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NON-HODGKIN'S LYMPHOMATA: CLINICAL FEATURES IN RELATION TO HISTOLOGY

J. A. M. VAN UNNIK, K. BREUR, J. M. V. BURGERS, F. CLETON, A. A. M. HART, W. F. STENFERT KROESE, R. SOMERS AND J. M. M. P. M. VAN TURNHOUT

From the Netherlands Cancer Institute, Antoni van Leeuwenhoek Ziekenhuis, Plesmanlaan 121, *Amsterdam, and Rotterdam Radiotherapeutic Institute, Groene Hilledijk* 297, *Rotterdam, The Netherlands*

Summary.—An analysis is given of the clinico-pathological correlations of non-Hodgkin's lymphomata in 332 patients referred to the Netherlands Cancer Institute in Amsterdam and the Rotterdam Radiotherapy Institute. Clinical staging proved to be an important prognostic index. In Stage I the 5 year survival was 55%, in Stage II 25% and in Stages III and IV less than 10%.

The presence of follicular structures in non-Hodgkin's lymphomata has similarly an important prognostic significance especially in Stage I and II. In lymphocytic lymphomata a larger cell size is correlated with less favourable prognosis. The presence of macrophages in non-Hodgkin's lymphomata is found in patients with short survival. The histiocytic lymphomata have a different survival pattern from the lymphocytic lymphomata in Stages I and II.

PATIENTS AND METHODS

The records of 1050 patients with non-Hodgkin's lymphomata referred to the Netherlands Cancer Institute (N.K.I.) in Amsterdam and the Rotterdam Radiotherapy Institute (R.R.T.I.) between 1957 and 1970 were reviewed. In 332 cases sufficient pathological material was available for review up to this moment. More material is being collected. Hence this study has to be considered as a preliminary report.

In this study the Rappaport classification was used, differing in some respects from the same classification as it was used by Jones *et al.* (1973).

1. The mixed histiocytic lymphocytic type was not considered as a separate group. The cases designated as mixed histiocytic lymphocytic type by Jones *et al.* (1973) were probably labelled " lymphocytic " in our classification. In accordance with this supposition 34% of non-Hodgkin's lymphomata in our series belonged to the histiocytic variety, as against 36% in the study of Jones *et al.* (1973).

2. The lymphocytic lymphomata were not divided into well differentiated and poorly differentiated but according to cell size into small lymphocytic, intermediate lymphocytic and large lymphocytic.

3. The undifferentiated type was not considered as a separate group but incorporated into the large cell lymphocytic variety.

In addition to this classification, a number of histological features were noted, for example the presence of macrophages.

Clinical staging was carried out according to the Ann Arbor clinical staging classification (adopted from Jones *et al.*, 1973).

As lymphography and splenectomy were seldom performed during this period, they were not included in the staging.

Stage I Involvement of a single lymph node region or of a single extra-lymphatic organ or site.

Stage II Involvement of 2 or more lymph node regions on the same side of the diaphragm or localized involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm.

Stage III Involvement of lymph node regions on both sides of the diaphragm which may also be accompanied by localized involvement of the spleen, extra-lymphatic site, or both.

Stage IV Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node enlargement.

DIFFERENCE IN CLINICAL STAGE LYMPHOSARCOMA. CELL SIZE

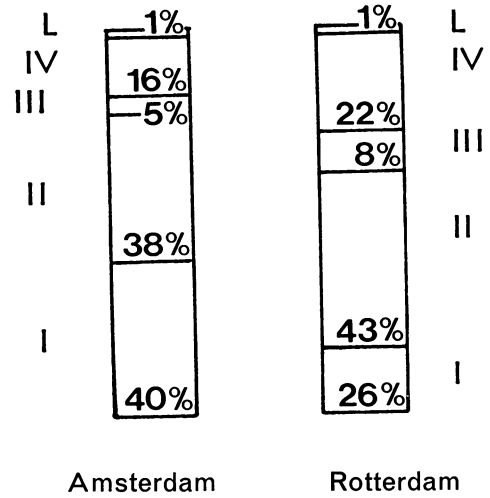

FIG. 1.—Difference in clinical stage between the Netherlands Cancer Institute (N.C.I. Amsterdam) and the Rotterdam Radiotherapy Institute (R.R.T.I.). I, II, III and IV: clinical stages I to IV. L.: leukaemia.

