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NON-HODGKIN LYMPHOMA — A REVIEW OF 590 PATIENTS

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Abstract — Five hundred ninety adult patients, 324 males and 266 females with non-Hodgkin lymphoma (NHL) who had their first treatment at the Oncological Institute in Ljubljana were analysed retrospectively; 189 patients were treated between 1968—1974, 190 between 1975—1979 and 217 between 1980—1983. All were followed 3—18 years. The statistical methods used were the Kaplan-Meier survival curves and Cox' models.
The survival improved significantly during the time under analysis. A patient diagnosed in 1983 had 2.6 (1.4—4.7) times better chance to survive the NHL than a patient with NHL diagnosed in 1968. Factor levels associated with significantly better survival were: female sex, age 36—65, stage I, extranodal primary site, radiation therapy in doses more than 20 Gy and surgery. »COP« or »CHOP« combination chemotherapy improved the survival only in patients in lower stages of the disease.

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At the 50-th anniversary of the Institute of Oncology, Ljubljana dedicated to dr. Tatjana Šumi-Križnik, originator of the »Lymphoma section« and its leader for almost 2-decades.

Introduction — The term non-Hodgkin lymphoma (NHL) includes great variation of the morphology as well as biology of the disease. Age, stage and histology have long been recognized as factors important for the prognosis of the NHL (11, 25, 33, 38, 40). Different staging systems and several histological classifications have been proposed for the prediction of the outcome of the disease (11, 12). With the development of chemotherapy and with availability of many new agents the possibility of more tailored treatment has increased. Choosing aggressive treatment for the group of patients with highly malignant disseminated tumors appears to be easier than choosing the treatment for less malignant localized tumors or for tumors of the intermediate group (24, 34). With multidrug chemotherapy the cure rates of patients with disseminated NHL of highly malignant diffuse histiocytic type have markedly improved (2, 16, 17, 19, 28, 30) while the cure rates of patients with disseminated NHL of low malignant histological types have not (7, 15, 24). Further, the problem of reliability and reproducibility of the histological classification remains, as well as the problem of tumor transformation from a more benign to a malignant histological type of tumor (1, 2, 12).

The progress made in the management of NHL during the last decade is mainly in better understanding of the disease, in the improvement of the diagnostic possibilities and in a wider choice of chemotherapeutic agents (10, 11, 18, 20, 21, 23, 42, 43).

The aim of this study was to establish the possible improvement of the survival and of the disease-free survival of patients treated at the Oncological Institute in Ljubljana, Slovenia, during a period of time when diagnostic procedures and treatment have undergone changes. We have also tried to find out what changes could have contributed most to the possible improvement of results.

Material — Between 1968 and 1983, 804 adult patients (more than 15 years old) with NHL were registered at the Cancer Registry of Slovenia;

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755 were admitted for their first treatment and 49 patients for recurrence. The medical documentation was lacking or deficient in 61 cases and 16 patients refused treatment. After the review of histological slides the diagnosis was changed in 55 patients, 16 had only cytological diagnosis and 6 were lost to follow up earlier than 3 years from diagnosis. Patients who had clinical diagnosis of chronic lymphocytic leukemia were not included in this study. There were thus 590 adult patients, 324 males and 266 females first treated at the Institute of Oncology in Ljubljana for histologically verified NHL and with a follow up of at least 3 years, who were suitable for statistical analysis. The study was completed in December 1986. All patients alive at the end of the study had their last check-up in December 1986.

The management has changed in several aspects during this period of time therefore the patients were divided into three groups according to the three periods of time.

During 1968—1974, the first period (183 patients), the majority (156) with NHL were classified as lymphosarcoma or reticulosarcoma. For determination of the extent of disease clinical examination, biochemistry and blood status, bone marrow aspiration of the sternum, isotope scanning of the skeleton, liver and spleen were performed. Chemotherapy was given only rarely. Radiation was the main treatment modality.

During 1975—1979, the 2nd period of time (190 patients), the majority (102) with NHL was classified according to the Rappaport classification. The diagnostic procedures remained essentially the same. Chemotherapy was regularly used, either one drug or a »COP« combination. Radiation to bulky lesions was added as a rule.

During 1980—1983, the 3rd period of time (217 patients), the majority (130) with NHL was classified either according to the Luke-Collins classification or a modified Kiel classification. CT scanning and ultrasonography of the abdominal organs were introduced for clinical staging. Aggressive multidrug chemotherapy was introduced. The »CHOP« combination was most often used for patients clinically or histologically recognized as the poor risk group, while on the other hand the use of chemotherapy for low risk patients has become more cautious. Radiation therapy was given to bulky lesions and surgery for gastrointestinal tumors was more favoured during this period of time than earlier.

The Ann-Arbor system was used for clinical staging during the whole period of time under investigation.

This analysis has the following two objectives:

1) to find out the main differences in survival and disease-free survival of NHL due to different levels of factors: sex, age, histology, radiotherapy and surgery, stage, primary site and methods of treatment;

2) to establish possible progress in survival and disease-free survival which could be attributed to changes in management during the different periods of time under observation.

