

blood

1981 58: 45-51

Factors predicting long-term survival in diffuse mixed, histiocytic, or undifferentiated lymphoma

RI Fisher, SM Hubbard, VT DeVita, CW Berard, R Wesley, J Cossman and RC Young

Information about reproducing this article in parts or in its entirety may be found online at:
http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub_requests

Information about ordering reprints may be found online at:
<http://bloodjournal.hematologylibrary.org/misc/rights.dtl#reprints>

Information about subscriptions and ASH membership may be found online at:
<http://bloodjournal.hematologylibrary.org/subscriptions/index.dtl>



Factors Predicting Long-Term Survival in Diffuse Mixed, Histiocytic, or Undifferentiated Lymphoma

By Richard I. Fisher, Susan M. Hubbard, Vincent T. DeVita, Costan W. Berard, Robert Wesley, Jeffrey Cossman, and Robert C. Young

Clinical and histopathologic material from 151 cases of diffuse mixed, diffuse histiocytic, and diffuse undifferentiated non-Burkitt's lymphomas have been reviewed to determine the factors that predict long-term survival. Median survival of all patients was 34 mo with 43% alive at 70 mo. Factors associated with a poor prognosis include: male sex, constitutional symptoms, advanced stage, bone marrow involvement, huge (>10 cm) abdominal masses with gastrointestinal involvement, hepatic involvement, hemoglobin <12 g/dl, or serum LDH >250 U. The best prediction of a given patient's survival was defined by a set of four variables, which includes sex, symptoms, bone marrow status, and the presence or absence of a huge

abdominal mass with gastrointestinal involvement. In contrast, classification of these patients according to the histopathologic categories of Rappaport or Strauchen did not define patient groups with significant differences in survival, nor did these categories correlate with the previously described clinical factors. Knowledge of the distribution of these prognostic factors in any clinical trial is needed before therapeutic results can be compared. In addition, such data may define subsets of patients for whom current therapy is inadequate and conversely those patients for whom current therapy yields excellent long-term survival.

DURING THE LAST 15 yr, the results obtained from the treatment of the aggressive forms of diffuse lymphomas have improved significantly. Diffuse histiocytic lymphoma has classically been selected as the prototype of these aggressive diffuse lymphomas since it is the most common type. During the 1960s, 10%–20% of all patients with diffuse histiocytic lymphoma were alive at 5 yr.¹ Radiation therapy did lead to 30%–50% survival at 5 yr when clinical stage I patients were treated.² With the advent of pathologic staging and improved radiotherapeutic techniques, 70%–80% of stage I patients are now alive and disease free at 5 yr.^{3,4}

Patients with more advanced stages of diffuse histiocytic lymphoma rarely achieved long-term survival with either radiation therapy or single agent chemotherapy. The first report that demonstrated that long-term disease-free survival could be obtained with combination chemotherapy was published in 1975.⁵ Subsequently, numerous other authors have demonstrated that a subset of patients with advanced stages of diffuse histiocytic lymphoma can achieve long-term disease-free survival after combination chemotherapy.^{6–10} In 1977, we analyzed 56 cases of advanced stage diffuse histiocytic lymphoma to determine what prognostic factors predicted the success or failure of combination chemotherapy.¹¹ That study demonstrated that the determination of the sites of tumor involvement and extent of tumor mass during the initial evaluation allow one to accurately predict a patient's prognosis.

This study, however, provided no information about patients with a Rappaport diagnosis of diffuse mixed or diffuse undifferentiated lymphoma (neither of these groups is rare). There is considerable histopathologic overlap between these three diagnoses and, indeed,

disagreement among expert pathologists is not uncommon. Often the subgroups are treated identically. Recently, several authors have also suggested that subclassification of these aggressive forms of diffuse lymphoma on histopathologic criteria may provide significant prognostic information.^{12,13}

Therefore, we have reviewed the clinical history and pathologic material from 151 patients with all stages of mixed, histiocytic, and undifferentiated lymphomas treated at the National Cancer Institute in order to determine the important prognostic factors influencing long-term survival. This information should also enable clinical investigators to determine the adequacy of current treatment programs for various subgroups of patients with diffuse lymphoma and should permit more accurate comparisons of the results obtained in different clinical trials.

