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NON-HODGKIN'S LYMPHOMA IN NORTHERN SWEDEN

Prognostic factors and response to treatment

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A total of 352 cases of non-Hodgkin's lymphoma reported to the Cancer Registry of Northern Sweden during 1978–1982 were retrospectively analysed. After morphologic review, 327 cases classifiable as low (n = 162) or high-grade (n = 165) according to the Kiel classification remained for further study. The purpose of the study was to evaluate the interrelations between some variables and their bearing on prognosis in an almost unselected clinical material. Age, morphological grade of malignancy, clinical stage, systemic symptoms, bulk of disease and serum lactate dehydrogenase (LDH) level turned out to be associated with the clinical outcome in terms of response to treatment, disease-free survival and survival. In the hetrogenous group of low-grade lymphoma, six pretreatment characteristics were negatively associated with survival in a univariate analysis, namely; stage II–IV, systemic symptoms, bone marrow infiltration, two or more extranodal sites, elevated LDH and age above 65 years. In high-grade lymphoma, stage II–IV, bone marrow infiltration and elevated LDH predicted a worse prognosis in a multivariate analysis. The impact of the number of these prognostic factors on survival in high-grade lymphoma was demonstrated.

In the past two decades important advances have been achieved concerning classification, staging techniques and treatment of non-Hodgkin's lymphomas (NHL). Today several various classifications are used. In USA the Lukes and Collins classification (1) or the so-called Working Formulation (2) are generally accepted while most countries in Europe use the Kiel classification (3). This leads to some difficulties when comparing results from different centers. However, all classifications show a clear prognostic difference between two major subgroups morphologically characterized as low-grade (LG) and high-grade (HG) malignancy (4–6). The most obvious treatment progress has been combination chemotherapy containing anthracyclines in patients with generalized HG lymphoma. Twenty years ago few of these patients survived more than 2 years while today more than 60% achieve complete remission and 30% remain obviously cured from the disease (6–9). In LG lymphomas more aggressive therapy has not markedly influenced the survival and discussions continue about the best therapy (10–12).

Most reports on treatment results in NHL concern selected materials in which patients above the age of 70 often have been excluded (2, 9, 13–17). About 50% of the malignant lymphomas in Sweden are seen in patients above the age of 65 years (18). Thus the average patient with NHL is an elderly person who often suffers from concomitant diseases which makes the choice of therapy, especially combination chemotherapy, more difficult.

To illustrate the true incidence, prognostic factors and treatment outcome in NHL we retrospectively analysed all reported cases in three northern counties of Sweden (Norrbotten, Västerbotten and Västernorrland) diagnosed during 5 years and with a follow-up of more than 8 years.

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Material and Methods

Patients. A retrospective review was performed of all patients reported as NHL to the regional cancer registry during the 5-year period 1978–1982 in the three mentioned

counties. Histologic and/or cytologic materials were reevaluated and all clinical records were collected for analyses of data. The number of evaluable patients was 352, of whom 327 patients were classifiable according to the original Kiel classification as LG or HG lymphomas (3). Staging was performed according to the Ann Arbor classification (19). In a previous report we described the material in detail concerning morphological diagnosis and clinical staging (20). The treatment of this unselected material was not uniform. In general, radiotherapy was given to patients with stage I lymphomas with 'involved field' technique, to the LG lymphomas 30–40 Gy and to the HG lymphomas 40–45 Gy. Approximately 20% of these patients also received chemotherapy as initial treatment. Twenty patients with stage IE and IIE (gastrointestinal involvement 19 pts, thyroid 1 pt) had the bulk of the tumor surgically resected before chemo- or radiotherapy. Seventeen of 162 patients with LG and 7 of 165 patients with HG lymphomas received no therapy. In the LG patients the reason usually was indolent disease without serious symptoms. In the HG patients the reason was advanced age, poor general condition and/or rapid deterioration. Single agent chemotherapy (chlorambucil or prednimustine with or without corticosteroids) or COP (cyclophosphamide, vincristine and prednisone) was given to 78 of the 121 LG patients in stages II–IV (10), while the remaining ones received other chemotherapy combinations, such as CHOP (COP + doxorubicine) regimen (19 pts) and/or radiotherapy (27 pts). Fifty-five of 100 patients with HG lymphoma stage II–IV received combinations with cyclophosphamide, e.g. COP or MEV (methotrexate, cyclophosphamide and vincristine) (21) and 38 received CHOP or CHOP-methotrexate. Combinations of radio- and chemotherapy was given to 35 of these HG patients as initial treatment. Distribution according to stage, extranodal involvement and systemic symptoms in LG and HG lymphoma cases were detailed in a previous report (20). All patients were followed until death or until September 1990. The median follow-up for living patients was 115 months (range 94–154).

