Malignant Lymphomas

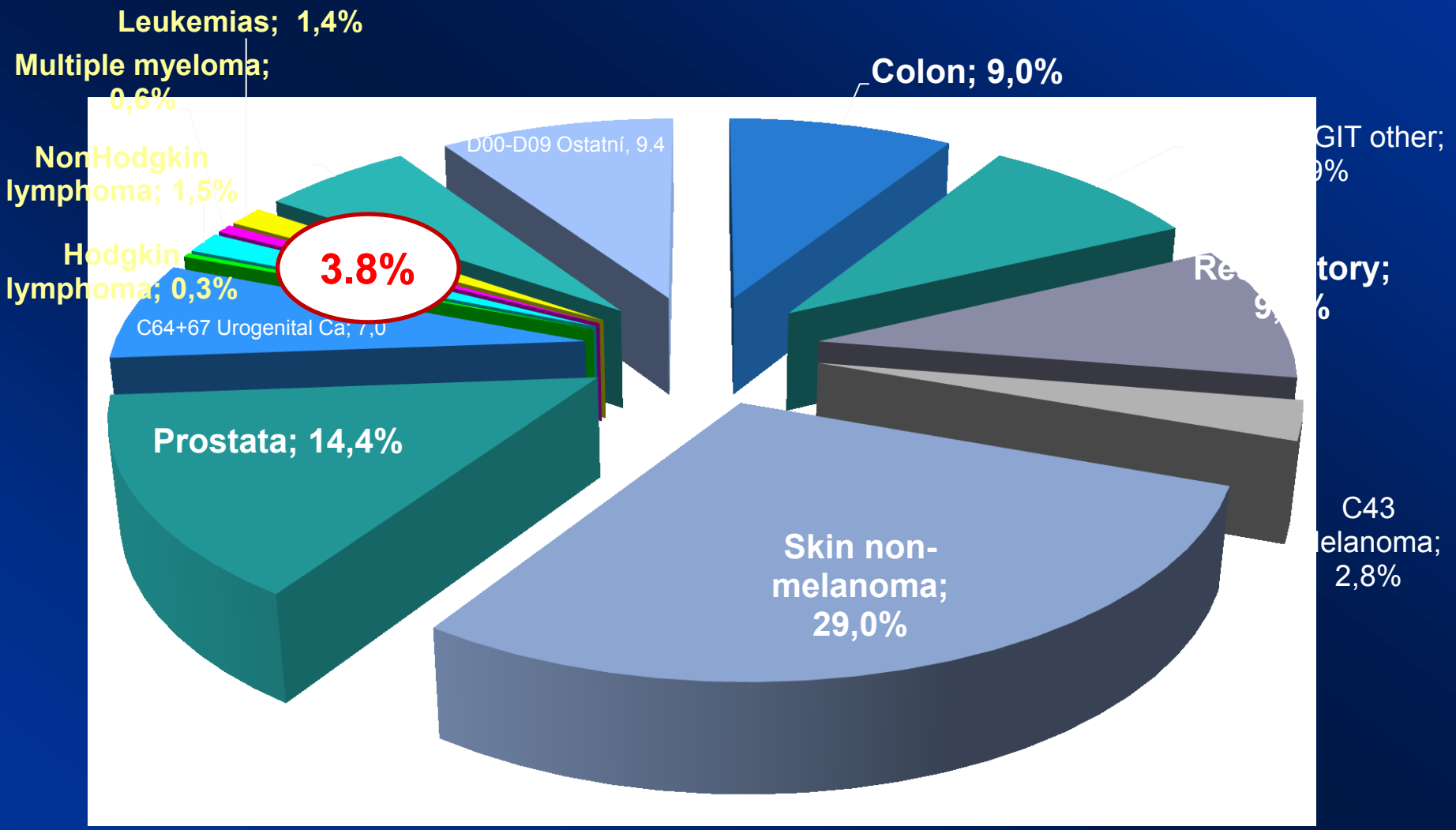
Janikova A et al

What´s essential to remember – „Take home message“

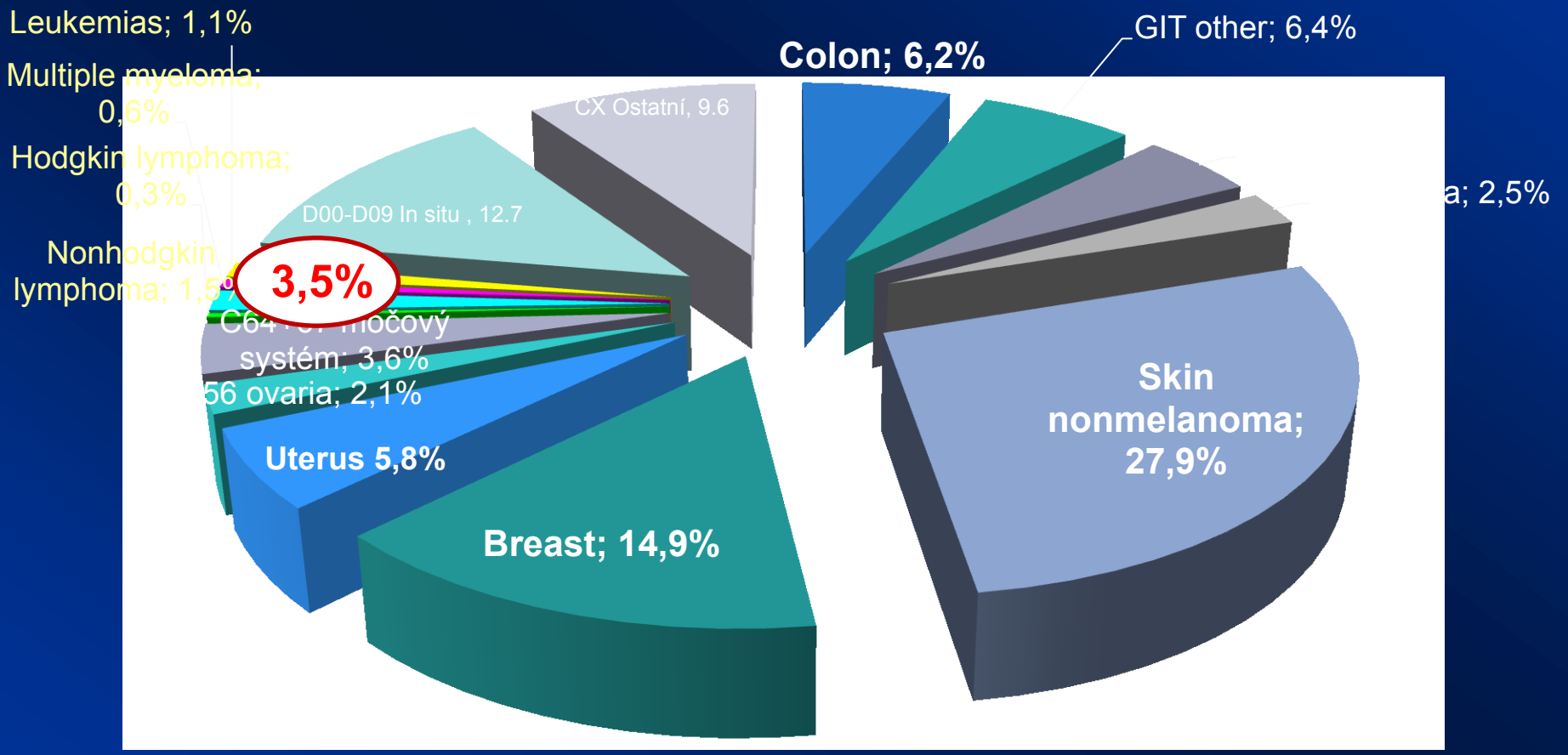
- For students and non-hematologists:
- Clinical manifestation – when the disorder is to be suspected
- Diagnostic algoritm – how the correct diagnosis to be made
- Basic overview of disorders – nosological units, treatment , prognosis

- For hematology specialists:
- Recent optimal treatment algoritms

CANCER INCIDENCE CZECH REPUBLIC 2016 (men; ÚZIS)



CANCER INCIDENCE IN CZECH REPUBLIC 2016 (women; ÚZIS)



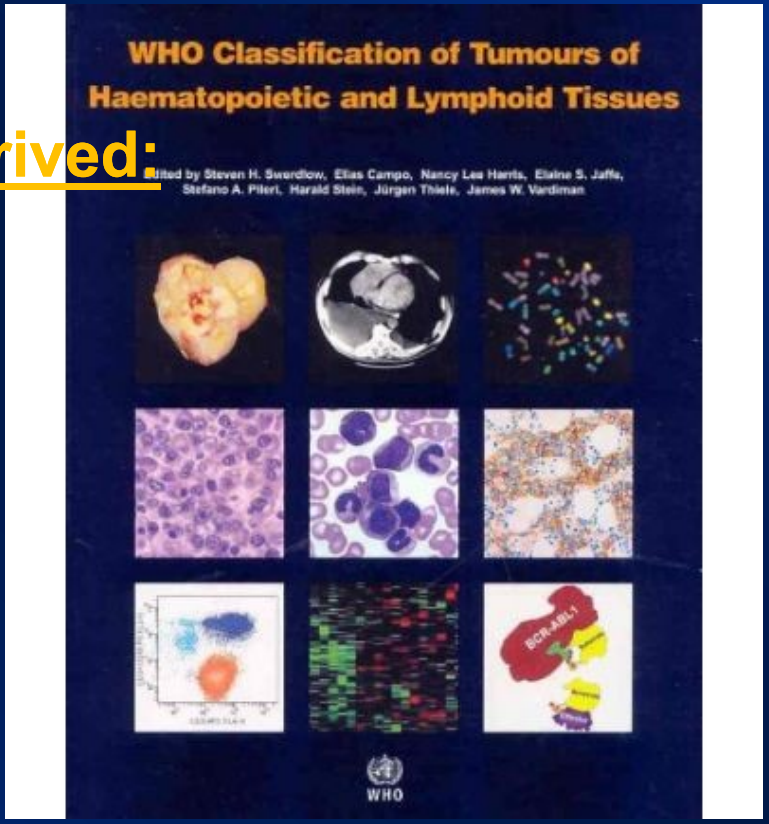
Overview of hematological malignancies

WHO classification of Haematopoietic and Lymphoid system (last update 2018)

