THE NON-HODGKIN'S LYMPHOMAS

CURRENT STATUS

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DEFINITION

The lymphomas are a diverse group of malignant disorders sharing in common their origin in lymphoid tissues. Those lymphomas which do not fit the histologic criteria for Hodgkin's disease are termed the nonHodgkin's lymphomas. As a matter of convention and for the purposes of this discussion, certain disease entities are excluded from the term nonHodgkin's lymphoma. These include:

1. Acute lymphocytic leukemia
2. Chronic lymphocytic leukemia
3. Malignant histiocytoses
4. Leukemic reticuloendotheliosis (Hairy cell leukemia)
5. Mycosis fungoides and Sezary syndrome.

It is clear that there is a close interrelationship between the non-Hodgkin's lymphomas and the above named disorders. In some instances, actual identity may exist.

CLASSIFICATION

One of the most important advances in our understanding of the nonHodgkin's lymphomas was the recognition by Rappaport that the histologic heterogeneity of these diseases could be,in part, correlated with the clinical variability. His classification of the nonHodgkin's lymphomas is shown in Table I along with the relative incidence of each subtype (1, 2). This classification has become the most widely utilized and has served as a basis for most of the recent prospective studies in this area.

TABLE 1 (Ref. 1)

RAPPAPORT CLASSIFICATION OF NON-HODGKIN'S LYMPHOMA

	% Frequency	
	NODULAR	DIFFUSE
WELL DIFFERENTIATED LYMPHOCYTIC (WDL)	<1	2*
POORLY DIFFERENTIATED LYMPHOCYTIC (PDL)	30	20
MIXED HISTIOCYTIC LYMPHOCYTIC (M)	10	5
HISTIOCYTIC (H)	5	25
UNDIFFERENTIATED (U)	0	3
UNCLASSIFIABLE	0	<1
	45	55

*C.L.L. NOT INCLUDED

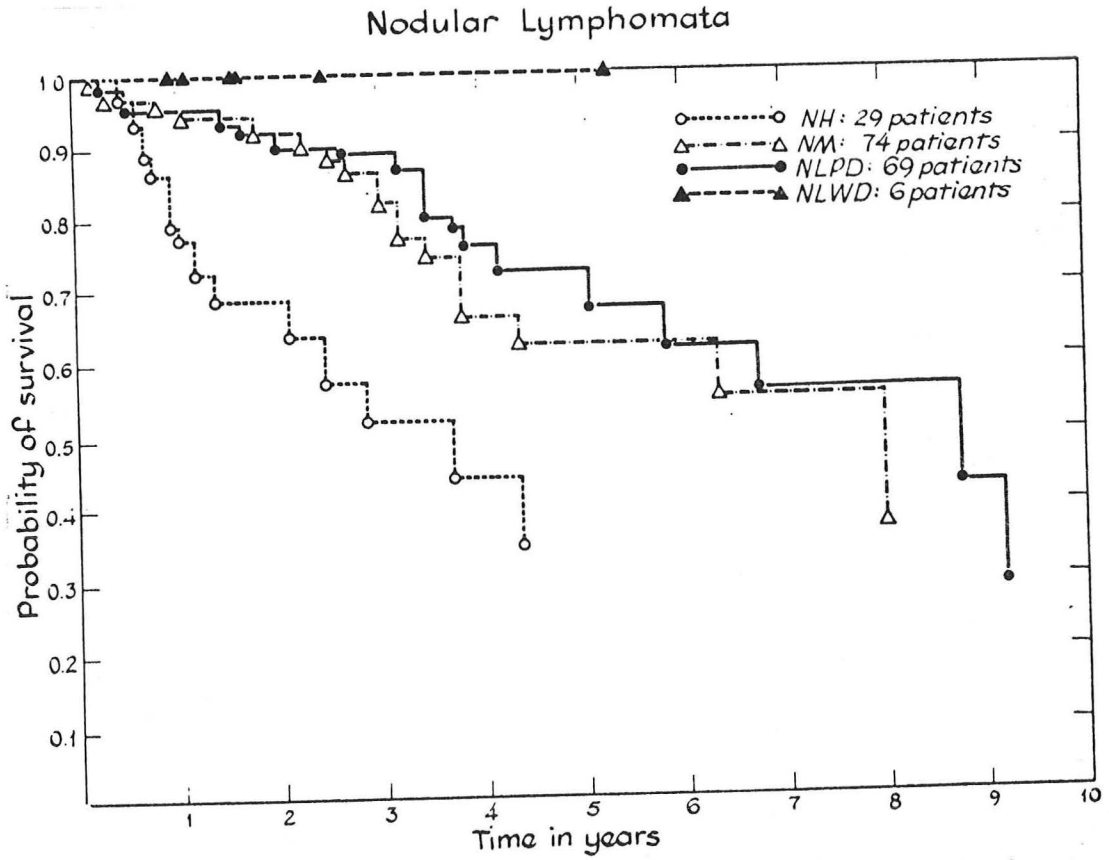
The following comments can be made regarding the utility of the Rappaport classification:

1. Retrospective and prospective studies have demonstrated that it has a workable application to the initial evaluation, therapy, and prognosis. This is especially true in the separation of nodular versus diffuse patterns but also, to some extent, in terms of cell type.(3) (Figures 1 and 2)

2. This classification does not delineate groups of patients within certain categories, which appear to behave in clearly different ways.

3. Certain tumors which appear to be well defined entities, both histologically and clinically, are not accounted for as separate types in this classification (e.g. Burkitt's lymphoma)