Statistical methods. Survival was calculated from the date of diagnosis to the end of follow-up or to death. Survival was presented as crude, when all deaths were taken into account. When survival was defined as cause-specific, deaths from clearly documented causes not associated with lymphoma were excluded. Deaths from possible treatment-related causes, e.g. infections or postoperative complications or from other diseases where the lymphoma contributed to the deterioration, were considered as death from lymphoma. Complete remission (CR) was defined as absence of residual clinical or radiological evidence of disease. Disease-free survival (DFS) was calculated from the date of clinical CR to relapse or to end of follow-up. Patients with partial remission (PR) showed substantial but not total reduction of measurable disease for at least one month. Survival rates were calculated according to Kaplan–Meier (22) and differences in survival were analyzed with the log-rank test (23). Multivariate analyses were performed by Cox's proportional hazards model (24) to identify subsets of independent prognostic factors for survival. Initially, the model included the following eight factors: Age, gender, clinical stage, systemic symptoms, bone marrow involvement, bulky disease, number of extranodal sites, and LDH. The hypothesis that the coefficient of each variable was equal to 0 was tested. The coefficients with a non-significant p-value (more than 0.10) were excluded from the model in an iterative process (at each step the variable with the least statistical signficance was excluded). In the final model, each excluded variable was tested again for reinclusion, with a criterion of p-value for inclusion of less than 0.05. However, with this criterion in no instance a previously excluded variable was reintroduced into the model (25). Relative survival was determined according to Hakulinen (26). A risk score consisting of no, one, two or three of the significant risk factors was applied on HG lymphomas.

Results

Survival

The median crude survival of the whole material was 29 months. In the LG lymphomas the survival curve showed a continuous downward slope while the curve in the HG lymphomas fell steeply the first 2 years to level off into a plateau phase after approximately 3 years. Median survival in LG lymphomas was 55 months and in HG 13 months. After 11 years of follow-up the crude survival was similar—22% in the two groups. Analysis of relative survival showed that LG lymphomas had an increased risk of dying during the whole follow-up time whereas the risk of HG lymphomas decreased and was the same as for the general population after approximately 3 years (Fig. 1).

The subgroups of the LG lymphomas had varying prognosis. In patients with follicular lymphomas (median age 58 years) the prognosis was favourable with a median crude survival of 7 years. The lymphocytic lymphomas (LC) with high median age (67 years) often had an indolent course and a median survival of more than 5 years. However, there was an obvious discrepancy between crude and cause specific survival in LC lymphomas, reflecting the fact that the lymphoma was often diagnosed in patients with other, serious diseases. The immunocytic (IC), centrocytic (CC) and diffuse centrocytic/centroblastic (Cb/Cc) lymphomas formed an intermediate group (median age 59–67 years) with median survival 2.5–4 years. With the exception of lymphoblastic (LB) lymphomas the survival in the HG subgroups was rather uniform with a median survival of 13 months (Table 1). Five of 9 patients with LB lymphomas were children (1–10 years old), all of them alive in complete remission (CR) after treatment according

