Acta Radiologica Oncology 20 (1981) Fasc. 3

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CLINICO-PATHOLOGIC CORRELATION IN NON-HODGKIN'S LYMPHOMA

IV. Analysis of patients with clinically localized disease

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Different opinions concerning the classification of non-Hodgkin's lymphoma exist at present. Several new classifications have been proposed recently (BENNETT et coll. 1974, DORFMAN 1974, GERARD-MARCHANT et coll. 1974, LUKES & COLLINS 1974, LENNERT et coll. 1975, MATHÉ et coll. 1976). However, the clinical and practical usefulness of the new classifications is not yet fully settled. The classification of LUKES & COLLINS was, somewhat modified, applied to a patient series analyzed retrospectively. The results of the whole series, previously reported in three parts (LENNER et coll. 1979 a, b, c) indicated a good correlation between the cell types thus defined and clinical features including prognosis.

In one of the previous communications (LENNER et coll. 1979 c) different mechanisms of spread were discussed. Lymphomas with cells similar to normal circulating small lymphoid cells often had a systemic or leukaemic spread, whereas large cell lymphomas seemed to disseminate by a mechanism more related to the metastatic process of solid tumours. Relapse outside the treatment field after radiation therapy for apparently localized disease may be regarded as a result of spread undetected at the primary evaluation of the patient. Thus, rates and localizations of recurrences after irradiation of early stage lymphoma reflect the process of spread.

The present report describes the results of such a retrospective analysis applied to a series of patients with non-Hodgkin's lymphoma in apparently localized stages, classified according to a modified LUKES & COLLINS scheme, including an analysis of sites at presentation, response to treatment, and survival. The findings are discussed in terms of their implications for staging and treatment of patients with non-Hodgkin's lymphoma.

Material and Methods

Of 302 adult, previously untreated patients with non-Hodgkin's lymphoma referred to this Department between 1959 and 1975, 140 were found to have apparently localized disease (stage I or II according to the Ann Arbor staging classification; CARBONE et coll. 1971). Staging methods were simple, based on clinical examination including history, physical status, chest films, peripheral blood and marrow examination. Lymphography was performed in 27 patients, 14 being in stage I or II before the procedure. Of these 14 cases, 4 were changed from stage II to stage III as a result of the procedure. However, this finding was disregarded in the present analysis in order to make all cases comparable with respect to staging procedures. Staging laparotomy was not performed in any patient. Extranodal spread was determined by open biopsy or fine needle aspiration biopsy.

The therapy was not uniform. Radiation therapy was recorded in terms of dose, time and volume, and chemotherapy in terms of drugs, doses and time.

Accepted for publication 13 February 1981.

Whether the patient achieved a complete remission or not was principally evaluated by the same simple methods as in the pretreatment evaluation. Time and site of the first relapse were recorded. All patients were followed to death or to December 31, 1978, giving a minimum observation time for living patients of 3 years. No patient was lost to follow-up.

All pretreatment microscopic material was reviewed by two of the authors (EL and PL) and classified according to a modified LUKES & COLLINS system (Table 1). The growth was recorded as nodular or diffuse. A minimally nodular (grade III; LENNER et coll. 1979b) was regarded as nodular. Further details of the microscopic and clinical review were given previously (LENNER et coll. 1979a).

Statistical significance of differences, except those pertaining to survival curves, was tested according to the two-tailed proportional test (COLTON 1974). Survival and relapse-free survival curves were generated as described by PETO et coll. (1976, 1977). Differences in survival were tested by the log-rank test (PETO et coll. 1976, 1977). A p-value less than or equal to 0.05 was considered as significant. Statistical analysis of this type may, of course, be somewhat dubious in a heterogeneous, retrospective material. However, it is in this context considered to have some value for the evaluation of the significance of differences found in the material.

Table 1

Modified Lukes & Collins classification

Small lymphocytic (CLL)
Plasmacytoid lymphocytic
Follicular centre cell (FCC) types
Small cleaved
Large cleaved
Mixed small/large cleaved
Large non-cleaved
Immunoblastic
With plasmacytoid differentiation
Without plasmacytoid differentiation
Lymphoblastic
Convoluted
Non-convoluted
Burkitt's lymphoma
Unclassifiable

Table 2

Clinical stage on admission

	No. stage I	No. stage II	No. stage I and II/ Per cent all stages
FCC type			
Small cleaved	19	17	36/84 (43)
Mixed small/ large cleaved	13	6	19/31 (61)
Large cleaved	12	17	29/42 (69)
Large non-cleaved	17	12	29/51 (57)
Total	61	52	113/208 (54)
Non-FCC type			
Small lymphocytic	8	0	8/43 (19)
Plasmacytoid lymphocytic	2	0	2/7 (29)
Immunoblastic	8	2	10/25 (40)
Lymphoblastic	1	2	3/11 (27)
Total	19	4	23/86 (27)
Unclassifiable	2	2	4/8 (50)
Total	82	58	140/302 (46)

Results

Follicular centre cell (FCC) lymphomas had a stronger tendency to be in localized stages on admission than non-FCC lymphomas ($p<0.001$, Table 2). Fewer patients with the small cleaved FCC subtype presented in early stages than with the other FCC subtypes ($p=0.006$).

Thirty-nine patients of 78 (50%) with nodular FCC lesions had stage I or II on admission. The corresponding figure for diffuse FCC lymphomas was 74/130 (57%). Median age was 62 years (range 25–84) for patients with nodular FCC, 64 years (range 29–87) for those with diffuse FCC, and 65 years (range 17–85) for those with non-FCC tumours. The percentages of females were for those three groups 51, 39 and 35 per cent, respectively. In the early stage nodular lymphomas had a stronger tendency to be located in lymph nodes than those growing diffusely ($p=0.03$, Table 3). The opposite was found when regarding the localization in Waldeyer's ring ($p=0.04$).

The therapy varied greatly, reflecting the fact that the observation period was rather long, and that these tumours represent a wide spectrum requiring a corresponding great variability in clinical management. Radiation therapy was the only treatment in

Table 3

Tumour localization

	Nodular FCC		Diffuse FCC		Non-FCC		Total	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Lymph nodes	25	64	31	42	13	57	69	51
Waldeyer's ring	3	8	18	24	0	0	21	15
Other ENT	0	0	6	8	2	9	8	7
Stomach	2	5	6	8	1	4	9	7
Intestine	4	10	4	5	3	13	11	8
Spleen	0	0	0	0	2	9	2	1
Other extranodal*	5	13	9	12	2	9	16	12
Total	39	100	74	99	23	101	136	101

* Includes the following sites: Thyroid n=6, orbita n=3, skin n=2, skeleton n=2, testis n=1, urinary bladder n=1, mammary gland n=1.

