Radiol Oncol 1994; 28: 26-33.

Prognosis of patients with non-Hodgkin's lymphoma (NHL), the influence of Kiel classification on survival

Berta Jereb[1], Janez Stare[2], Gabrijela Petrič-Grabnar[1], Janez Jančar[1]

[1] The Institute of Oncology, Ljubljana, [2] The Institute for Biomedical Information, Medical Faculty, University of Ljubljana, Slovenia

The effect of treatment modalities on the survival of patients with NHL and the prognostic impact of Rappaport's and Kiel classifications was analysed with the multivariate Cox model. Between 1978 and 1986, 482 adult patients received their first treatment for non Hodgkin's lymphoma at the Institute of Oncology in Ljubljana. We compared a group of 317 patients classified according to both Rappaport and Kiel classification (Group K) with a group of 165 patients classified according the Rappaport classification alone (Group R). Group K was divided into subgroups of high grade or low grade lymphomas, which again were analysed separately. The Kiel group patients had 1.5 times better chances for cure than the R- group. Stage was significant for the predicting of outcome. Chemotherapy and radiation significantly improve the survival in the high-grade (K) group but do not seem to have any bearing on the outcome in the low-grade (K) group of patients.

Key words. iymphoma, non-Hodkins; prognosis; Kiel classification

Introduction

In recent decades, considerable progress has been achieved in the management of patients with non Hodgkin's lymphoma (NHL). The biology of this disease with its multitude of biologic variations has become better understood.[1-10] New chemotherapeutic regimens have been introduced, enabling the treatment to be more "individualized"[11-18], i.e. adjusted to the aggressiveness of the disease.[19-26] As a result, the survival has improved, mainly in the group of patients with highly malignant lymphomas.[17] A number of new prognostic factors have been recognized. While the significance of some of these is undisputed (extent of the disease, primary site), there is still some diversity of opinions concerning others: age, sex, histology of the tumor, its cellular proliferation and DNA content.[27, 28]

In an earlier report, we analysed patients with NHL by means of a multivariate model and have found sex, age, stage and some treatment methods to be of significance for the

Correspondence to: Berta Jereb, Ph. D., M.D., Institute of Oncology, Ljubljana, Zaloška 2, Slovenia. Tel.: (+ 386 61) 323-063 (ext. 37-17). Fax: (+ 386 61) 1314 180.

UDC: 61.6-006.441-036

outcome. We could also show the survival to have significantly improved during the long period of time under investigation. In that analysis, however, neither the primary site nor the histological type of the tumor were included among the variables.[29] In this paper we report on the results of our analysis of a more recent group of patients, with these two variables included in the multivariate model. We aimed to find out whether Kiel classification serves us better in daily work with these patients. Therefore, no reclassification was attempted. We also tried to establish the effect of treatment methods on the survival in different groups of patients. The prognostic impact of Rappaport's[30] as well as Kiel classification[31] has been evaluated separately.

Material and methods

Between 1978 and 1986, 482 adult patients had their first treatment for NHL at the Institute of Oncology in Ljubljana. Patients younger than 15 years, those with chronic lymphocytic leukemia (CLL) and those admitted for recurrent disease were not included in the study. The extent of disease was assessed by clinical examination, biochemistry and blood status, chest X-ray, bone marrow aspiration of the iliac crest, and radionuclide scanning of the liver and spleen. After 1980, the investigations also included an abdominal sonogram, or CT and bone marrow biopsy. For histological classification the Rappaport system was used before 1980, and an updated Kiel classification after 1980. The treatment approaches used during these two periods were different: in the earlier period, one drug or a COP combination (Cyclophosphamide, Vincristine, Prednison) was, as a rule, complemented by radiation to the bulky lesions. After 1980, CHOP (including also Adriamycin) combination was most often used for high grade NHL. Patients with low grade histology and stages I and II were treated by radiation, whereas those with advanced stages were often only observed and treated only if symptomatic. Radiation therapy was applied to bulky lesions, and surgery for gastrointestinal tumors was more favoured after 1980 than before. Ann Arbor system was used for clinical staging throughout.[32]

Our aims were:

1. to find out whether the histological classification system did influence the survival and disease free survival presumably owing to better adjustment of treatment methods to the biological behaviour of disease;

2. to find out whether the independent variables significant for survival were the same in Group K (classified according to Kiel) and Group R (classified according to Rappaport);

3. to find out whether the variables significant for the survival of patients with high grade tumors were the same as for those with low grade tumors.