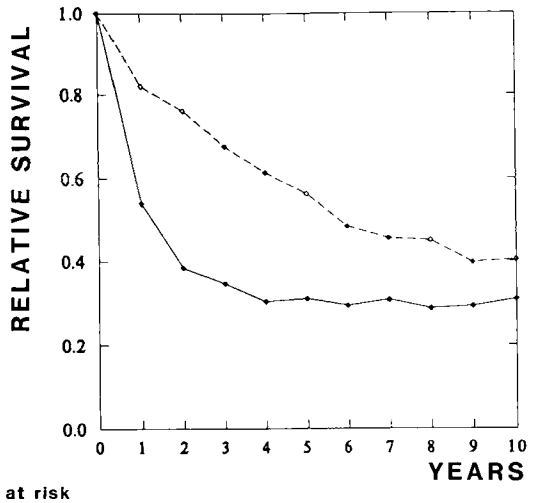

Fig. 1. Relative survival for patients with low (– – –, n = 162) and high (——, n = 165) grade of malignancy.

to Wollner et al. (27). Four adult patients with LB lymphomas (age 28–64 years) died from lymphoma 5, 6, 18 and 44 months after diagnosis.

In LG lymphoma stage I the crude 5-year survival rate in patients older than 65 years was 50%, compared to 85% in patients younger than 65 years. In stage II–IV 4% of LG patients older than 75 years, 41% of those 55–74 years and 63% of patients younger than 55 years survived more than 5 years. Among 45 HG patients older than 75 years, 5 of the 22 patients in stage I (all had extranodal lymphoma) were alive 5 years after diagnosis. None of the 23 patients in stage II–IV lived for more than 19 months. Five-year survival in HG patients in age 55–74 years was 33% and in those younger than 55 years 70% in stage I. In stage II–IV the survival was comparable in the two age groups, 17% and 20% respectively.

Prognostic factors

Age. Figs 2 and 3 and Tables 2 and 3 show the importance of age in LG and HG lymphomas respectively, in

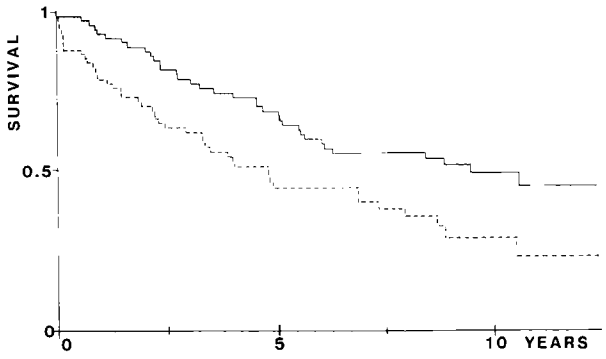

Fig. 2. Cause specific survival for patients with low-grade lymphomas according to age (p = 0.006). Age < 65 years (——) n = 86; ⩾65 years (– – –) n = 76.

Table 1

Survival according to the Kiel classification

	Number of patients	Median survival, months		10 year survival, %	
		Crude	Cause specific	Crude	Cause specific
Low grade					
LC	26	61	106	27%	53%
IC	27	28	35	18%	25%
Foll. ± diff.					
Cb/Cc	58	80	106	35%	47%
CC	13	47	48	23%	23%
Diff. Cb/Cc	30	39	60	17%	33%
Myc. fung.	5	120	124	80%	80%
Unclass.	3				
Total low grade	162	55	73	27%	41%
High grade					
CB	73	11	17	20%	33%
IB	54	11	12	20%	24%
LB	9	not reached		56%	67%
Unclass.	29	19	19	10%	39%
Total high grade	165	13	15	18%	33%

Abbreviations: LC: lymphocytic lympoma; IC: immunocytic lymphoma; Cb/Cc: centrocytic/centroblastic; CC: centrocytic lymphoma; Myc. fung.: mycosis fungoides; CB: centroblastic; IB: immunoblastic; LB: lymphoblastic.