-separated system from ICD (MKN)

Hematological malignancies are derived:

- from lymphoid cell-line
- from myeloid cell-line
- from histiocytic cell-line
- from monocytoid- macrofagocytic system



SURVIVAL OF PATIENTS WITH HEMATOLOGICAL MALIGNANCIES
-world data

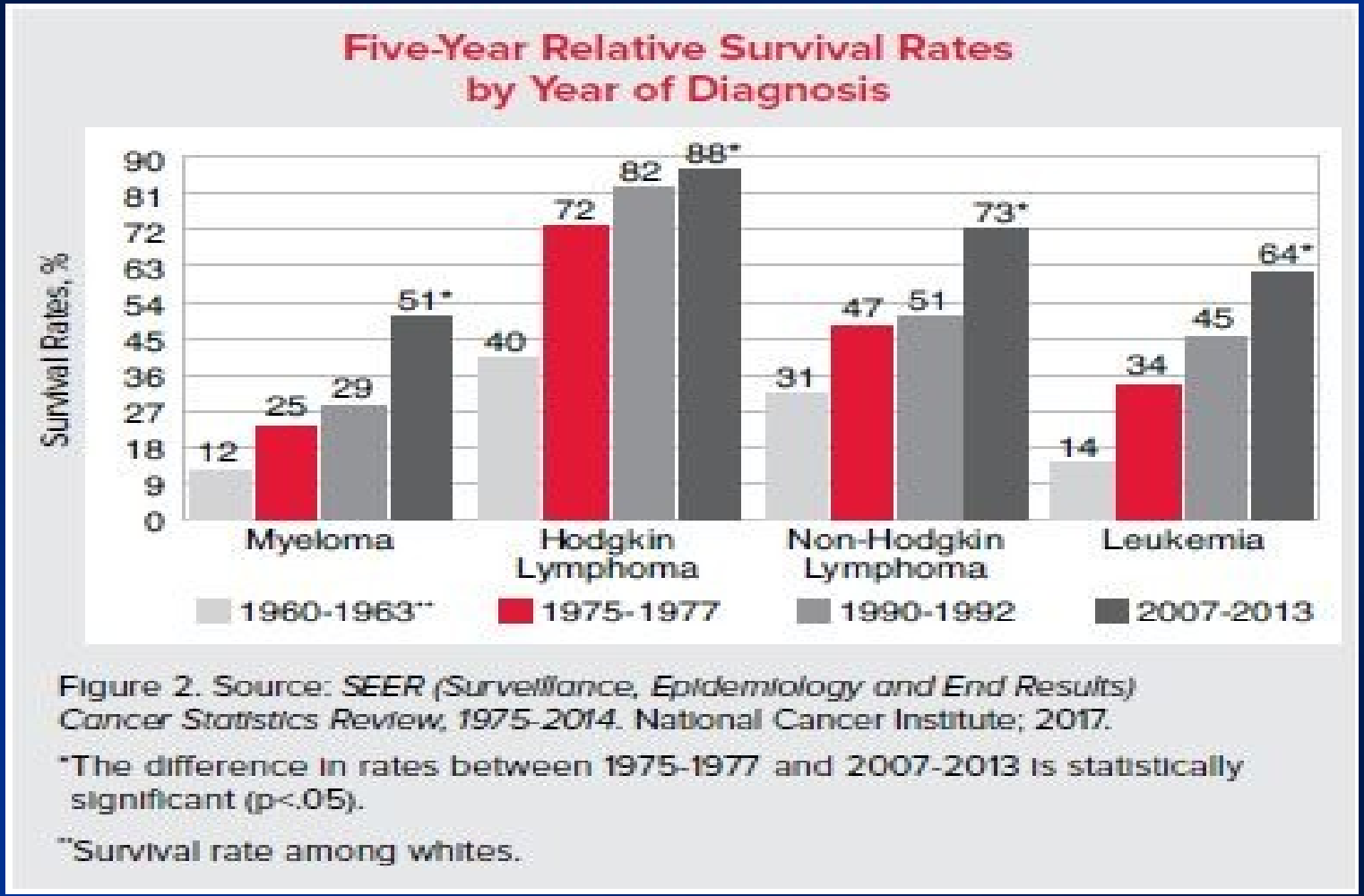


Figure 2. Source: *SEER (Surveillance, Epidemiology and End Results) Cancer Statistics Review, 1975-2014*. National Cancer Institute; 2017.

*The difference in rates between 1975-1977 and 2007-2013 is statistically significant ($p<.05$).

**Survival rate among whites.

LYMPHOPROLIFERATIONS = malignancies from lymphoid tissue

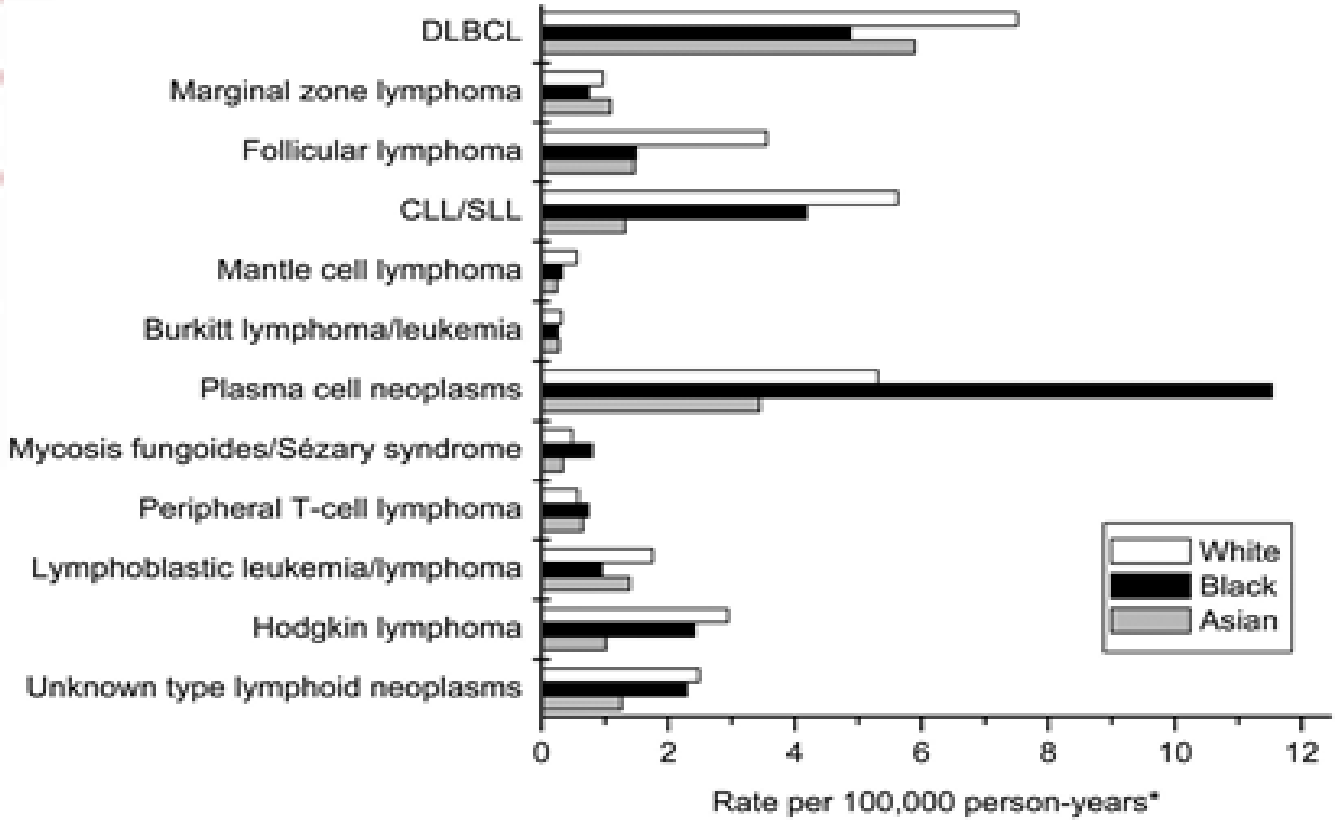
WHO 2018 > 60 nosological units

- LYMPHOMAS
  - Hodgkin lymphoma (Hodgkin´s lymphogranuloma) ~30%
    - Classical (~95%)
    - Nodular lymphocyte predominant (~ 5%)
  - NonHodgkin´s lymphomas (NHL) ~70%
    - B-NHL (~90%)
    - T-NHL (~10%)
- LYMPHOCYTIC LEUKEMIAS
  - B-line: B-CLL, Hairy cell, prolymphocytic leukemia
  - T-line: T-prolymphocytic leukemia, T-LGL, adult T-cell leukemia
- MULTIPLE MYELOMA

ETHNICAL DIFFERENCES IN LYMPHOID NEOPLASM DISTRIBUTION

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

ce of lymphoid neoplasms by subtype and race, 12 SEER registries, 1992-2001. *All incidence rates are age adjusted to the 2000 United States population.



