 trial. *International Journal of Radiation Oncology * Biology * Physics*, **51**, 1209–1218.

Supplementary data

Supplementary introduction:

Summary of evolution of treatment in the paediatric trials:

In the GPOH-HD95 trial, all patients received 2 cycles of induction chemotherapy with OEPA (vincristine, etoposide, prednisolone, and doxorubicin) or OPPA (vincristine, procarbazine, prednisolone, and doxorubicin) and patients with intermediate and advanced stage disease received an additional 2 or 4 cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone), respectively. Radiotherapy was omitted for patients in CR by conventional radiology criteria after chemotherapy and, although the results showed a promising 5-year EFS and overall survival (OS) of 89% and 97%, respectively, more relapses were identified in intermediate and advanced stage patients who did not receive radiotherapy suggesting that these patients were undertreated. (Dorffel, Ruhl et al. 2013). In the GPOH-HD-2002 trial, radiotherapy was omitted only for early stage patients in CR after 2 cycles of chemotherapy. The fertility sparing regimen COPDAC (in which dacarbazine replaced procarbazine) was used instead of COPP in males, giving 5 year EFS and OS of 92.0% and 99.5% in treatment group (TG) 1 and 87.7% and 96.2% for TG2 and TG3 combined, respectively (Mauz-Korholz *et al.* 2010).

Further differences between paediatric and adult treatment regimens:

The paediatric regimens have a higher initial intensity but lower cumulative dose of anthracycline than ABVD; 2 cycles of OEPA over 8 weeks contains the equivalent anthracycline dose as 3 cycles of ABVD over 12 weeks. Despite the initial high intensity

of treatment, patients with advanced stage disease receive a lower total dose of anthracycline with 2 cycles of OEPA followed by COPP than if treated with 6 cycles of ABVD (160mg/m^2 compared to 300mg/m^2). Corticosteroids are used in high doses in the paediatric regimens with 15 days of prednisolone in each cycle whereas ABVD does not include steroids.

Supplementary methods:

Inclusion and exclusion criteria:

Inclusion Criteria

i. Biopsy proven de-novo classical Hodgkin lymphoma

ii. No previous chemotherapy or radiotherapy

iii. Age 18-30 years

iv. Any stage

v. Able to give informed consent

vi. Agreement to take adequate precautions to prevent conception during chemo-/radiotherapy and for up to one year afterwards

Exclusion criteria

i. Nodular Lymphocyte Predominant Hodgkin lymphoma

ii. Previous chemotherapy or radiotherapy

iii. Known or suspected HIV infection

iv. Pre-existing neurological disorder

v. Serious co-morbidity which may prevent administration of study treatment

vi. Prior organ transplant

vii. Previous malignancy

viii. Pregnancy or lactation

ix. Creatinine >1.5 upper limit of normal (ULN) not due to the lymphoma

x. ALT/AST/Bilirubin >2.5 ULN not due to the lymphoma. Patients with Bilirubin levels of >2.5 ULN due to Gilberts syndrome will be included.

Staging and response assessment

All patients were staged with a contrast-enhanced CT scan of the neck, chest, abdomen and pelvis and FDG-PET. Bone marrow biopsy was performed if the stage was greater than 2A. Stage was determined according to the Cotswold revision of the Ann Arbor staging system taking into account the results of the FDG-PET scan (Lister, Crowther et al. 1989) . Areas of abnormal FDG uptake identified on the FDG-PET scan were only considered as involved sites of disease if there was evidence from conventional imaging to support the FDG-PET findings.

PET Protocol

Patients fasted for 6 hours prior to scanning and drank 2-3 glasses of water to ensure adequate hydration. 4.5MBq/Kg of FDG was injected with uptake time of 90 minutes prior to scan acquisition. Whole body (vertex to upper thighs) PET data was acquired and reconstructed using OSEM. A low dose CT without IV contrast was acquired with the same coverage as the PET scan. Local site protocol determined use of PET in 2D or 3D mode and CT imaging parameters. Baseline and subsequent scans were acquired on the same scanner for each patient using the same patient preparation and imaging parameters.

Baseline scans were submitted for central review within 4 weeks of trial entry for confirmation of staging and final allocation of treatment group. Scans performed at end-of-chemotherapy were centrally reviewed by two independent reviewers to confirm the response to treatment and to determine radiotherapy volumes.

Central review of staging differed from local review in 2 cases and in both cases the patients were allocated to TG3 whereas local review had indicated that they should be in TG1 or TG2.