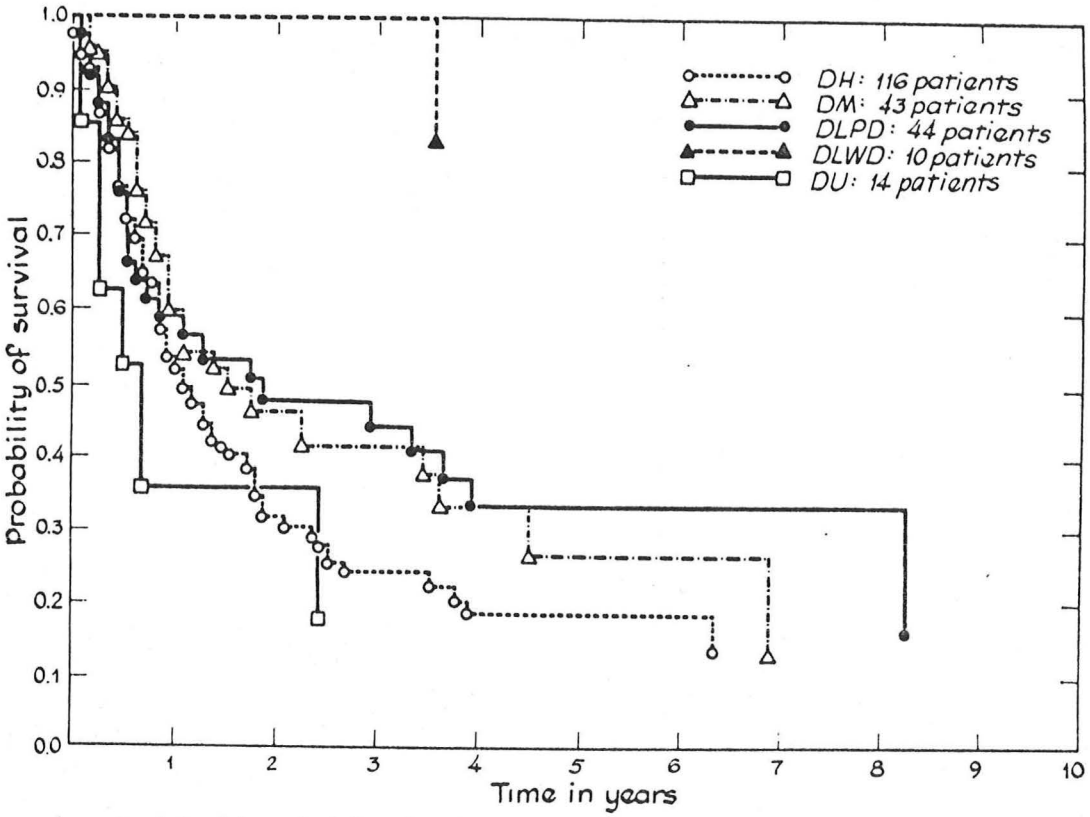
FIGURE 1 (Ref. 3)



Actuarial survival for all patients in each histological category of nodular lymphoma. (Reprinted from Jones *et al.*, *Cancer, N.Y.*, 1973, **31**, 806, with permission of the publisher.)

FIGURE 2 (Ref. 3)

Diffuse Lymphomata



Actuarial survival for all patients in each histological category of diffuse lymphoma. (Reprinted from Jones *et al.*, *Cancer, N.Y.*, 1973, **31**, 806, with permission of the publisher.)

Because of the recognized inherent deficiencies in the clinical application of the Rappaport classification, other approaches to the delineation of the nonHodgkin's lymphomas are under active investigation. These are being evaluated both in terms of their application to the Rappaport system, as well as totally different modes of separation. Examples of such studies are as follows:

1. By applying the techniques of several cellular markers, such as the presence of surface immunoglobulin, complement receptors, E. rosette formation and histochemical stains, the site of origin and/or function of the malignant cells are being evaluated. (4-7) (Figure 3). The following types of information has so far emerged:

   a) T cell disorders - in addition to the previous recognition that Sezary syndrome and mycosis fungoides are T cell malignancies, it appears that one subgroup of poorly differentiated lymphocytic diffuse lymphomas are T cell in origin as well as a small percentage of histiocytic diffuse. It has been proposed that these tumors arise from the inter-follicular or paracortical regions of the lymph node.

b) B cell disorders - it has been previously recognized that the majority of cases of chronic lymphocytic leukemia are B cell in origin and along with such immunoglobulin producing neoplasms as Waldenstrom's macroglobulinemia may be malignancies of the medullary cords of the lymph node. Similar studies suggest that well differentiated lymphocytic diffuse lymphoma may be of similar origin. In addition, essentially all of the nodular nonHodgkin's lymphomas mark as B cells, as well as many of the poorly differentiated lymphocytic diffuse, histiocytic diffuse and undifferentiated lymphomas. It has been proposed that these are tumors arising from cells of the germinal centers of the lymphoid follicles.

c) Histiocyte disorders - only a rare tumor marks as a true histiocyte and these fall into the category of histiocytic diffuse lymphoma. It is thus apparent that the term histiocytic lymphoma, as used in the Rappaport classification, is generally a misnomer.

d) In a number of cases the site of origin and/or function of the lymphoma studied is not identifiable.

FIGURE 3 (Ref. 7)

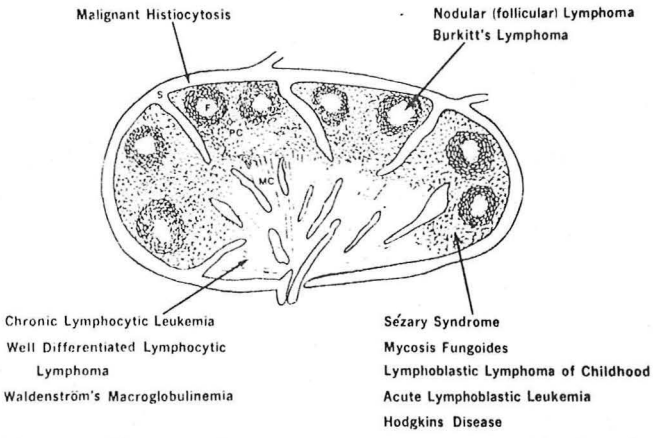


Figure 2. Diagrammatic representation of a normal lymph node, showing the anatomic and functional compartments of the immune system. The malignant lymphomas are related conceptually and functionally to each of the above compartments. S = sinuses; F = follicles; PC = paracortex; MC = medullary cords.

2. Several studies are in progress attempting to define histologic subtypes within the Rappaport classification, which in themselves, may have prognostic and therapeutic significance. (4, 8) (Table 2) Examples of such histologic subclassification include diffuse lymphomas of intermediate differentiation, lymphoblastic lymphoma, Burkitt's lymphoma and immunoblastic sarcoma.

TABLE 2

TRENDS IN HISTOLOGIC SUBCLASSIFICATION
OF NON-HODGKIN'S LYMPHOMA

NODULAR TYPES - HISTIOCYTIC VS. OTHERS

DIFFUSE TYPES -

WELL DIFFERENTIATED:	CHRONIC LYMPHOCYTIC LEUKEMIA ASSOCIATED PARAPROTEIN NEITHER
POORLY DIFFERENTIATED LYMPHOCYTIC:	INTERMEDIATE DIFFERENTIATED LYMPHOBLASTIC
UNDIFFERENTIATED:	LYMPHOBLASTIC BURKITT'S LYMPHOMA
HISTIOCYTIC:	IMMUNOBLASTIC SARCOMA TRUE HISTIOCYTIC

3. A third area of investigation that has been of very limited yield at this time has been the attempt to delineate specific etiologic agents in nonHodgkin's lymphomas. The most important example of this approach has been the recognition of the relationship of the EB virus to African Burkitt's lymphoma (9).

