# Poor outcome in adolescents with high-risk Hodgkin lymphoma

R.A. HERBERTSON[2], L.S. EVANS[2], J. HUTCHINSON[1], J. HORSMAN[1] and B.W. HANCOCK[1]

[1]Yorkshire Cancer Research Academic Unit of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ; [2]Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ, UK

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**Abstract.** This retrospective study looks at the differences between adolescents (15-19 years) and young adults (20-25 years), diagnosed with Hodgkin lymphoma and treated at the same adult institution. Outcome according to risk category was evaluated, and although there were no significant differences in the whole cohort, or low and intermediate-risk categories, high-risk adolescent patients had a significantly worse outcome compared to that of young adults. In these high-risk patients, 5-year event free survival was 43.6% in adolescents compared to 58.7% in young adults (log-rank survival p=0.03), and the 5-year overall survival in adolescents was 66.7% compared to 84.4% in the young adults (p=0.04). Possible contributing factors to this inferior outcome in these high-risk patients were explored. The difference could not be explained in terms of differences in histological subtype (p=0.5), proportion of patients with bulky (p=0.6) or extranodal disease (p=0.6), initial treatment received (chemotherapy alone compared to combination therapy, p=0.2), or proportion proceeding to high-dose treatment after initial treatment failure (p=0.6). There was no difference in the documented number of delays, dose reductions or episodes of non-compliance during initial treatment in the two high-risk age groups. A significantly greater proportion of high-risk adolescents had primary progressive disease (PPD) [eight high-risk adolescents (33.3%) compared to two high-risk young adults (7.7%), p=0.02].

## Introduction

'Adolescent' is usually used to describe someone who has undergone puberty but not reached full maturity, referring to those aged between 13-19 years of age. The outcome of adolescents with cancer is becoming an increasingly important issue, as when adolescents are compared with children higher incidence, lower mortality reduction, and even a worse outcome have been reported in a number of cancers (including Hodgkin lymphoma (HL) (1,2). Some published data suggests adolescents may also have a worse outcome compared to young adults, but evidence focusing specifically on this age group is scarce (2-5). Hodgkin lymphoma is one of the commonest cancers to be diagnosed in adolescents (3,6) with an annual incidence per million in England between 1968-1995 of 28.2 (7) compared to 32.5 in the United States between 1986-1995 (6,8). Adolescents in paediatric series seem to have a much better outcome than those evaluated in adult series. 'Paediatric' risk adapted, combined modality treatment with regimens such as OEPA/OPPA induction (vincristine, etoposide, prednisolone and doxorubicin/ vincristine, prednisolone, procarbazine and doxorubicin) ± COPP (cyclophosphamide, vincristine, procarbazine, prednisolone) and involved field radiotherapy (IFR), have led to a high-5-year event free survival (EFS) with apparent minimal long-term toxicity, even in advanced or 'high-risk' disease (9). Directing treatment towards prognostic score or risk stratification is increasingly important in all ages, but especially in children and adolescents as this ensures that those with good prognosis, low-risk disease can be managed with regimens associated with minimal toxicity, whilst those at high risk of treatment failure can be treated more aggressively (10). Low-risk disease is defined as localised disease (stage I and II), no bulky disease and absence of B symptoms. Intermediate-risk disease is defined as all stage I and stage II patients not classified as early stage (i.e. those that have one or more unfavourable feature) and stage IIIA. High-risk disease is those patients with stage IIIB and IV disease at presentation.

Five-year EFS and overall survival (OS) for high-risk patients in paediatric series (which included adolescents) are quoted to be 77-91 and 82-99%, respectively (9,11-20), which is superior to adolescent containing adult series (50-78 and 66-89% respectively) (21-24). Age analysis was performed in some of these studies, but no statistical significance was found (9,11,12,19). Few studies have focused specifically on adolescents, but some support the hypothesis that they have an inferior outcome. The retrospective study of Yung *et al* of adolescents with HL found the 5- and 20-year EFS was 50 and 41% respectively, and the 5- and 20-year OS was 81 and 68% (4). Possible factors contributing to this apparently inferior outcome could include differences in disease at presentation, the use of treatments designed for adults, delays in diagnosis and low accrual into clinical trials (2,4,25). Foltz *et al* found no differences when outcome was compared in adolescents (16-21 years) and young adults