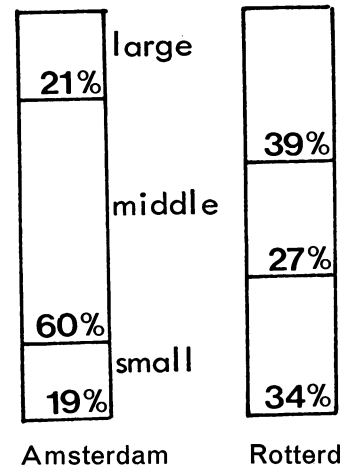

FIG. 2.—Difference in cell size of malignant lymphomata lymphocytic type between the N.C.I. (Amsterdam) and the R.R.T.I. (Rotterdam).

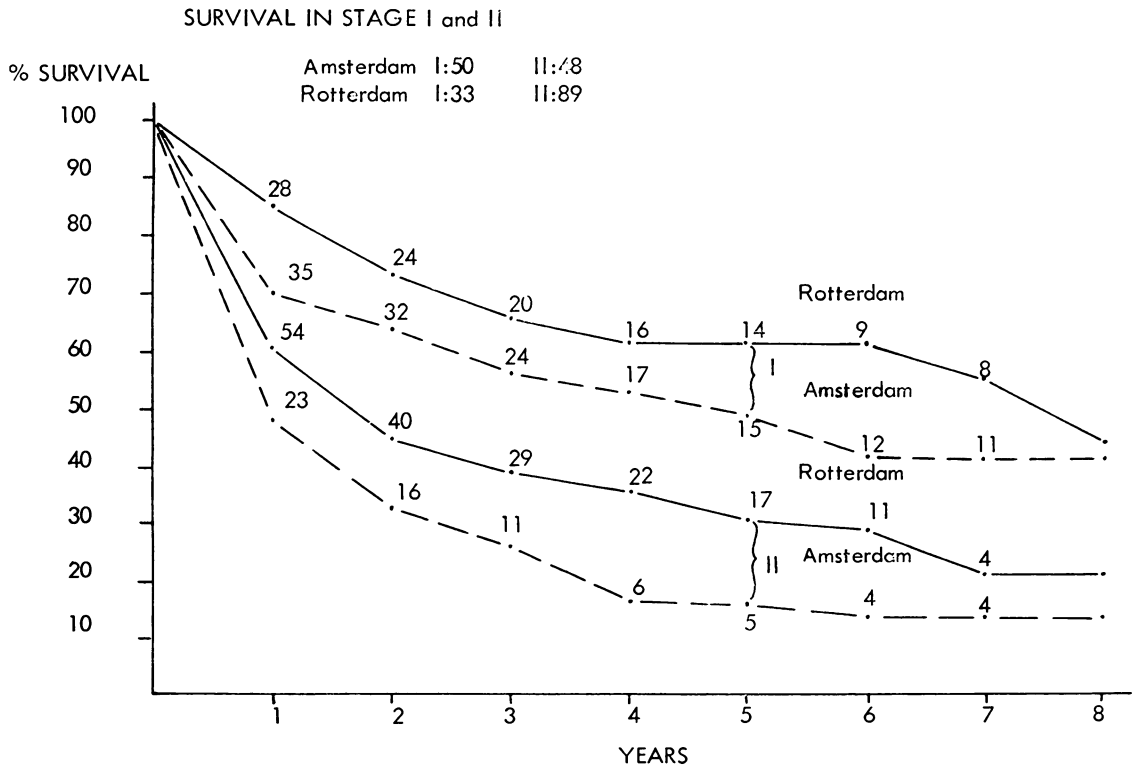

FIG. 3.—Survival in non-Hodgkin's lymphomata (All histologic types). Clinical stage I and II. The figures of the N.C.I. (Amsterdam) and R.R.T.I. (Rotterdam) are given separately.

