

Symposium article

Lymphoma classification – from controversy to consensus: The R.E.A.L. and WHO Classification of lymphoid neoplasms

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Summary

Background: Controversy in lymphoma classification dates back to the first attempts to formulate such classifications. Over the years, much of this controversy arose from the assumption that there had to be a single guiding principle – a ‘gold standard’ – for classification, and from the existence of multiple different classifications.

Design: The International Lymphoma Study Group (I.L.S.G.) developed a consensus list of lymphoid neoplasms, which was published in 1994 as the ‘Revised European–American Classification of Lymphoid Neoplasms’ (R.E.A.L.). The classification is based on the principle that a classification is a list of ‘real’ disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. The relative importance of each of these features varies among diseases, and there is no one ‘gold standard’. In some tumors morphology is paramount, in others it is immunophenotype, a specific genetic abnormality, or clinical features. An international study of 1300 patients, supported by the San Salvatore Foundation, was conducted to determine whether the R.E.A.L. Classification could be used by expert pathologists and had clinical relevance. Since 1995, the European Association of Pathologists (EAHP) and the Society for Hematopathology (SH) have been developing a new World Health Organization (WHO) Classification of hematologic malignancies, using an updated R.E.A.L. Classification for lymphomas and applying the principles of the R.E.A.L. Classi-

fication to myeloid and histiocytic neoplasms. A Clinical Advisory Committee (CAC) was formed to ensure that the WHO Classification will be useful to clinicians.

Results: The International Lymphoma Study showed that the R.E.A.L. Classification could be used by pathologists, with inter-observer reproducibility better than for other classifications (>85%). Immunophenotyping was helpful in some diagnoses, but not required for many others. New entities not specifically recognized in the Working Formulation accounted for 27% of the cases. Diseases that would have been lumped together as ‘low grade’ or ‘intermediate/high grade’ in the Working Formulation showed marked differences in survival, confirming that they need to be treated as distinct entities. Clinical features such as the International Prognostic Index were also important in determining patient outcome. The WHO Clinical Advisory Committee concluded that clinical groupings of lymphoid neoplasms was neither necessary nor desirable. Patient treatment is determined by the specific type of lymphoma, with the addition of grade within the tumor type, if applicable, and clinical prognostic factors such as the International Prognostic Index (IPI).

Conclusions: The experience of developing the WHO Classification has produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world, which should facilitate progress in the understanding and treatment of hematologic malignancies.

Key words: classification, lymphoma, pathology

Principles of lymphoma classification

Controversy in lymphoma classification dates back to the first attempts to formulate such classifications [1–7]. Over the years, much of this controversy arose from the assumption that there had to be a single guiding principle – a ‘gold standard’ – for classification. Many early classifications were based purely on morphology (Gall and Mallory, Rappaport); others utilized primarily treatment response and survival (Working Formulation); and others were based primarily on cell lineage and differentiation, in the belief that each neoplasm corresponded to a recognizable normal cell or differentiation stage (Kiel, Lukes and Collins). Recently, the introduc-

tion of the new techniques of immunophenotyping and molecular genetic analysis have led to further controversy about what, if anything, should be the modern ‘gold standard’ for defining disease entities.

The Revised European–American Classification of Lymphoid Neoplasms (R.E.A.L.), developed by the International Lymphoma Study Group (I.L.S.G.), adopted a new approach to lymphoma classification. In this approach, *all* available information – morphology, immunophenotype, genetic features, and clinical features – is used to define a disease entity. The relative importance of each of these features varies among diseases, and there is no one ‘gold standard’. Morphology is always important, and some diseases are primarily de-

finer by morphology – follicular lymphoma, angioimmunoblastic T-cell lymphoma, nodular sclerosis Hodgkin's disease – with immunophenotype as backup in difficult cases. Some diseases have a virtually specific immunophenotype – small lymphocytic lymphoma, mantle-cell lymphoma, anaplastic large-cell lymphoma – such that one would hesitate to make the diagnosis in the absence of the immunophenotype. In some lymphomas a specific genetic abnormality is an important defining criterion – t(11;14) in mantle-cell lymphoma, t(14;18) in follicular lymphoma, t(8;14) in Burkitt's lymphoma – while others lack specific genetic abnormalities – MALT lymphoma and diffuse large B-cell lymphoma. Still others require a knowledge of clinical features as well – e.g., nodal vs. extranodal presentation in marginal zone lymphomas and peripheral T-cell lymphomas, and mediastinal location in mediastinal large B-cell lymphoma.