Morton L M et al. Blood 2006;107:265-276

CLINICAL SYMPTOMS OF MALIGNANT HEMATOLOGICAL DISEASES

We can recognise:

- *Systemic (General) symptoms*
- *Symptoms of local expansion*
  - *Nodal*
  - *Extranodal*

GENERAL SYMPTOMS

(the most frequent)

- WEIGHT LOSS

  (≥10% during 3 months; GIT disorders, chronic inflamatory diseases…)

- SUBFEVER/FEVER

  (lasting > 3 weeks, dif dg infections, other tumors or autoimunity disorders)

- ITCHING (with or without skin lesions)

- NIGHT SWEAT (need to change clothes/pyjama during sleeping)

- FATIGUE (pathological tiredness interfering with usual daily activity)

SYMPTOMS OF LOCAL EXPANSION

NODAL:

- **Peripheral (palpable) lymphadenopathy:**
  - „lumps“
- **Mediastinal lymphadenopathy:**
  - irritative dry cough, feeling of pressure, vena cava superior syndrom
- **Abdominal lymphadenopathy:**
  - stomach and intestinal dyspepsia, hydronephrosis due to uretheral compression.
- **Splenomegaly:**
  - enlarged spleen compressing stomach, feeling of fullness after small meal

EXTRANODAL:

- **Bone marrow infiltration:** (pan)cytopenia
- **Osteolytic destruction of bones:** pain (backbone), pathol. fractures
- **Organ specific symptoms:** ~30% primary extranodal lymphomas
  - mimicking relevant carcinoma **(different therapy approach!)**

Diagnostic algoritm

Periferal lymphadenopathy

Non-specific (general) symptoms

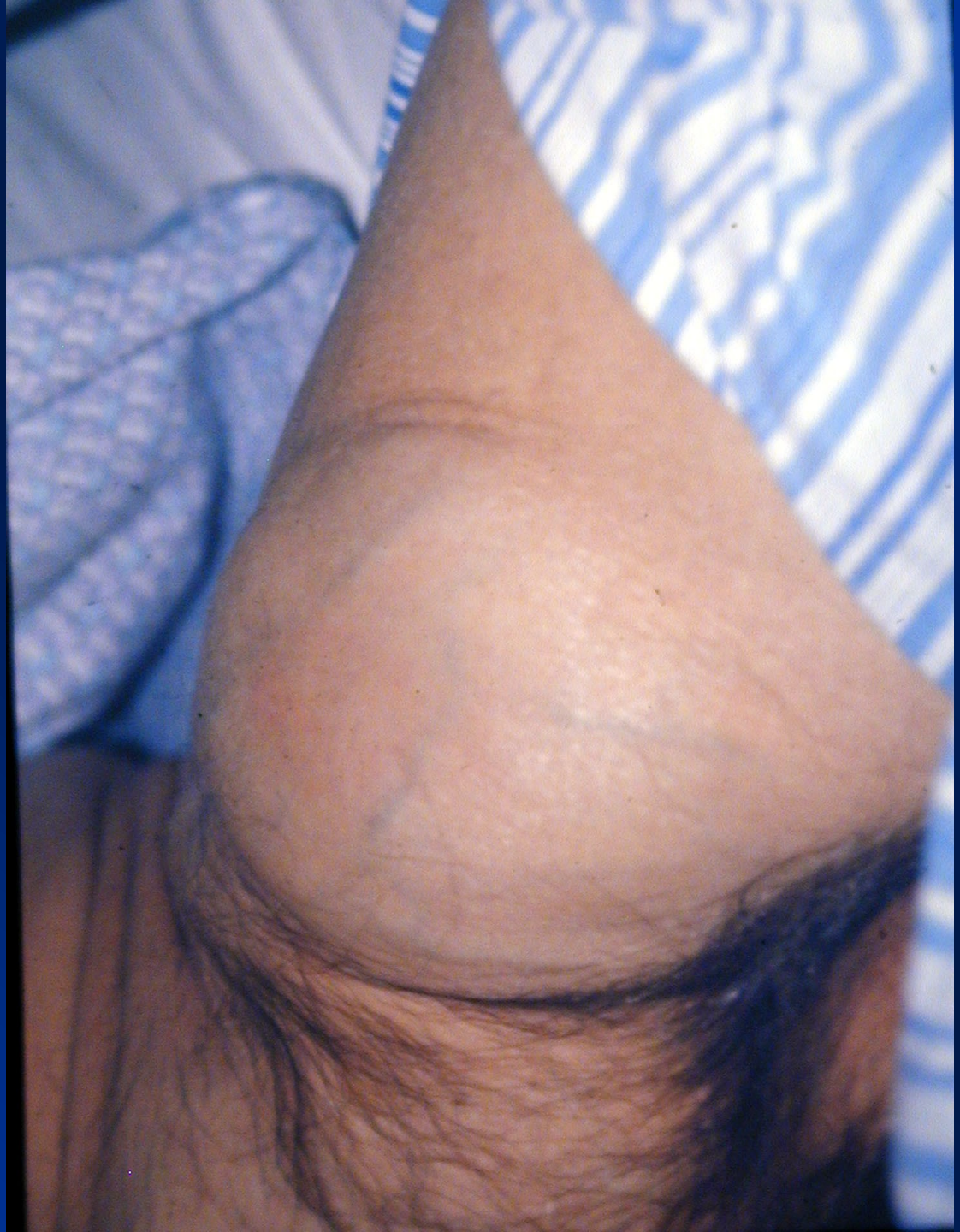
Clinical examination (lumps)

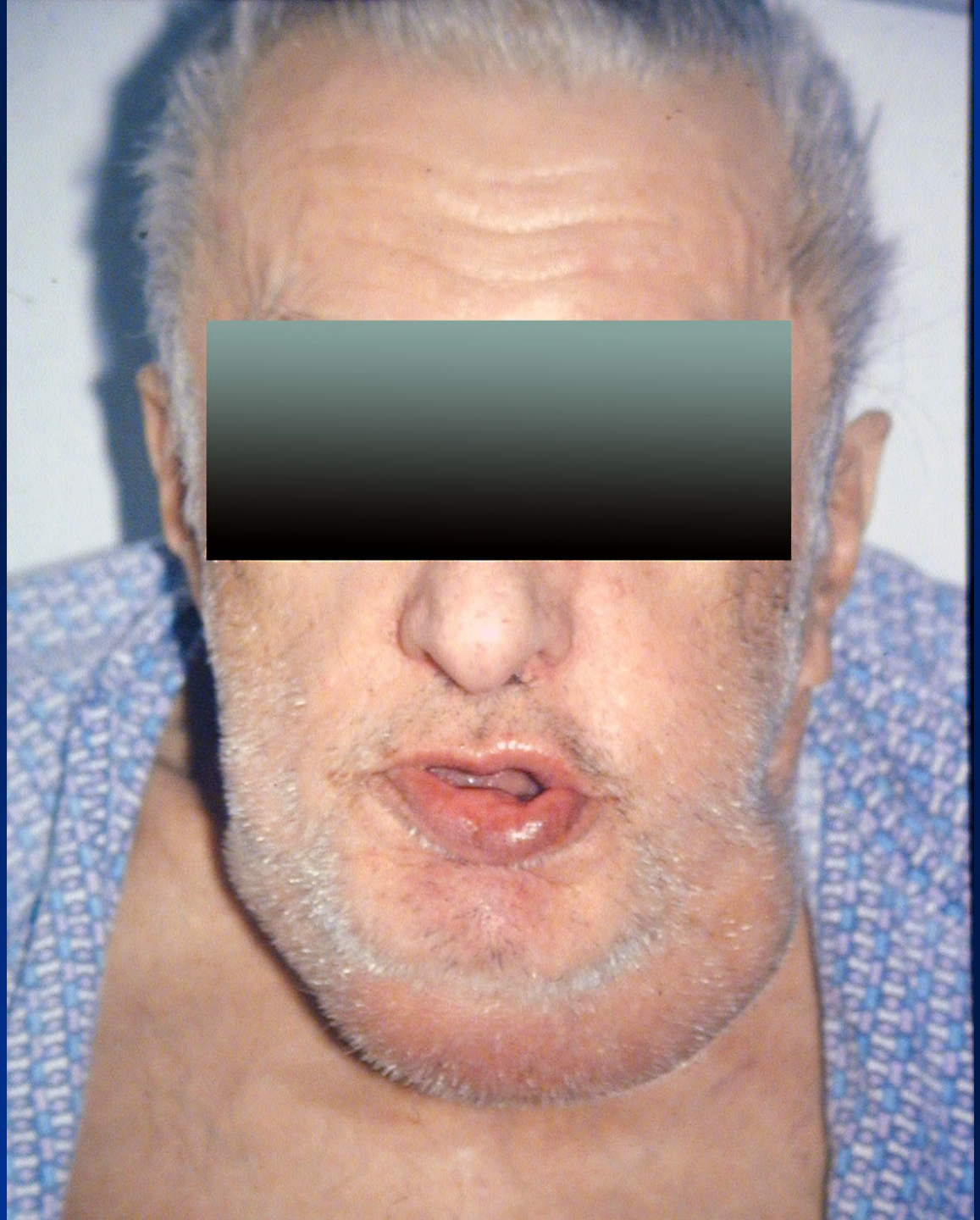
Infection must be excluded
EBV, HIV, toxoplasma