The role of these alternative attempts at the classification of the non-Hodgkin's lymphomas in terms of delineating separate clinical pathologic entities and, in particular, their application to the therapy and prognosis of patients remains in doubt. For these reasons, despite its obvious drawbacks, the Rappaport classification remains the "gold standard" for prospective evaluation of patients with the nonHodgkin's lymphomas.

STAGING

One of the most notable advances leading to improved survival and cure rates in Hodgkin's disease was the development and evaluation of several diagnostic procedures, including staging laparotomy, which allowed a precise definition of the extent of disease. It became apparent that critical therapeutic decisions depended principally on knowing the stage of the disease as defined by the Rye staging system.

In an analogous manner, a number of prospective investigative series have been carried out to assess the significance of obtaining similar data in patients with nonHodgkin's lymphoma. The Rye staging system has also been used in these studies. (Table 3) (10).

TABLE 3 (Ref. 10)

Hodgkin's Disease: Ann Arbor Modification of Rye Staging System (1971)	
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E).
Stage 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 or site (III_E) or by involvement of the spleen (III_S) or both (III_{SE}).
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Reasons for classifying the patient as Stage IV should be identified.
Note: In Hodgkin's disease, all patients are subclassified A or B to indicate the absence or presence, respectively, of (1) unexplained weight loss of more than 10 percent body weight; (2) unexplained fever with temperatures above 38°C; (3) night sweats.	

The studies have been designed to answer the following specific questions:

1. Do the extent and patterns of involvement vary in relationship to the histologic type according to the Rappaport classification?
2. What is the relative frequency of localized versus disseminated nonHodgkin's lymphomas?
3. What is the reliability of certain staging procedures in identifying the presence or absence of involvement?

A. Lymph Node Involvement (11-15) (Figure 4, Table 4 and Table 5)

1. Lymph node involvement of Stage III extent is seen more frequently in the nonHodgkin's lymphomas, occurring in over 60% of patients with the nodular lymphomas and in nearly 50% of patients with diffuse lymphomas.

2. Paradoxically, mediastinal lymph node involvement is rather infrequent in the nonHodgkin's lymphomas as compared to Hodgkin's disease. The one exception to this is the lymphoblastic lymphoma or T cell lymphoma in the poorly differentiated lymphocytic diffuse category which has at least 50% mediastinal masses. (8).

3. The use of the lymphangiogram to identify intraabdominal lymph node involvement has proven to be highly accurate when positive, ranging from 83 to 95% in several studies. False negatives occur approximately one third of the time however.

4. The inferior venacavagram is also highly accurate when positive, but has over 50% false negatives.

5. The gallium scan has added nothing significantly to the radiologic procedures and is less sensitive than the lymphangiogram.

6. Frequently false negative radiologic evaluation of intraabdominal node involvement is accounted for by the presence of mesenteric and porta hepatis nodes which are not visualized by these techniques.

B. Spleen Involvement (11, 14)

1. Approximately one third of patients have splenic involvement.

2. When the spleen is clinically palpable it is 80 to 90% accurate in predicting involvement. This contrasts to the reliability of palpable splenomegaly in Hodgkin's disease.

3. The absence of palpable splenomegaly is not a reliable indicator of non-involvement.

TABLE 4 (Ref. 13)

Yield of Non-Surgical Procedures in Staging Non-Hodgkin's Lymphoma*

	Lymphangiogram		Bone Marrow Biopsy		Percutaneous Liver Biopsy		Peritoneoscopy Liver Biopsy	
	no. +/no. tested	%	*no. +/no. tested*	%	*no. +/no. tested*	%	*no. +/no. tested*	%
Nodular								
PDL	38/42	90	19/48	40	14/45	31	6/28	21
Mixed	18/20	90	11/24	46	4/21	21	7/17	41
HIST	6/7	86	1/7	14	0/6	0	3/6	50
Total	62/69	90	31/79	39	18/72	25	16/51	32
Diffuse								
WDL	5/5	100	6/6	100	2/4	50	0/1	0
PDL	10/16	63	15/28	54	5/15	33	5/7	71
Mixed	6/7	86	2/6	33	1/4	25	2/5	40
HIST	21/37	57	6/39	15	2/33	5	3/26	12
Stem	3/3	100	4/7	57	0/3	0	0/1	0
Total	45/68	66	33/86	38	10/59	17	10/40	25

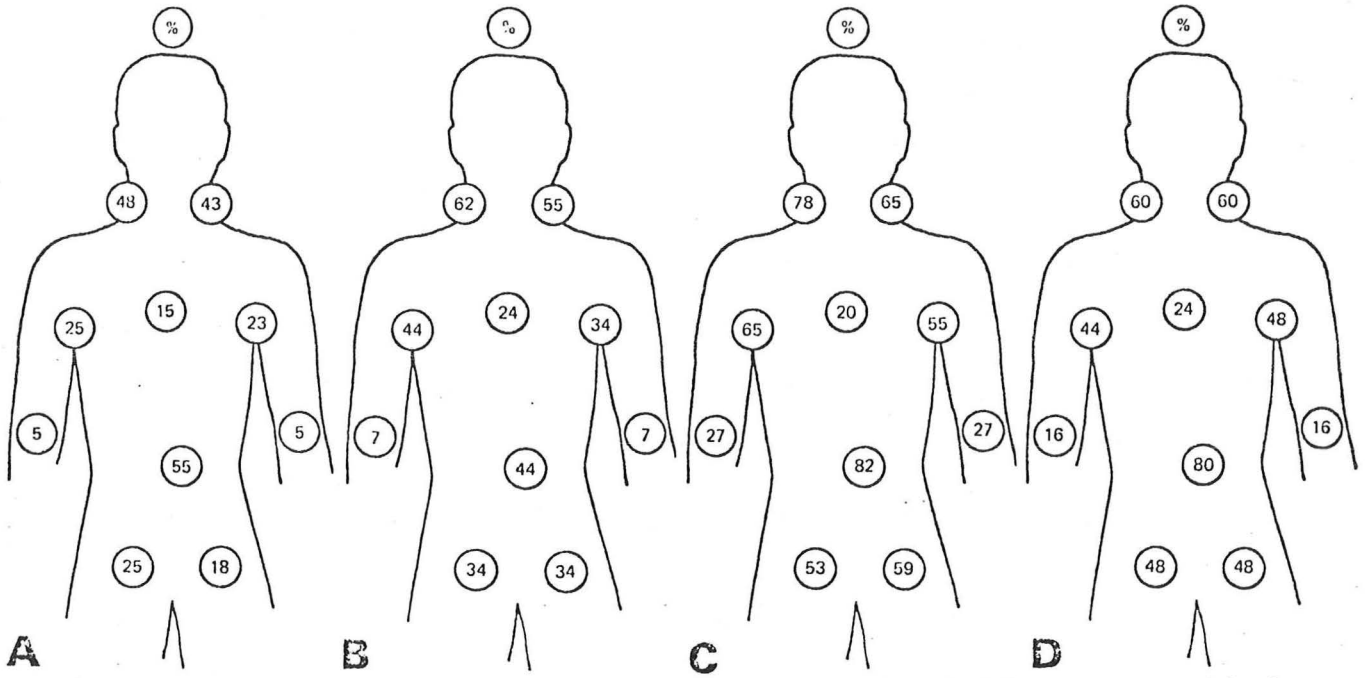
* WDL = well-differentiated lymphocytic; PDL = poorly differentiated lymphocytic; Mixed = mixed lymphocytic-histiocytic; HIST = histiocytic; Stem = pleomorphic or stem cell lymphoma.

