Tumori Emolinfopoietici: il punto di vista dell'Ematologo

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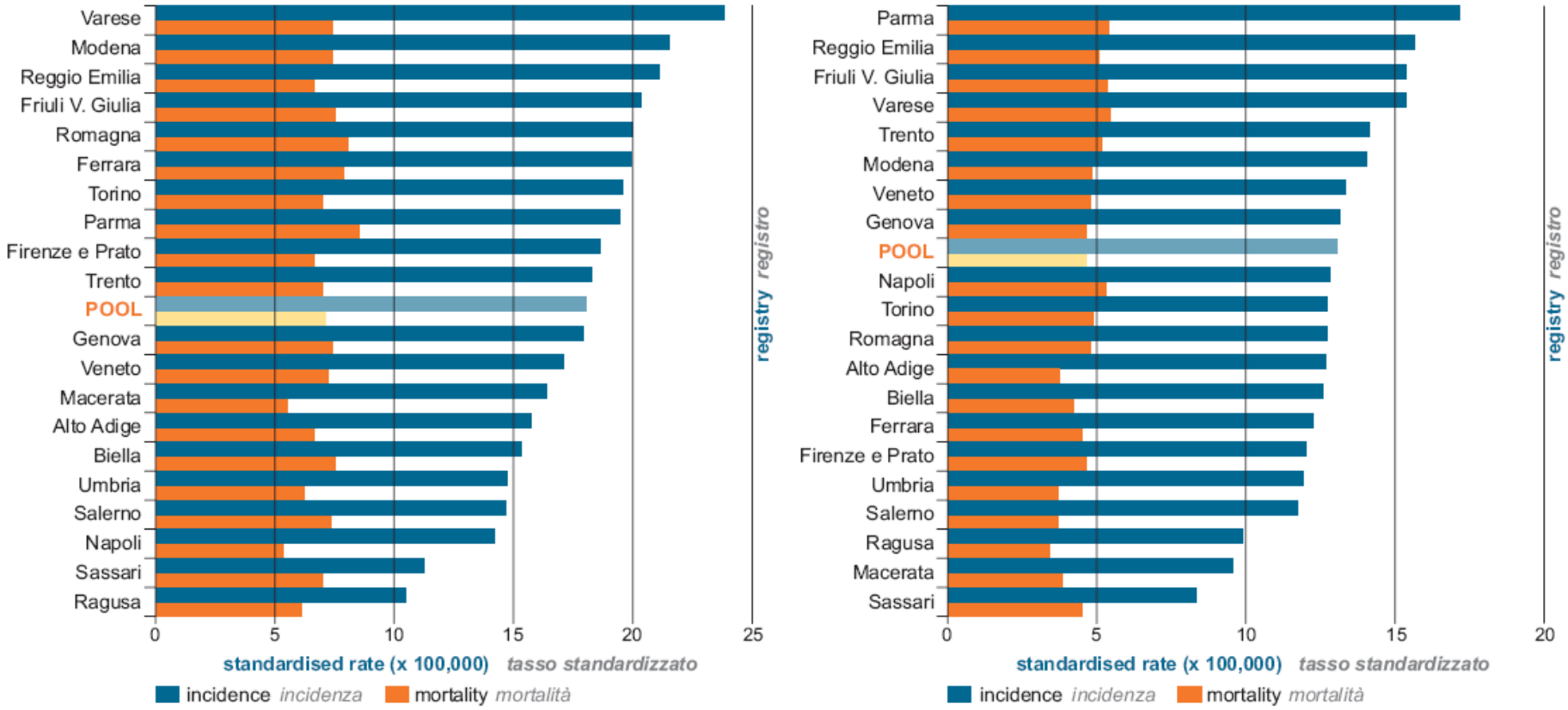
I TUMORI IN ITALIA - RAPPORTO 2006

LINFOMA NON HODGKIN



Basis of diagnosis *Modalità di diagnosi*	**n. cases**	**%**
histology *istologica*	5,548	91%
cytology *citologica*	320	5%
clinical *clinica*	228	4%
DCO *solo certificato di morte*	25	0%
	6,121	

More frequent morphologies among histologically verified cases

Morfologie più frequenti tra i casi con conferma istologica

9591	Malignant lynphoma, non Hodkin, NOS *Linfoma maligno, non Hodgkin, NAS*	1529	28%
9680	Malignant lynphoma, large B-cell, diffuse, NOS *Linfoma maligno, a grandi cellule B, diffuso, NOS*	917	17%
9590	Malignant lynphoma, NOS *Linfoma maligno, NAS*	602	11%
9700	Mycosis fungoides *Micosi fungoide*	360	6%
9670	Malignant lymphoma, small B lymphocitic, NOS *Linfoma maligno, piccoli linfociti B*	315	6%

I TUMORI IN ITALIA - RAPPORTO 2006

LINFOMA NON HODGKIN

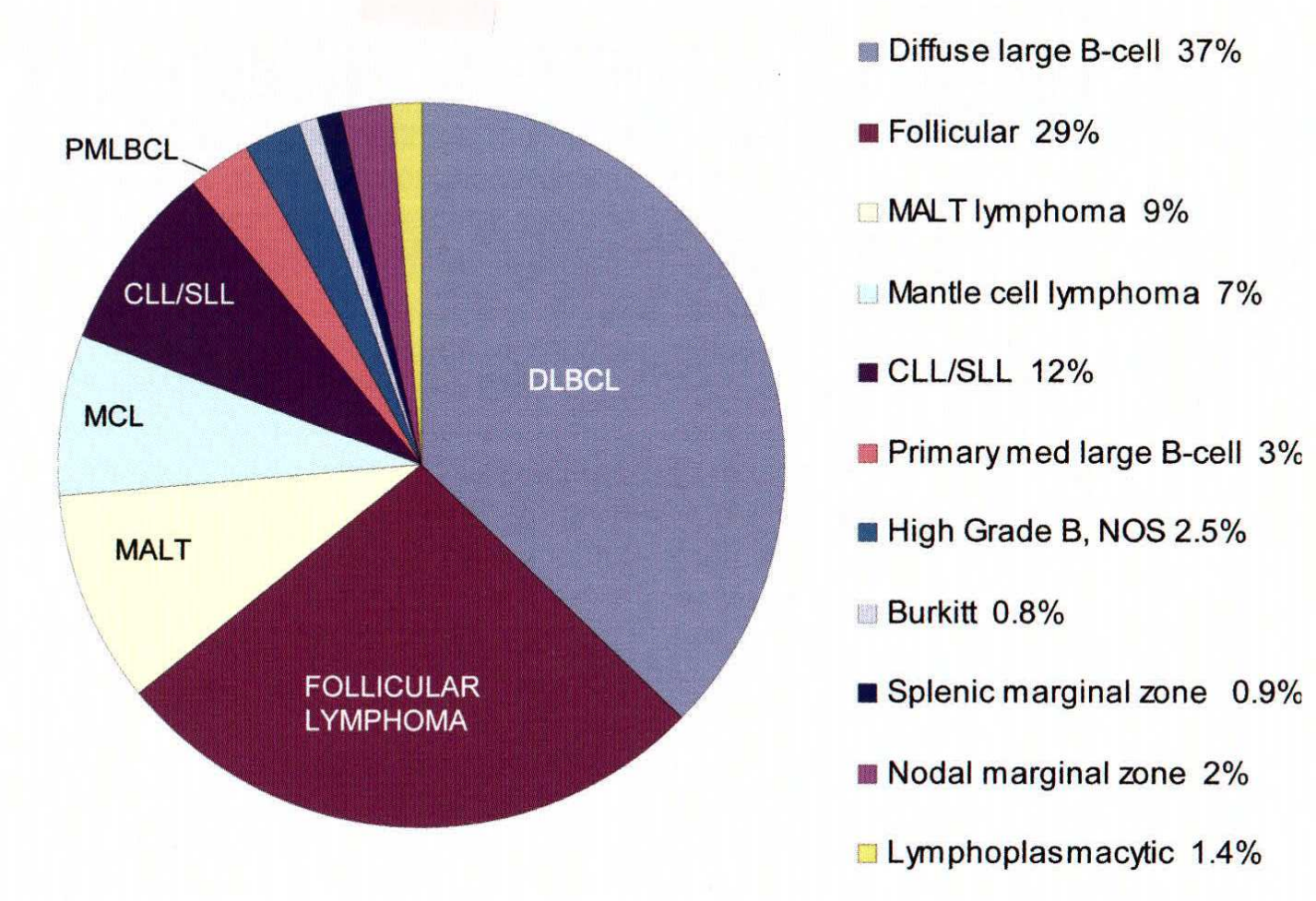
♀ Femmine Females

Basis of diagnosis *Modalità di diagnosi*	n. cases	%
histology *istologica*	5041	89%
cytology *citologica*	337	6%
clinical *clinica*	242	4%
DCO *solo certificato di morte*	41	1%
	5661	

