Principles of the revised European–American lymphoma classification
(from the International Lymphoma Study Group)

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Summary
The International Lymphoma Study Group has proposed a consensus classification for lymphoid neoplasms. Lymphoid neoplasms are defined as distinct biological entities, based on a combination of morphologic, immunophenotypic, genetic, and clinical features. Each distinct disease may have a range of histologic grade and clinical aggressiveness. Although many distinct diseases can now be recognized, three of them (follicular lymphoma, diffuse large B-cell lymphoma, and Hodgkin’s disease) account for the majority of the cases seen in Europe and the USA. Recognition of distinct disease entities is essential in order to develop and test effective therapies.

Key words: classification, Hodgkin’s disease, immunophenotype, lymphoma

Introduction
Since the 1970s, different lymphoma classifications have been in use in different parts of the world [1–6]. This lack of consensus on lymphoma classification and terminology has caused problems for practicing pathologists and clinicians and creates difficulty in interpreting published studies. Ideally, lymphomas, like other tumors, should be classified according to their presumed cell of origin: this should provide the best information about disease biology, natural history, and response to treatment. However, our current understanding of the immune system and the lymphomas is insufficient to permit this to be done in all cases, so that the ultimate, biologically 'correct' lymphoma classification is beyond our reach for the time being. Nonetheless, many hematopathologists agree on a large number of distinct lymphoma entities, which they recognize and diagnose in daily practice, using a combination of available morphologic, immunologic, and genetic information [7]. The International Lymphoma Study Group (ILSG) – a group of 19 hematopathologists from the US, Europe, and Asia – recently developed a consensus on the diseases that can be recognized with the currently available techniques. This list of well-defined, ‘real’ disease entities, which can serve as an updated, practical lymphoma classification, was published in 1994 [8]. The list of lymphoid neoplasms is shown in Table 1. Since this compilation represented a revision of current or prior European and American lymphoma classifications, it is called the ‘Revised European–American Classification of Lymphoid Neoplasms’ (REAL).

Disease categories
There are three major categories of lymphoid malignancies: B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin’s disease (HD). Both lymphomas and lymphoid leukemias are included in this classification, since both solid and circulating phases are present in many lymphoid neoplasms, and distinction between them is artificial. Thus, B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma are simply different manifestations of the same neoplasm, as are lymphoblastic lymphomas and acute lymphoid leukemias. In addition, Hodgkin’s disease and plasma-cell myeloma are now recognized as lymphoid, and therefore belong in a compilation of lymphoid neoplasms. Within the B- and T-cell categories, two major categories are recognized – precursor neoplasms, corresponding to the earliest stages of differentiation, and peripheral neoplasms, corresponding to more differentiated stages.

Histologic grade and clinical aggressiveness
Prior to the advent of immunophenotyping and genetic studies that led to the recognition of many distinct lymphoid neoplasms, it was generally assumed that ‘non-Hodgkin’s lymphoma’ was a single disease, with a spectrum of morphology and clinical aggressiveness; thus, it seemed feasible to develop a single grading system that would be predictive of clinical behavior. This principle was applied in the Working Formulation (WF) [5]: in the WF, tumors are divided into three prognostic groups, based on the survival of the patients in the original study; these prognostic groups are commonly referred to as
to attempt to sort different lymphoid neoplasms accord-

and clinical aggressiveness. Thus, it is now no more useful

phoma, there may be a spectrum of morphologic grade

bodies. Furthermore, within a specific type of lym-

may have quite different presentations, natural histories,

broad categories contains several distinct diseases, which

Clinical groupings of non-Hodgkin’s lymphomas

Within the broad category of non-Hodgkin’s lymphomas, there are a large number of distinct lymphoid neoplasms that can now be recognized with a combination of morphology, immunophenotype, and genetic studies (Table 1). These are associated with distinctive epidemiology, etiol-

ogies, clinical features, and often, distinctive responses to therapy. These lymphoid neoplasms can be sorted ac-

indolent nodal lymphoma. Clinically indolent lymphoid

are always systemic diseases, often with leukemic manifesta-

tion; others are primarily extranodal, and may remain

of grades within the tumor type, if applicable, and clinical features such as stage, age, performance status, etc.

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logies, clinical features, and often, distinctive responses to therapy. These lymphoid neoplasms can be sorted ac-

ording to various principles, including their postulated normal counterpart in the immune system, their mor-

phologic features, or their clinical features. For practicing oncologists, the most practical sorting is according to predicted clinical behavior. It is possible to sort patients with lymphoid neoplasms into three major groups, based on their clinical features at presentation, and on their general expectation of survival, as proposed by Longo and colleagues [9, 10] (Table 2).  