TABLE 5 (Ref. 14)

Accuracy of Diagnostic Tests in Non-Hodgkin's Lymphomas*		
Test	Accuracy on positives (percent)	Accuracy on negatives (percent)
Inferior venacavagram	93	47
Lymphangiogram	83	67
Liver scan	50	82
Spleen scan	77	61
Gallium scan	82	59

*Based on a series of 57 staging laparotomies performed at the University of Chicago. Accuracy indicates clinical impression of test confirmed by pathologic stage. For example, 93 percent of inferior venacavagrams interpreted as positive were confirmed on pathologic section; 47 percent considered clinically negative were found to be negative and the balance, 53 percent, were positive.[6]

FIGURE 4 (Ref. 13)



. Body diagrams showing the percentage of patients with lymph node involvement in each of the major lymph node-bearing areas, including epitrochlear, axillary, cervical and supraclavicular, mediastinal or hilar, para-aortic, and inguinal. Nodal involvement was determined by clinical examination, chest X ray, and lymphangiogram and does not include results of surgical staging. A. 40 patients with diffuse histiocytic lymphoma. B. 29 patients with diffuse poorly differential lymphocytic lymphoma. C. 49 patients with nodular poorly differentiated lymphocytic lymphoma. D. 25 patients with nodular mixed lymphocytic-histiocytic lymphoma.

C. Bone Marrow Involvement (11, 13, 14, 16-19) (Table 4, 6 and 7).

Because of its benign nature, the utilization of bone marrow examination as a means of detecting Stage IV disease has been widely investigated. The following general conclusions can be drawn from these studies:

1. Table 6 demonstrates an example of an observation that has been uniformly made in all series. The needle biopsy of the bone marrow is a much more reliable indicator of involvement than a bone marrow aspirate. In a few instances, however, the aspirate material will give a positive result when the needle biopsy has been negative. Thus the ideal circumstance is to obtain both an aspirate and needle biopsy of the bone marrow.

2. Table 7 demonstrates the frequency of bone marrow involvement in nonHodgkin's lymphoma in the three largest reported series. Approximately 30% of all patients will have marrow involvement at the time of initial diagnosis. This is in direct contrast to observations in Hodgkin's disease where generally less than 10% of patients will have bone marrow involvement initially.

3. The frequency of bone marrow involvement is clearly related to the histologic type of the lymphoma. Forty to fifty percent of patients with poorly differentiated lymphocytic lymphoma, either nodular or diffuse, will demonstrate positive biopsies. On the other hand less than 10% of patients with histiocytic diffuse lymphoma demonstrate this finding.

TABLE 6 (ref. 18)

Comparison of Open, Needle, and Aspirate Techniques in Demonstrating Lymphoma in the Bone Marrow

	No.	No. with positive needle	No. with negative needle	No. with positive aspirate	No. with negative aspirate
Positive open biopsy	17	1 (1 equivocal)	5	0	16
Positive needle biopsy	22	—	—	4	17
Positive aspirate	11	4	2	—	—

TABLE 7 (Ref. 13, 17, 18)

BONE MARROW INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA

% POSITIVE NEEDLE BIOPSIES

HISTOLOGY	NCI(165)	CHICAGO(116)	STANFORD(212)	TOTAL(493)
ALL	39	38	17	29
DIFFUSE	38	32	15	27
NODULAR	39	50	18	31
PDL-D	54	61	29	50
H-D	15	5	5	8
PDL-N	40	59	30	42
H-N	14	-	5	8

D. Hepatic Involvement (11-14) (Tables 4, 8 and 9)

Several investigators have attempted to determine the frequency of hepatic involvement in the nonHodgkin's lymphomas primarily by carrying out relatively unselected staging laparotomies. The percentage of patients with hepatic involvement under these circumstances varied from series to series depending upon the weight of the various histologic subtypes and also the criteria for selecting patients for laparotomy. A more practical and applicable approach to the question has been carried out at the National Cancer Institute where a series of 170 consecutive patients with nonHodgkin's lymphoma underwent a series of prelaparotomy staging procedures. Included in this investigation was an evaluation of the usefulness and yield of the percutaneous needle liver biopsy and liver biopsy by peritoneoscopy. One hundred and thirty three of the one hundred and seventy patients were subjected to percutaneous needle biopsy of the liver. Subsequently, ninety one of the patients whose needle biopsy was negative underwent peritoneoscopy with liver biopsies under visualization. Their observations, which are consistent with others as well, can be summarized as follows:

1. Twenty one percent of the percutaneous needle biopsies were positive. In those patients with negative needle biopsies 29% had positive liver biopsies at the time of peritoneoscopy. Finally, 44 patients with negative liver biopsies and negative bone marrow biopsies underwent staging laparotomy. Wedge liver biopsies in these patients were positive in 20%. Thus, both percutaneous needle biopsy and peritoneoscopy have a significant yield of positive results in patients with nonHodgkin's lymphoma, which is in direct contrast to the circumstance in Hodgkin's disease where percutaneous needle biopsy is notoriously unable to identify hepatic involvement.

2. Table 9 demonstrates the approximate frequency of hepatic involvement in nonHodgkin's lymphomas overall and by histologic type. At least 50% of the patients in this series had hepatic involvement and this was slightly more frequent in the nodular lymphomas than the diffuse. Of greater significance was the relative frequency in different specific histologic subtypes. For example, in patients with poorly differentiated lymphocytic nodular or diffuse lymphomas one half to two thirds had hepatic involvement, whereas patients with histiocytic diffuse lymphoma had approximately 15% incidence.

3. In several series in which hepatic involvement was delineated by staging laparotomy, 90% of patients with hepatic involvement also had splenic involvement. A similar observation has been made in patients with Hodgkin's disease.

4. When the lymphangiogram is negative, hepatic lesions are infrequent.

5. It is apparent from all studies that clinical evaluation, including physical examination, liver scan, and liver function tests are highly inaccurate for determining the presence or absence of hepatic involvement. This again is similar to observations in Hodgkin's disease.

