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Long-term survival in Hodgkin's disease patients: a comparison of relative survival in patients in trials and those recorded in population-based cancer registries

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Abstract

The prognosis of Hodgkin's disease (HD) has improved during the last 30 years. This study was planned to analyse long-term survival of HD patients and to compare survival rates estimated from clinical trials and population-based data. Individual data were analysed on 2755 adult HD patients entering randomised clinical trials of the British National Lymphoma Investigation (BNLI) between 1970 and 1987, and 5064 patients with HD incident 1978–1984 recorded in the UK population-based cancer registries participating in the EUROCARE study. Relative survival of Hodgkin's disease patients allowing for mortality expected from general population rates was analysed by a proportional hazards regression model including covariates. Although relative mortality decreased with longer follow-up, it was still significantly positive at 9–10 years after diagnosis in both the clinical trials and the population-based data sets. Relative mortality was worse for late stage than for early stage patients even at 10–15 years after first treatment (BNLI data). Whereas 10-year relative survival was identical in trials and population-based patients at ages under 45 years (>69%), it was much higher in BNLI older patients than in the population-based patients. In the older age group (65–74 years) the BNLI patients had 39% relative survival whilst for the population-based patients it was only 27%. Generalisation of clinical trials results to the general population must be done with caution, especially for older patients.

Keywords: Hodgkin's disease; Survival; Prognostic factors

1. Introduction

The prognosis of Hodgkin's disease (HD) has greatly improved during the last 30 years, and as a consequence it has become important to determine the extent of long-term survival, and whether after several years survival, mortality approximates that of the general population. Crude survival analysis [1,2], as frequently used in the analysis of trials, gives only partial information because, especially as the patients grow older, some deaths would be expected if the patients simply suffered general population mortality rates (i.e. if they ceased to suffer adverse mortality as a consequence of their past Hodgkin's disease). Adjustment for competing causes of death is then necessary if one wants to analyse the late effects of treatment on survival.

Survival is most often estimated from clinical series, but such series are selected to meet entry criteria for the trials and also may be unrepresentative of general population survival because they may receive better care within the trials. At a public health level, it would be interesting to know how survival rates obtained from clinical trial series compare with survival rates from population-based data, and hence the extent to which trial results may imply prognosis for patients generally. Although studies comparing the prognosis of patients included in clinical trials with those not included have been published for several sites [3], there appear to have been no studies for Hodgkin's disease.

To address these questions, we analysed survival in patients participating in the randomised clinical trials of

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the British National Lymphoma Investigation (BNLI) [4,5] between 1970 and 1987, and compared their long-term relative survival [6,7] with that in population-based UK data [8].

2. Patients and methods

2.1. BNLI data

The BNLI is a large British clinical collaborative group which since 1970 has conducted clinical trials of treatment of lymphoma. Approximately two-thirds of patients at the collaborating centres are entered into the trials, a greater proportion at younger than at older adult ages. The present analyses were conducted on the records of 2755 HD patients aged 15–79 years, all of the subjects included in BNLI trials between 1970 and 1987. Demographic, clinical, and biological variables were available. The demographic variables were sex, age at diagnosis, and year of diagnosis. The clinical variables were clinical stage (CS) and pathological type. The pathological review was done using a modification of the criteria proposed by Lukes and Butler [9], including mixed cellularity (MC), lymphocyte depleted (LD), and lymphocyte predominant (LP) groups, and subdividing the nodular sclerosis form (NS) into two groups (NSI and NSII) [10,11]. The biological variables were the erythrocyte sedimentation rate (ESR), haemoglobin level, and albumin level at diagnosis. Values were missing for ESR in 409 cases (15%), for albumin in 498 cases (18%), and for haemoglobin in 214 cases (8%). Missing values were taken into account using three extra binary covariates, keeping all the patients in the analysis.

2.2. Population-based cancer registry data

Data were obtained from the UK contributors to a European collaborative study of survival in data from population-based cancer registries (EUROCARE) [8]. Records from 5064 cases aged 15–79 years, and registered between 1978 and 1984 in Yorkshire, Wessex, Wales, Trent, Southwest, Oxford, Northwest, Northern, Mersey and East Anglia cancer registries were analysed. The cases were those patients whose tumour morphology was coded to HD according to the International Classification of Diseases for Oncology [12].

2.3. Population mortality data

To provide estimates of the mortality to be expected in general population subjects of the age and sex of the HD patients, we used age-specific mortality tables for males and females in the general population of England and Wales 1980–1982 [13].

