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RAPID COMMUNICATION

A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma

By The Non-Hodgkin's Lymphoma Classification Project

The recognition of several new types of non-Hodgkin's lymphoma (NHL) in recent years has led to proposals for changing lymphoma classifications, including a new proposal put forth by the International Lymphoma Study Group (ILSG). However, the clinical significance of the new entities and the practical utility of this new proposal have not been studied. Therefore, we performed a clinical evaluation of the ILSG classification. A cohort of 1,403 cases of NHL was organized at nine study sites around the world and consisted of consecutive patients seen between 1988 and 1990 who were previously untreated. A detailed protocol for histologic and clinical analysis was followed at each site, and immunologic characterization as to T- or B-cell phenotype was required. Five expert hematopathologists visited the sites and each classified each case using the ILSG classification. A consensus diagnosis was also reached in each case, and each expert rereviewed a 20% random sample of the cases. Clinical correlations and survival analyses were then performed. A diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. The most common lymphoma types were diffuse large B-cell lymphoma (31%) and follicular lymphoma (22%), whereas the new entities comprised 21% of the cases. Diagnostic accuracy was at least 85% for most of the major lymphoma types, and reproducibility of the diagnosis was 85%. Immunophenotyping improved the diagnostic accuracy by 10% to 45% for a number of the major types. The clinical features of the new entities were distinctive. Both the histologic types and the patient characteristics as defined by the International Prognostic Index predicted for patient survival. In conclusion we found that the ILSG classification can be readily applied and identifies clinically distinctive types of NHL. However, for clinical application, prognostic factors as defined by the International Prognostic Index must be combined with the histologic diagnosis for appropriate clinical decisions.

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BECAUSE OF the increasing incidence of non-Hodgkin's lymphoma (NHL), with approximately 53,000 new cases occurring annually in the United States,[1,2] the diagnosis and classification of these disorders is an increasingly important clinical issue. The classification of NHL has evolved steadily throughout the twentieth century. An early system proposed by Gall and Mallory[3] used the terms giant follicular lymphoma, lymphosarcoma, and reticulum cell sarcoma, but proved too imprecise for clinical application. In the 1950s, Rappaport et al[4] recognized the importance of the growth pattern in some types of NHL and used pattern, in addition to cell size and shape, as the basis of a new and clinically relevant classification. In the 1970s, recognition that NHLs were tumors of the immune system and were derived from T or B cells led to the immunologically based classifications of Lukes and Collins,[5] and later Lennert and associates (Kiel classification).[6-8] In an attempt to unify terminology and improve the effectiveness of communication between pathologists and clinicians, the Working Formulation was proposed in 1982.[9] Over the next two decades, however, the Kiel classification dominated clinical practice in Europe, whereas the Working Formulation became the main classification system used in North America.

In the last two decades, increased understanding of the immune system and the genetic abnormalities associated with NHL have led to the identification of several previously unrecognized types of lymphoma. These include mantle cell lymphoma,[10-20] monocytoid B-cell lymphoma,[21-28] extranodal lymphoma of mucosa-associated lymphoid tissue (MALT),[16,29-34] splenic marginal zone lymphoma,[35-38] primary mediastinal large B-cell lymphoma,[39-47] and a variety of T-cell lymphomas,[48-73] including anaplastic large cell lymphoma.[74-83] The recognition of these new and supposedly clinically relevant types of NHL has led to proposals for changing lymphoma classifications. Modifications of the existing classifications, and a new proposal by the International Lymphoma Study Group (ILSG)[84] incorporating some aspects of the Kiel classification and Working Formulation, have been put forward. However, the clinical significance of the new lymphoma entities and the practical utility and clinical relevance of this new proposal needed to be tested.

The histologic diagnosis of specific subtypes of NHL is widely believed to be imprecise. Previous studies have identified high rates of diagnostic discrepancy between different pathologists (interobserver variability) and for the same pathologist (reproducibility) when reviewing the same case at different times.[85-88] This inaccuracy in diagnosis has made treatment decisions difficult. In the past two decades, the widespread use of immunophenotyping has led to increased insight into the diagnosis and classification of tumors of the immune system. However, the value of immunophenotyping in the day-to-day practice of lymphoma diagnosis and clinical care has not been clearly shown.

With this background, we set out to perform a retrospective clinical evaluation of the newly proposed ILSG classification.[84] Although the ILSG classification is a proposal for classifying all lymphoid neoplasms (Table 1), our study was

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Table 1. International Lymphoma Study Group Classification (including provisional categories)

B-Cell Lymphoma	T/NK-Cell Lymphoma	Others
Precursor B-lymphoblastic	Precursor T-lymphoblastic	Composite lymphoma (types specified)†
Small lymphocytic (CLL)	T-cell chronic lymphocytic leukemia	Malignant lymphoma, unclassifiable low grade
Lymphoplasmacytic	Large granular lymphocyte leukemia	Malignant lymphoma unclassifiable high grade
Mantle cell	Mycosis fungoides	Malignant lymphoma, unclassifiable
Follicle center, follicular	Peripheral T cell, unspecified	
*Grade 1**	*Medium-sized*	Hodgkin's disease
*Grade 2**	*Mixed medium and large cell*	Diagnosis other than lymphoma
*Grade 3**	*Large cell*	Case unclassifiable
Follicle center diffuse, small cell	*Lymphoepithelioid*	
Marginal zone B-cell, MALT type	*Hepatosplenic*	
Marginal zone B-cell, nodal	*Subcutaneous panniculitic*	
Marginal zone B-cell, splenic	Angioimmunoblastic	
Hairy cell leukemia	Angiocentric, nasal	
Plasmacytoma	Intestinal	
Diffuse large B-cell	Adult T-cell lymphoma/leukemia	
Diffuse mediastinal large B-cell	Anaplastic large cell (including null phenotype)	
Burkitt's	*Anaplastic large cell, Hodgkin's-like*	
High grade B-cell, Burkitt-like	Unclassifiable low grade	
Unclassifiable low grade	Unclassifiable high grade	
Unclassifiable high grade		

Provisional categories are indicated in italic type.
Abbreviations: CLL, chronic lymphocytic leukemia; MALT, mucosal-associated lymphoid tissue.
* Follicular lymphomas are designated as such and were graded according to the Berard method.[90]
† Composite lymphomas consisted of two distinctly different cytologic subtypes of lymphoma.
Data from Harris et al.[84]

designed to only assess the ILSG classification of NHL. Specific goals of our study were the following: (1) to evaluate the ability of hematopathologists to apply the ILSG classification to a retrospective group of cases collected at sites around the world; (2) to determine the role of immunophenotyping and clinical data in the diagnosis of the various entities; (3) to determine the clinical importance of immunophenotyping; (4) to determine the intraobserver and interobserver reproducibility of diagnosis of the various entities; (5) to determine clinical correlations for the various entities, including clinical features at presentation and survival outcomes; and (6) to determine whether certain entities can be grouped for prognostic or therapeutic purposes.

PATIENTS AND METHODS

Nine institutions in eight countries were chosen to provide up to 200 consecutive cases of previously untreated NHL that were representative of the geographic region during the time between January 1, 1988 and December 31, 1990. The first 200 cases at each site that fulfilled the following criteria were selected for the study. In all cases, tissue biopsy samples that were adequate for diagnosis and classification were required, and all diagnostic pathology materials obtained before initial therapy, including positive bone marrow (BM) specimens, were included in the pathology review. Immunologic characterization as to B- or T-cell origin, by whatever means in use at the institution, was also required in all cases. Leukemias were excluded from the study unless a tissue biopsy, other than BM, was performed before therapy. Clinical characteristics, treatment data, and some follow-up information were also required in all cases. The nine study sites, which provided a total of 1,403 cases, are shown in Table 2.

