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# A CLINICO-PATHOLOGICAL AND PROGNOSTIC ANALYSIS OF NON-HODGKIN LYMPHOMA

## A study of 203 patients

J.-M. NABHOLTZ, S. FRIEDMAN, H. BASTIEN, J. CUISENIER, J.-C. HORIOT and J. GUERRIN

**Abstract**

In a retrospective analysis of 203 patients with non-Hodgkin lymphoma (NHL) treated between 1975 and 1985, the relationship between pathology, clinical presentation and course, was studied, using the Kiel classification. This classification was a much better predictor of prognosis than clinical stage and within the different pathology groups there was no significant difference between the stages concerning the survival rate. In the group with low grade malignancy this latter was positively associated with nodular architecture, bone marrow involvement and complete or partial response to therapy. In the high grade group, the survival was positively correlated to complete remission, but no plateau was seen in the survival curve. All extranodal sites had poor survival. For both grades, age (>60 years), systemic symptoms and biologic signs (Ann Arbor 'B' and 'b') were unfavorable prognostic factors.

*Key words*: Lymphoma, non-Hodgkin; clinical signs, histopathology, Kiel classification, prognosis.

Non-Hodgkin lymphomas (NHL) are a group of heterogeneous diseases in terms of pathology, clinical presentation, treatment and prognosis (1, 8, 10, 29, 32, 39, 42, 47, 48, 51). There have been many attempts to classify these tumors according to prognostic groupings (6, 21–23, 34, 37, 38, 43, 46), that more recently have involved such fields as immunology, morphometry, cell kinetics and immunohistochemistry.

Few of these investigative techniques have resulted in improvements of therapy. Practical considerations require a simple, inexpensive, and reproducible prognostic categorization of NHL for the application of effective therapy. Using the Kiel classification, we have analysed the correlation between pathology, clinical presentations and prognosis in a group of 203 patients admitted in 1975 to 1985.

### Material and Methods

A retrospective analysis of 321 patients with NHL seen between 1975 and 1985 at the Georges-François Leclerc Institute, Dijon was performed. Of these, 118 patients were excluded from this study due to uncertain pathology (n=18), incomplete initial evaluation (n=5), insufficient follow-up (n=24) and treatment in other institutions (n=71). This left 203 patients for analysis.

All pathology slides were read or reviewed by 2 experienced pathologists of our institution (Dr H. Bastien and Dr F. Collin) and graded according to the Kiel classification and architectural pattern (nodular or diffuse). For any doubtful cases, a panel of experts was consulted: Profs. R. Michiels, Dijon, J. Diebold, Paris, and K. Lennert, Kiel.

Staging was performed according to the Ann Arbor classification (15) in similar fashion in all patients and consisted of a history and physical examination, chest radiogram, ENT examination if there were any symptoms in this area, blood counts, routine blood chemistry and urine tests, bone marrow aspiration and biopsy, and sonography or CT scan of the liver. In all patients staged I–III the abdominal lymph nodes were studied by lymphography or CT scan. Biologic signs ('b') were evaluated (15) by ESR, serum fibrinogen, $\alpha$-2 globulin and iron binding studies.

The treatment methods varied only slightly over the years. In general, involved field radiotherapy alone was employed for stage I patients, combinations of radiotherapy and chemotherapy for stage II patients, and chemo-

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therapy alone for stage III and IV patients. Chemotherapy consisted of CVP (cyclophosphamide, vincristine, prednisone) or CVP-like protocols for low grade (LG) (4, 45), and CHOP (cyclophosphamide, doxorubicine, vincristine, prednisone) or similar protocol (19) for high grade lymphomas (HG).

The median follow-up of all patients was 5.8 years. Survival rates were calculated by Kaplan-Meier and actuarial methods and differences between survival were analysed with the log rank test.

## Patient Characteristics

According to the Kiel classification, 117 patients (57.6%) were classified as LG, and 86 (42.3%) as HG. In the LG group, 48 patients (41%) had a nodular and 69 (59%) a diffuse pattern. In the HG group, all were diffuse. The pathology types are shown in Table 1.