Statistical analysis

1. Description of the data

For each patient the following data were recorded for the statistical analysis:

— sex

— age at the time of the diagnosis. For the purpose of statistical analysis the patients were divided into 3 age groups: 76 patients were 16—35 years old, 304 were between 36 and 65 years, and 210 patients were more than 65 years old.

— stage:

I A	— 134 patients
II A + B	— 172 + 6 patients
III A + B	— 88 + 14 patients
IV A + B	— 136 + 30 patients
not classified	10 patients

— primary site (localization): nodal or extranodal

with subgroups:	peripheral nodes	261
	mediastinum	34
	abdomen	34
	head and neck	124
	skin	22
	bone	16
	gastrointestinal tract	60
	other extranodal	29
	unknown	10

— histology: lymphosarcoma or reticulosarcoma (194 patients), diffuse or nodular (160), low grade or high grade (143), and the remaining 93 non-classified. Ninety-nine patients were classified according to both the Rappaport's and Kiel classifications;

— methods of first treatment: chemotherapy, radiotherapy and surgery. The distribution of patients according to the combinations of first treatments is given in Table 1.

For statistical analysis, in some cases initially recorded categories had to be merged due to small number of patients. Ten patients with unknown stage of tumor were included in stage IV group. The cathegory »other« for chemotherapy consists of 24 patients with monochemotherapy, 7 with MOPP, 40 initially declared as »others« and 1 with unknown type of chemotherapy.

Dose of radiation	Chemotherapy				Total	Surgery		Total
	none	COP	CHOP	other CHT		none	surgery	
none	29 12%	57 33%	27 25%	18 25%	131 22%	104 21%	27 28%	131 22%
<2000 cGy	16 7%	28 16%	18 16%	16 22%	78 13%	68 14%	10 11%	78 13%
≥2000 cGy	188 81%	90 51%	65 59%	38 53%	381 65%	323 65%	58 61%	381 65%
TOTAL	233	175	110	72	590	495	95	590

Surgery	Chemotherapy				Total
	none	COP	CHOP	other CHT	
none	178 76%	160 91%	93 85%	64 89%	495 84%
surgery	55 24%	15 9%	17 15%	8 11%	95 16%
TOTAL	233	175	110	72	590

Table 1 — Number and column percentage of patients according to combinations of two treatments.

When studying the dose of radiation, 1 patient with unknown dose of radiation was included with the patients having the highest dose.

2. Definition of the failure time and censoring — The failure time and censoring of patients were defined in three different ways: analysis A and B were devoted to the study of survival, analysis C to the study of disease-free survival.

— For analysis A, the starting point of observation was the date of diagnosis, the end-point, the date of last check-up or death. 50% of the patients who died of cancer (283) or complications due to cancer treatment (11) were taken as events, the rest 50% were censored (Table 2).

— For analysis B, death of any cause is considered as a failure. 69% of patients who died of cancer (283), complications due to cancer treatment (11), other diseases (50) or of unknown cause (63) were taken as events, the rest 31% were censored.

— Analyis C is devoted to the tumor recurrence. 66% of patients in the study with recurrence (388) were included as failures and were followed from the day of diagnosis up to their recurrence date, if it was known. If the date was not known, day one was taken as the failure time. Patients without recurrence (34%), were censored (202). Their failure time was from the date of diagnosis to the date of last check-up or death.

3. Statistical methodology — To achieve the objectives specified in the previos section the following statistical methodology was applied to analysis A, B and C.

a. Survivor curves (27) based on Kaplan-Meier estimates of survival function were plotted for each factor under study. Survivor curves are good descriptive tools to summarize differences between survival function estimators for subgroups of patients. For example, when analysing sex in analysis A, Figure 2 reflects better survival for female patients comparing to male patients. The last event i.e. death of cancer or treatment for females happened nearly 10 years after the diagnosis, for males 12 years after diagnosis. Censoring times are presented in the subplot and range up to 18.5 years, where 19 years is the maximal follow-up time.

When studying a particular factor it is of interest to determine if the samples of patients with different factor levels could have arisen from populations with identical survival functions. The most commonly used statistic to answer this question is the logrank chi-square statistic. Its value and its significance level for each particular factor in analysis A, B and C is presented in tables 3, 4 and 5, respectively. For example, for sex in analysis A, the value of logrank chi-square statistic is 9.1 ($p < 0.003$). Thus, the survival function for males is significantly different from the survival function for females.

The effects of independent variates on the failure time were analysed by the Cox's proportional hazard regression models (9,27). The proportional hazard model is appropriate for censored data if the hazards are proportional throughout the study period. To find out if this assumption was fulfilled, for each particular factor the plot of ln(-)n F(t)) against ln(t) was obtained; F(t) is the Kaplan-Meier estimator of the survival function. These plots suggested that proportional hazards model is an acceptable assumption for each factor under study.