The clinical information for each case was abstracted from the medical record by a clinician or data manager and recorded on a standardized form for direct computerized data entry. These data included coded patient and site identifiers; patient sex, ethnic origin, and date of birth; the date and site of the diagnostic biopsy; and a tabulation of nodal and extranodal sites of involvement and Ann Arbor stage at the time of initial diagnosis. Laboratory data were recorded, including the serum lactate dehydrogenase level, absolute lymphocyte count, presence of circulating lymphoma cells, presence of a monoclonal serum Ig, and a history of immunodeficiency and viral (human T-cell leukemia virus-1 [HTLV-1], human immunodeficiency virus [HIV]) status. Also recorded were the performance status and maximum diameter of the largest tumor mass. The initial therapy and therapeutic response, details of remission, progression, or relapse, and subsequent therapies and follow-up were tabulated in each case. For this report, all cases with clinical data were included regardless of the specific therapies given. In 73 of the cases, sufficient data was not available for the clinical and survival analyses.

At each institution, the pathology slides and reports for each case were carefully reviewed by a designated site pathologist. The original stained slides and immunostains were organized for review, and additional sections, immunostains, and other studies were performed if deemed necessary by the site pathologist. The results of the immunologic studies for each case, as well as any available cytogenetic or molecular genetic data, were recorded on a standardized form for direct computerized data entry. Five expert hematopathologists then traveled as a group to each of the nine sites to review and classify

Table 2. Number of Cases by Study Site

Site	Cases
Omaha, NE	200
Vancouver, Canada	202
Cape Town, South Africa	196
London, UK	120
Locarno, Switzerland	80
Lyon, France	195
Würzburg/Göttingen, Germany	210
Hong Kong	200

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each case in each of the three major classifications.[9,84,89] The site visits occurred over a period of 8 months beginning in June 1995. All expert pathologists used a standard Nikon Labophot-2 microscope (Nikon, Inc, Melville, NY), including a 10× plan achromat objective (high-power field = 0.159 mm^2). The diagnostic categories in each of the three classifications were used according to published criteria.[9,84,89] More specific criteria were developed for some of the entities with Nancy L. Harris providing consultation regarding the ILSG classification. The criteria of Mann and Berard[90] were used to grade follicular lymphoma in the ILSG classification.

At each site, the diagnostic slides were reviewed and classified independently by each expert hematopathologist. The initial classification was based on examination of the hematoxylin-eosin and/or Giemsa stained slides with only the following clinical information from the time of initial diagnosis: patient age and sex, site of the biopsy, and the major site of disease (ie, diagnosis 1). After recording a diagnosis in each classification, the expert was then presented with the immunophenotypic profile, along with any available cytogenetic and molecular genetic data, and the immunostains and/or flow cytometry report. After review, a second diagnosis was rendered in each classification (ie, diagnosis 2). Then, the expert was presented with all of the pretreatment clinical information and a third diagnosis was made in each classification (ie, diagnosis 3). No previous diagnosis could be changed based on information subsequently revealed. If a case was considered unclassifiable in any of the classifications, the expert was required to give a reason, ie, inadequate material, poor slide preparation, additional phenotyping needed, additional information needed, or other reasons. The expert was allowed to change the phenotype of a case if he interpreted the immunostains and/or phenotype data differently than the site pathologist. For some diagnostic categories, a research protocol was also completed by the expert pathologists. All of this information was recorded on standardized forms for direct computerized data entry. Approximately 40 to 50 cases were reviewed by each pathologist each day.

In addition to the independent diagnoses rendered by each of the expert pathologists, a consensus diagnosis was also reached in each case. A consensus was considered to have been reached if at least four of the five expert pathologists agreed on the third diagnosis (diagnosis 3) in the ILSG classification. A diagnosis of follicular lymphoma of any grade was considered an agreement, and a diagnosis of peripheral T-cell lymphoma of any type was also considered an agreement. In these latter two categories, agreement by three of the five expert pathologists with regard to the specific type was considered the consensus diagnosis; if there was no agreement with regard to the type, the case was arbitrated by D. Weisenburger based on the individual diagnoses and the research protocol. All other cases without a consensus diagnosis were jointly reviewed on a multi-headed microscope and discussed by the five expert pathologists and the site pathologist in a consensus conference at the end of each day, and an attempt was made to reach a consensus of at least four expert pathologists in each case. If additional sections, immunostains, molecular studies, or other information was required, a diagnostic algorithm was developed by the group and the additional materials were obtained, if possible, and reviewed at a subsequent consensus conference at the site. If the additional materials could not be obtained during the site visit, the required materials and information were subsequently sent to D. Weisenburger who arbitrated the case based on the algorithm.

At the end of each site visit, after all cases had been reviewed, each expert pathologist rereviewed 20% of the cases. The cases for rereview were randomly selected by the statisticians. These cases were classified a second time by each expert, without knowledge of his initial interpretation, using all available pathology materials and pretreatment clinical information. Cases in which a consensus diagnosis had not yet been reached were excluded from the rereview.

Table 3. Distribution of NHL Cases by the Consensus Diagnosis

Consensus Diagnosis	No. of Cases	% of Total Cases
Diffuse large B-cell	422	30.6
Follicular	304	22.1
Grade 1	131	9.5
Grade 2	85	6.2
Grade 3	88	6.4
Marginal zone B-cell, MALT	105	7.6
Peripheral T-cell	96	7.0
Medium-sized, mixed, and large	51	3.7
Angiocentric, nasal	19	1.4
Angioimmunoblastic	17	1.2
Intestinal	5	<1
Lymphoepithelioid	2	<1
Hepatosplenic	1	<1
Adult T-cell leukemia/lymphoma	1	<1
Small B-lymphocytic (CLL)	93	6.7
Mantle cell	83	6.0
Primary mediastinal large B-cell	33	2.4
Anaplastic large T/null-cell	33	2.4
High grade B-cell, Burkitt-like	29	2.1
Marginal zone B-cell, nodal	25	1.8
Precursor T-lymphoblastic	23	1.7
Lymphoplasmacytoid	16	1.2
Marginal zone B-cell, splenic	11	<1
Mycosis fungoides	11	<1
Burkitt's	10	<1
All other types	84	6.1

Abbreviation: CLL, chronic lymphocytic leukemia.