TABLE 8 (Ref. 13)

Staging Laparotomy: 44 Patients with Negative Closed Liver Biopsies and Negative Marrow*

	Wedge Liver Biopsy Positive	Porta Hepatis or Mesenteric Nodes Positive†	Ascites Positive‡	Patients with Positive Finding/Total Patients
Nodular				
PDL	7	5	0	12/18
Mixed	1	5	2	8/9
HIST	0	1	0	1/2
Total	8	11	2	21/29 (72%)§
Diffuse				
PDL	1	0	0	1/2
Mixed	0	1	0	1/2
HIST	0	2	0	2/11
Stem	0	0	0	0/0
Total	1	3	0	4/15 (27%)§

* PDL = poorly differentiated lymphocytic; Mixed = mixed lymphocytic-histiocytic; HIST = histiocytic; Stem = pleomorphic or stem cell lymphoma.
† In patients with liver and ascites (negative).
‡ In patients with liver and nodes (negative).
§ $P < 0.05$.

TABLE 9 (Ref. 13)

APPROXIMATE FREQUENCY OF HEPATIC INVOLVEMENT
IN NON-HODGKIN'S LYMPHOMA

HISTOLOGY	% EXPECTED INVOLVEMENT
ALL	54
NODULAR	63
DIFFUSE	46
PDL-N	67
PDL-D	50-67
H-D	15

E. Blood Involvement (8, 19-22)

Although chronic lymphocytic leukemia is generally excluded from consideration of the nonHodgkin's lymphomas, circulating malignant cells in the remaining histologic cell types may occur. The frequency and significance varies due to several factors.

1. Lymphoma cells in the peripheral blood of patients with nodular lymphomas at the time of diagnosis may occur in as many as one third. This feature does not appear to have any effect on the expected prognosis of patients with nodular lymphoma.

2. A leukemic picture is uncommon at the time of diagnosis in the other nonHodgkin's lymphomas with the one exception of the histologic subtype, lymphoblastic lymphoma.

3. A leukemic picture developing in patients with diffuse lymphomas or late in the course of patients with nodular lymphomas imparts a grave prognosis in general. This is primarily due to the fact that the leukemic conversion is frequently followed shortly by the presence of meningeal lymphoma. This latter complication is associated with a median survival of less than three months.

F. Other Sites of Involvement

Less commonly a number of other extralymphatic sites may be involved in nonHodgkin's lymphoma at the time of presentation. These include lung, bone, CNS, gastrointestinal tract, gonads, kidney, breast and skin. Almost no systematic evaluation of the prognostic and therapeutic significance of these areas of involvement are available since the development of the Rappaport histologic classification and the use of refined staging procedures.

G. Conclusions Regarding Results of Staging Procedures Including Staging Laparotomy. (Table 10 - 12)

It will be seen subsequently that the major impact of the stage of disease at the time of diagnosis in patients with nonHodgkin's lymphomas primarily involves the recognition of those patients with very localized disease (generally Stage I) versus those with disease beyond this extent. With this point as a background the following comments can be made related to the necessity of, and approach to, the staging of patients with nonHodgkin's lymphoma:

1. Table 10 demonstrates the clinical stage on referral of patients in the NCI series and the relative usefulness of the various staging procedures described above in delineating the presence of more extensive disease than initially appreciated. Approximately one third of patients had apparently localized (Stage I or II) disease after initial physical evaluation. The sequential use of the lymphangiogram, bone marrow biopsy and closed liver biopsies including peritoneoscopy reduced this number to 17%. After selected exploratory laparotomy in this residual group of patients, the final observation was that only 6% of patients had Stage I disease and 8% Stage II disease. Thus the overall incidence of localized disease in nonHodgkin's lymphomas is very small. It is therefore apparent that a staging laparotomy is only infrequently necessary in patients with nonHodgkin's lymphomas and that such a procedure should be performed only after very careful sequential staging procedure and then only if the likelihood of very localized disease still remains.

2. The frequency of localized versus disseminated disease is strikingly related to the histologic type by the Rappaport classification (Table 11). In the NCI study, 94% of patients with nodular lymphoma were Stage III or IV. Eighty six percent of patients with diffuse lymphomas other than histiocytic diffuse were also Stage III or IV. In significant contrast, however, 30% of patients with histiocytic diffuse lymphoma were found to be localized to Stage I or II.

3. Based upon the extensive evaluations published in the literature, a suggested procedure for the staging evaluation of patients with nonHodgkin's lymphoma is outlined in Table 12. There is little information available as to the value of performing hilar tomography in patients with negative chest x-rays. It has been our experience that positive results occasionally occur and will thus allow the avoidance of other more invasive staging procedures in some patients. The bone marrow biopsy is suggested as an early procedure both because of its high yield in demonstrating Stage IV disease and also because it is frequently of value in determining the patient's bone marrow cellularity as a parameter in determining therapeutic modalities and dosages. It would appear to be a prudent suggestion that the sequence of staging procedures be terminated at any point where further positive information would have no bearing on therapeutic decisions.

TABLE 10 (Ref. 13)

Change in Patient Stage During Sequential Work-Up

Percent of Patients Each Stage After Indicated Procedure				
	Stage I	Stage II	Stage III	Stage IV
	←	%		→
Clinical stage on referral	13	21	42	24
After lymphangiogram	8	15	54	24
After bone marrow	7	13	33	48
After closed liver biopsies	6	11	25	58
After laparotomy	6	8	21	65

TABLE 11 (Ref. 14)

Relationship Between Histology and Stage of Disease at Presentation

Histology	Stage		
Non-Hodgkin's Lymphoma	**Stages I and II (Percent)**	**Stage III (Percent)**	**Stage IV (Percent)**
Poorly differentiated lymphocytic lymphoma-nodular	15	<15	>70
Poorly differentiated lymphocytic lymphoma-diffuse	15	<15	>70
Histiocytic lymphoma	<50	>50	
Hodgkin's Disease	60	30	10

TABLE 12

PROPOSED STAGING SEQUENCE

1. HISTORY AND PHYSICAL EXAMINATION
2. CHEST X-RAY - HILAR TOMOGRAMS IF NEGATIVE
3. BONE MARROW BIOPSY
4. LYMPHANGIOGRAM
5. CLOSED LIVER BIOPSY
6. STAGING LAPAROTOMY

THERAPY AND PROGNOSIS

A clear cut improvement in the systematic approach to the treatment of, and the prognostic predictability for, the nonHodgkin's lymphomas has been generated by the application of the Rappaport histologic classification. Systematic approach to the evaluation of extent of disease has also lent a hand in the progress towards dealing with these disorders. Nevertheless, major holes are apparent in our therapeutic strategies when we are faced with decisions in dealing with individual patients. This area is one of major flux and very few specific conclusions can be expressed which are likely to be acceptable within the very near future. This section, therefore, will deal in generalizations regarding therapeutic modalities which are available for the treatment of nonHodgkin's lymphomas and will also give some selected examples of how our most recent knowledge of classification in staging has allowed us to develop more rational therapeutic approaches to at least some patients, as compared to previously.

