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REVIEW

# RELATIONSHIP BETWEEN PROGNOSTIC FACTORS AND THERAPY IN HIGH-GRADE NON-HODGKIN'S LYMPHOMAS OVER TWO DECADES

MASSIMO FEDERICO, PAOLO G. GOBBI, FAUSTO BARBIERI, VITTORIO SILINGARDI

**We considered the prognostic factors in high-grade non-Hodgkin's lymphomas (HG-NHL) over the past two decades. In an effort to clarify the relationship between prognostic factors and therapy, we pooled the literature reports concerning 3,480 patients into four different periods according to the mean years of the clinical trials. The most important prognostic factors discovered in period A (mean year prior to 1970) were histology, symptoms and stage. In period B (1970 through 1975), in addition to the former indicators, two new factors were pointed out: bone marrow involvement and serum lactic dehydrogenase. In period C (1976 through 1980) the significance of stage was reduced, while bulk and measures of lymph nodal and extranodal involvement (LSI, ESI) were found to be better prognostic factors. In studies related to this period the prognostic role of albumin, hemoglobin and erythrocyte sedimentation rate were also emphasized. Period D (1980 through 1985) was characterized by a decrease in the importance of the Kiel and Working Formulation (WF) classifications by virtue of the better outcome, in different reports, of HG-NHL with respect to low-grade NHL. The conclusion of our analysis is that symptoms, ESI, bulk, LDH, albumin and hemoglobin should be the most important factors used today in planning the therapy and management of patients with HG-NHL. In addition, an update of the WF is necessary.**

KEY WORDS: Non-Hodgkin's lymphomas, prognostic factors, therapy.

*From the Istituto di Clinica Medica, Divisione di Oncologia, Università di Modena, and the Dipartimento di Medicina Interna, Sezione di Clinical Medica II Univesità di Pavia, Italy.*

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*Correspondence: Dr. M. Federico, Istituto di Clinica Medica, Divisione di Oncologia, Policlinico, via del Pozzo 71, 41100 Modena, Italy.*

The non-Hodgkin's lymphomas (NHL) are a diverse group of tumors that affect people from early childhood to old age. In recent years, increased understanding of the biology of lymphomas has resulted in the successful application of new staging and treatment programs. Combination chemotherapy is capable of producing complete remissions and long-term disease-free survival in an increasing number of patients [1-12] and is proposed as the treatment for early stage aggressive histologic type NHL either alone [13 14] or in combination with radiotherapy [4,15-20]. The American Cancer Society reported that the 5-year survival rate for patients with NHL increased from 31% in 1963 to 41% in 1973, and to 49% in the period from 1979 to 1984 [21]. This improvement in survival is among the best posted for any cancer type during the same period, second only to Hodgkin's disease.

The Kiel classification [22] and the Working Formulation (WF) [23], two of the most diffuse classification of NHL, have their grading systems based upon survival characteristics because of the close relation between morphological pattern and clinical outcome. The Kiel classification groups all NHL into two categories [low-grade (LG) and high-grade (HG) lymphomas], while the WF has also incorporated an intermediate grade (IG) of malignancy. In both these systems, HG-NHL is synonymous with poor prognosis.

However, patients with HG-NHL can achieve a complete remission with appropriate therapy, and an increasing proportion will have long-term survival [1-5 15 16]. Paradoxically, the long-term prognosis of HG-NHL now seems better than that of LG-NHL [1-4], therefore histological classification are losing their prognostic significance.

In addition to histology, some other traditional parameters (e.g. stage) seem to be less important to-

day as prognostic indicators. New factors have recently been discovered, however, and have been found to provide better prognostic information.

The prognostic variability of a disease is a function of both factors due to the disease and factors due to the therapy [24]. Therefore, when analyzing prognostic factors in HG-NHL, it is most important to define the period over which patients were treated because the treatment closely reflects the type of prognostic factors discovered.

Reports on prognostic factors often reflect the experience of a single institution over a long period (ten years or more, in most cases). This fact sometimes confuses the analysis because important changes in therapy occur and, consequently, the life expectancy or the response rates of patients treated at the beginning of the interval may be very different from those toward the end.