Table 4

Distribution of morphologic types in patients given both irradiation and chemotherapy

	No.	Total number stage I and II	Per cent
Small cleaved	3	36	8
Mixed small/large cleaved	1	19	5
Large cleaved	10	29	34
Large non-cleaved	6	29	21
Small lymphocytic and plasmacytoid lymphocytic	0	10	0
Immunoblastic	0	10	0
Lymphoblastic	2	3	67
Nodular FCC	3	39	8
Diffuse FCC	17	74	23

109 patients. The tumour dose ranged between 8.8 and 65.5 Gy (mean 38.3 Gy), delivered with approximately 10 Gy per week. Most patients were treated with extended field technique, implying that the involved area and adjacent lymph nodes were included. Mean values for the different lymphoma types were the following: large cell (large cleaved and large non-cleaved FCC, and immunoblastic types) 42 Gy, small cell (small and plasmacytoid lymphocytic, and small cleaved FCC) 33.6 Gy, mixed small/large cleaved FCC 39.4 Gy. The same figures for diffuse and nodular FCC lymphoma were 40.1 Gy and 36.6 Gy, respectively.

Two patients received chemotherapy alone (10 and 7 courses of COP, i.e. Cyclophosphamide, Vincristine and Prednisone), one had a diffuse lesion composed of large cleaved cells and the other of large non-cleaved cells.

In 22 cases the primary treatment consisted of both irradiation and chemotherapy. The radiation dose in these cases ranged between 10.0 and 62.5 Gy (mean 37.5 Gy). The chemotherapy consisted of a single drug in 12 of these cases; 9 patients were given Cyclophosphamide in doses between 900 and 4000 mg (mean 2600 mg) in 5 to 18 days (mean 9 days), 2 patients Nitrogen mustard (18 mg in 4 days and 26 mg in 2 days, respectively), and one patient was given 70 mg Melphalan as a single dose. Ten patients received multiple drug therapy in the form of COP in 2 to 12 courses (mean 6 courses), with one course approximately every 3 weeks. The distribution of the lymphoma types in the cases that received irradiation and chemotherapy is demonstrated in Table 4. Three patients were treated by surgery only; one by gastrectomy, one by hemicolectomy and one by cervical node extirpation.

Complete remission was achieved in the majority of cases (Table 5). However, within the group of large cell lymphomas a significant proportion of patients either did not obtain complete remission or died within the treatment period. Nodular FCC lymphomas were more sensitive to treatment than diffuse FCC lymphomas ($p=0.001$). The group of nodular FCC tumours also included fewer patients who died within the first 6 months than the diffusely growing group ($p=0.004$).

Table 5

Effects of treatment

	Complete remission		Remaining disease		Dead within 6 months		Total
	No.	Per cent	No.	Per cent	No.	Per cent	
FCC							
Small cleaved	33	92	0	0	3	8	36
Mixed small/large cleaved	17	89	1	5	1	5	19
Large cleaved	19	66	5	17	5	17	29
Large non-cleaved	17	59	3	10	9	31	29
Total	86	76	9	8	18	16	113
Non-FCC							
Small and plasmacytoid lymphocytic	9	90	1	10	0	0	10
Immunoblastic	6	60	1	10	3	30	10
Lymphoblastic	1	33	0	0	2	67	3
Total	16	70	2	9	5	22	23
Nodular FCC	37	95	1	3	1	3	39
Diffuse FCC	49	66	8	11	17	23	74

Further analysis of the treatment failures showed that these patients were somewhat older (range 45–82, median 66 years) than within the whole series (range 17–87, median 63 years). Two cases of 80 (3%) in stage I failed, compared with 9 of 56 (16%) of those in stage II. The treatment was more intense in the patients with treatment failure. Of patients who received both irradiation and chemotherapy 5 of 22 (23%) had remaining disease, whereas the corresponding figure for those only irradiated was 5/109 (5%).

No significant difference was found between FCC subgroups with regard to site of first relapse in relation to localization of the primary, early stage tumour (Table 6). When comparing FCC tumours of different types, nodular lesions had a stronger tendency to relapse in contradiaphragmatic lymph nodes, or in otherwise distant sites. The few non-FCC lymphomas seemed to have a high propensity for distant relapse. Two patients relapsed within the treatment field, the tumours were small cleaved, nodular, and large non-cleaved, diffuse.

Among the FCC lymphomas the relapse rate was higher for the small cleaved subtype than for the other subgroups (Table 7). No significant difference was found between nodular and diffuse FCC tumours.

The most favourable subtypes with respect to relapse-free survival and survival were the small cleaved and mixed small/large cleaved FCC lymphomas, and the tumours composed of small or plasmacytoid lymphocytes (Table 7, Figs 1a, b, 2a). On the contrary, the large cell lymphomas were associated with short time to the first relapse, and a short period between relapse and death (Table 7, Figs 1c, d, 2b). The small cleaved FCC subgroup had, on the whole, the most prolonged survival after relapse, but almost all patients relapsed sooner or later (Fig. 1a).

Statistically significant difference was not found in survival or relapse-free survival when testing between the small cleaved and mixed small/large cleaved, mixed small/large cleaved and large cleaved, or between large cleaved and large non-cleaved subgroups. However, significant differences in survival were found when pooling large cell lymphomas (large cleaved, large non-cleaved and immunoblastic) and testing against mixed small/large cleaved cell lymphomas ($p=0.04$) and against small cell lymphomas (small cleaved, small and plasmacytoid lymphocytic; $p=0.001$). No significant difference in survival was found between small cell and mixed small/large cleaved cell tumours.

Many patients with nodular lesions also relapsed

Table 6

Localization of first relapse

	Within treatment field (n=2) or ipsidiaphragmatic lymph nodes		Contradiaphragmatic nodes or distant (haematogenous)	
	No./total No. of relapses within each subgroup	Per cent	No./total No. of relapses within each subgroup	Per cent
Small cleaved	9/23	39	14/23	61
Mixed small/ large cleaved	2/7	29	5/7	71
Large cleaved	3/9	33	6/9	67
Large non-cleaved	2/7	29	5/7	71
Nodular FCC	4/18	22	14/18	78
Diffuse FCC	13/28	46	15/28	54
Non-FCC	1/6	17	5/6	83

