National Comprehensive Cancer Network®

Diagnosis of NHL: What's New in the WHO?

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Why Classify?

- Classification is the "language" of medicine
  - Diseases must be described and defined before they can be diagnosed and treated
- Consensus on terminology and definitions
  - Essential for both clinical practice and research
- Diseases should be clearly defined and clinically distinctive
  - Mutually exclusive (non-overlapping categories)
  - Collectively exhaustive (all diseases should be identified)
    - "MECE"
- The classification should serve as a basis for further investigation

WHO Classification: History

- 1970s: Multiple lymphoma classifications
  - Rappaport, Kiel, Lukes-Collins, BNLI, Dorfman, WHO
- 1982: Working formulation (led by exasperated clinicians)
  - Designed to translate between classifications
  - Prognostic groups more important than specific pathological categories
- 1994: “Revised European-American Classification of Lymphoid neoplasms” (REAL classification) (ILSG)
  - Consensus list of lymphoid neoplasms that could be recognized by pathologists and were clinically distinctive
  - Included input from a meeting with clinicians

WHO Classification: History

- 1997: International clinical study of REAL classification
  - Categories reproducible, covered >95% of lymphomas, clinically relevant
- 2001: WHO Classification, 3rd Edition
  - Broader consensus on lymphoid neoplasms
  - Applied principles of REAL to myeloid, histiocytic neoplasms
  - Clinical advisory committee
  - First international consensus on classification of hematologic malignancies

The REAL/WHO Classification: Principles

- Define distinct disease entities that can be recognized by pathologists and that have clinical relevance
- A constellation of features (morphologic, immunophenotypic, genetic, and clinical) defines each disease entity
- Since we do not know the underlying cause of most lymphomas, the relative importance of each feature varies among diseases – no "gold standard"
- Diseases are stratified according to postulated normal counterpart and stage of differentiation to the extent possible, and sorted according to clinical and morphologic similarities

The World Health Organization Classification (WHO), 4th Edition: The Process

- American (SH) and European (EAHP) Hematopathology Societies
  - Persuaded WHO to continue the series, with help from hematology & oncology societies
- 8 editors selected by EAHP & SH
  - Myeloid: J. Vardiman (US), J. Thiele (DE)
  - Lymphoid: S. Swerdlow, E. Jaffe, N.L. Harris (US); E. Campo (ES), S. Pileri (IT), H. Stein (DE)
  - ~110 authors: U.S., Canada, Europe, Asia, Australia
- The WHO Clinical Advisory Committees
  - Myeloid and acute leukemias: Chicago, Feb. 2007
  - Lymphoid: Airlie House VA, March 2007
  - ~100 international hematologists and oncologists
- Consensus meeting of pathologists: Lyon, Sept. 2007
- Published in Sept. 2008; first printing sold out (10,000 books); second printing now available (almost gone!) – WHO Web site

WHO 2008: What's New?

- Genetically defined categories of leukemias
- New diseases/subtypes/variants/grading
- Small clonal lymphoid populations
- Consensus guidelines for some diseases
- Borderline (grey zone) categories
- Provisional categories

WHO 2008 vs. WHO 2001: What's New?

- More diseases recognized (108 in all!)
  - Myeloid and acute leukemias: 50
  - Mature B, T, HL: 53
  - Histiocytic: 5
- Many defined by genetic and immunophenotypic features as well as morphology
- Correct classification required to determine treatment

WHO Lymphoid 2008: Implications for Practice

- Immunophenotyping more important than ever
- Cytogenetics/FISH increasingly important to detect genetic abnormalities associated with specific diseases
- Detection of viruses (EBV, HHV8) often necessary
- Morphology +/- clinical features drive both the choice and the interpretation of special studies

Small Clonal Populations ?Early/Precursor Lesions

- New technology allows detection of small clones of lymphoid cells in blood, bone marrow, and lymph nodes of healthy persons
  - Immunophenotype (light-chain restriction, CD5, CD10, BCL2 in GC)
  - Genetics (IGH-r, BCL2-r)
- May not indicate presence or risk of progressive malignancy
- Analogous to MGUS 30 years ago
- Guidelines included in discussions of respective lymphoma subtypes (myeloma, CLL, FL)

