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The World Health Organization Classification of Lymphomas

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The Revised European-American Classification of Lymhoid Neoplasms (REAL) classification has been validated by a multi-institutional study, and project data showed that it is both reproducible and clinically relevant. The new World Health Organization (WHO) Classification of Neoplastic Diseases of Hematopoietic and Lymphoid Tissues, as a joint project of the Society of Hematopathology and European Association of Hematopathologists, is an update of the REAL classification, with minor changes based on newly available information. We analyzed the incidence of different histological types of non-Hodgkin's lymphomas diagnosed in Zagreb University Hospital Center, which were reclassified according to the WHO classification. Furthermore, we present a conceptual grouping of lymphomas into four categories (indolent, aggressive, highly aggressive, and localized indolent).

Key words: *classification; immunohistochemistry; lymphoma; molecular biology; World Health Organization*

The histological categorization of lymphoma has been a source of frustration for many years for both clinicians and pathologists. Ideally, lymphomas, like most other tumors, should be classified according to their presumed normal counterpart. This should provide the best information about disease biology, natural history, and response to treatment. However, despite extensive research, there are still many uncertainties in the definition of lymphoid compartments in humans and movement of cells between these compartments. Furthermore, there are difficulties in defining the full size of a neoplastic clone in individual cases of lymphoma, and some well-defined lymphoma types do not have their obvious normal counterparts. Consequently, although differentiation schemes provide useful conceptual frameworks for understanding lymphomas and suggest important new lines of research, our current understanding of both the immune system and lymphomas appears to be inadequate to support a biologically "correct and justifiable" lymphoma classification. Thus, a classification strictly based on a theoretical relationship of tumors to normal stages of differentiation is both unrealistic and unnecessary for the practical categorization of human lymphomas. In the last 10 years, a lot of updated information on lymphomas has become available, resulting in the recognition of new entities and raising the question whether it was time for a new lymphoma classification. Most hematopathologists agree that there are more classification schemes than entities they recognize and diagnose in daily practice. Historically, many lymphoma classifications were used in clinical practice, such as the Rappaport Classification, Kiel Classification, the Lukes-Collins Classification, Working Formulation, British National Lymphoma Investigation Classification, and Revised European-American Classification (REAL). Most were based on the histological appearance of tumor growth (nodular or diffuse), size of cells (small, medium, or large), and cell immunophenotype (B, T, NK, or null). Many lymphoma entities recognized in different classification systems often go by different names and their diagnostic criteria vary. For that reason, most hematopathologists had doubts about both practical feasibility and scientific validity of distinguishing certain subtypes in different classification systems.

The most practical approach to lymphoma categorization at this time is simply to define the diseases that we think we can recognize using the currently available morphologic, immunologic, and genetic techniques. Thus, lymphoma classification becomes simply a list of well-defined, real disease entities, which are associated with distinctive clinical presentations and natural histories. Cases that do not fit into one of these defined entities are best left unclassified, reflecting the fact that we do not yet understand everything about lymphomas or the immune system.

The World Health Organization (WHO) has adopted the REAL classification, which was published in 1994 by the International Lymphoma Study Group, as the classification of lymphoid neoplasms (1-6). This classification contains a list of "real" disease entities, which are defined by a combination of morphologic, immunophenotypic, genetic, and clinical features (Table 1). The relative importance of each

Table 1. Cytogenetic findings in different types of lymphoma

Lymphoma type	Specific chromosomal translocations	Implicated oncogene or tumor suppressor gene
Follicular lymphoma	t(14;18)(q32;q21)	BCL2
Lymphoplasmacytic lymphoma	(t9;14)(p13;q32)	PAX5
Mantle cell lymphoma	t(11;14)(q13;q32)	BCL1
Extranodal marginal zone B-cell lymphoma of MALT type[a]	t(11;18)(q21;q21)	API2,MLT
	t(1;14)(p22;q32)	BCL10
Diffuse large B-cell lymphoma	t(3;14)(q22;q32), and translocations involving 3q27 with a number of chromosome partners	BCL6
Burkitt lymphoma	t(8;14)(q24;q32) t(8;22)(q24;q11) t(2;8)(p12;q24)	C-myc
Myeloma	t(6;14)(p25;q32)	MUM1
Precursor T-lymphoblastic lymphoma/leukemia	t(1;14)(p32;q11)	TAL1
Anaplastic large cell lymphoma, primary systemic form	t(2;5)(p23;q35)	ALK and other partner genes, such as TPM3, TGF, ATIC, and CLTCL
	variant translocations involving 2p23, e.g. t(1;2), t(2;3), and inv(2)(p23;q35)	

