LYMPHOMAS

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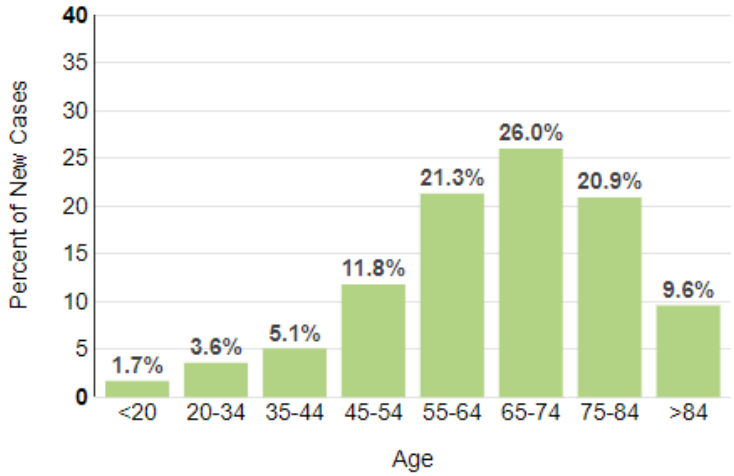
version 2020

Non-Hodgkin's Lymphomas (NHL)

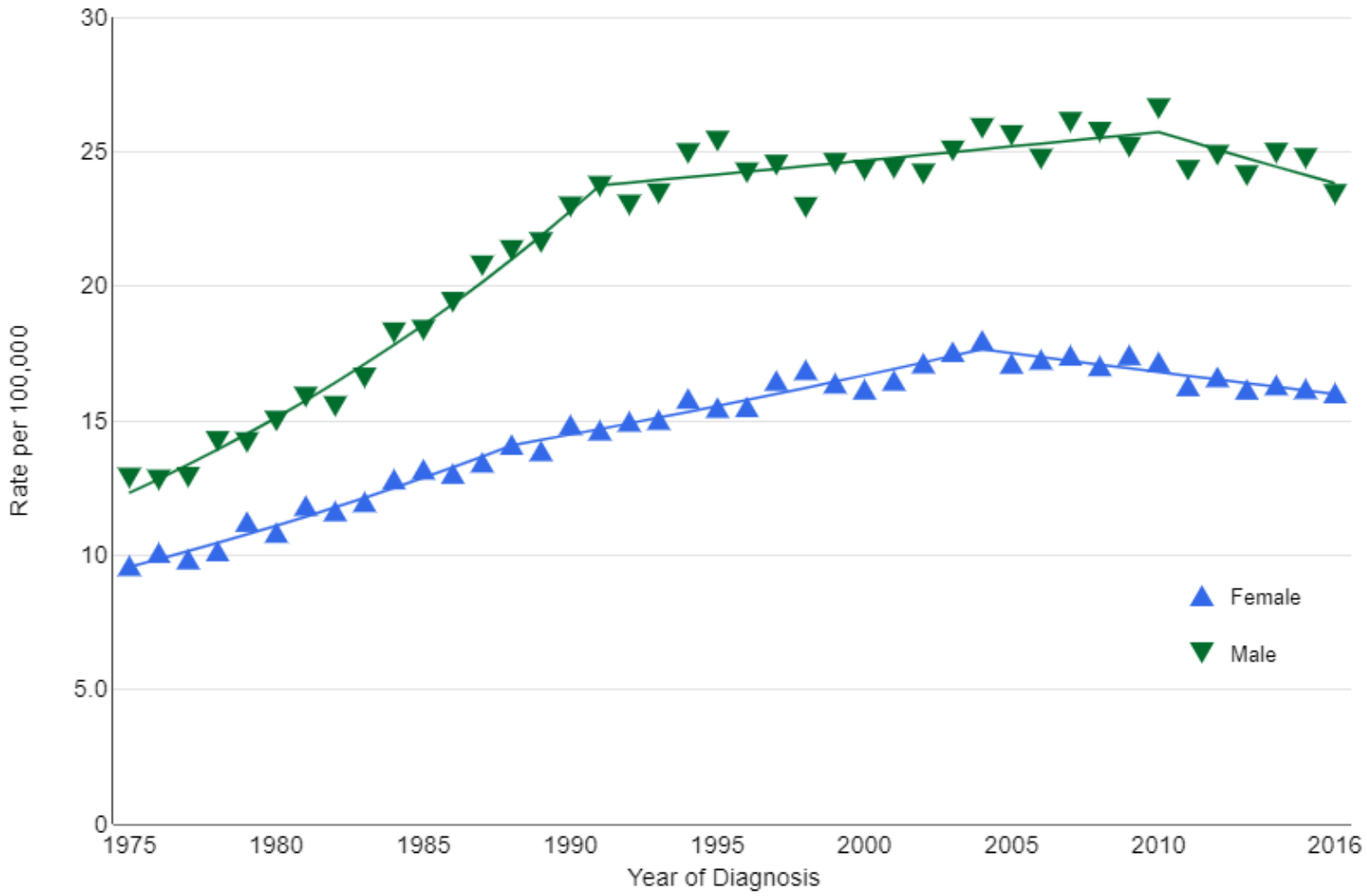
Epidemiology

- male > female
- incidence:
  - increases with age
  - increasing in recent decades (highest increase of all hematological malignancies) x M.Hodgkin
- median age at diagnosis ~ 67 let



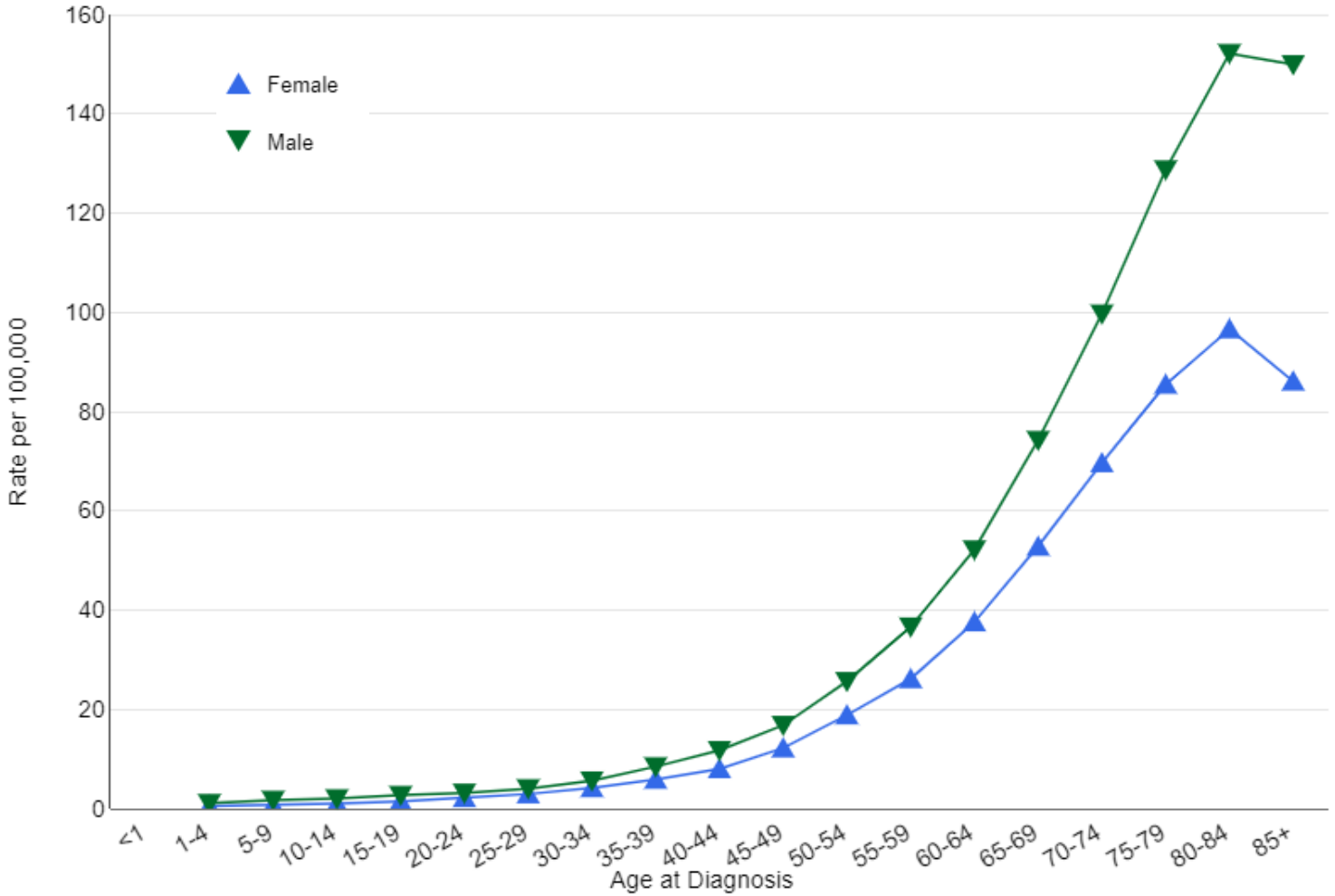
data seer.cancer.gov

Development of NHL incidence over time



data seer.cancer.gov 1975 - 2016

Age distribution of patients with NHL



data seer.cancer.gov 1975 - 2016

Patogenesis NHL I.

- Some lymphomas may be involved:
- **viruses:**

HTLV 1	(T-NHL)
EBV	(Burkitt, extranodal nasal, Hodgkin lymphomas)
HCV	(lymfoplasmocytic lymphoma)
HIV	(agresive NHL)
Helicobacter pylori	(gastric MALT lymphoma)

- **immunodeficiency**: congenital, immunosuppression, transplant patients (solid organs and haemopoietic stem cells)
- **environmental factors:** pesticides, smoking?
- **autoimmune diseases:** SLE, rheumatoid arthritis, Crohn's disease

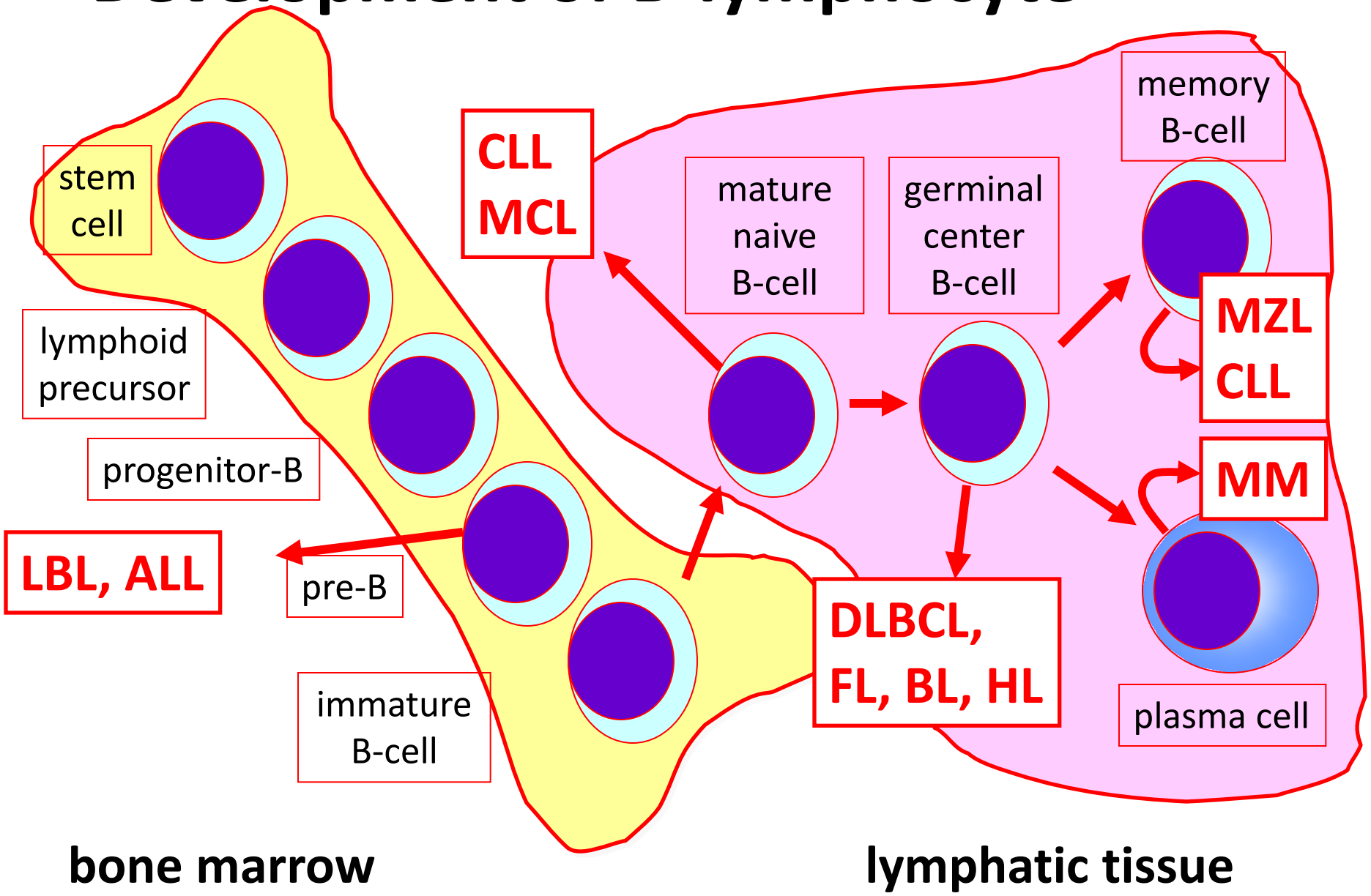
Patogenesis NHL II.

- precursor cell mutations ➡ clonal expansion of lymphocytes in their various developmental stages
- the most common mutation - chromosomal translocation
- translocation occurs during the normal process of "gene rearrangement" (IgH, TCR)
- some translocations characteristic of certain lymphomas:

  t(14,18) …… follicular lymphoma

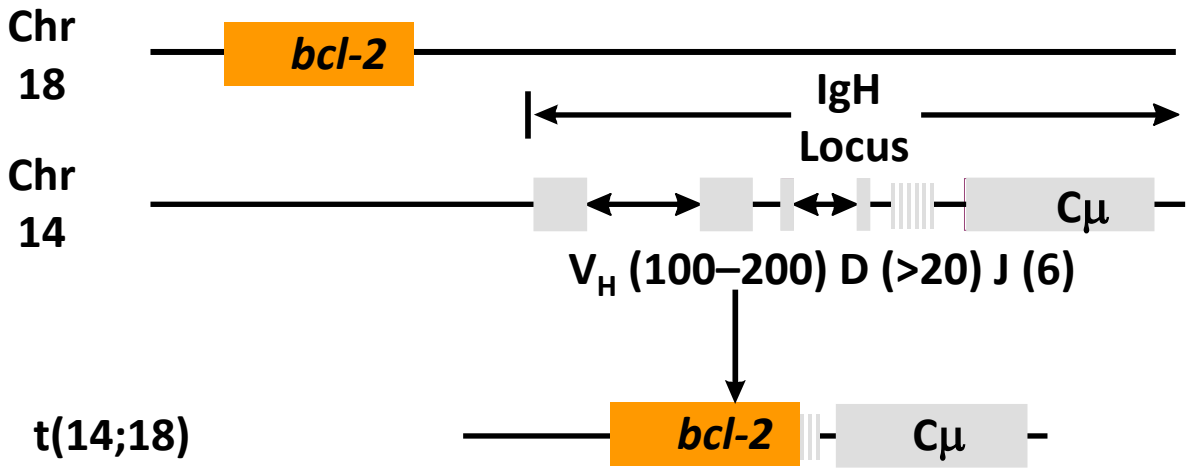
  t(8.14) …… Burkitt's lymphoma
- often occur other mutations leading to "tumor progression"

Development of B-lymphocyte



Chromosomal translocation t(14:18) in follicular lymphoma

example:



- present in> 90% FCL ➡ bcl-2 protein overexpression ➡ inhibition of apoptosis
- important role in the diagnosis and monitoring of treatment efficacy

upraveno podle Liu Y, PNAS 1994

Histological classification of NHL

1956 Rappaport classificacation

1974 Dorfman classificacation

1974 British National Lymphoma Investigation

1976 WHO classificacation

1974 Lukes and Collins classificacation

1974 Kiel (later Lennert) classificacation

1982 Working Formulation for Clinical Usage - WF

1994 Revised European - American Classification of Lymphoid Neoplasm - REAL classificacation

2001 WHO classification of tumors of hematopoietic and lymphoid tissues

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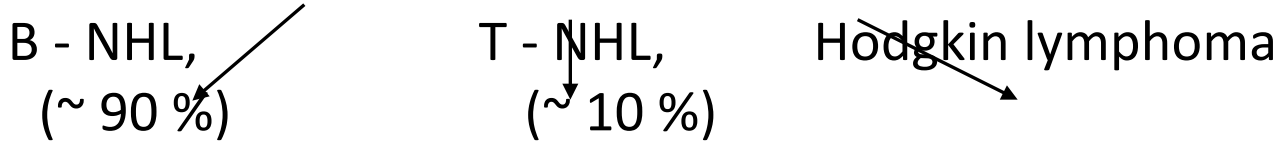
➡ in modern history many classifications of lymphomas now used ➡ <u>WHO classification</u> of lymphatic malignancies

WHO classification

basic principles:

- basic division into 3 groups



- with regard to the development of the normal immune system, a further division of B-NHL and T-NHL into 2 groups:

- precursor neoplasia: correspond to lymphoblastic lymphoma / leukemia
- peripheral (mature) neoplasia: include all other B- and T-lymphomas

takes into account morphological, clinical, immunological and genetic information ➡ divides lymphomas into units with different clinical behaviors ➡ has clinical and therapeutic implications

WHO classification of lymphatic malignancies

B-cell neoplasms

Precursor B-cell neoplasm

- Precursor B-lymphoblastic leukaemia/lymphoma (precursor B-cell acute lymphoblastic leukaemia)

Mature (peripheral) B-cell neoplasms†

- B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (+/− villous lymphocytes)
- Hairy cell leukaemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone B-cell lymphoma (+/− monocytoid B cells)
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
  - Mediastinal large B-cell lymphoma
  - Primary effusion lymphoma
- Burkitt lymphoma/ Burkitt cell leukaemia

T and NK-cell neoplasms

Precursor T-cell neoplasm

- Precursor T-lymphoblastic lymphoma/leukaemia (precursor T-cell acute lymphoblastic leukaemia)

Mature (peripheral) T-cell neoplasms‡

- T-cell prolymphocytic leukaemia
- T-cell granular lymphocytic leukaemia
- Aggressive NK-cell leukaemia
- Adult T-cell lymphoma/leukaemia (HTLV1+)
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell, primary systemic type

Hodgkin's lymphoma (Hodgkin's disease)

- Nodular lymphocyte predominance Hodgkin's lymphoma
- Classical Hodgkin's lymphoma

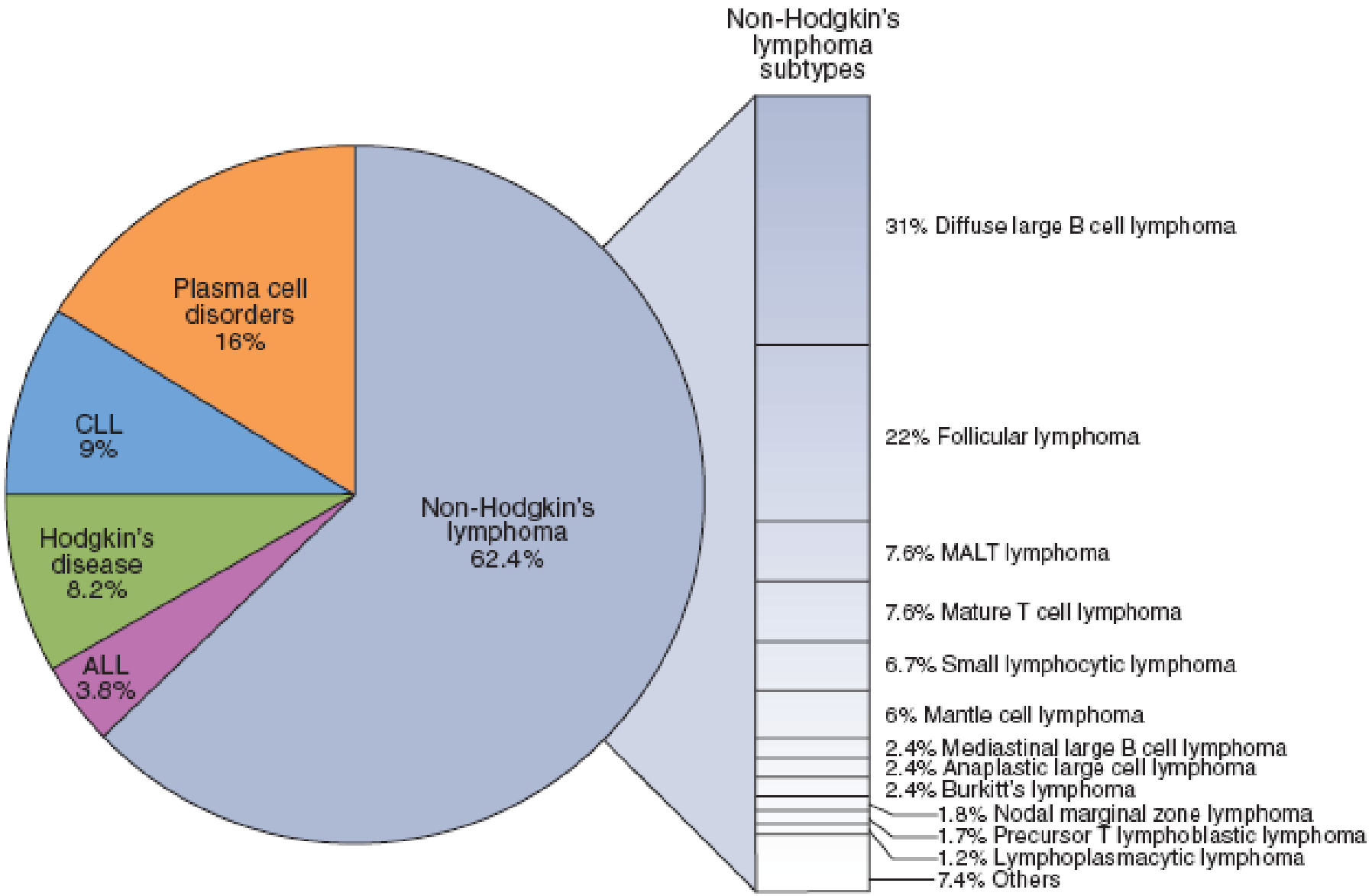
  Nodular sclerosis Hodgkin's lymphoma (Grades 1 and 2)

  Lymphocyte-rich classical Hodgkin's lymphoma

  Mixed cellularity Hodgkin's lymphoma

  Lymphocyte depletion Hodgkin's lymphoma

Relative representation of lymphoid malignancies



The importance of accurate diagnosis of lymphoma

- it is important to distinguish between Hodgkin's or non-Hodgkin's lymphoma, because the treatment method is different and the treatment procedures for HD ineffective in NHL and vice versa !!