Consensus Guidelines

- Chronic lymphocytic leukemia
  - "In the absence of tissue involvement there must be ≥5 × 10^9/L monoclonal lymphocytes with CLL phenotype in peripheral blood."
  - Others: "monoclonal B lymphocytosis/MBL"
- Waldenström's macroglobulinemia
  - Paraprotein of any size in a patient with LPL in bone marrow
- Plasma cell myeloma
  - Symptomatic vs. asymptomatic
    - End-organ damage (CRAB)
    - If symptomatic, no minimum plasma cell #, paraprotein level
  - International staging system (albumin, β2 microglobulin)
  - TC groups (Translocations-Cyclin D genes)
  - Cytogenetic prognostic groups (favorable, unfavorable)
- Cutaneous lymphomas: EORTC classification

Follicular Lymphoma: Issues

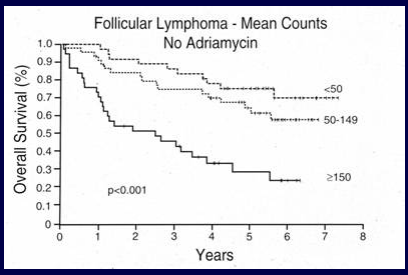
- Grading
- Diffuse areas
- Subtypes/variants
  - Gastrointestinal FL
  - Pediatric FL
  - "Intrafollicular neoplasia (FL in situ)"
- Primary cutaneous follicle centre lymphoma
  - Now recognized as a distinct disease

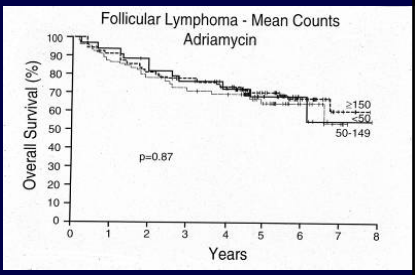
FL Grading: Issues

- CAC: simplify or eliminate grading
  - FL1-3A: “follicular lymphoma” - one disease with no grades
  - FL3B: “follicular” variant of diffuse large B-cell lymphoma
- *But* grading is the only pathological predictor of outcome in FL
  - Many studies: worse prognosis for Grade 3 (large cell) cases
  - *But* poorly reproducible among pathologists
- Evidence that FL3B is genetically closer to DLBCL than FL1-3A
  - *But* mainly true for FL3B+DLBCL (BCL6-R, CD10-, Mum1+)@
- Suspicion that FL3B is more aggressive than FL3A
  - *But* 3B more often associated with DLBCL than 3A (~60% vs. 30%)
  - *And* no difference in survival of 3A vs. 3B if purely follicular#
- Since FL3B is rare (25% of FL3, 5% of FL), most studies of clinical behavior of FL3 (large cell) are based mainly on FL3A cases

#Hans CP, et al. *Blood*. 2003;101:2363-2367.
@Katzenberger T, et al. *Am J Pathol*. 2004;165:481-490.

Follicular Lymphoma: Clinical Impact of Grading





- Grades 1 & 2: equal survival, not affected by doxorubicin
- Grade 3: improved OS and FFS with doxorubicin
- Grade 3A and 3B: no difference

Weisenburger DD, et al. Abstract.

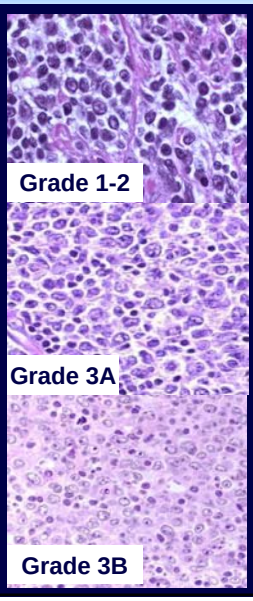
FL Grading: Pathologists' Conclusions

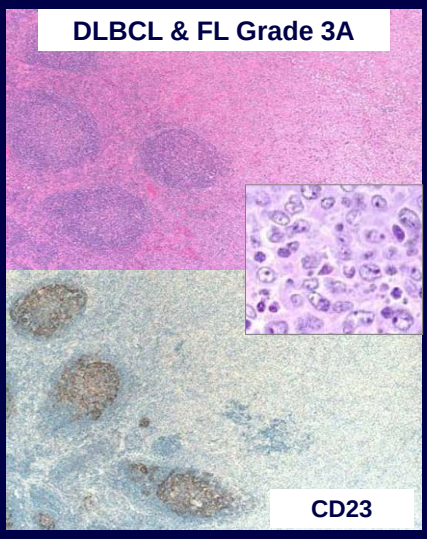
- Insufficient data at this time to warrant:
  - Lumping FL3B with DLBCL, or
  - Eliminating grading altogether
- FL1 and FL2 do not differ from one another
  - Could call them both FL1
    - FL3A becomes FL2
    - FL3B becomes FL3
  - *But* using same grades with new definitions confusing
- Could change nomenclature
  - FL low-grade (FL1-2)
  - FL intermediate-grade (FL3A)
  - FL high-grade (FL3B)
    - *But* not clear that FL3B is more aggressive than FL3A