[a]MALT – mucosa-associated lymphatic tissue.

of these features varies among diseases, and there is no "gold" standard. The major advantage of this classification is that clinical groupings of lymphoid neoplasms are neither necessary nor desirable, since patient treatment is determined by the specific type of lymphoma, grade of the tumor type – if applicable, and clinical prognostic factors, such as the International Prognostic Index (IPI) (Table 2). The development of the WHO classification, which has intensified the cooperation of and communication between oncologists and pathologists from around the world, should facilitate progress in the understanding and treatment of hematological malignancies. The proposed WHO classification of lymphoid neoplasms has a goal to define disease entities as such that can be recognized by pathologists, and also have clinical relevance (Table 3). In the application of the WHO classification, immunohistochemical studies play a key role in the delineation of the entities. Another important aspect of the classification is that clinical information is an integral part of the definition of many entities; when such information is not available, the definitive classification may not be possible. The proposed classification recognizes and differentiates between B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin's disease. The T- and B-cell neoplasms are stratified into *precursor* (lymphoblastic lymphomas), or lymphoblastic neoplasms, and *mature* (peripheral) B- and T-cell neoplasms. The mature B- and T-cell neoplasms are grouped according to their major clinical presentations: *predominantly disseminated* (leukemic), *primarily extranodal,* and *predominantly nodal* diseases.

Table 2. Parameters of International Prognostic Index, applicable to practically all non-Hodgkin's lymphomas

Age
Advanced stage (III or IV)
> 1 extranodal sites of involvement
Performance status > 2
Serum lactate dehydrogenase level increased
Risk group stratification:
0-1 low risk
2 low-intermediate risk
3 high-intermediate risk
4-5 high risk

Table 3. World Health Organization lymphoma classification (2001)

Precursor cell lymphoma:
Lymphoblastic lymphoma, T cell, B cell
Peripheral B-cell neoplasms:
B-chronic lymphocytic leukemia/small lymphocytic lymphoma
B-prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Mantle cell lymphoma
Follicular lymphoma
Extranodal marginal zone B-cell lymphoma of MALT type[a]
Nodal marginal zone B-cell lymphoma
Splenic marginal zone B-cell lymphoma
Hairy cell leukemia
Diffuse large B-cell lymphoma
Burkitt's lymphoma (including Burkitt-like lymphoma)
Plasmacytoma/plasma cell myeloma
Peripheral T and NK cell neoplasms; T-prolymphocytic leukemia:
T-cell granular lymphocytic leukemia
Aggressive NK cell leukemia
Mycosis fungoides/Sezary syndrome
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Extranodal NK/T cell lymphoma, nasal and nasal-type
Enteropathy-type T-cell lymphoma
Hepatosplenic γδ T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Anaplastic large cell lymphoma, T/null cell systemic type
Anaplastic large cell lymphoma, T/null cell cutaneous type

[a]MALT – mucosa-associated lymphatic tissue.

Precursor Neoplasms

There was a consensus that the terms L1, L2, and L3 morphology did not predict immunophenotype, genetic abnormalities, or clinical behavior of the neoplasm. L3 is generally equivalent to Burkitt lymphoma in leukemic phase, and should be diagnosed as such. There was also a consensus that the precursor neoplasms presenting as solid tumors and those presenting with marrow and blood involvement were biologically the same disease, but with different clinical presentations. The involvement of bone marrow and peripheral blood is principally a prognostic, and not classification, issue, although the biological basis for the different clinical presentations is not fully under-

stood. Since most precursor lymphoid neoplasms present as leukemia, it was agreed that the classification should retain the term acute lymphoblastic leukemia (ALL) for the leukemic phase of precursor neoplasms of T and B types. Genetic abnormalities are important prognostic factors within precursor B lymphoblastic neoplasms t(9;22), q(34;q11), BCR/ABL, 11q23, MLL, t(1;19)(q23;p13), E2A/PBX1, t(12;21)(p12;q22), ETV/CBFα, so pathologists who undertake to diagnose these neoplasms should be familiar with the types and significance of genetic abnormalities occurring in these tumors. The genetic analysis should be included in the pathology report whenever feasible.

