A

NON-HODGKINS LYMPHOMA

A retrospective analysis of 314 cases

Proefschrift ter verkrijging van de graad van doctor in de geneeskunde aan de Erasmus Universiteit te Rotterdam, op gezag van de Rector Magnificus Prof. Dr. P.W. Klein en volgens besluit van het college van dekanen. De openbare verdediging zal plaats vinden op woensdag 9 april, des namiddags te 4.15 uur

Door

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Geboren te Geldrop.

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Van de velen die mij behulpzaam waren bij het vervaardigen van dit proefschrift wil ik speciaal noemen J.M.H.G. Brouwers, mevrouw W.M. van der Luit-van Vianen, W.F. Stenfert Kroese en J.A.M. van Unnik.

Zij zijn voor mij een bijzondere steun geweest.

Non-Hodgkins Lymphoma, a retrospective study of 314 cases.

Appendices: page

1. INTRODUCTION.

Of all the malignant lymphomas Hodgkin's disease has been studied most extensively. A clear-cut natural history emerged; this induced new philosophies of treatment, which resulted in a better survival (Kaplan, 1972; Clinics in Haematology, 3: 1).

The other malignant lymphomas, a larger group, have not been studied as thorougly. It seems therefore appropirate to apply to these lymphomas the proved techniques, which have been used for the study of Hodgkin's disease. By this method their subtypes, natural history and resemblance to Hodgkin's disease may appear.

The clinical data of 314 patients with a malignant non-Hodgkin's lymphoma have been studied, using Rappaport's histological classification and the Ann Arbor staging method. It is the largest study in the Netherlands originating from one single institute.

The following points have been studied especially:

- the prognostic value of Rappaport's histological subdivisions.
- the prognostic value of the Ann Arbor staging classification, which has been originally developed for Hodgkin's disease.
- primary symptoms and signs.
- frequency of concurrent neoplasms.
- the frequency of extranodal primary sites, their prognosis as compared to nodal origins.
- method of spread: contiguity, mediastinal skipping, therapeutic consequences.
- results of treatment: overall and detailed per type of treatment.
- side-effects of treatment.

- complete remission: its quality expressed as the product of frequency and duration, interrelation of the durations of subsequent remissions.
- local recurrence.
- frequency of bone marrow invasion.
- the prognostic significance of clinical and therapeutical data, their importance alone or in combination with others.

II. SELECTION OF PATIENTS, DATA HANDLING.

The studied material consists of a review of the case history and biopsy material of 314 patients seen at the Rotterdam Radiotherapy institute (R.R.T.I.).

1. THE PATIENTS.

Years of study.

The patients were seen for the first time in the years between 1950 and 1971. The closing date of the study was August 1st, 1973, which means a minimum follow-up period of 2 years and 7 months.

The patients in this study represent about one third of the total number of patients with a malignant lymphoma who were seen at the institute during the time of the study (Annual Reports R.R.T.I.). The total number of patients who entered the study per annum is given in Fig. 2.1.

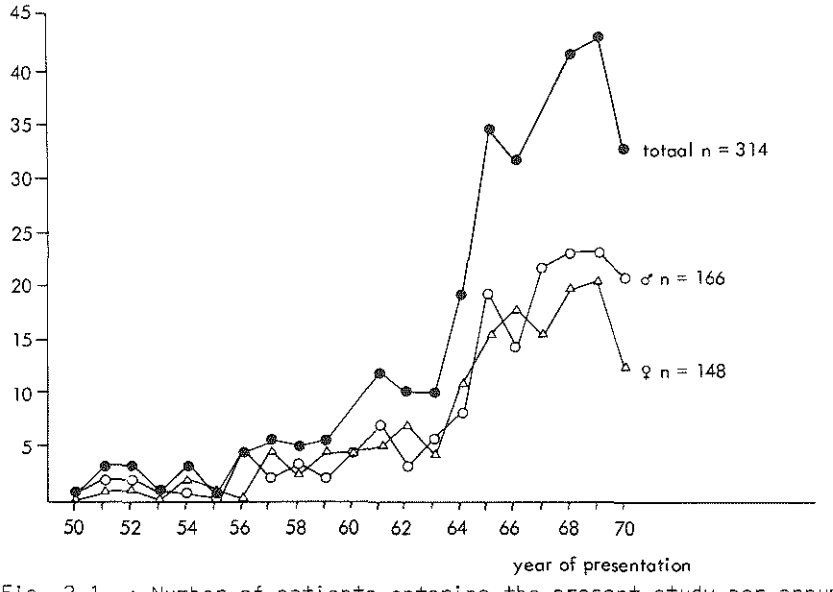


Fig. 2.1. : Number of patients entering the present study per annum.

Patients were excluded from the study when it was not possible to obtain the original biopsy material for review within four months.

Referral area.

The R.R.T.I. is the largest oncological centre in the Netherlands, where at present about 2.600 new patients are seen each year; of these about 135 have a malignant lymphoma. The referral area is Rotterdam and suburbs with about one million inhabitants; many patients were also sent from secondary centres throughout the country.

Reasons for inclusion.

All patient records with a diagnosis of non-Hodgkin's lymphoma from the study period were drawn from the files. In each case it was tried to recover the biopsy slide from which the original diagnosis had been made. These slides were 'blindly' reviewed by J.A.M. van Unnik, who is the consultant pathologist in this field for the European Organisation for Research and Treatment of Cancer in the Netherlands. If the reviewing pathologist could not confirm the diagnosis of malignant non-Hodgkin's lymphoma, even after new microscopic slides were made from stored material, the patient was omitted from further study. This occurred in 21 cases.

2. DATA HANDLING.

Relevant information from a case history, was noted on specially prepared optical reading charts (Appendix A). Later on these were converted into punch cards. The data on these cards were stored on computer background memory. Appendix B, which is a translation of Appendix A, shows which factors were considered relevant and the code which was employed.

Punchcard No. 1 contains the basic unchanging information about the patient, this can be easily updated.

Cards 2 and 3 together represent the first episode of the illness. A second episode is recorded on a new set of cards 4 and 5 which resemble card 2 and 3; subsequent episodes on 6 and 7 , 8 and 9 , and so on. This makes it possible to record all relapses separately. Not more than three episodes have been analysed. The criteria of the Ann Arbor conference (Carbone, et al., 1971; Rosenberg, et al., 1971) have been used for staging: Table 2.2.

I. Involvement of one single lymph node region (I), or of a single extralymphatic organ or site (IE).

II. Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of an extralymphatic organ and of one or more lymph node regions on the same side of the diaphragm (IIE).

III. Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ (IIIE), or by involvement of the spleen, or both.

IV. Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

A = Without symptoms.

B = With general symptoms:

1. unexplained weight loss > 10 % in 6 months.
2. unexplained fever.
3. night sweats.

Table 2.2: Staging criteria of the Ann Arbor Conference, 1971.

Complete remission means no signs of activity on physical or X-ray investigation, also the E.S.R. has to be below 30 milim. in the first hour. Partial remission means significant improvement.

The computations were done on an I.B.M. computer (Type 1130). As exact information on the computing programs is given in detail in Appendix C, only a general outline is given here. All data were checked for errors (e.g. incorrect data, staging errors, wrong dates) by special programs. After correction the final calculations were made, using a system which made cross tabulation possible up to seven dimensions.

III. PATHOLOGY OF NON-HODGKIN'S LYMPHOMAS.

1. BRIEF HISTORICAL REVIEW.

The first description of lymphoreticular tumors was given by Hodgkin in 1832 and subsequently by Wilks in 1865. A part of the cases described by them would, by modern standards, be classified as "genuine Hodgkin's disease", another part as cases of non-Hodgkin's lymphomas.

Later on the existence of malignant lymphomatous disease differing from lymphatic leukemia and Hodgkin's disease was described especially by Virchow (1858, 1863) thereby introducing the clinical entity 'lymphosarcoma' (Billroth, 1871).

The distinction between Hodgkin's disease and the other malignant lymphomas was more precisely drawn by the work of Kundrat (1893), Dreschfeld (1893), Paltauf (1896), and especially by Sternberg and Reed, who called attention to the characteristic giant cell of Hodgkin's disease (1898 and 1902).

Beside the typical lymphosarcoma there was also recognized a type consisting of cells cytologically more resembling reticular or reticulum cells; this type was finally named reticulum cell sarcoma by Roulet (1930, 1932) after having been given a great variety of names (Oberling, 1928; Ghon and Roman, 1916, Goormagchtigh, 1926).

A period followed in which a confusing chaos of names (Willis, 1948) emerged, because many pathologists proposed a new classification. However, each classification only remained useful in the hands of its originator.

After the recognition of the giant follicular lymphoma as a separate entity by Brill (1925) and Symmers (1927), there emerged in 1966 from the "happy marriage" (Gall, 1958) between cytologic views of Gall and Mallory (1942), and the concept of nodular versus diffuse lymphoma of Rappaport, et al. (1956) a final classification by Rappaport (1966). This widely used classification is used in the present study. After the classification of Rappaport only a few rare separate types of lymphoma have been described (Rosai and Dorfman, 1969 and 1972; leading article Lancet 1973, Frizerra, et al., 1974; Lukes and Tindle, 1975; Schultz and Yunis, 1975; Rappaport and Moran, 1975).

2. RAPPAPORT'S CLASSIFICATION (1966).

This classification is based on two sets of criteria:

1. the proliferation patters in the lymph node.
2. the cytological type and its degree of differentiation.

2.1. Proliferation patterns.

It is presumed that each cytological type - with the exception of the undifferentiated type - may present itself in a diffuse or a follicular form. Instead of the term follicular the somewhat confusing equivalent nodular is used too. The follicular malignant lymphoma is distinguished from the 'reactive' lymph node according to criteria laid down by Rappaport, et al. (1956). Usually the follicular type progresses to the corresponding diffuse form in the course of the disease (Hurst and Meyer, 1961; Dorfman, 1964); and also the cytologically mixed types have a tendency to become more histiocytic.

2.2. Cytologic type and degree of differentiation.

Rappaport distinguishes between lymphocytic and histiocytic lymphomas, each with varying degrees of differentiation - also a mixed type consisting of both cell types exists:

Well differentiated lymphocytic lymphoma.

This type consists of rather small, mature, uniformly appearing lymphocytes, which are hardly distinguishable from normal lymphocytes. One should be careful to distinguish this lymphoma from its systemic morphological counter-part: chronic lymphocytic leukemia. Some of these tumors produce monoclonal immunoglobulins (Kim, et al., 1973).

Poorly differentiated lymphocytic lymphoma (P.D. Ly Ly).

The lymphocytes in this tumor show varying degrees of nuclear atypia, immaturity and high mitotic activity. It is felt (Berard and Dorfman, 1974) that the classification poorly differentiated is too broad, and that in this category finer subdivisions should be made. In children the lymphocytes often resemble those of acute lymphoblastic leukemia, but in adults this is seen less often. Adults mostly display: 1) more differentiation in cell size, 2) small cleaved cells (follicular centre cells according to the Lukes terminology, 1974), 3) "leukosarcoma cells" in the bone marrow and/or peripheral blood (see Schnitzer, et al., 1970). In children the follicular pattern is extremely rare in contrast to adults; however progression to leukemia occurs more often (Sullivan, 1962).

It should be kept in mind that the distinction between well differentiated and poorly differentiated lymphomas is in essence an artificial one, and serves for convenience only. Some investigators are testing the value of further morphologic subdivision, especially in the poorly differentiated class (Van Unnik, 1973). Also differentiation in the degree of nodularity probably has practical use (Patchefsky, et al., 1974).

Histiocytic lymphoma (H Ly).

This consists of neoplastic histiocytes in various stages of maturation and differentiation, sometimes with phagocytosis and/or "fibroblastic" differentiation. The spectrum may range from the poorly differentiated forms, to the well differentiated type. The poorly differentiated forms are characterised by:

a) more or less round nuclei

b) rather prominent eosinophilic nucleoli

c) scanty cytoplasm.

The well differentiated type shows one or more of the following features:

a) deeply indented or oval nuclei

b) abundant, and often eosinophilic cytoplasm, with phagocytosis

c) increased reticulin formation.

Undifferentiated lymphoma (U Ly).

This is formed of pleomorphic cells without any appreciable histiocytic or lymphocytic differentiation: large nuclei containing a delicate chromatin structure and one single distinct nucleolus, and varying amount of cytoplasma. The cells may seem cohesive. Sometimes the term "stem-cell" has been used for these cells, but this term implies a non-existing potential (Maximow and Bloom, 1942).

Mixed (lymphocytic histiocytic) lymphomas (M Ly).

This group includes mixed forms of lymphocytic and histiocytic lymphomas, they are mostly follicular.

3. CLASSIFICATION USED IN THIS STUDY.

Based on Rappaport's classification some minor modifications (Van Unnik, 1973) were made by J.A.M. van Unnik who reviewed all material of the patients under discussion.

a) The lymphocytic types are not subdivided in well differentiated and poorly differentiated, but - according to cell-size into small, intermediate, large, and polymorphocellular lymphocytic. The small lymphocytic type which corresponds with Rappaport's well differentiated lymphocytic lymphosarcoma is called lymphocytosarcoma (L.C.S.) and the remaining types together are called lymphoblastosarcoma (L.B.S.).

b) The mixed lymphocytic - histiocytic type is considered as lymphocytic (as done by Dorfman, 1974).

c) The others are divided into histiocytosarcoma (H.C.S.), i.e. Rappaport's histiocytic lymphomas, and histioblastosarcoma (H.B.S.), an expression from Mathé, et al. (1970).

d) The follicular mixed group was considered apart because of its special interest. This classification is only used when lymphocytes and histiocytes are equally represented.

e) The division into diffuse and follicular is in accordance with Rappaport's method. Partial follicular is considered as follicular. A problem has arisen due to the retrospective nature of the present study. In some cases it was impossible to obtain adequately stained slides for determining the presence of follicular structures or to obtain the original biopsy material. Because special reticulin stains were not always available only H.E. stained slides were used for determination of the structure. The problems arising thereby are discussed later.

In the actual data extraction more detailed subdivisions were made - which have not been used in this study, but remain available for later studies. The computer has rearranged these subdivisions into the present classification. For comparison Rappaport's classification is shown in Table 3.1.

As the histological classification is made on the first diagnostic slide, two histological aspects have not been studied. These are:

a) the similarity of multiple biopsies done at the same time,

b) the similarity between subsequent biopsies during the course of the disease. They have not been studied, because multiple biopsies have been done in a limited number of patients.

Rappaport, 1966	Present study: v.Unnik, 1973
Well differentiated lymphocytic	LCS = Lymphocytosarcoma
Poorly differentiated lymphocytic	LBS = Lymphoblastosarcoma
Histiocytic	HCS = Histiocytosarcoma
Undifferentiated	HBS = Histioblastosarcoma
Diffuse	Diffuse
Nodular/Follicular	Follicular
Follicular mixed	Follicularmixed
Diffuse mixed	→ Corresponding lymphocytic type

Table 3.1. : The classification used in the present study compared with Rappaport's classification.

4. RECENT DEVELOPMENTS IN LYMPHOMA CLASSIFICATIONS.

Ultrastructural studies of the respective morphological presentations and functions of the lymphocyte and histiocyte and their place in the normal lymph node, and data obtained from immunological and functional studies, have resulted in considerable further developments (Hansen and Good, 1974).

The normal lymph node.

A brief review of the structure and function of the normal lymph node is necessary in order to understand subsequent classification of tumors originating from lymph nodes which are "in fact all - more or less caricaturally - derived from their parent cells" (Diebold, 1970).

4.1. The normal lymph node.

The lymph node starts with an afferent lymph vessel, which enters at the subcapsular sinus. From there on the lymph may pass through the maze of interfollicular sinuses to the marrow sinus, or through the lymph follicles. The interfollicular tissue consists of a network of "marrow-macrophages", which show much pinocytosis and phagocytosis (Ned. Ver. voor de Immunologie, 1971). Surrounding the lymph follicles is the parafollicular zone consisting of small lymphocytes. The follicles do not exist in germ-free animals (Humphrey and Frank, 1967; Akazaki, 1973), but are formed by the antigenic stimulus of the normal environment.

The following types of cells have - as yet - been distinguished in the lymph follicles:

a) Desmosome-bearing reticulum cells forming together a reticular structure by means of desmosomes (Lennert, 1964; Lennert, et al., 1966). They form the majority of the follicle, in which they arrive and fuse together from their diffuse spread throughout the lymph node, after the first exposure to infection. These dendritic macrophages (White, 1963) trap the antigen, not by real phagocytosis, but by surface binding facilitated by opsonins (Nossal, 1967; Nossal, et al., 1968). It is supposed that the lymphocytes, which pass from the parafollicular zone along these antigen-laden dendritic reticulum cells, pick up a message to transform (Nossal, et al., 1968; Lukes and Collins, 1971) into large blast like cells.

b) Normal phagocytically active macrophages (settlers from the phagocytic system) which may contain phagocytosed nuclear remnants.

c) Follicular centre cells or germinal centre cells, whose exact origin is not yet completely clear. It is thought that they are transformed B-lymphocytes, which got instructions on their way to the germinal centre from the dendritic "reticulum cells". Once they are triggered by some antigenic stimulus, they undergo transformation in the follicular centre to large blast like cells of the same light-microscopic appearance as stimulated lymphocytes.

The different types of lymphocytes and reticulum cells have an important function in the immune response.

4.2. The lymphocytes.

They are divided up into B-lymphocytes and T-lymphocytes with different origin and function, although in close coöperation (Keuning, 1972).

a) The immunoglobulin carrying B-lymphocytes may be transformed into large blast like cells in the germinal centre, which are called germinoblasts by Lennert, 1964. They are morphologically identical to the cells observed in irritated lymph nodes, which are called non cleaved cells by Lukes and Collins (1971). Lukes and Collins (1974) distinguish between five separate morphological steps during this transformation: small lymphocyte, small cleaved cell, large cleaved cell, small non cleaved cell, and finally large non cleaved cell. They all transform in the parafollicular areas of the lymph nodes (Van Buchem, 1962; leading article Lancet, 1974) into plasmacells. During their transformation they are already producing antibodies (Gowens and Knight, 1964; Oort and Turk, 1965). In vitro this transformation is especially stimulated by pokeweed (Roitt, et al., 1969).

b) The T -lymphocytes, which form rosettes with sheep erythrocytes, are located in the deep cortical areas.

They are responsible for the cellular immunity; they sometimes help the B cells in starting immunoglobulin synthesis (Mulder, 1972); they also respond to PHA stimulation. Some lymphocytes never show the characteristics of B- or T-lymphocytes; they are called null cells.

4.3. The reticulum cell.

There has always been some uneasiness about the term reticulum cell sarcoma; some people thought that it was being misused as a "wastebasket" for poorly differentiated malignant neoplasms of lymph nodes (Butler, 1970); others thought that it encompassed different types of cells: "true" histiocytes, and lymphocytes, which resemble histiocytes because of special influences (see 4.2). Instead of Ashoff's (1924) unitarian concept and its later versions (Cline, 1973) a different concept of the "reticulum cell" has arisen (Van Furth, 1970). Now this cell is divided into two groups. The first consists of the mononuclear phagocytes, including the monocytes and their offspring which have settled in the tissues: histiocytes, Kupffer cells and macrophages. The other group consists of cells belonging to the connective tissue, e.g. fibroblasts. The dendritic reticulum cells of the germinal centre have not yet found a place in any category (Diebold, 1970).

4.4. Recent trends in malignant lymphoma classification.

As all tumor types - more or less caricaturically - resemble their parent cell, new classifications based on the newer concepts of cellular origin have been attempted.

It is now clear that the former reticulum cell sarcoma (or histiocytic lymphomas) contained the following cell types:

a) Lymphocytes in transformation, whether B-, T- or null-cells.

b) Desmosome-bearing dendritic reticulum cells.

c) Poorly differentiated fibroblasts ("structured elements").

d) A remnant of poorly differentiated other tumor types with lymph node metastases.

This concept stems from studies by Stein, et al. (1972), Levine and Dorfman (1974), Dorfman (1974), and Mennemeyer, et al. (1974), who show on the basis of enzymocytochemical, ultrastructural, and immunological studies that many reticulum cell sarcomas do not originate from reticulum cells at all. Follicular lymphomas are thought to originate from B-lymphocytes on the basis of immunologic cell markers (Shevach, et al., 1972; Jaffe, et al., 1974; Hansen and Good, 1974) and the presence of dendritic reticulum cells (Levine and Dorfman, 1974). The large and small follicular centre cell produce the follicular lymphoma (they are called germinoblast and germinocyte by Lennert, 1964). The occurrence of the true reticulum cell sarcoma, which consists of dendritic reticulum cells, and the occurrence of true lymphocytic follicular lymphoma are rare (leading article Lancet 1974). However not all authors agree on the assumption that all follicular lymphomas are of B-cell origin (Peter, et al., 1974).

It may similarly be presumed that a regrouping of the diffuse lymphomas will take place in the near future when the exact origin of the malignant lymphocytic cell has been more firmly established (Seligman, 1974; Gajl-Peczalska, et al., 1973; Michlmayr, et al., 1974; Piessens, et al., 1973). Attempts in this direction have been made by Dorfman (1974; 2 papers), Farrer-Brown (1973), Gérard Marchant, et al. (1974); however they were based only partially on these new data. Another attempt was made by Lukes and Collins, who consider the various subtypes of the transforming B-lymphocytes in the follicular centre as the origin of follicular lymphomas. About the diffuse lymphomas and the T-cell lymphomas they have no definite opinion.

At present Rappaport's classification is the only useful clinical guide (Bradfield, 1974).

5. PATHOGENESIS.

The exact pathogenetic mechanism is still unknown. Probably a lymphoma cell is triggered into malignant degeneration by a multitude of influencing factors - although the exact place and importance of each of them is still being debated.

The most important factors are probably infectious agents and genetic factors although both may seem to be geographic factors (Freeman, et al., 1972; Banfi, et al., 1968), the latter because of the fact that the same susceptible genes are common in the whole population of that area. The genetic factor may be expressed in a special tissue antigen composition. or impaired immune response of autoimmune disease (Cummings, 1971). It may be possible that an infectious agent, for instance a virus (Dmochowski, 1970; Gerber, et al., 1972) induces some change in the lymphocytes, probably with the help of other unknown factors (Ramboud and Matuchansky, 1973), in a susceptible individual who does not have the proper immunological defence - whether the fault be congenital or acquired (Penn and Starzl, 1972). Lukes and Collins (1974) suppose, that in the case of the B-cell lymphomas, a block or derepression somewhere during the transition from small lymphocyte to large non cleaved follicular centre cells exists.

IV. CLINICAL FEATURES AND HISTOLOGY.

1.1. Presenting complaint.

The first single spontaneous complaint, which after proper evaluation could be ascribed to the lymphoma is listed in Table 4.1. A few remarks about this table are the following:

a. abdominal complaints: these encompass a very wide spectrum such as abdominal masses, a change in bowel habits, gastric problems, etc.

b. ear-nose-throat problems: hoarseness, swallowing difficulties, deafness, etc.

c. respiratory symptoms: dyspnea, hemoptoe, etc.

d. it should be noted that complaints about constitutional symptoms in this table are only those which were spontaneously told; later (Table 4.3) the results of explicit questioning in this regard are given.

The chief presenting complaints are painless lymphadenopathy, E.N.T. problems, and abdominal complaints. These are followed at a distance by skin abnormalities and no complaints, the last of which means that the disease was discovered accidentally.

These results were compared with those of Rappaport, et al. (1956), Rosenberg, et al. (1961), Molander and Pack (1963) and Ibbott, et al. (1966). Rappaport's cases, which also contain 18 nodular sclerosing forms of Hodgkin's disease, are all follicular; he has only noted the chief complaint instead of the first complaint. In Ibbott's cases, which are all lymphocytic, all first symptoms have been noted. The fact that some patients have more than one first symptom explains the total of more than one hundred per cent. The comparison is given in Table 4.2, which shows their data in a similar way as has been done in this study.

Presenting complaint	Percentage of Total	Tot	♂	♀
None	8.3	26	10	16
Lymph node enlargement	35.7	112	63	49
Painless	32.8	103	58	45
Painfull	2.9	9	5	4
Abdominal complaints	13.7	43	23	20
Fatigue-malaise	2.5	8	5	3
Fever	0.6	2	1	1
Skeletal pain	1.9	6	4	2
Weight-loss o.u.c.	0	0	0	0
E.n.t.-problems	21.6	68	30	38
V.cava.syndrome	0.3	1	0	1
Respiratory symptoms	2.5	8	7	1
Skin-lesions	6.7	21	11	10
Salivary glands	0.3	1	0	1
Urogenital complaints	1.9	6	4	2
Muscle weakness	0.3	1	0	1
Unknown	3.5	11	6	5
Total	100 %	314	166	148

Table 4.1. : A survey of the presenting complaints.

Author	Rappaport 1966	I.B. Bott 1966	Rosenberg 1961	Molander 1963	Present study
Total number	247	107	1269	567	314
None	6	6			8
Unknown	10	21	4	6	0
Lymph node-enlargement	57	52	64	46	36
Painless	55		56		33
Painfull	2		8		3
Abdominal complaints	9	8	21	20	14
Fatigue malaise		10	15	14	3
Fever	4	5	5	11	1
Skeletal pain			3		2
Weight-loss o.u.c.		8	9	15	0
E.N.T. problems					22
Vena cova syndrome					1
Respirato-ry symptoms	8	3	11	9	3
Skin-lesions	2			3	7
Salivary glands					1
Urogential complaint					2
Muscle weakness	4				1

Table 4.2. : Presenting complaints in the literature, expressed as percentages.

Notwithstanding the sampling differences, here too the enlarged lymph nodes are the most frequent complaint, followed by abdominal distress. Only the E.N.T. problems show a definitely higher frequency in this study. This may be caused by the fact that others have not filed these under the heading first complaint but included them in the first localization, or by the fact that the coöperation with the E.N.T. surgeons in the Rotterdam area is very intensive. In other studies the involvement of Waldeyer's ring is a relatively frequent occurrence too; e.g. Rosenberg, et al. (1961) 7,4 %, Jones, et al. (1973) 2 % (follicular type) and 11 % (diffuse type), Lattuda and Milani (1973) 11 %. The relatively low frequency of complaints about constitutional symptoms is probably caused by the fact that only the very first complaint has been noted and a closer questioning about systemic symptoms was made later.

1.2. Constitutional symptoms.

Constitutional or systemic symptoms (fever, sweats, weight loss) occur in 25 % of all cases: Table 4.3. The total number of patients in this table is 267 instead of 314, because many patients could not remember exactly, even after pertinent questioning. This is in accordance with the literature which states percentages ranging from 14 % (Lattuda and Milani, 1973) to 25 % (Rosenberg, et al., 1961; Molander and Pack, 1963). Probably the real value of the occurrence of systemic symptoms lies in its prognostic significance (Jones, 1974). This will be discussed in chapter 8: "Factors influencing Prognosis".

1.3. Primary localization, nodal vs. extranodal.

The primary localization is most often found in the lymph nodes, as can be seen in Table 4.4.

symptoms	♂	♀	tot	% tot
neg.	105	96	201	75
pos.	41	25	66	25
total	146	121	267	100

Table 4.3. : Frequency of constitutional symptoms.

	♂	♀	tot ⟶	%	
Nodal	66	65	131	42,5	85% at least
Nodal and extranodal	74	57	131	42,5	nodal component
Extranodal	23	18	41	13	13% extranodal only
Leukemic transform.	2	4	6	2	
Total	165	144	309	100	

Table 4.4. : Frequency of primary localizations.

This can be expected in a lymphomatous disease; however the percentage of primary organ localizations is quite high in contrast to Hodgkin's disease (Kaplan, 1972). The extranodal occurrence of 13 % overall is in agreement with the data of Lattuda and Milani (1973): 10 % of 556 cases, Banfi, et al. (1968): 11 % of 300 cases, Rosenberg, Diamond and Jaslowitz (1961): about 15 % of 126 cases, and 12 % of 405 cases (Jones, et al., 1973). It is however somewhat less than described by Melander, et al. (1963): 31 % of 567 cases, and considerably less than the figures given by Peters, et al. (1968), which vary from 40 % of 631 cases (lymphosarcoma) to 61 % of 270 cases (reticulum cel sarcoma).

Primary localization will be discussed later with regard to pathology and other factors.

1.4. Primary localization, detailed.

A survey is given in Fig. 4.5 (all data in this subdivision are derived from Appendix D). Comparison with data from the literature enforced these different presentations, because many authors used different points of view when discussing the same problem. In Table 4.6 the data are compared with those of studies by Rosenberg, et al. (1961), Peters, et al. (1963), Banfi, et al. (1972) and Lattuda and Milani (1973). It should be noted beforehand, that comparing these figures with those of earlier studies can be misleading because of the differences in diagnostic refinements available to the respective authors - e.g. the rise in bone-marrow positivity is a function of sampling technique and number of punctures (Jones, et al., 1972). Nevertheless, when comparing these data with caution, some similarities do appear. The adenopathies figure very strongly with cervical lymph nodes occurring most frequently; the frequencies of the other lymph nodes are still in doubt, but significantly less. They are closely followed by primary localizations in the skin, gastro-intestinal tract, respiratory tract and bone-marrow - all others seem to be infrequent.