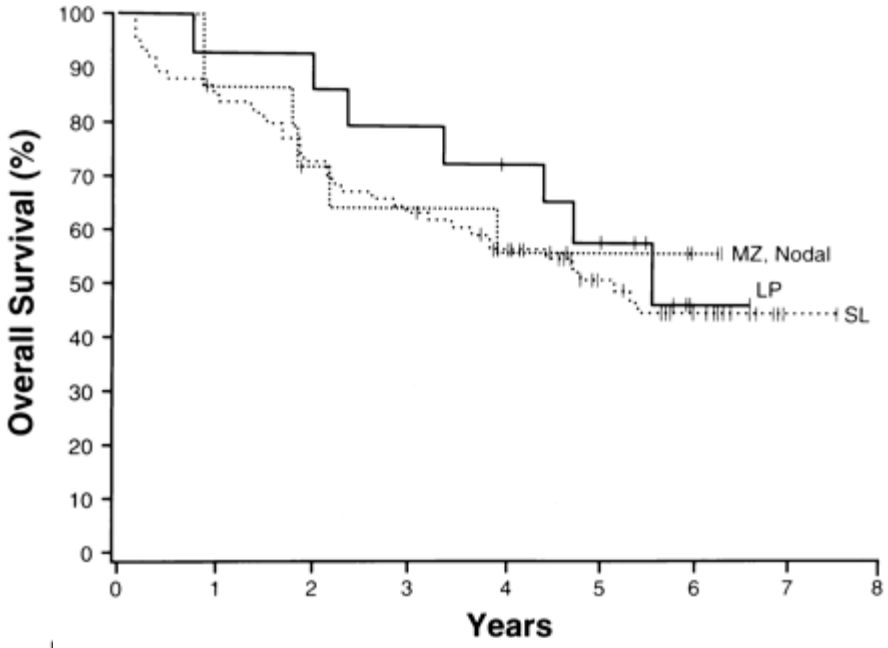
- equally important is the determination of the NHL subtype - individual NHL subtypes have a completely different prognosis, are treated quite differently and treatment of a given type of NHL is not universally applicable to another type of NHL

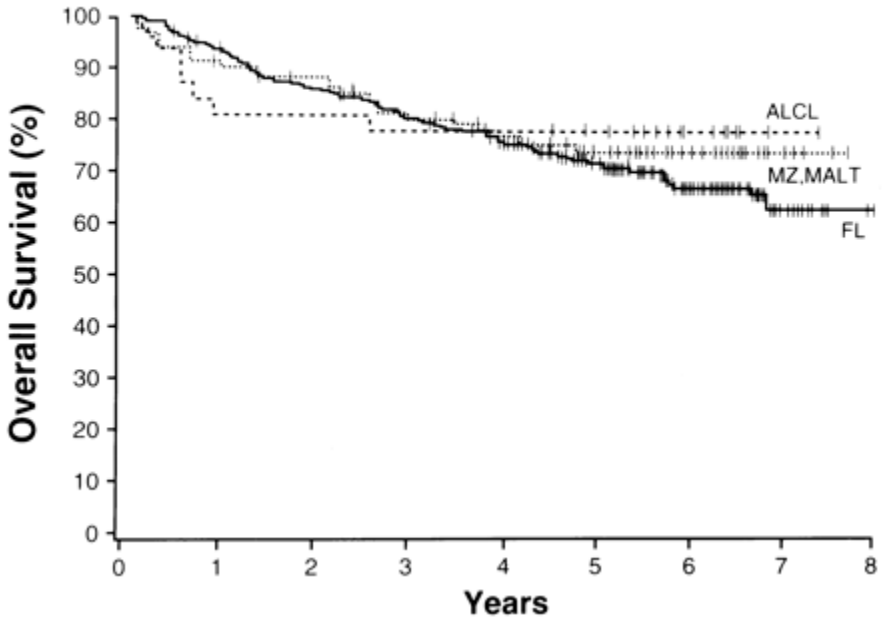
Prognosis of individual NHL types according to WHO

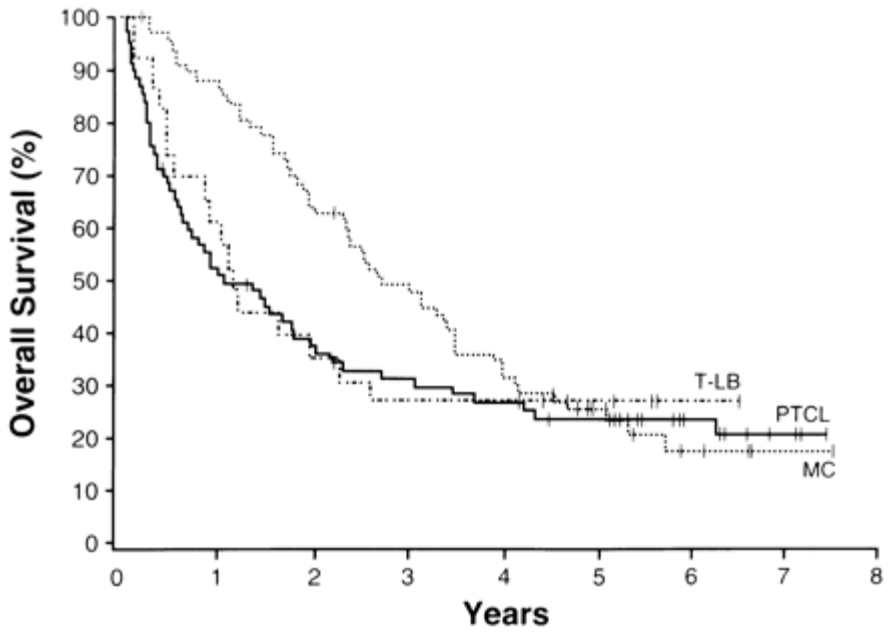
5-year overall survival:

from more than 70% to less than 30%

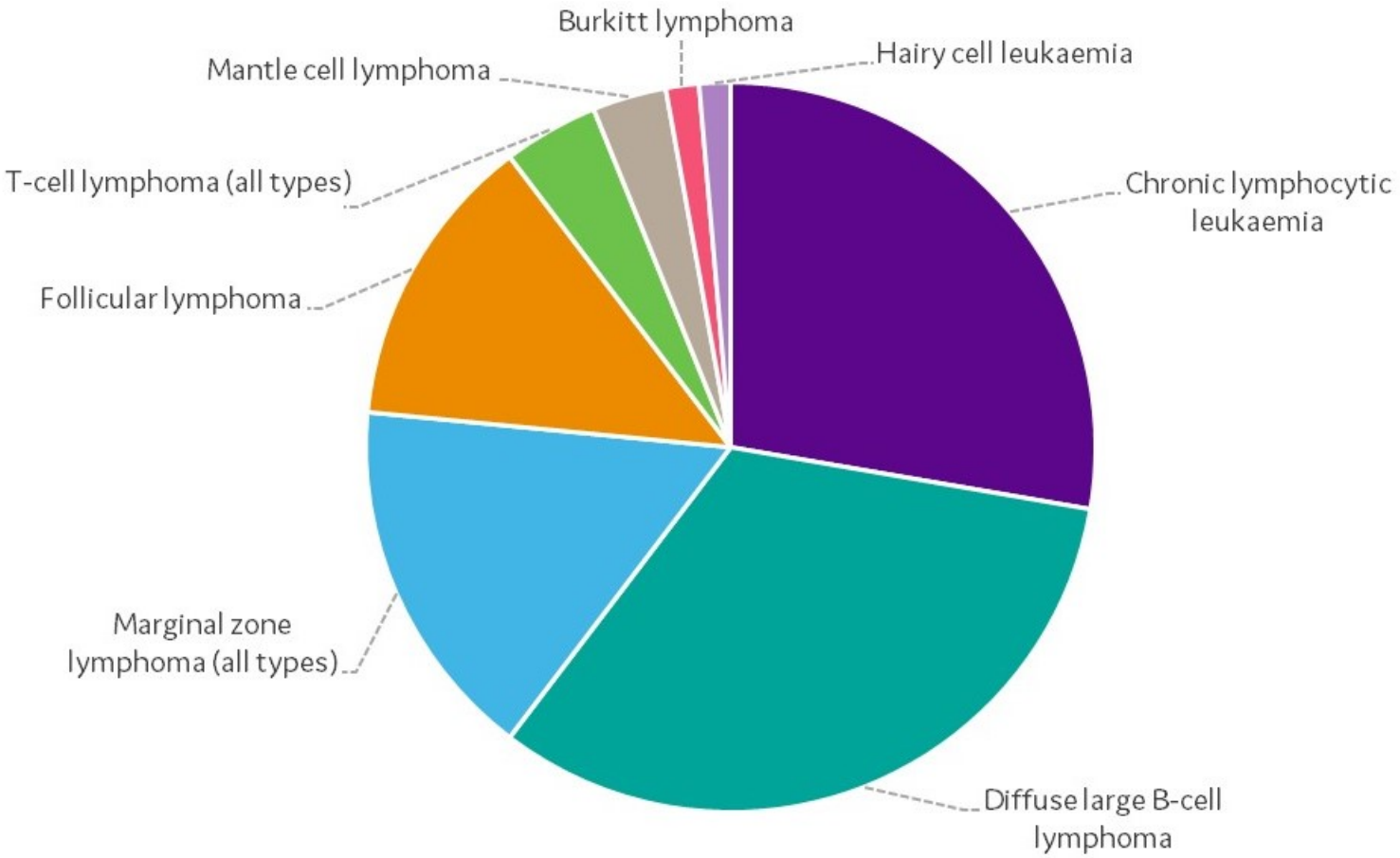
the type of lymphoma (by WHO) itself determines the prognosis







The most common non-Hodgkin lymphomas



https://lymphoma-action.org.uk/

Clinical manifestations

system symptoms:

- weight loss, subfebrile, night sweats
- anorexia

} B- syptoms

local manifestations:

- enlarged lymph nodes (lymphadenopathy, adenomegaly)
- splenomegaly, hepatomegaly
- almost any tissue can be infiltrated

manifestations of the disease are variable:

- asymptomatic to severe condition
- it can develop in weeks, months to years

Classification of lymphomas according to clinical behavior

- **low malignant:** grow slowly, less responsive to treatment

  eg: follicular lymphoma

- **aggressive:** faster growing, potentially curative

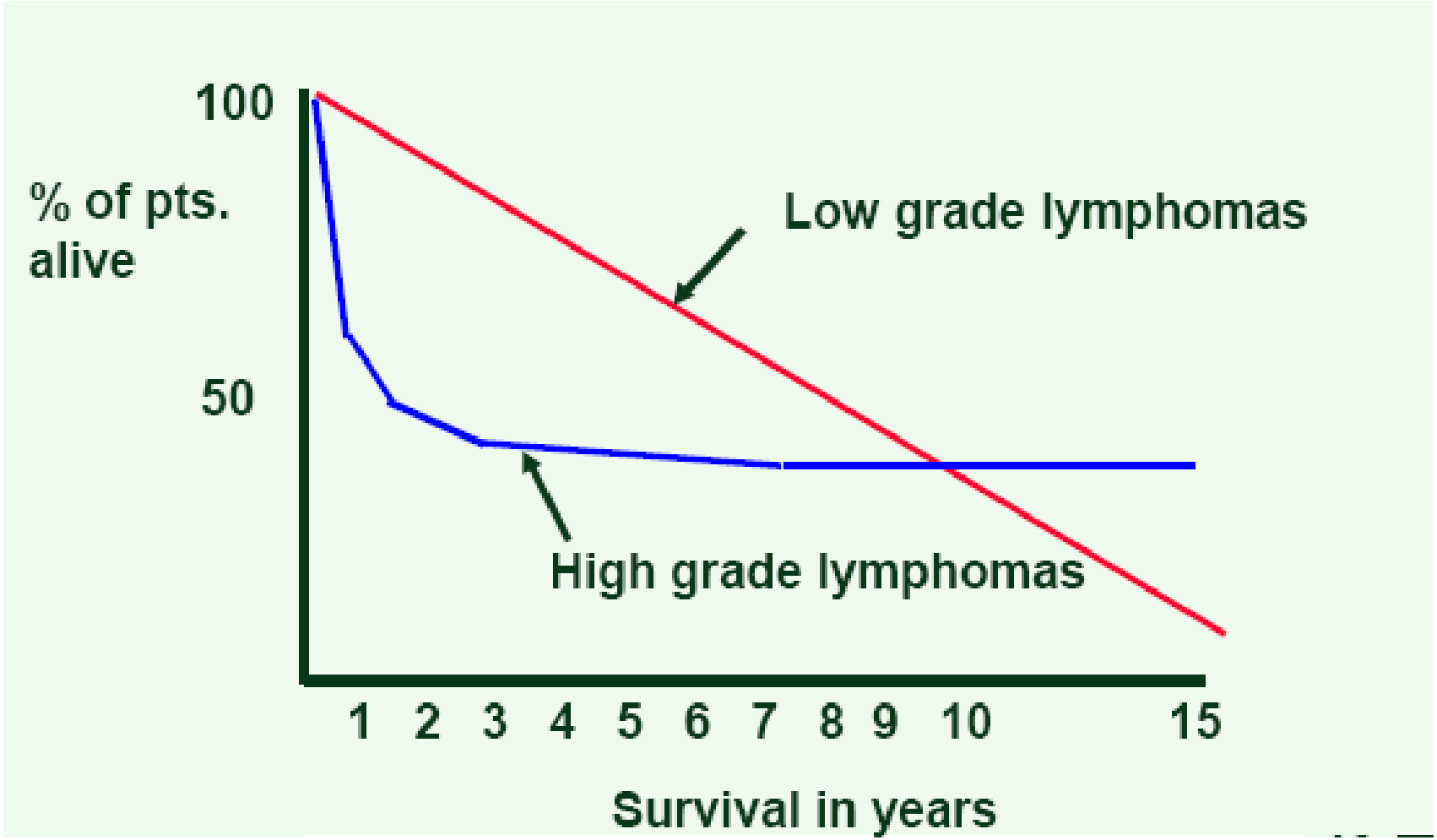
  eg: diffuse large cell lymphoma

- **highly malignant:** grow rapidly, without lethal treatment

they behave and treat themselves like leukemia

  eg: lymphoblastic lymphoma

Low vs. highly malignant lymphomas



Diagnostic procedure

1.refine diagnosis according to WHO classification

➡ node exscision (histology)

2. determining the extent of disability (stage, staging)

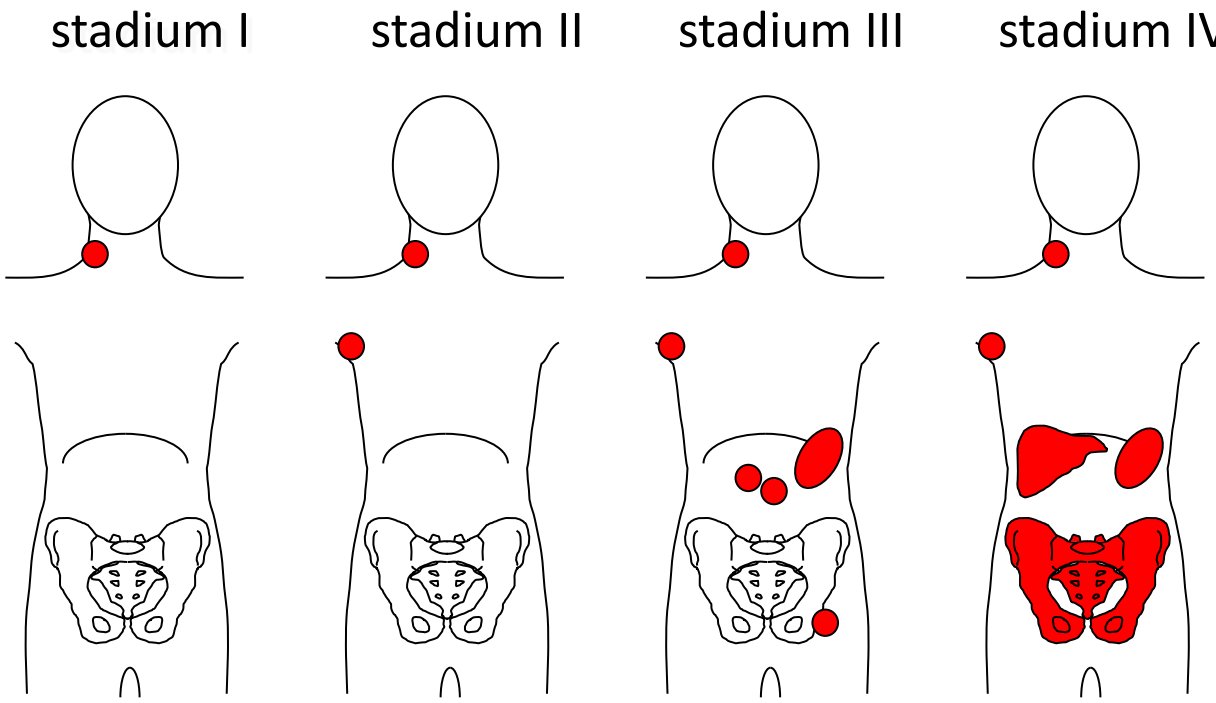
➡ CT, PET-CT (mediastinum and retroperitoneum)

➡ bone marrow infiltration?

3. **determination of clinical prognostic factors**

➡ International Forecasting Index (IPI)

Staging of lymphoma



A: absence of B symptoms

B: temperature, night sweats, weight loss

Ann Arbor staging system:

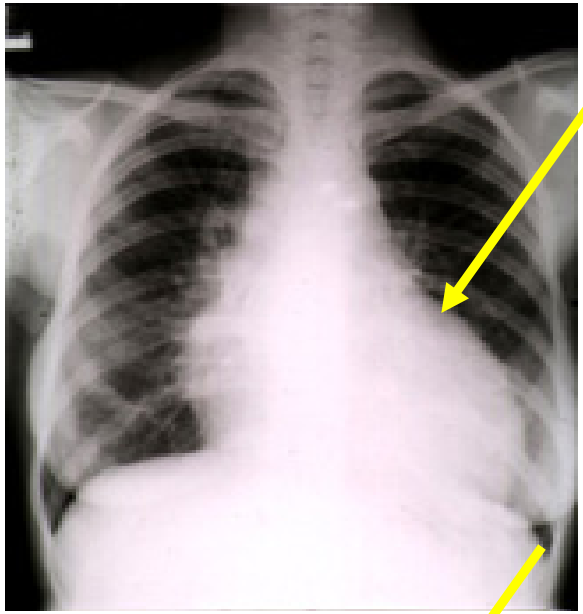
St. I: involvement of 1 node or "nodal" localization

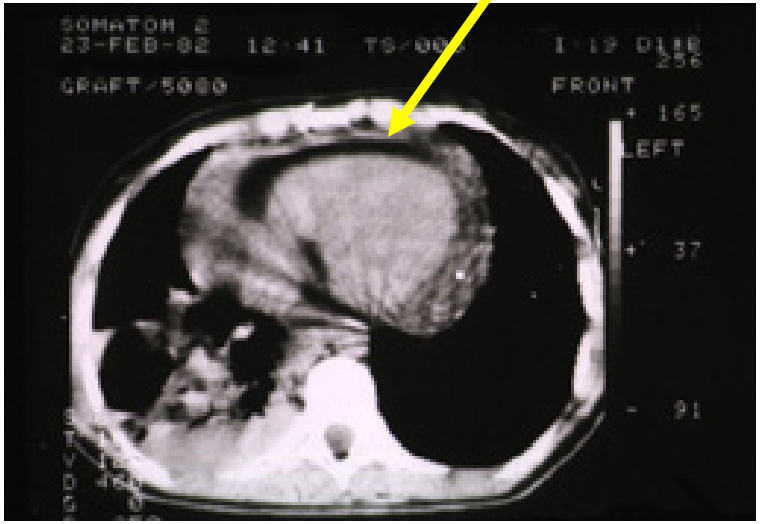
St. II: multiple node involvement multiple sites on one side of the diaphragm

St. III: multiple node involvement on both sides of the diaphragm.

