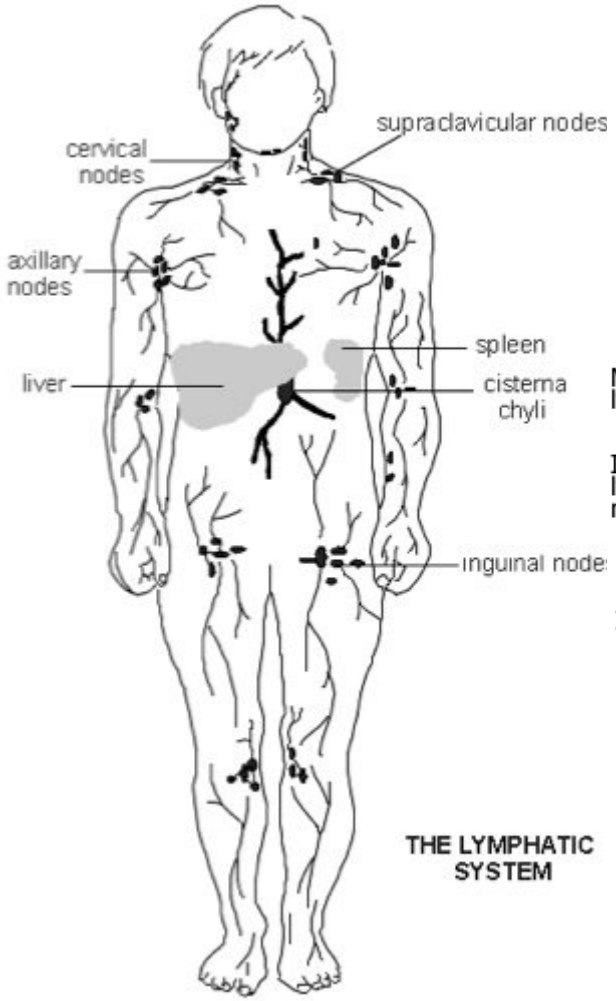
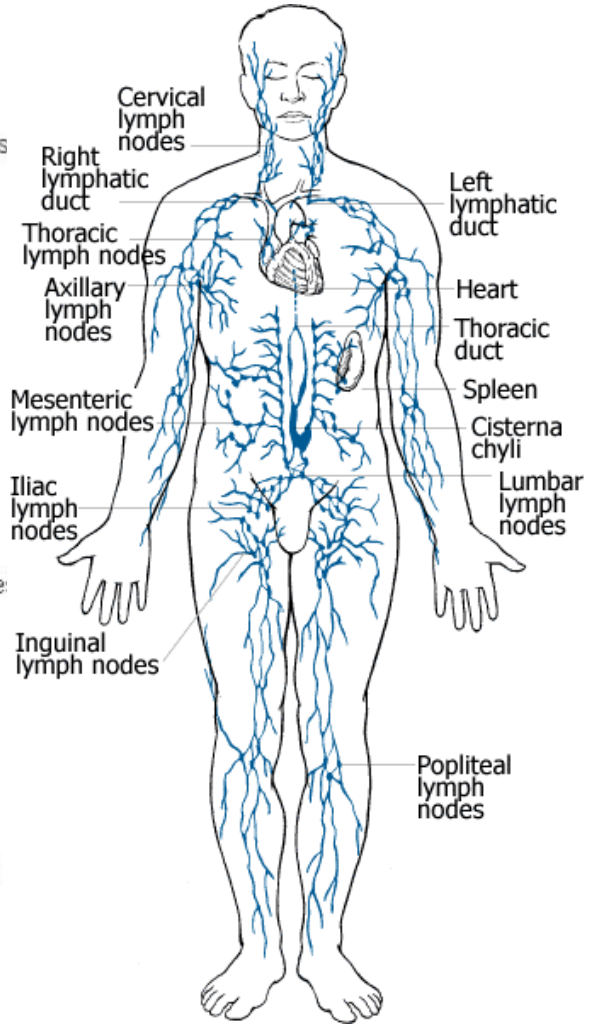
Ente Ospedaliero Cantonale