The frequencies of nodal and extranodal initial sites in their respective category are compared with the literature in Table 4.7. This table includes authors, who are not present in Table 4.6., because not all have data on all aspects, e.g. Freeman, et al. (1972) present data on extranodal localizations only. Regarding the lymph nodes there seems to be a good agreement on the relative frequency, except for the frequencies of positive spleens and abdominal lymph nodes in Banfi's series.

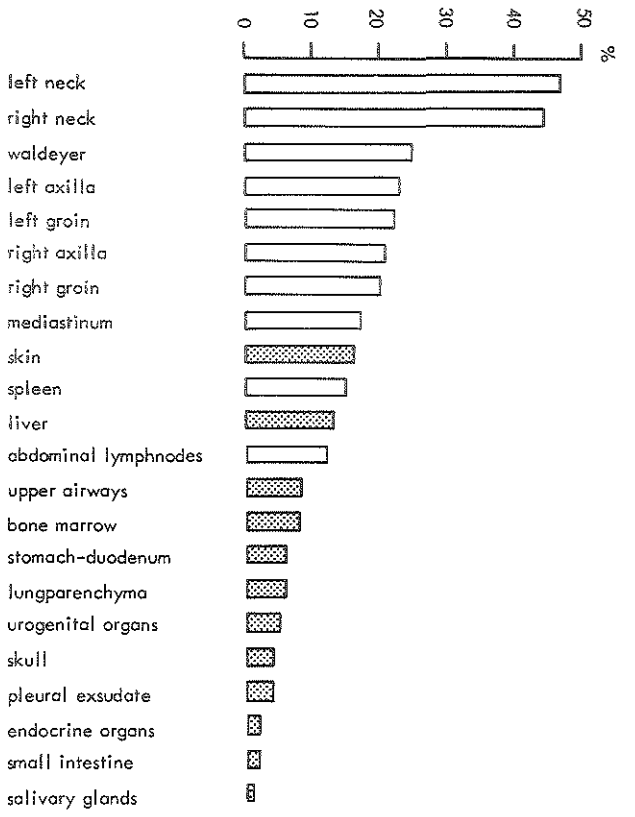


Fig. 4.5. : Frequency of primary localizations.

Note : the shaded boxes represent organ localizations, the others nodal localizations.

Author Date	Rosen-berg 1961	Pe-ters 1963	Lattu-da 1973	Pre-sent study
Total nr.	1269	901	556	314
LE Neck	>37	22	14	47
RI Neck			14	44
LE Axilla	>9	5	5	23
RI Axilla			5	21
LE Groin	>12	11	4	22
RI Groin			4	20
Waldeyer	7	10	11	25
Mediastinum	3	2	4	17
Spleen	?	1	1	15
Abdominal lyno	?	6	15	12
U.R.I.	?	?	?	8
Esophagus	?	16	?	0
Stomach	2		?	6
Sm. Intestine	1		?	2
Colon	0		?	0
Liver	0	0	3	13
Skin	5	6	5	16
Skeleton	4	4	4	4
Lung parench.	0	1	2	6
Pleural exsud.	0	?	1	4
U.G.	1	3	1	5
Bone-Marrow	?	?	3	8
Salivary glands	?	2	2	1
Endocrine glands	?	1	0	2

Table 4.6. : Frequency of primary localizations in the literature and this study.

Rosenberg 1961	Molander 1963	Banfi 1968: L.S.	Banfi 1968: R.S.	Present study	Author and date
1269	567	102	53	314	Total number of patients
38	24	37	31	37	Cervical
9	16	21	20	18	Axillary
3	4	5	7	7	Mediastinum
12	11	18	17	17	Inguinal
nd	nd	2	2	6	Spleen
nd	7	17	24	5	Abdominal

nd = no data

Table 4-7[1]: Distribution of initial lymphadenopathy in percentages

Note: In volvement of Waldeyers ring is 10% in the present study, it is not mentioned seperctely in the other studies.

Peters 1968	Freeman 1972	Lattuda 1973	Present Study	Author and date
418	1467	163	314	Total number of patients
↑	24	nd	7	Stomach
35	8	nd	3	Intestine
↓	6	nd	0	Colon
1	nd	12	18	Liver
12	8	16	21	Skin
9	5	13	5	Skeleton
2	4	7	8	Lung
	nd	nd	6	Pleural exsudate
6	nd	nd	11	Respiratory tract
nd	nd	4	6	Urogenital organs
nd	nd	11	11	Bone marrow
4	5	6	2	Salivary glands
2	4	1	2	Endocrine glands
nd	16	nd	0	Other

Table 4-7[2]: Distribution of initial extranodal presentations in percents

nd = no data

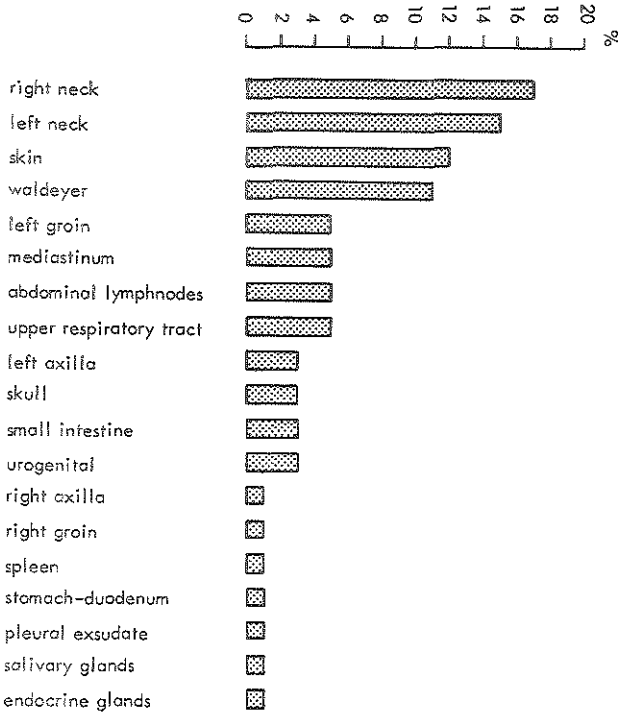


Fig. 4.8. : Frequency of single presenting sites.

In the extranodal presentations there is little doubt about the predominance of the skin, the gastro-intestinal tract (most frequently the stomach), respiratory tract and bone-marrow. Finally, in order not to be confused by the many primary sites present at the same time in one patient, one may wish to look at the real primary sites (as far as can be ascertained clinically) by considering the primary sites in stage I only (Fig. 4.8). There is very little comparison possible with other studies. Only the study of Scheer (1963) is comparable in this respect. Other studies, who consider this, have used the Rye staging classification, which has a different interpretation of stage I. As shown in Table 4.9 the frequencies of nodal presentations are similar; about extranodal presentations nothing meaningful can be said because both series are too small.

2. CLINICAL STAGE.

The clinical stages of the patients according to the Ann Arbor scheme (Carbone, et al., 1971; Rosenberg, et al., 1971) are given in Table 4.10. It should be noted that in this material some patients were not staged as sophisticated as they would have been nowadays. In the earlier years not all diagnostic methods, which are considered necessary today, e.g. lymphangiography and laparotomy (Moran, 1973; Jones, et al., 1974; Ferguson, 1973) were used. This will probably have resulted in some understaging (Veronesi, 1974), as these two procedures are especially useful for diagnosing involvement of the spleen, para-aortic and mesenteric lymph nodes. A comparison with data from Lattuda and Milani (1974), and Jones, et al. (1974) does not render essential differences except for a dip in stage III in the present series. This is a consistent feature of the Rotterdam material, because almost the same frequency of stage III was also seen in an earlier study (Van der Werf-Messing, 1968) on other patients from the same institute.

Source	Scheer 1963	Present study
Total number of patients	130	70
Neck LE	31	15
Neck RI		17
Axilla LE	10	3
Axilla RI		1
Groin LE	7	5
Groin RI		1
Waldeyer	11	11
Mediastinum	3	5
Spleen		1
U.Resp.Tract	2	5
Stomach	10	1
Skin		12
Skeleton		3
Pleural exsud.		1
Lung parench.		3
Urogential organs		3
Salivary glands		1
Endocrine glands	2	1

Table 4.9. : Frequency of single primary sites, in percentages.

Author	I	II	III	IV	total number of patients
Jones, 1974	10	25	25	40	405
Lattuda, 1974	27	37	25	11	556
Patchefsky, 1974	48		62		293
Present study	23	36	10	29	311

Table 4.10. : Frequency of clinical stage, in percentages.

3. HISTOLOGY.

3.1. Cell type.

The distribution is given in Table 4.11. Both sexes are equally represented in the total series of 314 patients except for a male predominance in H.C.S.

3.2. Structure.

Table 4.12. In this table the total number is 221, because for this study only H.E. stains were used, on which it is not always possible to give an opinion about structure. All cases where the structure was doubtful were omitted here. This may have caused some underrepresentation of the follicular type, because a concurrent prospective series in the Netherlands, in which all sections were seen with reticulin stains, gives a slightly higher percentage 34 % (Van Unnik, 1973) instead of 25 %.

In the present series diffuse lymphoma affects males considerably more often than females. There are 3.6 times as many men in the diffuse than in the follicular group (96 vs. 26) but only 2.3 times as much diffuse women (69 vs. 30). This difference is in agreement with the findings of others (Gall and Mallory, 1942; Jones, et al., 1973). The reason for this is still a matter of speculation. In the follicular type the sexes are equally distributed (Dorfman, 1964).

When these results are compared to those of Veronesi, et al. (1974) and the augmented series of Jones (1974) there does not seem to be much agreement: in the present series the lymphoblastic variety is rather frequent and in Veronesi's series the histiocytic type predominates: Table 4.13.

	Numbers			Percentages		
	♂	♀	tot	♂	♀	tot
LCS	44	42	86	53	47	100
LBS	61	61	122	50	50	100
HCS	39	22	61	64	36	100
HBS	18	20	38	47	53	100
FM	4	3	7	57	43	100
Tot	166	148	314	53	47	100

Table 4.11. : Distribution of cell types.

structure / cell type	Diffuse				Follicular				Both			
	n	%	♂	♀	n	%	♂	♀	n	%	♂	♀
LCS	21	40	13	8	32	60	17	15	53	100	30	23
LBS	85	83	49	36	17	17	6	11	102	100	55	47
HCS	38	93	22	16	3	7	1	2	41	100	23	18
HBS	21	84	12	9	4	16	2	2	25	100	14	11
Total	165	75	96	69	56	25	26	30	221	100	122	99

Table 4.12. : Cell type and structure.

Structure	Diffuse			Follicular		
Author / Cell type	Jones 1974	Veronesi 1974	Present Study	Jones 1974	Veronesi 1974	Present Study
LCS	3	7	10	1	6	14
LBS	20	7	38	37	10	8
HCS	28	54	17	7	19	1
HBS	4	0	10	4	0	2
Total	55	77	75	45	33	25

Table 4.13. : Cell type and structure as percentages of the total number of patients in different studies.

This also occurs in another series from the same institute (Lattuda and Milani, 1974) in which the histiocytic type amounts to 66 %. It should be noted that in this caomparison the mixed cell type has been included in the L.B.S. class (poorly differentiated lymphocytic lymphoma), which is common practice nowadays.

3.3. Presence of macrophages.

Table 4.14. The presence of large pale reticulum cells containing predominantly nuclear debris is thought to be a prognostic index. These cells first studied by Diamandopoulos and Smith (1964) who identified them in 10 % of reticulum cell sarcomas using Rappaport's classification. However, they felt that the distinction between histiocytic and undifferentiated was often so subjective that it should be omitted. Their findings are comparable to the 8.5 % in the present series when H.B.S. and H.C.S. are combined together. The large-cell variety and the diffuse structure most often contain macrophages. Multiple regression analysis will show that their presence has a distinct prognostic influence (see chapter VIII).

3.4. Concurrent neoplasia.

It has often been stated (Gunz and Angus, 1965; Hyman, 1969) that patients with lymphoproliferative disorders have more chance to develop other malignancies, but htere are at least as many authors (Moertel, 1957; Watson, 1953; Berg, 1967; Warren and Ehrenreich, 1944) who deny this increased incidence.

Most patients have, once their lymphoproliferative disorder has been discovered, an excellent follow-up, which favours early detection.

	Negative		Positive	
Cell-type	nr	%	nr	%
LCS	74	90	9	10
LBS	102	84	19	16
HCS	58	97	2	3
HBS	31	82	7	18
Total	265	88	37	12
Structure				
Diffuse	139	85	25	15
Follicular	60	97	2	3
Total	199	88	27	12

Table 4.14. : Presence of macrophages.

Second tumor / Lympho-ma type		skin	other	Percentage of total number
LCS	n = 86	4	1	5/86 = 6
LBS	n = 122	2	5	7/122 = 6
HCS	n = 61	0	1	1/61 = 1
HBS	n = 28	0	0	0/28 = 0
FM	n = 7	1	2	3/7 =40
Total	n = 314	7	9	16/314 = 5

Table 4.15. : Occurrence of a second tumor.

When this influence is eliminated by comparing them with a group having a similar intensive follow-up (Moertel, 1957; Berg, 1967) the incidence of cancer is about the same as in the general population, except for malignancies of the skin. The frequency of the latter, most often in the form of basal cell carcinoma, is about tenfold higher than normal. It is not clear whether this is due to the same carcinogen, or to the loss of immunologic function (Hyman, 1969), or to the effect of potentially carcinogenic treatment.

In the present series, in which the patients have a lifelong follow-up, five per cent developed another malignancy after the diagnosis of malignant non-Hodgkin's lymphoma: Table 4.15. In view of the intensive and long follow-up this does not seem to be an important rise in frequency. It is not clear whether any value must be attached to the fact that most new malignancies arise in the lymphocytic types; an explanation could be that the patients with the more malignant histiocytic types did not live long enough to develop other malignancies.

4. BONE-MARROW INVASION.

Fifty eight per cent of the patients with initial stage IV had a bone-marrow evaluation by aspiration. Tumor infiltration was seen in 36 per cent. In the diffuse lymphoma there is a higher frequency of bone-marrow invasion than in the follicular type: 67 vs. 22 per cent: Table 4.16. It was felt that further subdivision of each cell type in its structural variants would produce unrealistic percentages because of the very small number in each category.

From Jones, et al. (1972, 1974) and Dick, et al. (1974) we know that the chance of finding of marrow invasion by a marrow aspiration is only half of that when more aggressive techniques such as Westerman needle bone biopsy or open surgical biopsy are used: 8 per cent vs. 16-18 per cent.

	positive		negative		total	
	N	%	N	%	N	%
LCS	10	67	5	33	15	100
LBS	3	14	18	86	21	100
HCS	3	33	6	67	9	100
HBS	0	0	3	100	3	100
FM	2	67	1	33	3	100
Tot	18	36	33	64	51	100
Foll	6	22	21	78	17	100
Diff	8	67	4	33	12	100
Tot	14	36	25	64	39	100

Table 4.16. : Bone-marrow invasion in stage IV.

Age	M	F	Tot
0 - 10	3	4	7
10 - 20	6	2	8
20 - 30	9	4	13
30 - 40	12	7	19
40 - 50	21	21	42
50 - 60	33	25	58
60 - 70	39	35	74
70 - 80	31	34	65
80 - 90	10	14	24
90 -100	2	2	4
Total	166	148	314

Table 4.17. : Age at presentation.

The percentage of positive bone-marrows in aspirations from all stages is 8; this consists of 18 stage IV patients with bone-marrow infiltration and 6 with leukemic development.

The overall yield of 8 per cent positive results is derived from only 38 per cent of the total number of patients. About the distribution of the positives over the pathology types no firm opinion is possible because the total figures are too small.

5. AGE AND SEX.

Table 4.17. In contrast with moste authors (Rosenberg, et al., 1961; Lattuda, et al., 1974; Lee, et al., 1973; Molander and Pack, 1973; Hansen, 1969; Molander, 1965; Jones, 1973) who state a male/female-ratio ranging from 1.5-2 to 1, the sexes are about equally distributed in the present series, 53 per cent are men, and 47 per cent are women. It is tempting to see the equal distribution of the sexes in the present study as specific for Northern Europe. However, a smaller study carried out at the same time at the Dutch Cancer Institute in Amsterdam (Hart, 1973) gives a percentage of 60 per cent men out of a total of 126 patients. The age distribution of the age at presentation is in close agreement with the literature. There is a predilection for the later decades in both sexes. The average age for women is slightly nigher than for men (55.2 years vs. 51.6 years).

APPENDIX D.

A review of the most important primary localizations cross-tabulated against stage, pathology, structure and sex.

Notes on Appendix D.

1. The column totals may exceed 314 because many patients had multiple presenting primary sites.
2. The column totals may be less than 314 (e.g. in "structure") because on some patients there are no data available about the aspect under discussion.
3. There are 24 positive bone-marrows of which 18 are stage IV; the other 6 are of course stage IV too, but are subclassified in the group lymphoma with leukemic development.

V. FURTHER CLINICAL INTERRELATIONS.

1. STAGE, CELL TYPE AND STRUCTURE.

The relation between cell type and structure has already been discussed (see Table 4.3). It remains to be seen whether any histology subclass has a tendency to skip stages. This would suggest a rapid, probably haematogenic, dissemination, in contrast with the orderly spread along the lymphatic pathways (Goffinet, et al., 1973) that has clearly been established in Hodgkin's lymphoma (Kaplan, 1972). Most authors subdivide the pathologic material in two parallel series according to structure. Although the value of the structural division cannot be denied, in this study both possibilities are considered as the ends of a structural spectrum and the aspect of structure is treated separately.

1.1. The relation between cell type and clinical stage is shown in Fig. 5.1 (see also Appendix E). It is hard to find comparable groups in the literature because in most series the Rye staging classification or pre-Rappaport histological classification has been used. In the series of Jones, et al. (1973) - see Table 5.2 - stage IV is more frequent than stage III. This is especially true for the histiocytic type. Although the studies of Lattuda, et al., and Patchefsky, et al. (1974) are recent, they cannot be used for comparison because the stages are grouped together. In the present study stage III is also underrepresented as compared with the other stages. This may be explained as a tendency for quick generalization from localized to disseminated forms. However, comparisons should be made with care because in small numbers a large percentage shift can be caused by a few patients. Therefore it seems best to conclude only that there is a trend, of early non-lymphatic, probably hematogenous spread.

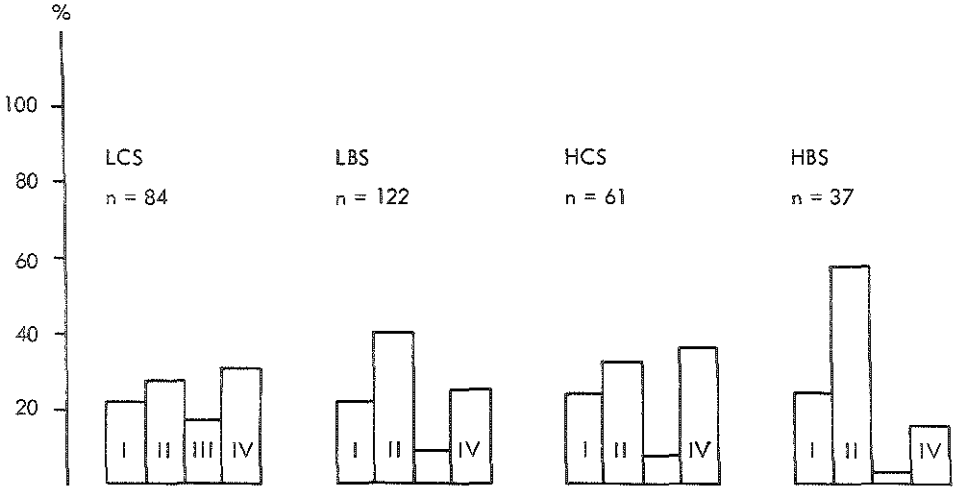


Fig. 5.1. : Cell type and clinical stage.

Source	Jones 1974				Present Study			
Stage	I	II	III	IV	I	II	III	IV
Cell type								
LCS	25	12	19	44	21	28	17	35
LBS	12	21	30	37	22	40	9	29
HCS	11	32	19	38	24	33	7	36
HBS	60	40	10	0	24	57	3	16

Fig. 5.2. : Cell type and clinical stage in the literature.

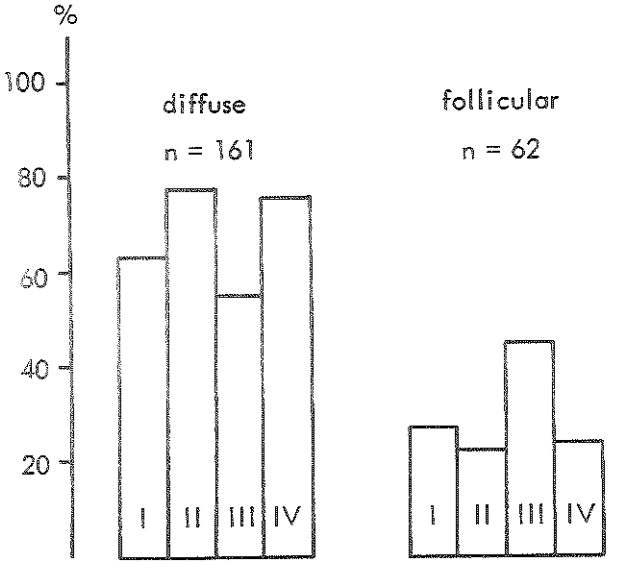


Fig. 5.3. : Structure and clinical stage.

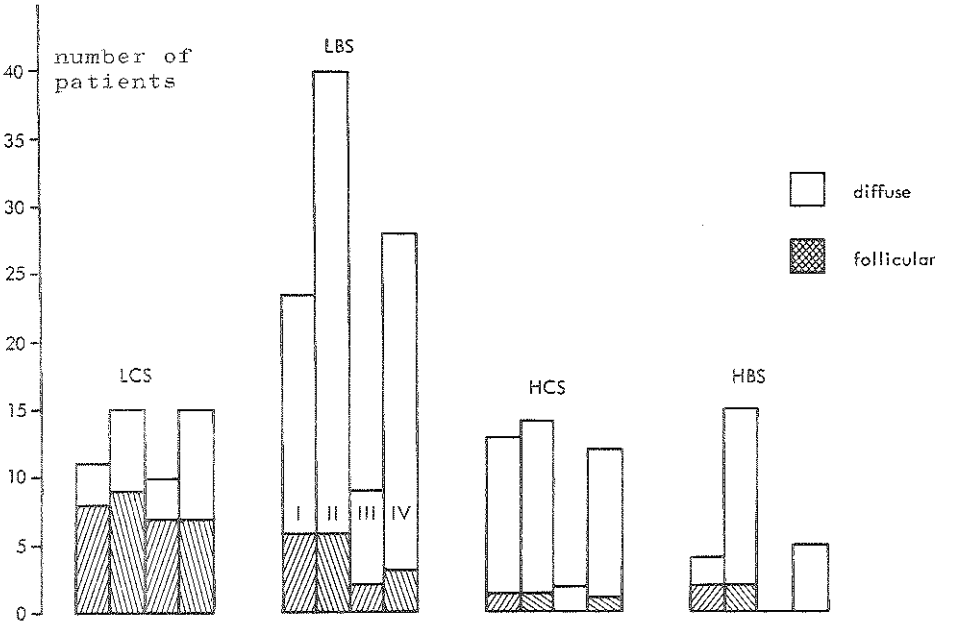


Fig. 5.4. : Cell type and structure per stage.

1.2. Table 5.3 shows the frequency of diffuse and follicular structures in each stage (see also Appendix F). It seems that the distribution between diffuse and follicular in the different stages is of the same order except for stage III, which however consists of a small group of patients.

1.3. The rather equal distribution of the diffuse and nodular types over all stages makes the factor structure unimportant when the distribution of histology (cell type and structure together) over the stages is considered: Table 5.4.

Summarizing we can state that in the present series:
The percentage of diffusely structured lymphomas in each cytologic type is the same in all stages. This may indicate that the aggressiveness of the diffuse type is the same as that of the follicular type because otherwise one of the two would predominate in the higher stages.
The follicular type is infrequent and occurs from 10 to 20 per cent, except for the L.C.S.-variant where it is present in 60 per cent.
There is a tendency towards early dissemination compared with the spread in Hodgkin's disease because there the frequency of stage III and IV together is lower (Kaplan, 1972).

2. AGE, CELL TYPE, STRUCTURE AND STAGE.

2.1. The distribution of the cell types over the age groups is shown in Fig. 5.5 (see also Appendix G).

It is apparent that the lymphocytic types are evenly spread over the different age groups, whereas the histiocytic types seem to be rare below the age of twenty. All cytological types have about the same average age at the time of diagnosis: 55 years.

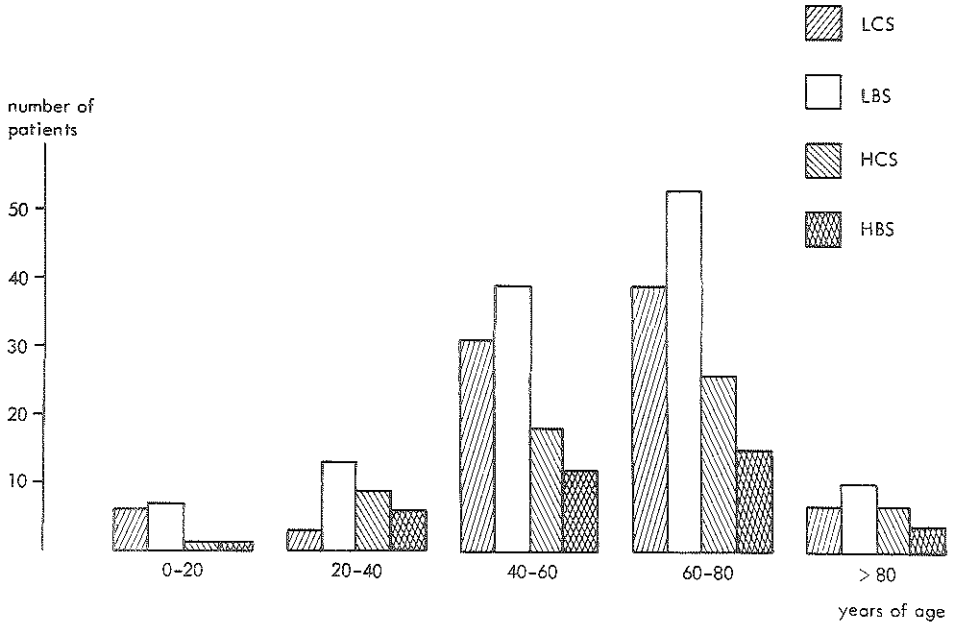


Fig. 5.5. : Cell type and age.

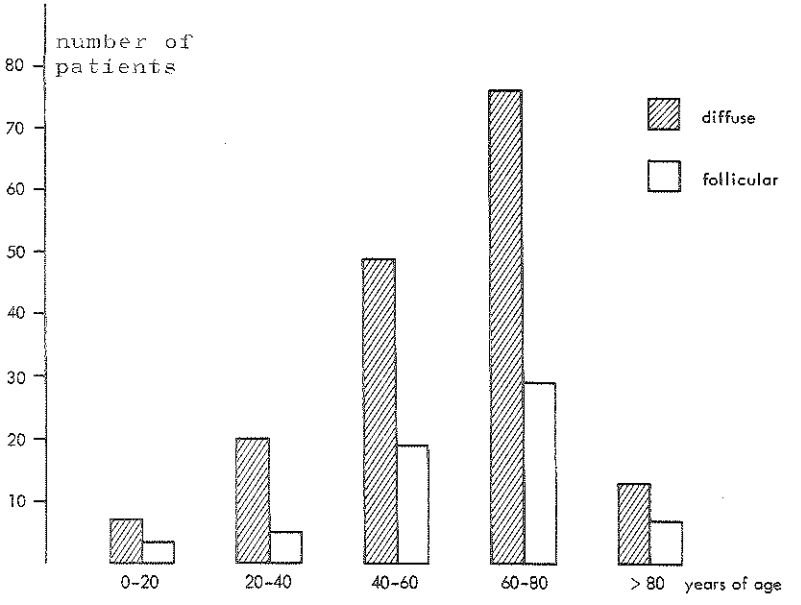


Fig. 5.6. : Structure and age.

2.2. Follicular structures are evenly distributed over the different age groups, as shown in Fig. 5.6. The percentages range around 25 (see also Appendix H).

Data from the literature (Rosenberg, et al., 1961; Lee, et al., 1973; Molander and Pack, 1963; Hansen, 1969; Gall and Mallory, 1942; Lattuda, 1974; Patchefsky, et al., 1974) agree with the results of the present study; they show the same frequency curve, which is similar to the age distribution of most malignancies (Ackerman and del Regato, 1970), but different from the bimodal age distribution curve in Hodgkin's disease (McMahon, 1957). This difference suggests a pathogenesis which is different from that of Hodgkin's disease.

2.3. Fig. 5.7 demonstrates that within each stage the age distribution is similar except for stage III, which shows an unexpected peak in the years from fifty to seventy and a relative deficit after that. As it does not seem likely that a certain stage can be detected earlier at a certain age, the stage/age distribution should follow the age distribution. The reason why stage III shows a different distribution is probably the fact that in this relatively small group a few patients have caused disproportional percentage shifts.

The average age for all stages varies from 51 to 56 years.