A. Therapeutic Modalities (3, 24-29) (Figure 5, Tables 13 and 14).

The armamentarium for the treatment of the nonHodgkin's lymphomas is rather broad. That is, these tumors are in general relatively responsive to a number of different approaches when compared to neoplastic disorders as a whole. The design of new therapeutic programs are dependent upon recognition of some of the following basic principles.

1. Surgery: except for the obvious primary role of surgical removal of tissue for histologic diagnosis, this modality serves essentially no primary position. On the other hand, with our present knowledge of the improvement in responsiveness of small amounts of tumors as compared to more gross cell numbers, the adjunctive use of surgical "debulking" does play a role, in particular in dealing with some extranodal sites of disease.

2. Radiation therapy: as might be expected in tumors that are of lymphoid origin, the nonHodgkin's lymphomas as a group are relatively quite radiosensitive. As has been previously demonstrated for Hodgkin's disease, the dose response curve for most of the non-Hodgkin's lymphomas allows for very low recurrence rates when doses of 4,000 - 5,000 r can be delivered. There are exceptions to this rule, and the group at Stanford have clearly demonstrated the dependence of the histologic type by the Rappaport classification and the specific radiation therapy dose response curve. As a corollary to this observation, one would predict that if disease is well localized enough and of the proper histologic cell type, the utilization of radiation therapy as a primary approach with curative intent would be logical. Such information has evolved from several centers. Thus, the practical application of radiation therapy for either curative or adjunctive "debulking" is of major importance in the therapeutic approach to the nonHodgkin's lymphomas.

3. Chemotherapy: the systemic administration of chemotherapeutic agents has, in general, proven to be the most important part of the treatment program in most patients with nonHodgkin's lymphoma. Most of the nonHodgkin's lymphomas have some degree of responsiveness to a wide variety of chemotherapeutic agents. Again, however, the frequency of response and the degree of response are quite dependent upon the histologic subtype as generated by Rappaport. The nonHodgkin's lymphomas are also one of the groups of disorders in which the basic principles of combination chemotherapy utilizing agents of different toxicities for additive or synergistic purposes have been substantiated.

FIGURE 5 (Ref. 25)

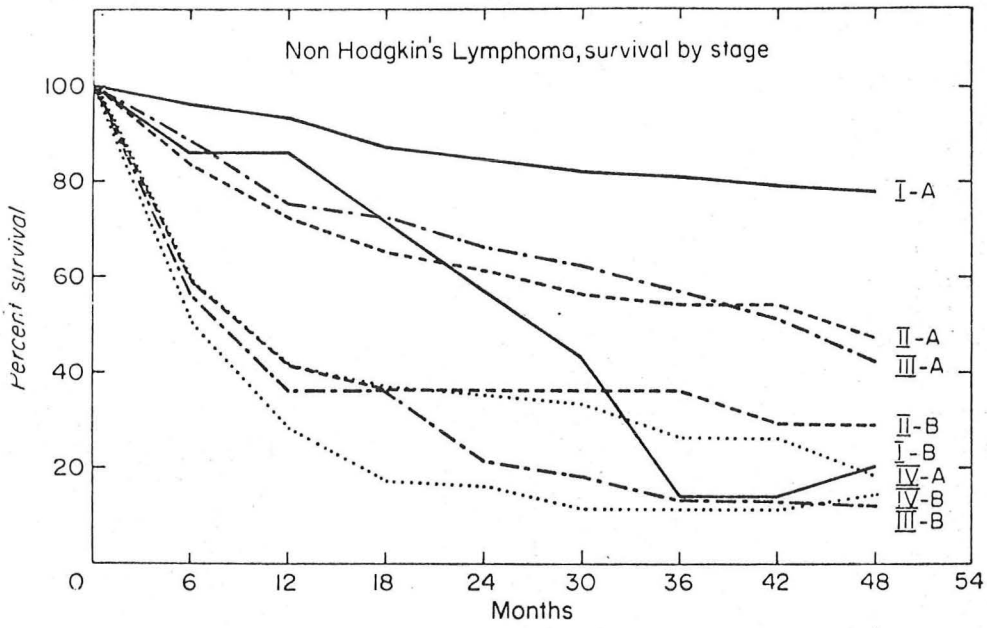


TABLE 13 (Ref. 29)

Percentage of Response by Histologic Type to Either Cyclophosphamide or Chlorambucil

Histology	No. treated	Percentage		
		NR	PR	CR
NH	7	28	44	28
NM	16	19	50	31
NLPD	19	26	26	48
DH	19	26	69	5
DM	15	40	47	13
DLPD	9	33	45	22

NR = no response; PR = partial response; CR = complete response.

TABLE 14 (Ref. 28)

Non-Hodgkin's Lymphoma, Single Agent vs. Combination[10]

Therapy	Lymphocytic		Histiocytic	
	No. patients	Per cent response	No. patients	Per cent response
Cyclophosphamide	14	43	11	45
High-dose combination*	16	100	13	85
Low-dose combination*	21	90	13	54

* Cyclophosphamide, vincristine, and prednisone.

B. Localized Disease (23, 26, 30, 31) (Table 15)

More specific comments regarding the therapy of the nonHodgkin's lymphomas requires attention to both the stage of the disease and the histologic type. From the preceding discussion regarding stages of disease, it is apparent that truly localized disease is rather uncommon in patients with nonHodgkin's lymphoma. When one is faced with such a patient, however, certain points appear to be apparent.

1. A true cure rate may be achieved in patients with Stage I disease when that stage has been confirmed by laparotomy. It would appear that patients with Stage I diffuse lymphomas may be curable more than one half of the time with radiation therapy alone. Since patients with histiocytic diffuse lymphoma are most frequently that localized, they make up the greatest bulk of apparent radiation therapy cures.

2. For radiation to be successful with a curative intent, sufficient doses must be delivered which are dependent upon histology and, thus, the site of Stage I disease will also be significant in predicting radiation curability.

3. It can be seen from Table 15 that more than one site of disease i.e. Stage II or worse, imparts a prognosis which makes irradiation therapy as the only modality not practical.

4. Most of the nodular lymphomas, with perhaps the exception of histiocytic nodular, demonstrate a high frequency of relapse and thus a probable lack of significant curability by radiation alone.

5. Thus, as is true for Hodgkin's disease, the potential for radiation curability does exist in nonHodgkin's lymphoma. The major difference, however, is that the frequency of localized disease of favorable histology is low.

