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MORPHOLOGIC CLASSIFICATION OF NON-HODGKIN'S LYMPHOMA

I. Retrospective analysis using the Kiel classification

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The clinical manifestations and the prognosis among the non-Hodgkin's lymphomas (NHL) vary considerably. Therefore, the therapy must be correspondingly differentiated. In some cases, the disease is indolent and the therapy can be mild or even expectant, in others it is rapidly fatal, and the therapy must be intensive, and then usually toxic. It is therefore of great importance for the clinician to obtain an appropriate prediction of the behaviour of the disease. In NHL it is a well known fact that the morphology is an important prognostic factor.

One of the more recently proposed classifications based on modern immunologic concepts, the Kiel classification (GÉRARD-MARCHANT et coll. 1974), was applied to a retrospective series of 334 cases of confirmed or possible NHL.

Material and Methods

The series included 334 patients with confirmed or possible NHL registered at this Department of Oncology and diagnosed between 1969 and 1978. In 20 of the cases, the diagnosis was initially based only upon cytologic material. Of the remaining 314 cases, the initial diagnosis of NHL was changed in 34 cases (benign 7, metastatic carcinoma 7, Hodgkin's disease 7, malignant histiocytosis 5, miscellaneous 8). In 30 (11%) of the remaining 280 cases of NHL, it was not possible to make a subclassification according to the Kiel classification; in the majority of these cases, the material was not technically sufficient for a complete review.

Clinical records. Patients who turned out to have a microscopically proven NHL were all subject to a complete physical examination, blood laboratory tests and chest radiography. In 245 (98%) patients, a bone marrow puncture with cytologic or histopathologic examination from at least one location was performed. Scintigraphy of the liver and spleen was performed in 118 (47%) patients. In 37 cases, the primary diagnosis was made after an explorative laparotomy. An abdominal lymphangiography was performed in 57 patients, a vena-cavo-urography in an additional 11 and computed tomography in 4 patients. An adequate examination directed to disclose intra-abdominal disease other than liver–spleen scintigraphy was not carried out in 52 patients initially in stage I or II. The patients were divided into clinical stage according to the definitions given by the Ann Arbor classification system (CARBONE et coll. 1971).

The majority of patients with stage I and stage II disease (106 of 126 patients) was given radiation therapy alone to approximately 40 Gy (range 24–55). The remaining 20 patients initially in stage I or II either received no tumour specific therapy, surgery alone, or chemotherapy in addition to irradiation. The treatment regimens for patients in stage III or

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IV, and for irradiation failures varied considerably during the period. Except for the first years, when the treatment mainly was based upon radiation, single drugs or simple drug combinations, patients with a lymphoma of a more favourable microscopic appearance initially received, in addition to irradiation against bulky disease, simple drug combinations like CVP (cyclophosphamide, vincristine, prednisone) or no tumour specific therapy. Those with a lymphoma of higher grade of malignancy usually received more intense treatment with chemotherapy combinations like MOPP (nitrogen mustard, vincristine, procarbazine, prednisone), MEV (methotrexate, cyclophosphamide, vincristine) or CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) besides irradiation of bulky disease.

All patients were followed from admission to death, or to completion of follow-up, i.e. April 1982. The observation time was at least 36 months for all living patients. No patient was lost to follow-up.

Statistical methods. The survival curves were generated as described by PETO et coll. (1977). Differences in survival were tested using the log-rank test, also described by PETO et coll. Patients dead from intercurrent diseases are not included in the population at risk after their death provided they were in complete clinical remission; if not, they were regarded as dead from malignant lymphoma.

Histopathology. All specimens were recut in 3 μm thick sections and examined after staining with Hematoxylin-eosin (Htx), Giemsa, PAS, and Laidlaw. The reviewing pathologist (C. S.) knew the age of the patient, and the site of the biopsy. The reviewed specimens originated from the site on which the initial diagnosis was based.

Lymphomas of follicular centre cell (FCC) origin were classified as follicular (LENNERT et coll. 1975) if they were totally follicular in all available material, as follicular and diffuse if any diffuse areas were present, and as diffuse if no follicular portion was present. The proportions of centrocytes and centroblasts were scored in FCC lymphomas. Purely centrocytic lymphomas contained less than approximately one per cent centroblasts, and purely centroblastic lymphomas more than 30 per cent centroblasts, or sheets of centroblasts. The centroblastic-centrocytic lymphomas were further subdivided into 3 classes with approximately one to 10, 11 to 20 and 21 to 30 per cent centroblasts, respectively.

The Kiel classification was used only as a morphologic classification. No additional examinations, e.g. immunologic, of the biopsy material could be done.