3. PRIMARY LOCALIZATION, CELL TYPE, STAGE.

The clinical stage at first presentation gives some information about the primary localization. Study of the frequency of extranodal primary localization in each cytological category gives additional data. It shows if a cell type has a tendency to start extranodally.

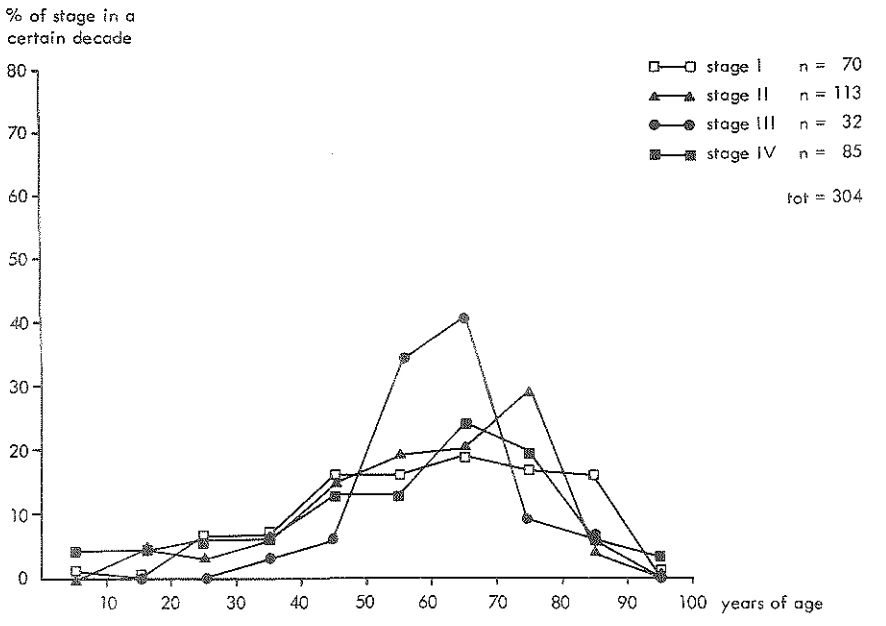


Fig. 5.7. : Clinical stage and age.

Cell type	total number	nodal	extra nodal	both	"leuke-mic"
LCS	85	40	12	43	5
LBS	120	43	15	40	2
HCS	61	33	15	52	0
HBS	37	62	11	27	0

Table 5.8. : Frequency of primary site within each cytological group in percentages.

It may be argued that the same conclusions can be derived from the construction: "cell type vs. structure vs. stage vs. primary localization" as was done by Jones, et al. (1973). However the total number of patients in the present study does not allow such a four-dimensional division because the groups become too small for realistic interpretation.

Table 5.8 shows the frequency of nodal and extranodal primary sites for each cell type. It appears that there is no preference for an extranodal start in any of the cytological types. The frequency of about 13 per cent extranodal primary sites is in agreement with the data of Jones, et al. (1974).

4. CONSTITUTIONAL SYMPTOMS, STAGE AND CELL TYPE.

The frequency of constitutional symptoms rises sharply with the clinical stage, as is shown in Fig. 5.9.A. There is no significant difference between the percentage with B symptoms in the different cytological classes: Fig.5.9.B. Therefore it may be concluded that within each cytological class the patients with constitutional symptoms are concentrated in the higher stages: Fig.5.9.C. Only a few remarks are made in the literature about the frequency of systemic symptoms in different stages of cytological groups (Hansen, 1969; Jones, 1974) but nothing definite is known. The importance of constitutional symptoms lies in their prognostic significance. Some people (Jones, et al., 1973) regard them as unimportant subsidiaries of the clinical stage; others (Bloomfield, et al., 1974; Patchefsky, et al., 1974) think that they have independent prognostic significance. In the present study (see chapter: Factors influencing prognosis) the presence of constitutional symptoms also emerges as an independent prognostic factor.

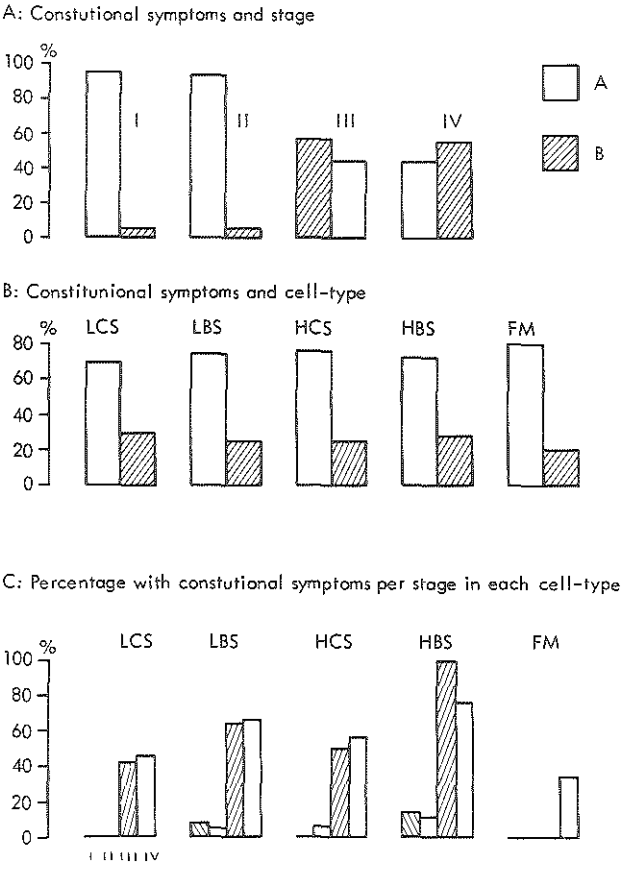


Fig. 5.9. : Constitutional symptoms, stage and cell type.

VI. TREATMENT OF NON-HODGKIN'S LYMPHOMAS.

1. INTRODUCTION.

The modern treatment schemes for Hodgkin's disease cannot be applied to the non-Hodgkin's lymphomas (McElwain, 1974). The latter lymphomas show a less predictable spread, they are usually more disseminated, and they tend - especially in the lymphocytic variants - to involve bone-marrow earlier. Some of the localized lymphomas are curable with adequate irradiation, others however have certainly, but as yet undetectably, spread more widely, and need more extensive treatment, e.g. chemotherapy after irradiation (Peckham, 1974). Somehow a certain natural aggressiveness of each tumor-type has also to be taken into account in the treatment (Kim and Dorfman, 1974). At present many different opinions are presented about the treatment of non-Hodgkin's lymphomas. However, most studies are of little value because they do not give information about histology criteria according to Rappaport, exact radiation schemes, or the Ann Arbor staging. Moreover the total number in each subgroup, when modern classification is used, is often so small that survival curves become statistically insignificant (Jones, Kaplan, et al., 1972). Therefore possible prognostically favourable groups can remain unnoticed.

2. SURVEY OF TREATMENT METHODS.

The therapy concept at the Rotterdam Radiotherapy Institute is to treat locoregional disease with radiotherapy, and surgery when needed. Disseminated disease is treated with chemotherapy sometimes together with radiotherapy and/or surgery. The role of surgery as a single treatment is insignificant. Locoregional disease may be translated as clinical stage I and II, whether A or B. Disseminated, means stage IV or leukemic degeneration.

The treatment of stage III has been variable, sometimes in a case with limited stage III disease only radiatherapy has been given without subsequent chemotherapy. A survey of treatment is given in Table 6.1.

Irradiation type		ortho			mega			mepro			no			total		
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
First attack	chemo +	0	5	5	1	14	15	1	2	3	0	11	11	2	32	34
n = 314	chemo -	2	62	64	22	110	132	2	32	34	13	9	22	39	13	252
	total	2	67	69	23	124	147	13	20	37	13	20	33	41	245	286
Second attack	chemo +	0	3	3	0	8	8	0	2	2	0	24	24	0	37	37
n = 184	chemo -	0	35	35	1	58	59	0	10	10	5	25	30	6	128	134
	total	0	38	38	1	66	67	0	12	12	5	49	54	6	165	171
Third attack	chemo +	0	2	2	0	5	5	0	0	0	0	20	20	0	27	27
n = 99	chemo -	0	21	21	0	25	25	0	1	1	1	17	18	1	64	65
	total	0	13	23	0	30	30	0	1	1	1	37	38	0	91	92

Note: 1 = also surgical treatment
2 = no surgery
3 = total

Table 6.1. : A survey of treatment. The number of patients receiving a certain form of radiotherapy (ortho = orthovoltage, mega = megavoltage, mepro = megavoltage with "prophylactic" extended fields) is given for each attack; concurrent chemotherapy and/or surgery are also indicated.

2.1. Radiotherapy.

Orthovoltage was most often used in the earlier years. The dosage was about 3000 roentgen in 3 to 4 weeks. Later high energy irradiation or megavoltage was applied, supplied by a Co^{60}-source or a linear accelerator. The dosage was 4000 rads administered in 20 fractions during 4 weeks - or equivalents.

The megavoltage irradiation, with the same dosage, was sometimes electively applied to the surrounding area or adjacent lymph node stations too. Megavoltage irradiation with and without elective "prophylactic" irradiation are abbreviated as mega respectively mepro in the illustrations. The exact irradiation data have partly been published elsewhere (Van der Werf-Messing, 1968), the other data will be published in 1975 by the E.O.R.T.C.

2.2. Surgery.

Surgery varied considerably in scope from a simple tumor excision or a diagnostic exploration, to extensive palliative laparotomies. Surgery was used in 13½ % of all cases, in 3½ % it was the only form of treatment. In the remaining 10 % it was palliative.

2.3. Chemotherapy.

All patients were treated in the time before the more powerful (cyclical) chemotherapeutic combinations came into use in the R.R.T.I. Treatment consisted most often of single sequential chemotherapy sometimes concurrent with corticosteroids in high dosage. As can be seen from Table 6.2 alkylating agents, corticosteroids, procarbazine, and vinca alkaloids were most frequently used.

3. RESULTS OF TREATMENT.

3.1. Overall results are depicted in Fig. 6.3. The number of patients in each group is given in Table 6.1.

Alkylating agents	
Nitrogen mustard	21
Chlorambucil	6
Cyclophosphamide	24
Triethyleen melamine	2
Vinca alkaloids	
Vincristin	3
Vinblastin	1
Methotrexate	1
Corticosteroids	28
Bleomycin ^{R}	4
6-Mercaptopurine	2
Daunomycin ^{R}	1
Procarbazine	5
Urethane	1
Total number	99

Table 6.2. : Summary of chemotherapy.

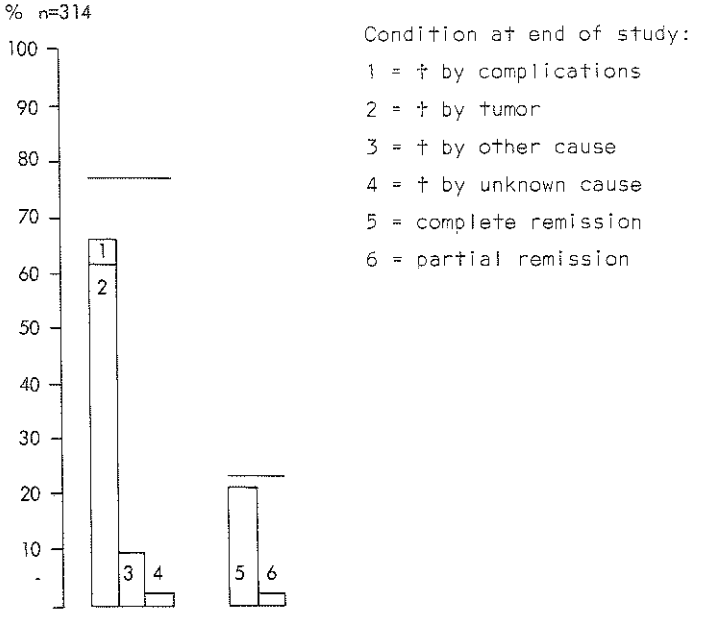


Fig. 6.3. : Results of treatment.

The results must be interpreted with some caution, because in the patients, who were entered into the study late, the follow-up may have been too short. This might make the survival figures only slightly worse, because the minimal follow-up is 2¾ years and most patients in whom the disease was fatal died within three years. With a therapeutic approach of predominantly regional megavoltage irradiation, and single agent chemotherapy as practised at that time at the R.R.T.I., 66 % of the patients (Fig. 6.3) die with non-Hodgkin's lymphoma. The three and five year survival percentages (Fig. 6.4) are about 37 and 25 % respectively. Comparable and almost similar data are given by Rosenberg, et al. (1962) in their very extensive study.

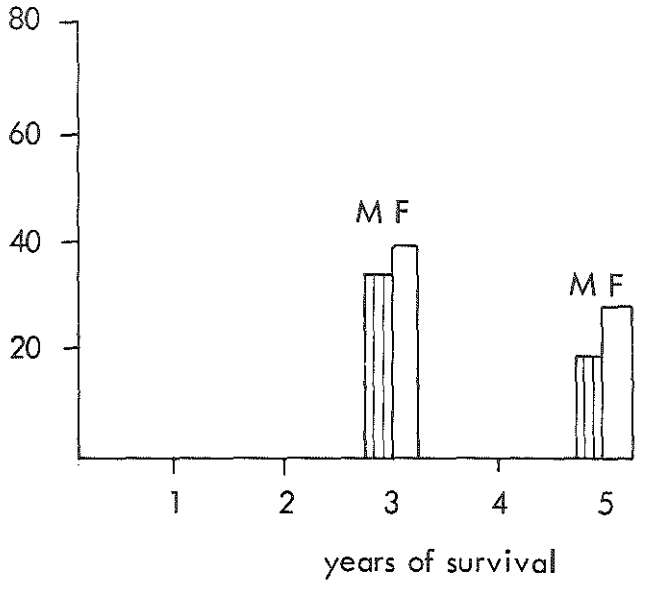


Fig. 6.4. : Three and five year survival of males (M) and females (F), expressed as percentages of their numbers at the beginning of the study.

The survival data are comparable with those of Molander and Pack (1963), who had almost the same therapeutic concept. It is apparent from this study, that non-Hodgkin's lymphoma has a high mortality rate.

3.2. The result of each specific treatment type.

The percentages of complete remission, partial remission, and therapeutic failures for all single treatment forms (orthovoltage, megavoltage, megavoltage with extended "prophylactic" field, chemotherapy, and surgery).

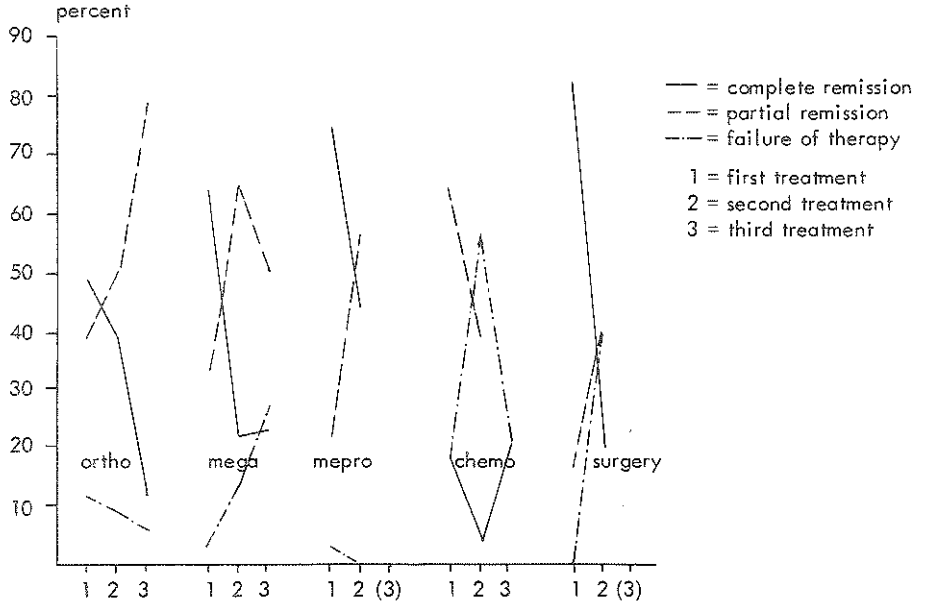


Fig. 6.5. : Effect of each single treatment per relapse.

3.2.1. Radiotherapy.

There appears a trend (see Fig.6.5) of improving results (higher frequency of complete remission) as the irradiation gets more aggressive (voltage, extension of involved fields). However, it should be borne in mind that the change from orthovoltage to megavoltage irradiation coincided with improved diagnostic tools. Therefore understaging in the orthovoltage time is a distinct possibility - with the consequence of undertreatment. The better result of prophylactic extended field irradiation is in some contrast with the findings of Jones, et al. (1973) and also with results of the latest E.O.R.T.C. trial (January 1975).

It becomes obvious that the effectiveness of irradiation decreases in the treatment of relapses because previous radiotherapy may limit irradiation fields and/or dosage. Therefore the initial treatment should be of maximal curing potency because a second attempt at cure (here expressed as the percentage of complete remissions at each relapse) is much less effective.

3.2.2. Surgery.

This is rarely (see table 6.1) used as a single treatment, in fact only for the excision of very small local lesions. As a purely local treatment it has a high succes rate (83 % complete remissions, see Fig.6.5). Therefore primary surgery may incidentally be performed for the treatment of some small stage I lymphomas. At present it would probably be followed by irradiation

3.2.3. Chemotherapy.

The results of sequential single agent chemotherapy are poor, because complete remission is only obtained in 18 per cent (see Table 6.5).

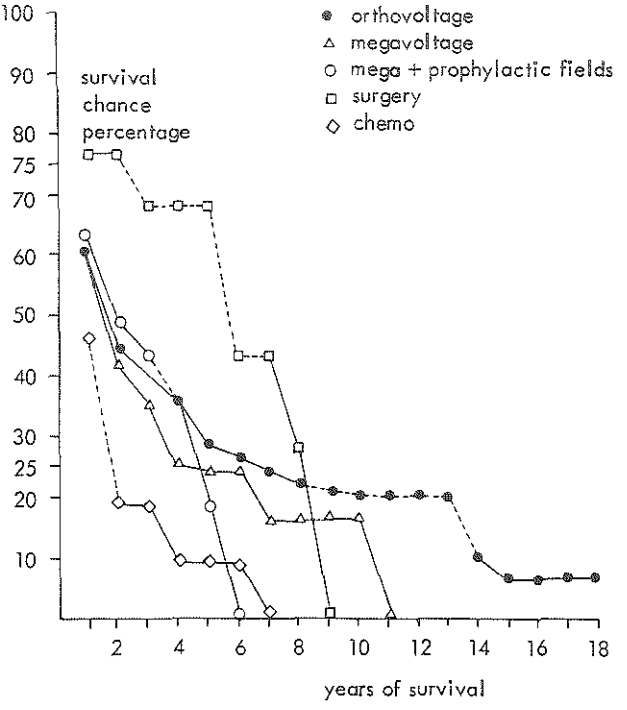
With the same agents used in about the same frequency, Jones, Rosenberg, et al. (1972), and Monfardini, et al. (1973) obtained comparably low rates of 17 and 20 per cent. These results are worse than those obtained with intermittent or continuous multiple chemotherapy by Hoogstraten, et al. (1973), Luce, et al. (1971), Bagley, et al. (1972), and Stein, et al. (1974): they achieve about sixty per cent complete remissions. It is clear that single agent chemotherapy will be of very minor importance in the future.

Therapy can also be evaluated against survival, as has been done by many authors (Lee, et al., 1973; Monfardini, et al., 1973), when they discuss particular forms of treatment. These data are usually of little value because they have been derived from nonrandomized studies or because they compare different and incomparable forms of treatment (e.g. high voltage irradiation, which is only used in the favorable lower stages, with multiple chemotherapy, which is used in disseminated disease). However, in Fig. 6.6 all single (first) treatments are evaluated against survival.

4. RESPONSE DIFFERENCE PER CELL TYPE.

As shown in Fig. 6.7, it was possible to achieve over 50 % complete remissions at the first treatment, with the larger cell types marking the upper limit; the failure rate was about the same for all. The high rate of cure in follicular mixed lymphoma once more proves that this type of lymphoma is an outsider.

These data may give the impression that the cell type does not significantly influence the curability of a non-Hodgkin's lymphoma.



Note : The solid line indicates when the total number of patients is above ten (left hand side) or below five (right hand side).

Fig. 6.6. : Survival and single treatment.

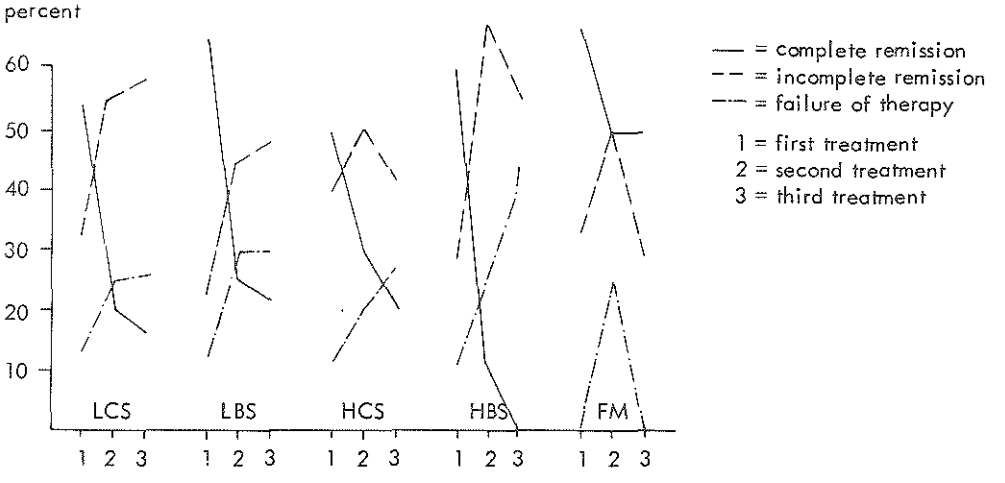


Fig. 6.7. : Effect of treatment in each attack.

However, the complementary factor of disease-free time after treatment, i.e. duration of remission, must be taken into account also, because it gives another indication of the curability (see below).

5. DURATION OF COMPLETE REMISSION.

Table 6.8 shows that the treatment response of each cell type is different, when it is related to the duration of complete remission. The L.C.S. emerges quite good, and the histiocytic variants suffer setback because of the short duration of remission. From Table 6.9, which correlates duration of remission and structure of the lymphoma, it appears that the follicular variants attain more and longer remissions.

A search was made for a relationship between the duration of the first and second remissions, as it appeared that the second complete remission was much longer than the first. It could be supposed that a long first complete remission predicts a long second complete remission, because the duration of the first remission is an indication of the relative benignity. The relation between the duration of the second complete remission and the duration of the first is given in Table 6.10. There is no clear relation between the remission durations in the present small series. There are no data in the literature about a relation between the subsequent remission durations.

Cell type	LCS	LBS	HCS	HBS	FM
n total (=100%)	86	122	61	38	7
% in remission after: 1 month	30	12	10	11	14
2 months	13	5	7	3	14
3	8	1	3	0	0
4	2	1	3		
5	1	0	2		
6	1		2		
7	0		0		

Table 6.8. : Duration of first complete remission, related to cell type.

Structure	Diffuse	Follicular
N total (=100%)	165	63
% in remission		
after: 1 month	12	27
2 months	5	13
3	2	6
4	2	3
5	1	2
6	1	0
7	0	

Table 6.9. : Duration of first complete remission, related to structure

Duration of first remission in months:	<1	1	2
Total number (=100%)	128	26	11
Percentage in second			
remission after 1 month	49	58	54
2 months	40	58	45
3	28	42	36
4	21	35	36
5	13	35	18
6	8	27	18
7	8	15	0
8	6	15	
9	5	12	
10	3	12	
11	2	0	
12	0		

Table 6.10. : Relation between duration of first and second complete remission

6. LOCAL RECURRENCE.

The recurrence rate in regions, which had received adequate irradiation, is shown for each cytological and structural type in Table 6.11. The histiccytic variants do much worse in overall frequency and in reappearance time, as shown in Table 6.12. This can be an indication that they are more aggressive or that they require a higher irradiation dose than the lymphocytic variants. Difference in structure is not an important factor, although the recurrences appear earlier in the diffuse type than in the follicular type. When the data of Fuks and Kaplan (1973), who have rougly the same irradiation philosophy, are compared with the results of the present study, it appears that the recurrence rates are about the same, whether looked at per cell type, or per structure variant (see Table 6.13). They also note, as does Hansen (1969), a quick recurrence. The very quick recurrence of the histiocytic variants occurs in their series too.

In general it can be said that local recurrence appears more often and earlier in the histiocytic variants. There is no difference in the final total between diffuse and follicular structures, but in the diffuse type recurrence is faster.

	recurrence	none	n
LCS	25 %	75 %	← 84
LBS	19 %	81 %	←120
HCS	27 %	73 %	← 60
HBS	34 %	66 %	← 38
FM	0 %	100 %	← 7
n tot =	73	236	309
diffuse	22 %	78 %	←162
follicular	19 %	81 %	← 63
n tot =	48	177	225

Table 6.11. : Frequency of local recurrence in relation to cell type and structure.

Appearance time in mounths	cell type				structure	
	LCS	LBS	HCS	HBS	diffuse	follicular
<1	52%	83%	94%	92%	83%	50%
1	81%	87%	94%	92%	89%	75%
2	86%	97%	94%	92%	92%	84%
3	100%	100%	94%	92%	97%	100%
4			100%	92	100%	
~~						
8				100%		
total number	21	23	16	13	36	12

Table 6.12. : Appearance time of local recurrence, in relation to cell type and structure.

Author Histology	Fuks 1973	Present study
LCS	35 %	25 %
LBS	21 %	19 %
HCS	27 %	27 %
HBS	28 %	36 %
Diffuse	26 %	22 %
Follicular	21 %	19 %

Table 6.13. : Frequency of local recurrence.

VII. SIDE EFFECTS OF TREATMENT, INFECTIONS.

1. SIDE EFFECTS.

Iatrogenic complications are a very important aspect of the treatment of malignancy. At present with the increasing availability of more potent therapy the incidence of iatrogenic side effects rises correpondingly (Meyler and Peck, 1972; Moser, 1969). In the case of the present cytostatics the therapeutical range is small and therefore each beneficial effect has to be paid for with many side effects (Zwaveling, et al., 1973). The same applies to irradiation therapy (Kaplan, 1972; Sykes, et al., 1974; Vogel and Lunde, 1968; Bull, et al., 1969).

In the case of radiotherapy the most prominent side effects are ulceration of skin and mucous membranes, bone-marrow depression, pneumonitis, and myelopathy. The main chemotherapeutic agents used in this study were 1) the alkylating agents nitrogen mustard, cyclophosphamide and chlorambucil, 2) corticosteroids, 3) procarbazine, and 4) vinca alkaloids (see table 6.2). Their most frequent side effects are bone-marrow depression, neurotoxicity, haemorrhagic cystitis, diarrhoea and nausea. The frequency of side effects occurring in this series is given in Table 7.1.

All therapeutic side effects occurring in individual patients during the treatment are included, so that side effects cannot be pinpointed to a particular treatment at any precise moment, but only an overall picture can be obtained. One rather special side effect occurred, the source of which could be ascertained: the only case of lungfibrosis was in a patient who received bleomycin ^{R}, and this as we now know is quite a common complication of this type of drug (Oldhoff and Schraffordt Koops, 1972; Dragoni, et al., 1971). Three other patients on bleomycin ^{R} did not develop lungfibrosis.

Fourty per cent of patients receiving corticosteroids developed complications, ranging from mild Cushings' syndrom to fatal gastric bleeding. Haemorrhagic cystitis which is fairly specific for cyclophosphamide occurred in 33 % of those using it. Neurotoxicity, expressing itself as paraesthesias, pareses, or paralytic ileus occurred solely in patients on vinca-alkaloids; in fact all patients using vinca-alkaloids in the present series developed this complication at least once. Bone-marrow depression may occur as a consequence of cytostatics, and/or irradiation (large field with much bone-marrow in it, bone-marrow previously compromised by therapy), so no special offender may be singled out. In the present study a significant decrease of the leucocytes and thrombocytes, to below values of 1.000 and 30.000 respectively, was considered to be an indication of bone-marrow depression.

2. DEATH DUE TO COMPLICATIONS OF THERAPY.

In twelve patients treatment clearly shortened the life span of the patient. These twelve patients form 4 % of the total number. This frequency once more shows the small therapeutic range left for the clinician treating lymphomas.

3. INFECTIONS.

The lymphoma is a ideal candidate for infections for many reasons (Klastersky, 1974):

- abnormal body flora: more resistant and virulent types of bacteria and viruses acquired from the hospital, or altered through selective growth under former antibiotic treatment (Feingold, 1970).

Side effect	% of total number of patients
Lung fibrosis Pneumonitis	0,3
Skin ulceration Mucositis	8
Bone marrow Depression	23
Corticosteroid Side effect	3,5
Haemorrhagic Cystitis	1
Neuritis Ileus	5
Total % of side effects	41

Table 7.1. : Side effects of treatment.

% of positive infection of total number, of which information about that type of infection excists

Infection type	% of total*
Bacterial	22
Herpes 7	3
Other viral	0
Opportunistic	3
Total %	22

* Total, in which a search was made for this type of infection.

