

SPREAD ACCORDING TO HISTOLOGY IN NON-HODGKIN'S LYMPHOMATA

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Summary.—The spread of non-Hodgkin's lymphomata was investigated in a group of 323 cases. Differences were sought between 4 histological groups: lymphocytic *vs* histiocytic lymphomata and diffuse *vs* follicular types.

Histiocytic and follicular types were rare in childhood. Histiocytic lymphomata, compared with lymphocytic ones, were more often confined to sites above the diaphragm. They exhibited a higher rate of loco-regional recurrences within the first 3 months and also of late recurrence after 4 years. Lymphocytic lymphomata of the follicular type more commonly presented with nodal involvement below the diaphragm as primary or secondary site than the diffuse form. Follicular types of lymphoma compared with diffuse types, occurred more frequently in women. They were more seldom seen as primary or secondary sites in extranodal localizations. They had a smaller chance of late disease recurrence and were associated with a longer survival time after first recurrence. The mediastinum often remained clinically uninvolved. With regard to this mediastinal "skip" no differences were found between the histological groups.

IN CONTRAST with Hodgkin's disease, until recently very few data have been published with regard to the spread of the disease in different histological types of non-Hodgkin's lymphomata. Recently Jones *et al.* (1973) have published an analysis of their clinical material.

Staff members of the Netherlands Cancer Institute in Amsterdam and the Radiotherapeutic Institute in Rotterdam have co-operated in studying the records of their patients with non-Hodgkin's lymphomata (van Unnik *et al.*, 1975).

In this paper we present data with regard to the spread of the disease in relation to age, sex, site(s) of disease and histology. Histology is divided into 4 groups: lymphocytic and histiocytic lymphomata on the one hand and diffuse and follicular (or nodular) types of lymphoma on the other hand.

Age distribution

On the whole, no striking differences were found in the age distribution between

lymphocytic and histiocytic lymphomata, though histiocytic lymphomata were relatively rare in childhood.

Follicular types of lymphomata are exceptional in young children. The pattern for older age groups did not show marked differences between follicular and diffuse forms.

Sex

Of a total of 323 cases, 139 were women and 184 men, so there were slightly more men than women (factor 1.3).

In our material the follicular type of lymphoma occurs significantly more frequently in women than in men (24% and 15% respectively).

Localization of the primary involved sites at the time of staging

In Stage I, comprising 94 cases, the distribution over the various nodal and extranodal single sites leaves too small a number of cases in each particular site to permit an analysis of the differences

for the different histological groups. Relatively frequently involved in Stage I were the right side of the neck, with 14 cases compared with 9 cases in the left side of the neck, Waldeyer's ring with 11 cases and the upper air passages with 11. Waldeyer's ring and both sides of the neck were primary sites of rather more than one third of the total number of cases in Stage I.

In order to obtain sufficient numbers to analyse the influence of the histological type on spread, we combined the various sites in groups above, below and on both sides of the diaphragm. By distinguishing between extranodal and nodal localizations, we categorized (apart from lymph nodes) other lymphocytic organs like Waldeyer's ring and spleen as "nodal".

Histiocytic lymphomata were confined to supradiaphragmatic sites in a significantly higher percentage than the lymphocytic lymphomata, which occur more frequently below and on both sides of the diaphragm.

In Stage II nodal lymphocytic lymphomata the follicular type more often presents below the diaphragm than the diffuse form (Table I).

TABLE I.—*Stage II, Lymphocytic Lymphomata. Below Diaphragm (Initial or Second Site)*

Diffuse	17/47	(36%)
Follicular	11/14	(79%)

Mediastinal involvement

The mediastinum was primarily affected in 53 cases (16% of the total). The percentage increases more or less with increasing stage: Stage I 5/94 (5%); Stage II 20/126 (16%); Stage III 9/27 (30%); Stage IV 18/70 (26%).

Considering the cases primarily staged as III and IV with nodal involvement both above and under the diaphragm, no mediastinal involvement could be demonstrated in 65% of them. In this respect no significant difference could be found between lymphocytic and histiocytic lym-

phomata, nor between diffuse and follicular types (Table II).

TABLE II.—*Mediastinal Involvement (Primary Stages III and IV)*

Lymphocytic lymphomata	27/42	(64%)
Histiocytic lymphomata	7/12	(58%)
Total	34/54	(63%)
Diffuse type	23/38	(61%)
Follicular type	10/13	(77%)
Total	33/51	(65%)

The small difference in total numbers, respectively 54 and 51, is due to the fact that in 3 cases the typing in diffuse or follicular type was not possible.

These findings already suggest that there is a tendency for mediastinal "skipping". Such a phenomenon can, however, be studied better during the follow up of the patient by looking at the secondary involved sites after the initial treatment.

The pattern of spread

Of 75 cases in Stage I with nodal or extranodal involvement, 16 subsequently demonstrated disease on the other side of the diaphragm and thus had moved into Stage III or IV. In 13 of these 16 cases (81%) the mediastinum remained clinically uninvolved.

