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Original Paper

Survival Analysis of Patients with Clinical Stages I or II Hodgkin's Disease Who Have Relapsed After Initial Treatment with Radiotherapy Alone

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To aid treatment choice in early stage of Hodgkin's disease, we analysed patients registered in the IDHD Database with clinical stages I or II Hodgkin's disease who were not staged with laparotomy and whose initial treatment was with radiotherapy alone. The factors analysed for outcome after first relapse included initial stage, age, sex, histology, number of involved areas, mediastinal involvement, E-lesions, B-symptoms, erythrocyte sedimentation rate, alkaline phosphatase, serum albumin and haemoglobin. As well as presentation variables, we analysed the disease-free interval after initial radiotherapy and the extent of disease at relapse. A total of 1364 patients with clinical stage I or II Hodgkin's disease were treated with initial radiotherapy, of whom 473 relapsed. The probability of survival 10 years after relapse was 63%. For cause-specific survival (CSS), both multivariate and univariate analysis identified the importance of age at presentation and histological subtypes. When all causes of death were considered, the multivariate analysis identified age as the only significant factor. The length of initial disease-free interval had no influence on prognosis after relapse, but the 169 patients with nodal relapse had a higher cause-specific survival than those with an extranodal component of relapse (74% versus 51% at 10 years, $P < 0.005$). Thus, the important factors for outcome after initial treatment with radiotherapy are those factors predicting the risk of relapse after initial treatment together with those predicting outcome after relapse, namely age, histologic subtype and extent of disease at relapse. © 1997 Elsevier Science Ltd.

Key words: Hodgkin's disease, radiotherapy, salvage of relapse

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INTRODUCTION

THERE ARE a number of approaches to the management of the patient who presents with early stage Hodgkin's disease. These include radiotherapy, chemotherapy or a combined modality approach incorporating both. Issues underlying the treatment decision include not only the risk of recurrence, but also an estimate of the probability of successful salvage after recurrence [1–7]. We have previously used the International Database on Hodgkin's Disease to analyse salvage of relapse after radiotherapy in patients with laparot-

omy-staged Hodgkin's disease [5]. This study analyses clinical stage I and II patients who did not have a staging laparotomy with the aim of defining the presentation variables that might indicate the probability of successful treatment of patients relapsing after initial radiotherapy.

MATERIALS AND METHODS

The International Database on Hodgkin's Disease (IDHD) comprises more than 14000 patients with Hodgkin's disease treated since the early 1960s by five cooperative trials groups or within 13 cancer centres (see Appendix). The database contains 9091 patients with clinical stages I or II Hodgkin's disease, of whom 3750 patients were initially treated with radiotherapy alone. 1364 of these

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Table 1. CS I and II HD: presentation variables and disease-free survival after radiotherapy

Variables	Number of patients	Relapse (% DF at 5 years)	Significance (log-rank)
Gender			
Male	761	68%	NS
Female	603	67%	
Age*			
<25 years	375	69%	NS
25-39 years	472	68%	
>39 years	516	66%	
Histology*			
LP	171	79%	} $P < 0.025$
NS	836	67%	
MC	326	64%	
LD	12	58%	
Number of sites*			
1	658	72%	} $P < 0.005$
2	416	68%	
3	170	55%	
>3	67	57%	
Mediastinal involvement*			
Med-	888	70%	} $P < 0.05$
Med+	470	64%	
Symptom stage			
A	1215	70%	} $P < 0.005$
B	149	52%	
ESR*			
<20	498	76%	} $P < 0.005$
20-39	253	66%	
40-59	134	61%	
≥60	191	53%	
Haemoglobin*			
Normal	903	70%	} $P < 0.005$
Low	109	54%	

*Some data missing. Haemoglobin (low in males if <8 mmol/l, low in females if <7 mmol/l).