Table 1

Distribution of histopathologic subgroups according to the Kiel classification

Type of malignant lymphoma	Abbreviation	No. of patients	Per cent
Lymphocytic	LC	20	8
Immunocytic	IC	49	20
Lymphoplasmacytic/-cytoid		31	12
Polymorphic		18	7
Centrocytic	CC	4	2
Centroblastic-centrocytic	CB-CC	91	36
Follicular	CB-CC foll.	27	11
Follicular and diffuse	CB-CC foll. + diff.	37	15
Diffuse	CB-CC diff.	27	11
Without sclerosis	CB-CC, 0 scl.	64	26
With sclerosis	CB-CC, + scl.	27	11
Centroblastic	CB	45	18
Lymphoblastic	LB	18	7
Convoluted		2	1
Non-convoluted		16	6
Immunoblastic	IB	23	9
Total		250	100

Table 2

Age and sex distribution by histopathologic subgroup

	Median age	Range	Per cent males
LC	56	25–67	40
IC	64	31–77	61
CC	61	35–81	50
CB-CC	61	17–84	56
CB-CC foll.	57	25–84	41
CB-CC foll. + diff.	62	17–83	65
CB-CC diff.	66	37–82	59
CB	64	22–92	53
LB	51	2–84	78
IB	66	14–86	48

Results

Characterization of the series. The distribution of the 250 cases that could be subgrouped according to the Kiel classification appears in Table 1. The age distribution was uniform and unimodal in all subgroups except in the lymphoblastic lymphomas, where a bimodal age distribution was found. The median age was approximately 60 years in all sub-

Table 3

Clinical stage and systemic symptoms by histopathologic subgroup at presentation. Per cent in parentheses

	Stage				Systemic symptoms
	I	II	III	IV	
LC	–	–	1 (5)	19 (95)	5 (25)
IC	17 (35)	8 (16)	7 (14)	17 (35)	7 (14)
CC	–	2 (50)	1 (25)	1 (25)	–
CB-CC	31 (34)	14 (15)	22 (24)	24 (26)	12 (13)
CB-CC foll.	7 (26)	3 (21)	12 (44)	5 (19)	2 (7)
CB-CC foll. + diff.	15 (41)	4 (11)	8 (22)	10 (27)	7 (19)
CB-CC diff.	9 (33)	7 (26)	2 (8)	9 (33)	3 (10)
CB-CC, 0 scl.	16 (25)	11 (17)	19 (30)	18 (28)	6 (9)
CB-CC, + scl.	15 (56)	3 (11)	5 (19)	4 (15)	6 (22)
CB	18 (40)	10 (22)	7 (16)	10 (22)	2 (4)
LB	8 (44)	3 (17)	–	7 (39)	2 (11)
IB	5 (22)	10 (43)	3 (13)	5 (22)	3 (13)

Table 4

Extranodal involvement (stage I–III), and involvement of Waldeyer's ring and bone marrow (stage I–IV) at presentation. Per cent in parentheses

	Extranodal involvement	Involvement of Waldeyer's ring	Bone marrow involvement
LC	0	1 (5)	19 (95)
IC	17 (53)	11 (22)	13 (27)
CC	1 (33)	2 (50)	1 (25)
CB-CC	14 (20)	15 (16)	14 (15)
CB	13 (37)	9 (20)	2 (4)
LB	6 (55)	3 (17)	1 (6)
IB	9 (50)	4 (17)	1 (4)

groups except in the lymphoblastic lymphomas, where it was slightly lower (51 years, Table 2). In most subgroups, males preponderated slightly (Table 2).

The distribution by clinical stage at the time of diagnosis is indicated in Table 3. All patients with lymphocytic lymphoma with one exception were initially in stage IV due to bone marrow involvement (Table 4). The remaining patient was in stage III, and had no bone marrow involvement until after 84 months. In all other subgroups (except the 4 patients with centrocytic lymphomas), the proportion of patients with a localized disease (stage I) ranged between 22 and 44 per cent, and with regional disease (stage II) between 16 and 43 per cent. Centroblastic-centrocytic lymphomas with sclerosis were more often localized (56%, stage I) than those that did not contain sclerosis (25%, stage I, $p<0.005$).

Systemic disease was present in between 4 and 25 per cent with the highest figure in patients with lymphocytic lymphomas (Table 3). The frequency of extranodal involvement in patients with clinical stage I–III disease was lower among the FCC derived lymphomas (CC, CB-CC, CB; 20–37%) than among the other subgroups (50–55%; Table 4). The most frequent extranodal sites of involvement were the skin (8%) and the gastrointestinal tract (11%). The Waldeyer's ring (not considered extranodal) was involved in between 16 and 22 per cent of the patients, with no difference between groups (except in CC where 2 of 3 patients had such involvement). Except for the high incidence of bone marrow involvement in the lymphocytic lymphomas (95%), such involvement was rather infrequent with the lowest figures (4–6%) among the so-called high grade lymphomas (CB; LB, IB; Table 4).

Survival according to the Kiel classification

Influence of clinical stage. Clinical stage I disclosed an excellent prognosis irrespective of microscopic type (Fig. 1). No statistically significant difference could be found between any subgroups. The majority (87%) of these patients was given radiation therapy alone.

