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Localized non-Hodgkin's Lymphoma

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Abstract—*Radiation was the primary therapy in* 100 *patients with clinically localized non-Hodgkin's lymphoma. The histological pattern was nodular in* 20 *and diffuse in* 80. *Thirty-five had nodal disease and* 65 *had extranodal involvement. The predicted* 10 yr *survival was* 64% *for stage I and* 43% *for stage II, with disease free survival of* 43% *and* 32%, *respectively. A proportion of patients with clinically localized non-Hodgkin's lymphoma may be cured with radiation alone.*

INTRODUCTION

THE non-Hodgkin's lymphomas (NHL) comprise a heterogeneous group of diseases with varying histological patterns and clinical presentations. Unlike Hodgkin's disease (HD), localised NHL is uncommon, and when it occurs, frequently involves extranodal sites [1–3]. High cure rates have been reported for apparently localized disease treated by conventional radiotherapy [3–5], although interpretation of results from the majority of studies has been hampered by inconsistencies in staging and histological classification [6]. Recent improvement in our understanding of the NHL has been aided by the introduction of the revised Rappaport histological classification [7] which has been shown to have prognostic significance [8]. In addition, more intensive staging studies [1, 9] have underlined the importance of adequate pretreatment investigation of patients in whom disease appears localized clinically, thereby avoiding treatment failures as a result of inadequate initial management.

This study is a retrospective analysis of patients with clinically localized (stage I) or regional (stage II) NHL seen at St. Bartholomew's Hospital between 1961 and 1977.

MATERIALS AND METHODS

Patients

One hundred and twelve previously untreated patients with localized NHL referred to St. Bartholomew's Hospital between 1961 and 1977 form the basis of this review. Cases primarily involving the gastrointestinal tract were not included and 12 cases in whom follow-up was inadequate were subsequently excluded from the analysis. There were no recorded cases of primary testicular, bone or breast lymphoma.

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Histopathology

Haematoxylin and eosin sections of all original biopsy specimens were examined (DK) and classified according to the Rappaport classification [7] (Table 1).

Staging

The Ann Arbor staging classification was used, although in the majority of cases the extent of disease was not assessed by intensive investigation. Patient details are shown in Tables 2 and 3.

Clinical examination revealed 35 cases to have disease localized to lymph nodes and 65 to have extranodal involvement. The site of presentation was supradiaphragmatic in 88 out of 100 cases.

Lymphangiography was performed in 36 patients. During the latter part of the study, bone marrow examination became routine: bone marrow aspiration was performed in 51 cases and unilateral bone marrow trephine biopsy (Gardner needle) was performed in 22, although inadequate material was obtained in two patients. Laparotomy and splenectomy were only undertaken in two cases.

Treatment

All patients were treated initially with radiotherapy. The majority of patients received

Table 1. *Localized non Hodgkin's lymphoma stages* I+II (*Rappaport classification*)

Stage	Nodular			Diffuse				
	P.D.L.	Mixed	Histio.	W.D.L.	P.D.L.	Mixed	Histio.	Undiff.
IA	1	3	1	2	7	1	8	—
IIA	1	2	—	1	1	—	7	—
I+IIA	2	5	1	3	8	1	15	—
IE	4	3	—	8	8	2	6	3
IIE	1	4	—	—	13	2	11	—
I+IIE	5	7	—	8	21	4	17	3
All	7	12	1	11	29	5	32	3

Table 2. *Localized non-Hodgkin's lymphoma* (*St. Bartholomew's Hospital* 1961–1977

Patient details		
Total No. of patients		100
Male:female		48:52
Age range (yr)		10–85 (median=58)
Male		10–77 (median=53)
Female		13–85 (median=63)
Stage I	Nodal	23
	Extranodal	34
Stage II	Nodal	12
	Extranodal	31

megavoltage irradiation using ^{60}Co or 4 MeV or 15 MeV linear accelerator with minimum tumour doses of 2500 rad at the rate of 800–1000 rad/week in five daily fractions. Twenty-three patients with either skin or orbital lesions received tumour doses of less than 2500 rad. Forty-one cases with clinical stage I disease received treatment to the involved site only (IF), 14 received treatment to the involved site and the clinically uninvolved adjacent (regional) nodes (EF), and two received wide field (WF), 'mantle' or 'inverted Y' irradiation. Thirty-three cases with stage II disease received involved field (IF), six received extranodal field (EF) and four received wide field irradiation (Table 4).