Follicular Lymphoma Grading: Decision – Still 3 Grades

- Estimate number/proportion of centroblasts
  - FL1-2 = CB rare ("low-grade")
  - FL3A = CB numerous (>15/hpf); centrocytes still present
  - FL3B = sheets of centroblasts (no longer optional)
  - *This issue needs to be revisited when more data are available on gene expression and prognosis; will change in next edition*
- Diffuse areas:
  - If meets criteria for FL3 (A/B): separate diagnosis of DLBCL
  - No such thing as "FL Grade 3 with diffuse areas"!

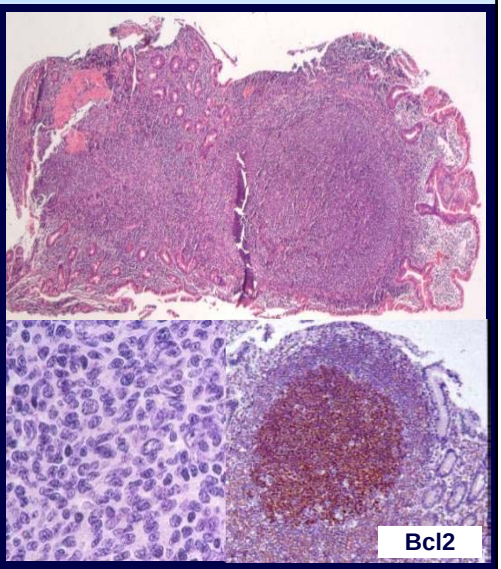
Follicular Lymphoma: Grading and Diffuse Areas





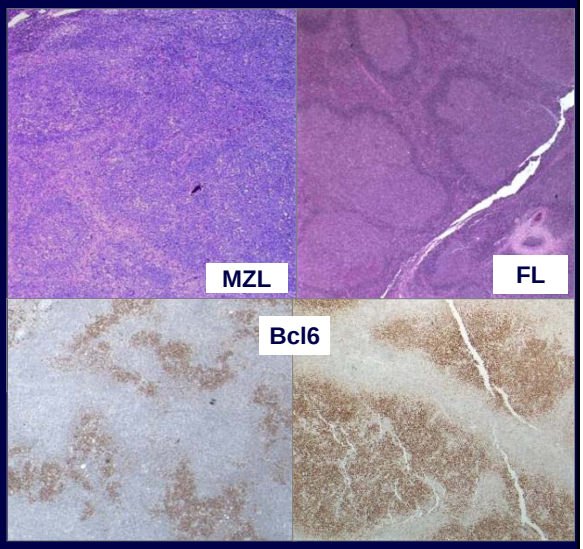
Follicular Lymphoma of the Gastrointestinal Tract

- Small intestine
  - Duodenum: 85%
- Morphology, immunophenotype, genetics similar to nodal FL
  - Bcl2+ CD10+ Bcl6+, often IgA+
- Clinically indolent, localized
  - Asymptomatic (incidental); abdominal pain
  - Most localized (Stage I/II)
  - Curable with resection, often no treatment
  - Systemic recurrence unusual
- ?Arise from follicular component of MALT



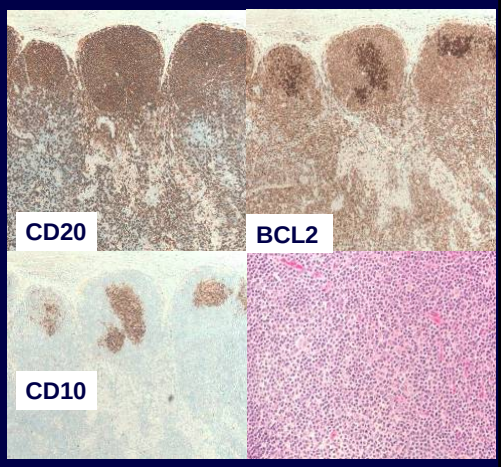
Pediatric Follicular Lymphoma
Pediatric Nodal Marginal Zone lymphoma

- Adolescent or young adult males; localized peripheral lymph nodes
- Large follicles, PTGC-like, follicle lysis; effacement of architecture
- Clonal (immunophenotype, genetic analysis)
- FL:
  - CD10+ Bcl6+ CD43+ Bcl2-
- MZL:
  - CD10- Bcl6- (residual GC present) Bcl2 +/- clg +/-
- DDX:
  - Reactive LN with clonal CD10+ cells
- Often cured with minimal therapy; no dissemination
- Are these really malignant?



