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Staging and Classification of Lymphoma

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In 2004, new cases of non-Hodgkin's lymphoma in the United States were estimated at 54,370, representing 4% of all cancers and resulting 4% of all cancer deaths, and new cases of Hodgkin's lymphoma were estimated at 7,880. The appropriate staging and management of lymphomas greatly depend on an accurate pathological diagnosis and classification. The recently established Revised European–American Classification of Lymphoid Neoplasms (REAL) and the subsequently adopted and updated World Health Organization (WHO) classification include modern cytogenetic, molecular, and immunologic techniques and knowledge and reach an international consensus on the classification of lymphomas. This classification scheme represents an advance in our understanding of lymphomas and serves as an operative guideline for studying and diagnosing lymphomas. Imaging techniques always have served as staging and monitoring tools for the clinical management of lymphomas. The understanding and adoption of the current classification system is important in refining the role of imaging modalities in the management of specific lymphoma. To help one understand the current classification, this current review gives a brief history of lymphoma classifications and summaries the recent classification schemes, including new entities, clinical staging methods, and clinical prognostic criteria.
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During past decades, because of the lack of knowledge in the lymphoma biology, the diagnosis and classification of lymphoma were based solely on morphology. Different lymphoma classifications have been used in the United States and in other countries, for example, the Rappaport, Lukes and Collins, Kiel, and Working Formulation classifications of lymphomas.[1-5] This lack of consensus on lymphoma classification and terminology has caused problems not only for pathologists but also for clinicians, radiologists, and nuclear medicine physicians. It has been difficult to compare and to understand published research data, including imaging modalities data in lymphoid neoplasms, especially in the field of non-Hodgkin's lymphomas. Since the 1980s, 2 predominant classification systems have been adopted widely. Classification of non-Hodgkin's lymphomas by Working Formulation has been accepted in Unites States, whereas the Kiel classification of non-Hodgkin's lymphomas has been adopted widely in Europe and elsewhere. The Working Formulation classification of non-Hodgkin's lymphomas is based on clinical presentation and morphology and groups lymphomas into low, intermediate, and high grade according to their natural history, their response to therapy, and their survival in the patients recruited in the original study. The Working Formulation was described after conducting a multi-institutional study of 1175 cases of non-Hodgkin's lymphoma to evaluate the 6 competing classifications. It is a means of translation from one classification system to another among those classifications in the early 1980s. According to the Working Formulation, non-Hodgkin's lymphoma is a single generic disease with different degrees of aggressiveness. In contrast, based on the Kiel classification, non-Hodgkin's lymphomas are divided into B-cell and T-cell lineages based on available immunophenotypic data and into low or high grades based on cell morphology. The Kiel classification divides lymphomas into individual entities based largely on the similarity of their cells to normal lymphocyte counterparts, presumably with unique biologic characteristics. However, each category of non-Hodgkin's lymphoma defined by the Working formulation and Kiel classification contains a wide range of clinical presentation, etiology, and response to treatment.

The development of techniques in cytogenetic, molecular, and immunologic methods has yielded new insights into the pathogenesis of lymphoid neoplasms. New entities have been recognized that were not included previously in those classification systems. In 1994, the International Lymphoma Study Group, a group of 19