Twenty-one patients (13 stage I and 8 stage II) received adjuvant chemotherapy, 19 with combination regimes and two with single agents.

Statistical analysis

Survival and disease free survival are calculated from completion of initial radiotherapy to the time of death or first relapse using standard life table formulae. Statistical significance was determined by the Wilcoxan test modified to deal with life table data by Gehan [11].

Table 3. *Localized non-Hodgkin's lymphoma* (*extra nodal sites*)

	IE	IIE	Total
Orbit	9	—	9
P.N.S.	2	7	9
Tonsil	4	9	13
Thyroid	3	5	8
Oro-pharynx	3	1	4
Vallecula	—	2	2
Nasal cavity	1	1	2
Sinuses	2	—	2
Skin	7	4	11
Extra-dural	2	—	2
Thymus	—	1	1
Salivary gland	1	1	2
Total	34	31	65

Table 4. *Localized non-Hodgkin's lymphoma* (*St. Bartholomew's hospital* 1961–1977, *site of relapse following radiotherapy*)

	Radiotherapy	No.	Local	Contiguous	Distant
Stage I	I.F.	41	2(5%)	2(5%)	12(29%)
	E.F.	16	1(6%)	—	2(12.5%)
Stage II	I.F.	33	6(18%)	4(12%)	12(36%)
	E.F.	10	1(10%)	—	3(30%)

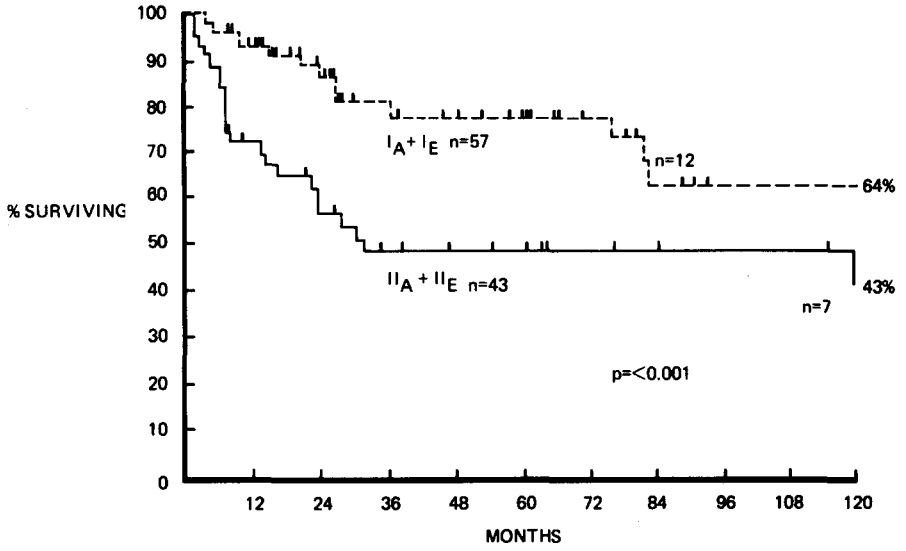

Fig. 1. Survival data for stage I *and stage* II *patients.*

RESULTS

Survival

Thirty-eight patients have died at the time of this analysis. NHL was the primary cause of death in 31. Seven patients died of intercurrent disease, one from carcinoma of the bronchus and one from carcinoma of the rectum, at 26 and 126 months, respectively. Bronchopneumonia and cardiovascular disease accounted for the remaining five deaths, only one of whom had evidence of active lymphoma at the time of death.

