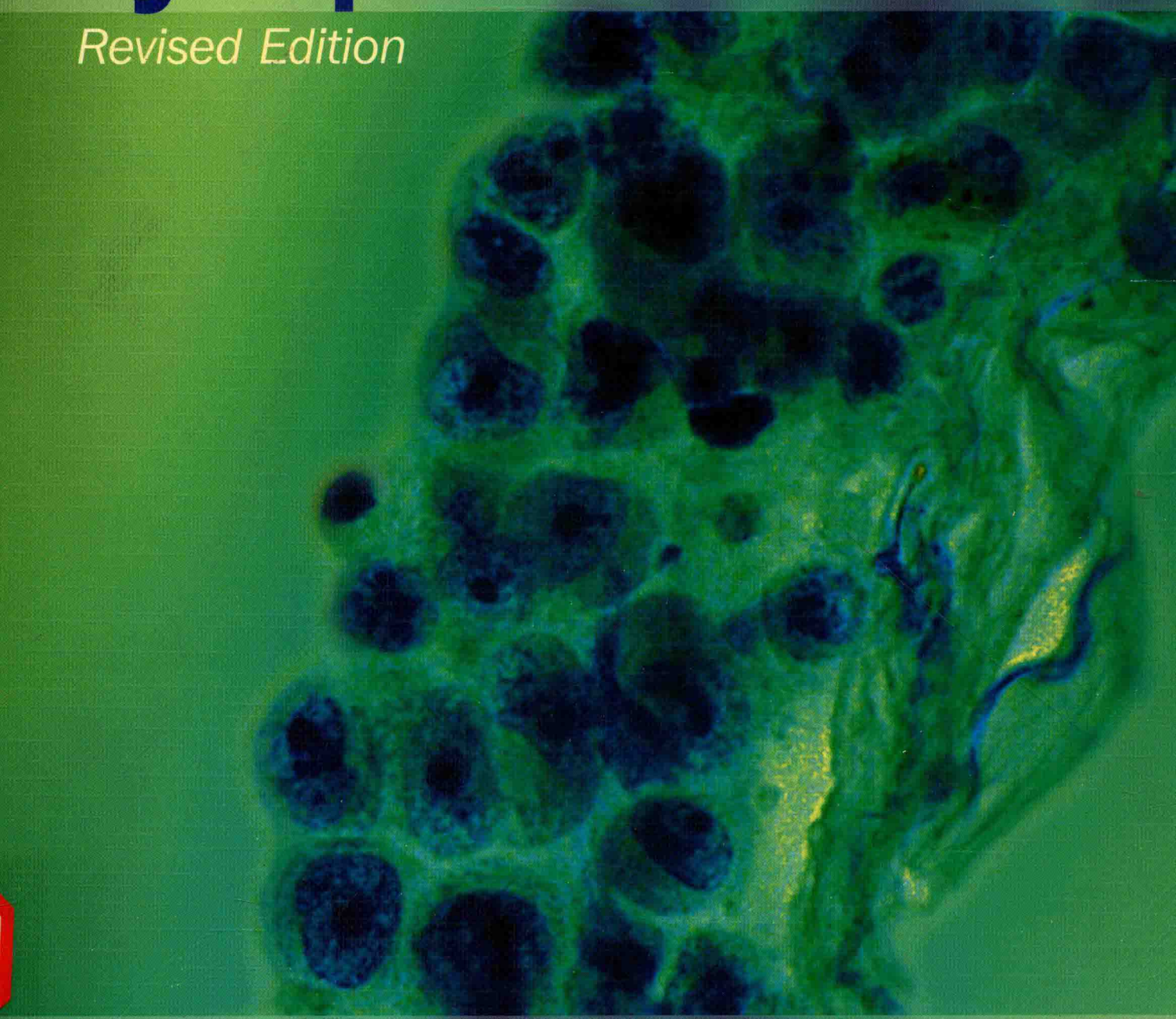
Text Atlas of Lymphomas

Revised Edition



James O Armitage • Franco Cavalli
Emanuele Zucca • Dan L Longo

Illustrations provided by Judith A Ferry

MARTIN DUNITZ

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James O Armitage, MD
Dean of the School of Medicine
Joe Shapiro Professor
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, NE, USA

Franco Cavalli, MD, FRCP
Professor and Director
Department of Oncology
Oncology Institute of Southern Switzerland
Ospedale San Giovanni
Bellinzona, Switzerland

Emanuele Zucca, MD
Department of Oncology
Oncology Institute of Southern Switzerland
Ospedale San Giovanni
Bellinzona, Switzerland

Dan L Longo, MD, FACP
Scientific Director
National Institute on Aging
National Institutes of Health
Baltimore, MD, USA

Illustrations provided by

Judith A Ferry, MD
Associate Professor of Pathology
Massachusetts General Hospit
Boston, MA, USA

MARTIN DUNITZ

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Preface

Our understanding of the 'solid' tumors of the immune system, namely, Hodgkin's disease and the non-Hodgkin's lymphomas, continues to evolve. These tumors have provided insights into tumor biology and therapy that have been widely applied in other malignancies. However, there is still considerable room for improvement in our ability to help patients afflicted by the lymphomas.