Intrafollicular Neoplasia
("In-Situ" Follicular Lymphoma)

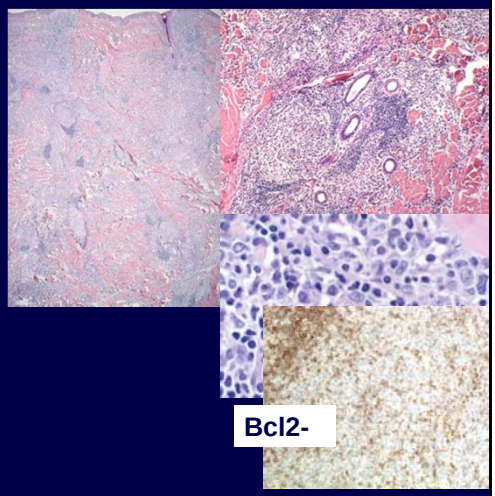
- Architecturally normal-appearing lymph node or other lymphoid tissue
  - One or more follicles with Bcl2+ CD10+ clonal B cells, IGHr, BCL2r
  - Often an incidental finding
- Clinical
  - Minority with overt FL elsewhere (earlier, concurrent, later)
  - Most no FL
- Nodal equivalent of small clones of BCL2R cells in blood of normal subjects?
  - 2nd "hit" required for FL
- Evaluate for FL; don't treat!



Cong P, et al. *Blood*. 2002;99:3376-3382.

Primary Cutaneous Follicle Center Lymphoma

- Definition
  - A tumor of neoplastic follicle center cells, usually a mixture of centrocytes and variable numbers of centroblasts, with a follicular, a follicular and diffuse, or a diffuse growth pattern, which generally present on the head or trunk
  - Lymphomas with a diffuse pattern and sheets of centroblasts/ immunoblasts are excluded (DLBCL leg type)
- Morphology
  - Centrocytes (may be large) and centroblasts, often diffuse; no grading
- Immunophenotype
  - Bcl6+ CD10-/+Bcl2-/dim+ Mum1-
- Clinical
  - Indolent, cutaneous relapse, no systemic dissemination
  - Local therapy sufficient (excision, radiation)



WHO 4th Edition Changes: Aggressive B-cell Neoplasms

- DLBCL – new categories
  - Extranodal primary sites
  - Virus-associated (EBV, HHV8)
- Borderline categories
  - BL and DLBCL
  - PMBL and NSCHL

WHO 4th Edition: Diffuse Large B-cell Lymphomas

- Diffuse large B-cell lymphoma, not otherwise specified
  - GCB/ABC, morphologic variants
  - T cell/histiocyte rich large B-cell lymphoma
  - Primary CNS DLBCL
  - Primary cutaneous DLBCL ("leg type")
  - EBV+ DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive DLBCL
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease

Borderline between BL and DLBCL

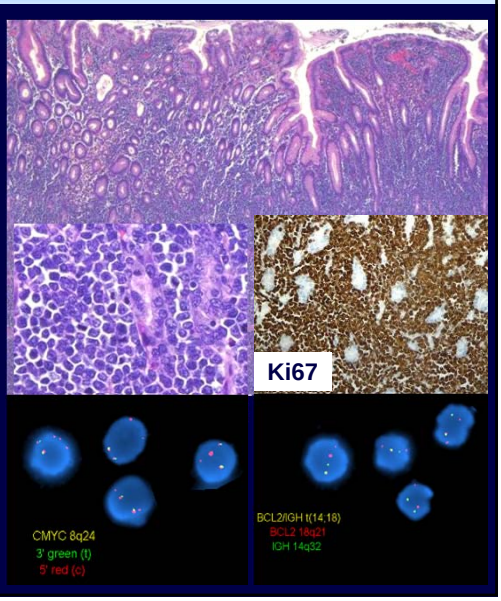
- Most cases straightforward, but some morphologically intermediate (mix of medium and large cells, mitoses, starry-sky pattern)
- WHO 3rd edition: "atypical Burkitt's lymphoma"
  - Morphologically intermediate between BL and DLBCL
    - >95% Ki-67 fraction
    - Immunophenotype of BL (CD10+ Bcl6+ Bcl2-)
    - MYC rearranged, BCL2 germline [if available]
  - *Should not make this diagnosis unless you really think it is more likely Burkitt's than large B-cell lymphoma*
- Others: classify as DLBCL

