

Long-term survival after treatment for Hodgkin's disease (1973–2002): improved survival with successive 10-year cohorts

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BACKGROUND: The Nottinghamshire Lymphoma Registry contains the details of all the patients diagnosed with lymphoma (since 1 January 1973) within a defined geographical area with a population of 1.1 million. It was therefore possible to study the outcome of treatment for Hodgkin's disease for three 10-year cohorts (1973–1982, 1983–1992 and 1993–2002). The aims of the study were to compare survival time among the three patient cohorts, to identify prognostic factors and to estimate relative survival.

METHODS: A total of 745 patients diagnosed between 1973 and 2002 were analysed for survival. Survivorship was estimated by the Kaplan-Meier method and parametric survival models. An accelerated failure-time regression was used for multivariate analysis.

RESULTS: Overall, patients were observed for 9.8 (0.3–34.82) years (median(range)), on average. One, five and fifteen-year disease-specific survival was found to be 87% (85–90%), 77% (74–80%) and 70% (67–74%), respectively. For those for diagnosed between 1973 and 1982, the 15-year survival was found to be 57%; for 1983–1992, it was 74% and for 1993–2002, it was 83% ($P < 0.001$). The difference remained significant after adjusting for prognostic factors. The actuarial risk of developing a second malignancy at 20 years was for the 1973–1982 cohort, 12.4%, and for the 1983–1992 cohort, 18.8%.

CONCLUSION: Treatment advances and effective management of toxicities of treatment over time, have resulted in a significantly longer survival for patients with Hodgkin's disease diagnosed within a defined population.

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The majority of patients with Hodgkin's disease (HD) have been cured of their disease in the UK since the introduction of combination chemotherapy for advanced disease in the early 1970s (Roy *et al*, 2000). Before this, in many centres in the UK, single-agent chemotherapy was used as a palliative treatment. The only potentially curative treatment was radiotherapy. In Nottinghamshire, with the introduction of the Medical School in the University of Nottingham, combined chemotherapy was routinely used for Hodgkin's disease from 1972 onwards. For the start of this study, 1 January 1973 was chosen, because 1973 was the first full year using combination chemotherapy as standard therapy for patients with advanced HD. Nottinghamshire has a relatively stable population so that it has been possible to follow patients long term (over 30 years).

Survival data from large referral centres and from trial organisations tends to overestimate the survival, particularly in an older age group (Roy *et al*, 2000). The aim of this observational cohort study was to investigate the long-term survival of patients with Hodgkin's disease.

In particular, we were interested in whether statistical differences between three separate cohorts (1973–1982, 1983–1992, 1993–2002) could be identified, and whether such differences would remain significant after adjusting for known prognostic factors.

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MATERIALS AND METHODS

The Lymphoma Registry in Nottinghamshire

Most of the population of Nottinghamshire and adjacent parts of Derbyshire, Lincolnshire and Leicestershire are served by three hospitals: University Hospital (UHN) and City Hospital (NCH) Nottingham (now both part of Nottingham University Hospitals NHS Trust) and Kings Mill Hospital (KMH) (part of Sherwood Forest NHS Trust), Sutton-in-Ashfield. The served population is 1.1 million and has been stable during 1973–2002.

The registry was set up by Dr EM Bessell and AJ Moloney (now Head of Radiotherapy Physics, Clinical Director, Department of Clinical Oncology, Stoke-on-Trent, Staffordshire) in 1986, and data was entered prospectively from this date. Data from 1973–1986 was added retrospectively from radiotherapy notes held in the department and hospital notes from the three hospitals involved. The majority of patients were alive when the retrospective data were added. From 1986–1999, the data was entered from lymphoma clinics in each of the three hospitals; laptop computers were used in each clinic and the main computer updated every 6 months.

A printout from each histopathology department was obtained annually to ensure completeness of the registry. A dedicated data administrator has been employed since the registry was established. Since 1999, the data has been entered from the lymphoma multidisciplinary team meetings at the City Hospital (NCH).