Among the group of high grade lymphomas, a marked difference ($p<0.001$) was noticed between stage I on the one hand and stage II–IV on the other (Fig. 2). No difference was noticed between stages

II, III, and IV and no difference between the 3 morphologic subgroups (CB, LB, IB) in this respect. The same finding of a more marked difference between stage I and stage II–IV, than between stages II, III, and IV, respectively, was found also among the lymphomas with more favourable prognosis (not illustrated).

In the following comparison between different histopathologic types, only stages II–IV are included.

Influence of cell type. All subgroups that make up the high grade malignant lymphomas (CB, LB, IB) within the Kiel classification, as proposed and described by GÉRARD-MARCHANT et coll., had a poor prognosis. Fifty per cent of the patients were dead within 12 months after diagnosis (Fig. 3). No statistically significant difference in survival between the different high grade lymphomas was found.

The prognosis for the various low grade malignant lymphomas was more variable. Lymphocytic lymphomas had the most favourable prognosis with a median survival of 7 years or more, whereas the centroblastic-centrocytic and the immunocytic lymphomas, respectively, were significantly ($p<0.002$) less favourable (50% alive after 3–4 years; Fig. 4). The number of centrocytic lymphomas was so few that no firm conclusion about their prognosis can be drawn.

The proportion of centrocytes and centroblasts within the FCC derived lymphomas did not seem to influence the survival rate (not illustrated).

The survival curve for the polymorphous subtype of the immunocytic lymphomas indicated a slightly worse prognosis, but did not significantly differ from those of the lymphoplasmacytoid and lymphoplasmacytic subtype (not illustrated).

Influence of growth pattern and sclerosis. Subdivision of the centroblastic-centrocytic lymphomas on the basis of growth pattern (Table 1) greatly influenced survival (Fig. 5). Those with a purely diffuse growth had an unfavourable prognosis, and, in fact, as poor as for the high grade lymphomas (cf. Figs 3 and 5). In contrast, a purely follicular growth indicated a favourable prognosis comparable to the lymphocytic lymphomas, whereas the lymphomas that showed both a follicular and a diffuse growth behaved in an intermediate way. The presence or absence of sclerosis among the centroblastic-centrocytic lymphomas did not influence the prognosis (not illustrated).

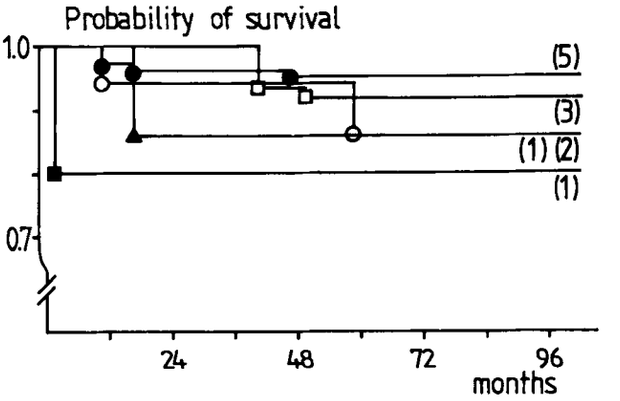

Fig. 1. Actuarial survival for patients in clinical stage I. Immunocytic (□, n=17), centroblastic-centrocytic (●, n=31), centroblastic (○, n=18), lymphoblastic (▲, n=8) and immunoblastic (■, n=5). Within parentheses, the number of patients after an observation time of 108 months.

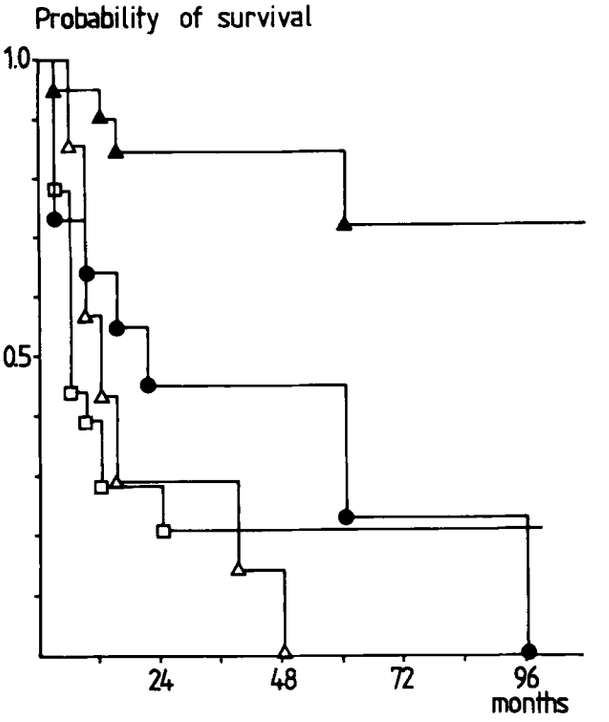

Fig. 2. Actuarial survival for patients with high-grade lymphomas (CB, LB, IB) in different initial clinical stages. Stage I (▲, n=31), stage II (□, n=23), stage III (●, n=10), and stage IV (△, n=22).