Table 7.2. : Types of infections.

- compromised inflammatory response: bone-marrow depression, corticosteroids (Levine, et al., 1972), impaired neutrophil function (Rosner, et al., 1970; Lehrer and Cline, 1971), inhibition of macrophage function (Cohen, et al., 1974).
- decreased immunoresponse: bone-marrow depression or the R.E.S.-disease itself (Levine, et al., 1972).
- "broken" anatomic barriers which are no longer infection-resistant: invasive diagnostic techniques, catheters (Kass and Scheiderman, 1957), epithelial lesions by radiotherapy (Craig and Farberm, 1953), surgery.

In the present series 22 % of the patients had severe infections; they are presented in Table 7.2. Bacterial infections are most prominent, only a minor rôle exists for herpes virus and the more exotic infections (fungi, protozoa, non-herpes virus). It may be expected in the future that infection and especially by the exotic pathogens will increase further, as supportive measures improve, life expectancy lengthens, and treatment becomes more aggressive. Therefore sophisticated bacteriological surveillance methods and antibiotic treatment will be necessary to get the maximum benefit from lymphoma treatment, without losing the patient to fatal infections.

4. DISCUSSION.

There is little systemic information about side effects in the literature, as only a few studies give a factual account. The study of Rosenberg, et al. (1961) presents a very wide spectrum of side effects, possibly because their series is larger (1,269 patients) and therefore contains unfrequent side effects such as radiation ostitis and liver cirrhosis caused by cytostatic drugs. From their study too however the chief therapy-related problems emerge: bone-marrow depression, corticosteroid effects, skin and mucosal ulcerations.

A few fatal outcomes are mentioned. The incidence of side effects, in the study of Rosenberg, et al., seems to be lower than in the present study; but the survival rate is lower too. The data of Luce, et al. (1971) using combined chemotherapy (cyclophosphamide, vincristine, prednisone) in advanced lymphoma show a very high percentage of undesirable side effects: bone-marrow depression 88 % (severe 9 %, fatal 1 %), neuropathy 48 % (in 13 % requiring complete cessation of therapy), steroid effects 29 %, severe infections 4 % and fatal toxicity in 4 patients out of a total of 262 patients. These authors state that in order to be succesful any chemotherapeutic regime must have an "intrinsic" high percentage of toxicity. The study of Stein, et al. (1974) based on cyclical courses with cyclophosphamide, vincristine, procarbazine and prednisone describes toxic effects in all (!) patients.

VIII. FACTORS INFLUENCING PROGNOSIS.

1. INTRODUCTION.

Survival is the fact of most interest to both patient and physician. By carefully altering certain treatment modalities, and studying their effect on survival results the physician may improve his treatment methods. The ideal for a survival study is a very large number of patients, all entering the study simultaneously. The study is concluded when all patients have died. Then a real survival curve can be made, after subtracting those patients who did not die of the disease under study. In practice this ideal cannot be attained.

In this type of study it is impossible to gather complete data on all patients, because they enter the study at different times; there is considerable variation in duration of follow-up; the number of entries per year varies; and it is also possible that in some patients the disease has not run its full course at the conclusion of the study

For this reason three of five-year survival rates are often used; sometimes they are even presented as "cure rate". The term cure rate is better avoided, because many patients die of the disease later. A better method to make the maximal use (Cutler and Eberer, 1958) of all available data is the employment of actuarial life-table methods. The survival in life-table methods is given as an estimate of the survival chance. It is expressed as survival percentage per year, or as the percentage of the total number of patients, who survive a specified number of years after the initial diagnosis or treatment.

2. STATISTICAL METHODS.

In this study the actuarial life-table method of Kaplan and Meier (1958) was used to analyze the decrease in the number of patients during the time of study. Kaplan's method considers the number of patients, who enter an observation period (in this study one whole year), and compares this with the number of survivors at the end of that period. The survival chance for a period is defined as the quotient of the number of surviving/entering patients in that particular period. The chance of survival for a specified number of years is the cumulative product of all separate survival chances of the previous years. Any patient, who leaves the study during a certain observation period for reasons not related to the disease, is not entered in the computations for that period. With this method patients are studied as long as their follow-up permits; when their follow-up ends, it is not automatically assumed that they have died of the disease, as is done in simple survival curves. The number of patients under consideration decreases more quickly, as the survival becomes longer. Therefore the standard error in the "last" survival years increases, and it is hazardous to interpret survival percentages computed from groups which contain less than five or even ten patients. All survival tables in this chapter indicate when the remaining number of patients becomes too low. The survival line is solid as long as the total number of patients exceeds ten; it is broken when the number of patients lies between ten and five.

3. SEPARATE SURVIVAL FACTORS.

3.1. Introduction.

Much has been written about the influence on survival of cell type, structure, stage, sex, constitutional symptoms, age, bone-marrow invasion, extranodal start, presence of macrophages, and of course the type of treatment. Most authors have constructed for all these factors a regression coëfficient against survival, i.e. a measure of prognostic value, has been constructed, expressed as a three or five year survival rate or more recently as an actuarial survival chance percentage. Instead of using multiple regression analysis of survival factors it is also possible as done by Jones, et al. (1973) to compare the survival characteristics of multi-dimensional categories, e.g. cell type x structure x stage x presence of constitutional symptoms. A disadvantage of this method is the intense fragmentation of the case material, which may result in groups, which are to small for statistical evaluation. Also these subgroups, which are compared in their survival rates, may differ widely in other characteristics, and comparison of their survival rates can produce erroneous results. Categorisations of this kind will not be made in this study but the influence of all factors together is considered in a multiple regression analysis.

In this chapter the prognostic value of the above factors will be considered to select the most important for a multiple regression analysis in the next chapter.

3.2. Clinical stage.

The influence of the clinical stage according to Ann Arbor on survival is depicted in Fig. 8.1. It is evident that the prognosis worsens as the clinical stage rises. This is in agreement with the results of Peckham (1974), Jones, et al. (1974), Lee, et al. (1973) and Fayos, et al. (1974).

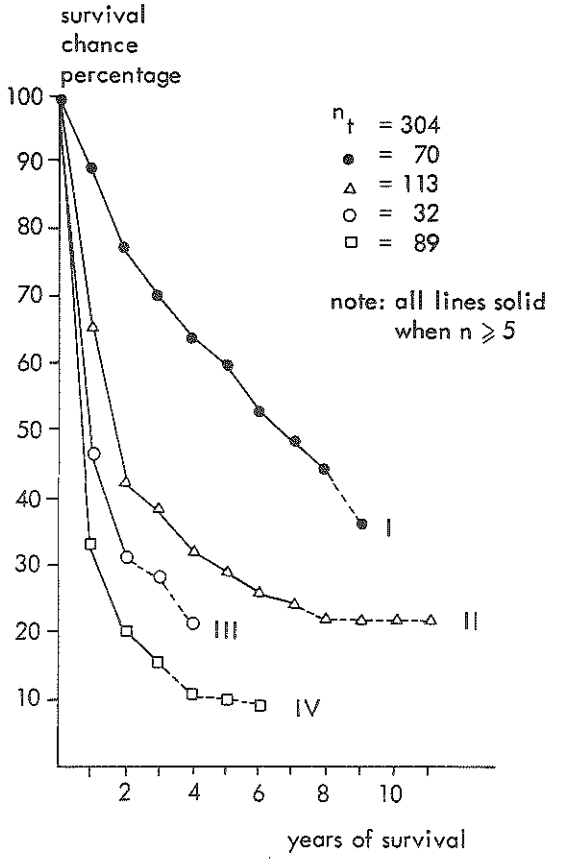


Fig. 8.1. : Clinical stage and survival.

3.3. Cell type.

Fig. 8.2. The smaller lymphocytic type (L.C.S.) has the best prognosis, the smaller histiocytic type (H.C.S.) the worst. The larger variants of both cell types (L.B.S., H.B.S.) show about the same survival. Similar conclusions are reached by Rappaport (1956) for follicular cases only, Jones, et al. (1973), Monfardini, et al. (1973), and Patchefsky, et al. (1974).

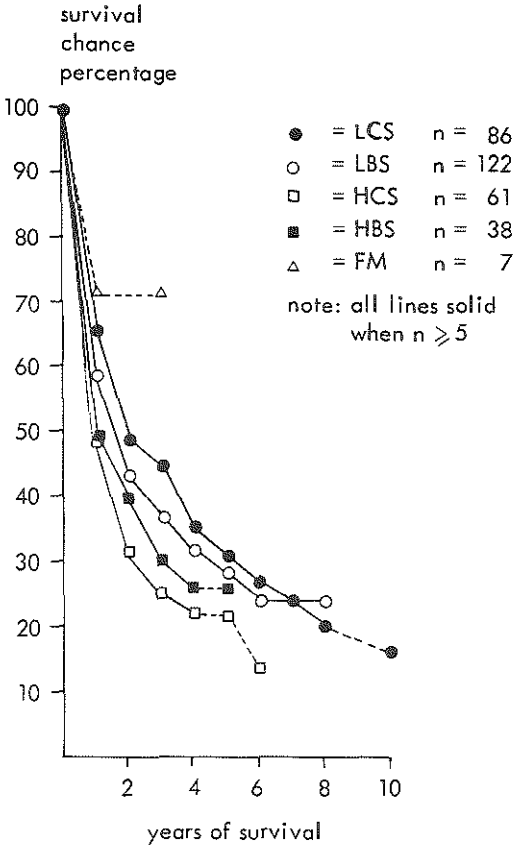


Fig. 8.2. : Cell type and survival.

3.4. Structure.

Fig. 8.3. The follicular type has a better prognosis than the diffuse type. This observation has repeatedly been made since the original publication by Rappaport, et al. (1956). Patchefsky, et al. (1974) even subdivide the follicular type and note an improved survival rate as the degree of nodularity increases.

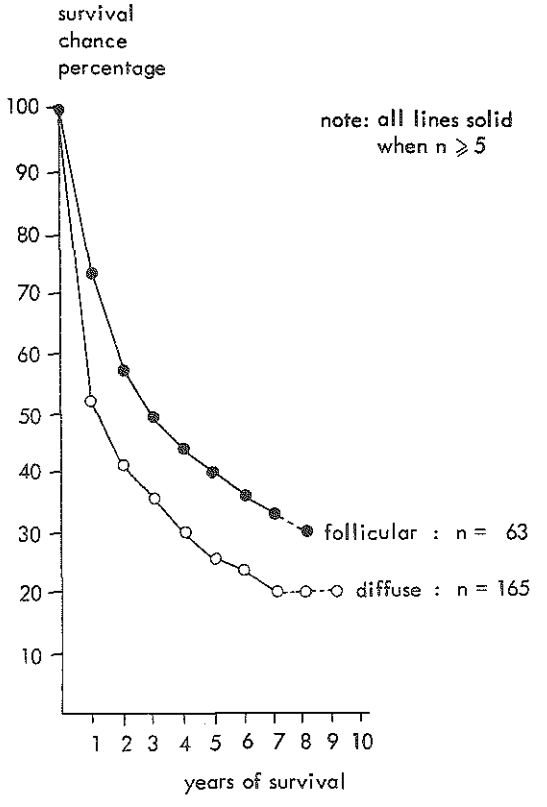


Fig. 8.3. : Structure and survival.

3.5. The presence of macrophages.

Fig. 8.4. Because macrophages were seen in only 12 %, no finer subdivision was made on the basis of the number of macrophages. There is a negative correlation between presence of macrophages and survival. The same was found by Diamandopoulos and Smith (1964) and Van Unnik (1973). The reason for the presence of macrophages and their function is not clear. According to Diamandopoulos they are reactive cells, which reflect the immaturity of the lymphoma cells. However in the newer light of the newer facets about different types of histiocytic malignant lymphomas (Lancet, 1974), the entire problem may need reconsideration.

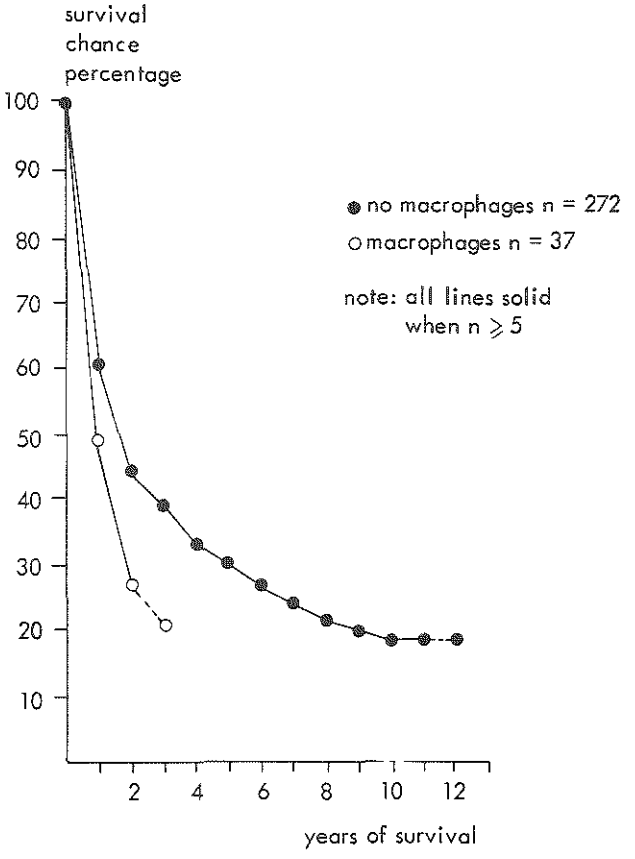


Fig. 8.4. : Macrophages and survival.

3.6. Bone-marrow invasion.

Fig. 8.5. There is no clear effect of bone-marrow invasion on survival: initially the positives do better than the negatives, but do worse in the ultimate survival. Although there are some data about the frequency and significance of bone-marrow involvement (Jones, et al., 1972; Jones, et al., 1973), only Bloomfield, et al. (1974) give exact information on its prognostic influence. In their study the bone-marrow invasion appears to be a separate negative prognostic factor in patients with stage IV. In the present study there does not seem to be much difference in survival figures in stage IV, whether the bone-marrow is positive or not. However, the total numbers are too small to justify a strong opinion, they only permit an impression.

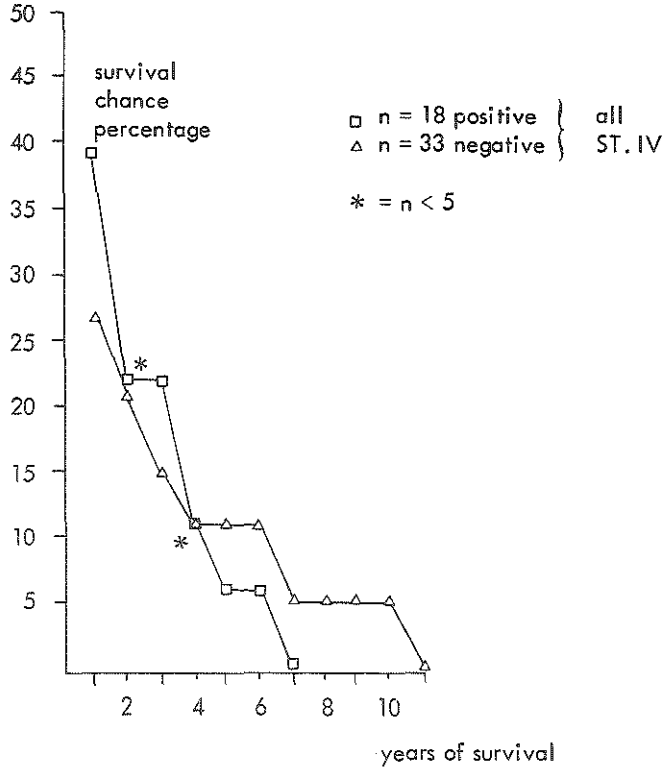


Fig. 8.5. : Bone-marrow invasion and survival.

3.7. Constitutional symptoms.

Fig. 8.6. There is a strong negative correlation between survival and the presence of B-symptoms. In Hodgkin's disease the unfavorable prognostic effect of B-symptoms is well known (Tubiana, et al., 1971; Kaplan, 1972), but in the case of the other malignant lymphomas some divergence of opinion exists. Jones, et al. (1973) state that there is no significant influence but Bloomfield, et al. (1974) and Patchefsky, et al. (1974) note a strong correlation independent of the clinical stage.

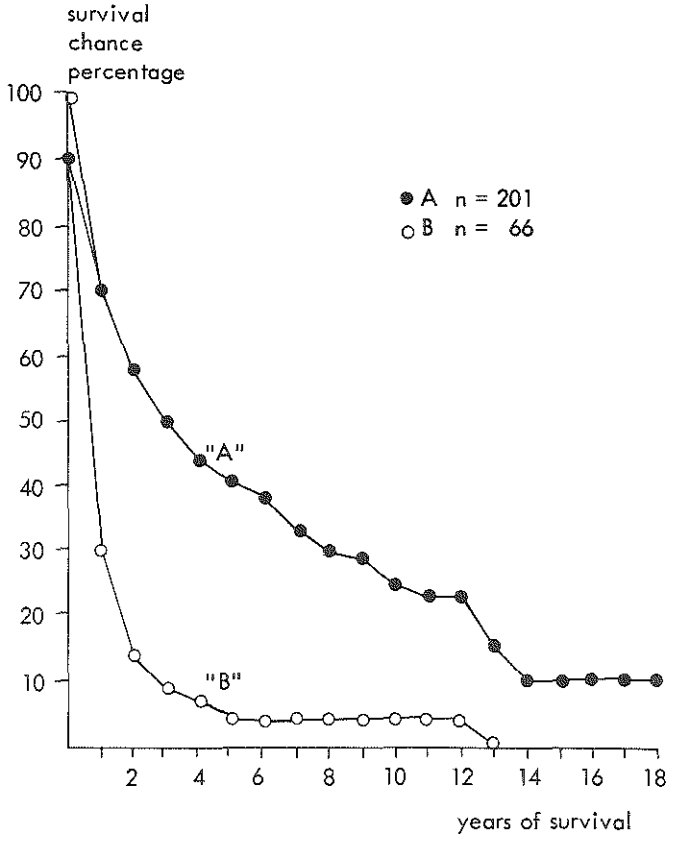


Fig. 8.6. : Constitutional symptoms and survival.

Because of Jones' remark that B-symptoms probably have a bad prognostic influence because of their well known association with higher clinical stages, the effect within each clinical stage was computed. It appeared that within each stage the unfavorable influence of B-symptoms was present. The same applies within each cytological class. These data are presented in Appendix J.

3.8. Sex.

Fig. 8.7. The women appear to do slightly better. The same trend is seen by Lee, et al. (1973), Rosenberg, et al. (1961), Molander and Pack (1963), Hansen (1969), and Patchefsky, et al. (1974); however, in many other studies no difference has been noted.

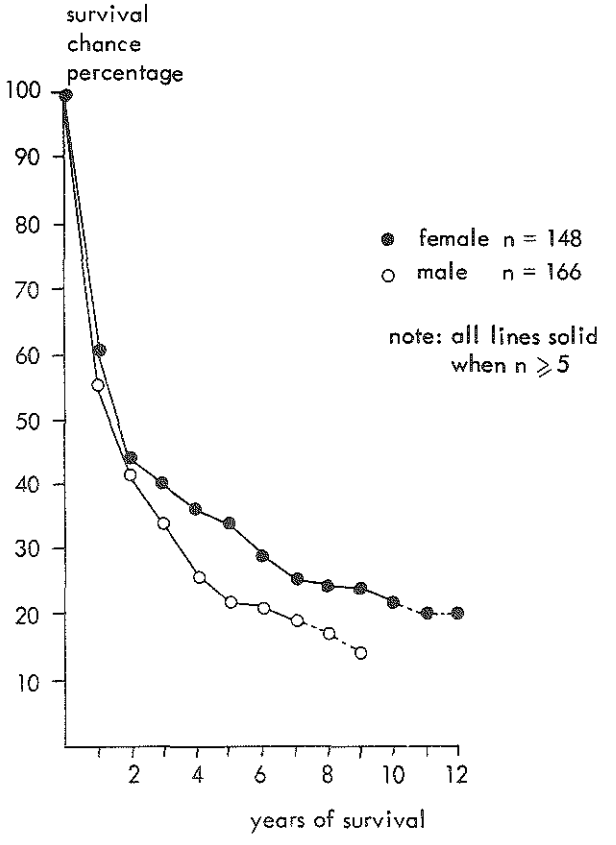


Fig. 8.7. : Sex and survival.

3.9. Age.

Fig. 8.8. There is no important difference between the different age groups, except for the seventh decade. Only the part of the curves on the left-hand side of the asterisks should be considered. Perhaps the seventh decade-group shows a shorter survival because of the intrinsically much shortened life span of this age group as compared to the younger ones: death by other reasons occurs significantly more often. This is in close agreement with the authors mentioned in section 3.7 of this chapter and also with Jones, et al. (1973), and Bloomfield (1974). In fact nowhere in the literature is the suggestion offered, that age significantly affects the survival.

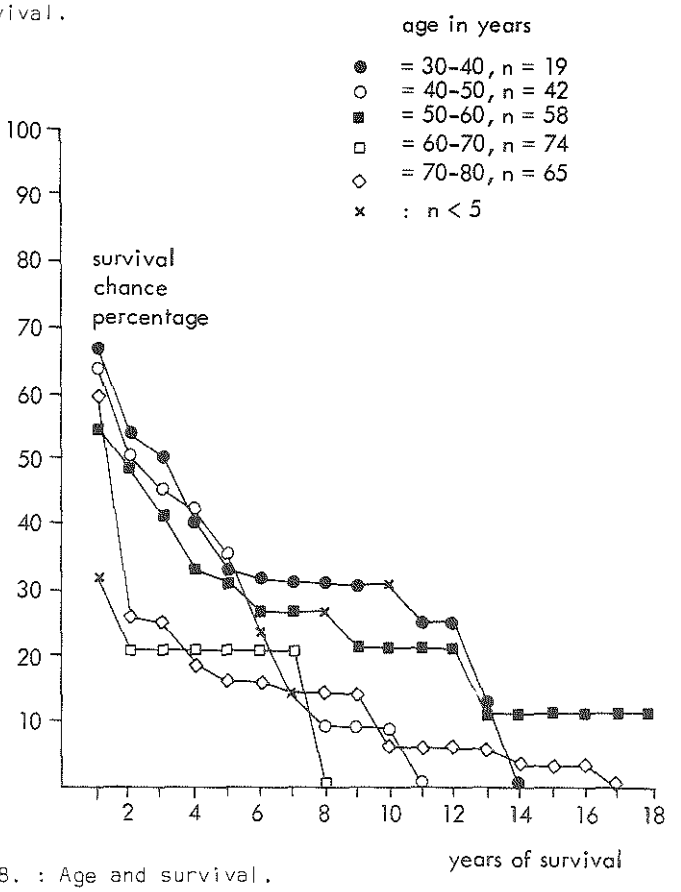


Fig. 8.8. : Age and survival.

3.10. Extranodal or nodal primary site.

Fig. 8.9. The primary site here is only nodal or extranodal without regional lymph nodes. No difference emerges between nodal and extranodal in their influence on survival.

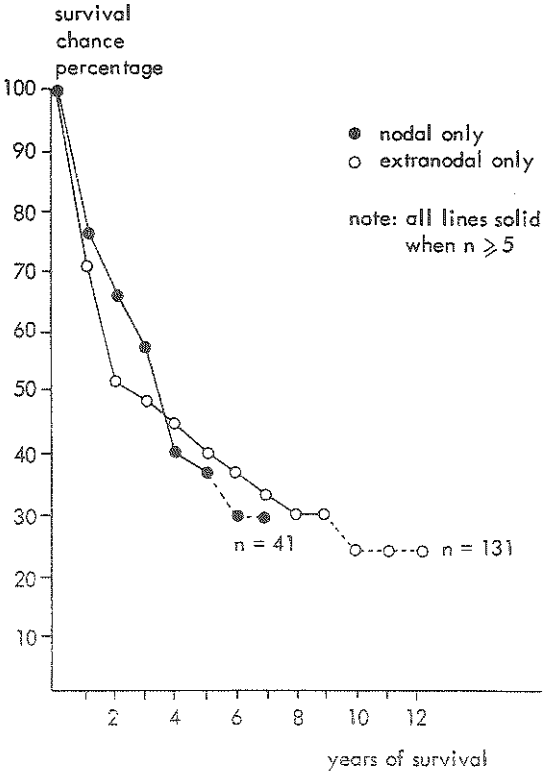


Fig. 8.9. : Nodal or extranodal primary site and survival.

4. PROGNOSTIC IMPORTANCE OF EACH SEPARATE FACTOR.

The prognostic importance of each separate factor, expressed as the simple regression coëfficient, can be calculated by standard computer programs (e.g. I.B.M.-SSP). However the dependent variable, survival, cannot be entered as a chance percentage, but has to be in real years or months. Therefore Kaplan's method cannot be applied to these calculations. It would produce an unrealistic worsening of the survival data. Now every patient, in whom the disease cannot yet have run its full course, will be presumed to have died of the disease at the moment that the follow-up ends. This phenomenon will notably affect the survival data of those patients having entered the study in the last few years. In the last two years 76 patients entered the study (last year 33). The minimal follow-up to closing date is two years and seven months (chapter 2). Another unfavorable factor is death from other causes. This has not been eliminated beforehand, because the major cause of death is the malignant lymphoma itself. For comparison purposes however, the computer program can be modified to disregard those who died of other causes. This results in two survival curves: total survival and a second survival curve, composed only of those, who did not die of other causes (Fig. 8.10). The correlation coefficients are calculated on the basis of survival data in months instead of years. This is done, because conversion from months to years, which is normally done by dividing the number of years by twelve and disregarding the fractions, will shorten the survival. The single correlations make it possible to select the most significant prognostic factors for a multiple regression analysis. They also show the relative importance of each factor. These correlations are shown in descending order in Table 8.11.

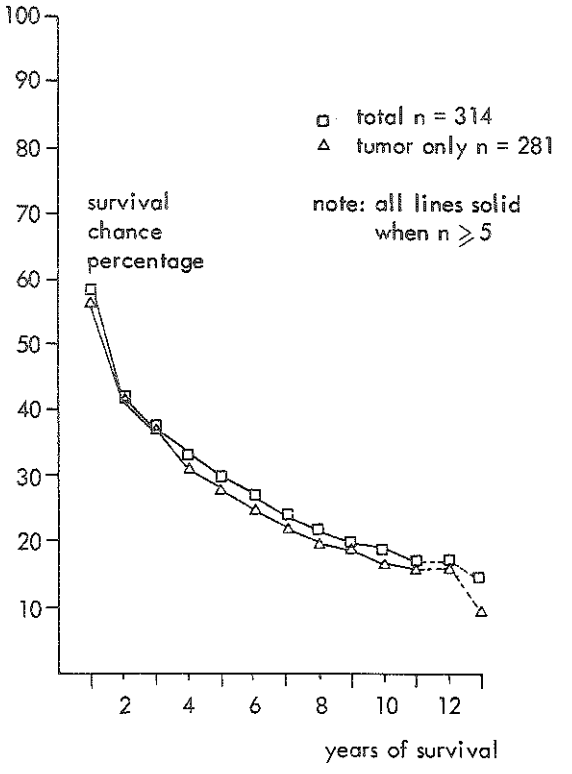


Fig. 8.10. : Total survival and tumor survival.

Prognostic Factor	single correlation coeffioient
Stage	0.34
Const.symptoms	0.31
Cell-type	0.15
Structure	0.14
Age	0.11
Macrophages	0.11
Sex	0.09
Bone-marrow	0.08
Nodal/extranodal	0.04

Table 8.11. : Prognostic importance of each separate factor.

IX. MULTIPLE REGRESSION ANALYSIS OF PROGNOSTIC FACTORS.

1. INTRODUCTION.

Although there are many reports on prognostic factors and the effect of different methods of treatment on survival, little is known about the effect of all these factors together. In fact it is only mentioned in the study of Bloomfield, et al. (1974). When all factors are considered simultaneously, it is possible that some factors will cancel out the effect of others, which in single correlation analysis seemed to be important. For instance it may be possible that constitutional symptoms occur more often in a certain cell type, and therefore the influence on survival of this independent variable will diminish the importance of the cell type and vice versa. The importance of the type of treatment per se will probably be small. This is caused by the fact, that the type of treatment is chosen according to the progression of the disease. However, the progression is already expressed in the other prognostic indices.

As conventional life-table analysis of all prognostic factors separately can give a distorted view because these factors are often inter-dependent, it is useful to perform a multi-variate analysis, which considers the effect of all these prognostic factors together (Snedecor and Cochran, 1972). This can be achieved by multiple linear regression methods as used by standard computing programs; I.B.M.-S.S.P. was used in this study. A problem is created by the fact that these programs do not differentiate between death caused by the disease and "considered to be dead" for lack of follow-up; this will artificially depress the survival rate.

Multiple linear regression computer programs will first compute all single correlation coefficients, which in this study are the prognostic factors.

Subsequently the most important one will be singled out, and the relative prognostic effect of the second most important one will be calculated in view of the known effect of the first. This continues until all possible factors have been reviewed. Factors, which are taken into account later, will add very little prognostic information, because they are already relatively unimportant in single correlation analysis. This makes it possible to give nearly as good a prognostic indication with the first few prognostic factors. Various combinations of risk factors have to be tried in order to find the most useful prediction (Dunn and Clark, 1974). This was done in accordance with the method of Daniel and Wood (1971).