DLBCL vs. BL: Clinical Advisory Committee 4th Edition

- Gene expression studies (2006) showed true "grey zone" between BL and DLBCL
- Many cases, especially in adults, cannot be definitively classified as BL vs. DLBCL
- Should not "contaminate" these categories with cases that may be biologically and clinically different
- Provisional category: B-cell lymphoma, intermediate between BL and DLBCL
  - A heterogeneous category that needs to be further refined; not a distinct entity
  - Allows classification of cases not meeting criteria for classical BL or DLBCL
  - Individualized decisions about treatment

High-Grade B-Cell Lymphoma, Intermediate between BL and DLBCL (Provisional Category)

- **Definition:**
  - Lymphomas with features of both DLBCL and BL, but that for biological and clinical reasons should not be included in these categories
  - Morphology:
    - Intermediate between BL and DLBCL (medium-sized cells, large cells)
  - Immunophenotype:
    - GCB (CD10+ Bcl6+) but may be Bcl2+
    - Ki67 high or intermediate
  - Genetics:
    - *MYC*, *BCL2*, both (double hit), complex karyotypes
  - Clinical:
    - May occur in pts w/ hx FL
    - Aggressive, short survival (especially double hit cases)



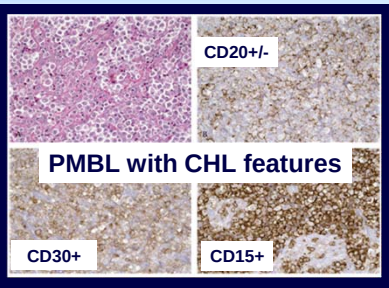
B-Cell Lymphoma, Intermediate between DLBCL (PMBL) and CHL (NSCHL)

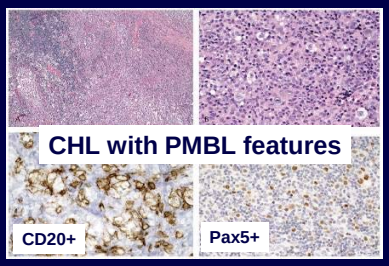
- Mediastinal lymphomas common in young adults
- Share immunophenotypic and gene expression profiles
  - Ig-, loss of B-cell receptor signaling
  - Activation of cytokine JAK-STAT pathway
  - Expression of TNF family members (CD30, TRAF1)
  - Constitutive NF-kappa B activation (cREL nuclear localization)
  - Activation of tyrosine kinases and the PI3K/ATK pathway
- Borderline cases are increasingly recognized by pathologists
- This may be a real disease…

Traverse-Glehen A, et al. *Am J Surg Pathol*. 2005;29:1411-1421.
Savage KJ, et al. *Blood*. 2003;102:3871-3879.
Rosenwald A, et al. *J Exp Med*. 2003;198:851-862.

B-Cell Lymphoma, Intermediate between DLBCL and CHL (Provisional Category)

- Definition:
  - A B lineage lymphoma with overlapping features between classical Hodgkin lymphoma (CHL) and diffuse large B-cell lymphoma (DLBCL), especially primary mediastinal large B-cell lymphoma (PMBL)
- Morphology:
  - Large cells, lacunar, R-S like, in sheets; variable sclerosis, fibrous bands, inflammatory background
  - CD45+ CD30+ Pax5+ CD20+/- CD79a+/- CD15+/- CD10- Bcl6-/+
- Clinical:
  - Young men (20-40), mediastinal
  - Aggressive, often fatal
  - ?Treat as CHL or PMBL