MATERIALS AND METHODS

All patients with diffuse mixed, histiocytic, and undifferentiated non-Burkitt's lymphoma treated at the National Cancer Institute between 1964 and 1977 were evaluated for entry into this study. The medical records were completely reviewed and interpreted by two of the authors (R.I.F. and S.M.H.). All pathologic material was reviewed by the two experienced pathologists (C.W.B. and J.C.) and a consensus interpretation reached. In order to be included in this study, the initial pathologic material had to include at least one biopsy site that contained one of the previously mentioned forms of diffuse lymphoma. Any biopsy containing areas of nodular lympho-

From the Medicine Branch, Laboratory of Pathology, and Biometric Research Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

Submitted November 25, 1980; accepted March 4, 1981.

Address reprint requests to Richard I. Fisher, M.D., Building 10, Room 12N226, National Cancer Institute, Bethesda, Md. 20205.

© 1981 by Grune & Stratton, Inc.

0006-4971/81/5801-0007\$01.00/0

ma, in addition to diffuse lymphoma, was considered a nodular lymphoma and, therefore, not included in this analysis. One hundred and fifty-one patients met the above criteria.

The clinical and histologic characteristics of these 151 patients are shown in Table 1. Sixty-two percent of the patients were male. The median age was 49 yr with a range from 8 to 74 yr. Only 9% of all patients were less than 20 yr old. Constitutional symptoms (fever, night sweats, or loss of 10% of total body weight) were present in 45%. The initial pathologic diagnoses according to the Rappaport classification¹⁴ were diffuse mixed, 20%; diffuse histiocytic, 60%; diffuse undifferentiated non-Burkitt's, 13%; and unclassifiable lymphoma, 7%.

Staging procedures were performed at the time of admission, as defined in prior reports.^{5,7,11,15} For this analysis, all staging data were reinterpreted according to our current criteria for pathologic staging that have been defined by Chabner et al.¹⁶ If an adequate evaluation of a given organ site had not been performed, then that organ was considered not evaluable. As outlined by the Ann Arbor Conference,¹⁷ 13% of patients were stage I, 23% stage II, 14% stage III, and 50% stage IV.

Initial therapy following referral to the National Cancer Institute consisted of radiation alone in 37 patients (25%). Involved field or extended field radiation was given to 29 of the 37 radiation patients, while the remainder received more extensive fields. Combination chemotherapy was initial treatment for 93 patients (61%). Of these 93 patients, 14 received cyclophosphamide, vincristine, and prednisone (CVP);¹⁸ 37 received cyclophosphamide or mechlorethamine, vincristine, procarbazine, and prednisone (C-MOPP or MOPP);⁵ and 40 received cyclophosphamide, doxorubicin, vincristine, bleomycin, and prednisone (BACOP).⁷ For patients with stage I or II disease, 30/54 (56%) received radiation alone and 11/54 (20%)

radiation plus C-MOPP. For the 97 patients with stage III or IV disease, 83 (86%) received combination chemotherapy, 7 (7%) received extensive radiation therapy, 5 (5%) received radiation plus combination chemotherapy, and 2 (2%) received single agents.

Only those patients with no evidence of residual tumor at restaging have been called complete responders. Those in whom there was a 50% decrease in tumor size and those attaining a complete clinical remission with microscopic disease present at restaging were considered partial responders. All other patients were classified as nonresponders.

Survival was calculated from the start of therapy and plotted by the life table method. Survival curves were analyzed by the generalized Wilcoxon test of Gehan¹⁹ or the generalized Kruskal-Wallis test of Breslow.²⁰ Response rates were compared statistically by the Fisher exact test.²¹ All *p* values are of the two-sided type. To assess the relative effect of different prognostic factors on survival, the proportional hazards model of Cox²² was used. A modified forward stepwise regression method was applied to find the most important set of factors for predicting survival. Of the prognostic factors found to be individually important, all subsets of size two are analyzed to find the best pair, then a stepwise procedure was used to continue. A backward stepwise regression method was also used to check the results and gave the same final subset of prognostic factors.