TABLE 15

RESULTS OF INITIAL RADIATION THERAPY ALONE IN NHL
MEDIAN SURVIVAL (YEARS)

HISTOLOGY	STAGE I	STAGE II	STAGE III AND IV
HD	10+	1.8	1.5
HN	7+	3+ (1.2)*	2
PDLD and MD	10+	1.8	1
PDLN and MN	7+ (4.8)	8+ (3)	III 9 IV 6

* Where median survival has not been reached, numbers in parenthesis are median disease free survival if that has been reached.

C. Disseminated Disease

More than 85% of patients with nonHodgkin's lymphoma have their disease of an extent greater than a single lymph node bearing area. It is apparent from the results with irradiation therapy alone that this group of patients require other forms of therapy. Within the group of patients with disseminated disease, the greatest differences between the nodular and diffuse histologic patterns becomes apparent. This applies not only to survival potential but also to therapeutic responsiveness.

1. Nodular lymphomas (29, 32-38) (Figures 6, 7 and Table 16)

The disseminated nodular lymphomas present a distinct contrast to the disseminated diffuse lymphomas. The nodular lymphomas are indolent in nature

with rather long survival times, but are infrequently curable. On the other hand the disseminated diffuse lymphomas are rapidly aggressive in their natural history but with recent therapeutic advances, appear to have a significant cure rate. The following general comments can be made in relationship to the nodular lymphomas as a whole:

a) Almost all patients with nodular lymphomas will respond to therapy and over 50% will achieve a complete remission. Of interest, these results appear to be essentially the same no matter what the therapeutic modality; that is single agent chemotherapy, combination chemotherapy, total nodal irradiation (Stage III) or whole body irradiation.

b) Median survivals are long, exceeding at least 5 years, and do not appear to be related to the therapeutic modality which was initially utilized.

c) Despite the longterm survivorship, most patients do not remain disease free. Thus, there is a significant discrepancy between survival and disease free survival beginning at two to three years after diagnosis.

d) As a consequence of the above features of the nodular lymphomas, these patients have a comparatively good duration of survival, yet paradoxically, a very low rate of cure.

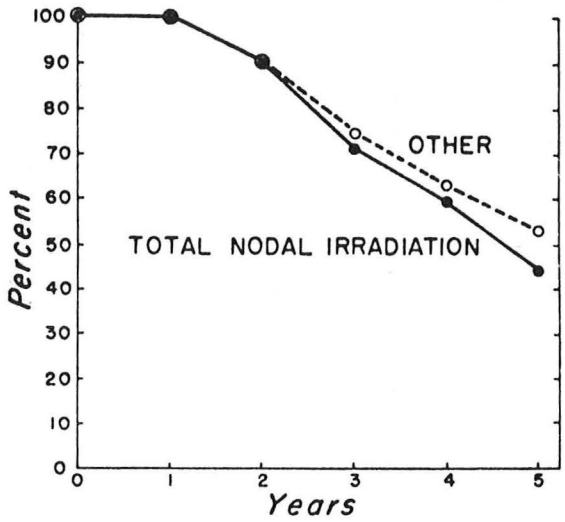
e) Although numbers of patients are small, it is probable that patients with histiocytic nodular lymphoma have a more aggressive disease than other cytologic types of nodular disease.

TABLE 16 (Ref. 36)

Reported Therapeutic Results in Advanced Nodular Lymphoma

Authors (Reference)	Stages	Number of patients	Treatment	Survival	Relapse-free survival
Johnson[13]	III & IV	30	Whole body irradiation	70% at 5 yr	—
Chaffey et al.[4]	III IV	10 4	Whole body irradiation	100% at 3 yr	65% at 3 yr
Schein et al.[21]	III IV	6 19	CVP chemotherapy	65% at 3 yr	—
Portlock et al.[18]	IV	63	Randomized: 1-CVP chemotherapy 2-CVP-total nodal Irradiation-CVP 3-single agent chemo-therapy	87% at 4 yr	35% at 4 yr
Present series	III	51	Total nodal irradiation	75% at 5 yr 65% at 10 yr	43% at 5 yr 33% at 10 yr

FIGURE 6 (Ref. 38)



Survival of patients treated with total nodal irradiation (solid line) and those treated with other modalities.

FIGURE 7 (Ref. 38)

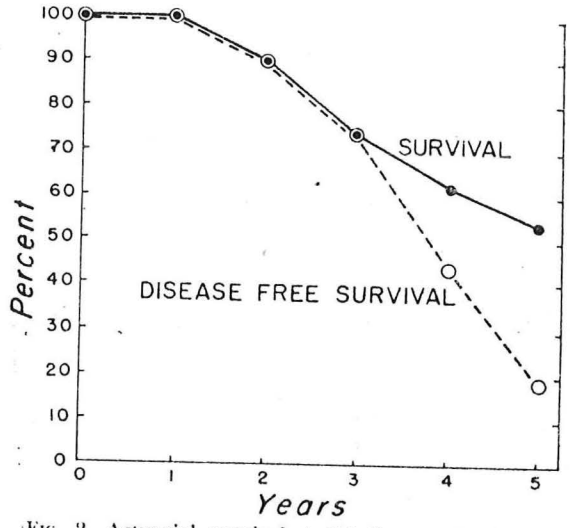


FIG. 2. Actuarial survival (solid line) and disease-free survival (broken line) for all patients.

2. Diffuse lymphomas (7, 8, 32-35, 37, 39, 40-47) (Table 17, Figure 8-10)

Not only are the diffuse lymphomas clearly different in their clinical behavior, prognosis, and therapeutic responsiveness from the nodular lymphomas, but they are also clearly a group of distinct entities within themselves, based on histologic type. The examples described below illustrate the striking differences between the various diffuse lymphomas and also contrast their behavior with the nodular lymphomas.

a) Histiocytic diffuse lymphoma

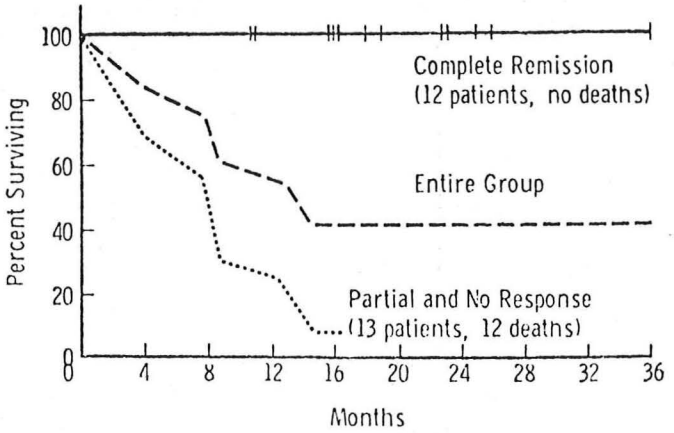
- as seen in Table 13 single agent chemotherapy results in a very low and unsatisfactory complete response rate.
- Table 17 demonstrates that with aggressive combination chemotherapy regimens of various types, complete remission rates of 50% or greater can be achieved in this disorder.
- Figures 8 and 9 demonstrate a phenomenon that has been noted with all of the combination therapy programs for histiocytic diffuse lymphoma. If the patient achieves a complete remission, the subsequent relapse rate is small, occurs prior to two years and the remaining patients appear to have a long survival if not cure.
- those patients who do not achieve a complete remission demonstrate the previously recognized natural history of this disease, that is a very brief survival.
- thus in approximately 50% of patients with histiocytic diffuse lymphoma a complete remission and possible cure occurs. The remaining 50% of patients have a very brief survival. It is not clear at this time whether any of the histologic or functional subclassifications of the histiocytic lymphomas accounts for this strikingly different behavior between the two groups of patients. Studies of this type are ongoing.