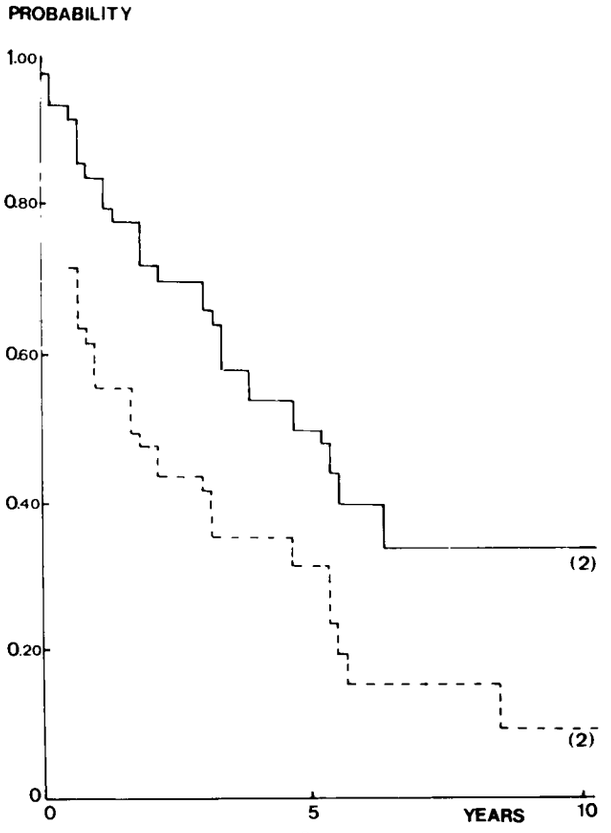
Table 7

Relapse and survival

	No. of relapses/ No. of complete remissions	Per cent	Median time to first relapse (months)	Median survival (months)
FCC				
Small cleaved	23/33	70	21	61
Mixed small/large cleaved	7/17	41	16	109
Large cleaved	9/19	47	10	19
Large non-cleaved	7/17	41	7	12
Non-FCC				
Small and plasmacytoid lymphocytic	2/9	22	51	59
Immunoblastic	3/6	50	8	21
Lymphoblastic	1/1	100	4	4
Nodular FCC	18/37	49	26	56
Diffuse FCC	28/49	57	9	14

(Fig. 3a), but the survival curve was relatively favourable, with a long period between the first relapse and death. On the contrary, diffuse FCC tumours (Fig. 3 b) were unfavourable both with respect to relapse-free survival and survival. The difference between nodular and diffuse lymphomas was statistically significant according to both relapse-free survival ($p=0.04$) and survival ($p=0.001$).

The clinical course was more beneficial for patients presenting in stage I than for those in stage II. The difference was valid with respect to relapse-free survival and survival, and when dividing the material into the major groups with favourable (Fig. 4a, b) and unfavourable (Fig. 4c, d) prognosis. Differences in survival between patients in stage I and stage II were: for favourable subtypes $p=0.04$, for unfavourable subtypes $p=0.02$. Corresponding figures for relapse-free survival were for favourable subtypes $p=0.001$ and for unfavourable subtypes $p=0.04$.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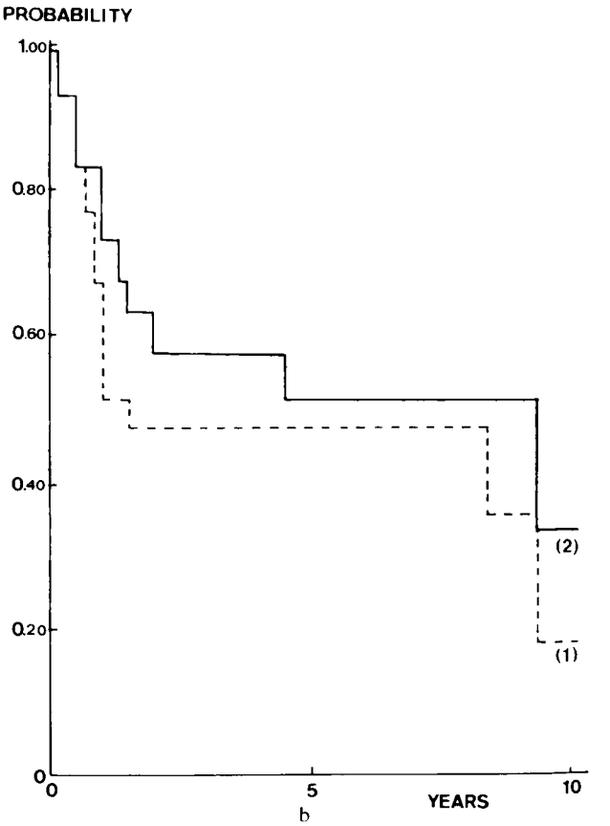
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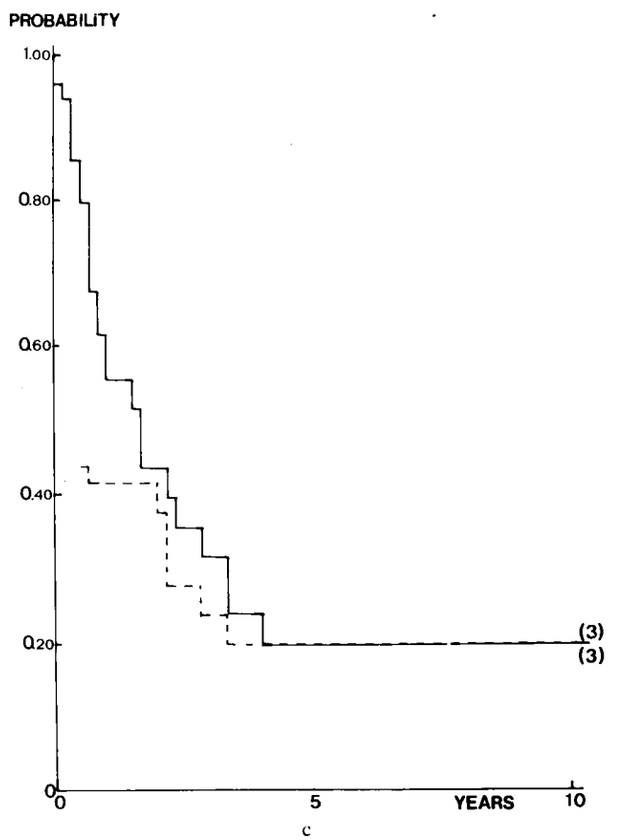
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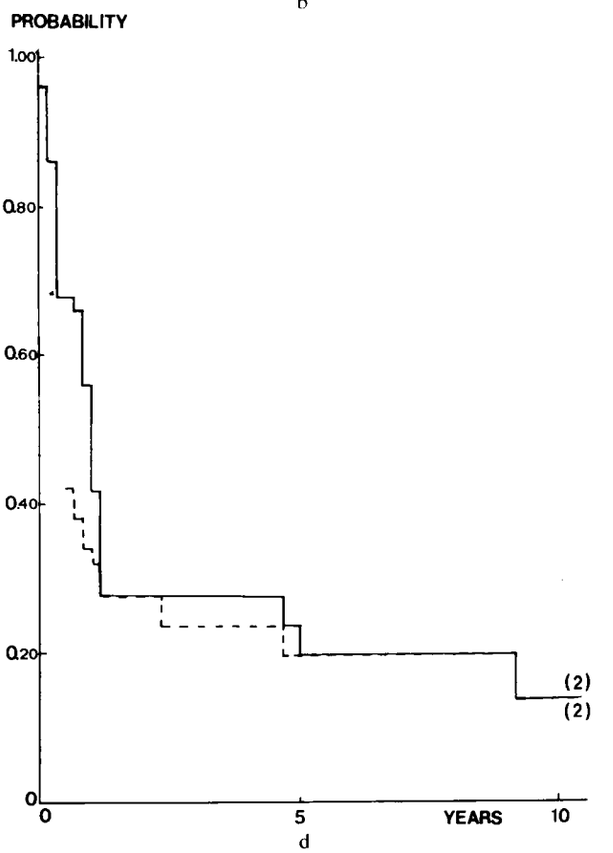
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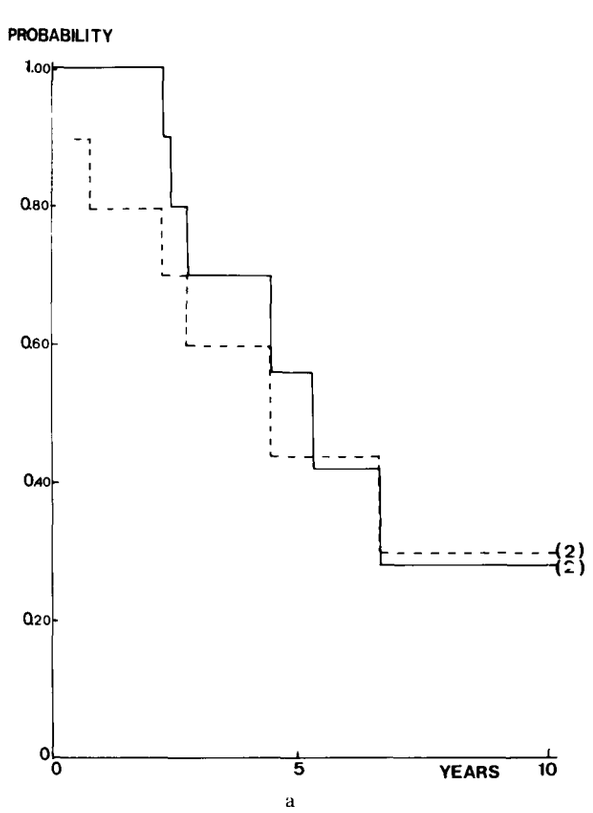