RESULTS

The median follow-up for all patients on the study now exceeds 6 yr. The actuarial survival for all 151 patients is shown in Fig. 1. Median survival is 34 mo with 43% of patients alive greater than 70 mo. As noted in previous studies,^{11,23} only those patients achieving a complete remission had prolonged disease-free survival. Fifty-four percent of all patients achieved a complete remission, and their median survival has not been reached, with 76% of the complete responders alive at 70 mo. The median survival of the 37% of patients who achieved a partial response and the 9% who had no response are 6 and 7 mo, respectively. Complete response rates according to

Table 1. Clinical and Histologic Characteristics of Patients With Diffuse Lymphomas

Characteristic	Number	Percent
Total Patients	151	100
Sex		
Males	93	62
Females	58	38
Age (yr)		
Less than 20	13	9
20-40	40	26
40-60	70	46
Greater than 60	28	19
Constitutional symptoms*		
A	83	55
B	68	45
Histologic diagnosis†		
Diffuse mixed	31	20
Diffuse histiocytic	91	60
Diffuse undifferentiated non-Burkitt's	19	13
Unclassifiable	10	7
Stage		
I	20	13
II	34	23
III	21	14
IV	76	50
Initial therapy		
Radiation	37	25
Combination chemotherapy	93	61
Combined modality	16	11
Other	5	3

*Fever, night sweats, or loss of 10% of total body weight.

†According to Rappaport classification.

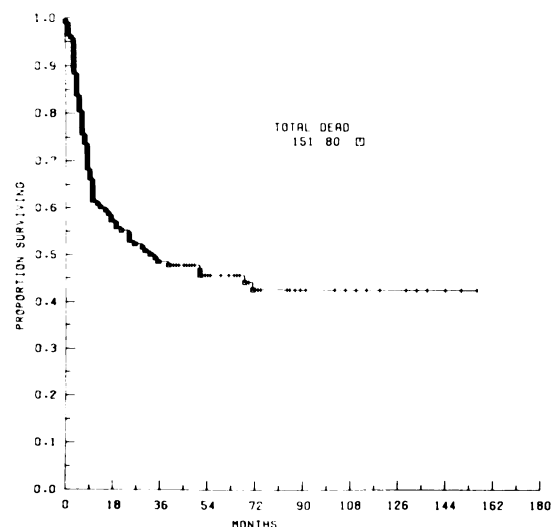


Fig. 1. Actuarial survival curve for all patients with aggressive forms of diffuse lymphoma.

stage were as follows: stage I, 100%; stage II, 56%; stage III, 66%; and stage IV, 38%,

Eight clinical factors, easily determined prior to the initiation of therapy, can be utilized to predict the survival of patients with these diffuse lymphomas. The relationship of the patients' sex to his survival is shown in Fig. 2. Survival of female patients exceeded that of male patients ($p = 0.05$). Of interest, sex is the only clinical factor that significantly affected patient survival without affecting the complete remission rate. Furthermore, there was no significant association of females with any particular stage of disease, site of tumor involvement, or histology.

The presence of fever, night sweats, or weight loss greater than 10% of the total body weight was associated with both a lower complete response rate and survival. The complete response rate for patients with constitutional symptoms was 38% compared to 67% for asymptomatic patients ($p < 0.002$). Likewise, median survival for patients with constitutional symptoms is 10 mo, while the median for asymptomatic patients has not been reached ($p = 0.002$) (data not shown).

A patient's initial stage was inversely correlated with the complete response rate and also survival, as shown in Fig. 3 ($p < 0.002$). The only exception is the fact that patients with stage II disease had a lower complete response rate and survival than those patients with stage III lymphoma. This fact is partially explained by the inclusion of 5 patients with huge abdominal masses involving the gastrointestinal tract in the stage II category. These patients had a poor prognosis and will be discussed later.