Response assessment according to GPOH criteria

The protocol was designed before the introduction of international standardised response criteria incorporating PET results. Response assessment was performed according to the GPOH-HD definitions in use at the time the protocol was devised in which CR was attained if all sites of disease decreased in size by >95% and any residual masses measured ≤2ml in volume, non-measurable sites of disease were undetectable, disease symptoms had abated, and FDG-PET was negative. Good partial remission (GPR) was achieved when all sites of measurable disease had reduced by >75% but the criteria for CR were not met. Partial remission (PR) was achieved when all sites of disease had reduced by 50-75% from baseline (Mauz-Korholz *et al.* 2010). FDG-PET scans were defined as negative if there was complete resolution of all sites of uptake identified at baseline and as positive if abnormal FDG uptake was seen (Table S5).

Treatment details:

OEPA consisted of vincristine 1.5mg/m^2 IV (capped at a maximum of 2mg) on days 1, 8, and 15, etoposide 125mg/m^2 IV on days 1 to 5, prednisolone 60mg/m^2 orally on days 1 to 15, and doxorubicin 40mg/m^2 IV on days 1 and 15. COPP consisted of cyclophosphamide 500mg/m^2 IV on days 1 and 8, vincristine 1.5mg/m^2 IV (capped at a maximum of 2mg) on days 1 and 8, procarbazine 100mg/m^2 orally on days 1 to 15, and prednisolone 40mg/m^2 orally on days 1 to 15. Cycle duration of both OEPA and COPP was 28 days.

Supportive care was recommended with anti-*pneumocystis jiroveci*, and anti-viral prophylaxis during treatment. Granulocyte colony stimulating factor (GCSF) was recommended if neutropenia was experienced to prevent treatment delays.

Radiotherapy delivery:

All radiotherapy patients were planned using 3D-CRT. An involved site Clinical Target Volume (CTV) was delineated on CT following the Involved Site Radiotherapy (ISRT) principles described in the National Cancer Research Institute Lymphoma Radiotherapy Group Guidelines (Hoskin *et al.* 2013). Patients in TG2 or TG3 in CR received 20Gy ISRT to all initially involved sites of disease regardless of the FDG-PET scan result at end-of-chemotherapy. Patients in good PR (GPR) with >75% reduction of all sites of disease (regardless of PET findings) or PR (50-75% reduction in sites of disease volume) with a negative PET scan received 20Gy ISRT plus a 10Gy boost to residual masses measuring >50ml. Residual disease was outlined as the Gross Tumour Volume and a boost CTV defined as an expansion of this, by 15mm in all directions, constrained to anatomical boundaries. Patients in PR with PET-positive sites of disease received 30Gy ISRT to all initial sites of disease with no additional boost to residual sites of disease (Figure 1). Radiotherapy was delivered in 2Gy fractions, 5 days a week, and was subject to a central quality assurance assessment.

Statistical considerations:

Sample size calculation was based on a Fleming single stage design. With a 90% power, one-sided 10% significance level and assuming the true neurotoxicity rate in the experimental treatment is ≤4%, 45 patients would be required to exclude a neurotoxicity rate of >15%. Also, with one sided significance level of 10% and 90% power, 45 patients would be sufficient to exclude a response rate of <80%, assuming that the true response is ≥93%.

For adverse events and neurotoxicity, the worst grade for each patient is presented. ORR is reported with respective 2-sided 80% CI. Time-to-event endpoints were DFS

(defined as the time from documentation of CR to relapse or death from any cause) and OS (defined as the time from registration to death from any cause), and standard survival analysis was implemented.

QoL values for each of the scales obtained at each timepoint were compared with baseline values using paired t-tests. 99% CI were used and statistical significance was only assumed if $P<0.01$ for all QoL data to account for multiple testing.

Supplementary tables:

Characteristic	No of patients	%
All patients	47	100
Sex		
Female	22	47
Male	25	53
Stage		
II	28	60
III	6	13
IV	13	28
B symptoms		
Absent	25	53
Present	22	47
ECOG performance status		
0	41	87
1	5	11
2	1	2
Extranodal involvement		
Yes (E lesion)	7	15
Yes (Stage IV)	6	13
No	32	68
Not reported	2	4
Treatment group		
TG1 (early stages)	16	36