2. "PROGNOSTIC" EFFECT OF THE TYPE OF TREATMENT.

Although the type of treatment is dependent on some other prognostic factors, an attempt has been made to evaluate treatment as an independent prognostic factor. For the effect of treatment a scale was constructed from the data on the effect of the first single treatment. Some data on combined treatments had to be approximated. The total effect (Table 9.1) is therefore somewhat unsatisfactory, but may be the best possible one can achieve. The single correlation coefficient, or the prognostic effect of the treatment type is 0.07. This places the type of treatment nearly at the bottom of the list of prognostic factors (see Table 8.11).

3. RESULTS OF MULTIPLE REGRESSION ANALYSIS.

Multiple regression analysis identifies clinical stage, constitutional symptoms and cell type as the most important prognostic factors: Table 9.2.

100	Surgery *
90	Megavoltage + prophylactic fields
70	Megavoltage
55	Orthovoltage
40	Surgery + mega + prophylaxis
40	Surgery + megavoltage
35	Surgery + orthovoltage
25	Chemotherapy
15	Chemo + surgery
15	Chemo + irrad, any type
15	Chemo + irrad, anytype + surgery
0	No treatment

* Note: These 13 cases treated by surgery alone are very selected as they cousist of small localized tumors.

Table 9.1. : "Prognostic effect" of treatment.

Prognostic Factor	Multiple regression coefficient
Stage	0.28
Constitutional symptoms	0.18
Cell type	0.14
Macrophages	0.09
Nodal/Extranodal	0.08
Treatment	0.07
Age	0.05
Structure	0.05
Sex	0.02
Bone-marrow	0.02

Table 9.2. : Multiple regression analysis of all prognostic factors.

They alone produce 93 % of the possible prediction. Addition of "presence of macrophages" gives some improvement, as the total prediction force now rises to 96 %. Age, sex, extranodal involvement, bone-marrow invasion and structure do not influence prognosis significantly. These findings indicate a downward shift in importance of structure and a rise of the presence of macrophages, when compared to the single correlation coefficient results as shown in the last chapter. Therefore the major part of the prognostic message of the structure is probably contained in the three most important parameters. In the study of Bloomfield, et al. (1974) bone-marrow positivity appears to be very important; this is not so in the present study. The total multiple correlation or the prediction value, which can be obtained by combining histology, clinical symptoms and bone-marrow as, indicated by Bloomfield, is in this study 83 %, which is considerably lower than the one in which bone-marrow is replaced by clinical stage: 93 %. This discrepancy can have several reasons: different patient population, too short follow-up in Bloomfield's study, insufficient bone-marrow sampling in the present study. The importance of macrophages has not been noted before, probably because not much attention has been focused on this phenomenon. Only Diamandopoulos and Smith (1964) have studied their effect in depth; they considered their presence an unfavorable sign.

X. PATTERNS OF SPREAD.

1. METHODS OF SPREAD.

How non-Hodgkin's lymphomas spread has long been considered as unpredictable (Scheer, 1968; Han and Stutz, 1967; Banfi, et al., 1968), and resulted in some therapeutic nihilism (Newall, et al., 1968). However the finding of Rosenberg and Kaplan (1966) that Hodgkin's disease is potentially curable, since it begins as an unicentric focus and disseminates in an orderly progression via the lymphatic channels, has caused a review of the mechanism of spread in the other lymphomas. Patterns of spread can be studied in two ways:

a. the first method maps all initially involved sites and notes whether they are contiguous. Contiguous lymph node regions are listed in Table 10.1. This method requires a routine laparotomy, because quite a few lymph nodes may be positive (Veronesi, et al., 1974), which seemed negative on the basis of lymphography or which are otherwise undetectable (e.g. mesenteric nodes). Veronesi's study (1974) shows contiguity of lymphatic involvement in 73 %. Moran (1973) who also uses staging laparotomy finds contiguous spread too (notably in lymphosarcoma). The same conclusion is reached by Goffinet, et al. (1973).

b. The second method starts with the localized involvement only (i.e. stage I) and notes where the next manifestation of the disease occurs. All recent studies which start from a single point, show contiguous spread via the lymphatic channels (Peters, et al., 1968; Al-Saleem, et al., 1970; Rosenberg and Kaplan, 1968; Lipton and Burton, 1971; Jones, et al., 1973) in about 70 %; distant spread occurs in 30 %.

In the present series the pattern of spread of all unifocal primary sites was studied. Table 10.2 summarizes the results. It appears that the supradiaphragmatic lymph nodes (except the mediastinum) show contiguous spread, which means either the next lymph node or an adjacent organ, in 64 % (80 % *). The diaphragm is passed in 36 %; 69 % (78 % *) of the spread involves lymph nodes. No evaluation was done on the very few stage I infradiaphragmatic nodal presentations.

The localized organ involvements (stage I without regional lymph nodes) show a different behavior. Only 28 % (43 %) show regional spread; 50 % pass the diaphragm, 64 % of the spread is to a lymph node. The results of this study also show a very clear tendency towards contiguous spread in the case of primary nodal involvement. The behavior of the primary organ localizations is more erratic and therefore unpredictable. This last fact may be a real function of primary organ involvements, or it may be caused by either insufficient staging in the present study or the bias which a few abnormal cases may introduce in such a small total number of cases. However the findings presented here are one more argument for irradiation therapy, which includes the adjacent lymphatic region.

2. MEDIASTINAL SKIPPING.

Although a malignant lymphoma spreads via the lymphatic channels to the next lymph node, one exception occurs to be present: the skipping of the mediastinum. In fact (see below) the mediastinum of often passed silently when a stage I becomes a stage III. However, this is not a real exception, because para-aortic lymph nodes are connected directly to the nodes of the left side of the neck (Rouvière, 1932).

* Note : the number in parentheses includes local recurrence.

Thus spread from neck lymph nodes to para-aortic nodes may or may not involve the mediastinum and still be contiguous. This has an important therapeutic consequence. If the mediastinum is skipped very often during spread, it is not useful to include it in routine prophylactic regional irradiation and thus not to impair the hematopoietic activities of a considerable part of the bone-marrow, but better to remain watchful and perform regular tomographic controls of this "region at risk" (Van der Werf-Messing, 1968). In the completely staged cases of Veronesi, et al. (1974) mediastinal skipping occurred in 97 %. The study of Jones, et al. (1973) shows 72 %, that of Van der Werf-Messing (1969), shows 94 %, and that of Han and Stutzman (1967) shows 100 % mediastinal skipping.

To study the frequency of this skipping phenomenon mediastinal tumor involvement as seen on X-rays was investigated in the following (only nodal) cases:

1. first presentation stage III.
2. first relapse corresponding to stage III, but at first presentation stage I or II without mediastinal involvement.
3. second relapse corresponding to stage III, but at first relapse corresponding to stage I or II without mediastinal involvement.

The results are given in Table 10.3. Mediastinal skipping occurs in 71 %. The lymphocytic types have a higher tendency to involve the mediastinum when passing to the other side of the diaphragm: 33 % versus 16 % for the histiocytic types. There is no difference between diffuse and follicular structured types. This study too shows a very clear tendency to mediastinal skipping, especially in the histiocytic types. Probably the percentage of mediastinal skipping would have been even higher, if more drastic staging procedures had been used in each case. However, even these data urge restraint when considering mediastinal irradiation as a prophylactic regional treatment.

Primary site	Secondary involvement
Cervical or supraclavicular	- Supraclavicular - Ipsil ateral axillary - Mediastinal - Contralate ral neck, supraclavi cular
Mediastinal	- Cervical - Supraclavicular - Para aortic - Axillary
Axillary	- Ipsilateral cervical, supraclavicular - Mediastinal
Inguinal	- Ipsilateral iliac, femoral - Para aortic
Para aortic	- Mediastinal - Iliac - Left cervical

Table 10.1. : Contiguous lymph nodes (after Molander and Lacayo, 1970).

	Supradiaphragmatic nodes, except mediastinum		Organs	
Contiguous	64 %	* 80 %	28 %	* 43 %
To any lymphnode	69 %	* 78 %	64 %	
Via diaphragm	36 %		50 %	
Total number	44			

*Note: The numbers preceded with an asterik include local recurrence

Table 10.2. : Spread patterns from stage I.

Mediastinal	LCS	HBS	HCS	HBS	FM	Tot	Diff	Foll	Tot
Skipped	11	13	5	0	2	31	12	11	23
Not-skipped	7	5	0	1	0	13	4	4	8
Total	18	18	5	1	2	44	16	15	31

Table 10.3. : Occurrence of mediastinal skipping.

XI. LEUKEMIC DEVELOPMENT, SOME LOCALIZED ORGAN INVOLVEMENTS.

1. INTRODUCTION TO LEUKEMIC DEVELOPMENT.

The occurrence of a leukemic phase in lymphosarcoma is well known (Molander and Pack, 1963) and relatively frequent (Rosenberg, et al., 1961; Ibbot and Whitelaw, 1966); in reticulum cell sarcoma this is rarer (Loewenbaum, et al., 1971) and here the cytological type of the circulating cell is different (Schnitzer and Kass, 1973) from that of lymphocytic malignant lymphoma.

The lymphosarcoma cell leukemia (L.S.C.L.) has now gained acceptance as a separate entity to chronic lymphatic leukemia, and is probably a dissemination into the peripheral blood of malignant lymphocytic lymphoma cells (Schwartz, et al., 1965). The differentiation is made on the basis of the total number, and in particular the cytological aspects (Dick, et al., 1974) of the circulating lymphocytes, as there is little significant difference in clinical presentation (Zacharski and Linman, 1969). The invasion of the bone-marrow is not decisive for the diagnosis (Dick, et al., 1974; Ryrolin, et al., 1974). The pathological peripheral lymphocytes consistently display atypical features which distinguish them from normal lymphocytes: there is considerable cytological pleomorphism, and often nuclear clefting and folding. Hyperchromatic nuclei, a large cell-diameter, the presence of one and rarely two or more nucleoli are seen. Leukemic development is most often described in diffuse lymphoma (Schnitzer and Kass, 1973; Stenfert Kroese, et al., 1973). The prognosis of those L.S.C.L. arisen from follicular lymphomas appears to be better than those arising from diffuse lymphomas although the original lymphomas very often convert to a diffuse type finally (Schnitzer and Kass, 1973). However the survival from the onset of leukemia is very short, varying from 9 months in the diffuse lymphoma to 18 months in the follicular lymphoma.

Leukemic development occurs more often in children (Schey, et al., 1973) than in adults.

Occurrence of leukemic development in reticulum cell sarcoma is rarer - although Mathé, et al. (1970) disagree at this point. The peripheral leukemic cells may remain a more primitive histiocytic cell or closely resemble the monocyte as seen in Schilling's leukemia (Butler, 1970). Once the leukemic phase has begun the prognosis is measured in a very few months (Zeffren and Ultmann, 1960; Loewenbraun, et al., 1971; Schnitzer and Kass, 1973). There are also some case reports (Gunz, et al., 1973; Pal, et al., 1973) of malignant lymphoma with later (therapy induced?) myeloid leukemia.

2. LEUKEMIA DEVELOPMENT IN THE PRESENT STUDY.

In the present study leukemic development was also present in a number of cases. To be considered as such, in the differential count of the peripheral (May-Grünwald-Giemsa stained) blood film, at least 25 % of the cells had to be pathological. At first presentation 2.5 % of the patients were in the leukemic phase, at first relapse 4.2 %, and at the second relapse 2 %. The overall percentage is 5.5 - only one of these cases being coexistent with a reticulum cell sarcoma: Table 11.1. The structure of the original lymphoma was diffuse in twelve out of fourteen cases of L.C.S.L., in which the structure is known for certain; i.e. 89 %. The age distribution is given in Fig. 11.2. Leukemic development, when not present at the first presentation, always occurred within one year; the mean appearance time for those derived from diffuse lymphoma is 3.8 months, for the others it is 4.8 months. This is another confirmation of the diffuse lymphoma. Survival after the diagnosis of the leukemic development (Table 11.3) is very short. One very interesting case of leukemia and lymphoma was present. This patient had a diffuse histioblastosarcoma (Rappaport: "diffuse undifferentiated malignant lymphoma") of the nasopharynx. It was treated by orthovoltage.

	At start	First relapse	Second relapse	Total
Lymphatic lymphoma	7	7	2	16
Histiocytic lymphoma	"1"	0	0	"1"
Total n	314	180	94	-

Table 11.1. : Leukemic development.

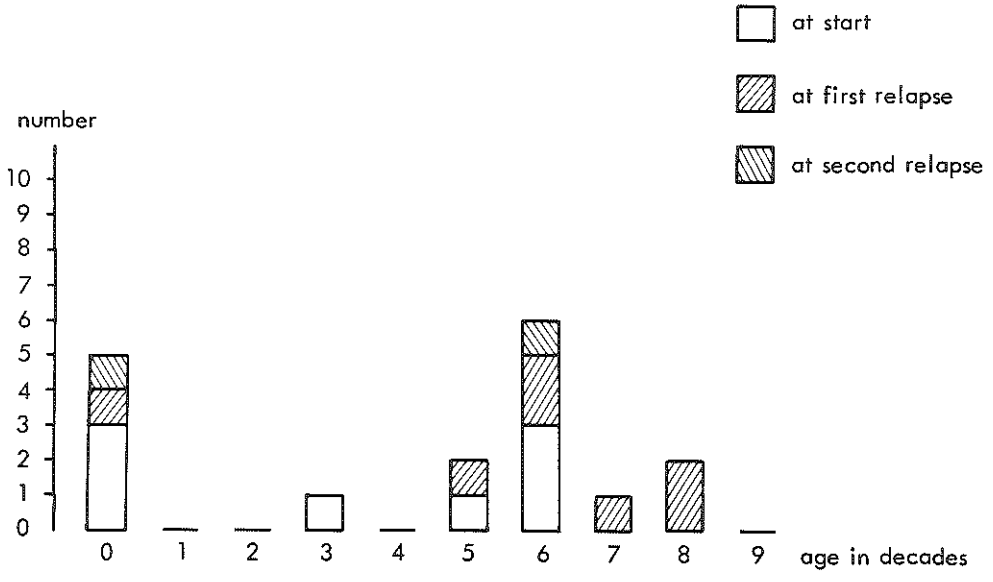


Fig. 11.2. : Age distribution of patients showing leukemic development.

Years :	0	1	2	3	4	5	6
At start n =	7	2	1	1	0		
1st Relapse n =	7*		1	1	1	1	0
2nd Relapse n =	2	0					

* One case, a histioblastosarcoma discussed separately in the text

Table 11.3. : Survival since leukemic development.

At the time of presentation there was also a chronic lymphatic leukemia (152.000 leukocytes with 98 % of small mature lymphocytes). The leukemia had only been treated elsewhere with splenic irradiations. The patient lived for 12½ years after the diagnosis, and died of myocardial infarction at the age of 82 years. Three of his close relatives died of (non-skin) malignancies, so there was probably some genetic (?) predisposition in this family.

In conclusion: the frequency, age distribution, cell type and structure of the original lymphoma, appearance time, and prognosis all closely agree with other studies (Stenfert Kroese, et al., 1973; Schnitzer and Kass, 1973). The occurrence of two different malignant lymphoproliferative diseases is rare, but not unknown (Kim and Dorfman, 1974). There are, however, some case reports (Gunz, et al., 1973; Pal, et al., 1973) of lymphosarcoma coexistent with later (therapy-induced?) myeloid leukemia.

3. SOME LOCALIZED ORGAN INVOLVEMENTS.

It has often been stated that some extranodal primary sites, whether accompanied by regional lymph nodes or not, have a better prognosis than others with a comparable stage. This would appear to be especially so in the case of gastrointestinal lymphomas (Sherrick, et al., 1965; Peters, et al., 1968). To evaluate these statements a comparison was made between the prognosis of some primary extranodal lymphomas (stage I or II), which are especially mentioned in these reports, and the rest of stage I or II.

4. UPPER RESPIRATORY TRACT, EXCEPT WALDEYER'S RING.

Involvement in stage I or II is 8 % (13 patients: 2 L.C.S., 4 L.B.S., 4 H.C.S. and 3 H.B.S.). The survival rate seems worse than average for these stages. However this can only be an impression, as the total number is small.

There are a few studies which give comprehensive survival curves for involvement of the upper respiratory tract (Ennuyer, et al., 1963; Van der Werf-Messing, 1968), but it is not possible to separate those cases with involvement of Waldeyer's ring from the others. Moreover the staging is not comparable.

5. GASTROINTESTINAL TRACT.

5.1. Stomach.

Much has been written about primary lymphoma of the stomach. This tumor is frequent among the primary sarcomas of the stomach. Its symptoms are non-specific, being those of any gastric malignancy (Molander and Pack, 1963; Zwaveling, et al., 1969). A preoperative diagnosis has become possible because of the availability of fiber-endoscope biopsy techniques. In a study carried out at the Mayo Clinic (Stobbe, et al., 1966) localized lymphomas formed 2½ % of all gastric malignancies. Surgical treatment with subsequent results in 5 and 10 year survival percentages of respectively 65 and 50. A study of Zwaveling, et al. (1969) mentions a 5 year survival of approximately 50 % in case of resectable lymphomas. In the present series 11 primary gastric lymphomas occur (3 L.C.S., 7 L.B.S. and 1 H.C.S.), representing 6 % of all stage I or II lymphomas. The diagnosis was never made preoperatively. The 5 year, with the same methods of treatment as Zwaveling, survival in this small series is high: 73 %: Fig. 11.4.

5.2. Small intestine.

Malignant lymphoma of the small intestine also is diagnosed most often during surgery. Foremostly it occurs in the terminal ileum (Wheelock, et al., 1963).

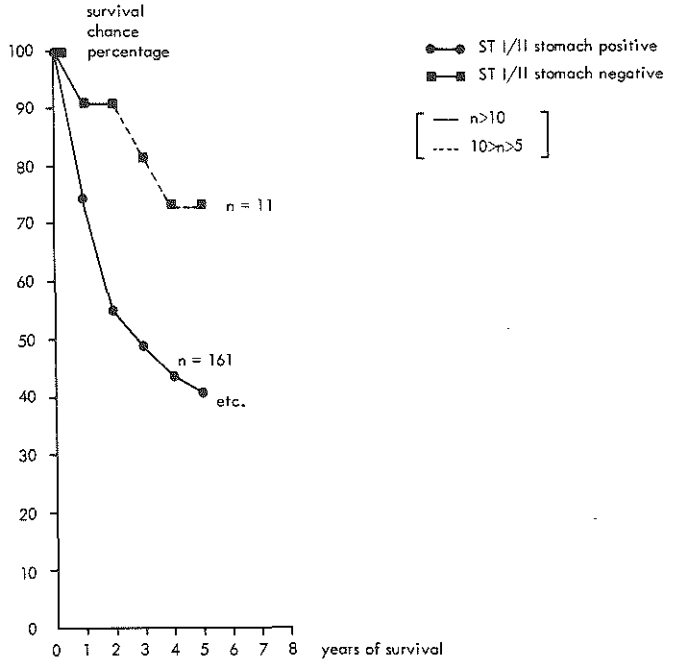


Fig. 11.4. : Survival of localized malignant lymphoma of the stomach.

The symptoms are non-specific; malabsorption (Al-Saleem and Al-Bahrani, 1973; Eidelman, et al., 1966), loss of weight, malaise, secondary anemia or intussusception (Marcuse and Puraly Stout, 1950). Sometimes the barium meal gives a diagnostic clue (Friedell, 1954; Messinger, et al., 1973). Tumor extension is usually longitudinally along the mucosa (Molander and Pack, 1963), and this may give a different picture from that normally seen with an adenocarcinoma. In the latter case obstruction is prominent; dilatation of the lumen, polyposis and thickening of the rugae however, point to malignant lymphoma.

In the present series 4 % (6 patients: 2 L.C.S. and 4 L.B.S.) had localized intestinal involvement. In no case the diagnosis was made before surgery. Treatment by surgery and intensive irradiation has resulted in a better survival percentage than that of the other cases with stage I and II, namely: 67 versus 42 %.

5.3. Colon.

Primary involvement occurs in 5 patients (2 L.C.S. and 3 L.B.S.) representing 3 % of all stage I and II patients. The result of treatment by surgery and subsequent radiotherapy was unimpressive: 3 patients died within one year, all within three years.

5.4. Conclusion on gastrointestinal involvement.

Gastrointestinal primary involvement occurs quite often, stomach and small intestine, being favoured sites. In nearly all cases the exact diagnosis is made after surgery since the symptoms are those of any gastrointestinal malignancy. Except for gastric lymphomas prognosis is comparable with other localized forms (stages I and II together).

XII. SUMMARY AND CONCLUSIONS.

CHAPTER 1 gives a short introduction.

A comparison is made between Hodgkin's disease and the other lymphomas. Some questions are posed to be solved by the techniques which have proved themselves to be so succesful in the case of Hodgkin's disease.

CHAPTER 2 discusses the material and methods.

The 314 patients are from the Rotterdam Radiotherapy Institute. They represent one-third of all patients with a malignant non-Hodgkin's lymphoma in the years 1950 to 1971. The original histology slides of each patient have been reviewed and reclassified according to Rappaport. The clinical and therapeutical data (Appendix B) about the first three attacks have been put on computer punchcards. The clinical staging has been done in accordance with the criteria of the Ann Arbor conference. The closing date of the study was 1st September, 1973; this gives a minimum follow-up of at least two years and seven months. Cross-tables in maximally seven dimensions have been compiled by means of specially designed computer programs (Appendix C) using an I.B.M. 1130 computer.

CHAPTER 3 discusses the histology.

After a short review which gives an outline of the concepts lympho sarcoma and reticulum cell sarcoma, the classification of Rappaport is discussed, who differentiates between two structural possibilities: diffuse and nodular (or follicular). There are two different cell types: lymphocyte and histiocyte, which both may show different degrees of differentiation. This results in four cytological types: well differentiated lymphocytic, poorly differentiated lymphocytic, histiocytic and histioblastic or undifferentiated. There are also cytologically mixed forms.

In the present study Rappaport's cytological view is slightly modified. The equivalents are:

L.C.S. : lymphocytosarcoma = Rappaport's well differentiated lymphocytic lymphoma.

L.B.S. : lymphoblastosarcoma = Rappaport's poorly differentiated lymphocytic lymphoma.

H.C.S. : histiocytosarcoma = Rappaport's histiocytic lymphoma.

H.B.S. : histioblastosarcoma = Rappaport's undifferentiated lymphoma.

Diffuse mixed has been considered as diffuse lymphocytic; follicular mixed as a separate category.

A problem, caused by the retrospective nature of this study, is a probable underrepresentation of the follicular structural variant; this is caused by the fact that the histological review has been done without the special reticulin stains which are sometimes necessary for the decision on the exact structure.

The current views on structure and function of the normal lymph node are discussed. These are on some points in contrast with the ideas of Rappaport. The lymph node contains dendritic macrophages, normal macrophages, T-lymphocytes and B-lymphocyte-derivates. From the B-lymphocyte the larger immunoblasts are formed in the follicle centre after antigenic stimulus. They form via an intermediate stage of "cleaved cell"; later they may develop into plasma cells.

Little remains of the former group of reticulum cell sarcoma: only a small group of phagocytosing histiocytes. The biggest part of the group consists of tumors formed by transforming lymphocytes, dendritic reticulum cells, poorly differentiated fibroblasts and lymph node metastases of anaplastic carcinomas.

These views originate from studies with immunological cell-markers, enzymo cyto hemistry, electron-microscopic and especially from careful light-microscopic observation of all stages of the transforming lymphocyte.

A better and more physiologic classification is still hotly debated. The follicular lymphomas probably originate from B-lymphocytes in the germinal centre, or from their derivates: the cleaved and non-cleaved follicle centre cells. The diffuse lymphomas may arise from B- or T-lymphocytes; there is as yet no common opinion about this. The real reticulum cell sarcomas, originating from the phagocytosing histiocyte, are rare.
The pathogenetic mechanisms also are still partly unclear. Most probable is a combination of viral infection and immuno-genetic predestination. This will start the malignant degeneration, e.g. by blocking further normal development of the lymphocyte or derepression of certain stages of development. Immune mechanisms are very important as can be deducted from the very high frequency of malignant lymphomas in patients who are treated by immuno suppressive drugs.

CHAPTER 4 reviews the histological and clinical data; they are compared with the literature.

The most important presenting complaints are (painless) lymph node enlargement, ENT problems, and abdominal complaints; skin abnormalities are relatively frequent too. In 25 % there are constitutional symptoms.

The tumor localization at presentation is nodal in 85 %, and exclusively nodal in 42 %. Of these lymph nodes the nodes of the neck are the most important; after these in descending order of frequency: axillary, mediastinal, inguinal, splenic and abdominal. In primary extranodal presentations, which are much less frequent, the frequency order is: skin, gastrointestinal, respiratory tract, bone-marrow.

The localizations in stage I are discussed separately because it is impossible to determine the origin of the lymphoma in an overall review of all presenting sites. The localizations in stage I do give, per definition, the primary origin of the tumor. In stage I the lymph nodes also predominate - especially those of the neck; also there is the same frequency order of organ localizations.

The distribution of the clinical stages shows an unexplained dip in stage III.

The histology is divided into cell type and structure. Men and women are evenly distributed over the cell types; but in the diffusely structured category men predominate. The frequency of cell types is: W.D.Ly.Ly. (L.C.S.) 27 %, P.D.Ly.Ly. (L.B.S.) 39 %, H.Ly. (H.C.S.) 19 %, U.Ly. (H.B.S.) 12 %, follicular mixed (F.M.) 2 %. The W.D.Ly.Ly. has a follicular structure in 40 %, the others have a predominantly diffuse structure (83-93 %).

Macrophages are present in 10 % of all cases.

Five per cent of all patients develop a second neoplasm after the diagnosis of the malignant lymphoma; it occurs especially in patients with lymphocytic lymphomas. Half of these second neoplasms are localized in the skin. It is unclear whether malignant lymphoma favors a higher incidence of other tumors. Bone-marrow aspiration has been carried out in 38 %; the result of these aspirations was positive in 21 %. Diffuse lymphomas show a higher incidence of bone-marrow infiltration. According to the current opinion both the intensitivity and the method of sampling could be improved.

There is no difference between the sexes regarding the frequency of malignant lymphoma. The age distribution of both sexes shows a predominance of the later decades; however the average age of women is somewhat higher (55 versus 52 years).

CHAPTER 5 discusses the relation between cell type, structure, primary localization, constitutional symptoms and age.

The follicular structure is infrequent (approximately 10 %) except for W.D.Ly.Ly. or L.C.S. (40 %). In each stage the percentage of follicular lymphomas is nearly the same. This implicates that the follicular lymphoma is just as aggressive as the diffuse type, because otherwise the diffuse type would have predominated in the higher stages. The low frequency of stage III is interesting; it occurs with all cell types and is independent of the structure. It seems that all lymphomas skip this stage and disseminate quickly - probably hematogenously. This is clearly different from Hodgkin's disease.

Although the average age at presentation is the same for all cell types, the histiocytic types seldom occur below the age of 20. The age distribution curve resembles those of most solid tumors, and does not have the bimodal form of Hodgkin's disease. Within each age group the distribution of clinical stages is nearly the same.

No cell type shows a higher tendency for extranodal primary origin than the others; the frequency for all is approximately 13 %.

Constitutional symptoms increase with the clinical stage. The percentage is the same within each cell type. Therefore the patients with constitutional symptoms are concentrated in the higher stages in each cell type.

CHAPTER 6 discusses the treatment forms and results.

Locoregional lymphomas, stage I and II with or without constitutional symptoms, have been irradiated; sometimes surgery has been employed too. More disseminated lymphomas have been treated by chemotherapy; sometimes localized radiotherapy or surgery has been used as well.

In the earlier years radiotherapy has predominantly consisted of orthovoltage; later megavoltage has been used. In some megavoltage irradiations the surrounding areas or contiguous lymph node stations have been irradiated electively. Surgery has been used in 10 % of all treatments but mostly for palliation; curative surgery without any other treatment has been used in only 3½ %. Chemotherapy was mainly given as a single agent: corticosteroids, alkylating agents, procarbazine, vinca-alkaloids.

Death by tumor occurs in 66 % of all patients - minimal follow-up almost 3 years. The 3 and 5 year survival are 37 and 25 % respectively. The frequency of complete remission is highest after the first treatment, which has to be planned with maximum curability potential.

The frequency of complete remission rises with the increase in intensity of the radiotherapy, expressed in dosage and radiation field: orthovoltage 50 %, megavoltage 65 %, megavoltage with prophylactic irradiation 74 %. It should be noted that the orthovoltage-irradiation has been given in the earlier years, when clinical staging was not as sophisticated as nowadays.

Surgery has been employed as single treatment in some very selected cases; such as excision of a small localized tumor. In this case the success rate is high: 83 % complete remissions.

Chemotherapy has a success rate of only 18 % complete remissions.