Clinically staged patients. Thirteen deaths have occurred in 57 patients with stage I and 25 in the 43 patients with stage II disease (Fig. 1). A significant survival difference was demonstrated between localized (stage I) and regional (stage II) cases with projected 10-yr survivals of 64% and 43%, respectively ($P=0.001$).

Staging with lymphangiography and bone marrow biopsy. Lymphangiography was negative in 23 out of 57 patients with clinical stage I disease. Only three of these patients have relapsed and there is a trend, although not statistically significant, for this group to have a better survival than those in whom lymphography was not performed at presentation. Both bone

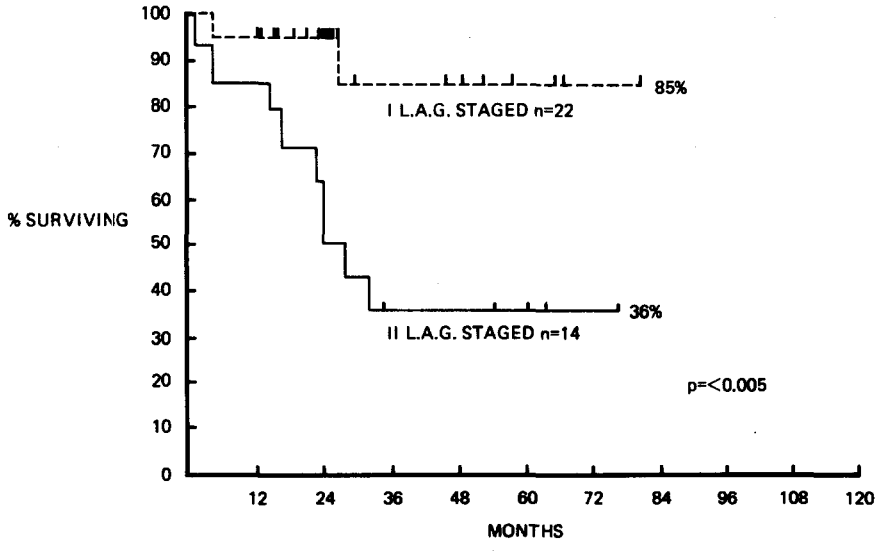

Fig. 2. Comparison of survival rates for lymphangiogram stage I *and* II *patients.*

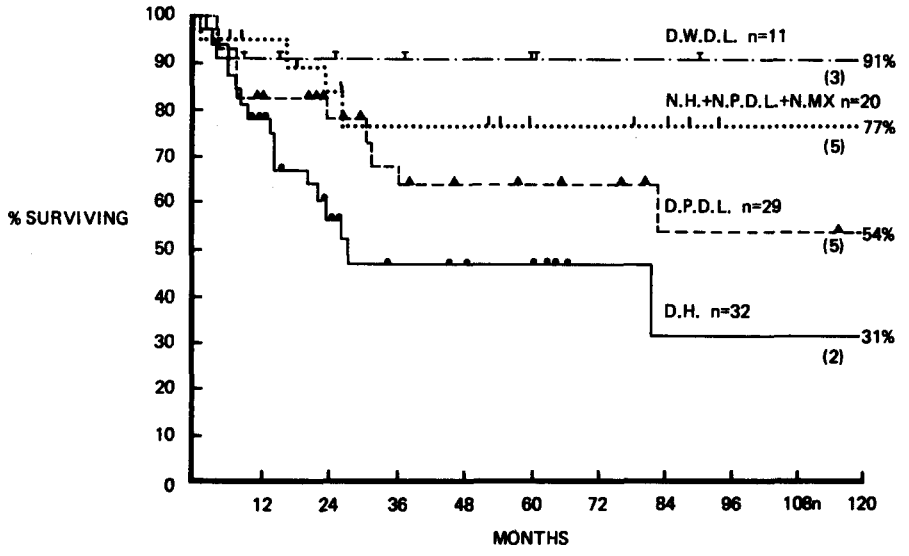

Fig. 3. Survival by histology.

marrow biopsy and lymphangiography was performed in 14 of these patients: one has relapsed.