Prognostic relevance of the Kiel classification

When the prognosis among different subgroups was compared for stages II–IV, 3 major prognostic groups could be identified. The most favourable prognosis was found for the lymphocytic lymphomas, and the follicular centroblastic-centrocytic

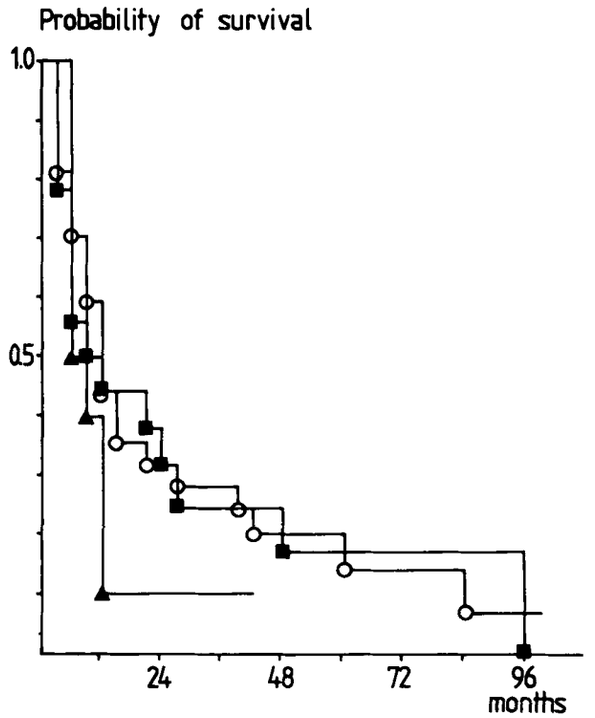

Fig. 3. Actuarial survival for patients in stages II–IV with so-called high-grade lymphomas. Centroblastic (○, n=27), lymphoblastic (▲, n=10), and immunoblastic (■, n=10).

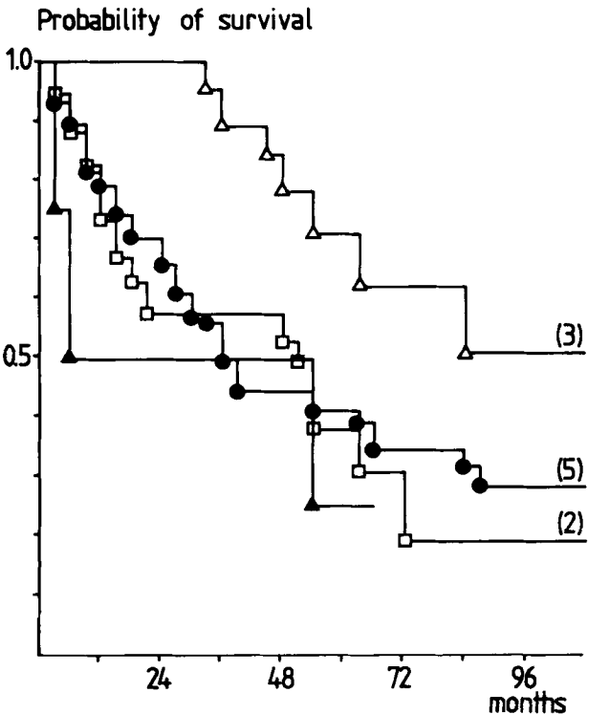

Fig. 4. Actuarial survival for patients in stages II–IV with so-called low-grade lymphomas. Lymphocytic (△, n=20), immunocytic (□, n=32), centrocytic (▲, n=4), and centroblastic-centrocytic (●, n=61).

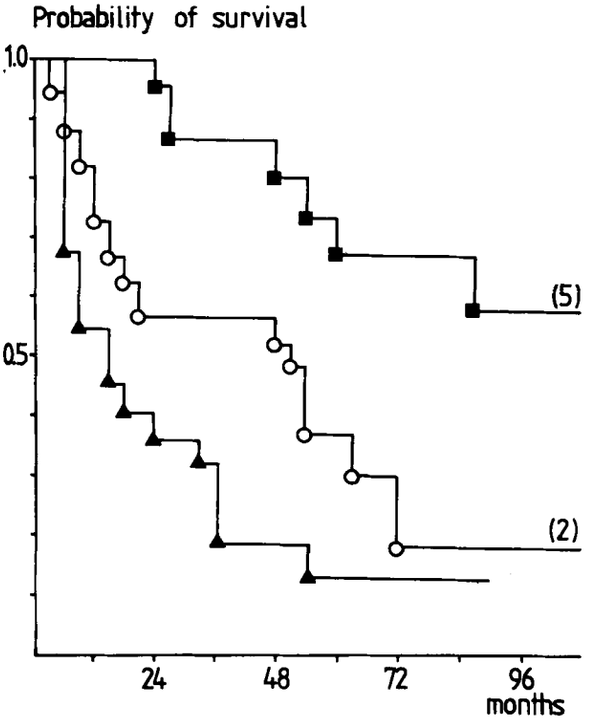

Fig. 5. Actuarial survival for patients in stages II–IV with centroblastic-centrocytic lymphomas with different growth pattern, follicular (■, n=20), follicular and diffuse (○, n=22), and diffuse (▲, n=19).