A complete remission is obtained in 50 to 60 % by the first treatment in all cell types; the upper limit is given by P.D.Ly.Ly. (L.B.S.) and U.Ly. (H.B.S.). The duration of the complete remission however is clearly shorter in the histiocytic cell types and the diffusely structured ones. Therefore the quality of the first complete remission (expressed as the product of frequency and duration) is poorest in the case of diffuse histiocytic lymphomas. There is no clear relation between the duration of the first and the second complete remission.

Local recurrences arise more often and faster in the case of histiocytic lymphomas. Although the local recurrence occurs more rapidly in the diffuse structures, the ultimate number is the same as in the follicular structures. The relation between local recurrence and irradiation data has not been studied.

CHAPTER 7 discusses the detrimential side effects of the treatment, and the infections.

Serious side effects of treatment are almost unavoidable because the treatment has to be at least as aggressive as the tumor. In the present study 41 % of the patients have shown serious side effects. Most frequent are bone-marrow depression, ulceration, neuritis and corticosteroid effects. Neuritis has occurred in all patients, using vinca-alkaloids. Corticosteroid effects have occurred in 40 % of its users, and haemorrhagic cystitis in 33 % of the cyclophosphamide users.

In 12 patients, i.e. 4 % of the total number, the treatment has markedly shortened the life-span.

Infections occur very easily in this type of patient; there are many causes for this: lowered immunity and inflammation defence, abnormal body flora, broken anatomic barriers. Twenty-two per cent of all patients have had an infection, most often a bacterial infection; herpes zoster and more exotic infections are unimportant. This may be caused by the fact that during the present study the diagnosis of these last two was still rather difficult.

CHAPTER 8 discusses the relative importance of prognostic factors.

Survival is expressed as survival chance per year in accordance with the method of Kaplan and Meier.

This actuarial method makes it possible to get maximum information from incomplete data, which are per se produced by a study with this set-up. This is caused by the fact that the follow-up is different, and may be too short in some cases for the disease to have run its full course. A number of so-called prognostic factors are derived from the literature. Each factor has been correlated with the survival rate; the correlation coefficient is also calculated.

Clinical stage appears to be the most important factor (correlation coefficient 0.34), closely followed by the presence of systemic symptoms (0.31). Cell type and structure follow at some distance (0.15 and 0.14 respectively). The prognostic order of the cell types is: F.M., L.C.S., L.B.S., H.B.S. and H.C.S. The diffuse usely structured lymphomas have a worse prognosis than the follicular ones.

Age at presentation (0.11), presence of macrophages (0.11), sex (0.09), bone-marrow invasion (0.08) and nodal start (0.04) all have a low prognostic influence.

CHAPTER 9 discusses the interdependence of the prognostic factors.

Since some prognostics are closely related with other prognostic factors, and sometimes even derived from them, it is useful when considering the total prognosis for one particular patient to compute the effect of all factors together; after this calculation the most important factors may be singled out for clinical use.

It appears that consideration of a) clinical stage, b) presence of systemic symptoms, and c) cell type, provide 93 % of the total prognosis. If the presence of macrophages is taken in account as well, the prediction rises to 96 %. Structure, age, sex, bone-marrow invasion, and extranodal start all are relatively unimportant.

CHAPTER 10 discusses the methods of spread.

Starting from stage I at first presentation the way of spread leading to the first relapse has been studied.

In the case of the primary nodal presentation, there is a very high tendency to orderly spread along the lymphatic channels. In contrast, the primary organ localizations definitely do not show this trait. This can be an argument to irradiate the adjacent lymph nodes, when the primary presentation is nodal.

The mediastinum is skipped in a very high percentage, when the tumor spread passes the diaphragm. The lymphocytic types have a slightly higher tendency to attack the mediastinum than the histiocytic ones; structure makes no difference. Prophylactic mediastinal irradiation is not useful, because of the tendency for mediastinal skipping during spread.

CHAPTER 11 discusses leukemic development and some primary organ localizations.

The lympho sarcoma cell leukemia is differentiated from chronic lymphatic leukemia on cytological grounds. In the present study 16 patients do have or develop leukemic development of their lymphocytic lymphoma; in 90 % the original lymphoma has a diffuse structure. The appearancetime of the leukemic development is always less than one year. The survival after the leukemic dissemination is about 4 months - somewhat longer when the parent lymphoma has a follicular structure.

One patient with a stage I histioblastosarcoma was known years before this diagnosis to have a quiet chronic lymphatic leukemia; he died 12 years later of a myocardial infarction. Probably the concurrence of two lymphatic malignancies is merely a coincidence.

It has been said that some primary organ localizations have a more favorable prognosis. In this series the survival of some of these so-called special localized cases is compared with the survival of all stages I and II, i.e. all localized lymphomas together.

The survival of primary lymphomas of the skin and of the ENT region (minus Waldeyer's ring) is not longer than average. It may be even somewhat shorter; however the small total numbers do not permit an exact conclusion.

Of all primary gastrointestinal lymphomas - of which the diagnosis was incidentically never made preoperatively - those originating from the small intestine and from the colon do have a slightly better, respectively worse prognosis than average. However, because here too the total number is small, this remark is only anecdotal.

The primary gastric lymphomas, eleven in number, have been treated by surgery and extensive irradiation. Here the survival rate is clearly higher than average for their stage: more than 70 % showed 5 year survival.

CONCLUSIONS.

The practical conclusions from this study are these:

- Rappaport's cytological and structural subclassifications have prognostic value.
- the Ann Arbor staging criteria, which have been developed for Hodgkin's lymphoma, are also valid for the other lymphomas.
- there is a higher tendency to unpredictable spread than in Hodgkin's disease; there are indications that this spread is more often hematogenous.
- spread from primary nodal localizations mostly occurs via the lymphatic channels; this is not as clear in the case of primary organ localizations; striking is the mediastinal skipping during spread.

- the chance at obtaining a complete remission gets smaller at each relapse.

The therapeutic implications are the following:

Optimal staging is necessary. A staging scheme has to be followed systematically to the end, unless a definitive stage IV has been reached before. The staging procedure is as follows: physical examination including inspection of Waldeyer's ring; X-ray studies: chest (anterior, transverse, tomography), lymphangiography, skeletal survey; liver biochemistry, liver and spleen-scanning; two bone biopsies; liver biopsy: percutaneous or during laparoscopy (in this case aspiration of the spleen should be performed as well); exploratory laparotomy with splenectomy (scheme E.O.R.T.C.-trial, spring, 1975). As the fate of the patient is decided by the first treatment, this has to be optimal. For the lower stages this means intensive mega-voltage irradiation. The practical use of elective irradiation of adjacent lymph nodes is as yet unclear, and has to be evaluated in clinical trials. If prophylactic irradiation of adjacent lymph nodes is given, the mediastinum can be skipped. It is useful to evaluate the effect of some years of chemotherapy after irradiation in patients with stage I and higher. Treatment in a specialized centre is desirable because of the dangers of aggressive treatment and because of the complicated investigation techniques.

XIII. SAMENVATTING EN GEVOLGTREKKINGEN.

HOOFDSTUK EEN geeft een korte inleiding.

Er wordt een parallel getrokken tussen ziekte van Hodgkin en de andere lymphomen. Een aantal problemen wordt gesteld om te trachten deze met de bij de ziekte van Hodgkin zo succesvol gebleken methodieken op te lossen.

HOOFDSTUK TWEE geeft een overzicht over de verzameling en verwerking van de gegevens afkomstig van 314 patienten met maligne lymphomen uit het Rotterdams Radio-Therapeutisch Instituut. Zij vormen één derde van de patienten met een maligne non-Hodgkin's lymphoom uit de jaren 1950 tot en met 1971. De originele histologische coupes van iedere patient zijn herbeoordeeld en gereclassificeerd volgens Rappaport. De klinische en therapeutische gegevens omtrent de eerste drie aanvallen der ziekte (Appendix B) zijn overgebracht op ponskaarten. De klinische stagering is verricht volgens de criteria van de Ann Arbor conferentie. De afsluitingsdatum van de studie is september 1973; dit resulteert in een minimale vervolg periode van twee jaar en zeven maanden. Met speciaal ontwikkelde computerprogramma's (Appendix C) zijn kruistabellen in maximaal zeven dimensies gemaakt door een I.B.M. 1130.

HOOFDSTUK DRIE bespreekt de histologische indeling.

Na een kort historisch overzicht, dat het ontstaan en de betekenis van de begrippen lymphosarcoom en reticulosarcoom schetst, wordt de indeling volgens Rappaport besproken.

Deze onderscheidt twee structurele mogelijkheden: diffuus en nodulair (folliculair). Ook zijn er twee celltypes: lymphocyt en histiocyt, die in verschillende mate van differentiatie voorkomen.

Dit resulteert derhalve in vier cytologische types: goed gedifferentieerd lymphocytair, weinig gedifferentieerd lymphocytair, histiocytair, histioblastair of beter weinig gedifferentieerd histiocytair. Naast de cytologisch enkelvoudige tumoren zijn er ook mengvormen.

In de huidige studie wordt Rappaport's celindeling gering gemodificeerd toegepast. De equivalenten zijn als volgt:

L.C.S. = lymphocytosarcoom : Rapp : goed gedifferentieerd lymphocytair lymphoom.

L.B.S. = lymphoblastosarcoom : Rapp : weinig gedifferentieerd lymphocytair lymphoom.

H.C.S. = histiocytosarcoom : Rapp : histiocytair lymphoom.

H.B.S. = histioblastosarcoom : Rapp : histiocytair, weinig gedifferentieerd.

Diffuus gemengd wordt beschouwd als lymphocytair.

Follicul air gemengd wordt apart bezien; deze classificatie is alleen gebruikt indien lymphocyten en histiocyten gelijkelijk aanwezig waren. Alle gradaties van nodulariteit zijn tesamen gevoegd.

Een probleem bij de retrospectieve beoordeling is een vermoedelijke onderpresentatie van de follicul aire variant, omdat de beoordeling is verricht zonder de hiervoor soms noodzakelijke speciale reticulinekleuringen. De huidige visie over bouw en functie van de normale lymfeklier wordt besproken. Deze weerspreekt in een aantal opzichten de ideeën van Rappaport. De lymfeklier bevat dendritische macrophagen, gewone macrophagen, T-lymphocyten en de B-lymphocyten-derivaten. Uit de B-lymphocyt ontwikkelen zich na antigene stimulatie in het follikelcentrum de grotere immunoblasten, via een tussenstadium van "cleaved-cell"; later kunnen zij zich verder tot plasmacellen ontwikkelen.

Van de vroegere reticulumcelsarcomen blijft slechts weinig over. Deze groep blijkt nu te bestaan uit tumoren van transformerende lymphocyten, dendritische reticulumcellen, en weinig gedifferentieerde fibroblasten; ook zijn kliermetastasen van anaplastische carcinomen vroeger vaak als zodanig beschouwd. Deze ideeën zijn ontstaan naar aanleiding van studies met immunologische cel-merkers, enzymcytochemie, electronenmicroscopische en vooral ook zorgvuldige lichtmicroscopische observatie van alle stadia van de transformerende lymphocyt.

Over een nieuwe en zinvoller indeling zijn de pennen nog druk in beroering. Vermoedelijk ontstaan de folliculaire lymphomen uit de B-lymphocyten in de kiemcentra of uit hun derivaten, de "cleaved" en "non-cleaved" follikelcentrum cellen. De diffuse lymphomen kunnen uit B- of T-lymphocyten ontstaan. Hierover bestaat nog geen communis opinio. De echte reticulumcelsarcomen zijn gering in aantal - zo zij al bestaan.

Ook de pathogenetische mechanismen zijn nog gedeeltelijk duister. Meest waarschijnlijk is een combinatie van viraal infekt en immuungenetische voorbeschikking. Dit ontketent de maligne ontaarding, bij voorbeeld door blokkade van de verdere normale ontwikkeling of door depressie van bepaalde ontwikkelingsstadia. Immunologische mechanismen spelen een zeer grote rol gezien de hoge frequentie van maligne lymphomen bij patienten, die behandeld worden met immuunsuppressiva.

HOOFDSTUK VIER geeft een overzicht over de histologische en klinische aspecten en vergelijkt deze met gegevens uit de literatuur.

De voornaamste klachten bij presentatie zijn (pijnloze) klierzwelling, K.N.O.-problemen, en buikklachten; ook huidklachten zijn relatief frequent. In 25 % zijn er constitutionele symptomen.

De tumorlocalisatie bij presentatie is in 85 % nodaal, en in 42 % uitsluitend nodaal. Van deze klieren zijn de halsklieren de belangrijkste, daarna komen in aflopende volgorde axillair, mediastinaal, inguinaal, milt, abdominaal. Bij de minder vaak voorkomende extranodale localisaties in de volgorde: huid, maagdarmstelsel, luchtwegen, beenmerg.

De localisaties in stadium I zijn apart beschouwd, omdat het bij een totaal overzicht van alle aangedane plaatsen niet na te gaan is waar de oorsprong van het lymphoom is. De localisaties in stadium I geven wel de oorsprong van de tumor aan. Ook hier blijkt de sterke overheersing van de lymphekliéren - met name die van de hals, en tevens dezelfde relatieve volgorde van de orgaanlocalisaties.

De verdeling der klinische stadia toont een onverklaard dal in stadium III. De histologie valt uiteen in celtype en structuur. Mannen en vrouwen zijn gelijk verdeeld qua celtype, doch de diffuus gestructureerde categorie bevat meer mannen. De frequentie der celtypen is L.C.S. 27 %, L.B.S. 39 %, H.C.S. 19 %, H.B.S. 12 %, F.M. 2 %. Het L.C.S. is in 40 % folliculair, de anderen zijn overwegend (83 - 93 %) diffuus van structuur.

Macrophagen zijn aanwezig in 10 %.

Vijf % der patienten ontwikkelt na de diagnose van het maligne lymphoom nog een tweede tumor; het betreft voornamelijk patienten met een lymphocytair lymphoom. De helft dezer tweede tumoren zijn huidcarcinomen. Het is niet zeker of de kans op een tweede tumor verhoogd is bij patienten met een maligne lymphoom.

Beenmergaspiratie is in 38 % verricht; het resultaat is in 21 % hiervan positief. Bij diffuse lymphomen is de frequentie van beenmerginfiltratie duidelijk hoger. Het zij opgemerkt dat volgens de huidige inzichten de intensiviteit en techniek der aspiraties voor verbetering vatbaar zijn.

Er is geen verschil tussen mannen en vrouwen wat betreft de frequentie van maligne lymphomen. De leeftijdsverdelingscurve toont bij beiden een overwegen der latere decaden, doch de gemiddelde leeftijd van vrouwen is iets hoger (55 versus 52 jaar).

HOOFDSTUK VIJF bespreekt de relatie van celtype, structuur, primaire localisatie, constitutionele symptomen en leeftijd.

De folliculaire structuur is weinig frequent (± 10 %) behalve bij het L.C.S. (40 %). In ieder stadium komt een nagenoeg gelijk percentage folliculair voor. Dit houdt in dat het folliculaire lymphoom even aggressief is als het diffuse, omdat waarschijnlijk anders het aggressievere type in de hogere stadia zou hebben overheerst. Opvallend is de lage frequentie van stadium III; dit geldt voor alle celtypes en is ook onafhankelijk van de structuur. Het lijkt alsof alle typen lymphoom dit stadium overslaan, en zich snel uitzaaien - waarschijnlijk haematogeen. Dit is duidelijk anders bij de Morbus Hodgkin.

Alhoewel de gemiddelde leeftijd voor alle celtypes gelijk is, komen de histiocytaire types zelden voor beneden de twintig jaar. De leeftijds-verdelingscurve gelijkt op die van de meeste solide tumoren en heeft niet de bimodale vorm van die der Morbus Hodgkin. Binnen iedere leeftijdsgroep (decade) is de onderlinge verhouding der stadia vrijwel stabiel.

Geen enkel celtype toont een verhoogde neiging tot een uitsluitend extranodale start; de frequentie is bij allen rond de 13 %.

Constitutionele symptomen nemen toe naarmate het klinisch stadium stijgt. Het percentage is in ieder celtype vrijwel gelijk. Derhalve zijn in ieder celtype de patienten met constitutionele symptomen geconcentreerd in de hogere stadia.

HOOFDSTUK ZES bespreekt de verschillende behandelingswijzen en de resultaten.

Locoregionale lymphomen, d.w.z. stadium I en II al dan niet met constitutionele symptomen, zijn bestraald; soms is tevens chirurgie toegepast. Meer uitgebreide lymphomen zijn behandeld met chemotherapie; al dan niet met locale hulp van radiotherapie of chirurgie. De radiotherapie heeft in de begin jaren bestaan uit voornamelijk orthovoltage; later is megavoltage toegepast. Bij sommige megavoltage bestralingen zijn ook het omliggende gebied of de volgende klierstations prophylactisch bestraald. Chirurgie is weliswaar bij 10 % van alle behandelingen toegepast, doch meestal palliatief; enkelvoudige en curatief opgezette chirurgie vormt slechts 3½ %. De chemotherapie is voornamelijk enkelvoudige middelen: alkylerende stoffen, corticosteroiden, procarbazine, vinca-alkaloiden.

Van alle patienten - minimum follow-up bijna drie jaar - sterft 66 % door de tumor; 21 % is (nog?) in een complete remissie. De drie en vijf jaarsoverleving zijn 37 en 25 %.

De kans op een complete remissie is na de eerste behandeling het grootst; deze moet dan ook in opzet maximaal zijn.

Naarmate de bestraling intenser wordt qua dosis en veldgrootte, neemt de kans op complete remissie toe: orthovolt 50 %, megavolt 65 %, megavolt met electieve bestraling van omliggende velden 74 %. Het zij wel opgemerkt dat de orthovolt is gegeven in een vroeger tijdvak, waarin de stagering nog niet zo verfijnd was. Chirurgie wordt in een enkel zeer geselecteerd geval als enige therapie toegepast: exisie van een totaal locale tumor. Het heeft dan een redelijk succesfrequentie: 83 % complete remissie. Chemotherapie is weinig succesvol: 18 % complete remissie.

Bij alle celtypen wordt in 50 tot 60 % na de eerste behandeling een complete remissie bereikt; de bovengrens wordt gevormd door L.B.S. en H.B.S. De duur evenwel van de complete remissie is duidelijk korter bij de histiocytaire celtypes en bij de diffuus gestructureerden. Derhalve is de qualiteit van de eerste complete remissie, gezien als het product van frequentie en duur, het slechts bij de diffuse histiocytaire lymphomen. Er is geen duidelijke relatie tussen de duur van de eerste en tweede complete remissie.

Locale recidieven ontstaan vaker en sneller bij de histiocytaire lymphomen. In diffuse typen treedt het locale recidief weliswaar sneller op, doch het slot aantal is gelijk bij de folliculaire. Een relatie tussen locaal recidief en bestralingsgegevens is niet bestudeerd.

HOOFDSTUK ZEVEN bespreekt de schadelijke bijwerkingen van de behandeling en de infekties.

Schadelijke bijwerkingen van de behandeling zijn welhaast onvermijdelijk, omdat deze minstens even aggressief moet zijn als de ziekte. In deze studie ondervindt 41 % der patienten dit. Meest voorkomend zijn beenmergdepressie, ulceraties, neuritiden, en corticosteroideffecten. Neuritis is voorgekomen bij alle patienten welke vincaalkaloiden gebruikten. Corticosteroideffecten bij 40 % der gebruikers hiervan. Haemorrhagische cystitis bij 33 % der cyclophosphamide gebruikers.

In twaalf patienten, d.w.z. 4 % van het totale bestand, heeft de behandeling de levensduur duidelijk verkort.

Infekties komen zeer gemakkelijk voor bij dit type patient; er zijn vele oorzaken: verminderde immuun- en ontstekingsafweer, abnormale lichaamsflora, doorbroken anatomische barrières.

Van de patienten heeft 22 % een infektie doorgemaakt. Meest frequent is het bacteriële infekt; herpes zoster en opportunistische infekties spelen een kleine rol. Dit laatste mogelijk omdat de diagnostiek van dezen in de studieperiode nog moeizaam was.

HOOFDSTUK ACHT bespreekt het relatief belang van factoren met prognostische invloed.

De overleving is uitgedrukt als overlevingskans per jaar volgens de methode van Kaplan en Meier. Deze actuariële methode maakt het mogelijk ten volle profijt te trekken uit partiële data, welke een studie als deze altijd oplevert. Immers de follow-up is verschillend en kan bij sommigen nog te kort zijn om de volle effecten van de ziekte te kunnen zien.

Aan de literatuur zijn een aantal zogeheten prognostische faktoren ontleend. Elk dezer is apart afgezet tegen de overleving om zijn invloed na te gaan; tevens is de correlatie coëfficient berekend.

Klinisch stadium blijkt het belangrijkst (correlatie coëfficient 0.34), op de voet gevolgd door het aanwezig zijn van constitutionele symptomen (0.31). Celtype en structuur volgen op enige afstand (0.15 respectievelijk 0.14). De prognostische volgorde der celtypen is als volgt: F.M., L.C.S., L.B.S., H.B.S. en H.C.S. De diffuus gestructureerde lymphomen hebben een mindere prognose dan de folliculaire.

Er gaat slechts een vrij matige prognostische invloed uit van leeftijd bij presentatie (0.11), aanwezigheid van macrophagen (0.11), geslacht (0.09), beenmerginvasie (0.08) en het feit of de tumor al dan niet nodaal begint (0.04).

HOOFDSTUK NEGEN bespreekt de interdependentie der prognostische faktoren.

Omdat sommige prognostische factoren nauw verbonden zijn met anderen - ja zelfs hieruit afgeleid - is het zinvol om voor de totale prognose per individuele patient het effect van allen tesamen te beschouwen en er dan de meest belangrijke van de hele groep uit te halen voor het dagelijks gebruik. Dit is gedaan middels een multiple regressie-analyse.

Het blijkt dat met de beschouwing van slechts klinisch stadium, aanwezigheid van constitutionele symptomen, en celtype al 93 % van de totale prognose mogelijk is. Beziet men hier de aanwezigheid van macrophagen ook bij dan loopt dit op tot 96 %. Structuur, leeftijd, geslacht, beenmerginvasie en extranodale start blijken vrij onbelangrijk in het gehele beeld.

HOOFDSTUK TIEN bespreekt de wijze van uitzaaiing.

Uitgaande van stadium I bij eerste presentatie is de verspreiding bij de eerste relaps bestudeerd. Bij de primair nodale presentaties is er een zeer sterke tendens tot ordelijke verspreiding via de lymphebanen naar de volgende lymphekliersta tions. Daarentegen tonen de primaire orgaanlocalisaties deze tendens zeker niet. Dit kan een argument zijn om bij primair nodale presentatie de volgende klierstations ook te bestralen.

Het mediastinum wordt in een zeer hoog percentage overgeslagen als de tumor uitzaaiing het diaphragma passeert. De lymphocytaire typen hebbem iets meer neiging het mediastinum toch aan te tasten dan de histiocytaire; verschil in structuur heeft geen invloed. Gezien deze tendens tot overslaan van het mediastinum is bestraling hiervan niet zinvol als prophylactische maatregel.

HOOFDSTUK ELF bespreekt het voorkomen van leukemische uitzaaiing; tevens komen enkele primaire orgaanlocalisaties aan de orde.

De lymphosarcoomcel leukemie onderscheidt zich op cytologische gronden van de chronische lymphatische leukemie. Zestien patienten hebben of krijgen in deze studie een leukemische uitzaaiing van hun lymphocytair of lymphoblastair lymphoom; in 90 % heeft het oorspronkelijke lymphoom een diffuse structuur. De verschijningstijd van de leukemische uitzaaiing is steeds minder dan een jaar. De levensduur na de leukemische uitzaaiing is ongeveer vier maanden - iets langer bij de leukemisch uitgezaaide folliculaire lymphomen.

Een patient met een stadium I histioblastosarcoom had reeds jaren tevoren een rustige chronische lymphatische leukemie; hij stierf op hoge leeftijd aan een hartinfarct. Waarschijnlijk is dit samenvallen van twee lymphatische tumoren een toeval.

Van sommige primaire orgaanlocalisaties is beschreven, dat zij een gunstiger prognose hebben. In deze serie is de overleving van enkele van deze genoemde speciale gelocaliseerde gevallen vergeleken met die voor alle gelocaliseerde lymphomen; d.w.z. alle stadia I en II tesamen. De overleving van primaire lymphomen van zowel huid als K.N.O.-gebied (minus Waldeyer's ring) is zeker niet beter. Mogelijk is hij zelfs iets minder, doch de kleine totale aantallen staan geen exacte uitspraak toe. Van de primaire gastrointestinale lymphomen, waar overigens de diagnose nooit pre-operatief is gesteld, hebben die uitgaande van dunne en dikke darm een iets betere respectievelijk slechtere prognose dan gemiddeld. Evenwel, omdat ook hier de totale aantallen zeer klein zijn is deze uitspraak vrijwel alleen anecdotisch.

De primaire maaglymphomen, elf in getal, zijn chirurgisch behandeld met uitvoerige nabestraling. Hier is de overleving duidelijk verhoogd t.o.v. de stadiumgenoten: na vijf jaar meer dan 70 %.

CONCLUSIE

De praktische gevolgtrekkingen uit deze studie zijn:

- de cytologische en structurele subclassificaties van Rappaport geven reële prognostische informatie.
- de voor de Morbus Hodgkin ontwikkelde Ann Arbor stadium indeling is ook voor de andere lymphomen zeer wel bruikbaar.
- er is een grotere neiging tot onvoorspelbare uitzaaiing dan bij de Morbus Hodgkin; er zijn aanwijzingen dat deze ook vaker haematogeen is.
- de verspreiding vanuit primaire klierlocalisaties verloopt meestal via lymphebanen; bij primaire orgaanlocalisaties is dit veel minder duidelijk; opvallend is het overslaan van het mediastinum (mediastinal skipping) tijdens de verspreiding.
- de kans op complete remissie wordt bij elk recidief kleiner.

De therapeutische implicaties zijn:

Optimale stadiumindeling is noodzakelijk. Men dient systematisch een stageringsschema te volgen tot het einde, tenzij tevoren reeds definitief een stadium IV bereikt wordt. Dit schema is als volgt: lichamelijk onderzoek inclusief inspectie van Waldeyer's ring; röntgenonderzoek: X-thorax (VA, DW, tomogram), lymphangiographie, skeletoverzicht; uitvoerige leverchemie, lever- en miltscintigrafie; 2 x botboring; leverbiopt per-cutaan of laparoscoop (dan tevens miltbiopt); proeflaparotomie met splenectomie (zie schema E.O.R.T.C. trial, lente 1975).

Daar het lot van de patient beslist wordt door de eerste behandeling moet deze optimaal zijn. Dit betekent voor de lagere stadia een intensieve megavoltage bestraling. Het nut van prophylactische bestraling van aangrenzende klierstations is nog onduidelijk, en dient nog eëvalueerd te worden in klinische trials. Zo er toch prophylactische bestraling der aanliggende klierstations wordt verricht dan kan het mediastinum hierbij worden overgeslagen. Het is zinvol om bij patienten in stadium I, en zeker bij patienten met hogere stadia, het effect van enige jaren chemotherapie na de bestraling te evalueren. Vanwege de grote gevaren door de aggressieve behandeling en vanwege de gecompliceerde onderzoekmethodieken, is behandeling in een gespecialiseerd centrum wenselijk.

XiV. LITERATURE.

Ackerman, L.V., del Regato, J.A. (1970): Cancer: Diagnosis, Treatment and Prognosis. 4th edition, Mosby, St. Louis.

Akazaki, K. (1973): Reticulosarcoma in Japan. In: Malignant diseases of the haematopoietic system. Gann Monograph on Cancer Research, no. 15, 1973. Japanese Cancer Association, University Park Press, Tokyo.

Al-Saleem, T., Harwick, R., Robbins, R. (1970): Malignant Lymphomas of the pharynx. Cancer, 26: 1383-1387.

Al-Saleem, T., Al-Bahrani, Z. (1973): Cancer, 31: 291-295.

Annual Reports, Rotterdam Radiotherapy Institute, 1950-1971.

Aschoff, L. (1924): Das Retikuloendotheliale System. Ergebnisse Inn. Medizin und Kinderheilkune, 26: 1-118.

Bagley, C.M., De Vita, V.T., Berard, C.W., et al. (1972): Ann. Int. Med., 76: 227-234.

Banfi, A., Bonadonna, G., Carnevali, G., et al. (1968): Preferential Sites of Involvement and Spread in Malignant Lymphoma. European J. Cancer, 4: 319-324.

Banfi, A., Bonadonna, G., Carnevali, G., Oldini, C., Salvini, E. (1969): Malignant Lymphomas: further studies on their preferential sites and possible mode of spread. Lymphology, 2: 130-138.

Banfi, A., Basso-Ricci, S., Bonadonna, G. (1972): Malignant Lymphoma of the Waldeyer's ring: Natural History and Results of Radiotherapy. Abstracts XIV International Congress of Haematology, no. 583, Sao Paulo, Brasil.

Berard, C.W., O'Connor, G.T., Thomas, L.B., Torloni, H. (1969): Histopathological Definition of Burkitt's Tumor. Bulletin W.H.O., 40: 601-607.

Berard, C.W. and Dorfman, R.F. (1974): Histopathology of Malignant Lymphomas. Clinics in Haematology, 3: 39-77.

