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## Hodgkin lymphoma in children, adolescents and young adults – a comparative study of clinical presentation and treatment outcome

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### ABSTRACT

**Background:** Hodgkin lymphoma (HL) treatment protocols for children, adolescents and young adults traditionally differ, but the biological and clinical justification for this remains uncertain.

**Material and methods:** We compared age-dependent clinical presentation and treatment and outcome for 1072 classical HL patients 0–24 years diagnosed in Denmark (1990–2010) and Sweden (1992–2009) in pediatric ( $n=315$ , Denmark <15 years, Sweden <18 years) or adult departments ( $n=757$ ). Distribution of clinical characteristics was assessed with Pearson's  $\chi^2$ -test and Mantel–Haenszel trend test. The Kaplan–Meier method was used for survival analyses. Hazard ratios (HR) were used to compare the different treatment groups and calculated using Cox regression.

**Results:** Children (0–9 years) less often presented with advanced disease than adolescents (10–17 years) and young adults (18–24 years) (stage IIB–IV: children 32% vs. adolescents 50%, and adults 55%;  $p < .005$ ). No variation in overall survival (OS) was seen between pediatric and adult departments or by country. Danish pediatric patients received radiotherapy (36%) less frequently than Swedish pediatric patients (71%) ( $p < .0001$ ). Ten-year event-free survival (EFS) was lower among Danish pediatric patients (0–14 years) (0.79; 95% confidence interval (CI) 0.70–0.86) than among Swedish pediatric patients (0–17 years) (0.88; 95% CI 0.83–0.92), HR (1.93; 95% CI 1.08–3.46). A similar pattern was seen between adult patients in the two countries: Denmark 10-year EFS 0.85 (95% CI 0.81–0.88), Sweden 0.88 (95% CI 0.84–0.91), adjusted HR 1.51 (95% CI 1.03–2.22).

**Conclusion:** Adolescents and young adults shared similar clinical presentation suggesting a rationale of harmonized treatment for these groups. Both adult and pediatric protocols provided high OS with no significant difference between the departments. The less frequent use of radiotherapy in Danish pediatric patients corresponded to a lower EFS, but comparable OS in all groups confirmed effective rescue strategies for the relapsing patients.

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## Introduction


The treatment of adolescents and young adults with cancer has attracted increased attention in recent years. Specifically, it has become evident that, compared with younger and older age groups, less progress has been made for cancer survival among adolescents and young adults [1,2]. The causes of this lack of improvement in treatment outcome are not completely understood, but may involve both age-dependent variation in clinical characteristics and the challenges posed by the complex psychological and physiological characteristics of the adolescent and young adult patient [3].

Dependent on the patient's age at diagnosis, cancer treatment conventionally falls under the auspices of either pediatric or adult oncologists. Consequently, patients with clinically identical disease presentations but at opposite ends of the age spectrum may receive different treatment.

Randomized clinical trials comparing outcome between pediatric and adult classical Hodgkin lymphoma (cHL) treatment strategies are lacking [4,5]. A few older retrospective analyses have indicated similar outcomes in adolescents and young adults treated with adult protocols independent of age at diagnosis [6,7]. One study including 245 patients described higher EFS in adolescents treated according to

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 Supplemental data for this article can be accessed [here](#).

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pediatric compared with adult protocols [8]. This raises the question of whether improved outcomes could be achieved by treating adolescent and young adult cHL patients according to similar protocols.

To further inform discussions on protocols of choice for children (0–9 years), adolescents (10–17 years) and young adults (18–24 years) with cHL, we used population-based cancer registers and clinical data to characterize clinical presentation in different age groups and compare outcomes between patients treated in pediatric (<15 years Denmark, <18 years Sweden) and adult departments, in the two countries.

## Study population and methods

### Study population and clinical presentation

We included all individuals diagnosed with cHL before 25 years of age in the period 1990–2010 in Denmark and 1992–2009 in Sweden in the nationwide Danish and Swedish Cancer registers ( $n = 1345$ ). Clinical information on disease stage, blood counts, B-symptoms, bulky and extra-nodal disease was ascertained from clinical databases or through scrutiny of medical records and was available for 1072 cHL patients. Data sources used are presented in Supplementary Table S1.

Patients were staged according to the Ann Arbor system modified in Cotswold [9]. Ann Arbor stages I–IIA were considered as limited disease and stages IIB–IV as advanced disease. Recognition of organ involvement including bone marrow and extra nodal disease was based on active reporting to the clinical registers and therefore considered absent in patients with no registrations hereof. Bulky tumor was either registered as such or in the present project defined as registrations of tumor diameter >10 cm. Blood counts at time of diagnosis were only available for Danish patients.