The results of Cox's regression analysis of the effects of independent variables on the survival time of NHL in analysis A, B and C are presented in tables 3, 4 and 5, respectively. Maximising the partial likelihood function gives the beta-estimates (β), their variances and the deviance for a particular model. In these tables β coefficients, their 95 % confidence intervals, their exponential transformations and the deviance of the model is presented. The exponential transformation of beta-estimates is referred to as the hazard ratio i.e. the ratio between the hazard of patients in a specific group and the hazard of patients in the reference group. For example: the hazard ratio for females in analysis A is 0.70 which means that hazard of females is 0.70 of the hazard of males. The beta coefficient $\beta = -0.36$ with confidence interval (-0.59, -0.12) is significantly different from 0, according to the logrank test ($p = 0.003$).

To find out a possible progress in survival and disease-free survival in the period 1968—1983, year of diagnosis is considered as the main variable of interest. It was analysed as a continous variate. For each analysis A, B, C three different Cox's models were constructed:

— model 1: univariate model for year of diagnosis;

— model 2: year of diagnosis adjusted for covariates: sex, age, histological diagnosis, stage, primary site, chemotherapy, radiation, surgery;

— model 3: covariates only.

For analysis A, the results are presented in table 6, for example:

— the change in deviance for model 1 and model 2 is 113.1 on 16 degrees of freedom which is highly significant. This means that β coefficient for year of diagnosis in model 2 (-0.063) is significantly different from β coefficient for year of diagnosis in model 1 (-0.071). Hence covariates have a significant effect on the β coefficient.

— model 3 is included to examine if β coefficient for the year of diagnosis in model 2 (-0.063) is significantly different from 0. The change in deviance for model 2 and model 3 is 9.48 on 1 degree of freedom which is significant ($p = 0.01$), thus β coefficient in model 2 is significantly different from 0.

b. Software support — Survivor curves presented in this paper are based on Kaplan-Meier estimates of survival function and were obtained using LIFETEST procedure in SAS (35). Results of Cox's regression were obtained by COXREGR procedure in SUGI Supplemental Library (40).

Results — At the end of the study (December 1986) 407 (69 %) patients were dead — 294 (50 %) of NHL or of treatment; 177 (30 %) were alive, of these 150 (25 %) were without signs of NHL, and 6 (1 %) patients were to lost follow up 3—10 years after treatment. The majority of patients who are alive without disease have been without recurrence from the first treatment. The majority of patients with recurrence died of cancer. About a half of the patients who died of an unknown cause or of other causes had recurrence of NHL (Table 2).

Patients treated in the 3rd period of time did better than those treated earlier (Fig. 1).

The survival in women is better than that in men (Fig. 2), their median survival time is 8 years, while in men it is 3—4 years.

Recurrence	STATUS							Total
	Alive no sympt.	Alive + sympt.	Died of NHL	Died of other causes	Died of treatment	Died of unknown cause	Lost to follow-up	
No recurrence	125	2	8	27	5	31	4	202 34 %
Recurrence	25	25	275	23	6	32	2	388 66 %
TOTAL	150 25 %	27 5 %	283 48 %	50 8 %	11 2 %	63 11 %	6 1 %	590 100 %

Table 2 — Number and percentages for patients by status at the end of the study and their recurrence.

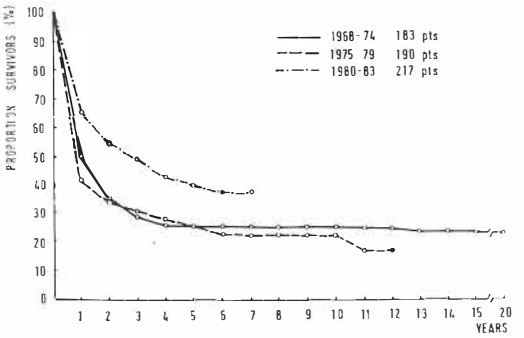

Fig. 1 — Survival by periods of time

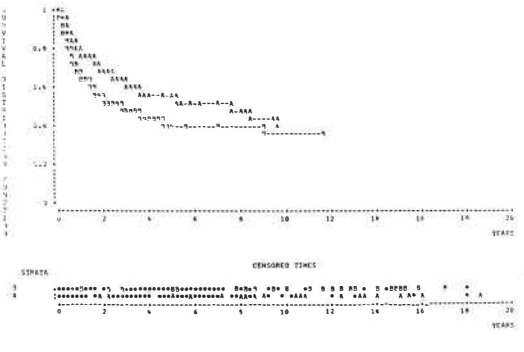

Fig. 2 — Survival by sex

Age did influence the survival of patients with NHL; those who were between 36—65 years old had the highest survival. There was no significant difference in the survival of the younger and older patients (Fig. 3). Patients with extranodal primary sites did better than those with nodal primary sites (Fig. 4). Patients with stage I NHL have the highest survival as compared to other stages, and the hazard ratio increases with

