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Long-term outcome in children with Hodgkin's lymphoma: The United Kingdom Children's Cancer Study Group HD82 trial

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ABSTRACT

Background: The aim of United Kingdom Children's Cancer Study Group (UKCCSG) HD82 was to establish the efficacy of chlorambucil/vinblastine/procarbazine/prednisolone (ChlVPP) in the treatment of childhood Hodgkin's lymphoma stages II–IV and radiotherapy (RT) alone in stage I patients. We report on the status of these patients to a follow-up of 20 years.

Methods: Treatment consisted of 35 Gy involved-field RT for stage I and ChlVPP alone for stages II–IV. Adjuvant RT (35 Gy) was administered to those with bulky mediastinal disease.

Results: Of the 358 patients, the 10-year EFS/OS per stage is I (65.4%/92.6%), II (80.0%/93.3%), III (68.8%/85.0%), IV (45.5%/72.7%). The corresponding 20-year OS rates are similar with a combined (all stage) rate dropping from 89.3% to 89.0% over the decade. The cumulative 20-year malignancy rate is 7.29%.

Conclusion: Single modality treatment provided relatively low EFS at 10-years but comparable long-term OS, relative to contemporary published combined modality regimens, for stages I–III but not for stage IV patients.

1. Introduction

Radiotherapy (RT), using high doses (up to 45 Gy) and extended volumes, was the standard treatment for Hodgkin's lymphoma (HL) in adults and children in the early 1960s. Children shared a similar prognosis with their adult counterparts but demonstrated a greater incidence of the musculo-skeletal consequences of RT.[1] An attempt was made to reduce this toxicity by lowering the dose of RT and introducing chemotherapy – mechlorethamine, oncovin, prednisone and procarbazine (MOPP). Results from trials confirmed the role of this combined modality approach with overall survival (OS) rates of approximately 90%.[2–5] However, with the use of mechlorethamine, a relatively high rate of toxicity persisted and second-malignancies became apparent. To overcome these problems alternative treatment strategies were considered.

It was with this background in 1982 that the United Kingdom Children's Cancer Study Group (UKCCSG) developed its

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first HL trial (HD82), in an attempt to establish an effective, predominantly single modality, non-mechlorethamine containing chemotherapy regimen.

Adverse treatment consequences, including the development of second malignancies, appear to be more prevalent in patients with HL as compared to those with any other malignancies.[6,7] Most co-operative groups are now focussing on similar issues of effectiveness of treatment and long-term sequelae by addressing the relative merits of combined or single modality treatment. The German Society for Pediatric Oncology (GPOH) and the Children's Cancer Group (CCG), historically utilising a combined modality approach as standard treatment for children for HL, have attempted to decrease the potential radiation-related burden of treatment by decreasing, or omitting, radiation in patients relative to their response to chemotherapy. The GPOH omitted radiotherapy in patients, regardless of the extent of disease at presentation, who were in complete remission (CR) following chemotherapy.[8] Patients not in CR received either 20 Gy or 30 Gy involved field RT (IFRT) relative to their chemotherapy response. Relapse free survival was superior in patients receiving RT although there was no significant reduction in overall and event free survival compared to previous GPOH trials when RT was administered to all patients. In the CCG trial, patients in CR following chemotherapy were randomised to receive 21 Gy IFRT or no RT. Event free survival in the former group was superior although there was no significant difference in overall survival (at 3 years) between the groups.[9] The long-term implications with respect to treatment related toxicity are not available due to relatively short follow-up periods in both studies at the time of publication. The need for long-term data are therefore important.

The objectives of this report are to update our preliminary reports[10,11] with survival rates as well as the second malignancy rate in this cohort of patients following extensive follow-up. Our aim is to contribute to the current debate on the most appropriate treatment for children with HL by presenting long-term outcome.