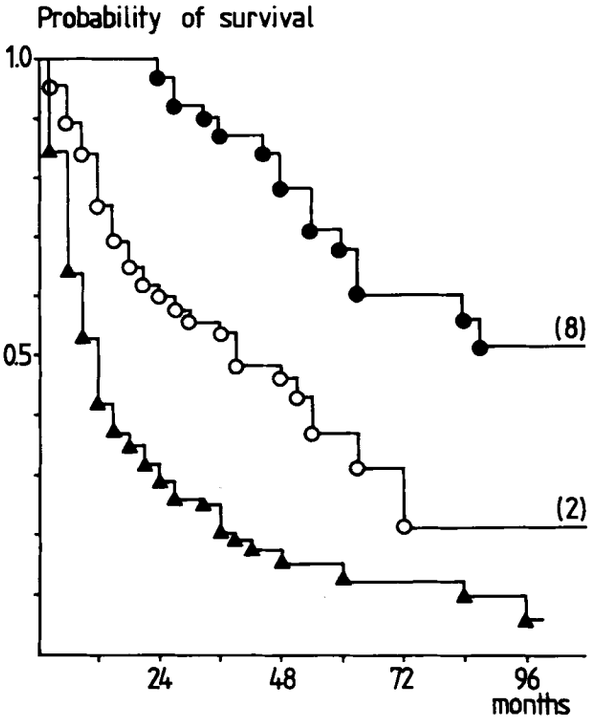

Fig. 6. Actuarial survival for patients in stages II–IV with a favourable (●; n=40), intermediate (○; n=54), and unfavourable (▲, n=74) prognosis, respectively. The four cases of centrocytic lymphomas are not included in the figure.

lymphomas, where 50 per cent of the patients survived 7 years or more (Fig. 6). An intermediate prognosis was found for the immunocytic lymphomas, and for the mixed follicular and diffuse centroblastic-centrocytic lymphomas with 50 per cent surviving 3 to 4 years. A poor prognosis was found for the centroblastic, immunoblastic, lymphoblastic, and the diffuse centroblastic-centrocytic lymphomas. After about one year, 50 per cent of those patients were dead.

The differences between the three prognostic groups were statistically highly significant ($p<0.001$), and further, one subtype within a prognostic group differed significantly from any other subtype in the other prognostic groups. This meant that follicular centroblastic-centrocytic lymphomas differed from the follicular and diffuse subtype ($p<0.005$), which in turn differed from the diffuse variant ($p<0.05$). A clear difference between the lymphocytic lymphomas and the immunocytic lymphomas was found ($p<0.02$). Similar statistically significant differences were also noted if prognosis was compared only for stages III and IV, or stage IV alone. In fact, the survival curves for any prognostic group were virtually identical whether stages II–IV or only stages III–IV were included (not illustrated). These differences were, however, not always statistically significant when also the patients in stage I, with its excellent prognosis irrespective of morphologic appearance were included in the comparison.

Discussion

Two facts revealed in the present series have necessitated a different approach to the comparison of survival of the different subgroups of non-Hodgkin's lymphoma. One fact is the differences in prognosis between stages, the other is the different distribution of stages among the subgroups. The comparison was therefore made for groups of prognostically or therapeutically related stages separately, and not for all stages grouped together. To include stage I disease, which had an excellent prognosis irrespective of morphology, in a comparison of survival together with the other, usually considerably less favourable stages, will dilute differences in the biologic properties (grade of malignancy) of different subtypes. The rate of survival will then not only reflect this grade of malignancy, but also the proportion of stage I disease. Most recent reports that have dealt with the prognostic relevance of a morphologic classification of NHL, have only presented data for all stages grouped together (e.g. LENNERT et coll., MEUGÉ et coll. 1978, NATHWANI et coll. 1978, LENNER et coll. 1979a, b, GARVIN et coll. 1980, BRITTINGER et coll. 1981, KRÜGER et coll. 1981).

According to the data presented in the present retrospective analysis, it was found relevant to group stage II, III and IV together. The survival rates were similar for these stages within the group of unfavourable lymphomas. Also, the difference between stage I and II was greater than between any other stage. This subdivision also seemed therapeutically relevant, since stage I may in a high proportion of cases be regarded as truly localized and thus possible to cure with local irradiation, whereas the other stages, including stage II, should be considered disseminated and should thus not primarily be treated only locally (cf. also HAGBERG et coll. 1982).