All patients diagnosed at the three hospitals are discussed at this meeting. The cause of death was determined by examination of the hospital notes (rather than the death certificate). The data administrator discussed all uncertain cases with the lead clinician (EM Bessell). The date, but not the type of any second malignancy, was recorded. Non-melanomatous skin cancers were not recorded.

Histopathology

The histopathology in Nottingham has been reported by histopathologists with a special interest in lymphoma throughout the study period (C Elston, IO Ellis, KA MacLennan and others), and has been reviewed at multidisciplinary team meetings since the 1980s. All cases are now seen by three haematopathologists (S O'Connor, D Clark and V Sovani). Patients have been entered into trials of the British National Lymphoma Investigation (BNLI) and other national trial organisations in the UK, where histological review was routine. Four major Nottingham reviews have been carried out on patients with Hodgkin's disease. The slides were reviewed on 212 patients with Stage IA or IIA disease. In 188 patients, Hodgkin's disease was confirmed (89%) and 24 were found not to be Hodgkin's disease (22, non-Hodgkin's lymphoma (NHL); 1, reactive; 1, carcinoma). The details of two patients were therefore removed from the registry and 22 patients were reclassified as NHL (Bessell *et al*, 1991; Bessell *et al*, 1998). All patients, aged 70 years and over, diagnosed with Hodgkin's disease were reviewed. The histological sections of 39 patients were therefore reviewed. There were then 28 patients with Hodgkin's disease, 10 with NHL (mostly peripheral T cell) and one was a carcinoma (Forsyth *et al*, 1997).

The third review was of 11 patients with advanced Hodgkin's disease who were treated with chemotherapy and relapsed locally. These patients then received involved field radiotherapy. All 11 patients on review had Hodgkin's disease (MacMillan and Bessell, 1994). The fourth review was done for this paper. The histological sections of ten patients with lymphocyte-depleted Hodgkin's disease were reviewed (by S O'Connor). All 10 were reviewed as Hodgkin's disease (six nodular sclerosing grade I, three nodular sclerosing grade II, 1 classical Hodgkin's disease, not otherwise specified).

Management of patients with Hodgkin's disease in the 3 separate 10-year periods

1973–1982 Advanced Hodgkin's disease was treated with either MOPP (DeVita *et al*, 1970), MVPP (Nicholson *et al*, 1970) or LOPP (Hancock *et al*, 1992). Stages IA, IIA, IIIA were treated initially with radiotherapy alone in most cases. Staging laparotomy was carried out in 51 (29%) of the 176 patients without B symptoms. The chemotherapy was supervised mostly by general physicians with an interest in haematology; some chemotherapy and all the radiotherapy was given in the Department of Radiotherapy and Oncology in Nottingham. The radiotherapy given was mostly a mantle field, inverted Y or total nodal irradiation except for patients entered into the randomised BNLI trial of involved field vs extended field radiotherapy (Hoskin *et al*, 2005).

1983–1992 Advanced Hodgkin's disease was treated with LOPP, LOPP/EVAP (Hancock *et al*, 1992), ChIVPP/PABLOE (Hancock *et al*, 2001) or ABVD (Canellos *et al*, 1992). Radiotherapy alone was given to patients with IA or non-bulky IIA (<10 cm) disease. Bulky IIA, IIB and IIIA/B with most of the disease above the diaphragm was treated with chemotherapy and radiotherapy. High-dose chemotherapy (BEAM and autologous bone marrow transplantation) was started in 1986. Seven patients had a staging laparotomy between 1983 and 1985. The radiotherapy given was mostly involved field. When a mantle field was used, the inferior border was 5 cm below the lower limit of disease (usually T7/T8 or T8/T9 to reduce cardiac irradiation).

1993–2002 Advanced Hodgkin's disease was treated mostly with CHIVPP/PABLOE or ABVD (Johnson *et al*, 2005). Radiotherapy was replaced by ABVD (3–4 cycles) and involved field radiotherapy, alone in this period, except for patients with IA or IIA lymphocyte predominant disease (Fermé *et al*, 2007).