Completed clinical and pathology forms were reviewed and edited to detect any inconsistencies, and additional information and/or clarification was obtained when needed. After completion of the editing, the clinical and pathology data forms were entered into a computer for data analysis. The International Prognostic Index[91] was used to stratify patients within the various disease entities. Treatment outcome was measured using failure-free survival and overall survival. Failure-free survival was defined as the time from diagnosis to the first occurrence of progression, relapse after response or death from any cause. Follow-up of patients not experiencing one of these events was censored at their date of last contact. Overall survival was measured from diagnosis to death from any cause, with surviving patient follow-up censored at the last contact date. Estimates of failure-free survival and overall survival distribution were calculated using the method of Kaplan and Meier.[92] Time to event distributions were compared using the log-rank test.[93]

RESULTS

Twenty-five of the 1,403 cases (1.8%) were found to have a diagnosis other than NHL and, thus, were excluded from further analysis. The types of NHL found in the remaining 1,378 cases are presented in Table 3. Approximately 31% of the cases were forms of diffuse large B-cell lymphoma and approximately 22% of the cases were types of follicular lymphoma. All types of T-cell processes, including natural killer (NK) cell disorders, made up only 12% of the cases. Small lymphocytic lymphoma was observed in 6.7% of the cases, a higher percentage than is sometimes appreciated. The major newly recognized types of lymphoma that occurred most frequently were marginal zone B-cell lymphoma of MALT type (7.6%), mantle cell lymphoma (6.0%), pri-

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Table 4. Expert Pathologist Agreement With the Consensus Diagnosis

Consensus Diagnosis	Dx 1* (%)	Δ Dx 2-1 (%)	Dx 2† (%)	Δ Dx 3-2 (%)	Dx 3‡ (%)
Follicular, any grade	93	1	94	0	94
Follicular, grade 1	72	1	73	0	73
Follicular, grade 2	61	0	61	0	61
Follicular, grade 3	60	1	61	0	61
Marginal zone B-cell, MALT	84	2	86	0	86
Small lymphocytic (CLL)	84	3	87	0	87
Lymphoplasmacytoid	53	3	56	0	56
High grade B-cell, Burkitt-like	47	6	53	0	53
Primary mediastinal large B-cell	51	7	58	37	85
Marginal zone B-cell, nodal	55	8	63	0	63
Mantle cell	77	10	87	0	87
Diffuse large B-cell	73	14	87	0	87
Precursor T-lymphoblastic	52	35	87	2	89
Anaplastic large T/null-cell	46	39	85	0	85
Peripheral T-cell, all types	41	45	86	0	86

Abbreviation: CLL, chronic lymphocytic leukemia.

* Diagnosis 1 based only on histology.

† Diagnosis 2 based on histology and immunophenotype.

‡ Diagnosis 3 based on histology, immunophenotype and clinical data.

mary mediastinal large B-cell lymphoma (2.4%), and anaplastic large T/null-cell lymphoma (2.4%). Only 2.8% of the 1,378 cases of NHL could not be specifically classified using this system, usually because of technical factors.

Three diagnoses were made by each expert pathologist in each case: one based on only histology, the second based on histology and immunophenotype data, and the third based on a combination of histology, immunophenotype, and clinical data. In Table 4, the percentages of the review diagnoses that agreed with the consensus diagnosis are given for each major histologic type. For most of the histologic types, the percentage of third review diagnoses (using all available data) that agreed with the consensus diagnosis equaled or exceeded 85%. The percent agreement was only 53% for high-grade B-cell Burkitt-like tumors, where distinctions between Burkitt's lymphoma and diffuse large B-cell lymphoma often proved difficult. The percent agreement was also below 85% for lymphoplasmacytoid lymphoma and nodal marginal zone B-cell lymphoma, also due at least in part to the imprecise definitions of these entities. Whereas the accuracy of diagnosis of follicular lymphoma was 94%, the percent agreement for the various grades of the follicular lymphoma was only 61% to 73%. However, the agreement in follicular lymphoma, grade 3, increased to 74% if cases with a diffuse component were also considered as an agreement.

The usefulness of immunophenotyping in making the correct diagnosis was dependent on the specific disease (Table 4). For some lymphomas, such as follicular lymphoma, marginal zone B-cell lymphoma of MALT type, and the small lymphocytic and lymphoplasmacytoid lymphomas, information on the immunophenotype did not increase the diagnostic accuracy significantly. However, for the mantle cell, diffuse large B-cell, and the T-cell lymphomas, immunophenotyping was helpful in many cases in reaching the correct diagnosis and improved the diagnostic accuracy by some 10% to 45%. For many of these cases, the initial diagnosis based on histology only was unclassifiable malignant lymphoma. Immunophenotyping allowed the classification of such cases into specific categories. Detailed clinical data was helpful only in distinguishing primary mediastinal large B-cell lymphoma from the other diffuse large B-cell lymphomas, because there were no characteristic histologic or immunologic differences between these two categories.

The expert pathologists' rereview of a 20% sample of the cases at each site showed that they could reproducibly make a diagnosis of NHL (Table 5). Overall, the rereview diagnosis agreed exactly with the pathologist's initial diagnosis 3 or the consensus diagnosis (including the grading of follicular lymphoma) in 85% of the cases (range, 82% to 89%). Because the consensus diagnosis for all of these cases was reached before the time of the rereview, the consensus process may have influenced the assessment of some cases at rereview. Therefore, the pathologists were allowed to agree with either their original diagnosis 3 or the consensus diagnosis at the time of rereview. For an additional 9% of the cases, the rereview diagnosis was nearly the same as the original diagnosis (ie, follicular, grade 1, *v* follicular, grade 2; or, follicular, grade 3, *v* follicular, grade 3, plus diffuse large B-cell). Thus, for 94% of the cases rereviewed (range, 92% to 97%), the expert pathologists made a diagnosis consistent with either their original diagnosis 3 or the consensus diagnosis. In only 6% of the cases (range, 3% to 8%) the pathologist's rereview diagnosis would likely have led to a different approach to therapy than the original diagnosis.

The clinical characteristics of the more common types of lymphoma are presented in Table 6. It is important to recognize that, although the average results vary between the various types, there was considerable overlap between the types for any particular characteristic. The newly recognized types of lymphoma appear to be distinctive. Marginal zone B-cell lymphoma of MALT type was characterized by a high frequency of localized extranodal disease and a prolonged survival, whereas nodal marginal zone (monocytoid) B-cell lymphoma more often presented with advanced-stage disease and had a worse survival. Mantle cell lymphoma had

Table 5. Pathologist Agreement Upon Rereview of 20% of the Cases

	Dx 3/Consensus* (%)	Near-miss† (%)	None (%)
Overall agreement	85	94	6
Expert pathologist			
A	89	97	3
B	87	96	4
C	85	93	7
D	82	93	7
E	82	92	8

* Agreement with either diagnosis 3 or the consensus diagnosis.

† Agreement including near-miss diagnoses (see text for explanation).

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Table 6. Patient Characteristics by Histologic Type

Consensus Diagnosis	% Male	Median Age	% Stage 1 or 2	% Marrow Positive	% PI 0/1	% PI 4/5	% 5-yr OAS	% 5-yr FFS
Follicular, all grades	42	59	33	42	39	6	72	40
Mantle cell	74	63	19	63	19	19	27	11
Marginal zone B-cell, MALT	45	61	66	14	38	5	74	60
Marginal zone B-cell, nodal	41	58	18	41	36	9	57	29
Small lymphocytic (CLL)	53	65	6	73	17	10	51	25
Lymphoplasmacytoid	53	63	20	73	20	13	59	25
Diffuse large B-cell	55	64	51	17	31	16	46	41
Primary mediastinal large B-cell	34	37	66	3	44	9	50	48
Burkitt's	89	31	56	33	44	22	44	44
High-grade B-cell, Burkitt-like	59	55	50	21	25	18	47	43
Precursor T-lymphoblastic	74	25	13	43	35	22	26	24
Peripheral T-cell, all types	56	61	18	37	14	27	25	18
Anaplastic large T/null-cell	69	33	50	12	50	19	77	58

Abbreviations: PI, International Prognostic Index; OAS, overall survival; FFS, failure-free survival; CLL, chronic lymphocytic leukemia.

a striking male predominance, a high frequency of advanced-stage disease with marrow involvement, and the lowest 5-year survival of any type of lymphoma. Primary mediastinal large B-cell lymphoma occurred more frequently in young females and was often of low stage, but the survival was no different from that of other diffuse large B-cell lymphomas. Anaplastic large T/null-cell lymphoma occurred mainly in young patients and had a surprisingly high 5-year survival when compared to other lymphomas with large cell histology or a T-cell phenotype. This was not due to inclusion of a high proportion of patients with only skin involvement, a group that represented just 6% of these patients.

