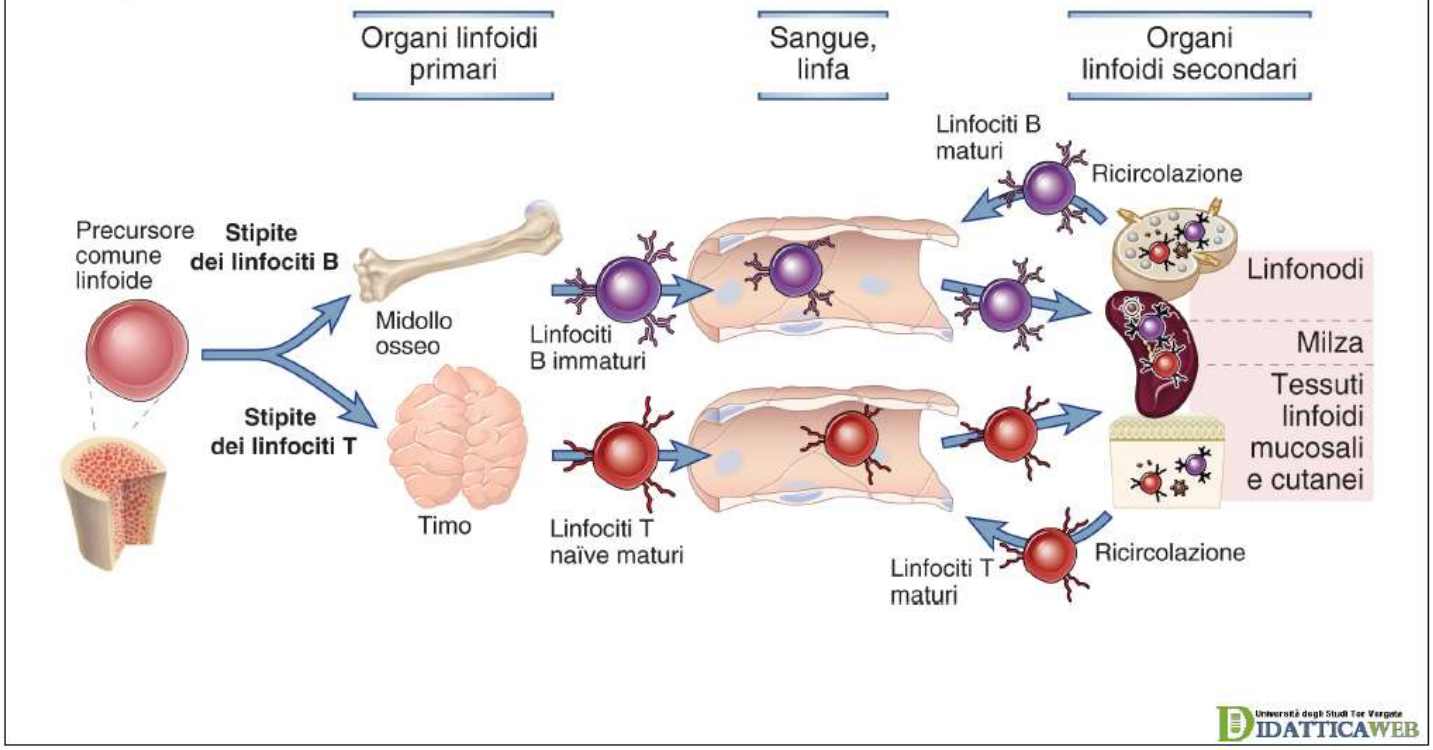
Il percorso di maturazione dei linfociti



Linfomi: definizione

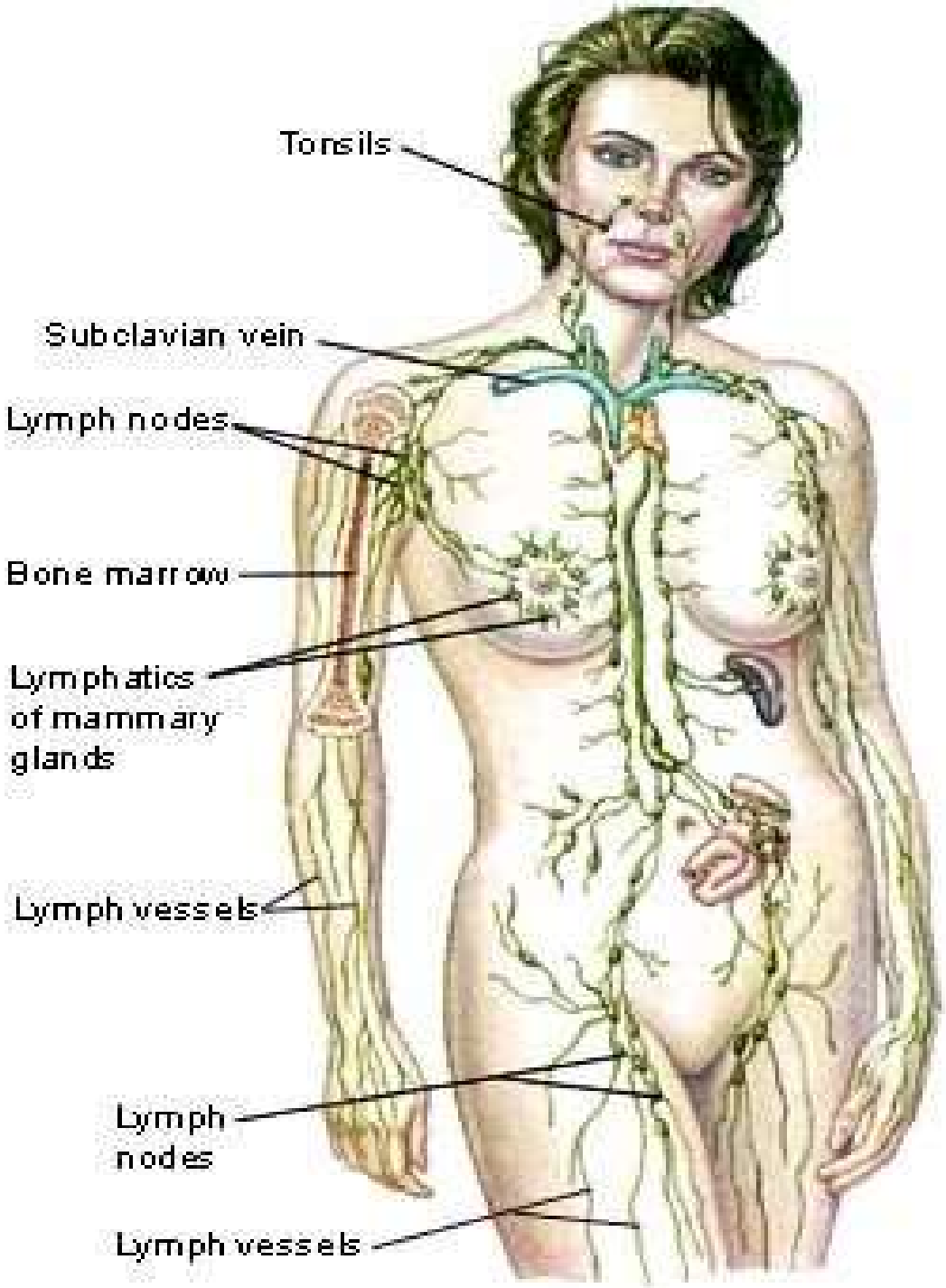
Tumori del sistema linfatico

Gruppo eterogeneo di malattie che si differenziano per:

- Epidemiologia
- Eziologia
- Biologia
- Aggressività
- Presentazione clinica
- Risposta alle terapie
- Prognosi

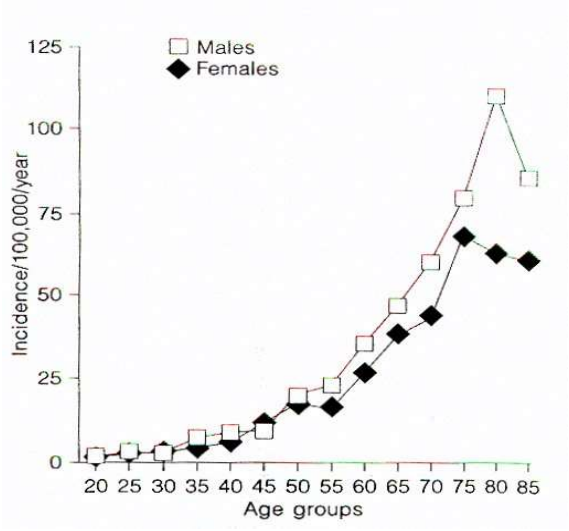
Sistema Immunitario Primario
- Midollo osseo
- Timo

Sistema Immunitario Secondario
- Linfonodi
- Milza
- Tessuto linfatico cute
- Tessuto linfatico intestino
- Tessuto linfatico faringe