The mean age of the patients in both groups was 61 years; 120 patients (59.1%) were 60 years or older. The sex ratio (M/F) was 1.18 without apparent difference between the 2 grades.

In 148 patients (72.9%), the disease initially appeared as purely nodal while 55 (27.1%) patients also had obvious extra-nodal involvement. After complete evaluation, however, 55 (47.0%) patients in the LG group had disease localized to the lymph nodes, 22 (18.8%) nodal involvement with bone marrow invasion and 44 (37.6%) other extra-nodal involvement. In the HG group, 24 patients (27.9%) had disease localized to the lymph nodes, 5 (5.8%) had nodal and bone marrow involvement, and 57 (66.3%) other extra-nodal manifestations in addition to nodal involvement. Tables 2a and 2b show the sites of extra-nodal involvement in the two grades and their subtypes.

Table 3 summarizes the clinical stages according to pathology.

Forty patients (19.7%) presented with 'B' symptoms. Of these, 17 patients (42.5%) had LG disease, and 23 (57.5%) HG. Overall, 14.5% with LG disease had 'B' symptoms compared with 26.7% with HG. Of the 17 LG patients with 'B' symptoms, 15 had stages III or IV, compared with 15 of 23 HG patients.

Forty-three patients had 2 or more abnormal biologic tests ('b'); 17 of them had LG, of which 13 belonged to stages III and IV. In the HG group, 26 patients had abnormal biologic tests, 16 of whom had stage III or IV disease. Of the 17 'b' patients in the LG group, 9 had 'B' symptoms. Of the 26 'b' patients in the HG group, 14 had 'B' symptoms.

## Results

Overall 92 patients (45.3%) achieved complete remission (CR), 56 in the LG group (60.9%) and 36 in the HG group (39.1%). Forty-eight patients (23.6%) had partial

**Table 1**

*Kiel classification and architectural pattern*

| Kiel classification | Architectural pattern | No. | Percentage |
|---|---|---|---|
| Low grade | | | |
| Lymphocytic | Diffuse | 31 | 15.3 |
| Lymphasmocytic | Diffuse | 22 | 10.8 |
| Centrocytic | Diffuse | 4 | 2.0 |
| Centroblastic-centrocytic | Nodular | 48 | 23.6 |
| | Diffuse | 12 | 5.9 |
| High grade | | | |
| Centroblastic | Diffuse | 32 | 15.8 |
| Immunoblastic | Diffuse | 32 | 15.8 |
| Lymphoblastic | Diffuse | 21 | 10.3 |
| Undifferentiated | Diffuse | 1 | 0.5 |

**Table 2a**

*Extra-nodal involvement in low grade lymphomas*

| Low grade | Lc | Lpc | Cc | Cb-cc | Total (%) |
|---|---|---|---|---|---|
| No. | 31 | 22 | 4 | 60 | 117 |
| Bone marrow | 19 | 4 | 4 | 12 | 39 (33.3) |
| Liver | 2 | 1 | 0 | 4 | 7 (6.0) |
| Lung | 2 | 1 | 0 | 2 | 5 (4.3) |
| G.I. tract | 1 | 5 | 0 | 1 | 7 (6.0) |
| E.N.T. | 3 | 9 | 1 | 9 | 22 (18.8) |
| Uro-genital | 0 | 2 | 0 | 1 | 3 (2.6) |

Lc=Lymphocytic, Lpc=Lymphoplasmocytic, Cc=Centrocytic, Cb-cc=Centroblastic-centrocytic.

**Table 2b**

*Extra-nodal involvement in high grade lymphomas*

| High grade | Cb | Lb | Ib | Ud | Total (%) |
|---|---|---|---|---|---|
| No. | 32 | 21 | 32 | 1 | 86 |
| Bone marrow | 7 | 6 | 2 | 0 | 15 (17.4) |
| Liver | 3 | 2 | 5 | 0 | 10 (11.6) |
| Lung | 0 | 1 | 1 | 0 | 2 (2.3) |
| G.I. tract | 3 | 2 | 5 | 0 | 10 (11.6) |
| E.N.T. | 9 | 2 | 8 | 1 | 20 (23.2) |
| Uro-genital | 3 | 0 | 2 | 0 | 5 (5.8) |
| C.N.S. | 2 | 2 | 2 | 0 | 6 (7.0) |
| Skin | 4 | 1 | 4 | 0 | 9 (10.5) |

Cb=Centroblastic, Lb=Lymphoblastic, Ib=Immunoblastic, Ud=Undifferentiated.