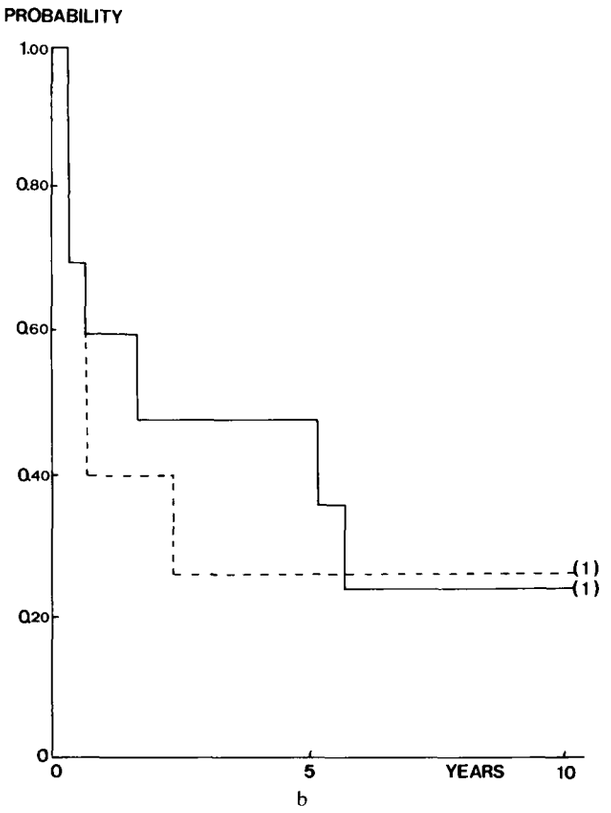


Fig. 2. Actuarial relapse-free survival and survival for patients with non-FCC lymphomas. a) Small and plasmacytoid lymphocytic (n=10), b) immunoblastic (n=10). Survival —, relapse-free survival - - -.

Discussion

Variation in the clinical course between morphologic subgroups could theoretically be attributed to non-uniform staging, differences in treatment, or different natural course of the disease. A retrospective analysis is of course insufficient when the purpose is to evaluate different treatment regimens. However, if the aim is to elucidate the natural course of different tumour entities, a retrospective analysis may have an advantage over a prospective investigation. since in a prospective one the therapy will cause a systematic error, if different treatment regimens were used for different tumour entities. In the present series the treatment methods were not uniform. The more malignant (large cell) lymphomas received, generally, more extensive treatment. Notwithstanding, survival was more unfavourable in these groups as compared with the small cell or mixed small/large cleaved FCC subgroups. It is not known whether the more extensive treatment improved survival significantly, but the overall impression of differences between the major groups is still quite obvious.

The problem of non-uniform staging can be reduced by retrospective staging that only takes into account the simple methods that were uniformly performed throughout the observation period. In the present series staging was uniform and simple, and this factor could be ruled out as a major cause of the differences found in prognosis.

Therefore, the natural course associated with the different morphologic types was probably the most important factor for the results.

The majority of non-Hodgkin's lymphomas can be separated into three main groups with different biologic features: Those with small cell morphology (small and plasmacytoid lymphocytic, small cleaved FCC), those with predominating large cells (large

Fig. 1. Actuarial relapse-free survival and survival for patients with FCC lymphomas. a) Small cleaved (n=36), b) mixed small/large cleaved (n=19), c) large cleaved (n=29), d) large non-cleaved (n=29). Figures within parentheses at the end of curves indicate number of living patients after a 10-year observation time. Survival —, relapse-free survival - - -.