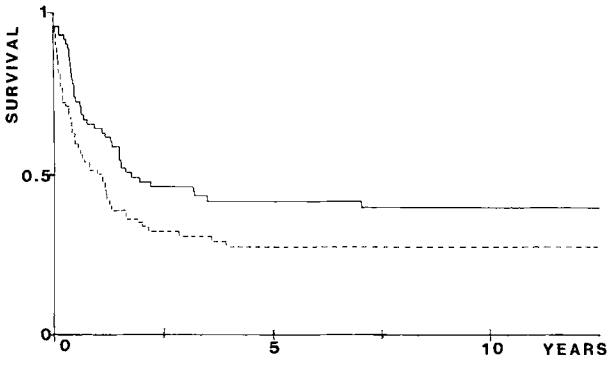

Fig. 3. Cause specific survival for patients with high-grade lymphomas according to age ($p = 0.027$). Age < 65 years (——) $n = 90$; ≥ 65 years (– – –) $n = 75$.

terms of cause specific survival, and significantly better prognosis in patients below 65 years of age. The median age of patients below 65 years was 55 years and for patients 65 years or older it was 74 years.

Table 2

Univariate analysis of pretreatment clinical factors in LG lymphoma (n = 162)

	No. of patients	Cause specific survival, %		p-value
		5 years	10 years	
Age				
<65	76	68	49	
>65	86	44	29	<0.001
Gender				
Female	65	59	42	
Male	97	54	38	0.587
Stage				
I	41	89	79	
II, III, IV	121	46	26	<0.001
Systemic symptoms				
Absent	129	65	49	
Present	33	21	4	<0.001
Bone marrow involvement				
No	88	69	50	
Yes	52	44	27	0.005
Bulky disease (largest tumor diameter > 10 cm)				
No	136	60	45	
Yes	26	37	17	0.009
No of extranodal sites				
0 or 1	143	61	45	
2 or more	19	26	0	<0.001
LDH (normal limit <7.5 ukat/l)				
Normal	67	72	51	
Elevated	67	42	25	<0.001

Table 3

Univariate analysis of pretreatment clinical factors in HG lymphoma (n = 165)

	No. of patients	Cause specific survival, %		p-value
		5 years	10 years	
Age				
<65	75	41	40	
>65	90	27	27	<0.001
Gender				
Female	71	38	38	
Male	94	31	29	0.572
Stage				
I	65	50	50	
II, III, IV	100	23	22	<0.001
Systemic symptoms				
Absent	118	41	41	
Present	47	15	12	<0.001
Bone marrow involvement				
No	117	40	39	
Yes	15	0	0	<0.001
Bulky disease (largest tumor diameter >10 cm)				
No	124	34	33	
Yes	35	20	20	0.002
No of extranodal sites				
0 or 1	148	35	35	
2 or more	17	27	18	0.268
LDH (normal limit <7.5 ukat/l)				
Normal	50	55	52	
Elevated	92	21	21	<0.001

Stage. In LG lymphoma, 41/162 (25%) were in clinical stage I and in HG lymphomas 65/165 (39%). The survival differences between stages II, III and IV were not statistically significant, and in the following these patients will be discussed as a joint group (Tables 2 and 3). The long-term prognosis in LG stage I was favourable. In HG stage I, however, half of the patients died from lymphoma within 5 years. Approximately three-fourths of the patients in stage II–IV died from lymphoma during the follow-up period, in LG within 10 years and in HG within 5 years after diagnosis.