Over the past decade, a number of investigations into the immunology, genetics and etiology of non-Hodgkin's lymphoma have resulted in the identification of new subtypes. These entities, including mantle-cell lymphoma, anaplastic large cell lymphoma, and MALT lymphoma, are clinically as well as histopathologically distinct. Their recognition provided the stimulus for a new classification of non-Hodgkin's lymphoma. This classification, termed the Revised European American Lymphoma (REAL) classification, divided non-Hodgkin's lymphomas into clinical/pathological entities (i.e. real diseases!), rather than simply morphological groupings. A subsequent test of the clinical applicability of the REAL classification showed it to be highly reproducible and clinically relevant.

The REAL classification provided the basis for the lymphoma classification within the recently published *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Indeed, the *lymphoid tissues* section of the WHO classification can be regarded as an updated and improved REAL classification.

This volume is meant to provide a guide to understanding this REAL/WHO classification of lymphoid neoplasms. It provides the clinical characteristics, survival data and histological appearance of the major lymphoma subtypes. The ability to use this lymphoma classification will be key to providing optimal patient care for the foreseeable future.

The editors wish to thank Alison Campbell and Martin Dunitz of the publishers.

JOA, FC, EZ, DLL

Summary of the WHO classification of tumors of lymphoid tissues*

The number to the right of each disease entity is the morphology code of the Internal Classification of Diseases (ICD-O), 3rd edn. Behavior is coded /3 for malignant tumors and /1 for lesions of low or uncertain malignant potential.

B-CELL NEOPLASMS

Precurosor B-cell neoplasm

Precursor B-lymphoblastic leukemia[1]/ lymphoma[2]	9835/3[1] 9728/3[2]

Mature B-cell neoplasms

Chronic lymphocytic leukemia[1]/ small lymphocytic lymphoma[2]	9823/3[1] 9670/3[2]
B-cell prolymphocytic leukemia	9833/3
Lymphoplasmacytic lymphoma	9671/3
Splenic marginal-zone lymphoma	9689/3
Hairy cell leukemia	9940/3
Plasma-cell myeloma	9732/3
Solitary plasmacytoma of bone	9731/3
Extraosseous plasmacytoma	9734/3
Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Nodal marginal-zone B-cell lymphoma	9699/3
Follicular lymphoma	9690/3
Mantle-cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Mediastinal (thymic) large B-cell lymphoma	9679/3
Intravascular large B-cell lymphoma	9680/3
Primary effusion lymphoma	9678/3
Burkitt lymphoma[1]/leukemia[2]	9687/3[1] 9826/3[2]

B-cell proliferations of uncertain malignant potential

Lymphomatoid granulomatosis	9766/1
Post-transplant lymphoproliferative disorder, polymorphic	9970/1

T-CELL AND NK-CELL NEOPLASMS

Precurosor T-cell neoplasms

Precursor T-lymphoblastic leukemia[1]/ lymphoma[2]	9837/3[1] 9729/3[2]
Blastic NK-cell lymphoma[a]	9727/3

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukemia	9834/3
T-cell large granular lymphocytic leukemia	9831/3
Aggressive NK-cell leukemia	9948/3
Adult T-cell leukemia/lymphoma	9827/3
Extranodal NK/T-cell lymphoma, nasal-type	9719/3
Enteropathy-type T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sézary syndrome	9701/3
Primary cutaneous anaplastic large cell lymphoma	9718/3
Peripheral T-cell lymphoma, unspecified	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3
Anaplastic large cell lymphoma	9714/3

T-cell proliferation of uncertain malignant potential

Lymphomatoid papulosis	9718/1

HODGKIN'S DISEASE

Nodular lymphocyte-predominant Hodgkin's disease	9659/3
Classical Hodgkin's disease	9650/3
Nodular sclerosis classical Hodgkin's disease	9663/3
Lymphocyte-rich classical Hodgkin's disease	9651/3
Mixed-cellularity classical Hodgkin's disease	9652/3
Lymphocyte-depleted classical Hodgkin's disease	9653/3

HISTIOCYTIC AND DENDRITIC-CELL NEOPLASMS

Macrophage/histiocytic neoplasm

Histiocytic sarcoma	9755/3

Dendritic cell neoplasms

Langerhans cell histiocytosis	9751/1
Langerhans cell sarcoma	9756/3
Interdigitating dendritic cell sarcoma[1]/tumor[2]	9757/3[1] 9757/1[2]
Follicular dendritic cell sarcoma[1]/tumor[2]	9758/3[1] 9758/1[2]
Dendritic cell sarcoma, not otherwise specified	9757/3

[a]Neoplasm of uncertain lineage and stage of differentiation.

†Reproduced from Jaffe ES et al, *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press: Lyon, 2001.

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1 Introduction and background

The history of lymphoma classification

The distinction between Hodgkin's disease and non-Hodgkin's lymphoma became practical with the description of the Reed–Sternberg cell early in the 20th century. Since that time, the terminology to describe the non-Hodgkin's lymphomas has changed frequently and has often been confusing. The terms 'lymphosarcoma' and 'reticulum cell sarcoma' were developed to describe different types of non-Hodgkin's lymphoma. The description of follicular lymphoma by Brill et al and by Symmers set the stage for the first 'modern' lymphoma classification. This was proposed by Gall and Mallory, and divided non-Hodgkin's lymphomas into lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma.