Statistical analysis

For each patient the following data were recorded for statistical analysis and used as independent variables:

– sex:
245 males, 237 females
– age at the time of diagnosis:
between 16 and 89 years
mean 55.6
median 58.0
– stage:

stage I –	117
stage II –	147
stage III –	76
stage IV –	142

429 were classified as A and 53 had B symptoms.
– primary site:

nodal	250
extranodal	217
unknown	15

– with subgroups:

peripheral nodes	185

mediastinum	26
abdominal	32
head and neck	75
skin	16
bone	10
gastrointestinal tract	88
other extranodal (breast 11, testis 6, spleen 7, soft tissue 6, central spinal 3, and ovary, kidney, uterus, parotis one each)	37
unknown	13
– histology: Rappaport's classification only (R-group):	165
nodular	20
diffuse	95
other	50
Kiel classification (K-group):	317
low grade	163
high grade	124
other	30

There were 174 cases classified according to both systems, and 31 could not be histologically classified.

– methods of treatment:
chemotherapy, radiotherapy and surgery.

The methods of first treatment are given in Table 1.

– duration of chemotherapy:
< 6 months
6 months – 1 year
>1 year

The data were statistically evaluated by survival analysis methods, the time from diagnosis until death being the outcome of interest. The survival curves were calculated according to Kaplan-Meier method.[33]

To reduce the number of potential prognostic variables to a manageable level, we first did univariate analysis, subdividing the data by prognostic variables and comparing the survival curves by log-rank test. The variables which proved to be significantly associated with survival, as well as some other variables considered important by clinicians, were then included in Cox proportional hazards model[34] which was used for the following two purposes:

1) to follow other prognostic variables when trying to confirm the connection between survival and histological classification,

Table 1. Treatment, combination of the 3 methods.

Chemotherapy/ /RT	Number of patients percent of patients none	mono	MOPP	COP	CHOP	other	Total
no RT	38	20	0	36	40	21	155
	27	72		37	26	36	32
< 2000 cGy	7	4	0	17	30	11	69
	5	14		18	19	19	14
≥ 2000 cGy	97	4	4	43	84	26	258
	68	14	100	45	55	45	54
Total	142	28	4	96	154	58	482
Surgery/ChT							
none	113	24	3	80	121	44	385
	80	86	75	83	79	76	80
surgery	29	4	1	16	33	14	97
	20	14	25	17	21	24	20
Total	142	28	4	96	154	58	482

Surgery/ /RT	Number of patients percent of patients none	surgery	Total
	136	19	155
	35	20	32
	50	19	69
	13	20	14
	199	59	258
	52	60	54
	385	97	482

Table 2. Survival according to histological calssification.

	STATUS							
Histological classification	Alive no sympt.	Alive with disease	Died of NHL	Died of other causes	Died of treatment	Died of unknown causes	Lost to follow-	Total
Kiel	127	23	112	13	5	28	9	317 66 %
No Kiel	48	2	75	12	3	21	4	165 34 %
Total	175 36 %	25 5 %	187 39 %	25 5 %	8 2 %	49 10 %	13 3 %	482 100 %

2) to identify important prognostic variables in some subgroups. We did this in order to see if the importance of prognostic variables varied between the subgroups.

Results

By the end of the study in December 1990, 200 patients were alive, 269 dead and 13 were lost to follow up (Table 2).