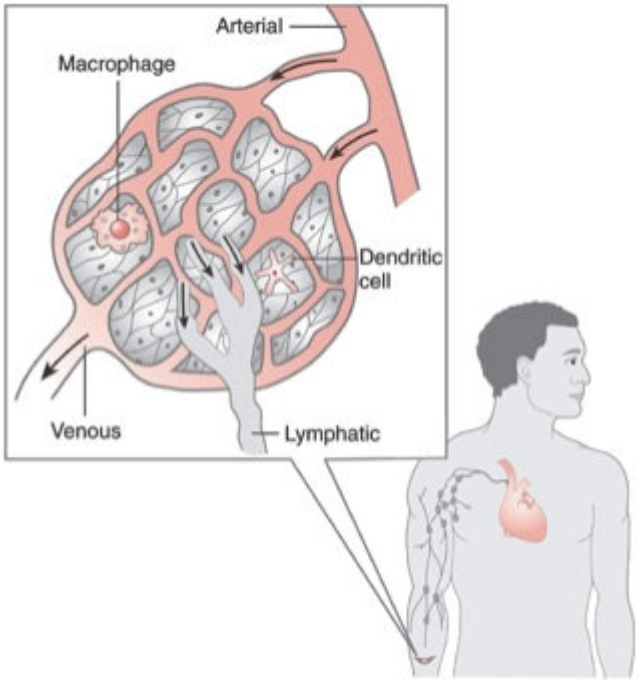
Linfomi indolenti e CLL

Georg Stüssi, Ematologia IOSI
Laboratorio di Ematologia EOLAB

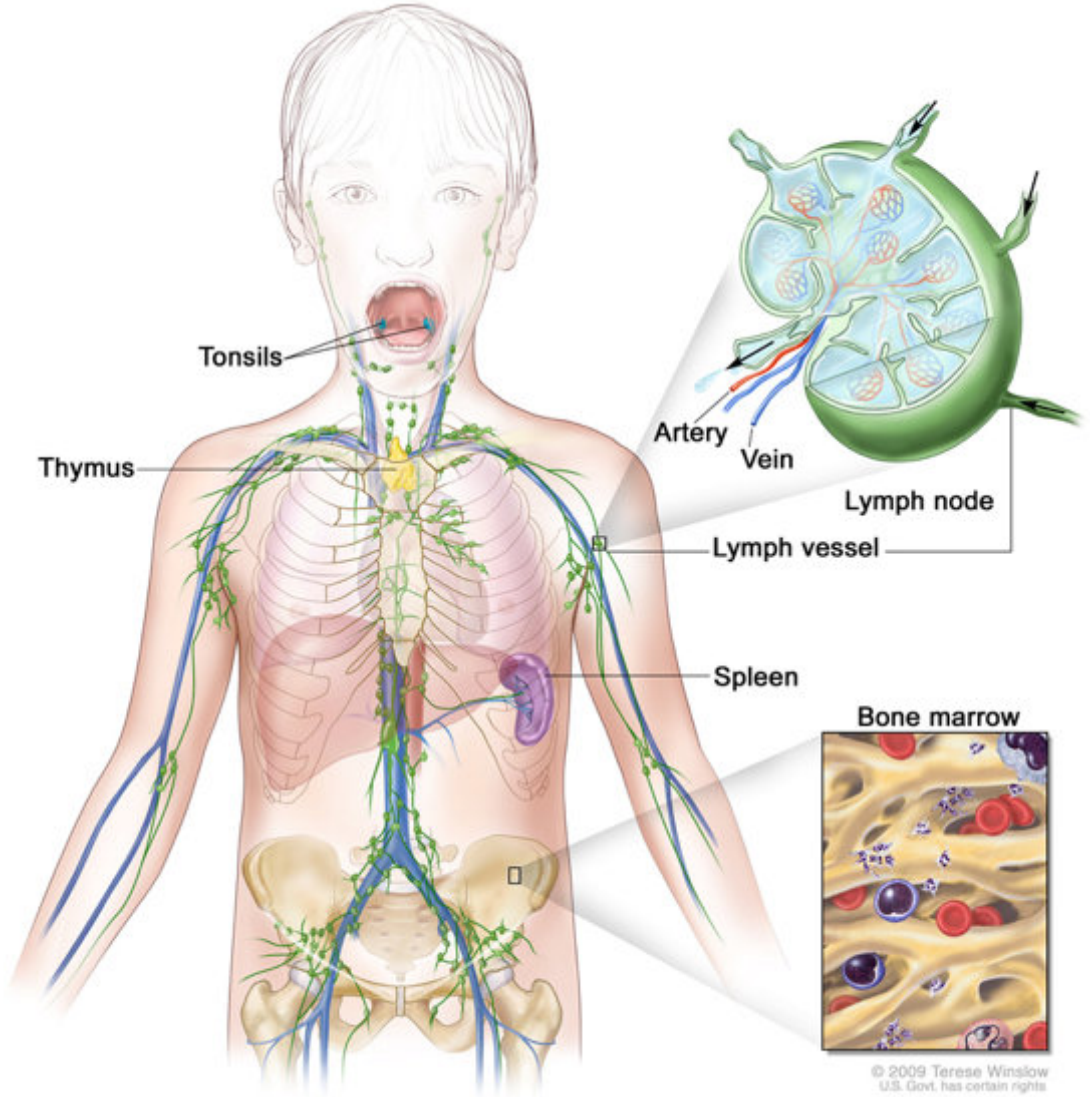
Il sistema linfatica





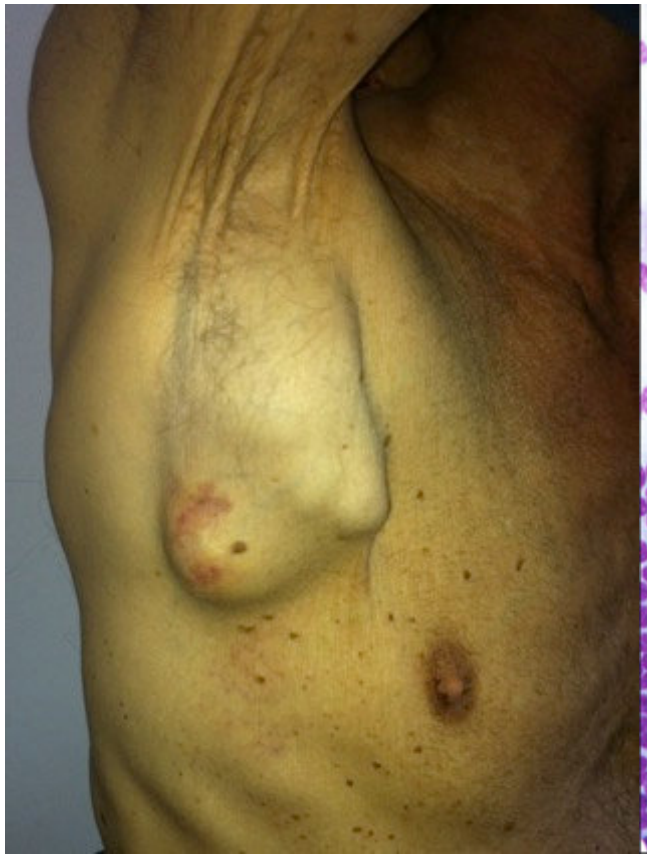


I viaggi dei linfociti

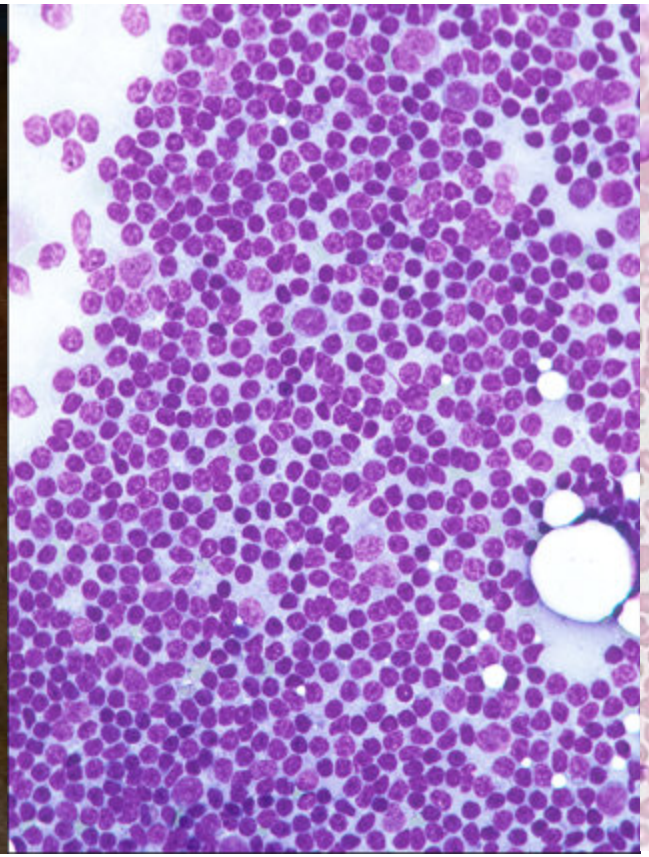


Localizzazione dei linfomi

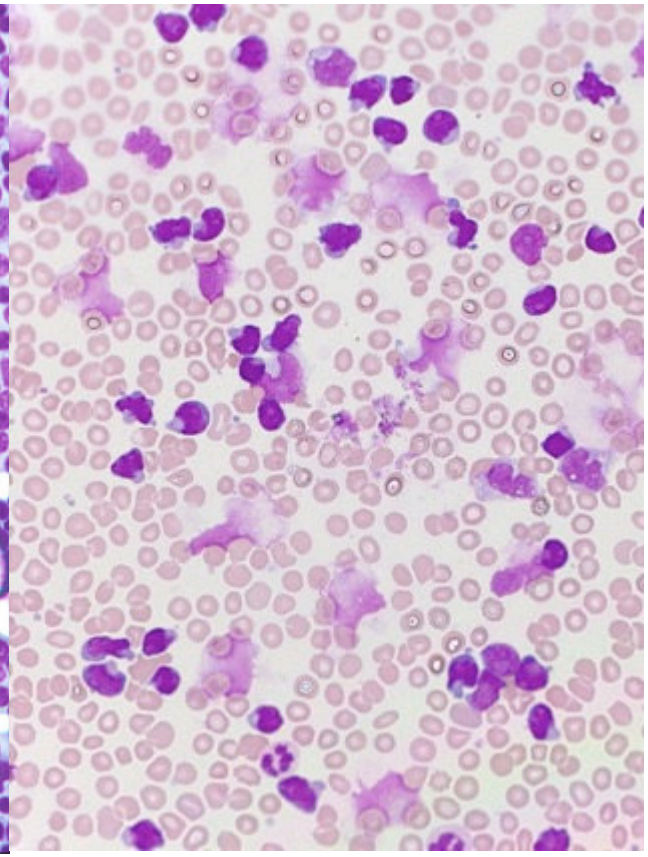
Linfonodi

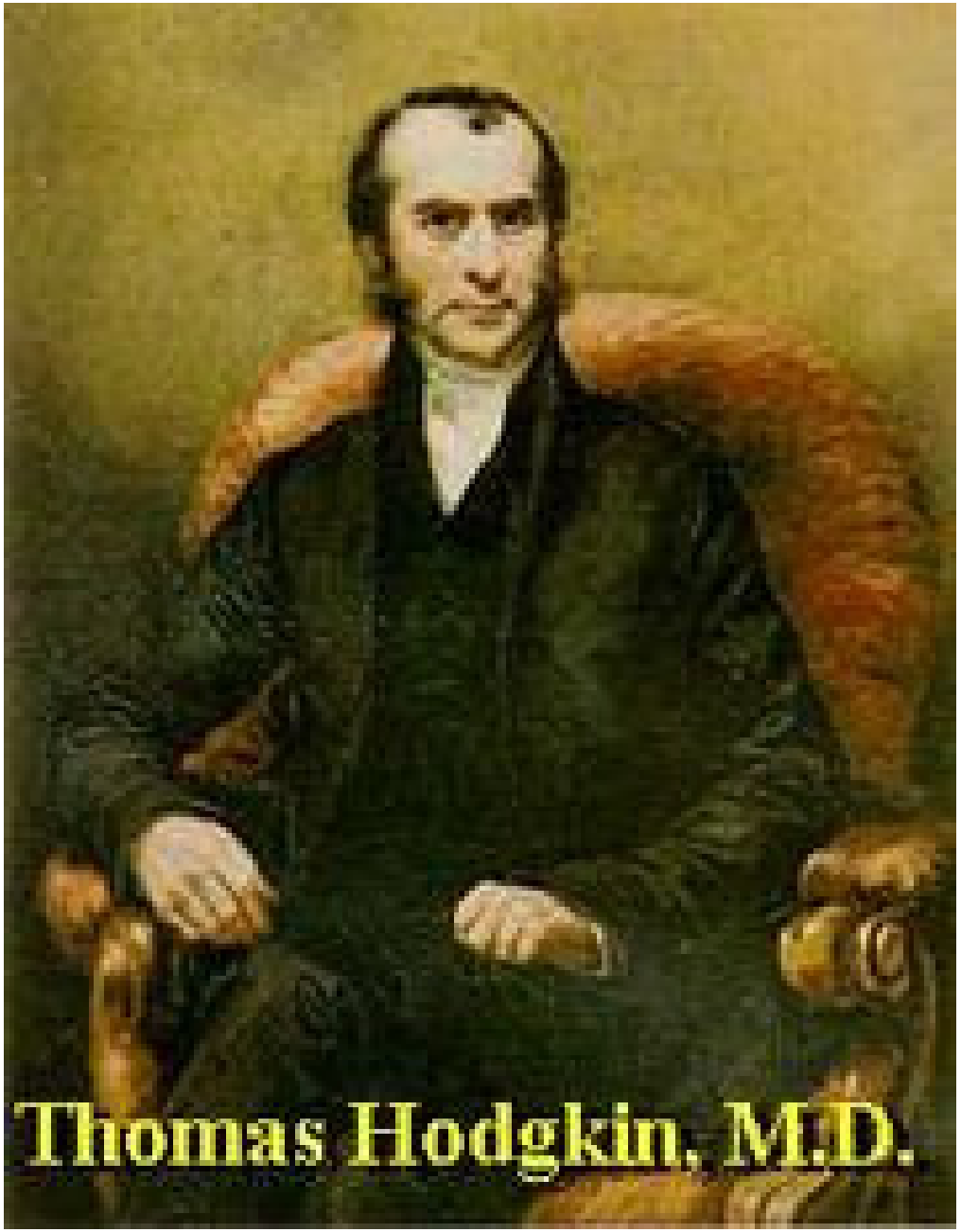


Midollo



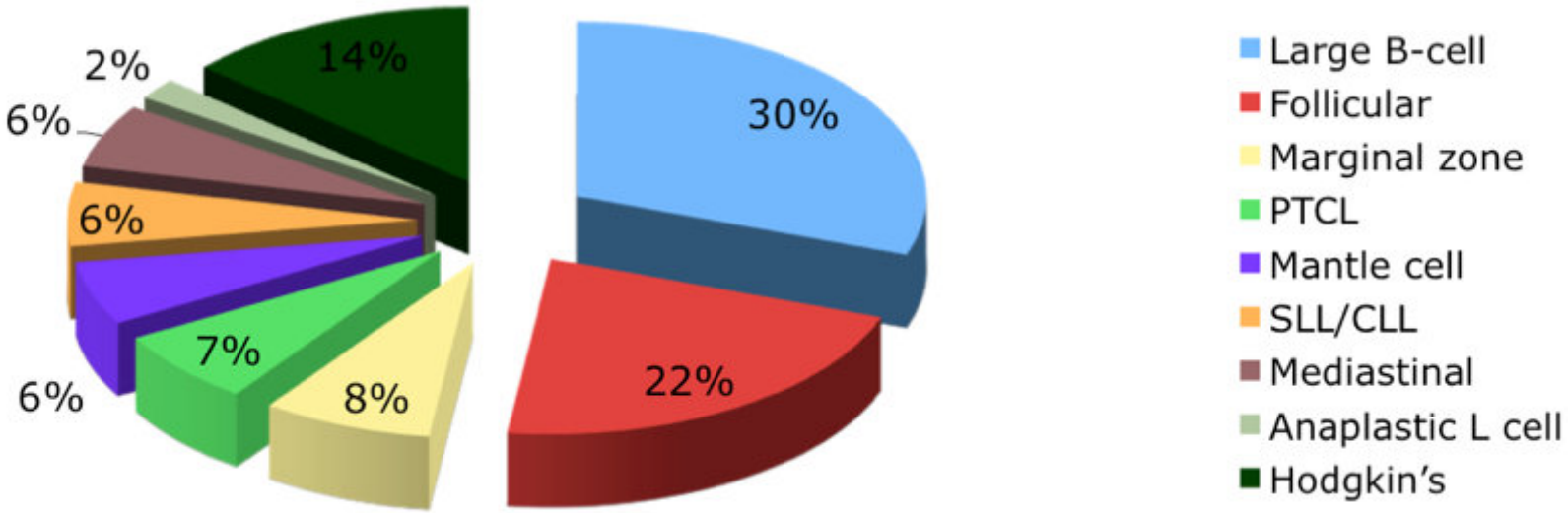
Sangue

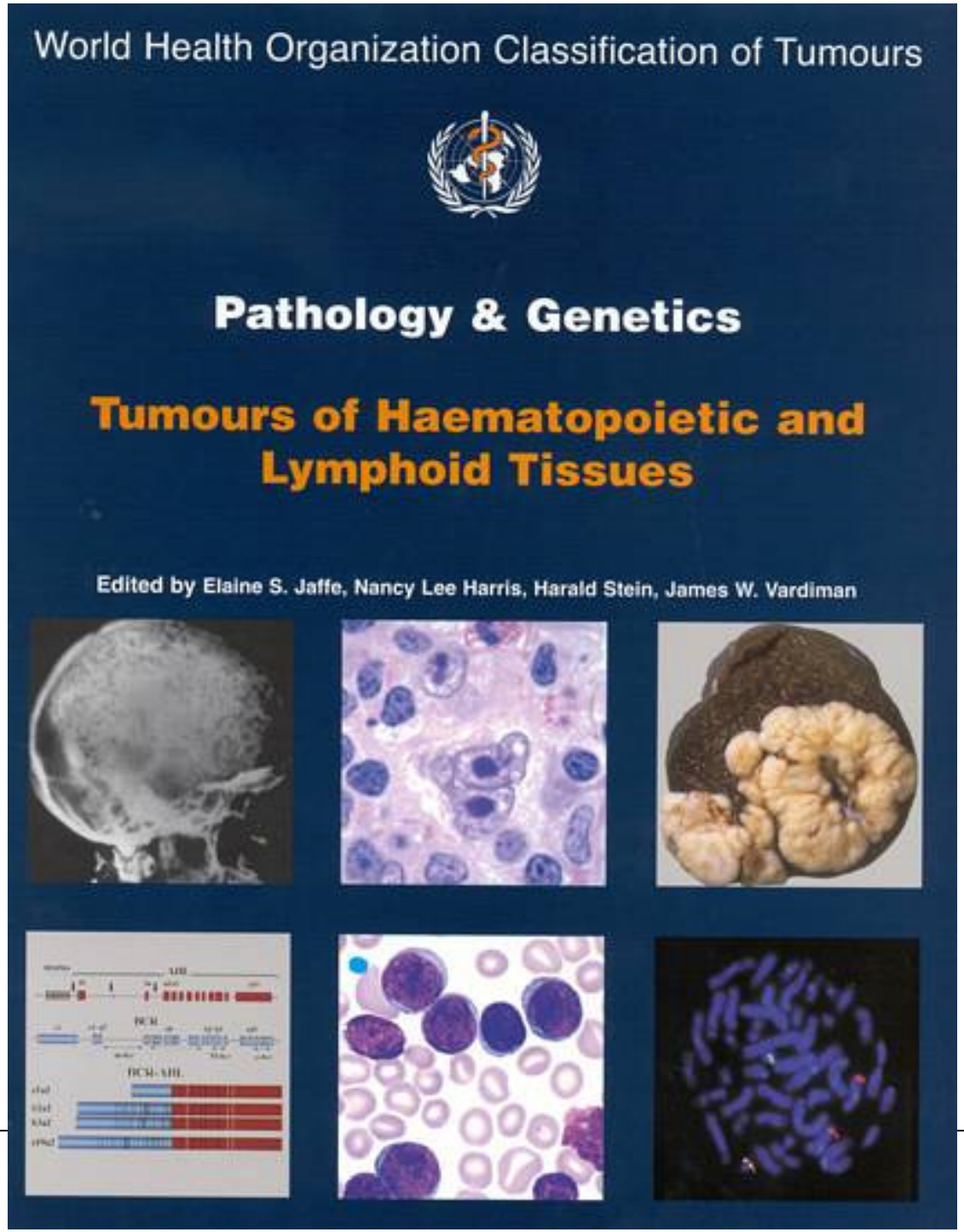



Thomas Hodgkin, M.D.