The radiotherapy technique did not change significantly from the previous decade. The dose of radiotherapy throughout the 30-year period has been 35–40 Gy in 20 fractions over 4 weeks.

Statistical analysis

Long-term survival studies may be analysed using either the traditional approach (cohort survival) (Cox, 1972), or a relatively recent alternative method (period survival, not presented here) that corrects for recent survival experiences by using the expected survival of a reference population, based on common characteristics (age, gender, area etc) (Brenner *et al*, 2004). As the primary endpoint of the analysis, survival time was considered as disease-specific (DSS), cancer-specific (CSS) and overall (OS) survival since the date of diagnosis. Alive patients were censored at the date of the last follow-up.

Univariate approaches, including Kaplan–Meier survival curves and life-tables, were implemented for estimating unadjusted survival probabilities. Survival tests (Cox–Mantel and Peto–Peto) were used for assessing differences among the patient cohorts having explored test hypotheses (e.g., proportionality).

Finally, a multivariate regression model was selected, among various candidates and an adjusted analysis was conducted. It should be noticed that a robust model evaluation was developed to assess model fit of the four most favourable survival models: Semiparametric (Cox) (Cox, 1972), flexible-parametric (Royston and Parmar, 2002), parametric Accelerated-time failure (gamma) (Kleinbaum and Klein, 2005) and parametric piece-wise (exponential) (Blossfeld and Rohwer, 1995). Model fit can be seen in Figure 1.

Despite the popularity of the Cox regression in cancer research, a thorough evaluation suggested that it was not the best model. Both the Akaike information criterion (AIC) and the model-fit graph indicated the AFT model as the most recommended (Collett, 2000). As the major assumption of this model (proportional hazards) was rejected for two covariates (age and stage),

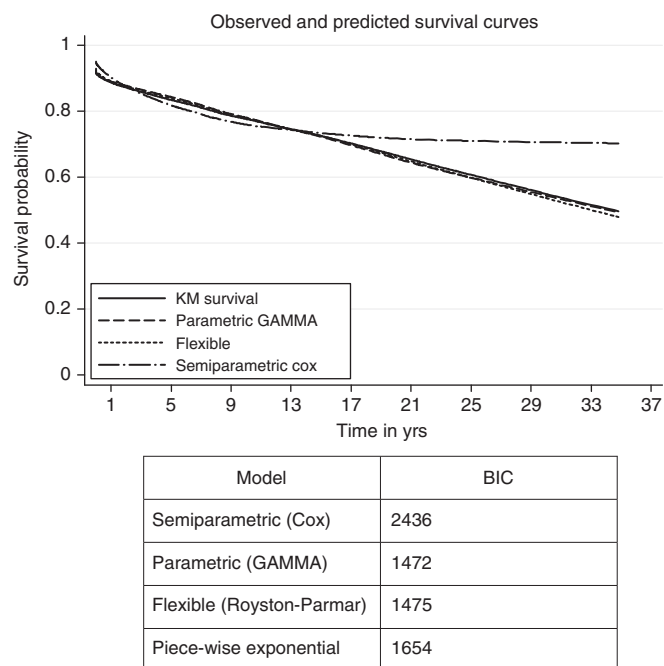


Figure 1 Comparison of fit using cohort-adjusted survival curves.

a parametric alternative model was explored. Because of non-proportional-hazard erroneous assumption, AFT models avoid bias; however, they require a suitable distribution approximation of the survival time (parametric). In this study, a generalised gamma distribution was used in the multivariate analysis. The independent variables were patient (age, sex), disease (stage, histology, B-symptom) and treatment (therapy type) characteristics and a cohort-indicator variable (1973/82, 1983/92, 1993/02). Time ratios were estimated for facilitating interpretation. Such ratios are exponential coefficients (as the hazard ratios) known as acceleration factors. However, they declare an increase/decrease in delay of experiencing an event (death), rather than an increase/decrease in risk of such event, depending on whether the ratio is greater/lower than 1. Thus, a time ratio greater than one indicates that the exposure to that factor is beneficial as it delays death (Kleinbaum and Klein, 2005).