CS, clinical stage; LP, lymphocyte predominant; Med, mediastinum; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depleted; ESR, erythrocyte sedimentation rate.

patients were staged without laparotomy and treated between 1970 and 1983, of whom 473 (35%) relapsed. Patient characteristics are summarised in Table 1. Of the 473 relapsing patients, 161 died of Hodgkin's disease, 7 died of treatment-related complications with no evidence of Hodgkin's disease, 26 deaths were due to second malignancies of which 10 were leukaemias, 3 lymphomas and 13 solid tumours. 28 deaths were of other or unknown causes. The second malignancies on the IDHD have been analysed

and reported separately [8]. Limited recorded data relating to initial radiotherapy is shown in Table 2.

The initial disease-free interval was measured from the time of start of therapy to the time of first relapse. Survival after relapse was measured from the time of relapse until death from Hodgkin's disease (for cause-specific survival, counting all deaths with active Hodgkin's disease as events), or until death irrespective of cause (for overall survival). The median follow-up after first relapse in patients still alive

Table 2. CS I and II HD: treatment variables and disease-free survival after radiotherapy

Variables	Number of patients	Relapse (% DF at 5 years)	Significance (log-rank)
1st RT			
1970-1974	584	63%	} $P < 0.005$
1975-1979	447	70%	
1980-1983	333	74%	
Field			
IF*	301	64%	} $P < 0.005$
M or Y	636	66%	
(S) TNI	415	73%	

*Some data missing.

RT, radiotherapy; IF, involved field; M, mantle field; Y, inverted-Y field; (S) TNI, (subtotal) total nodal irradiation.

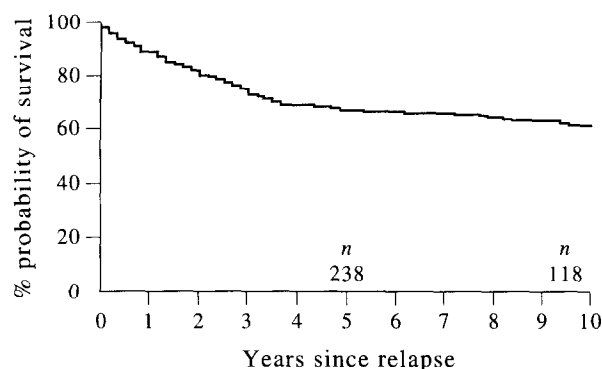


Figure 1. Cause-specific survival after first relapse following radiotherapy for clinical stage I and II Hodgkin's disease in 473 patients.

was 9 years (range 0–17 years). Survival curves were calculated according to the method of Kaplan and Meier [9], and comparisons in the univariate analyses were performed by the log-rank test (for trend if appropriate) [10]. To estimate the independent contribution of different factors to prognosis, multivariate analyses were performed using Cox's method [11]. In the multivariate analyses, the factors analysed were scored according to their natural order. For factors where no natural order existed (e.g. histological subtype), indicator variables were used comparing each subgroup with the one with the best prognosis. Age and length of the initial disease-free interval were entered as number of years and analysed as continuous variables. For tables and figures, arbitrary cut points were chosen for the sake of illustration.

RESULTS

As shown in Figure 1, the cause-specific survival after first relapse in 473 patients were 68% at 5 years and 63% at 10 years and corresponding figures for overall survival were 61% and 50%. Univariate analysis of pretreatment variables

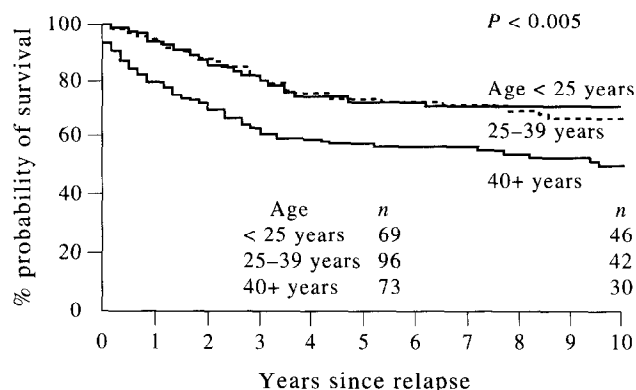


Figure 2. Cause-specific mortality after first relapse following radiotherapy for clinical stage I and II Hodgkin's disease, comparing 375 patients aged <25 years at presentation, 472 patients aged 25–39 years and 516 patients aged >39 years ($P < 0.005$).