Berg, J.W. (1967): The incidence of multiple primary Cancers. Development of further Cancers in patients with Lymphomas, Leukemias en Myeloma. J. Nat. Cancer Inst., 38: 741-753.

Billroth, T. (1871): Multiple Lymphome. Wiener Medizinische Wochenschrift, 21: 1066-1967.

Bloomfield, C.D., Goldman, A., Dick, F., Brunning, R.D., Kennedy, B.J. (1974): Multivariate analysis of prognostic factors in the non-Hodgkin's Lymphoma. Cancer, 33, 3: 870-880.

Bradfield, J.W.B. (1974): Classification of Non Hodgkin's Lymphomas. Lancet, 2: 652-653.

Brill, N.E., Baehr, G., Rosenthal, N. (1925): Generalized giant lymph follicle hyperplasia of the lymphnodes and spleen. J.A.M.A., 84: 668-671.

Buchem, F.L. van. (1962): Histologisch onderzoek van de plasmacellulaire reactie en zijn plaats in de histophysiologie van de lymphklier. Thesis, Groningen.

Bull, E.G., McAfee, J.G., Constable, W.C. (1969): Radiology, 92: 1083-1088.

Butler, J.J. (1970): Histopathology of Malignant Lymphomas and Hodgkin's Disease. In: Leukaemia-Lymphoma: A collection of papers presented at the 14th Annual Clinical Conference on Cancer, 1969, Houston, Texas. Year Book Medical Publishers, Chigaco.

Carbone, P.P., Kaplan, H.S., Musshoff, K., Smithers, D.W., Tubiana, M. (1971): Report of the Committee on Hodgkin's disease Staging Classification. Cancer Research, 31: 1860-1861.

Cline, M.J., Golde, D.W. (1973): A review and re-evaluation of the histiocyte disorders. Am.J.Med., 55: 49-60.

Clinics in Haematology (1974): 3, 1: Ed. S.A. Rosenberg.

Cohen, S., Fisher, B., Yoshida, T. (1974): N.E.J.M., 290, 16: 882-886.

Craig, J.M., Farber, S. (1953): American Journal of Pathology, 29: 601.

Cummings, N.A. (1971): Sjögrens Syndrome, newer aspects of research, diagnosis and therapy. Am. Int. Med., 75: 937-950.

Cutler, S.J., Eberer, F. (1958): J. Chron. Diseases: 699-712.

Daniël, C. and Wood, F.A. (1971): Fitting Equations to data. Wiley Interscience, New York.

Diamandopoulos, G.Th. and Smith, E.B. (1964): Cancer, 17, 3: 328-337.

Dick, F., Bloomfield, C.D., Brunning, R.D. (1974): Incidence, Cytology and Histopathology of Non-Hodgkin's Lymphoma in the bone-marrow. Cancer, 33: 1382-1398.

Diebold, J. (1973): Affections malignes lympho-plasmocytaires et reticulo-histiocytaires. Propositions pour une nouvelle classification. Arch. Path. Anat., 21: no. 2: 103-112.

Dmochowski, L. (1970): Current Status of the relationship of virus to leukemia, lymphoma and solid tumors. In leukemia-lymphoma. A collection of papers presented at the fourteenth annual Clinical Conference on Cancer, 1969, at the University of Texas: 37-52. Chicago, Year Book Medical.

Dorfman, R.F. (1964): Follicular Lymphoma in South-Africa. In: Symposium on Lymphoreticular Tumors in Africa. Ed. F.C. Roulet. Publ. Karger, Basel/New York. 211-228.

Dorfman, R.F. (1974): Lancet, 1: 1295-1296.

Dorfman, R.F. (1974): Lancet, 2: 961-962.

Dragoni, F., et al. (1971): Radiol. Med., 57: 497-510.

Dreschfeld, J. (1893): Ein Beitrag zur Lehre von den Lymphosarkomen. Deutsche Medizinische Wochenschrift, 17: 1175-1177.

Dunn and Clark (1974): Applied Statistics. Wiley Interscience. New York.

Eidelman, S., Parkins, A., Rubin, C.E. (1966): Medicine, 45: 111-137.

Enueyer, A., Helary, J., Bataini, P. (1963): Bulletin du Cancer, 50: 113-122.

European Organisation for Research and Treatment of Cancer. (1975): to be published.

Farrer-Brown, G., Bennett, M.H., Henry, K. (1973): Workshop on Classification of non-Hodgkin's Lymphoma. Chigaco-Illinois, June.

Fayos, J.V., Edlund, J.H., Knapp, W.T., et al. (1974): Cancer, 34, 1: 212-222.

Feingold, D.S. (1970): Hospital acquired infections. New England J. of Medicine, 283: 1384-1391.

Ferguson, D.J., Allen, L.W., Griem, M.L., et al. (1973): Surgical Experience with staging laparotomy in 125 patients with Lymphoma. Arch. Int. Med., 131: 356-361.

Freeman, C., Berg, J.W., Cutler, S.J. (1972): Occurrence and prognosis of extranodal Lymphomas. Cancer, 29: 252-260.

Friedell, H.L. (1954): In: Cancer Seminar, 1, 5: 161-163. Ed. Del Regato.

Friedman, A.I. (1959): American Journal of Medicine, 26: 783-796.

Frizzera, G., Moran, E.M., Rappaport, H. (1974): Angio-immunoblastic lymphadenopathy with dysproteinemia. Lancet, 1: 1070-1074.

Fuks, Z., Kaplan, H.S. (1973): Radiology, 108: 675-684.

Furth, R. van, ed. (1970): Mononuclear Phagocytes. Blackwell, Oxford.

Gajl-Peczalska, K.J., Hansen, J.A., Bloomfield, C.D., Good, R.A. (1973): B lymphocytes in untreated patients with malignant lymphoma and Hodgkin's disease. J. Clin. Invest., 52: 3064-3073.

Gall, E.A., Mallory, T.B. (1942): Malignant lymphoma, a clinical pathological survey of 618 cases. American Journal of Pathology, 18: 381-429.

Gall, E.A., Rappaport, H. (1958): Seminars on diseases of lymphnodes and the spleen. In: Proc. of 23rd Seminar of the American Society of Clinical Pathology; ed. McDonald, J.R., Chicago.

Gérard-Marchant, R., Hamlin, J., Lennert, K., et al. (1974): Classification of non-Hodgkin's Lymphomas. Lancet, 7877: 406-408.

Gerberg, M.J. (1972): Reticulosarcoma in gold hamsters caused by murine leukemia virus. Cancer Research, 32: 2075-2081.

Gershwin, M.E., Steinberg, A.D. (1973): Loss of suppresor function as a cuase of lymphoid malignancy. Lancet, 11: 1174-1175.

Ghon, A., Roman, B. (1916): Ueber das Lymphosarkom. Frankf. Zeitschrift für Pathologie, 19: 1-138.

Goffinet, D.R., Gastellino, R.A., Kim, H., et al. (1973): Staging laparotomies in previously unselected patients with non-Hodgkin's Lymphomas. Cancer, 32: 672-681.

Goormagchtigh, N. (1926): Bulletin de l'Academie Royale de Medicine de Belgique.

Goudie, R.B. (1974): Lancet, 1: 292-293.

Gowans, J.L., Knight, E.J. (1964): The route of recirculation of lymphocytes in the rat. Proc. Royal. Soc. London, Series B, 159: 257-282.

Gunz, F.W., Angus, H.B. (1965): Leukemia and Cancer in the same patient. Cancer, 18: 145-152.

Gunz, F.W., Levi, J.A., Lind, D.E., et al. (1973): New Zealand Medical Journal, 79, 495: 71-75.

Han, T., Stutzman, L. (1967): Mode of spread in patients with localised malignant lymphoma. Arch. Int. Med., 120, 1: 1-7.

Hanssen, H.S. (1969): Reticulumcell sarcoma treated by radiotherapy. Acta Radiologica, 8: 439-459.

Hansen, J.A., Good, R.A. (1974): Malignant disease of the lymphoid system in immunological perspective. Human Pathology, 5, 5: 567-600.

Hellman, S. (1974): Current Studies in Hodgkin's disease. New Engl. J. of Med., 290: 894-898.

Hill, I.D., Pike, M.C. (1967): Algorithm 299: Chi-squared integral, Comm. of the A.C.M., 10, 4: 243-244.

Hodgkin, T. (1832): On some morbid appearances of the absorbent glands and the spleen. Transactions of the Medical and Chirurgical Society of London, 17: 68-114.

Hoogstraten, B., Owens, A.H. Lenhard, R.E., et al. (1969): Combination Chemotherapy in Lymphosarcoma and Reticulumcellsarcoma. Blood, 33: 370-378.

Humphrey, J.K., Frank, M.M. (1967): The localisation of non-microbial antigens in the draining lymph nodes of the tolerant, normal and primed rabbits. Immunology, 13: 87-100.

Hurst, D.W., Meyer, O.O. (1961): Giant follicular lymphoblastoma. Cancer, 14: 753-778.

Hyman, G.A. (1969): Increased incidence of neoplasia in association with chronic lymphocytic leukemia. Scan. J. Haematol., 6: 99-104.

I.B.M. (1968): System/360 Scientific Subroutine Package (360A-OM-03X) Version III.

Ibbetson, D. (1963): Algorithm 209: Comm. of the A.C.M., 6, 10: 616.

Ibbot, J.W., Whitelaw, D.M. (1966): The relation between lymphosarcoma and leukemia. Canad. Med. Ass. J., 94, 11: 517-528.

Jacobs, D.S., et al. (1963): American Journal of Clinical Pathology, 40: 379-394.

Jaffe, E.S., Shevach, E.M., Frank, M.M., Berard, C.W., Green, I. (1974): Nodular lymphoma-evidence for origin from follicular B-lymphocytes. New Engl. J. of Med., 290: 813-815.

Johnson, R.E. (1972): Cancer, 29: 1473-1476.

Jones, S.E., Kaplan, H.S., Rosenberg, S.A. (1972): Radiology, 193: 657-662.

Jones, S.E., Rosenberg, S.A., Kaplan, H.S. (1972): Non-Hodgkin's Lymphomas: Bone-Marrow Involvement. Cancer, 29: 954-960.

Jones, S.E., Rosenberg, S.A., Kaplan, H.S., et al. (1972): Non-Hodgkin's Lymphomas: Single Agent Chemotherapy. Cancer, 30: 31-38.

Jones, S.E., Fuks, Z., Bull, M., a.o. (1973): Non-Hodgkin's Lymphomas: Clinicopathological Correlations in 405 cases. Cancer, 31: 806-823.

Jones, S.E., Fuks, Z., Kaplan, H.S., et al. (1973): Non-Hodgkin's Lymphomas: Results of Radiotherapy. Cancer, 32: 682-691.

Jones, S.E. (1974): Clinical Features and Course of the Non-Hodgkin's Lymphomas. Clinics in Haematology, 3, 1: 131-161.

Jordan, G.L., Bolton, B.F., Heard, J.G., et al. (1955): Surg. Gyn. Obst., 100: 453-457.

Kaplan, E.L., Meier, P. (1958): J. Am. Statistical Ass., 53: 457-482.

Kaplan, H.S. (1972): Hodgkin's Disease. Harvard University Press, Cambridge, Massachussets.

Kass, E.H., Scheiderman, L.J. (1957): Entry of bacteria into the urinary tracts of patients with inlying catheters. New England J. of Med., 256: 556-559.

Keuning, F.J. (1972): Dynamics of immunoglobulin forming cells and their precursors. In: Immunoglobulins, ed. Ballieux, R.E. Vol. 26. Fed. European Bioch. Societies. North Holland Publishing Company.

Kim, H., Heller, P., Rappaport, H. (1973): Monoclonal gammopathies associated with lymphoproliferative disorders. American J. Clinical Pathology, 59: 282-294.

Kim, H. and Dorfman, R. (1974): Cancer, 33: 657-674.

Klastersky, J. (1973): Incidence and Management of Infections occuring in Malignant Lymphomas. In: I Linformi Maligni. Ed. Bucalosi, Casa Ambrosiana, Milano, 1974.

Kundrat, H. (1973): Ueber Lymphosarkomatosis. Wiener Klinische Wochenschrift, 6: 211-213; 234-239.

Lancet. (1973): Leading article, 1: 139-140.

Lancet. (1974): Leading article, 1: 1088-1089.

Lattuda, A., Milani, F. (1974): Quadro Clinico ed Evoluzione dei Linfomi Maligni Linfo-Istiocitari. In: Linformi Maligni, 95-111. Ed. Bucalossi, P., Ambriosiana, Milano.

Lee, Y.N., Say, C., Hori, J.M., Spratt, J.S. (1973): Clinical Course of Hodgkin's Disease and other malignant lymphomas. Am. J. Roentgenology, 67: 19-30.

Lehrer, R.I., Cline, M.J. (1971): Leukocyte Candidacidal activity and resistance to systemic Candidiasis in patients with Cancer, 27: 1211-1217.

Lennert, K. (1964): Pathologie der Halslymphknoten. Springer, Berlin.

Lennert, K., Caesar, R., Muller, H.K. (1966): Germinal Centers in Immune Responses. H. Cottier, ed. Berlin.

Levine, G., Dorfman, R.F. (1974): J. Lab. Investig., 30, 3: 381.

Levine, A.S., Graw, R.G., Young, R.C. (1972): Seminars in Hematology, 9, 2: 141-181.

Lipton, A., Lee, B.J. (1971): Prognosis of stage I Lymphosarcoma and Reticulum-cell Sarcoma. New Engl. J. Med., 284: 230-233.

Loewenbraun, S.A., Sutherland, J.C., Marvin, J., et al. (1971): Cancer, 27: 579-587.

Luce, J.K., Gamble, J.F., Wilson, H.E. (1971): Cancer, 28: 306-317.

Lukes, R.J., Collins, R.D. (1971): Am. J. Pathology, 62: 63A.

Lukes, R.J., Collins, R.D. (1974): Cancer, 34: 1488-1503.

Lukes, R.J., Tindle, B.H. (1975): New Engl. J. Med., 292, 1: 1-8.

MacMahon, B. (1957): Cancer, 10: 1045-1055.

Marcuse, P., Purdy Stout, A. (1950): Cancer, 3: 459-475.

Mathé, G., Gérard-Marchant, R., Texier, J.L., et al. (1970): Br. J. Cancer, 24: 687-696.

Maximow, A.A., Bloom, W. (1942): A Textbook of Histology. Saunders, Philadelphia. Second Edition.

McElwain, T.J. (1974): Sem. in Haem., 11, 1: 59-73.

Mennemeyer, R., Hammar, S.P., Cathey, W.J. (1974): New Engl. J. Med., 31 October, 960-963.

Messinger, N.H., Bodroff, L.M., Beneventono, T.C. (1973): American J. Roentgen., 117, 2: 281-287.

Meyler, L., Peck, H.M. (1972): Drug Induced Diseases, vol. 4. Excerpta Medica, Amsterdam.

Michlmayr, G., Huber, C.H., Fink, V., Falkensommer, M., Huber, H. (1974): Schweizerische Medizinische Wochenschrift, 104, no. 23: 815-820.

Moertel, C.G. (1957): Multiple primary malignant neoplasms. In: Recent results in cancer research. Ed. Reutschnik, P., 41-43. Springer, New York.

Molander, D.W. and Lacayo, G. (1970): Am. J. Roentgenology, 108, 2: 348-353.

Molander, D.W. and Pack, G.T. (1963): Rev. Surgery, 20, 1: 3-31.

Molander, D.W., Pack, G.T. (1965): Am. J. Roentgenology, 93: 154-160.

Monfardini, S., Tancini, G., Gasparini, M., et al. (1973): Tumori, 59: 219-238.

Moran, E.M. (1974): Staging Classification for non-Hodgkin's Lymphomas. In: I Linfomi Maligni. Ed. Bucalossi, P., et al., Ambrosiana, Milano.

Moser, R. (1969): Diseases of Medical Progress. Springfield, Illinois.

Mulder, N.H. (1972): Thymus dependency of antibody response. Thesis, Groningen.

Ned. Ver. Immunologie. Inleiding tot de Immunologie. Publ. Oosthoek. Second Edition. 1971.

Newall, J., Friedman, M., Navarez, F. de (1968): Extra-Lymph-Node Reticulum-cell Sarcoma. Radiology, 91: 708-712.

Nossal, G.J.V. (1967): Mechanisms of Antibody production. Ann. Rev. Med., 18: 81-86.

Nossal, G.J.V., Abbot, A., Mitchell, J., Lummus, Z. (1968): Antigens in immunity. Ultrastructural features of antigen capture in primary and secondary lymph-follicles. J. Exp. Med., 127: 277-289.

Oberling, C. (1928): Les réticulosarcomes et les réticulo-endotheliosarcomas de la moelle ossense (sarcomes d'Ewing). Bull Ass. Française Etude Cancer, 17.

O'Brien, W.M., Wood, J. (1968): Certification of algorithm 299: Comm. of the A.C.M., 11, 4: 271.

Oldhoff, J., Schraffordt Koops, H. (1972): Nederlands Tijdschrift voor Geneeskunde, 116, 19: 779-783.

Oort, J., Turk, J.L. (1965): A histological and autoradiographic study of lymph-nodes during the development of contact sensitivity in the guinea pig. Brit. J. Exp. Path., 46: 147-155.

Pal, A.K., Chopra, S.K., Rastogi, J.K. (1973): Indian Journal of Medical Science, 27: 24-27.

Paltauf, R. (1896): Ergebnisse Algemeiner Pathologie, Lubarsh and Ostertag, 3.

Patchefsky, A.S., Brodovsky, H.S., Menduke, H., et al (1974): Cancer, 34: 1173-1186.

Pearson, E.S. (1962): Biometrics for Statisticians, 2nd ed., 1: 122-129, Cambridge.

Peckham, M.J. (1974): Sem. in Haem., 11, 1: 41-59.

Penn, I., Starzi, T.E. (1972): Malignant tumors arising de novo in immuno-suppressed organ transplant recipients. Transplantation, 14: 407-417.

Peter, C.R., MacKenzie, M., Glassy, F.J. (1974): T or B cell origin of some non-Hodgkin's lymphomas. Lancet, 2: 686-689.

Peters, M.V., Hasselback, R., Brown, T. (1968): The natural history of the lymphomas related to clinical classification. In: Proceedings of the International Conference on Leukemia - Lymphoma. Ed. Zarafonetis, Philadelphia, Lea and Febiger, 357-371.

Piessens, W.F., Schur, P.H., Moloney, W.C., Churchill, W.H. (1973): Lymphocyte surface immunoglobulins. Distribution and frequency in lymphoproliferative diseases. New Engl. J. Med., 288: 176-180.

Ramboud, J.C., Matuchansky, C. (1973): Alpha-Chain Disease. Lancet, 1: 143-1433.

Rappaport, H., Winter, W.J., Hicks, E.B. (1956): Follicular Lymphoma. A re-evaluation of its position in the scheme of malignant lymphoma. Cancer, 9: 792-821.

Rappaport, H. (1966): Tumors of the haematopoietic system. In: Atlas of Tumor Pathology, Section III, fasc., 8, 91-206. Washington D.C.: Armed Forces Institute of Pathology.

Rappaport, H., Moran, E.M. (1975): New Engl. J. Med., 292, 1: 42-43.

Reed, D.M. (1902): On the pathological changes in Hodgkin's disease, with special reference to its relation to tuberculosis. Johns Hopkins Hospital Reports, 10: 133-196.

Roitt, I.M., Greaves, M.F., Torrigani, G., Brostoff, J., Playfair, J.H.L. (1969): The cellular basis of immunological responses. The Lancet, 11: 367-371.

Rosai, J., Dorfman, R.F. (1969): Arch. Path., 87: 63-70.

Rosai, J., Dorfman, R.F. (1972): Cancer, 30: 1174-1188.

Rosenberg, S.A., Diamond, H.D., Craver, L.F. (1961): Am. J. Roentgen., 85: 521-532.

Rosenberg, S.A., Diamond, H.D., Jaslowitz, B., Craver, L.F. (1961): Lymphosarcoma, a review of 1269 cases. Medicine, 40: 31-84.

Rosenberg, S.A., Kaplan, H.S. (1966): Evidence for an orderly progression in the spread of Hodgkin's disease. Cancer Research, 26: 1225-1231.

Rosenberg, S.A., Kaplan, H.S. (1968): The results of radical radiotherapy in Hodgkin's disease and other lymphomas. In: Proceedings of the international Conference on leukemia-lymphoma, ed. Zarafonetis, C.J.D., Lea and Febiger, Philadelphia.

Rosenberg, S.A., Boiron, M., De Vita, V.T., Johnson, R.E., Lee, B.J., Ultman, J.E., Viamonte, M. (1971): Report of the Committee on Hodgkin's disease Staging Classification. Cancer Research, 31: 1862-1863.

Rosner, F., Valmont, I., Kozmin, P.H. (1970): Leukocyte function in patients with leucaemia. Cancer, 25: 835-895.

Roulet, F. (1930): Das primäre Retothelsarkom der Lymphnoten. Virchows Arch. Anat. Physiol., 277: 15-47.

Roulet, F. (1932): Weitere Beitrage zur Kenntinis des Retothelsarkoms der Lymphnoten und andere Lymphoiden Organe. Virchows Arch. Path. Anat. Physiol., 286: 702-732.

Rouvière, H. (1932): Anatomie des lymphatiques de l'homme. Masson, Paris, 157 and 298.

Ryrolon, A.M., Ortega, R.S., Dominguez, C.J. (1974): Blood, 43: 389-401.

Scheer, A.C. (1963): The course of stage I malignant lymphoma following local treatment. Am.J.Roentgenology, 90: 939-943.

Schey, W.L., White, H., Conway, J.J., et al. (1973): American Journal of Roentgenology, 117: 59-72.

Schnitzer, B., Loesel, R.S., Reed, R.E. (1970): Lymphosarcoma cell leukemia. Cancer, 26: 1082-1096.

Schnitzer, B., Kass, L. (1973): Cancer, 31: 547-560.

Schultz, D.R., Yunis, A.A. (1975): N.E.J.M., 292, 1: 8-13.

Schwartz, D.L., Pierre, R.V., Scheerer, P., et al. (1965): American Journal of Medicine, 38: 778-787.

Seligman, M. (1974): B-cell and T-cell markers in lymphoid proliferations. N.E.J.M., 290: 1483-1484.

Sherrick, D.W., Hodgson, J.R., Dockerty, M.R. (1955): Radiology, 84: 925-932.

Shevach, E.M., Herberman, R., Frank, M.M. (1972): J. Clin. Invest., 51: 1933-1938.

Snedecor, G.W., Cochran, W.G. (1972): Multiple regression in statistical methods. Ames, Iowa State University Press. Chapter 13.

Stein, H., Lennert, K., Porwaresh, M.R. (1972): Malignant lymphomas of B-cell type. Lancet, 721: 855-857.

Stein, R.S., Moran, E.G., Desser, R.K., et al. (1974): Ann. Int. Med., 81: 601-609.

Stenfert Kroese, W.F., Cleton, F.J., Somers, R. (1973): "Leukemic Progression in Lymphomas". Personal Communication.

Sternberg, C. (1898): Ueber eine eigenartige unter dem Bilde einer Pseudo leukämie verlaufende Tuberkulose des lymphatischen Apparates. Zeitschrfit für Heilkunde, Berlin, 19: 21-90.

Stobbe, J.A., Dockerty, M.B., Bernetz, P.E. (1966): Obst.Am.J.Surgery, 122: 10-19.

Sullivan, M.P. (1962): Leukemic transformation of lymphosarcoma in childhood. Pediatrics, 29: 589-599.

Sykes, M.P., Chu, F.C.H., Sovel, H., et al. (1964): Radiology, 83: 1084-1087.

Symmers, D. (1927): Follicular lymphadenopathy with splenomegaly. Archives of Pathology, 3: 816-820.

Symmers, D. (1938): Giant follicular lymphadenopathy with or without splenomegaly. Archives of Patholo y, 26: 603-647.

Tubiana, M. (1971): Cancer Research, 31: 1801-1810.

Van der Werf-Messing, B. (1968): Europ. J. Cancer, 4: 549-557.

Van der Werf-Messing, B. (1969): Nederlands Tijdschrift voor Geneeskunde, 113: 688-693.

Van Unnik, J.A.M. (1973): Personal Communication.

Van Unnik, J.A.M. (1973): Proceedings of the Conference on non-Hodgkin's Lymphomas. London, October, 1973.

Veronesi, U., Musumeci, R., Pizetti, F., a.o. (1974): The value of laparotomy in Non-Hodgkin's Lymphomas. Cancer, 33: 446-459.

Virchow, R.L.K. (1858): Die Zellular pathologie in ihrer Begruendung auf physiologische und pathologische Gewebelehre. Hirschwald, Berlin.

Virchow, R.L.K. (1863): Die krankhaften Geschwülste. Hirschwald, Berlin, 2: 728-738.

Vogel, C.L., Lunde, M.N. (1968): Cancer, 23: 614-618.

Warren, S., Ehrenreich, T. (1944): Multiple Primary Malignant Tumors and Susceptability to Cancer. Cancer Research, 4: 554-570.

Watson, T.A. (1953): Incidence of multiple Cancer. Cancer, 6: 365-371.

Wheelock, M.C., Atkinson, A.J., Pizzo, A. (1950): Gastroenterology, 15: 158-161.

White, R.C. (1963): The immunologically competent cell; its nature and origin. In: Wolsenholme, G.E.W., Knight, J., The Immunologically competent cell: its nature and origin. Ciba Foundations Study Group, no. 16, London.

Wilks, S. (1865): Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease). Guy's Hospital Reports, 11: 56-67.

Willis, R.A. (1948): Pathology of Tumors, chapter 49: 700. Ed. Mosley, St. Louis.

Yam, L.T., Li, C.Y., Crosby, W.H. (1971): American Journal of Clinical Pathology, 55: 283-290.

Zacharski, L., Linman, J.W. (1969): American Journal of Medicine, 47: 75-81.

Zwaveling, A., Stenfert Kroese, W.F., Van Unnik, J.A.M., et al. (1969): Nederlands Tijdschrift voor Geneeskunde, 113: 148-151.

Zwaveling, A., Stenfert Kroese, W.F., Van Gilse, H.A. (1973): Kankerchemotherapie in de Praktijk; 3e ed. Ed. St. Kroese, Leiden.

Zeffren, J.L., Ultmann, J.E. (1960): Blood, 15: 277-284.

LYMFOMEN-ONDERZOEK / HAEMATOLOGIE I.

Nr.											
	Kaart nr.										
1	0	1	2	3	4		5	6	7	8	9
2	0	1	2	3	4		5	6	7	8	9
	Statusnr.										
3	0	1	2	3	4		5	6	7	8	9
4	0	1	2	3	4		5	6	7	8	9
5	0	1	2	3	4		5	6	7	8	9
6	0	1	2	3	4		5	6	7	8	9
7	0	1	2	3	4		5	6	7	8	9
8	0	1	2	3	4		5	6	7	8	9
	Code instituut										
9		A	R	L							
	PA - nr.										
10	0	1	2	3	4		5	6	7	8	9
11	0	1	2	3	4		5	6	7	8	9
12	0	1	2	3	4		5	6	7	8	9
13	0	1	2	3	4		5	6	7	8	9
14	0	1	2	3	4		5	6	7	8	9
15	0	1	2	3	4		5	6	7	8	9
	Cytologie nr.										
16	0	1	2	3	4		5	6	7	8	9
17	0	1	2	3	4		5	6	7	8	9
18	0	1	2	3	4		5	6	7	8	9
19	0	1	2	3	4		5	6	7	8	9
20	0	1	2	3	4		5	6	7	8	9
21	0	1	2	3	4		5	6	7	8	9
	Sexe										
22		M	V								
	Geboortedatum omgekeerd										
23	0	1	2	3	4	Jr	5	6	7	8	9
24	0	1	2	3	4		5	6	7	8	9
25	0	1	2	3	4	Mnd	5	6		8	9
26	0	1	2	3	4		5	6	7	8	9
27	0	1	2	3	4	Dag	5	6	7	8	9
28	0	1	2	3	4		5	6	7	8	9
	Datum 1e symptoom omgekeerd										
29	0	1	2	3	4	Jr	5	6	7	8	9
30	0	1	2	3	4		5	6	7	8	9
31	0	1	2	3	4	Mnd	5	6	7	8	9
32	0	1	2	3	4		5	6	7	8	9
33	0	1	2	3	4	Dag	5	6	7	8	9
34	0	1	2	3	4		5	6	7	8	9
	Datum PA diagnose omgekeerd										
35	0	1	2	3	4	Jr	5	6	7	8	9
36	0	1	2	3	4		5	6	7	8	9
37	0	1	2	3	4	Mnd	5	6	7	8	9
38	0	1	2	3	4		5	6	7	8	9
39	0	1	2	3	4	Dag	5	6	7	8	9
40	0	1	2	3	4		5	6	7	8	9
	Instituut diagnose										
41		A	R	L							
	Datum presentatie instituut omgekeerd										
42	0	1	2	3	4	Jr	5	6	7	8	9
43	0	1	2	3	4		5	6	7	8	9
44	0	1	2	3	4	Mnd	5	6	7	8	9
45	0	1	2	3	4		5	6	7	8	9
46	0	1	2	3	4	Dag	5	6	7	8	9
47	0	1	2	3	4		5	6	7	8	9
	Datum overlijden omgekeerd										
48	0	1	2	3	4	Jr	5	6	7	8	9
49	0	1	2	3	4		5	6	7	8	9
50	0	1	2	3	4	Mnd	5	6	7	8	9
51	0	1	2	3	4		5	6	7	8	9
52	0	1	2	3	4	Dag	5	6	7	8	9
53	0	1	2	3	4		5	6	7	8	9
	Overleving in maanden op censusdatum										
54	0	1	2	3	4		5	6	7	8	9
55	0	1	2	3	4		5	6	7	8	9
56	0	1	2	3	4		5	6	7	8	9
	Toestand op censusdatum										
57		D.1	D.2	D.3	D.?		LC	LIC	L?		?
	Volgnummer van de remissie										
58	0	1	2	3	4		5	6	7	8	9
	Therapie-complicaties :										
59	Longfibrose-pneumonitis								+	-	?
60	ulceratie-mucositis								+	-	?
61	beenmerg depressie								+	-	?
62	steroideffect								+	-	?
63	haemorrhagische cystitis								+	-	?
64	neuritis defaecatiest								+	-	?
65	infecties								+	-	?
66	andere								+	-	?
67	andere								+	-	?
	Infecties										
68			+	-	B		V	H	O		?
	Leucemie										
69									+	-	?
	Interval in maanden sinds primaire therapie										
70	0	1	2	3	4		5	6	7	8	9
71	0	1	2	3	4		5	6	7	8	9
72	0	1	2	3	4		5	6	7	8	9
	Soort leucemie										
73											
74											
	Recidief in bestraald gebied										
75								C	R	-	?
	Interval in maanden na irradiatie										
76	0	1	2	3	4		5	6	7	8	9
77	0	1	2	3	4		5	6	7	8	9
78	0	1	2	3	4		5	6	7	8	9

EUR/5930 nr. 46

OPTICAL READING CHART FOR PUNCHCARD 2

LYMFONEN-ONDERZOEK / HAEMATOLOGIE 2

81 Kaart nr. 0 1 2 3 4 5 6 7 8 9

82 0 1 2 3 4 5 6 7 8 9

Statusnummer

83 0 1 2 3 4 5 6 7 8 9

84 0 1 2 3 4 5 6 7 8 9

85 0 1 2 3 4 5 6 7 8 9

86 0 1 2 3 4 5 6 7 8 9

87 0 1 2 3 4 5 6 7 8 9

88 0 1 2 3 4 5 6 7 8 9

Eerste klacht

89 0 1 2 3 4 5 6 7 8 9

90 0 1 2 3 4 5 6 7 8 9

P.A.