Although only 15% of all evaluable patients had bone marrow infiltration with malignant lymphoma,

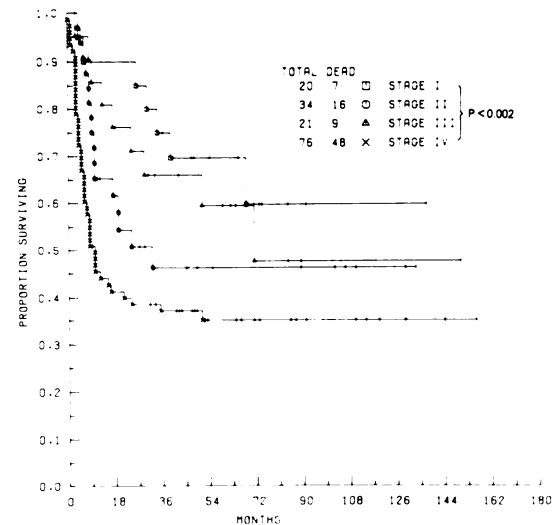


Fig. 3. Survival of all patients according to their stage.

the prognosis of these patients was extremely poor. The complete response rate was only 9% for patients with bone marrow infiltration versus 62% for all other patients without marrow lymphoma ($p < 0.002$). As shown in Fig. 4, median survival drops from 51 mo for all other patients without marrow involvement to 6 mo for patients with it ($p < 0.002$). This detrimental effect of bone marrow involvement was also present in the subset of patients with diffuse histiocytic lymphoma. No other histologic category had sufficient numbers of patients with marrow involvement to be analyzed independently.

The prognosis of patients with huge abdominal mass and gastrointestinal involvement is shown in Fig. 5. For this analysis we have again defined a huge abdominal mass as one greater than 10 cm in diameter.¹¹

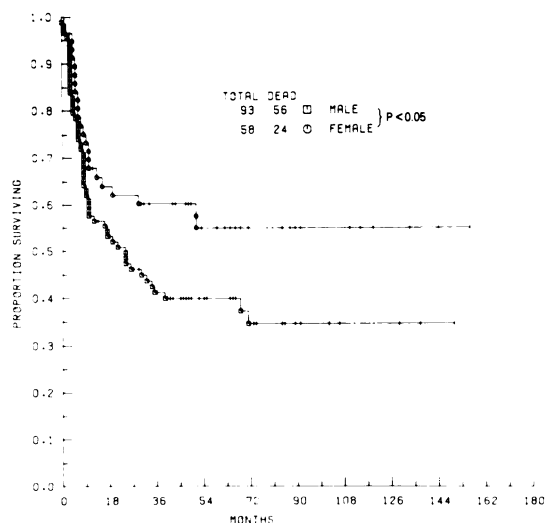


Fig. 2. Survival of all patients according to their sex.

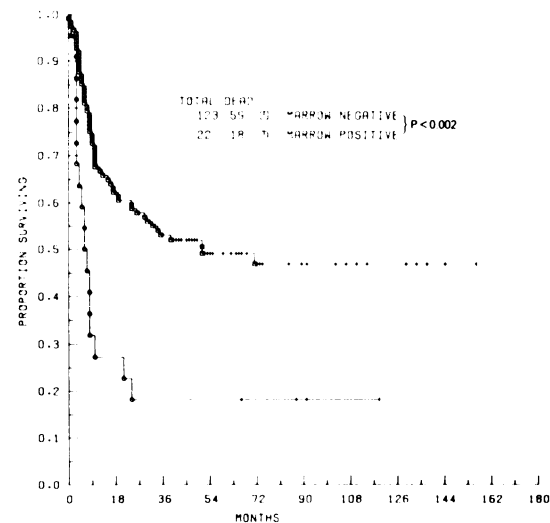


Fig. 4. Effect of bone marrow involvement on survival.

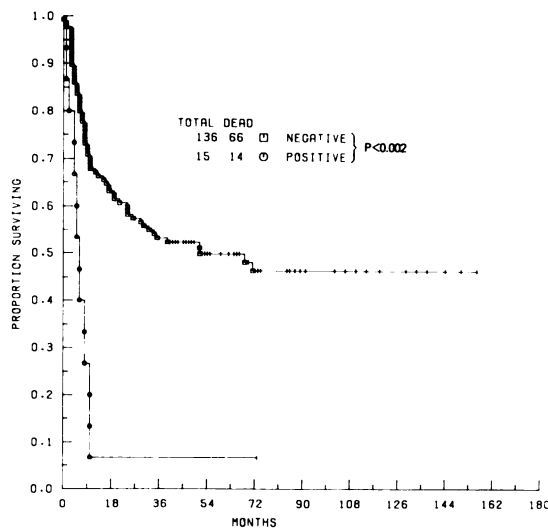


Fig. 5. Effect of huge abdominal mass with gastrointestinal involvement on survival.