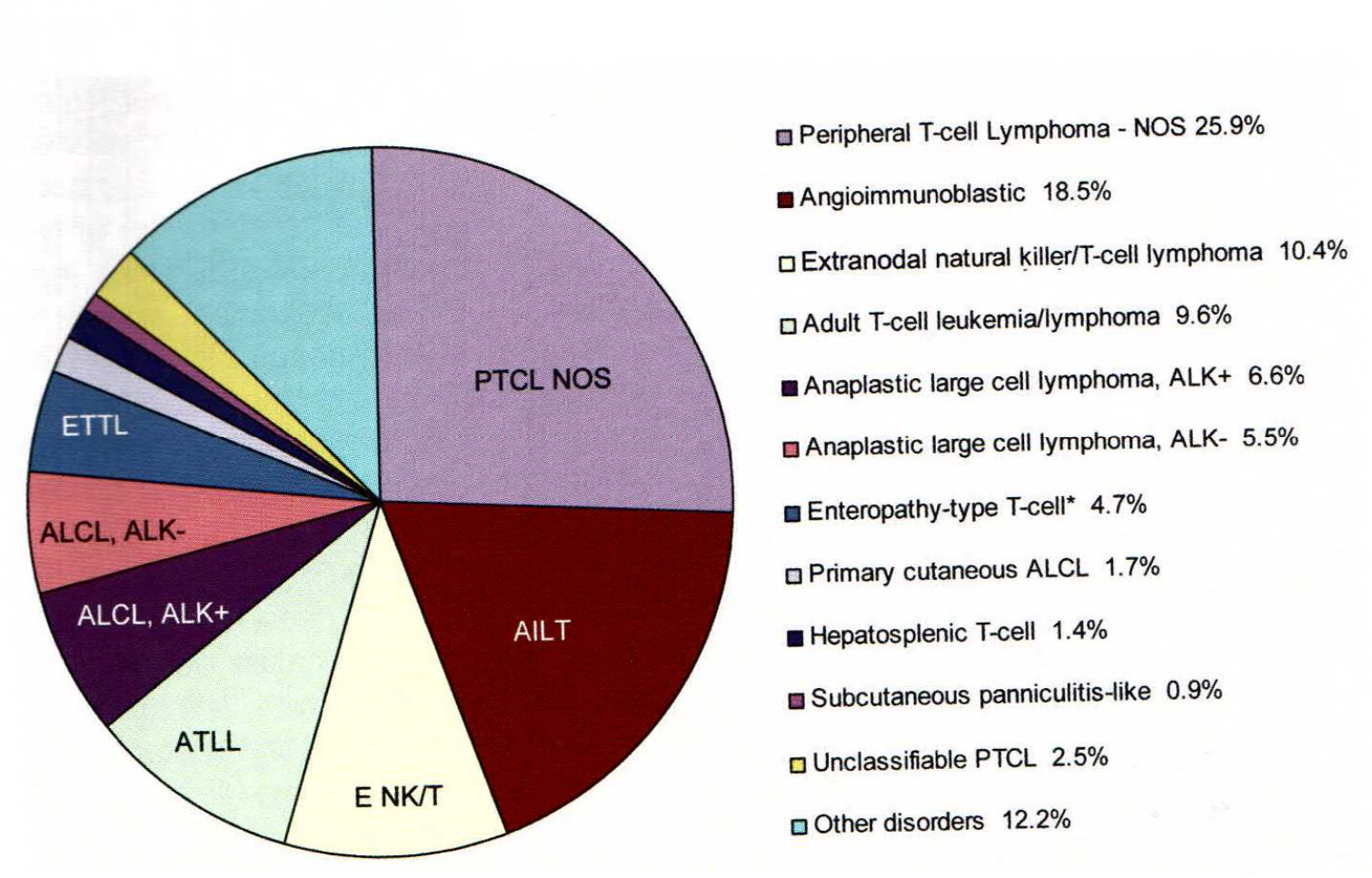
More frequent morphologies among histologically verified cases
Morfologie più frequenti tra i casi con conferma istologica

9591	Malignant lynphoma, non Hodkin, NOS *Linfoma maligno, non Hodgkin, NAS*	1494	30%
9680	Malignant lynphoma, large B-cell, diffuse, NOS *Linfoma maligno, a grandi cellule B, diffuso, NOS*	887	18%
9590	Malignant lynphoma, NOS *Linfoma maligno, NAS*	580	12%
9690	Follicular lymphoma, NOS *Linfoma maligno nodulare, NAS*	330	7%
9670	Malignant lymphoma, small B lymphocitic, NOS *Linfoma maligno, piccoli linfociti B*	263	5%

Relative frequencies of B-cell lymphoma subtypes in adults



Relative frequencies of mature T-cell lymphoma subtypes in adults



Why do we need a lymphoma classification?

- There are several subtypes of lymphoma
- Not all lymphomas share the same clinical behaviour and prognosis
- Treatment depends on specific histologic features
- Allows the comparison of clinical trial results
- Essential to study etiology, pathogenesis, risk factors, and epidemiology of lymphomas

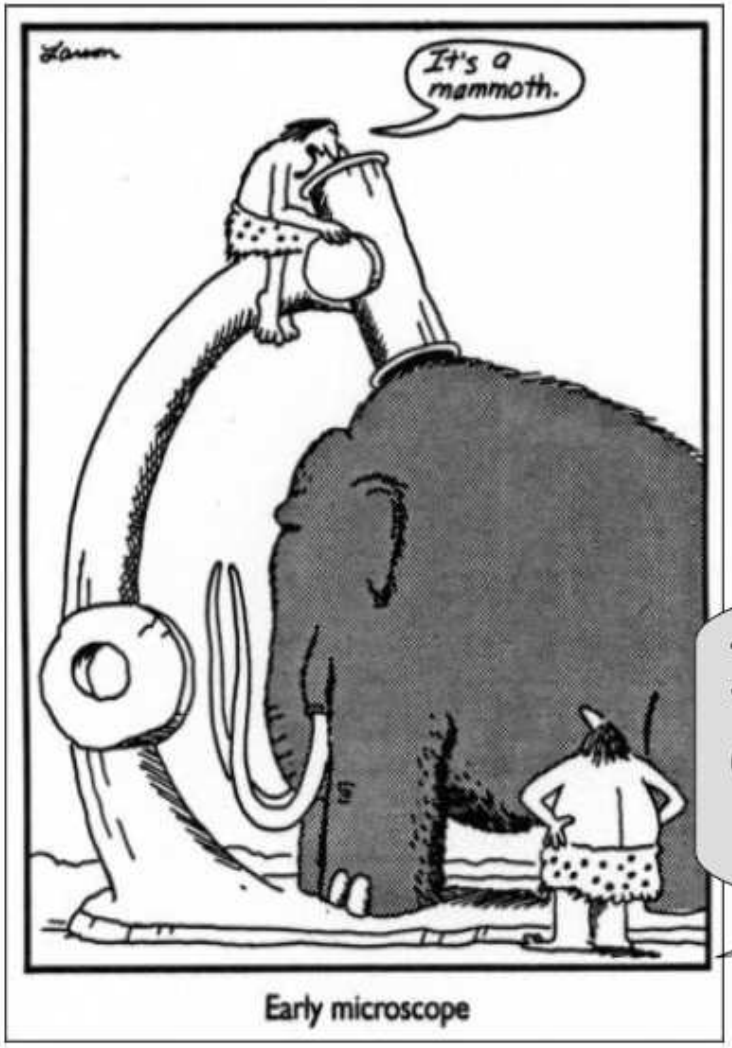
Requisites of a Classification

- Easy to apply
- Minimal intra-and inter observer variability
- Must give relevant clinical information relating to pathogenesis and prognosis
- Must be validated in prospective studies
- Must be a dynamic process that can integrate clinical(prognosis, therapy) and pathological advances(immunology, genetics)

Evolution of Lymphoma Classification

- Rappaport (considered cytological and architectural features)
- Lukes and Collins (immunophenotype)
- Kiel Classification(Europe)
- Working Formulation(USA)
- REAL Classification(1992)
- WHO classification(2001)
- Update of WHO classification(2008)

Principles of the WHO classification

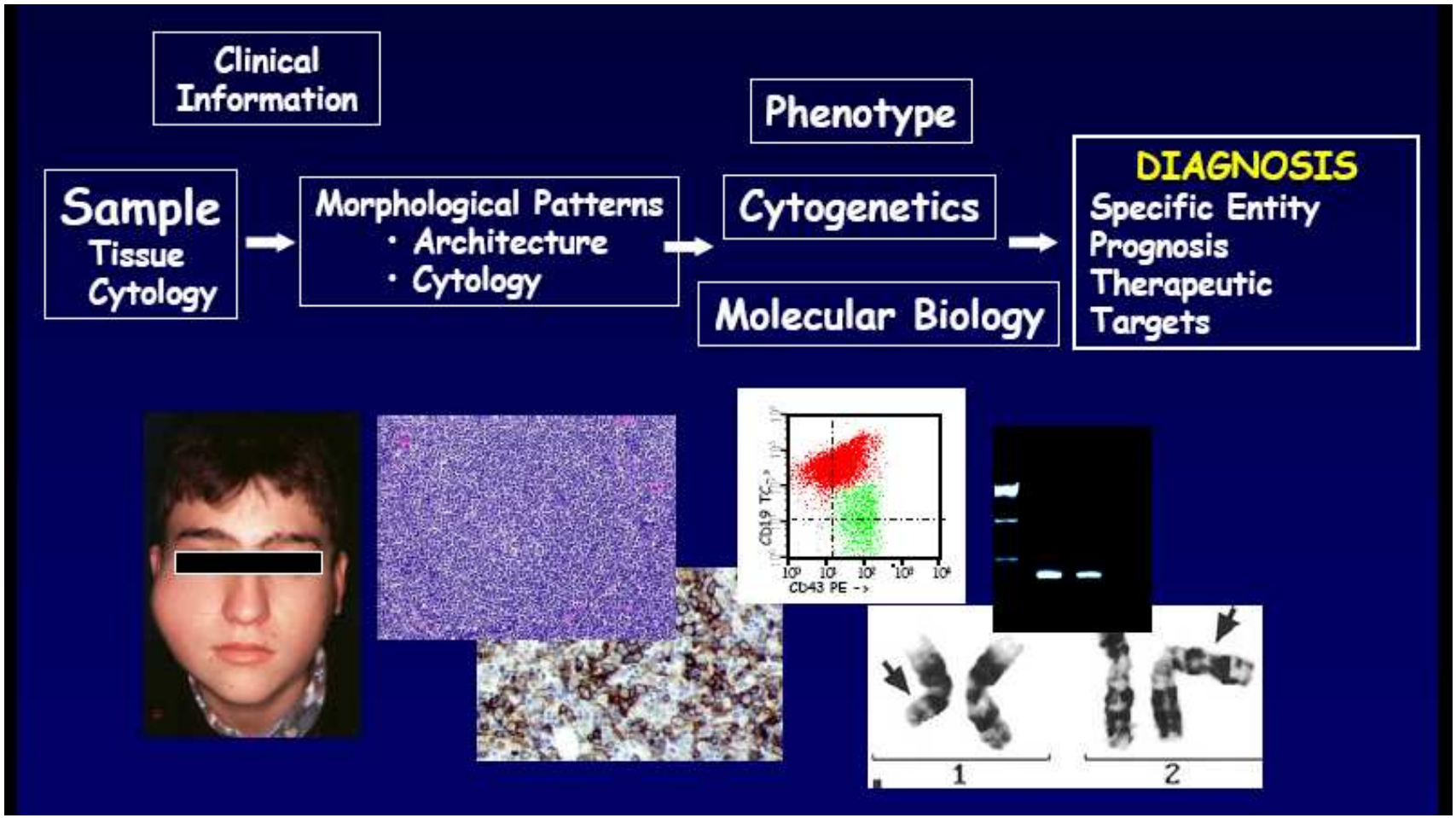


1. Morphology
2. Immunophenotype
3. Molecular biology
4. Genetic
5. Clinical presentation and course

Revised WHO classification (2008)
What changed?