2. Patients and methods

2.1. Patients

Children under the age of 16 years with histologically proven HL were eligible for entry. Patients were clinically staged according to the Ann Arbor classification.[12] Histological determination, utilising the Rye classification[13], was undertaken in local centres. Staging was based on imaging, predominantly by CT scan, with no patients undergoing staging laparotomies or splenectomies. Patients with a mediastinal mass greater than one third of the transverse thoracic diameter at the level of the mass were considered to have bulky mediastinal disease (BMD). There was no comprehensive central pathology, radiological or radiotherapy review.

2.2. Protocol treatment

2.2.1. Stage I cervical/neck disease

Apart from those with BMD, patients were treated with RT at a dose of 35 Gy. The dose was calculated at 2 cm from the supraclavicular fossa and at the midplane for the upper cervical nodes. Bilateral neck irradiation was performed using anterior and posterior opposing fields, extending from the mastoid process to immediately below the clavicle. The lateral field extended to the outer third of the clavicle. The larynx and cervical spine were recommended to be shielded as was the floor of the mouth unless high cervical node involvement was present.

2.2.2. Stages II, III and IV disease

All patients, except those with BMD, were treated with chemotherapy alone, using cycles of ChlVPP. This consisted of chlorambucil (6 mg/m^2 orally for 14 days), vinblastine (6 mg/m^2 intravenous push on days 1 and 8), procarbazine (100 mg/m^2 orally for 14 days) and prednisolone (40 mg/m^2 orally for 14 days). The duration of each cycle was 28 days with no treatment being administered over the final 14 days. A minimum of 6 and a maximum of 8 cycles were to be given. It was recommended that cycles were continued until remission was achieved and followed by a further 4 cycles thereafter if possible within the total maximum of 8.

2.2.3. Patients with bulky mediastinal disease

These patients received the above chemotherapy with the subsequent addition of RT. A dose of 35 Gy was administered to the midplane. The original volume of the mediastinal mass was to be included in the treatment fields, extending from the suprasternal notch to the level of T10 vertebra.

2.3. Follow-up

Following completion of treatment patients were monitored at least biannually for 5 years, then annually until 10 years post diagnosis. However, in view of interest in long-term consequences, a request to all participating centres was made in December 2003, for current survival status, and a similar request was made to the Childhood Cancer Research Group, University of Oxford, UK, for updated follow-up and second malignancy information.

2.4. Statistical methods

Overall survival (OS) was computed from the date of diagnosis to the date of death from any cause or the last date of contact if still alive. Similarly EFS was computed from the date of diagnosis but now to the date of the first event (whether relapse, second malignancy or death) or the last date of contact for those who are still alive and believed to be free of disease. The Kaplan–Meier method was used to estimate the OS and EFS curves.

To reliably estimate long-term OS rates, and their associated 95% confidence intervals (CI), statistical models[14] were fitted to the survival curves (see Figs. 3 and 4) using Stata.[15] These models (often termed 'cure' models) allow the influence of stage and the presence of BMD on long-term OS to be quantified (Table 5).