In the past two decades we can distinguish at least four different periods characterized by radical modification in NHL therapy. During period A (up to the late 1960s) the treatment for NHL was essentially palliative. Period B, from 1970 to 1975, was characterized by the use of earlier protocols of combination chemotherapy. Doxorubicin was introduced in the mid 1970s and marked the beginning of period C. Finally, period D (from the late 1970s until today) has been characterized by the use of alternating, non cross-resistant chemotherapy.

In this review we try to analyze the evolution of prognostic factors in HG-NHL across these four periods. Because published reports do not refer to the above indicated periods, we have grouped the literature according to the mean year of trial dates. If the mean year was prior to 1970 we placed the study in period A, if it was 1971 through 1975 we placed it in period B, 1976 through 1980 in period C, and, finally, if the mean year was later than 1980 we placed it in period D (Fig. 1). In this way we obtained four fairly homogeneous groups of reports, helpful in clarifying the relationship between therapy and prognostic factors in HG-NHL.

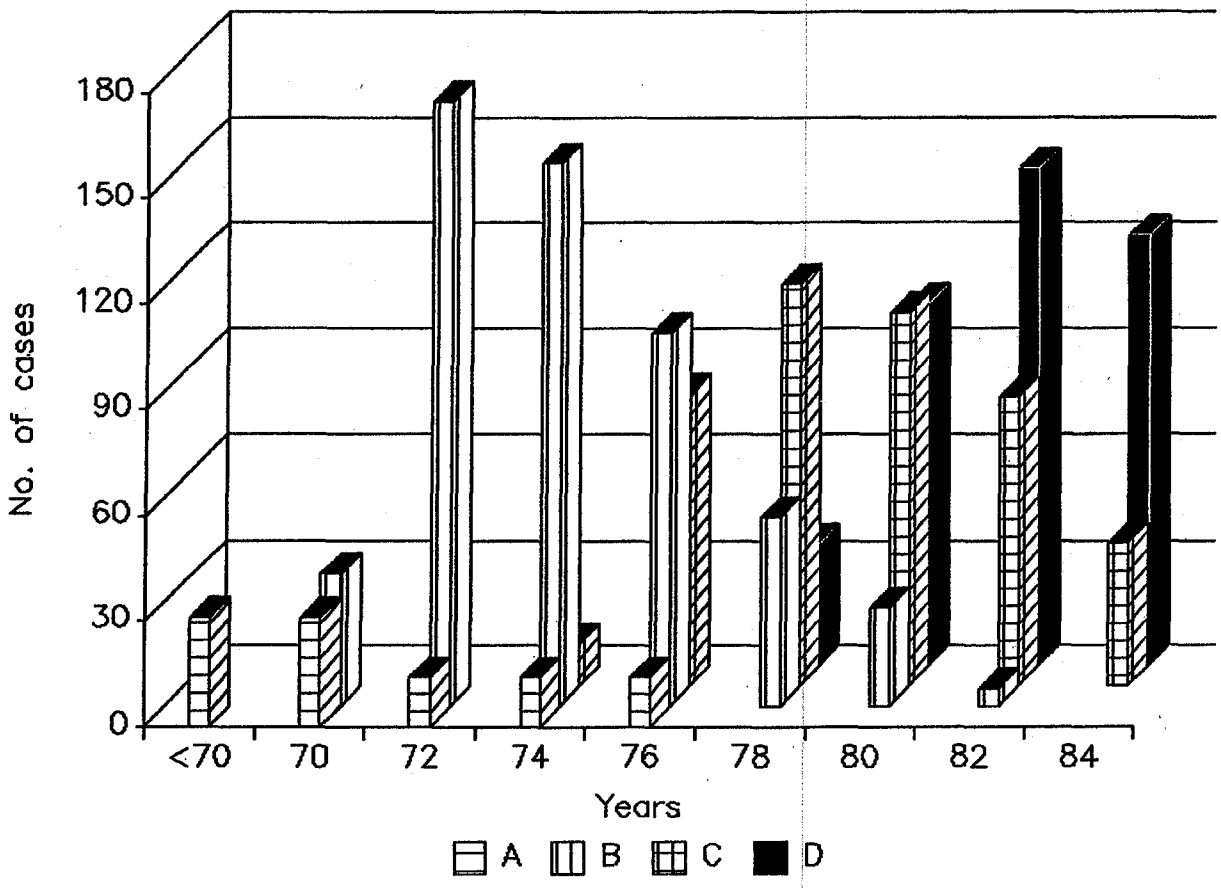


Fig. 1. - Estimated distribution of patients considered in the four different periods (see text), according to the year of treatment. Each column covers a two-year interval (70 = 1970-1971; 84 = 1984-1985).

PERIOD A STUDIES

Until the late 1960s results in the treatment of HG-NHL were very poor, with a median survival of less than one year in most cases. Five-year survival rates are similar among the different reports in period A (Table 1). We estimated a 5-year survival rate of 24.8% for all 459 cases considered in this period. The most important prognostic factors in this period were histopathologic pattern, stage and symptoms as defined at the Ann Arbor conference for Hodgkin's disease (unexplained fever of greater that 38°C, weight loss of more than 10% of body weight in the 6 months prior to admission, and night sweats) [25]. In these studies, NHL were usually named according to the Rappaport classification [26]. Rappaport's HG-NHL [diffuse poor differentiated lymphocytic (DPDL), mixed diffuse (MD), histiocytic diffuse (HD), Burkitt's and diffuse undifferentiated (DU) lymphomas] had the worst prognosis, while nodular or diffuse but well-differentiated lymphomas showed a better outcome. The presence of systemic symptoms and an advanced stage at diagnosis adversely affected the prognosis. In a report on 473 patients with malignant lymphomas treated between 1953 and 1975 at the NCI [27], it was possible to evaluate the clinical outcome of 105 patients with HG-NHL treated before 1968. For this purpose we considered 29 patients with DPDL, 34 with DH, 11 with DM, 19 with Burkitt's, and 12 with DU lymphoma. Five-year survival rates were 25, 10, 10, 35, and 0%, respectively. There was a significant difference in survival rates between these lymphomas and other diffuse but well-differentiated or nodular lymphomas. In all histological types, complete response rates, and then survival, correlated well with disease stage. In the group of patients with DPDL, however, the presence of systemic symptoms was still associated with a worse prognosis. In conclusion, only a few cases in well-documented early stages without systemic symptoms showed a better prognosis.

The median survival of 133 patients with HG-NHL treated at the Memorial Sloan Kettering Cancer Center (MSKCC) between 1958 and 1969, and reported recently by Lieberman [28], was less than 9 months, while it was more than 2 years for LG-NHL. The median survival in different subgroups of HG-NHL, classified according to the Kiel classification, was 9 months for 46 patients with centroblastic primary, 6 months for 29 patients with centroblastic polymorphous, 8 months for 25 patients with immunoblastic, and 5 months for 30 patients with lymphoblastic lymphoma. The overall five-year survival rate was less than 20%. In this report, too, clinical stage was highly significant ($p = 0.006$) as a prognostic factor within HG-NHL.

The study performed by Rosenberg, who analyzed 221 cases of HG-NHL, reached different conclusions. The histological pattern was the only indicator of prognostic information in this series, with stage failing to supply any useful information for identifying different prognostic groups [29].