In the 1950s, Henry Rappaport first proposed the lymphoma classification for which he remains well known. This classification divided lymphomas based on the pattern of cell growth and the size and shape of the tumor cells. It was shown to predict treatment outcome in a way that made it clinically useful. Unfortunately, the terminology in the Rappaport classification quickly became outdated when it became apparent that all non-Hodgkin's lymphomas were tumors of lymphocytes and that lymphocytes could be divided into those of T-cell origin and those of B-cell origin. The common large cell lymphoma with a diffuse growth pattern was termed 'diffuse histiocytic lymphoma' in the Rappaport classification.

Application of new understanding of the biology of the immune system led to new classifications. In the USA, Lukes and Collins proposed such a classification, and a similar system (the Kiel classification) was proposed by Lennert and colleagues in Europe. The Kiel classification became widely used and has remained popular up to the present time. For the first time, it defined lymphomas as being of low grade or high grade.

The use of widely different lymphoma classifications in different parts of the world hindered clinical research and clinical care. Because of this, an attempt was made by physicians from the US National Cancer Institute to reach a consensus system. This led to the development of the Working Formulation, which was not meant to be a classification per se but rather a means of translation between existing classifications. However, the Working Formulation became the most widely used system for classifying lymphomas in North America, while the Kiel classification remained popular in Europe. Since the development of the Working Formulation in the 1970s, new insights

into the biology of the immune system have continued to be obtained. In particular, these include the identification of specific antigens associated with certain subsets of lymphocytes and their corresponding lymphomas, and the recognition of specific genetic abnormalities in certain subtypes of lymphoma. In several circumstances, these observations made it possible to recognize new subtypes of lymphoma that had not been widely accepted on purely morphological grounds. For example, the recognition of the t(11;14) and the resultant overexpression of the *BCL1* oncogene confirmed the existence of mantle-cell lymphoma. The discovery of the Ki-1 or CD30 antigen and the subsequent discovery of the t(2;5) cytogenetic abnormality that leads to overproduction of the ALK protein led to wide acceptance of anaplastic large T/null cell lymphoma as a specific entity.

In the 1990s, a group of hematopathologists from around the world proposed a new system of lymphoma classification that included the newly recognized entities. These pathologists, who referred to themselves as the International Lymphoma Study Group, proposed that specific lymphoma entities should be recognized on the basis of a combination of morphological and clinical characteristics. This is a major change from the purely morphological classifications of the past. For example, recognition of the entity of mediastinal diffuse large B-cell lymphoma requires knowledge of the existence of a large mediastinal mass. That tumor, morphologically, represents an otherwise typical diffuse large B-cell lymphoma. When this entity is recognized separately, the patients are found to be younger than those with other aggressive non-Hodgkin's lymphomas and have an unusual female predominance.

This classification, termed the Revised European American Lymphoma (REAL) classification (Table 1.1), became the basis of the lymphoma classification within a new World Health Organization classification for tumors of hematopoietic and lymphoid tissues; a summary of the lymphoid tissues classification is shown on page viii.

Table 1.1
Summary of the REAL classification of non-Hodgkin's lymphomas[a]

B-cell lymphomas

Precursor B-cell lymphomas:
- B-lymphoblastic

Mature B-cell lymphomas:
- B-cell CLL/small lymphocytic
- Follicular
- Marginal-zone–nodal
- Extranodal marginal-zone (MALT)
- Splenic marginal-zone
- Lymphoplasmacytic
- Mantle-cell
- Diffuse large B-cell
- Primary mediastinal large B-cell[b]
- Burkitt-like[b]
- Burkitt's

T-cell lymphomas

Precursor T-cell lymphomas:
- T-lymphoblastic

Mature T-cell lymphomas:
- Mycosis fungoides/Sézary syndrome
- Peripheral T-cell (many subtypes)
- Anaplastic large T/null cell
- Adult T-cell leukemia/lymphoma

[a]Harris NL, Jaffe ES, Stein H et al, A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**: 1361–92.
[b]These are not included in the WHO classification as distinct entities.

Clinical applications

Non-Hodgkin's lymphomas were almost uniformly fatal diseases early in the 20th century. The use of radiotherapy produced long survival on some rare occasions. However, the use of combination chemotherapy regimens in the early 1970s led to the recognition that some patients with diffuse large cell lymphoma could be cured, even when widespread disease was present. The development of an increasing number of chemotherapeutic agents and biologic therapies such as interferon and antibodies (with or without radiolabels) increases the importance of accurate lymphoma diagnosis. All the subgroups of non-Hodgkin's lymphoma do not respond equally to the same therapy.