Indolent lymphoid neoplasms

Indolent neoplasms are those in which survival is mea-

ured in years, with or without treatment. These disorders have a variety of clinical presentations. Some are virtually always systemic diseases, often with leukemic manifesta-

tion; others are primarily extranodal, and may remain localized for prolonged periods, with or without treat-

ment; and others are primarily nodal diseases, which are also often widespread at the time of the diagnosis. This, it is useful to recognize three clinical subgroups of indolent lymphoid neoplasms: (1) indolent disseminated lymphoma/leukemia, (2) indolent extranodal lymphoma, and (3) indolent nodal lymphoma. Clinically indolent lymphoid neoplasms usually have ‘low-grade’ histologic appear-
Indolent disseminated lymphoma/leukemia

These tumors usually present with involvement of bone marrow, with or without peripheral blood and solid tissues such as lymph nodes and spleen. They include in the B-cell system B-cell chronic lymphocytic leukemia (CLL), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, and plasma-cell myeloma, and in the T-cell system, T-cell CLL and large granular lymphocyte leukemia (LGL).

Indolent extranodal lymphomas

There are two indolent lymphomas that virtually always present in extranodal sites, and appear to correspond to normal lymphoid cells specific for extranodal immunologic reactions. These are extranodal marginal-zone B-cell lymphoma (MALToma) and mycosis fungoides, a T-cell neoplasm. Because their clinical presentation and treatment options differ dramatically from the more common

ance, with a predominance of small cells bearing a close resemblance to some normal lymphoid cell stage, with a minor population of large, transformed lymphoid cells (blasts). A feature common to many diverse types of indolent lymphoma is the propensity to undergo eventual histological transformation to a high-grade malignancy, with a correspondingly accelerated clinical course.

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Table 4. Comparison of the Kiel classification with the REAL classification.

<table>
<thead>
<tr>
<th>Kiel classification</th>
<th>REAL classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell neoplasms</td>
<td>B-cell neoplasms</td>
</tr>
</tbody>
</table>

### Low-grade malignant lymphomas

#### Lymphocytic
- Chronic lymphocytic leukemia
- Prolymphocytic leukemia
- Hairy-cell leukemia

#### Lymphoplasmacytic/lytoid (immunocytoma)
- Lymphoplasmacytoid
- Plasmacytic
- Centroblast centrocytic
- Follicular
- Diffuse

#### Lymphoid cell neoplasm, including marginal zone

### High-grade malignant lymphomas

#### Centroblastic
- Follicular
- Diffuse

#### Immunoblastic
- Burkitt's lymphoma

#### Large cell anaplastic (Ki-1+)

#### Lymphoblastic

### T/NK-cell neoplasms

#### Low-grade malignant lymphomas

#### Lymphocytic
- Chronic lymphocytic leukemia

#### Prolymphocytic leukemia
- Small cell cerebriform (mycosis fungoides, Sézary syndrome)

#### Lymphoproliferative disorder (Lennert's lymphoma)

#### Angioimmunoblastic (AILD, LgX)

#### T-zone lymphoma

#### Pleomorphic, small cell

### High-grade malignant lymphomas

#### Pleomorphic, medium-sized and large cell

#### T-immunoblastic

#### T-large cell anaplastic (Ki-1+)

#### T-lymphoblastic

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### Diseases not specifically recognized in the Kiel classification

<table>
<thead>
<tr>
<th>Kiel equivalent</th>
<th>REAL entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocytoma or monocytoid B-cell lymphoma</td>
<td>Extramedullary B-cell lymphoma</td>
</tr>
<tr>
<td><strong>SLL</strong></td>
<td><strong>Low-grade lymphoma of MALT type</strong></td>
</tr>
<tr>
<td>Large-cell, sclerosing B-cell lymphoma of the mediastinum</td>
<td>Primary mediastinal (thymic) B-cell lymphoma</td>
</tr>
<tr>
<td>Pleomorphic small, medium, or large, immunoblastic</td>
<td>Intestinal T-cell lymphoma</td>
</tr>
<tr>
<td>Pleomorphic small, medium-sized, large, and immunoblastic</td>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
</tbody>
</table>

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Table 5. Approximate relative frequency of lymphomas in adults: US and Europe (nodal presentations).