Linfomi: epidemiologia

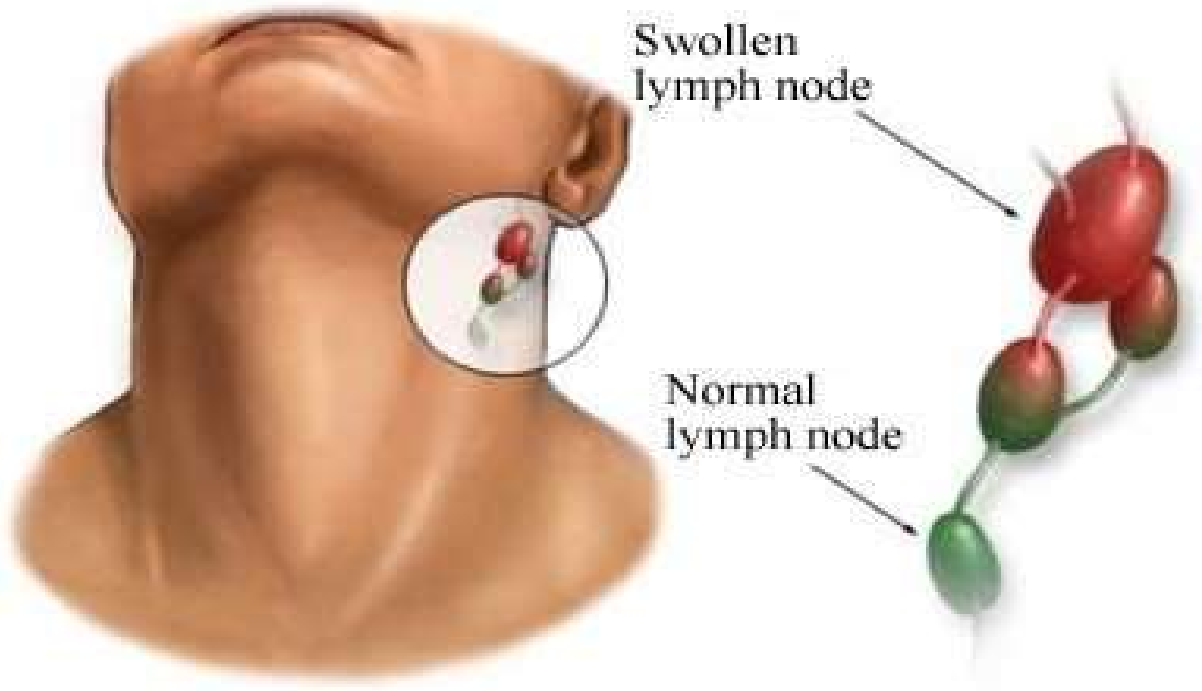
- 4% delle nuove diagnosi di tumore maligno;
- Incidenza: circa 30 nuovi casi su 100.000 abitanti anno;
- Incidenza in incremento;



- Età di insorgenza: variabile a seconda del tipo di linfoma; età media intorno ai 60-70 anni;
- Lieve prevalenza nel sesso maschile;
- Categorie a rischio: pazienti con stato di immunosoppressione o affetti da patologie del sistema immunitario (malattie autoimmuni);