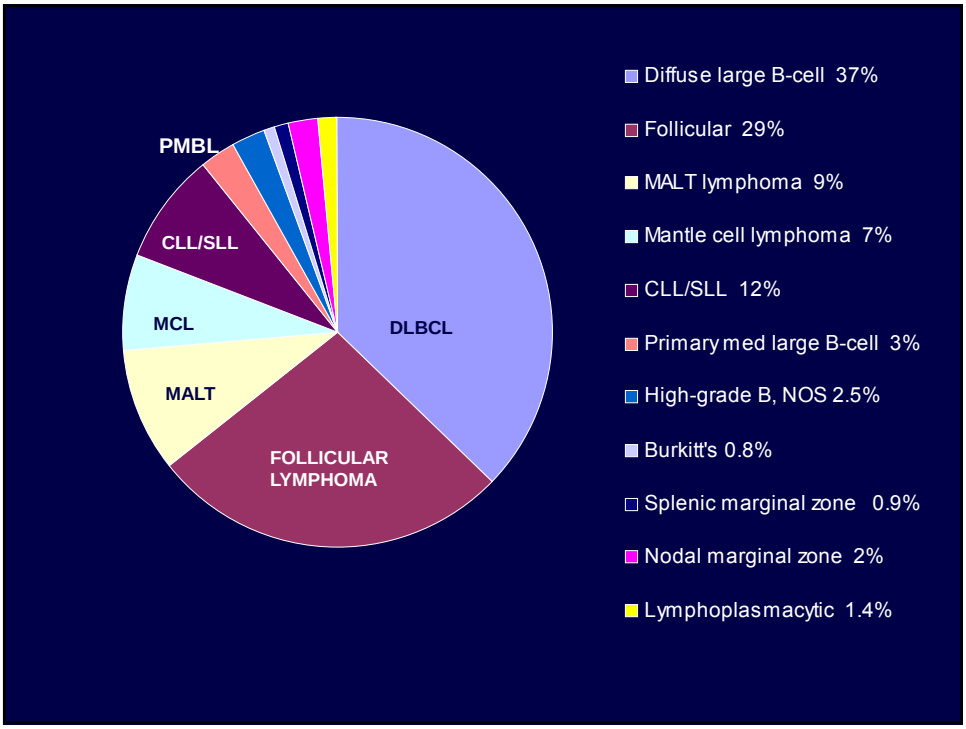


Traverse-Glehen A, et al. *Am J Surg Pathol*. 2005;29:1411-1421.

WHO 4th Edition: Classification of Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/Small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable^
- Lymphoplasmacytic lymphoma
- Heavy chain diseases
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Primary cutaneous follicle centre lymphoma
- Follicular lymphoma
- Nodal marginal zone B-cell lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphomas
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma^
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma^

^=provisional entities



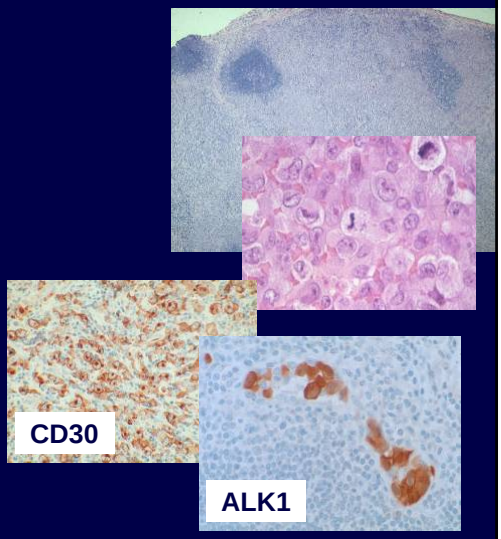
WHO 4th Edition: Mature T-Cell Neoplasms

- EBV-associated T-cell clonal lymphoproliferations (pediatric, Asian)
  - Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
  - Hydroa vacciniforme-like lymphoma
- New categories of cutaneous T-cell lymphomas (EORTC)
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma^
  - Primary cutaneous small/medium CD4-positive T-cell lymphoma^
- ALCL, ALK+ vs ALK-
  - ALK+ = a well-defined clinicopathologic entity
  - ALK- = should it be distinguished from PTCL-NOS?