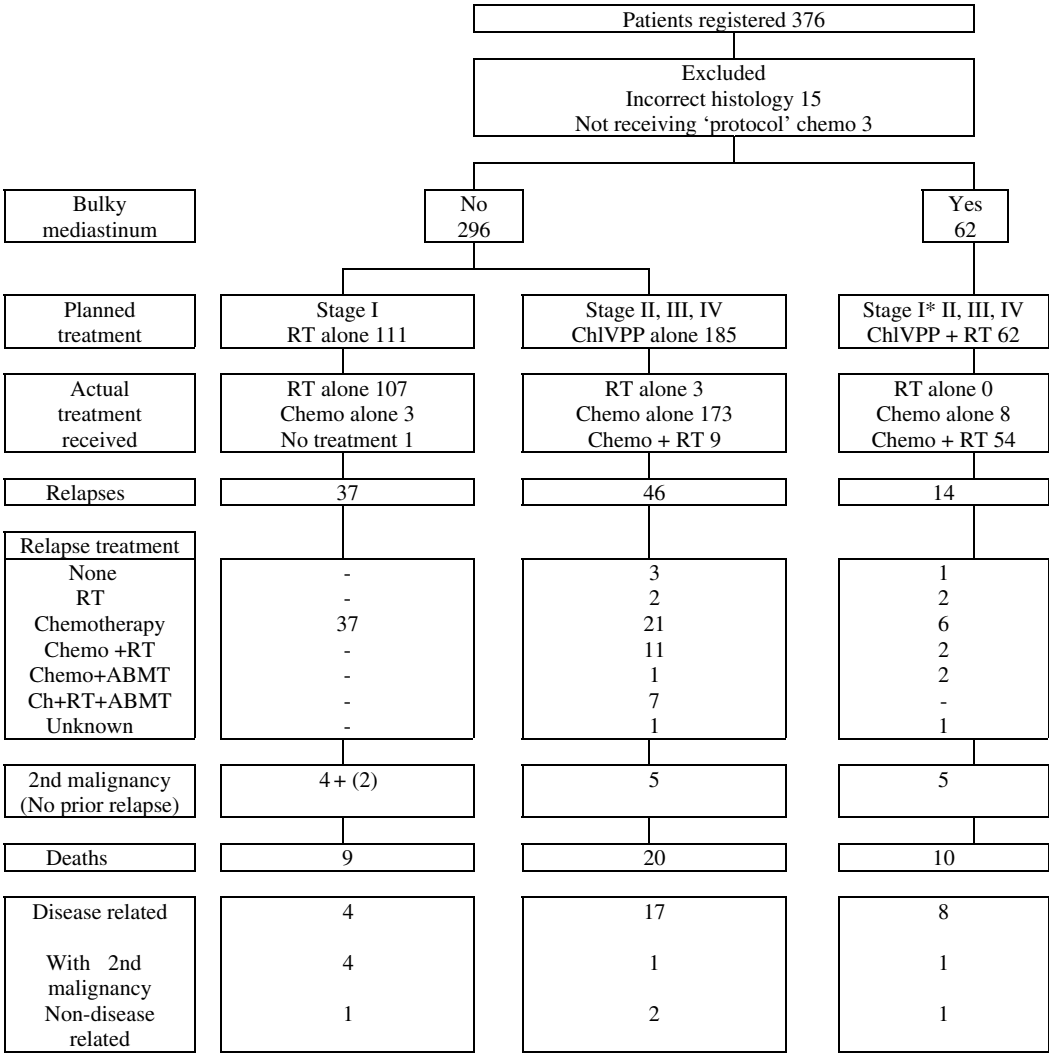
The second malignancy rate per 1000 years of patient follow-up is expressed relative to the overall survival time accumulated in successive 5-year intervals and the Kaplan–Meier method used to obtain the cumulative rate at 20 years.

3. Results

Over the period 11th January 1982 to 12th May 1992, 376 patients from 20 centres were entered into the trial of which 358 (95%) were deemed eligible and of these 319 remain alive at a median follow-up of 15.5 years (range: 0.3–22.2 years). In total 89% of patients have a 'date-last-seen' of 2000 or later, 64% within the year 2003, while 11% have not been traced for more than 4 years and are essentially lost to follow up via the referral centre although any second malignancies or deaths will have been reported by the national systems. The patient flow through the study is summarised in Fig. 1. Of the 18 patients not eligible, 15 were excluded for a histological diagnosis other than HL and 3 were treated with VEEP chemotherapy (there was no intention to treat these according to the HD82 protocol). One patient, 16.1 years at the time of initial diagnosis is included in the analysis. The majority of the patients received treatment as the protocol intended for their stage, RT alone 95.5%, ChlVPP alone 85.8% and ChlVPP with adjuvant RT 76.1%, respectively. Of patients receiving chemotherapy, 167 (94%) patients in the ChlVPP alone arm received between 6 and 8 cycles of chemotherapy as compared to 50 (80.6%) in the chemotherapy with RT arm. The principal reasons recorded for departure from protocol were clinician preference.