All of the features that we now use to define disease entities are probably secondary phenomena, or surrogates, for the underlying causative abnormality – the 'true' defining feature of the disease. However, this 'true' defining abnormality is not known at present for most diseases, and we do not know which of the features we recognize are most closely related to this biological 'truth'. Therefore, it behooves us to use all the available information, and we must recognize that we will not be able to use the same approach for each disease. Insisting on a single 'gold standard' as the basis for a classification at this time is impractical, and can impede progress. The emphasis on defining 'real' disease entities – which can be recognized by pathologists and are clinically relevant – and the recognition that no single feature can define all diseases, represents a new paradigm in lymphoma classification.

A second historical problem in lymphoma classification was that most of them represented the work of one or a few individuals, and there was no theoretical limit to the number of competing classifications that could be – and were – published. For most of the 20th century, different lymphoma classifications were used in different parts of the world – most recently, the Kiel Classification in Europe and the Working Formulation and Lukes–Collins Classifications in the US. This lack of consensus on lymphoma classification and terminology caused chronic problems for both pathologists and clinicians, created difficulty in interpreting published studies, and resulted in a lack of credibility for pathologists with their clinical colleagues. The I.L.S.G. recognized that the complexity of the field in the 1990s made it impossible for a single person or small group to be completely authoritative, and also that broad agreement – even if it requires compromise – is necessary if the result is to be used by multiple pathologists. Thus, the R.E.A.L. Classification, which represented a revision of current or prior European and American lymphoma classifications, was developed as a consensus of 19 international expert hematopathologists – arguably the largest group of pathologists ever to agree on a disease classification [8].

Since 1995, members of the European and American

Table 1. B-cell neoplasms in the updated R.E.A.L./WHO Classification.^a

Precursor B-cell neoplasm
<i>Precursor B-lymphoblastic leukemia/lymphoma (B-ALL/LBL)</i>
Mature (peripheral) B-cell neoplasms
<i>B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma</i>
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)
Hairy-cell leukemia
<i>Plasma cell myeloma/plasmacytoma</i>
<i>Extranodal marginal zone B-cell lymphoma of MALT type</i>
<i>Mantle-cell lymphoma</i>
<i>Follicular lymphoma</i>
Nodal marginal zone B-cell lymphoma (+/- monocytoid B cells)
<i>Diffuse large B-cell lymphoma</i>
<i>Burkitt lymphoma</i>

^a More common entities are in italics.

Hematopathology societies have been collaborating on a new World Health Organization (WHO) Classification of hematologic malignancies (Tables 1–3). It will use an updated version of the R.E.A.L. Classification for lymphomas and will expand the principles of the R.E.A.L. Classification to the classification of myeloid and histiocytic neoplasms [9, 10]. This effort involves a Steering Committee of 6 individuals (3 from each Society), and includes a total of 52 hematopathologists from around the world, as well as a clinical advisory committee of 36 international expert hematologists and oncologists. Proponents of most major lymphoma and leukemia classifications are involved in the process, and have agreed to adopt the WHO Classification when it is complete. Thus, this will represent the first true international consensus on the classification of hematologic neoplasms.

In addition to its emphasis on a multi-parameter approach to defining real diseases and the importance of consensus, the R.E.A.L./WHO approach differs in another important way from the Kiel Classification and the Working Formulation. Both of these classifications attempted to stratify lymphomas into broad categories (grades or prognostic groups) according to either common histologic features (nuclear size, proliferation) or clinical features (survival). This approach is reassuring to clinicians and pathologists who do not wish to remember a large number of categories, but it is a deceptive simplicity, based on the old idea that 'lymphoma' or 'non-Hodgkin's lymphoma' was a single disease with a range of histologic grade and clinical aggressiveness. In fact, we are dealing with over 20 diseases that are in most cases unrelated to one another. One of the corollaries of defining distinct lymphoma entities is that it is neither possible nor helpful to sort them precisely according to histologic grade or clinical aggressiveness. For example, although it is true that many lymphomas composed of relatively small cells with a low proliferation fraction have a generally indolent course, at least one of them – mantle-cell lymphoma – is rather aggres-