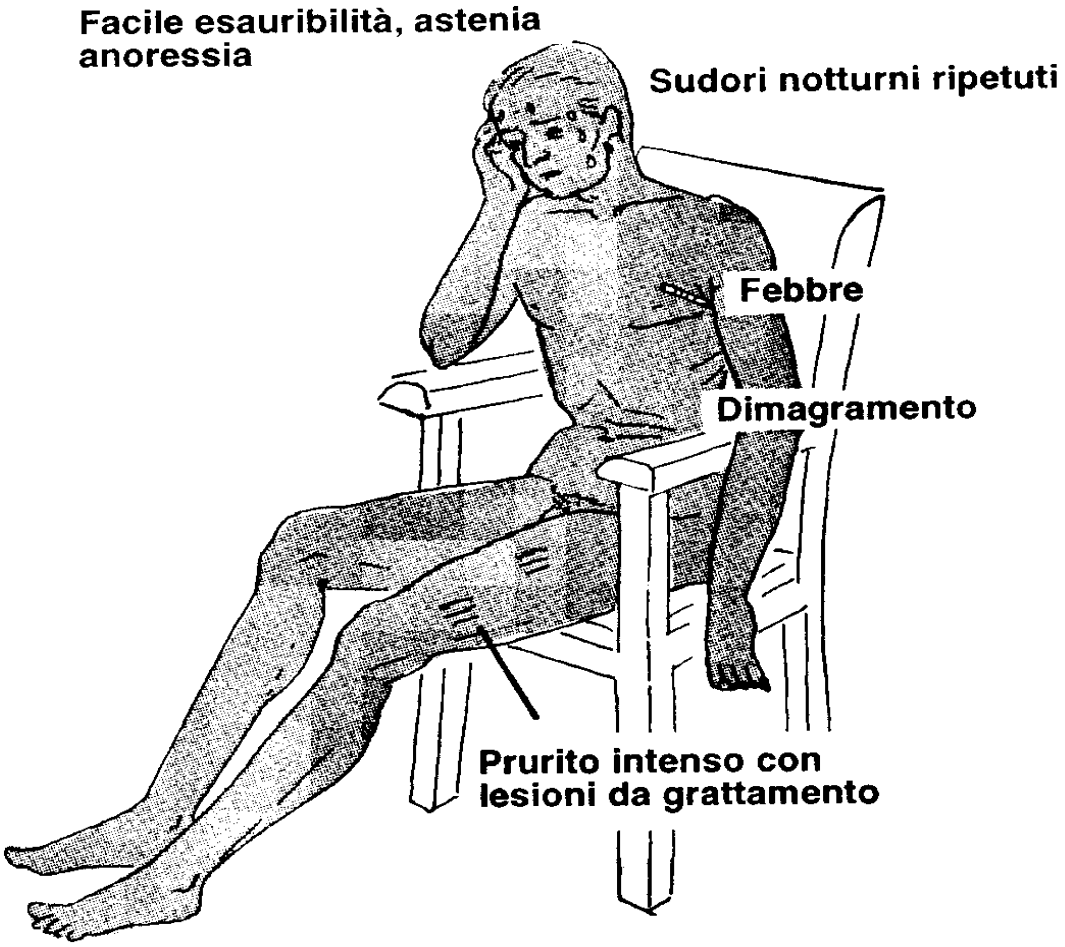
Linfomi: presentazione

1. Tumefazione delle sedi linfatiche coinvolte



Linfomi: presentazione

2. Sintomi generali



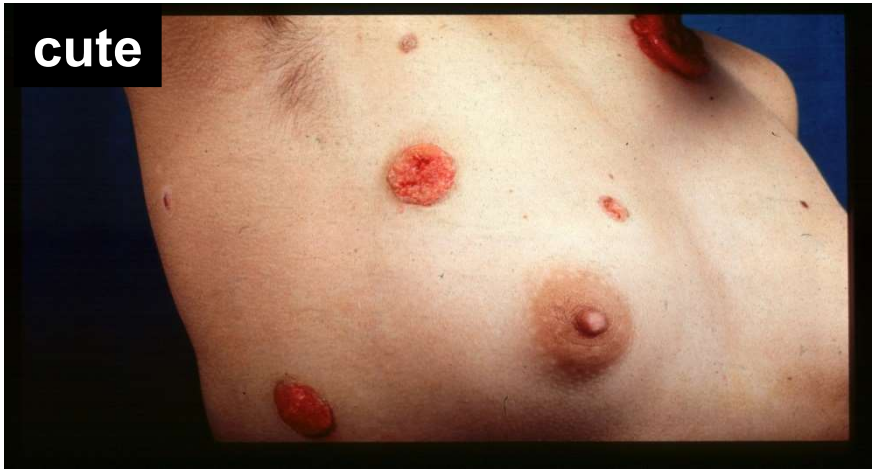
Linfomi: presentazione

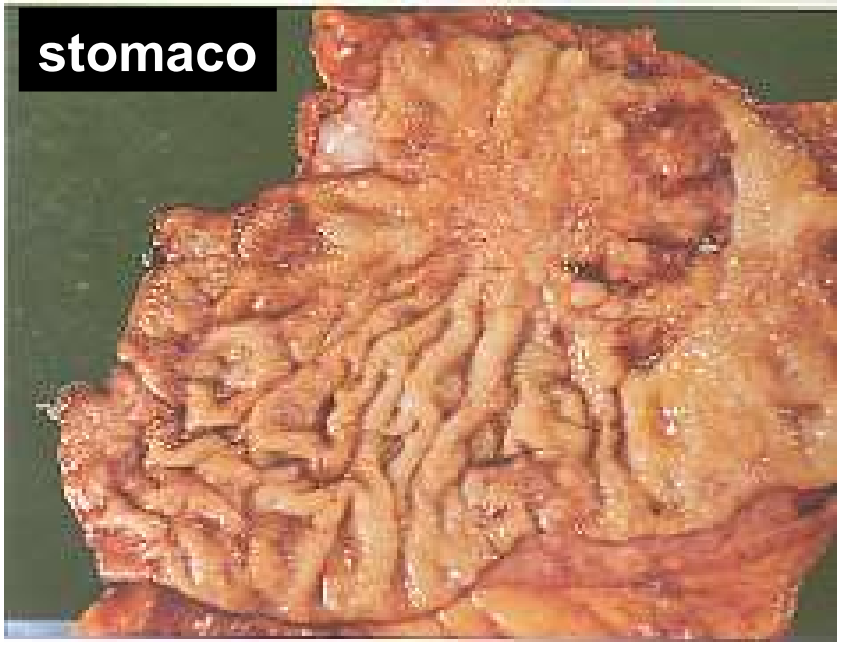
3. Stato di immunosoppressione

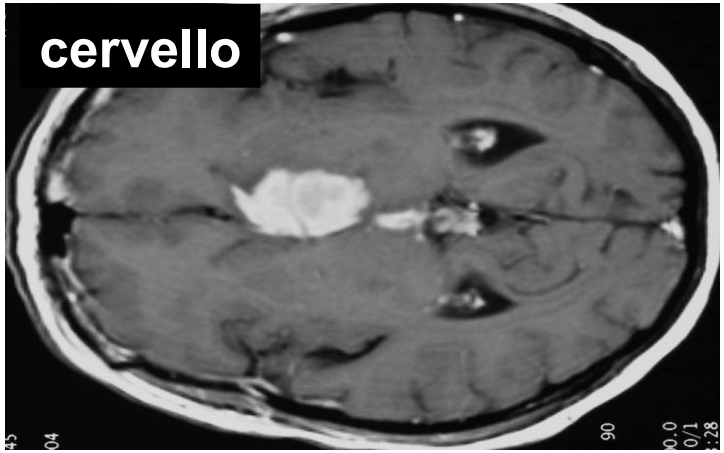
Maggiore ricettività alle infezioni

Linfomi: presentazione

4. Possibile interessamento anche di organi non linfatici

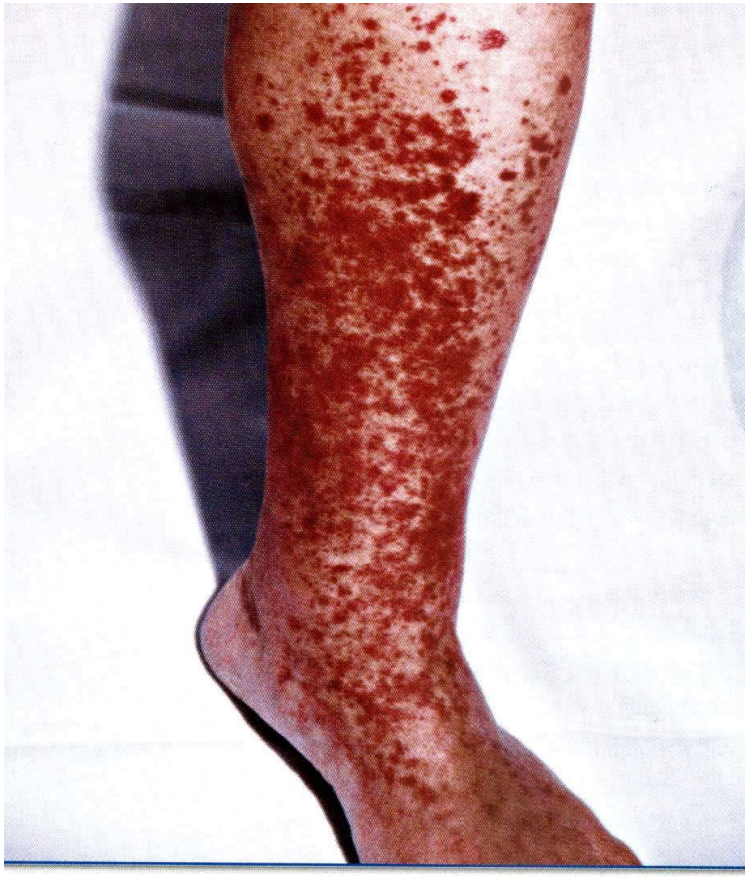


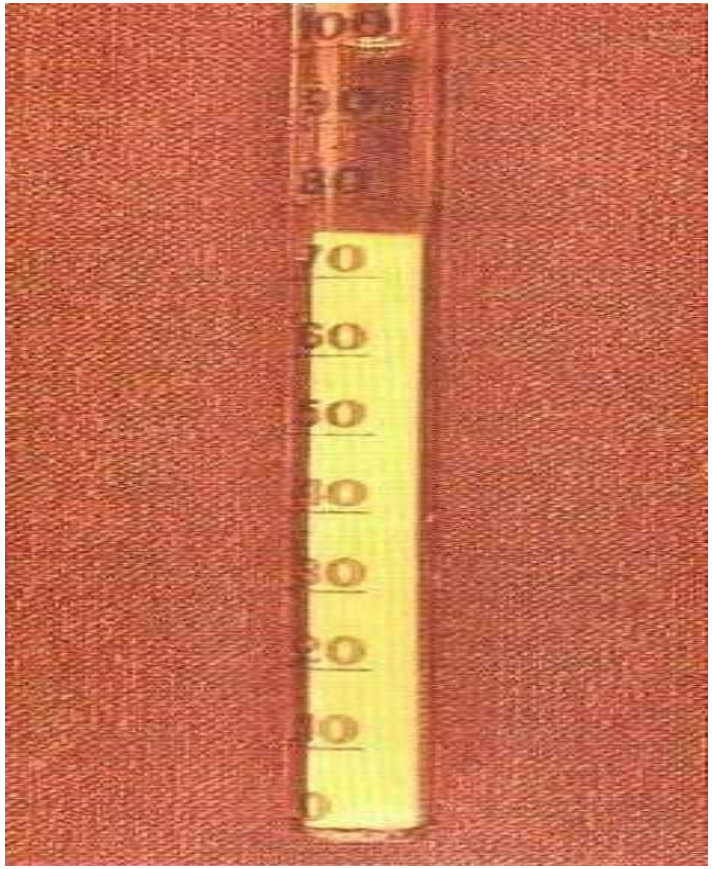




Linfomi: presentazione

5. Fenomeni particolari





Linfomi: eziologia

1. Sconosciuta nella maggior parte dei casi
2. Agenti “inquinanti” in genere (fumo, pesticidi, radiazioni)
3. Alcuni farmaci (chemioterapici, farmaci immunosoppressori)
4. Agenti infettivi:
   - Virus (HCV, EBV, HIV, …)
   - Batteri (Helicobacter Pilori, Clamidia Psittaci, …)

DIAGNOSI

La diagnosi di linfoma deve essere

SEMPRE

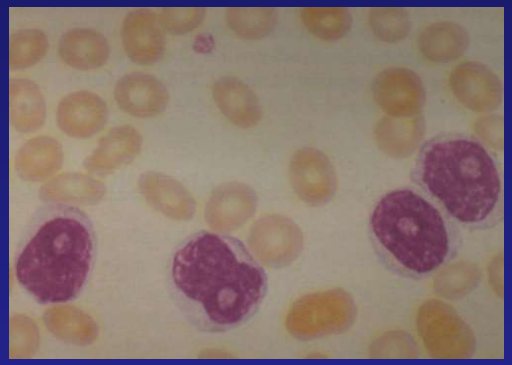
documentata istologicamente

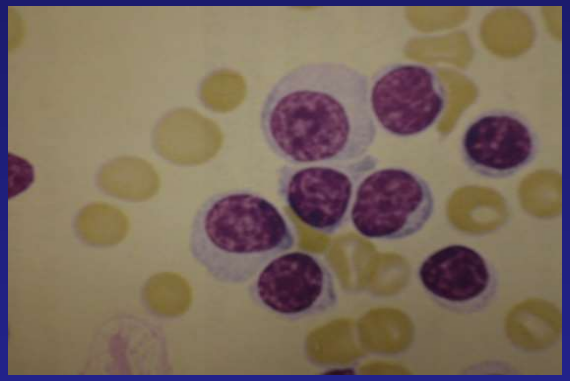
~~AGOASPIRATO LINFONODALE~~

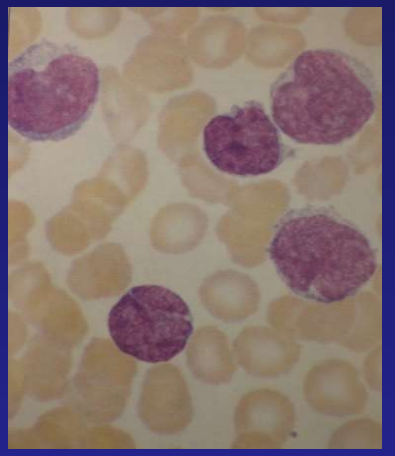
- insufficiente per iniziare una chemioterapia antitumorale
- può alterare l'architettura strutturale del linfonodo e rendere quindi problematica la diagnosi sulla successiva biopsia
- elevata percentuale di falsi positivi o negativi
- inadeguato ai fini della precisazione classificativa del linfoma
- quanto tempo ci fa perdere?

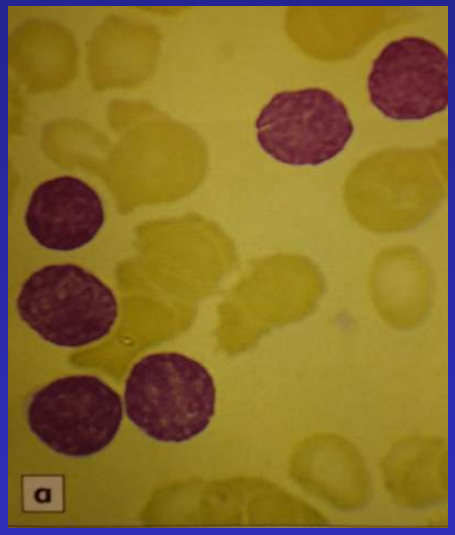
ACCERTAMENTI DI LABORATORIO

- esame emocromocitometrico completo, con formula ed osservazione dello striscio al microscopio
- tests sierologici (mononucleosi, toxoplasmosi, HIV, CMV)
- LDH
- β_2 microglobulina
- protidemia con elettroforesi, immunodiffusione e immunofissazione