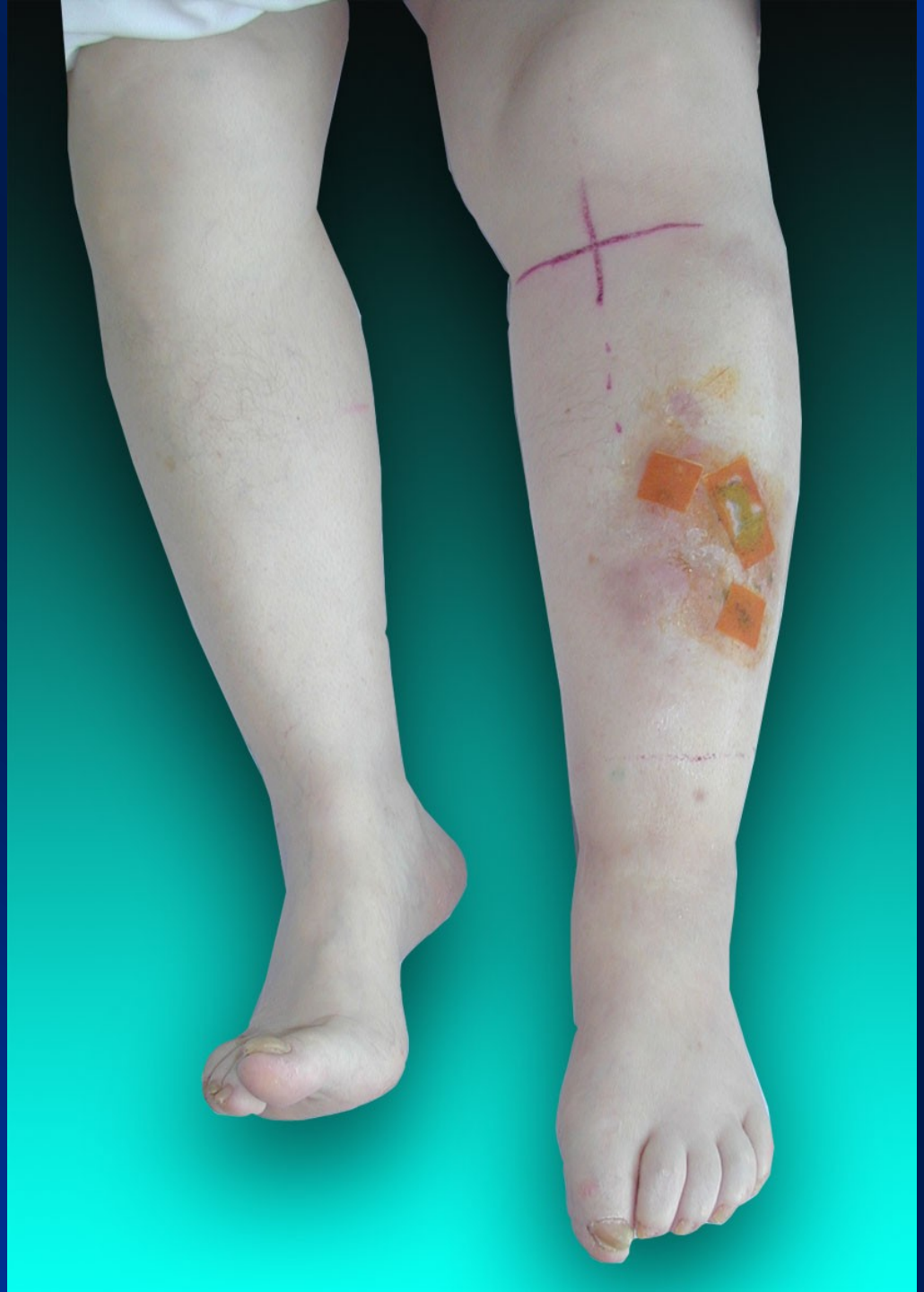
Lymph node biopsy and histological examination

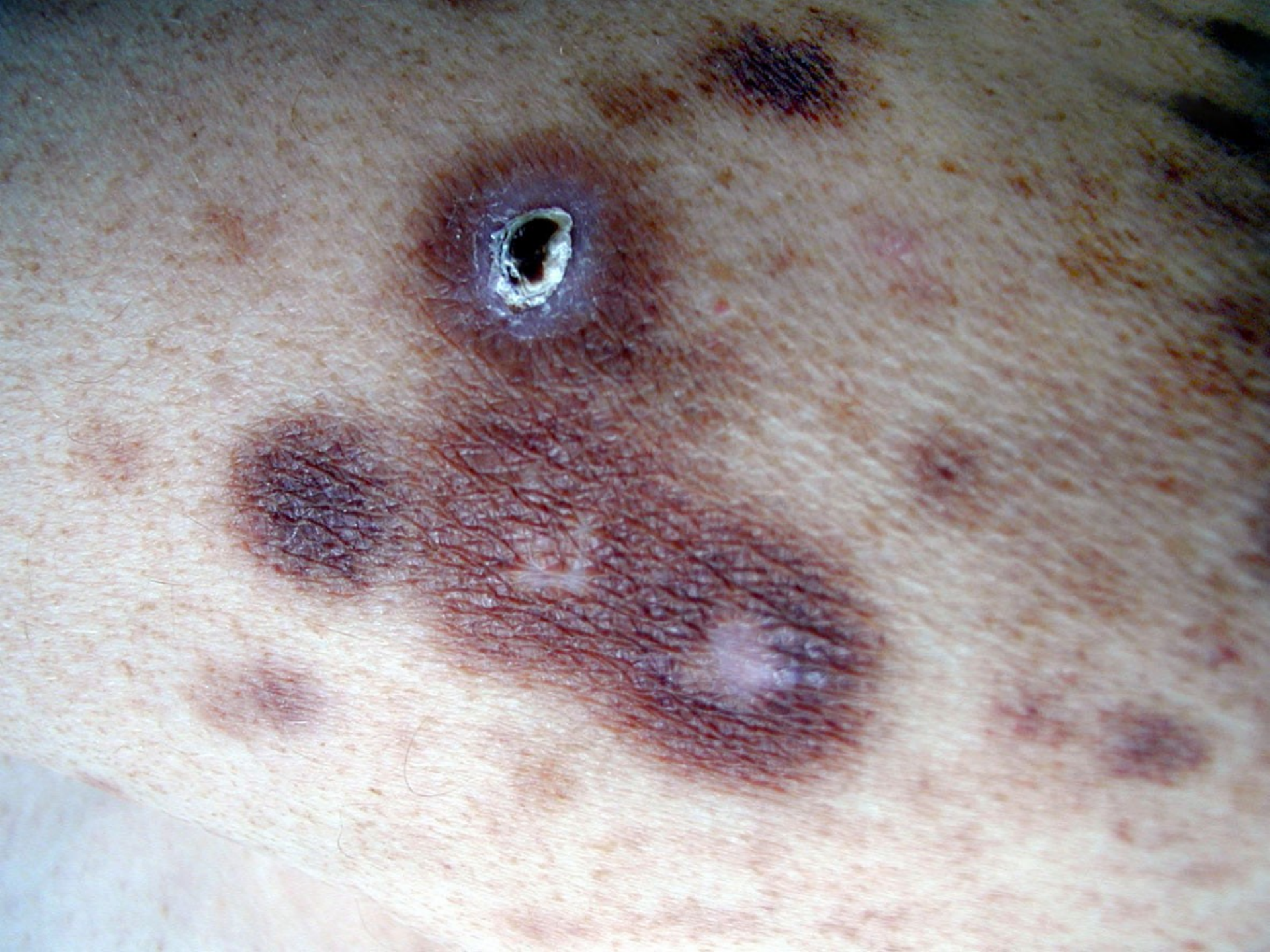
Native sample is prefered

Imaging examination:
Ultrasonogrphy- peripheral lymph node, abdomen
CT mediastinum + retroperitoneum
PET
MR