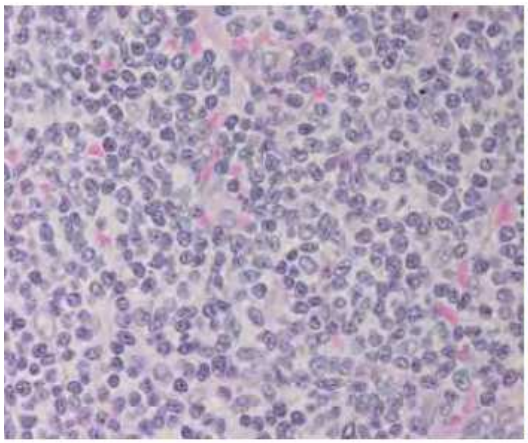
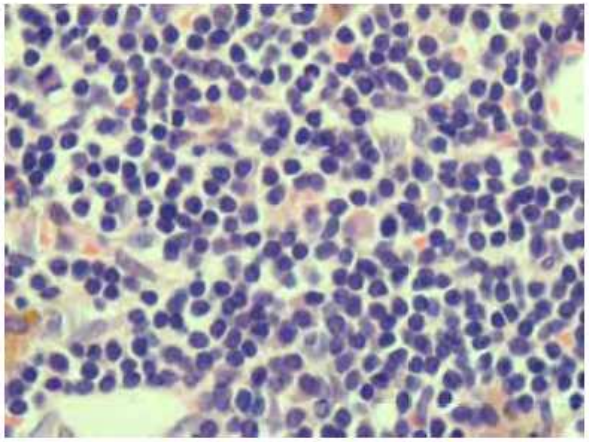
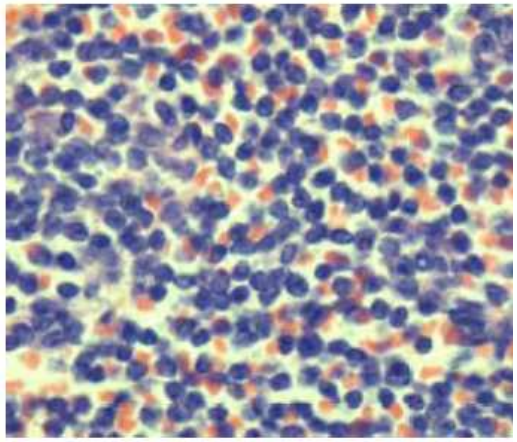
Hodgkin lymphoma	Minor changes
Mature B cell neoplasms	Some changes!
Mature T-cell and NK-cell neoplasms	Minor changes (unfortunately!)

Approccio integrato alla diagnosi



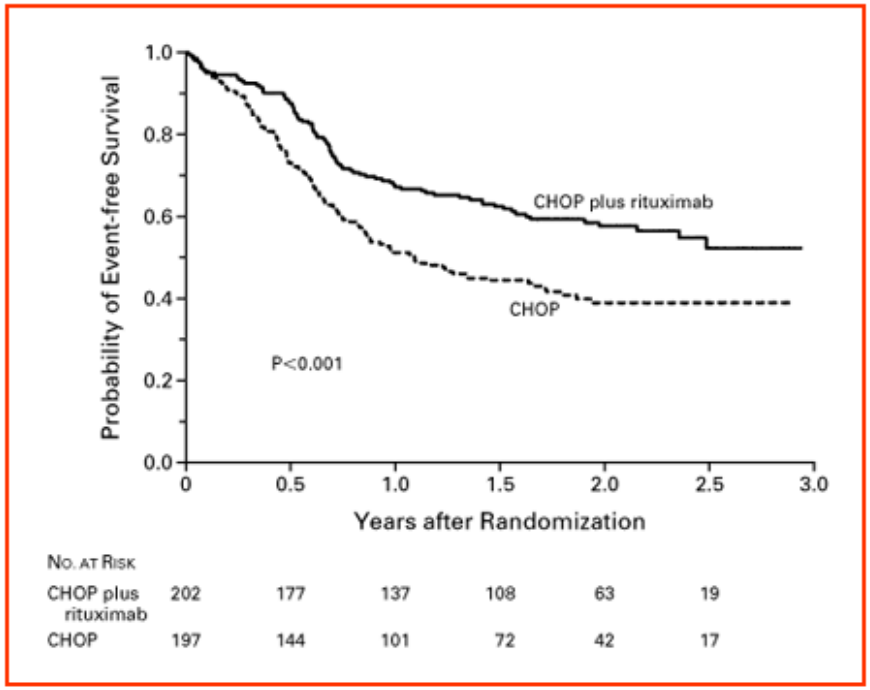
Courtesy of Prof. S.A. Pileri

Immunophenotype

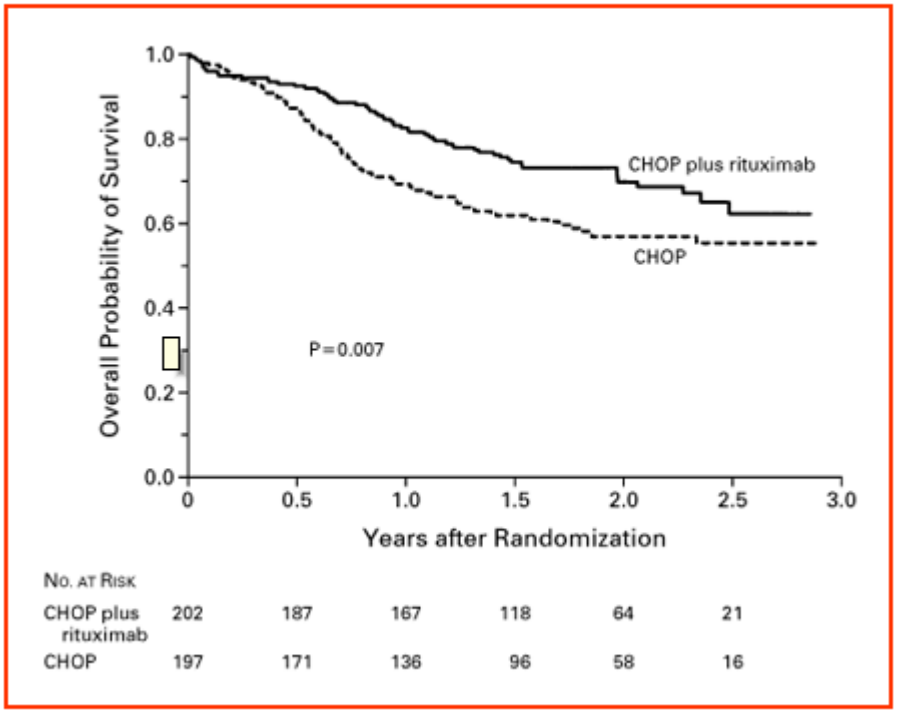




	CD5	CD23	CD10	Cyclin D1
CLL	+	+	-	-
Marginal zone lymphoma	-	-	-	-
Mantle cell lymphoma	+	-	-	+
Follicular lymphoma	-	-	+	-

Event-Free Survival



Overall Survival

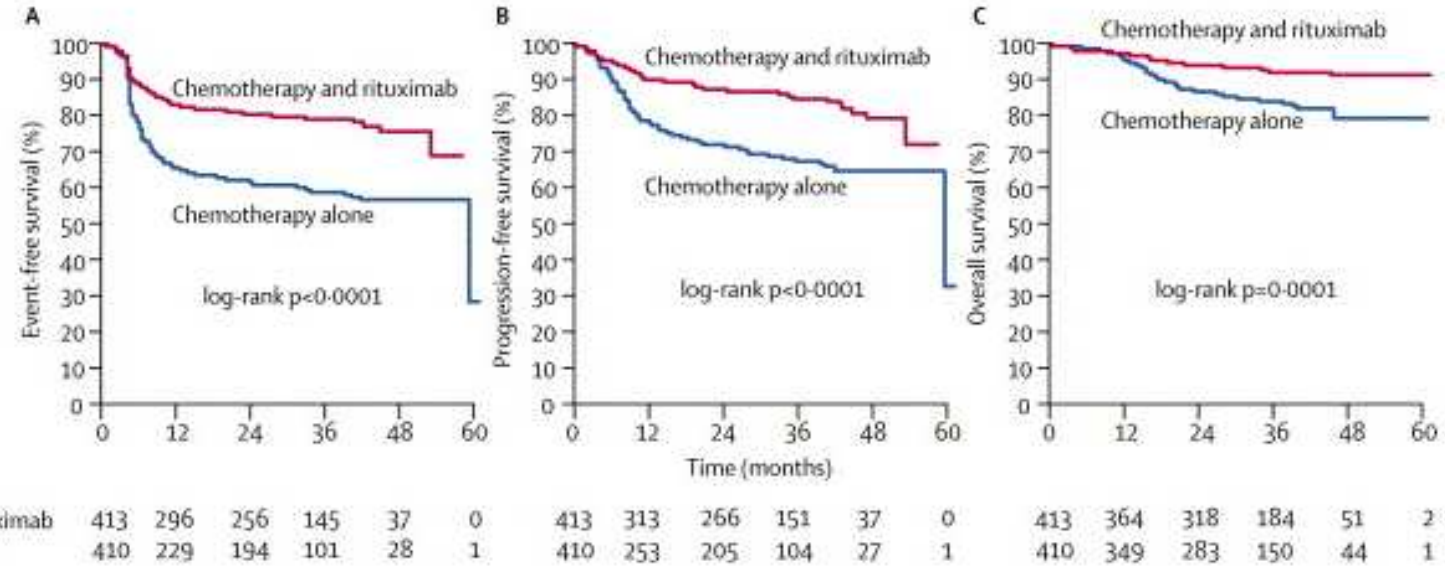


CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma

Coiffier et al. NEJM,2005 346 (4): 235

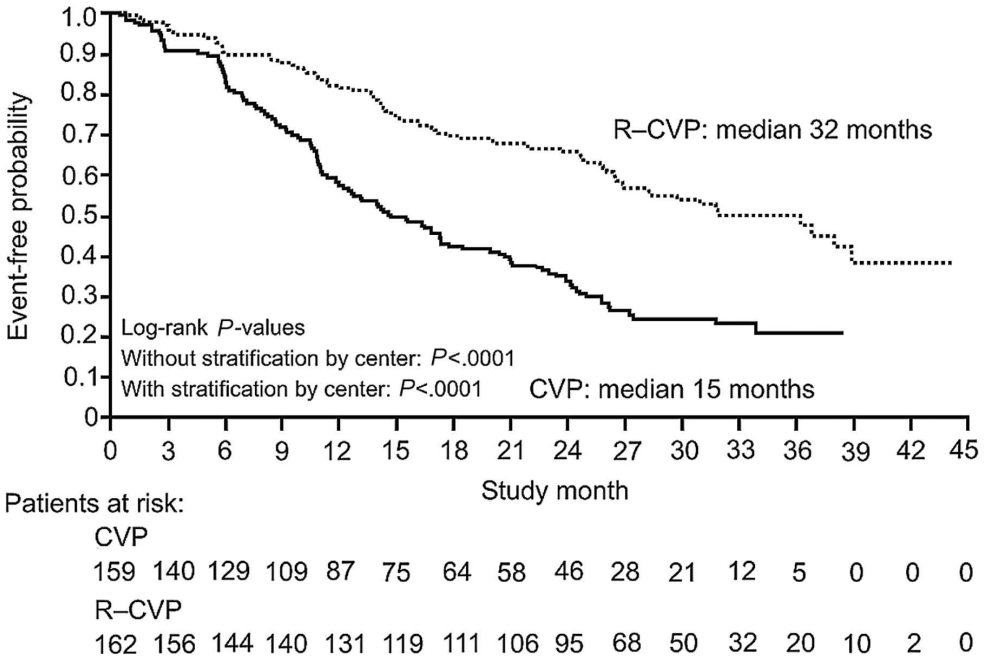
CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group