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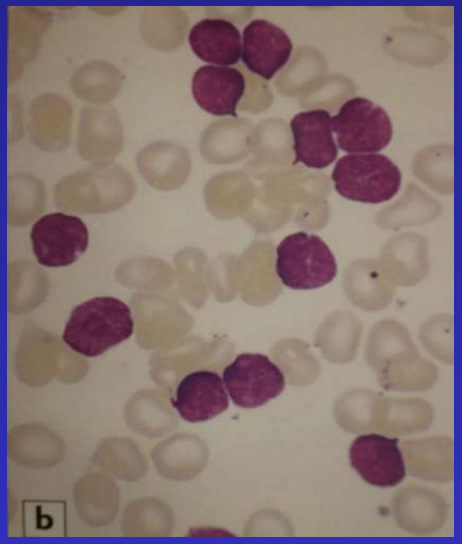
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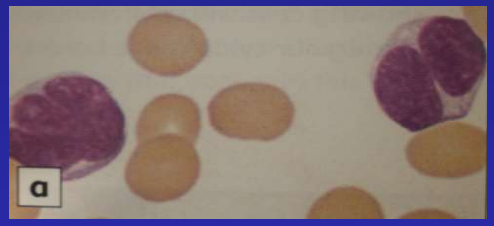
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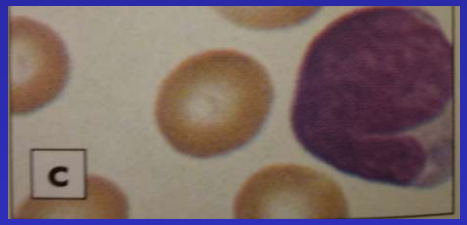

c

Linfomi: diagnosi e inquadramento

- Biopsia: linfonodo e midollo osseo, altri organi
- Esame clinico
- Esami di laboratorio
- Indagini radiologiche:
  - TAC collo-torace-addome
  - Risonanza Magnetica
  - PET (TC-PET)

Indagini particolari:

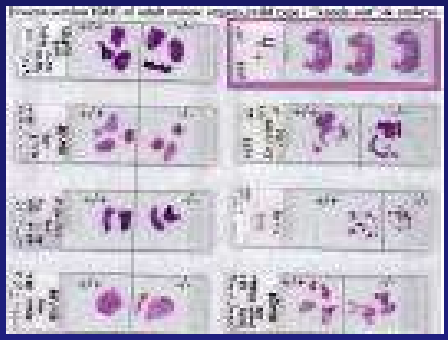
  - Puntura lombare
  - Endoscopia (stomaco, intestino)
  - Diagnostica molecolare

Ottimizzare:
- diagnosi
- prognosi
- terapia

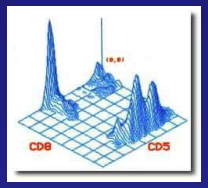
Biopsy

Lymph node

Laboratory



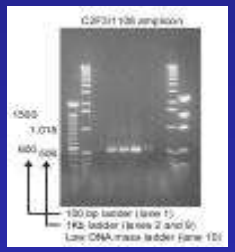
Histology



Flow Cytometry

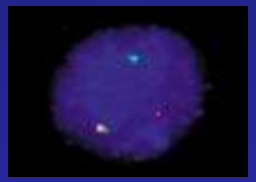
fresco

inclusione



Molecular diagnosis

Citogenetics



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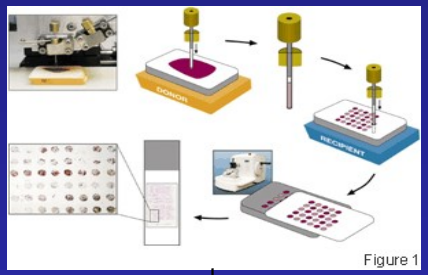
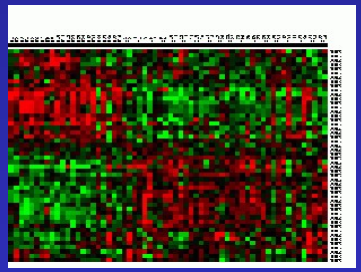
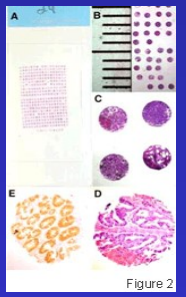




Gene profiling

Proteomics

Antibodies



Tissue microarray

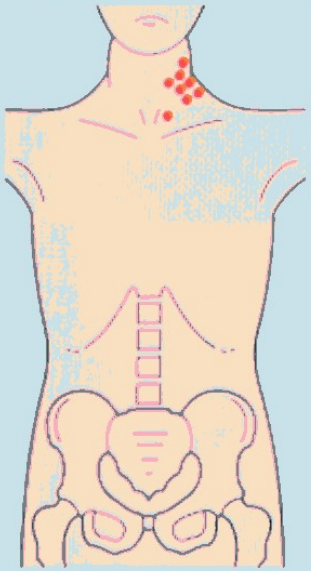
STADIAZIONE

Poter stratificare, attraverso l'accurata valutazione della estensione e della diffusione della neoplasia, gruppi di pazienti a diversa prognosi a lungo termine per i quali, quindi, sia possibile proporre approcci terapeutici diversificati.

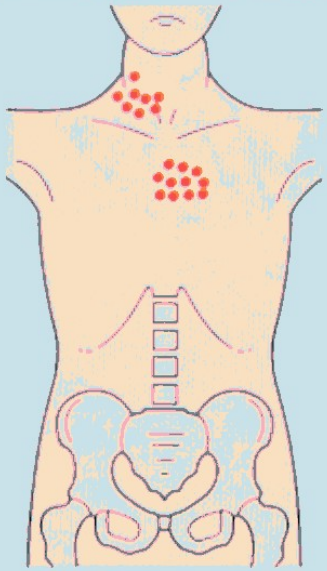
The Ann Arbor Staging System for HL (1974)

Stage	Anatomic Description
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or a site (IE)
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm without (III) or with (IIIE) localized involvement of an extralymphatic organ or site
Stage IV	Diffuse involvement of >/= 1 extralymphatic organ or site, with or without lymphatic involvement

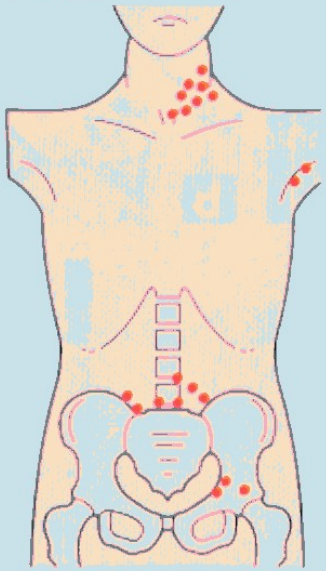
ANN ARBOR STAGING



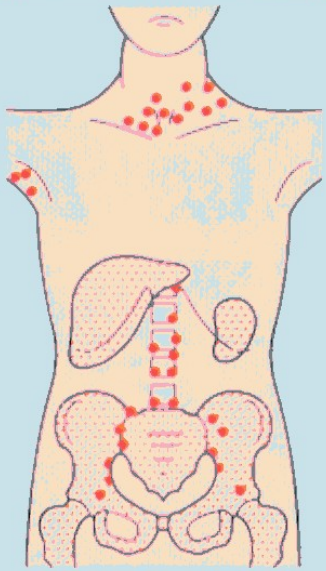
Stage I:
involvement of single lymph node region or single extralymphatic site (I_E)



Stage II:
involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic involvement on same side of diaphragm (II_E)



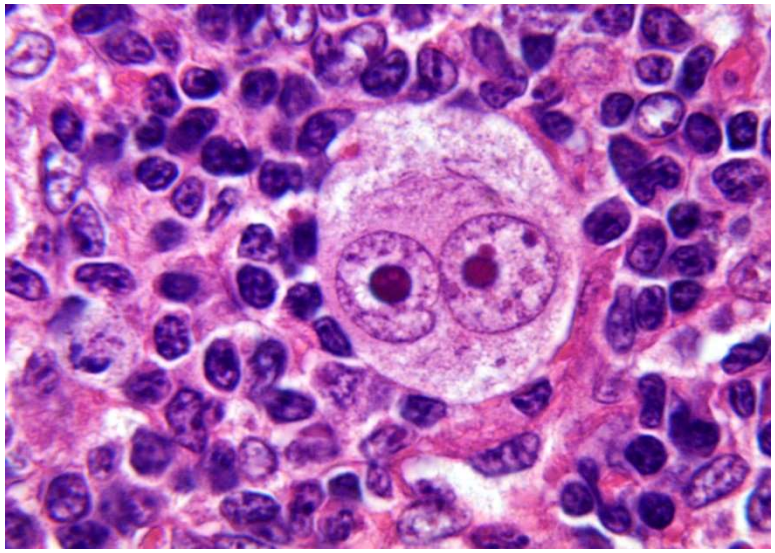
Stage III:
involvement of lymph node regions on both sides of the diaphragm; may include spleen (III_S) or localized extranodal disease (III_E)

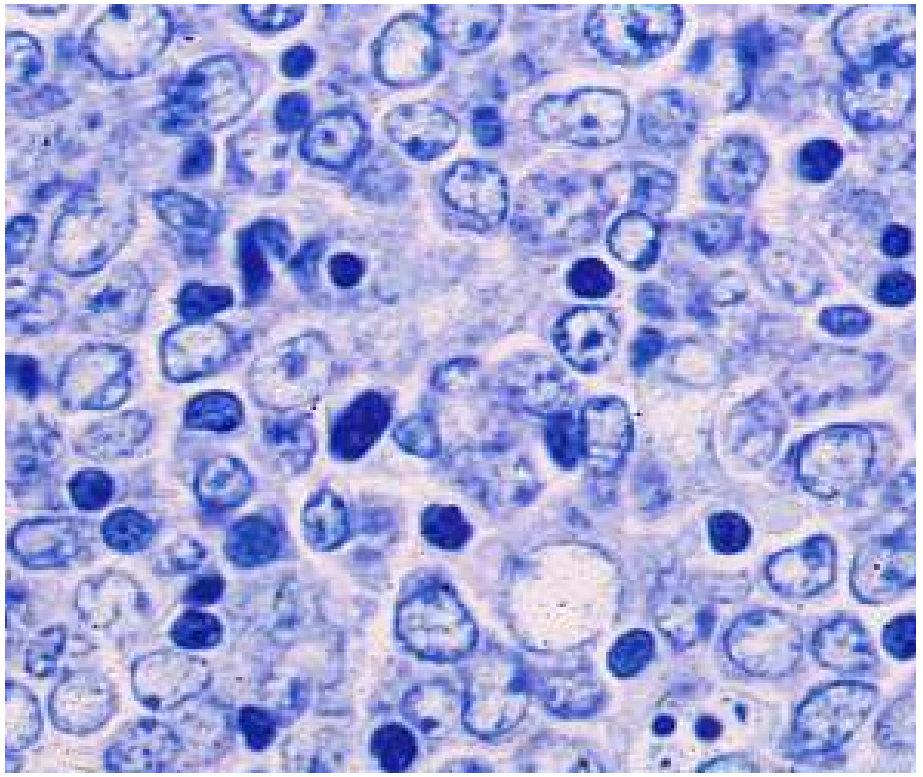


Stage IV:
diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)