Classificazione dei linfomi

- Classificazioni storiche: Rappaport, Kiel, Working formulation, “R.E.A.L.”, altre…
- World Health Organization ha sviluppato da 2001 una classificazione unica al livello mondiale
- WHO 2001: 23 NHL separati e 5 linfomi di Hodgkin




World Health Organization Classification of Tumours
Pathology & Genetics
Tumours of Haematopoietic and Lymphoid Tissues
Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman

Classificazione WHO 2016 linfomi maturi

Mature B-cell neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- μ heavy-chain disease
- γ heavy-chain disease
- α heavy-chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- [illegible]
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- *Large B-cell lymphoma with IRF4 rearrangement**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type*
  - Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV⁺ DLBCL, NOS*
- *EBV⁺ mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK⁺ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8⁺ DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV⁺ T-cell lymphoma of childhood*
- Hydroa vacciniforme-like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30⁺ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8⁺ T-cell lymphoma**
- *Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK⁻

Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma
- [illegible]
- [illegible]
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)
- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD*
- [illegible]
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease*

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Non esiste la diagnosi di linfoma o di leucemia...

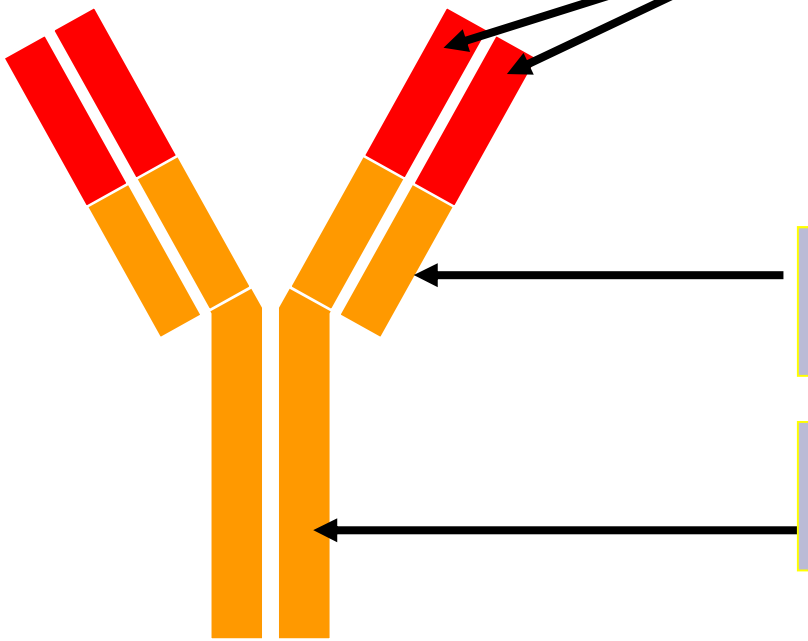
>90 malattie differenti

Swerdlow SH, Campo E, Pileri Stefano A, et al. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. *Blood*. 2016.

Il trattamento dei linfomi

I risultati nel trattamento di pazienti con NHL sono migliorati in un modo impressionante con l’introduzione di rituximab

Rituximab (Mabthera®) : Anticorpo monoclonale contro CD20

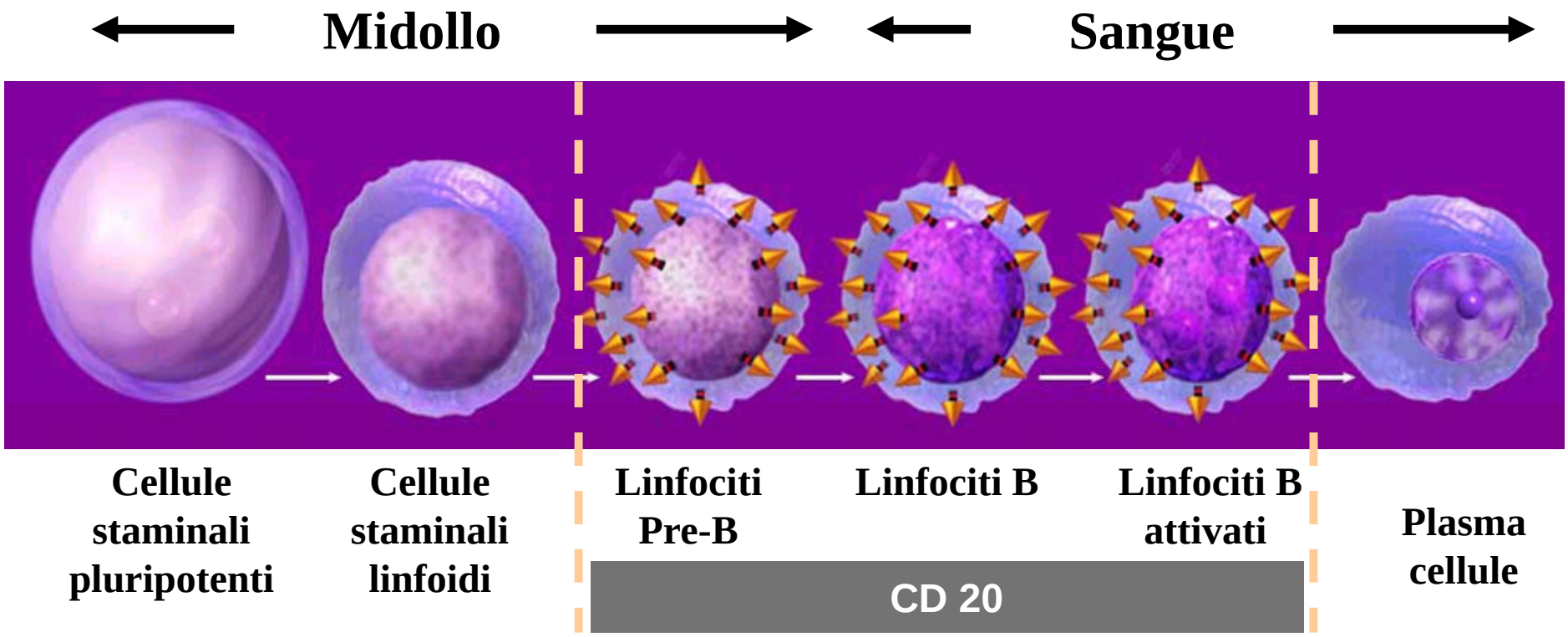


parte murina che si lega contro CD20 di linfociti B

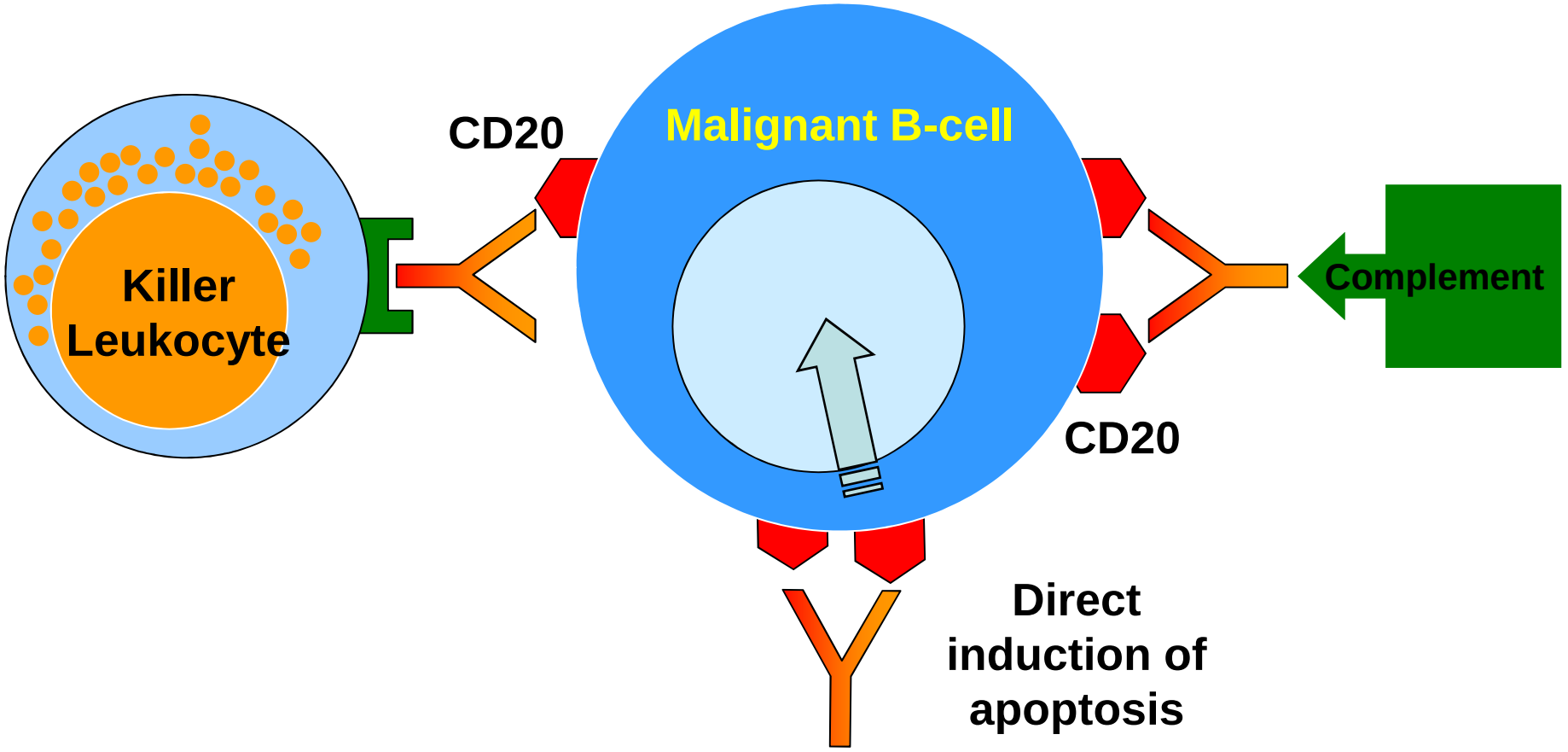
Parte umana: Regione costante

Parte umana che interagische con le cellule effetori

Espressione di CD20 durante la maturazione di linfociti B



Come funziona Rituximab?