*Correspondence to:* Professor Barry W. Hancock, Yorkshire Cancer Research Academic Unit of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ, UK
E-mail: b.w.hancock@sheffield.ac.uk

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Table I. Event free survival and overall survival according to age group.

| | All risk categories | | | Low-risk category | | | Intermediate-risk category | | | High-risk category | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (years) | | | (years) | | | (years) | | | (years) | | |
| Outcome | 15-19 | 20-25 | p-value | 15-19 | 20-25 | p-value | 15-19 | 20-25 | p-value | 15-19 | 20-25 | p-value |
| 5-year EFS | 59.9 | 69.7 | 0.38 | 65.9 | 80.5 | 0.64 | 75.0 | 66.7 | 0.29 | 43.6 | 58.7 | 0.03 |
| 20-year EFS | 56.1 | 54.6 | | 65.9 | 61.9 | | 75.0 | 43.9 | | 16.6 | 58.7 | |
| 5-year OS | 85.4 | 91.4 | 0.25 | 96.4 | 93.8 | 0.76 | 100 | 95.8 | 0.25 | 66.7 | 84.4 | 0.04 |
| 20-year OS | 76.3 | 86.9 | | 89.0 | 93.8 | | 100 | 85.7 | | 52.5 | 80.2 | |

(22-45 years) (5), concluding that the two age groups had similar baseline characteristics, and achieved similar outcomes when treated with the same protocols, but no analysis on high-risk patients was performed.

This retrospective study was designed to help identify any differences in the outcome of adolescents (15-19 years) and young adults (20-25 years) with HL treated in a single institution, and explore potential influential factors that might explain any potential differences.

## Patients and methods

Although adolescents are often counted as those between 13-19 years of age, this study focused on those patients treated in an adult institution, and hence the definition of adolescent was 15-19 years (those younger than 15 years were treated at the region's paediatric centre). The Sheffield Teaching Hospital NHS Trust Ethics Committee approved the use of data collected on the Weston Park Hospital (WPH) lymphoma database over a 30-year period, and patients diagnosed with HL when aged 15-25 years between 1/1/69 and 31/12/98 and treated at the single institution were identified. Adolescents were compared to those 20-25 years of age as this age group was thought to be most likely to have the least amount of confounding factors (such as additional medical problems). Where possible, the date of diagnosis was taken as the date of biopsy, but when unavailable, date of the first outpatient appointment at WPH was used. Date of relapse was documented in a similar way. The time to relapse was taken as the time between the date of diagnosis and the date relapse was confirmed. Bulky disease was taken as one site of disease measuring 5 cm or more. EFS was documented as the time between date of diagnosis and date of first event; progression, relapse or death. The date of progression in those that never achieved a remission was the date progression was confirmed. Primary progressive disease was defined as patients with progressive disease during induction treatment or within 90 days after the end of treatment. CRu was defined as a clinical complete response, but with evidence of residual disease on post treatment imaging of uncertain significance.

*Statistical methods*. Life-table calculations were performed using the Kaplan Meier methods (26). EFS was calculated with respect to the following events: progression during therapy, relapse, death (before and in first remission). OS was calculated as death from any cause. Survival differences were compared using the log-rank test (27). Potential differences in variables between the two age groups was analysed using the $\chi^2$ test. Univariate analysis was used to assess the influence of different variables on EFS and OS in the high-risk patients.