PERIOD B STUDIES

The introduction of combination therapy in the early 1970s resulted in increased survival of patients with HG-NHL [23,30-34]. Analyzing the results of the treatment of more than 1200 cases reported in the literature, we estimated the 5-year survival rate to be 33.1% during this period (Table 2). Histology, stage and symptoms are still referred as good predictors of clinical outcome. In the National Cancer Institute (NCI) sponsored study of classification of NHL, a clinicopathologic study of 1175 previously untreated patients seen at four institutions between 1971 and 1975 is reported. Out of the 1175, 475 cases were classified in the HG-NHL group. A significant difference in survival among LG-, IG-, and HG-NHL was found. The 5-year survival rate for the four subgroups of HG-NHL (diffuse large cell, im-

Table 1. - *Prognostic factors discovered in patients with high-grade non-Hodgkin's lymphomas treated during period A.*

| Author | Trial dates | Mean year | No. of patients | 5-year survival (%) | Median survival (Mo.) | Prognostic factors | Ref. |
|---|---|---|---|---|---|---|---|
| Lieberman | 58-69 | 64 | 133 | < 20 | 9 | Histology, stage | 28 |
| Rosenberg | 61-76 | 69 | 221 | 30 | N.A. | Histology, stage, symptoms | 29 |
| Anderson | 53-68 | 61 | 105 | 20 | 23 | Histology, symptoms | 27 |
| Total | | | 459 | 24.8 * | | | |

Legend: N.A. = not assessed; * = calculated mean value.

Table 2. - *Prognostic factors discovered in patients with high-grade non-Hodgkin's lymphomas treated during period B.*

| Author | Trial dates | Mean year | No. of patients | 5-year survival (%) | Median survival (Mo.) | Prognostic factors | Ref. |
|---|---|---|---|---|---|---|---|
| Fisher | 64-77 | 71 | 151 | 43 | 34 | Histology, stage, symptoms, BM, LDH | 30 |
| Blanco | 64-81 | 73 | 155 | 30 | 15 | Histology, stage | 31 |
| Bloomfield | 69-72 | 70 | 78 | 30 | N.A. | Histology, stage, symptoms, BM | 32 |
| Working F. | 71-75 | 73 | 475 | 35 | 24 | Histology | 23 |
| Ersboll | 70-79 | 75 | 342 | 30 | N.A. | Histology | 33 |
| Mauri | 68-79 | 74 | 70 | 30 | 13 | Histology, stage, symptoms | 34 |
| Total | | | 1271 | 33.1 * | | | |

Legend: BM = bone marrow; N.A. = not assessed; * = calculated mean value.

munoblastic, lymphoblastic, and small non-cleaved cell lymphomas) was 35, 32, 26, and 23%, respectively. For the same groups, median survival was 1.5, 1.3, 2.0 and 0.7 years [23]. Other retrospective studies, considering patients treated between 1964 and 1981, pointed out the importance of the WF of Kiel classification in terms of prognostic value [31 33 34]. A few, but significant, new prognostic indicators were also discovered during this period. Bloomfield stressed the role of bone marrow (BM) involvement in determining a poor prognosis [32]. Fisher, in a study of 151 patients with HG-NHL treated at NCI between 1964 and 1977 (with a median survival of 34 months and a 5-year survival rate of 43%) [30], found that huge abdominal mass with gastrointestinal (GI) involvement, hemoglobin, and serum lactic dehydrogenase (LDH) also had good prognostic value. In this study, GI involvement adversely affected the survival only when a huge abdominal mass was present, and patients with normal LDH had a better prognosis than those with higher LDH. This supports the correlation of serum LDH with prognosis suggested by Ferraris in 1979 [35]. The prognostic values of LDH was subsequently reported by several more authors [1 7 36-41] and appears to be the most important new factor, along with BM involvement, discovered in studies of patients treated with combination chemotherapy in the early 1970s.

### Period C studies

In the middle 1970s doxorubicin was introduced into the most commonly used chemotherapeutic protocols (CHOP, BACOP), and an increase in survival was seen. The estimated 5-year survival rate of 905 cases treated with similar protocols but published by different groups, between 1977 and 1987 was 39.7%, ranging from 19% of 86 cases described by Nabholtz [42] to 60% of 79 cases reported by Fisher [30] (Table 3). In these studies histology and symptoms appear to be important prognostic factors, but the value of stage proved to be less useful than in the past.