TG2 (intermediate stages)	11	24
TG3 (advanced stages)	18	40

Supplementary Table 1 Baseline patient characteristics

Treatment group	Cycles	Chemotherapy drugs			
TG1 (N=16)		Vincristine or Vinblastine**	Etoposide	Prednisolone*	Doxorubicin
	OEPA 1	2	0	2	0
	OEPA 2	0	0	2	0
TG2 (N=11)		Vincristine or Vinblastine	Etoposide	Prednisolone	Doxorubicin
	OEPA 1	0	0	0	0
	OEPA 2	0	0	0	0
		Vincristine or Vinblastine	Cyclophosphamide	Prednisolone	Procarbazine
	COPP 1	0	0	0	0
	COPP 2	1	0	1	0
TG3 (N=18)		Vincristine or Vinblastine	Etoposide	Prednisolone	Doxorubicin
	OEPA 1	1	0	2	0
	OEPA 2	1	0	1	1
		Vincristine or Vinblastine	Cyclophosphamide	Prednisolone	Procarbazine
	COPP 1	1	0	0	0
	COPP 2	3	0	1	1
	COPP 3	4	0	0	0
	COPP 4	4	0	0	0

* 5 patients in OEPA cycle 1 received less than 90% of the intended dose of the prednisolone. One of those patients was the patient who withdrew in first cycle of OEPA and was not classified into a treatment group.

** Vinblastine was administered in place of vincristine in 3 of 45 (7%) patients receiving OEPA cycle 2, 5 of 29 (17%) patients receiving COPP cycles 1 and 2, and 3 of 18 (17%) patients receiving COPP cycles 3 and 4.

Supplementary table 2 Number of patients who received less than 90% of the intended dose for each of the drugs in each cycle by treatment group

	Baseline	Prior to each cycle of chemotherapy	After 2 x OEPA	After final cycle of chemotherapy	After all treatment	3 months after completion of all treatment	6 months after completion of all treatment	9 months after completion of all treatment	12 months after completion of all treatment	Follow-up[b]
Toxicity	X	X		X	X	X	X	X	X	X
QOL	X	X	X	X	X	X	X	X	X	X
CT/MRI scan	X		X	X		X				
FDG-PET	X		X[a]	X						

Supplementary Table 3 **Schedule of investigations and follow up.**

[a] FDG-PET required after 2 cycles of OEPA in TG1 only

[b] Follow-up every 4 months for years 2 and 3, every 6 months in years 4 and 5 and annually thereafter

Minor variations	***No. of Patients***	***Major variations***	***No. of Patients***
SUP and/or INF margin variation <2.0 cm	3	SUP and/or INF margin variation ≥2.0 cm	3
Liver disease should not be treated	1	Skeletal sites uninvolved in CT & MR should not be treated	1
Splenic hilum inclusion	1	Nodal region missed	1

Supplementary Table 4 Radiotherapy outlining protocol variations (one major variation patient displayed 2 types of variation)

FDG-PET Result	**Definition**
Negative (1)	Complete disappearance of all abnormal uptake, highest residual uptake in tumour site less than or equal to mediastinal background

Positive (2)

Partial Response	Reduction in abnormal uptake but residual tumour activity greater than mediastinal background
Stable	No significant change compared to baseline
Progression	Increase in level of abnormal uptake or appearance of new sites

Supplementary Table 5 FDG-PET Response Categories

Neurotoxicity	Ever Worst Grade (CTCAE grade criteria*) N (%**)				Total
	1	2	3	4	
Motor	9 (20%)	6 (13%)	2 (4%)	0 (0%)	17 (37%)
Sensory	16 (35%)	17 (37%)	3 (7%)	0 (0%)	36 (78%)
Ileus/GI	8 (17%)	6 (13%)	1 (2%)	0 (0%)	15 (33%)
Other not specified	2 (4%)	1 (2%)	1 (2%)	0 (0%)	4 (9%)
Any neurotoxicity	15 (33%)	18 (39%)	5 (11%)	0 (0%)	38 (83%)

* Patients who reported neurotoxicity related adverse events are taken into account in the table

** Percentages based on a total of 46 patients (47 patients were registered into the trial, one withdrew consent before receiving treatment)

Supplementary Table 6 Worst grade of neurotoxicity during the trial

Toxicities (CTCAE grade criteria)	Grades	
	3	4
	N (%)	N (%)
HAEMATOLOGICAL		
Haemoglobin decreased	1 (2%)	0 (0%)
Neutrophil count decreased	9 (20%)	29 (63%)
Platelet count decreased	5 (11%)	3 (7%)
White blood cell decreased	7 (15%)	0 (0%)
NON-HAEMATOLOGICAL		
Constitutional symptoms		
Fatigue	2 (4%)	0 (0%)
Fever	2 (4%)	0 (0%)
Gastrointestinal		
Nausea	3 (7%)	0 (0%)
Vomiting	3 (7%)	0 (0%)
Diarrhoea	2 (4%)	0 (0%)