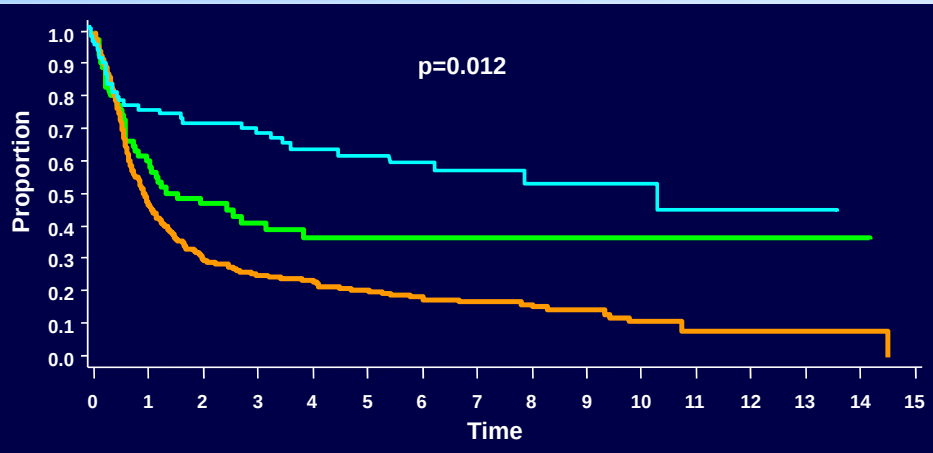
^=provisional entity

Anaplastic Large-Cell Lymphoma, ALK+

- Morphology: sinusoidal, large cells, eccentric, kidney-shaped nuclei, abundant cytoplasm with eosinophilic paranuclear region ("hallmark cells")
  - Small cell, histiocyte-rich variants
- Immunophenotype:
  - T-cell Ag+/- CD30+ ALK+
  - EMA+ CD25+ CGP+
- Genetics:
  - t(2;5) and variants
- Clinical: children and young adults, M>>F, nodal or extranodal; aggressive but curable



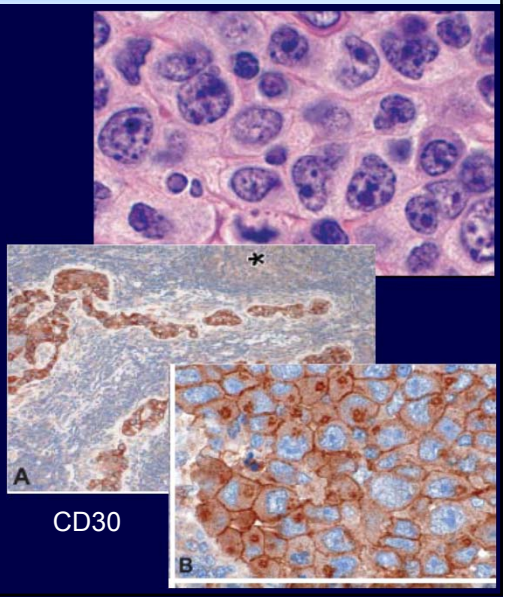
Failure-Free Survival: ALCL ALK+, ALCL ALK-, PTCL-U



Diagnosis	CENSOR	FAIL	TOTAL	MEDIAN
ALCL, ALK-	31	40	71	1.53
PTCL-U	72	258	330a	0.91
ALCL, ALK+	45	33	78	10.4

ALCL, ALK- (Provisional Category)

- Morphology:
  - Identical to ALK+ ALCL
  - Large cells with abundant cytoplasm, cohesive growth, horseshoe-shaped nuclei (“hallmark cells”)
- Immunophenotype:
  - CD30+ strong, diffuse
  - No B-cell antigens (Pax5-)
  - ALK-
- Clinical:
  - Adult (med 60y)
  - Prognosis intermediate between ALK+ and PTCL-NOS



CD30

WHO 4th Edition: Mature T/NK-Cell Neoplasms

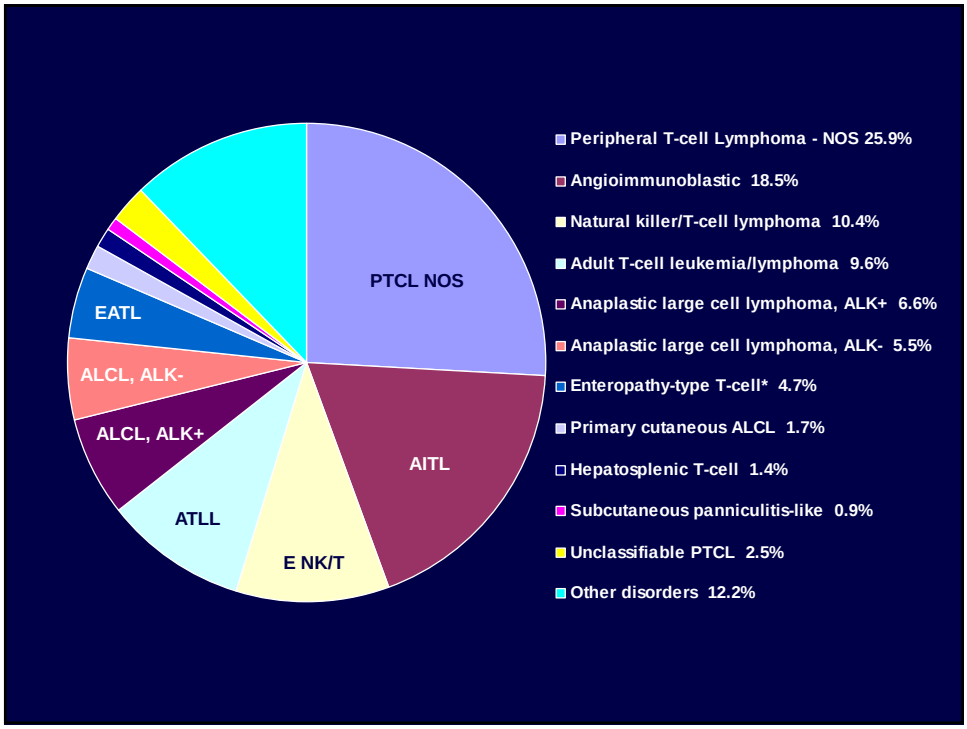
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic NK-cell lymphoproliferative disorder^
- Aggressive NK cell leukemia
- Adult T-cell leukemia/lymphoma
- Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
- Hydroa vacciniforme-like lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative^