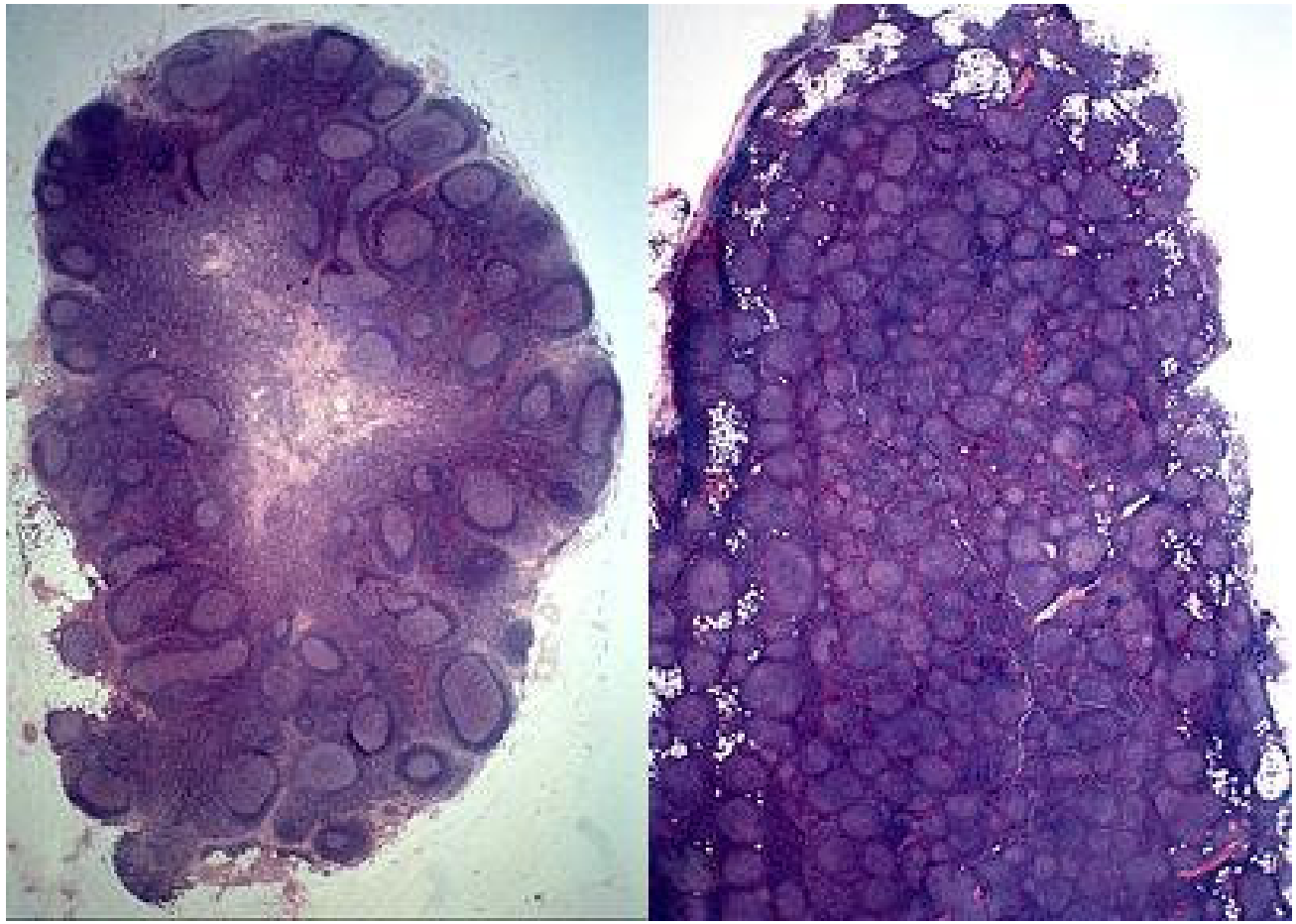


Adapted from Male D, *et al., Advanced Immunology* 1996: 1.1–1.16

LINFOMA FOLLICOLARE

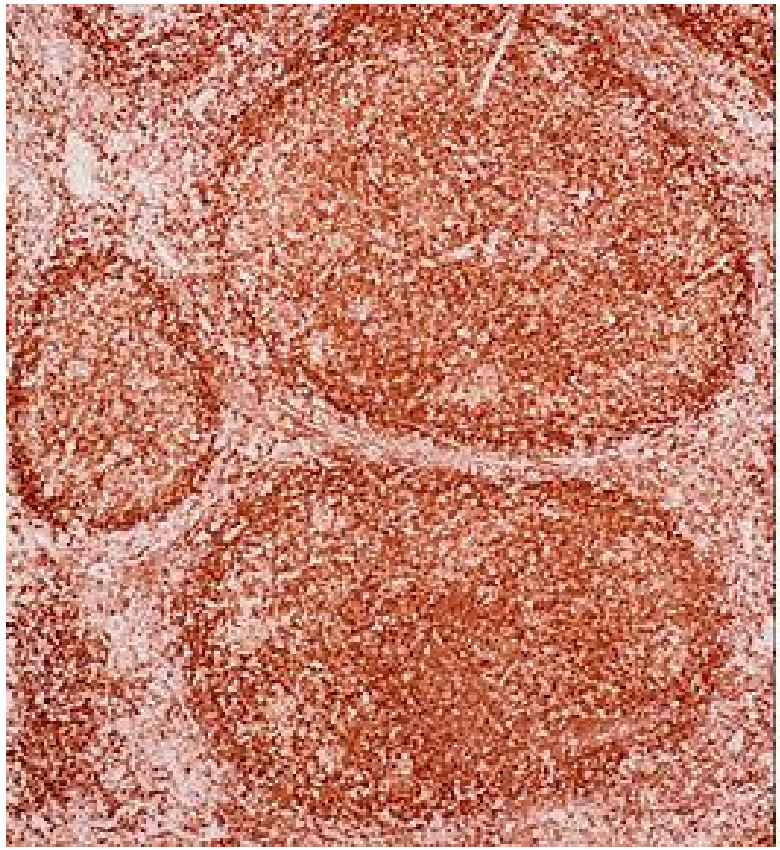
Perché si chiama linfoma follicolare

Linfonodo normale reattivo **Linfoma follicolare**

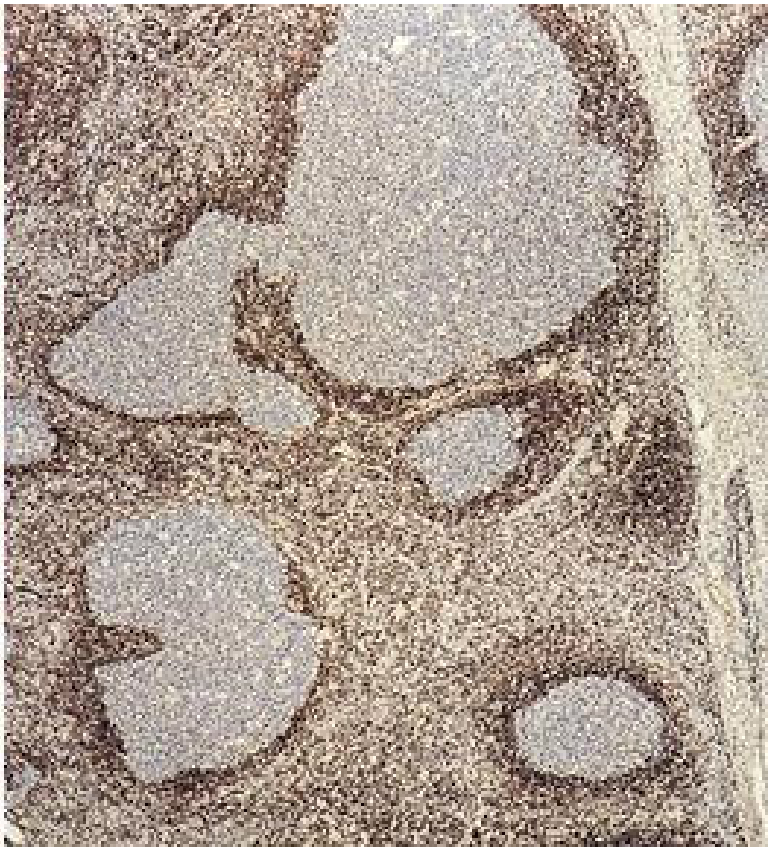


Linfoma follicolare esprima Bcl-2

Linfoma follicolare

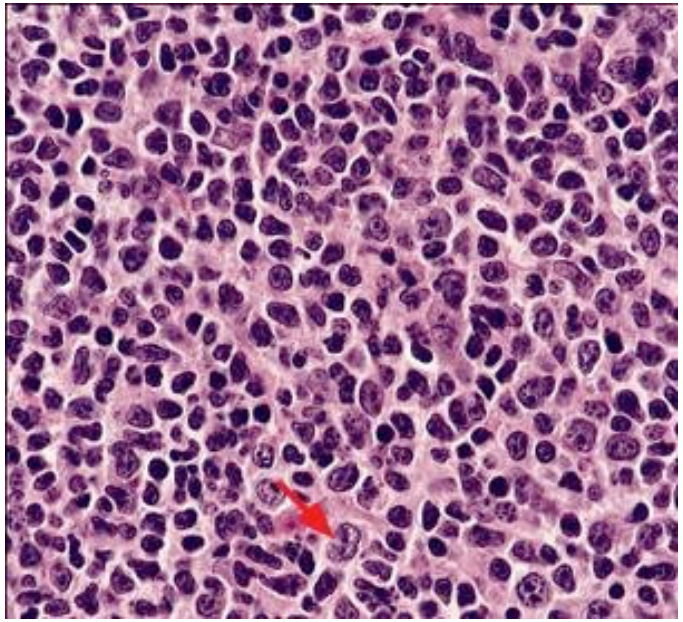


Follicolo normale reattivo



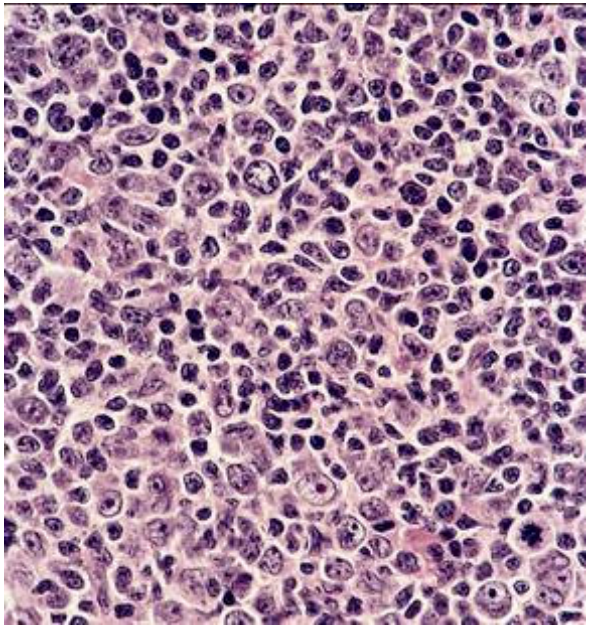
Graduazione del linfoma follicolare

Grado I
0-5 centroblasts/HPF



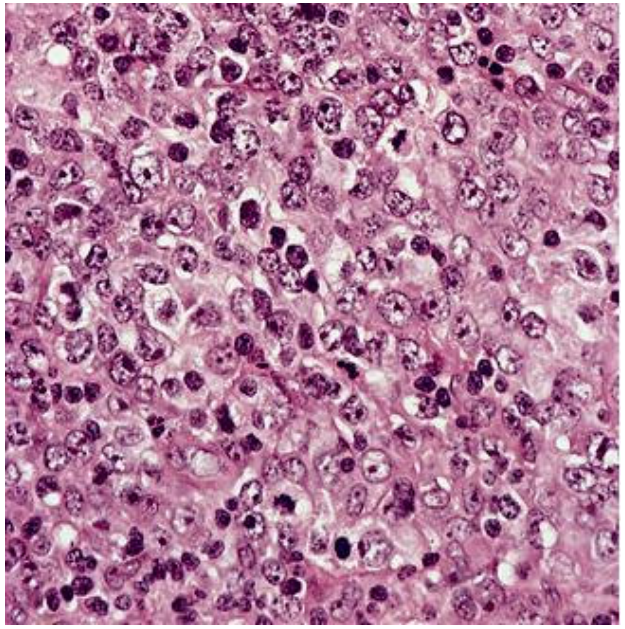
Centrociti

Grado II
6-15 centroblasts/HPF



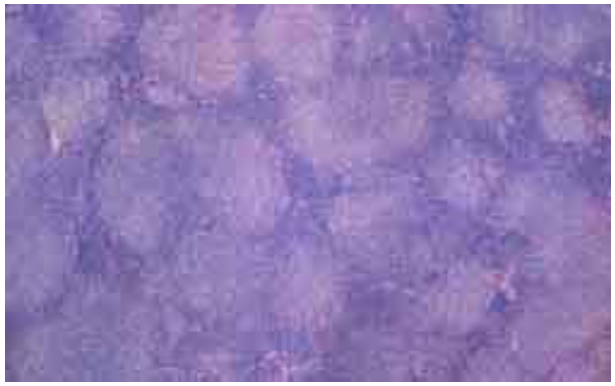
Misto

Grado III
>15 centroblasts/HPF



Centroblasti

Linfoma follicolare



- Il linfoma indolente più frequente
- Linfadenopatie asintomatiche
- Spesso malattia generalizzata alla diagnosi
- Età mediana: 59 anni
- Natura indolente
  - Sopravvivenza a lungo tempo
- Non curabile con chemio
- Trattamento solamente se sintomatico
- Radioterapia in malattia localizzata
- Spesso Watch-and-wait

Terapia linfoma follicolare

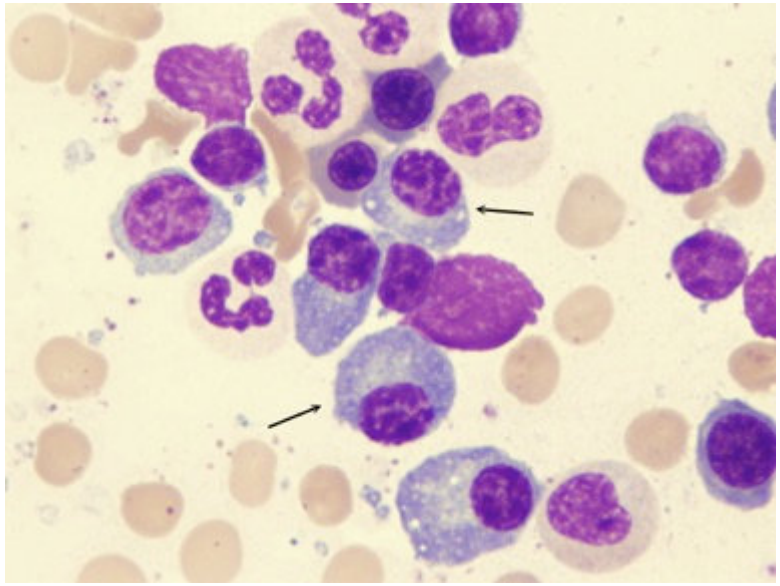
Terapia di prima linea

Malattia localizzata Stadio I o stadio II con non più di 2 stazioni contigue	RT (IF)
Malattia disseminata	
Pazienti asintomatici	Osservazione ("wait and see")
Pazienti sintomatici: - sintomi B - malattia Bulky > 6 cm - coinvolgimento viscerale, linfadenopatia o splenomegalia con sintomi presenti o incipienti - versamento pleurico o ascitico dovuto a linfoma - anemia o piastrinopenia clinicamente significativa (Hb < 10 e Tc < 100)	<u>Gradi 1-2</u> - Studio SAKK 35/14 (Rituximab ± Ibrutinib) oppure - Rituximab monoterapia (chiedere CM) - R-Bendamustina oppure - R-Chlorambucil <u>Gradi 3a</u> - R-CHOP x 6 (± mantenimento con Rituximab) <u>Gradi 3b</u> - R-CHOP x 6 (vedi DLBCL)