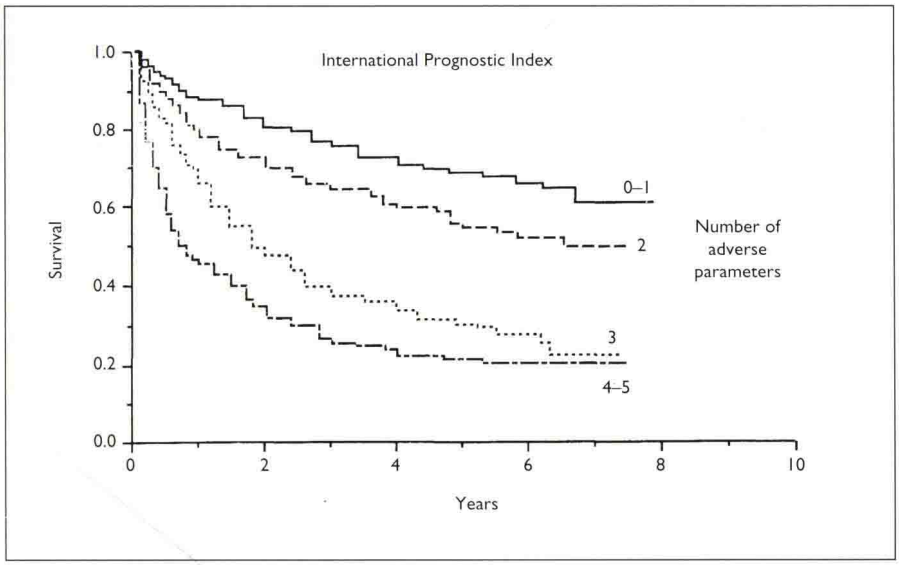

Figure 1.1
Overall survival with all types of non-Hodgkin's lymphoma grouped together by International Prognostic Index Score: 1254 lymphoma patients included in the ILSG Trial.

Table 1.2
International Prognostic Index[a]

Factor	Adverse prognosis
Age	≥60 years
Ann Arbor stage	III or IV
Serum LDH	Above normal
Number of extranodal sites of involvement	≥2
Performance status	≥ECOG 2 or equivalent

[a]International Non-Hodgkin's Lymphoma Prognostic Factors Project, A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329**: 987–94.

Even in any particular, distinctive subgroup, all patients do not respond equally to a particular therapy. The best way to predict treatment outcome in a uniform group of patients is using the International Prognostic Index (Table 1.2). By simply summing the number of adverse characteristics, it is possible to divide patients into clinically relevant subgroups. As shown in Figure 1.1, this information divides non-Hodgkin's lymphomas of all subgroups into clinically relevant groups. However, the best distinction is when a particular subtype of non-Hodgkin's lymphoma as recognized in the REAL classification is subdivided based on the prognostic characteristics of the patients. Therapeutic decisions should currently be based on these two factors.

The following chapters illustrate the important characteristics of the major subtypes of non-Hodgkin's lymphoma recognized in the REAL classification. The order of the chapters is not entirely arbitrary. The non-Hodgkin's lymphomas (and lymphoid leukemias) are discussed in roughly their order of frequency. In addition, chapters are included on extranodal lymphomas, Hodgkin's disease and rare entities, some of which are not specifically included in the new classification schemes, but may nevertheless occasionally be diagnosed. We do not discuss plasma-cell disorders. The relevant histological, biological and clinical characteristics are presented, along with characteristic photomicrographs. This information should be used routinely by clinicians in the care of patients with non-Hodgkin's lymphoma.

Bibliography

Athan E, Foitl D, Knowles D, Bcl-1 rearrangement: frequency and clinical significance among B cell chronic lymphocytic leukemias and non-Hodgkin's lymphomas. *Am J Pathol* 1991; **138:** 591–9.

Brill NE, Baehr G et al, Generalized giant follicle hyperplasia of lymph nodes and spleen: a hitherto undiagnosed type. *J Am Med Assoc* 1925; **84:** 668–71.

DeVita VT Jr, Canellos GP, Chabner B et al, Advanced diffuse histiocytic lymphoma, a potentially curable disease. *Lancet* 1975; **i:** 248–50.

Ewing J, Reticulum cell sarcoma. *J Med Res* 1913; **32:** 1.

Gall EA, Mallory TB, Malignant lymphoma: a clinicopathological survey of 63 cases. *Am J Pathol* 1942; **18:** 381–432.

Harris NL, Jaffe ES, Diebold J et al, The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November, 1997. *Ann Oncol* 1999; **10:** 1419–32.

Harris NL, Jaffe ES, Stein H et al, A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84:** 1361–92.

International Non-Hodgkin's Lymphoma Prognostic Factors Project, A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987–94.

Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press: Lyon, 2001.

Lennert K, Mohri N, Stein H, Kaiserling E, The histopathology of malignant lymphoma. *Br J Haematol* 1975; **31**(Suppl): 193–203.

Levitt M, Marsh JC, DeConti R et al, Combination sequential chemotherapy in advanced reticulum cell sarcoma. *Cancer* 1972; **29:** 630–6.

Lukes RJ, Collins RD, Immunologic characterization of human malignant lymphomas. *Cancer* 1974; **34:** 1488–503.

Mason D, Bastard C, Rimokh R et al, CD30-positive large cell lymphomas ('Ki-1 lymphoma') are associated with a chromosomal translocation involving 5q35. *Br J Haematol* 1990; **74:** 161–8.

Non-Hodgkin's Lymphoma Pathologic Classification Project, National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982; **49:** 2112–35.

Oberling C, Les reticulo-sarcoma et les reticulo-endotheliosarcoma de la moelle ossense (sarcoma d'Ewing). *Bull Assoc France Etude Cancer* 1928; **17:** 259.

Rappaport H, Malignant lymphomas. In: *Tumors of the Hematopoietic System*. Publication 91, Armed Forces Institute of Pathology: Washington, DC, 1966.

Rappaport HW, Winter J, Hicks E, Follicular lymphoma: a re-evaluation of its place in the scheme of malignant lymphoma based on a survey of 253 cases. *Cancer* 1956; **9:** 792–821.