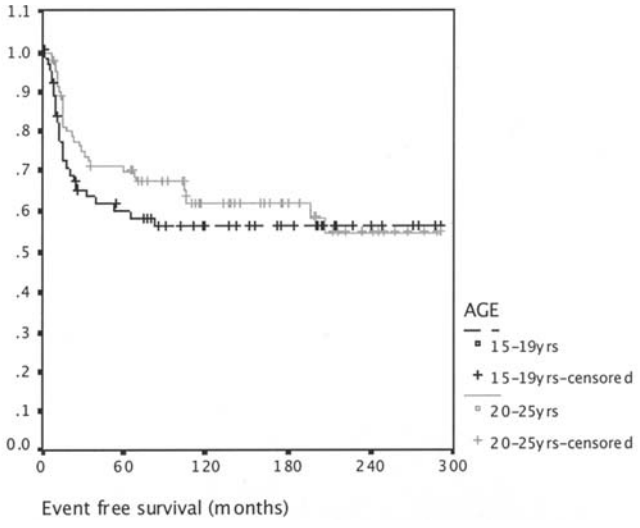


Figure 1. Event free survival in whole cohort.

## Results

Of the 145 patients in the study population, 63 were 15-19 years old and 82 were 20-25 years. In the whole study population (all risk categories), the mean EFS for adolescents was 172 months (95% CI 138-207), compared to 187 months (95% CI 159-215) in young adults. The 5- and 20-year EFS for adolescents was 59.9 and 56.1% compared to 69.7 and 54.6%, respectively in young adults. The 5- and 20-year OS for adolescents was 85.4 and 76.3% compared to 91.4 and 86.9% respectively in young adults. There was no statistically significant difference in EFS (p=0.38) or OS (p=0.25) between the two age groups when the whole sample was evaluated. Differences were seen however, when outcome was assessed according to risk category. Table I documents the 5- and 20-year EFS and OS in the whole cohort and according to risk category. Figs. 1 and 2 show the Kaplan Meier curves for EFS and OS in the whole study population.

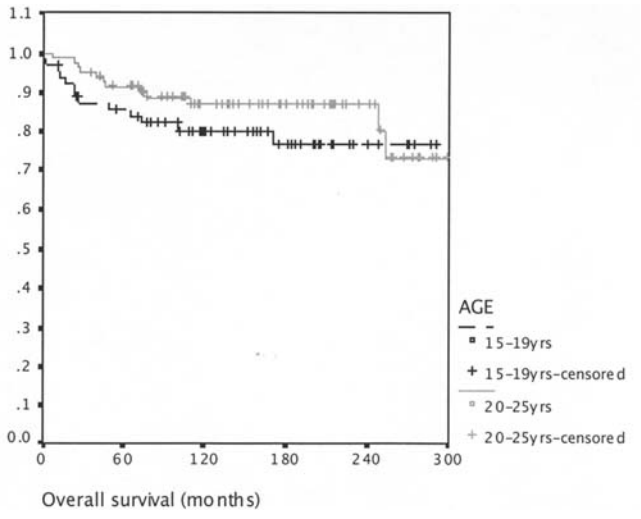


Figure 2. Overall survival of whole cohort.

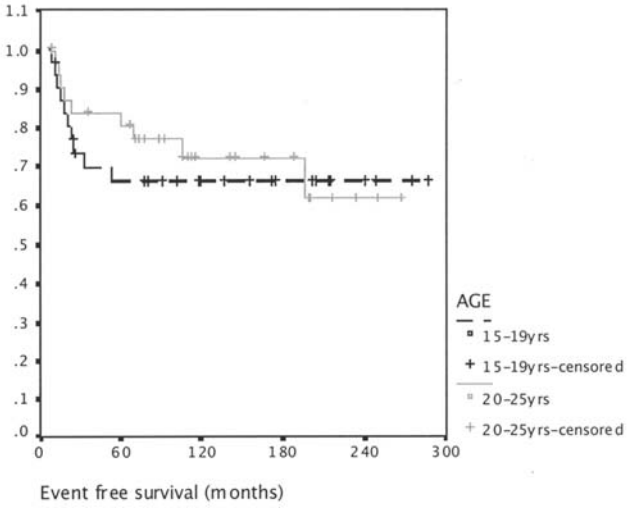


Figure 3. Event free survival in low-risk category.