Histology is the most important prognostic factor in those series with poorer survival rates [6 42 43]. Steward, who reported a 5-year survival of 37% with a median survival of 20 months, performed a Cox's multivariate analysis to identify those variables with the most significant effect on the length of survival [41]. The first three characteristics ranked in order of importance by the stepwise method showed that a complete remission with initial therapy was the most important factor, followed by LDH levels and liver involvement. Analysis of factors associated with higher complete remission rates and better survival include lack of systemic symptoms, absence of BM involvement, high serum albumin level and female sex (although less important). Gobbi, who reported a 5-year survival of 37% in a series of 161 patients [44], using a multivariate approach also found that albumin is a very sensitive prognostic factor. Danieu et al. from MSKCC proposed a model for prognosis in advanced DH lymphoma [38]. In this report the median survival of 127 patients was 20 months, with a 5-year survival of 50% for 24 patients in stage II, 54% for 26 patients in stage III, and 38% for 77 patients in stage IV (estimated 5-year survival of the group as a whole was 43%). Parameters of prognostic value, as determined by univariate analysis, included age, LDH, bulky disease and level of site involvement (LSI). With a multivariate analysis they constructed a model based on LDH and LSI. This model discriminated between four different prognostic

Table 3. - *Prognostic factors discovered in patients with high-grade non-Hodgkin's lymphomas treated during period C.*

| Author | Trial dates | Mean year | No. of patients | 5-year survival (%) | Median survival (Mo.) | Prognostic factors | Ref. |
|---|---|---|---|---|---|---|---|
| Fisher | 77-81 | 79 | 79 | 60 | — | BM, GI | 2 |
| Shipp | 76-83 | 80 | 121 | 50 | 68 | Tumor bulk, ESI, LDH, symptoms, stage | 36 |
| Somers | 75-82 | 79 | 49 | 35 | N.A. | Histology, stage, tumor bulk | 6 |
| Jagannath | 74-81 | 78 | 105 | 48 | 58 | Tumor bulk, ESI, LDH, symptoms | 37 |
| Nabboltz | 75-85 | 80 | 86 | 19 | 12 | Histology | 42 |
| Danieu | 74-84 | 79 | 127 | 40 | 20 | LSI, LDH | 38 |
| Steward | 75-82 | 79 | 111 | 37 | 20 | Stage, LDH, symptoms, BM, albumin | 41 |
| Leonard | 76-79 | 78 | 66 | 25 | 15 | Histology, stage, symptoms, hemoglobin | 43 |
| Gobbi | 75-85 | 80 | 161 | 37 | N.A. | Histology, stage, ESR | 44 |
| Total | | | 905 | 39.7 * | | | |

Legend: BM = bone marrow; GI = gastrointestinal tract; ESI = extranodal sites of involvement; LSI = level of site involvement; Hb = hemoglobin; ESR = erythrocyte sedimentation rate; N.A. = not assessed; * = calculated mean value.

groups with actuarial median survivals ranging from 211 to 12 months.

Stage lost its importance as a prognostic factor in the analysis performed by Jagannath [37]. In this study the median survival time was 58 months with a 5-year survival of 48%. A proportional hazard model identified LDH level and tumor burden as independent risk factors for survival. Normal LDH and low tumor burden (one extranodal site of disease and, at most, one area of extensive nodal involvement) were associated with 87% survival at 5 years. The worst results occurred in patients with high LDH and heavy tumor burden (two or more areas of extensive nodal disease, three or more extranodal sites, or a combination of one extensive nodal and two extranodal sites), who displayed a 5-year survival of 20%. This model classified the remaining 40% of patients in an intermediate group with a 5-year survival of 48%.

In the series of Shipp [36], median survival (58 months) and 5-year survival (50%) were similar to those of Jagannath [37] and similar prognostic indicators were reported: tumor bulk, number of extranodal sites, LDH, stage, systemic symptoms and performance status. Tumor bulk, number of extranodal sites and performance status were the three prognostic factors selected by a Cox's regression analysis of survival to construct a model for identifying patients at low, moderate or high risk. This model also placed 40% of the cases in the moderate risk group.