EFS **PFS** **OS**

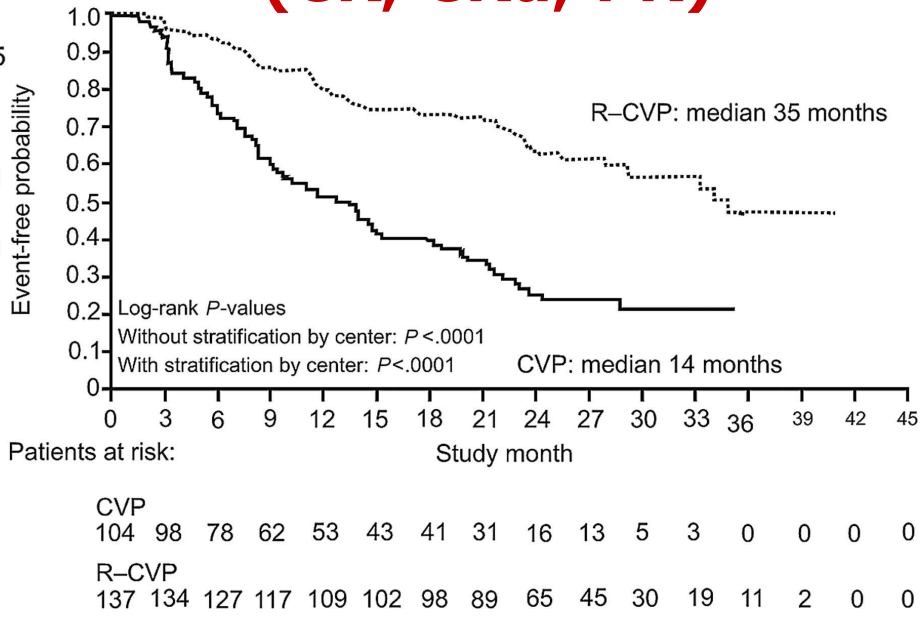


M. Pfreundschuh, Lancet Oncology, 2006

Time to disease progression, relapse or death



Duration of response (CR, CRu, PR)



Marcus, R. et al. Blood 2005;105:1417-1423

Chromosomal translocations in B-NHL

Lymphoma Type	*Chromosomal Alteration*	*Oncogene Involved*	*Mechanism of Oncogene Activation*
Follicular	t(14;18)(q32;q21)	BCL2	Transcriptional deregulation
MALT	t(11;18)(q21;q21)	API2/MALT1	Fusion protein
	t(1;14)(p22;q32)	BCL10	Transcriptional deregulation
	t(14;18)(q32;q21)	MALT1	Transcriptional deregulation
Mantle cell	t(11;14)(q13;q32)	BCL1	Transcriptional deregulation
B-DLCL	3q27 translocations	BCL6	Transcriptional deregulation
Burkitt's	t(8;14)(q24;q32)	c-MYC	Transcriptional deregulation

Chromosomal translocations in T-NHL

Lymphoma Type	*Chromosomal Alteration*	*Oncogene Involved*	*Mechanism of Oncogene Activation*
Anaplastic large cell	**t(2;5)(p23;35) t(1;5)(q25;p23) t(2,3)(p23;q35)**	**ALKNPM**	**Fusion protein**

Working formulation, 1982

Malignant Lymphoma

Low-grade

A. Small lymphocytic (consisted with CLL, plasmacytoid)

B. Follicular (predominantly small cleaved, diffuse areas, sclerosis)

C. Follicular (small cleaved and large cell, diffuse areas, sclerosis)

Intermediate-grade

D. Follicular (predominantly large cell)

E. Diffuse (small cleaved cell, sclerosis)

F. Diffuse (mixed, small and large cell, sclerosis, epithelioid component)

G. Diffuse (large cell, cleaved and non-cleaved)

High grade

H. Large cell (immunoblastic: plasmacytoid, clear cell, polymorphous, epithelioid component)

I. Lymphoblastic (convoluted, non-convoluted)

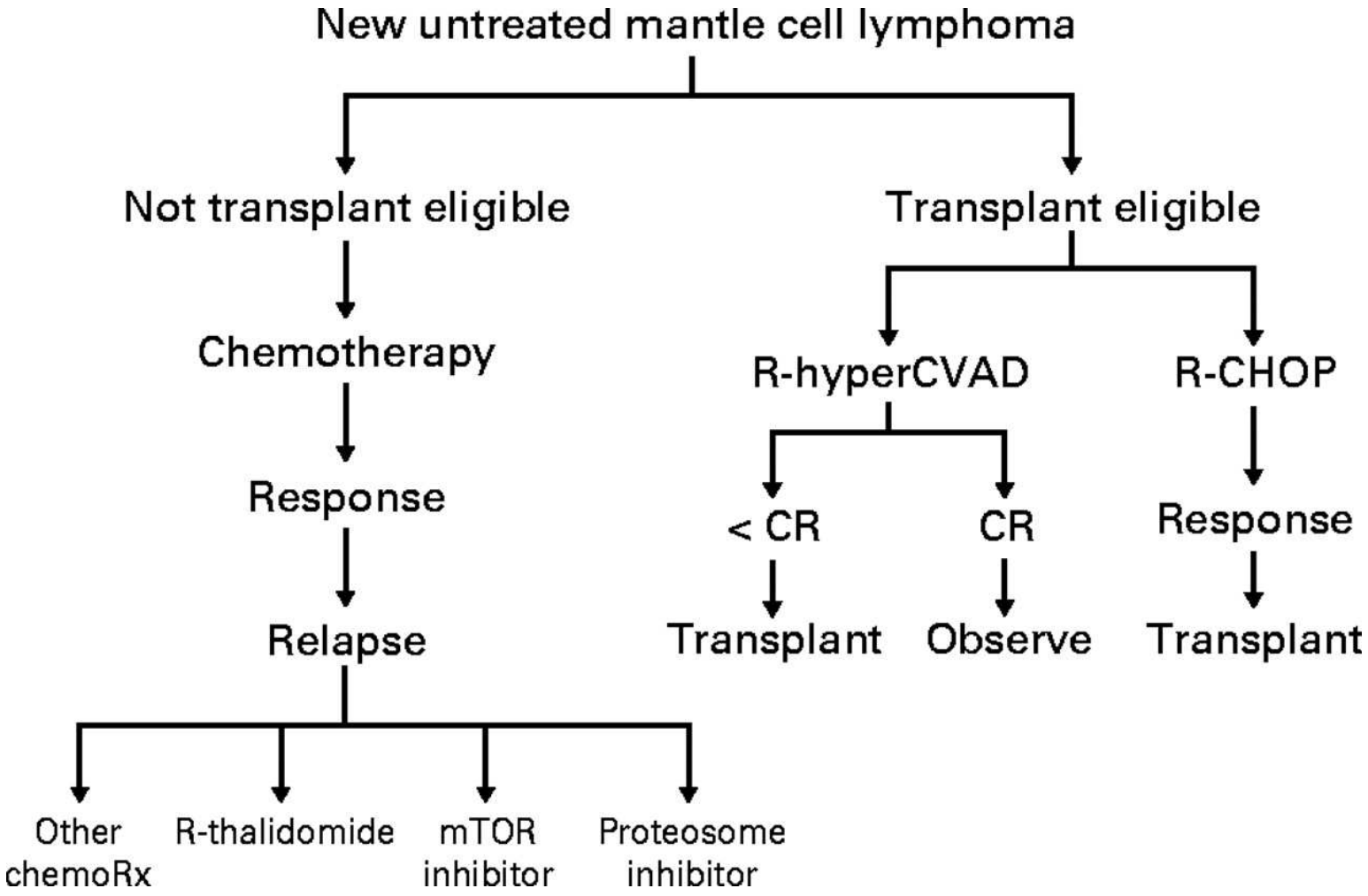
J. Small non-cleaved cell (Burkitt's, follicular areas)

Courtesy of Prof. S.A. Pileri

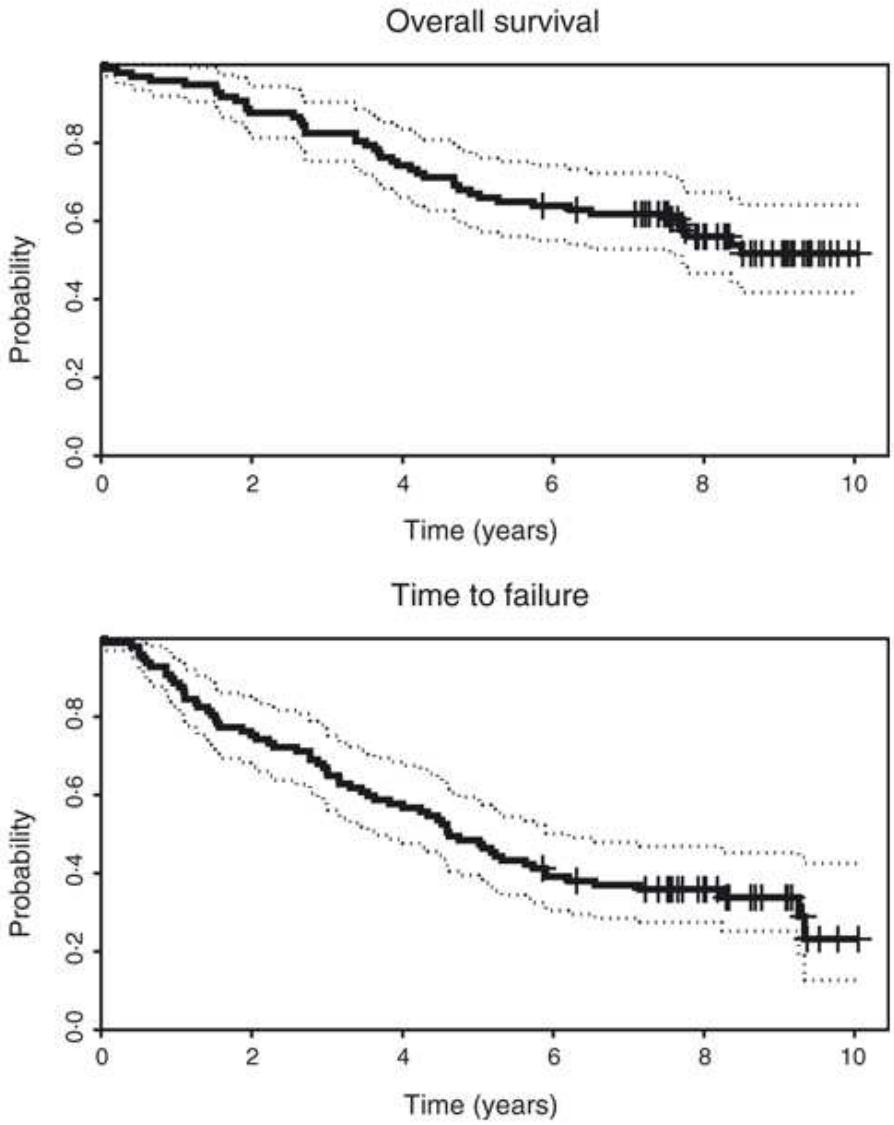
Mantle Cell Lymphoma

- **Aggressive variants**
  - Blastoid (cells resemble lymphoblasts). Mitosis and ki-67 index are prognostic important
  - Pleomorphic
- **Other variants**
  - Small cell(cells resemble cells of CLL)
  - Marginal zone-like