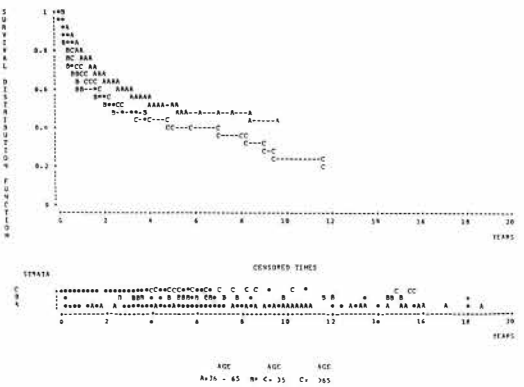

Fig. 3 — Survival by age

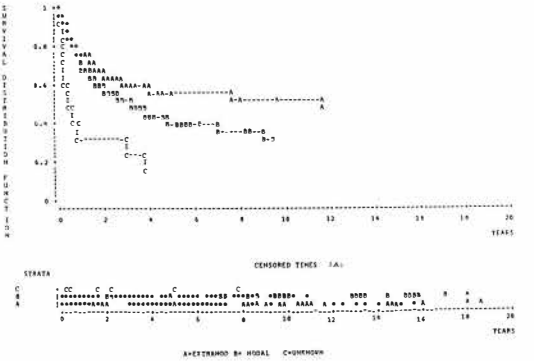

Fig. 4 — Survival by primary site

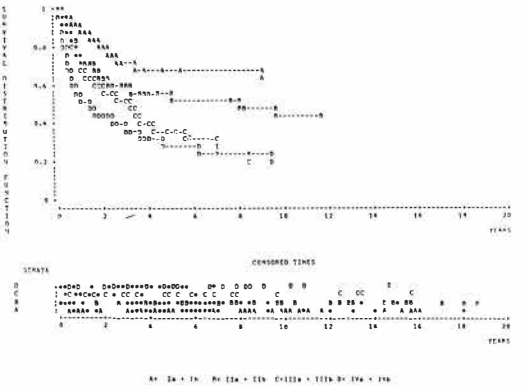

Fig. 5 — Survival by stage

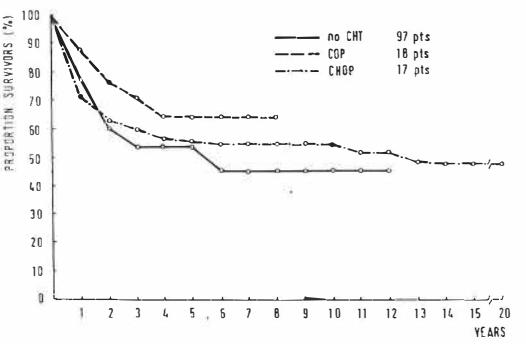

Fig. 6 — Survival by chemotherapy — stage Ia + Ib

higher stages (Fig. 5). The survival of patients who received either the COP or the CHOP combination of chemotherapy was not better from the survival of patients who had no chemotherapy, while the group of patients with »other« chemotherapy did significantly worse (Fig. 6). When the effect of chemotherapy adjusted for radiotherapy was studied, the results showed

	No. of pts.				hazard	logrank		
	Total	Dead of NHL or treatment	β	95% CI for β	ratio	χ^2	p value	deviance
SEX								
male*	324	178 (55%)			1.00			
female	266	116 (44%)	−0.36	(−0.59, −0.12)	0.70	9.1	0.003	3449.6
AGE AT DIAGNOSIS (in years)								
≤35*	76	40 (53%)			1.00			
36—65	304	147 (48%)	−0.21	(−0.56, 0.14)	0.81			
>65	210	107 (51%)	0.14	(−0.23, 0.51)	1.15	7.29	0.026	3451.6
LOCALISATION OF TUMOR								
nodal*	329	177 (54%)			1.00			
extran	240	102 (42%)	−0.38	(−0.61, −0.15)	0.68			
unknown	21	15 (71%)	0.91	(0.05, 1.77)	2.48	26.6	0.000	3437.3
STAGE OF TUMOR								
I*	134	42 (31%)			1.00			
II	178	81 (45%)	0.54	(0.17, 0.91)	1.71			
III	102	57 (56%)	0.96	(0.56, 1.36)	2.62			
IV	176	114 (65%)	1.29	(0.93, 1.65)	2.48			
CHEMOTHERAPY								
none*	233	104 (45%)			1.00			
COP	175	85 (49%)	0.23	(−0.06, 0.52)	1.26			
CHOP	110	55 (50%)	0.15	(−0.18, 0.48)	1.16			
other	72	50 (69%)	0.75	(0.07, 1.09)	2.11	19.0	0.000	3441.6
RADIOTHERAPY (dose in cGy)								
0*	131	75 (57%)			1.00			
<2000	78	46 (59%)	0.16	−0.20, 0.52)	1.17			
≥2000	381	173 (45%)	−0.54	(−0.81, −0.27)	0.68	4.94	0.026	3458.7
SURGERY								
no*	495	256 (52%)			1.00			
yes	95	38 (40%)	−0.38	(−0.72, −0.04)	0.68	4.94	0.026	3458.7

* Reference group

Table 3 — Relationship between independent variates and disease-free survival of patients with non-Hodgkin lymphoma — Analysis A.

decreased hazard ratio for those patients who had radiotherapy as well.