Reed DM, On the pathological changes in Hodgkin's disease, with especial reference to its relation to tuberculosis. *Johns Hopkins Hosp Rev* 1902; **10:** 133–96.

Stein H, Mason D, Gerdes J et al, The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed–Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985; **66:** 848–58.

Sternberg C, Uber eine eigenartige unter dem Bilde der Pseudoleukamie verlaufende Tuberculose des lymphatichon Apparates. *Ztschr Heilk* 1898; **19:** 21.

Symmers D, Follicular lymphadenopathy with splenomegaly: a newly recognized disease of the lymphatic system. *Arch Pathol* 1927; **3:** 816–20.

Vandenberghe E, De Wolf-Peeters C, Van den Oord J et al, Translocation (11;14): a cytogenetic anomaly associated with B-cell lymphomas of non-follicle centre cell lineage. *J Pathol* 1991; **163:** 13–18.

Virchow R, *Die Krankenhaften Geschwülste*. Herschwald: Berlin, 1864.

2 Diffuse large B-cell lymphoma

Definition and classification

Diffuse large B-cell lymphoma is an aggressive neoplasm with a short survival in the absence of effective therapy. However, it has been known for 25 years that this lymphoma can sometimes be cured with combination chemotherapy. Early reports of cure used older nomenclature, including the terminology 'diffuse histiocytic lymphoma', 'diffuse large cell lymphoma', 'large transformed cell lymphoma', 'centroblastic lymphoma' and 'immunoblastic lymphoma'.

The most common non-Hodgkin's lymphoma is diffuse large B-cell lymphoma. This lymphoma often presents de novo, but can also be seen as a result of histologic transformation of most low-grade B-cell lymphomas. Transformation to diffuse large B-cell lymphoma is a common occurrence in follicular lymphoma, and is also seen in small lymphocytic lymphoma and the marginal-zone lymphomas, including MALT lymphoma.

Diffuse large B-cell lymphoma can arise in essentially any site in the body. The most common site is in lymphatic tissue, but any organ system can be involved. With some sites of involvement, unique clinical problems or unusual clinical courses are often observed. Primary central nervous system diffuse large B-cell lymphoma is an increasingly important clinical problem. While seen often in patients with human immunodeficiency virus (HIV) infection, diffuse large B-cell lymphoma involving the central nervous system is being seen increasingly frequently in patients with normal immune function. Central nervous system presentation is associated with an aggressive clinical course. In contrast, diffuse large B-cell lymphomas confined to the skin sometimes pursue an indolent clinical course. Diffuse large B-cell lymphomas involving the sinuses, epidural tissue and, probably, testes have an unusual predilection to spread to the central nervous system. The unique characteristics of specific sites of involvement need to be taken into account in planning the management of any particular patient.

Frequency

Diffuse large B-cell lymphoma makes up approximately 40% of all non-Hodgkin's lymphomas; the frequency varies little geographically. It is the predominant non-Hodgkin's lymphoma in all parts of the world.

Diffuse large B-cell lymphoma is increasing in frequency. This is the major explanation for the dramatic increase in the incidence of non-Hodgkin's lymphoma that has occurred over the last several decades. In the USA, the increase in incidence has been 4% per year since 1950. The

cause of this 'epidemic' remains a mystery. The frequency of diffuse large B-cell lymphoma is higher in patients with defective immune function. It is a frequent tumor in patients with HIV infection, but it also is seen with increased frequency in patients with other immune disorders such as rheumatoid arthritis. Diffuse large B-cell lymphoma occurs more frequently in individuals exposed to a variety of chemicals, including many used in agriculture. Despite this knowledge of predisposing factors, the reason for the development of the disorder in most patients is not known.

Pathology

Histology (Table 2.1)

Diffuse large B-cell lymphoma can be recognized accurately by pathologists. In the International Lymphoma Classification Study, diffuse large B-cell lymphoma could be diagnosed accurately 87% of the time when both histologic features and immunophenotype were taken into account.

Diffuse large B-cell lymphoma is a neoplasm of large cells growing in a diffuse (i.e. non-follicular) pattern. The nuclei of the tumor cells are usually at least twice as large as the nucleus of a small lymphocyte. The tumor cells have nuclei that are vasicular and often contain prominent nucleoli, and have basophilic cytoplasm. They usually represent a mixture of centroblasts and immunoblasts. Occasionally, the tumor cells can have an 'anaplastic' appearance similar to that seen in anaplastic large T/NK-cell lymphoma. In this situation, the tumors display B-cell antigens. There is usually a moderate to high growth fraction in diffuse large B-cell lymphoma.

Occasionally, diagnosis can be complicated by a predominance of infiltrating T lymphocytes. This can lead to confusion in immunophenotyping, if it is not recognized that the tumor cells mark as B cells. This entity, often called T-cell-rich B-cell lymphoma, follows the same clinical course as other diffuse large B-cell lymphomas.

Immunophenotype (Table 2.2)

The only characteristic immunophenotypic finding in diffuse large B-cell lymphoma is that the tumors mark as B cells and thus display the CD20 antigen. They stain negatively with T-cell markers such as CD3. As noted above, care must be taken to be certain that it is the immunophenotype of the tumor cells that is being observed and not that of infiltrating normal cells. Knowing the immunophenotype increases the accuracy of diagnosis by 10%.