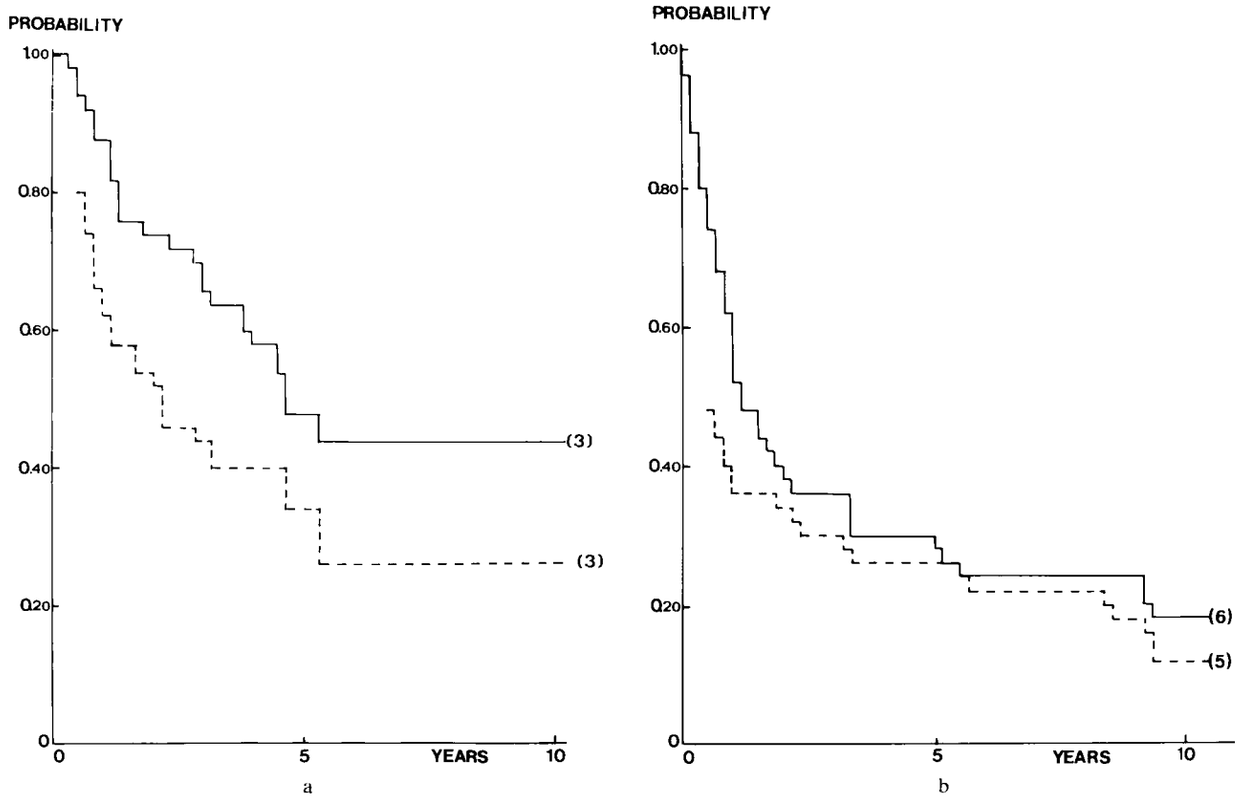


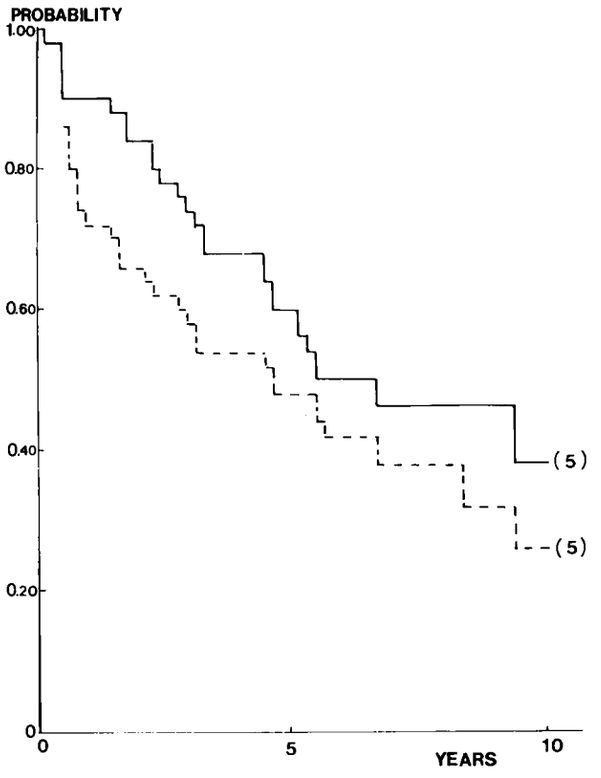
Fig. 3. Actuarial relapse-free survival and survival for patients with FCC lymphomas with different morphology. a) Nodular (n=39), b) diffuse (n=74). Survival —, relapse-free survival - - -.

cleaved and large non-cleaved FCC, and immunoblastic), and those composed of a mixture (with more than 1/3 of each) of small and large cleaved cells (LENNER et coll. 1979 a, c). These major groups have significantly different clinical and pathologic features, including proliferative capacity, mechanisms of spread and prognosis. The same features appear to be responsible for the present results; thus, a more detailed discussion of the main groups seems to be warranted.

Extensive staging procedures from several institutions have established the wide spread disease at the time of initial presentation of patients with small cell lymphoma (JONES et coll. 1972, GOFFINET et coll. 1973, KIM et coll. 1974, CHABNER et coll. 1975, 1976, JOHNSON et coll. 1975, ROSENBERG et coll. 1975, STEIN et coll. 1976, CASTELLANI et coll. 1977, COLLER et coll. 1977, MENON & BUCHANAN 1979, RIBAS-MUNDO & ROSENBERG 1979). Many of these tumours present with bone marrow and peripheral blood involvement. However, despite a great propensity for dissemination, these lymphomas are by virtue of a rather indolent and benign natural course associated with a relatively favourable survival. Convincing evidence for the slowly progressing course in these types has been presented previously (JONES et coll. 1973 a, STEIN et coll. 1974, SCHEIN et coll. 1975).

There appears to be no report analysing response to treatment and relapse rates in early stage non-Hodgkin's lymphomas, based on the LUKES & COLLINS classification. The small cell lymphomas, particularly the small cleaved FCC subgroup, appear to have a high relapse rate. Reports based on older classifications also confirm the high rate of systemic relapse associated with favourable, i.e. mainly lymphocytic lymphomas, following radiation thera-