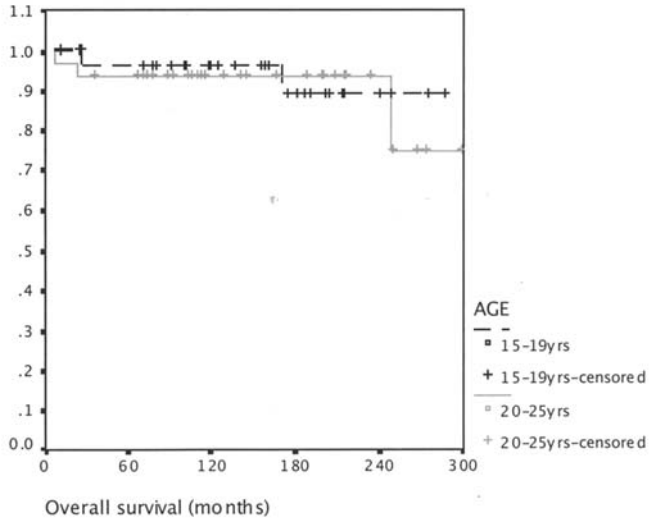


Figure 4. Overall survival in low-risk category.

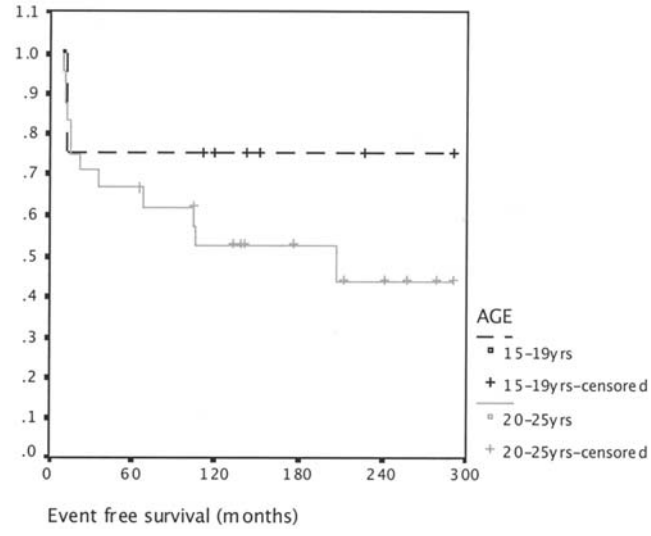


Figure 5. Event free survival in intermediate-risk category.

*Low-risk category patients*. There were 63 patients in low-risk category, 32 in 20-25-year age group and 31 adolescents. For these patients the mean EFS and OS was very similar in both age groups. Mean EFS was 196 months (95% CI 151-242) for adolescents and 197 months (95% CI 159-235) for young adults. Mean OS was 268 months (95% CI 245-292) for adolescents and 271 months (95% CI 243-299) for young adults). The 5- and 20-year EFS for adolescents was 65.9% (there were no late relapses), compared to 80.5 and 61.9%, respectively, in young adults. This did not reach statistical significance (p=0.64). The 5- and 20-year OS was very similar in both age groups, being 96.4 and 89.0% in adolescents and 93.8% in young adults (the only late death in this group occurred >20 years later). There were 5 documented deaths in this risk category. Two adolescents, one whom died of progressive disease at 27 months, and one of cardiac sarcoma at 172 months (following prior mantle radiotherapy). Of the 3 young adults who died, one developed Acute Respiratory Distress Syndrome after high-dose therapy (HDT), one developed metastatic adenocarcinoma >20 years after initial diagnosis, and one died in a traffic accident (8 months after diagnosis). Figs. 3 and 4 demonstrate the survival curves for EFS and OS respectively).