The average overall survival by histologic type allowed for division of the NHLs into four broad groupings (Fig 1). Those with a 5-year overall survival of greater than 70% included follicular lymphoma, marginal zone B-cell lymphoma of MALT type, and anaplastic large T/null-cell lymphoma. Lymphomas within a 50% to 70% 5-year overall survival included the small lymphocytic, lymphoplasmacytoid, and nodal marginal zone B-cell lymphomas. Lymphomas with a 30% to 49% 5-year overall survival included diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and the high-grade B-cell Burkitt-like and Burkitt lymphomas. Lymphomas with less than a 30% 5-year overall survival included peripheral T-cell lymphoma, precursor T-lymphoblastic lymphoma, and mantle cell lymphoma.

Whereas the histologic diagnosis of a specific type of lymphoma provides clinically important information, equally important prognostic information was obtained from the clinical characteristics of the individual patients. We found considerable variation within any particular histologic type for both overall survival and failure-free survival based on patient clinical characteristics using the International Prognostic Index (Table 7). For example, patients with follicular lymphoma had significantly different outcomes depending on their clinical prognostic characteristics (Fig 2). Moreover, patients with follicular lymphoma with a high (unfavorable) prognostic index had a far worse overall and failure-free survival (ie, 17% and 6%) than patients with a diffuse large B-cell lymphoma and a low (favorable) prognostic index (ie, 73% and 63%). In contrast, the histologic diagnosis of anaplastic large cell lymphoma was important because it was associated with a surprisingly good survival, even with a high prognostic index. In contrast, patients with mantle cell lymphoma had a relatively poor outcome despite apparently good clinical characteristics. The prognostic index also did not predict survival in precursor T-lymphoblastic lymphoma, although the number of cases was small.

DISCUSSION

This study shows that, using the definitions proposed in the ILSG classification, it is possible to accurately identify most of the major types of NHL. The major types recognized by this classification are also clinically distinctive, with the possible exception of high-grade B-cell Burkitt-like lymphoma, which appears to be very similar clinically to diffuse large B-cell lymphoma (Table 6). This classification was, in general, easily and accurately applied by the expert hematopathologists. In fact, this study suggests that when expert pathologists work from clear definitions, with the use of immunologic markers, the diagnosis of NHL can be made more accurately than had been thought. Previous studies, using morphology only, found that the diagnosis of specific types of NHL could only be made accurately 50% to 60% of the time.[85-88] In contrast, we have shown that, when expert pathologists work from clear and agreed upon criteria, the diagnosis of NHL can be at least 85% accurate for most of the common types. However, the methods used to reach a consensus diagnosis in our study certainly had a positive influence on these agreement rates. Because treatment depends on the diagnosis, it must be made as accurately as possible. We believe that the diagnosis of NHL should always be made by a hematopathologist who is experienced in lymphoma classification.

Immunophenotyping added significantly to the accuracy of diagnosis of many of the lymphoma types, including mantle cell lymphoma, diffuse large B-cell lymphoma, and the T-cell lymphomas. However, immunophenotyping did not add significantly to the accuracy of diagnosis of some lymphomas, such as follicular lymphoma, small lymphocytic lymphoma, and marginal zone B-cell lymphoma of MALT

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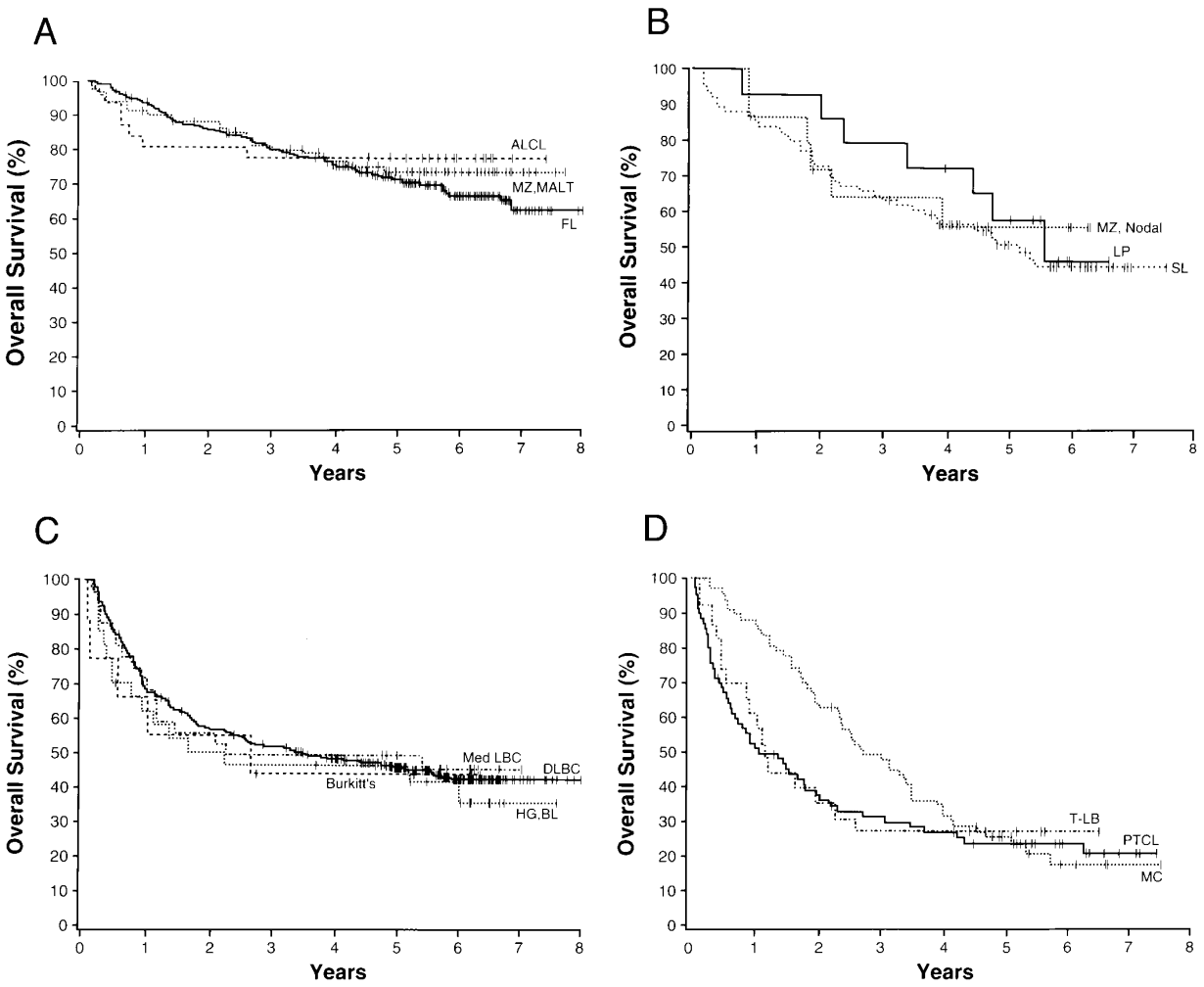

Fig 1. NHLs with a 5-year overall survival of greater than 70% (A), 50% to 70% (B), 30% to 49% (C), and less than 30% (D); ALCL, anaplastic large T/null-cell lymphoma; MZ, MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; FL, follicular lymphoma; MZ, nodal, marginal zone B-cell lymphoma of nodal type; LP, lymphoplasmacytoid lymphoma; SL, small lymphocytic lymphoma; Med LBC, primary mediastinal large B-cell lymphoma; DLCBL, diffuse large B-cell lymphoma; HG, BL, high-grade B-cell Burkitt-like lymphoma; T-LB, precursor T-lymphoblastic lymphoma; PTCL, peripheral T-cell lymphoma; MC, mantle cell lymphoma.