Several of the newer classifications including the Kiel classification (DORFMAN 1974, GÉRARD-MARCHANT et coll., LUKES & COLLINS 1974) subdivide small lymphocytic lymphomas into 2 categories, depending upon the presence or absence of plasmacytoid differentiation. Whether this subdivision is of prognostic relevance has not been shown, although there have been certain trends to a less favourable prognosis for the lymphomas with this feature (STACHER et coll. 1976, LENNER et coll. 1979a, GARVIN et coll., HEINZ et coll. 1981). In the present material, there was a statistically significantly (stages II–IV compared; $p<0.02$; stages III–IV, $p<0.003$) less favourable prognosis for the immunocytic lymphomas. When stage I, only present for those with plasmacytoid differentiation was included in the comparison, only a trend ($p=0.3$) was noticed. Therefore it was concluded that the appearance of plasmacytoid differentiation is of prognostic relevance. Those without all have an indolent course, whereas the immunocytic lymphomas, if initially disseminated (stages II–IV), have a considerably less favourable prognosis in the majority of cases.

The degree of nodularity within the nodular lymphomas has been the subject of several investigations with conflicting results. Several authors (PATCHEFSKY et coll. 1974, BUTLER et coll. 1975, LENNER et coll. 1979b, COLBY et coll. 1980) have noticed a less favourable prognosis for lymphomas with a mixed nodular and diffuse growth compared with those with a predominantly nodular growth. WARNKE et coll. (1977) also found a correlation

between the degree of nodularity and prognosis, but only within the histiocytic subgroup and not among the poorly differentiated lymphocytic and mixed lymphomas, respectively. In contrast, BAGLEY et coll. (1972), COX et coll. (1974), NATHWANI et coll. and GARVIN et coll. found no such correlation. Much of this confusion may arise in the fact that the degree of nodularity was defined in several different ways, and that the patients were selected differently. In the present series, a clear prognostic importance of the extent of nodularity was noticed. The difference was highly statistically significant when stages II–IV ($p<0.005$), III–IV ($p<0.01$) or only stage IV ($p<0.005$) were included for comparison but not when all stages were included ($p=0.3$).

Nodularity in NHL has in numerous reports been shown to indicate a better prognosis compared with a diffuse growth (e.g. RAPPAPORT et coll. 1956, JONES et coll. 1973, EZDINLI et coll. 1978, NATHWANI et coll. 1978, LENNER et coll. 1979b, GARVIN et coll.). On the other hand, LUKES (1977) and LENNERT (1978) have claimed that nodularity is only a feature secondary to cell type, and of no primary prognostic significance. Since a follicular growth was found in virtually only one cytologic type as defined by the Kiel classification (centroblastic-centrocytic), growth seemed to be secondary to cell type. However, the present results, as well as those reported by LENNER et coll. (1979b) and GARVIN et coll., oppose the view that growth pattern was of no primary prognostic significance, since any degree of nodularity within one cytologic type indicated a significantly better survival. Further, the proportion of centrocytes (or centroblasts) seemed to be of no primary importance for prognosis among the centroblastic-centrocytic and centroblastic lymphomas, respectively, only growth pattern was. The reason for these discrepancies against what has been reported by LENNERT and co-workers (see LENNERT) is not known. However, major differences in the incidence of the different subtypes of the FFC derived lymphomas exist between the materials. In the present material, purely centrocytic lymphomas were rare, whereas centroblastic lymphomas were common in contrast to previous series (LENNERT et coll., DÜHMKE & QUÄCK 1977, DELBRÜCK et coll. 1978, MEUGÉ et coll., KÖNIG et coll. 1981). Also the finding that 30 per cent of the centroblastic–centrocytic lymphomas had a diffuse growth pattern is contrary to previous series, where only a few per cent were diffuse. The reasons for these differences are not known, but they may represent regional differences in the incidence of different NHL subtypes and should not reflect diagnostic differences.

The differences in prognosis in the present series probably mirror biologic properties of the subgroups, and not differences in treatment or a non-uniform staging procedure. Apart from primary irradiation for the majority of patients in stage I and II, treatment varied considerably during the period. On the whole, the more aggressive microscopic types received a more intensive treatment, and therefore the observed differences probably do not reflect treatment differences. The centroblastic–centrocytic lymphomas of diffuse type, which were considered to be included with the high grade lymphomas, were treated with the same overall intensity as the highly malignant lymphomas as defined by the Kiel group (GÉRARD-MARCHANT et coll.). Apart from an examination to detect intra-abdominal disease, which was not always adequate, the patients were uniformly staged. The differences in survival found in the present series were present even if the results from lymphangiography were omitted, or if the patients that were not completely staged were excluded, thus ruling out this factor as a major cause for differences in survival.

The possibility to subgroup the NHL into 3 major, clearly separated prognostic groups using the Kiel classification may have great clinical implications. The treatment strategies can now be so differentiated that there could be room for more than the 2 prognostic groups proposed in the Kiel classification (GÉRARD-MARCHANT et coll.). It was possible to identify a group that seemed to be homogeneous with a truly favourable clinical course. The 2 other groups, the intermediate and unfavourable groups appeared less homogeneous. Both groups, although in different proportions, contained cases both with a rapidly fatal behaviour, and with an indolent course. This calls for other and better prognostic parameters.