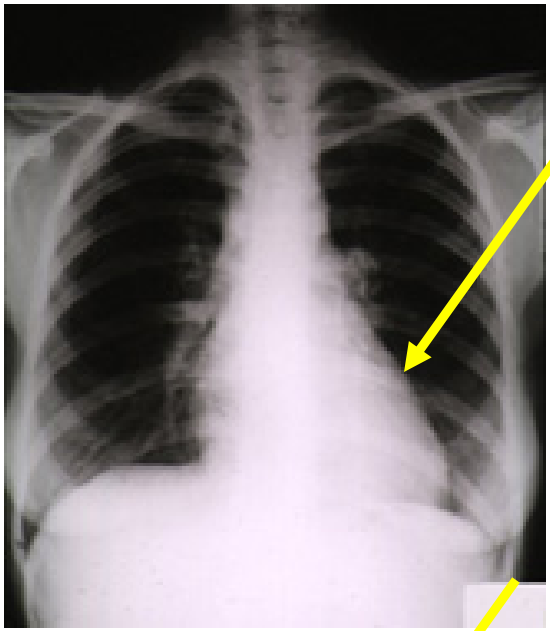
St. IV: generalized disability - even outside the lymph nodes (bone marrow, spleen)

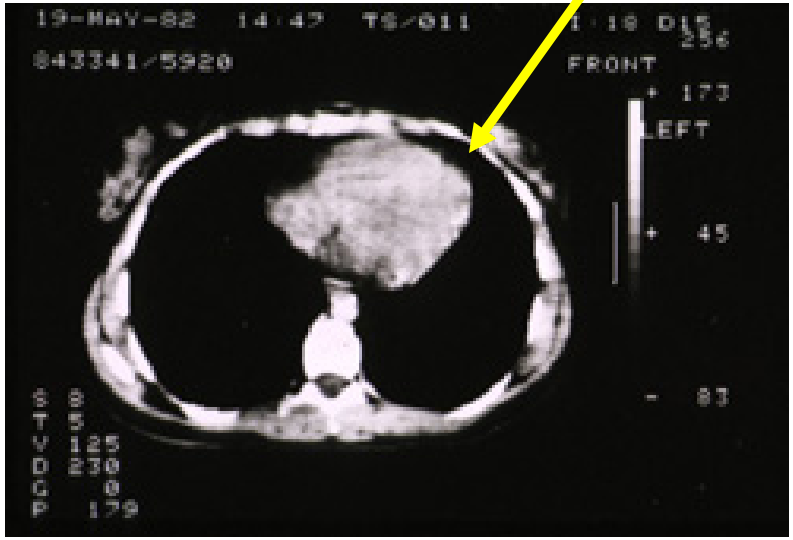
staging – involvement of pericardium and lymphoma lymph nodes - X-ray + CT





after treatment - complete regression





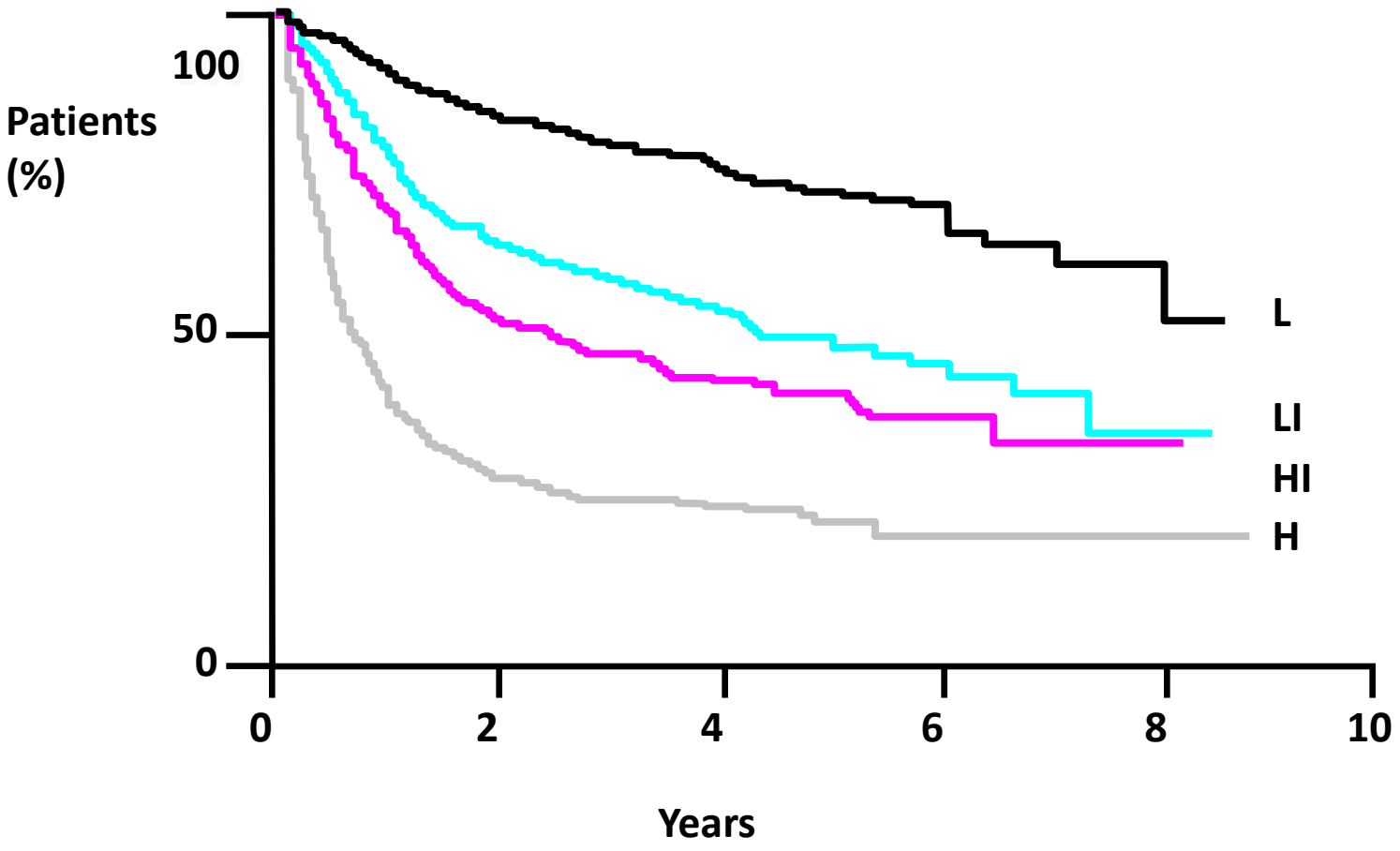
Prognostic stratification of NHL according to clinical characteristics

- determined by: age (≥ 60 years), LDH, general condition (ECOG ≥ 2), stage (III / IV), presence of extranodal infiltration
- the result is the so-called IPI (International Prognostic Index)

IPI ↓

		5 years survival
low risk	**0-1**	**73%**
low intermediate risk	**2**	**51%**
high intermediate risk	**3**	**43%**
high risk	**4-5**	**26%**

Overall survival by risk group



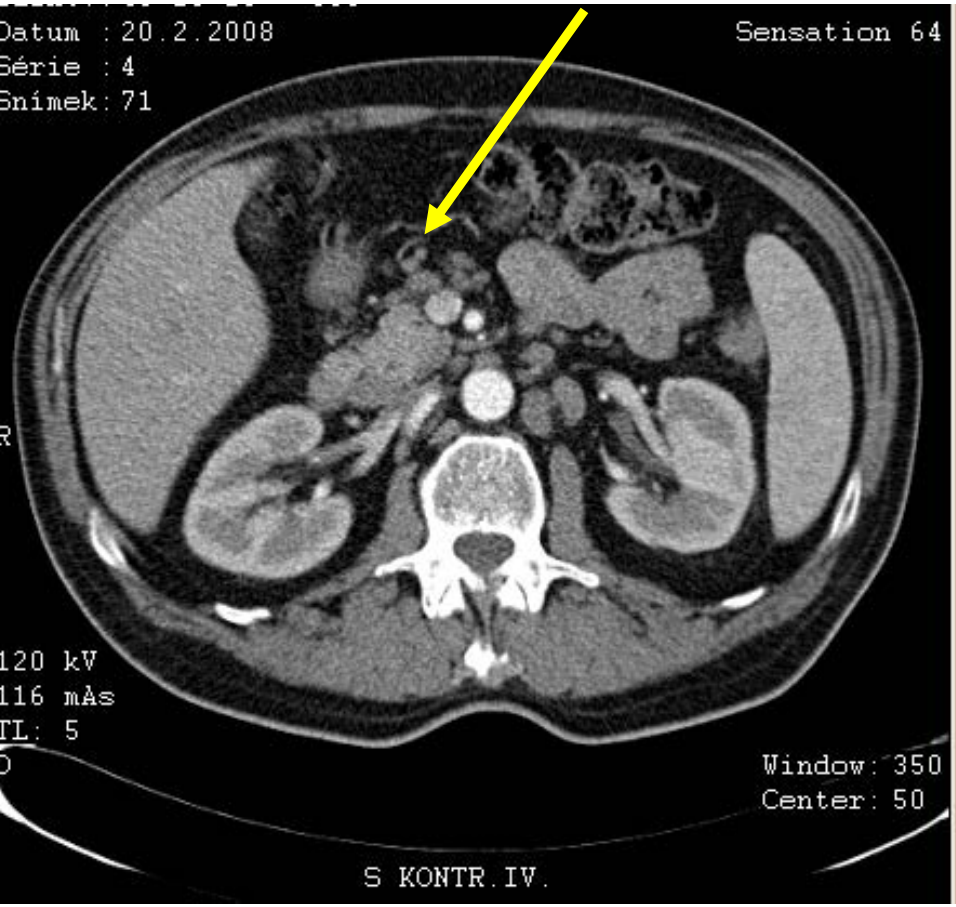
The International Non-Hodgkin's Lymphoma Prognostic Factors Project, NEJM 1993

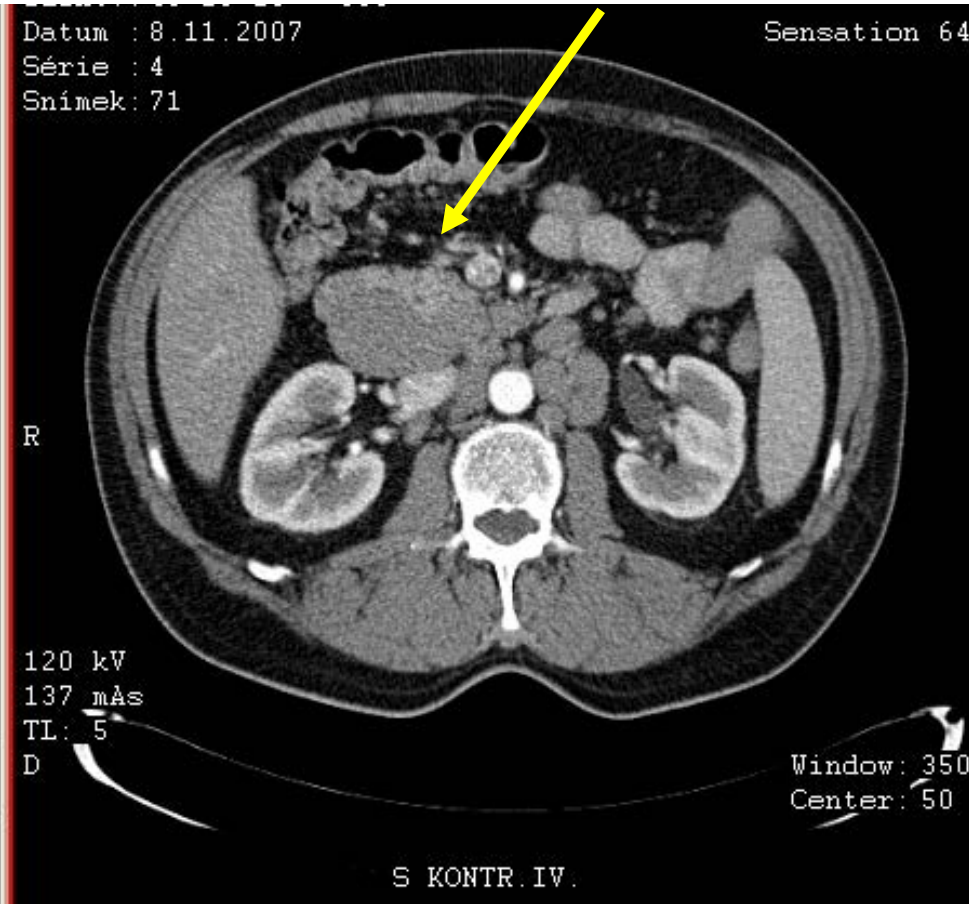
Complications of lymphomas

- bone marrow failure (infiltration) with decrease in blood count
- CNS infiltration
- immune hemolysis or thrombocytopenia
- compression of surrounding structures (blood vessels, spinal cord, ureters) by enlarged nodes
- pleural or pericardial effusions, ascites

NHL - treatment options

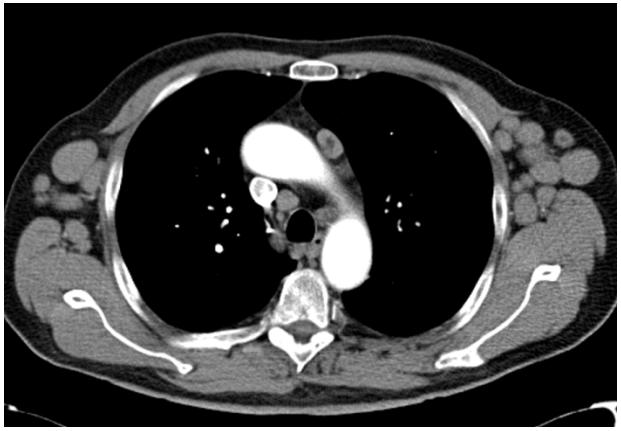
- chemotherapy
  - eg CHOP (cyclophosphamide, adriamycin, vincristine, prednisone)
- immunotherapy (anti-CD20) ➡ chemoimmunotherapy (R-CHOP) R = rituximab
- actinotherapy
- autologous or allogeneic transplantation
  a combination of the above

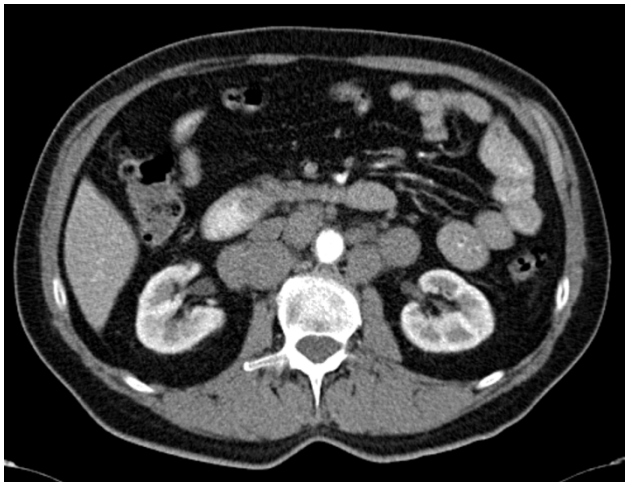


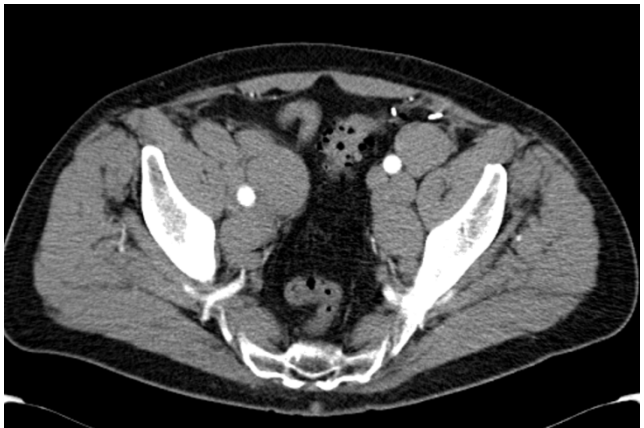


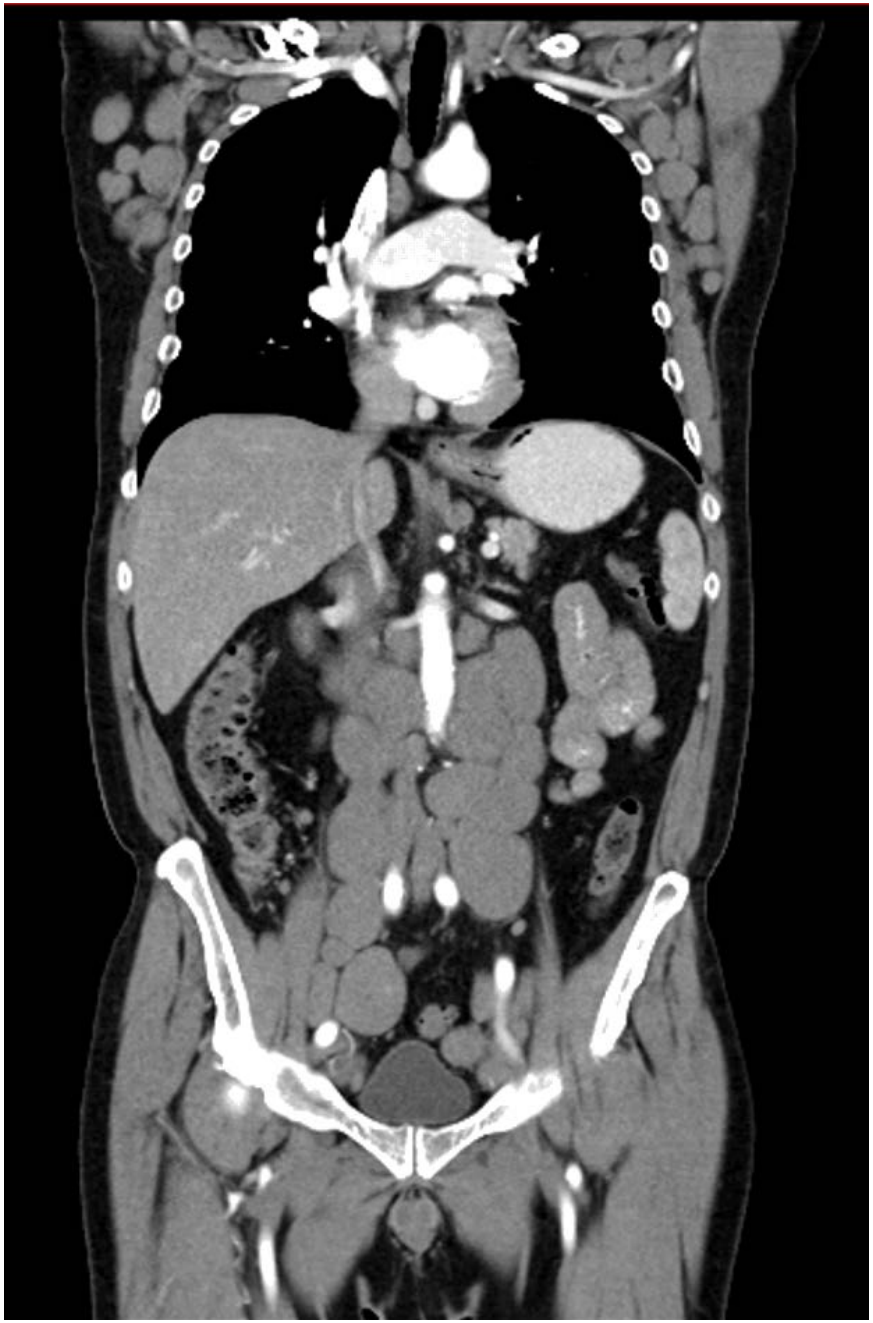
regression of lymph node involvement in retroperitoneum after treatment by 60 - 70%