Peripheral B-cell Neoplasms

As for the precursor neoplasms, the proposed classification considers lymphomas and lymphoid leukemias of the same cell type as a single disease with different clinical presentations or stages. When the mature B-cell neoplasms are concerned, this question is primary relevant to B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma. The experts agree that further studies are needed to determine whether plasmacytoid differentiation is an adverse prognostic factor in chronic lymphocytic leukemia. Therefore, recognition of this feature is not required for the diagnosis for clinical purposes, but criteria for diagnosing plasmacytoid differentiation should be agreed upon, if possible, for future studies.

Follicular Lymphoma

The WHO committee proposed to change the nomenclature. Thus, previous "follicle center lymphoma" is now called "*follicular lymphoma*", and criteria recommended for grading are those developed by Mann and Berard (7), in which the number of large cells (centroblasts) are counted. Follicular lymphomas are graded as grade 1 (1-5 centroblasts per high-power field), grade 2 (6-15 centroblasts per high-power field), and grade 3 (more than 15 centroblasts per high-power field). The grade 3 group tends to show earlier relapse but similar overall survival, although this occurrence may be reduced by the use of adriamycin-containing therapeutic regimens. There are also interesting recent data to support the addition of a new subgroup (grade 3b), characterized by exclusive presence of centroblasts: biologically it appears to be much more related to diffuse large B-cell lymphoma than follicular lymphoma. In summary, there was a consensus that follicular lymphoma should be graded into at least two grades, and that neoplasms currently recognized as grade 3 follicular lymphomas should be discriminated from grades 1 and 2. Although there are minor differences in the natural history and response to treatment between grades 1 and 2 follicular lymphomas, there was a consensus that these did not mandate different approaches to the treatment, and thus were not of great clinical importance. According to this classification, it is also accepted that diffuse areas should be reported and quantified according to the recommendations of the REAL classification, as follows: predominantly follicular (>75% follicular), follicular and diffuse (25-75% follicular), and predominantly diffuse (<25% follicular). However, it is not clear what will be the implications of these features for treatment.

Marginal Zone B-cell Lymphoma

Marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue (MALT) type is reserved for small cell gastrointestinal lymphomas with indolent clinical behavior. The term "high-grade MALT lymphoma", which is used by some pathologists to denote either transformation of a low-grade MALT lymphoma or any large B-cell lymphoma in a MALT site, is confusing to clinicians, to whom the term MALT lymphoma is synonymous with a lesion that may respond to antibiotic therapy. For that reason, the oncologists preferred the term MALT lymphoma for the low-grade lymphoma, originally described as "low-grade B-cell lymphoma of MALT." Areas of large-cell lymphoma, if present, should be separately diagnosed as "diffuse large B-cell lymphoma." Primary large-cell lymphomas of MALT sites should be diagnosed as "diffuse large B-cell lymphoma," not as "high grade MALT lymphoma." The issue of grading MALT lymphoma has not been extensively studied. On the basis of available data, the Committee agreed that increased large cells might be of prognostic importance in MALT lymphoma. WHO classification should specify criteria for grading so that its significance can be tested in future clinical studies. Splenic marginal zone lymphoma (SMZL) appears to be the tissue counterpart of splenic lymphoma with villous lymphocytes (SLVL). Patients are typically older adults, with bone marrow and blood involvement, and a very indolent clinical course. Nodal marginal zone lymphoma, which often has a prominent monocytoid B-cell component, must be distinguished from MALT lymphoma with lymph node involvement as well as from other lymphomas (follicular and mantle cell lymphoma) with a marginal zone pattern or a component of monocytoid B cells. Nodal marginal zone lymphoma appears to have a high rate of early relapse and overall survival similar to or slightly worse than that of follicular lymphoma.