Although only 10% of all evaluable patients actually had a huge abdominal mass with gastrointestinal involvement, their complete response rate of 7% and median survival of 6 mo were significantly less than that of all other patients (60% and 51 mo, respectively, $p = 0.002$). We have previously reported that both gastrointestinal involvement *and* huge masses appear to adversely affect the survival of patients treated with combination chemotherapy.¹¹ In the present study with a larger number of patients, we found that only a huge abdominal mass with gastrointestinal involvement adversely affects prognosis. We cannot demonstrate that gastrointestinal involvement without a huge abdominal mass or huge masses in other sites are important prognostic factors. The poor prognosis of these patients with huge abdominal masses and gastrointestinal involvement could also be demonstrated in the subset of patients with diffuse histiocytic lymphoma. There were insufficient numbers of these patients in other histologic categories to analyze them independently.

Involvement of the liver by these forms of diffuse lymphoma also adversely affects the prognosis. Twelve percent of evaluable patients had documented hepatic parenchymal involvement. Of these patients, 25% had a complete response, and median survival was 6 mo. This is significantly worse than the results from all other patients without liver involvement, i.e., 59% and 51 mo, respectively ($p = 0.01$).

In this analysis, we were unable to demonstrate that other common sites of extranodal involvement with diffuse lymphomas, such as the skin, lung, bone, spleen, or central nervous system, resulted in a significantly lower survival.

The patient's initial hemoglobin level predicted

response to therapy and survival. Patients whose hemoglobin was less than 12 g/dl had a 41% complete response rate and 10 mo median survival compared to 63% and 71 mo for patients whose hemoglobin was greater than or equal to 12 g/dl ($p < 0.002$).

Finally, patients' initial serum LDH (lactic dehydrogenase) values provided useful prognostic information. Patients with an LDH greater than 250 U had a 39% complete response rate and a median survival of 13 mo. In contrast, patients with a normal LDH, i.e., less than 250 U, had a 74% complete response rate and a median survival that was not reached with 57% of the patients alive at 70 mo ($p = 0.003$).

The patients could also be analyzed to determine whether these seven clinical factors were as important in patients with localized disease (stage I or II) or advanced disease (stage III or IV). When comparisons were made among stage III and IV patients only, sex, symptoms, marrow involvement, huge abdominal masses with gastrointestinal involvement, LDH, and hemoglobin all significantly affected survival. Liver involvement was also associated with a lower survival, although this difference did not reach statistical significance ($p = 0.10$). Obviously, bone marrow or liver involvement caused the patients to be classified as stage IV and thus were not found in stages I or II patients. Of the remaining factors, only symptoms and huge abdominal masses with gastrointestinal involvement were predictive of lower survival for stage I or II patients. Sex and level of LDH or Hgb did not statistically predict survival for stage I or II patients.

In addition to the clinical factors discussed previously, we have attempted to determine whether histopathologic subclassification of these diffuse lymphomas provides additional useful prognostic information. Survival of all patients, according to the Rappaport classification, is shown in Fig. 6. Although the prognosis worsens from diffuse mixed to diffuse histiocytic to diffuse undifferentiated lymphoma, there is no significant difference among the categories ($p = 0.27$).

In 1978, Strauchen et al. proposed a new histopathologic system of classifying patients with these types of diffuse lymphoma.¹² The authors retrospectively reviewed a series of 66 cases and divided the patients into the five categories: large cleaved, large noncleaved, mixed follicular center cell, blastic, and pleomorphic pyroninophilic. In the initial report, this classification appeared to delineate good, intermediate, and poor prognostic groups. The pathologic material from this initial report has been re-reviewed by one of the original authors (C.W.B.). In only 67% of the cases were the original interpretations reproducible. This classification was then applied to the larger series of 151 cases. The results are demonstrated in