*Intermediate-risk category patients*. Thirty-two patients presented with intermediate-risk disease. Eight were adolescents and 24 were young adults. No statistically significant difference was found between the EFS (p=0.29) and OS (p=0.25) in the two age groups. The mean EFS for adolescents was 221 months (95% CI 138-304) compared to 165 months (95% CI 114-216) in young adults. Five- and 20-year EFS was 75.0% in adolescents (no late relapses), compared to 66.7 and 43.9% respectively, in young adults (p=0.29). Five- and 20-year OS was 100% in adolescents (surprisingly no deaths were documented in this age group), compared to 95.8 and 85.7% respectively, in young adults (p=0.25). There were four young adult deaths, three were a result of progressive disease, and one late death (254 months after diagnosis) was secondary to the treatment of a secondary malignancy (neutropenic sepsis). It was not clear

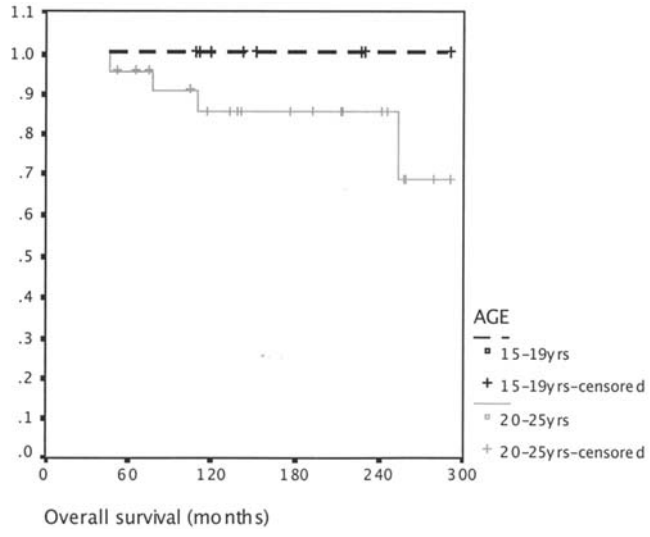


Figure 6. Overall survival in intermediate-risk group.

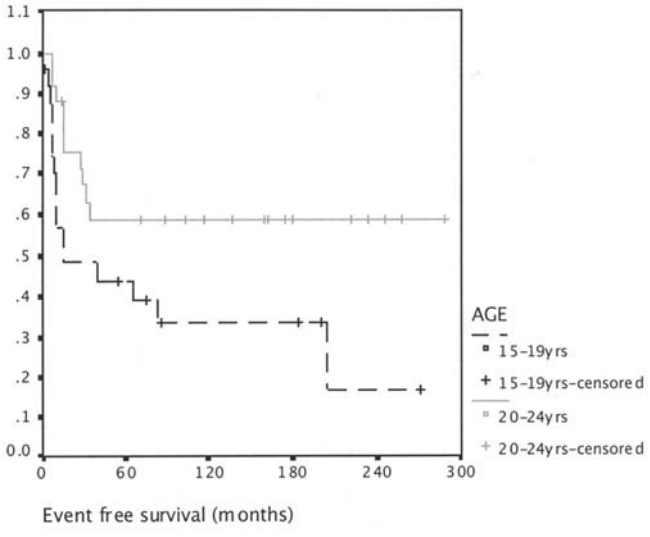


Figure 7. Event Free survival in high-risk patients.

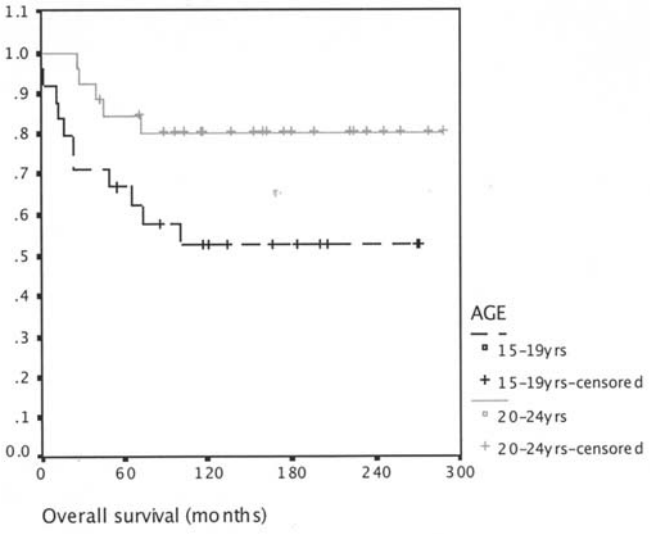


Figure 8. Overall survival in high-risk patients (months).