### Treatment

The clinical registers and medical record reviews also provided information on treatment, that is, number and type of chemotherapy courses and radiation therapy.

*Pediatric departments:* The majority of the pediatric HL patients were treated according to protocols in clinical trials organized by the German Pediatric Oncology & Hematology Group (GPOH) (1998–2007 Denmark, 1996–2005 Sweden), and since 2006 in Sweden and 2008 in Denmark by the European Euro-Net Paediatric Hodgkin's Lymphoma Group (Euro-Net PHL). Chemotherapy used was OEPA/OPPA [vincristine, etoposide (OEPA) or procarbazine (OPPA), prednisone, doxorubicin] and COPP/COPDAC [cyclophosphamide, vincristine, prednisone, procarbazine (COPP) or dacarbazine (COPDAC)], given as 2–6 courses [10]. Radiation therapy 20–30 Gy to involved field was given to patients after completed chemotherapy depending on remission or not. Remission was defined as >95% tumor volume reduction (GPOH-95, GPOH-HD-2002) and in Euro-Net PHL-C1 depending on fluorodeoxyglucose (FDG) positron emission tomography-computer tomography (PET-CT) response after two courses of chemotherapy. In the period until 1998 and 1996

in Denmark and Sweden, respectively, patients received MOPP/ABVD (mechlorethamine, vincristine, procarbazine and prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine) with or without radiotherapy. For the Swedish pediatric patients, the planned treatment and disease stage were used to extrapolate the number of chemotherapy courses since this was not always stated in the registers.

*Adult departments:* Adults with limited stage disease were treated with 2–4 courses of chemotherapy and 30 Gray (Gy) involved field/node/site radiotherapy; at the beginning of the study period (until approximately 1994) doses up to 36–40 Gy were applied and a small proportion of the patients with stage I disease received radiotherapy as the only treatment modality. Adults with advanced stage disease received 6–8 courses of chemotherapy, and radiotherapy to residual lymphoma, if disease was bulky initially or in case of slow tumor regression [11]. Chemotherapy used was MOPP/ABV (mechlorethamine, vincristine, procarbazine and prednisone/doxorubicin, bleomycin, vinblastine) in the period 1992–1998 and henceforth ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Since 2005 (Denmark) and 1999 (Sweden), high-risk patients with an international prognostic score of >2 were treated with either BEACOPP-14 (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) or BEACOPP-escalated [12].

### Outcome and follow-up

Outcomes considered were primary progressive disease, first relapse after end of treatment and death from all causes. Absence of all three outcomes defines event-free survival (EFS), absence of the latter defines overall survival (OS). The relapse information was retrieved from the clinical registers and medical records in both countries. Autologous and allogeneic stem-cell transplantations identified from the National Patient Register ([www.socialstyrelsen.se](http://www.socialstyrelsen.se)) were used as an additional means of identifying relapses for Swedish adult patients. Information on vital status was retrieved from the nationwide death registers by means of the national civil registration number. Patients were followed from diagnosis until outcome, emigration or end of follow-up, in Denmark March 2015, in Sweden December 2013. All analyses of OS and EFS were restricted to the first 10 years after diagnosis.

### Statistical modeling

Variation in distribution of clinical characteristics was shown for patients in different age groups (children 0–9 years, adolescents 10–17 years and young adults 18–24 years) and assessed with Pearson's  $\chi^2$ -test and Mantel-Haenszel trend test (ordinal variables). Treatment outcome analyses were stratified by treatment in pediatric (children: 0–14 years Denmark, 0–17 years Sweden) or adult departments (adults: 15–24 years Denmark, 18–24 years Sweden) and by country (Denmark and Sweden). The Kaplan-Meier method was used to estimate survival. Confidence intervals (CIs) for 5- and 10-year survival were calculated in SAS proc lifetest using the default complementary log-log transformation of

**Table 1.** Distribution of patient characteristics in the clinical cohort of classical Hodgkin lymphoma patients ( $n = 1072$ ).