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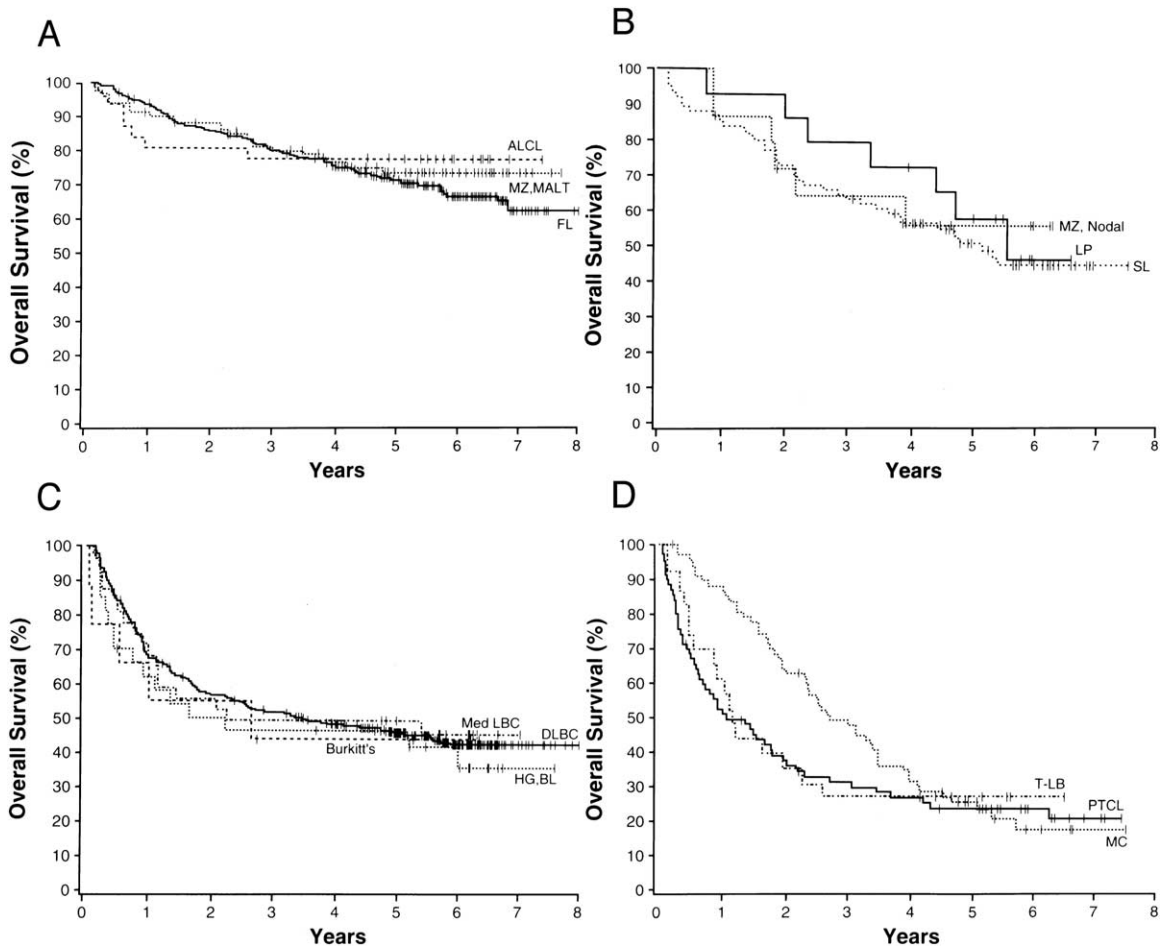

Figure 1 A 5-year overall survival of non-Hodgkin's lymphomas defined by Revised European and American Classification: (A) >70%; (B) 50% to 70%; (C) 30% to 49%; (D) <30%. ALCL, anaplastic large T/null-cell lymphoma; MZ, MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; FL, follicular lymphoma; MZ, nodal, marginal zone B-cell lymphoma of nodal type; LP, lymphoplasmacytoid lymphoma; SL, small lymphocytic lymphoma; MED LBC, primary mediastinal large B-cell lymphoma; DLCBL, diffuse large B-cell lymphoma; HG, BL, high grade B-cell Burkitt-like lymphoma; T-LB, precursor T-lymphoblastic lymphoma; PTCL, peripheral T-cell lymphoma; MC, mantle cell lymphoma. (Adapted and reprinted with permission from the Non-Hodgkin's Lymphoma Classification Project.[7])

hematopathologists from the United States, Europe, and Asia, developed a consensus on the classification of lymphomas based on the currently available morphologic, immunologic, and genetic techniques to provide a single classification system for international communication and to attempt to define distinct disease entities. The resulting classification system is the Revised European–American Classification of Lymphoid Neoplasms (REAL).[6] Studies have shown that most entities in the REAL classification can be diagnosed reproducibly by experienced pathologists and that it provides clinically distinctive types of lymphoma and stratifies patients into different prognostic groups (Fig. 1).[7] In 1997, this classification was adopted with minimal modification by WHO, which consists of more than 50 expert hematopathologists and hematologists.[8] The WHO classification not only encompasses lymphoid neoplasms but extends to myeloid, mast cell, and histiocytic cell neoplasms.[8,9] The WHO classification may be considered as an updated version of the REAL classification of lymphoid neoplasms. The classification divides lymphomas first according to their lineage and second according to the stage of differentiation at which lymphoma transformation has occurred. The lymphoid neoplasms are divided into B-cell neoplasms, T-cell/natural-killer cell neoplasms, and Hodgkin's disease, now more appropriately termed Hodgkin's lymphoma. The B- and T-cell neoplasms are further stratified into precursor or lymphoblastic neoplasms and mature (peripheral) neoplasms (Table 1). At first glance, the reader may be discouraged by new system because of its diverse entities listed in the classification and by its somewhat lack of user friendliness. However, in fact, 6 entities account for 80% of those non-Hodgkin's lymphoma entities (Fig. 2).