**Table 3**

*Clinical stages and pathology grades*

| | Total series (n=203) | Low grade (n=117) | High grade (n=86) |
|---|---|---|---|
| Stage I | 47 (23.1%) | 20 (17.1%) | 27 (31.4%) |
| Stage II | 34 (16.7%) | 20 (17.1%) | 14 (16.3%) |
| Stage III | 39 (19.2%) | 26 (22.2%) | 13 (15.1%) |
| Stage IV | 83 (41.0%) | 51 (43.6%) | 32 (37.2%) |

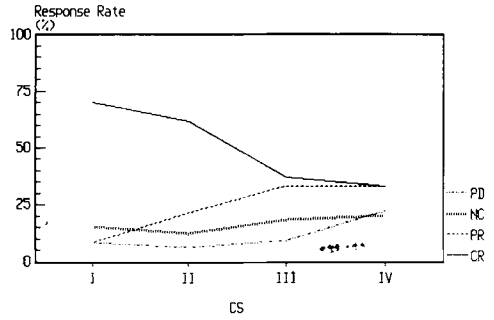


Fig. 1. Response rates to therapy according to clinical stage (Ann Arbor classification). CR=Complete response, PR=Partial response, NC=No change, PD=Progressive disease.

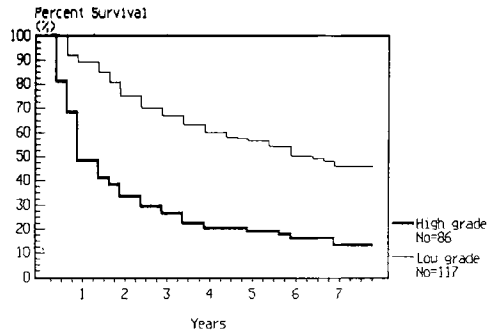


Fig. 2. Survival probability according to Kiel classification ($p<0.001$).

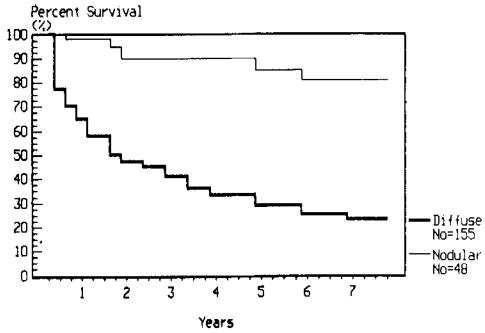


Fig. 3. Survival probability according to architectural pattern ($p<0.001$).

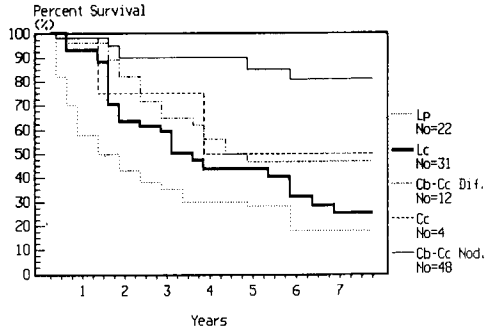


Fig. 4. Survival probability according to Kiel low-grade subtypes. Cb-Cc Nod.=Centroblastic-centrocytic (nodular), Cb-Cc Dif.=Centroblastic-centrocytic (diffuse), Cc=Centrocytic (diffuse), Lc=Lymphocytic (diffuse), Lp=Lympho-plasmocytic (diffuse).