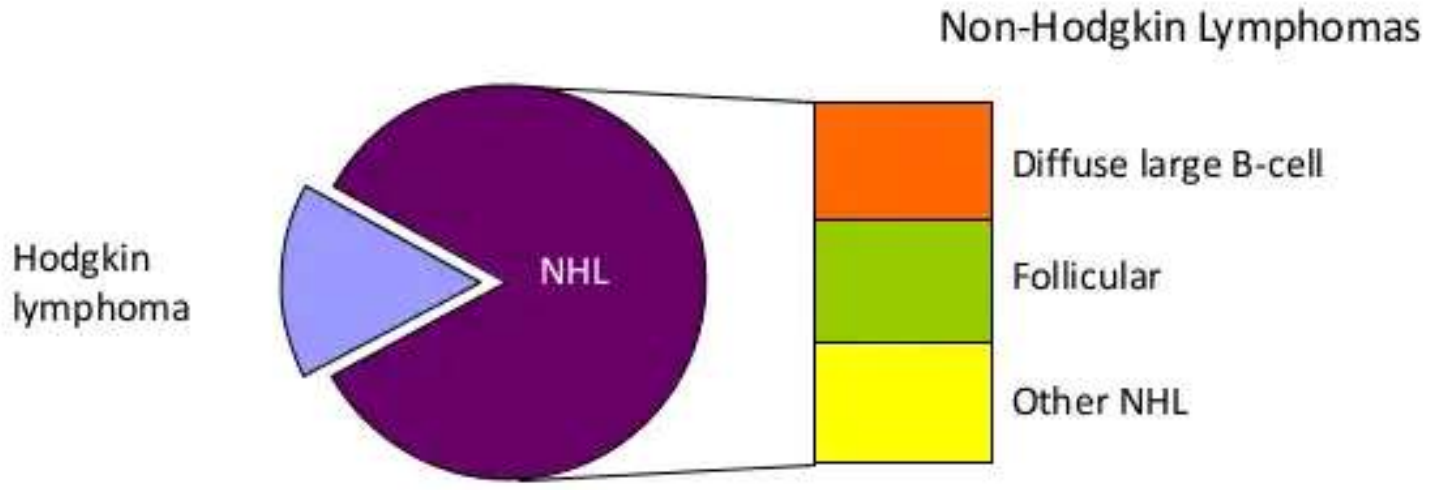
NB: if unexplained weight loss of >10% body weight in preceding 6 months and/or fevers of >38°C and night sweats, classified as 'B'; if absent, 'A'.

Linfomi: *Hodgkin vs non Hodgkin ?*





Relative frequencies of different lymphomas



~85% of NHL are B-lineage

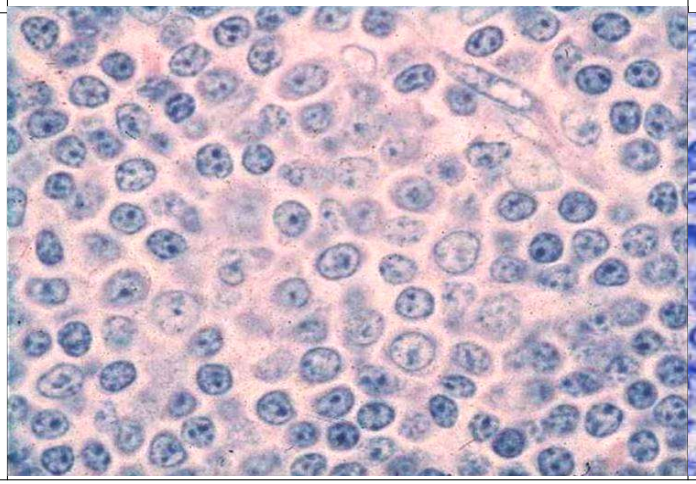
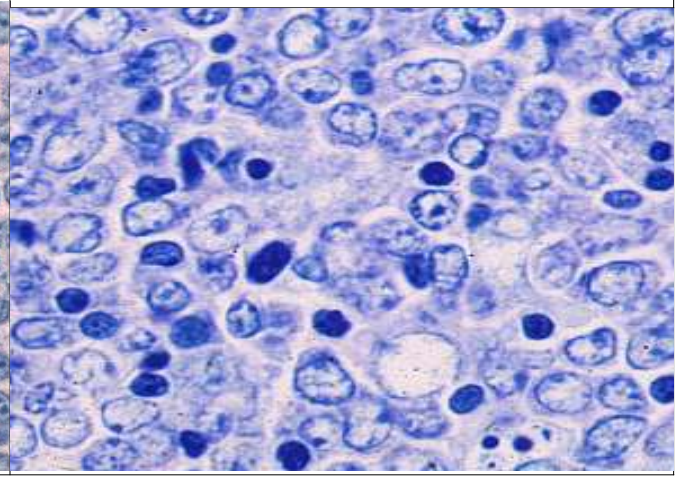
SISTEMI CLASSIFICATIVI DEI LINFOMI NON HODGKIN

Classificazione	Data
Rappaport Classification[8]	1956 e 1966
Lukes e Collins Classification[15]	1974
Kiel Classification[16,17]	1974
British National Lymphoma Invest. *[21]	1974
Dorfman Classification*[22]	1974
WHO Classification*[23]	1976
Working Formulation[24]	1982
Updated Kiel Classification[18]	1988

UPDATED KIEL CLASSIFICATION

Derivazione linfocitaria B	*Derivazione linfocitaria T*
A basso grado di aggressività • Leucemia linfatica cronica • Leucemia prolinfocitica • Leucemia a tricoleucociti • Linfoplasmo-citico/citoide (Lp immunocitoma) • Plasmocitoma extramidollare • Centroblastico/centrocitico: follicolare ± diffuso, diffuso • Centrocitico	**A basso grado di aggressività** • Leucemia linfatica cronica • Leucemia prolinfocitica • A cellule cerebriformi: micosi fungoide e sindrome di Sézary • Linfoma linfoepitelioideo (linfoma di Lennert) • Linfoma simil-angioimmunoblastico • Linfoma della zona T • Linfoma a cellule T periferiche polimorfe, piccole (HTLV±)
Ad alto grado di aggressività • Centroblastico • Immunoblastico • A grandi cellule anaplastiche CD30+ • Linfoma di Burkitt • Linfoblastico	**Ad alto grado di aggressività** • Linfoma a cellule T periferiche polimorfe, medie-grandi (HTLV±) • Immunoblastico • A grandi cellule anaplastiche CD30+ • Linfoblastico

Linfomi: evoluzione

	Linfomi basso grado	Linfomi alto grado
Accrescimento	**lento**	**rapido**
Espansione tumorale	**accumulo, ↓ apoptosi**	**replicazione**
Indice di proliferazione	**basso**	**alto**
Presentazione clinica	**indolente**	**aggressiva**
Eradicazione	**difficile**	**~ 50%**
Morfologia		

REAL classification of lymphoma (1994)

REAL = Revised European American Lymphoma classification

REAL = reale, riproducibile

Criteri morfologici

Espressione di marcatori immunofenotipici

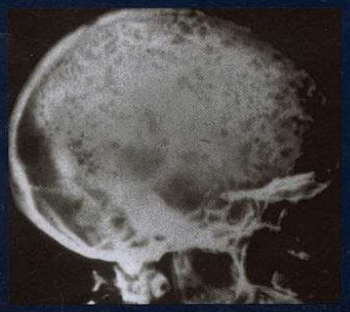
Espressione di marcatori cariotipici/molecolari

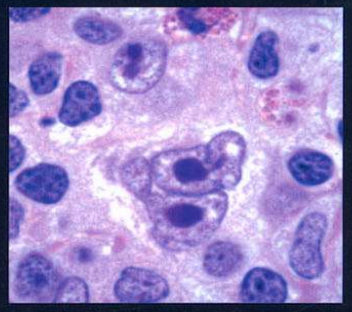
World Health Organization Classification of Tumours

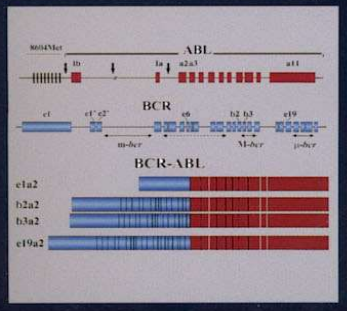
Pathology & Genetics

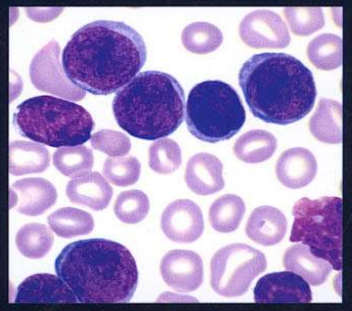
Tumours of Haematopoietic and Lymphoid Tissues