Mucositis/stomatitis	6 (13%)	0 (0%)
Ascites	1 (2%)	0 (0%)
Pain		
Gastrointestinal	4 (9%)	0 (0%)
Musculoskeletal	2 (4%)	1 (2%)
NOS	1 (2%)	0 (0%)
Other *	1 (2%)	0 (0%)
Infection		
Febrile neutropenia	9 (20%)	1 (2%)
Vascular		
Thrombosis/embolism	2 (4%)	0 (0%)
Cardiac		
Hypotension	1 (2%)	1 (2%)
Respiratory		
Pleural effusion	1 (2%)	0 (0%)
Osteonecrosis		
Osteonecrosis **	2 (4%)	0 (0%)

* Patient with grade 3 pain had pelvic pain due to osteonecrosis

** One other patient had grade 2 of osteonecrosis

Supplementary Table 7 Non-neuropathy toxicities: worst toxicity grade at any point in time of the trial (excluding neurotoxicity).

Worst grade reported of radiotherapy toxicity (RTGO criteria)	Patients who received radiotherapy (N=41)						Total (%)
	Mild		Moderate		Severe		
	N	%	N	%	N	%	
Skin problems §	3	7	2	5	0	0	5 (12%)
Mucositis ∫	8	20	2	5	2	5	12 (29%)
Gastrointestinal ‡	5	12	2	5	0	0	7 (17%)
Other acute toxicity*	10	24	2	5	2	5	14 (34%)
Any radiotherapy toxicity	16	39	4	10	3	7	23 (56%)

§ Skin problems: 2 patients with moderate Erythema

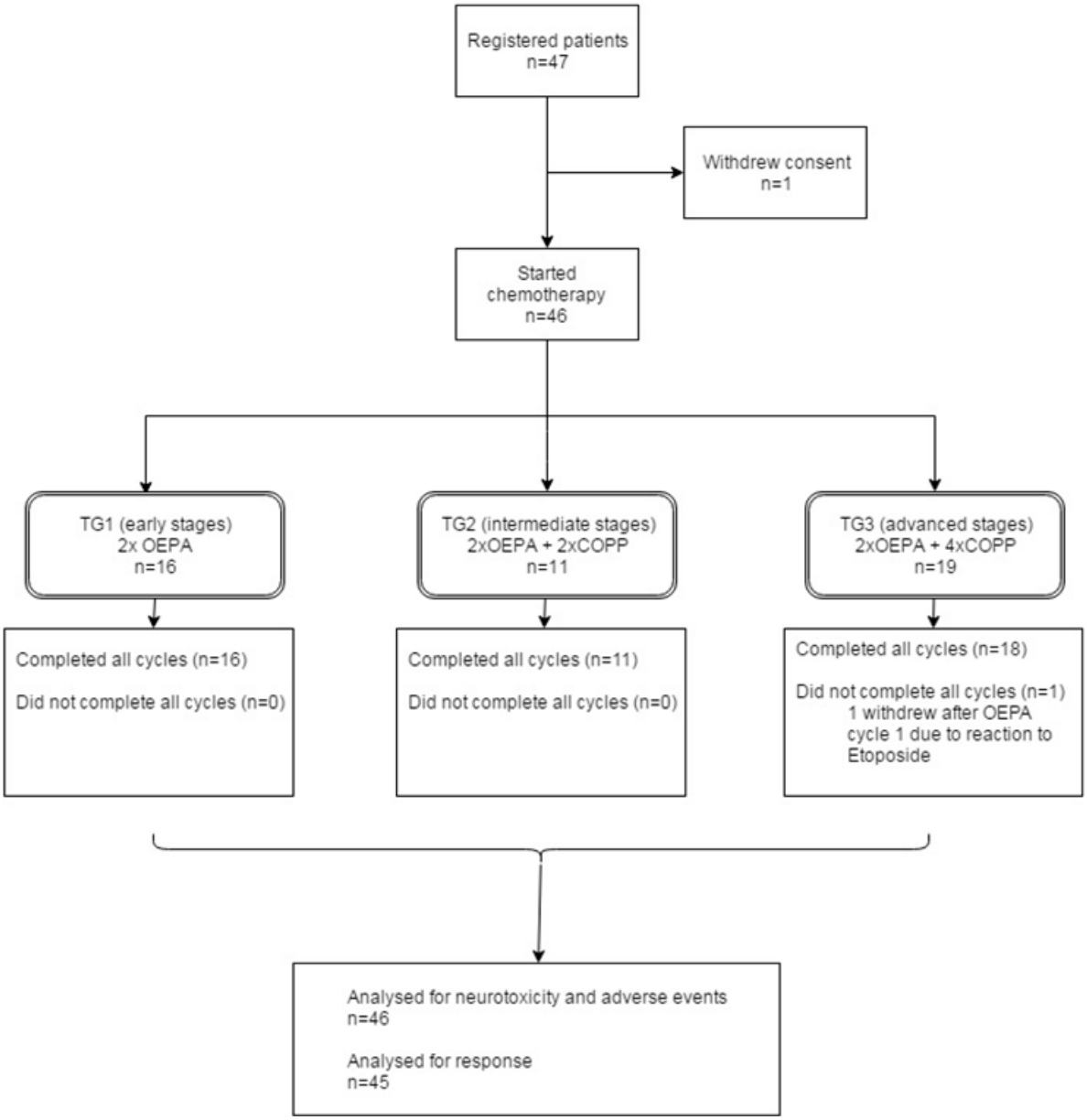
∫ Mucositis: 1 patient with moderate oral mucositis, 1 patient with moderate mouth mucositis, 1 patient with severe throat and mouth mucositis, 1 patient with severe mouth and oesophagus mucositis