Among those patients who had irradiation, those who received < 2000 cGy did significantly better. The addition of chemotherapy did not improve the survival in either group significantly. Patients who had undergone surgery did better than those who had not (Table 3).

The results of analysis B show that the effect of different variables on the survival is mainly the same as in analysis A, while the survival on the whole is lower as compared with analysis A. Differences are detected when studying age: hazard of the middle group is not significantly different from the hazard of the youngest group. The highest hazard has the eldest group. This is probably due to the fact that death of any cause is considered as a failure in analysis B (Table 4).

The influence of the different variables under study on the disease-free survival are not much different from the influence of the same variables on the survival (analysis A and B). The percent of disease free survival is nearly the same as the percent of survivals in analysis B, only the oldest age group is an exception; this group of patients probably does not live long enough to experience the recurrence of NHL (Table 4 and 5).

Discussion — Reports on the influence of some factors on the prognosis in patients with NHL are controversial (4, 8, 23). The reasons for this might be among others:

1. The strong relationship between some factors such as histological type of NHL and age (13, 34).

	No. of pts.							
	Total	Dead of any cause	β	95% CI for β	hazard ratio	logrank χ^2	p value	deviance
SEX								
male*	324	233 (72%)			1.00			
female	266	174 (65%)	−0.23	(−0.42, −0.03)	0.80	5.1	0.024	4714.7
AGE AT DIAGNOSIS (in years)								
⩽35	76	43 (57%)			1.00			
36—65	304	190 (63%)	−0.00	(−0.33, 0.33)	1.00			
>65	210	174 (83%)	0.60	(0.27, 0.94)	1.83	36.7	0.000	4718.2
LOCALISATION OF TUMOR								
nodal*	329	241 (73%)			1.00			
extran	240	147 (61%)	−0.35	(−0.54, −0.15)	0.71			
unknown	21	19 (90%)	0.86	(0.11, 1.60)	2.37	30.1	0.000	4695.2
STAGE OF TUMOR								
I*	134	68 (51%)			1.00			
II	178	109 (61%)	0.36	(0.06, 0.66)	1.43			
III	102	86 (84%)	0.93	(0.61, 1.28)	2.54			
IV	176	144 (82%)	1.10	(0.78, 1.42)	3.00	75.3	0.000	4645.4
CHEMOTHERAPY								
none*	233	157 (67%)			1.00			
COP	175	126 (72%)	0.26	(0.02, 0.49)	1.29			
CHOP	110	67 (61%)	−0.00	(−0.27, 0.27)	1.00			
other	72	57 (79%)	0.50	(0.16, 0.85)	1.65	13.7	0.003	4707.0
RADIOTHERAPY								
0*	131	98 (75%)			1.00			
<2000	78	63 (81%)	0.22	(−0.10, 0.54)	1.25			
⩾2000	381	246 (65%)	−0.49	(−0.73, −0.25)	0.61	34.6	0.000	4688.4
SURGERY								
no*	495	352 (71%)			1.00			
yes	95	55 (58%)	−0.33	(−0.61, −0.05)	0.72	5.4	0.020	4714.0

* Reference group

Table 4 — Relationship between independent variates and disease-free survival of patients with non-Hodgkin lymphoma — Analysis B.

2. The complexities concerning histopathologic classifications (23, 31, 32).

3. Small selected groups of patients reported (6, 18, 35, 37, 39).

4. Too short follow-up (2, 4, 6).

5. Variability of the treatment methods.

It is therefore hard to find out how much the progress in management and the widened choice of treatment have improved the survival in patients with NHL on the whole. Further, the factors that are recorded and analysed are only those that are recognised at the time of analyses, some appreciated only recently and many probably still unknown (3, 14, 29, 41, 44).

In our study the follow-up time is long in a great majority of patients and the group is relatively large. There is, however, no uniform histological classification; the diagnostic and therapeutic procedures varied considerably and only a few prognostic factors could be used for the analysis.

The impact of age on the prognosis in patients with NHL is in accordance with the findings of other authors while the better outcome for women found in our series has not been found in some other studies (6, 23, 33).

The extent of the disease is a significant prognostic factor in this and other series. The number of patients with systemic symptoms in this series was relatively small. Since it has not been shown of major importance, it has not been investigated in our series (23, 25, 37).