Outline of treatment approaches for patients with MCL



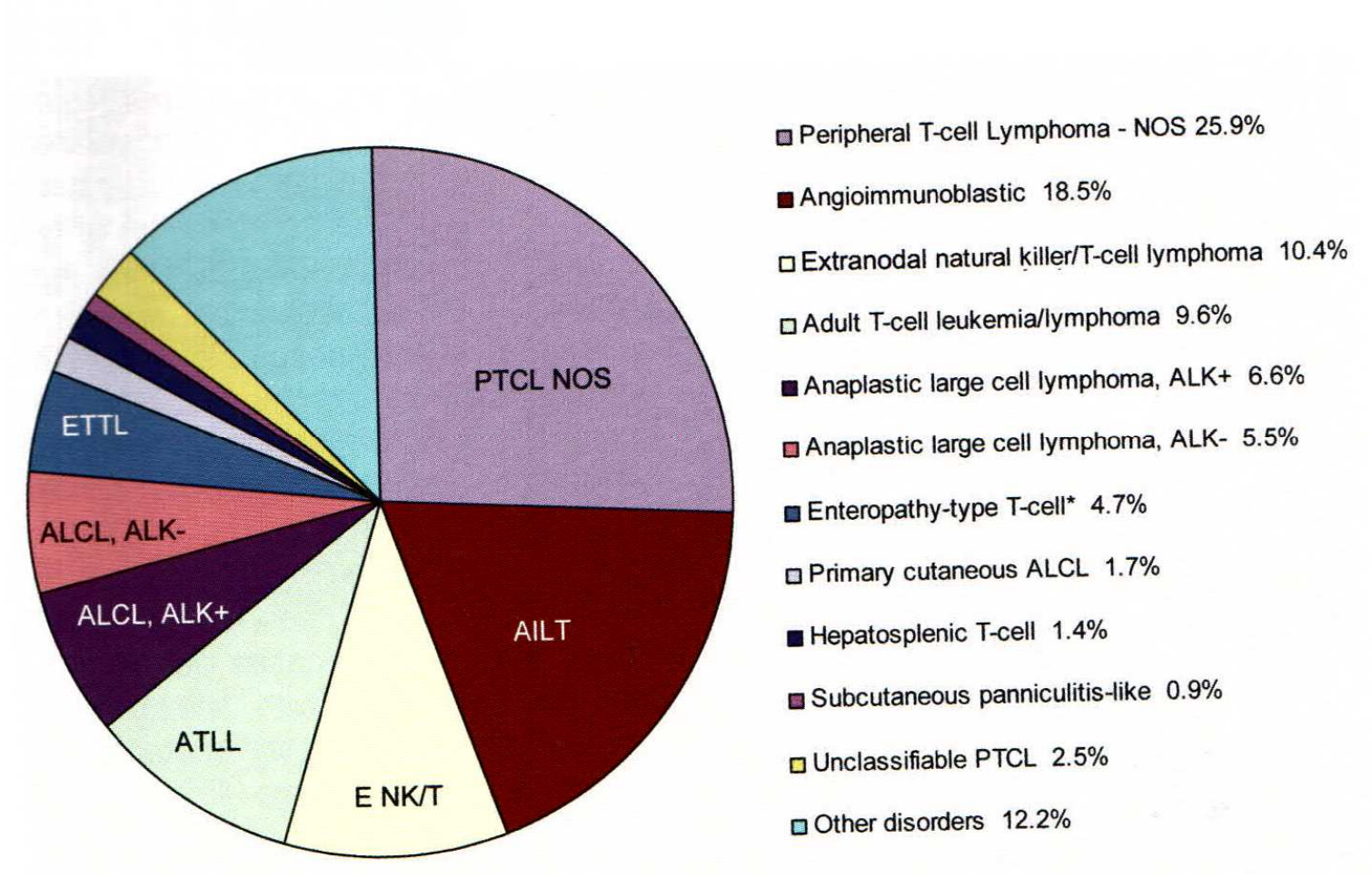
Witzig, T. E. J Clin Oncol; 23:6409-6414 2005



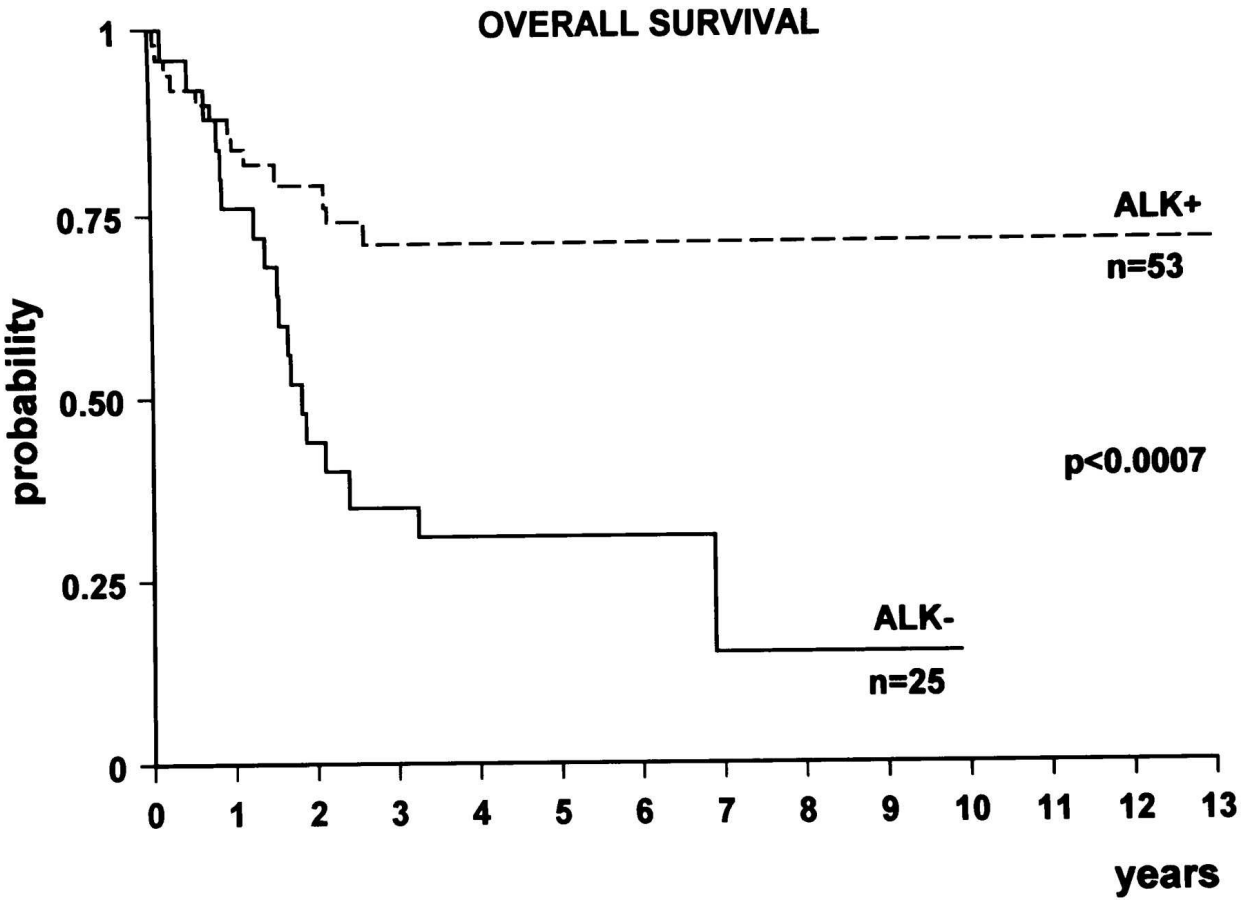
OS and TTF in 97 patients treated with R hyper-CVAD alternating with R M/A