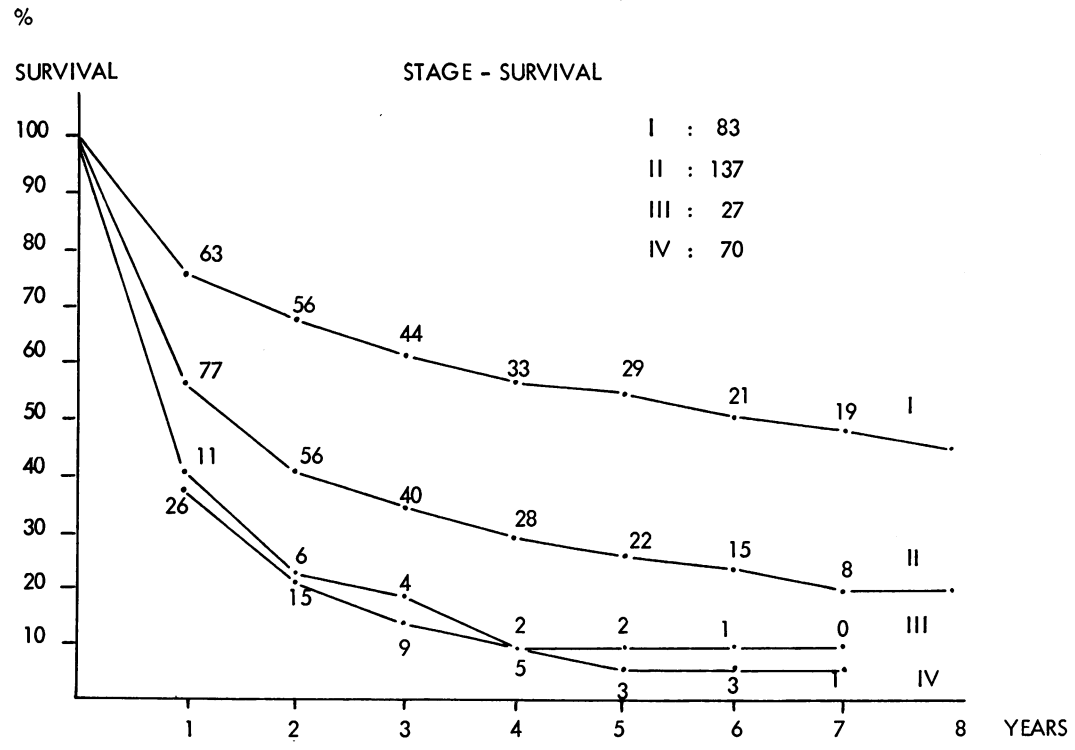

FIG. 4.—Survival in non-Hodgkin's lymphomata (all histological types). Clinical stages I to IV. The figures of the N.C.I. (Amsterdam) and the R.R.T.I. (Rotterdam) are taken together.