Fisher [30] achieved the best results of period C with the ProMACE-MOPP flexible protocol, reporting a 4-year survival of 65% (we estimated a 5-year survival of 60%). No statistical analysis was reported; however, three different groups were considered with complete remission rates of 50% for patients with the worst prognosis (BM or GI involvement), 71% for patients with other sites of extranodal involvement, and 89% for patients having stage II, III, or IV by virtue of skin disease only.

Summarizing the results of the studies conducted on series of patients treated in period C, we can conclude that the most useful prognostic features were LDH and, as new factors, bulky disease and sites of extranodal involvement.

Several studies have shown that bulk is an important prognostic factor in patients with HG-NHL, while there is less evidence to support the importance of local bulk in the low-grade lymphomas. Early or advanced stage bulky disease is an important prognostic factor, and is particularly unfavorable at certain sites such as the gastrointestinal tract. Bulky disease is a very important variable associated with a poor prognosis; however, a standardized definition of bulky disease is needed for a better indication of prognostic impact. An additional problem is how to score bulky disease that has been surgically excised.

Jagannath [37] and Shipp [36] emphasized the adverse effect of increased numbers of sites of extranodal involvement on both response rate and survival. Fisher [30] further pointed out the relevance of different organ involvement in predicting outcome. We agree with them and others that a simple definition of stage IV does not give useful prognostic information in HG-NHL treated with combination

chemotherapy. Definition of sites of extranodal involvement must be kept in mind when planning clinical trials and reporting results.

Albumin [41 44] and hemoglobin [43] have also been suggested as useful factors in predicting the outcome of patients with HG-NHL. Although these are easily measured parameters, they have been tested in only a few studies on prognostic factors.

In some reports of studies referred to this period, performance status and response to initial treatment are suggested as important prognostic indicators. While these findings may be useful in clinical practice, their prognostic significance is obvious, and we think that these parameters should not enter into any multivariate analysis of prognostic factors.

### Period D studies

An intensification of induction therapy has resulted in a further increase in survival in recent years. Almost all studies on prognostic factors during this last period were conducted on patients treated with CHOP or CHOP-derived protocols. Only a few reports are available on prognostic factors detected in patients treated with more recent regimens. We estimated the 5-year survival rate of patients treated in this period to be 43.8% (Table 4), ranging from 40 to 52% in different series [1 3 7 45-50]. In some studies, with a median follow-up shorter than 5 years, we considered the results in terms of complete remission and relapse rate (both useful indicators of disease outcome).

In a recent report of the ECOG on 332 patients with HG-NHL treated between 1978 and 1983 with COPA or COPA-Bleo, the 5-year survival was 41% for all patients, with a median survival of 36 months [47]. A multivariate analysis of survival according to prognostic factors indicated that DH histology, advanced age (> 60 yr.), systemic symptoms, and involvement of the mediastinum and GI tract are strongly correlated with poor survival. No evaluation of LDH was done in this study.

In a series of 117 patients with advanced HG-NHL treated in a collaborative group between 1980 and 1985 with CHOP, CHOP-BLEO and BACOP, we investigated the prognostic factors using a regression tree model for survival data recently proposed by Segal [51]. Symptoms, hemoglobin, nodal sites of involvement and ESI appeared to be the most relevant factors emerging from this approach [52]. In addition, albumin and erythrocyte sedimentation rate were also statistically significant prognostic factors in a preliminary univariate analysis. Five-year survival rates ranged from 76% in the best prognostic group (absence of systemic symptoms, normal hemoglobin levels and less than 3 sites of nodal involvement) to 32% in the worst group (presence of systemic symptoms and 2 or more extranodal sites of involvement). Only response rate (not survival) was reported in another cooperative study on 51 patients treated with a 6-drug protocol by the Nebraska Lymphoma Study Group between 1982 and 1984 [48]. The only variable significantly associated with a decreased probability of complete remission and a worse prognosis was tumor bulk. Patients with high LDH, systemic symp-