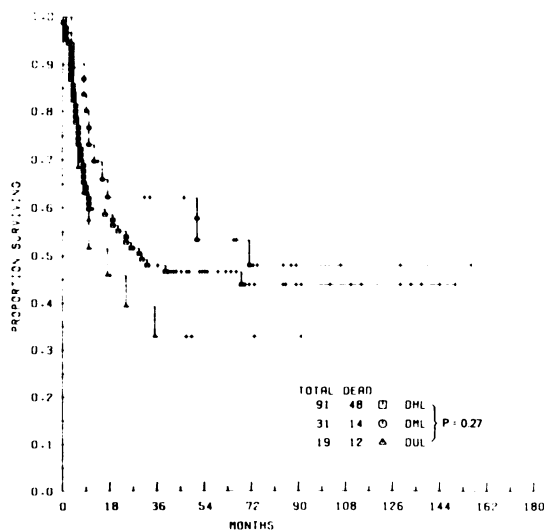


Fig. 6. Survival of the aggressive forms of diffuse lymphomas according to the classification of Rappaport.

Fig. 7. Although the curves appear in the same order as described in the initial report, Strauchen's categories do not separate these patients into significantly different prognostic groups ($p = 0.16$). In addition, none of Strauchen's categories correlated with the previously described clinical prognostic factors.

A multifactor Cox regression analysis was performed to delineate the relative strength of any of these eight clinical prognostic factors while taking into account the contribution of all the other factors listed above. Because each of the eight variables was individually highly predictive of survival, it was not possible to unequivocally define the exact order of importance of each of these factors. Moreover, the model may give equal weight to a factor that is strongly predictive for poor survival but present in relatively few patients and a factor that is associated with a moderate decrement in survival but is present in a larger proportion of the population. However, the best prediction of the patient's course was achieved using a set of four prognostic variables that defined the patient's status in regard to bone marrow, huge abdominal masses with gastrointestinal involvement, symptoms, and sex.

CONCLUSIONS

We have studied the factors that predict long-term survival in patients with diffuse mixed, histiocytic, or undifferentiated non-Burkitt's lymphoma in a retrospective review of 151 patients who have been followed for a median time in excess of 6 yr. Indeed, improved results have been obtained during the last 15 yr, since 43% of all patients are alive at 70 mo. Eight clinical factors that can be determined prior to the initiation of therapy adversely affected the prognosis. They

include: (1) male sex; (2) constitutional symptoms; (3) advanced stage; (4) bone marrow involvement; (5) huge abdominal masses with gastrointestinal involvement; (6) liver involvement; (7) hemoglobin less than 12 g/dl; and (8) serum LDH greater than 250 U. These clinical factors, with the exception of sex, all affected the survival of patients because fewer complete remissions were achieved. Indeed, there was no evidence that the survival of patients with poor prognostic factors who achieved a complete remission was less than that of other complete responders. This once again emphasizes the concept that improved survival of patients with diffuse lymphoma will result when larger numbers of complete remissions are obtained.

In contrast to these clinical factors, histopathologic subclassification of these patients according to the systems proposed by Rappaport¹⁴ or Strauchen¹² did not add significant additional prognostic information. In fact, the interpretations established by the Strauchen system were not satisfactorily reproducible. Armitage et al. used a similar classification scheme and applied it to patients with a Rappaport diagnosis of diffuse histiocytic lymphoma.¹³ They reported an 86% concurrence rate between two pathologists reading the slides independently but did not determine the reproducibility of a given pathologists' reading. The survival of patients with four of the subcategories was identical but inferior to the group with large noncleaved cells. Whether other histopathologic classifications can provide prognostic information comparable to or greater than that provided by the clinical factors remains to be determined.