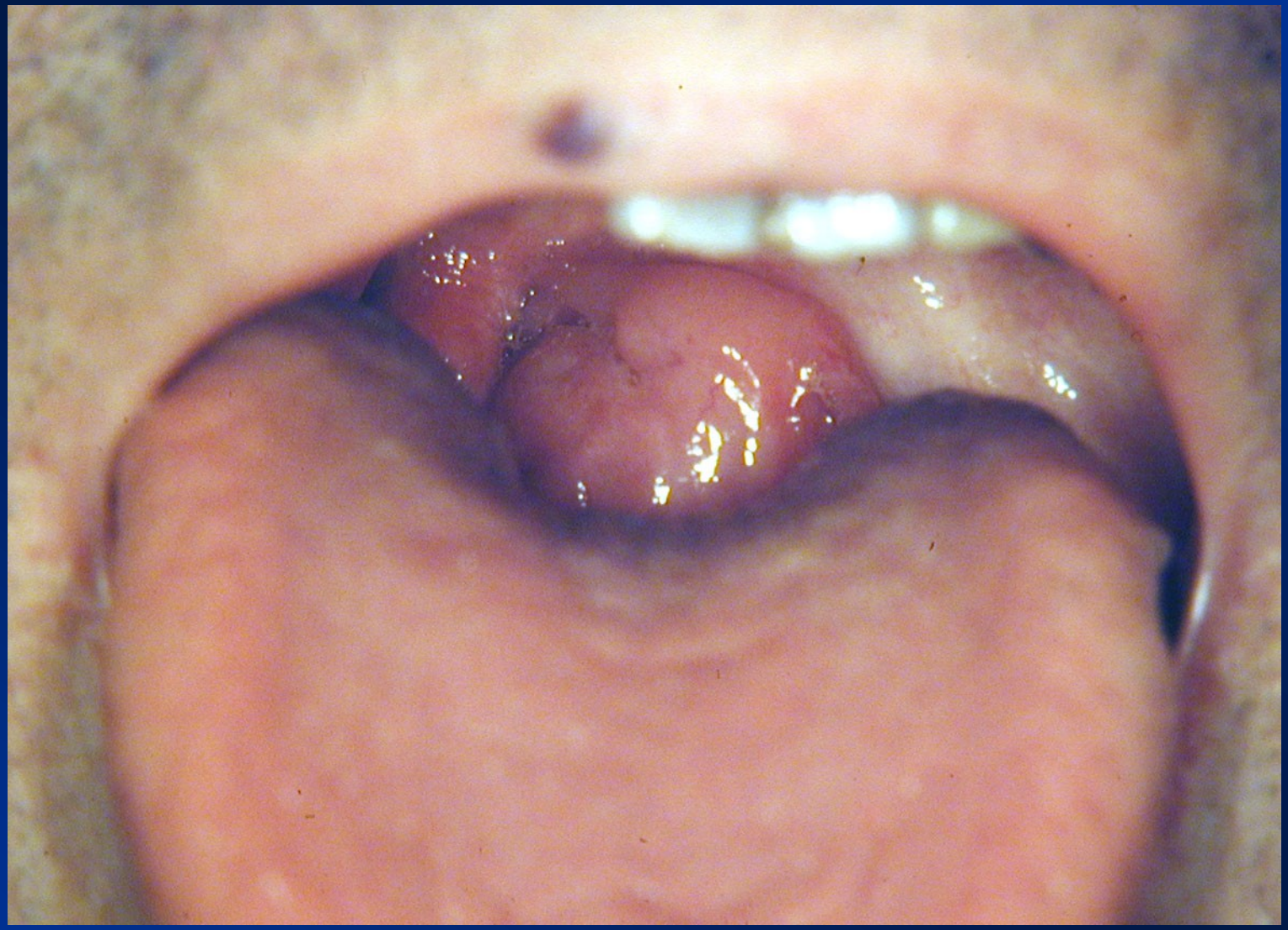


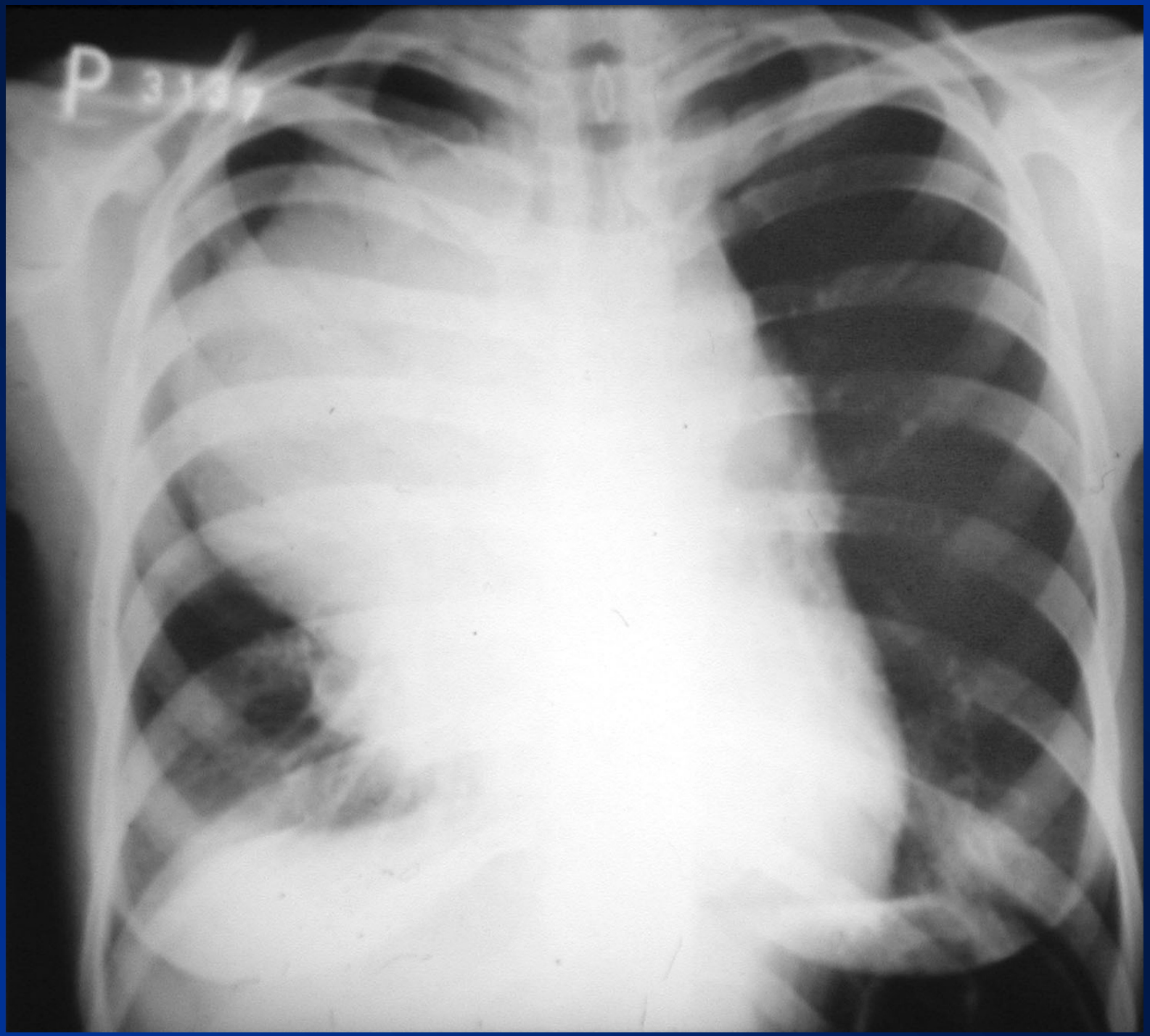


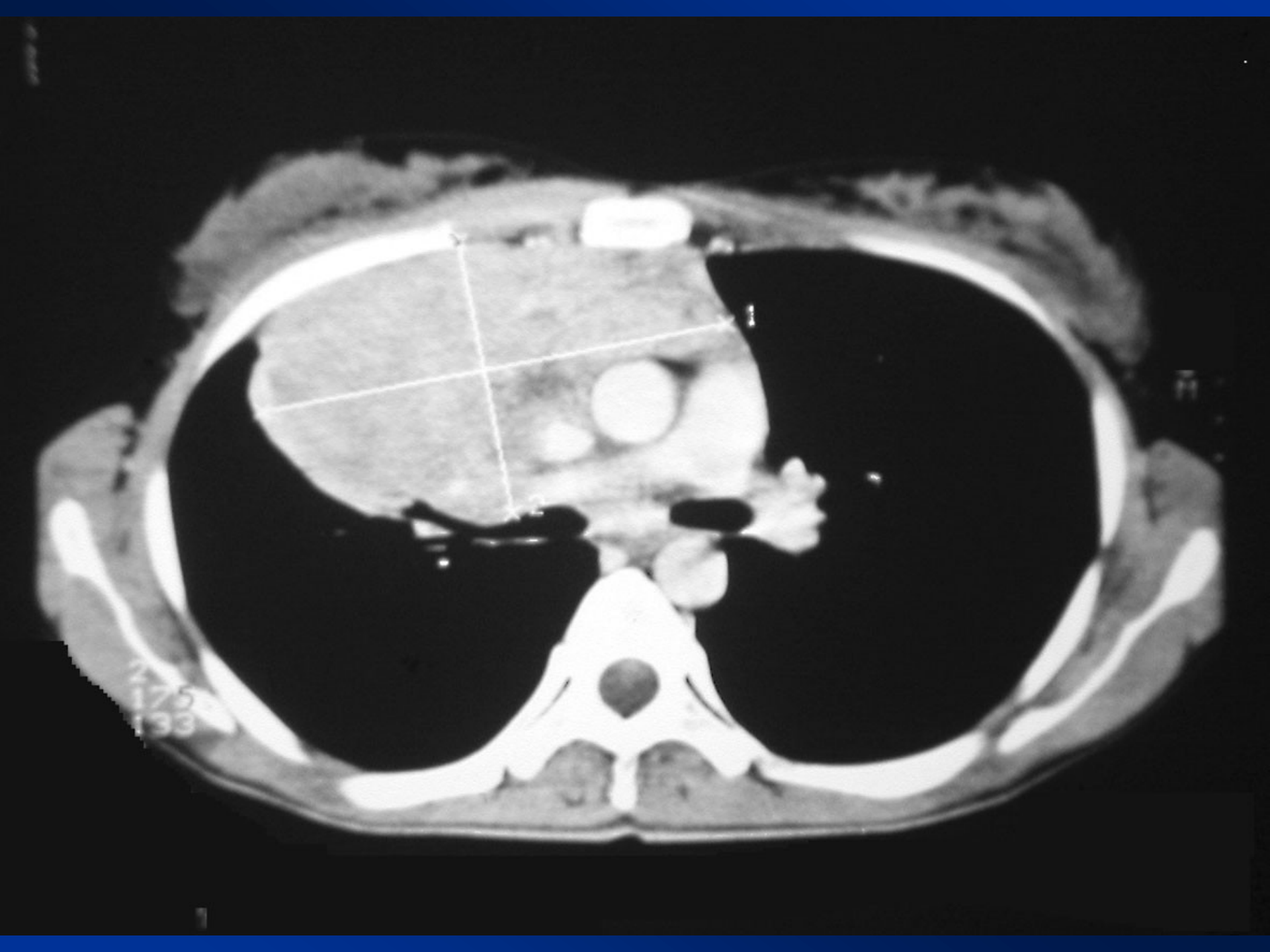
Vena cava superior syndrom

Swelling of face, enlarged volume of neck

Visible collateral veins between vena cava superior and inferior





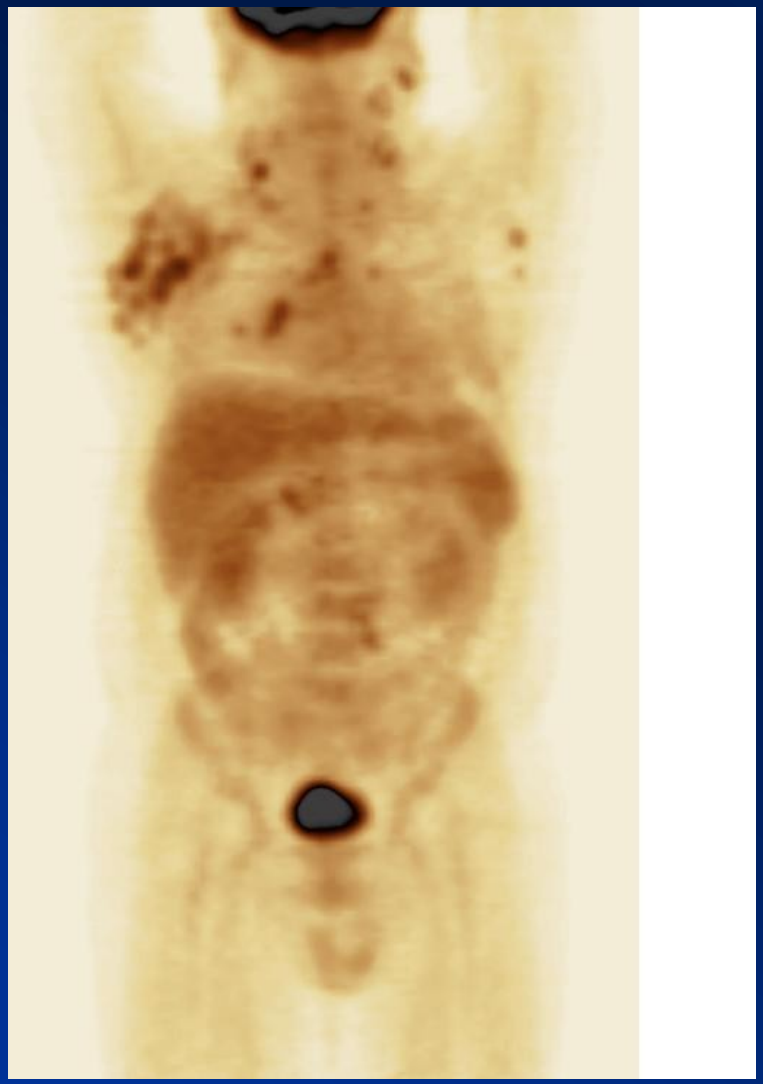


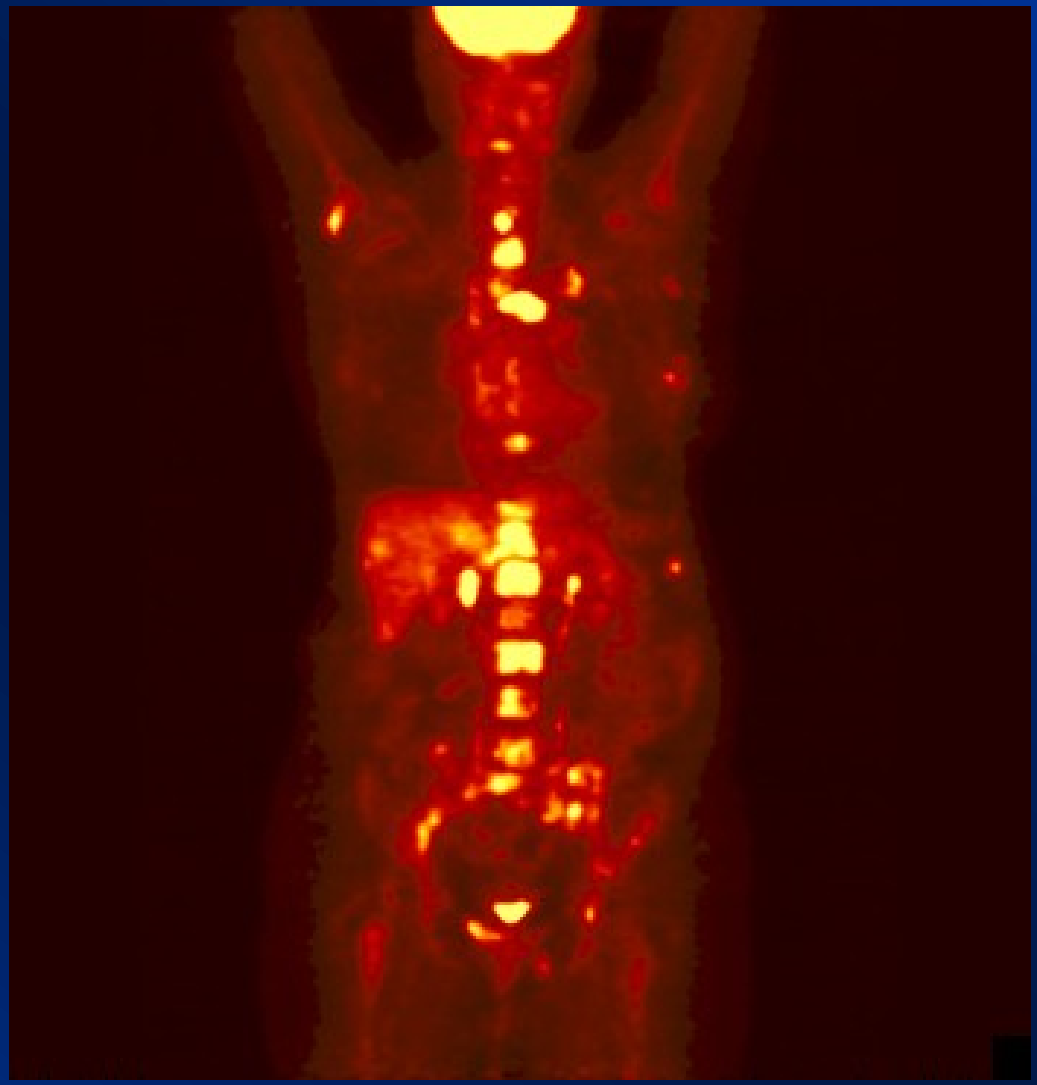
PROGNOSIS OF PATIENT WITH MALIGNANT LYMPHOMA IS BASED ON:

- Histology subtype
- Performance status (according to ECOG/WHO)
- Laboratory examination
- Extent of disease = **clinical stage**

- Imaging (CT±PET ev. MRI±PET)
  - CT usually „gold standard“
- Bone marrow examination (trephine biopsy)
  - Not necessary in some lymphomas

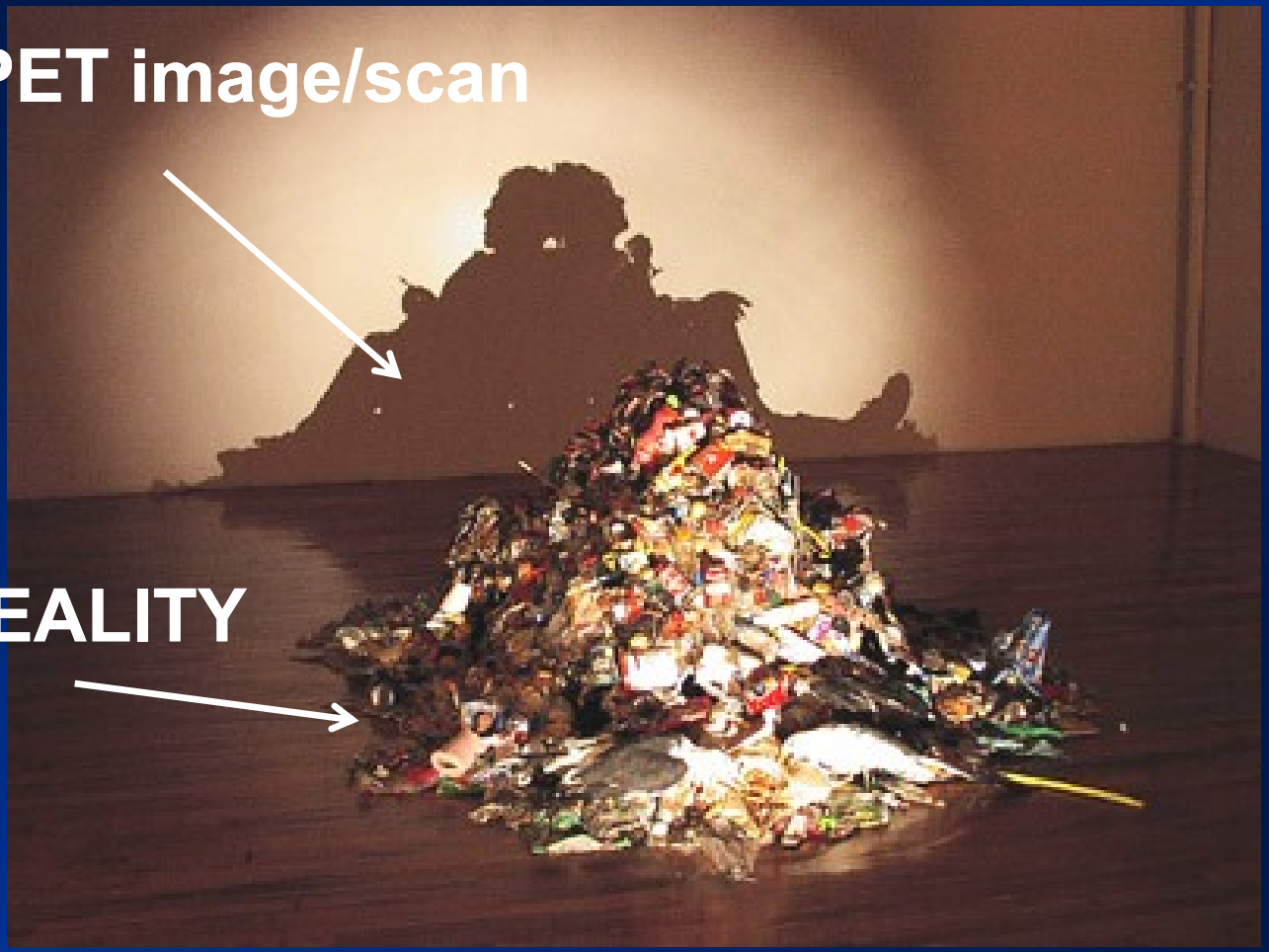
STAGING: FDG-PET (^{18}Fluordeoxyglucose - positrone emission tomography)