Table 4. - *Prognostic factors discovered in patients with high-grade non-Hodgkin's lymphomas treated during period D.*

| Author | Trial dates | Mean year | No. of patients | 5-year survival (%) | Median survival (Mo.) | Prognostic factors | Ref. |
|---|---|---|---|---|---|---|---|
| Coiffier | 80-84 | 82 | 48 | 52 | — | Tumor bulk, ESI, LDH, BM | 1 |
| Klimo | 81-84 | 83 | 61 | 70 ** | — | N.A. | 3 |
| Young | 79-84 | 82 | 111 | 45 | 36 | Proliferative activity | 46 |
| Pereira | 78-85 | 82 | 47 | 40 | 40 | Tumor bulk, ESI, LDH, symptoms | 7 |
| O'Connell | 78-83 | 81 | 332 | 41 | 36 | Tumor bulk, symptoms, BM, GI | 47 |
| Armitage | 82-84 | 83 | 51 | 45 | 36 | Tumor bulk | 48 |
| Del Bino | 78-85 | 82 | 78 | 40 | N.A. | Labeling index | 50 |
| Ail-LG | 80-85 | 83 | 117 | 41 | 39 | Symptoms, hemoglobin, NSI, ESI | 52 |
| Total | | | 845 | 43.8 * | | | |

Legend: N.A. = not assessed; BM = bone marrow; ESI = extranodal sites of involvement; NSI = nodal sites of involvement; NSI = nodal sites of involvement; * = calculated mean value; ** = 3-year survival.

toms, or extranodal sites of involvement had lower but not significantly different remission rates. In this study the actuarial 5-year survival was 45%, with a median survival of 36 months.

Coiffier and coworkers [1] performed an analysis of prognostic factors in a series of 100 patients with IG- or HG-NHL treated with the LNH-80 protocol, but their results are not clear. Those authors reported that there was no statistical difference in survival duration between IG and HG-NHL. Morphological subtypes, age and BM involvement were, however, significantly important predictors of poor prognosis in a multivariate Cox regression analysis «where all the factors with some significance were included». Nevertheless we think that an incorrect deduction regarding the predictive value of stage on the response rate was made in this report. A comparision of stage I+II vs III vs IV shows a non significant level of difference but if stages I+II+III are compared with stage IV a statistically significant difference is found using the same chi-square test employed by the authors (chi square = 8.24; degrees of freedom = 1; $p < 0.01$).

Immunologic phenotype [49], cytogenetic abnormalities [45], proliferative activity and cell kinetics [46 50 53] serum alkaline DNase activity [54], transferrin receptor expression [55 56] have also been reported recently in small series as predictors of clinical outcome in HG-NHL. However, the difficulty in evaluating them on large series and the conflicting results that sometimes are reported [57] limit their effective usefulness as prognostic factors in clinical practice.

## Sex and age

In almost all studies on NHL sex and age are evaluated as prognostic factors, and male sex has often been associated with a poorer prognosis [1 15 30 43]. Steward [41] found female sex to be a positive indicator of complete remission but not of increased survival. Survival of female patients exceeded that of male patients ($p = 0.05$) in a study by Fisher [30] but no information was given about other clinical factors in the two groups of patients. Therefore, the difference between male and female survival rates may have been due to differences in age, stage, systemic symptoms, or other prognostic factors. Several reports indicate that sex is not a significant variable [9 27 36 37 47 58 59]. Danieu [38] and Bloomfield [32] have even reported a better outcome for males. We think that it is impossible to rule out a subtle effect of gender. Even if such a difference exists, however, it is minor and sex should not be included in the analysis of prognostic factors.

Age is indeed a complex factor that influences prognosis in different ways, yet it is also hard to standardize. Its relevance for survival prediction is obvious, but in many reports the cut-off values vary widely. Often increased age is associated with drug dose reduction, and this influences the prognosis [5 59]. In a report of 307 cases treated by the SWOG [60], it was demonstrated that older patients treated with full chemotherapy dosage had complete response rates equivalent to younger patients and that inferior response was correlated primarily with drug dose reduction. We agree with Hoppe that age itself is not an important factor for predicting response rate [15]. We prefer to consider patients in relation to chemoteraphy dosage rather to age when performing multivariate analysis of response or survival.