Table II. $\chi^2$ analysis of the high-risk category patients in the two age groups.

| Characteristics | 15-19 years n=24 | 20-25 years n=26 | $\chi^2$ P-value |
|---|---|---|---|
| Subtype | | | |
| NS | 20 | 17 | 0.5 |
| MC | 3 | 6 | |
| LR | 1 | 1 | |
| LD | 0 | 1 | |
| NLP | 0 | 0 | |
| Not documented | 0 | 1 | |
| Documented bulky disease | 8 | 13 | 0.6 |
| Documented extranodal disease | 14 | 13 | 0.6 |
| Initial treatment | | | |
| Chemotherapy alone | 18 | 15 | 0.2 |
| Combination therapy | 6 | 11 | |
| Documented delays during initial treatment | 5 | 10 | 0.1 |
| Documented dose reductions during initial treatment | 2 | 5 | 0.3 |
| Documented non-compliance during initial treatment | 1 | 3 | 0.3 |
| Response to first line therapy | | | |
| CR | 15 | 20 | 0.02[a] |
| PR | 2 | 6 | |
| PD | 6 | 0 | |
| Died during treatment | 1 | 0 | |
| Number in CR after initial treatment | 15 | 20 | 0.3 |
| HDT after initial treatment (those with PD or PR after initial treatment) | 6 | 5 | 0.6 |
| Primary progressive disease | 8 | 2 | 0.02[a] |

NS, nodular sclerosing; MC, mixed cellularity; LR, lymphocyte rich; LD, lymphocyte depleted; NLP, nodular lymphocyte predominant; CR, complete response; PR, partial response, PD, progressive disease.

why there were differences, with the young adults having an inferior outcome. Figs. 5 and 6 demonstrate the survival curves for EFS and OS respectively in the intermediate-risk patients.

*High-risk disease*. Fifty patients presented with high-risk disease. Twenty-six were 20-25 years and 24 were 15-19

Table III. First line treatment modality of high-risk patients.

| | Number of patients receiving treatment (% of age group) | | | | |
|---|---|---|---|---|---|
| Age | C | C, HDT | C, XRT | C, XRT, HDT | Total |
| 20-25 years | 15 (57.7) | 0 | 6 (23.1) | 5 (19.2) | 26 |
| 15-19 years | 15 (62.5) | 4 (16.7) | 4 (16.7) | 1 (4.2) | 24 |
| Total | 30 | 4 | 10 | 6 | 50 |

C, chemotherapy; HDT, high-dose therapy; XRT, radiotherapy.

Table IV. First line chemotherapy in high-risk patients.

| Chemotherapy regimen | 15-19 years n=24 | 20-25 years n=26 |
|---|---|---|
| ABVD | 0 | 1 |
| ChlVPP | 1 | 0 |
| ChlVPP/PABlOE | 6 | 3 |
| LOPP | 8 | 3 |
| LOPP/EVAP | 5 | 8 |
| Mixed hybrid | 1 | 1 |
| MOPP | 1 | 6 |
| MOPP/ABV | 0 | 1 |
| PABlOE | 2 | 2 |
| VAPEC-B | 0 | 1 |

ChlVPP, chlorambucil, vincristine, procarbazine, prednisolone; PABlOE, prednisolone, doxorubicin, bleomycin, vincristine; ChlVPP/PABlOE, chlorambucil, vinblastine, procarbazine, prednisolone/prednisolone, doxorubicin, bleomycin, vincristine, etoposide; LOPP, chlorambucil, vincristine, procarbazine, prednisolone; EVAP, etoposide, vinblastine, doxorubicin, prednisolone; MOPP, mechlorethamine, vincristine, procarbazine, prednisolone; MVP, methotrexate, vinblastine, prednisolone; ABVD, doxorubicin, vinblastine, bleomycin, dacarbazine; VAPEC-B, vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; Mixed hybrid, LOP-EVA.