Lymphangiography advanced the stage from I to II in three patients with clinical stage I disease, and was negative in 14 patients with clinical stage II disease. Bone marrow biopsy was negative in six of these cases. The survival of those patients with lymphangiography staging was the same as that of those in whom it was not performed.

Site of presentation. There was no statistical difference in survival between patients with nodal and extranodal presentations.

Histology. Seven of the 20 patients with nodular lymphoma have died (35%), 5 out of 12 with nodular mixed (N-M) at 138, 120, 25, 23 and one month and two nodular poorly differentiated lymphocytic (N-PDL) at 126 and 16 months. The only patient with nodular histiocytic lymphoma is alive in remission at 18 months.

Thirty one patients with diffuse lymphoma have died (39%), 10 (34%) with diffuse poorly differentiated lymphocytic (D-PDL) and 16 (50%) with diffuse histiocytic (DH). The median survival for D-DPL has not yet been reached but is in excess of 82 months

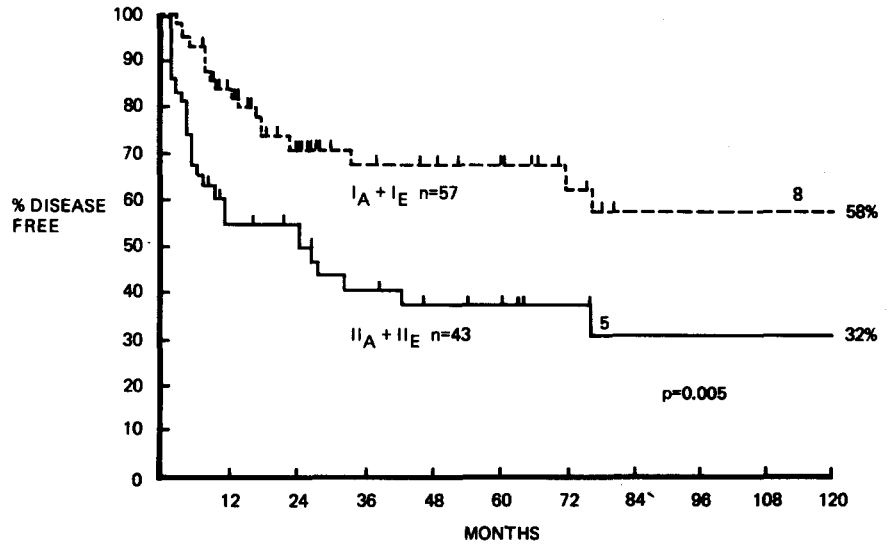

Fig. 4. Disease free survival data for stage I *and stage* II *patients.*

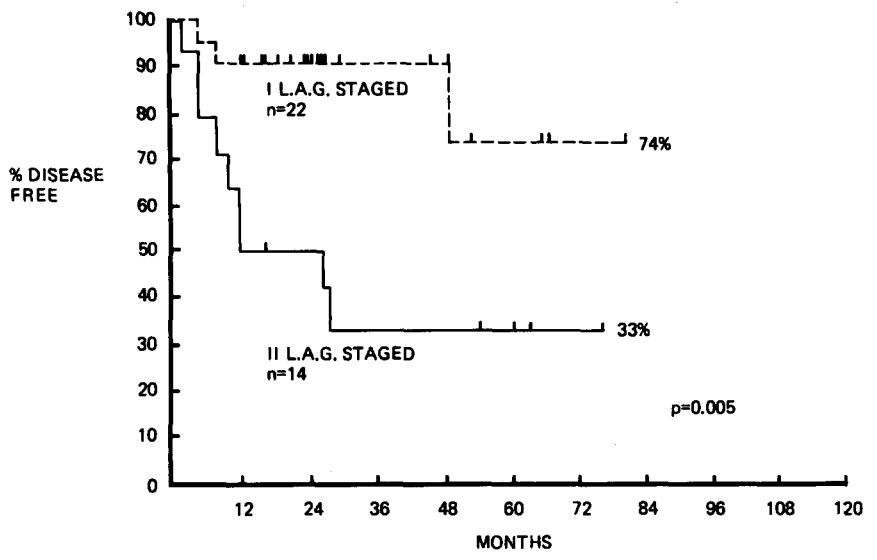

Fig. 5. Comparison of disease free survival rates for lymphangiogram stage I *and* II *patients.*

whereas for DH patients with median survival was only 27 months (Fig. 3). Two of the 11 patients with diffuse well differentiated lymphocytic lymphoma (D-WDL) have died, at 4 months and 131 months from diagnosis.