	Children 0–9 years N (%)	Adolescents 10–17 years N (%)	Young adults 18–24 years N (%)	$p$ Value children vs. adolescents/ young adults grouped
All patients	55 (100)	364 (100)	653 (100)	
Sex				
Male	42 (76)	187 (52)	304 (47)	$p < .001$
Female	13 (24)	177 (48)	349 (53)	
Histology				
Nodular sclerosis	35 (64)	298 (82)	473 (72)	$p < .002$
Mixed cellularity	18 (33)	46 (13)	107 (16)	
Other or unspecified	2 (4)	20 (6)	73 (11)	
Stage				
I	10 (18)	22 (6)	81 (12)	$p = .07$
II	34 (61)	221 (61)	339 (52)	
III	8 (14)	67 (18)	147 (23)	
IV	3 (5)	51 (14)	83 (13)	
Missing	–	3 (1)	3 (0.5)	
Stage low/high				
Limited (IA–IIA)	37 (67)	173 (48)	290 (44)	$p < .001$
Advanced (IIB–IVB)	18 (33)	187 (51)	358 (55)	
Missing	–	4 (1)	5 (1)	
Bone marrow				
Yes	0	14 (4)	14 (2)	$p = .21$
No/not reported	55 (100)	343 (94)	632 (97)	
Missing	–	7 (2)	7 (1)	
B-symptoms				
Yes	14 (25)	135 (36)	290 (44)	$p < .02$
No/not reported	41 (73)	226 (61)	362 (55)	
Missing	1 (2)	12 (3)	2 (0)	
Extra nodal disease				
Yes	2 (4)	50 (14)	101 (15)	$p = .007$
No/not reported	53 (95)	314 (86)	552 (85)	
Missing	–	–	–	
Spleen involvement (DK)				
Yes	3 (15)	21 (12)	46 (16)	$p = 1$
No	17 (85)	145 (85)	232 (82)	
Missing	–	5 (3)	5 (2)	
ESR rate $>30$ (DK)				
Yes	4 (20)	64 (37)	104 (37)	$p = .16$
No	10 (50)	51 (30)	92 (33)	
Missing	6 (30)	56 (33)	87 (31)	
Bulky (DK)				
Yes	4 (20)	44 (26)	40 (14)	$p = .85$
No	14 (70)	97 (57)	165 (58)	
Missing	2 (10)	30 (17)	78 (28)	

N: number; ESR: erythrocyte sedimentation rate; DK: data on Danish patients only.

survival estimates. Hazard ratios (HR) with 95% CIs were used to compare pediatric and adult departments, Denmark and Sweden, sex, stage, calendar period and first-line treatment concepts. HRs were presented with adjustments for sex, stage (limited/advanced), country and calendar period (before and after year 2000) and calculated using Cox regression with time since diagnosis as the underlying time scale. CIs were based on Wald tests. SAS version 9.4 (SAS Inc., Cary, NC) was used for all analyses.

## Ethics

The study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2014/539) and by the Danish scientific ethics committee system (H2-2011-107).

## Results

The 1072 cHL patients with clinical information were followed for a mean of 13.1 (0.3–25.1) years in Denmark and 11.7 (0.1–22.0) years in Sweden. The male:female ratio varied by age from a male preponderance among children to a

more even sex distribution in the older ages (Table 1). Disease severity increased with age. Specifically, the likelihood of presenting with advanced stage (IIB–IV) increased with age (children 32%; adolescents 50%; adults 55%;  $p < .005$ ). Likewise, the frequencies of B-symptoms and extra nodal disease were lower in children than among adolescents and young adults (Table 1), as were the erythrocyte sedimentation rates. The distribution of clinical characteristics of patients treated in pediatric ( $n = 315$ ) and adult ( $n = 757$ ) departments, respectively, is shown in Table 2.

## Treatment outcome

*Pediatric versus adult treatment protocols:* Similar proportions of patients treated in pediatric (13% and 5%) and adult (14% and 6%) departments experienced relapse or died during follow-up (Table 2). Consistent with this, adjusted HRs showed no difference in EFS and OS between the groups (Table 3).

*Denmark versus Sweden:* Analyses stratified by country revealed a more complex pattern. Relapse was more common in Denmark (pediatric patients 22%, adults 16%) than in Sweden (pediatric patients 10%, adults 12%) and the Danish pediatric patients had lower EFS (10-year EFS 0.79; 95% CI

**Table 2.** Comparison of outcome for classical Hodgkin lymphoma (cHL) patients treated at either pediatric or adult departments.