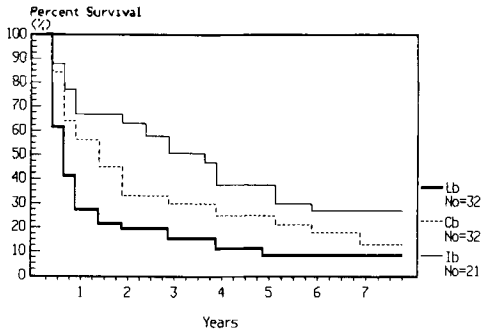


Fig. 5. Survival probability according to Kiel high-grade subtypes. Lb=Lymphoblastic, Cb=Centroblastic, Ib=Immunoblastic.

response (PR), 37 with LG (77.1%), and 11 with HG disease. Sixty-three patients (31.1%) had either minimal or no response (NR), 24 with LG (38.1%) and 39 with HG disease (61.9%).

In the total series, the proportion of CR was highest in stage I and then progressively decreased with advancing stage (Fig. 1).

In the total series, the 5-year survival rate was 41.9%. The LG group had a 56.4% survival rate and the HG group 18.6% ($p<0.001$) (Fig. 2). The 5-year survival rate was 85.1% for lymphomas with nodular pattern and 28.4% for patients with lymphomas with diffuse pattern ($p<0.001$) (Fig. 3). Among the patients with LG histology the survival rate was higher in the group with nodular pattern ($p<0.05$). When all patients with diffuse pattern were compared to those with HG histologies, it was found that the survival rate was higher in the diffuse group ($p<0.01$).

The survival curves for the different pathology subtypes within the LG group showed a large spread (Figs 4 and 5). Therefore we studied a third group within the Kiel classification, consisting of patients with LG lymphoma and diffuse architecture (40). This resulted in separations of survival curves between LG nodular and LG diffuse and between LG diffuse and HG which were significant ($p<0.001$ and $p<0.05$ respectively) (Fig. 6).

Contrariwise, the HG group showed a close clustering of survival rates with time (after 4 years) when divided according to pathology sub-types (Fig. 5).

Survival rates at five years according to stage were not significantly different (Fig. 7). When separated into grades, there was a difference between LG and HG ($p<0.001$) but still not between the stages within the respective grades.

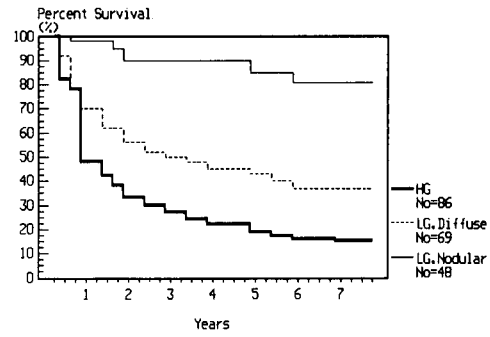


Fig. 6. Survival probability according to Kiel classification and architectural pattern.

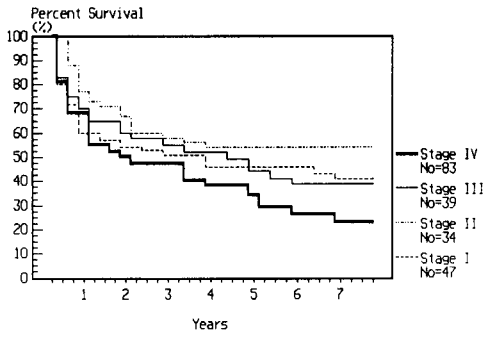


Fig. 7. Survival probability according to clinical stage (Ann Arbor classification).

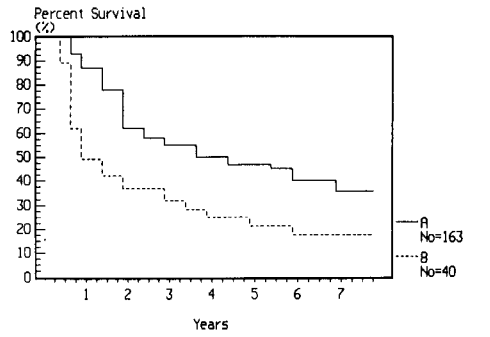


Fig. 8. Survival probability according to systemic symptoms (A, B; Ann Arbor classification) ($p<0.02$).