Table 7. Survival by Histologic Type and the International Prognostic Index

	% 5-yr OAS		% 5-yr FFS	
Consensus Diagnosis	Index 0/1	Index 4/5	Index 0/1	Index 4/5
Follicular, all grades	84	17	55	6
Mantle cell	57	0	27	0
Marginal zone B-cell, MALT	89	40	83	0
Marginal zone B-cell, nodal	76	50	30	0
Small lymphocytic (CLL)	76	38	35	13
Diffuse large B-cell	73	22	63	19
Primary mediastinal large B-cell	77	0	69	0
High grade B-cell, Burkitt-like	71	0	71	0
Precursor T-lymphoblastic	29	40	29	40
Peripheral T-cell, all types	36	15	27	10
Anaplastic large T/null-cell	81	83	49	83

Abbreviations: PI, International Prognostic Index; OAS, overall survival; FFS, failure-free survival; CLL, chronic lymphocytic leukemia.

type, all of which have very distinctive histologic features which usually facilitate the diagnosis without a need for immunologic data. For other types, such as the lymphoplasmacytoid, nodal marginal zone B-cell, and high-grade B-cell Burkitt-like lymphomas, imprecise histologic criteria and the lack of specific immunologic markers led to a diagnostic accuracy of only 53% to 65%. Further definition of these entities is clearly needed. Because the need for immunophenotyping cannot be predicted before biopsy, it is vital that each patient have tissue available for immunophenotyping and other special studies to facilitate proper patient care. In many cases, this will require communication between the oncologist, the surgeon, and the pathologist.

The 13 major types of NHL shown in Fig 1 made up over 90% of the cases in our study, with diffuse large B-cell lymphoma and follicular lymphoma comprising over 50% of the cases and the newly recognized entities comprising 21% of the cases (Table 3). The clinical features of the various lymphoma types were remarkably different, as were

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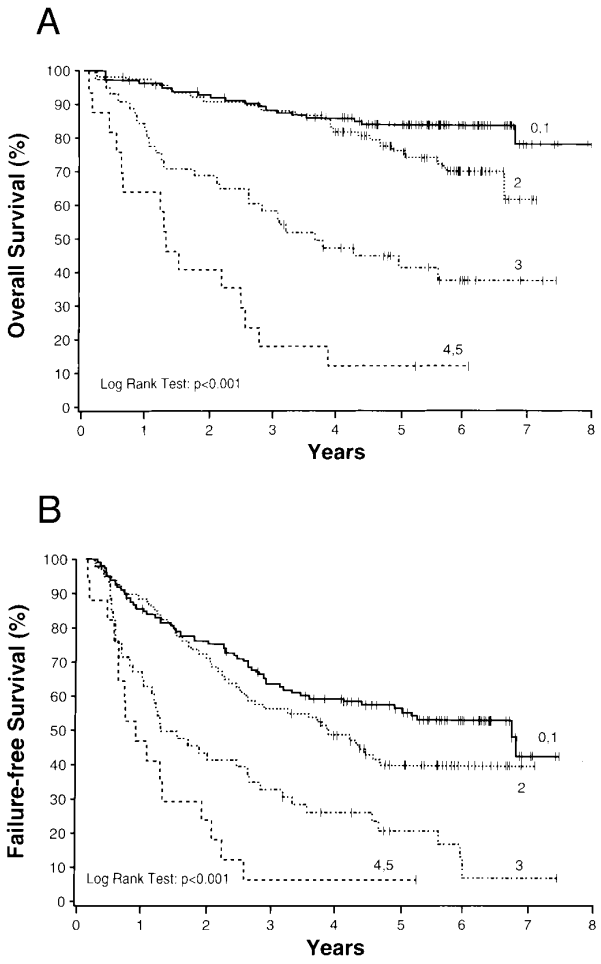

Fig 2. Overall (A) and failure-free (B) survivals of patients with follicular lymphoma grouped according to International Prognostic Index scores.

the survivals (Table 6). Using overall survival, the various lymphoma types could be divided into four broad groups for prognostic purposes (Fig 1). The groups consist of the those with a 5-year survival of greater than 70% (Fig 1A), those with a 5-year survival between 50% and 70% (Fig 1B), those with a 5-year survival of 30% to 49% (Fig 1C), and those with a 5-year survival of less than 30% (Fig 1D). Although such groupings may be useful for planning or interpreting future clinical studies, important differences in the approach to treatment and the potential curability of the various lymphoma types in these broad groups are well known. However, we believe that patient-specific information is also very important for clinical decision making, with the histologic diagnosis being only the first step in ''classification'' for proper patient management. The prognostic factors used in the International Prognostic Index[69] provide important information in most of the major types of NHL. Whereas the pathologic entities are distinctive, the variation in outcome within a particular entity by clinical prognostic characteristics is great. ''Good prognosis'' pathologic entities contain patients with a poorer outcome than the better patients in the ''poor prognosis'' entities. Therefore, to make proper clinical decisions, it is necessary to consider both the histologic type and the various prognostic factors present in an individual patient. Any useful clinical grouping of the NHLs must take both types of information into account.

Although the ILSG classification could be accurately applied and appears to be useful clinically, there are a number of areas that could be improved. Changes in organization and terminology have been suggested by others.[94-96] In addition, more specific criteria for some of the lymphoma types are clearly needed, such as the lymphoplasmacytoid, nodal marginal zone B-cell, and high-grade B-cell Burkitt-like lymphomas. The cellular origin of so-called splenic ''marginal zone'' lymphoma, along with diagnostic criteria, also need to be elucidated.[97] Subtyping of the diffuse large B-cell lymphomas into immunoblastic and nonimmunoblastic types may be useful, and the clinical and pathologic features of anaplastic large B-cell lymphoma need to be more carefully studied before combining it into the generic category of diffuse large B-cell lymphoma. Precise criteria for grading within the various lymphoma types are clearly needed, such as for the follicular lymphomas, mantle cell lymphomas, and marginal zone B-cell lymphomas of MALT type. Finally, the number of categories of peripheral T-cell lymphoma, for which the diagnostic criteria are imprecise and difficult to apply, seems excessive when there is little evidence to support subdividing for clinical purposes. Hopefully, these issues will be addressed by the working groups of the new World Health Organization classification project.

In conclusion, the ILSG classification was readily applied and identified clinically distinctive types of NHL. Immunophenotyping added significantly to the accuracy of diagnosis in certain major lymphoma types and was clinically important. For clinical application, however, prognostic factors as defined by the International Prognostic Index[91] must be combined with the histologic classification for appropriate clinical decisions.