It has been found in this seried and by others in better defined groups that combination therapy gives better results than either chemotherapy or radiation therapy alone (21, 22, 35, 36). In our series the combined treatment might have been given to patients with lesser disease, with better

	No. of pts.							
	Total	Events with occurrence	β	95 % CI for β	hazard ratio	logrank χ^2	p value	deviance
SEX								
male*	324	223 (69 %)			1.00			
female	266	165 (62 %)	−0.25	(−0.45, −0.05)	0.78	5.8	0.017	4414.3
AGE AT DIAGNOSIS (in years)								
≤35*	76	45 (59 %)			1.00			
36—65	304	199 (65 %)	−0.01	(−0.31, 0.33)	1.01			
>65	210	144 (69%)	0.41	(0.07, 0.75)	1.51	15.0	0.001	4405.9
LOCALISATION OF TUMOR								
nodal*	329	232 (71 %)			1.00			
extran	240	139 (58 %)	−0.39	(−0.60, −0.18)	0.68			
unknown	21	17 (81 %)	−0.83	(0.34, 1.32)	2.29	29.9	0.000	4394.8
STAGE OF TUMOR								
I*	134	60 (45 %)			1.00			
II	178	108 (61 %)	0.48	(0.16, 0.80)	1.62			
III	102	78 (76 %)	0.02	(0.68, 1.36)	2.77			
IV	176	142 (81 %)	1.29	(0.98, 1.60)	3.63	90.6	0.000	4332.2
CHEMOTHERAPY								
none*	233	144 (62 %)			1.00			
COP	175	120 (69 %)	0.34	(0.09, 0.59)	1.40			
CHOP	110	67 (61 %)	0.15	(−0.15, 0.44)	1.16			
other	72	57 (79 %)	0.64	(0.33, 0.95)	1.90	19.1	0.000	4401.1
RADIOTHERAPY (dose in cGy)								
0*	131	98 (75 %)			1.00			
<2000	78	59 (76 %)	0.16	(−0.16, 0.48)	1.17			
≥2000	381	231 (61 %)	−0.60	(−0.84, −0.36)	0.55	42.2	0.000	4381.8
SURGERY								
no*	495	338 (69 %)			1.00			
yes	95	50 (53 %)	−0.39	(−0.69, −0.09)	0.68	6.6	0.010	4412.8

* Reference group

Table 5 — Relationship between independent variates and disease-free survival of patients with non-Hodgkin lymphoma — Analysis C.

performance status, younger ones and also therefore yield better results. The same might be true for the higher doses of irradiation being more effective than lower doses. Although also this observation has been reported earlier (21, 23, 29) in selected groups of patients (5, 21, 23) it might be so that lower doses of radiation were used in our patients often for palliation only.

Also patients who have undergone surgery were selected, therefore the positive efect of surgery on the outcome is likely to be correlated with other factors, such as one primary site and early stage (26, 45).

Chemotherapy, the way it was used in our patients, did not emerge as a factor improving the survival in this analysis. When the whole group is broken down according to stages (Fig. 6, Fig. 7) it becomes evident that patients with early stages but not those with stage III and IV

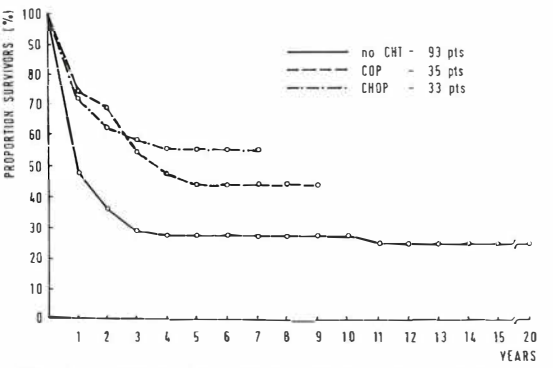

Fig. 7 — Survival by chemotherapy — stage IIa + IIb

who had COP or CHOP did better than those who had not. The survival curve of patients who had no chemotherapy shows a decrease in sur-

Variable of interest	Covariates	β	95 % CI for β	hazard ratio	logrank χ^2	DF	p	deviance
MODEL 1 year of diagn.	none	−0.071	(−0.096, −0.046)	0.932	31.2	1	0.000	3429.1
MODEL 2 year of diagn.	***	−0.063	(−0.103, −0.022)	0.939	149.9	17	0.000	3316.0
MODEL 3 none	***							3325.5

*** = sex, age, histological, diagnosis, localisation, stage, chemotherapy, radiation, surgery

Table 6 — Analysis by Cox' models for variable of interest, year of diagnosis adjusted for specific covariates. Analysis A.

vival even after 15 years, probably because this group includes patients with disease that was not primarily treated with combination chemotherapy. Also the group of patients who received chemotherapy is smaller and is followed for a shorter time.

Conclusions — The following few conclusion can be made on the basis of the present study:

Clinical factors that influenced the prognosis in our patients with NHL were:

1. Sex: women did better than men.
2. Age: patients between 36—65 years old did better than either younger or older patients.
3. Stage: patients in stage I and II did better than those in higher stages.
4. Primary site: patients with extranodal primary sites did better than those with nodal primary sites.
5. Dose of irradiation: patients treated with more than 2000 cGy did better than those who were treated with lower doses.
6. Only patients in stages I and II did benefit from additional »CHOP« or »COP« and »CHOP« chemotherapy respectively.
7. There has been a significant improvement in the survival of patients with NHL during the period under investigation and the compounded impact of the analysed variables on the improvement was significant.

Because several of the variables have changed during the whole period and because some might have been correlated to each other as well as to the results, it is not possible to conclude how much the change in the methods of treatment alone might have induced this improvement.