Age and sex. Neither age nor sex had a significant influence on survival.

Adjuvant chemotherapy. Twenty-one patients received adjuvant chemotherapy, 16 with cyclophosphamide, vincristine and prednisolone, two with cytosine arabinoside and prednisolone, one cytosine arabinoside, adriamycin, vincristine and prednisolone, and two with chlorambucil. Twelve of 13 stage I and 6 of 8 stage II patients remain alive at follow up periods of 12–76 months (median=24 months).

Disease free survival

Clinically staged patients. Forty-five patients have relapsed, 19 stage I and 26 stage II with projected disease free survival figures at 10 yr of 58% and 32%, respectively (Fig. 4. $P = 0.005$). Thirty-six of the 45 relapses (80%) occurred within 24 months from initial treatment. One patient with nodular and two with diffuse disease relapsed at periods in excess of 72 months from treatment.

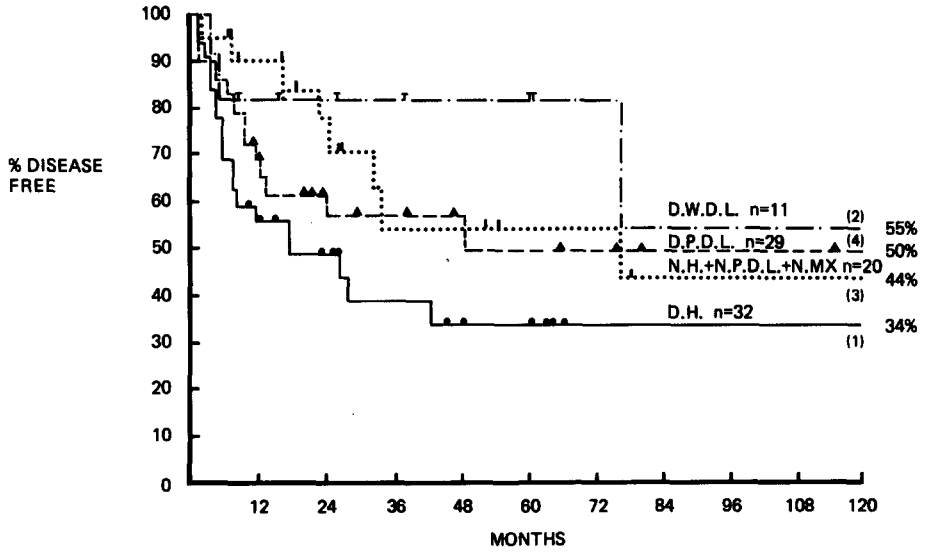

Fig. 6. Disease free survival by histology.