Celtype

91 0 1 2 3 4 5 6 7 8 9

necrose

92 0 1 2 3 4 5 6 7 8 9

macrofagen

93 0 1 2 3 4 5 6 7 8 9

kwaliteit

94 0 1 2 3 4 5 6 7 8 9

epitheloïden

95 0 1 2 3 4 5 6 7 8 9

structuren

96 0 1 2 3 4 5 6 7 8 9

fibrose

97 0 1 2 3 4 5 6 7 8 9

herkomst

98 0 1 2 3 4 5 6 7 8 9

eo-granulos

99 0 1 2 3 4 5 6 7 8 9

cytologie

100 0 1 2 3 4 5 6 7 8 9

extra maligniteit

101 0 1 2 3 4 5 6 7 8 9

Klieren:

hals totaal li

102 1 2 8 9

hals totaal re

103 1 2 8 9

cervicaal li

104 1 2 8 9

cervicaal re

105 1 2 8 9

kin li

106 1 2 8 9

kin re

107 1 2 8 9

st.cl.mast li

108 1 2 8 9

st.cl.mast re

109 1 2 8 9

clavicula li

110 1 2 8 9

clavicula re

111 1 2 8 9

oksel li

112 1 2 8 9

oksel re

113 1 2 8 9

lies li

114 1 2 8 9

lies re

115 1 2 8 9

weldeyer li

116 1 2 8 9

mediastinum

117 1 2 8 9

milt

118 1 2 8 9

mesenterlaal

119 1 2 8 9

paraortaal li

120 1 2 8 9

paraortaal re

121 1 2 8 9

lumbaal li

122 1 2 8 9

lumbaal re

123 1 2 8 9

biceps li

124 1 2 8 9

biceps re

125 1 2 8 9

knie li

126 1 2 8 9

knie re

127 1 2 8 9

Organen:

bovenste luchtwegen

128 1 2 8 9

oesofagus

129 1 2 8 9

maagduodenum

130 1 2 8 9

dunderm/appendix

131 1 2 8 9

dikkedarm/rectum

132 1 2 8 9

lever (...)

133 1 2 8 9

galsysteem

134 1 2 8 9

huid

135 1 2 8 9

long

136 1 2 3 4 5 6 7 8 9

longparenchym

137 1 2 8 9

longexsudaat

138 1 2 3 5 6 9

speekselklieren

139 1 2 8 9

endocrien

140 1 2 4 5 9

urmenitaal

141 1 2 4 5 6 7 9

elders extranodaal

142 1 2 9

Röntgen-lymphogram

143 1 2 3 4 8 9

radio-lymphogram

144 1 2 3 4 8 9

botboring

145 1 3 8 9

beenmergpunctaat

146 1 3 8 9

leverscan

147 1 3 8 9

miltscan

148 1 3 8 9

klinisch stadium

149 I II III IV 9

150 A B ?

primaire localisatie

151 N E B L ?

pathologisch stadium

152 I II III IV V 9

laparotomie

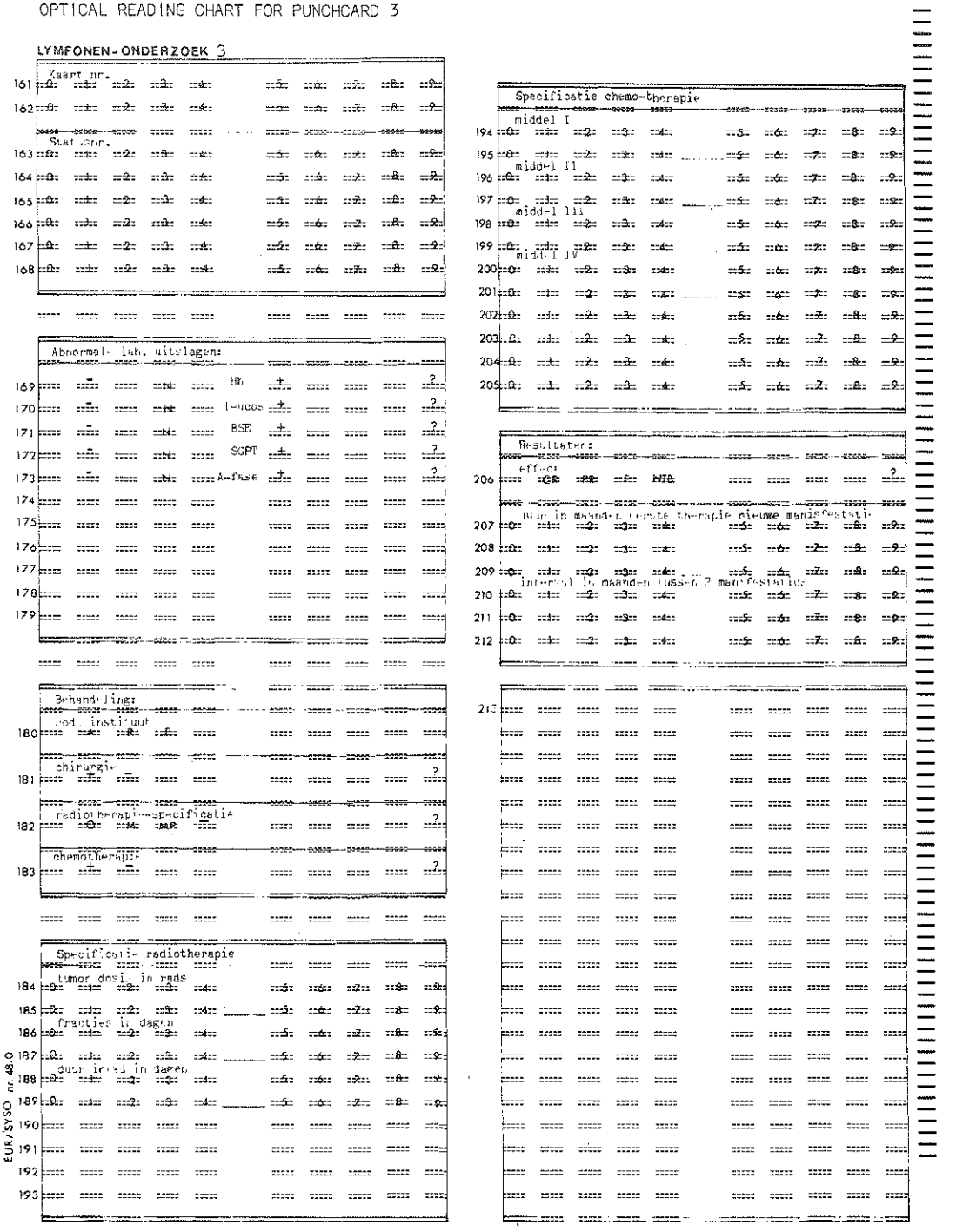
153 1 2 9

laparoscopie

154 1 2 9

EUR / SYSO nr 47.0

OPTICAL READING CHART FOR PUNCHCARD 3



Punchcard no. 1 CODE ON OPTICAL READING CHART AND PUNCHCARDS Appendix B

NO. ON CARD	INTERPRETATION
1 - 3	CARD-NUMBER
3 - 9	PATIENT FILE-NUMBER
9	INSTITUTE CODE
10 - 16	PATHOLOGY FILE-NUMBER
16 - 22	CYTOLOGY FILE-NUMBER
22	SEX M = MALE , F = FEMALE
23 - 29	BIRTHDATE - INVERTED (: YEAR, MONTH, DAY)
29 - 35	DATE OF FIRST SYMPTOMS - INVERTED
35 - 41	DATE OF PATHOLOGY DIAGNOSIS - INVERTED
41	INSTITUTE OF DIAGNOSIS
42 - 48	DATE OF PRESENTATION AT INSTITUTE - INVERTED
48 - 54	DATE OF DEATH, (IF KNOWN) - INVERTED
54 - 57	SURVIVAL IN MONTHS AT CLOSING-DATE
57	CONDITION AT CLOSING-DATE
	D = deceased
	1 : D 1 = by tumor
	2 : D 2 = by other illness
	3 : D 3 = iatrogenic complications
	4 : D 4 = cause unknown
	5 : LC = alive, complete remission
	6 : LIC = alive, partial remission
	7 : L? = alive, remission unknown
	9 : ? = no follow-up
58	NUMBER OF REMISSIONS ATTAINED

NO. ON CARD	INTERPRETATION	
	COMPLICATIONS	
59	LUNGFIBROSIS - PNEUMONITIS	
60	DERMATITIS	7 = positive
61	BONE-MARROW DEPRESSION	8 = negative
62	STEROID SIDE EFFECTS	9 = unknown
63	HAEMORRHAGIC CYSTITIS	
64	NEURITIS	
65	INFECTION, UNCLASSIFIED	
66		
67	VIRTUAL FOLLOW-UP (ACCORDING TO KAPLAN)	
68	INFECTION : 2 = + , 3 = - , 4 = bacterial, 5 = viral (minusherpes), 6 = herpes, 7 = opportunistic, 9 = unknown	
69	LEUKEMIA : 7 = + , 8 = - , 9 = unknown	
70 - 73	INTERVAL IN MONTHS FROM PRIMARY THERAPY TILL LEUKEMIA-APPEARANCE	
73 - 75	LEUKEMIATYPE IN CODE	
75	RECURRENCE IN IRRADIATED AREA : 7 = central, 8 = peripheral, 9 = unknown	
76 - 79	INTERVAL IN MONTHS BETWEEN IRRADIATION AND RELAPSE IN IRRADIATED AREA	
79 - 80	AGE IN YEARS	

Card nr. 2

1 - 2	CARD NUMBER
3 - 9	FILE NUMBER

NO. ON CARD	INTERPRETATION
9 - 10	FIRST COMPLAINT
	1 = none
	2 = painless lymphnodes
	3 = painfull lymphnodes
	4 = gastrointestinal complaints
	5 = fatique, malaise
	6 = fever, night-sweats
	7 = bone pain
	8 = unexplained weight loss
	9 = E.N.T.-problems
	11 = vena cava superior syndrome
	12 = respiratory tract abnormalities
	13 = unknown
	14 = skin manifestations
	15 = salivary gland abnormalities
	16 = urogenital symptoms
	17 = muscle weakness
11	HISTOLOGY
	1 = small-cell }
	2 = polymorph-cell }
	3 = medium sized cell } Lymphoblastosarcoma
	4 = large cell }
	5 = histiosarcoma
	6 = histioblastosarcoma
	7 = polymorph-cell histiosarcoma

NO. ON CARD	INTERPRETATION
11	HISTOLOGY
	8 = mixed follicular
	9 = no malignant lymphoma
12	NECROSIS
	1 = none
	2 = positive
	3 = grade I
	4 = grade II
	5 = grade III
	9 = unknown
13	PRESENCE OF MACROPHAGES
	1 = none
	2 = grade I
	3 = grade II
	4 = grade III
	9 = unknown
14	QUALITY OF SLIDES
	1 = good
	2 = poor
	3 = rather small
	4 = 2 + 3
	5 = wrong slide?
	9 = no opinion possible

NO. ON CARD	INTERPRETATION
15	PRESENCE OF EPITHELOID CELLS
	1 = none
	2 = few
	3 = many
	9 = no opinion possible
16	STRUCTURE
	1 = diffuse
	2 = follicular, well structured
	3 = follicular, poorly structured
	4 = partial follicular
	5 = follicular, deposits of eosinophilic material
	6 = mixed follicular = 11.8
	9 = no opinion possible
17	FIBROSIS
	1 = none
	2 = nodular fibrosis
	3 = bandlike fibrosis
	4 = hyaline fibrosis
	5 = 2 + 4
	6 = diffuse fibrosis
	8 = positive, no further score
	9 = no opinion possible
18	ORIGIN
	1 = lymph node
	2 = extranodal
	3 = 1 + 2

NO. ON CARD	INTERPRETATION
18	ORIGIN
	4 = bone-marrow
	5 = post mortem
	9 = unknown
19	EOSINOPHILIC CELLS
	1 = none
	2 = few
	3 = many
	9 = no opinion
20	CYTOLOGY
21	OTHER MALIGNANCY
	0 = no
	1 = positive, except skin
	6 = skin
	9 = unknown
	LYMPH NODES
22	NECK, TOTAL, LEFT — 1 = clinically positive
23	NECK, TOTAL, RIGHT — 2 = negative
24	CERVICAL, LEFT — 8 = histology positive
25	CERVICAL, RIGHT — 9 = unknown
26	SUBMANDIBULAR, LEFT
27	SUBMANDIBULAR, RIGHT
28	ANTERIOR CERVICAL TRIANGLE, LEFT — 1 = + (clinically)
29	ANTERIOR CERVICAL TRIANGLE, RIGHT — 2 = -
30	SUPRA- AND INFRACLAVICULAR, LEFT — 8 = PA +
31	SUPRA- AND INFRACLAVICULAR, RIGHT — 9 = ?

NO. ON CARD	INTERPRETATION	
32	AXILLARY, LEFT	
33	AXILLARY, RIGHT	
34	INGUINAL, LEFT	
35	INGUINAL, RIGHT	
36	WALDEYER	
37	MEDIASTINUM	
38	SPLEEN	
39	MESENTERIC	
40	PARA-AORTAL, LEFT	
41	PARA-AORTAL, RIGHT	
42	LUMBAR, LEFT	
43	LUMBAR, RIGHT	
44	BICEPITAL, LEFT	
45	BICEPITAL, RIGHT	
46	POPLITEAL, LEFT	
47	POPLITEAL, RIGHT	
	ORGANLOCALIZATIONS	
48	UPPER RESPIRATORY TRACT	
49	ESOPHAGUS	
50	STOMACH-DUODENUM	
51	SMALL INTESTINE-APPENDIX	
52	COLON-RECTUM	1 = + (clinically)
53	LIVER	2 = -
54	BILIARY TRACT	3 = PA +
55	SKIN	9 = ?

NO. ON CARD	INTERPRETATION
56	SKELETON
	1 = positive
	2 = negative
	3 = central skeleton
	4 = upper leg
	5 = lower leg
	6 = upper arm
	7 = lower arm
	8 = skull
	9 = unknown
57	LUNG
58	PLEURAL EXSUDATE
	1 = positive, no cytology known
	2 = negative
	5 = positive, cytology negative
	6 = positive, cytology positive
	9 = unknown
59	SALIVARY GLANDS
	1 = clinically positive
	2 = negative
	8 = histology positive
	9 = unknown
60	ENDOCRINE GLANDS
	1 = positive
	2 = negative

NO. ON CARD	INTERPRETATION
60	ENDOCRINE GLANDS
	4 = thyroid gland
	5 = adrenal glands
	9 = unknown
61	UROGENITAL SYSTEM
	1 = positive
	2 = negative
	4 = kidney
	5 = ureter - bladder
	6 = penis - prostate - vagina - uterus
	7 = testis - ovary
	9 = unknown
62	OTHER EXTRA-NODAL
63	LYMPHANGIOGRAPHY
	1 = $A^{+}L^{-}$
	2 = $A^{-}L^{+}$
	3 = $A^{-}L^{-}$
	4 = $A^{+}L^{+}$
	8 = suspect
	9 = not performed
	A = para-aortic
	L = para-lumbal
64	RADIOLYMPHANGIOGRAPHY (CODE SEE: 63)

NO. ON CARD	INTERPRETATION	
65	BONE-MARROW BIOPSY	1 = positive
66	BONE-MARROW ASPIRATION	2 = negative
		8 = suspect
		9 = not performed
67	LIVER SCAN	1 = positive
68	SPLEEN SCAN	3 = negative
		8 = suspect
		9 = not performed
69	CLINICAL STAGE I - II - III - IV , IV with leukemic phase	
70	SYSTEMIC SYMPTOMS	
	1 = A	
	2 = B	
71	PRIMARY LOCALIZATION	
	2 = nodal	
	3 = extra nodal	
	4 = both	
	5 = leukemic phase	
72	PATHOLOGICAL STAGE I - II - III - IV , IV with leukemic phase	
73	LAPAROTOMY	1 = performed
74	LAPAROSCOPY	2 = not performed
		9 = unknown
75 - 80		

Card nr. 3

1 - 2	CARD NUMBER
3 - 9	FILE NUMBER

Card no. 3, continued

NO. ON CARD	INTERPRETATION	
9	HEMOGLOBINE	1 = lowered
10	LEUKOCYTES	3 = normal
11	E.S.R.	5 = raised
12	S.G.P.T.	9 = unknown
13	SERUM ALKALINE PHOSPHATASE	
14 - 20		
20	INSTITUTE OF TREATMENT	
21	SURGICAL TREATMENT	
	1 = done	
	2 = not done	
	9 = unknown	
22	RADIOTHERAPY	
	1 = orthovoltage	
	2 = megavoltage	
	3 = megavoltage + wide field prophylaxis	
	4 = none	
	9 = unknown	
23	CHEMOTHERAPY	
	1 = yes	
	2 = no	
24 - 27	IRRADIATION DOSE IN RADS	
27 - 28	NUMBER OF IRRADIATIONS	
28 - 30	IRRADIATION TIME IN DAYS	
30 - 34		

NO. ON CARD	INTERPRETATION
34 - 35	FIRST CHEMOTHERAPY
36 - 37	SECOND CHEMOTHERAPY
38 - 39	THIRD CHEMOTHERAPY

1 = adriamycin
2 = BCNU
3 = bleomycin
4 = CCNU
5 = corticosteroids
6 = cytosine arabinoside
7 = rubidomycin
8 = cyclophosphamide
9 = chlorambucil
10 = methyl-CCNU
11 = nitrogen-mustard
12 = methotrexate
13 = busulfan
14 = procarbazin
15 = vincristin
16 = thiotepa
17 = vinblastin
18 = ACOP
19 = COP, continuous
20 = COP } pulse dosage
21 = COPP }
22 = MOPP } pulse dosage
23 = MABOP }
24 = mercaptopurin
25 = triethylene melamine
26 = urethane

39 - 46	RESULT OF TREATMENT

1 = complete remission
2 = partial remission
3 = failure
4 = non-evaluable
9 = unknown

NO. ON CARD	INTERPRETATION
47 - 50	INTERVAL IN MONTHS BETWEEN PRIMARY TREATMENT AND RELAPSE
50 - 53	INTERVAL IN MONTHS BETWEEN TWO SUCCESSIVE MANIFESTATIONS OF DISEASE
>53	

Note: All open numbers can be filled in with further data, if necessary.

Appendix C

PROGRAMS USED FOR COMPUTING AND STATISTICAL ANALYSIS.

A. INTRODUCTION.

All programs are especially developed for this study. However, they are designed in such a way that it is easy to add more patients and episodes of the disease, that may have occurred after the closing date. The checking programs make it possible, by limiting the permitted values, to retain only the correct data; all punchcards showing filing errors or logical deficiencies are put apart for correction. Filing errors are omissions of important data, such as length of follow-up or result of treatment. Logical deficiencies are present when impossible results are derived from correct data, e.g. leukemic development staged as II. The statistical program produces a set of 24 parameters from the files of all patients, and puts these combined data in computer storage. Between any desired pair of these parameters cross-tabulations can be made, complete with statistical analysis. Furthermore 5 other variables can be "frozen" into specified positions; this makes cross-tabulations in 7 dimensions possible, e.g. radiotherapy methods (1) cross-tabulated against treatment results (2) on the basis of the following criteria: male (3), more than 30 years of age (4), diffuse (5), well differentiated lymphocytic lymphoma (6), stage I or II (7).

B. CHECKING PROGRAMS.

1. EEN : checks punchcard number one on logical deficiencies and filing errors.
2. ONEVen : checks odd numbered cards except for the first card.
3. EVEN : checks even numbered cards.
4. ELLEnde : checks for missing data cards.

5. ZOEK : collects all data cards with a given file number (e.g. a patient whose data need correction or updating) and puts them apart.

6. WENS : puts all cards apart that have a specified value at one particular place; this is in fact lifting of selected files.

C. STATISTICAL PROGRAMS.

7. COMP : puts 24 specified data from each patient in computer storage (e.g. disk-storage). From this matrix cross-tabulations are made.

8. KRUIS : computes cross-tables from specified data compiled by COMP. The following side features are incorporated in this program:

a. 5 "frozen" dimensions are possible, therefore 7 dimensional tabulations can be effected.

b. this program, unless directed not to do so, calculates with each tabulation also the sums, standard error, standard deviation, probability, X-square and L-test; also it indicates whether the X-square or the L-test is the more useful. To do this some subroutines were used:

9. GAUS T : gives the integral of a Gaussion distribution by polynomial approximations (Ibbetson, 1963).

10. CHI P : uses GAUS T to compute probabilities (Hill and Pike, 1967; O'Brien and Wood, 1968).

11. CHIP test : tests COMP, KRUIS and CHIP together against a set of known values (Pearson, 1962). Besides it tests the decimal accuracy of the entire computing system.

c. correction of the raw survival figures according to the life-table method of Kaplan and Meier.

12. FREQ : this is a simplified version of program KRUIS which presents multiple cross-tabulations in one table - without statistical evaluation of the results. In effect it cross-tabulates all known (or permitted) values of the first X data, against all known (or permitted) values of the last Z data, for each known (or permitted) value of Y; the sum of X, Y and Z is maximally 24.

13. REGR T : performs multiple regression analysis after data transformation in a way comparable to the I.B.M.-S.S.P. programs (I.B.M., 1968).

Appendix D: A Survey of Primary Localizations

Primary Localisation	Neck LE	Neck RI	Axilla LE	Axilla RI	Groin LE	Groin RI	Waldeyer	Mediastinum	Spleen	Lymphogram	Upper Airways	Stomach Duodenum	Colon Rectum	Liver	Skin	Skull	Lung Parenchyma	Pleural Exsudate	Small Intestine	Kidney	Ureter Bladder	Penis Prostate Vagine Uterus	Testis Ovary	Bone Marrow	Salivary Glands	Thyroid	Adrenals
Tot	148	137	71	65	69	62	77	52	46	38	25	17	0	41	49	12	18	13	6	1	6	1	7	24	4	3	2
st I	11	12	2	1	4	1	8	4	1	4	4	1	0	0	9	2	0	1	2	0	0	0	2	0	1	1	0
st II	54	45	13	11	10	12	38	12	2	15	9	10	0	0	12	4	3	2	4	0	3	1	1	0	1	0	1
st III	27	22	16	14	20	17	7	11	7	10	1	0	0	0	1	0	2	0	0	0	0	0	0	0	0	0	0
st IV	50	50	37	35	32	29	21	23	33	8	10	6	0	41	26	5	13	10	0	1	3	0	4	18	2	2	1
LCS	47	45	24	22	28	26	18	23	18	10	5	3	0	10	14	3	6	5	2	0	0	0	0	13	2	1	0
LBS	51	47	20	17	22	23	33	13	16	19	9	10	0	17	15	5	3	1	4	0	3	1	5	6	1	1	1
HCS	25	22	16	12	12	7	13	9	10	6	8	4	0	10	13	2	6	5	0	1	2	0	2	3	1	1	1
HBS	21	20	8	11	3	2	13	6	1	2	3	0	0	2	5	2	2	1	0	0	1	0	0	0	0	0	0
FM	4	3	3	3	4	4	0	1	1	1	0	0	0	2	2	0	1	1	0	0	0	0	0	2	0	0	0
Diff	75	66	36	33	29	27	46	27	25	24	13	10	0	26	23	7	7	2	5	1	6	0	7	8	3	2	2
Foll	37	27	17	19	19	18	7	10	16	10	2	3	0	7	9	0	6	4	1	0	0	0	0	9	0	1	0
♂	82	73	44	43	41	38	38	27	30	22	11	10	0	30	27	5	11	8	3	1	3	0	5	14	1	3	1
♀	66	64	27	22	28	24	39	25	16	16	14	7	0	11	22	7	7	5	3	0	3	1	2	10	3	0	1

Clinical stage	I	II	III	IV	"L"	All
Cell type						
LCS	18	22	14	26	4	84
LBS	27	49	12	31	3	122
HCS	15	20	4	22	0	61
HBS	9	21	1	6	0	37
FM	1	1	1	4	0	7
All	70	113	32	89	7	311

Appendix E: Cell type and Clinical Stage.

Clinical stage	I	II	III	IV	All
Structure:					
Diffuse	35	66	12	48	161
Follicular	18	19	10	15	62
All	53	85	22	63	221

Appendix F : Structure and Clinical Stage.

Age \ Cell type	LCS	LBS	HCS	HBS	FM	All
0 - 20	6	7	1	1	0	15
20 - 40	3	13	9	6	1	32
40 - 60	31	39	18	12	0	100
60 - 80	39	53	26	15	6	139
>80	7	10	7	4	0	28
All	86	122	61	38	7	314

Appendix G : Cell type and age (in years).

Age \ Structure	Diffuse	Follicular	All
0 - 20	7	3	10
20 - 40	20	5	25
40 - 60	49	19	68
60 - 80	76	29	105
>80	13	7	20
All	165	63	228

Appendix H : Structure and age (in years).

Appenx J: The effect of constitutional symptoms within each clinical stage and within each cell type.

Survival Chance Percentage

Years of survival	Clinical Stage								Histology							
	I		II		III		IV		LCS		LBS		HCS		HBS	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
n=	64	3	90	6	16	12	31	39	50	19	78	25	40	14	24	7
0	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
1	92	67	69	50	37	50	45	18	73	47	73	28	65	21	62	14
2	81	67	49	0	25	33	39	5	58	32	58	8	47	0	54	14
3	73	67	44		25	25	32	0	56	21	51	4	39		44	14
4	65	67	38		19	25	29		49	14	44	4	39		37	14
5	57	33	35		12	12	25		45	7	41	0	34		37	14
6	51	33	33		12	12	25		39	7	38		34		37	14
7	46	33	30		6	12	20		34	7	38		19		37	14
8	38	33	27		6	12	20		28	7	38		19		37	14
9	19	33	27		6	0	20		25	0	38		19		37	14
10	19	33	27		6		20		22		38		13		37	14
11	0	33	27		6		13		18		38		13		37	14
12		0	27		6		13		18		38		13		37	14
13			21		0		13		18		0		13		37	0
14			14				0		9				0		37	
15			14						9						17	

Note: Below this sign o n <10
Below this sign - n < 5

Appendix J

CURRICULUM VITAE

Jacques van Turnhout was born in Geldrop on August 15th, 1943.

He graduated from the 'gymnasium β' in July 1961.

He studied medicine in Nijmegen, becoming an M.D. in February 1969.

He passed the E.C.F.M.G. examination in July 1972.

He received his training as an internist in Arnhem (Gemeente Ziekenhuis, Dr. L. Schaim) and Rotterdam (Sint Clara Ziekenhuis, Dr. E.E. Twiss; Rotterdam Radio Therapy Institute, W.F. Stenfert Kroese).

He was registered as a specialist in internal medicine in March 1974.

He is now at the hematology department of the Academic Hospital, Rotterdam.