2.4. Survival analysis

Survival analysis was performed by fitting relative survival models which correct the survival probability for competing causes of death [7,14]. The approach is equivalent to a proportional hazards model for net survival. Since the mortality hazard in the general population is subtracted from the hazard in the study population, the results may be interpreted in terms of the relative rate of death of different groups of HD patients (actually relative hazard) after allowing for the mortality to be expected from general population rates. The maximum follow-up time was 20 years (237 months) for BNLI cases and 12 years (144 months) for the population-based cases. All the explanatory variables were categorised. Biological variables were dichotomised using a priori chosen thresholds. Polytomous variables were recoded using dummy covariates. Significance of parameters was tested using the likelihood ratio test, or a Wald test in the case of variables with missing values. Statistical tests (two-tailed) with a P value smaller than 5% were considered as significant. Relative survival models were fitted including all the covariates. The relative survival analyses were performed over 15 years for BNLI data and 10 years for population-based cancer registry data. A partition of 22 intervals for BNLI (21 for the population-based data) of the follow-up was used comprising 12 3-month intervals up to 3 years, four 6-month intervals up to 5 years, five 1-year intervals between 5 and 10 years, and one interval (none for the population-based data) for 10–15 years.

The survival experience of the BNLI cohort was compared with that of the patients from the general UK population (EUROCARE UK registries) by restricting the former to the period 1978–1984. Survival models were fitted to eight subsets of data defined by four age classes (age limits: 15, 25, 45, 65, 74 years) within the two cohorts. Each model enabled the prediction of survival for any 5-year age group within the sub-cohort. These were used to provide age-standardised survival for each sub-cohort. The age standard was the age structure of EUROCARE and allowed the comparison of BNLI patients with EUROCARE patients of the same age class if the former had the same age structure within the age class.

3. Results

3.1. Distribution of cases by age

Fig. 1 shows the distribution by age of the BNLI cases (median = 32 years; 15–79) and population-based cases (median = 41 years; 15–79). The median values of age in the four age groups (15–24; 25–44; 45–64; 65–79) were

respectively 20, 32, 54 and 69 years for BNLI patients and 20, 33, 56 and 71 years for population-based cases.

3.2. Long-term survival and net annual mortality

To follow current practice in the analysis of Hodgkin's disease data [15], results were presented distinguishing BNLI early stages (CS I and CS II) and advanced stages (CS III and CS IV). In early stage HD, the 10-year relative survival rate was 78.6% standard error of the mean (SEM) 1.5% and the 15-year relative survival rate was 74.2% (SEM 2.1%). The net annual mortality rate (i.e. corrected for general population expectations) was still significantly positive up to 15 years after diagnosis, although it was close to zero. It was estimated to be 2.2% per year (SEM 0.8%) between 9 and 10 years and 1.2% per year (SEM 0.4%) between 10 and 15 years. In advanced stage HD, the 10-year relative survival rate was 56.1% (SEM 1.7%) and the 15-year relative survival rate was 48.4% (SEM 2.3%). The net annual mortality rate was estimated to be 3.3% per year (SEM 1.1%) between 9 and 10 years and 2.9% per year (SEM 0.7%) between 10 and 15 years.

In general population patients, the 10-year relative survival rate (all stages) was 58.0% (SEM 0.9%). The net annual mortality rate between 9 and 10 years was 3.1% per year (SEM 0.6%).

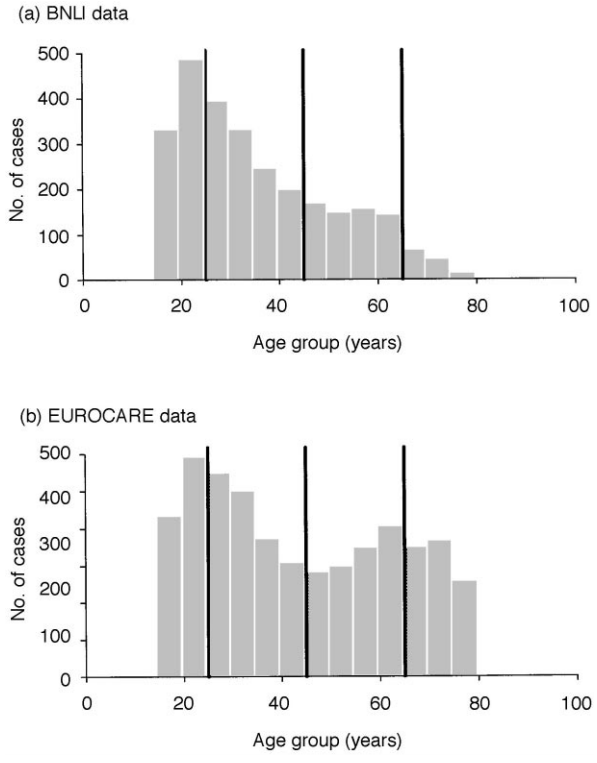

Fig. 1. Distribution of patients by age group. (The vertical lines correspond to the thresholds used to define the age groups for analysis). (a) British National Lymphoma Investigation (BNLI) data; (b) Population-based (EUROCARE) data.