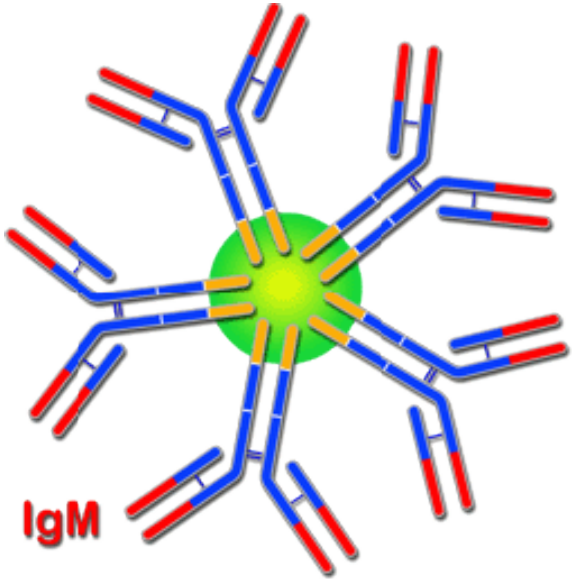
WALDENSTRÖM MACROGLOBULINEMIA

LINFOMA LINFOPLASMOCITICO

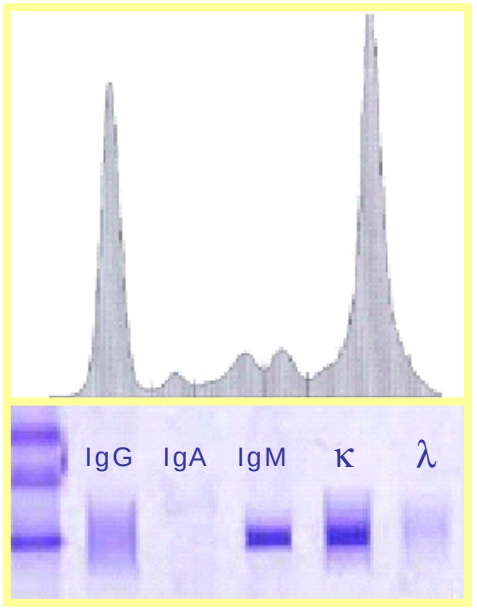
Waldenström macroglobulinemia
“Due problemi principali”



Infiltrati linfoplasmocitici



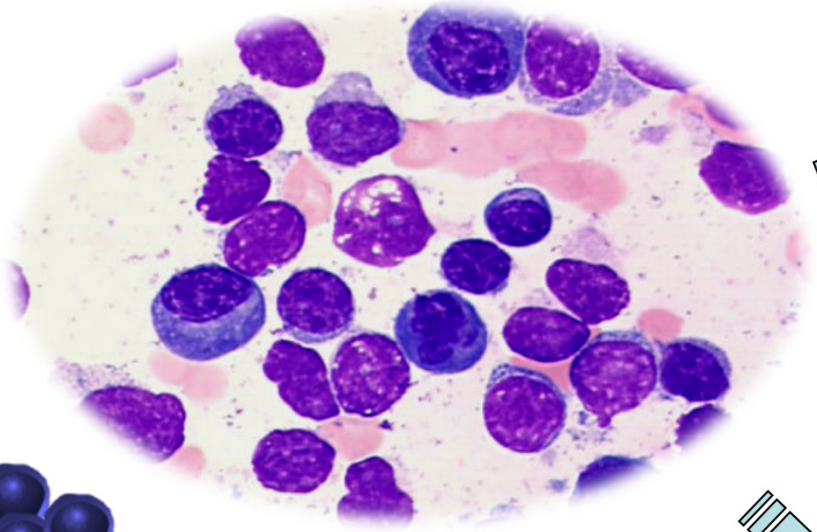
Secrezione di IgM



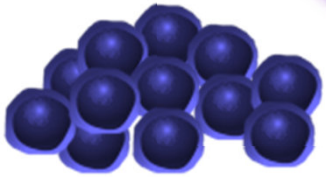
Elettroforesi del siero

Manifestazioni

↓HCT, ↓PLT, ↓WBC



Iperviscosità:
Epistassi, anemia emolitica,
Peggioramento del viso



Linfadenopatia,
Splenomegalia
≤20%

Anemia ferripriva

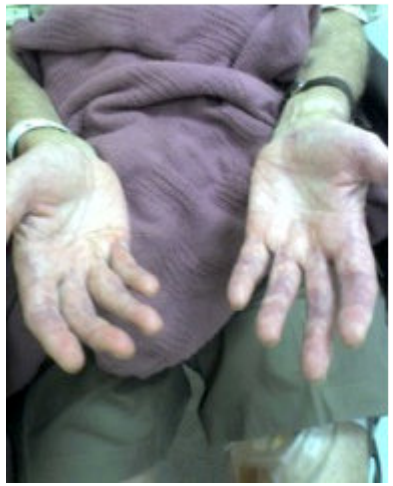
Neuropatia (22%)
Crioglobulinemia (10%)
Agglutine a freddo (5%)

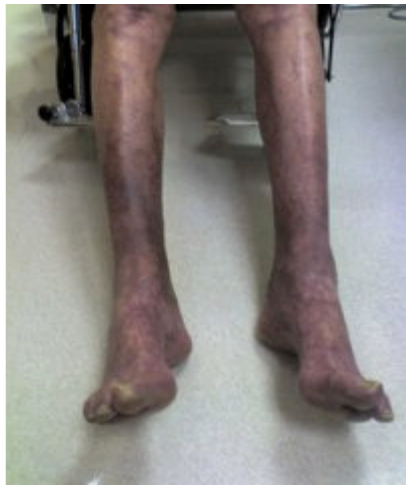
Treon Hematol Oncol 2013

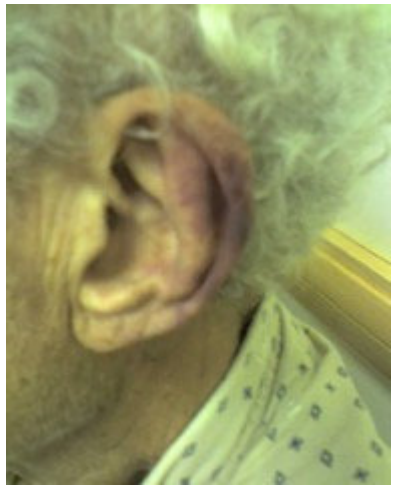
Crioglobulinemia

Pheresis

Pre

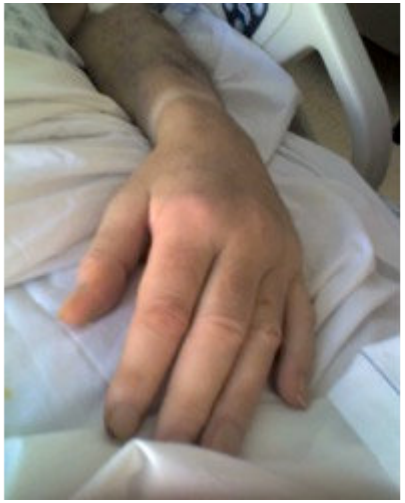


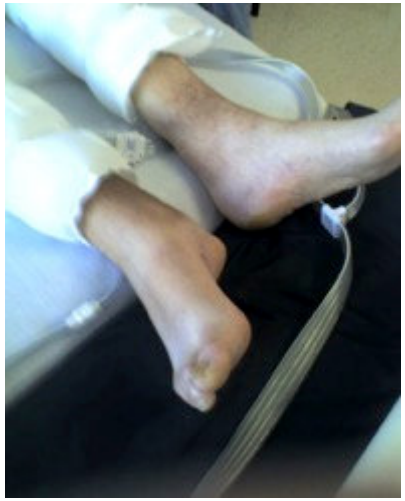


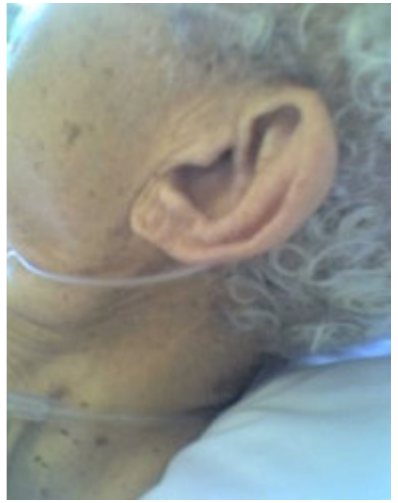


Pheresis

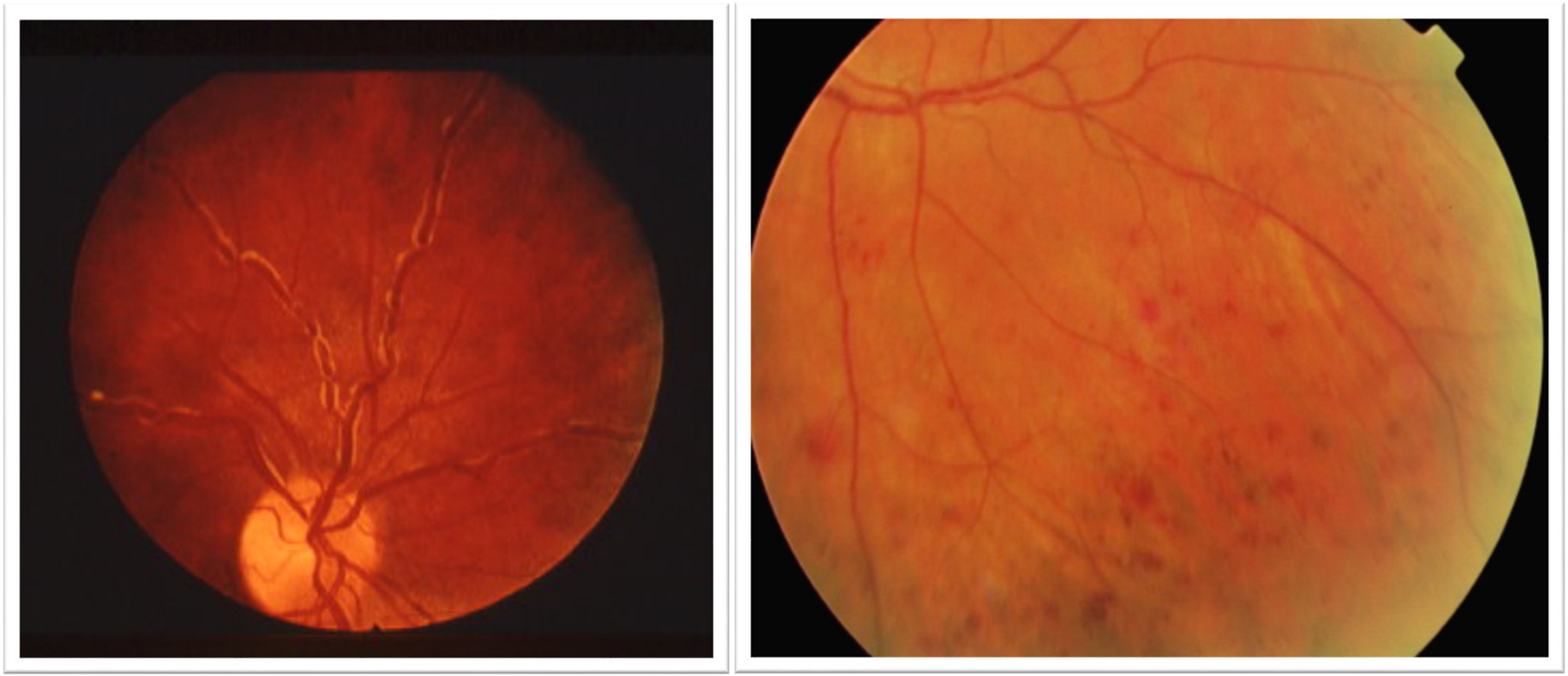
Post







Alterazioni della retina dovute all'iperviscosità



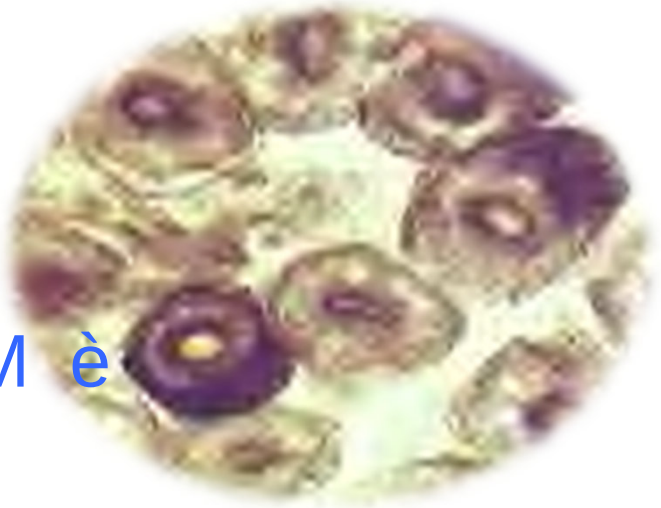
- Dilatazione delle vene IgM >3,000 mg/dL
- Flusso retrogrado e sanguinamenti >6,000 mg/dL