Fig. 4. Actuarial relapse-free survival and survival according to clinical stage and cell type. a) Favourable cell type (small cleaved FCC, mixed small/large cleaved FCC, small and plasmacytoid lymphocytic), stage I (n=42), b) favourable cell type, stage II (n=23), c) unfavourable cell type (large cleaved FCC, large non-cleaved FCC, immunoblastic), stage I (n=37), d) unfavourable cell type, stage II (n=31). Survival —, relapse-free survival - - -.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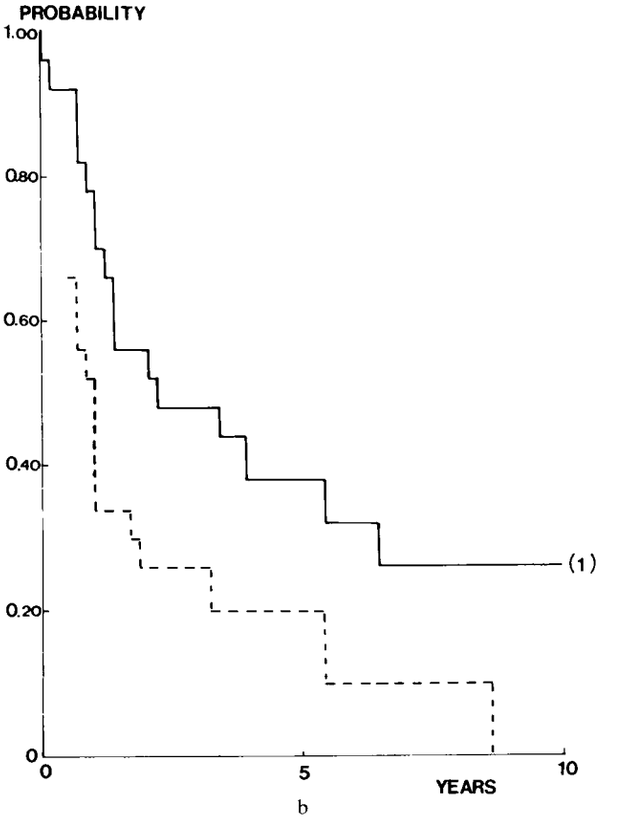
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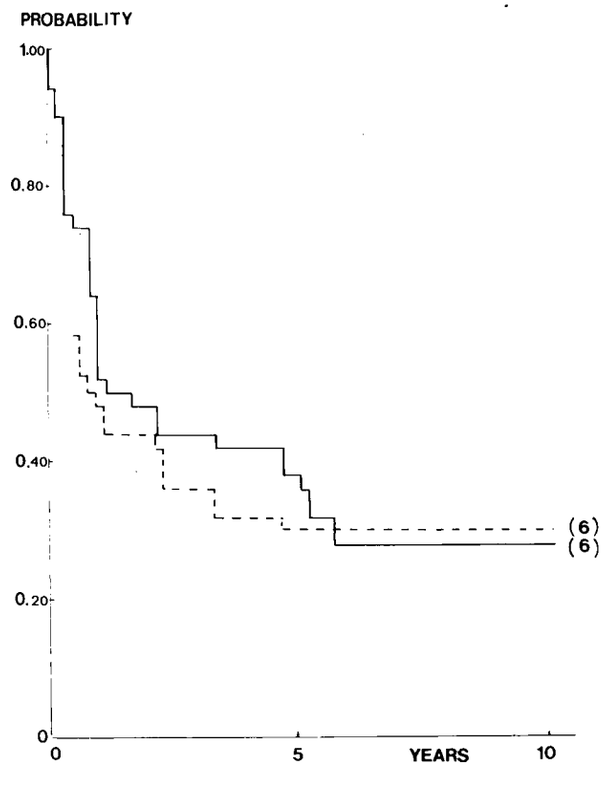
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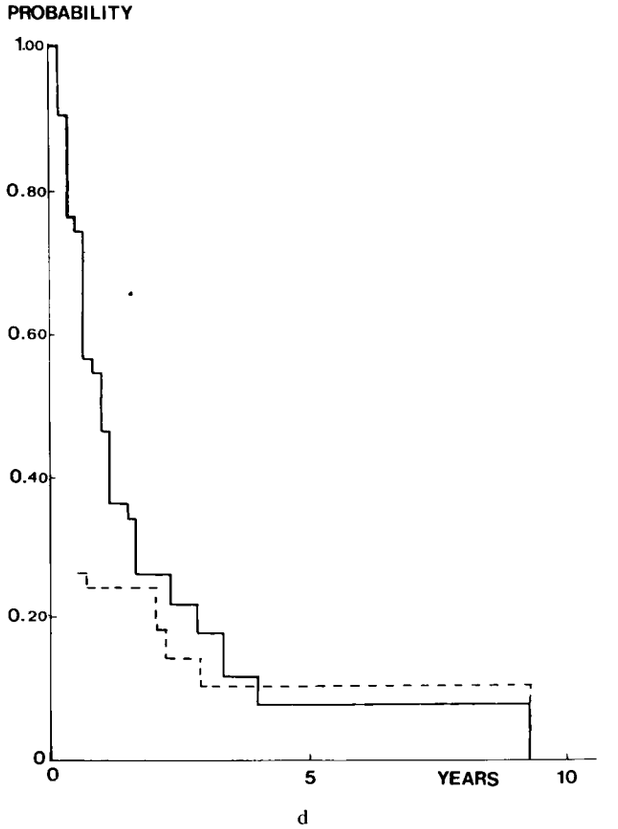
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py for apparently localized disease (JONES et coll. 1973 b, FUKS et coll. 1975, CHEN et coll. 1979).

GARRETT et coll. (1979) and TURESSON et coll. (1979) have described a high incidence of monoclonal B lymphocytes in peripheral blood of patients with lymphomas of 'favourable' morphology, previously thought to have no abnormal blood cells according to standard morphologic procedures. Thus, evidence is accumulating that small cell lymphomas are always, or almost always, systemic diseases at presentation. This feature appears to represent retention of the property of normal small lymphocytes to circulate in the organism. The practical conclusion concerning these tumours must be that extensive staging procedures do not appear to be of critical importance, a standpoint which has been expressed previously (LENNER 1980).

Patients with large cell lymphoma had, in the present series, a lower tendency to relapse compared with those with small cell lymphoma. On the other hand, time to relapse was shorter, and so was survival after relapse. However, there was a fraction of patients (about 1/5) with long-term disease-free survival, and it seems realistic to assume that at least some of these patients were cured. The finding of a more malignant biologic behaviour, but potential curability, in large cell (histiocytic) lymphomas is in good agreement with other reports (DEVITA et coll. 1975, COLTMAN et coll. 1977). It has also been demonstrated that the fraction of patients in all stages with long-term survival is increased with modern chemotherapeutic regimens (SCHEIN et coll. 1974, 1976, BERD et coll. 1975, DURANT et coll. 1975, SWEET et coll. 1976, FISHER et coll. 1977, RODRIGUEZ et coll. 1977, SKARIN et coll. 1977, JONES et coll. 1979, MILLER & JONES 1979, 1980). There is also evidence in favour of a beneficial effect of adjuvant chemotherapy after irradiation for an early stage of histiocytic lymphoma (LANDBERG et coll. 1979, MONFARDINI et coll. 1980).

The clinical attitude towards these rather highly malignant, but potentially curable, large cell lymphomas should be active. It appears important to define subgroups that do not respond well to current therapeutic regimens, as exemplified by BLOOMFIELD et coll. (1979). They demonstrated a more unfavourable course in lymphomas composed of cells without demonstrable immunologic markers, than in tumours of the same morphology but with such markers.

In the present series the mixed small/large cleaved FCC subgroup had the most favourable survival curve. This subgroup also had a high proportion of cases in stage I, a high rate of complete remisssion, and a comparably low relapse rate. This seems to be in agreement with the series of ANDERSON et coll. (1977), in which the patients were classified according to RAPPAPORT (1966), and treated with multiple drug chemotherapy. The nodular mixed lymphocytic-histiocytic subgroup had a high rate of complete remission, a long remission duration, and a favourable survival. The concept of a 'mixed' neoplasm may be confusing, since the entity is defined by the proportion of cells with different morphology. Due to varying definitions it may be difficult to compare results from different institutions concerning such tumours. However, the entity as defined in the present work seems to deserve recognition, since it was associated with the most favourable clinical course, obviously separated from the other main groups.