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APPENDIX

Study Participants: The pathologists and clinicians at each institution were, respectively, Wing C. Chan and James O. Armitage (Omaha, NE), Randy Gascoyne and Joseph Connors (Vancouver, Canada), Pauline Close and Peter Jacobs (Capetown, South Africa), Andrew Norton and T. Andrew Lister (London, UK), Ennio Pedrinis and Franco Cavalli (Locarno, Switzerland), Francoise Berger and Bertrand Coiffier (Lyon, France), Faith Ho and Raymond Liang (Hong Kong), German Ott/Alfred Schauer and Wolfgang Hiddemann (Würzburg/Göttingen, Germany). The five visiting expert hematopathologists were Jacques Diebold (Paris, France), Kenneth A. MacLennan (Leeds, UK), H. Konrad Müller-Hermelink (Würzburg, Germany), Bharat N. Nathwani (Los Angeles, CA), and Dennis D. Weisenburger (Omaha, NE). Nancy L. Harris (Boston, MA) participated as a consultant regarding application of the International

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Lymphoma Study Group classification. James R. Anderson (Omaha, NE) and Pascal Roy (Lyon, France) provided statistical expertise regarding the study design and data analysis.

REFERENCES

1. Weisenburger DD: Epidemiology of non-Hodgkin's lymphoma: Recent findings regarding an emerging epidemic. Ann Oncol 5:19, 1994 (suppl 1)

2. Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics 1996. CA Cancer J Clin 46:5, 1996

3. Gall EA, Mallory TB: Malignant lymphoma. A clinicopathologic survey of 618 cases. Am J Pathol 18:381, 1942

4. Rappaport H, Winter WI, Hicks EB: Follicular lymphoma: A re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 9:792, 1954

5. Lukes RF, Collins RD: Immunologic characterization of human malignant lymphomas. Cancer 34:1488, 1974

6. Lennert K, Mohri N, Stein H, Kaiserling E: The histopathology of malignant lymphoma. Br J Haematol 31:193, 1975 (suppl)

7. Lennert K: Malignant Lymphomas Other Than Hodgkin's disease. New York, NY, Springer-Verlag, 1978

8. Stansfeld A, Diebold J, Kapanci Y, Kelenyi G, Lennert K, Mioduszewska O, Noel H, Rilke F, Sundstrom C, van Unnik J, Wright D: Updated Kiel classification of lymphomas. Lancet 1:292, 1988

9. The Non-Hodgkin's Lymphoma Classification Project: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer 49:2112, 1982

10. Weisenburger DD, Nathwani BN, Diamond LW, Winberg CD, Rappaport H: Malignant lymphoma, intermediate lymphocytic type. A clinicopathologic study of 42 cases. Cancer 48:1415, 1981

11. Weisenburger DD, Kim H, Rappaport H: Mantle-zone lymphoma. A follicular variant of intermediate lymphocytic lymphoma. Cancer 49:1429, 1982

12. O'Briain D, Kennedy M, Daly P, O'Brian A, Tanner W, Rogers P, Lawlor E: Multiple lymphomatous polyposis of the gastrointestinal tract. A clinicopathologically distinctive form of non-Hodgkin's lymphoma of B-cell centrocytic type. Am J Surg Pathol 13:691, 1989

13. Lardelli P, Bookman MA, Sundeen J, Longo DL, Jaffe ES: Lymphocytic lymphoma of intermediate differentiation. Morphologic and immunophenotypic spectrum and clinical correlations. Am J Surg Pathol 14:752, 1990

14. Banks PM, Chan J, Cleary M, Delson G, De Wolf-Peeters C, Gator K, Grogan T, Harris N, Isaacson P, Jaffe E, Mason D, Pileri S, Ralfkiaer E, Stein H, Warnke R: Mantle cell lymphoma: A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol 16:637, 1992

15. Zucca E, Stein H, Coffier B: European Lymphoma Task Force (ELTF). Report of the workshop on mantle cell lymphoma (MCL). Ann Oncol 5:507, 1994

16. Berger F, Felman P, Sonet A, Salles G, Bastion Y, Bryon PA, Coiffier B: Nonfollicular small B-cell lymphomas. A heterogeneous group of patients with distinct clinical features and outcome. Blood 83:2829, 1994

17. Norton AJ, Mathews J, Pappa V, Shamash J, Love S, Rohatiner AZ, Lister TA: Mantle cell lymphoma. Natural history defined in a serially biopsied population over a 20-year period. Ann Oncol 6:249, 1995

18. Fisher RI, Dahlberg S, Nathwani BN, Banks PM, Miller TP, Grogan TM: A clinical analysis of two indolent lymphoma entities: Mantle cell lymphoma and marginal zone lymphoma (including mucosa-associated lymphoid tissue and monocytoid B cell categories): A Southwest Oncology Group study. Blood 85:1075, 1995

19. Zucca E, Roggero E, Pinotti G, Pedrinis E, Cappella C, Venco A, Cavalli F: Patterns of survival in mantle cell lymphoma. Ann Oncol 6:257, 1995

20. Weisenburger DD, Armitage JO: Mantle cell lymphoma—An entity comes of age. Blood 87:1483, 1996

21. Sheibani K, Sohn CC, Burke JS, Winberg CD, Wu AM, Rappaport H: Monocytoid B-cell lymphoma. A novel B-cell neoplasm. Am J Pathol 124:310, 1986

22. Cousar J, McGinn D, Glick A, List A, Collins R: Report of an unusual lymphoma arising from parafollicular B lymphocytes or so-called ''monocytoid'' lymphocytes. Am J Clin Pathol 87:121, 1987

23. Sheibani K, Burke J, Swartz W, Nademanee A, Winberg C: Monocytoid B-cell lymphoma. Clinicopathologic study of 21 cases of a unique type of low grade lymphoma. Cancer 62:1531, 1988

24. Cogliatti S, Lennert K, Hansmann M, Zwingers T: Monocytoid B cell lymphoma: Clinical and prognostic features of 21 patients. J Clin Pathol 43:619, 1990

25. Ngan B-Y, Warnke R, Wilson M, Takagi K, Cleary M, Dorfman R: Monocytoid B-cell lymphoma. A study of 36 cases. Hum Pathol 22:409, 1991

26. Nizze H, Cogliatti S, von Schilling C, Feller A, Lennert K: Monocytoid B-cell lymphoma. Morphological variants and relationship to low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue. Histopathology 18:403, 1991

27. Shin S, Sheibani K, Fishleder A, Ben-Erza J, Bailey A, Koo C, Burke J, Tubbs R, Rappaport H: Monocytoid B-cell lymphoma in patients with Sjögren's syndrome. A clinicopathologic study of 13 patients. Hum Pathol 22:422, 1991

28. Davis G, York J, Glick A, McCurley T, Collins R, Cousar J: Plasmacytic differentiation in parafollicular (monocytoid) B-cell lymphoma. A study of 12 cases. Am J Surg Pathol 16:1066, 1992

29. Isaacson P, Wright D: Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive B-cell lymphoma. Cancer 52:1410, 1983

30. Isaacson P, Spencer J: Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 11:445, 1987

31. Cogliatti S, Schmid U, Schumacher U, Eckert F, Hansmann M-L, Heddrich J, Takahashi H, Lennert K: Primary B-cell gastric lymphoma: A clinicopathologic study of 145 patients. Gastroenterology 101:1159, 1991

32. Radaszkiewicz T, Dragosics B, Bauer P: Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: Factors relevant to prognosis. Gastroenterology 102:1628, 1992

33. Wotherspoon A, Doglioni C, Diss T, Pan L, Moschini A, de Boni M, Isaacson P: Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 342:575, 1993

34. Roggero E, Zucca E, Pinotti G, Pascarella A, Capella C, Savio A, Pedrinis E, Paterlini A, Venco A, Cavalli F: Eradication of Helicobacter pylori infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. Ann Intern Med 122:767, 1995