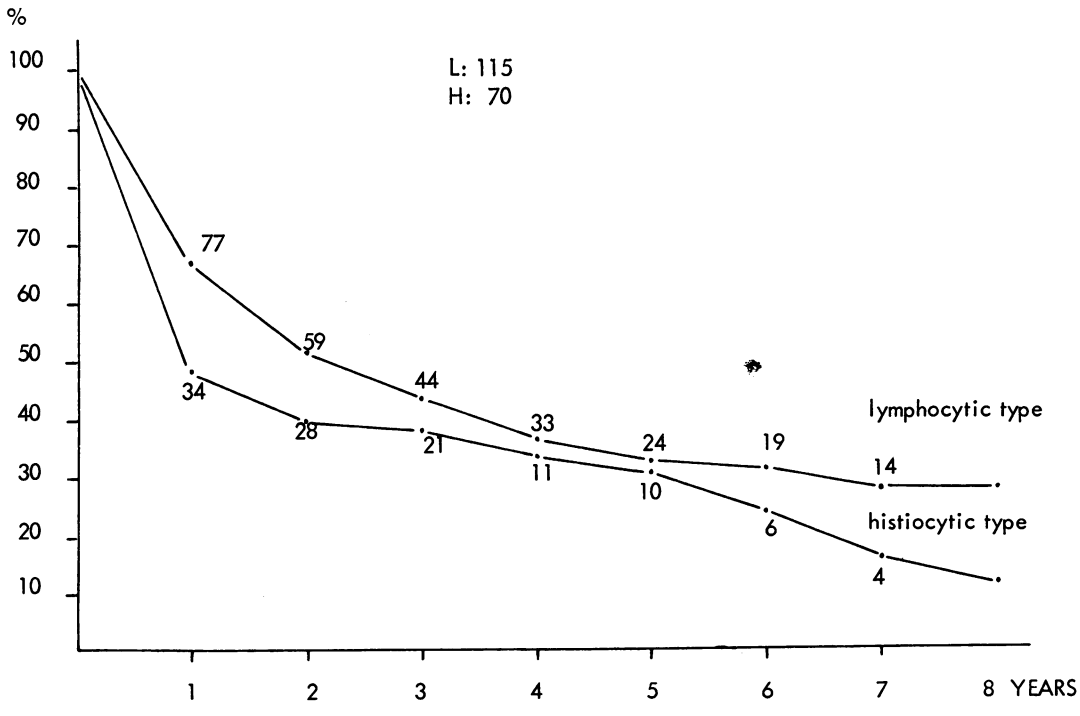

FIG. 5.—Survival in clinical stages I and II of malignant lymphomata of different cell type (lymphocytic and histiocytic types respectively).

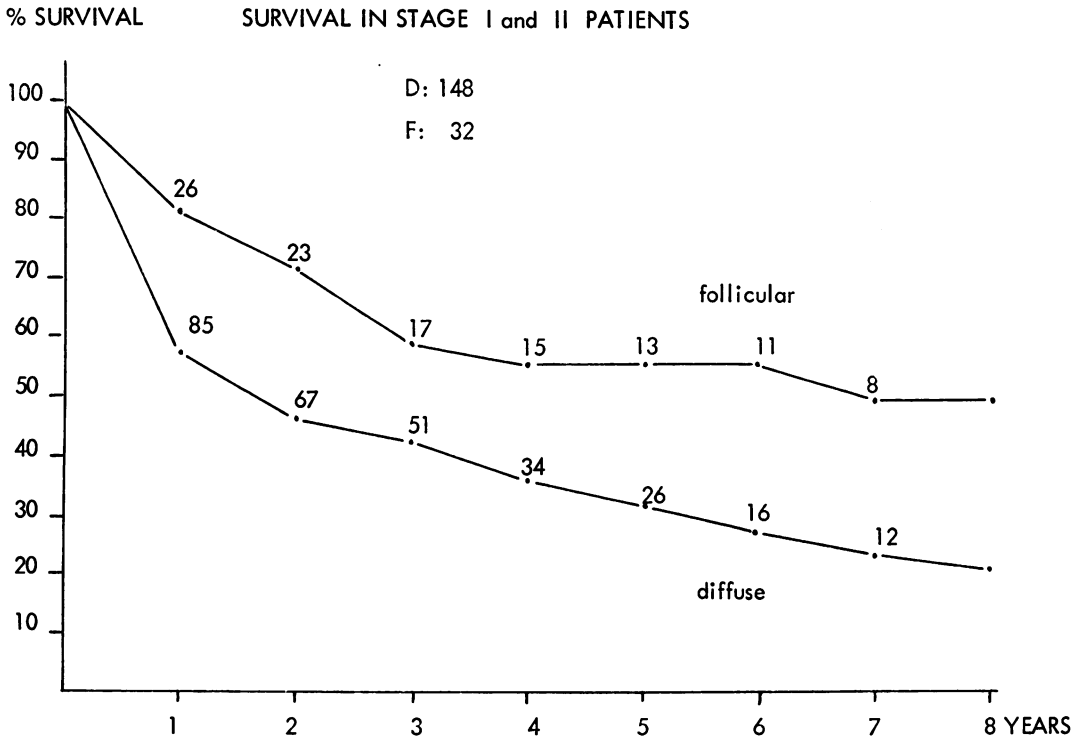

FIG. 6.—Survival in clinical stages I and II of malignant lymphomata of different structure (follicular and diffuse).