The nodular lymphoma was associated with approximately the same relapse frequency as the diffuse one. However, survival was significantly more favourable for patients with nodular lymphomas, reflecting the well-known benign course of these tumours (RAPPAPORT et coll. 1956, LUMB & NEWTON 1957, JONES et coll. 1973 a, b, PATCHEFSKY et coll. 1974, SCHEIN et coll. 1974). Based on the LUKES & COLLINS classification it has previously been shown (BUTLER et coll. 1975, NATHWANI et coll. 1978, LENNER et coll. 1979 b) that nodularity is correlated with cell type, but even within the same cell type patients with nodular tumours survive longer than those with corresponding diffuse lymphomas.

In conclusion, the results of this analysis of patients in apparently localized stages further confirm the value of a modified LUKES & COLLINS classification, as applied on a purely morphologic basis, in terms of correlation with clinical features including response to therapy, relapse rates and mode of relapse, and survival. Nodularity is associated with significantly better prognosis compared with the corresponding diffusely growing tumours. Finally, the results emphasize the importance of separating the majority of non-Hodgkin's lymphomas into three main groups with different clinico-pathologic features, and that the clinical approach in terms of staging and treatment should be different for these major groups.

SUMMARY

A retrospective analysis of 140 patients with non-Hodgkin's lymphoma in clinical stage I or II classified according

to a modified LUKES & COLLINS scheme was performed. Three major groups were found according to cell type, with different clinical features: (1) Small cell lymphomas with a relatively favourable survival in spite of high relapse rates. (2) Large cell lymphomas with lower relapse rates, but short time between relapse and death, and unfavourable survival. (3) Mixed small/large cleaved follicular centre cell lymphoma which was most favourable with respect to relapse and survival. Nodular lymphoma had the same overall relapse rate as diffuse lymphoma, but had a significantly longer survival. Tumours stage I were associated with significantly longer relapse-free survival and survival than stage II. The importance of separating the majority of non-Hodgkin's lymphomas into three main groups according to cell type is emphasized. These major groups require different clinical approaches in terms of staging and treatment.

ACKNOWLEDGMENT

The authors thank Prof. Lars-Gunnar Larsson and Dr Per Westling for critical evaluation and comments. This work was supported by grants from the Swedish Cancer Society and Lion's Research Foundation, Department of Oncology, University of Umeå, Sweden.

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REFERENCES

ANDERSON T., BENDER R. A., FISHER R. I., DEVITA V. T., CHABNER B. A., BERARD C. W., NORTON L. and YOUNG R. C.: Combination chemotherapy in non-Hodgkin's lymphoma: results of long-term follow-up. Cancer Treat. Rep. 61 (1977), 1057.

BENNETT M. H., FARRER-BROWN G., HENRY K. and JELLIFFE A. M.: Classification of non-Hodgkin's lymphomas. Lancet 2 (1974), 405.

BERD D., CORNOG J., DECONTI R. C., LEVITT M. and BERTINO J. R.: Long-term remission in diffuse histiocytic lymphoma treated with combination sequential chemotherapy. Cancer 35 (1975), 1050.

BLOOMFIELD C. D., GAJL-PECZALSKA K. J., FRIZZERA G., KERSEY J. H. and GOLDMAN A. I.: Clinical utility of lymphocyte surface markers combined with the Lukes-Collins histologic classification in adult lymphoma. New Engl. J. Med. 301 (1979), 512.

BUTLER J. J., STRYKER J. A. and SHULLENBERGER C. C.: A clinicopathological 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), 1890.

CASTELLANI R., BONADONNA G., SPINELLI P., BAJETTA E., GALANTE E. and RILKE F.: Sequential pathologic staging of untreated non-Hodgkin's lymphomas by laparoscopy and laparotomy combined with marrow biopsy. Cancer 40 (1977), 2322.

CHABNER B. A., JOHNSON R. E., YOUNG R. C., CANELLOS G. R., HUBBARD S. P., JOHNSON S. K. and DEVITA V. T.: Sequential nonsurgical and surgical staging of non-Hodgkin's lymphoma. Ann. intern. Med. 85 (1976), 149.

— — CHRETIEN P. B., SCHEIN P. S., YOUNG R. C., CANELLOS G. P., HUBBARD S. H., ANDERSON T., ROSENOFF S. H. and DEVITA V. T.: Percutaneous liver biopsy, peritoneoscopy and laparotomy: An assessment of relative merits in the lymphomata. Brit. J. Cancer 31 (1975) Suppl. No. II, p. 242.

CHEN M. G., PROSNITZ L. R., GONZALES-SERVA A. and FISCHER D. B.: Results of radiotherapy in control of stage I and II non-Hodgkin's lymphoma. Cancer 43 (1979), 1245.

COLLER B. S., CHABNER B. A., and GRALNICK H. R.: Frequencies and patterns of bone marrow involvement in non-Hodgkin's lymphomas: observations on the value of bilateral biopsies. Amer. J. Hematol. 3 (1977), 105.

COLTMAN C. A., LUCE J. K., MCKELVEY E. M., JONES S. E. and MOON T. E.: Chemotherapy of non-Hodgkin's lymphoma: 10 years experience in the Southwest Oncology Group. Cancer Treat. Rep. 61 (1977), 1067.

COLTON T.: Statistics in medicine, p. 163. Little, Brown & Co, Boston 1974.

DEVITA V. T., CANELLOS G. P., CHABNER B., SCHEIN P., HUBBARD S. P. and YOUNG R. C.: Advanced diffuse histiocytic lymphoma, a potentially curable disease. Results with combination chemotherapy. Lancet 1 (1975), 248.

DORFMAN R. F.: Classification of non-Hodgkin's lymphomas. Lancet 1 (1974), 1295.

DURANT J. R., LOEB V., DORFMAN R. and CHAN Y.: 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), Cyclophosphamide, Vincristine and Prednisone (BCOP). A new therapeutic regimen for diffuse histiocytic lymphoma. Cancer 36 (1975), 1936.

FISHER R. I., DEVITA V. T., JOHNSON B. L., SIMON R. and YOUNG R. C.: Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. Amer. J. Med. 63 (1977), 177.

FUKS Z., GLATSTEIN E. and KAPLAN H. S.: Patterns of presentation and relapse in the non-Hodgkin's lymphomata. Brit. J. Cancer 31 (1975) Suppl. No. II. p. 286.

GARRETT J. V., SCARFFE J. H. and NEWTON R. K.: Abnormal peripheral blood lymphocytes and bone marrow infiltration in non-Hodgkin's lymphoma. Brit. J. Haemat. 42 (1979), 41.

GERARD-MARCHANT R., HAMLIN I., LENNERT K., RILKE F., STANSFELD A. G. and VAN UNNIK J. A. M.: Classification of non-Hodgkin's lymphomas. Lancet 2 (1974), 406.