TABLE 17

RESPONSE AND SURVIVAL IN DISSEMINATED HISTIOCYTIC DIFFUSE LYMPHOMA

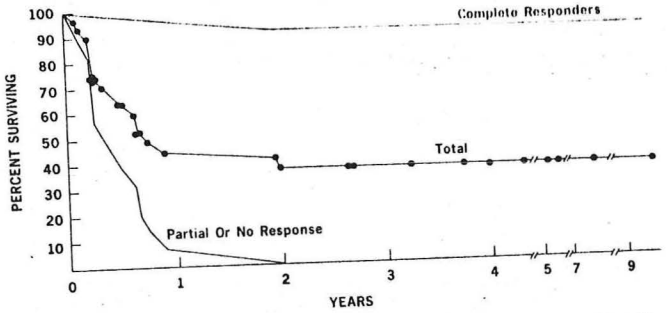
Regimen (Ref.)	CR%	Probable 5 yr. survival %
COPP (7, 34, 39)	41	37
COMA (40-42)	71	60
BACOP (43)	48	?
HOP-CHOP (35, 44)	65	?

FIGURE 8 (Ref. 43)



Life-table analysis of survival for the entire group of 25 previously untreated patients. Twelve patients achieved a complete remission, and 13 patients obtained a partial response or no response.

FIGURE 9 (Ref. 3, 39)

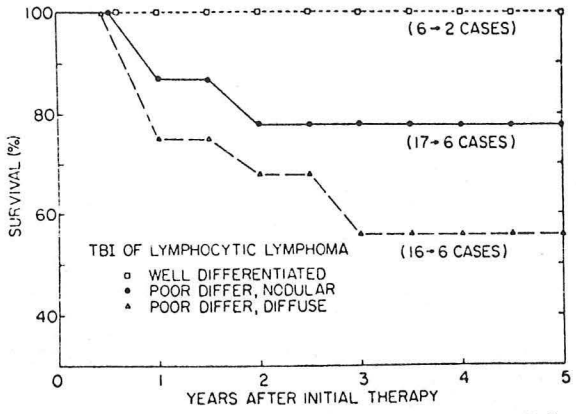


Survival of patients with advanced diffuse histiocytic lymphoma in the National Cancer Institute series.

b) Poorly differentiated lymphocytic diffuse lymphoma

- as a group, patients with lymphoma of this histologic type demonstrate a poor response rate to both single and combination agent chemotherapy. This is particularly true of regimens which are known to be effective in the histiocytic diffuse patients. Complete remission rates average approximately 33% or less in most studies.
- as would be predicted, because of the low complete remission rate, the median survival of patients with poorly differentiated lymphocytic diffuse lymphoma is short, averaging one year. On the other hand, a small fraction of patients will demonstrate very long survivals suggestive of cure.
- there is strong evidence that at least one histologic and functional subclass of this group demonstrates a distinct clinical entity. Histologically this has been described as the lymphoblastic lymphoma variant and appears to almost invariably mark as a T cell lymphoma. The clinical course closely mimics acute lymphoblastic leukemia and preliminary data would suggest that a therapeutic approach similar to that used in acute childhood leukemia is most appropriate.
- preliminary data suggests that the use of total body irradiation (TBI) results in response rates and survival times that are superior to any other form of therapy so far described. Careful controlled evaluation of this mode of therapy is imperative. (Figure 10).

FIGURE 10 (Ref. 37)



The survival curves shown are actuarially calculated. The median observation time for the entire series is 4 years. There was a single death from intercurrent disease, so the rates for the first several years are essentially absolute survival.

c) Well differentiated lymphocytic diffuse lymphoma

- this group of lymphomas demonstrate the exception to the rule that diffuse lymphomas follow a natural history which is rapidly progressive. Median survival times in patients with this histologic diagnosis is similar to, if not better than, the nodular lymphomas.
- this histologic type is rather infrequent, but both histologic and functional studies indicate that the malignant cell in this disorder has all of the characteristics of the cell in chronic lymphocytic leukemia. It is probable that this is basically the same disease as CLL during a nonleukemic phase. Prospective data are now being accumulated to determine whether the therapeutic responsiveness and prognosis are similar for these two diagnoses.

D. Immunotherapy (48 - 50)

Unlike patients with solid tumors or Hodgkin's disease, the immune functional status of patients with nonHodgkin's lymphomas is poorly understood. Very few studies have carefully evaluated this parameter. The most recent study indicates that some impairment of immune function does exist in patients with the nonHodgkin's lymphomas, especially those with diffuse types. Evidence of both T cell and B cell abnormalities was elicited with the former being most obvious. Even less information is available related to the application of a variety of immunotherapy techniques to this group of diseases. The fact that these are in themselves tumors of the cells of the immune system raises provocative questions relative to immunological manipulation of these patients.

SUMMARY

The nonHodgkin's lymphomas are a heterogeneous group of neoplastic disorders in which our present state of knowledge is insufficient to adequately classify.

It is clear that at the present time the most significant parameter in planning therapeutic strategy and predicting prognosis is the histologic appearance of the tumor as judged by the experienced hematopathologist.

Although most patients with the nonHodgkin's lymphomas present with rather generalized disease, the identification of the small group of patients with localized disease by appropriate staging techniques is also imperative.

The therapeutic approach to patients with the nonHodgkin's lymphomas is in constant flux as new observations are being rapidly reported.

It is also apparent that additional supplementary means of identifying groups of patients with disorders requiring different therapeutic approaches must be pursued.

One thus would conclude from these statements that the initial diagnosis and evaluation of the patient is the most important stage of dealing with the disorder. Such an appropriate evaluation clearly requires an experienced hematopathologist, radiotherapist and medical oncologist. Additionally, it would seem wise in most instances that appropriate functional studies be performed and that the patient be evaluated in a prospective sense to obtain additional information regarding these disorders.

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