The patients who had their tumors classified according to Kiel system (treated more recently) had significantly better chances for survival than those who had their tumors classified according to Rappaport system (Figure 1). On the whole, patients with extranodal primary sites did not fare better than those with primary nodal disease (Figure 2). However, patients with extranodal primary tumors of the bone, skin, head and neck, and gastrointestinal organs did significantly better than those with some rare "other extranodal" tumors and those with the primary site in the lymph nodes. The patients with primary abdominal lymph node involvement had the worst prognosis while the prognosis of those with primary bone NHL was the best (Figure 3). Neither age nor sex appeared to be prognostically significant factors.

The results of the multivariate analysis are presented in Tables 3- 6; the hazard ratio is the ratio between the hazard of patients in a specific group and the hazard of patients in a reference group; it is of statistical significance according to the log-rang test. The multivariate analysis confirmed the result of the univariate analysis, showing a 1.5 higher hazard ratio (risk value) for Group R than for Group K.

The same prognostic variables were than used in the multivariate analysis for Groups K and R separately. Table 3 shows the values for Group K. The stage of disease, which emerged as a highly significant factor, was followed by the mediastinum as the primary nodal site, and

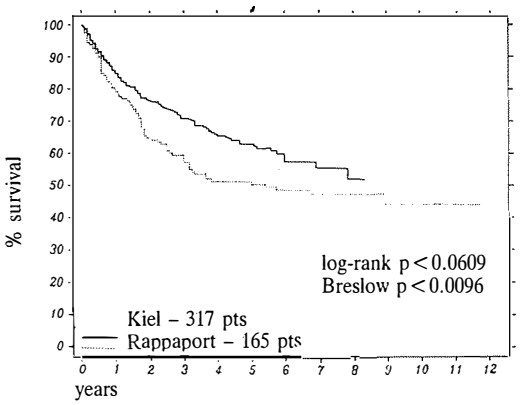

Figure 1. Survival by histologic classification system.

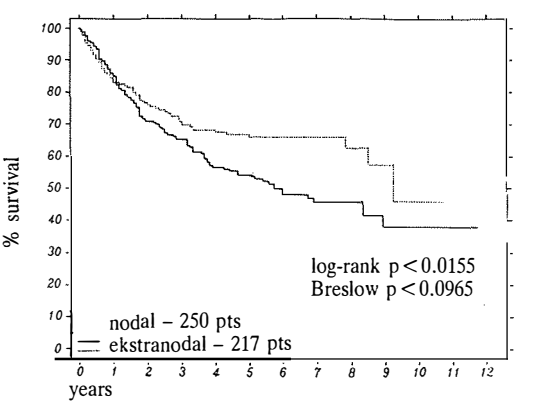

Figure 2. Survival by primary site.

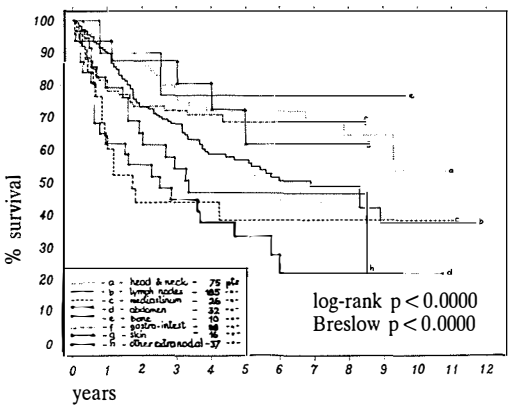

Figure 3. Survival by primary site.

by sex and histological type, respectively. The influence of chemotherapy did not emerge as significant.

The results for Group R are similar, however, radiotherapy appeared among the significant factors while histology did not (Table 4).

As to the survival of Group K patients with low-grade NHL, stage was the only variable which emerged as significant while for Group K patients with high grade NHL the results are quite different, the main difference being the impact of treatment on prognosis, which was significant in patients with high grade tumors but not in those with low grade tumors (Table 5, 6).

Table 3. Results of multivariate analysis for K-group patients.