Combining the nodal forms of Stages I and II, we found 29 out of 117 cases in which the primary site and the first recurrence were on opposite sides of the diaphragm. Mediastinal "skipping" was found in 90% of these 29 cases. There was no significant difference observed with regard to this phenomenon between lympho- and histiocytic lymphomata, nor between diffuse and follicular types (Table III).

The patho-physiological basis for mediastinal "skipping" is not clear.

In our material the right side of the neck was more frequently involved than the left side and extension to a secondary site was found only twice on the left side of the neck, compared with 9 times on the right side. This suggests that spread

TABLE III.—*Secondary Involvement on Opposite Side of Diaphragm*

		Mediastinal "skipping"	
Stage I (nodal + extra nodal)	16/75	13/16 (81%)	
Stage I and II (nodal)	29/117	26/29 (90%)	
Lymphocytic type		17/18 (94%)	
Histiocytic types		9/11 (82%)	
Diffuse lymphomata		18/21 (86%)	
Follicular lymphomata		8/8 (100%)	

via the thoracic duct does not play an important role.

The tendency for mediastinal "skipping" has already been noticed by a number of authors (Tin Han and Stutzman, 1967; van der Werf-Messing, 1968; Scheer, 1963).

Lymphomata in Stage I with a follicular structure were seen less commonly in extranodal localizations. For the combined nodal forms of Stages I and II, it was evident that the follicular type gave rise to secondary extranodal involvement in a far smaller percentage of the cases than was the case for diffuse lymphomata (20/31 (65%) vs 6/16 (37%)).

Lymphocytic lymphomata of the follicular type show more of a tendency to extend to infradiaphragmatic nodal areas than is the case for diffuse lymphocytic lymphomata.

Spread in time of evolution of the disease

The survival curves for the combined Stages I and II are different for histiocytic and lymphocytic forms (van Unnik *et al.*, 1975, Fig. 5).

In quite a number of cases local recurrence or extension of the disease outside the irradiated area was discovered shortly after and sometimes even during treatment. Such loco-regional recurrences within the first 3 months occurred in about 30% of all cases in Stages I and II. As most of the patients were treated locally with x- or gamma rays, these recurrences are probably due either to inadequate doses or inadequate field sizes.

We did not succeed in establishing a dose-effect relation with respect to local recurrence, as the percentages did not differ significantly for the various dose levels.

The histiocytic lymphomata had a greater chance of local recurrence within the first 3 months compared with the lymphocytic lymphomata (Table IV).

TABLE IV.—*Local Recurrence Within 3 Months—Stages I and II*

Lymphocytic type	28/108	(26%)
Histiocytic type	26/68	(38%)

This suggests that the histiocytic lymphomata are less radiosensitive.

There was no clear difference between diffuse and follicular types with regard to the chance of local recurrence (Table V).

TABLE V.—*Local Recurrence Within 3 Months—Stages I and II*

Diffuse types	43/140	(31%)
Follicular types	9/32	(28%)

If one does not take into account the patients in Stages I and II who had a recurrence within the first 3 months and follows the percentages of patients remaining clinically free of tumour for one, 2 or more years, there proves to be not much difference between lymphocytic and histiocytic types during the first 4 years. After 5 years, however, histiocytic lymphomata appear to relapse with a new tumour localization with greater frequency than lymphocytic lymphomata (Fig. 1).

For those patients not recurring within the first 3 months, the chance of developing a new localization of the disease was less for follicular than for diffuse types of lymphomata (Fig. 2). Moreover, the survival time after the discovery of a recurrence is better for patients with follicular types of lymphoma (Fig. 3). Both the lower rate of late recurrence and the longer survival afterwards contribute

PERCENTAGE FREE OF TUMOUR IN STAGE I and II
(without cases of recurrence within 3 months)

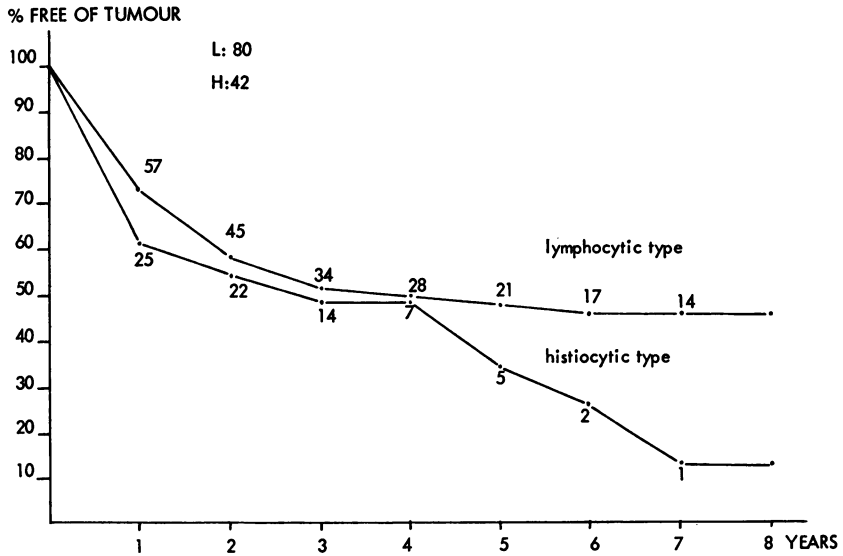


FIG. 1.—Combined Stages I and II. Excluded are the patients, who had loco-regional recurrence within the first 3 months after treatment. Percentages of patients remaining clinically free of tumour. Comparison between lymphocytic and histiocytic types of lymphoma.