3.3. Multivariate survival analysis for BNLI data

In the multivariate analysis of factors affecting survival, age had a strong impact on relative survival, with prognosis over three times worse for patients over age 65 years than those aged 15–24 years, even allowing for the greater mortality expected at older ages on the basis of general population death rates (Table 1). Male gender, advanced stage, and pathological types LD and NSII were associated with poor prognosis as were high ESR (in early stages) and low albumin level. The prognosis of early stage HD improved during the observation period (P for trend = 0.040) but that for late stage did not significantly.

3.4. Multivariate survival analysis for population-based cancer registry data

Only age and sex covariates were available for a multivariate analysis, and both were associated with the outcome (Table 2). Relative survival rates by age group showed the adverse prognostic value of greater age, especially in patients older than 45 years.

3.5. Comparison of survival of BNLI and population-based patients

The worse prognostic value of advanced age for population-based data could only partly be explained by a difference between the distributions of age within the age groups (Fig. 1). When 10-year survival by age groups (adjusted within age groups) were compared, survival rates of BNLI patients and population-based cases were similar at ages under 45 years, but at older ages survival rates were lower in the population-based patients than in the BNLI patients (Table 3 and Fig. 2).

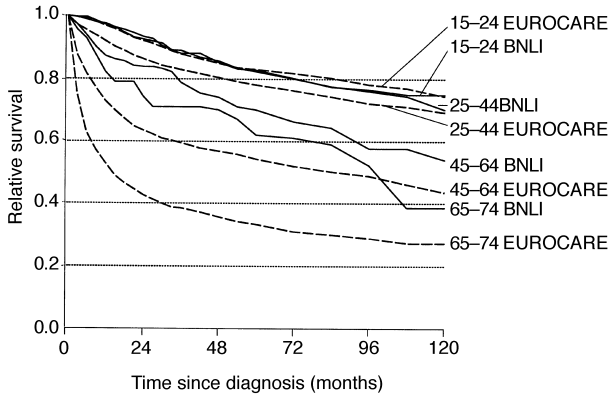

Fig. 2. 10-year relative survival by age group (adjusted within age groups). British National Lymphoma Investigation (BNLI) and population-based (EUROCARE) cases (1978–1984 period and 15–74 years age class).

Table 1
Prognostic factors in early stage (CS I and CS II) and advanced stage (CS III and CS IV) Hodgkin's disease patients: British National Lymphoma Investigation data ($n=2755$)

		CS I–II ($n=1450$)			CS III–IV ($n=1305$)		
Factor	Level	*n*	RR (95% CI)	*P*	*n*	RR (95% CI)	*P*
Age (years)	15–24	444	1.00	<0.001[b]	377	1.00	<0.001[b]
	25–44	639	1.22 (0.87–1.73)		538	1.11 (0.88–1.41)	
	45–64	303	1.93 (1.29–2.89)		322	1.98 (1.53–2.56)	
	65–79	64	3.57 (1.78–7.12)		68	3.22 (2.15–4.84)	
Sex	Males	877	1.00	0.050[a]	850	1.00	0.049[a]
	Females	573	0.74 (0.54–1.01)		455	0.82 (0.67–1.00)	
Stage (CS)	I	636	1.00	0.033[a]			<0.001[a]
	II	814	1.42 (1.02–1.98)				
	III				786	1.00	
	IV				519	1.46 (1.21–1.78)	
Histology	NS I	678	1.00	<0.001[a]	617	1.00	<0.001[a]
	NS II	361	2.45 (1.73–3.48)		366	1.66 (1.33–2.06)	
	MC	273	1.99 (1.33–3.00)		258	1.16 (0.89–1.51)	
	LD	4	6.80 (1.49–31.02)		35	1.93 (1.18–3.15)	
	LP	134	0.54 (0.20–1.41)		29	1.35 (0.71–2.57)	
ESR (mm)	⩽40	832	1.00		494	1.00	
	>40	408	1.78 (1.26–2.52)	0.001[a]	612	1.20 (0.94–1.52)	0.144[a]
	m.v.	210	1.39 (0.93–2.07)		199	1.13 (0.83–1.53)	
Haemoglobin (g/dl)	⩾12	1174	1.00		698	1.00	
	<12	210	1.10 (0.74–1.62)	0.643[a]	459	1.04 (0.81–1.33)	0.755[a]
	m.v.	66	0.79 (0.39–1.59)		148	1.03 (0.68–1.55)	
Albumin (g/l)	>35	1085	1.00		746	1.00	
	⩽35	117	1.74 (1.13–2.67)	0.012[a]	309	1.47 (1.14–1.89)	0.003[a]
	m.v.	248	1.45 (1.00–2.09)		250	1.16 (0.84–1.61)	
Calendar period	1970–75	380	1.00	0.040[b]	387	1.00	0.263[b]
	1976–81	501	0.87 (0.63–1.19)		485	0.83 (0.67–1.03)	
	1982–87	569	0.62 (0.39–0.97)		433	0.89 (0.68–1.16)	