Predictors	b	hazard ratio	p
low grade	+	1.00	
high grade	0.1985	1.65	0.0472
other	0.6889	1.99	0.0228
sex			
female	+	1.00	
male	0.4450	1.56	0.0238
stage			
A	+	1.00	
B	0.5641	1.76	0.0402
chemotherapy			
yes	+	1.00	
no	0.4785	1.61	0.0977
stage			
I	+	1.00	
II	1.1497	3.16	0.0028
III	1.7490	5.75	0.0000
IV	1.7630	5.83	0.0000
primary site			
hand & neck	+	1.00	
peripheral lymph node	0.2486	1.28	
mediastinum	1.0601	2.89	0.0182
abdomen	0.3884	1.47	
bone	-0.3253	0.72	
gastro	0.3044	1.36	
skin	-0.1448	0.87	
other	0.4467	1.56	

+ = reference group

Table 4. Results of multivariate analysis for R-group patients.

Predictors	b	hazard ration	p
stage			
A	+	1.00	
B	0.9767	2.66	0.0109
radiation			
yes	+	1.00	
no	0.6798	1.97	0.0137
stage			
I	+	1.00	
II	-0.0128	0.96	
III	1.1267	3.09	0.0135
IV	0.3602	1.43	
primary site			
head & neck	+	1.00	
peripheral lymph nodes	0.1124	1.12	
mediastinum	0.8817	2.41	0.1482
abdomen	1.7929	6.01	0.0002
bone	-0.6023	0.55	
gastro	0.4293	1.53	
skin	0.5259	1.69	
other	1.2896	3.63	0.0151

+ = reference group

Discussion

This study confirms our previous report on better results in patients treated more recently. This time, however, the primary site of the tumor and its histological type according to Kiel and Rappaport classifications have been included among the investigated parameters.

Table 5. Results of multivariate analysis for patients with low-grade tumors.

Predictors	b	hazard ratio	p
stage			
I	+	1.00	
II	1.2940	3.65	0.0252
III	1.7150	5.56	0.0252
IV	1.8709	6.49	0.0005

+ = reference group

Table 6. Results of multivariate analysis for patients with high-grade tumors.

Predictors	b		hazard ratio	p
sex				
female	+		1.00	
male		0.8107	2.25	0.0142
chemotherapy				
yes	+		1.00	
no		2.0786	8.00	0.0013
radiation				
no	+		1.00	
yes		0.7647	2.15	0.0457
surgery				
yes	+		1.00	
no		1.2860	3.62	
stage				
I	+		1.00	
II		2.0496	7.77	0.0039
III		2.4621	11.73	0.0008
IV		2.2096	24.77	0.0000
primary site				
head & neck	+		1.00	
peripheral lymph nodes		0.5562	1.74	
mediastinum		1.7580	5.80	0.0127
abdomen		0.0392	1.04	
bone		-0.5180	0.60	
gastro		0.9686	2.63	
skin		-0.0268	0.97	
other		0.4575	1.58	

+ = reference group

The finding that Kiel classification system had favourable impact on the prognosis (the patients of Group K had a 1.5 better chance for survival than those in Group R) suggest that the use of Kiel system enabled better identification of low-risk and high-risk patients, resulting in better adjustment of treatment to the patient and his condition than in Group R (Table 3, 4). However, regarding other factors, the results in this series were not in full agreement with those in the previous one. We could not confirm age or sex as significant for prognosis in the univariate analysis of the whole series of 482 patients nor did the group of patients with all extranodal primary sites have better survival than those with nodal ones. It is possible that the rather high proportion of patients who died of other causes made the evaluation of survival curves in the univariate analysis less accurate, thus rendering the differences less significant. In the univariate analysis, the following factors were found to be prognostically significant: stage of the disease, primary site and the system of histological classification. They were also confirmed by multivariate analysis of the whole group. On separate analysis of Groups K and R, stage and primary site remained significant in both, stressing their independent influence on the prognosis. There have been reports on a correlation of histological subgroups according to Rappaport system, but in our Group R histology did not emerge as a significant predictor of the outcome. In Group K, however, it did, thus confirming the reviews. The finding that males had a worse outcome in Group K but not in Group R is hard to explain.