Stone, Clin Lymphoma 2005; Menke et al, Arch Opthal 2006

Neuropatie periferiche

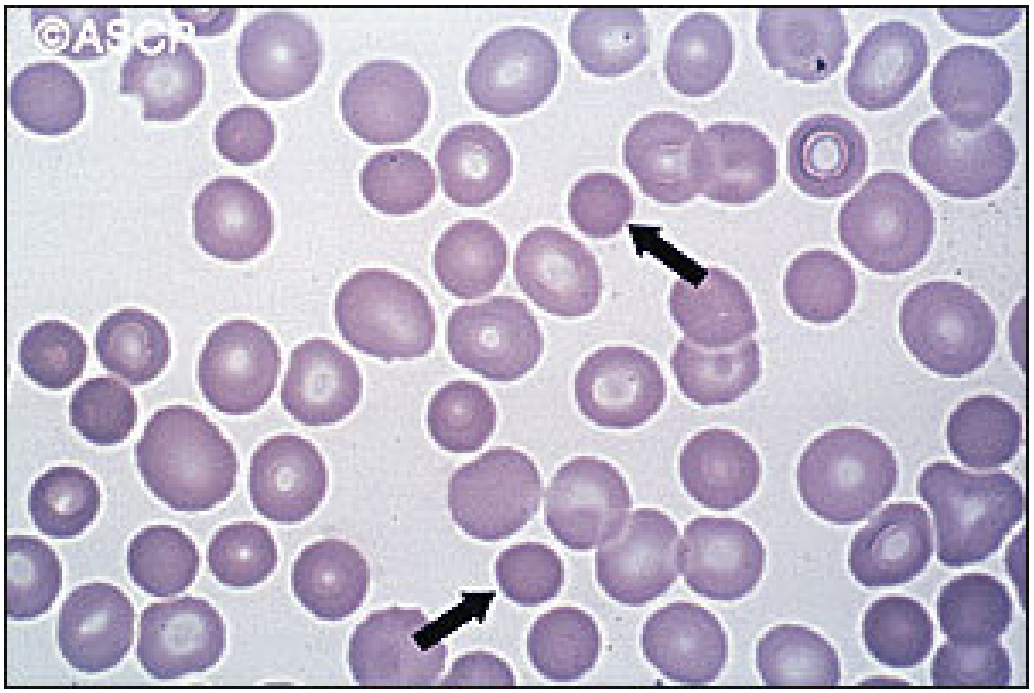
- 22% dei pazienti con WM
- Di solito neuropatia sensitoria dovuto all'IgM mirata contro:
  - Myelin Associated Glycoprotein
  - Ganglioside M1
  - Sulfatide

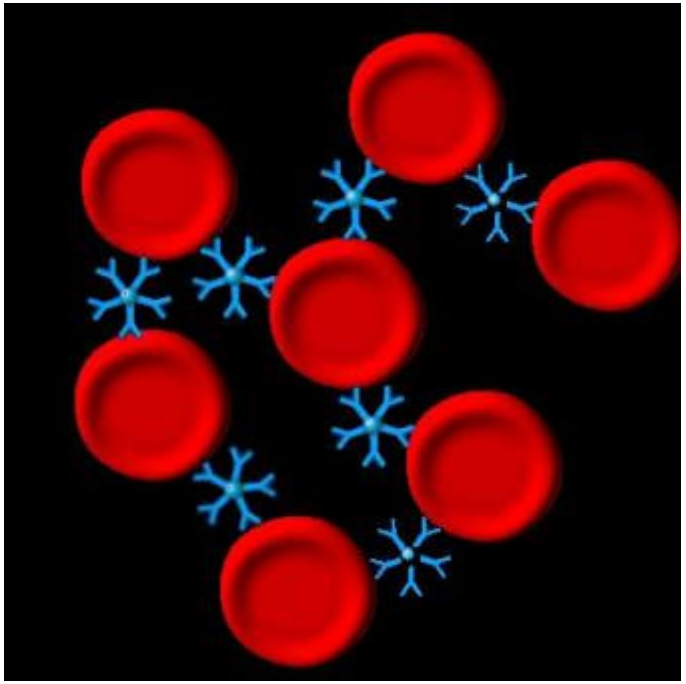
MAG IgM è



Treon et al, ASCO 2010; Photomicrograph Courtesy Todd Levine, MD

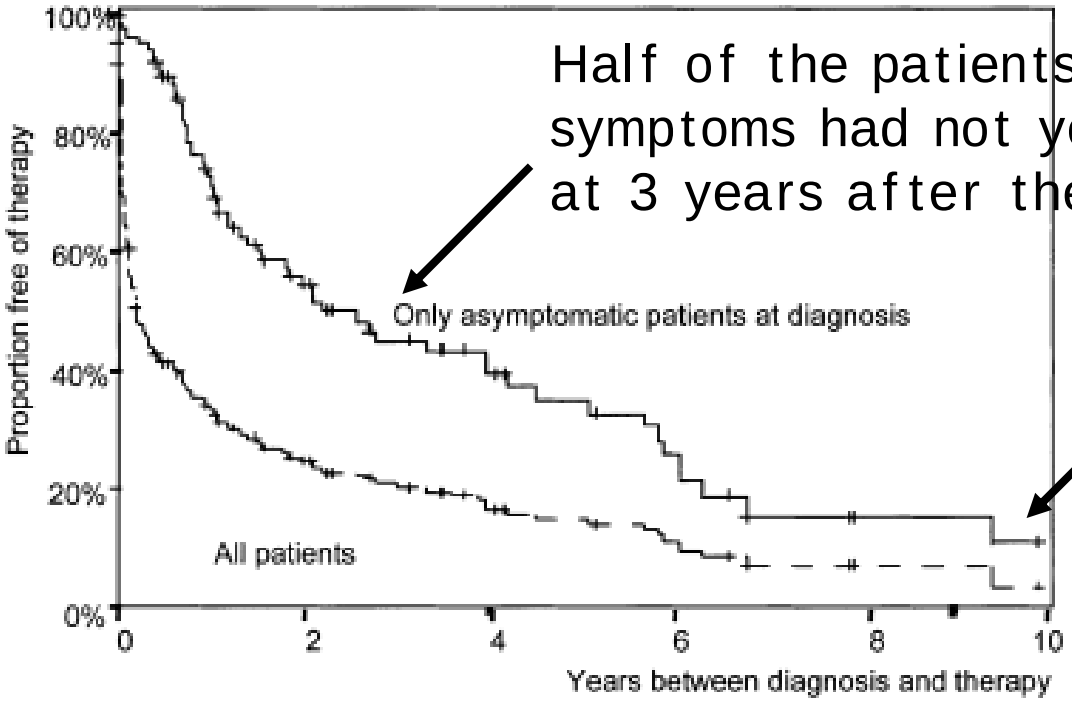
Emolisi autoimmunitaria





CHI RICHIEDE TERAPIA?

Watch and wait in pazienti con Waldenström



Half of the patients who had no symptoms had not yet been treated at 3 years after their diagnosis

10% of the patients had not yet been treated at 10 years

García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

Sintomi che suggeriscono necessità per trattamento

- Febbre, sudurazioni notture, calo ponderale
- Linfadenopatia, splenomegalia
- Anemia (<100g/L) o trombocitopenia (>100G/L)
- Iperviscosità, neuropatie, insufficenza renale, crioglobulinemia

Kyle et al. Semin Oncol. 2003 Apr;30(2):116-20

Opzioni terapeutiche

- Watch and wait
- Rituximab monoterapia
- Combinazioni Chemoimmunoterapie
- Plasmaferesi
- Nuovi farmaci: ibrutinib
- Trapianto cellule staminali

- **L’opzione migliore?**

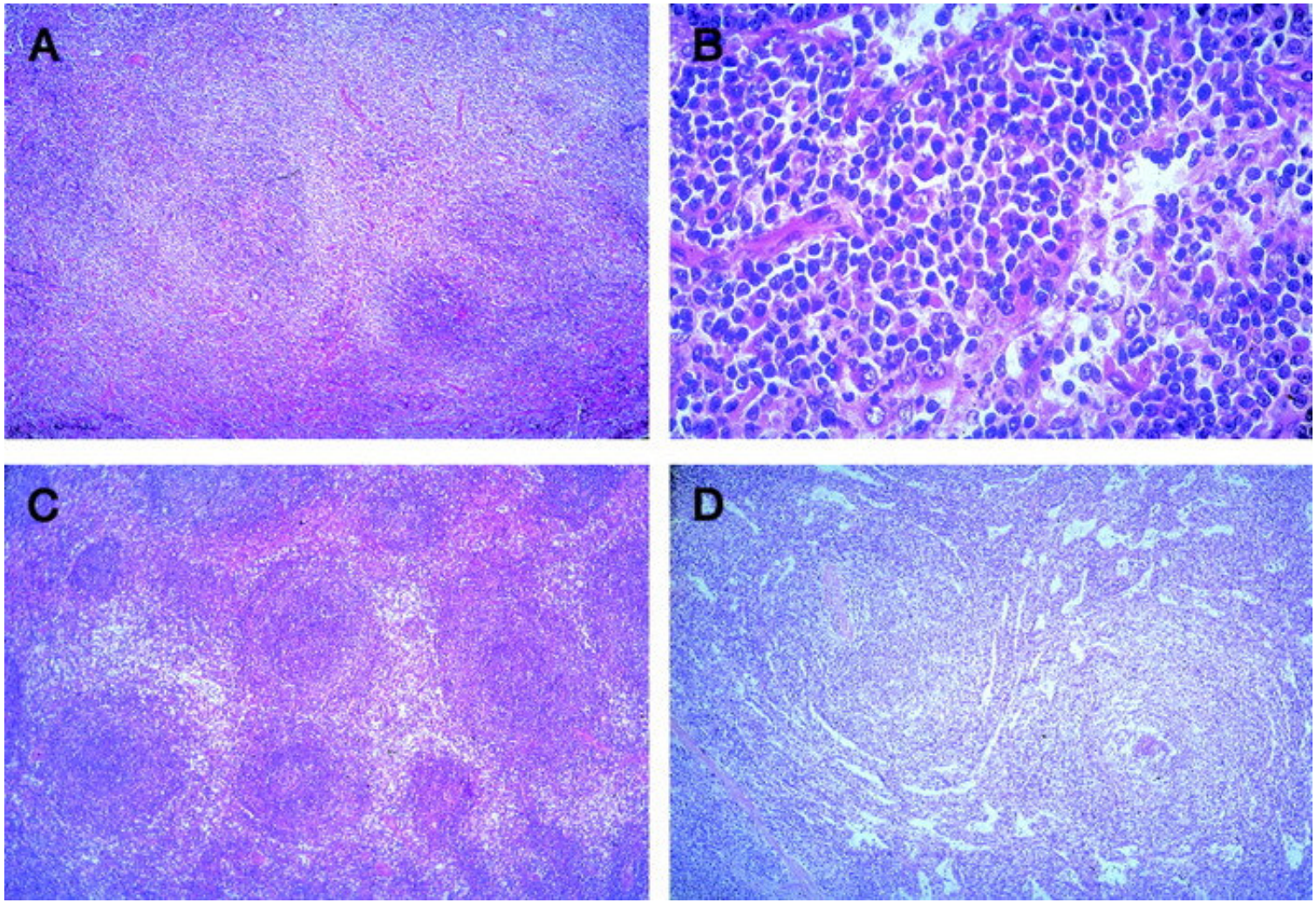
LINFOMI DELLA ZONA MARGINALE

Linfomi della zona marginale (MZLs)

Classificazione WHO

- MZL splenico ~ 1% of all NHLs
- MZL nodale ~ 2% of all NHLs
- MZL estranodale (MALT Lymphoma) ~ 8% of all NHLs

Linfomal della zona marginale

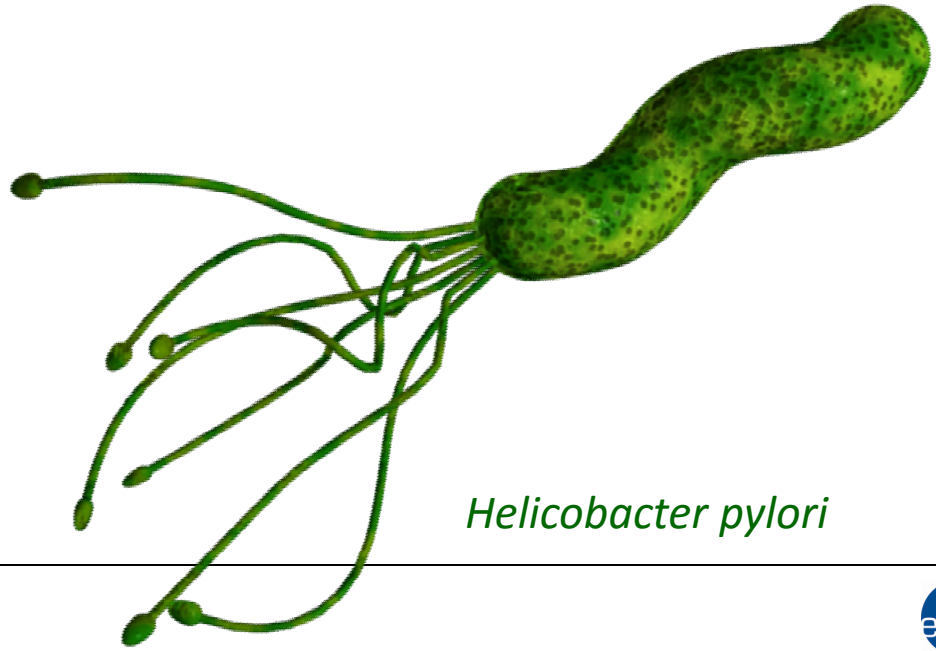


Françoise Berger et al. Blood 2000;95:1950-1956

Crescita causata di HP

- Morfologia di un linfoma MALT

- Associazione della malattia cronica con un processo autoimmune
- Effetto terapeutico degli antibiotici.