	Pediatric (0–14 Denmark, 0–17 Sweden)			Adult (15–24 Denmark, 18–24 Sweden)		
	Total N (%)	Number of relapses (%)	Number of deaths (%)	Total N (%)	Number of relapses (%)	Number of deaths (%)
Clinical cohort cHL	315 (100)	41 (13)	17 (5)	757 (100)	99 (14)	45 (6)
Country						
Sweden	228 (70)	22 (10)	11 (5)	370 (49)	43 (12)	26 (7)
Denmark	87 (30)	19 (22)	6 (7)	387 (51)	64 (16)	19 (5)
Sex						
Male	168 (54)	28 (17)	11 (6)	365 (48)	57 (16)	21 (6)
Female	147 (46)	13 (9)	6 (4)	392 (52)	50 (13)	24 (6)
Period						
1990–1999	134 (42)	14 (10)	10 (8)	269 (36)	46 (17)	20 (7)
2000–2010	181 (58)	27 (15)	7 (4)	488 (64)	61 (12)	25 (5)
Stage						
Limited (IA–IIA)	153 (47)	17 (11)	6 (4)	347 (46)	34 (10)	12 (4)
Advanced (IIB–IVB)	159 (49)	23 (14)	10 (6)	405 (53)	73 (18)	32 (8)
Missing	13 (4)	1 (8)	1 (8)	6 (1)	0	1 (17)
Radiotherapy						
Sweden no RT	51 (22)	8 (16)	3 (6)	110 (30)	9 (8)	2 (2)
Sweden RT	162 (71)	13 (8)	7 (4)	209 (57)	27 (13)	13 (6)
Missing	15 (7)	1 (7)	1 (7)	51 (14)	7 (14)	4 (8)
Denmark no RT	56 (64)	12 (21)	5 (9)	128 (33)	31 (24)	13 (10)
Denmark RT	31 (36)	7 (23)	1 (3)	258 (67)	33 (13)	13 (5)
Missing	0	0	0	1 (0.3)	0 (0)	0 (0)
Treatment overall						
Radiotherapy (RT) only	3 (1)	0	0	31 (4)	7 (23)	3 (10)
2–4 courses	71 (22)	11 (16)	5 (7)	23 (3)	6 (26)	1 (4)
2–4 courses + RT	121 (38)	15 (12)	4 (3)	213 (28)	16 (8)	6 (3)
6+ courses	36 (11)	9 (25)	3 (4)	215 (28)	34 (16)	14 (6)
6+ courses and RT	68 (22)	5 (7)	4 (6)	223 (30)	37 (17)	17 (8)
Missing	16 (5)	1 (6)	1 (6)	52 (7)	7 (14)	4 (8)

**Table 3.** Hazard ratios of event free and overall survival by treatment and age for patient with classical Hodgkin lymphoma.

	Number of patients	Crude EFS Hazard ratio 95% CI	Crude OS Hazard ratio 95% CI	Adjusted EFS <sup>a</sup> Hazard ratio 95% CI	Adjusted OS <sup>a</sup> Hazard ratio 95% CI
Treatment					
Ped depart.	315 (29)	0.97 (0.68–1.38)	1.01 (0.55–1.85)	1.07 (0.74–1.54)	1.01 (0.53–1.90)
Adult depart.	757 (71)	ref	ref	ref	ref
Country					
Pediatric					
Sweden	228 (70)	ref	ref	ref	ref
Denmark	97 (30)	<b>1.96 (1.07–3.58)</b>	1.32 (0.45–3.86)	<b>1.90 (1.03–3.52)</b>	1.12 (0.35–3.58)
Adult					
Sweden	370 (49)	ref	ref	ref	ref
Denmark	388 (51)	<b>1.51 (1.03–2.21)</b>	1.19 (0.62–2.30)	<b>1.51 (1.03–2.22)</b>	1.24 (0.64–2.39)
Sex					
Male	533 (50)	ref	ref	ref	ref
Female	539 (50)	0.73 (0.51–1.0)	1.11 (0.64–1.93)	0.74 (0.54–1.02)	1.10 (0.63–1.92)
Calendar period					
1990–1999	403 (38)	0.97 (0.70–1.35)	0.92 (0.52–1.63)	0.94 (0.68–1.31)	0.96 (0.54–1.72)
2000–2010	669 (62)	ref	ref	ref	ref
Stage					
Limited	500 (46)	ref	ref	ref	ref
Advanced	564 (52)	<b>1.83 (1.31–2.56)</b>	<b>2.61 (1.39–4.90)</b>	<b>1.84 (1.32–2.57)</b>	<b>2.61 (1.39–4.91)</b>
Treatment					
RT yes	660 (61)	ref	ref	ref	ref
RT no	348 (32)	<b>1.64 (1.18–2.28)</b>	1.54 (0.86–2.77)	1.32 (0.93–1.86)	1.08 (0.58–2.0)

EFS: event-free survival; OS: overall survival; CI: confidence interval; depart: department.