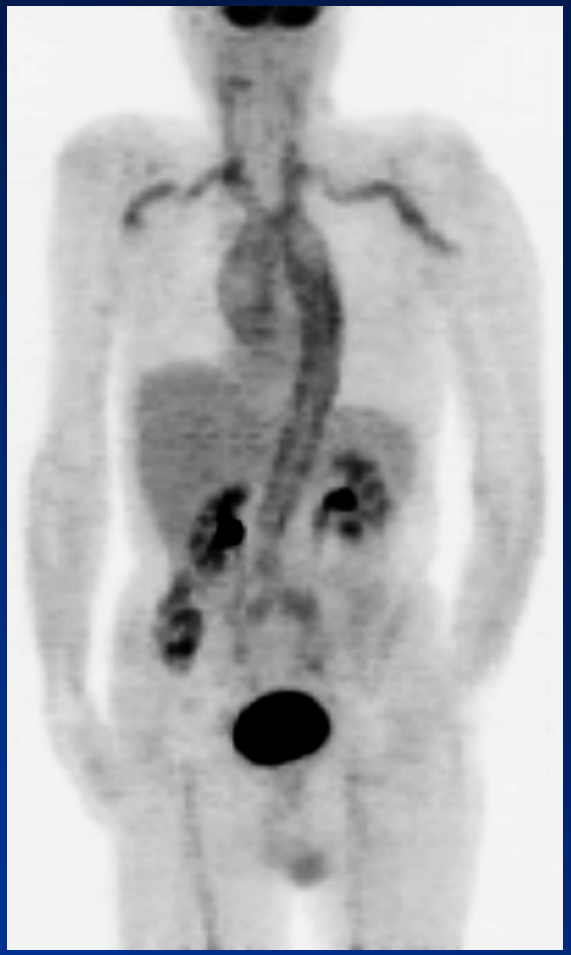
FDG-PET – BUT, what can we really see???

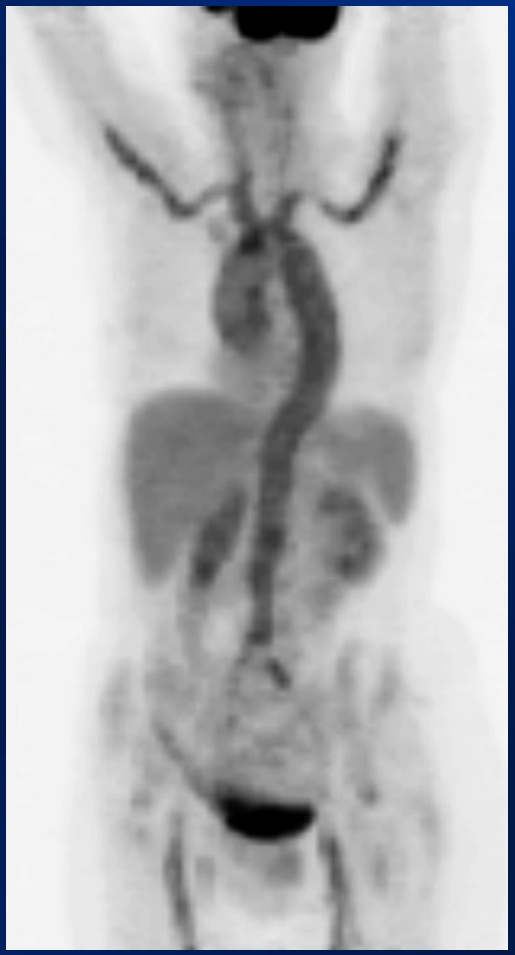
Be cautious with the interpretation of PET scan!



PET is sensitive but not specific for tumor!

Fever of unknown origin – vasculitis descovered by FDG-PET





STAGING -
ANN ARBOR CLASSIFICATON (modified)

Stage I	Involvement of 1 lymph nodes (LU) group or 1 extralymfatic organ (EN) (IE)
Stage II	Involvement 2 or more LN regions on the same side of diaphragma or LOCALISED involvement of 1 EN organ (IIE) including lymph node involvement of 1 or more groups LN on the same side of diaphragma
Stage III	Involvement of LN or lymphatic organs (spleen, Waldayer circle) on both side of diaphragma, which can be accompanied with LOCALISED involvement of 1 EN organ (IIIE)
Stage IV	Difuse or diseminated involvement of 1 or more EN organs or tissues with or without LN involvement

[1]Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971; 31(11):1860-61.
[2]Rosenberg SA. Report of the committee on the staging of Hodgkin's disease. Cancer Res 1966; 26: 1310.
[3]Lister TA, Crowther D, Sutcliffe SB, et al. Report of a commitee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 1989; 7(11):1630-36.

WHY IS IMPORTANT TO KNOW STAGE (~EXTENT) OF THE LYMPHOMA?

Limited stages:
I and II

vs.

Advanced stages:
III a IV

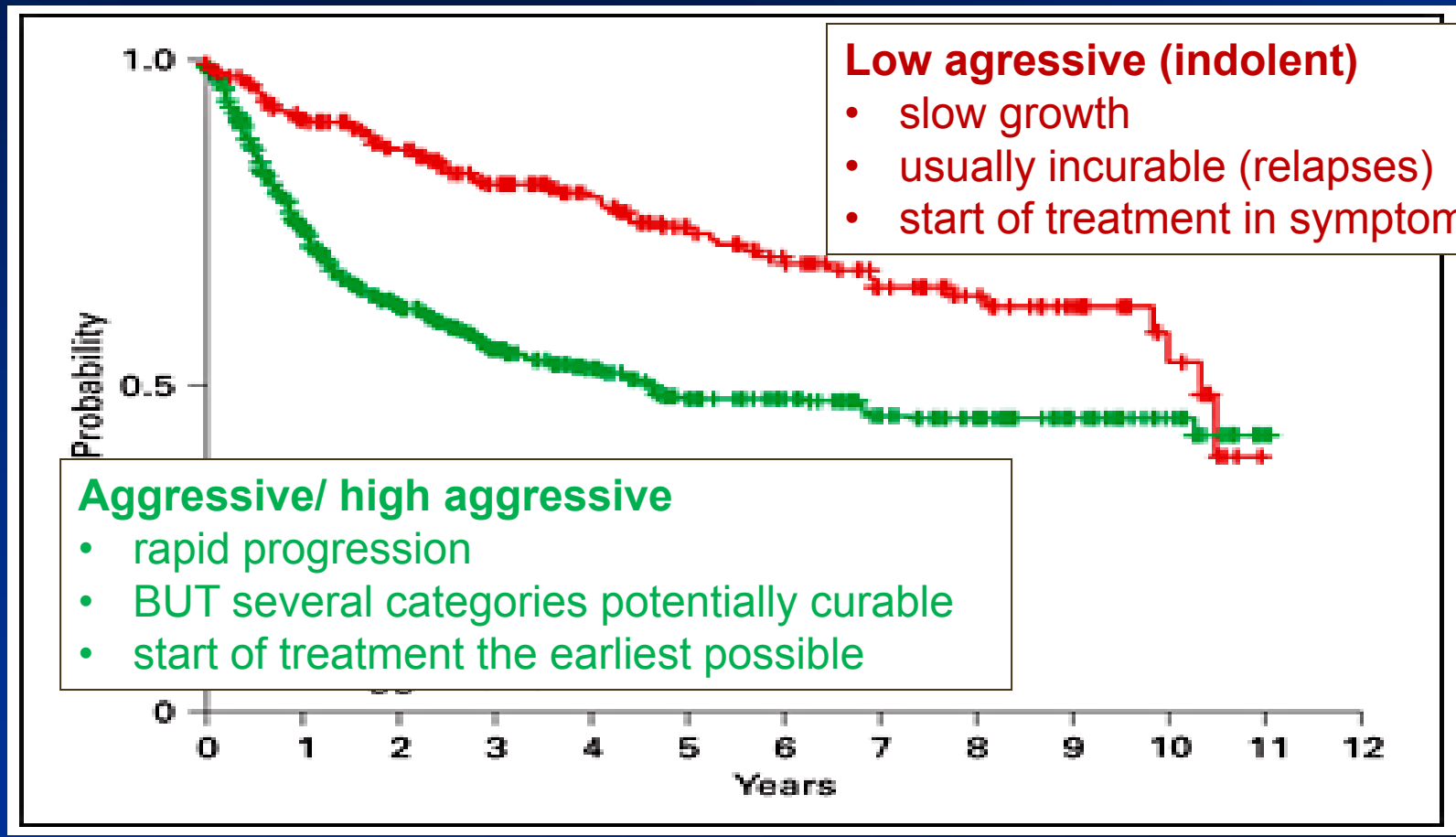
IF-RT- based / IF-RT containing therapy

Systemic therapy (immuno-, chemo-, or immunochemotherapy)