Table 2. T- and NK-cell neoplasms in the updated R.E.A.L./WHO Classification.^a

Precursor T-cell neoplasm
<i>Precursor T-lymphoblastic lymphoma/leukemia (T-ALL/LBL)</i>
Mature (peripheral) T-cell neoplasms
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic $\gamma\delta$ T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
<i>Mycosis fungoides/Sezary syndrome</i>
Anaplastic large-cell lymphoma, primary cutaneous type
<i>Peripheral T-cell lymphoma, unspecified</i>
<i>Angioimmunoblastic T-cell lymphoma</i>
<i>Anaplastic large-cell lymphoma, primary systemic type</i>

^a More common entities are in italics.

Table 3. Hodgkin's disease (Hodgkin's lymphoma) in the R.E.A.L./WHO Classification ^a

Lymphocyte predominance, nodular \pm diffuse areas
Classical Hodgkin's disease
<i>Nodular sclerosis</i>
<i>Mixed cellularity</i>
Lymphocyte depletion
Lymphocyte-rich classical Hodgkin's disease

^a Common entities are in italics.

sive. In addition, they each have a distinctive set of presenting features and, often, different treatments – e.g., hairy-cell leukemia vs. B-CLL vs. MALT lymphoma. Several of the lymphomas that we can now recognize have within themselves a range of histologic grade (number of large cells or proliferation fraction) and clinical aggressiveness – e.g., follicular lymphoma, mantle-cell lymphoma, and probably MALT lymphoma. Thus, histologic grade is just one of many prognostic factors, which should be applied *within* a disease entity, not across the whole range of lymphoid neoplasms. Both the pathologist and the oncologist must ‘get to know’ each disease entity and its spectrum of morphology and clinical behavior.

A clinical test of the R.E.A.L. Classification

An initial criticism of the R.E.A.L. Classification was that it had not been tested in a clinical study. To address this issue, an international group of oncologists and pathologists devised a clinical study of the classification, in which 5 expert pathologists reviewed over 1300 cases of non-Hodgkin's lymphoma at centers around the world [11–15]. The aims of the study were: 1) to see whether the classification could be used in practice, 2) to test its inter-observer reproducibility, 3) to determine the need for immunophenotyping in diagnosis, 4) to

determine whether the categories of disease identified in the classification were clinically distinctive either at presentation or in outcome, and 5) to determine the relative frequency of these diseases in the populations studied. The five pathologists traveled to nine sites, and independently reviewed diagnostic slides on all cases. Immunophenotyping sufficient to confirm the diagnosis of lymphoma and determine lineage (B or T/NK) was available in all cases. Diagnoses were made first without and then with knowledge of the immunophenotype, genetic features, and clinical features, using both R.E.A.L., WF, and Kiel Classifications. A consensus diagnosis was reached for each case. Clinical data at presentation, treatment and five years of follow-up were available for all patients.

This study convincingly demonstrated that the classification could be used by expert hematopathologists: over 95% of the cases with adequate material could be classified into one or another of the categories. The inter-observer reproducibility, which for lymphoma classifications has been poor [7, 16, 17], was substantially better than that for other classifications – greater than 85% for most diseases. Immunophenotyping was helpful in some diseases, such as mantle cell lymphoma and diffuse large B-cell lymphoma, where it improved accuracy by 10%–15%, and was essential for all types of T-cell lymphoma, improving reproducibility from around 50% to over 90%. It was not required for many diseases, such as follicular lymphoma, B-cell small lymphocytic lymphoma, and MALT lymphoma. However, it is important to note that this study did not address the need for immunophenotyping to establish the diagnosis of lymphoma initially; these techniques may be critically important in first establishing the diagnosis of a lymphoid neoplasm.