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphomas</td>
<td>Follicular lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mantle-cell lymphoma</td>
<td>B-CLL/SLL</td>
</tr>
<tr>
<td></td>
<td>Lympplasmyctoid lymphoma</td>
<td>Lympplasmyctoid lymphoma</td>
</tr>
<tr>
<td></td>
<td>Diffuse large B-cell lymphoma</td>
<td>Blastoid variant</td>
</tr>
<tr>
<td></td>
<td>Mantle-cell lymphoma, blastoid variant</td>
<td>Marginal zone</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td>Peripheral T-cell lymphomas</td>
<td>Anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Angioimmunoblastic lymphoma</td>
<td>Precursor T-LBL</td>
</tr>
<tr>
<td></td>
<td>Precursor B-Lymphoblastic lymphoma/leukemia</td>
<td>All others</td>
</tr>
</tbody>
</table>

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Table 6. Approximate relative frequency of lymphomas in children: US and Europe.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphomas</td>
<td>Burkitt's lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td></td>
<td>T-LBLb</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td>Precursor T-LBL</td>
<td>Anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Peripheral T-cell lymphomas</td>
<td>Peripheral T-cell lymphomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral T-cell lymphomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unspecified (medium-sized cell)</td>
</tr>
</tbody>
</table>

* Precursor B-ALL is the most common childhood neoplasm, but most present as acute leukemia; presentation as solid tumor ('lymphoma') is rare.

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Cally present with disseminated disease predominantly involving lymph nodes, but with frequent involvement of bone marrow, spleen, and liver; they may involve other extranodal sites as part of disseminated disease, but rarely present with localized extranodal disease. Follicular lymphoma comprises the vast majority (80% or more) of low-grade lymphomas reported in most American and European clinical trials of low-grade lymphoma. Thus, our understanding of the clinical features and response to treatment of 'low-grade lymphoma' is essentially that of follicular lymphoma. Mantle-cell lymphoma has been recognized relatively recently; it can be classified as indo-
lent since its survival is measured in years, but its median survival is significantly shorter than that of follicular lymphoma. Removal of this distinctive entity from studies of follicular lymphoma is essential if treatment modalities are to be studied and defined for each type of tumor.

Aggressive lymphomas

Aggressive lymphomas are defined as tumors whose survival if untreated is measured in months (i.e., median of one year or less). Paradoxically, in contrast to most of the indolent lymphoma/leukemias, aggressive lymphomas are often curable with aggressive therapy. Thus, the treatment approach is urgent and curative in intent. In general, clinically aggressive lymphomas are composed predominantly of cells that are larger than normal circulating lymphocytes, with a high proliferation fraction; they tend to correspond to proliferating stages of antigen-dependent B- or T-cell differentiation. Although most aggressive lymphomas arise de novo, they may develop from a pre-existing low-grade lymphoma/leukemia, such as B-CLL, follicle-center lymphoma, marginal-zone B-cell lymphoma, T-LGL, mycosis fungoides, or even Hodgkin's disease. These secondary aggressive lymphomas are often less susceptible to cure. By far the most common aggressive lymphoma is diffuse large B-cell lymphoma, accounting for 60%-70% of the cases in the US and Europe; anaplastic large-cell lymphoma, peripheral T-cell lymphoma unspecified, and angioimmunoblastic lymphoma, in descending order of frequency, make up the bulk of the remainder.

Highly aggressive/acute lymphoma/leukemia

Highly aggressive or acute lymphoid neoplasms are defined as tumors that will likely kill the patient in a matter of weeks if untreated. These tumors have in common a tendency to become widely disseminated, often with leukemia and CNS involvement. Histologically most are composed of primitive-appearing cells with a high proliferation fraction. The most common neoplasm in this group is precursor B-cell acute lymphoblastic leukemia, followed by precursor T-cell lymphoblastic lymphoma (either of these may present as solid tumors or leukemia or both, but leukemic presentations are much more common in the former and lymphomatous in the latter). The other major entity in this group in the US and Europe is Burkitt's lymphoma, which also has endemic foci in Africa. All of these neoplasms are more common in children than in adults. The HTLV-1-associated adult T-cell lymphoma/leukemia is also placed in the highly aggressive group, because of its often very rapid fatal course.