A significant level of 5% was adopted for all analyses. The analysis was performed in Stata v.10. (Cleves, 2008).

Table 1 Patient characteristics

	1973–82	1983–92	1993–2002	Total
	Freq. (%)	Freq. (%)	Freq. (%)	Freq. (%)
Age group				
< 26	66 (26.1)	72 (26.6)	61 (25.1)	199 (25.9)
26 to 45	81 (32)	105 (38.7)	94 (38.7)	280 (36.5)
46 to 65	70 (27.7)	60 (22.1)	65 (26.7)	195 (25.4)
66 +	36 (14.2)	34 (12.5)	23 (9.5)	93 (12.1)
Pearson $\chi^2(6) = 6.3939, P = 0.381$				
Gender				
Female	80 (31.6)	105 (38.6)	100 (41.2)	285 (37.1)
Male	173 (68.4)	167 (61.4)	143 (58.8)	483 (62.9)
Pearson $\chi^2(2) = 5.2278, P = 0.073$				
Treat				
Chemo	126 (49.8)	133 (48.9)	129 (53.8)	388 (50.7)
Combi	29 (11.5)	65 (23.9)	56 (23.3)	150 (19.6)
Radio	98 (38.7)	74 (27.2)	55 (22.9)	227 (29.7)
Pearson $\chi^2(4) = 24.7184, P < 0.001$				
Stage				
I	62 (24.5)	53 (19.5)	63 (25.9)	178 (23.2)
II	44 (17.4)	97 (35.7)	110 (45.3)	251 (32.7)
III	78 (30.8)	65 (23.9)	36 (14.8)	179 (23.3)
IV	30 (11.9)	40 (14.7)	29 (11.9)	99 (12.9)
Unsp.	39 (15.4)	17 (6.3)	5 (2.1)	61 (7.9)
Pearson $\chi^2(8) = 77.3425, P < 0.001$				
B symptoms				
No	188 (74.3)	193 (71.2)	146 (61.3)	527 (69.2)
Yes	65 (25.7)	78 (28.8)	92 (38.7)	235 (30.8)
Pearson $\chi^2(2) = 10.4978, P = 0.005$				
Who				
Lymphocyte Pred.	24 (9.5)	22 (8.1)	24 (9.9)	70 (9.1)
Mixed Cell.	61 (24.1)	54 (19.9)	39 (16)	154 (20.1)
Nodular Scl.	127 (50.2)	184 (67.6)	177 (72.8)	488 (63.5)
Unsp.	41 (16.2)	12 (4.4)	3 (1.2)	56 (7.3)
Pearson $\chi^2(6) = 58.5400, P < 0.001$				
Status				
Alive	71 (28.1)	132 (48.5)	168 (69.1)	371 (48.3)
Died of disease	105 (41.5)	70 (25.7)	35 (14.4)	210 (27.3)
Died of other cancer	30 (11.9)	12 (4.4)	8 (3.3)	50 (6.5)
Died of other causes	30 (11.9)	40 (14.7)	9 (3.7)	79 (10.3)
4. Lost to follow-up	17 (6.7)	18 (6.6)	23 (9.5)	58 (7.6)
Pearson $\chi^2(8) = 111.5255, P = 0.000$				
Sample size	253	272	243	768

RESULTS

Although 768 patients were found to be diagnosed and treated between January 1973 and December 2002, after a careful data-cleaning, only 745 patients were taken into the analysis stage (the main exclusion was deaths occurring within one week of diagnosis).