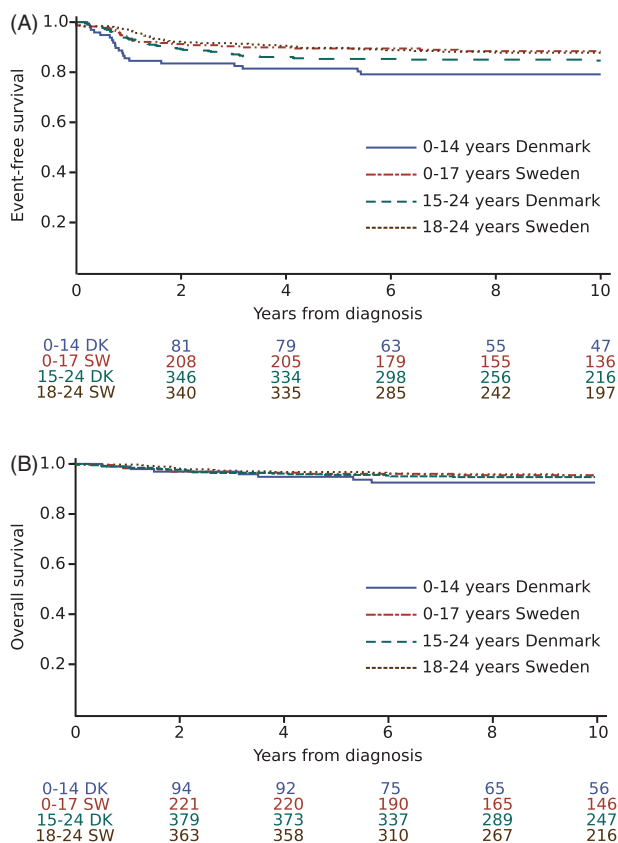
<sup>a</sup>Adjusted for sex, stage (limited/advanced), country and time period (before and after year 2000).

Bold indicates statistically significant results ( $p < 0.05$ ).

0.70–0.86) than Swedish pediatric patients (0.88; 95% CI 0.83–0.92), adjusted HR: 1.90 (95% CI 1.03–3.52) (Table 3, Figure 1(A)). A similar pattern was seen between adult patients in the two countries: Denmark 10-year EFS 0.85 (95% CI 0.81–0.88), Sweden 0.88 (95% CI 0.84–0.91), adjusted HR 1.51 (95% CI 1.03–2.22). The OS was similar across all age groups in the two countries (Figure 1(B)).

*Clinical characteristics and treatment intensity:* Patients with advanced stage disease experienced more events (adjusted

HR: 1.84; 95% CI 1.32–2.57) and more deaths (adjusted HR: 2.61; 95% CI 1.39–4.91, Table 3) than patients with limited stage disease. The most prominent difference in treatment was the lesser use of RT among Danish pediatric patients compared to Swedish pediatric patients (36% vs. 71%,  $p < .0001$ , Table 2). The proportion of irradiated patients was stable in Denmark throughout the study period, while it was declining in Sweden during the same period. Pediatric treatment protocols allowed for 2–4 courses of chemotherapy



**Figure 1.** (A) Event-free survival (EFS) in Denmark: 10 year EFS pediatric department 0.79 (95% CI 0.70–0.86), adult department 0.85 (95% CI 0.8–0.88) and Sweden: pediatric department 0.88 (95% CI 0.83–0.92), adult department 0.88 (95% CI 0.84–0.91). (B) Overall survival in Denmark: pediatric department 0.93 (95% CI 0.85–0.96), adult 0.95 (95% CI 0.92–0.98) and Sweden: pediatric department 0.95 (95% CI 0.92–0.98), adult department 0.95 (95% CI 0.93–0.97).

without radiotherapy, while for adults this was given only to a very limited number of patients ( $n = 20$ , 3%) and the majority were treated with combined modality treatment or full chemotherapy (Table 2). Chemotherapy regimens for adults were similar between the countries, although BEACOPP was introduced earlier in Sweden. For pediatric patients, ABVD was used in Denmark and MOPP-ABV in Sweden in the beginning of the study period. Chemotherapy regimens used are presented in detail in Supplementary Table S2.