The relative frequency of the different B- and T/NK-cell lymphomas in the study population was similar to previous patterns reported in the literature (Table 4). The most common lymphoma was diffuse large B-cell lymphoma, followed by follicular lymphoma; together these comprised 50% of the lymphomas in the study. New entities not specifically recognized in the Working Formulation accounted for 27% of the cases: MALT lymphoma 8%, mantle-cell 7%, peripheral T-cell 6%, nodal marginal zone 2%, mediastinal large B-cell 2%, anaplastic large T/null-cell 2%. These results are reassuring, confirming that the majority of the cases that will be encountered by oncologists and pathologists will be only a few subtypes, with which they are already familiar. However, they also underscore the need for recognizing the more recently described entities, which although less common, have important clinical differences.

The different entities recognized by the classification had significantly different clinical presentations and survivals. For example, diffuse aggressive lymphomas, which would be lumped as intermediate/high grade in the Working Formulation, include diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, periph-

Table 4 Presenting features of common B- and T-cell neoplasms.

Neoplasm	Frequency (%)	Age (Med)	Male (%)	Stage (%)				B Sx (%)	EN ^a (%)	BM	GI (%)	IPI (%)		
				I	II	III	IV					0/1	2/3	4/5
Large B-cell	31	64	55	25	29	13	33	33	71	16	18	35	46	9
Mediastinal	2	37	34	10	56	3	31	38	56	3	0	52	37	11
Follicular	22	59	42	18	15	16	51	28	64	42	4	45	48	7
SLL/CLL	6	65	53	4	5	8	83	33	80	72	3	23	64	13
MALT	8	60	48	39	28	2	31	19	98	14	50	44	48	8
Mantle-cell	6	63	74	13	7	9	71	28	81	51	9	23	54	23
Peripheral T-cell	7	61	55	8	12	15	65	50	82	36	15	17	52	31
ALCL	2	34	69	19	32	10	39	53	59	13	9	61	18	21

Abbreviations: BSx – B-symptoms; EN – any extranodal site, including bone marrow; BM – bone marrow; GI – gastrointestinal tract; IPI – international prognostic index.

Data from Armitage J, Weisenburger D. J Clin Oncol 1998; 16: 2780–95

eral T-cell lymphoma, and anaplastic large T/null-cell lymphoma. The clinical features at presentation were strikingly different, with a younger age group for mediastinal large T-cell lymphoma and anaplastic large T/null lymphoma, and striking differences in male/female ratios, suggesting that these are distinctive biological entities (Table 4). When overall survivals were analyzed, entities that would have been lumped together as 'low grade' or 'intermediate/high grade' in the WF showed marked differences in survival, again confirming that they need to be recognized and treated as distinct entities.

A critical finding in this study was that classification is not the only predictor of clinical outcome. Patients with any of these diseases could be stratified into better and worse prognostic groups according to the International Prognostic Index [18]. For example, although patients with follicular lymphoma typically have IPI scores of 1–3, those patients with scores of 4 or 5 had a predicted median overall survival of only 18 months. Thus, to plan treatment for an individual patient, the oncologist must know not only the diagnosis, but the clinical prognostic factors that will influence that patient's course.

The WHO Clinical Advisory Committee

In order to ensure that the proposed WHO Classification will be of maximal use to oncologists, the Steering Committee invited expert hematologists and oncologists to form a Clinical Advisory Committee, with American and European co-chairs. The charge to the committee was to review the proposed classification (Tables 1–3) and advise the pathologists on its clinical utility. Over 30 hematologists and oncologists from around the world agreed to participate. The proposed classification was circulated, and all participants were invited to submit topics and questions for discussion. A meeting was held in November 1997, at Airlie House, Virginia, to which the Clinical Advisory Committee and all pathologists involved in the WHO committees, as well as the Execu-

tive Committees of the two hematopathology societies, were invited.

The meeting was organized around a series of questions. Participants were invited to present data relevant to each question, and open discussion followed. At the end of each session, the clinicians present were asked to arrive at a consensus regarding each question (as well as on other issues raised at the meeting); if necessary a show of hands was taken as a vote. Following the meeting, a poll of the participants, as well as several additional meetings of the pathology Steering Committee and the co-chairs of the Clinical Advisory Committee were held to resolve residual questions. Some of these questions and the consensus of the Committee are discussed below.