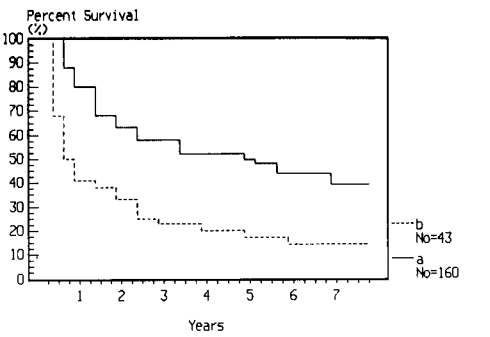


Fig. 9. Survival probability according to biologic signs (a, b; Ann Arbor classification) ($p<0.01$).

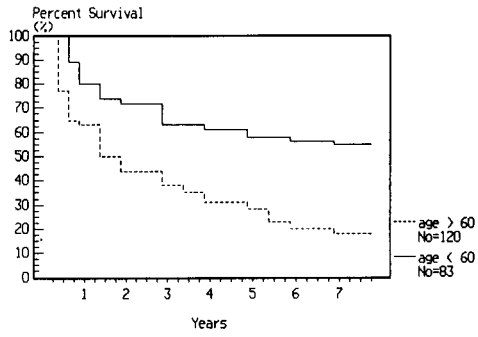


Fig. 10. Survival probability according to age ($p<0.02$).

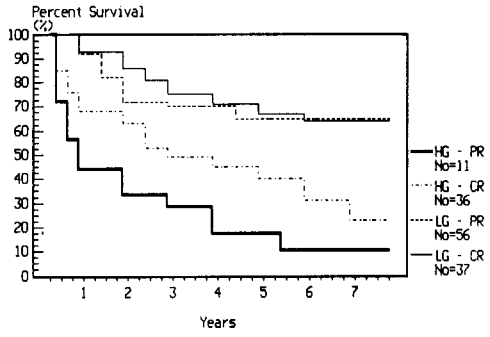


Fig. 11. Survival probability according to Kiel classification and response to therapy. CR=Complete response, PR=Partial response.

Both systemic symptoms ('B') and 2 or more biologic signs ('b') were correlated to poor survival ($p<0.02$ and $p<0.01$ respectively) (Figs 8 and 9). Patients over 60 years had a poorer survival ($p<0.02$) than patients younger than 60 years (Fig. 10). There was no survival difference between the sexes (males/39.2%, females/41.9% at 5 years).

In the LG group, patients with complete response (CR) and partial response (PR) had similar survivals (66.7% and 63.7% respectively at 5 years) (Fig. 11). In the HG group, patients with CR lived longer than those with PR (40.5% and 16.7% 5-year survival rate respectively) (Fig. 11); however, there were only 11 patients in the PR group, and no statistical analysis of this difference was performed. A general experience in our series was that patients with HG lymphoma either achieved CR or rapidly progressed. When the response was less than a 50% shrinkage of the tumor mass (NC, PD), there was no survival difference between the 2 grades (Fig. 12).

In stage IV disease, the survival in patients with and without bone marrow invasion was compared. Within the LG group the 5-year survival was 71.9% in patients with bone marrow involvement and 12% in the patients with-

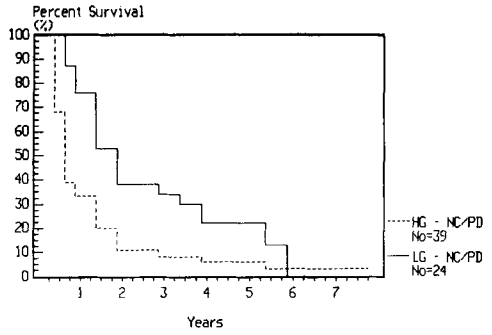


Fig. 12. Survival probability according to Kiel classification and response to therapy. NC=No change, PD=Progressive disease.

out involvement (p=0.02). No such difference was seen in patients with stage IV HG lymphomas with and without bone marrow invasion, both of which had a 5-year survival of 12.5%.