There were 111 (31.0%) stage I patients, all with cervical/neck primary site disease, and none with BMD (Table 1) while 134, 80 and 33, respectively had stages II, III and IV disease of whom 62 (17.3%) had BMD (36 male, 26 female). A large proportion (47.5%) had nodular sclerosis (NS), 23.5% were of mixed cellularity (MC), 20.7% lymphocyte predominant (LP), and the remainder were either combined pathology (8.1%) or lymphocyte depleted (0.8%).

The proportion with B symptoms increased with stage and was 1.8%, 22.4%, 38.8% and 60.6% in stages I–IV, respectively. Patients with nodular sclerosis subtype had the highest incidence of B symptoms (31.2%).



* Although the protocol was inclusive of Stage I patients with bulky disease, none were entered.

Fig. 1 – Patient progress through key stages of the study.

Table 1 – Demographic and clinical characteristics of patients by protocol treatment recommended

	Treatment			
	RT alone	Chemo alone	Chemo + RT	Total
Number of patients				
n	111	185	62	358
Mediastinal				
Involved				
Bulky	–	–	62	62 (17.3%)
Not bulky	3	84	–	87
Not involved	102	89	–	191
Unknown	6	12	–	18
Stage				
I	111	–	–	111 (31.0%)
II	–	104	30	134 (37.4%)
III	–	58	22	80 (22.3%)
IV	–	23	10	33 (9.2%)
Gender				
Male	95	126	36	257
Female	16	59	26	101
Age (years)				
0–4	12	14	4	30
5–9	48	63	9	120
10–15	51	108	49	208
Pathology				
LP	44	29	1	74 (20.7%)
LD	0	2	1	3 (0.8%)
NS	35	94	41	170 (47.5%)
MC	25	48	11	84 (23.5%)
Other	7	12	8	27 (7.5%)
Symptoms[a]				
A	99	113	32	244
B	2	55	26	83
Unknown	10	17	4	31

LP, lymphocyte predominant; LD, lymphocyte depleted; NS, nodular sclerosis; MC, mixed cellularity.
a 'B symptoms' were recorded if the patient had one or more of – fever, loss of weight or night sweats.

3.1. *Relapses*

There have been a total of 97 (71 alive, 26 dead) relapses (Table 2) of whom all survivors received salvage treatment.

Of the 37 patients (33.3%) relapsing from initial stage I disease, 24 relapsed within 3 years of diagnosis, whilst 7 relapsed after 5 years – range 5.1–14.5 years. All were treated initially with RT alone, followed by chemotherapy at the time of relapse. Six (16%) have subsequently died. There were 15 (62.5%) stage I patients with mixed cellularity who relapsed compared to 13 (28.2%) lymphocyte predominant and 9 (28.1%) with nodular sclerosis. The proportion relapsing was 17.2%, 26.3% and 48.5% in stages II, III and IV, respectively; 46 (24.9%) scheduled for ChlVPP alone and 14 (22.6%) of those scheduled for ChlVPP and RT. Treatment for relapse (Fig. 1) was by RT alone 4, RT with autologous bone marrow transplantation (ABMT) 7, chemotherapy of many different modalities 27, both chemotherapy and RT in 13, chemotherapy with ABMT 3 and chemotherapy with RT and ABMT in 7.

3.2. *Second malignancies*

A total of 16 second malignancies have been reported (Table 3) of whom six had previously relapsed. The overall cumulative second malignancy rate at 10-years is 2.45% (95% confidence interval [95% CI]: 0.76–4.14%) and at 20 years 7.29% (CI: 2.8–11.7%) (Fig. 2). The malignancy rate appears greatest at 5.90 per 1000 years, in the period 11–15 years post diagnosis.