Are lymphomas and lymphoid leukemias different manifestations of the same disease entity? Yes

The R.E.A.L./WHO Classification considers lymphomas and lymphoid leukemias of the same cell type as one disease, with different clinical presentations or stages. This question is primarily relevant to lymphoblastic lymphoma and leukemia of precursor B- and T-cell type, Burkitt's lymphoma and 'B-ALL/L3' and B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma. Although patients in some locations may be seen by different physicians based on their presentation (e.g., those presenting with peripheral blood involvement – leukemias – being seen by hematologists and those presenting with tissue involvement – lymphomas – by oncologists), there was a consensus that they are biologically the same diseases.

Should follicular lymphoma be graded? Yes *How many grades are clinically relevant? Two*

There was a consensus that follicular lymphoma should be graded, at least into two grades, with what is currently recognized as grade 3 (follicular large cell) being discriminated from lower grade cases (grades 1 and 2; follicular small cleaved cell and mixed small and large

cell). Although there are minor differences in natural history and response to treatment between grades 1 and 2, there was a consensus that these did not mandate different approaches to treatment, and thus were not of great clinical importance. Nonetheless, there was concern that changing the nomenclature would be potentially confusing, so that a three-grade system should be retained. The pathologists concluded that since only the Berard cell-counting method has been repeatedly tested in the literature, it should be recommended for use (grade 1: 0–5 centroblasts/hpf; grade 2: 6–15 centroblasts/hpf; grade 3: > 15 centroblast/hpf) [19].

Should diffuse areas in follicular lymphoma be reported?
Yes

Diffuse areas in all grades of follicular lymphoma may impact on prognosis. There was a consensus that diffuse areas should be reported and quantified according to the recommendations of the R.E.A.L. Classification: predominantly follicular (> 75% follicular) follicular and diffuse (25%–75% follicular), and predominantly diffuse (< 25% follicular). However, it is not clear what the implications of these features for treatment would be. In grade 3 follicular lymphoma, diffuse areas represent areas of diffuse large B-cell lymphoma. DLBCL, and should be reported as such. The presence of DLBCL in any follicular lymphoma will dictate more aggressive therapy. A separate category – follicle center lymphoma, diffuse – will be retained for the rare purely diffuse cases.

Should the term, MALT lymphoma, be applied only to a lymphoma composed mostly of small cells? **Yes**

The term, ‘high-grade MALT lymphoma’, which is used by some pathologists to denote either transformation of a low-grade MALT lymphoma (extranodal marginal zone lymphoma) or any large B-cell lymphoma in a MALT site, is confusing to clinicians, who regard MALT lymphoma as a lesion that may respond to antibiotic therapy for eradication of *Helicobacter pylori*. Since patients with a component of large-cell lymphoma do not respond to antibiotic therapy, the use of this term may result in cases of extranodal large-cell lymphoma being undertreated. Therefore, the term, MALT lymphoma, should be used only for the 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’.

Should morphologic subclassification of DLBCL be required? **No**

There was a consensus that neither biological nor clinical data at present support a requirement for subclassi-

fication of 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% immunoblasts) has a worse prognosis than centroblastic lymphoma. Other data suggest that staining for *BCL-6* (centroblastic) and syndecan-1/CD138 (immunoblastic) or evidence of *BCL-6* rearrangement (centroblastic) may help to discriminate between them. Nonetheless, neither reliable pathological or biological criteria for subclassification nor distinctive therapies that can be recommended for clinical practice are available at this time. For these reasons, the committee felt that these categories should remain optional at this time. However, the pathologists should develop criteria for subclassification, so that these categories can be tested in future clinical studies.

Should ‘Burkitt-like’ lymphoma be a subtype of DLBCL?
No

There was a consensus that it would be a mistake to consider Burkitt-like lymphoma as a subtype of large B-cell lymphoma. In children, cases classified as Burkitt-like (or non-Burkitt) behave identically to Burkitt lymphoma, and would be undertreated if treated like large B-cell lymphoma. In adults, the biology of cases classified as Burkitt-like is less clear, but this may reflect the heterogeneity of the diagnostic criteria. The oncologists concluded that the category of Burkitt-like lymphoma should be reserved for tumors that should be treated ‘like Burkitt lymphoma’ – that is, very high-grade tumors, with *cMYC* rearrangement and a proliferation fraction of 100%. The Burkitt-like category will be eliminated; cases should be classified as either large B-cell lymphoma or Burkitt lymphoma. Burkitt lymphoma will have two morphologic categories – *typical* and *atypical* – to reflect the morphologic heterogeneity. In addition, three subcategories – *endemic*, *non-endemic*, and *immunodeficiency-associated* – were proposed to reflect the major clinical and genetic subtypes of this disease.