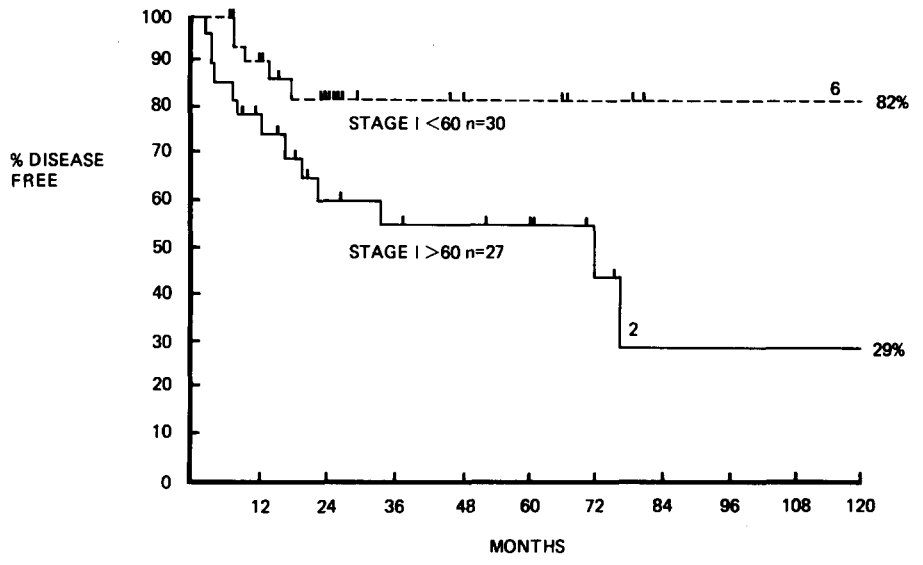

Fig. 7. Disease free survival for stage I patients according to age.

Staging by lymphangiography. In the stage I patients who underwent preliminary investigation by lymphangiography there were fewer relapses during the first 48 months after therapy, although the difference between these and the group of patients who did not have a lymphangiogram was not significant (Fig. 5). Staging by lymphangiography showed no benefit in the stage II patients.

Site of presentation. No significant difference was apparent in terms of disease free survival between nodal and extranodal (E) presentations.

Histology. Eight patients with nodular lymphoma have relapsed, seven N-M and one N-PDL with follow up from 7 to 173 months. In the diffuse group, 19 of 32 (60%) of DH patients have relapsed and 13 of 29 (45%) with D-PDL. Projected 10-yr disease free survival figures are shown in Fig. 6.

Age and sex. In the stage I patients, those less than 60 years of age at presentation had a significantly improved relapse-free survival duration compared with those over 60 ($P=0.02$). This difference could not be explained on the basis of histological bias and was not shown in the stage II group.

There was no difference in disease-free survival when analysed according to sex.

Adjuvant therapy. One patient in the stage I group (13) has relapsed at 7 months and two in stage II (8) at 4 and 26 months respectively with median follow-up of 24 months (12–76 months).

Site of relapse. Twenty-nine relapses (64%) occurred in areas distant to the initial site of involvement, six in contiguous node groups and 10 were classified as local failures (Table 5). No contiguous recurrences were observed in the group receiving extended field irradiation but the rate of distant recurrences was not significantly different between EF and IF treated patients. Nine of the 10 local recurrences were in diffuse histology tumours (DH 4, D-PDL 3, D-M 3) and six of these had received tumour doses in excess of 4000 rad.

DISCUSSION

It is clear from these data and from the literature that localized or regional radiotherapy may result in prolonged disease free survival and possibly cure a proportion of patients with stage I and II NHL [3–6].

Three factors make the results of treatment for NHL at different centres difficult to compare: the intensity of the staging procedures, the interpretation of the histopathological classification, even if the same classification is used at the different centres, and the type of therapy employed.

In this analysis, patients with clinically localized disease (stage I) have shown a significantly better actuarial disease-free survival rate at 10 yr (58%) compared to the more extensive regional (stage II) cases (32%) ($P=0.005$), figures in close agreement with data reported by others [3,6]. The improved disease-free survival rates for localized disease support the hypothesis that NHL may arise as a solitary focus and although spreading in-

itially in contiguous fashion (stage II) rapidly becomes disseminated, accounting for the high percentage of patients with generalised disease at presentation.

More intensive staging will exclude patients with otherwise undetected disease at distant sites in whom localized therapy is inappropriate. While pretreatment lymphangiography resulted in an improvement in early relapse figures for a small group of stage I patients, other workers have confirmed the inadequacy of lymphangiography as the sole staging procedure but have demonstrated that for the majority of patients evidence of dissemination of disease may be obtained by non-surgical methods [1]. Staging laparotomy should be reserved for the few cases with clinically localized disease below the diaphragm in whom all other investigations are negative.