Mantle Cell Lymphoma

Many studies found morphological heterogeneity in both pattern and cytology of mantle cell lymphoma (MCL), and suggested that some features may predict outcome. For example, cases with a mantle zone pattern behaved less aggressive in some studies than in some other research, and cases with blastic or blastoid morphology had a worse prognosis (8,9). The consensus of the Committee has been that stratification by morphological features is not required for clinical diagnostic purposes, since no effective therapy currently exists for any type of mantle cell lymphoma. However, different cytological types and patterns should be included in the text of the classification, so that variant cases can be recognized as MCL for diagnosis and graded similarly for research purposes (4).

Diffuse Large B-Cell Lymphoma

The Clinical Advisory Committee agreed that, at present, neither biological nor clinical data support a requirement for subclassification of diffuse large B-cell lymphoma (DLBCL) according to the criteria of the Working Formulation or the Kiel classification. Data from the Kiel group suggest that immunoblastic lymphoma, as defined in the updated Kiel classification (>90% immnoblasts), has worse prognosis than centroblastic lymphoma. Other data suggest that staining for bcl-6 (centroblastic) and syndecan-1/CD138 (immunoblastic) may help to discriminate between them. Nonetheless, neither reliable pathological or biological criteria for subclassfication nor distinctive therapies that can be recommended for clinical practice are available at this time. For that reasons, the Committee felt that these categories should remain optional at this time. However, there was agreement that pathologists should develop criteria for subclassification, so that these categories can be tested in future clinical studies. The pathologists proposed to define "Burkitt-like" lymphoma as a subtype of large B-cell lymphoma. However, there was a clear consensus among the oncologists that this would be a mistake. There are abundant data indicating that lymphomas classified as Burkitt-like (or non-Burkitt) in children behave identically to Burkitt lymphoma, and would be undertreated if treated like B-cell lymphoma. In adults, the biology of cases classified as Burkitt-like is less clear, but this may reflect the heterogeneity of diagnostic criteria. The committee concluded that Burkitt-like lymphoma should be listed as a morphological variant of Burkitt lymphoma in the WHO classification. The "gold standard" for the diagnosis of Burkitt lymphoma should be the presence of the t(8;14)(q24;q32) and its variants of c-myc rearrangement. Cytogenetic analysis is recommended in all leukemic cases. If cytogenetic or Southern blot analysis is not available, it seems likely that the most reasonable surrogate for c-myc rearrangement is proliferation fraction. Therefore, it was suggested that cases in which cytogenetic analysis is not available should not be diagnosed as Burkitt lymphoma or Burkitt-like lymphoma without a Ki-67 fraction close to 100%. Thus, the definition of Burkitt-like lymphoma is a lymphoma that morphologically resembles Burkitt lymphoma, but has more pleomorphism or large cells than classic Burkitt lymphoma, and a proliferative fraction of >99%.

There are multiple distinct clinical presentations of DLBCL, several of which have unique clinical behavior. These include mediastinal/thymic large B-cell lymphoma, primary central nervous system lymphoma, and primary effusion lymphoma. Of particular concern to pathologists is the category of cutaneous B-cell lymphoma, most of which have a very indolent clinical course. Pathologists easily recognize one category of marginal zone/MALT lymphoma as a low-grade lymphoma. However, the other major category, called cutaneous follicle center lymphoma in the recently proposed EORTC classification, has a range of morphology from a clearly low-grade lesion resembling nodal follicular lymphoma to a diffuse proliferation with numerous large cells, which may be specified by pathologists as DLBCL (10). This type of lymphoma, which is typically localized to the head and trunk, responds well to local therapy (excision or radiation), and typically does not disseminate to lymph nodes, comprises 70% of cutaneous B-cell lymphomas. There is concern that if those distinctive histological and clinical features are not recognized by pathologists and oncologists, these patients will be over-treated with aggressive chemotherapy (10,11).

The consensus of the Committee was that separate classifications of lymphomas at specific extranodal sites were not needed for clinical purposes. However, the site of involvement should be clearly stated in the pathology report, and oncologists are obliged to understand the distinctive clinical features of lymphomas at various sites. Distinct entities, such as primary mediastinal (thymic) B-cell lymphoma, primary effusion lymphoma, and intravascular lymphoma are considered as subtypes of DLBCL. The Committee recommended that the distinctive clinical features of B-cell lymphomas in the skin be indicated in the text describing each lymphoma subtype.