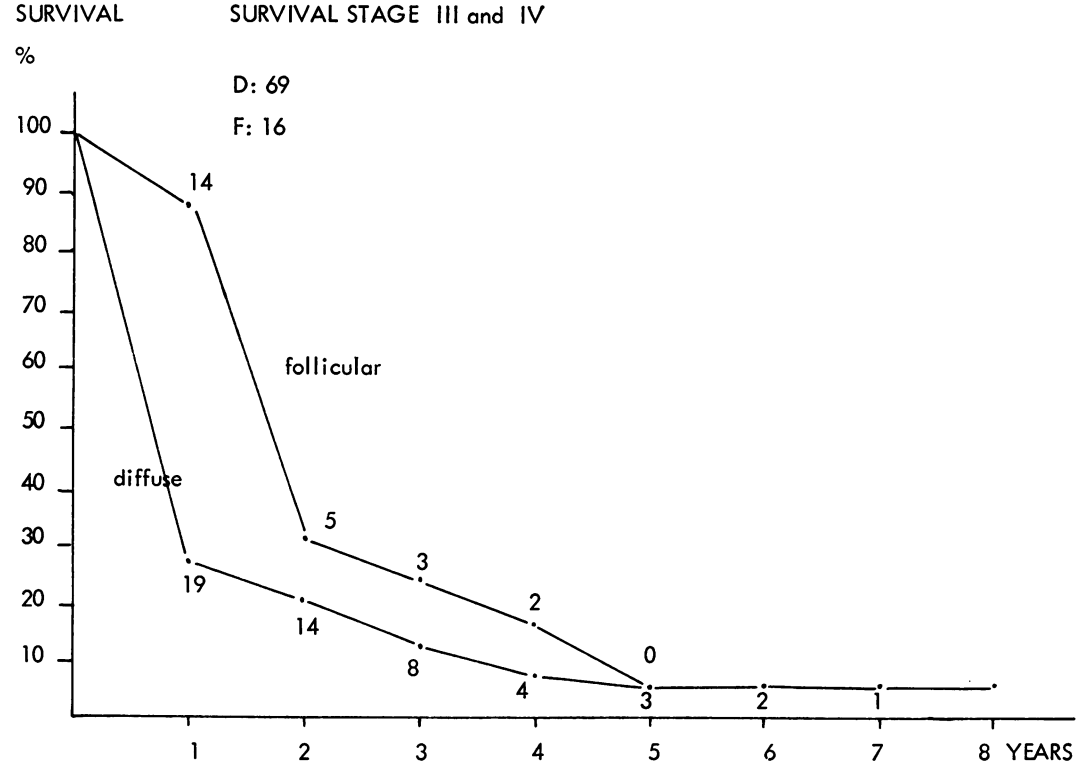

FIG. 7.—Survival in clinical stages III and IV of malignant lymphomata of different structure (follicular and diffuse).

RESULTS

A difference was found in the frequency of follicular lymphomata compared with the figures of Jones *et al.* (1973). In our study 19% follicular lymphomata were seen as against 44% in the series of Jones *et al.* This difference may be at least partly attributable to the application of other criteria. In the older pathological material of this report it was not possible to obtain reticulin stains in each case. In order not to introduce a bias, we decided to rely solely on haematoxylin and eosin stained sections. Consequently a number of cases of follicular lymphomata in which the follicular structures are only convincingly demonstrable in reticulin stained sections were missed as such.

In the series of 58 consecutive cases of non-Hodgkin' lymphomata included in the O.E.R.T.C. trial, where sufficient sections for additional staining procedures were available 34% follicular lymphomata were found. Excluding the extranodal cases and the cases in which a biopsy of Waldeyer's ring was done, 45% follicular lymphomata were found. It may be concluded that the difference in this respect between the Dutch patients and the United States patients as presented by Jones *et al.* (1973) is certainly less than may be concluded from our retrospective study.

