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PROGNOSTIC FACTORS IN HEAD AND NECK NON-HODGKIN'S LYMPHOMA WITH SPECIAL REFERENCE TO SERUM LACTIC DEHYDROGENASE AND SERUM COPPER

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Abstract

An analysis of prognostic variables was performed in a retrospective study of 121 patients with Ann Arbor stage I–II head and neck non-Hodgkin's lymphoma admitted from 1973 to 1988. The overall actuarial 5-year survival rate was 58.8% and the minimum follow-up 15 months. Nine clinical and laboratory parameters were studied, including serum lactic dehydrogenase (LDH) and serum copper (SCL), and subjected to univariate and multivariate analyses. In univariate analysis, histology and LDH were found to be significant prognostic variables. Evaluation by Cox's multivariate proportional hazard model revealed histology, SCL and sex to be of prognostic significance.

Key words: Non-Hodgkin's lymphoma, head and neck, prognostic factors, serum LDH, serum copper.

With improved treatment methods for non-Hodgkin's lymphoma (NHL), pretreatment prognostic assessment is becoming increasingly important as a guideline for selection of appropriate treatment. Several retrospective studies have proposed various factors to be associated with the prognosis of NHL. However, reports on prognostic factors in head and neck NHL are rare and only a few authors have used multivariate analysis (1, 2). Among various factors, stage, site of disease, histology, age, tumor bulkiness, and type of chemotherapy have been reported to be associated with prognosis (1–14). The association for some of these factors, however, is still controversial (3, 6, 10, 13).

The purpose of the present report was to evaluate the prognostic value of some parameters in head and neck NHL by use of both univariate analysis and Cox's multivariate regression analysis. Special attention was paid to the levels of serum lactic dehydrogenase (LDH) and serum copper (SCL).

Material and Methods

Between 1973 and 1988, 121 previously untreated patients with stage I–II head and neck NHL received radiotherapy and chemotherapy or radiotherapy alone in our department. The age of the patients ranged from 7 to 85, with a median of 53.2 years. Nine patients were ≤ 15 years and 9 were >80 years old. There were 75 males and 46 females. Sites of origin were lymph nodes in 43, extranodal site in 41 and Waldeyer's ring in 37 patients. Pretreatment assessment consisted of physical examination, chest radiography, routine blood counts and blood chemistry, radiography of the GI tract, lymphography, radionuclide bone scanning, computed tomography and ultrasonography of the abdomen, bone marrow biopsy and sometimes also more invasive procedures, such as hepatosplenic biopsy (15). Clinical staging was performed using the Ann Arbor classification; 67 patients were classified as stage I and 54 as stage II. Histological classification was done according to the working formulation for clinical usage (WF).

Involved regions were treated by a conventional fractionation scheme with 2.5 Gy per day, 4 times a week using 4 MV x-rays or ^{60}Co gamma rays. The total dose for involved regions was as a rule 45 Gy while non-involved necks received 30 Gy as 'prophylactic' treatment. Forty-one patients with lymphoma of intermediate malignancy received three courses of chemotherapy with COP (cyclophosphamide, vincristine, prednisolone: 20 cases) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone: 21 cases). Forty-seven patients out of 88 with intermediate or low-grade lymphoma were treated by irradiation alone.

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Follow-up examinations were regularly performed and included not only physical examination but also, when indicated, other examination modalities as used during the initial staging. All cases obtained complete remission and no patient was lost to follow-up. The minimum follow-up was 15 months. Complete remission was defined as disappearance of all recognizable tumor and absence of subjective symptoms.

The patients were subdivided with respect to stage of disease, sex, age, primary site, histology, type of chemotherapy, size of tumor, and levels of LDH and SCL. Serum LDH levels were determined according to the L-P, UV method (normal value: 125–220 U/l) and SCL by the bathocuproin method (normal value: 780–1 310 μg/l). Pretreatment LDH and SCL values were simultaneously determined for 69 of the 121 patients.

All 121 cases were first analysed by univariate analysis. Cox's multivariate proportional analysis was then performed for all 121 patients and separately for the 69 patients with pretreatment LDH and SCL values (16). In the univariate analysis, the cases were divided into two or three groups (quantal data) and the survival difference between each group was analysed. In the Cox's proportional hazard model, LDH and SCL values were analysed as sequential data (19). The survival time was calculated from the start of the initial therapy and estimated according to the actuarial life-table method of Kaplan-Meyer. The statistical significance of survival difference was evaluated by the generalized Wilcoxon's test. The correlation coefficient between initial LDH, SCL and histology was calculated, and the differences between the groups were evaluated by Student's t-test and Welch's test for heterogeneity.