Summary

In the REAL classification, a group of experienced hematopathologists, none of whom had been involved in developing an existing classification, compiled a summary of what they actually did in their daily practice in their approach to lymphoma diagnosis. The focus has been on determining which disease entities exist and can be recognized with available techniques, and then agreeing on criteria for diagnosis and on terminology. The group assumed that entities that they could all agree on could be recognized by others, and that entities that they could not define or diagnose reliably would likely cause difficulty for other pathologists. This approach has built on existing classifications and many other published studies, simply compiling existing knowledge in a practical form. Most of the entities listed are already included in the updated Kiel classification. This list can be used in conjunction with the Working Formulation, since many of the diseases recognized fall within one or another of the Working Formulation categories. Conversely, American hematologists and oncologists may conclude that the Working Formulation has outlived its usefulness and that more specific disease entities, such as those listed here, should be recognized in clinical trials. This classification includes a large number of disease entities, which may alarm those who believe that a lymphoma classification must be simple. Given the complexity of the immune system, it should not be surprising that its tumors are numerous and complex. It is necessary to 'split' before meaningful 'lumping' can occur. If several morphologically, immunologically, and genotypically distinct neoplasms prove to respond identically to currently available treatment, they can be 'lumped' for the purposes of clinical treatment selection. However, if new forms of treatment become available, it will be important to recognize and study each disease separately. For those who argue that oncologists cannot possibly remember a large number of diseases or incorporate new ones into their thinking, we call to mind the large and (to pathologists) bewildering array of new drugs and combinations

<table>
<thead>
<tr>
<th>Site</th>
<th>Lymphoma</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Diffuse large B cell</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Low-grade B cell, MALT type</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Burkitt's and Burkitt-like</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Mantle cell</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Follicular</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Intestine</td>
<td>Diffuse large B cell</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Low-grade B cell, MALT type</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Burkitt's and Burkitt-like</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Peripheral T-cell lymphomas</td>
<td>15%</td>
</tr>
<tr>
<td>Bone</td>
<td>Diffuse large B cell, often multilobated</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>CNS and eye</td>
<td>Diffuse large B cell</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Ocular adnexae</td>
<td>Low-grade B cell, MALT type</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Follicular</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Diffuse large B cell</td>
<td>20%</td>
</tr>
<tr>
<td>Skin</td>
<td>Mycosis fungoides</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>CD30+ lymphomas (ALCL, LyP; PTCL)</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Peripheral T-cell lymphomas, CD30-</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Follicle center and diffuse large B cell</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Low-grade B cell, MALT type</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
that oncologists seem to understand and remember without difficulty. If the entities that we describe here are indeed real diseases, the relevance and utility of this approach will be readily apparent, and no one will complain about the large number of diseases to study and treat. If appropriate studies are conducted, proposed entities that are not real diseases will soon be eliminated.

This study should be regarded as an effort to bring some order to the chaos of lymphoma categorization and constitutes a basis for further study. The reproducibility of diagnosis of these various categories, either among different pathologists or by the same pathologist over time, remains to be determined. No prior tumor classification has been based on reproducibility, and when such studies have been done with existing classifications of lymphoma, they have shown disappointing results [5, 11, 12]. We expect that recognition of clearly defined entities, which have characteristic immunophenotypes and in some cases genetic features, as well as characteristic morphology, will facilitate reproducibility among pathologists [13].

The clinical features of these lymphomas are taken from studies already published in the literature, many of them conducted by pathologists rather than clinicians. A pathologic classification of neoplasms is, by definition, a listing of distinct disease entities, based on features that can be recognized by pathologists: chiefly morphology, buttressed to a variable extent by special techniques. For pathologists to make the diagnoses, the entities must be defined by these clinical features. Studies to define their clinical spectrum and optimal treatment are essential, but these cannot be conducted until pathologists can recognize the entities. Clinical studies that group together entities that are biologically distinct may obscure important observations regarding prognosis and interaction with treatment, and can hinder development of novel therapeutic strategies for individual diseases. The emphasis on broad prognostic groups that are defined by survival rather than by pathologic features, as in the Working Formulation, can lead to the belief that all entities within a group can be considered as a single disease, rather than as distinct entities, simply because they have similar survival curves. Survival is not the only defining feature of a disease, since patients with the same disease may have different survivals, depending on a variety of prognostic factors, and on the type of treatment, and conversely, patients with entirely different tumors may by chance have similar survivals. We do, however, believe that systematic application of the criteria presented here to define groups of patients, in collaboration with our clinical colleagues, is imperative. Several of us are associated with cooperative clinical groups studying lymphomas in both the US and Europe, and have already undertaken such studies [14, 15].

Finally, a critical feature of any tumor classification is that it be periodically reviewed and updated to incorporate new information. A model for this activity has been the French–American–British (FAB) group in its approach to leukemias [16]. A project is currently underway to prepare a new WHO classification of hematologic neoplasms, under the joint sponsorship of the American and European Societies of Hematopathology. This project should achieve wider consensus on the spectrum and definitions of currently recognizable lymphoid neoplasms.

References


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