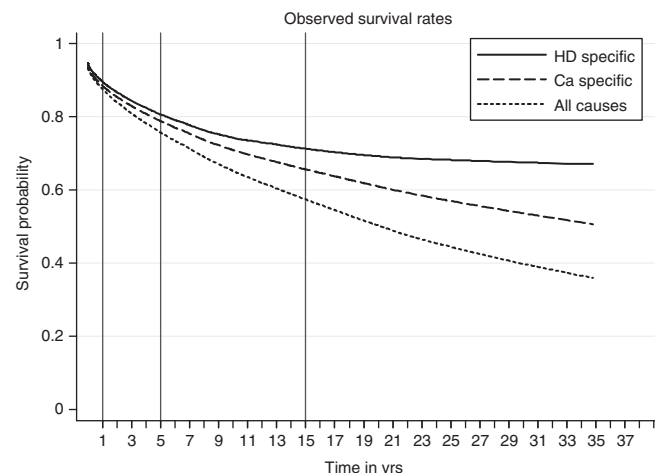
Table 1 presents patient characteristics stratified by the three patient-cohorts. Early cohorts, mid-cohort and late-cohort included 253 (33%), 272 (35%) and 243 (32%) patients correspondingly. The median (range) time of observation was 9.8 years (max 34.82).

Table 2 presents one, five and fifteen-year survival rates (and 95% confidence intervals) for three types of survivorship: DSS, CSS and OS. In addition to this, corresponding Kaplan–Meier survival curves are illustrated at Figures 1 and 2.

Next, cohort differences were investigated. Survival differences across the three cohorts found to be highly significant as both Wilcoxon and Cox–Mantel (log-rank) test indicated. It should be noted that the hypothesis of proportional hazards was marginally rejected, in the case of late-cohort. As a result, univariate analysis encouraged a multivariable analysis based on disease and patient factors.

Table 2 Patient survival

Survival	Year 1	Year 5	Year 15
DSS			
Cohort 1973–82	0.7808	0.647	0.5742
Cohort 1983–92	0.8849	0.7926	0.7363
Cohort 1993–2002	0.9536	0.8822	0.8258
Log-rank ($\chi^2 = 37.82, P < 0.001$), Peto–Peto ($\chi^2 = 40.6, P < 0.001$), Wald test ($\chi^2 = 34.60, P < 0.001$)			
CaSS			
Cohort 1973–82	0.7549	0.6217	0.5226
Cohort 1983–92	0.8816	0.7822	0.7096
Cohort 1993–02	0.9495	0.8696	0.7524
Log-rank ($\chi^2 = 40.38, P < 0.001$), Peto–Peto ($\chi^2 = 45.29, P < 0.001$), Wald test ($\chi^2 = 35.67, P < 0.001$)			
Any cause			
Cohort 1973–82	0.751	0.5968	0.4503
Cohort 1983–92	0.8709	0.7417	0.6112
Cohort 1993–02	0.9334	0.845	0.7115
Log-rank ($\chi^2 = 32.22, P < 0.001$), Peto–Peto ($\chi^2 = 40.6, P < 0.001$), Wald test ($\chi^2 = 31.2, P < 0.001$)			

**Figure 2** Survival probabilities for all patients.

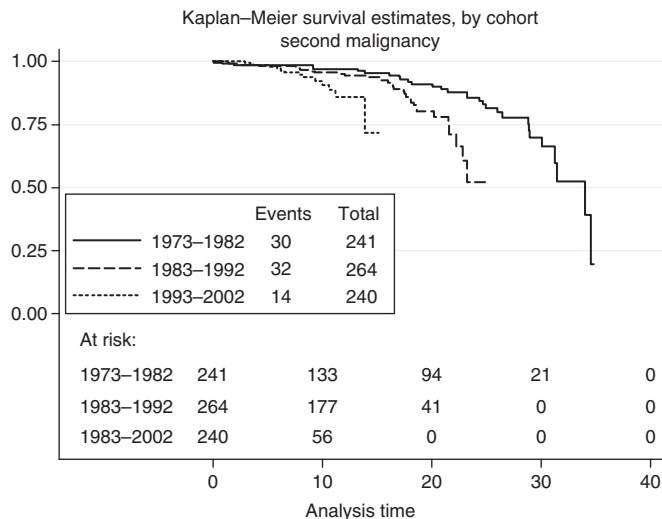


Figure 3 Time (between diagnosis) and second malignancy stratified by cohort.