Prognostic terms, such as high grade-unfavourable or low grade-favourable have been integrated into some of the modern classifications of NHL including the Kiel classification (GÉRARD-MARCHANT et coll.). This seems to be unsatisfactory for several reasons. The prognosis may vary between different geographic regions, and with time due to different or newer treatment regimens. The present results, as well as recent data from the Kiel Lymphoma Study Group (BRITTINGER et coll.) also im-

plicate that not only 2 prognostic groups could be identified, but rather 3 prognostic groups. The present results also point to a divergent place within the prognostic groups for some of the individual subgroups, compared with what has been proposed (GÉRARD-MARCHANT et coll.).

SUMMARY

In a retrospective analysis of 334 cases of non-Hodgkin's lymphoma observed between 1969 and 1978, 250 cases could be classified according to the Kiel classification. Clinicopathologic correlation was analysed for these latter cases. Irrespective of the morphologic appearance, all cases initially in stage I showed an excellent prognosis after radiation therapy alone, whereas the prognosis for stage II was similar to stages III and IV. For stages II–IV, 3 major prognostic groups with significantly differing survival curves were identified. The median survival times were one, 3 and more than 7 years, respectively. The pathologic and clinical significance of the Kiel classification is discussed.

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REFERENCES

BAGLEY C. M., DEVITA V. T. JR, BERARD C. W. and CANELLOS G. P.: Advanced lymphosarcoma. Intensive cyclical combination chemotherapy with cyclophosphamide, vincristine, and prednisone. Ann. Intern. Med. 76 (1972), 227.

BRITTINGER G., SCHMALHORST U., BARTELS H., FÜLLE H. H., GERHARTZ H., GREMMEL H., GRISAR T., GRUPP H. J., GUNZER U., HUHN D., KOEPPEN K.-M., KUBANEK B., LEOPOLD H., LÖFFLER H., LÖHR G. W., NOWICKI L., RUHL U., SCHMIDT M., STACHER A., THEML H. and LENNERT K. (Kiel Lymphoma Study Group): Principles and present status of a prospective multicenter study on the clinical relevance of the Kiel classification. Blut 43 (1981), 155.

BUTLER J. J., STRYKER J. A. and SHULLENBERGER C. C.: A clinico-pathological study of stages I and II non-Hodgkin's lymphomata using the Lukes-Collins classification. Brit. J. Cancer 31 (1975) Suppl. No. II, p. 208.

CARBONE P. P., KAPLAN H. S., MUSSHOFF K., SMITHERS D. W. and TUBIANA M.: Report of the committee on Hodgkin's disease staging classification. Cancer Res. 31 (1971), 1860.

COLBY T. V., HOPPE R. T. and BURKE J. S.: Nodular lymphoma. Clinico-pathologic correlations of parafollicular small lymphocytes and degree of nodularity. Cancer 45 (1980), 2364.

COX J. D., KOEHL R. H., TURNER W. M. and KING F. M.: Malignant lymphoid tumors of lymph nodes in the adult. Arch. Pathol. Lab. Med. 97 (1974), 22.

DELBRÜCK H., WEICHERT H. C., SCHMITT G., FIRUSIAN N. und WETTER O.: Der Zusammenhang zwischen Prognose und Kieler Klassifikation der malignen Non-Hodgkin-Lymphome. Eine katamnestische Studie über 201 Patienten. Klin. Wschr. 56 (1978), 539.

DORFMAN R. F.: Classification of non-Hodgkin's lymphomas. Lancet I (1974), 1295.

DÜHMKE E. und QUÄCK J.: Retrospektive Analyse von malignen Non-Hodgkin-Lymphomerkrankungen der Radiologischen Klinik der Universität Kiel von 1969 bis 1975. Strahlentherapie 153 (1977), 229.

EZDINLI E. Z., COSTELLO W., LENHARD R. E., BAKEMEIR R., BENNETT J. M., BERARD C. W. and CARBONE P. P.: Survival of nodular versus diffuse pattern lymphocytic poorly differentiated lymphoma. Cancer 41 (1978), 1990.

GARVIN A. J., SIMON R., YOUNG R. C., DEVITA V. T. and BERARD C. W.: The Rappaport classification of non-Hodgkin's lymphomas. A closer look using other proposed classifications. Semin. Oncol. 7 (1980), 234.

GÉRARD-MARCHANT R., HAMLIN I., LENNERT K., RILKE F., STANSFELD A. G. and VAN UNNIK J. A. M.: Classification of non-Hodgkin's lymphomas. Lancet II (1974), 406.

HAGBERG H., GLIMELIUS B. and SUNDSTRÖM S.: Radiation therapy of non-Hodgkin's lymphoma stage I and II. Acta radiol. Oncology 21 (1982), 145.