Results

Univariate analysis with 5-year survival rate as endpoint was performed for stage, sex, age, primary site, histology, chemotherapy, tumor size, LDH and SCL. Histology and LDH values were significantly ($p < 0.05$) associated with 5-year survival rate (Table 1). There was no correlation between histology and pretreatment values of LDH or SCL, nor between pretreatment SCL and LDH values ($p > 0.05$).

Table 1

Single factor variate analysis of possible prognostic factors with 5-year survival rate as endpoint

	Stage I		Stage II		Stage I–II		
	No.	Surv. %	No.	Surv. %	No.	Surv. %	
Stage	67	58.5	54	59.1	121	58.8	
Sex							
Male	40	50.3	35	51.5	75	50.5	p = 0.06
Female	27	83.9	19	84.2	46	83.6	
Age							
< 53 years	30	60.9	21	75.9	51	65.9	
⩾ 53 years	37	58.6	33	47.3	70	53.9	
Primary site							
Waldeyer	14	62.2	23	75.8	37	68.9	
Extranodal	26	53.3	15	61.3	41	57.5	
Nodal	27	60.7	16	50.9	43	53.4	
Histology (WF)							
Low grade	13	100	4	100	17	100	p = 0.03
Intermediate grade	43	59.4	45	58.2	88	59.3	p = 0.01
High grade	9	0	7	42.9	16	25.0	p = 0.01
Chemotherapy							
None	45	46.1	26	60.5	71	56.6	
Adjuvant	22	75.2	28	65.0	50	68.3	
Doxorubicin	11	48.5	15	67.1	26	57.1	
No doxorubicin	11	90.0	13	64.2	24	73.2	
Tumor size							
⩽ 5 cm	51	61.7	26	52.5	77	59.3	
> 5 cm	17	57.9	27	61.9	44	59.4	
LDH							
⩽ 220 U/l					48	79.6	p = 0.05
⩾ 221 U/l					21	34.1	
SCL							
⩽ 1 310 μg/l					22	79.4	
⩾ 1 320 μg/l					47	64.7	

Multivariate analysis was performed for the same variables. Sex, histology and SCL were found to be significantly ($p < 0.05$) associated with survival (Tables 2 and 3). LDH and SCL values were in the univariate analysis treated as quantal data and in the multivariate analysis as sequential data, which may explain the discrepancy between the results of the two types of analysis.

Survival curves for the different histologic types are shown in Fig. 1. All 17 patients with low-grade lymphoma were alive and well. Age, site of disease, size of tumor, chemotherapy (adjuvant chemotherapy vs no chemotherapy), type of chemotherapy (doxorobicin vs no doxorubicin), stage of disease and LDH were not significantly associated with survival in the multivariate analysis. However, Waldeyer's ring lymphoma have a slightly higher 5-year survival rate (69%) than extranodal (58%) and nodal lymphoma (53%) (Fig. 2). No significant survival difference was observed between stage I and stage II patients. Patients given doxorubicin had no higher survival rate (5-year: 57%) than those not given doxorubicin (5-year: 73%). Relapses were frequent in high-grade (9/17) and intermediate-grade lymphoma (31/88) compared to low-grade lymphoma (2/16) patients. Nine secondary cancers occurred in 7 patients and 3 patients died of the secondary cancer. It was also observed that both LDH and

Table 2

Cox's multivariate analysis of possible prognostic factors in 121 cases with 5-year survival rate as endpoint

Variable	p
Age	0.41
Sex	0.06
Primary site	0.95
Stage	0.64
Histology	0.01
Tumor size	0.41
Chemotherapy	0.93
Chemotherapy with doxorubicin	0.62

Table 3

Cox's multivariate analysis of possible prognostic factors in 69 cases with pretreatment LDH and SCL values

Variable	p
Age	0.50
Sex	0.04
Primary site	0.82
Stage	0.73
Histology	0.01
Tumor size	0.67
Chemotherapy	0.66
Chemotherapy with doxorubicin	0.23
Serum copper	0.02
LDH	0.50

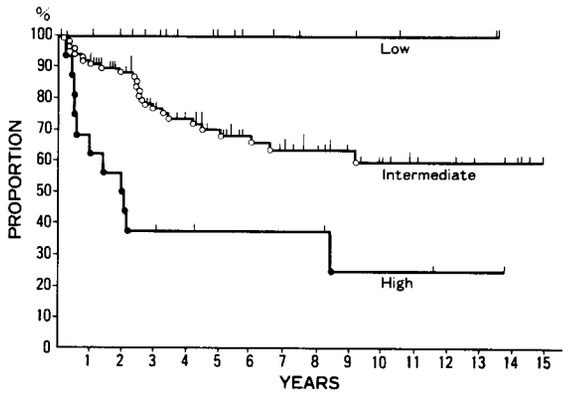

Fig. 1. Survival curves for head and neck stage I–II NHL patients according to histology (working formulation for clinical usage).