DLBCL, before treatment

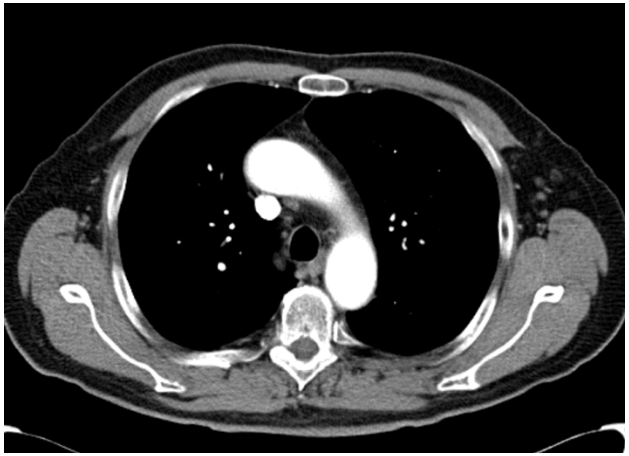


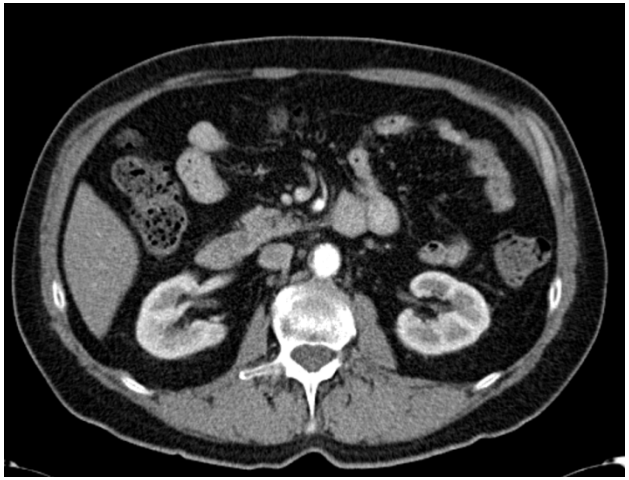


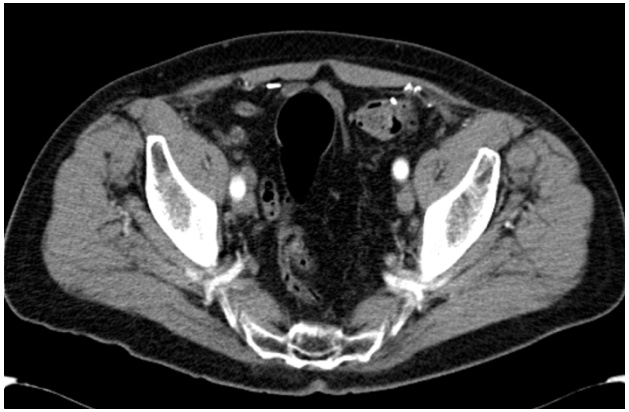


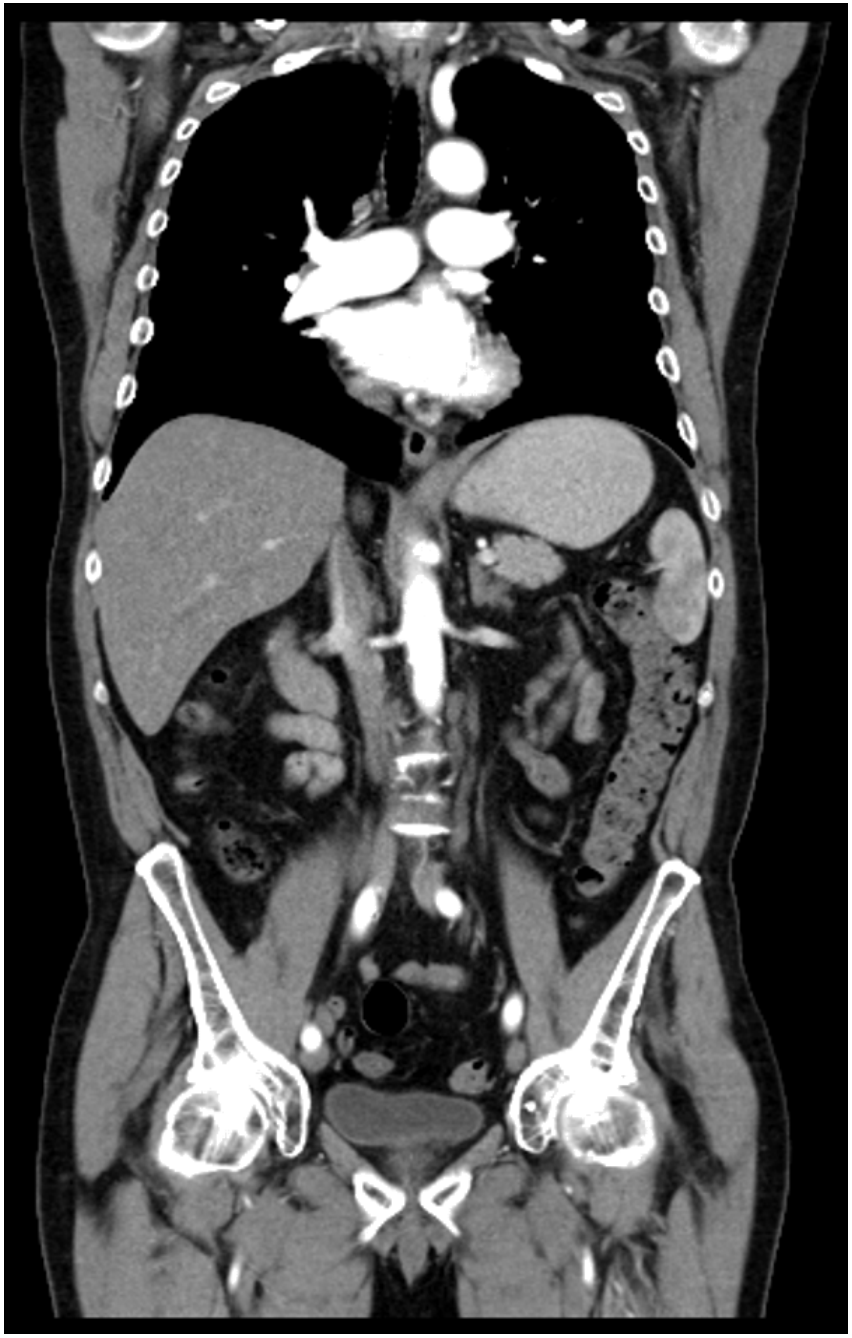


DLBCL, after treatment









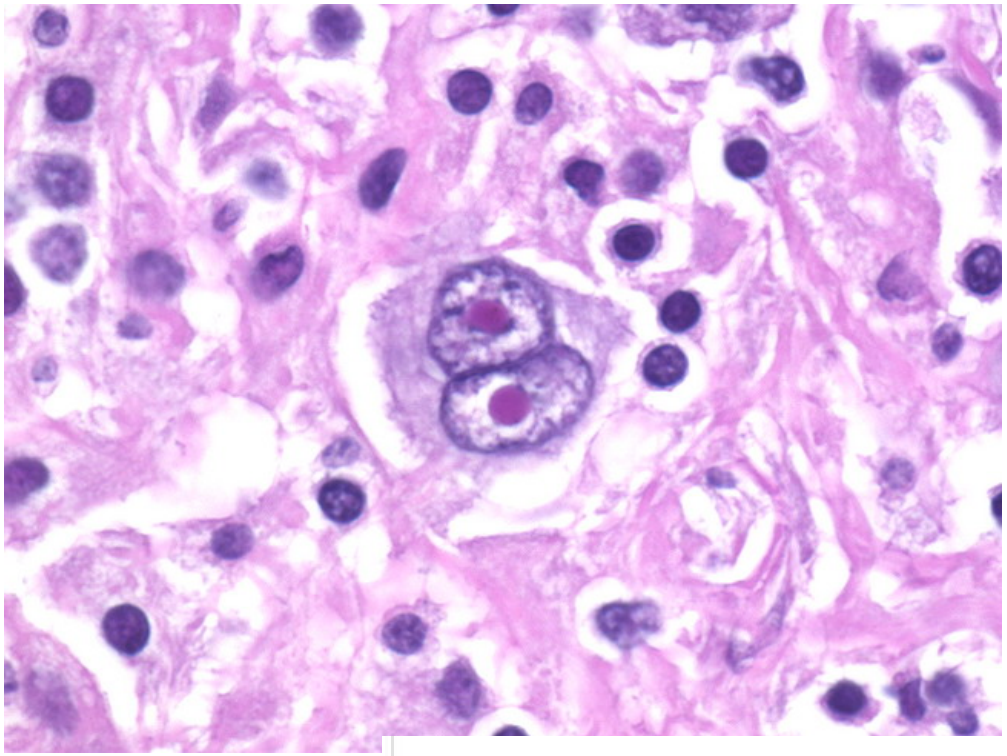
Hodgkin´s lymphoma (HD)

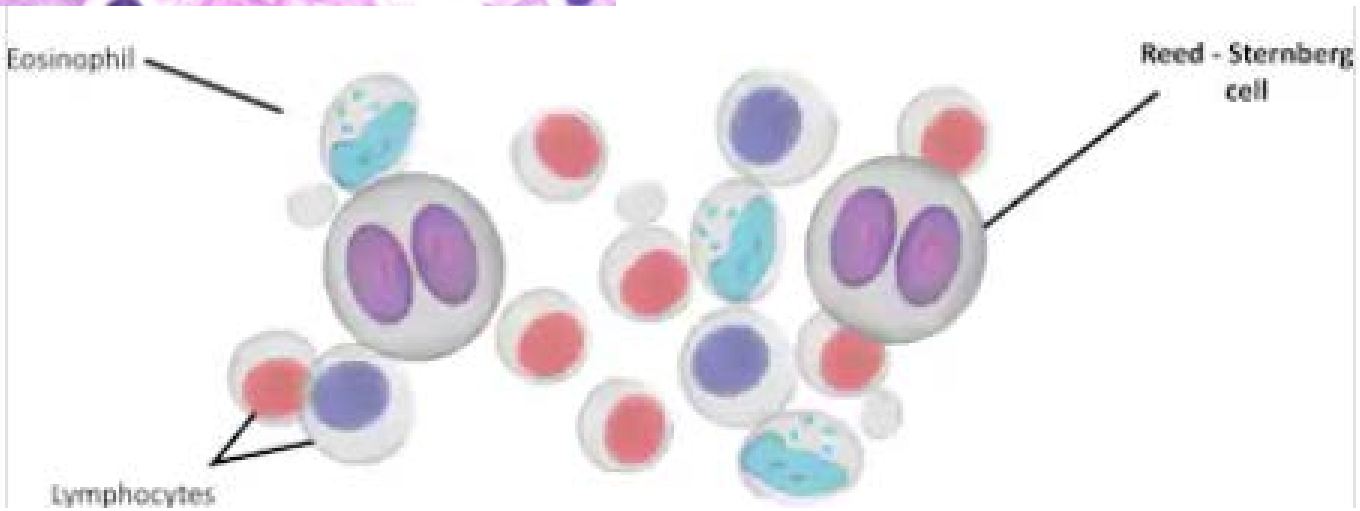
Thomas Hodgkin
(1798-1866)

Patogenesis I.

- the tumor cells originate from the B cells of the germinal node center
- Reed-Sternberg cells (RS cells) can be found in the affected node
- most node cells are polyclonal reactive lymphoid cells, not tumor cells

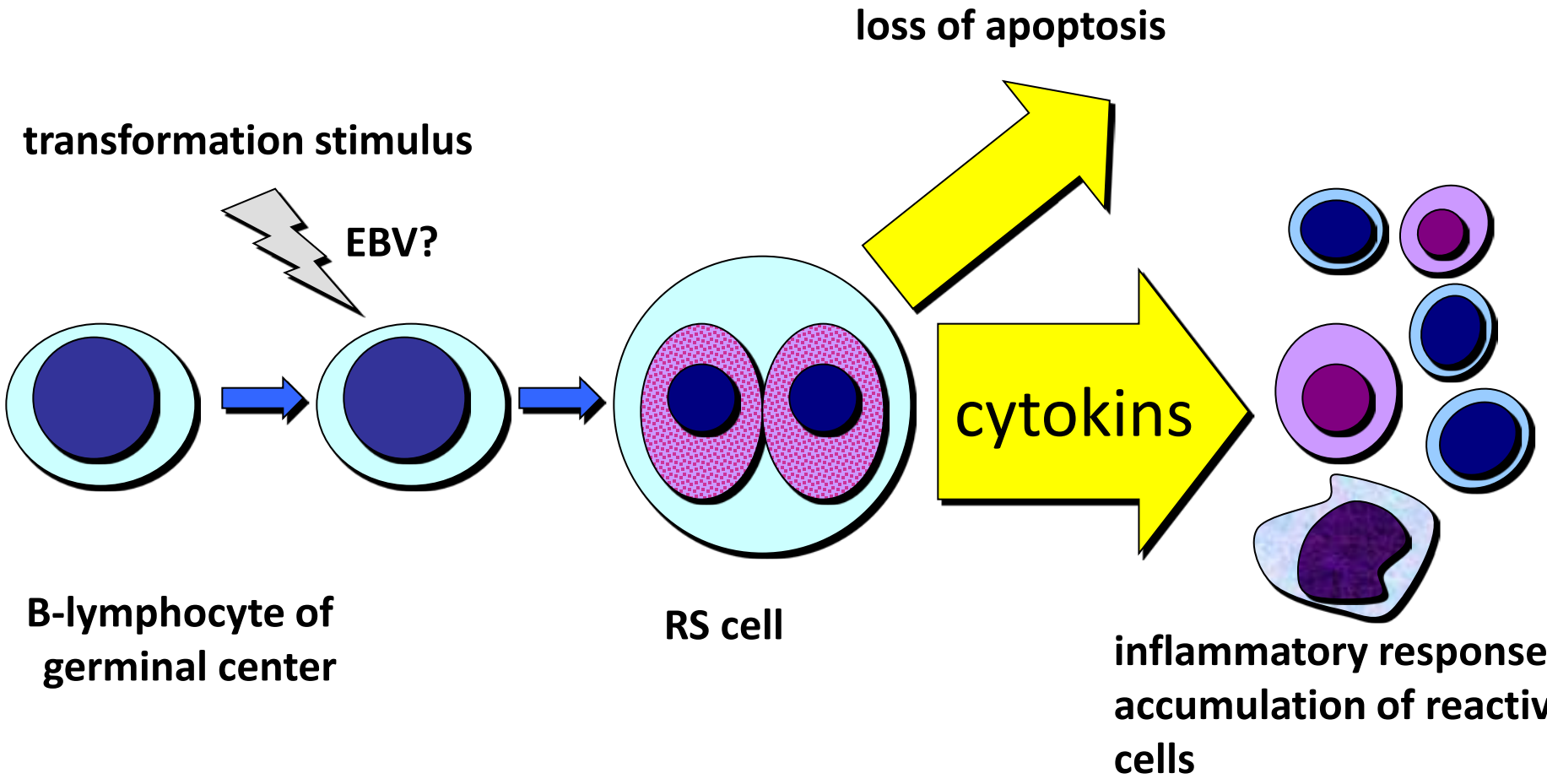
Reed-Sternberg cell





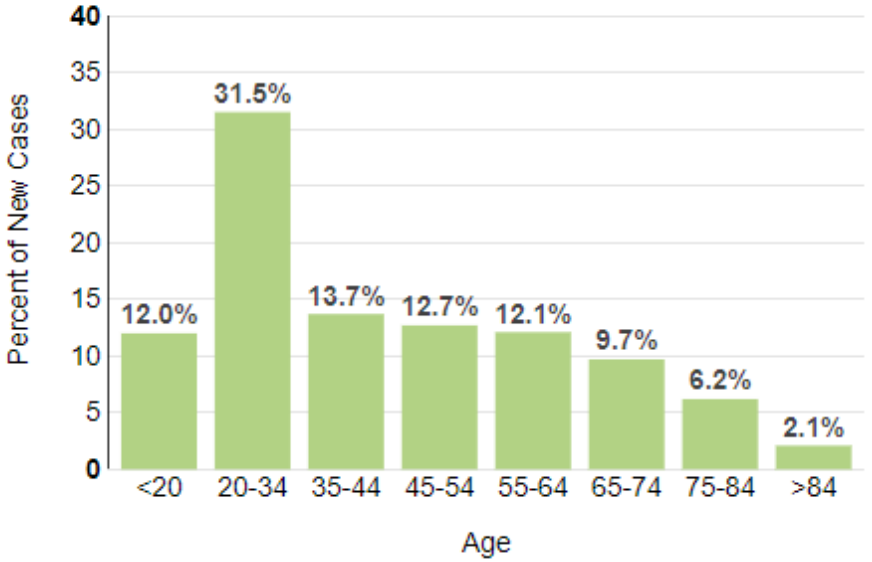
www.webpathology.com

Patogenesis II. – possible model



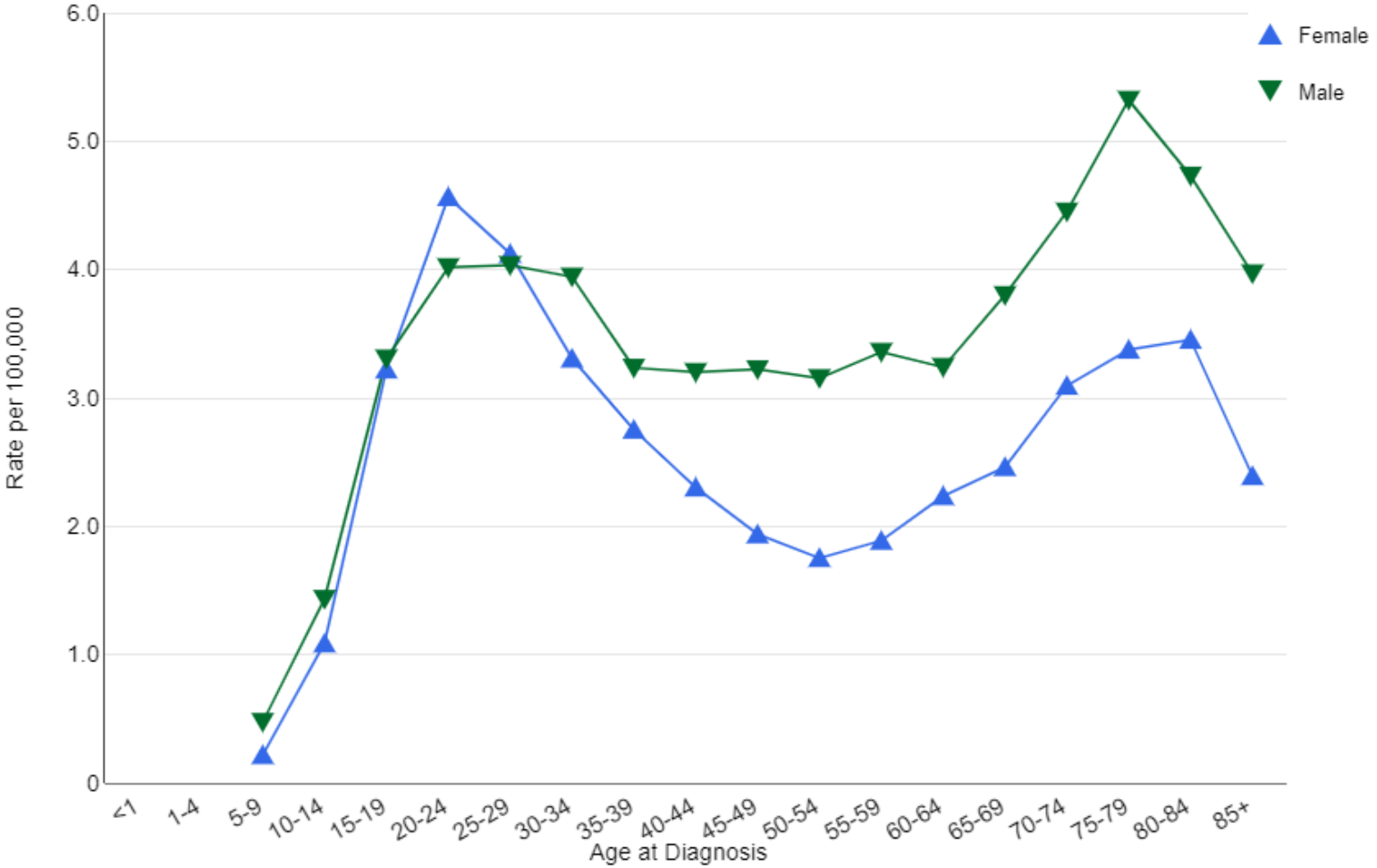
Epidemiology of Hodgkin's lymphoma

- less common than non-Hodgkin's lymphomas
- more often M> F
- median age at diagnosis of 39 years
- peak incidence in 3 decades of life and in old age



data seer.cancer.gov 1975 - 2016

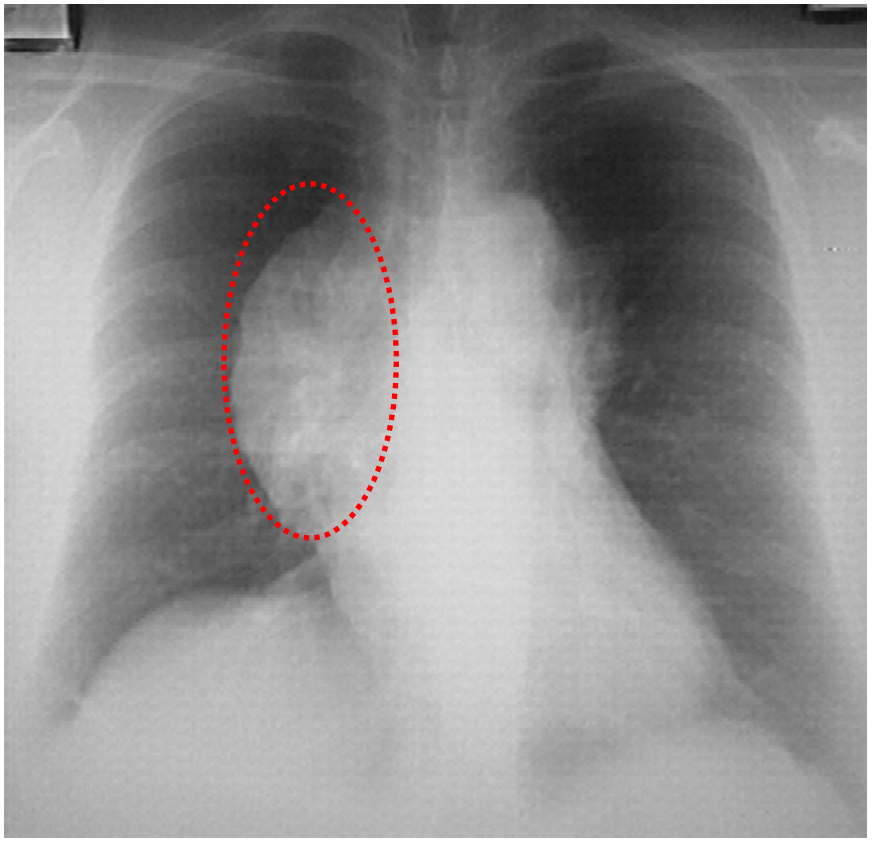
Age distribution of patients with HD

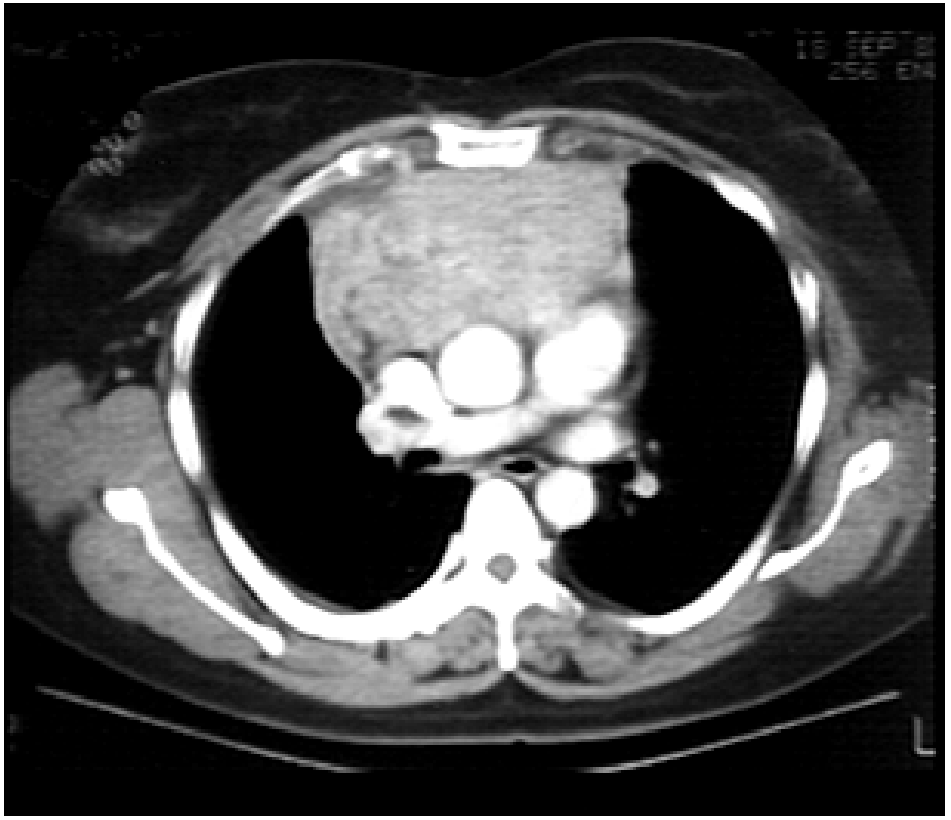


data seer.cancer.gov 1975 - 2016

Clinical picture

- lymphadenopathy (neck, axils, mediastinum ..)
- related disability (VCS syndrome, ..)
- extranodal involvement rather rare (except in advanced diseases)
- “B” symptoms (temperature, fatigue, weight loss)