‡ Gastrointestinal: 1 patient with moderate Nausea, 1 patient with moderate Diarrhoea

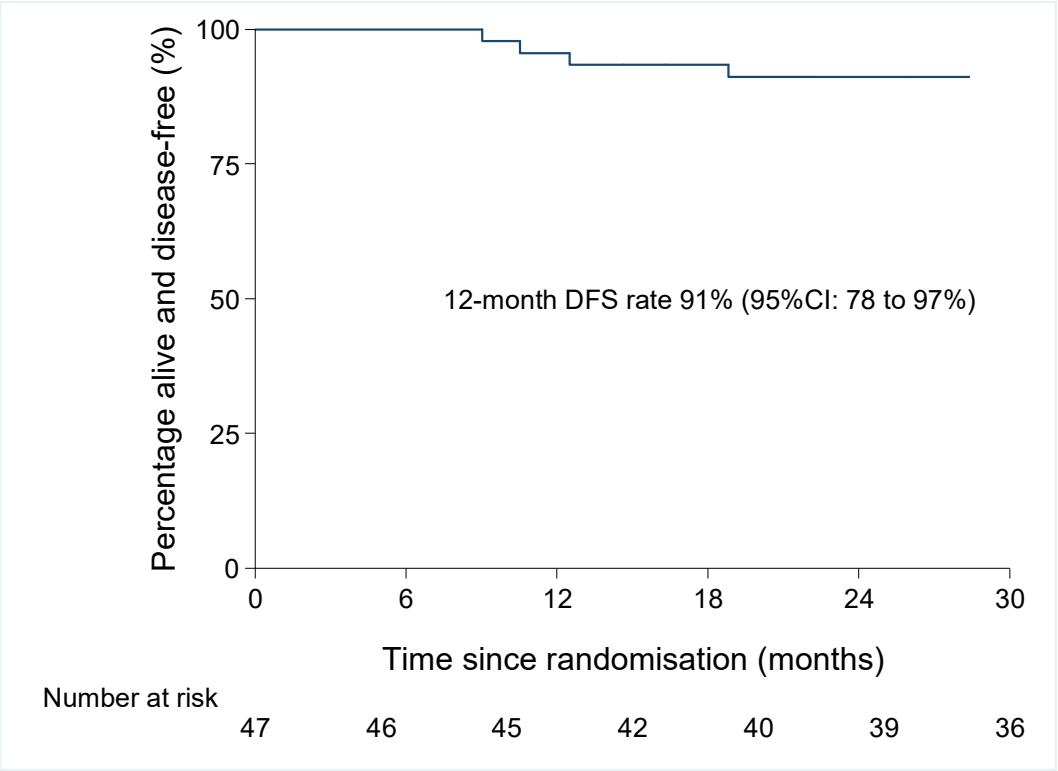
* Other acute toxicity: 1 patient with moderate Anorexia, 1 patient with moderate abnormal taste perception; 1 patient with severe Frontal headache, 1 patient with severe dysphagia