A further study will be done of recent patients, with uniform histological classification and primary tumor sites as additional variables, in order to address this question.

Povzetek

NE-HODGKINOV LIMFOM — ANALIZA POTEKA BOLEZNI PRI 590 BOLNIKIH

Retrospektivno smo analizirali potek bolezni 590 bolnikov z ne-Hodgkinovim limfomom (NHL), 324 moških in 266 žensk, ki so se prvič zdravili v Onkološkem inštitutu v Ljubljani: 189 v letih 1968—1974, 190 v letih 1975—1979 in 217 v letih 1980—1983. Vse bolnike smo redno kontrolirali; prihajali so različno dolgo, od 3—18 let. Za statistično analizo smo uporabili Kaplan-Meierjeve krivulje preživetja in Coxov model.

Čas preživetja bolnikov se je v analiziranem obdobju statistično značilno podaljšal. Bolnik, pri katerem je bil npr. NHL ugotovljen leta 1983, je imel 2,6-krat (1,4—4,7) večjo možnost, da bo bolezen preživel, kot pa bolnik, pri katerem so ugotovili NHL leta 1968. Ravni dejavnikov, ki so značilno vplivale na boljše preživetje, pa so bile: ženski spol, starost 36—65 let, stadij I, ekstranodalna primarna lokalizacija bolezni, obsevanje z dozami, ki so bile višje od 20 Gy, in kirurški poseg. S kemoterapijo po »COP« ali »CHOP« kombinaciji se je čas preživetja podaljšal le pri bolnikih z manj razširjeno boleznijo.

References

1. Armitage JO, Dick FR, Coreder MP. Diffuse histiocytic lymphoma after histologic conversion: a poor prognostic variant. Cancer Treat Rep 1981; 65: 413—8.
2. Armitage JO, Cheson BD. Interpretation of clinical trails in diffuse large-cell lymphoma. J Clin Oncol 1988; 6: 1335—134.
3. Akerman M, Brandt L, Johnson A, Olsson H. Mitotic activity in non-Hodgkin's lymphoma. Relation to the Kiel classification and to prognosis. Br J Cancer 1987; 55: 219—23.
4. 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.
5. Burgers JMV, Taal BG, van Heerde P, Somers R, den Hartog Jager FCA, Hart AAM. Treatment results of primary stage I and II non-Hodkin's lymphoma of the stomach. Radiother Oncol 1988; 11: 319—26.
6. Carbone A, Tirelli U, Volpe R et al. Non-Hodgkin's lymphoma in the elderly: a retrospective clinicopathologic study of 50 patients. Cancer 1986; 57: 2185—9.
7. Cheston BD, Wittes RE, Friedman MA. Low-grade non-Hodgkin's lymphomas revisited. Cancer Treat Rep 1986; 70: 1051—4.

8. Ciampi A, Bush RS, Gospodarowicz M, Till JE. An approach to classifying prognostic factors related to survival experience for non-Hodgkin's lymphoma patients: based on a series of 982 patients: 1967—1975. Cancer 1981; 47: 621—7.

9. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall, 1984.

10. Dardick I, Caldwell DR. Follicular center cell lymphoma: Morphologic data relating to observer reproductibility. Cancer 1986; 58: 2477—84.

11. De Wolf-Peeters C, Caillou B, Diebold J et al. Reproducibility 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.

12. Dick F, VanLier S, Banks P et al. Use of the working formulation for non-Hodgkin's lymphoma in epidemiologic studies: agreement between reported diagnoses and a panel of experienced pathologists. J Natl Cancer Inst 1987; 78: 1137—44.

13. Elias L. Differences in age and sex distributions among patients with non-Hodgkin's lymphoma. Cancer 1979; 43: 2540—6.

14. Egerter DA, Said JW, Epling S, Lee S. DNA content of T cell lymphomas. A flow-cytometric analysis. Am J Pathol 1988; 130: 326—34.

15. Ezindli EZ, Harrington DP, Kucuk O, Silverstein MW, Anderson J, O'Connell MJ. The effect of intensive intermittent maintenance therapy in advanced low--grade non-Hodgkin's lymphoma. Cancer 1987; 60: 156—60.

16. Fisher RI, deVita VT, Hubbard SM et al. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of proMACE and MOPP chemotherapy. Ann Intern Med 1983; 98: 304—9.

17. Gerhartz HH, Thiel E, Hiller E et al. CHOP and COPBLAM chemotherapy for diffuse large cell non-Hodgkin's lymphomas: a retrospective comparison. Hematol Oncol 1988; 6: 13—9.

18. Glick JH, McFadden E, Costello W, Ezindli E, Berard C, Bennett JM. Nodular histiocytic lymphoma: factors influencing prognosis and implications for aggressive chemotherapy. Cancer 1982; 49: 840—5.