Helicobacter pylori

Trattamento del MALT linfoma

HP **eradicazione HP come terapia standard per pazienti HP-positivi e malattia localizzata**

Evidence of for linking specific microorganisms to MALT lymphoma pathogenesis at different sites

Koch's postulates (1882)	*H. pylori* & Gastric MZL	*C. jejuni* & IPSID	*B. burgdorferi* & Cutaneous MZL	*C. psittaci* & Ocular adnexal MZL
Organism found in the lesion.	**most cases**	some cases	variable	variable
Organism can be isolated and grown *in vitro*.	**yes**	not yet	not yet	**yes**
Organism inoculation causes lesions in animals	**yes**	unknown	unknown	unknown
Organism can be recovered from the experimental animal	**yes**	unknown	unknown	unknown
Lymphoma regression after bacteria eradication	**yes**	**yes**	**yes**	**yes**

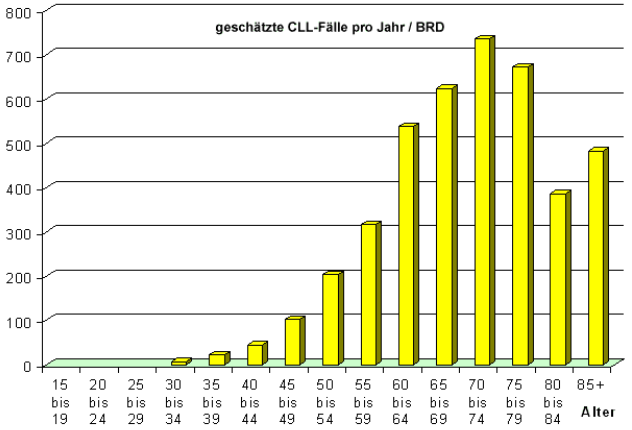
modified from: MQ Du, J Clin Exp Hematopathol 2007

LEUCEMIA LINFATICA CRONICA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA (SLL)

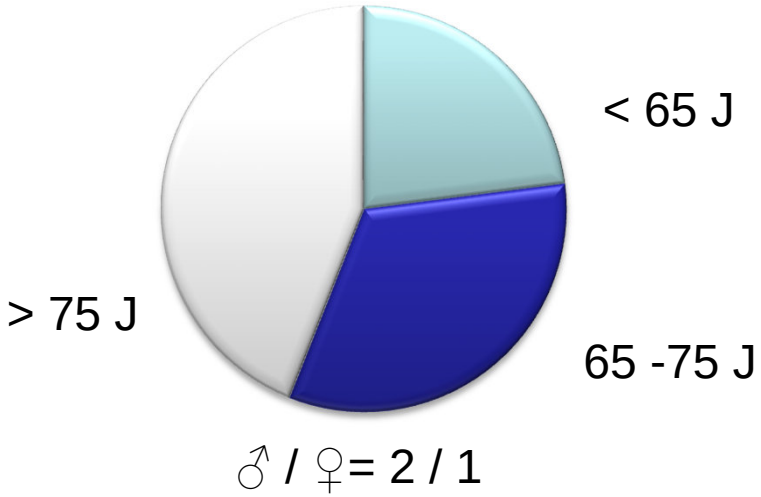
Leucemia linfatica cronica

Epidemiologia

- Incidenza: 3-4/100‘000
- ~ 200 nuove diagnosi/anno in Svizzera



Eta’ dei Pazienti



♂ / ♀= 2 / 1

- Maggioranza di stadi precoci di malattia

Eziologia

- Nessuna connessione con
  - Chemio e radioterapia
  - Fumo
  - Infezioni virali (EBV, HBV, HCV, HIV)
- Background genetico
  - Europei e africani >> Asiatici
- CLL familiare
  - Associazione piu` forte rispetto ad altri linfomi
  - raramente trasmissibile

Sintomi CLL

Sintomi non specifici

- Febbre, sudorazioni notturne, calo ponderale
- Citopenie
- Linfadenopatia, epatosplenomegalia
- Infezioni frequenti
- Emolisi

Senza sintomi

Diagnosi CLL

- **Conte cellulari**
  - Linfocitosi (clonale) > 5G/L (PB)
- **Morfologia**
  - Linfociti di taglia media o piccola, citoplasma scarso, nucleo denso e ombre di Gumprecht
- **Immunofenotipo**
  - CD19, CD20, CD23, CD5

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446–5456.

Scopi terapeutici nella CLL

- Sintomatico (miglioramento die sintomi)
- Allungamento della sopravvivenza libera da malattia
- Allungamento della sopravvivenza globale
- Guarigione

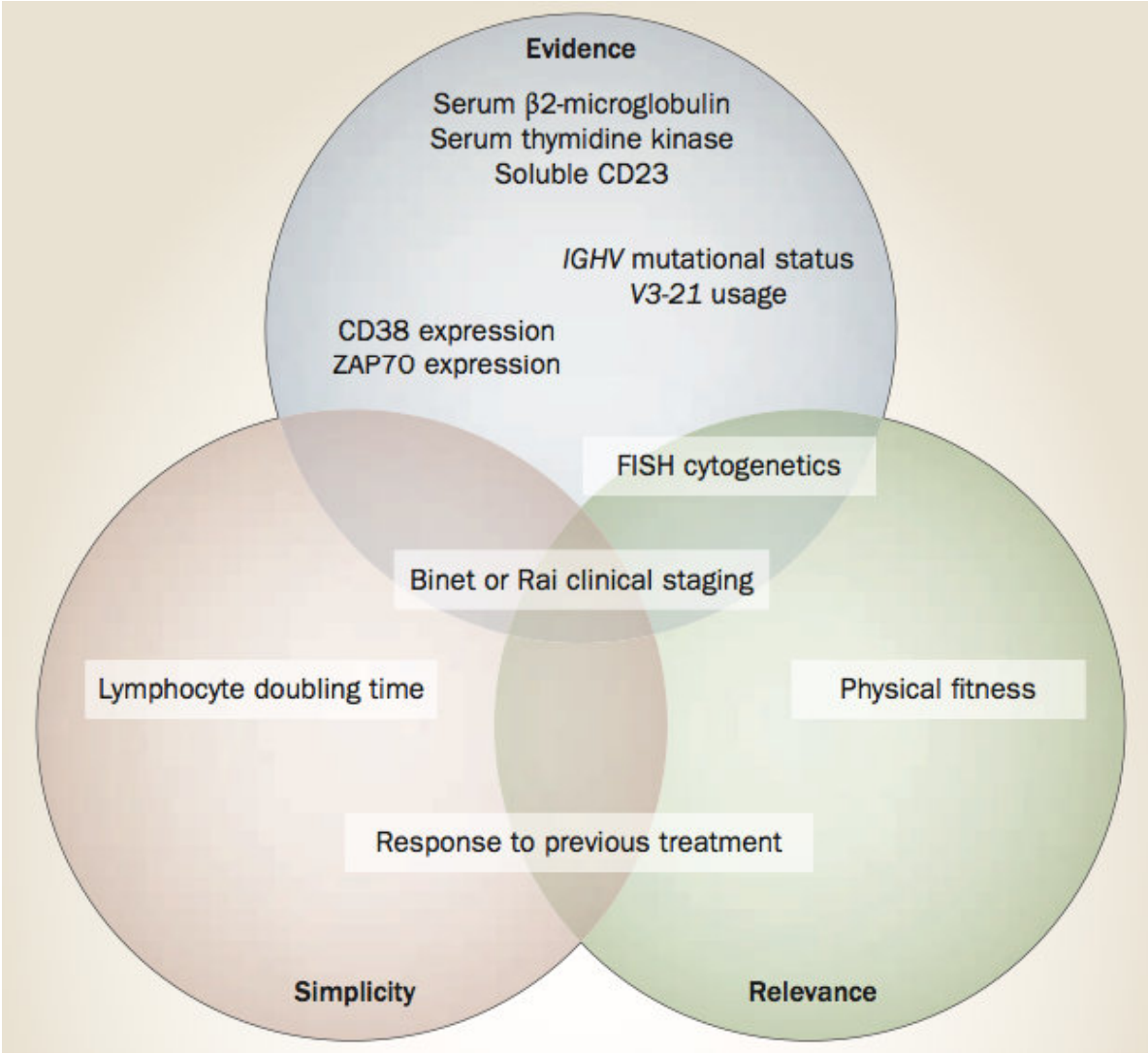
CLL asintomatica

Watch and wait

- Insufficienza midollare (Citopenie)
- Linfadenopatie o splenomegalia clinicamente significative
- Sintomi costituzionali (**raramente in CLL**)
- Linfocitosi importante / radoppio dei linfociti< 6 mesi

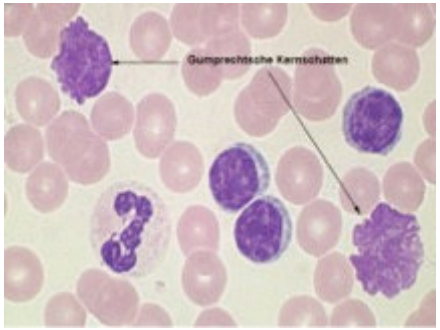
Hallek M, et al. Blood 2008

Fattori di rischio CLL



Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia-what do we need to know? *Nat Rev Clin Oncol*. 2011;8(1):38–47.