for prognostic significance with regard to cause-specific survival after relapse included age, sex, histology (local review) presentation (infra- or supradiaphragmatic), number of involved areas, mediastinal involvement, presence of extra nodal extension (E-lesions), presence of B-symptoms, erythrocyte sedimentation rate (ESR), alkaline phosphatase, serum albumin and haemoglobin. As shown in Table 3, log-rank analysis revealed a significant impact only for age at initial presentation, histology and initial mediastinal involvement. Mortality from Hodgkin's disease in presentation age groups is shown in Figure 2. Mortality from Hodgkin's disease in those with different histological subtypes is shown in Figure 3. The adverse impact of increasing age is notable in those over 40 years of age. Lymphocyte predominant and nodular sclerosis histologies had a better prognosis than those with mixed cellularity Hodgkin's disease. Those presenting with mediastinum involvement had better prognosis than those who did not have mediastinum involvement. There is no impact of disease stage on success of salvage

Table 3. Cause-specific survival after radiotherapy relapse: significant univariate analyses

Variables	Relapsed patients	HD deaths	% Survival		
			5 years	10 years	
Total	473	161	68	63	
Age					
<25 years	125	35	73	72	} $P < 0.005$
25–39 years	165	48	74	68	
>39 years	183	78	58	51	
Histology					
LP	45	17	65	61	} $P < 0.01$
NS	292	86	72	67	
MC	126	53	57	55	
LD	4	3	50		
Field					
IF	120	52	61	54	} $P < 0.05$ (Het not trend)
M or Y	227	73	71	65	
(S) TNI	125	36	67	67	
Mediastinal involvement					
Med–	296	109	64	59	} $P < 0.025$
Med+	182	52	72	68	
Nodal relapse only	169	41	77	74	} $P < 0.005$
Extranodal relapse	137	57	56	51	

*HD, Hodgkin's disease; med, mediastinal; LP, lymphocyte predominant; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; (S) TNI, (subtotal) total nodal irradiation; Het, heterogeneity.

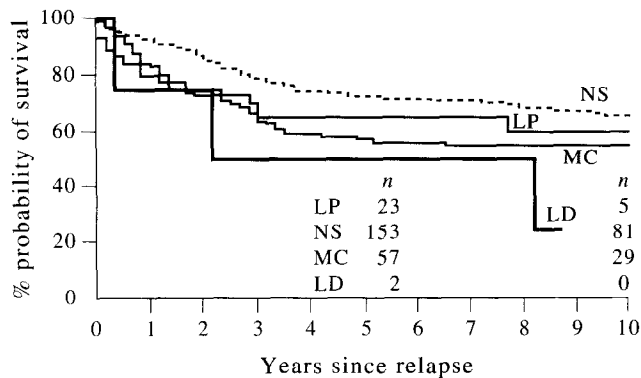


Figure 3. Cause-specific mortality after first relapse following radiotherapy for clinical stage I and II Hodgkin's disease comparing histological subtypes. (Lymphocyte predominant, LP $n = 45$; nodular sclerosing, NS $n = 292$; mixed cellularity, MC $n = 126$; lymphocyte depleted, LD $n = 4$) ($P < 0.01$).

therapy and no significant impact of number of involved nodal areas, although only 23 patients had 4 or more involved nodal areas at presentation.