GOFFINET D. R., CASTELLINO R. A., KIM H., DORFMAN R. F., FUKS Z., ROSENBERG S. A., NELSEN T. and KAPLAN H. S.: Staging laparotomies in unselected previously untreated patients with non-Hodgkin's lymphomas. Cancer 32 (1973), 672.

JOHNSON R. E., DEVITA V. T., KUN L. E., CHABNER B.

A., CHRETIEN P. B., BERARD C. W. and JOHNSON S. K.: Patterns of involvement with malignant lymphoma and implications for treatment decision making. Brit. J. Cancer 31 (1975) Suppl. No. II, p. 237.

JONES S. E., ROSENBERG S. A. and KAPLAN H. S.: Non-Hodgkin's lymphomas. I. Bone marrow involvement. Cancer 29 (1972), 954.

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

— — KAPLAN H. S., and ROSENBERG S. A. (b): Non-Hodgkin's lymphomas. V. Results of radiotherapy. Cancer 32 (1973), 682.

— GROZEA P. N., METZ E. N., HAUT A., STEPHENS R. L., MORRISON F. S., BUTLER J. J., BYRNE G. E., MOON T. E., FISHER R., HASKINS C. L. and COLTMAN C. A.: Superiority of Adriamycin-containing combination chemotherapy in the treatment of diffuse lymphoma. A Southwest Oncology Group study. Cancer 43 (1979), 417.

KIM H., and DORFMAN R. F.: Morphological studies of 84 untreated patients subjected to laparotomy for the staging of non-Hodgkin's lymphomas. Cancer 33 (1974), 657.

LANDBERG T., HÅKANSSON L., MÖLLER T., MATTSSON W., LANDYS K., JOHANSSON B., KILLANDER D., MOLIN B., WESTLING P., LENNER P. and DAHL O.: CVP-remission-maintenance in stage I or II non-Hodgkin's lymphomas—preliminary results of a randomized study. Cancer 44 (1979), 831.

LENNER P.: Non-Hodgkin's lymphoma (letter). New Engl. J. Med. 302 (1980), 635.

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

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

— — — (c): Clinico-pathologic correlation in non-Hodgkin's lymphoma. III. Biologic significance of a modified Lukes and Collins classification. Acta radiol. Oncology 18 (1979), 544.

LENNERT K., MOHRI N., STEIN H. and KAISERLING E.: The histopathology of malignant lymphoma. Brit. J. Haemat. (1975) Suppl. No. 31, p. 193.

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

LUMB G. and NEWTON K. A.: Prognosis of tumors of lymphoid tissue—An analysis of 602 cases. Cancer 10 (1957), 976.

MATHÉ G., RAPPAPORT H., O'CONOR G. T. and TORLONI H.: Histological and cytological typing of neoplastic diseases of hematopoietic and lymphoid tissues. *In*: WHO international histological classification of tumours, No. 14. World Health Organization, Geneva 1976.

MENON N. C. and BUCHANAN J. G.: Bilateral trephine bone marrow biopsies on Hodgkin's and non-Hodgkin's lymphoma. Pathology 11 (1979), 53.

MILLER T. P. and JONES S. E.: Chemotherapy of localised histiocytic lymphoma. Lancet 1 (1979), 358.

— — Is there a role for radiotherapy in localized diffuse lymphomas? Cancer Chemother. Pharmacol. 4 (1980), 67.

MONFARDINI S., BANFI A., BONADONNA G., RILKE F., MILANI F., VALAGUSSA P. and LATTUADA A.: Improved five year survival after combined radiotherapy-chemotherapy for stage I–II non-Hodgkin's lymphoma. Int. J. Radiat. Oncol. Biol. Phys. 6 (1980), 125.

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 clinicopathologic 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. I. Introduction and design. Brit. J Cancer 34 (1976), 585.

— — — — — — — — — — 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. *In*: Atlas of tumor pathology, sect. III, fasc. 8. Armed Forces Institute of Pathology, Washington. D.C. 1966.

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

RIBAS-MUNDO M. and ROSENBERG S. A.: The value of sequential bone marrow biopsy and laparotomy and splenectomy in a series of 200 consecutive untreated patients with non-Hodgkin's lymphoma. Europ. J. Cancer 15 (1979), 941.

RODRIGUEZ V., CABANILLAS F., BURGESS M. A., MCKELVEY E. M., VALDIVIESO M., BODEY G. P. and FREIREICH E. J.: Combination chemotherapy ('CHOP-Bleo') in advanced (non-Hodgkin) malignant lymphoma. Blood 49 (1977), 325.

ROSENBERG S. A., DORFMAN R. F. and KAPLAN H. S.: The value of sequential bone marrow biopsy and laparotomy and splenectomy in a series of 127 consecutive untreated patients with non-Hodgkin's lymphoma. Brit. J. Cancer 31 (1975) Suppl. No. II, p. 221.

SCHEIN P. S., CHABNER B. A., CANELLOS G. P., YOUNG R. C. and DEVITA V. T.: Non-Hodgkin's lymphoma: Patterns of relapse from complete remission after combination chemotherapy. Cancer 35 (1975), 354.

— — — — BERARD C. and DEVITA V. T.: Potential for prolonged disease-free survival following combination chemotherapy of non-Hodgkin's lymphoma. Blood 43 (1974), 181.

— DEVITA V. T., HUBBARD S., CHABNER B. A., CANEL-

LOS G. P., BERARD C. and YOUNG R. C.: Bleomycin, Adriamycin, Cyclophosphamide, Vincristine and Prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. Ann. intern. Med. 85 (1976), 417.

SKARIN A. T., ROSENTAHL D. S., MOLONEY W. C. and FREI E.: Combination chemotherapy of advanced non-Hodgkin's lymphoma with Bleomycin, Adriamycin, Cyclophosphamide, Vincristine and Prednisone (BACOP). Blood 49 (1977), 759.

STEIN R. S., MORAN E. M., DESSER R. K., MILLER J. B., GOLOMB H. M. and ULTMANN J. E.: Combination chemotherapy of lymphomas other than Hodgkin's disease. Ann. intern. Med. 81 (1974), 601.

— ULTMANN J. E., BYRNE G. E., MORAN E. M., GOLOMB H. M. and OETZEL N.: Bone marrow involvement in non-Hodgkin's lymphoma. Cancer 37 (1976), 629.

SWEET D. L., GOLOMB H. M. and ULTMANN J. E.: Disseminated malignant lymphoma, histiocytic type: the changing picture. Ann. intern. Med. 85 (1976), 521.

TURESSON I., BERNTORP E. and ZETTERVALL O.: The expression of a human B-lymphocyte antigen and surface membrane immunoglobulin by lymphoid cells from patients with lymphocytic lymphoma, multiple myeloma and benign monoclonal gammapathy. Acta med. scand. 206 (1979), 37.