The staging of lymphoid neoplasms requires a careful

Table 1 Summary of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues

Hodgkin's Lymphoma	B-Cell Neoplasms	T-Cell and NK-Cell Neoplasms
Nodular lymphocyte-predominant Hodgkin's lymphoma	**Precursor B-cell neoplasms**	**Precursor T-cell neoplasms**
Classic Hodgkin's lymphoma	Precursor B lymphoblastic leukemia/lymphoma	Precursor T lymphoblastic leukemia/ lymphoma
Nodular sclerosis classical Hodgkin's lymphoma		Blastic NK cell lymphoma
Lymphocyte-rich classic Hodgkin's lymphoma	**Mature B-cell neoplasms**	**Mature T-cell and NK-cell neoplasms**
Mixed cellularity classic Hodgkin's lymphoma	Chronic lymphocytic leukemia/small lymphocytic lymphoma	T-cell prolymphocytic leukemia
Lymphocyte-depleted classic Hodgkin's lymphoma	B-cell prolymphocytic leukemia	T-cell large granular lymphocytic leukemia
	Lymphoplasmacytic lymphoma	Aggressive NK cell leukemia
	Splenic marginal zone lymphoma	Adult T-cell leukemia/lymphoma
	Hairy cell leukemia	Extranodal NK/T cell lymphoma, nasal type
	Plasma cell myeloma	Enteropathy-type T-cell lymphoma
	Solitary plasmacytoma of bone	Hepatosplenic T-cell lymphoma
	Extraosseous plasmacytoma	Subcutaneous paniculitis-like T-cell lymphoma
	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)	Mycosis fungoides
	Nodal marginal zone B-cell lymphoma	Sezary syndrome
	Follicular lymphoma	Primary cutaneous anaplastic large cell lymphoma
	Mantle cell lymphoma	Peripheral T-cell lymphoma, unspecified
	Diffuse large B-cell lymphoma	Angioimmunoblastic T-cell lymphoma
	Mediastinal (thymic) large B-cell lymphoma	Anaplastic large cell lymphoma
	Intravascular large B-cell lymphoma	
	Primary effusion lymphoma	
	Burkitt lymphoma/leukemia	
	B-cell proliferations of uncertain malignant potential	**T-cell proliferation of uncertain malignant potential**
	Lymphomatoid granulomatosis	Lymphomatoid papulosis
	Post-transplant lymphoproliferative disorder, polymorphic	

Adapted from Jaffe et al.[9]

history and physical examination; imaging (chest x-ray, computed tomography [CT], gallium scan, bone scan, ultrasound, or magnetic resonance imaging) of the chest, abdomen, pelvis, and biopsy of the bone marrow; as well as blood tests, including lactate dehydrogenase, albumin, or possible β_2-microglobulin levels. ^{18}F-Fluorodeoxyglucose position emission tomography (^{18}F-FDG PET) has emerged as a more sensitive and promising imaging tool in staging and in monitoring early therapeutic responses. Figure 3 shows an example of stage IV non-Hodgkin's lymphoma detected by ^{18}F-FDG PET. The spread of Hodgkin's lymphoma usually is predictable. It involves first the lymph nodes, and then spreads to spleen, to liver, and to finally bone marrow and other extranodal sites. The accurate staging of Hodgkin's lymphoma is not only important for guiding the choice of therapy but also provides critical prognostic information. The Ann Arbor staging