^=provisional entities

WHO Cutaneous T-Cell Lymphomas

- Mycosis Fungoides
- Sézary Syndrome
- Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma^
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous small/medium CD4 positive T-cell lymphoma^

^=provisional entities



The WHO Classification: Summary

- An international consensus of pathologists and hematological oncologists
  - Uniform terminology and criteria standardize diagnoses for clinical trials and improve reproducibility
  - Updates by joint committees of hematopathology societies, with input from oncologists, can continue
- Multiparameter approach to disease definition
  - Morphology, immunophenotype, genetic, and clinical features
  - Clinically practical, biologically-oriented classification that can incorporate new information
- Emphasis on “real” diseases facilitates research into pathogenesis, prognosis, targeted therapies

How To Be Sure the Diagnosis is Correct: "4 Rules"

- Know the classification and diagnostic criteria for each disease
- Make sure an adequate specimen is obtained (avoid needle biopsies!)
- Read the pathology report and make sure all necessary studies have been done
- Communicate with pathologists
  - Make sure they have clinical information that may impact on diagnosis or management
  - Make sure you understand the level of certainty re: dx
  - Don't hesitate to ask for consultation
  - "A skeptical clinician is the pathologist's best friend!"

Algorithms for Immunophenotyping in Diagnosis of Mature Lymphoid Neoplasms

National Comprehensive Cancer Network

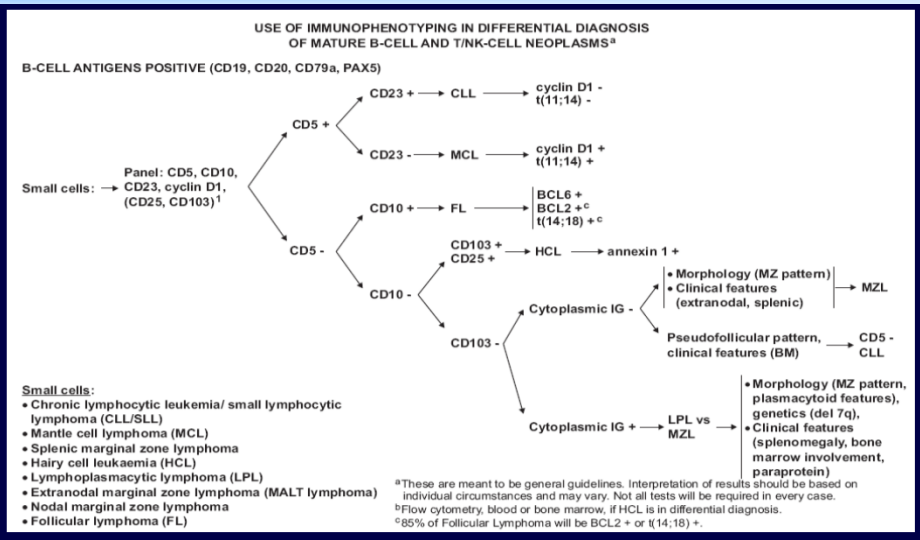
Clinical Practice Guidelines in Oncology

Non-Hodgkin's Lymphomas

www.nccn.org

Non-Hodgkin's Lymphomas

Clinical Practice Guidelines in Oncology – v.2.2009



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Things You Can Count On

- Death
- Taxes
- A new lymphoma classification!

L. Prosnitz, J. Armitage