## Conclusions

We found relevant changes in the predictive value of prognostic factors during the four periods considered. These changes seem closely related to therapeutic results. In fact, if we consider the same data with regard to treatment results, irrespective of the time of treatment, we find that when prognosis was very poor, histology, stage and systemic symptoms were the most important prognostic indicators in all series. When 5-years survival increased to 40-50% bulky disease, sites of extranodal involvement, and LDH level were more useful prognostic factors.

Today, chemotherapy regimens can produce complete remission rates of up to 80%, and the effect of this on the pattern of the prognostic factors is unknown. Fisher [2], who obtained 74% of remissions with ProMACE-MOPP, and Klimo [3] who reported 84% of remissions with MACOP-B, did not performed an analysis of the prognostic indicators of survival.

As more effective treatment programs are being developed, prognostic factors change and become more difficult to identify. This intrinsic difficulty is increased by the fact that the number of patients with HG-NHL seen per Institution in a one-year period is steadily declining, and in many instances is lower than a dozen. However, a large number of cases is necessary to properly evaluate the small differences expected between different therapeutic approaches. We think that if multicentric collaborative studies are not performed many, if not all, future attempts in this area will fail.

On the basis of the available data we conclude that stage, as defined at the Ann Arbor conference, is no longer a sensitive prognostic factor and should be integrated. More appropriate indicators of disease

diffusion include the specification of tumor bulk and the sites of nodal and extranodal involvement. Systemic symptoms still are useful indicators of prognosis, however, and LDH has been confirmed as a very sensitive marker. In addition, hemoglobin and albumin levels, whose prognostic value appears relevant, should be tested routinely in studies on prognostic factors.

Finally, the prognostic significance of current morphological classification deserves a comment. The conclusion of the Kiel classification and the WF were based on the survival of patients treated for lymphoma in the early 1970s. Treatment criteria and, consequently, therapeutic results are very different today. Therefore, we think that, as recently occurred with the Kiel classification [61], the other classification systems should also be updated.

## INTERAZIONE TRA PROGNOSI E TERAPIA NEI LINFOMI AD ALTA MALIGNITÀ LUNGO DUE DECENNI

**Abbiamo preso in esame i fattori prognostici individuati nei Linfomi non Hodgkin (LNH) ad alta malignità (AM) negli ultimi 20 anni. Per meglio chiarire i rapporti tra fattori prognostici e terapia, abbiamo esaminato numerosi studi apparsi in letteratura e li abbiamo raggruppati in 4 periodi (A,B,C,D). I fattori prognostici individuati nel periodo A (casistiche relative a pazienti trattati prima del 1970) erano istologia, sintomi e stadio. Nel periodo B (dal 1970 al 1975), in aggiunta ai precedenti, sono stati riconosciuti come importanti indicatori prognostici sia l'infiltrazione midollare che i livelli sierici di LDH. Nel periodo C (1976-1980), caratterizzato dall'introduzione in terapia delle antracicline, i fattori messi maggiormente in luce sono stati il volume tumorale, il numero delle localizzazioni linfonodali, il numero ed il tipo delle localizzazioni extranodali, mentre veniva sempre più ridimensionato il peso prognostico dello stadio (definito secondo i criteri di Ann Arbor). In alcuni studi relativi a pazienti trattati in questo periodo è stato evidenziato il valore predittivo di VES, emoglobina ed albumina sierica. L'ultimo periodo (1980-1985) è stato contrassegnato da una progressiva perdita di importanza prognostica delle classificazioni di Kiel e della WF, in virtù della miglior prognosi, in numerosi studi, dei LNH-AM rispetto ai LNH a bassa malignità.**

**I fattori attualmente provvisti di maggior significato prognostico nei LNH-AM sembrano essere: sintomi sistemici, numero e tipo di localizzazioni extranodali, volume tumorale, livelli di LDH, albumina ed emoglobina.**

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