The only treatment variable analysed was extent of initial radiation field, comparing involved field (IF) ($n = 120$), regional field (mantle or inverted Y) ($n = 227$) or subtotal/total nodal irradiation (TNI) ($n = 125$). As shown in Figure 4, the survival for those initially treated with involved field radiotherapy appeared to be poorer. There was evidence that IF radiotherapy was selected for older patients. In those aged >39 years, IF was used in 154 (30%), regional radiotherapy in 225 (44%) and (S) TNI in 132 (26%), compared to 147 (17%), 411 (49%) and 283 (34%), respectively ($P < 0.001$) in those under 39 years of age. The type of relapse was also a significant indicator of prognosis after relapse. The database allowed only the simple division into those with nodal relapse or those with extranodal (with or without nodal) relapse (Table 3). As shown in Figure 5, in 169 patients with nodal relapse, the probability of cause-specific survival at 10 years was 74%, whereas in 137 patients with a component of extra nodal relapse the 10-year cause-specific survival probability was 51% ($P < 0.005$). The disease-free interval (DFI) between initial treatment and first relapse did not influence survival

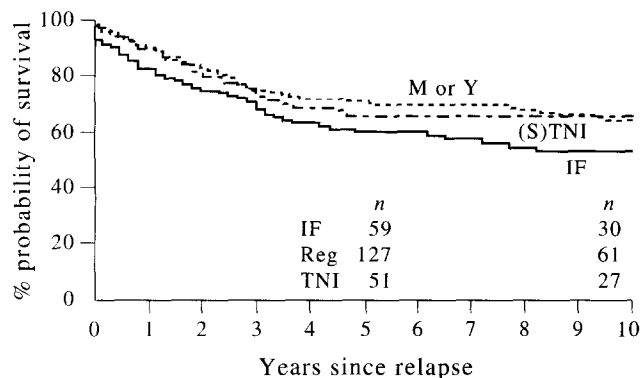


Figure 4. Cause-specific survival after first relapse following radiotherapy for clinical stage I and II Hodgkin's disease comparing those initially treated with involved field (IF, $n = 120$), regional (Reg) field, mantle (M) or inverted Y (Y) $n = 227$, or (sub)total nodal irradiation ((S) TNI, $n = 125$) ($P < 0.05$ heterogeneity).

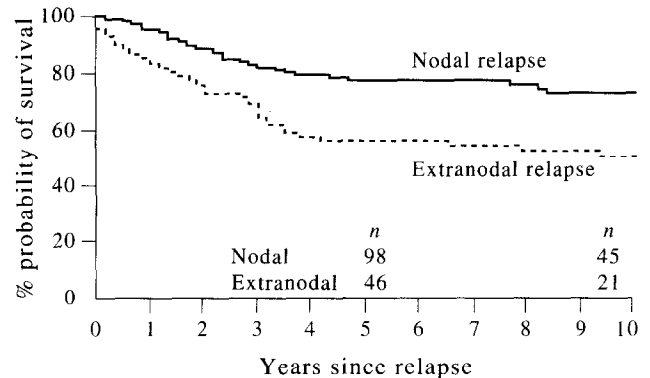


Figure 5. Cause-specific survival after first relapse following radiotherapy or clinical stage I and II Hodgkin's disease comparing those with only nodal relapse ($n = 169$) with those whose recurrence contained an extranodal component ($n = 137$) ($P < 0.005$).

after relapse. In 151 patients with DFI <1 year, the 10-year cause-specific survival was 62% compared to 65% in 197 patients with DFI between 1 and 3 years, and 58% in 125 patients with DFI >3 years.

On multivariate analysis of presentation variables for impact on cause-specific survival after relapse, age and histological subtype were independent significant factors with the relative risk of death increasing by a factor of 1.3 (95% CI, 1.1–1.4) for each 10 year increase of age and by 1.4 (95% CI, 1.0–2.0) for mixed cellularity (MC) or lymphocyte depleted (LD) histologies. However, in the analysis of survival after relapse, which included all causes of death, age was the only significant factor. Table 4 shows the multivariate analyses of presentation variables with the extent of disease at relapse. For cause-specific survival, it can be seen that age at original presentation, histological subtype and extent of disease at relapse are independently significant prognostic factors.