Peripheral T and NK Cell Neoplasms

Many distinct T- and/or NK-cell diseases have a wide range of cytological composition (small to large to anaplastic), show immunophenotypic variations, and share many antigens. For most of them, specific cytogenetic features are not defined, and even T-cell receptor types or T vs NK lineage are not sufficient to define distinct disease entities. To a greater extent than is appreciated for B-cell neoplasms, it seems that clinical syndromes, and particularly location (nodal vs extranodal and specific extranodal sites), are important in determining the biological behavior of the disease. Based on the available data, there seems to be no immediate justification or clear criteria for recognizing cytological subtypes within this broad category. However, given the pronounced differences in clinical behavior between primary extranodal T/NK-cell lymphomas and primary nodal lymphomas, it could be clinically relevant to subdivide the unspecified category into nodal and extranodal types. Both pathologists and oncologists will need to continue addressing this area in further studies (12).

Incidence of Different Types of Non-Hodgkin's Lymphomas in Our Material

We analyzed the incidence of different histological types of non-Hodgkin's lymphomas diagnosed in the Zagreb University Hospital Center, Croatia, in the period from January 1997 to July 2002. A total of 172 non-Hodgkin's lymphomas were diagnosed in that period. The REAL classification was used until 2000. After the WHO classification was published, all non-Hodgkin's lymphomas were classified according to the WHO classification. The distribution of histological types of non-Hodgkin's lymphomas during the 2000-2002 period shows that most lymphomas were diffuse large B-cell lymphomas (32.5%) and follicular lymphomas (29.4%) (Table 4). Although the classification list of non-Hodgkin's lymphomas in WHO classification is long, 6 entities already account for

more than 75% of all cases encountered in clinical practice. According to non-Hodgkin's WHO lymphoma classification project data, diffuse large B-cell lymphomas comprise 31%, follicular lymphomas 22%, B-cell chronic leukemia/small cell lymphoma 6%, mantle cell lymphoma 6%, peripheral T-cell lymphomas 6%, and extranodal marginal zone B-cell lymphomas of MALT type 5% of all diagnosed lymphomas (12). The distribution of histological types in our material is very similar to published project data (Table 4). We tried to compare and reclassify cases diagnosed and classified according to the REAL classification at the Department before 2000, and summarize our previous reports using WHO classification. For each case, we also assigned the corresponding histopathology category according to the WHO classification (Table 5). Of 70 lymphoid malignancies diagnosed during the 1997-1999 period, 62 (88.6%) were B-cell lymphomas, and 8 (11.4%) T-cell lymphomas. Among B-cell lymphomas, the commonest types were follicular lymphoma (54.3%) (Fig. 1) and diffuse large B-cell lymphoma (12.9%). Other less common lymphomas were mantle cell lymphoma (5.7%), peripheral T-cell lymphoma (4.3%), anaplastic large cell lymphoma (4.3%), and B-cell chronic lymphocytic leukemia (4.3%). Recent data showed that follicular lymphomas characterized by exclusive presence of centroblasts (grade 3b) are biologically more closely related to diffuse large B-cell lymphomas than follicular lymphomas (2,12). Indeed, rela-

Table 4. Types of non-Hodgkin's lymphomas according to the World Health Organization (WHO) classification in our material, 2000-2002

WHO classification	No. (%)
Extranodal marginal zone B-cell lymphoma of MALT type[a]	4 (3.9)
Nodal marginal zone B-cell lymphoma of MALT type	1 (1.0)
Splenic marginal zone B-cell lymphoma	2 (1.9)
B-chronic lymphocytic leukemia/small lymphocytic lymphoma	8 (7.8)
Mantle cell lymphoma	5 (4.9)
Diffuse large B-cell lymphoma	33 (32.5)
Follicular lymphoma	30 (29.4)
Lymphoplasmacytoid lymphoma	1 (1.0)
Burkitt lymphoma (including Burkitt-like lymphoma)	4 (3.9)
Peripheral T-cell lymphoma, not otherwise characterized	7 (6.9)
ALCL[b], T/null cell:	
systemic	3 (2.9)
primary cutaneous type	1 (1.0)
Enteropathy type T-cell lymphoma	1 (1.0)
Lymphoblastic lymphoma, T cell	2 (1.9)
Total	102 (100.0)

[a]MALT – mucosa-associated lymphatic tissue.
[b]ALCL – anaplastic large-cell lymphoma.