Response to treatment. Three hundred and five of 327 patients received treatment with radio- and/or chemotherapy. After treatment, 182 (60%) obtained complete remission (CR), 93/147 (63%) with LG and 89/158 (56%) with HG lymphomas. As expected the survival of patients with CR was significantly better than that of patients with partial remission (PR), stable disease (SD) and progressive disease (PD). The median survival in LG cases with

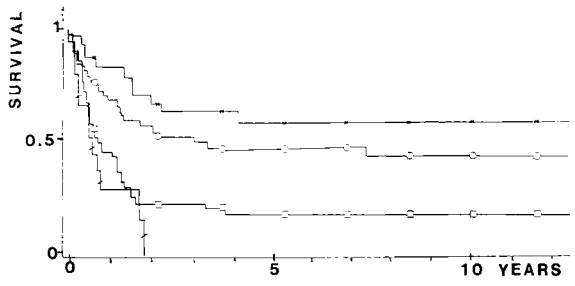

Fig. 4. Impact of number of risk factors on cause specific survival in 143 HG lymphoma patients. Twenty-two patients were excluded due to missing data. Number of risk factors: 0: —×— (31 pts), 1: —○— (44 pts), 2: —□— (54 pts), 3: —/— (14 pts).

(93 pts) or without (69 pts) CR was 88 vs 23 months. In the HG lymphomas the median survival in patients with CR (89 pts) was 43 months. In LG and HG patients with CR the 10-year survival was 39% vs. 36%. In patients not obtaining CR, 9% of the LG patients were alive after follow-up of 10 years while none of the 75 patients in the HG group survived more than 37 months. The median duration of the first CR was 62 months in the whole material. In stage II–IV the remission duration was more difficult to maintain compared to stage I (Table 4). Table 4 also shows the shorter remission duration in patients older than 65 years. Of the patients who received no treatment, median survival of the 15 LG patients was 8 months while all 7 HG patients died within 2 months.

Systemic symptoms. Systemic (B) symptoms were registered in 33/162 (20%) of the LG and in 47/165 (28%) of the HG patients. In both groups the survival of patients with B symptoms was significantly worse compared to those without systemic (A) symptoms (Tables 2 and 3).

Bone marrow (BM) infiltration. Bone marrow infiltration was seen in 52/144 (36%) investigated LG patients, and in 15/136 (12%) of the HG patients. BM involvement indicated a disease with worse prognosis. In HG lymphoma, all 15 patients with positive BM were dead within 22 months (Tables 2 and 3).

Extranodal involvement. In LG lymphomas extranodal involvement of two or more sites (ENS) was seen in 19/162 patients (12%). In these patients the prognosis was significantly worse than in those with none or only one ENS. Two or more ENS were seen in 17/165 (10%) HG lymphoma patients which did not affect the prognosis significantly (Tables 2 and 3).

Bulky disease. From the records a tumor mass of 10 cm or more could be assessed in 61/337 patients (18%) which implied a worse prognosis in both LG and HG lymphomas (Tables 2 and 3).

Serum lactate dehydrogenase. LDH (normal value <7.5 ukat/l) was measured in 89% of the LG and in 86% of the HG patients at the time of diagnosis. Survival was significantly longer for patients with low LDH levels than for those with high levels in both LG and HG lymphomas as seen in Tables 2 and 3. The response to treatment was also correlated to the LDH level with higher response rate in patients with normal LDH levels (Table 5).

Multivariate analysis. LG lymphomas constitute a heterogenous entity with several smaller subgroups. Thus, separate analysis for each subgroup was not reasonable, nor was multivariate analysis on the whole group of LG lymphomas. The eight clinical factors, indicated in Table 3 were included in a multivariate analysis in HG lymphomas. Clinical stage, LDH, and bone marrow status

Table 4

Duration of first complete remission

	CR of all treated pts n	CR duration median months	5-year crude DFS All pts
Low grade			
Stage I	36/40 = 90%	84	55%
Stage II–IV	57/107 = 53%	52	30%
LG < 65 years	53/74 = 72%	74	49%
LG > 65 years	40/73 = 55%	55	24%
High grade			
Stage I	45/63 = 71%	55	35%
Stage II–IV	45/95 = 47%	35	16%
HG < 65 years	44/73 = 60%	71	31%
HG > 65 years	46/85	23	16%