Genetics (Table 2.2)

Diffuse large B-cell lymphoma probably represents several subtypes of aggressive non-Hodgkin's lymphoma that have not yet been clearly delineated. This view is supported by the wide variety

Table 2.1
Histological features of diffuse large B-cell lymphoma

- Large cells (i.e. nuclei ≥ twice the size of a small lymphocyte) and diffuse growth pattern
- Vesicular nuclei, prominent nucleoli, basophilic cytoplasm
- Moderate to high growth fraction
- Usually a mixture of centroblasts and immunoblasts
- Can occasionally have an 'anaplastic' appearance
- Occasional predominance of infiltrating T cells can lead to confusion with peripheral T-cell lymphoma (i.e. T-cell-rich B-cell lymphoma)

Table 2.2
Typical immunophenotype and genetics of diffuse large B-cell lymphoma

Characteristic	Result
Immunophenotype	$CD20^+$
	$CD3^-$
Cytogenetics	t(14;18)(q32;q21)
	t(3;14)(q27;q32)
	t(8;14)(q24;q32)
Oncogenes	*BCL2*
	BCL6
	c-MYC

of cytogenetic abnormalities and oncogene abnormalities that are seen in this disorder. The most common cytogenetic abnormalities include the t(14;18)(q32;q21) that is characteristic of follicular lymphoma. This cytogenetic abnormality is seen in up to 30% of diffuse large B-cell lymphomas in various series. This cytogenetic abnormality is associated with overexpression of the *BCL2* oncogene. The protein overexpression rather than the translocation seems to have clinical significance.

Another common cytogenetic abnormality seen in diffuse large B-cell lymphoma is the t(3;14)(q27;q32). This cytogenetic abnormality is associated with overexpression of the *BCL6* oncogene. In some series, but not all, this has been reported to be associated with a good prognosis. A much less frequently seen cytogenetic abnormality in diffuse large B-cell lymphoma is the t(8;14)(q24;q32) that is associated with overexpression of the c-*MYC* oncogene. This cytogenetic abnormality is characteristic of Burkitt's lymphoma, but is also occasionally seen in patients with large B-cell lymphoma. A myriad other cytogenetic abnormalities have also been reported.

Molecular studies with DNA microarrays identified two major subsets of diffuse large B-cell lymphomas that, in relation to their patterns of gene expression, appeared to originate from different stages of B-cell development. One type showed the gene expression profile of the germinal center B cell, while the other type expressed genes normally induced during in vitro activation of peripheral blood B cells. Patients with germinal center B-cell-like diffuse large cell lymphoma had a significantly better survival than those with activated B-cell-like diffuse large cell lymphoma.

Clinical characteristics (Table 2.3)

Diffuse large B-cell lymphoma usually presents with lymphadenopathy, but extranodal presentations give a clinical picture that might be confused with carcinoma of the site of involvement. This lymphoma is more likely to be localized than other non-Hodgkin's lymphomas. While it can be seen in patients in any age, the median age is in the 60s. In the International Lymphoma Classification Study, the actual median age was 64 years, as seen in Table 2.3. This lymphoma is seen more frequently in males: 55% in the aforementioned study.

Approximately 50% patients with diffuse large B-cell lymphoma will have disease that is localized to one site (i.e. stage I) or confined to one side of the diaphragm (stage II). Approximately 50% of patients with localized lymphoma will have predominant extranodal involvement. The other 50% of patients with diffuse large B-cell lymphoma have more widespread disease. Approximately 60% of patients who present with stage III or stage IV disease will have extranodal involvement. Approximately 30% of patients will present with fevers, sweats or weight loss.

An elevation of the serum level of lactate dehydrogenase (LDH) is seen in approximately 50% of patients. While most patients will be fully active, approximately 25% of the patients have reduced performance status at the time of diagnosis. Thirty percent of patients will have a tumor mass of at least 10 cm diameter. The comparatively high frequency of elevated LDH, low performance status or large tumor mass account in part for the poorer prognosis associated with this lymphoma.

Table 2.3
Clinical characteristics of diffuse large B-cell lymphoma

Characteristic	Result
Median age	64 years
Percent male	55%
Stage I	12%
Stage IE	13%
Stage II	13%
Stage IIE	16%
Stage III	13%
Stage IV	33%
B symptom	33%
Elevated LDH	53%
Karnofsky score ≤ 70	24%
Tumor mass ≥ 10 cm	30%
Any extranodal site	71%
Bone marrow positive	16%
GI track positive	18%
IPI score: 0/1	35%
2/3	46%
4/5	19%

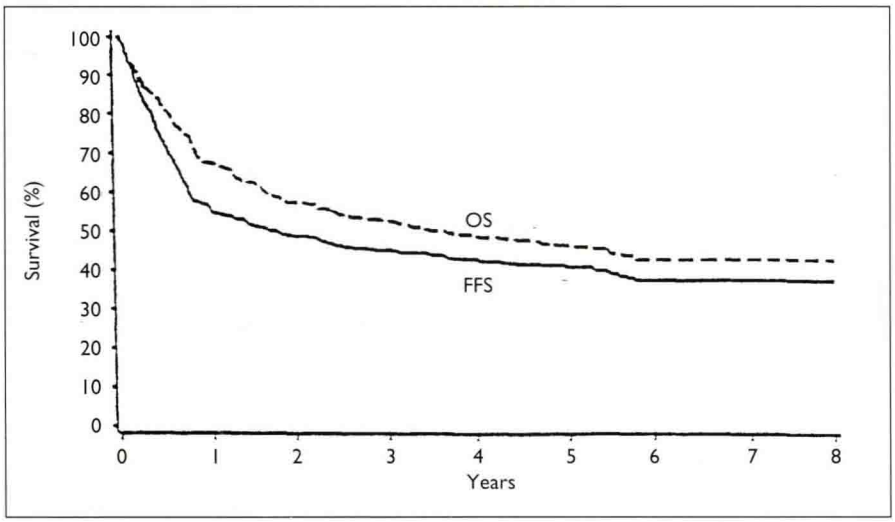

Figure 2.1
Overall survival (OS) and failure-free survival (FFS) for patients with diffuse large B-cell lymphoma.