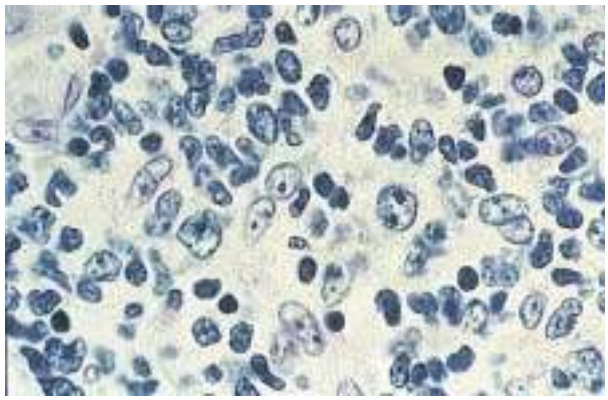

Figure 1. Malignant follicular (grade II) lymphoma. At this magnification, cytological examination revealed mixed small and large cell lymphoma. Giemsa staining, x600.

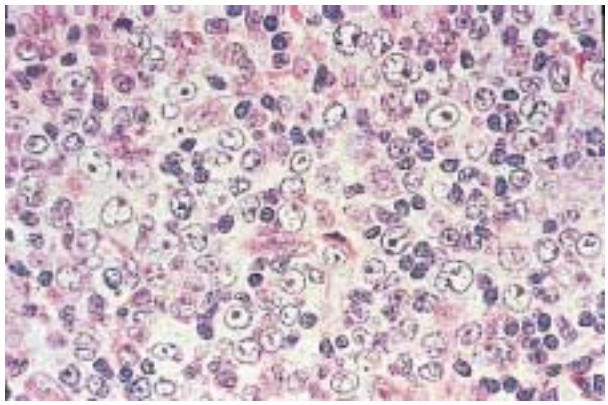

Figure 2. Malignant diffuse follicular lymphoma (grade III). This neoplasm completely affected normal lymph node architecture and was composed predominantly of large cells. Hematoxylin and eosin, x400.

Table 5. Comparison of non-Hodgkin lymphoma types in the 1997-1999 period according to the Revised European-American Classification of Lymhoid Neoplasms (REAL) and World Health Organization (WHO) classification in our material

REAL classification	No. (%)	Change	WHO classification	No. (%)
Marginal zone B-cell lymphoma				
extranodal	5 (7.1)	→	extranodal marginal zone B-cell lymphoma of MALT type[a]	5 (7.1)
nodal (provisional entity)	2 (2.9)	→	nodal marginal zone B-cell lymphoma of MALT type	2 (2.9)
B-chronic lymphocytic leukemia/small lymphocytic lymphoma	3 (4.3)	→	B-chronic lymphocytic leukemia/small lymphocytic lymphoma	3 (4.3)
Mantle cell lymphoma	4 (5.7)	→	mantle cell lymphoma	4 (5.7)
Diffuse large B-cell lymphoma	9 (12.9)	→	diffuse large B-cell lymphoma	24 (34.3) ↑
Follicular center cell lymphoma	38 (54.3)	→	follicular lymphoma	23 (32.9) ↓
Lymphoplasmacytoid lymphoma	1 (1.4)	→	lymphoplasmacytoid lymphoma	1 (1.4)
Peripheral T-cell lymphoma unspecified	3 (4.3)	→	peripheral T-cell lymphoma not otherwise characterized	3 (4.3)
			ALCL, T/null cell	
ALCL, T/null cell[b]	3 (4.3)	↗↘	systemic	2 (2.9)
			primary cutaneous type	1 (1.4)
Intestinal T-cell lymphoma	1 (1.4)	→	enteropathy type T-cell lymphoma	1 (1.4)
Lymphoblastic lymphoma, T cell	1 (1.4)	→	lymphoblastic lymphoma, T cell	1 (1.4)
Total	70 (100.0)			70 (100.0)