Although we initially had hoped that we could place the prognostic factors in sequential order of impor-

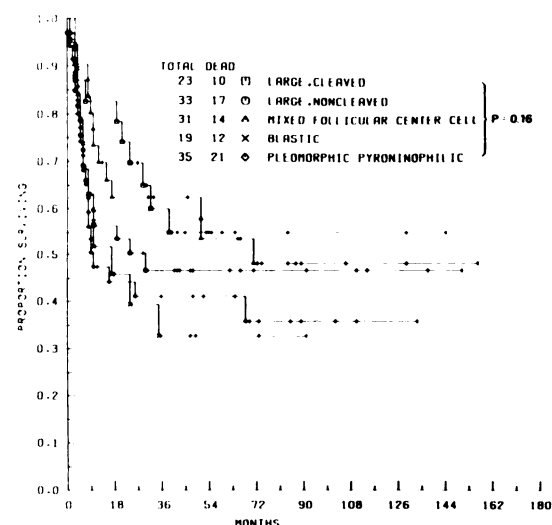


Fig. 7. Survival of the aggressive forms of diffuse lymphomas according to the classification of Strauchen.

tance by use of a Cox regression model, this goal was not possible. Part of the difficulty could be attributed to the fact that the regression model may give equal importance to two types of factors—one that is present in very few patients but has devastating impact, and a second one that may be present in about half of the patients but has only moderate negative impact. Nevertheless, when a patient's status was defined in regard to sex, symptoms, bone marrow involvement, and huge abdominal masses with gastrointestinal involvement, no other clinical variable provided significant additional prognostic information.

No truly comparable analysis of the factors predicting long-term survival in these diffuse lymphomas has been published. Our previous analysis dealt only with advanced stages of diffuse histiocytic lymphoma treated with intensive combination chemotherapy.¹¹ Stage IV disease, bone marrow involvement, gastrointestinal involvement, and a tumor mass greater than 10 cm in diameter in a single location were found to be poor prognostic factors. These factors are also important in the current study, although we can now demonstrate that it is a huge abdominal mass with gastrointestinal involvement that is important, not a huge mass in another site or a gastrointestinal involvement without a huge abdominal mass.

Cabanillas et al. studied the factors that influenced response and survival in patients with advanced stages of non-Hodgkin's lymphoma (approximately half nodular and half diffuse) treated with the less intensive combination chemotherapy, cyclophosphamide,

vincristine, and prednisone.²⁴ Factors that influenced prognosis included tumor bulkiness, prior therapy, nodular or diffuse pattern of growth, hemoglobin level, and presence or absence of constitutional symptoms. These results certainly are consistent with our findings when one notes that patients with prior treatment and those with nodular lymphoma were not part of our analysis. In addition, in the M.D. Anderson study, bone marrow biopsy and liver biopsy were not routinely performed, and serum LDH levels were not analyzed. Ferraris et al. have reported that an elevated serum LDH was a poor prognostic factor in all types of non-Hodgkin's lymphomas²⁵ and Arseneau reported similar results in Burkitt's lymphoma,²⁶ but otherwise there has been limited investigation of prognostic factors.

Numerous clinical trials are currently in progress throughout the world in an attempt to improve the therapy of diffuse lymphomas. In order to compare these regimens, it is important to know the distribution of clinical prognostic factors present in a given trial and the complete response rate for each category of patients. This is especially important since one can easily predict that differences in the prognosis of patients entering a given study could be of the same order of magnitude as the differences observed between two therapeutic modalities. Finally, it may now be appropriate to attempt to develop new treatment strategies for some patients with diffuse lymphomas—specifically those patients in whom we can prospectively predict poor therapeutic results.