JE. Romaguera et al, BJH, May, 2010

Relative frequencies of mature T-cell lymphoma subtypes in adults



Overall Survival of ALK-positive and negative patients



Falini, B. et al. Blood 1999;93:2697-2706

WHO Classification 2001: Mature Aggressive B-cell lymphoma

DLBCL variants

- ✓Centroblastic
- ✓Immunoblastic
- ✓T-cell/histiocyte rich
- ✓Anaplastic

Burkitt lymphoma

Burkitt-like

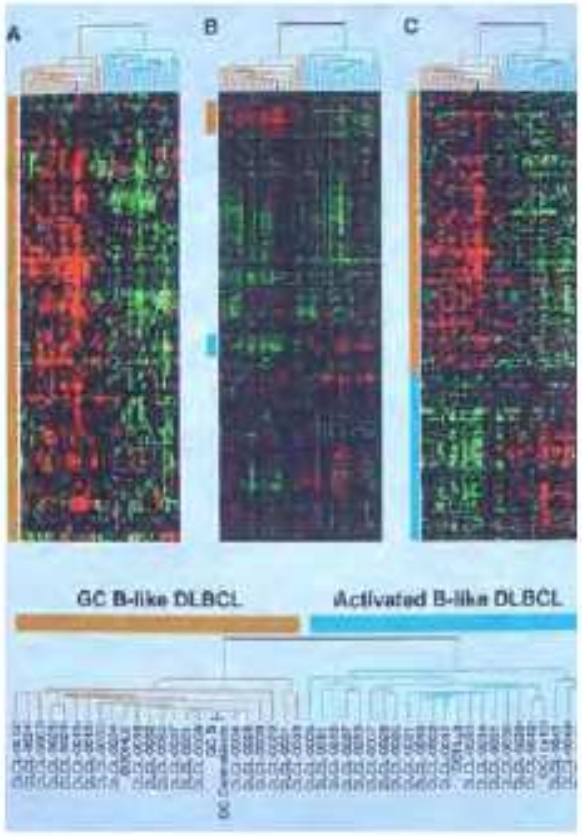
DLBCL subtypes

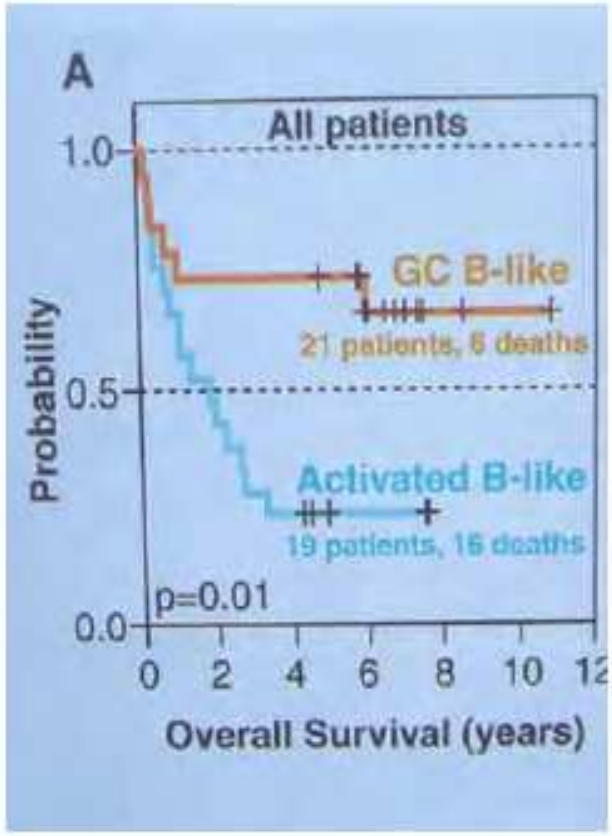
- ✓Mediastinal (thymic) large B-cell lymphoma
- ✓Intravascular large B-cell lymphoma
- ✓Primary effusion lymph.

Diffuse Large B-Cell Lymphoma

- **Common morphologic variants**
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- **Rare morphologic variants**
- **Molecular subgroups**
  - Germinal centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)
- **Immunohistochemical subgroups**
  - CD5-positive DLBCL
  - Germinal centre B-cell-like (GCB)
  - Non-germinal centre B-cell-like (non-GCB)

Diffuse Large B-Cell Lymphoma





Alizadeh AA et al.: Distinct type of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000, 403:503

Burkitt Lymphoma (WHO 2001)

- ✓ **Classical Burkitt Lymphoma**
  - ❑ **Endemic**
  - ❑ **Sporadic**
  - ❑ **Variant**
- ✓ **Burkitt Lymphoma with plasmacytoid appearance (HIV+)**
- ✓ **Atypical Burkitt lymphoma and Burkitt-like Lymphoma**

Burkitt lymphoma(WHO 2008)

- No single parameter can be used as a gold standard for the diagnosis (morphology, immunophenotype, genetic analysis)
- **CD10+, Bcl2-, bcl6+, ki67~100%**
- Most cases **(90%)** have a **MYC translocation**
- Gene profiling studies have demonstrated a consistent gene signature for BL, which his clearly distinct from DLBCL. However intermediate cases were also found.

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL

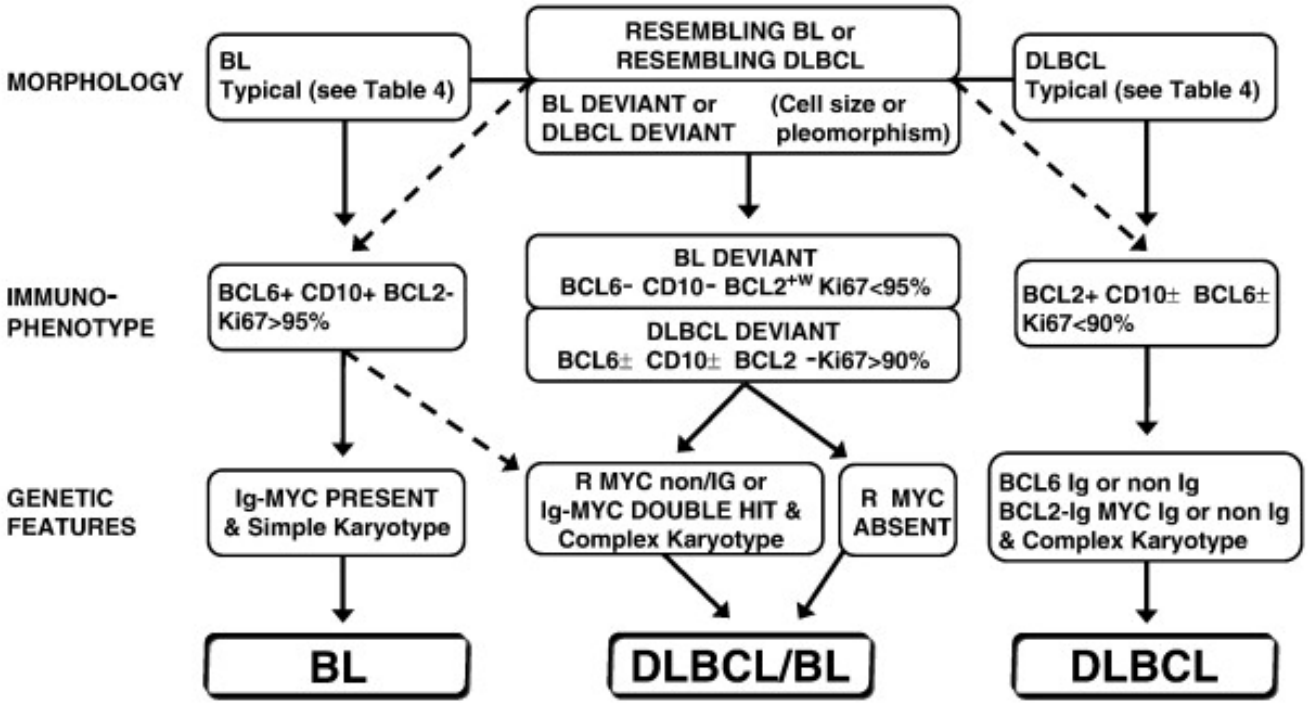
- This is a heterogeneous category that is not considered a distinct disease entity, but is useful in allowing the classification of cases not meeting criteria for classical BL or DLBCL
- This diagnosis should not be made in morphological typical DLBCL with MYC translocation
- This diagnosis should not be made in morphological typical BL without MYC translocation
- 30-50% have non-IG-MYC translocation and 15% have BCL2 translocation

Diagnostic features of DLBCL, BL and B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL ("gray zone").

	DLBCL	gray zone	BL
Morphology	Variable, ranging from medium-sized to large, pleiomorphic nuclei with a large morphological range	BL-like morphology wit or without large cells	Cohesive, starry-sky, medium-sized, round nuclei with multiple small nucleoli
Immunophenotype	BCL-2, CD10, BCL-6, MUM-1 highly variable Ki-67 30->95%	BCL-2 often strong, CD10 mostly+, BCL-6 mostly +, MUM-1 variable Ki-67 50->95%	BCL-2-, CD10+, BCL-6+, MUM-1 variable Ki-67 >95%
MYC translocation	5-15%	80%	90-100%
Non*IG* partner in *MYC* translocation	40%	40%	None
BCL2 translocation	20-30%	45%	No
BCL6 translocation	30%	9%	No
Simple karyotype	Rarely	Rarely	Typical
Complex karyotype	Generally	Generally	No

Haematologica. **2009 July; 94(7): 894–896**

Algorithm for diagnosis



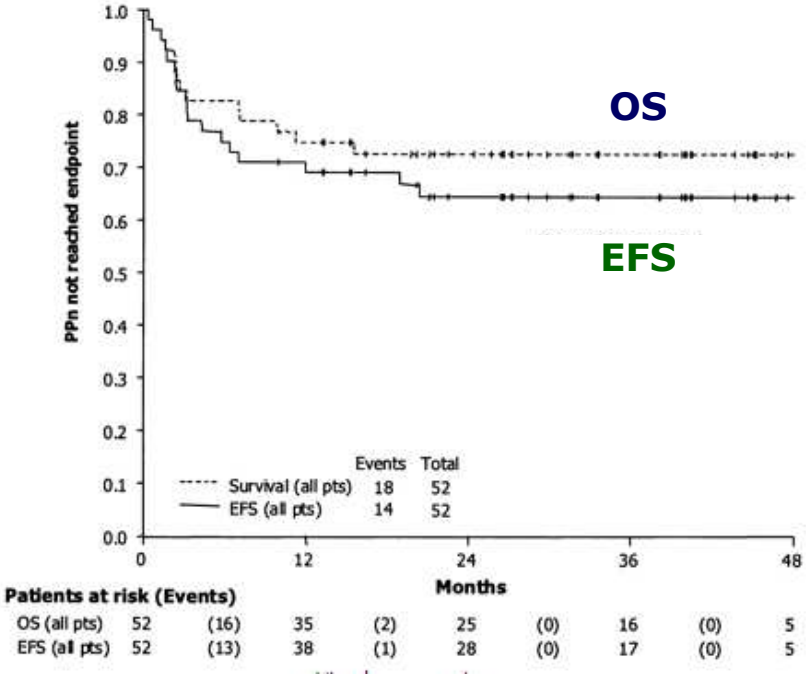
Carbone A., Human Pathology Vol 41 Issue 5
May 2010, Pages 621-631

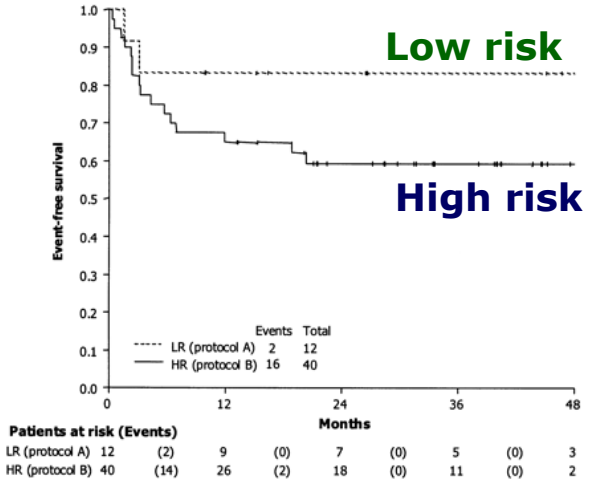
Algorithm for diagnosis in cases with intermediate morphology, and CD10 and BCL6 expression