[a]MALT – mucosa-associated lymphatic tissue.
[b]ALCL – anaplastic large-cell lymphoma.

tively high percentage (11.4%) of high-grade diffuse follicular center cell lymphomas in our material (Fig. 2) met criteria to be reclassified as diffuse large B-cell lymphomas. After reclassification, distribution of lymphomas is more similar to distribution in the 2000-2002 period, which is more likely to be correct. For other histological types of hematological malignancies, there was no difference after reclassification, except for a single case of anaplastic large cell lymphoma that was assigned as cutaneous form according to the localization of malignancy. The localization of malignancy is a very important part of the WHO classification. It is known that some hematological malignancies have predilection for specific sites. Additionally, the site of malignancy can be very important for prediction of clinical behavior, as in case of cutaneous anaplastic large cell lymphoma, which is likely to be of indolent clinical behavior (11,13-19).

Conceptual Grouping of Non-Hodgkin's Lymphomas by Natural History

Grouping according to survival is dangerous, because various entities with similar survival rates may have very different natural histories and require very different treatment approaches. For example, among the three types of lymphoma with the best survival figures, anaplastic large cell lymphoma has to be treated aggressively, whereas much milder forms of treatment are appropriate for follicular lymphoma and extranodal marginal zone B-cell lymphoma (12). The Clinical Advisory Committee for the WHO classification does not recommend clinical grouping on the grounds that it would hamper understanding of the specific features of some of the diseases. Nonetheless, a conceptual grouping of non-Hodgkin's lymphomas is proposed according to their natural history, which can provide a simple framework for learning these neoplasms (12). There are four major categories of non-Hodgkin's lymphomas in terms of biologic behavior: *indolent lymphoma*, *special group of localized indolent lymphoma, aggressive lymphoma*, and *highly aggressive lymphoma*. The treatment strategy is generally similar for the entities within each group, although the outcome of the individual entities within each group can be very different because some respond better to treatment than others. It is somewhat paradoxical that, in the long-term, the survival of the aggressive and highly aggressive lymphomas is better than that of indolent lymphomas because cure is practically not achievable in the indolent group.

Indolent Lymphomas

This group of lymphomas includes follicular lymphoma, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma (worst outcome in the group), splenic marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, mycosis fungoides, and T-cell granular lymphocytic leukemia. The patients are mostly older adults (almost always over the age of 40 years). Disease is often disseminated, with >80% having stage III/IV, with marrow and blood involvement. Natural history of diseases is slow growing and may have waxing and waning course. Even if left untreated, patients can survive for many years. Transformation to a large cell lymphoma can occur, and then the disease pursues a more aggressive course. Because of the low proliferative fraction, current therapy, such as radiotherapy or chemotherapy, usually fails to eradicate the tumor, except for the rare instances of early stage diseases. There is no evidence that treatment alters the outcome of the disease (20-24).

Special Group of Localized Indolent Lymphomas

Entities included in this category are extranodal marginal zone B-cell lymphoma of MALT type and primary cutaneous anaplastic large cell lymphoma. They can occur at any age, usually at early stage, and peripheral blood and marrow involvement are uncommon. Disease tends to remain localized. Anti-*Helicobacter pylori* therapy can bring remission in about 70% of gastric extranodal marginal zone B-cell lymphomas, and rare cases of cutaneous extranodal marginal B-cell lymphoma have also been reported to undergo remission with treatment of Borelia infection. Spontaneous remission occurs in about 30% of primary cutaneous anaplastic large cell lymphomas. These groups of lymphomas are apparently curable, at least in a proportion of cases, by locoregional therapy or sometimes by antibiotics. Occasionally, delayed relapse can occur (25,26).