About 70% of patients with diffuse large B-cell lymphoma will have involvement of at least one extranodal site. Approximately 30% of patients will have more than one extranodal site involved, and essentially any extranodal site can be involved. When the bone marrow biopsy is positive in these patients, the majority of patients will have small lymphocytes involving the marrow rather than large cells. The presence of small lymphocytes in the bone marrow in a patient with diffuse large B-cell lymphoma does not alter the overall prognosis. In contrast, the presence of large cells infiltrating the marrow has an adverse prognosis.

Approximately 30% of patients with diffuse large B-cell lymphoma will have none or only one adverse risk factor in the International Prognostic Index. About 50% of patients will have two or three adverse risk factors, and about 20% of patients will have four or five adverse risk factors.

Treatment and outcome

The treatment of patients with diffuse large B-cell lymphoma should emphasize the use of combination chemotherapy. The most popular regimen currently in use is the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) (Table 2.4), although a variety of other regimens have at least equal activity. Even in patients with localized disease, the initial treatment should be combination chemotherapy. However, in patients with stage I, the total number of chemotherapy cycles can be reduced and involved-field radiotherapy substituted.

It has been known for at least 25 years that diffuse large B-cell lymphoma can be cured with combination chemotherapy – even in some patients with widespread disease. Unfortunately, experimentation with a wide variety of chemotherapeutic agents in varying combinations over the last two decades has not led to a definite improvement in treatment outcome. The consequence is the failure-free and overall survival curves illustrated in Figure 2.1. Approximately 40% of all patients with diffuse large B-cell lymphoma can

Table 2.4
The CHOP regimen: usually administered at 3-weekly intervals

Regimen	Drug	Dose (mg/m^2)	Day of cycle
CHOP	Cyclophosphamide	750	1
	Doxorubicin	50	1
	Vincristine	1.4 (maximum 2 mg)	1
	Prednisone	100 mg total dose (not per m^2)	1–5

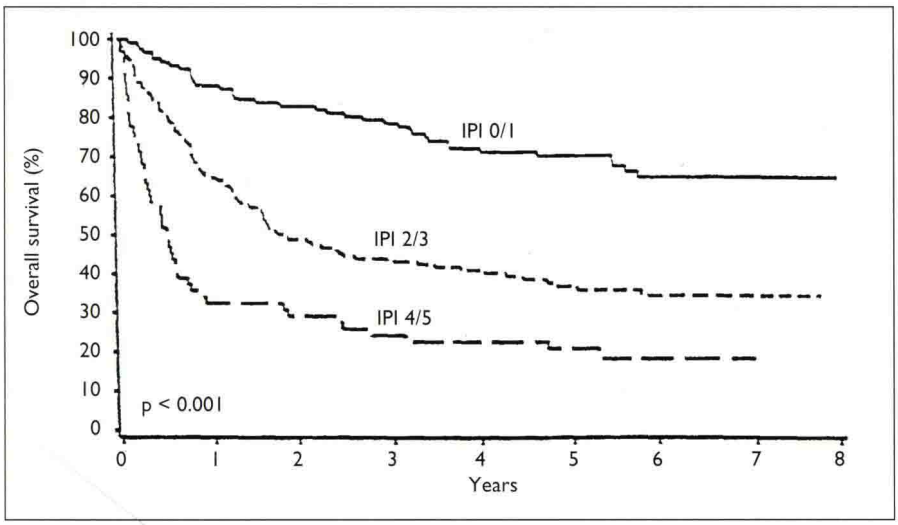

Figure 2.2
Overall survival according to International Prognostic Index (IPI) for patients with diffuse large B-cell lymphoma.

currently be cured. However, the chance for cure depends upon the risk factors in an individual patient. As illustrated in Figure 2.2, the International Prognostic Index can identify a subset of patients in which the five-year survival (i.e. usually very close to the five-year failure-free survival) is approximately 70%, and another subgroup of patients in which survival at five years is only approximately 20%.

There is preliminary evidence that the addition of rituximab (a chimeric anti-CD20 monoclonal antibody) to combination chemotherapy may be of some benefit.

Salvage therapy in patients with diffuse large B-cell lymphoma can occasionally be curative. It has recently been demonstrated that high-dose therapy and autologous hematopoietic stem cell transplantation can cure a significant proportion of patients with disease that remains chemotherapy-sensitive after relapse. In a randomized trial, this approach has been shown to be superior to standard-dose therapy. Studies conducted to see if earlier use of auto-transplantation can improve the outcome produced controversial results. Additional large randomized phase III studies are currently in progress.