35. Schmid C, Kirkham N, Diss T, Isaacson P: Splenic marginal zone cell lymphoma. Am J Surg Pathol 16:455, 1992

36. Isaacson PG, Manutes E, Burke M, Catovsky D: The histopathology of splenic lymphoma with villous lymphocytes. Blood 84:3828, 1994

37. Mollejo M, Menárquez J, Lloret E, Sanchez A, Campo E, Algara P, Cristobal E, Sanchez E, Piris MA: Splenic marginal zone lymphoma: A distinctive type of low-grade B-cell lymphoma. A clinicopathologic study of 13 cases. Am J Surg Pathol 19:1146, 1995

38. Hammer RD, Glick AD, Greer JP, Collins RD, Cousar JB:

Downloaded from http://ashpublications.org/blood/article-pdf/89/11/3909/1408169/3909.pdf by guest on 29 February 2024

Splenic marginal zone lymphoma. A distinct B-cell neoplasm. Am J Surg Pathol 20:613, 1996

39. Addis B, Isaacson P: Large cell lymphoma of the mediastinum. A B-cell tumor of probable thymic origin. Histopathology 10:379, 1986

40. Yousem S, Weiss L, Warnke R: Primary mediastinal non-Hodgkin's lymphomas. A morphologic and immunologic study of 19 cases. Am J Clin Pathol 83:676, 1985

41. Möller P, Lammler B, Eberlein-Gonska M, Feichter GE, Hofmann WJ, Schmitteckert H, Otto HF: Primary mediastinal clear-cell lymphoma of B-cell type. Virchows Arch A 409:79, 1986

42. Perrone T, Frizzera G, Rosai J: Mediastinal diffuse large-cell lymphoma with sclerosis: A clinicopathologic study of 60 cases. Am J Surg Pathol 10:176, 1986

43. Moller P, Moldenhauer G, Momburg F, Lammler B, Eberlein-Gonska M, Kiesel S, Dorken B: Mediastinal lymphoma of clear cell type is a tumor corresponding to terminal steps of B-cell differentiation. Blood 69:1087, 1987

44. Lamarre L, Jacobson J, Aisenberg A, Harris N: Primary large cell lymphoma of the mediastinum. A histologic and immunophenotypic study of 29 cases. Am J Surg Pathol 13:730, 1989

45. Todeshini G, Ambrosetti A, Meneghini V, Pizzolo G, Menestrina F, Chilosi M, Benedetti F, Veneri D, Cetto GL, Perona G: Mediastinal large B-cell lymphoma with sclerosis: A clinical study of 21 patients. J Clin Oncol 8:804, 1990

46. Lazzarino M, Orlandi E, Paulli M, Boveri E, Morra E, Brusamolino E, Kindl S, Rosso R, Astori C, Buonammo MC, Magrini U, Bernasconi C: Primary mediastinal B-cell lymphoma with sclerosis: An aggressive tumor with distinctive clinical and pathologic features. J Clin Oncol 11:2306, 1993

47. Cazals-Hatem D, Lepage E, Brice P, Ferrant A, d'Agay MF, Baumelou E, Briere J, Blanc M, Gaulard P, Biron P, Schlaifer D, Diebold J, Audouin J: Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA (''Groupe d'Etude des lymphomas de l'Adulte'') study. Am J Surg Pathol 20:877, 1996

48. Coiffier B, Brousse N, Peuchmaur M, Berger F, Gisselbrecht C, Bryon P, Diebold J: Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphoma. A prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. Ann Oncol 1:45, 1990

49. Patsouris E, Noël H, Lennert K: Histological and immunohistochemical findings in lymphoepithelioid lymphoma (Lennert's lymphoma). Am J Surg Pathol 12:341, 1988

50. Farcet J, Gaulard P, Marolleau J, Le Couedic J, Henni T, Gourdin M, Divine M, Haioun C, Zafrani S, Goossens M, Hercend T, Reyes F: Hepatosplenic T-cell lymphoma. Sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor $\gamma\delta$. Blood 75:2213, 1990

51. Gaulard P, Bourquelot P, Kanavaros P, Haioun C, Le-Couedic JP, Divine M, Goossens M, Zafrani ES, Farcet JP, Reyes F: Expression of the alpha/beta and gamma/delta T-cell receptors in 57 cases of peripheral T-cell lymphomas. Am J Pathol 137:617, 1990

52. Cooke CB, Krenacs L, Stetler-Stevenson M, Greiner TC, Raffeld M, Kingma DW, Abruzzo L, Frantz C, Daviani M, Jaffe ES: Hepatosplenic T-cell lymphoma: A distinct clinicopathologic entity of cytotoxic $\gamma\delta$ T-cell origin. Blood 88:4265, 19976

53. Alegre VA, Winkelmann RK: Histiocytic cytophagic panniculitis. J Am Acad Dermatol 20:177, 1989

54. Gonzalez C, Medeiros L, Braziel R, Jaffe E: T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 15:17, 1991

55. Watanabe S, Sato Y, Shimoyama M, Minato K, Shimosato Y: Immunoblastic lymphadenpathy angioimmunoblastic lymphodemopathy, and IBL-like T-cell lymphoma. Cancer 58:2224, 1986

56. Weiss L, Strickler J, Dorfman R, Horning S, Warnke R, Sklar J: Clonal T-cell populations in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Am J Pathol 122:392, 1986

57. Tobinai K, Minato K, Ohtsu T, Mukai K, Kagami Y, Miwa M, Watanabe S, Shimoyama M: Clinicopathologic, immunophenotypic, and immunogenetic analysis of immunoblastic lymphadenopathy-like T-cell lymphoma. Blood 72:1000, 1988

58. Siegert W, Nerl C, Agthe A, Engelhard M, Brittinger G, Tiemann M, Lennert K, Huhn D: Angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma: Prognostic impact of clinical observations and laboratory findings at presentation. Ann Oncol 6:659, 1995

59. Nathwani BN, Jaffe ES: Angioimmunoblastic lymphadenopathy (AILD) and AILD-like T-cell lymphomas, in Jaffe ES (ed): Surgical Pathology of the Lymph Nodes and Related Organs. Philadelphia, PA, Saunders, 1995, p 390

60. Lipford E, Margolick J, Longo D, Fauci A, Jaffe E: Angiocentric immunoproliferative lesions. A clinicopathologic spectrum of post-thymic T cell proliferations. Blood 5:1674, 1988

61. Chan J, Ng C, Lau W, Ho S: Most nasal/nasopharyngeal lymphomas are peripheral T cell neoplasms. Am J Surg Pathol 11:418, 1987

62. Ho F, Choy D, Loke S, Kung I, Fu K, Liang R, Todd D, Khoo R: Polymorphic reticulosis and conventional lymphomas of the nose and upper aerodigestive tract: A clinicopathologic study of 76 cases, and immunophenotypic studies in 16 cases. Hum Pathol 21:1041, 1990

63. Strickler JG, Meneses MF, Habermann TM, Ilstrup DM, Earle JD, McDonald TJ, Chang KL, Weiss LM: Polymorphic reticulosis: A reappraisal. Hum Pathol 25:659, 1994

64. Van Gorp J, de Bruin PC, Sie-Go DMDS, Van Heerde P, Ossenkoppele GJ, Rademakers LHPM, Meijer CJLM, Van Den Tweel JG. Nasal T-cell lymphoma: A clinicopathologic and immunophenotypic analysis of 13 cases. Histopathology 27:139, 1995

65. Liang R, Todd D, Chan TK, Chiu E, Lie A, Kwong YL, Choy D, Ho F: Treatment outcome and prognostic factors for primary nasal lymphoma. J Clin Oncol 13:666, 1995