Aggressive Lymphomas

Entities in this category include diffuse large B-cell lymphomas and various peripheral T-cell lymphomas and NK cell lymphomas except Mycosis fungoides (indolent lymphoma behavior), T-cell granular lymphocyte leukemia (behavior more likely indolent lymphoma), and primary cutaneous anaplastic large cell lymphoma (special group of localized indolent lymphoma). Patient's age in this group of lymphomas is not specified since they can be found in any age group. Extent of disease is variable, although peripheral T-cell lymphomas tend to have high-stage disease. Peripheral blood involvement is uncommon. Lymphomas in this group are characterized by rapid growth and usually kill the patient within one or two years if left untreated. Because of highly proliferative fraction, the lymphoma is potentially curable with chemotherapy or radiotherapy. The survival curve of patients who received treatment shows plateau, indicating the curability of the tumor. Approximately 70-80% of patients achieve complete remission, and about two-thirds of them will not relapse. The overall survival varies with the different lymphoma types, and is generally worse for peripheral T-cell lymphomas than for diffuse large B-cell lymphomas. The survival of primary systemic anaplastic large cell lymphoma is highly favorable due to good response to therapy (12,18,26).

Given the recent availability of an antibody to anaplastic lymphoma kinase (ALK) protein, which is highly associated with the t(2;5)(p23;q35), the question was raised whether this could be used as the de-

fining criterion for anaplastic large cell lymphoma. Clinically, cases with the t(2;5) and/or ALK positivity seem to represent a homogeneous group with a relatively good prognosis. However, the experience with ALK antibodies is limited since they have become commercially available only recently. In addition, there are cases with typical morphology and immunophenotype that are ALK or t(2;5) negative (27-30). The Committee concluded that a single "gold standard" for the diagnosis of anaplastic large cell lymphoma did not exist. The diagnosis requires both morphology and immunophenotype and restricting the diagnosis to ALK+ cases does not seem to be justified, at least for now. It was suggested that ALK staining be done in all cases to the extent possible, and that cases be designated as anaplastic large cell lymphoma, ALK+ or ALK-, at least for research purposes. In addition, pathologists need to be aware of the rather broad morphological spectrum of anaplastic large cell lymphoma.

Highly Aggressive Lymphomas

Burkitt lymphoma and lymphoblastic lymphoma, which occur almost exclusively in children and young adults, belong to the group of highly aggressive lymphomas. These lymphomas are often already in high stage when the disease presents, and peripheral blood and marrow involvement are common. Both are rapid growing tumors with early dissemination and usually kill patients within weeks to months if untreated. Central nervous system can also be involved. Use of aggressive chemotherapy can potentially lead to cure because of very high proliferative fraction. Shape of survival curve is similar to that of aggressive lymphomas, except for the initial downward slope, which is steeper due to deaths of those failing to achieve remission. Central nervous system prophylaxis is often recommended (4,12,31).

Unclassifiable Hematological Malignancies

Even with the advances in immunophenotyping and genetic analysis, some hematological malignancies are still unclassified. A case may be unclassifiable for various reasons: inadequate tissue sample, unavailability of special studies, or poorly preserved tissue; or it does not fit into one of the categories recognized in the classification even after complete analysis. For each case, the reason for the inability to classify it should be stated in the pathology report (4).

Future of Lymphoma Classification

Because of our incomplete understanding of the various lymphoma types there are still many imperfections in the new WHO lymphoma classification. Although a lot has been learned about the molecular genetics of B-cell lymphomas, knowledge of the specific molecular changes in T-cell lymphomas is extremely low, except for anaplastic large cell lymphoma in which ALK gene is implicated. Thus the classification of the T and NK lymphomas may require significant changes in the future when more will be known about genetic aberrations. Some categories, such as diffuse large B-cell lymphomas and peripheral T-cell lymphomas "unspecified", certainly require "purification" and identification of distinctive tumor types. There are some promising results from studies using DNA microarrays, which can simultaneously study the expression of thousands of genes by use of microchips (32,33). With this technique, two major groups among diffuse large B-cell lymphomas can be identified based on the pattern of gene expression. One group of these tumors expresses genes similar to those of germinal center B-cells (shows a much more favorable prognosis with 5-year overall survival 76%), and one expresses genes of activated B-cells (5-year overall survival 16%). The difference in survival remains significant even after the International Prognostic Index is taken into consideration (34). Since the number of studied patients was small (n = 42), further studies are required to validate this dramatic observation because previous attempts to subclassify diffuse large B-cell lymphomas using morphologic or immunogenetic approaches have never been successful in achieving significant separation in the survival curves. Certainly, information explosion in the field of molecular genetics of lymphomas can soon be expected, and we impatiently wait to see the development in this field.

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