years old. Mean EFS was 93 months (95% CI 48-139) for the adolescents and 177 months (95% CI 124-230) for young adults. Mean OS was 159 months (95% CI 111-208) compared to 239 months (95% CI 201-278) in young adults. Five- and 20-year EFS for adolescents was only 43.6 and 16.6% compared to 58.7% (with no late relapses) in young adults. Five- and 20-year OS was 66.7 and 52.5% in adolescents compared to 84.4 and 80.2% respectively, in young adults. EFS (p=0.03) and OS (p=0.04) were significantly worse in adolescents compared to young adults. Figs. 7 and 8 respectively demonstrate the survival curves for EFS and OS in the high-risk category patients. A number of variables were assessed to explore possible contributing factors for this inferior outcome. $\chi^2$ analysis of possible differences in patient or tumour characteristics within this group found no difference in the histological subtype (p=0.5), bulky disease (p=0.6), or extranodal involvement (p=0.6) at diagnosis between the two age groups, but did find significant differences in response to first line therapy and proportion of primary progressive disease (PPD) (Table II).

*First line treatment of high risk patients*. There was no statistically significant difference between initial treatment modality combination between the two age groups (p=0.2, when chemotherapy was compared to combination therapy). Fifteen young adults and 15 adolescents received chemotherapy alone as their first line therapy. A further 16 patients also received radiotherapy following chemotherapy, 11 of these were 20-25 years and 5 were 15-19 years. The commonest regimen was 35 Gy with a mantle or involved field. Five young adults and 1 adolescent went onto to HDT following chemotherapy and radiotherapy. Table III demonstrates the number of patients receiving each combination of first line treatment modality. There was a statistically significant difference in response to initial treatment between the two age groups (p=0.02). Initial treatment in adolescents resulted in 15 (62.5%) achieving a CR, 2 (8.3%) a PR, 6 (25.0%) progressed, and 1 died during treatment (4.2%). This compared to 20 (76.9%) CRs and 6 (23.1%) PRs in the young adults. A number of different chemotherapy regimens were used over the study period, and no one regimen seemed more frequently used in either age group (Table IV).

*Primary progressive disease*. Although the proportion of patients achieving CR with initial therapy was similar in both age groups (62.5% in adolescents, 76.9% in young adults, p=0.3), there was a significantly higher proportion of patients with primary progressive disease (PPD) in the high-risk adolescents (p=0.02). Eight adolescents had PPD (6 of these progressed during treatment, and 2 within 90 days of finishing), compared to only 2 young adults (both of these achieved an initial PR, but progressed soon after finishing treatment). This is 12.7% of the whole adolescent cohort, compared to 2.4% of the whole young adult cohort. There were no significant differences in documented delays in treatment (p=0.1), dose reductions (p=0.3), or non-compliance (p=0.3) to explain these differences.

Of the patients who developed PPD, no one regimen was clearly responsible. Of the 8 adolescents, 1 received ChlVPP/PABlOE, 2 PABlOE, 3 LOPP and 2 LOPP/EVAP. Of the 2 young adults 1 received MOPP and 1 received LOPP/EVAP. Of these 10 patients with PPD, only 3 had received combined modality therapy (2 adolescents, 1 young adult), but this was largely because progression had occurred

during initial chemotherapy for the majority of patients. Of those with PPD, 6 out of 8 adolescents received HDT, and 1 out of 2 young adults did. Eight out of 10 patients with PPD died, 7 of these from progressive disease and 1 from a cerebral haemorrhage during HDT. The 2 patients who remain in remission having achieved a CR following HDT were both in the adolescent age group.

*Deaths in high risk patients*. There were 16 deaths in the high-risk category patients. Five young adults died of progressive disease. Of the 11 adolescent deaths, eight had progressive disease, one developed sepsis following their first cycle of chemotherapy, 1 had a cerebral haemorrhage secondary to low platelets during HDT and in 1 the cause was unknown.

## Discussion

As adolescent HL is rare and the nature of the young, mobile study population meant some loss to follow-up was inevitable, a 30-year period was required to ensure a reasonable sample size. The evolution of HL management over this 30-year time period, however, meant that many of the chemotherapy regimen and radiotherapy protocols used to treat many of the study population are no longer used. Mantle field radiotherapy is no longer used because of the increased risk of secondary breast cancer, and not many of the patients in either group were treated with ABVD - the current gold standard (with or without radiotherapy). Despite this, response rates and outcome can be compared with other published data, as treatment in this Centre is likely to have be in line with the rest of the UK during that time period, although this is one likely explanation for inferior outcome when compared to more recent studies.