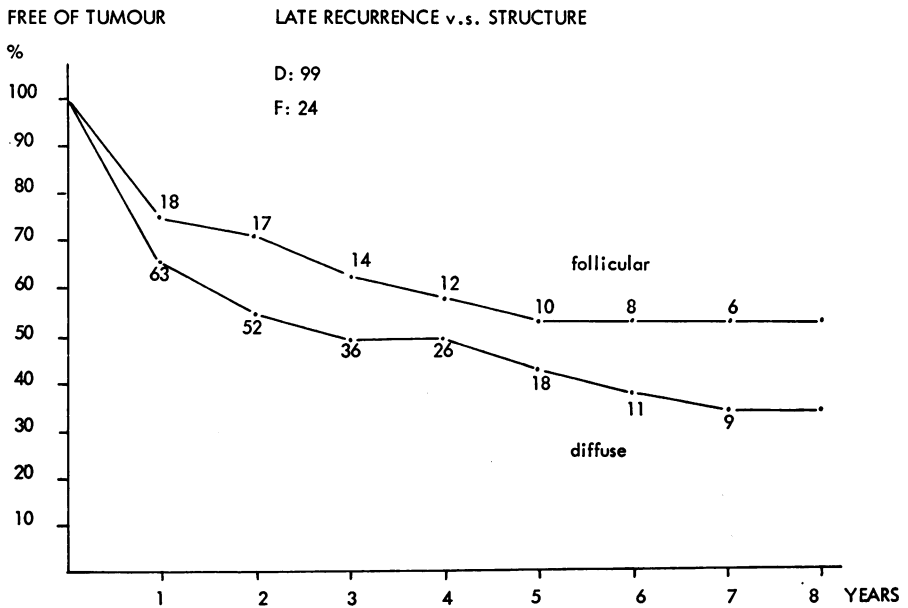


FIG. 2.—As Fig. 1. Comparison between follicular and diffuse types of lymphoma.

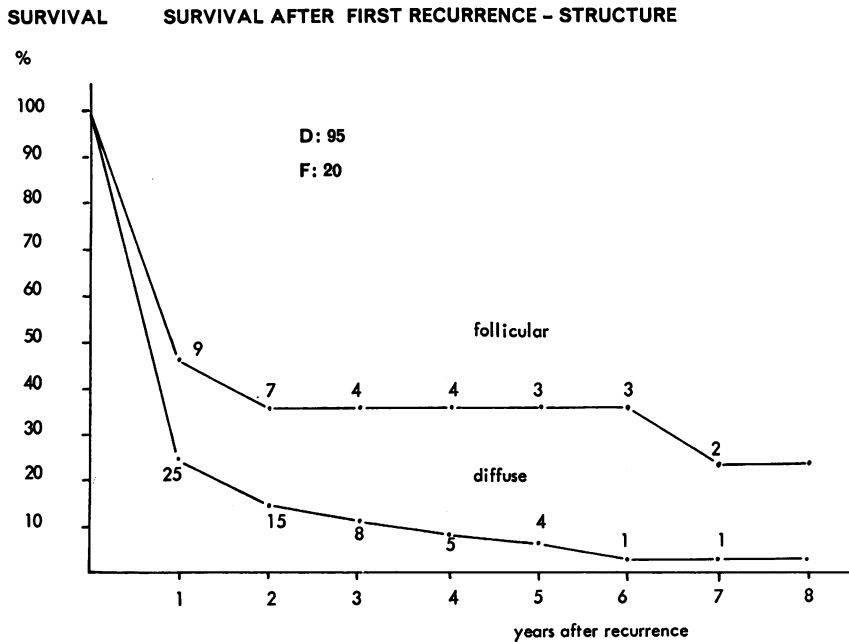


FIG. 3.—Combined Stages I and II. Comparison between follicular and diffuse types of lymphoma with regard to percentage survival after the first recurrence.

to the better prognosis of follicular types of lymphoma (van Unnik *et al.*, 1975, Fig. 6). They indicate a prolonged spread in time and probably a lower growth rate for follicular lymphomata.

Though we could demonstrate in our material a few striking differences in the spread of disease between 4 distinct histological groups, the present study underlines the limitations of retrospective analysis.

Well planned prospective studies will provide a clearer insight into the behaviour of non-Hodgkin's lymphomata in relation to their histological characteristics.

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