## Discussion

Our series showed similar proportion of LG and HG forms as reported in the literature (9, 32, 33). Also the distribution of histologic subtypes agreed in general with previous reports (32, 33). Noteworthy, however, was our high proportion (15.7%) of centroblastic lymphomas. While a similar high proportion has been found in 2 other series (10, 30), most other reported materials have contained a far lower proportion (3–6%) of centroblastic type (11, 32, 33, 35, 39). This discrepancy is probably not due to confusion between centroblastic and immunoblastic forms, since in our series the latter accounted for about 15%, which is similar to other reports (10, 11, 32, 33, 39).

According to our analysis the Kiel classification was a good predictor of survival, especially when the LG group was separated into nodular and diffuse forms with creation of an intermediate grade group (40). Other authors have also emphasized the importance of Rappaport's initial observation regarding prognostic implications of the architecture (20, 46). Separation of the groups according to pathology gave much better prognostic information than clinical staging in our series.

Within our LG group, the 22 lympho-plasmacytic lymphomas had a particularly poor survival, approximating that of the HG group. Furthermore, the lymphocytic type, considered to be relatively benign, had a poorer survival than several other forms.

As in most reports, the majority of patients with LG histology had advanced stage usually with nodal predominance. In the HG forms, extra-nodal involvement was more frequent, often with minimal nodal involvement (1).

Although we used the Ann Arbor classification for staging, we are well aware of its serious limitations. It takes into account neither several important prognostic factors, such as the tumor mass (28), nor the existence of localizations, such as CNS or mediastinum (9, 16, 24, 25, 41). Bone marrow invasion, considered as stage IV, is thought to yield a poor prognosis. This, however, appears not to be the case in the LG forms.

In our study the survival rates were not significantly different in the different stages. The literature is quite controversial on the usefulness of the Ann Arbor classification for NHL (30, 32, 35, 49). Clearly this staging is not as useful in NHL as in Hodgkin's disease for which it was initially devised (15).

Of interest was the finding that the Ann Arbor biologic signs did not correlate well with 'B' symptoms. However, both 'B' symptoms and 'b' signs were associated with unfavorable prognosis. While the majority of the authors have recognized 'B' as an unfavorable factor (7, 12, 17, 49), we have found no mention in the literature of 'b' signs as a prognostic factor.

Stage IV patients in the HG group had similar survival regardless of the site of involvement. In the LG group, patients with bone marrow involvement as the only extranodal manifestation had a 5-year survival of 71.9%, which was similar to the anatomically least advanced stages. This was in marked contrast to patients in stage IV LG with other sites of involvement, who had a 5-year survival rate of 12%, equal to the most unfavorable groups of HG lymphomas. This raises the question of whether routine bone marrow biopsies are necessary in the LG group. Similar observations have been reported from other studies (5, 27).

As in other series (2, 8, 17, 32), response to initial therapy was also an important predictive factor, particularly in the HG groups. Our HG patients had a CR rate of 40%, and 40% of the patients with CR were alive at 5 years. Only 16% of the patients with PR survived for 5 years. However, even in patients achieving a CR, the long-term results were not good, in agreement with the rather high rate of late relapses that have been reported in patients with CR after CHOP therapy (3). Clearly, therapy more aggressive than CHOP is necessary for this group (13, 14, 18, 26, 31, 36).

In the LG group, the survival in patients with CR and PR was similar, in agreement with other reports (44, 45, 48). Our patients with LG pathology who responded poorly to therapy (no response or less than 50% shrinkage) had a survival comparable to the poor responders in the HG group.

In our univariate analysis, the most important prognostic factors were the pathologic grade and architectural pattern. As these prognostic factors were presented in Rappaport's initial article (46), it is obvious that the therapies employed up to the present study have not been very successful. However, some subtypes of the HG lymphomas are clearly curable with more aggressive chemotherapy (13, 14, 18, 26, 31, 36, 50), and hopefully this type

of therapy will change the long-term prognosis in patients currently being treated.

*Request for reprints*: Dr J.-M. Nabholtz, Centre Georges-François Leclerc, 1, rue du Prof. Marion, F-21000 Dijon, France.

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