Of these malignancies, 6 (2 NHL, 1 Ewing's sarcoma, 1 brainstem glioma (BSG), 2 oral/salivary gland) were 5.4% of those with stage I disease scheduled for RT only; 5 (2 cervical carcinoma, 1 ovarian carcinoma, 1 AML, 1 thyroid sarcoma) were 2.7% of those with stages II/III/IV disease scheduled for chemotherapy only; and 5 (2 AML, 1 leiomyosarcoma of the thorax, 1 breast carcinoma, 1 cervical carcinoma) were 8.1% of those with bulky mediastinal disease scheduled for chemotherapy and RT (Table 4). Times to develop AML, one in each of stages II, III and IV, were 9.9, 5.4, and 4.0 years, respectively. The 20-year second haematological (AML/NHL) malignancy rate was 1.6%.

3.3. *Event free survival*

A relapse, secondary malignancy or death has occurred in 118 (33.0%) patients. Five and 10 years EFS for all patients are 74.2% (CI: 69.7–78.8%) and 69.7% (CI: 64.9–74.5%), respectively (Table 2). At 10 years the rates for those scheduled for radiotherapy alone, chemotherapy alone and the combined modality are 65.4%, 72.4% and 69.3%, respectively, and for stages I–IV the rates are 65.4%, 79.8%, 68.8% and 45.5%, respectively. Rates beyond 10-years are not reliable as reporting relapses are no longer routine beyond this time.

3.4. *Overall survival*

Thirty-nine patients have died, 20 as a direct result of HL, six from infection, six with secondary malignancies (AML 2, NHL 2, BSG 1, oral/salivary 1) and seven from other causes (suicide 2, murder 2, cerebrovascular accident following sagittal and lateral sinus thrombosis while on chemotherapy 1, complications arising from pre-existing neurofibromatosis 1, and cardio-respiratory arrest – underlying cause of death unknown 1). The 10- and 20-year OS figures within each treatment group are essentially the same. For all 358 patients combined, these are 89.3% (CI: 86.1–92.5%) and 89.0% (CI: 85.7–92.3%), respectively (Table 2). For stage I (none with BMD) patients scheduled for RT alone the 20-year OS rate is 91.2% (Fig. 3), while for those of stages II, III and IV scheduled for chemotherapy alone it is 89.2% and in those with BMD additionally receiving RT it is 5.3% lower at 83.9% (Fig. 4). OS is 93.8%, 86.3% and 74.9% for stages II, III and IV, respectively, but reduced to 91.2%, 81.2% and 67.1% in those with BMD (Table 5).

Table 2 – Survival status, presence of relapse, second malignancy and EFS and OS by scheduled treatment group

			Stage I RT alone	Chemo alone	Chemo + RT	Total
Number of patients		*n*	111	185	62	358
Survival status	Relapse	Malignancy				
Alive	No	No	71	129	40	240
		Yes	–	**4**[a]	**4**	**8**
	Yes	No	29	32	8	69
		Yes	**2**	–	–	**2**
		Subtotal alive	102	165	52	319
Dead	No	No	1	6	4	11
		Yes	**2**	–	–	**2**
	Yes	No	4	13	5	22
		Yes	**2**	**1**	**1**	**4**
		Sub total dead	9	20	10	39
Event free survival (EFS) (%)		5 years	72.8	75.1	74.2	74.2
		10 years	65.4	72.4	69.3	69.7
		15 years	62.8	68.7	65.2	66.3
Overall survival (OS) (%)		5 years	98.2	91.9	90.3	93.6
		10 years	92.6	89.2	83.9	89.3
		15–20 years	91.5	89.2	83.9	89.0

a Numbers with a second malignancy highlighted in **bold** type.

Table 3 – Risk of second malignancies by 5-year intervals

Treatment group	5-years					Total
	1–5	6–10	11–15	16–20	21–25	
RT alone	1	3	2	–	–	6
ChlVPP	–	2	3	–	–	5
ChlVPP + RT	1	1	2	1	–	5
Haematological	1	3	1	–	–	5
Non-haematological	1	3	6	1	–	11
Total	2	6	7	1	–	16
Total follow-up (y)	1720.3	1597.0	1186. 1	488. 7	43.2	5035.3
Rate per 1000 (y)	1.16	3.76	5.90	2.05	0.00	3.18
95%CI	0.14–4.20	1.38–8.18	2.37–12.16	0.05–11.40	0.00–85.31	
KM cumulative (%)	0.60	2.45	5.48	7.29	–	

4. Discussion

The debate on the most appropriate treatment for children with HL continues. Despite chemotherapy with low-dose radiation being adopted as the standard of care in the 1990s most co-operative groups continue to address similar issues specifically concerning the relative merits of combined or single modality treatment options. The need for long-term data are therefore important.