Table 3 Frequency of second malignancy

	1973–82		1983–92		1993–2002	
	Freq (N)	(%)	Freq (N)	(%)	Freq (N)	(%)
Second malignancy						
No	211	87.6	232	87.9	226	94.2
Yes	30	12.4	32	12.1	14	5.8

Pearson $\chi^2(2) = 7.3889$, $P = 0.025$

Table 4 Time to second malignancy

Survival	Year 1	Year 5	Year 15
Cohort 1973–82	0.7999	0.6627	0.5882
Cohort 1983–92	0.9049	0.8105	0.7530
Cohort 1993–2002	0.9536	0.8822	0.8258

Log-rank (χ^2) = 37.82, $P < 0.001$, Peto-Peto (χ^2) = 40.6, $P < 0.001$, Wald test (χ^2) = 34.60, $P < 0.001$

In addition to survivorship, time to second malignancy was also considered (Figure 3). Among the 745 patients, second malignancy was observed in only 76 (10.2%). Cohort estimates are presented in Tables 3 and 4. Univariate differences were found to be significant ($\chi^2 = 7.389$, $P = 0.025$). Also, time differences to second malignancy found to be significant (Wilcoxon $\chi^2 = 6.581$, $P = 0.0372$). We should note that the observation time for second malignancy was extended until June 2010. If a comparison is made with the data in Table 1, it can be seen that all the 30 malignancies diagnosed in the cohort of patients (1973–1982) resulted in death, whereas, in the cohort (1983–1992), only 12 of 32 malignancies resulted in death, and, in the cohort (1993–2002), only 8 of 14 malignancies resulted in death.

Finally, regression models were used to provide adjusted estimates for the three cohorts after controlling for age (at diagnosis), gender, tumour staging, treatment type, histological type and B symptoms. Results from the accelerated time-failure regression model are listed in Table 5 in the form of time ratios (exponentiated coefficients). Results indicated that after adjusting for related factors, cohort (survival) differences remained highly significant. In particular, the shift from the early cohort (1973–82,

Table 5 Accelerated-failure time model

Factor	Time ratio univariate	95% CI	Time ratio multivariate	95% CI	P-value
<i>Cohort</i>					
Cohort(73–82)	1.00		1.00		
Cohort(83–92)	4.85***	1.93, 12.22	1.92*	1.02, 3.62	0.045
Cohort(93–02)	22.58***	8.84, 57.71	4.60***	2.28, 9.30	<0.001
<i>Age group</i>					
Age gp (<26)	1.00		1.00		
Age gp(26–45)	0.64	0.26, 1.57	0.81	0.39, 1.66	0.556
Age gp(46–65)	0.07***	0.03, 0.18	0.14***	0.06, 0.30	<0.001
Age gp(66+)	0.004***	0.001, 0.011	0.02***	0.01, 0.06	<0.001
<i>Gender</i>					
Male	1.00		1.00	0.85, 2.51	
Female	1.26	0.51, 3.13	1.46	0.85, 2.51	0.170
<i>Treatment</i>					
Chemotherapy	1.00		1.00		
Combi (chemo + radio)	23.22***	9.36, 57.65	2.06	0.99, 4.28	0.053
Radiotherapy	27.14***	11.83, 62.28	2.63*	1.24, 5.57	0.011
<i>B symptom</i>					
No	1.00		1.00		
Yes	0.39*	0.17, 0.91	0.42**	0.23, 0.76	0.005
<i>Who</i>					
Lymphocyte	1.00		1.00		
Mixed Cell	0.22*	0.06, 0.88	0.31*	0.11, 0.85	0.022
Nodular Scl	0.49	0.14, 1.75	0.37*	0.15, 0.92	0.032
Unspecified	0.001***	0.0003, 0.008	0.03***	0.01, 0.14	<0.001
<i>Stages</i>					
Stage I	1.00		1.00		
Stage II	0.33*	0.13, 0.83	0.37*	0.16, 0.84	0.018
Stage III	0.06***	0.02, 0.15	0.29***	0.12, 0.68	0.005
Stage IV	0.02***	0.006, 0.089	0.22**	0.08, 0.63	0.005
Stage V	0.001***	0.0004, 0.004	0.06***	0.01, 0.26	<0.001