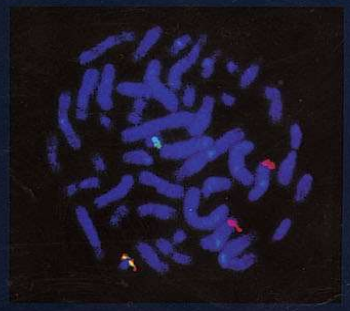
Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman











THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

[1]Division of Hematopathology, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Department of Pathology, Hospital Clinic, University of Barcelona, August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; [3]Haematopathology Unit, European Institute of Oncology, Milan, and Department of Experimental, Diagnostic and Specialty Medicine, Bologna University Medical School, Bologna, Italy; [4]Department of Pathology, Harvard Medical School and Massachusetts General Hospital, Boston, MA; [5]Pathodiagnostik, Berlin, Germany; [6]Institute of Human Genetics, Christian Albrechts University Kiel, Kiel, Germany; [7]Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; [8]Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [9]Department of Hematology, Hospices Civils de Lyon, and Université Claude Bernard Lyon-1, Lyon, France; [10]Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; and [11]Hematopathology Section, Laboratory of Pathology, National Cancer Institute, Bethesda, MD

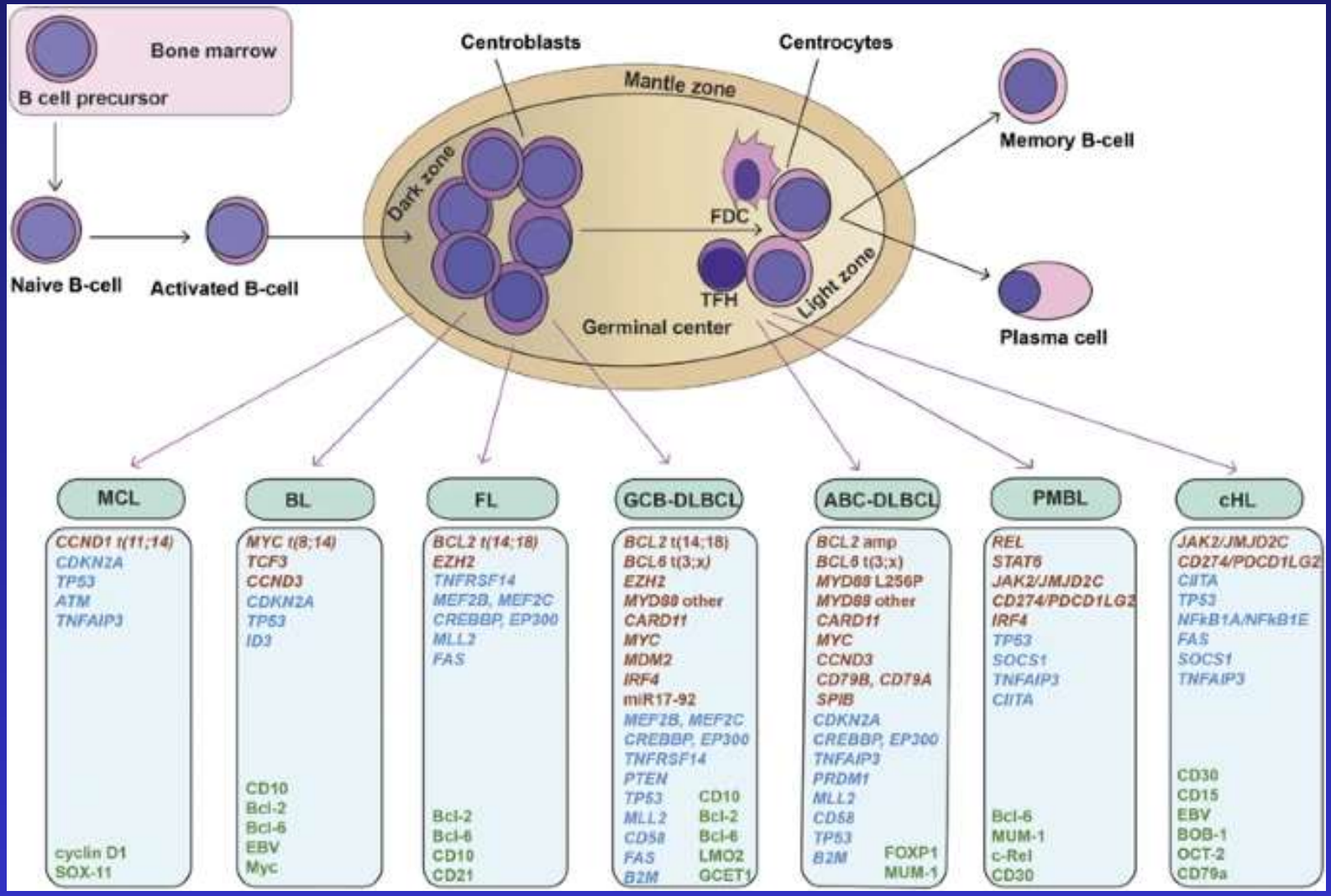
Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

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*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
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

Table 1. (continued)

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$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
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*

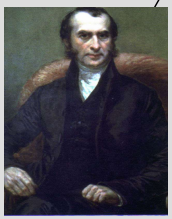
B CELL LYMPHOMA: CELLULAR ORIGIN



I LINFOMI DI HODGKIN

Introduction

- Are group of cancers which originate from lymphatic systems.
- It was named after Thomas Hodgkin who first described it in 1832.
- Dorothy Reed and Carl Sternberg first described the malignant cells of Hodgkin lymphoma call Reed Sternberg cells.
- Hodgkin lymphoma was the first cancer which could be successfully treated by radiation therapy and also by combination chemotherapy.



Hodgkin's Disease

1832 1865 1947 1966 1994 2001

Jackson-Parker

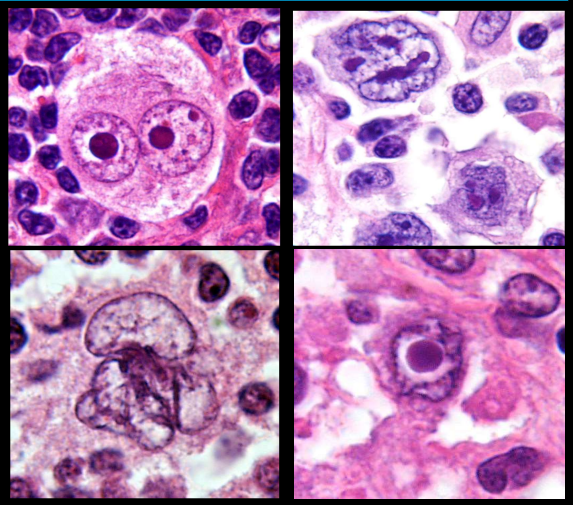
Lukes-Butler
Rye conference

REAL WHO

Linfoma di Hodgkin: natura cellulare

Endothelial cells
Histiocytes
Myeloid cells
Dendritic cells
Cell chimera

T Lymphocytes
B Lymphocytes



Reed Sternberg cell

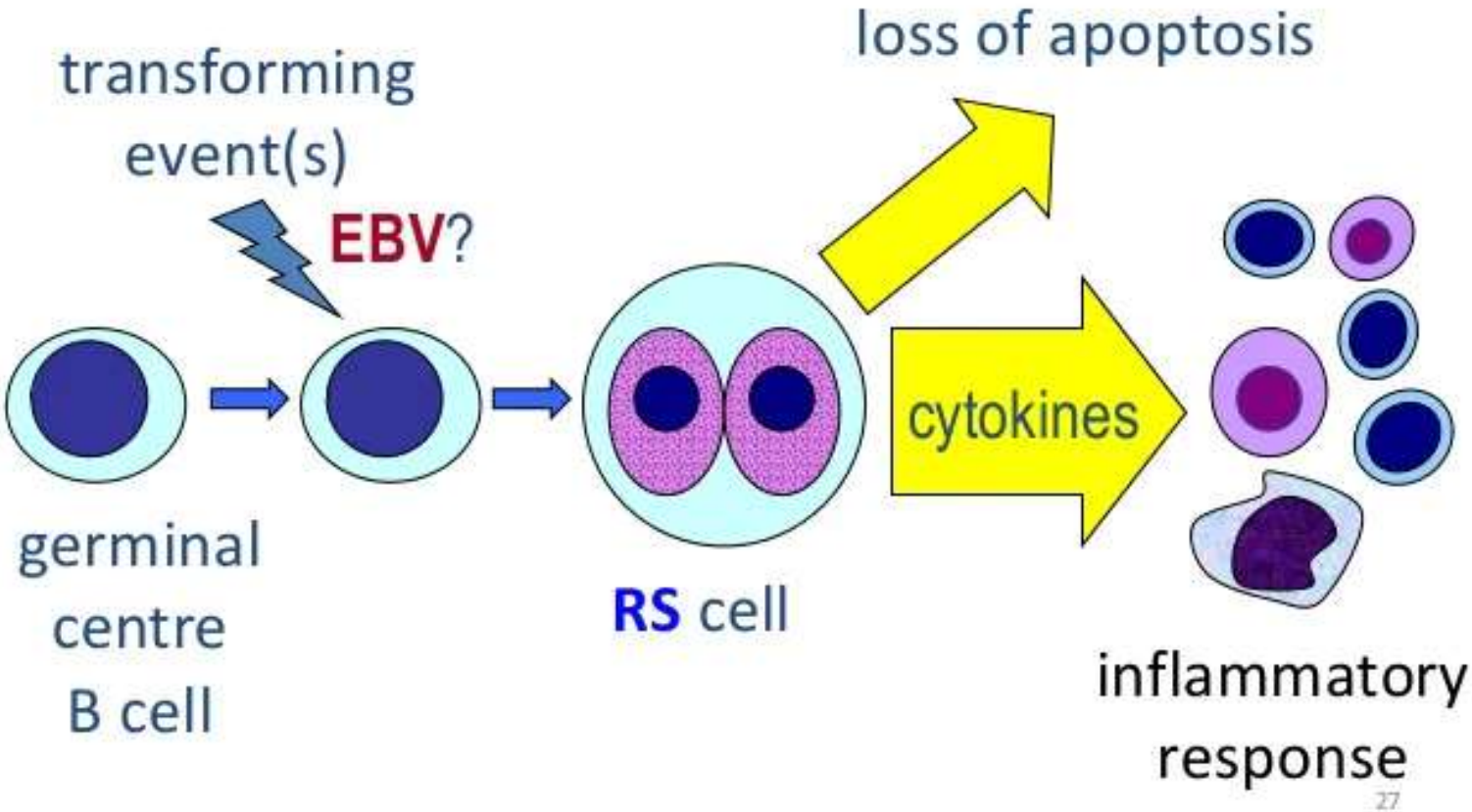
Common feature of ALL Hodgkin Lymphomas.