Table 5

Treatment results according to LDH/s at diagnosis

LDH ukat/l	Stage I		Stage II–IV	
	n	%CR	n	%CR
Low grade				
<8	22	100	47	55
8–15	9	89	54	37
>16	–		8	25
High grade				
<8	31	87	19	58
8–15	21	57	29	48
>16	4	(50)	38	42

Table 6

Multivariate analysis of predictive variables in HG lymphoma

Covariate	Estimate	Std	95% confidence interval		T-stat
			Lower	Upper	
Bone marrow	−0.56	0.34	−1.22	0.09	−1.69
LDH	0.78	0.28	0.23	1.33	2.28
Stage	0.73	0.73	0.19	1.27	2.64

Table 7

Survival and treatment outcome related to number of risk factors in HG lymphoma

Risk factors No.	Patients n	Complete remission,%	Cause specific survival	
			Median months	10 years, %
0	31	87	n.r	58
1	44	57	38	42
2	54	54	8	16
3	14	7	5	0

n.r = not reached
Risk factors: Stage II–IV, bone marrow involvement, elevated LDH

fell out as independent, statistically significant prognostic predictors (Table 6). Consequently, age, systemic symptoms and bulky disease lost their prognostic significance in the multivariate model. In HG lymphomas, the significant prognostic factors were the basis for a prognostic score in four levels, depending on the presence of 0, 1, 2, or 3 of these factors (Table 7 and Fig. 4).

Causes of death

During the follow-up period, 117/162 LG (72%) and 136/165 HG (82%) patients deceased. Most of the patients died from lymphoma (or from combinations of lymphoma and other diseases); 71% of the LG and 81% of the HG patients. However, among patients with LC and diff Cb/Cc lymphoma many deaths were caused by other diseases, reflected by a considerable difference between crude and cause-specific survival (Table 1). In LG patients lymphoma as cause of death was seen during the whole follow-up period while most of the patients with HG lymphomas died from the disease within the first 3 years after diagnosis. Among patients who died from serious infection within the first year after diagnosis 10/12 patients were more than 65 years old (Table 8). Table 9 shows causes of death not associated with lymphoma, predominantly cardiac disease or other malignancy. Among patients who died from intercurrent diseases the majority were 65 years or more at diagnosis; 85% of LG cases and 67% of HG cases. Other malignancy as cause of death was seen in 17 cases; acute non-lymphatic leukemia (n = 2), carcinoma of the stomach (n = 3), colon (n = 2), pancreas (n = 3), lung (n = 3), prostate (n = 2), urinary bladder

Table 9

Causes of death other than lymphoma

	Time after lymphoma diagnosis		
	<1 year	1–3 yrs	3–8 yrs
Low grade			
Cardiac disease	6	1	6
Other circ. dis.	1		1
Cerebral vasc. dis.			3
High age, unspec. cause	1		
Colitis			1
Other malignancy	2	5	3
Total LG	10	6	14
High grade			
Cardiac disease	5	2	2
Cerebral vasc. dis.		3	1
High age, unspec. cause			
Respiratory insuff.			1
Other malignancy		1	6
Suicide	1		
Total HG	6	6	10

Table 8

Mortality in lymphoma patients

	Cause of death	Time for death after diagnosis			Total
		<1 years	1–3 years	3–8 years	
Low grade (n = 162)					
	Lymphoma	21	18	33	72
	Infection + lymphoma	1	4	6	11
	Intercurrent disease	10	6	14	30
Total LG		32	28	53	113
High grade (n = 165)					
	Lymphoma	62	25	6	93
	Infection + lymphoma	11	4	6	21
	Intercurrent disease	6	6	10	22
Total HG		79	35	22	136

(n = 1), liver (n = 1) and uterine cervix (n = 1) respectively. In LG lymphomas about 50% of patients who died from intercurrent disease suffered from residual lymphoma with minor symptoms while 90% of the HG patients were in CR.