In the restrospective study where only those cases were accepted as follicular if the follicular structures were convincingly seen in haematoxylin and eosin stained sections, the same correlations were found as described by Jones *et al.* (1973). A greater frequency of follicular lymphomata was seen in nodal cases (26%) than in extranodal (6%).

Some differences were encountered between the data from the two institutes participating in this study, although they are situated rather close to each other in comparable highly urbanized areas.

The clinical data were compiled by a team from both institutes. A close collaboration in this field existed already in the past between the staff members of both institutes.

1. A difference was seen between the distribution of patients among the clinical stages (Fig. 1). This difference did not change in course of the years.

2. With regard to histology no difference was seen between cellular types (lymphocytic or histiocytic) and between follicular or diffuse. A clear difference, however, was found between the frequency of lymphocytic lymphomata of different cell size (Fig. 2). A difference in interpretation is not probable. A real difference is possible but most likely a different technique in preparing the histological sections is responsible.

In the R.R.T.I. material more nodal cases were seen in Stage 1 (73% *vs* 50%).

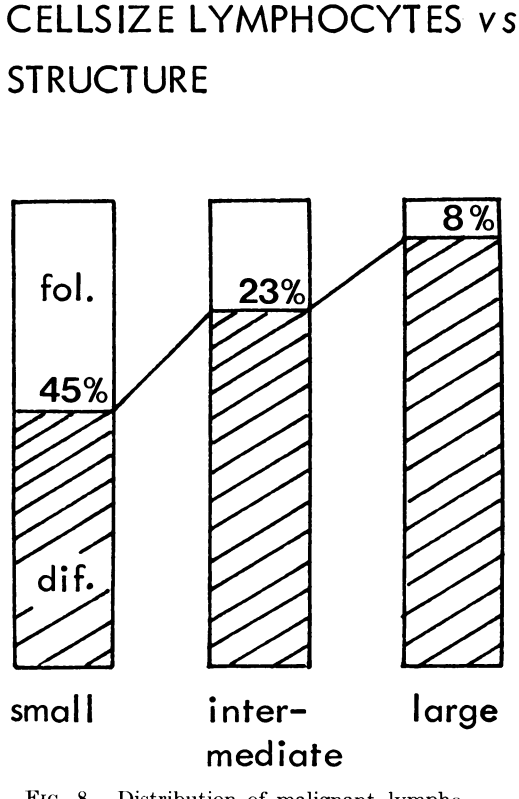

FIG. 8.—Distribution of malignant lymphocytic lymphomata of different cell-size among follicular and diffuse types.

Survival

Only those results were accepted in which the correlations were present in both institutes.

1. A difference in prognosis between the clinical stages is clearly demonstrable. Stage I has a better prognosis than Stage II. The difference between the stages in each institute is greater than the difference after summation (Fig. 3 and 4). The figures of each institute are essentially the same but on a different level. Stage III and IV have the worst prognosis; no convincing difference is demonstrable between these two stages (Fig. 4).

2. In the localized stages (I and II taken together) the histiocytic lymphomata show a different survival pattern from the lymphocytic lymphomata. There is a greater mortality in the first year in the histiocytic group. After 5 years the survival is roughly the same but subsequently the survival of histiocytic lymphoma patients continues to fall (Fig. 5). The clinical details of these different patterns are given by Breur *et al.* (1975).

3. In the localized stages (I and II) the follicular lymphomata show a better survival than the diffuse types (Fig. 6). This difference is obviously less clearly seen in the generalized stages (III and IV) (Fig. 7).

4. A smaller cell size in the lymphocytic lymphomata correlates with a better survival. Because the smaller cell types are seen more often in the follicular forms (Fig. 8), this correlation might be attributable to the difference in behaviour between follicular and diffuse lymphomata. If, however, we confine ourselves exclusively to the diffuse type the same correlation is found (Fig. 9).