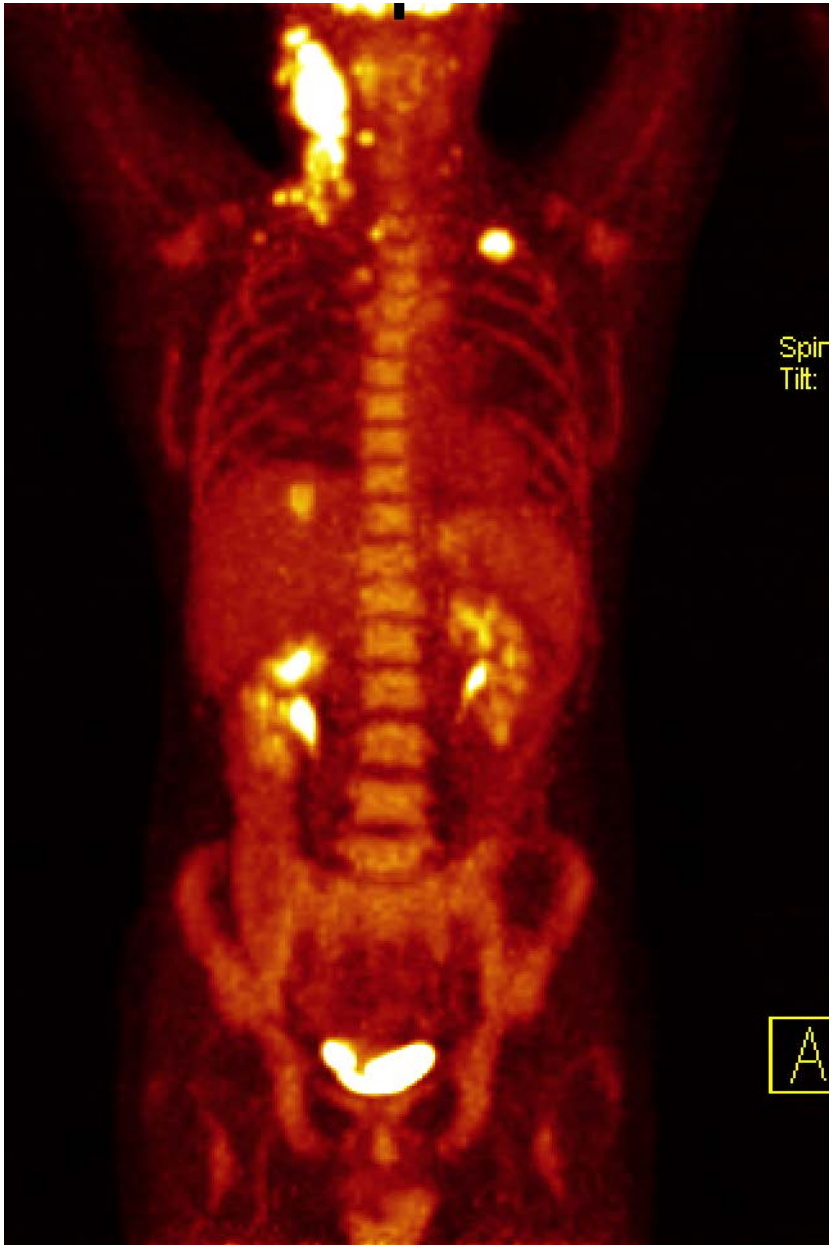


Treatment options

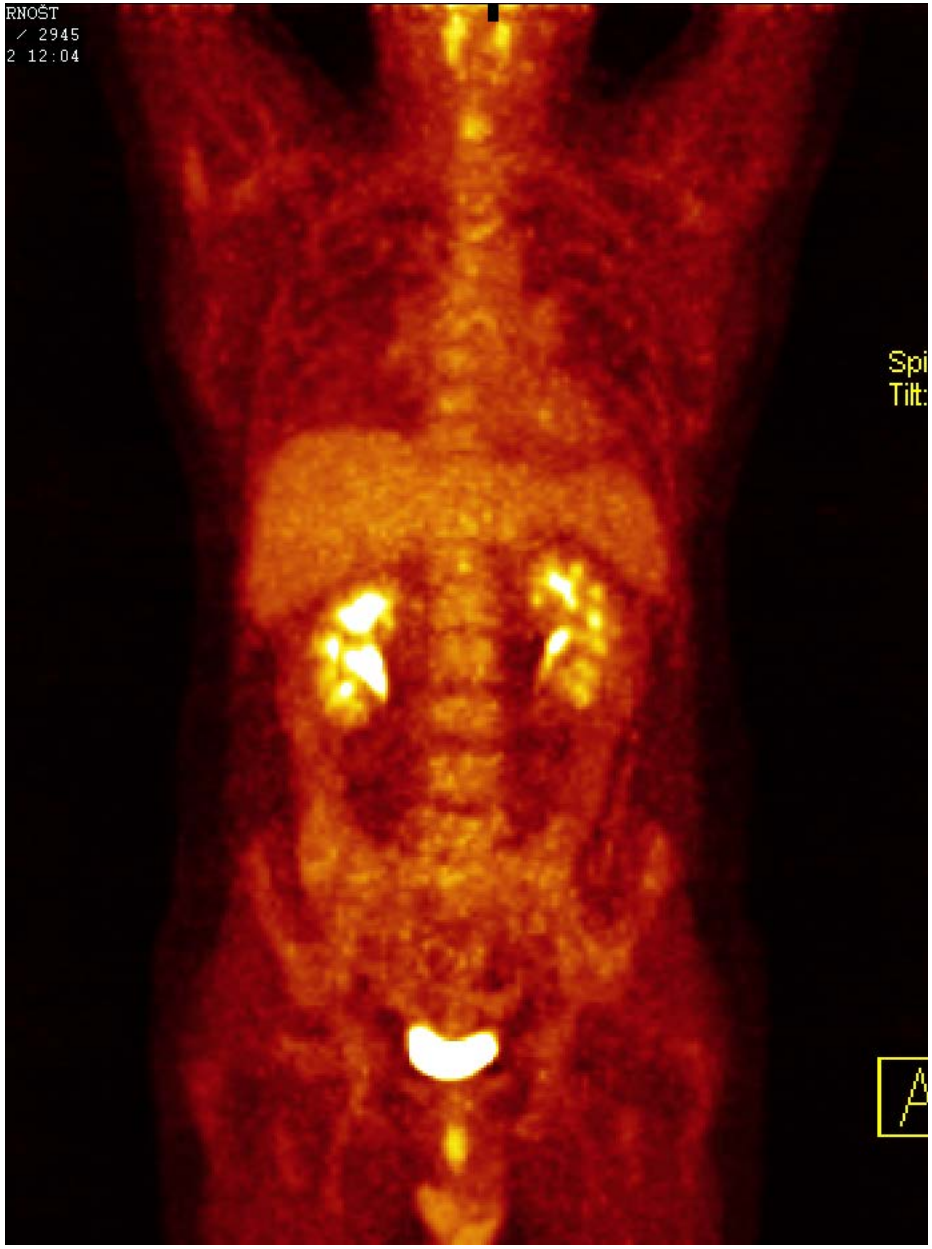
- chemotherapy
  - eg ABVD (doxorubicin, bleomycin, vincristine, dacarbazine)
- actinotherapy (site of the largest nodal affection)
- combination of chemotherapy and actinotherapy
- immunotherapy: anti-CD30 mAb (brentuximab vedotin) in relapses
- immunotherapy: PD-1 check-point inhibitor (nivolumab)

<u>in recurrent and advanced diseases</u>:

transplants autologous or even allogeneic

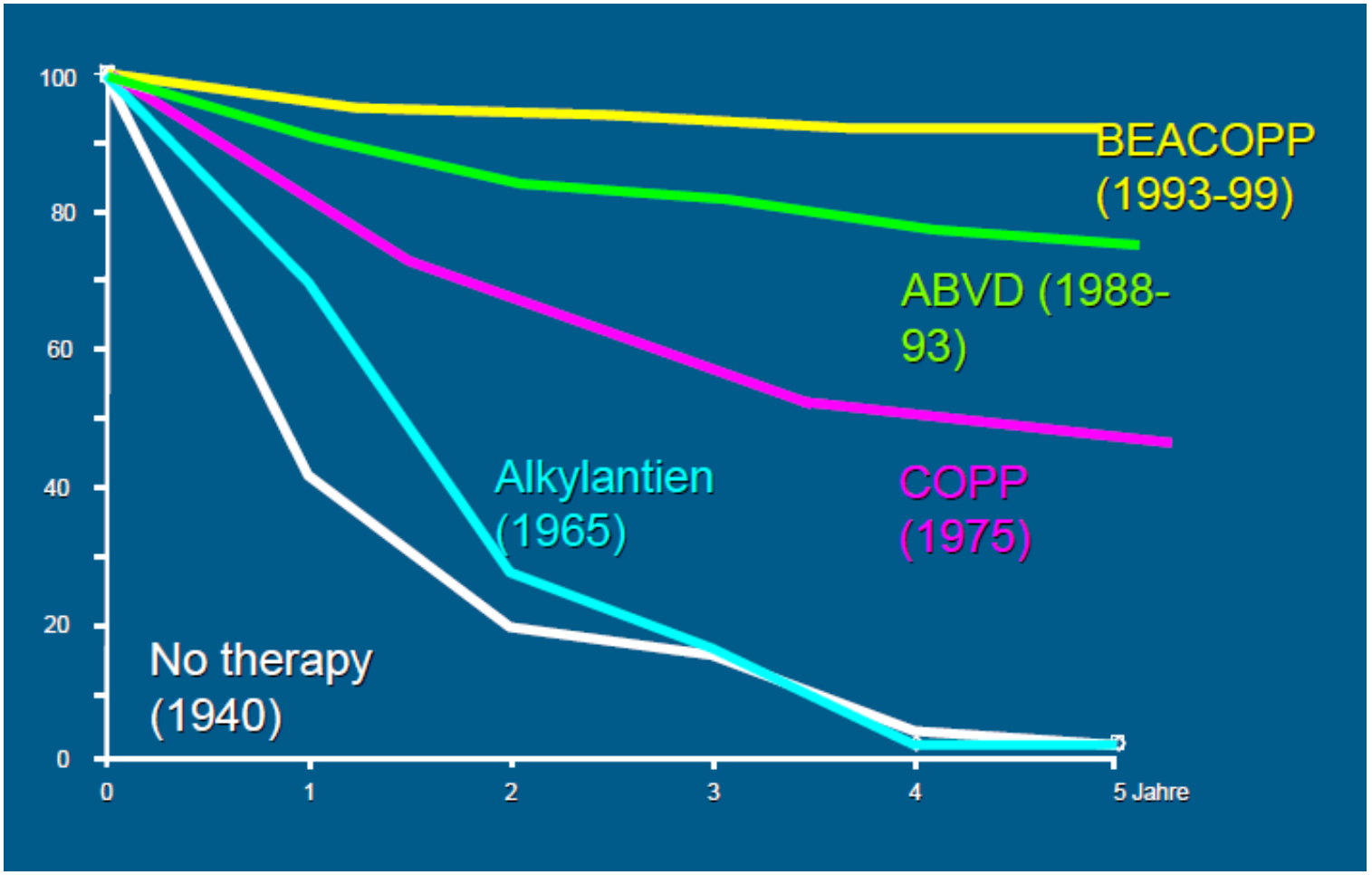


před léčbou (krk, nadklíček, játra)



kompletní remise po léčbě

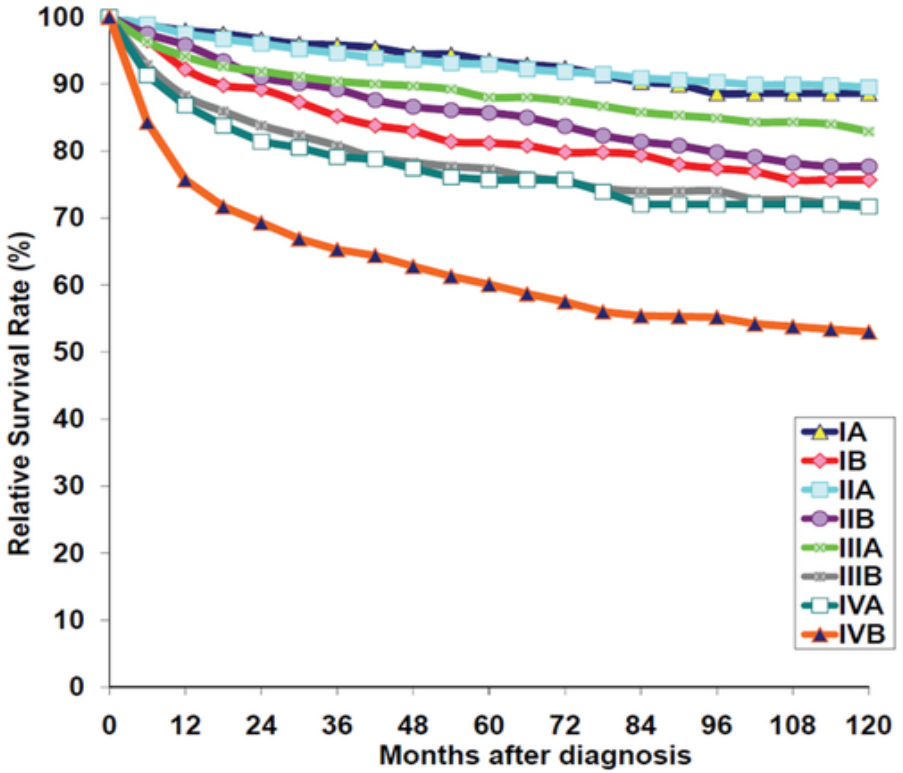
H.lymphoma= „success story“ 20. century

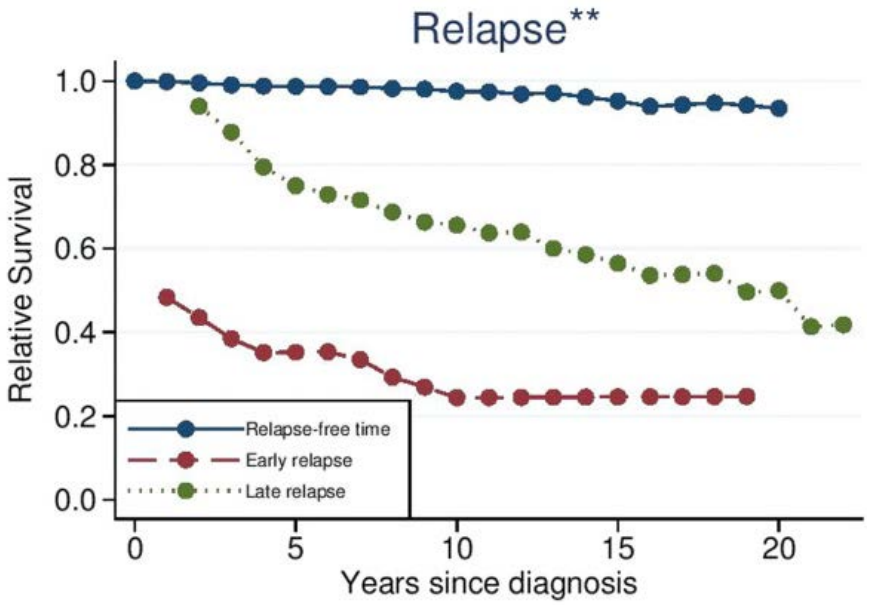


Two faces of H. lymphoma

excelent results:

- early stages - cure 90% of patients
- advanced stages - we treat 70-80% of patients





refractory disease and early relapses - poor prognosis: survival 20 - 30% !!

Shanbhag S, CA 2017; Glimelius I, Am J Hematol 2015

Long-term complications of lymphoma treatment

- **infertility:**
  - men> women
  - considering semen of “banking”
  - premature menopause
- **secondary malignancies:**
  - acute myeloid leukemia, myelodysplastic syndrome, lung ca, breast, thyroid ...
- **heart disease:**
    - cumulative dose of anthracyclines
    - chest actinotherapy

Radiotherapy I.

- success depends on the difference in radiosensitivity between tumor and normal tissue
- application of ionizing radiation in the form of X-rays or gamma radiation to the tumor
- application method: external (teletherapy) or internal (brachytherapy)

Radiotherapy II.

- radiotherapy: alone or in combination with chemotherapy
  - goal: curative x palliative

- in hemato-oncology:
  - Hodgkin's disease
  - non-Hodgkin's lymphomas
  - extramedullary leukemia (sarcoma)
  - CNS in acute lymphoblastic leukemia
  - TBI before allogeneic transplantation

- radioimmunotherapy:
  - a radioisotope-linked monoclonal antibody
  - accumulation of radionuclide at the tumor site

TBI = total body irradiation

Complications of radiotherapy

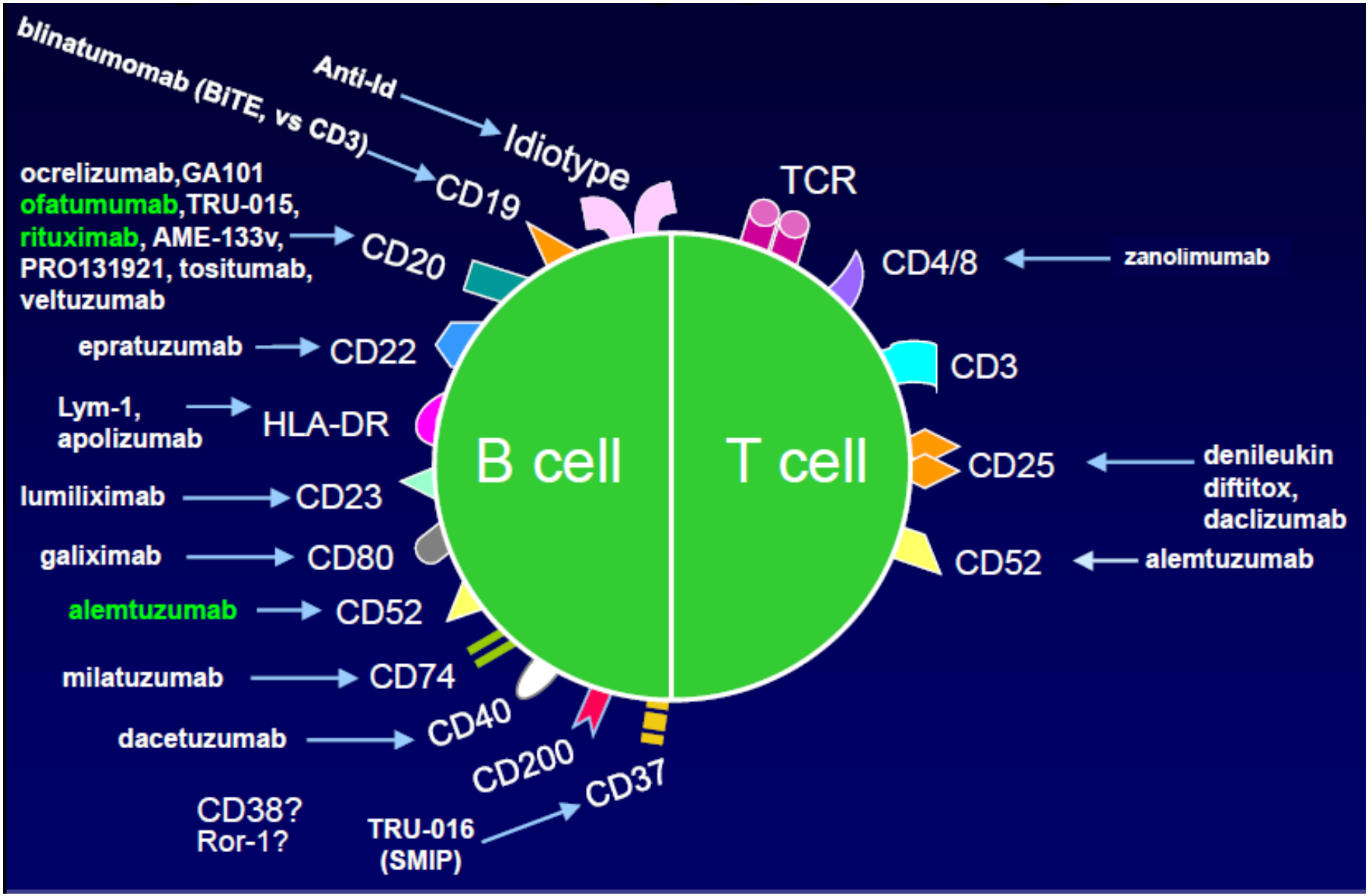
- acute and long-term toxicity
  - acute: general symptoms (fatigue), local skin reactions, GI toxicity, oropharyngeal mucositis, myelosuppression
  - long-term consequences: they appear months to years after treatment

- radiotherapy is:
  - mutagenic, carcinogenic, teratogenic
  - increased risk of secondary leukemia or solid tumors

Immunotherapy

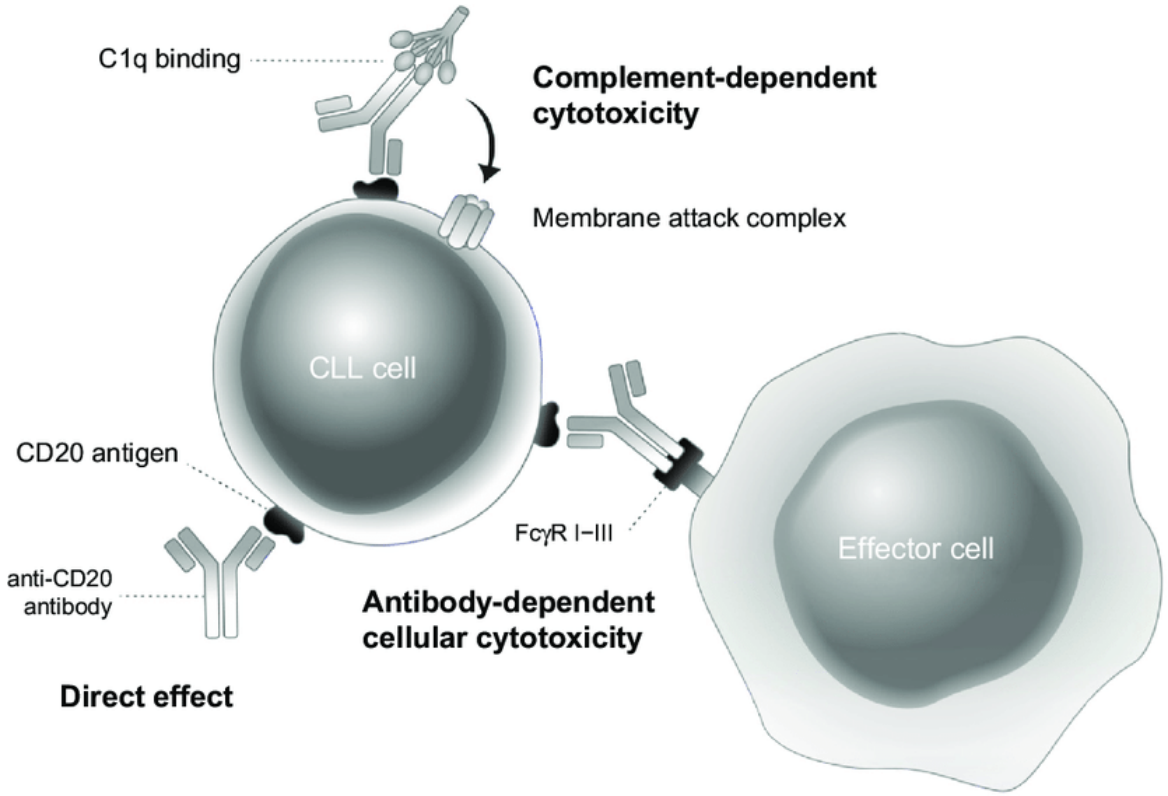
- monoclonal antibodies
- immunoconjugates: potentiation by toxin binding (ricin, diphtheria toxin…)
- radioimmunoconjugates: potentiation of effects by radioactive isotope binding