Are clinical syndromes integral to the definition of T/NK-cell neoplasms? **Yes**

Many distinct T- and or NK-cell diseases have a range of cytologic composition (small to large to anaplastic). Immunophenotypic variation exists within disease entities, and many antigens are shared by different diseases. Specific cytogenetic features are not defined for most entities, and even T-cell receptor types ($\alpha\beta$ vs. $\gamma\delta$) or T vs. NK lineage are not sufficient to define distinct disease entities. To a greater extent than for B-cell neoplasms, it appears that clinical syndromes, and particularly location (nodal vs. extranodal and specific extranodal sites) are important in determining the biological behavior of the disease.

Should peripheral T-cell lymphoma, unspecified, be subclassified for clinical purposes? No

Based on the available data, there appears to be no immediate justification or clear criteria for recognizing *cytologic* subtypes within this broad category. However, given the marked differences in clinical behavior between primary extranodal T/NK-cell lymphomas and primary nodal lymphomas, it is likely to be clinically relevant to subdivide the 'unspecified' category into nodal and extranodal types.

Should cutaneous and systemic ALCL be considered one disease or two? Two

Most cases of ALCL of T-cell type presenting with disease localized to the skin are distinct from systemic ALCL: the clinical course is indolent, they lack the t(2;5)(p23;q35) and are ALK protein negative, and appear to form a spectrum with lymphomatoid papulosis. Although some members of the committee felt that the clinical course was not predictably indolent, there was general agreement that at least for the purposes of further study, cutaneous and systemic ALCL should be considered distinct categories. There was concern about the proposed term, 'primary CD30+ cutaneous lymphoproliferative disorder' – which includes both lymphomatoid papulosis and cutaneous ALCL. Oncologists felt that including lymphomatoid papulosis in a classification of lymphomas would imply to patients and insurers that this is a malignancy, whereas it typically has a benign clinical course. Thus, the entity, primary cutaneous ALCL, will be included in the list of neoplasms, and a discussion of 'CD30+ cutaneous lymphoproliferative diseases' will be included in the text with a discussion of lymphomatoid papulosis and borderline lesions. Because of the difficulty in predicting by morphology alone which disease the patient has, pathologists will often be forced to use the term 'CD30+ cutaneous lymphoproliferative disease' on the pathology reports, with the understanding that clinical criteria must be added to determine whether the patient has a locally progressive disease that requires treatment (ALCL), or a relapsing condition that needs no treatment (lymphomatoid papulosis).

Is the t(2;5) or ALK expression the gold standard for defining ALCL? No

Clinically, cases of ALCL with the t(2;5) and/or ALK positivity appear to represent a homogeneous group with a relatively good prognosis. However, there are cases with typical morphology and immunophenotype that are ALK or t(2;5) negative. The committee concluded that a single 'gold standard' for the diagnosis of ALCL does not exist; the diagnosis requires both morphology and immunophenotype, and restricting the diagnosis to ALK+ cases does not appear to be justified. ALK staining should be done in all cases, and cases

should be designated as ALCL, ALK+ or ALK-. In addition, pathologists need to be aware of the rather broad morphologic spectrum of ALCL.

Should grading of nodular sclerosis be required for clinical use? No

Data on the clinical impact of grading nodular sclerosis Hodgkin disease (NSHD) according to the British National Lymphoma Investigation (BNLI) criteria (grade 1 = few RS cells; grade 2 = many RS cells) have shown conflicting results, with some studies showing that grade 2 cases are associated with a worse outcome and others showing no difference in outcome. The committee recommended that grading not be required for clinical purposes in routine diagnosis, but that the classification include clear criteria so that this question can be tested in future studies.