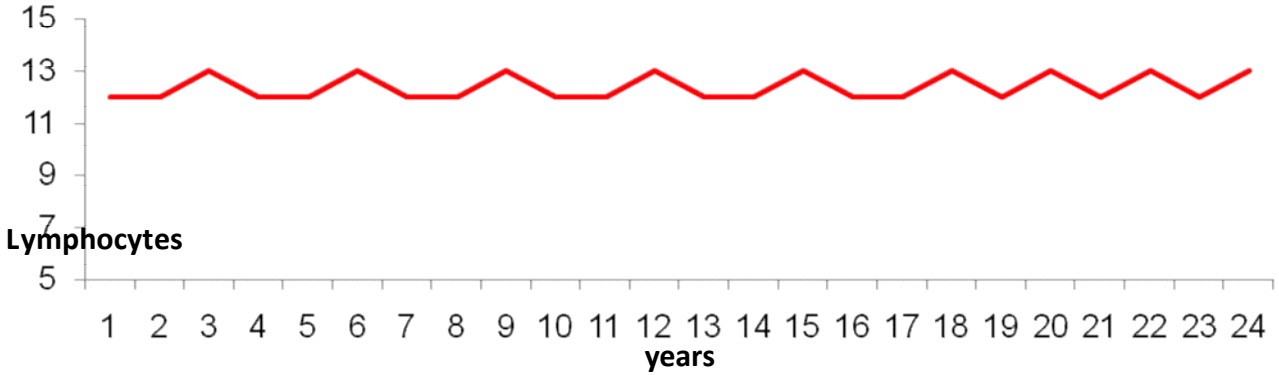
CLL – Raccomandazioni terapeutiche



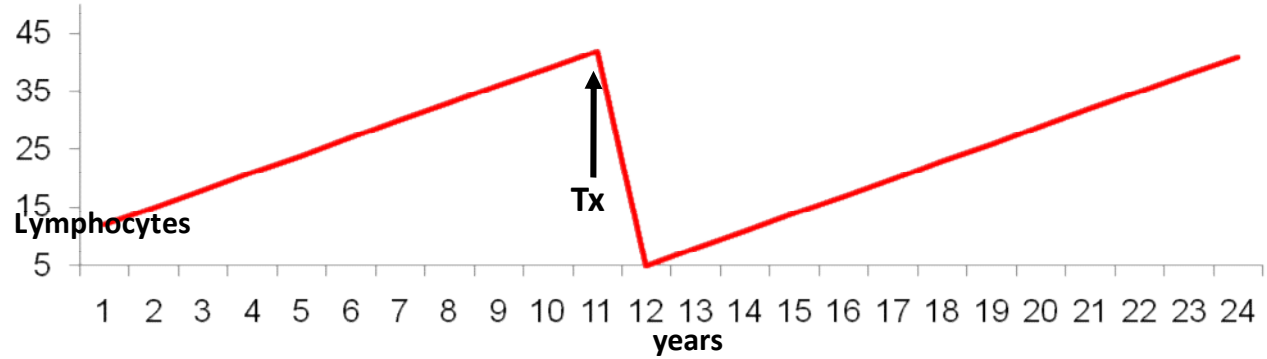
Group 1	Group 2	Group 3
• completely independent • no comorbidity • normal, age-matched life expectance	• somewhat impaired	• Severely handicapped • high comorbidity • reduced life expectance
„Go go“ Intensive therapy: FC, FCR, Tx → long lasting remissions! Cure?	„Slow go“ Mild therapy: CLB, F mono → control of symptoms	„No go“ Palliative care

CLL: decorsi eterogeni

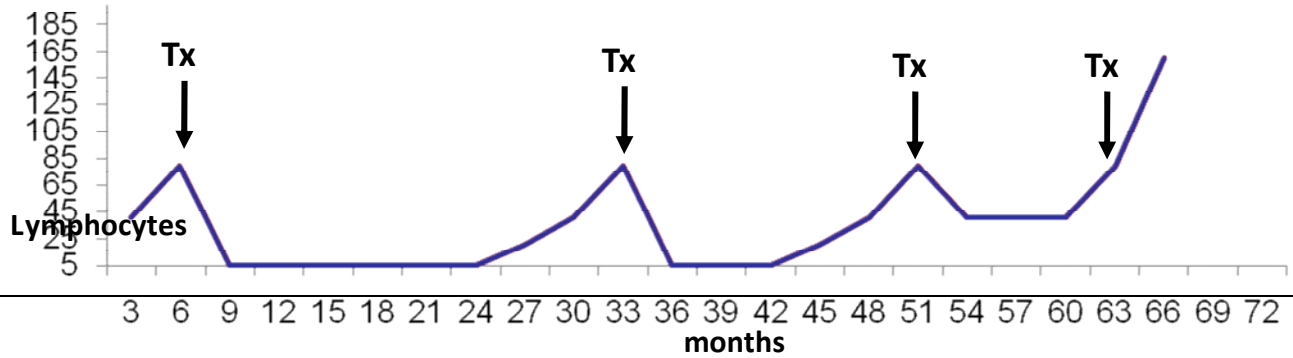
Highly stable



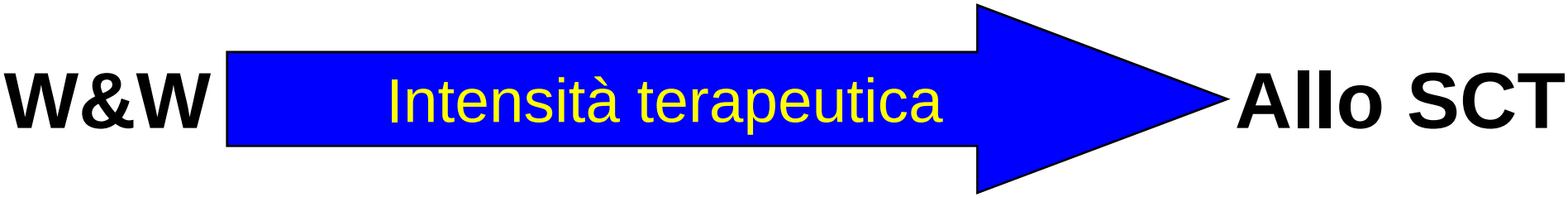
Slowly progressive



Rapidly progressive

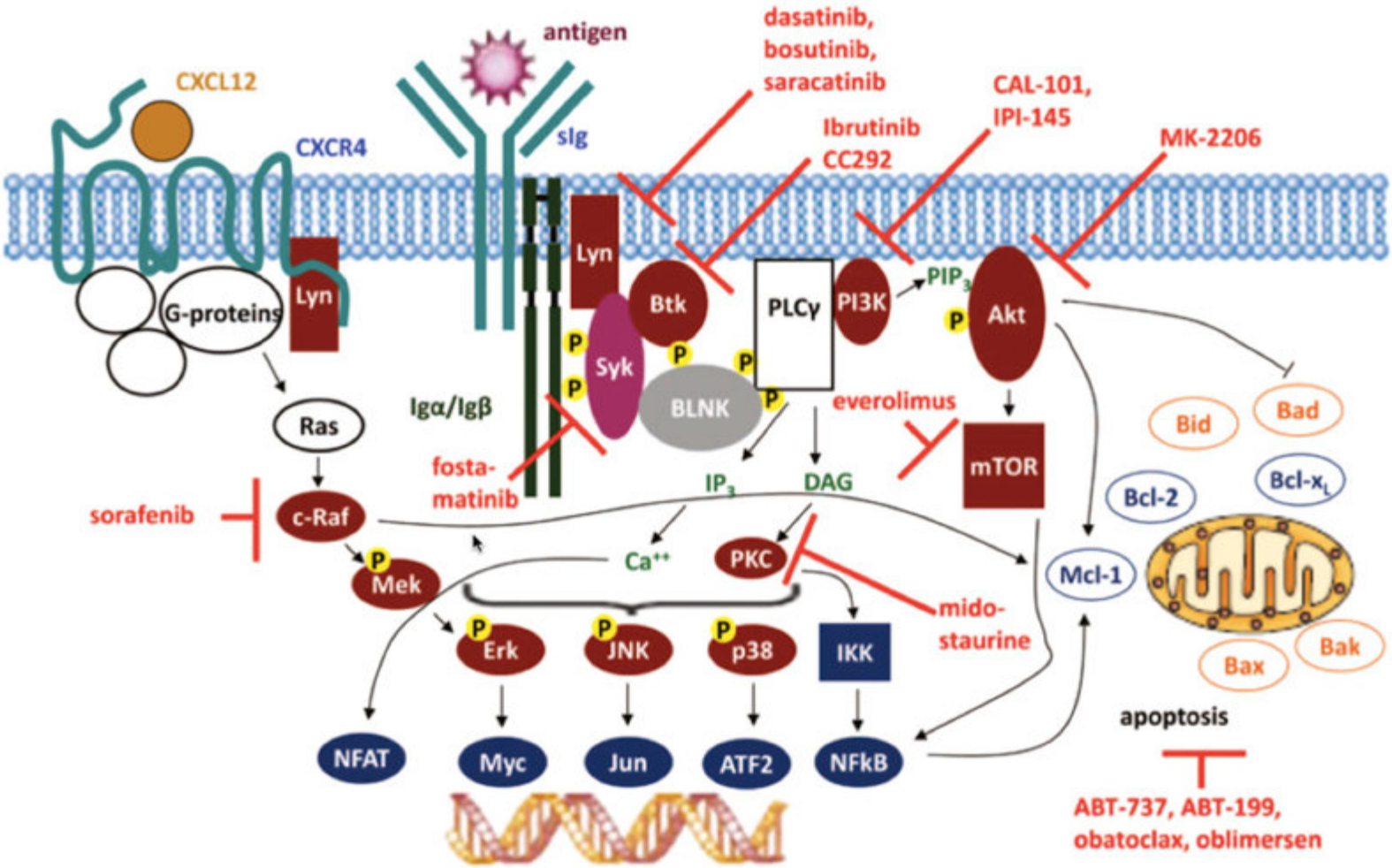


Terapia CLL

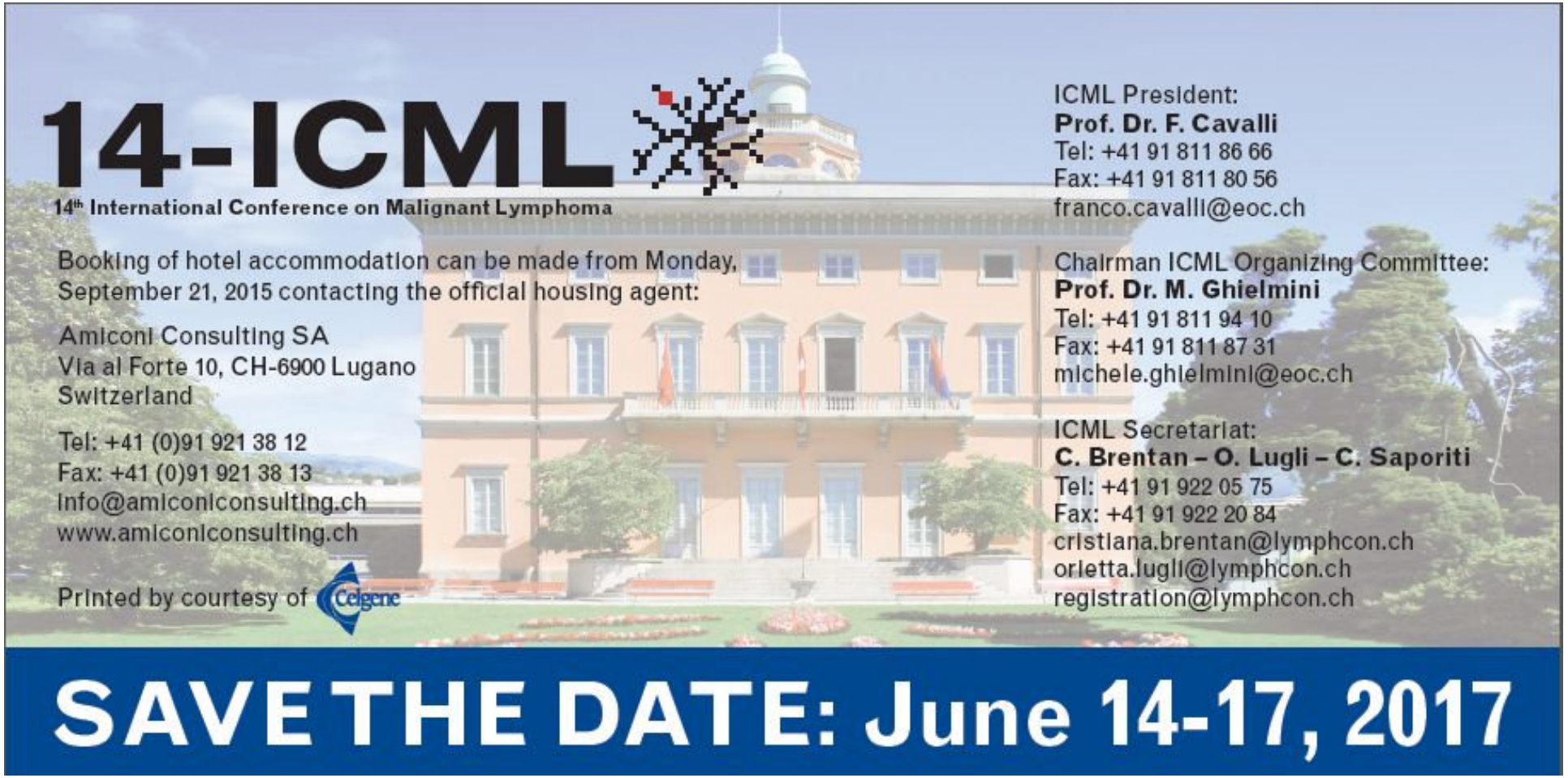


(R)-Chlorambucil
R-mono
Ofatumumab
(R)-Fludarabine (F)
(R)-Bendamustine (B)
R-FC
Alemtuzumab
Ibrutinib, Venetoclax, Idelalisib

BCR Targeting per trattare CLL



Hallek M. Signaling the end of chronic lymphocytic leukemia: new frontline treatment strategies. *Blood*. 2013;122(23):3723–3734.


14-ICML
14th International Conference on Malignant Lymphoma
Booking of hotel accommodation can be made from Monday, September 21, 2015 contacting the official housing agent:
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SAVE THE DATE: June 14-17, 2017