Target antigens in lymphoproliferations



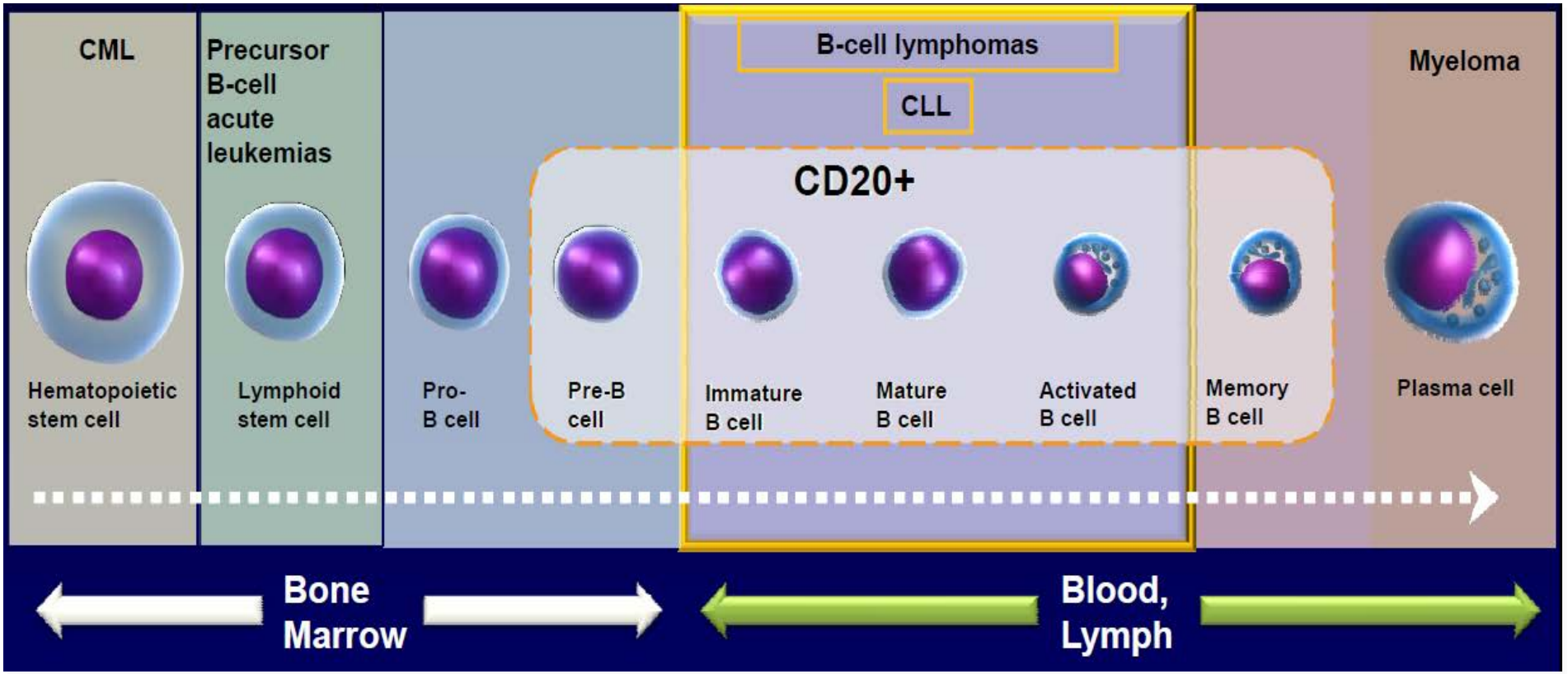
Rituximab (anti- CD20)

- chimeric murine anti-CD20 antibody
- approved by the FDA since 1997 for the treatment of B-non-Hodgkin's lymphomas



Smolej L, Pharmgenomics Pers Med 2014

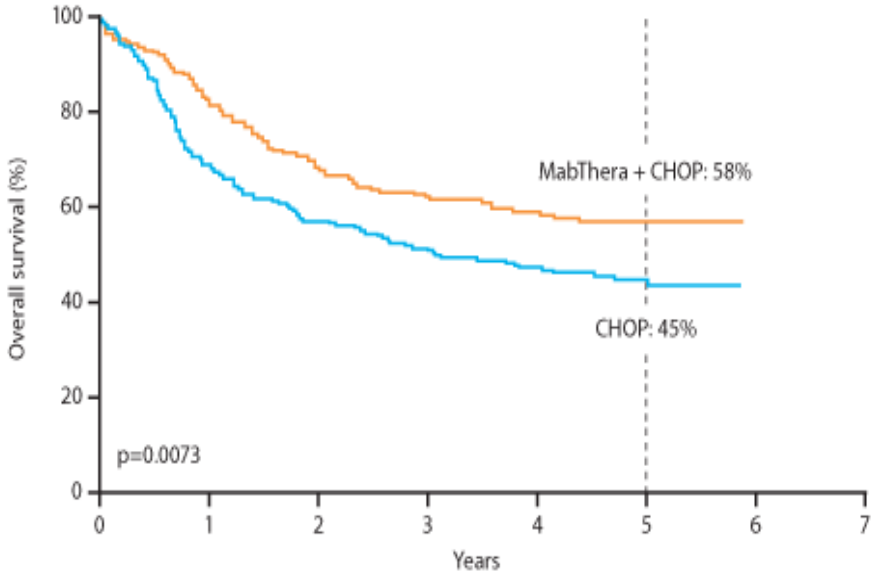
CD20 - the ideal target antigen



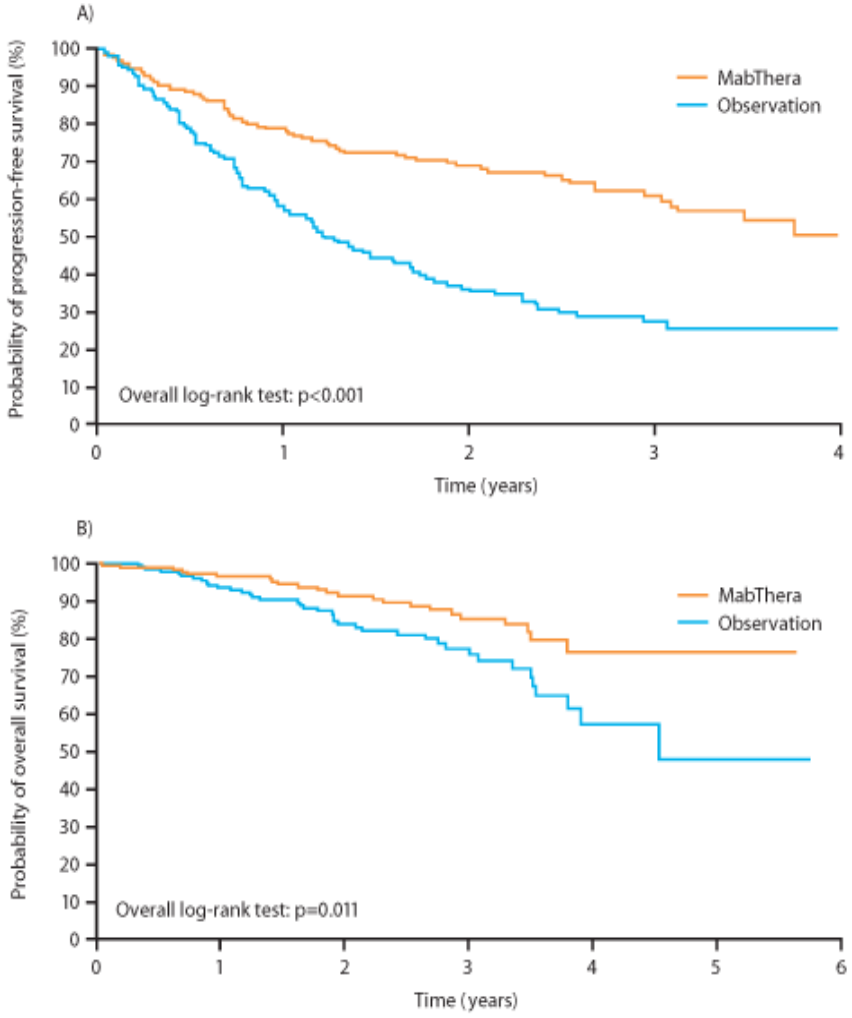
- is expressed on most tumor and normal B cells, not on stem cells and other tissues
- eradication of tumor population with relatively low toxicity (B-lymphocytes differentiate again from stem cells)

Addition of antibody improves survival

rituximab in DLBCL

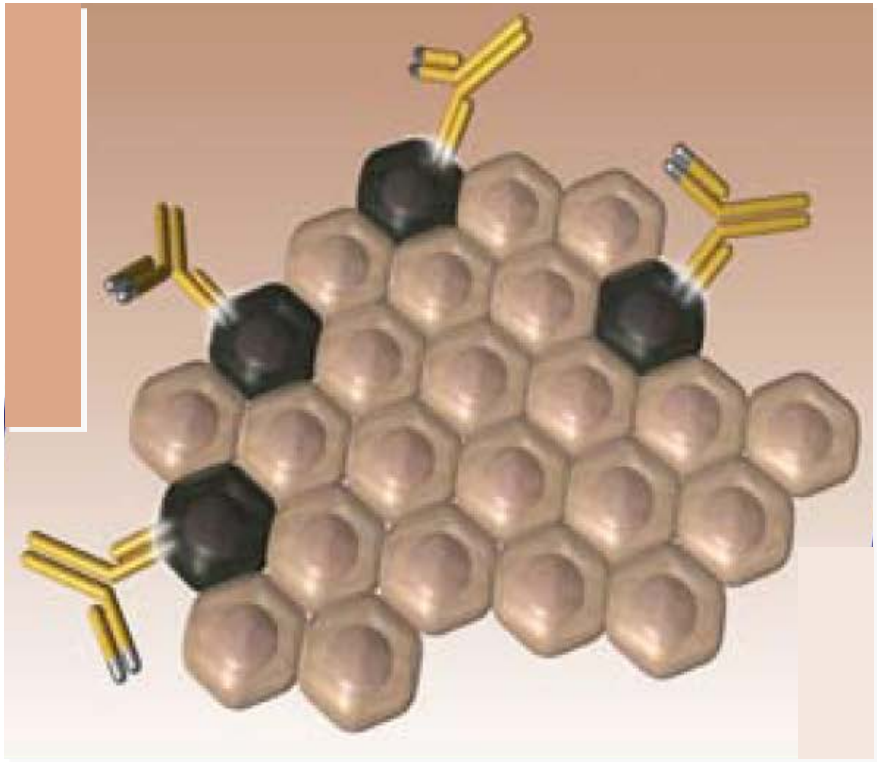


maintenance treatment of rituximab in FCL

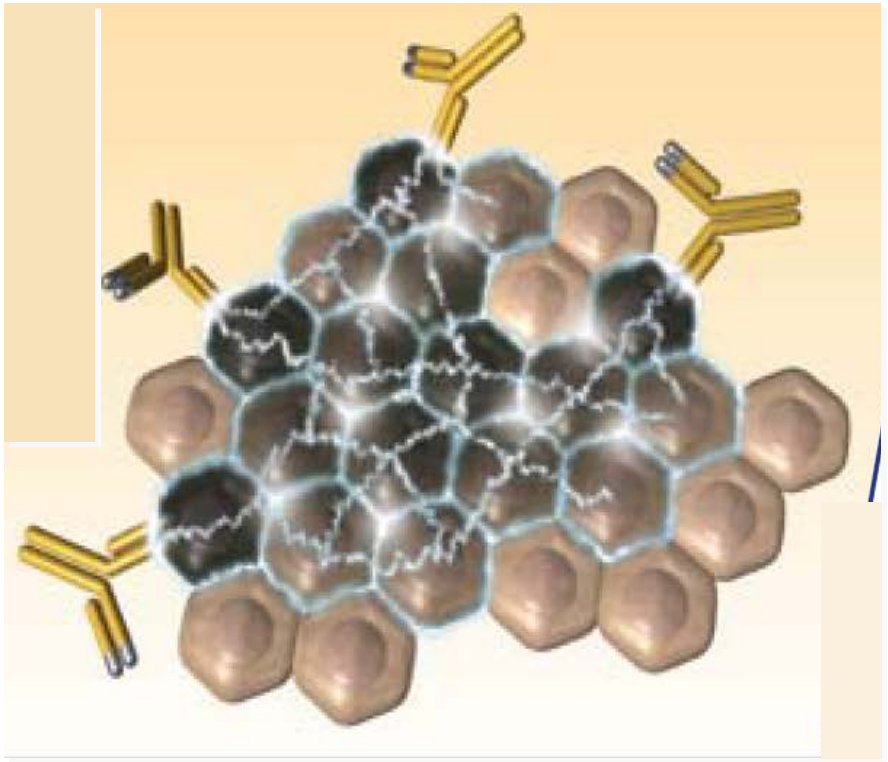


Feugler P, JCO 2005; van Oers Blood 2006

immunotherapy
anti- CD20



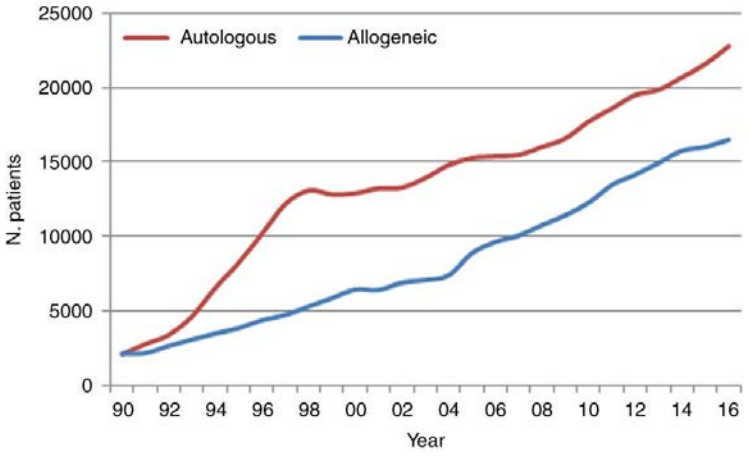
radio-immunotherapy
anti- CD20 + β radiation



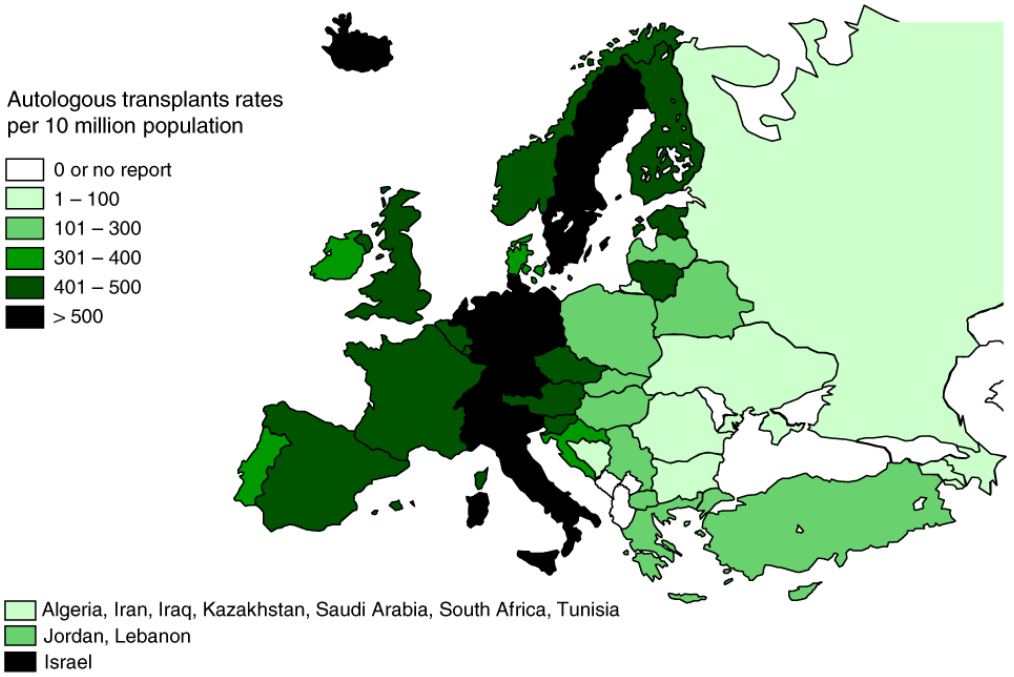
- radioimuniterapie kombinuje efekt imunoterapie a lokální radiace
- zasaženy jsou i lymfomové buňky nedosažitelné protilátkou

Autologous transplantation

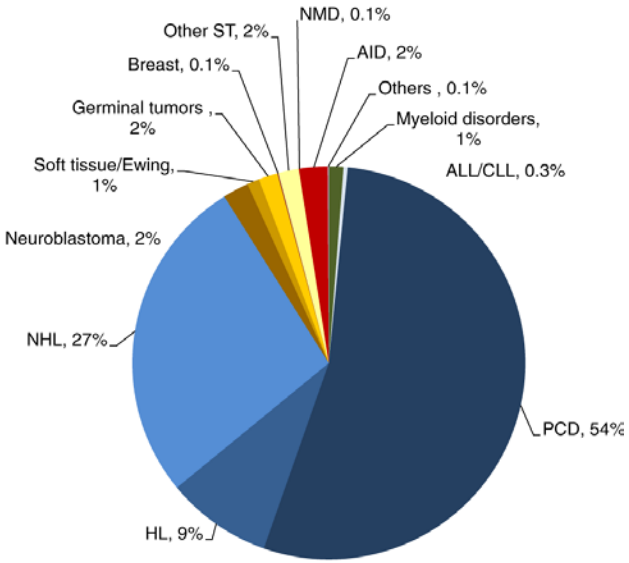
numbers of transplants in Europe (1990-2016)



autoTx per 10 million inhabitants (2018)



indications for autoTx (2018)



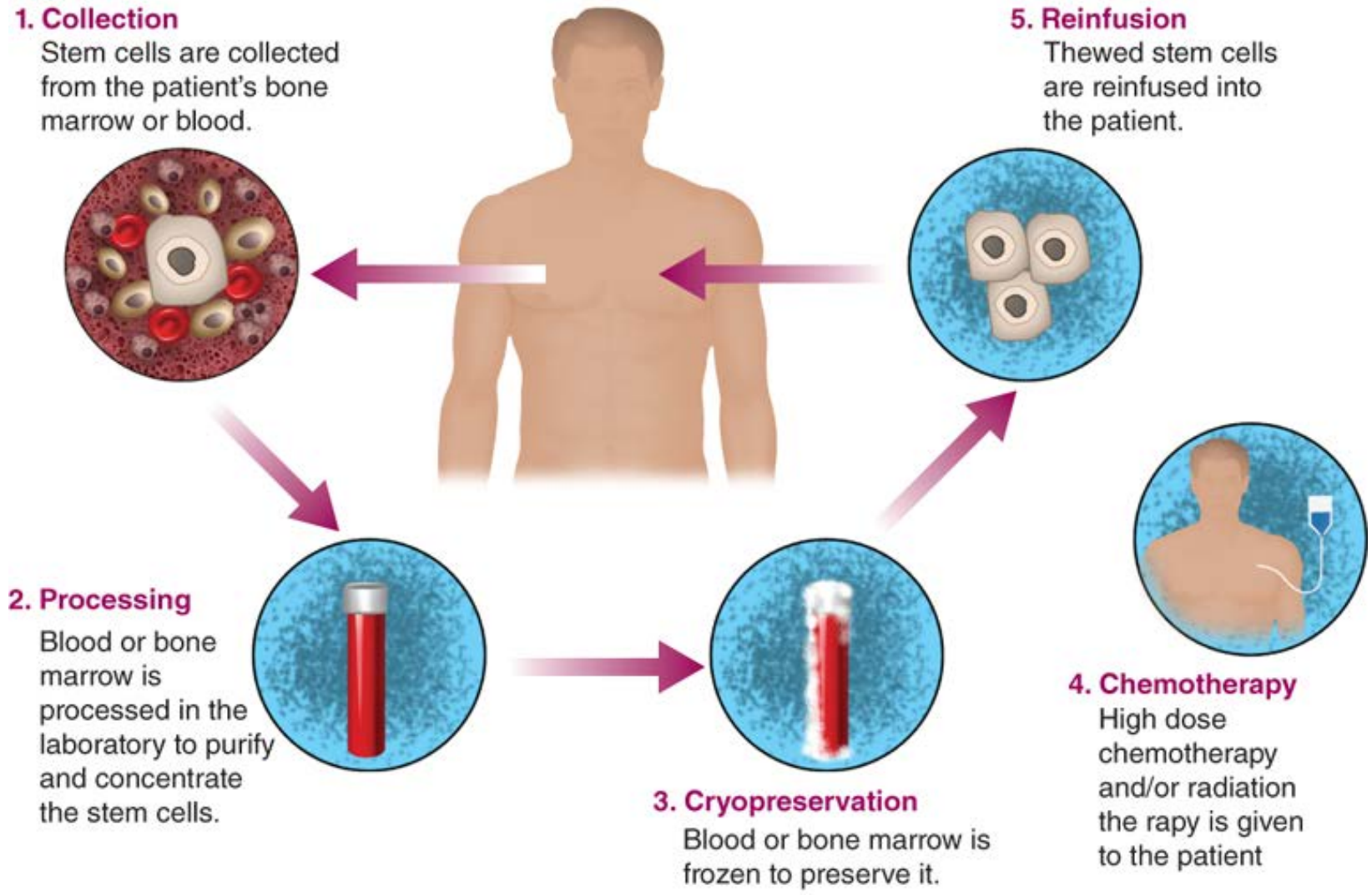
NHL – Non-Hodgkin lymphoma, HD – Hodgkin lymphoma, PCD – multiple myeloma

Passweg JR, BMT 2018, BMT 2020

Transplantation procedure

1. **collection of patient´s hematopoietic stem cells**
   - mobilization using combination of chemotherapy and granulopoiesis growth factor
   - washout of hematopoietic stem cells from bone marrow into peripheral blood
     apheresis collection
   - cell processing and cryopreservation
2. **freezing with cryoprotectant**
   - storage of transplants in liquid nitrogen (- 196 ºC)
   - long-term (years)
3. **high-dose chemotherapy**
   - pre-transplant chemotherapy (myeloablative) ⇨ pancytopenia
4. **cell thawing and application** (autologous transplantation)
   - transplant infusion
   - reconstitution of hematopoiesis and normalization of blood count

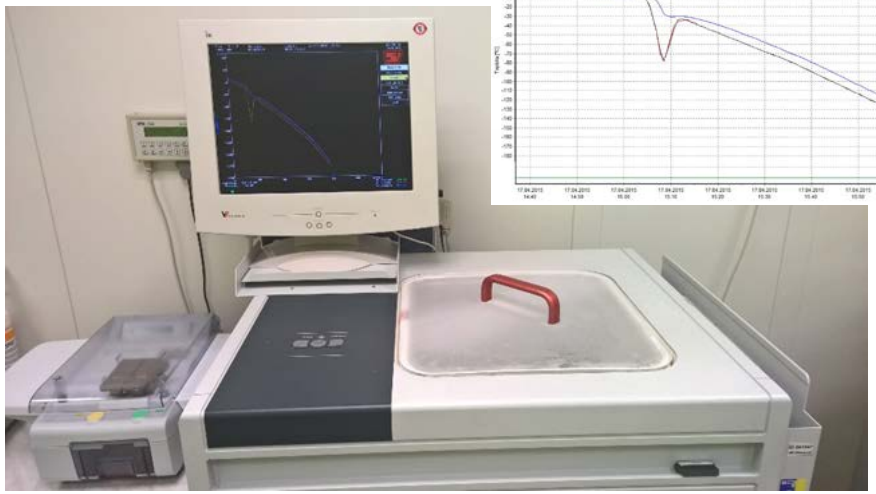
Autologous haematopoietic transplantation progenitor cells



Kantarjian H, The MD Anderson Manual of Medical Oncology, 3rd edition

Cryopreservation and storage

- clean space, aseptic technique
- cryomedium (dimethylsulphoxide)
- after closing the bag ➡ out of the clean room
- place the bag in a protective metal cassette
- immediately insert into the programmable freezer
- transfer to cryo-storage after freezing
- store in liquid nitrogen



Complication

transient bone marrow aplasia:

- thrombocytopenia, anemia, granulopenia (ERY substitution, thrombo, granulopoietic growth factors)

granulopenia infection:

- bacterial (prophylactic ATB)

toxic damage to the mucosa of the GIT:

- mucositis, diarrhea (hydration, parenteral nutrition, anodyne)

toxic action of cryopreservant (DMSO):
neurotoxicity, cardiotixicity

Supportive care I.

transfusion therapy:

- thromboconcentrates, erythrocyte resuspension
- irradiated and deleukotized

antibiotics, antifungals:

- predisposition to infection (neutropenia, mucosal barrier damage, immunosuppression)
- prophylaxis and treatment of infectious complications

nutrition:

- mucositis, enterocolitis
- total parenteral nutrition

granulocyte-colony growth factor (G-CSF):

- accelerates the regeneration of granulopoiesis
- reduces the duration of neutropenia

Supportive care II.