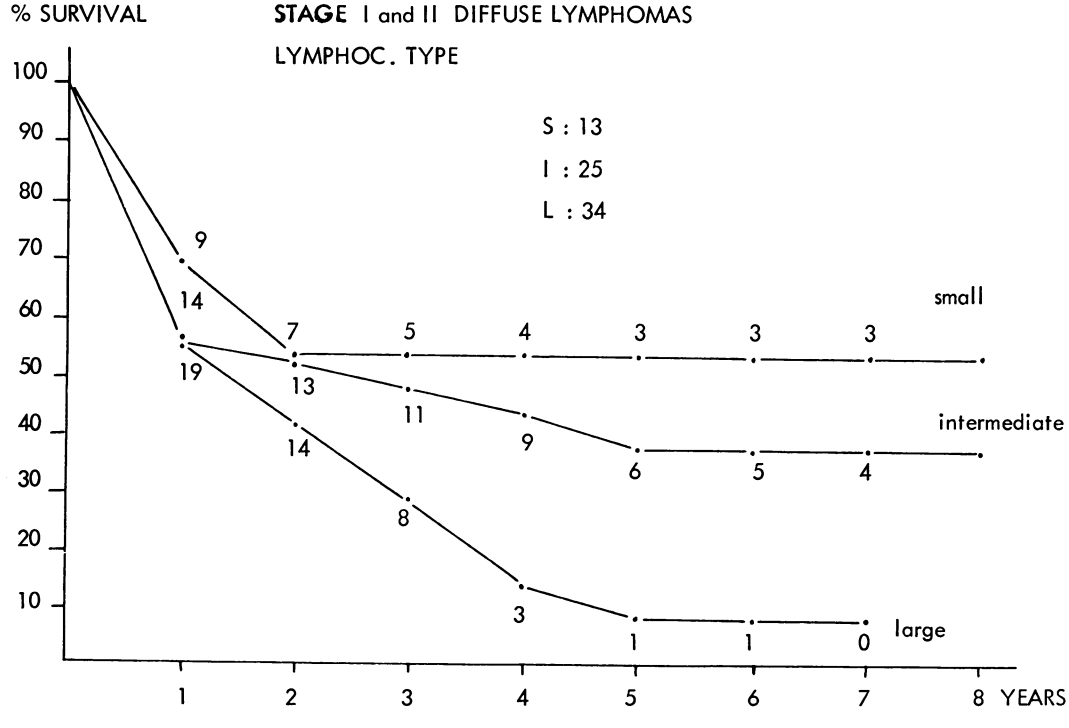

FIG. 9.—Survival of patients with diffuse malignant lymphomata lymphocytic type in clinical stages I and II. A division is made between small, intermediate and large average diameter of the lymphocytic cells.

5. An additional feature of some importance is the presence of macrophages. This is correlated with a bad prognosis. With one exception, no patient with macrophages in the lymphoma survived for more than one year after diagnosis. Generally these patients belonged to Stage IV clinically. This finding is in accordance with the publications of Diamandopoulos and Smith (1964) and Oels, Harrison and Kiely (1968).

Macrophages were found in diffuse and follicular lymphomata.

DISCUSSION

These data clearly demonstrate the significance of clinical staging. In Stage I the survival is about 55% after 5 years, dropping to 25% in Stage II and to less than 10% in Stages III and IV. The figures for Stages III and IV are essentially the same. Hence the additional involvement of extra-lymphatic organs or tissues in Stage III is not an important feature.

The presence of follicular structures in non-Hodgkin's lymphomata is an important characteristic, especially in Stages I and II. A further study on the significance of scarcely visible follicular structures or follicular structures shown by special stains is indicated.

In lymphocytic lymphomata cell size has a prognostic significance. Probably cell size as seen in the sections can be influenced by histological technique. Some standardization, for example in fixation methods, seems to be useful for comparison of sections from different laboratories. We found decisions about cell size not easily reproducible. New ways for a more objective judgment have to be sought.

Additional characteristics, such as the presence of macrophages, may have an important bearing on prognosis regardless of other features.

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