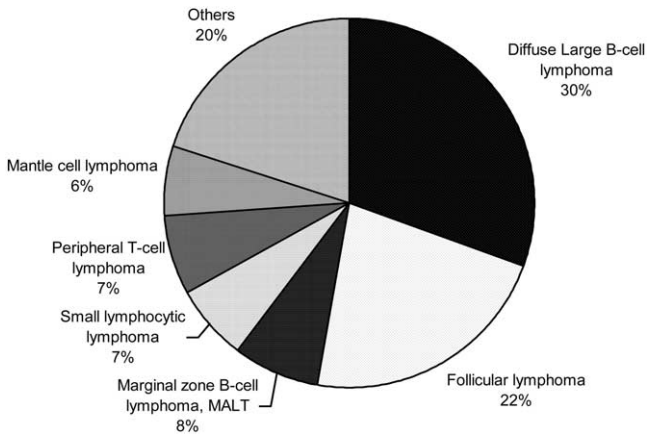

Figure 2 Distribution and frequencies of non-Hodgkin's lymphomas. (Adapted from the Non-Hodgkin's Lymphoma Classification Project.[7])

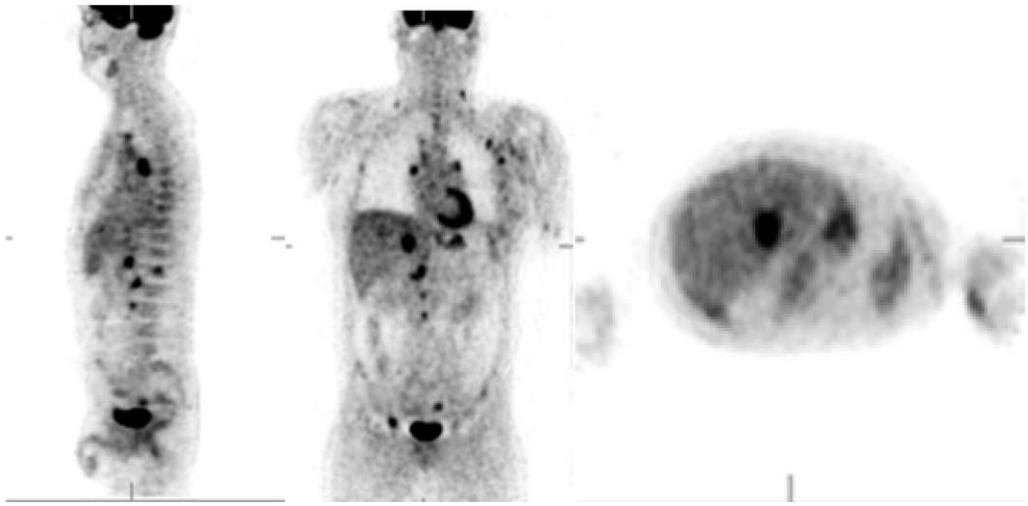

Figure 3 Multiple FDG avid foci were seen involving lymph nodes above and below the diaphragm, liver, and bone marrow. Left, sagittal view; middle, coronal view; right, transaxial view at liver level.

classification, originally proposed in 1971, has been used worldwide for the staging of Hodgkin's lymphoma (Table 2).[10] The Cotswold's modification of the Ann Arbor staging classification for Hodgkin's lymphoma incorporates a suffix "X" for the designation of bulky disease (greater than 10 cm maximum dimension of a mass of nodes or a mediastinal mass of greater than one third of the transthoracic width) and develops a new category of response to therapy: unconfirmed/uncertain complete remission (CR [u]), which was introduced because of the persistent radiologic abnormalities of uncertain significance.[11]

In contrast, non-Hodgkin's lymphomas are less predictable in their spreading patterns and frequently present as disseminated disease at the time of diagnosis. Nonetheless, the Ann Arbor staging classification also has been adopted for clinical staging of non-Hodgkin's lymphomas. This classification is less precise in identifying prognostic subgroups of patients with non-Hodgkin's lymphomas than those patients with Hodgkin's lymphoma. In 1993, a predictive model (international prognostic index) was developed, based on studies from 16 institutions and cooperative groups in the United States, Europe, and Canada, on 2031 patients with aggressive non-Hodgkin's lymphoma who were treated with combination chemotherapy regimens containing doxorubicin.[12] The international prognostic index has identified 5 independently significant risk factors associated with survival: age ($\leq$60 versus >60 years), tumor stage (stage I or II versus stage III or IV), the number of extranodal sites of disease ($\leq$1 versus >1), performance status (0 or l versus $\geq$2), and serum lactate dehydrogenase level ($\leq$1 times normal versus >1 times normal). The risk groups were defined as follows: low risk, 0 or 1; low-intermediate risk, 2; high-intermediate risk, 3, or high risk, 4 or 5. The prognostic index identified these 4 risk groups with significantly different rates of complete response, relapse-free survival, and overall survival (Table 3).[12] This approach provides additional information for deciding on a type of therapy for treatment, especially in choosing a subgroup of patients for experimental treatments, and facilitates the comparison of results among different centers. A recent clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma showed that pathological classification was not the only predictor of clinical outcome of individual cases, for example, patients with follicular lymphoma had more than a 70% overall survival, but less than 20% of patients with international prognostic index of 4 or 5 survived by the end of 5 years (Fig. 4).[7]