(hyper) hydration:

- protection of the kidneys and urinary tract from damage (toxicity of chemotherapy, antibiotics, ..)

allopurinol:

- decreases uric acid level (increased production - increased metabolic turnover of the tumor, tumor breakdown)
  xanthine oxidase inhibitor
  prevents formation of urinary stones (kidneys, urinary tract)

antiemetics:

- eliminate nausea and vomiting

Infectious complications

most common microorganisms:

- Gram-positive bacteria (up to 60%):
  - Staphylococcus epidermidis, aureus, Streptococcus viridans, pneumonia
  - wound infection, CVC, pneumonia, sepsis
- gram negative bacteria (about 20%):
  - Pseudomonas, Escherichia, Klebsiella
  - wound infections, rapidly developing sepsis
- Clostridium difficile:
  - it may outgrow other bacteria in the intestine during antibiotic treatment
  - pseudomembranous enterocolitis (diarrhea, abdominal pain ..)
- fungal infections:
  - candida: yeast, mouth infection
  - aspergillus: mold, pulmonary aspergillosis

MYELODYSPLASTIC SYNDROME

Introduction

acquired clonal hematopoietic disease characterized by:

- ineffective dysplastic haemopoiesis
- peripheral cytopenia (and the resulting complications)
- different risk of progression in acute myeloid leukemia

clinical manifestation:

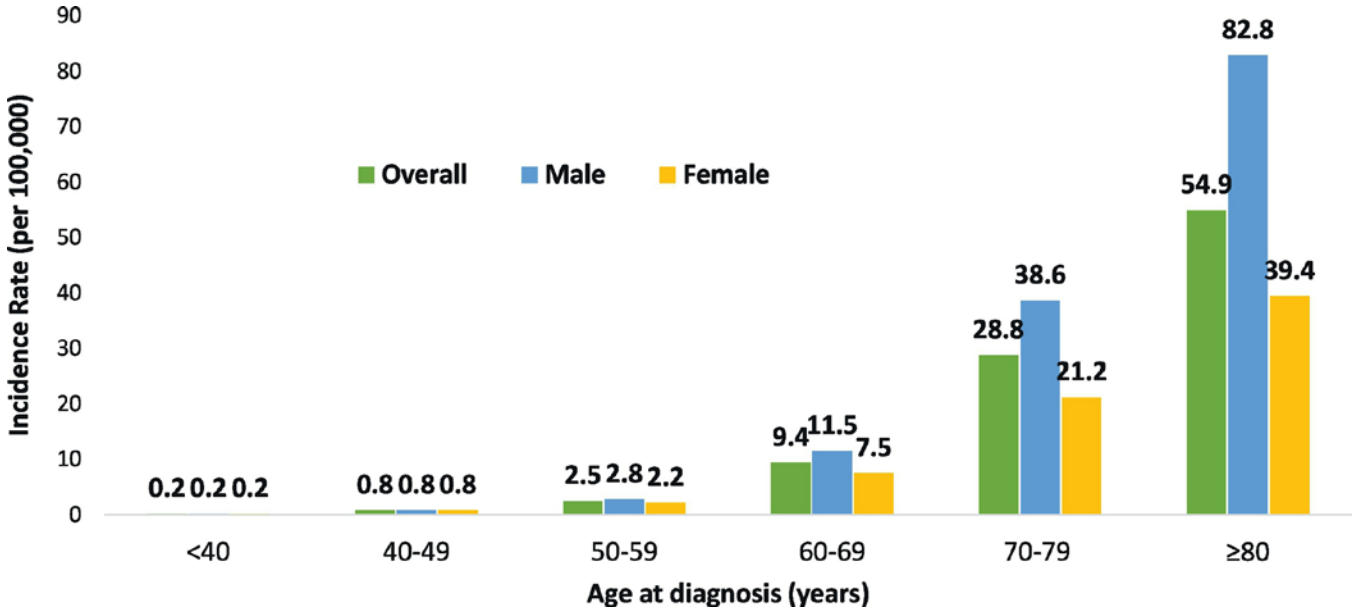
- failure of haemopoiesis with a tendency to leukemia transformation

morphological manifestation:

- morphological abnormalities of peripheral blood / bone marrow cells

Epidemiological data

- median age at dg. - 70 - 76 years
- incidence / 100,000 - 0.1% (<40 years), 9% (60-70 years) to 28% (70-80 years)
- > 80% of patients over 60 years old! at dg.
- MDS is age-independent and occurs in 10-15% of patients after intensive cancer chemotherapy



Zeidan A, Blood Reviews 2018

Development of incidence

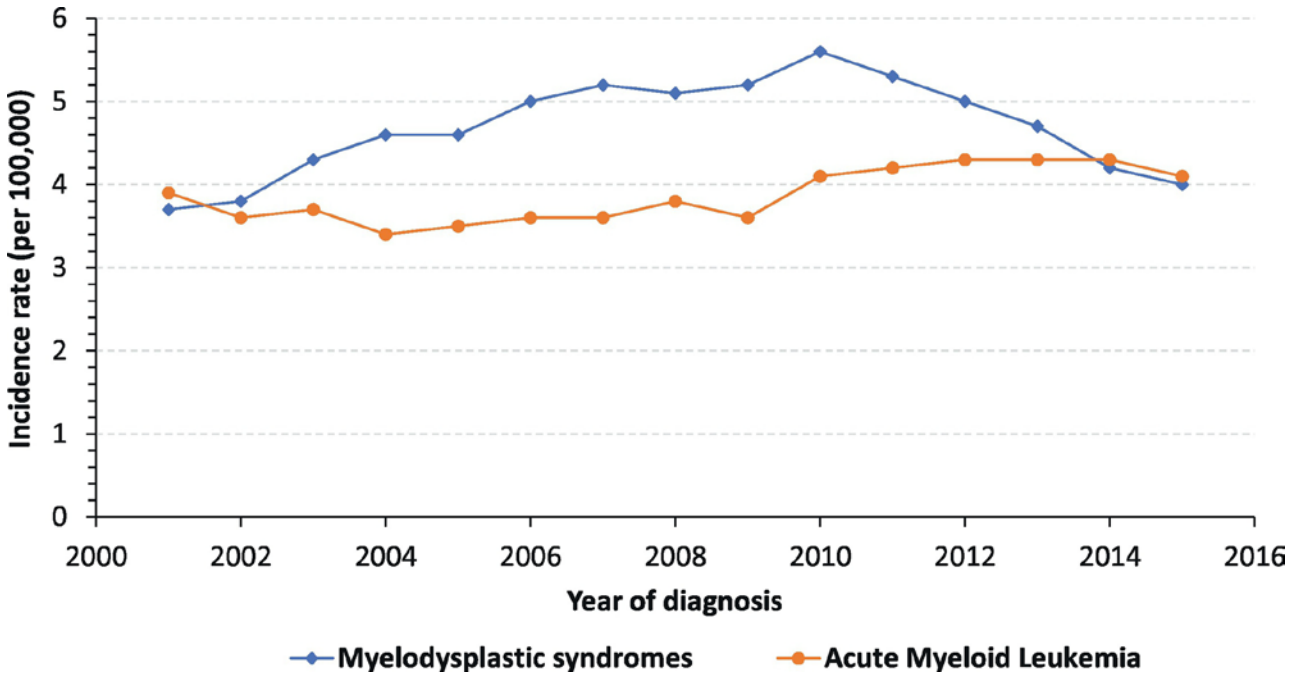
increase:

➡ aging population (improving geriatric care)

➡ increase in the use of cytostatics? ("Treatment related„ MDS)

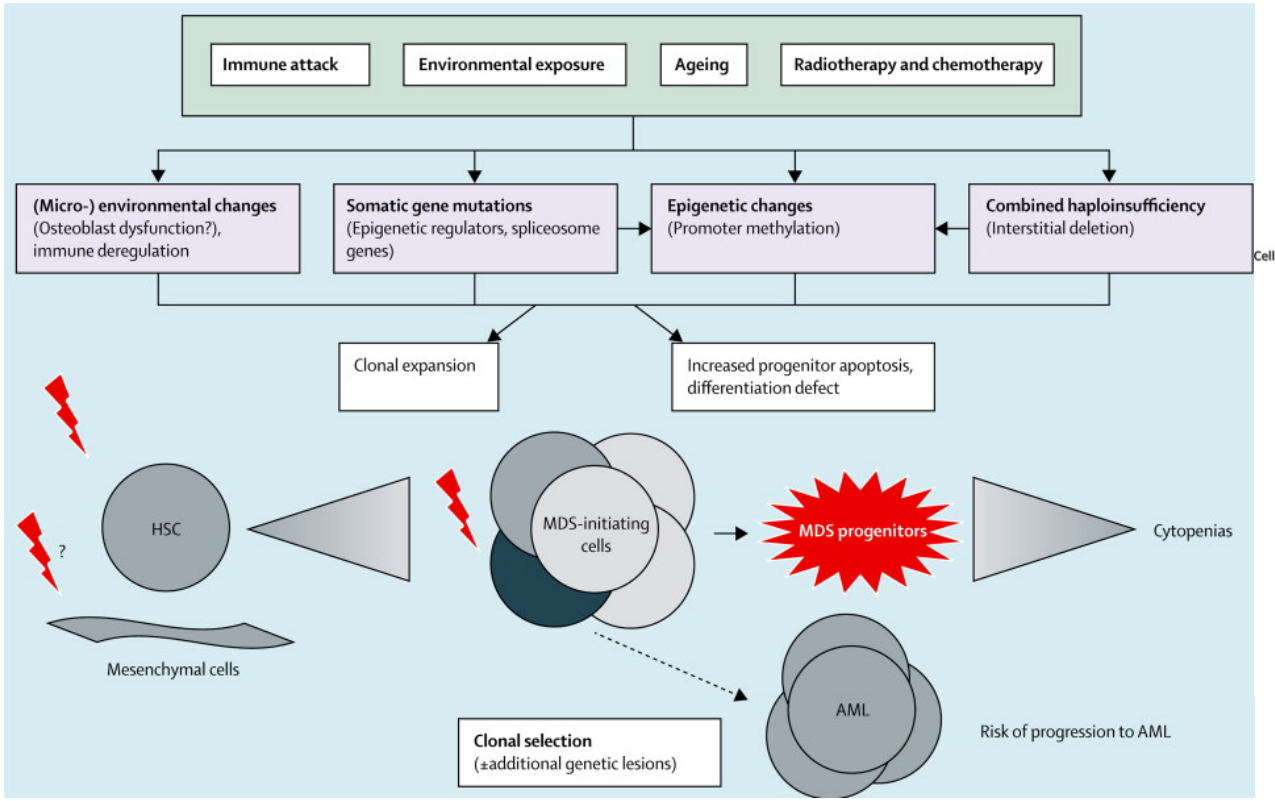
decrease:

➡in recent years thanks to the refinement of the classification

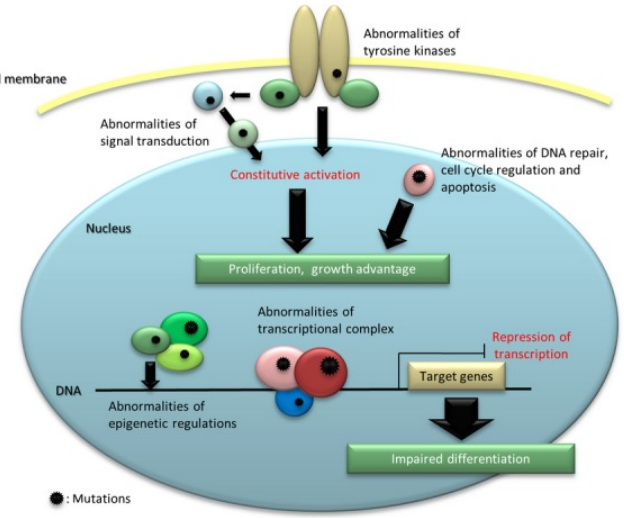


Zeidan A, Blood Reviews 2018

Etiopatogenesa



MDS-associated gene mutations

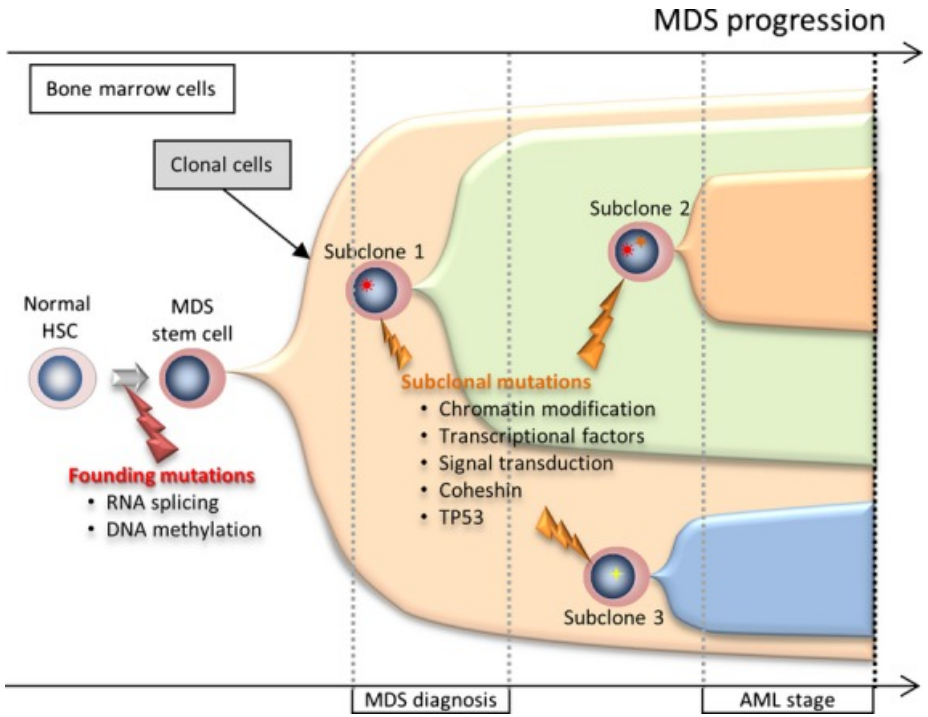


- it is a multistep process with sequential accumulation of oncogenic mutations
- haemopoietic cell mutations (age-related, external factors, immune changes) lead to oligoclonal expansion of myelodysplastic stem cells with defective differentiation and increased apoptosis
- there are changes in the microenvironment, immune dysregulation and cytokine imbalance, contributing to the defect of differentiation

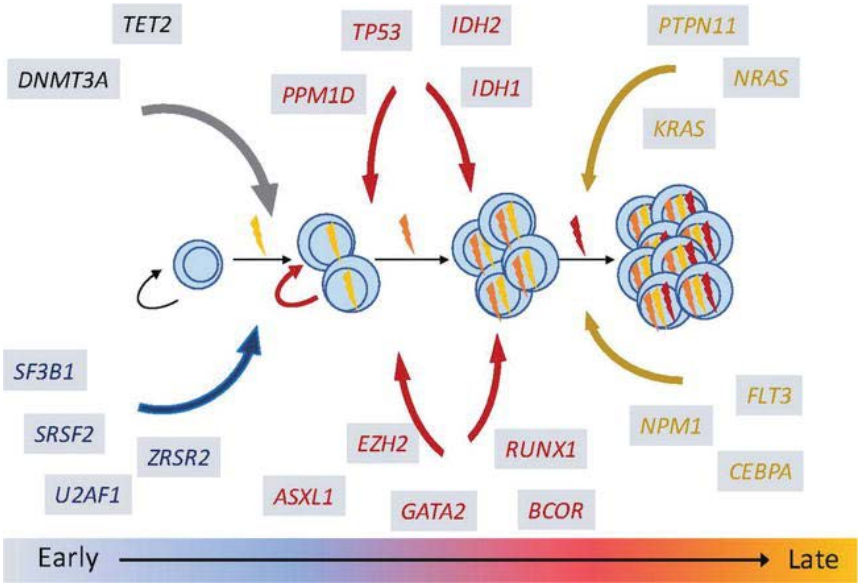
Ades L, Lancet 2014; Harada H, Cancer Sci 2015

Etiopathogenesis - progression to AML

clonal evolution from MDS to AML



mutations affecting epidenetic modification genes (DNMT3A, TET2) or RNA splicing (SF3B1) occur earlier, while mutations in growth factor signaling (NRAS, FLT3) occur later at the time of AML transition



- a number of mutations appear in stereotyped order during disease
- some of them are founding mutations and some are used as driver subclonal mutations

Chai-Ho W, Rec Dev in MDS, 2018; Harada H, Cancer Sci 2015

Diagnostics

- typically based on **pathological KO** (cytopenia in 1-3 lines)
- confirmed by bone marrow examination ➡ morphology (**dysplasia**) and blast count
- cytogenetics (molecular genetics) ➡ allows to specify dg. and prognosis
- recently defined a number of units preceding MDS ➡ MDS is a kind of outcome

- **CHIP <-> ICUS <-> IDUS <-> CCUS> MDS**

CHIP = Clonal Hemopoesis of Indeterminate Potential
IDUS = Idiopathis Dysplasia of Undetermined Significance
ICUS = Idiopathic Cytopenia of Undetermined Significance
CCUS = Clonal Cytopenia of Undetermined Significance

Blood count

B--Le	2,80	4 - 10	10^9/l
B--Ery	2,81	4 - 5,8	10^12/l
B--Hb	72	135 - 175	g/l
B--HTK	0,236	0,4 - 0,5	1
B--Obj ery.	84	82 - 98	fl
B--Hb ery	25,7	28 - 34	pg
B--Hb konc	306	320 - 360	g/l
B--Erytr.křivka	19,1	10 - 15,2	%
B--Trombo	74	150 - 400	10^9/l
B--shluky trombo	nejsou		
Dif mikr.			
B--Seg	0,61	0,47 - 0,7	1
B--Tyc	0,01	0 - 0,04	1
B--Ly	0,20	0,2 - 0,45	1
B--Mo	0,06	0,02 - 0,1	1
B--MMc	0,01	0 - 0	1
B--Mc	0,07	0 - 0	1
B--Blasty	0,04	0 - 0	1
B--Nbl	72/100	0 - 0	1

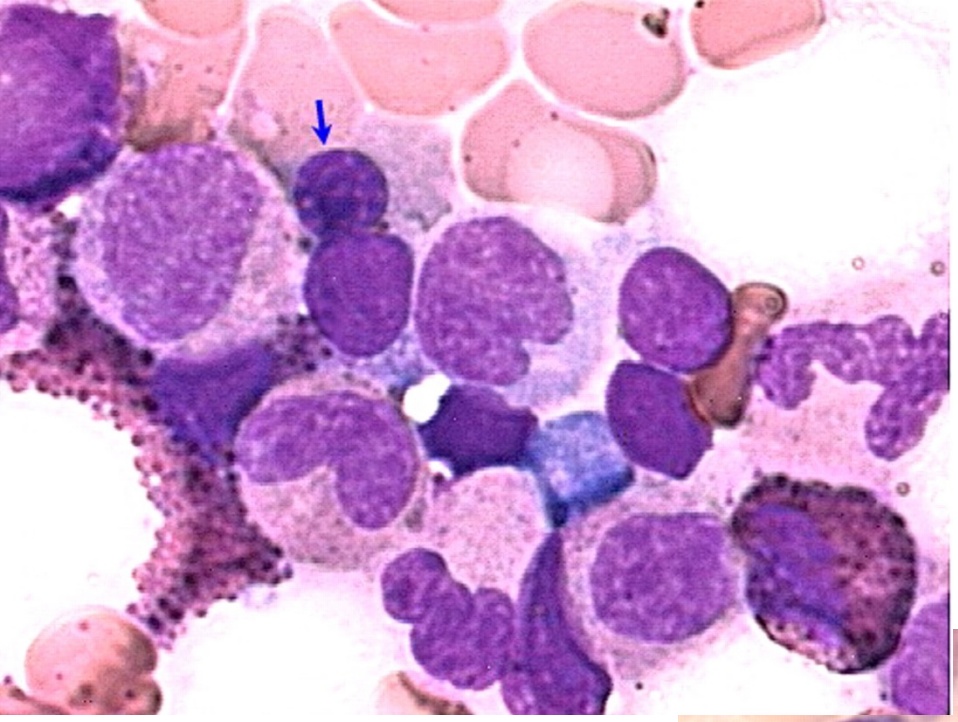
MDS EB1

B--Le	2,60	4 - 10	10^9/l
B--Ery	3,04	3,8 - 5,2	10^12/l
B--Hb	101	120 - 160	g/l
B--HTK	0,305	0,35 - 0,47	1
B--Obj ery.	100	82 - 98	fl
B--Hb ery	33,2	28 - 34	pg
B--Hb konc	331	320 - 360	g/l
B--Erytr.křivka	19,1	10 - 15,2	%
B--Trombo	96	150 - 400	10^9/l
B--shluky trombo	nejsou		
B--Nbl abs	0,00	0 - 0,02	10^9/l
B--Nbl rel	0,001	0 - 0,003	1
Dif aut			
B--Seg	0,696	0,45 - 0,7	1
B--Ly	0,125	0,2 - 0,45	1
B--Mo	0,140	0,02 - 0,12	1
B--Eo	0,025	0 - 0,05	1
B--Ba	0,014	0 - 0,02	1
B--Seg - abs	1,80	2 - 7	10^9/l
B--Ly - abs	0,30	0,8 - 4	10^9/l
B--Mo - abs.	0,40	0,08 - 1,2	10^9/l
B--Eo - abs	0,10	0 - 0,5	10^9/l
B--Ba - abs	0,00	0 - 0,2	10^9/l