The revised Rappaport histological classification introduced in 1966, provides a prognostically useful system for NHL and has allowed more valid comparison of results from different series [4, 8, 12]. Studies involving intensive staging have confirmed that the majority of cases with nodular histological pattern have disseminated disease at presentation and that diffuse histologic types make up the great proportion of stage I and II patients. In the present series, 80% of patients had diffuse pattern disease, the small number of nodular cases being evenly distributed between the nodal and extranodal presentations. The more indolent behaviour of nodular disease can be seen by comparison of the disease free survival curves in Fig. 3. Despite a high early relapse rate, many patients survive for long periods in the presence of active disease compared to the more aggressive diffuse histologic type where relapse carries a very poor prognosis.

Unlike HD, there is still considerable lack of information regarding the role of extended versus involved field treatment and the exact definition of 'adequate' tumouricidal dose appropriate to the various histological types of NHL [4, 12, 13].

The lack of contiguous recurrences in our own patients with EF irradiation suggests that it may be appropriate to treat at a minimum adjacent clinically uninvolved lymph node areas for localized disease, although the distant relapse rate was not significantly different between the IF and EF treated groups.

Analysis of the local failures shows that 90% involved diffuse tumours and many had received tumour doses in excess of 4000 rad. While this may be adequate to control nodular disease, Fuks and Kaplan reported significant local failures with even higher doses for diffuse histologies [13]. It appears, therefore, that despite high dose irradiation, local failures may still occur and the addition of cytotoxic chemotherapy may be required to gain control of the disease.

The poor disease free survival rate for those patients with two or more sites of involvement (stage II) probably reflects the high incidence of distant spread in this group and the need for systemic therapy. From the preliminary results of Bitran *et al.* [14] on a group of pathologically staged patients with localized NHL, the only relapses had occurred in patients with stage II disease and in sites distant from the initial area of involvement. Our own experience with adjuvant chemotherapy in NHL is very small and analysis of cases so treated is hampered by variations in quality of initial staging procedures. The majority received chemotherapy with cyclophosphamide, vincristine and prednisolone, a regime which has been shown to have only limited value in the management of advanced disease [15, 16].

Results from other groups using chemotherapy as an adjunct to radiation are conflicting [17, 18], but the uniformly poor results with radiotherapy alone in stage II disease suggest that the concept of systemic chemotherapy for this group is correct and it is the efficacy of the agents presently in use which is at fault. Increasing success with new combination chemotherapy regimes in patients with disease of aggressive histological type [19] offers hope for improved survival in those patients with occult disease at the time of presentation [20].

Although the investigation and treatment of patients in this review has varied over the period of observation, certain conclusions can still be drawn on the basis of the information available. It is apparent that localized NHL does exist and even with inadequate initial assessment over 60% of clinically localized cases of NHL treated by radiotherapy alone may expect to remain free of disease in excess of 5 yr.

Despite high dose irradiation local tumour recurrence remains a cause of failure and where disease is localized to one anatomical area, we still favour regional irradiation to reduce the risk of contiguous node recurrence.

For regional presentations, the failure rate following radiation therapy alone is consider-

able and effective chemotherapy is required to improve the chances of long term disease free survival in this group.

The small number of cases of localized NHL seen at most centres demands co-operative prospective studies in which adequate staging is mandatory and the role of varying radiotherapy techniques and adjuvant chemotherapy programmes can be adequately assessed.