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. If $TR < 1$, event occurs faster as time accelerates. If $TR > 1$, event delays as time decelerates.

base-category) to mid cohort (1983–92) is associated with an almost two-fold delay of death event otherwise, prolonged survival (i.e., experiencing of death decelerates over time by a factor of 1.92), and from early cohort to the late (1993–02), with an almost 5-times prolonged survival ($P < 0.001$). Covariates associated with accelerated (faster) time impact on death were increasing age, higher than stage I tumour, presence of B symptom and other-than lymphocyte predominant histology. In contrast, covariates of decelerated (delayed) time found to be female gender (not significant), combined chemotherapy and radiotherapy (not significant), and radiotherapy. The proportion of female patients increased with each successive cohort. Male-to-female ratio 2.16, 1973–1982; 1.59, 1983–1992; 1.43, 1993–2002.

Last, as a way to illustrate the survival disparities among the three cohorts, we attempted a between-cohort comparison of the fitted/predicted survival time of a typical HD patient in each of the three available cohorts. Figure 4 illustrates the predicted survival for a male, diagnosed with a stage II disease, at the age of 40 years, treated with chemotherapy and radiotherapy, having nodular sclerosing histology. As the graph suggests, transparent differences in predicted survival are observed over time.

DISCUSSION

The cure rate for HD in Nottinghamshire has improved significantly over a 30-year period with patients treated in the most recent cohort, (1993–2002) having a cure rate of 75% (15 year cause specific survival). This compares with a cure rate of 52% in the era 1973–1982. Our results suggest a clear improvement in survival time was observed. After adjusting for other factors,

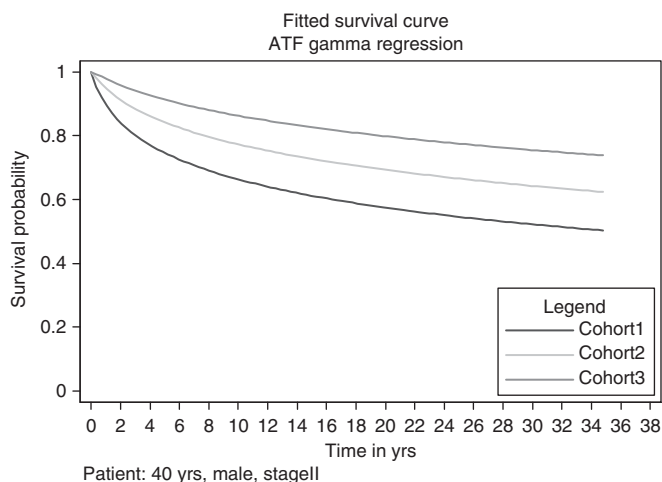


Figure 4 Comparison of survival probabilities for a typical patient.

regarding time to death, a 4-fold deceleration was found for the latest cohort compared with the earliest (95% CI 2.3–9.3).

This improvement in survival is likely to be due to the introduction of Doxorubicin in the early 1980s, better management of toxicity such as neutropenic sepsis, and possibly increased dose intensity of chemotherapy (this was not demonstrated for ABVD chemotherapy in the United Kingdom Lymphoma Group trial LY09, Owadally *et al*, 2010). There is insufficient data on the registry to clarify this situation further. There is no evidence supporting a change in the natural history of HD. It is not clear why the proportion of female patients with HD has been increasing in more recent cohorts except that, in the general population in Nottinghamshire (over the age of 70 years), the female-to-male ratio has been increasing (Forsyth *et al*, 1997).