Supplementary table 8 Worst grade of radiotherapy toxicity reported 6 months after completing radiotherapy

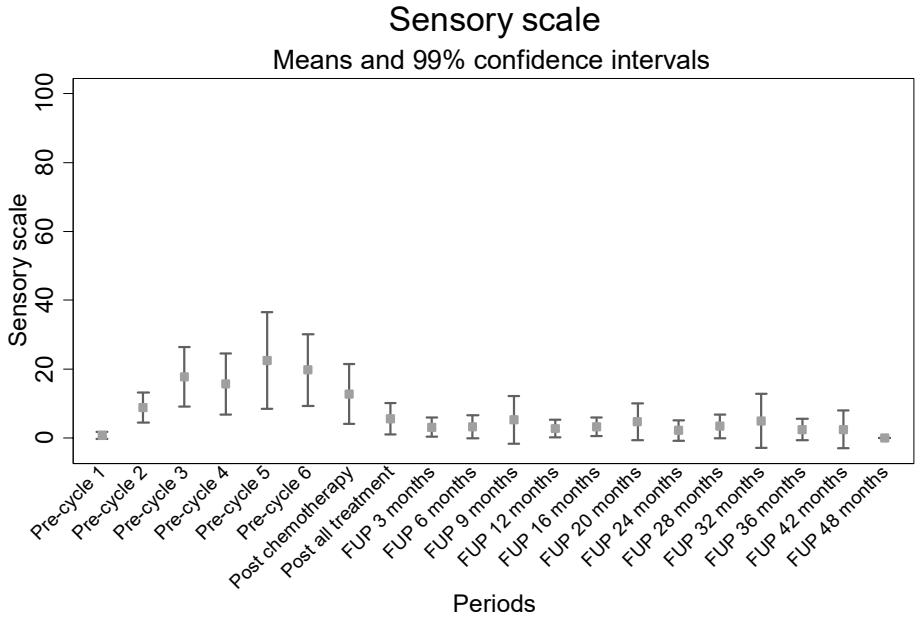
Supplementary figures:

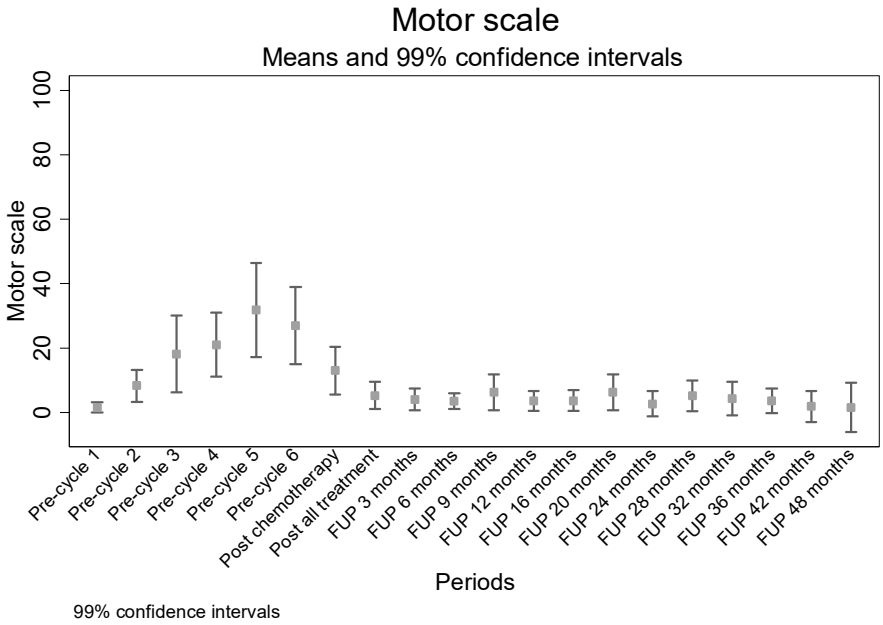


Supplementary Figure 1: Consort diagram



Supplementary Figure 2 **Disease free survival**





Supplementary Figure 3 Sensory and Motor quality of life scales. There was a significant deterioration in both scales between pre-treatment and post-chemotherapy. At 12 months post treatment, sensory scale was not significantly different to baseline but motor scale remained 2.6 points worse than at baseline.

Supplementary References:

Lister, T.A., Crowther, D., Sutcliffe, S.B., Glatstein, E., Canellos, G.P., Young, R.C., Rosenberg, S.A., Coltman, C.A. & Tubiana, M. (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *Journal of Clinical Oncology*, **7,** 1630–1636.