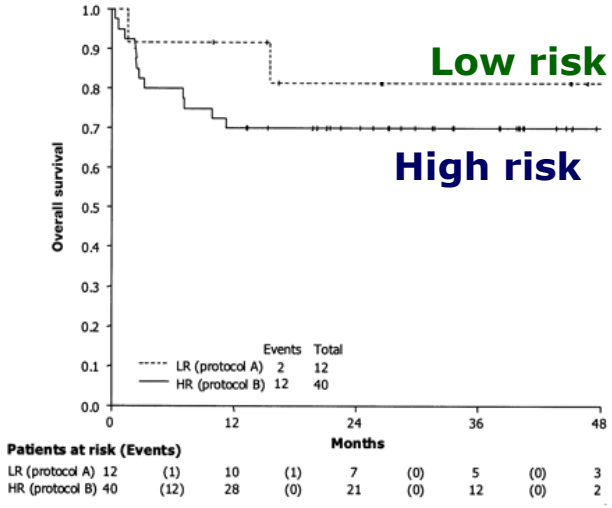
Favours diagnosis of BL	BCL2-negative
	Ki-67>95%
	IG-MYC rearrangement (simple karyotype)
Favours diagnosis of intermediate DLBCL/BL	BCL2-positive
	Ki-67<95%
	IG-MYC rearrangement
	non-IG-MYC rearrangement
	MYC&BCL2-rearrangements (double-hit)
	(complex karyotype)
Favours diagnosis of DLBCL	BCL2-positive
	Ki-67<90%
	MYC-negative rearrangement
	BCL6-rearrangement
	BCL2-rearrangement

Hematol Oncol 2009; 27: 182–185

An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study



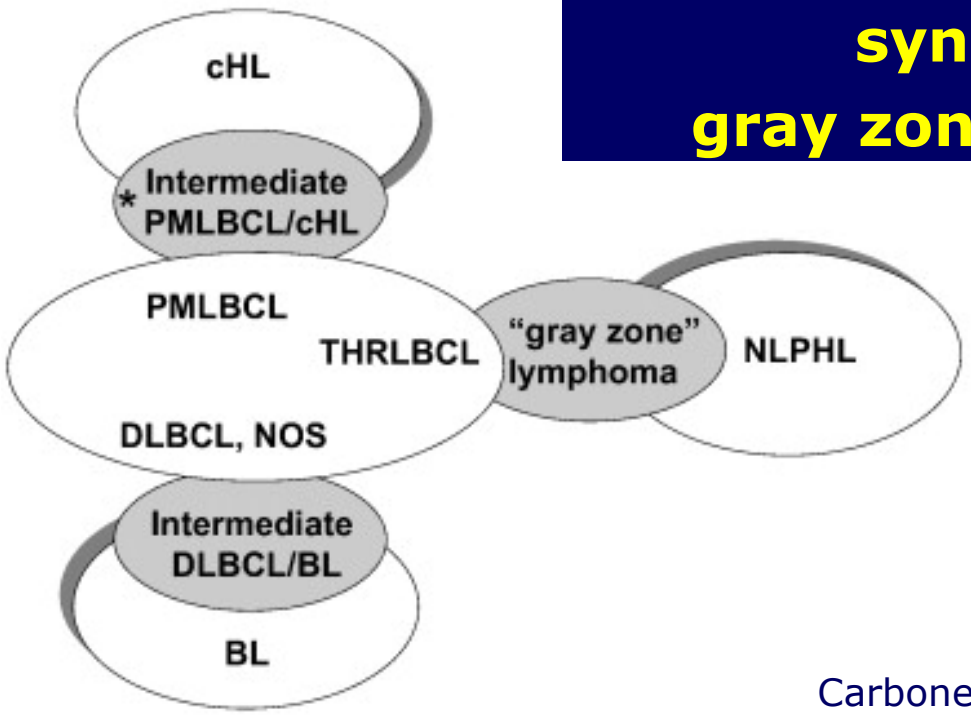




Mead GM, Annal oncol, 2002

Provisional borderline categories for B-cell lymphomas that do not clearly fit into one entity

The intermediate PMLBCL/cHL category is synonym of gray zone lymphoma.



Carbone A., Human Pathology Vol 41 Issue 5
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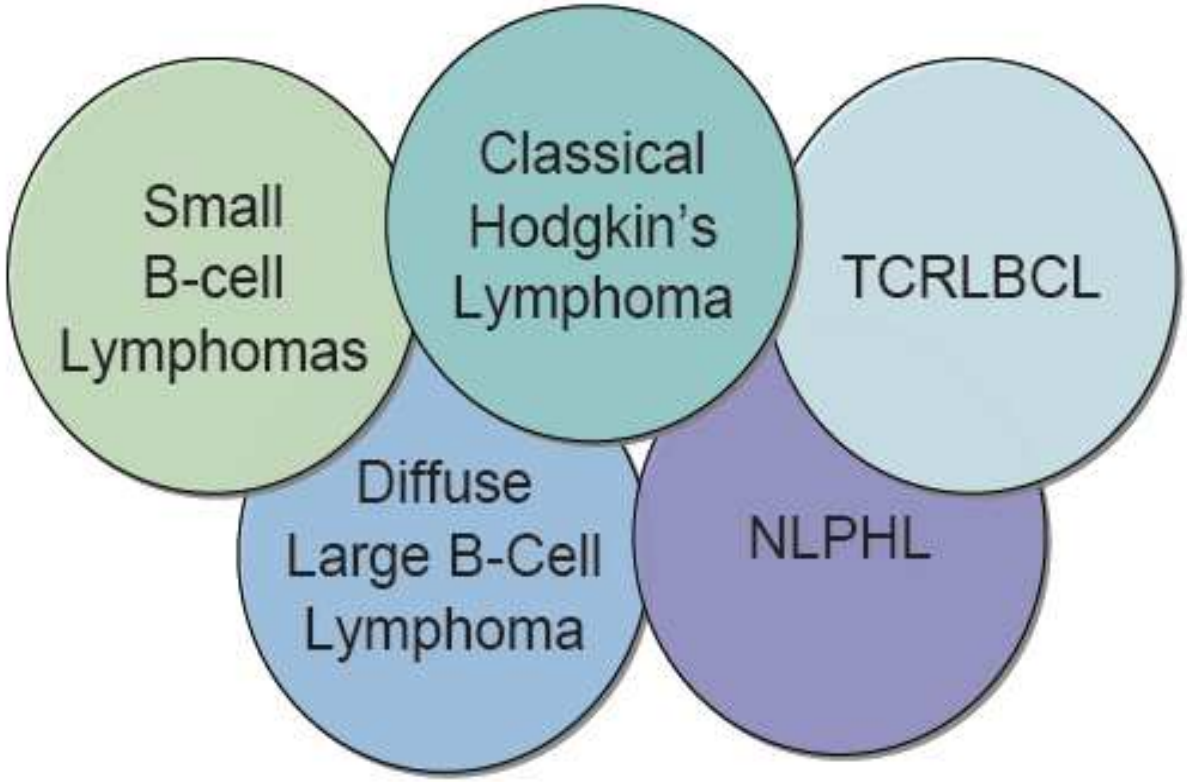
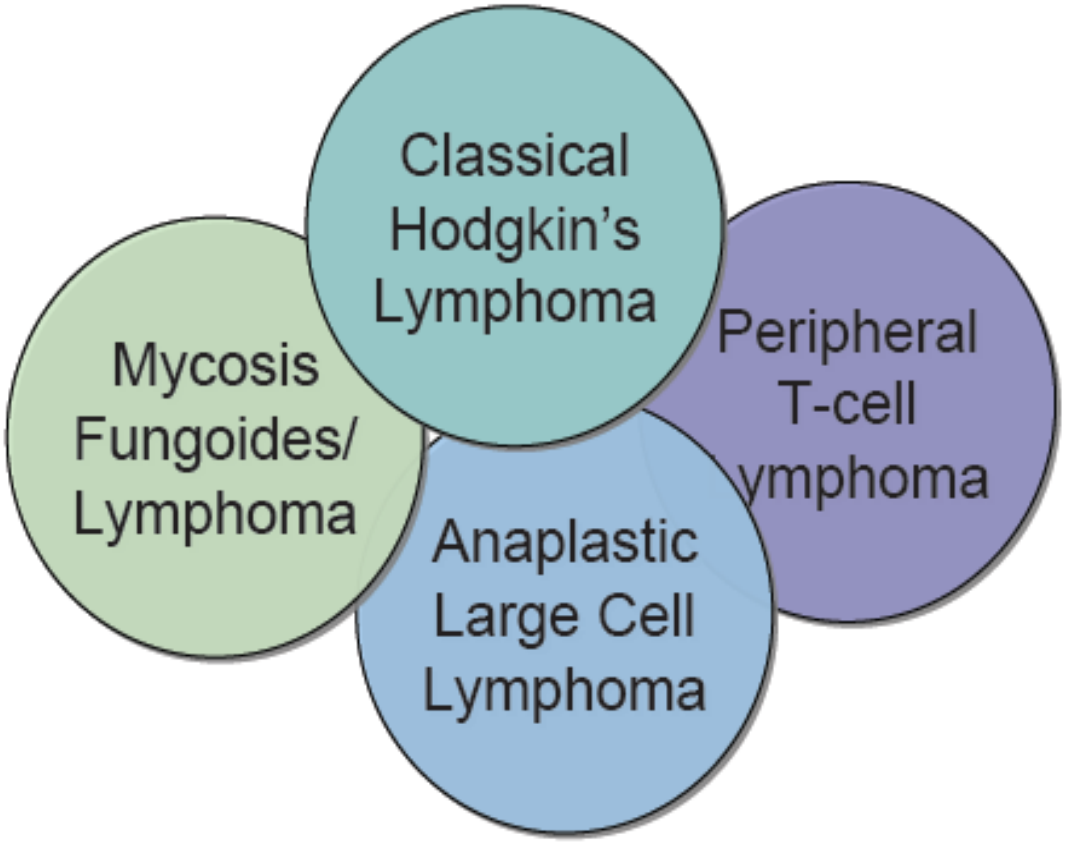
Biologic gray zones in HL and NHLs



HL is derived from an altered B lymphocyte. The precise molecular events that result in the Reed-Sternberg cell are not fully elucidated; however, it is likely that these events can occur *de novo*, in a normal B cell, or secondarily, in a neoplastic B cell. Therefore, biologic interfaces are indentified beetween HL and diverse subtypes of B-cell lymphoma. NLPHL, nodular lymphocyte-predominant HL; TCRLBCL, T-cell-rich B-cell lymphoma.

From E.S.Jaffe and W.H.Wilson, 2004

Morphologic gray zones in HL and NHLs



In contrast to true biologic interfaces, morphologic interfaces occur between HL and other non-Hodgkin lymphomas. These morphologic interfaces may cause problems in differential diagnosis, but they do not reflect an underlying biologic relationship.