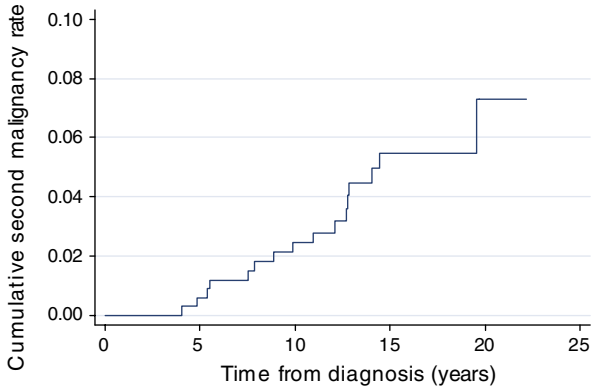


Fig. 2 – Overall Kaplan–Meier estimate of the cumulative second malignancy rate.

HD82 comprises a single modality, predominantly chemotherapy-only, regimen and has produced comparable overall survival figures with other studies utilising combined modality treatment regimens. The 5-year OS rate of 93.6% obtained is comparable to the rates documented in two contemporary national trials –92% 6-year OS in the MHD82 trial of the French Society of Paediatric Oncology and 96% 5-year OS in the DAL-HD-82 trial from the German-Austrian group.[16,17] However, the corresponding 5-year EFS rates of 86% and 96% of these trials are superior to the 74.2% reported here. This is most likely due to the intensive combined modality regimens administered upfront in both trials – ABVD/MOPP + 20–40 Gy RT and OPPA/COPP + 25–35 Gy RT, respectively. However, a subsequent Pediatric Oncology Group (POG) study demonstrated neither OS nor EFS advantage to

Table 4 – Details of second malignancies

Protocol schedule	Gender	Age	Stage	Chemo courses	Pathology	Time to relapse (y)	Treatment post relapse	Type of malignancy	Time to malignancy (y)	Status (alive, dead)	Survival (y)
RT alone	M	11.93	I	–	LP	4.79	Chemo	Oral/salivary	4.82	D	5.57
	F	6.51	I	–	MC	1.61	Chemo	ES	5.51	A	12.23
	M	8.34	I	–	LP	1.55	Chemo	NHL	7.53	D	8.11
	M	8.51	I	–	LP	–	–	BSG	8.90	D	9.58
	M	12.22	I	–	NS	–	–	NHL	10.93	D	11.70
	M	11.66	I	–	LP	0.93	Chemo	Oral/salivary	12.72	A	14.65
Chemo alone	M	10.43	III	6	LP	3.72	Chemo + RT	AML	5.41	D	5.47
	F	14.14	II	7	NS	–	–	Cervix	7.86	A	10.98
	F	14.39	II	6	NS	–	–	Ovary	12.78	A	17.89
	F	14.45	III	7	NS	–	–	Thyroid	12.85	A	13.66
	F	10.00	II	6	NS	–	–	Cervix	14.41	A	14.41
Chemo + RT	M	10.14	IV	8	NS	0.98	Chemo	AML	4.00	D	4.36
	F	14.08	II	6	NS	–	–	Thorax	12.10	A	12.10
	F	11.45	II	6	NS	–	–	AML	9.88	A	18.78
	F	9.52	IV	8	MC	–	–	Cervix	14.01	A	20.27
	F	13.48	IV	6	MC	–	–	Breast	19.52	A	21.11

LP, lymphocyte predominant; MC, mixed cellularity; NS, nodular sclerosis; AML, acute myeloid leukaemia, BSG, brain stem glioma; ES, Ewing's sarcoma; NHL, non Hodgkin's lymphoma.