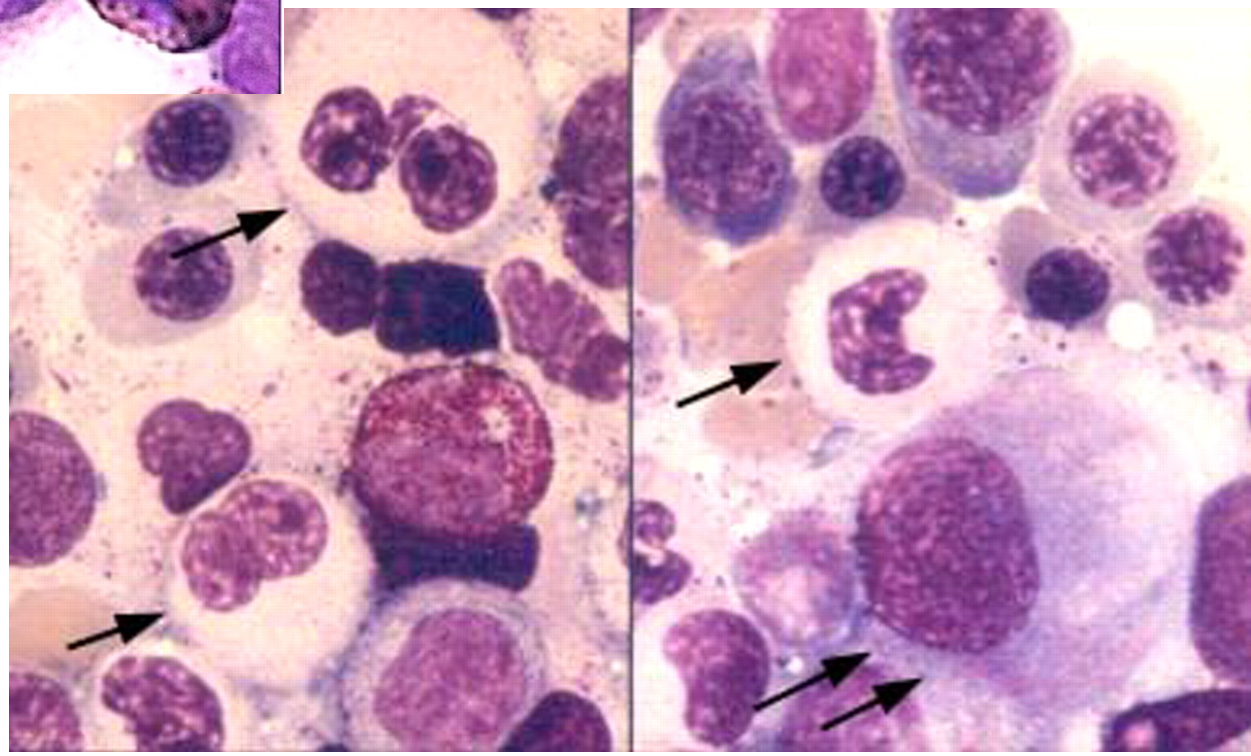
MDS 5q-

Bone marrow aspirate

- dysplastic changes in haemopoiesis - different number of affected lines (erythropoiesis / myelopoiesis / megakaryopoiesis)
- % blasts in BM / PB
- cytogenetics (cytogenetic abnormalities are present in about half of the patients)
- molecular genetics (NGS) - further refinement of prognostic stratification

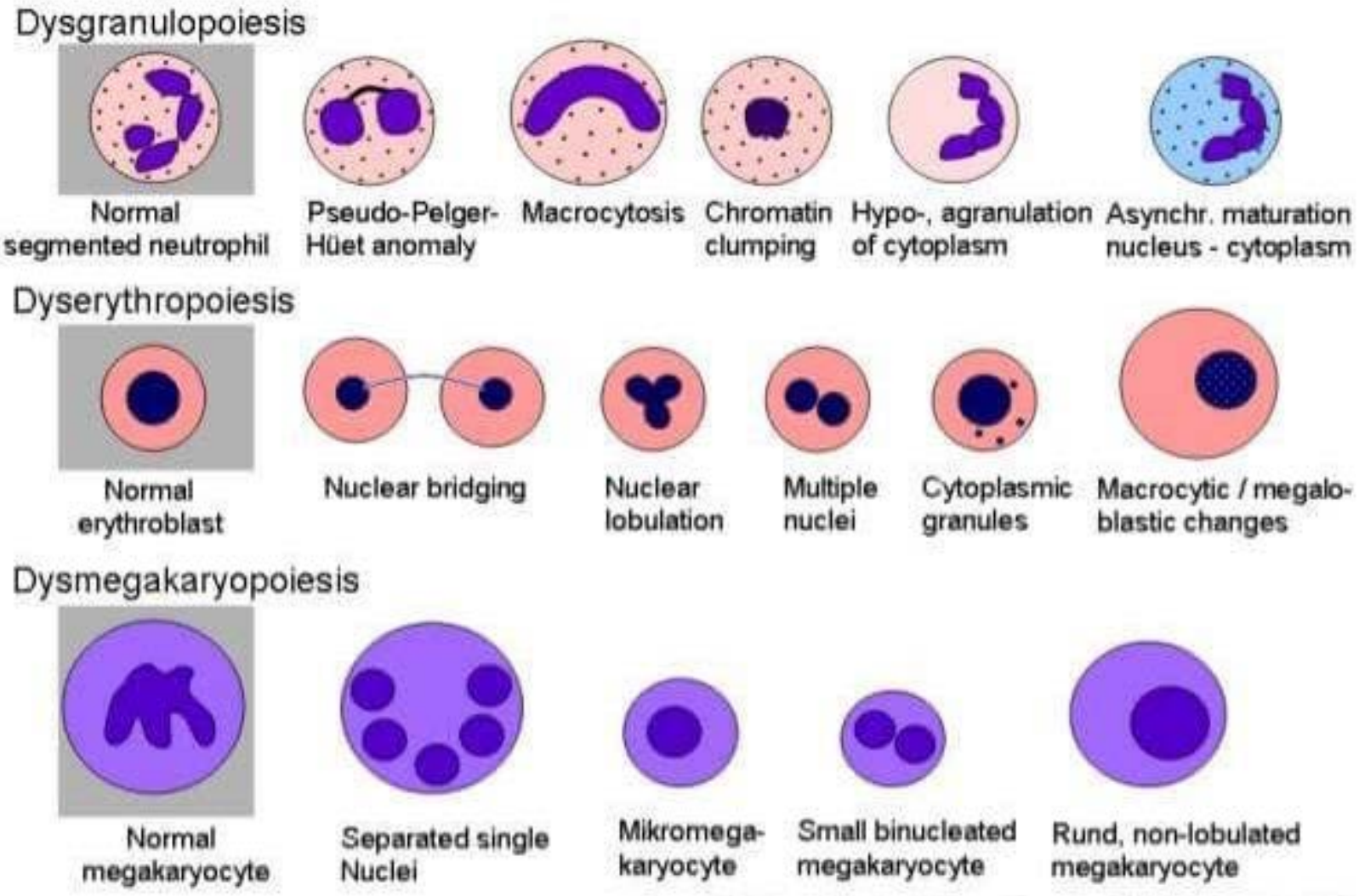


bone marrow apirate:
normal bone marrow



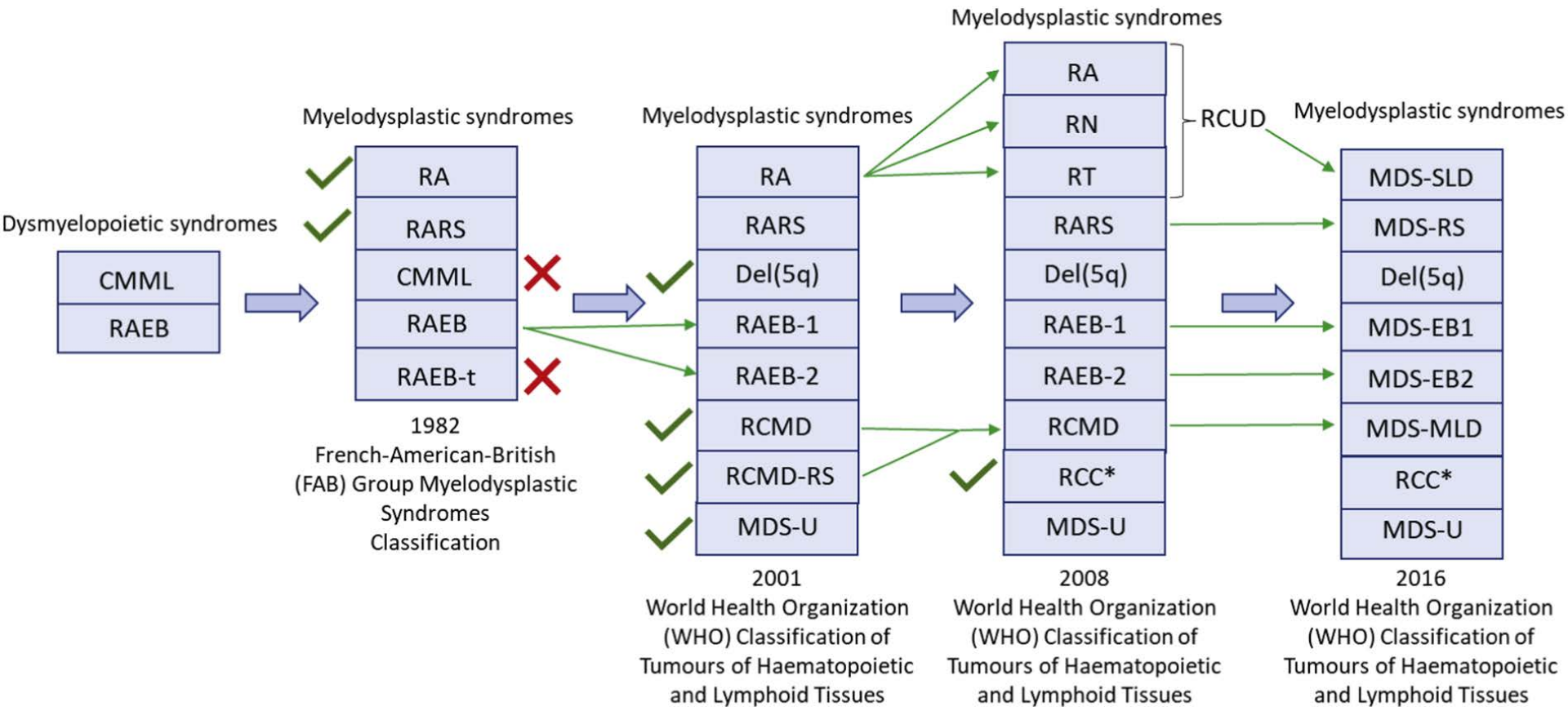
bone marrow apirate:
MDS with multi-line dysplasia

dysplastic changes (morphology)



Rajnoldi C, Ann Hematol 2005

Development of classification from FAB to WHO



- the classification of MDS is gradually being refined
- latest version from 2016 (7 subtypes)

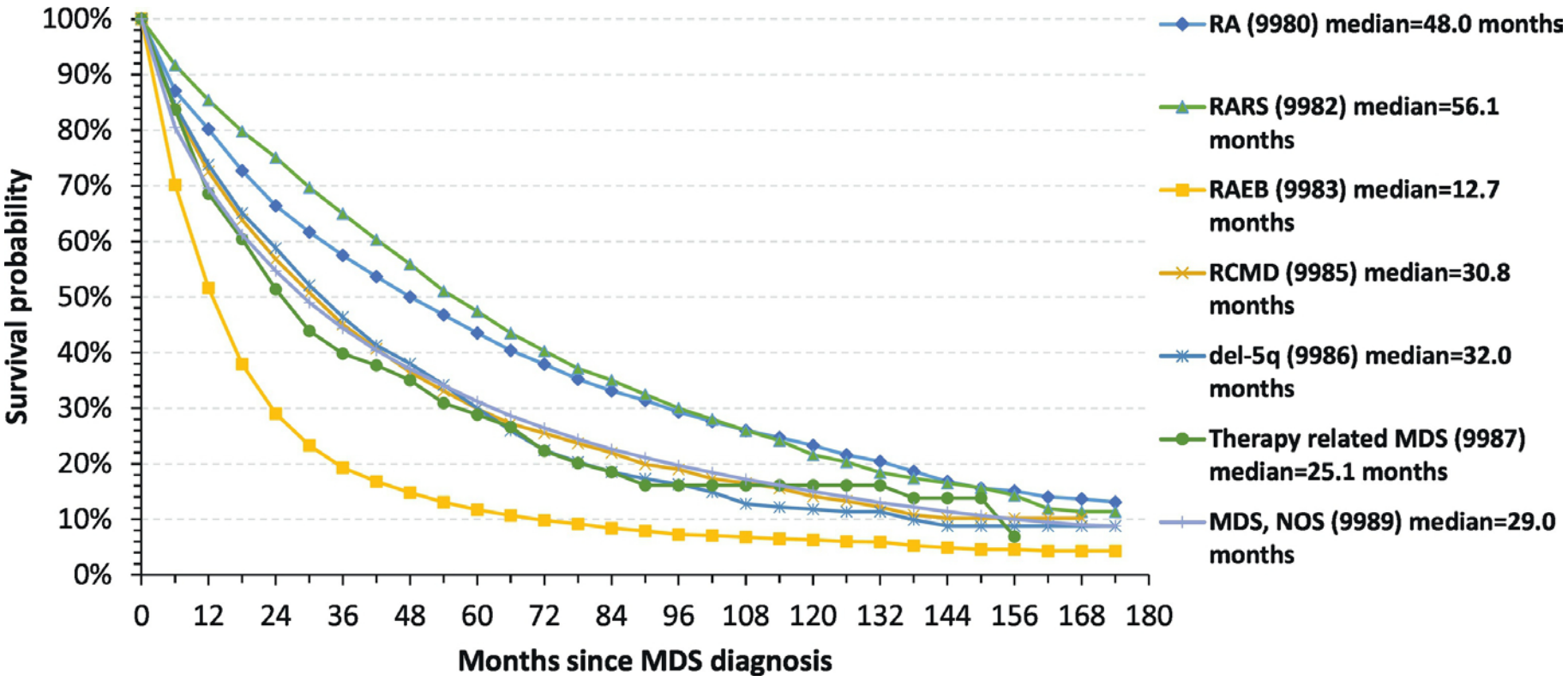
aktuální klasifikace

WHO classification

World Health Organization

type (abbreviation)	ring sideroblasts in BM	blasts number in BM
MDS with single-line dysplasia (MDS-SLD)	<15%	BM < 5%
MDS with multi-line dysplasia (MDS-MLD)	<15%	BM < 5%
MDS with ring sideroblasts (MDS-RS)	≥ 15%	BM < 5%
MDS with blast excess (MDS-EB) ▪ MDS-EB-1 ▪ MDS-EB-2	absent	BM 5-9% BM 10-19%
MDS with isolated del (5q)	absent	BM < 5%

Prognosis according to WHO



probability of survival according to WHO classification

Zeidan A, Blood Reviews 2018

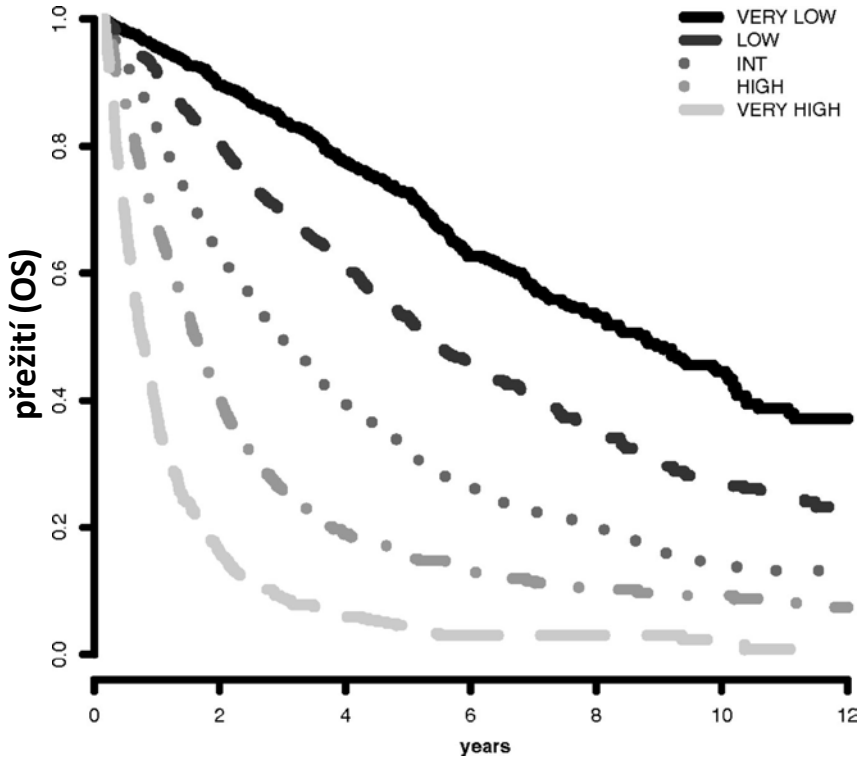
"Natural" course, complications

- MDS - Elderly Disease (more than 80% older than 60 years!)
  ➡ 20% die other than MDS

- ~1/3 transformation in AML ➡ fatal course

- most (~ 60%) die of infectious complications:
  - Granulocytopenia
  - granulocytic dysfunction

Prognostic stratification



5- RISK GROUPS:

- very low
- low
- medium
- hihg
- very gigh

MDS low risk

MDS hihg risk

median overal survival ~ 6-8 years ➡ less than 1 year

R-IPSS:

- percent blasts in BM
- karyotype
- blood count parameters (cytopenia)

R-IPSS = revised international prognostic scoring system for MDS

Schanz J, JCO 2012; Greenberg PL, Blood 2012

Treatment goals

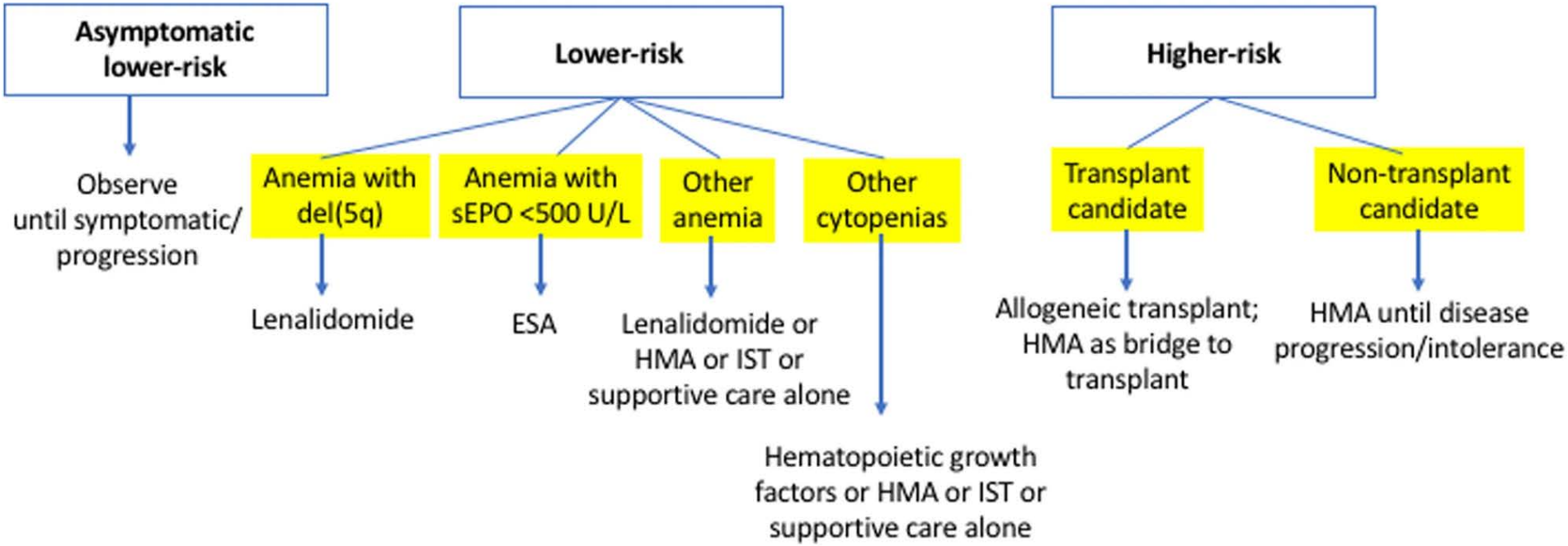
- relieve symptoms ➡ do not change the natural course of the disease
- permanently / temporarily cure ➡ change the natural course of the disease

- low risk / elderly patients: improving pancytopenia, improving quality of life
- high risk / younger patients: delaying progression, prolonging survival

Treatment options

treatment is based on:

- severity of cytopenia
- risks of progression to AML-R-IPSS
- age of the patient



EPO = erythropoietin, ESA = erythropoiesis-stimulating agent, HMA = hypomethylating agent, IST = immunosuppressive therapy (anti-thymocyte globulin, cyclosporine, or tacrolimus)

Steensma DP, Blood Cancer Journal 2018

Thanks for your attention