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REFERENCES

1. B. A. Chabner, R. E. Johnson, V. T. De Vita, G. P. Canellos, S. P. Hubbards, S. K. Johnson and R. C. Young, Sequential staging in non-Hodgkin's lymphoma. *Cancer Treat. Rep.* **61,** 993 (1977).
2. S. A. Rosenberg, H. D. Diamond, B. Jazlowitz and L. F. Craver, Lymphosarcoma: a review of 1269 cases. *Medicine (Baltimore)* **40,** 31 (1961).
3. S. Hellman, D. S. Rosenthal, W. C. Moloney and J. T. Chaffey, The treatment of non-Hodgkin's lymphoma. *Cancer (Philad.)* **36,** 804 (1975).
4. R. S. Bush, M. Gospodarowicz, J. Sturgeon and R. Alison, Radiation therapy of localized non-Hodgkin's lymphoma. *Cancer Treat. Rep.* **61,** 1129 (1977).
5. S. E. Jones, Z. Fuks, H. S. Kaplan and S. A. Rosenberg, Non-Hodgkin's lymphomas. V. Results of radiotherapy. *Cancer (Philad.)* **32,** 682 (1973).
6. M. J. Peckham, Radiation therapy of the non-Hodgkin's lymphoma. *Semin. Haematol,* **11,** 41 (1974).
7. H. Rappaport, Tumours of the haematopoietic system. Washington D. C. *Armed Forces Institute of Pathology,* **91** (1966).
8. S. E. Jones, Z. Fuks, M. Bull, M. E. Kadin, R. F. Dorfman, H. S. Kaplan, S. A. Rosenberg and H. Kim, Non-Hodgkin's lymphomas: clinicopathologic correlation of 405 cases. *Cancer (Philad.)* **31,** 806 (1973).
9. D. R. Goffinet, R. Warnke, N. R. Dunnick, R. Castellino, E. Glatstein, T. S. Nelson, R. F. Dorfman, S. A. Rosenberg and H. S. Kaplan, Clinical and surgical (laparotomy) evaluation of patients with non-Hodgkin's lymphomas. *Cancer Treat. Rep.* **61,** 981 (1977).
10. E. L. Kaplan and P. Meier, Non-parametric estimation from incomplete observation. *Amer. Stat. Ass. J.* **53,** 457 (1958).
11. E. A. Gehan, A generalised Wilcoxon test for comparing arbitrarily singly censored samples. *Biometrika* **52,** 203 (1965).
12. L. M. Fuller, F. L. Banker, J. J. Butler, J. F. Gamble and M. P. Sullivan, The natural history of non-Hodgkin's lymphomata stages I and II. *J. Cancer* **31,** 270 (1975).
13. Z. Fuks and H. S. Kaplan, Recurrence rates following radiation therapy of nodular and diffuse malignant lymphomas. *Radiology* **108,** 675 (1975).
14. J. D. Bitran, J. Kinzie, D. L. Swett, D. Variakojis, M. L. Green, H. M. Golob, J. B. Miller, N. Detlel and J. E. Ultmann, Survival of patients with localized histiocytic lymphoma. *Cancer (Philad.)* **39,** 342 (1977).
15. C. S. Portlock, S. A. Rosenberg, E. Glatstein and H. S. Kaplan, Treatment of advanced NHL with favourable histologies: preliminary results of a prospective trial. *Blood* **47,** 747 (1976).
16. T. A. Lister, M. H. Cullen, M. E. J. Beard, R. L. Brearley, J. M. A. Whitehouse, P. F. M. Wrigley, A. G. Stansfeld, S. B. Sutcliffe, J. S. Malpas and D. Crowther, Comparison of combined and single agent chemotherapy in non-Hodgkin's lymphoma of favourable histological type. *Brit. med. J.* **1,** 533 (1978).
17. G. Bonnadonna, M. de Lena, A. Lattuada, F. Milani, S. Monfardini and G. Beretta, Combination chemotherapy and radiotherapy in non-Hodgkin's lymphomata. *Brit. J. Cancer* **31,** 481 (1975).
18. S. A. Rosenberg and H. S. Kaplan, Clinical trials in the non-Hodgkin lymphomata at Standford University: experimental design and preliminary results. *Brit. J. Cancer* **31,** 456 (1975).

19. V. T. DE VITA, G. P. CANELLOS, B. CHABNER, P. SCHEIN, S. P. HUBBARD and R. C. YOUNG, Advanced diffuse histiocytic lymphoma, a potential curable disease. *Lancet* **ii,** 248 (1975).
20. T. P. MILLER and S. E. JONES, Chemotherapy of localised histiocytic lymphoma. *Lancet* **i,** 358 (1979).