Fig. 3 – Overall survival of stage I patients scheduled for RT alone and the corresponding fitted model.

Fig. 4 – Kaplan–Meier and cure model estimates of overall survival of stages II, III, and IV patients without BMD scheduled to receive chemotherapy alone (upper plots) compared to those with BMD receiving radiotherapy in addition to their chemotherapy (lower plots).

nodal radiotherapy being administered to patients following 8 cycles of alternating MOPP/ABVD[18] in those who had achieved CR. In contrast, radiotherapy was associated with superior EFS in the previously mentioned CCG study.[9] The authors of this prospective study with chemotherapy (COPP/ABV), using risk-adapted allocation to treatment, followed by randomisation to radiation therapy or discontinuing treatment had some 92% of patients who receive RT alone alive and disease free at 3-years compared with 87% with no further therapy. In fact, randomisation was stopped as a result of the inferior EFS in patients not receiving RT. The authors concluded that RT offered improved EFS but there was no survival advantage evident at the time of analysis. A meta-analysis of 8 trials in which predominantly adult patients with HL were randomised to receive chemotherapy only or chemotherapy and radiotherapy confirmed an 11% higher rate of continuous complete remission at 10 years for the latter group.[19] However, the overall survival in this group was inferior as a result of an increased rate of deaths (both non-Hodgkin's and Hodg-

Table 5 – Long-term (20-year) OS, with 95% CI, by stage and presence of BMD

BMD	Stage			
	I	II	III	IV
No				
n	111	104	58	23
OS%	91.2%	93.8%	86.3	74.9
95% CI	83.6–95.4	47.4–99.6	28.1–99.0	33.1–94.7
Yes				
n	–	30	22	10
OS%	–	91.2	81.2	67.1
95% CI	–	59.0–98.7	38.4–96.8	44.1–84.1

kin's related) in patients receiving radiotherapy prior to relapse.

The significance of EFS as a measure of effective treatment in patients with HL has become apparent over time. Relapsing survivors, although cured, would be at risk for multiple long term toxicities as a result of the high dose therapy eventually received, notwithstanding the emotional trauma involved in this process. In order to discuss the association between treatment and the outcome measures of survival, treatment-related toxicities and second malignant neoplasms (SMN) in our trial, it is beneficial to stratify the patients according to treatment groups. Analysis of these data have been made according to the *intended* treatment/protocol schedule, repeating the analyses omitting those who did not receive the intended regimen (see Fig. 1) made only marginal differences to the numerical results quoted and does not influence our conclusions in any way.

HD82 has succeeded in maintaining an excellent 5-year OS rate of 98.2% in stage I patients, albeit with an EFS of 72.8%. This was achieved by relapsing patients being effectively salvaged with ChlVPP chemotherapy. The aim of this approach was to avoid the effects of multimodal therapy for the majority of patients, while accepting the risk of full dose single-modal radiotherapy in all. This approach spared 72 of the 106 patients from receiving genotoxic chemotherapy. However, the estimated 10-year OS of stage I patients is 92.6%, marginally lower than 93.3% for the predominantly chemotherapy only treated stage II patients, raising the concern of treating such patients with radiotherapy alone. In order to establish the benefit of this approach, the burden of treatment in survivors needs to be accurately identified and individually assessed with appropriate quality of life tools. There were no reported cases of thyroid SMN in stage I patients who received radiotherapy. Further comprehensive treatment-related toxicity data, including for example, infertility rates, hypothyroidism, and soft tissue neck atrophy is not available from this trial, as such data were not prospectively collected when the trial commenced back in 1982. Modern chemotherapy regimens utilising low dosages of alkylator, and limited use of anthracyclines, together with low dose involved field radiation, now used by the majority of collaborative groups including the CCLG (formerly UKCCSG), have replaced the outdated single modal approach described above due primarily to the apparent consequent reduction of treatment-related toxicity.