Hodgkin's disease or Hodgkin's lymphoma? Either

Because it is now clear that Hodgkin disease is a clonal proliferation of (in most cases) B cells, and therefore qualifies as a lymphoma, the pathologists proposed that the name be changed to Hodgkin's lymphoma. Opinion of the committee was divided. No consensus was reached, and both terms will be allowed.

Is lymphocyte-rich classical HD (LRCHD) a 'real' subtype? Yes

The committee agreed that it was important to separate these cases from nodular lymphocyte predominance Hodgkin disease (NLPHD) for clinical purposes, and that it would be valuable to separate them from other types of classical HD for clinical research purposes.

Is anaplastic large-cell lymphoma, Hodgkin like real? No

There was a consensus that ALCL Hodgkin's-like is not a 'real' disease. Some cases of ALCL have a nodular growth pattern and areas of fibrosis, and thus resemble HD of nodular sclerosis type. Some cases of NSHD may have increased numbers of malignant cells and therefore resemble ALCL. However, this resemblance does not indicate a biological relationship. Pathologists should strive to resolve morphologically difficult cases by immunophenotyping and, if necessary molecular genetic studies. Cases that cannot be resolved should be considered unclassifiable. Clinical judgment should be used to determine whether to rebiopsy or to treat with a regimen that would be suitable for both HD and ALCL.

Are clinical groupings useful for clinical practice? No

The committee concluded that grouping the B- and T/NK-cell neoplasms into prognostic categories would serve no clear purpose and could hamper understanding of the specific features of some of the diseases. There are

no groups of diseases that require identical treatment, and if treatment must be individualized to a specific disease, grouping serves no purpose and may be misleading. The entities listed in the classification are clearly defined and clinically relevant, and it is necessary for oncologists and pathologists dealing with these diseases to understand each of them. In practice, treatment of a specific patient is determined not by which broad prognostic group the lymphoma falls into, but by the specific *histologic* type of lymphoma, with the addition of grade *within* the tumor type, if applicable, and *clinical prognostic factors* such stage, age, performance status, and/or the international prognostic index (IPI) [18].

Is a shorter list of diseases necessary for clinicians? No

There was a consensus that the complete list of neoplasms should have more common entities highlighted, to draw the attention of non-experts to the diseases they are likely to encounter in practice. Opinion was split on the need for a 'short list', and a poll taken after the meeting showed a majority of the oncologists favoring one comprehensive list with common entities highlighted.

The WHO Classification of lymphoid neoplasms: Disease categories

The classification stratifies lymphoid neoplasms primarily according to cell lineage and morphology into three major categories: B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin's disease (HD). Within the B- and T-cell categories, two major categories are recognized – precursor neoplasms, corresponding to the earliest stages of differentiation, and mature ('peripheral') neoplasms, corresponding to more differentiated stages. Within the categories of mature B- and T/NK-cell neoplasms, the diseases are informally grouped according to their major clinical presentations: predominantly disseminated/leukemic; primary extranodal, and predominantly nodal diseases.

Conclusions

The experience of developing the R.E.A.L. and WHO classifications has provided important lessons that may be applicable to other organ systems, and which should facilitate future progress in lymphoma classification. We must use all available information, including clinical features, to classify these disorders. No one modality is pre-eminent at present, and pathologists cannot make these diagnoses without sufficient data. A consensus among pathologists is essential if they are to provide useful information for patients. Although arriving at a consensus may require compromise and may introduce imperfections on occasion, most errors will become apparent with time. The only thing worse than an im-

perfect classification is multiple classifications. In order to achieve consensus, all participants must agree that a consensus will be the result. Voting on disagreements can be surprisingly useful. Finally, although the pathologic classification of neoplasms is primarily the responsibility of pathologists, the input of experienced clinicians is essential to ensure its usefulness in practice.

A critical feature of any tumor classification is that it be periodically reviewed and updated to incorporate new information. In the future, a joint classification committee of the major Societies of Hematopathology will undertake this as an ongoing project. The experience of developing the WHO Classification has produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world, which should facilitate progress in the understanding and treatment of lymphoid neoplasms. We have truly moved from controversy to consensus on lymphoma classification.

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