The adolescents in this study had a higher proportion of primary progressive disease compared to both the study's young adults (12.7% of all adolescents compared to 2.4% of all young adults), and other published series. The proportion of primary progressive disease quoted in published paediatric series ranges from 0-5.0% (9,12,14,16,28) and in adult series 1.9-6.0% (21,22,29). The higher proportion of adolescents with primary progressive disease in this study could not be explained in terms of differences in tumour or patient characteristics. Non-compliance and poor tolerance of initial treatment (reflected by delays or dose reductions) was negligible amongst all patients and therefore was not a likely contributing factor to this difference. The outcome of these patients was poor, which is in line with published data. Five out of six of these adolescents (83.3%) died of progressive disease despite salvage treatment, and only one achieved a remission (which followed-up front HDT). The 1 adolescent in this study who achieved a CR with salvage treatment, compares to the published long-term disease free survival in adults with primary progressive disease, of 0-10% (30,31). Josting *et al* found the 5-year OS of patients with primary progressive disease was 26% for all patients compared to 43% of those treated with HDT (32). HDT with autologous stem cell transplantation has shown promising results in a number of studies, with better reported disease free survival rates of 31-42% (33,34), and this approach is now often adopted for those who are chemo-responsive, although further confirmatory trials are needed. It is clear that the adolescents had more early deaths, most of which were secondary to refractory or primary progressive disease. With adolescents doing worse on relapse and having fewer late relapses, it seems that optimising initial treatment with a more dose intensive approach (for example with paediatric regimen or newer regimen like Stanford V or BEACOPP), and HDT for those who relapse early or do not achieve a CR, could be a way of improving outcome.

Studies focusing specifically on adolescents are scarce. Although Yung *et al* in a retrospective study of adolescents found a significantly inferior outcome (20 year EFS 41% and OS 68%) (4), Foltz *et al* compared adolescents (16-21 years) to adults (22-45 years), and found no difference in outcome, even in advanced stage disease (10-year PFS and OS 71 and 88% respectively for advanced stage adolescents compared to 75 and 86% of adults) (5). Other published data suggest the outcome of adolescents is significantly better when they are included in paediatric series compared to those in adult series (9,11-20), and one possible explanation for this is that paediatric style (combined modality) treatment is more dose-intensive. In the German-Austrian multi-centre trial DAL-HD-90 (90 patients <18 years of age were treated with OEPA/OPPA induction ± 2-4 cycles of COPP and low dose IFR, and 5-year EFS was high even in advanced disease (84-89%). These results are far superior to the 43.6% 5-year EFS in high-risk adolescents (and 58.7% of young adults) in this retrospective study (and many other published series). A comparison of outcome in adolescents and children in the UK would be informative in trying to confirm whether differences in survival are as striking as the literature currently suggests. If the high cure rates achieved by the German-Austrian group can be reproduced, then it can be argued that their risk adapted approach with OPPA/OEPA, COPP and IFR (or possibly similar dose intensive regimens such as BEACOPP) should be adopted more widely for adolescents.

This study was undertaken to determine whether the outcome of adolescent with HL is inferior to that of young adults treated in a similar way in the same institution, and explore possible factors contributing to this. In this study the 5-year EFS and OS for all ages is similar to that in many adult series spanning a similar time period (21-24,29). Although similar outcomes were found in both age groups in the whole population, this small retrospective study helps to confirm that despite presenting with the same disease and being treated similarly in the same institution, a higher proportion of high-risk adolescents develop PPD and have a significantly inferior outcome compared to young adults. Further trials involving these patients are needed to help confirm the role of HDT (for primary progressive disease and at first relapse) and more intensive initial multi-drug chemotherapy (±IFR). The outcome of adolescents may then move closer to that seen with the seemingly more successful paediatric style regimens.

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