**Male versus female:** Relapse was numerically more often seen in male than in female patients (16% vs. 12%), both when treated with pediatric (17% and 9%) and adult protocols (16% and 13%), Table 2. Irrespectively, the EFS did not differ significantly [adjusted HR 0.74 (95% CI 0.54–1.02), Table 3].

## Discussion

We compared clinical characteristics and treatment outcomes for 1072 children, adolescents and young adults with cHL treated according to pediatric or adult protocols in Denmark and Sweden in the period 1990–2010. Disease severity increased with age. Adolescents and young adults shared similar clinical characteristics, while children presented differently. OS did not differ between pediatric and adult departments and was comparable or superior to earlier published

results on this age group, which is satisfactory, especially considering that our study is population-based [6–8,13,14]. The most prominent finding was the lower degree of irradiation among Danish pediatric patients, which was reflected in lower EFS, both compared to Swedish pediatric patients and to Danish and Swedish adult patients.

The mechanisms underlying the correlation between disease burden and age are not fully understood, but might reflect age-dependent biological differences in HL pathogenesis possibly related to growth and puberty. Earlier disease detection in children than in adolescents and young adults has been described and could result from parental surveillance of children combined with patients' or doctors' delayed reaction to symptoms and signs in the adolescent and young adult age group [15,16]. The finding that adolescents and young adults shared similar clinical characteristics (Table 1) is in line with earlier studies [7,14] and provides a rationale for harmonizing treatments between these two groups.

Different selection to treatment between the countries enabled a unique possibility in this study to compare EFS and OS in groups treated with or without radiotherapy. Relapses were most frequently seen within the first 2 years, consistent with the definition of treatment failure. Radiotherapy is known to reduce the risk of relapse [17], but the striking difference in frequencies of relapses seen between children in Denmark and Sweden was unexpected. Importantly, however, this did not confer increased mortality for the Danish pediatric patients compared with the other strata of patients, implying that the relapsing patients could be saved by salvage treatment. The differences observed seemed more dependent on treatment traditions between countries, than between pediatric and adult departments within each country. The less intensive radiotherapy treatment in Denmark could potentially have resulted in fewer Danish patients being burdened by late treatment effects. However, the patients who experience a relapse are given more intensive treatment in the salvage situation, for example high-dose treatment with stem cell rescue with potentially more severe late effects as a result [18]. Moreover, a frequency of relapse of 22% in Danish pediatric patients is high from a psychological perspective suggesting the need for future efforts to decrease these numbers.

The later introduction of BEACOPP in Denmark might have contributed to the lower EFS seen for adult patients in Denmark. The BEACOPP regimen has proven to reduce relapses better than ABVD in high risk adult patients, but with equal OS between the groups [19], in line with our results.

Among the strengths of our investigation are its population-based approach, the number of patients followed, the level of clinical information available as well as the high quality of outcome assessments based on information from clinical registers or through scrutiny of hospital records. Still, the study also has limitations among which are the clinical data was not available for all patients in the cancer register. In addition, during the calendar period studied, treatment protocols were modified, although the main principles remained the same. Refined adjustment for calendar period (before and after year 2000) only had minor impact on the results. The differences in given treatment in Denmark and Sweden,

despite using the same protocols, probably reflect differences in protocol adherence and emphasize the value of enrolling patients in controlled trials to achieve stringent treatment decisions. In the GPOH-95 study, Sweden enrolled more patients than Denmark [20] and in the GPOH-HD-2002 [10] Denmark did not enroll patients at all. Since these protocols had recommendations on radiotherapy in the majority of arms this might have contributed to the higher extent of irradiated patients in Sweden. The proportion of irradiated patients was stable in Denmark and declining in Sweden throughout the study period. Thus, the difference in proportion of irradiated patients was most pronounced in the earlier period.

Since OS did not differ between the groups with the available follow-up time, this study calls for the need of investigating the occurrence of late effects, such as hospitalization [21], secondary AML [22], breast cancer and other secondary malignancies [23,24] heart and lung diseases [25], future fertility [26] and the risk of sick leave and disability pension [27] between children and adults receiving different treatment concepts.

In conclusion, adolescents and young adults shared similar clinical characteristics, supporting harmonization of treatment in these age groups. Both pediatric and adult treatment protocols are effective with high OS with no difference between the departments. Difference in selection of patients for particularly radiotherapy, but also for more intensive chemotherapy-regimens, in the two countries during the study period was reflected in higher EFS among Swedish than Danish patients.

## Disclosure statement

The authors report no conflicts of interest.

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