66. Emile JF, Boulland ML, Haioun C, Kanavaros P, Petrella T, Delfau-Larue M, Bensussan A, Farcet JP, Gaulard P: $CD5^-$, $CD56^-$ T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. Blood 87:1466, 1996

67. Harabuchi Y, Imai S, Wakashima J, Hirao M, Kataura A, Osato T, Kon S: Nasal T-cell lymphoma casually associated with Epstein-Barr virus. Clinicopathologic, phenotypic, and genotypic studies. Cancer 77:2137, 1996

68. Isaacson P, O'Connor NT, Spencer J, Bevan DH, Connolly CE, Kirkham N, Pollock DJ, Wainscoat JS, Stein H, Kirkham N, Wainscoat J, Mason DY: Malignant histiocytosis of the intestine. A T-cell lymphoma. Lancet 2:688, 1985

69. O'Farrelly C, Feighery C, O'Briain DS, Stevens F, Connolly CE, McCarthy C, Weir DG: Humoral response to wheat protein in patients with coeliac disease and enteropathy associated T-cell lymphoma. Br Med J 293:908, 1986

70. Chott A, Dragosics B, Radaszkiewicz T: Peripheral T-cell lymphomas of the intestine. Am J Pathol 141:1361, 1992

71. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H: Adult T-cell leukemia. Clinical and hematologic features of 16 cases. Blood 50:481, 1977

72. Jaffe ES, Blattner WA, Blayney DW, Bunn PA Jr, Cossman J, Robert-Guroff M, Gallo RC: The pathologic spectrum of adult T-cell leukemia/lymphoma in the United States. Human T-cell leuke-

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mia/lymphoma virus-associated lymphoid malignancies. Am J Surg Pathol 8:263, 1984

73. Shimoyama M, Ota K, Kikuchi M, Yunoki K, Konda S, Takatsuki K, Ichimaru M, Tomianga S, Tsugane S, Minato K, Tobinai K, Oyama A, Hisano S, Matsumoto M, Takiguchi T, Yamaguchi K, Kinoshita K, Tajima K, Suemasu K. for the Lymphoma Study Group: Major prognostic factors in adult patients with advanced T-cell lymphoma/leukemia. J Clin Oncol 6:1088, 1988

74. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, Gatterk, Falini B, Delsol G, Lemke H, Schwarting R, Lennert K: The expression of Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: Evidence that Reed-Stenberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 66:848, 1985

75. Agnarsson B, Kadin M: Ki-1 positive large cell lymphoma. A morphologic and immunologic study of 19 cases. Am J Surg Pathol 12:264, 1988

76. Kaudewitz P, Stein H, Dallenbach F, Eckert F, Bieber K, Burg G, Braun-Falco D: Primary and secondary cutaneous Ki-1+ (CD30+) anaplastic large cell lymphomas. Am J Pathol 135:359, 1989

77. Mason D, Bastard C, Rimokh R, Dastugue N, Huret JL, Kristoffersson U, Magaud JP, Nezelof C, Tilly H, Vannier JP: CD30-positive large cell lymphomas (''Ki-1 lymphoma'') are associated with a chromosomal translocation involving 5q35. Br J Haematol 74:161, 1990

78. Greer J, Kinney M, Collins R, Salhany K, Wolff S, Hainsworth JD, Flexner JM, Stein RS: Clinical features of 31 patients with Ki-1 anaplastic large-cell lymphoma. J Clin Oncol 9:539, 1991

79. De Bruin PC, Beljaards RC, van Heerde P, Van Der Valk P, Noorduyn LA, Van Krieken JH, Kluin Nelemans JC, Willemze R, Meijer CJ: Differences in clinical behavior and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T-cell or null cell phenotype. Histopathology 23:127, 1993

80. Shulman LN, Frisard B, Antin JH, Wheeler C, Pinkus G, Magauran N, Mauch P, Nobles E, Mashal R, Canellos G, Tung N, Kadin M: Primary Ki-1 anaplastic large cell lymphoma in adults: Clinical characteristics and therapeutic outcome. J Clin Oncol 11:937, 1993

81. Pileri S, Bocchia M, Baroni C, Martelli M, Falini B, Sabattini E, Gherlinzoni F, Amadori S, Poggi S, Mazza P, Burgio V, Zinzani P, Melilli G, Binni M, Saragoni L, Martelli M, Stein H, Mandelli F, Tura S: Anaplastic large cell lymphoma (CD30+/Ki-1+). Results of a prospective clinicopathologic study of 69 cases. Br J Haematol 86:513, 1994

82. Romaguera J, Garcia-Foncillas J, Cabanillas F: 16-year experience at MD Anderson Cancer Center with primary Ki-1 (CD30) antigen expression and anaplastic morphology in adult patients with diffuse large cell lymphoma. Leuk Lymphoma 20:97, 1995

83. Weisenburger DD, Gordon BG, Vose JM, Bast MA, Chan WC, Greiner TC, Anderson JR, Sanger WG: Occurance of the t(2;5)(p23;q35) in non-Hodgkin's lymphoma. Blood 87:3860, 1996

84. Harris NJ, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, DeWolf Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink HK, Pileri SA, Piris MA, Ralfkiaer E, Warnke RA: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361, 1994

85. Kim H, Zelman RJ, Fox MA, Bennett JM, Berard CW, Butler JJ, Byrne GE Jr, Dorfman RF, Hartsock RJ, Lukes RJ, Mann RB, Neiman RS, Rebuck JW, Sheehan WW, Variakojis D, Wilson JF, Rappaport H: Pathology panel for lymphoma clinical studies: A comprehensive analysis of cases accumulated since its inception. J Natl Cancer Inst 68:43, 1982

86. Whitcomb CC, Crissman JD, Flint A, Cousar JB, Collins RD, Byrne GE: Reproducibility of morphologic classification of non-Hodgkin's lymphomas using the Lukes-Collins system. The Southeastern Cancer Study Group experience. Am J Clin Pathol 82:383, 1983

87. NCI Non-Hodgkin's Classification Project Writing Committee: Classification of non-Hodgkin's lymphoma. Reproducibility of major classification systems. Cancer 55:91, 1985

88. Dick F, VanLier S, Banks P, Frizzera G, Witrak G, Gibson R, Everett G, Schuman L, Isacson P, O'Conor G, Cantor K, Blattner W, Blair A: Use of the Working Formulation for non-Hodgkin's lymphoma in epidemiologic studies: Agreement between reported diagnosis and a panel of experienced pathologists. J Natl Cancer Inst 78:1137, 1987

89. Lennert K, Feller AC: Histopathology of Non-Hodgkin's Lymphomas (based on the Updated Kiel classification). Berlin, Germany, Springer-Verlag, 1990

90. Mann RB, Berard CW: Criteria for the cytologic subclassification of follicular lymphoma. A proposed alternative method. Hematol Oncol 1:187, 1982

91. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987, 1993

92. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

93. Cox DR: Regression models and life-tables. J R Stat Soc 34:187, 1972

94. Mason DY, Gatter KC: Annotation: Not another lymphoma classification. Br J Haematol 90:493, 1995

95. Ioachim HL: The revised European-American classification of lymphoid lymphomas. A belated commentary. Cancer 78:4, 1996

96. Nathwani BN, Hernandez AM, Deol I, Taylor CR: Marginal zone B-cell lymphomas: An appraisal. Hum Pathol 28:42, 1997

97. Isaacson PG: Splenic marginal zone lymphoma. Blood 88:75, 1966

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