DISCUSSION

In this analysis of 1364 patients with clinical stage I or II Hodgkin's disease, staged without laparotomy, the major prognostic factors influencing risk of recurrence were year of first treatment, histological subtype, clinical stage and number of involved nodal areas, mediastinal involvement, systemic symptoms, extent of radiation field, haemoglobin level, ESR, alkaline phosphatase and albumin. Many of these have been reported in previous prognostic factor analyses [12–16].

Age was the major pretreatment variable predicting outcome after relapse, but it is unclear whether this reflects a more aggressive disease biology in older patients or whether a different treatment approach is undertaken in older patients because of the perception that their treatment tolerance is reduced. Since detailed information on relapse treatment is not available in the IDHD, we could not examine this further. In our analysis of survival from Hodgkin's disease, patients with mixed cellular histology had a slightly lower chance of survival after relapse than patients with lymphocyte predominant and nodular sclerosing disease. The significance of histological type is supported by an analysis of patients treated in Boston [17]. In 110 patients relapsing after initial radiotherapy alone, histological type was the single most important prognostic factor with 75%, 10-year

Table 4. Survival after radiotherapy relapse: multivariate analyses (including site of relapse)

Variables		Cause-specific survival		Overall survival	
		Relative risk	95% CI on relative risk	Relative risk	95% CI on relative risk
Age	(for each 10 year increase in age)	1.24	1.12–1.37	1.40	1.29–1.52
Relapse	Nodal only	1		1	
	Extranodal	1.51	1.08–2.10	1.54	1.16–2.04
Histology	NS/LP	1		1	
	MC/LD	1.41	1.02–1.97	1.60	0.95–1.68

Other variables included: age, sex histology, RT field, mediastinum, clinical stage, systemic symptoms.

survival for nodular sclerosis/lymphocyte predominant compared to 43% for mixed cellularity/lymphocyte depleted subtypes. In contrast, the report from Stanford [4] did not find histology to be a significant indicator of prognosis after relapse. However, only 13 of the 109 patients had mixed cellularity Hodgkin's disease and none were lymphocyte depleted. The important prognostic factors found from this analysis were age (>50 years) and extent of disease on relapse, and the multivariate analysis of freedom from second relapse suggested that a relapse treatment containing both chemotherapy and radiotherapy was more effective than treatment based on chemotherapy alone.

We did not find that the number of involved nodal sites at initial presentation influenced the outcome after relapse, in contrast to an analysis which also included stage III Hodgkin's disease [3]. The worse prognosis after relapse in patients initially treated with involved field radiotherapy may be due to a bias in the initial treatment selection, patients with poor general health or older age receiving the less extensive radiotherapy. It is unlikely to be a specific treatment effect since randomised studies of the extent of the radiation field have not demonstrated significant overall survival differences [18].

We found that patients relapsing with an extranodal component had a poorer prognosis than those with purely nodal relapse. This is entirely consistent with the study reported by Roach and associates [4], who found by multivariate analysis, which included pretreatment, treatment and relapse variables, that relapse stage was the most significant indicator of prognosis after relapse.

Previous analysis of patients with relapse after radiotherapy for laparotomy-staged Hodgkin's disease was based on 681 relapsed patients and similarly found that only age and histology were significant prognostic indicators on both univariate and multivariate analyses. Again patients with purely nodal relapse had a better prognosis and the length of the initial disease-free interval was unimportant [5].

We conclude that pretreatment variables are of very limited value in determining the prognosis in patients who relapse after radiotherapy for clinical stage I or II Hodgkin's disease. Our finding that older age was associated with a poor prognosis is compromised by the lack of treatment details, allowing the possibility that older patients were treated suboptimally. Thus, the important pretreatment determinants of outcome after initial treatment with radiotherapy for early Hodgkin's disease are those factors determining risk of recurrence. At the time of relapse, full restaging

assessments should be performed and prognosis judged by age, extent of disease and histological subtype.

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APPENDIX

International Database on Hodgkin's Disease

List of contributors, IDHD cooperating centres and cooperating groups.

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