Discussion

Many prognostic models for survival in NHL have been studied (28–32). The interpretation of the results is dependent on which factors are included in the model. Lately, considerable interest has been paid to the prognosis in relation to age at diagnosis (28, 31, 33–37). The significance of age as a prognostic factor must, however, be evaluated with due attention to the median age in the material. In the present study, where survival analysis was based on cause-specific survival, age was a significant prognostic variable in univariate analysis of HG lymphomas but not in the multivariate analysis. An explanation for this finding may be the fact that other factors, e.g. clinical stage and LDH, were correlated with age. Another interpretation may be that the disease is not, per se, worse in elderly people (in this case more than 65 years), in contrast to findings in Hodgkin's disease (38). One obvious implication in HG NHL is that the therapeutic strategy may be curative even in patients of high age with extensive disease. However, concomitant diseases in the elderly may be aggravated by NHL and its treatment impairing the survival (34).

In our material the CR rate was higher in patients below 65 years than in older patients in the LG lymphomas while the age did not significantly influence the initial response rate to therapy in HG patients. The time to relapse was, however, significantly shorter in the elderly HG patients. This may reflect the fact that the patients were not given optimal treatment, in many cases due to poor condition of the patient preventing adequate treatment.

Knowledge of the method for measuring survival is also of great importance. Crude survival may be biased by different age composition of the materials, since older patients will die from intercurrent diseases to a higher extent than younger patients. Thus, in this situation cause-specific or relative survival should be preferred. However, when using cause-specific survival, the assessment of the contribution of the lymphoma to the death may be a problem, especially in older patients with many concomitant diseases. In the present study, we considered death as caused by lymphoma if the patient's condition was considerably affected by lymphoma even if the immediate death cause was another acute disease, e.g. infection or circulatory complication. Most reports on LG lymphomas show a median survival of 4–7 years, in follicular lymphomas 7–10 years, which is comparable to our results. Newer treatment regimens have not yet prolonged survival markedly and frequent relapses cannot be avoided (6–9, 11, 12).

In stage I HG lymphomas more than 50% of the patients are cured by radiotherapy, sometimes in combination with chemotherapy (39, 40). The long-term results in our material showed relapses within three years in many patients. Incomplete staging procedures in older patients can explain these results (20). In generalized HG lymphomas long-term freedom from relapse has been reported in more than 30% of the patients in most materials after the institution of treatment with CHOP (41, 42). More intensive chemotherapy, 'third generation therapy', has improved the results in some centers, with more than 60% of the patients in complete remission more than 3 years after therapy (43). The median age in these materials was 50–55 years which probably reflects a high degree of selection of patients, especially in US materials. However, in some recent trials contradictory results have been achieved and treatment with newer models of chemotherapy have been reported to give similar response and survival rates as CHOP treatment (44).

In Europe the selection of patients seems to be lower, as the median age in most materials, including all stages, is around 60 years (6, 7, 10, 21). Survival in these studies is comparable to our results with 20–25% long-term survival in HG lymphomas.

In our series one-third of the patients were in stage I which is more than in other materials. This may reflect understaging especially in the older patients (21). The multivariate analysis of our material further confirms the prognostic risk of advanced stage and initial elevation of LDH (45, 46).

In a review of 294 NHL patients referred to our department 1959–1975 the median survival in LG lymphoma was 38 months and in HG patients 8 months (47). The results of treatment 1978–1982 showed improved survival (median survival for LG 55 months, for HG 13 months) although all the NHL patients from the cancer registry in the region were included in the present study.

NHL constitutes a heterogenous mixture of lymphatic disorders. In addition to separating the entity into LG and HG lymphomas, it is of importance to have knowledge of relevant prognostic factors even within these groups. The outcome highly depends on the distribution of these features. Since many therapy studies are based on highly selected materials, knowledge of the distribution of clinical factors associated with outcome is a prerequisite for the evaluation of results. Analysis of materials with a low grade of selection may therefore be of importance for providing such relevant background information concerning prognostic factors, as demonstrated by the present study.

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