- Large cells (>45um in diameter) with classically binucleate or bilobed central nucleus each with a large acidophilic central nucleoli surrounded by a clear halo. "owl's eye appearance"
- **Variants**: *mononuclear (Hodgkin's cell), mummified cell, lacunar cell, L/H cell.*
- Requirement of Reed-Sternberg cell for initial diagnosis is "absolute"(less strict for LPHL or recurrent disease)
- Classic Reed-Sternberg cell:

  + CD15, CD30, CD25

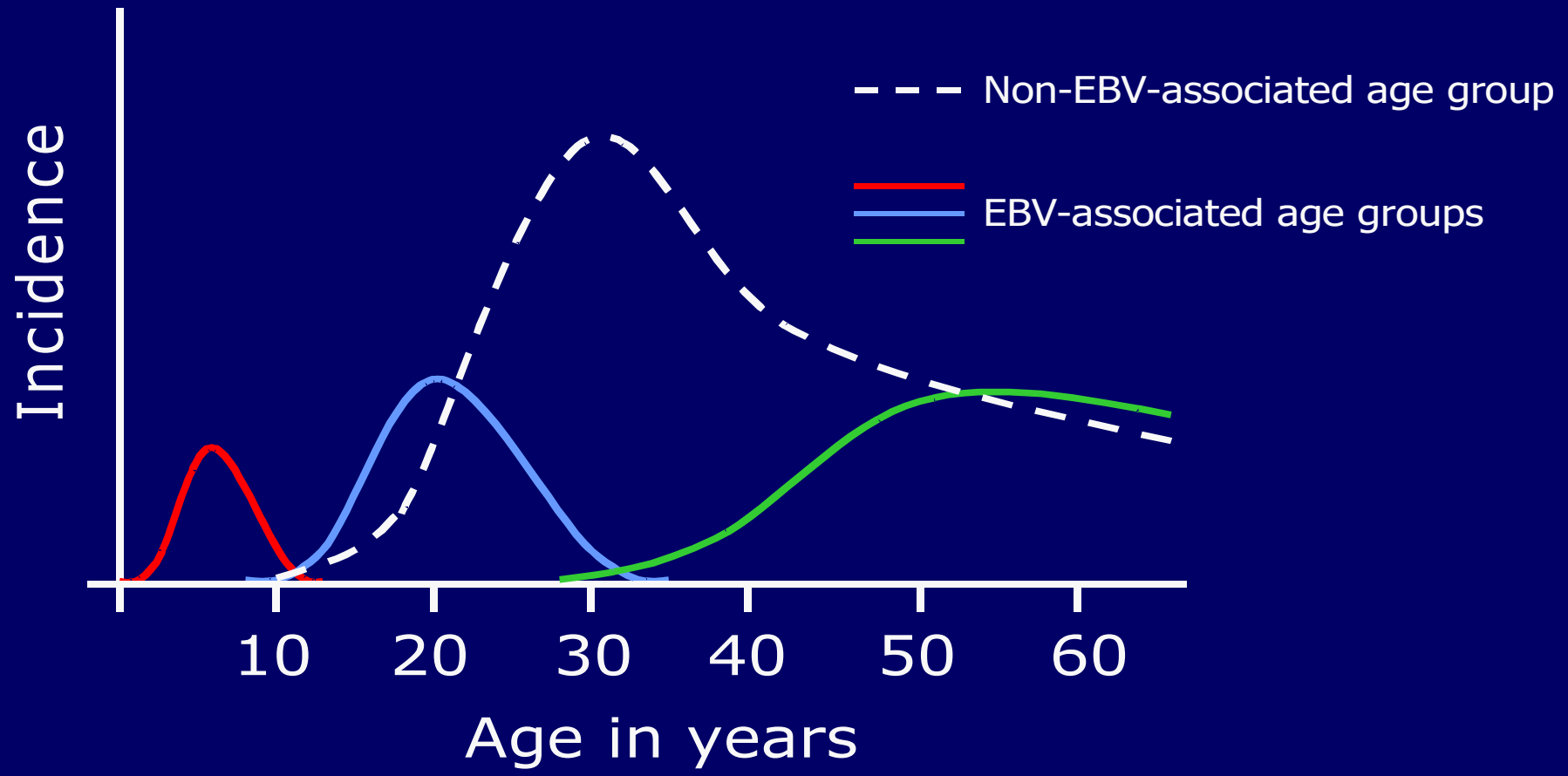
  – CD45, pan-B, S-100, keratin, EMA
- Most current studies indicate the RS cells of HL are lymphocytic in nature and, in the great majority of cases, are of B-cell origin.

A possible model of pathogenesis



Four disease model of HD

Jarret R.F., Annals of Oncology (2002)



Risk Factors

- No clear risk factors, several implicated
    - EBV (pathogen or passenger)
    - HIV
    - woodworking, farming
    - rare familial aggregations
- First degree relatives have five fold increase in risk for Hodgkin lymphoma.
- Associated with EBV infection mainly with mixed cellularity type.
- High socio economic status.
- Prolonged use of of human growth hormone.
- men > women
- whites > blacks > Asians

Clinical features

- Most common presentation is asymptomatic lymphnode enlargement, typically in the neck.
- Cervical lymphnodes are involved in 80% cases.
- Mediastinal involvement is seen in about 50% cases. They produce symptoms like chest pain, cough and dyspnoea.
- Infradiaphrgamatic involvement is seen in 5% cases and usually seen with older patients.
- Other less common symptoms are :

Pruritis, alcohol induced pain over involved lymphnodes, nephrotic syndrome, erythema nodosum, cerebellar degeneration, immune hemolytic anaemia, thrombocytopenia, hypercalcemia.

B symptoms

- About 33 % present with B symptoms overall
- Only 15-20% of stage I-III have B symptoms like

1. Fever(>38^C)

- May first present as fever of unknown origin
- Fever persists for days to weeks followed by afebrile intervals and then recurrence.
- This pattern is called Pel Ebstein fever.

2. Drenching night sweats

3. Weight loss (>10% in 6 months)

Diagnostic workup

- **History**
- **Complete physical examination**
- **Confirmatory workup**

➢ Excisional biopsy of the lymph node

❑ **Staging workup**

➢ Chest x ray(pa,lat)
➢ Usg neck,whole abdomen
➢ CT scan thorax,abdomen and pelvis
➢ FDG PET scan

- Routine blood investigations

- **Complete blood count**
- **Liver function**
- **Renal function**
- **Serum albumin**
- **ESR**
- **Lactate Dehydrogenase**

- OTHERS
- **Bone marrow biopsy**

Bone Marrow Biopsy

- Less commonly put into practice

- Overall involvement of bone marrow in Hodgkins lymphoma is 5%.

- Indicated in pts with
- B symptoms
- Clinical evidence of sub diaphragmatic disease
- Stage iii-iv
- Recurrent disease

2008 WHO Classification of Hodgkin Lymphoma

	Histologic Subtypes
	Nodular lymphocyte predominant Hodgkins lymphoma (NLPHL)
	Classical Hodgkins lymphoma(CHL)
1	Nodular sclerosis Hodgkins lymphoma
2	Lymphocyte rich classical Hodgkins lymphoma
3	Mixed cellularity Hodgkins lymphoma
4	Lymphocyte depletion Hodgkin lymphoma

I LINFOMI

PRINCIPI DI TERAPIA

Linfomi: terapia

- Non sempre necessaria (linfomi basso grado) nelle prima fasi della malattia;
- Chemioterapia;
- Immunoterapia;
- Radioterapia;

- Farmaci ad uso orale o ev;
- In monoterapia o in combinazione (cicli di terapia);
- Trapianto di cellule staminali emopoietiche;
- Nuovi farmaci in studio;

Linfomi: obiettivi della terapia

Funzione di:

- Tipo di linfoma;
- Età, caratteristiche e problematiche del paziente;

GUARIGIONE

CONTENIMENTO

LINFOMA DI HODGKIN

PASSATO

Curare la malattia

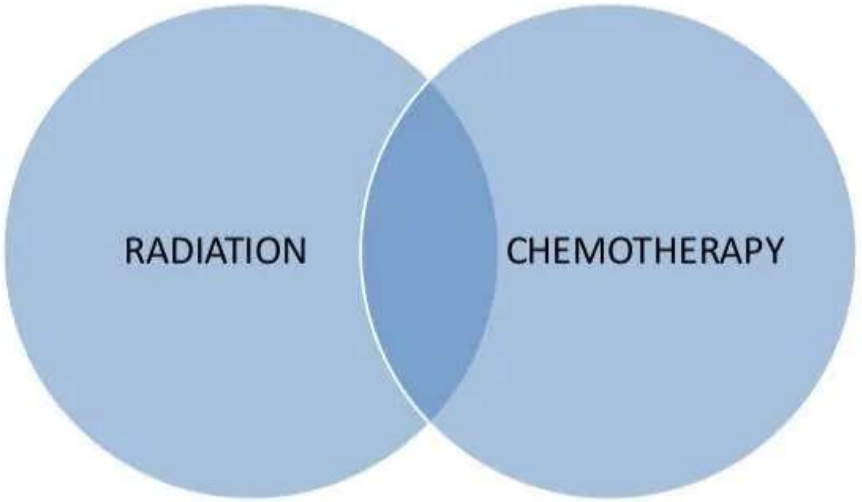
Eradicare la malattia ?