Chemotherapy as a predictor had only limited influence in Group K, while radiation in Group R was a stronger predictor of the outcome. Radiation was also used more often in the earlier group of patients and was to a lesser extent directed by different histological grading. The results of the separate analysis of the low-risk and the high-grade Group K patients are striking. Only stage I patients in the early stages, treated by radiation were curable, while the treatment had little or no effect on the course of the disease in more advanced stages.

In the high-risk group, stage was a highly significant predictor, however, chemotherapy as well as radiation had a significant impact on the outcome of the disease. It is evident that for the high-risk patients in Group K an effective treatment has been introduced while for the patients with advanced low risk tumors the question how to treat and whether to treat at all remains open.

We are well aware of the fact that treatment has changed over years, and full justification of our results could only be obtained by reclassification of the whole material. This being unfeasible, we nevertheless believe that the change of classification method had an influence on survival. We tried to check the possible effect of "treatment change" by including the year of diagnosis as a confounding variable. The "histological classification" variable remained significant in the multivariate regression model. We should also stress that all the patients diagnosed prior to the year 1978 were

excluded, so that only patients diagnosed between the years 1978 and 1986 were used in the analysis.

Conclusions

There are some conclusions that can be drawn from the analysis of the presented group of patients:

1. The group of patients that was classified according Kiel system and had their treatment adjusted to the histological grade had a 1.5 better chances for cure than the patients with tumors classified according Rappaport system.

2. Nodal abdominal primary site was associated with poor prognosis, while patients with gastrointestinal primary tumors did rather well.

3. Stage is a significant factor for predicting the outcome.

4. Chemotherapy and radiation are significantly improving the survival in the high-risk (K) group but do not seem to have any bearing on the outcome in the low risk (K) group of patients.

Acknowledgement

We are deeply indebted to Drs M. Vovk and M. Jenko for cooperation in the analysis of patients the great majority of whom have been under their care. The work has been supported by a grant from the Ministry for Science and Technology of the Republic Slovenia.

References

1. Bloomfield CD, Goldman A, Dick F, Brunning RD, Kennedy BJ. Multivariate analysis of prognostic factors in the non-Hodgkin's malignant lymphomas. *Cancer* 1974; **33:** 870-9.

2. Leonard RCF, Cuzick J, MacLennan ICM et al. Prognostic factors in non-Hodgkin's lymphoma: the importance of symptomatic stage as an adjunct to the Kiel histopathological classification. *Br J Cancer* 1983; **47:** 91-102.

3. D'Amore F, Christensen BE, Brincker H et al. Clinicopathological features and prognostic factors in extranodal non-Hodgkin lymphomas. *Eur J Cancer Clin Oncol* 1991; **27:** 1201-8.

4. Vose JM, Armitage JO, Weisenburger DD et al. The importance of age in survival of patients treated with chemotherapy for aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 1988; **6:** 1838-44.

5. Nabholtz J-M, Friedman S, Bastien H, Cuisenier J, Horiot J-C, Guerrin J. A clinico-pathological and prognostic analysis of non- Hodgkin lymphoma: a study of 203 patients. *Acta Oncol* 1988; **27:** 489-95.

6. De Wolf-Peeters C, Caillou B, Diebold J et al. Reproductibility and prognostic value of different non-Hodgkin's lymphoma classifications: study based on the clinicopathologic relations found in the EORTC trial (20751). *Eur J Cancer Clin Oncol* 1985; **21:** 579-84.

7. Heinz R, Fortelny A, Schneider B et al. Long term follow-up of 1520 NHL patients classified according to the Kiel classification - experiences of a single institution (meeting abstract). Fourth international conference on malignant lymphoma, Lugano, 1990:59.

8. Burgers VMJ, Somers R, Quasim MM, Glabbekke van M. Report on the EORTC lymphoma trial 20751. *Int J Radiat Oncol Biol Phys* 1983; **9:** 11-5.

9. Fyles A, Brada M, Ashley S, Horwich A. Localized low grade non-Hodgkin's lymphoma (NHL) (meeting abstract). 7th Annual meeting of the European society for therapeutic radiology and oncology. Den Haag, 1988.