Involvement of specific sites in patients with diffuse large B-cell lymphoma can provide unique clinical problems. For example, patients with sinus involvement, epidural involvement or testicular involvement need to have prophylactic therapy to the central nervous system incorporated into their initial treatment, otherwise they have a high risk for a meningeal relapse. Patients who present with primary diffuse large B-cell lymphoma in the brain provide a particularly difficult clinical problem. However, intensive chemotherapy regimens including the use of high-dose methotrexate and early irradiation of the brain seem to improve treatment results. Finally, patients who present with diffuse large B-cell lymphoma confined to the skin sometimes pursue an indolent clinical course. Some investigators would suggest that these patients be treated very conservatively, with only excision or involved field radiotherapy.

Bibliography

Alizadeh AA, Eisen MB, Davis RE et al, Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; **403:** 503–11.

Coiffier B, Lepage E, Brière J et al, CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346:** 235–42.

Conlan MG, Bast M, Armitage JO, Weisenburger DD, Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow: Nebraska Lymphoma Study Group. *J Clin Oncol* 1990; **8:** 1163–72.

Devesa SS, Fears T, Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992; **52:** 5432s–40s.

DeVita VT Jr, Canellos GP, Chabner B et al, Advanced diffuse histiocytic lymphoma, a potentially curable disease. *Lancet* 1975; **i:** 248–50.

Eby NL, Grufferman S, Flanelly CM et al, Increasing incidence of primary brain lymphoma in the US. *Cancer* 1988; **62:** 2461–5.

Filipovich AH, Mathur A, Kamat D, Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res* 1992; **52:** 5465s–7s.

Fisher RI, Gaynor ER, Dahlberg S et al, Comparison of CHOP vs m-BACOD vs ProMACE-CytaBOM vs MACOP-B in patients with intermediate or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1993; **328:** 1002–6.

Gatter KC, Warnke RA, Diffuse large B-cell lymphoma. In: *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues* (Jaffe ES, Harris NL, Stein H, Vardiman JW, eds). IARC Press: Lyon, 2001: 171–4.

Gianni AM, Bregni M, Siena S et al, High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med* 1997; **336:**1290–7.

Haioun C, Lepage E, Gisselbrecht C et al , Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol – a groupe d'Etude des Lymphomes de l'Adulte study. *J Clin Oncol* 2000; **18:** 3025–30.

Harris NL, Jaffe ES, Stein H et al, A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84:** 1361–92.

Hill ME, MacLennan KA, Cunningham DC et al, Prognostic significance of BCL-2 expression and *bcl-2* major breakpoint region rearrangement in diffuse large cell non-Hodgkin's lymphoma: a British National Lymphoma Investigation study. *Blood* 1996; **88:** 1046–51.

International Non-Hodgkin's Lymphoma Prognostic Factors Project, A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987–94.

Jones SE, Miller TM, Connors JM, Long-term follow-up and analysis for prognostic factors for patients with limited-stage diffuse large-cell lymphoma treated with initial chemotherapy with or without adjuvant radiotherapy. *J Clin Oncol* 1989; **7:** 1186–91.

Kinlen LJ, Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* 1985; **78**(Suppl 1A): 44–9.

Kluin-Nelemans HC, Zagonel V, Anastasopoulou A et al, Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. *J Natl Cancer Inst* 2001; **93:** 22–30.

Levine AM, Lymphoma in acquired immunodeficiency syndrome. *Semin Oncol* 1990; **17:** 104–12.

Levine AM, Shibata D, Sullivan-Halley J, Epidemiological and biological study of acquired immunodeficiency syndrome-related lymphoma in the county of Los Angeles: preliminary results. *Cancer Res* 1992; **52:** 5482s–4s.

Levitt M, Marsh JC, DeConti R et al, Combination sequential chemotherapy in advanced reticulum cell sarcoma. *Cancer* 1972; **29:** 630–6.

Longo DL, Glatstein E, Duffey PI et al, Treatment of localized aggressive lymphomas with combination chemotherapy followed by involved-field radiation therapy. *J Clin Oncol* 1989; **7:** 1186–91.

Non-Hodgkin's Lymphoma Classification Project, A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997; **89:** 3909–18.

Offit K, LoCoco F, Diane C, Rearrangement of the *bcl* gene as a prognostic marker in diffuse large cell lymphoma. *N Engl J Med* 1994; **14:** 74–80.

Pearce N, Bethwaite P, Increasing incidence of non-Hodgkin's lymphoma: occupational and environmental factors. *Cancer Res* 1992; **52:** 5496s–500s.

Philip T, Armitage JO, Spitzer G et al, High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1987; **316:** 1493–8.

Philip T, Guglielmi C, Hagenbeek A et al, Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; **333:** 1540–5.

Ramsay A, Smith W, Isaacson P, T-cell rich B-cell lymphoma. *Am J Surg Pathol* 1988; **12:** 433–43.

Snider WD, Simpson DM, Nielson S et al, Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol* 1983; **14:** 403–18.

Willemze R, Meister CJLM, Sentis HJ et al, Primary cutaneous cell lymphomas of follicular center-cell origin. *J Am Acad Dermatol* 1987; **16:** 518–26.

Vose JM, Link BK, Grossbard ML et al, Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2001; **19:** 389–97.

Yves Blay J, Conroy T, Chevreau C et al, High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol* 1998; **16:** 864–71.

Zahm SH, Blair A, Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 1992; **52:** 5485s–8s.