$P<0.05$ was taken to be significant. m.v., missing value; CS, clinical stage; RR, relative rate; CI, confidence interval; NS, nodular sclerosis form; MC, mixed cellularity; LD, lymphocyte depleted; LP, lymphocyte predominant.
[a] *P* value for heterogeneity. Wald test (erythrocyte–sedimentation rate (ESR), haemoglobin and albumin) or likelihood ratio test (other variables).
[b] *P* for trend.

Table 2
Relative survival analysis of population-based ($n=5064$) cases incident 1978–1984: relative rate of death by age group and sex

			Relative survival	
Factor	Level	*n*	RR (95% CI RR)	P^a
Age (years)	15–24	1027	1.00	<0.001
	25–44	1732	1.30 (1.10–1.52)	
	45–64	1333	3.14 (2.69–3.67)	
	65–79	972	6.98 (5.97–8.16)	
Sex	males	3022	1.00	0.018
	females	2042	0.89 (0.81–0.98)	

RR, relative rate.
[a] *P* for trend (age) or likelihood ratio test for heterogeneity (sex).

4. Discussion

An excess of mortality compared with that in the general population was still observed up to 15 years after diagnosis for advanced stage HD, and a smaller excess was also observed for early stage HD. HD incidence is higher in populations with elevated social status, who have a higher life expectancy than the general population. The use of general population mortality tables for comparison will, therefore, have tended to lead to overestimation of the relative survival rates of the patients. A relative survival analysis using mortality tables by social class would emphasise this, but could not be performed because the social status of the cases was unknown. A substantial proportion of late deaths in HD are due to second cancer and cardiac failure [16].

Age at diagnosis is an important prognostic factor for survival in HD patients [17–20]. In part this is because mortality unconnected with HD is greater at older ages, but the relative survival model shows that after removing this effect there is still a substantial remaining effect of age on the cumulative net hazard. The relative excess of mortality due to HD after 65 years of age was approximately three times (BNLI data) or six times (population-based data) that observed before 25 years

Table 3
5 and 10-year relative survival by age group, British National Lymphoma Investigation (BNLI), ($n=1106$) and population-based ($n=4807$) cases incident 1978–1984[a]

Age group at incidence (years)	BNLI			Population-based		
	No. of cases	Relative survival[b] 5-year	10-year	No. of cases	Relative survival[b] 5-year	10-year
15–24	318	0.83	0.75	1027	0.83	0.75
25–44	487	0.82	0.70	1732	0.78	0.69
45–64	250	0.70	0.54	1333	0.54	0.44
65-74	51	0.62	0.39	715	0.33	0.27

[a] After exclusion of 3 (BNLI data) and 257 (population-based data) cases older than 74 years.
[b] Age-adjusted within age groups according to the age structure of the population cases.

of age. Most of the BNLI cases were also recorded in population-based cancer registry data [21], and the BNLI centres include many district hospitals as well as certain referral centres. The population-based registries used as a comparison with the BNLI data include most of those in England and Wales, and cover over half its population (although not the London area), so should be reasonably representative of the BNLI catchment.

The worse prognosis for population-based cases at older ages may reflect selection of better-prognosis cases for inclusion in clinical trials and/or improved survival as a consequence of treatment within these trials. Stiller and Draper [22] analysed a population-based series of 4070 children with acute lymphoblastic leukaemia treated in Britain during 1971–1982 and found higher crude survival rates for children included in clinical trials. For children not in trials, they reported higher survival rates for centres treating at least 6 children a year. Davis and colleagues [23] compared the crude survival of 2278 HD patients recorded by comprehensive cancer centres and 3607 HD patients recorded by the population-based SEER programme in the USA. They found that the mortality rate among SEER patients (adjusted on sex, race, age, stage and histological type) was 1.5 higher than the mortality rate among comprehensive cancer centre patients. In our study, focused on the difference between population-based and clinical trials patient survival, the difference concerned essentially patients older than 45 years. This observation must be taken into account when generalisation of clinical trials results is considered.

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