10. Joensuu H, Klemi PJ, Soderstrom K-O, Jalkanen S. Comparison of S-phase fraction, working formulation, and Kiel classification in non-Hodgkin's lymphoma. *Cancer* 1991; **68:** 1564-71.

11. Federico M, Gobbi PG, Barbieri F, Silingardi V. Relationship between prognostic factors and therapy in high-grade non-Hodgkin's lymphomas over two decades. *Haematologica* 1989; **74:** 511-9.

12. McMaster M, Greer J, Greco A et al. Analysis of prognostic factors in patients (pts) treated with high dose , brief duration therapy for poor prognosis non-Hodgkin's lymphoma (NHL) (meeting abstract). *Proc Annu Meet Am Soc Clin Oncol 1989*; **8:** A1064.

13. Armitage JO, Cheson BD. Interpretation of clinical trials in diffuse large-cell lymphoma. *J Clin Oncol* 1988; **6:** 1335-47.

14. Epelbaum R, Faraggi D, Ben-Arie Y et al. Survival of diffuse large cell lymphoma: a multivariate analysis including dose intensity variables. *Cancer* 1990; **66:** 1124-9.

15. Stuart NS, Blackledge GRP, Child JA et al. A new approach to the treatment of advanced high-grade non-Hodgkin's lymphoma - intensive two-phase chemotherapy. *Cancer Chemother Pharmacol* 1988; **22:** 141-6.

16. Shimayama M, Ota K, Kikuchi M et al. Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M. *J Clin Oncol* 1988; **5:** 128- 41.

17. Inwards DJ, Armitage JO. Modern chemotherapeutic regimes in the management of aggressive non-Hodgkin lymphoma: can they be improved. *Eur J Cancer* 1991; **27:** 510-3.

18. Liang R, Todd D, Chan TK. HOAP-Bleo as salvage therapy for diffuse aggressive non-Hodgkin's lymphoma. *Cancer Chemother Pharmacol* 1988; **22:** 169-71.

19. Aviles A, Diaz-Maqueo JC, Sanchez E, Cortes HD, Ayala JR. Long-term results in patients with low-grade nodular non- Hodgkin's lymphoma. *Acta Oncol* 1991; **30:** 329-33.

20. Sutcliffe SB, Gospodarowicz MK, Bush RS et al. Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother Oncol* 1985; **4:** 211-23.

21. Heinz R. Long-term follow-up of CHOP-treated non-Hodgkin lymphoma of high-grade malignancy. *Blut* 1990; **60:** 68-75.

22. Hagberg H, Pettersson U, Glimelius B, Sundstrom C. Prognostic factors in non-Hodgkin lymphoma stage I treated with radiotherapy. *Acta Oncol* 1989; **28:** 45-50.

23. Brittinger G, Bartels H, Fulle HH et al. Grundlagen und bisherige Ergebnisse der perspektiven Studie der Kieler Lymphom gruppe uber Non-Hodgkin-Lymphome. In: Stacher A, Hocker P eds. Lymphknotentumoren. Munchen: Urban und Schwarzenberg, 1979: 1931- 200.

24. Scarantino CW, Greven KM, Buss DH. Single high dose-large field irradiation in drug resistant non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 1988; **14:** 1001-5.

25. Mackintosh JF, Cowan RA, Jones M, Harris M, Deakin DP, Crowther D. Prognostic factors in stage I and II high and intermediate grade non-Hodgkin's lymphoma. *Eur J Cancer Clin Oncol* 1988; **24:** 1617-22.

26. Cowan RA, Jones M, Harris M et al. Prognostic factors in high and intermediate grade non-Hodgkin's lymphoma. *Br J Cancer* 1989; **59:** 276-82.

27. Cowan RA, Harris M, Jones M, Crowther D. DNA content in high and intermediate grade non-Hodgkin's lymphoma - prognostic significance and clinicopathological correlations. *Br J Cancer* 1989; **60:** 904-10.