The 5-year OS for the 214 stages II and III patients (60% of all patients) was 95.5% and 91.3%, respectively, comparable with the 96% 3.5-year disease free survival of stages IIB/IIIA patients treated with OPPA/COPP and IFRT in the DAL-HD82 trial.[20] The 60 stages I and II patients who relapsed, partly reflected in the low 10-year EFS of 79.8% and 68.8%, respectively, were effectively salvaged with further treatment. Thirty-three patients in the chemotherapy only subgroup of stages II/III patients (total = 162), i.e. those without BMD, relapsed. This approach saved the majority the reported burden of radiotherapy in HL patients, including late thyroid, cardiac and pulmonary toxicity as well as SMN.[21–24]

Patients with stage IV disease ($n = 33$, 9%) in contrast had inferior OS of 75.8% at 5 years, below the 80% OS achieved using MOPP and RT[25] and the 87% disease free survival at 3.5 years with stages IIIB or IV disease using OPPA/COPP and IFRT.[20] Poor EFS rates, even with combined modality treatment, have been reported in multiple collaborative trials.[16,26,27] Further intensification of treatment for stage IV patients, possibly with intensified, or novel, chemotherapy approaches is required.

The relatively low cumulative risk of second malignancies, 7.3% overall and 1.6% for second haematological malignancies at 20-years, is encouraging. The latter compares favourably with a 4% rate reported by the Late Effects Study Group in which chemotherapy (predominantly mechlorethamine containing) was included in the treatment of 66% of 979 children with HL between 1995 and 1979.[28] This cohort was expanded and updated in 1994 to include 1380 patients in total, with a reported cumulative incidence of a second malignancy of 10.6% at 20 years.[29] A further extended follow-up study of nearly 700 young HL patients treated at Stanford over a 35-year period reported the strongest predictor for development of a SMN to be relapsing HL.[30] The small numbers of patients with SMN in our study, 16 in total of which six were treated for relapsing HL, exclude any meaningful analysis in this regard.

This study, initiated over 20 years ago in an attempt to treat patients uniformly, has many significant limitations relative to modern scientific rigour. There was no central radiology review at presentation or at the time of remission status decision-making. Likewise, pathology was not comprehensively centrally reviewed and specifically no distinction was made between lymphocyte rich classical HL and nodular lymphocyte predominant HL – now recognised as two different entities with proposed different treatment strategies. The opportunity to gather vital data pertaining to treatment-related toxicity was missed. Despite these significant deficiencies, extensive survival and second malignancy population based data spanning over two decades of follow-up is now available for future trials to take forward.

This study demonstrates that approximately a half of patients with HL can be treated with a single modality, chemotherapy only, regimen with a low prevalence of second malignancies. Planned collaborative future studies will attempt, by way of functional imaging, to identify in real time patients who can safely avoid radiotherapy and prospectively address the important issue of treatment-related sequelae.

Conflict of interest statement

The authors indicated no potential conflicts of interest.

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Pathology Review Panel Chair: Dennis Wright, Southampton General Hospital.
Clinical Centres Participating (the number of patients enrolled from each centre is given in parenthesis).
United Kingdom: Royal Aberdeen Children's Hospital (1), Addenbrooke's Hospital, Cambridge (15), Royal Belfast Hospital (5), Birmingham Children's Hospital (48), Bristol Royal Hospital for Sick Children (13), Llandough Hospital, Cardiff (16), Royal Hospital for Sick Children, Edinburgh (10), Royal Hospital for Sick Children, Glasgow (12), St James's University Hospital, Leeds (31), Leicester Royal Infirmary (11), Royal Liverpool Children's Hospital (22), Royal Manchester Children's Hospital (50), Royal Victoria Infirmary, Newcastle upon Tyne (30), Queen's Medical Centre, Nottingham (9), Barts and The Royal London Hospital (20), Great Ormond Street Hospital, London (21), Sheffield Children's Hospital (21), Southampton General Hospital (13), Royal Marsden Hospital, Sutton (4).
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