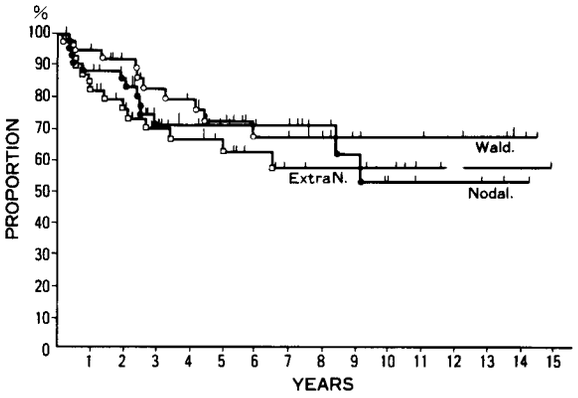

Fig. 2. Survival curves for head and neck stage I–II NHL patients according to the primary site.

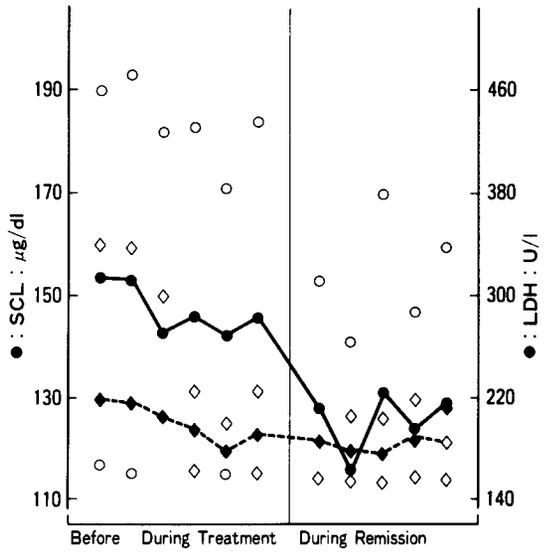

Fig. 3. Changes of LDH and SCL in 32 relapse-free patients. Filled circles (SCL) and diamonds (LDH) indicate mean values. Open circles (SCL) and diamonds (LDH) indicate standard deviation. The intervals between the determination were about a month.

SCL values as a rule decreased in patients with remission after treatment (Fig. 3). Increased values of LDH and SCL were often observed in patients with relapse but these observations are not reported in detail.

Discussion

Survival statistics on treatment results and prognostic influence of different variables in head and neck NHL have been reported by several authors (1, 2–6, 8–14). These reports suggest primary site, stage, histology, age and several other factors as being associated with the prognosis. According to our single factor analysis, histology and LDH values were significant prognostic variables. However, the pathologic type (Working Formulation) had the most striking association with survival. Previous authors dealing with stage I–II head and neck NHL have reported both good or poor correlation between WF type and prognosis (2, 7–10).

Mutlivariate analysis of possible prognostic factors in head and neck NHL has rarely been reported (1, 2). According to our Cox's porportional regression analysis, SCL, histology and sex seemed to be significant independent prognostic variables in contrast to site of disease and stage. It has been long discussed whether the site of head and neck NHL influences the prognosis and some authors have reported that Waldeyer's ring NHL has better prognosis than head and neck NHL in other sites (2, 7). In our study, Waldeyer's ring NHL had a somewhat higher survival than extranodal and nodal NHL, but the difference was not statistically significant. Some authors have found a better prognosis in stage I than in stage II (3–6, 8–10) head and neck NHL but this could not be verified in the present study. One reason may be that our patients were distributed over a long time period which might have influenced the staging. Ultrasonography and computed tomography were not used during the early years.

It has long been discussed whether chemotherapy could improve the results in early stage head and neck NHL but the results of combined chemotherapy and radiotherapy have rarely been analysed by multivariate methods (2, 4, 10, 18–22). Some authors have reported that initial multidrug chemotherapy improves the treatment outcome in stage I–II NHL (2, 19). In the present study, neither patients who received adjuvant chemotherapy nor those who got doxorubicin-containing combination chemotherapy had better prognosis. Age was not significantly associated with the prognosis in our analysis. However, some other investigators have reported that age influences the treatment outcome and should be taken into account when treatment modality is chosen (1, 6, 10–13). Our finding that females had a better prognosis than males is in agreement with a report from Cohen et al. (14). Ten among 16 patients with high-grade lymphoma in our study were male and they responded poorly to therapy.

In our study, SCL proved to be a significant prognostic indicator. LDH and SCL seem to be independent of each other and may both be of value as prognostic indicators and for early detection of relapse (23–25).

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