The REAL/WHO classification defines distinct lym-

Table 2 Clinical Staging of Hodgkin's and Non-Hodgkin's Lymphomas (Ann Arbor Classification)

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) and/or limited contiguous extralymphatic organ or site (IIIE, IIIES)
IV	Multiple or disseminated foci of involvement of one or more extralymatic organs or sites with or without lymphatic involvement

All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: fever (>38°C), night sweats, or weight loss of greater than 10% of body weight.

Table 3 Outcome Defined by the International Prognostic Index

All Patients (n = 2031)	No. of Risk Factors	Complete Response		Survival, 5 Years (%)
		Rate (%)	Relapse-Free Survival at 5 Years (%)	
Low	0 or 1	87	70	73
Low intermediate	2	67	50	51
High intermediate	3	55	49	43
High	4 or 5	44	40	26

Adapted from The International Non-Hodgkin's Lymphoma Prognostic Factors Project.[12]

phoma entities based not only on cell morphology but also on modern techniques, such as cytogenetic, molecular, and immunophenotyping methods. The distinct lymphoma entities are defined more precisely, and therapeutic strategies may be directed more specifically. It also is a remarkable achievement in reaching a consensus between oncologists and pathologists from around the world. It has become evident that our radiology and nuclear medicine communities have begun and will continue to adopt this classification scheme and to incorporate it into practice and research efforts.

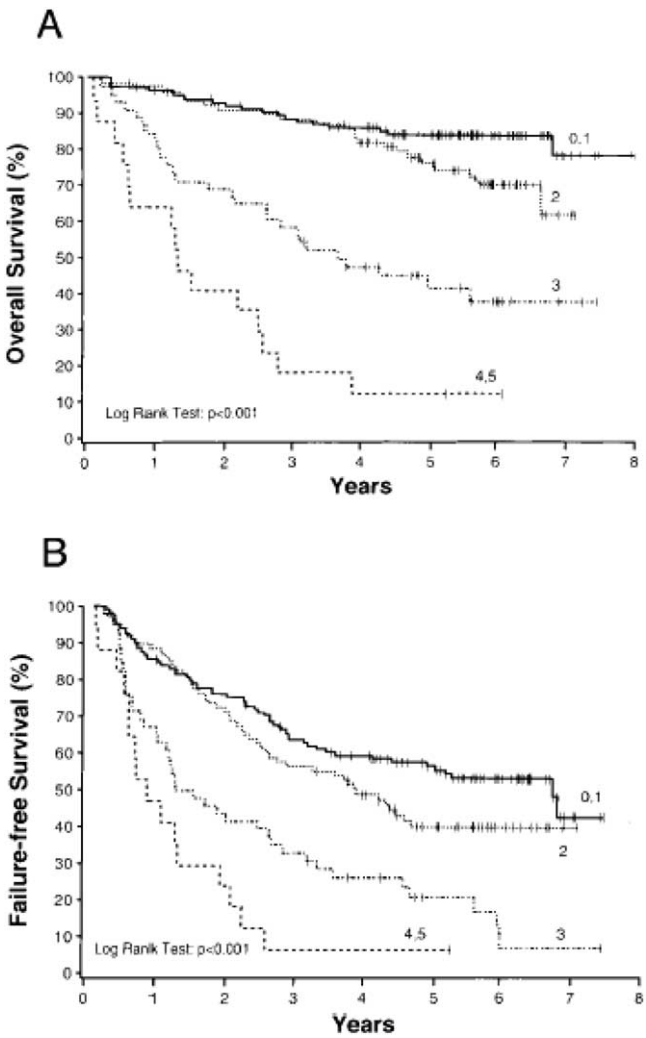

Figure 4 Overall (A) and failure-free (B) survivals of patients with follicular lymphoma grouped according to International Prognostic Index scores. (Adapted and reprinted with permission from the Non-Hodgkin's Lymphoma Classification Project.[7])

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