REFERENCES

1. Zuks Z, Bull M, Kadin ME, Dorfman HS, Rosenberg SA, Kim H: Lymphoma. IV. Clinicopathologic correlations. *Cancer* 31:806-823, 1973
2. Peckham MJ: Radiation therapy of the non-Hodgkin's lymphomas. *Semin Hematol* 11:41-58, 1974
3. Bitran JD, Kinzie J, Sweet DL, Variakojis D, Grien ML, Golomb HM, Miller JB, Oetzel N, Ultmann JE: Survival of patients with localized histiocytic lymphoma. *Cancer* 39:342-348, 1977
4. Toonkel LM, Fuller LM, Gamble JF, Butler JJ, Martin RG, Shullenberger CC: Laparotomy staged I and II non-Hodgkin's lymphomas: Preliminary results of radiotherapy and adjunctive chemotherapy. *Cancer* 45:249-260, 1980
5. DeVita VT, Canellos GP, Chabner BA, Schein P, Hubbard SP, Young RC: Advanced diffuse histiocytic lymphoma, a potentially curable disease. *Lancet* 1:248-250, 1975
6. Berd D, Cornog J, DeConti R, Levitt M, Bertino JR: Long term remission in diffuse histiocytic lymphoma treated with combination sequential chemotherapy. *Cancer* 35:1050-1054, 1975
7. Schein PS, DeVita VT, Hubbard SP, Chabner BA, Berard CW, Young RC: Bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphomas. *Ann Intern Med* 85:417-422, 1976
8. Skarin AT, Rosenthal DS, Maloney WC, Frei E: Combination chemotherapy of advanced non-Hodgkin's lymphoma with bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP). *Blood* 49:759-769, 1977
9. Jones SE, Grozea PN, Metz EN, Haut A, Stephens RL, Morrison FS, Butler JJ, Byrne GE, Moon TE, Fisher R, Haskins CL, Coltman CA: Superiority of adriamycin containing combination chemotherapy in the treatment of diffuse lymphoma. *Cancer* 43:417-425, 1979
10. Sweet DL, Golomb HM, Ultmann JE, Miller JB, Stein RS, Lester EP, Mintz U, Bitran JD, Streuli RA, Daly K, Roth NO: Cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and cytarabine (COMLA) combination sequential chemotherapy for advanced diffuse histiocytic lymphoma. *Ann Intern Med* 92:785-790, 1980
11. Fisher RI, DeVita VT, Johnson BL, Simon R, Young RC: Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Am J Med* 63:177-182, 1977
12. Strauchen JA, Young RC, DeVita VT, Anderson T, Fantone JC, Berard CW: Clinical relevance of the histopathological subclassification of diffuse histiocytic lymphoma. *N Engl J Med* 299:1382-1387, 1978
13. Armitage JO, Dick FR, Platz CE, Corder MP, Lennert JT: Clinical usefulness and reproducibility of histologic subclassification of advanced diffuse histiocytic lymphoma. *Am J Med* 67:929-934, 1979

14. Rappaport H: Tumors of the hematopoietic system, in: Atlas of Tumor Pathology, Section 3, Fascicle 8. Washington DC, Armed Forces Institute of Pathology, 1966
15. Lowenbraun S, DeVita VT, Serpick AA: Combination chemotherapy with nitrogen mustard, procarbazine, and prednisone in lymphosarcoma and reticulum cell sarcoma. *Cancer* 25:1018–1025, 1970
16. Chabner BA, Johnson RE, Young RC, Canellos GP, Hubbard SP, Johnson SK, DeVita VT: Sequential non-surgical staging of non-Hodgkin's lymphoma. *Ann Intern Med* 85:149–154, 1976
17. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M: Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 31:1860–1861, 1971
18. Bagley CM, DeVita VT, Berard CW, Canellos GP: Advanced lymphosarcoma: Intensive cyclical combination chemotherapy with cyclophosphamide, vincristine, and prednisone. *Ann Intern Med* 76:227–234, 1972
19. Gehan E: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika* 52:203–223, 1965
20. Breslow N: A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. *Biometrika* 57:579–594, 1970
21. Armitage P: *Statistical Methods in Medical Research*. New York, Wiley, 1971
22. Cox D: Regression models and life-tables. *J R Stat Soc B* 34:187–200, 1972
23. Anderson T, Bender RA, Fisher RI, DeVita VT, Chabner BA, Berard CW, Norton L, Young RC: Combination chemotherapy for non-Hodgkin's lymphoma: Results of long-term follow-up. *Cancer Treat Rep* 61:1057–1066, 1977
24. Cabanillas F, Burke JS, Smith TL, Moon TE, Butler JJ, Rodriguez V: Factors predicting for response and survival in adults with advanced non-Hodgkin's lymphoma. *Arch Intern Med* 138:413–418, 1978
25. Ferraris AM, Quintini P, Gaetani GF: Serum lactic dehydrogenase as a prognostic tool for non-Hodgkin's lymphomas. *Blood* 54:928–932, 1979
26. Arseneau JC, Canellos GP, Banks PM, Berard CW, Gralnick HP, DeVita VT: American Burkitt's lymphoma: A clinico-pathologic study of 30 cases. *Am J Med* 314–321, 1975