HEINZ R., STACHER A., PRALLE H., THEML H., BRUNSWICKER F., BURKERT M., COMMON H., FÜLLE H. H., GRISAR T., GRÜNEISEN A., HERRMANN F., LEOPOLD H., LIFFERS R., MEUSERS P., NOWICKI L., NÜRNBERGER R., RENGSHAUSEN H., RÜHL U., SCHOENGEN A., SCHMIDT M., WIRTHMÜLLER R., SCHWARZE E. W. and BRITTINGER G. (Kiel Lymphoma Study Group): Lymphoplasmacytic/lymphoplasmacytoid lymphoma. A clinical entity distinct from chronic lymphocytic leukaemia? Blut 43 (1981), 183.

JONES S. E., FUKS Z., BULL M., KADIN M. E., DORFMAN R. F., KAPLAN H. S., ROSENBERG S. A. and KIM H.: Non-Hodgkin's lymphomas. IV. Clinico-pathologic correlation in 405 cases. Cancer 31 (1973), 806.

KÖNIG E., BARTELS H., BREMER K., BURGER-SCHULER A., COMMON H., DÜHMKE E., ENGELHARD M., FÜLLE H. H., GUNZER U., KOPPEN K.-M., LEOPOLD H., NOWICKE L., OERTEL J., PAETZMANN S., RÜHL U., SCHMIDT M., SCHOENGEN A., SCHOLLE H., STACHER A., WOLF-HORNUNG B., SCHWARZE E.-W. and BRITTINGER G. (Kiel Lymphoma Study Group): Germinal center cell lymphomas. Prognostic significance of their histopathological differentiation. Blut 43 (1981), 193.

KRÜGER G. R. F., GRISAR T., LENNERT K., SCHWARZE E. W. and BRITTINGER G. (Kiel Lymphoma Study Group): Histopathological correlation of the Kiel with the original Rappaport classification of malignant non-Hodgkin lymphomas. Blut 43 (1981), 167.

LENNER P., LUNDGREN E. and DAMBER L. (a): Clinicopathologic correlation in non-Hodgkin's lymphomas. I. Retrospective analysis using the Lukes and Collins classification. Acta radiol. Oncology 18 (1979), 177.

— — — (b): Clinico-pathologic correlation in non-Hodgkin's lymphomas. II. Clinical and prognostic significance of nodularity. Acta radiol. Oncology 18 (1979), 417.

LENNERT K.: Malignant lymphomas other than Hodgkin's disease. *In:* Handbuch der speziellen pathologischen Anatomie und Histologie. Volume I. Part 3 B, p. 84. Springer, Berlin, Heidelberg, New York 1978.

— MOHRI N., STEIN H. and KAISERLING E.: The histopathology of malignant lymphoma. Brit. J. Haematol. 31 (1975), 193.

LUKES R. J.: Discussion II. Roundtable discussion of histopathologic classification. Cancer Treat. Rep. 61 (1977), 1042.

— and COLLINS R. D.: Immunologic characterization of human malignant lymphomas. Cancer 34 (1974), 1488.

MUEGÉ C., HOERNI B., DEMASCAREL A., DURANT M., RICHAUD P., HOERNI-SIMON G., CHAUVERGNE J. and LAGARDE C.: Non-Hodgkin malignant lymphomas. Clinico-pathologic correlations with the Kiel classification. Europ. J. Cancer 14 (1978), 587.

NATHWANI B. N., KIM H., RAPPAPORT H., SOLOMON J. and FOX M.: Non-Hodgkin's lymphomas. A clinicopathologic study comparing two classifications. Cancer 41 (1978), 303.

PATCHEFSKY A. S., BRODOVSKY H. S., MENDUKE H., SOUTHARD M., BROOKS J., NICKLAS D. and HOCH W. S.: Non-Hodgkin's lymphomas. A clinico-pathologic study of 293 cases. Cancer 34 (1974), 1173.

PETO R., PIKE M. C., ARMITAGE P., BRESLOW N. E., COX D. R., HOWARD S. W., MANTEL N., MCPHERSON K., PETO J. and SMITH P. G.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Brit. J. Cancer 35 (1977), 1.

RAPPAPORT H.: Tumors of the hematopoietic system. Atlas of tumor pathology, sect. III, fasc. B, p. 91. Armed Forces Institute of Pathology, Washington D.C. 1966.

— WINTER W. J. and HICKS E. B.: Follicular lymphoma. A reevaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 9 (1956), 792.

STACHER A., WALDNER R. und THEML H. (Kieler Lymphomgruppe).: Klinik der malignen Non-Hodgkin-Lymphome entsprechend der Kieler Klassifikation. Lymphoplasmozytoides Lymphom und chronisch lymphatische Leukämie. *In:* Maligne Lymphome und monoklonale Gammopathien. Hämatologie und Bluttransfusion. Volume 18, p. 199. Edited by H. Löffler. Lehmann, München 1976.

WARNKE R. A., KIM H., FUKS Z. and DORFMAN R. F.: The coexistence of nodular and diffuse patterns in nodular non-Hodgkin's lymphomas. Significance and clinicopathologic correlation. Cancer 40 (1977), 1229.