The risk of second malignancy has been estimated for each of the three cohorts. At 20 years, the risk of second malignancy is 12.4% for the 1973–1982 cohort, but because all second malignancies resulted in death, it is probable that this is an underestimate. The risk of second malignancy in the second cohort (1983–1992) at 20 years is 18.8%. The actuarial risk of second malignancy seems to be increasing (Figure 4), but this may be due to the more accurate registration of second malignancies on the lymphoma registry that do not result in death. The estimates for the actuarial risk of second malignancy are similar to other series of patients with Hodgkin's disease treated with radiotherapy, chemotherapy or chemoradiotherapy (Swerdlow *et al*, 1992; Mauch *et al*, 1996; Bonadonna *et al*, 2005; Allemanni *et al*, 2006; Franklin *et al*, 2006; Hodgson *et al*, 2007; Sénécal *et al*, 2008). These series give a long-term risk of 20–30% for second malignancy.

There are relatively few publications on the long-term survival of patients with HD. Some of these include patients treated in the 1960s, when combination chemotherapy was not used routinely and radiotherapy was used with larger fields and less precise imaging. In addition, even fewer publications are based on a defined population from a registry. Using national cancer registration data with limited access to the hospital notes may be

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more inaccurate for lymphomas than for solid malignancies (Trent Regional Cancer Registry data). There is agreement in the literature that, for the era 1973–2002, the 15-year disease-specific survival or relative survival is about 70% (Mauch *et al*, 1995; Van Spronsen *et al*, 1997; Aleman *et al*, 2003; Provencio *et al*, 2008). The survival of patients with HD entered onto the British National Lymphoma Investigation data base (which would have included some Nottinghamshire patients) during the period 1970–1987 was similar to that obtained from the population-based UK National Cancer Registry only for patients less than 45 years of age. Older patients were found to have a much better survival (relative survival 39%) than those from the National Cancer Registry (relative survival 27%). This demonstrates that data bases set up to analyse clinical trials often contain patients with a more favourable prognosis (Roy *et al*, 2000). There is evidence that the prognosis for patients over 45 years of age with HD is improving in recent cohorts but is still less favourable than for younger patients (Brenner *et al*, 2008).

The prognostic factors for HD are well known. The Hasenclever prognostic index is widely used in managing patients with advanced HD (Hasenclever and Diehl, 1998). This includes 7 factors, a serum albumin level of $<40 \text{ g l}^{-1}$, a haemoglobin level of $<10.5 \text{ g dl}^{-1}$, male sex, age ≥ 45 years, stage IV disease, leucocytosis ($\geq 15.0 \times 10^9 \text{ l}^{-1}$) and lymphopaenia ($<0.6 \times 10^9 \text{ l}^{-1}$).

For early stage HD (IA and IIA), the following factors associated with a good prognosis have been found: lymphocyte predominant and nodular sclerosing histology, young age <40 years, non-bulky disease ($<8 \text{ cm}$), three or fewer nodal sites and an erythrocyte sedimentation rate of $<30 \text{ mm h}^{-1}$ (Haybittle *et al*, 1985).

In our series, the covariates associated with a poorer prognosis (Table 5) in the accelerated-failure time model were earlier methods of treatment, increasing age of the patient (particularly over the age of 45 years), chemotherapy alone (without radiotherapy), B symptoms, histology other than lymphocyte predominant HD, and increasing stage of disease. Male gender was not associated with a worse prognosis. There has been much debate about the role of consolidation radiotherapy in the treatment of advanced HD, but in the UKLG LY09 trial of ABVD vs ChlVPP/PABLOE, consolidation radiotherapy was associated with better outcomes across all prognostic groups in multivariate analysis (Johnson *et al*, 2010). In our series, combined chemotherapy and radiotherapy compared with chemotherapy alone caused a two-fold delay in death (95% CIs 0.99–4.28).

The improvement in survival seen in the three consecutive cohorts in our series is independent of all of these prognostic factors.

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Conflict of interest

The authors declare no conflict of interest.

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