PRESENTE

Eradicare la malattia

Minimizzare gli effetti collaterali

Management



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Chemotherapy

Regimen	Medication	Regimen	Medication
1. ABVD (US)	•ADRIAMYCIN •BLEOMYCIN •VINBLASTINE •DACARBAZINE	2. STANFORD V (NEW)	•ADRIAMYCIN •BLEOMYCIN •VINBLASTINE •VINCRISTINE •PREDNISONE •MECHLORETHAMINE ETOPOSIDE
3. MOPP	•Mechlorethamine • Vincristine •Procarbazine • Prednisone	4. BEACOPP (EUROPE)	•BLEOMYCIN •ETOPOSIDE •ADRIAMYCIN •CYCLOPHOSPHAMIDE •ONCOVIN •PROCARBAZINE •PREDNISONE

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Radiotherapy

- Radiation therapy is the most effective single thrapeutic agent for treating Hodgkin lymphoma.
- The main objective of radiation in Hodgkin lymphoma is to treat involved and contiguous field.
- Radiotherapy can be given by

1. 2D planning
2. 3D planning
3. IFRT

- Involved field radiotherapy is the most commonly used technique at present. It targets a smaller area rather than a classical extended field.

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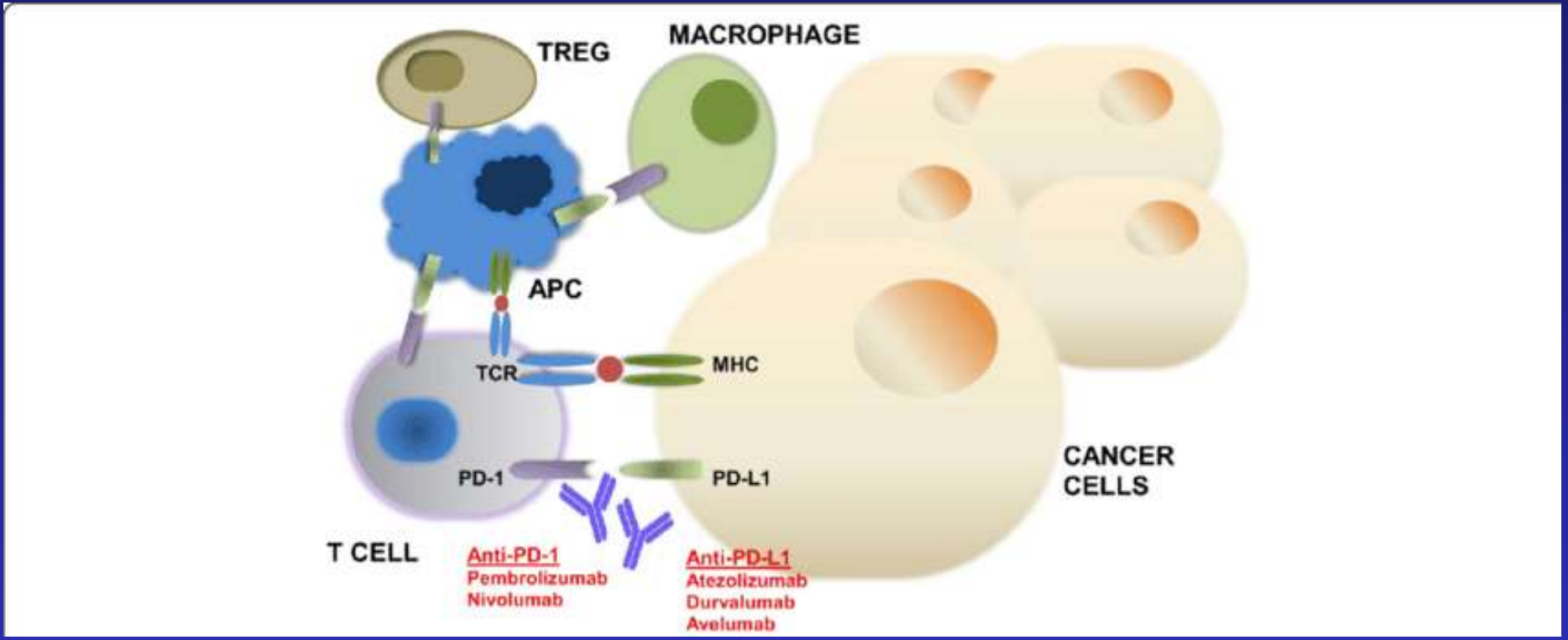
Immunotherapy (NIVOLUMAB)



I LINFOMI NON HODGKIN

PRINCIPI DI TERAPIA

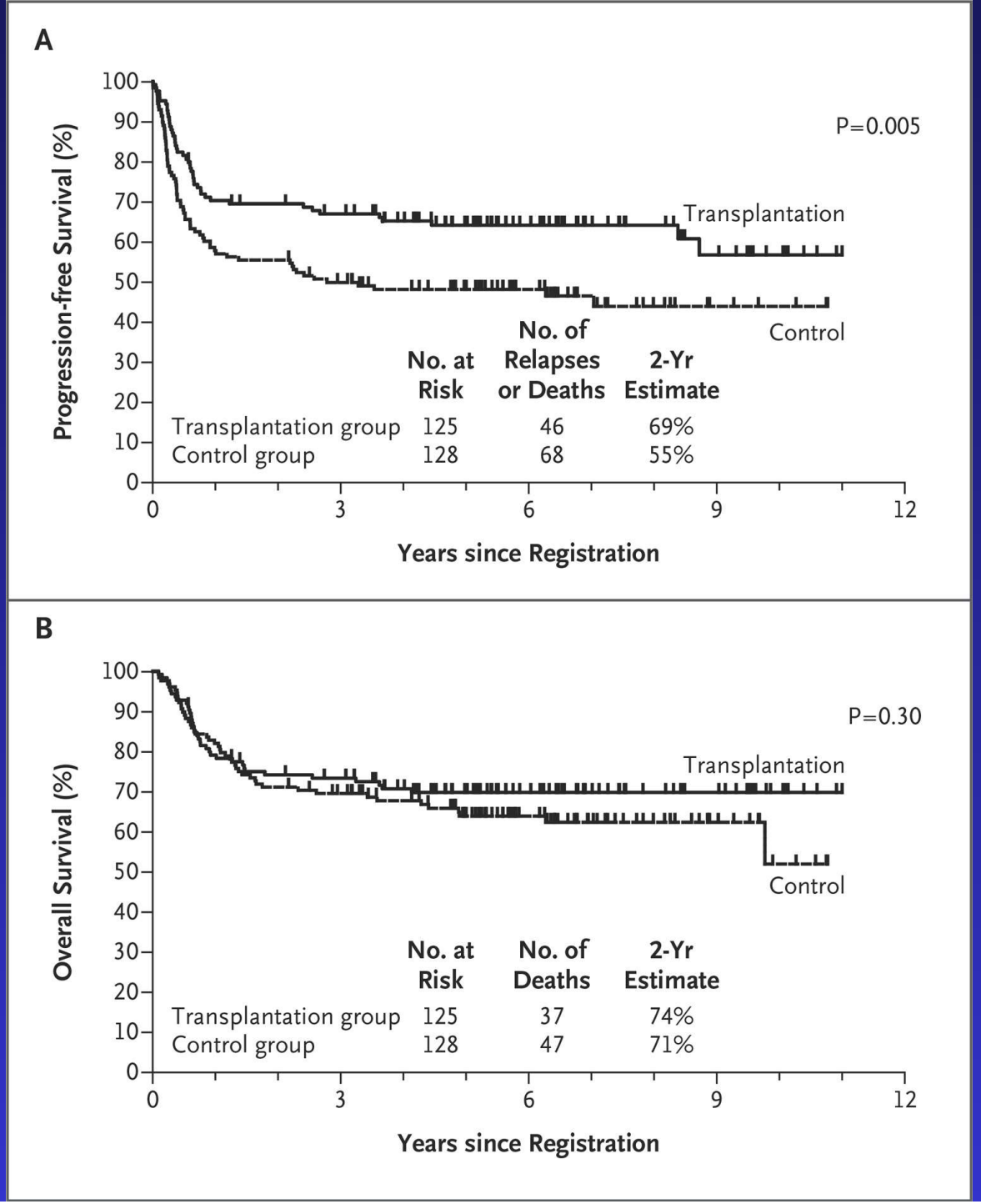
Table 1 The CHOP Regimen

Drug	Dose	Route	Treatment day
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin	50 mg/m^2	IV	1
Vincristine	1.4 mg/m^2	IV	1
Prednisone	100 mg	Oral	1-5

CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; IV, intravenous.
Sources: References 6, 7.

+ RITUXIMAB

Autologous SCT in high-risk patients



Radio-immunocojugate