19. Hagberg H, Bjorkholm M, Glimelius B, Lindemalm Ch, Mellstedt H, Killander A. CHOP vs MEV for the treatment of non-Hodgkin's lymphoma of unfavourable histopathology; a randomized clinical trial. Eur J Cancer Clin Oncol 1985; 21: 175—9.

20. Heinz R. Prognostic factors influencing the results of chemotherapy in treatment of malignant non Hodgkin lymphomas (NHL). 13th international congress of chemotherapy, Vienna 1983. Procedings 1983: 206/7-206/10.

21. Hoerni B, Trojani M, Eghbali H et al. Distinct entities among low-grade non-Hodgkin's malignant lymphomas. Analysis of a series of 377 cases. Eur J Clin Oncol 1987; 23: 1889—93.

22. Hoppe RT. The role of radiation therapy in the management of the non-Hodgkin's lymphomas. Cancer 1985; 55: 2176—83.

23. Horwich A, Peckham M. »Bad risk« non-Hodgkin's lymphomas. Semin Hematol 1983; 20: 35—56.

24. Jones SE. Follicular lymphoma — do no harm. Cancer Treat Rep 1986; 70: 1055—8.

25. Jones SE, Fuks Z, Bull M et al. Non-Hodgkin's lymphomas: IV. clinicopathologic correlation in 405 cases. Cancer 1973; 31: 806—23.

26. Kajanti M, Karkinen-Jaaskelainen, Rissanen P. Primary gastrointestinal non-Hodgkin lymphoma. Acta Oncol 1988; 27: 51—5.

27. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Baffins Lane: John Wiley and Sons, 1980.

28. Koziner B, Little C, Passe S et al. Treatment of advanced diffuse histiocytic lymphoma: an analysis of prognostic variables. Cancer 1982; 49: 1571—9.

29. Lenner P, Ross G, Johansson H, Lindh J, Dige U. Non-Hodgkin lymphoma: multivariate analysis of prognostic factors including fraction of S-phase cells. Acta Oncol 1987; 26: 179—83.

30. Miller TP, Jones SE. Initial chemotherapy in earlier stage of non-Hodgkin's lymphomas with unfavorable histology. 13th international congress of chemotherapy. Vienna 1983. Proceedings 1983: 206/14-206/19.

31. Monfardini S, Banfi A, Bonadonna G et al. Improved five year survival after combined radiotherapy-chemotherapy for stage I-II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1980; 6: 125—34.

32. Nabholtz J-M, Friedman S, Collin F, Guerrin J. Modification of Kiel and Working Formulation Classifications for improved survival prediction in non-Hodgkin's lymphoma. J Clin Oncol 1987; 5: 1634—9.

33. Patchefsky AS, Brodovsky HS, Menduke H et al. Non-Hodgkin's lymphomas: a clinicopathologic study of 293 cases. Cancer 1974; 34: 1173—86.

34. Portlock CS. »Good risk« non-Hodgkin lymphomas: approaches to management. Semin Hematol 1983; 20: 25—34.

35. SAS user's guide: Statistics. North Carolina: SAS Institute Inc. 1985.

36. Shepherd FA, Evans WK, Kutas G et al. Chemotherapy following surgery for stage IE and IIE non-Hodgkin's lymphomas of the gastrointestinal tract. J Clin Oncol 1988; 6: 253—60.

37. Shirato H, Tsujii H, Arimoto T et al. Early stage head and neck non-Hodgkin's lymphoma: the effect of tumor burden on prognosis. Cancer 1986; 58: 2312—9.

38. Somers R, Burgers JMV, Quasim M, Glabbeke van M, Duez N, Hayat M. EORTC trial non-Hodgkin lymphomas. Eur J Cancer Clin Oncol 1987; 23: 283—93.

39. Straus DJ, Filippa DA, Lieberman PH, Koziner B, Thaler HT, Clarkson BD. The non-Hodgkin's lymphomas: I. a retrospectiver clinical and pathologic analysis of 499 cases diagnosed between 1958 and 1969. Cancer 1983; 51: 101—9.

40. SUGI Supplemental Library. User's guide. Version 5 edition. North Carolina: SAS Institute Inc. 1986.

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

42. Taylor RE, Allan SG, McIntyre MA et al. Low grade stage I and II non-Hodgkin's lymphoma: Results of treatment and relapse pattern following therapy. Clin Radiol 1988; 39: 287—90.

43. Tirelli U, Carbone A, Zagonel V, Veronesi A, Canetta R. Non-Hodgkin's lymphomas in the elderly: prospective studies with specifically devised chemotherapy regimens in 66 patients. Eur J Cancer Clin Oncol 1987; 23: 535—40.

44. Vernoni S, Costa A, Motta R, Giardini R, Rilke F, Silvestrini R. Comparative analysis of (3H)-thymidine labelling index and monoclonal antibody Ki-67 in non-Hodgkin's lymphomas. Hematol Oncol 1988; 6: 21—8.

45. Wulfrank D, Speelman T, Pauwels C, Roels H, de Schryver A. Extranodal non-Hodgkin's lymphoma of the head nad neck. Radiother Oncol 1987; 8: 199—207.

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