From E.S.Jaffe and W.H.Wilson, 2004

Conclusioni (I)

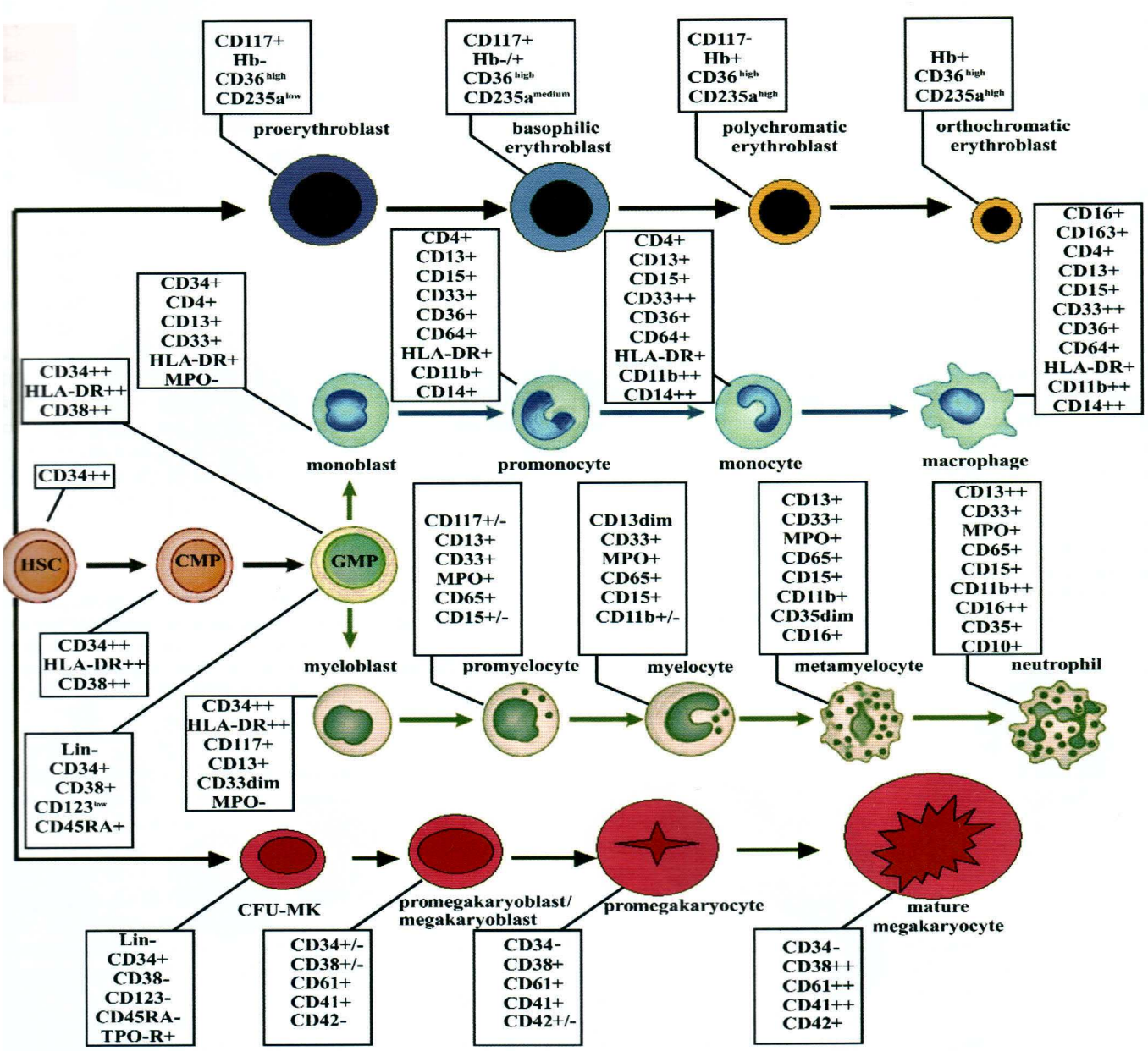
- Ci sono ancora diversi problemi aperti nella classificazione dei linfomi
- La WHO aggiornata del 2008 non chiarisce tutti i punti di discussione
- La classificazione del 2001 è stato un grande passo avanti verso una classificazione dei linfomi comprensiva di tutti gli aspetti connessi alla malattia (biologici, clinici ecc)

Conclusioni (II)

- E’ possibile per un Registro Tumori cogliere tutte le complessità presenti nella classificazione dei linfomi ?
- Le modifiche classificative che si susseguono periodicamente possono essere “assorbite” dal Registro Tumori ?
- Quali sono gli strumenti che possono facilitare il compito di chi lavora per un Registro Tumori ?
- Se vengono superate tutte queste criticità il Registro Tumori può diventare uno strumento insostituibile per fotografare la realtà dei linfomi in Italia

Myeloid Neoplasms

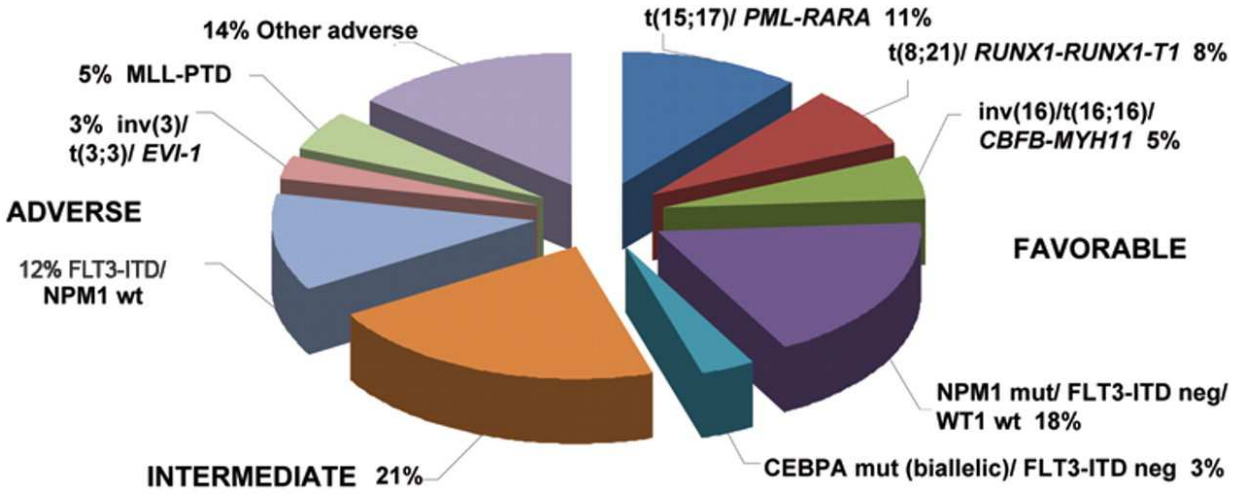
Antigen expression at various stages of normal myeloid differentiation



CORRELATION OF CYTOGENETIC AND MOLECULAR GENETIC WITH CLINICAL DATA

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q); –7; abnl(17p); complex karyotype‡

Frequency of prognostically relevant molecular and cytogenetic subgroups of AML arising in younger adults

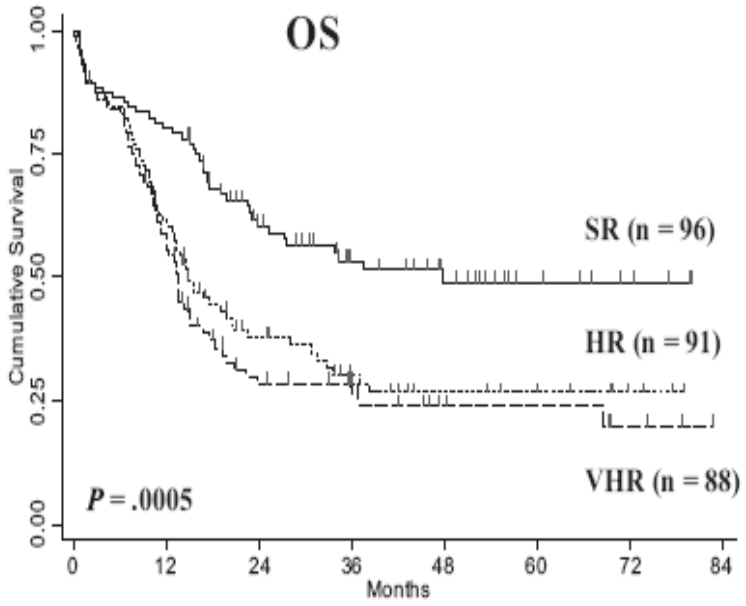


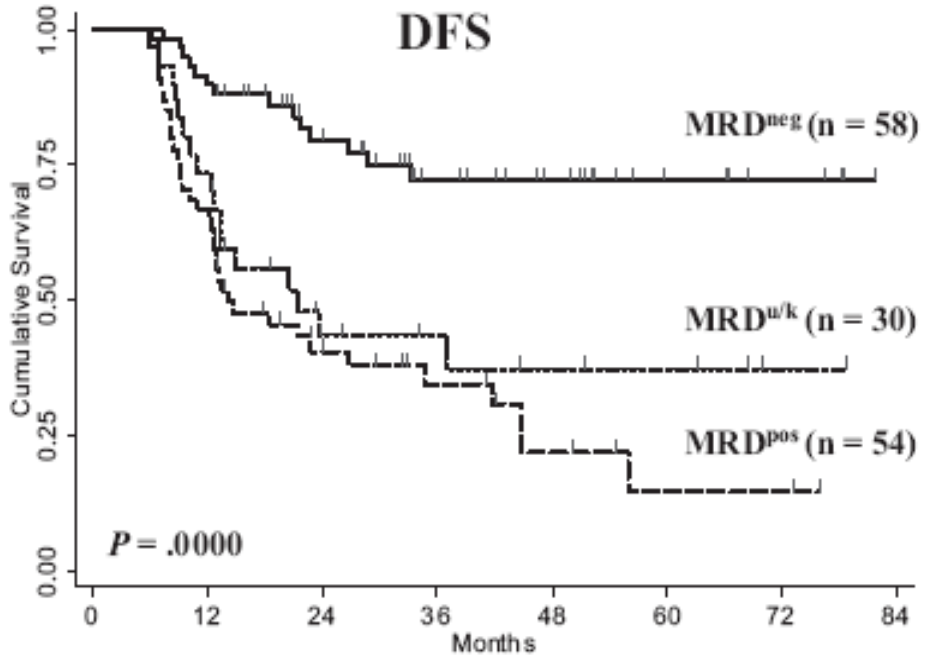
Grimwade, D. et al. Hematology 2009;2009:385-395

INDIPENDENT PROGNOSTIC FACTORS FOR AML OUTCOME

- Patient-related factors
- AML-related factors:
  - Cytogenetics
  - Molecular Genetics in CN-AML
  - Monitoring of MRD (risk stratification, post-remission therapy)
- Post-treatment Prognostic Factors: MRD

OS and DFs according to MRD status





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