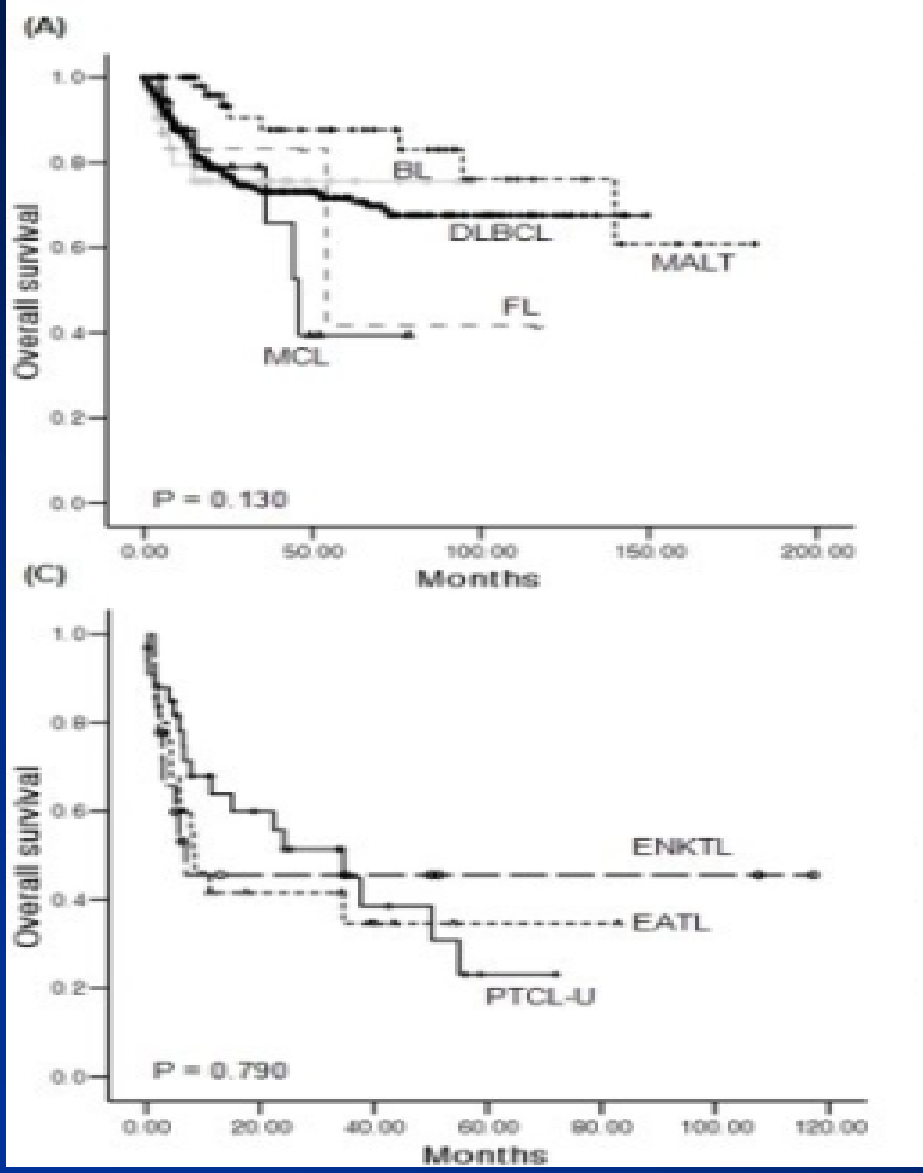
- TREATMENT STRATEGY DEPENDS ON THE STAGE IN THE MOST LYMPHOMA SUBTYPES!
- EXTENT OF DISEASE DYNAMICS IS USED FOR RESPONSE EVALUATION

MALIGNANT LYMPHOMAS - GENERAL SURVIVAL

- Clinical behavior (aggressive vs. indolent) is an important factor for therapy decision
- Irrespective of the lymphoma subtype



OVERALL SURVIVAL OF SELECTED NONHODGKIN LYMPHOMA SUBTYPES



B-NHL (~90% of NHLs):

MCL – mantle cell lymphoma
BL – Burkitt lymphoma
DLBCL- diffuse large B-cell lymphoma
FL –follicular lymphoma
MALT- mucosa associated lymphoma tissue lymphoma

T-NHL (~10% of NHLs):

ENKTL –extranodal NK/T lymphoma
EATL- enteropathy associated lymphoma
PTCL U –peripheral T-cell lymphoma (unspecified)

MALIGNANT LYMPHOMAS (overview of clinically important subtypes)

- **HODGKIN LYMPHOMAS (~30% of lymphomas)**
  - CLASSICAL (~95% of Hodgkin lymphoma)
  - NODULAR LYMPHOCYTE PREDOMINANT

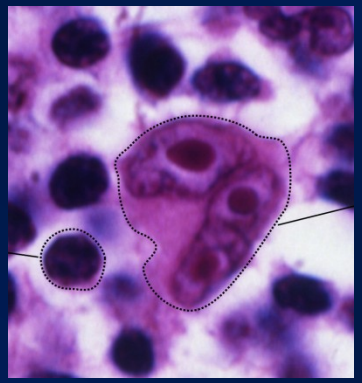
- **NON-HODGKIN LYMPHOMAS (~70% of lymphomas)**
  - **B-CELL LYMPHOMAS (~90% of NHLs)**
    - DLBCL (DIFFUSE LARGE B-CELL LYMPHOMA; 40% NHLs)
    - BURKITT LYMPHOMA (1% of NHLs)
    - FOLLICULAR LYMPHOMA (20% of NHLs)
    - MZL (MARGINAL ZONE LYMPHOMA; 10%of NHLs)
    - MCL (MANTLE CELL LYMPHOMA; ~7% of NHLs)
    - PCNSL (PRIMARY CNS LYMPHOMA; ~1%)
  - **T-CELL LYMPHOMAS (~10% of NHLs)**
    - ALCL (ANAPLASTIC LARGE CELL LYMPHOMA)
    - PTCL-NOS (PERIPHERAL T-CELL LYMPHOMA, NOS)
    - AITL (ANGIOIMMUNOBLASTIC LYMPHOMA)

HODGKIN LYMPHOMAS

CLASSICAL HODGKIN

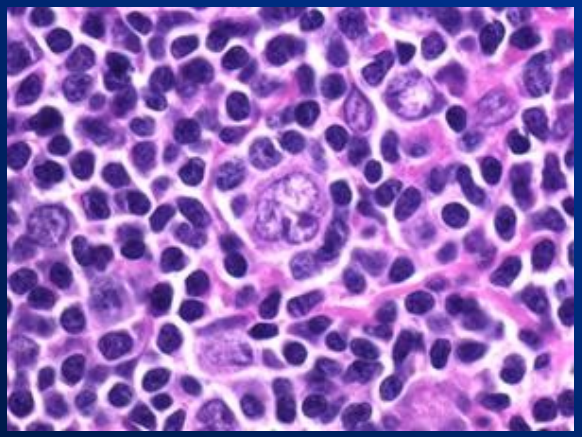
- **CD30+, CD15+**
- Reed-Sternberg cc.

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte-rich
- Lymphocyte-depleted



NODULAR LYMPHOCYTE PREDOMINANT

- **CD20+**
- „popcorn“ cells

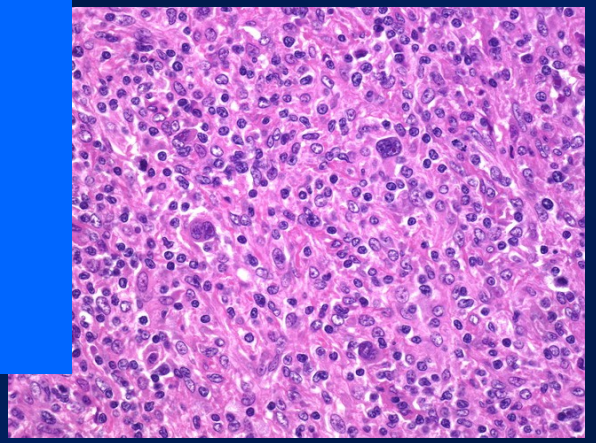


RS cells ~ derived from thymic B-lymphocytes

Peaks of incidence: 20-30yrs (75%), 60-80yrs (25%)

Symptoms similar like in NHLs with one exception:

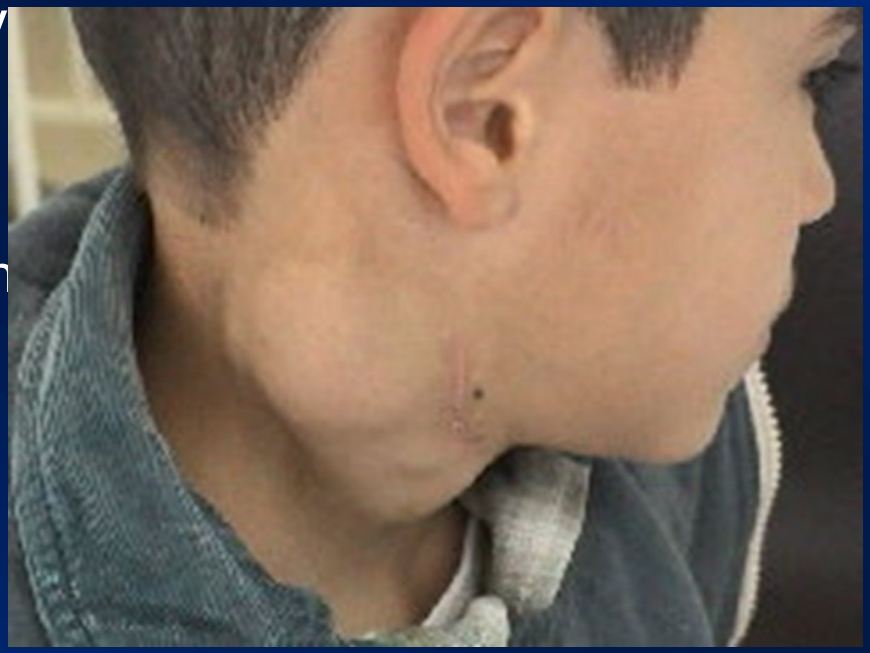
Alcohol-related pain (10-15% pts)



HODGKIN LYMPHOMAS – TREATMENT

- **Localised disease:** 2x cycle ABVD+ IF RT 20Gy
- **Intermediate disease:** 2x ABVD+ 2x BEACOPP escalated+ IF RT 30Gy
- **Advanced disease:** 6x BEACOPP escalated
- HODGKIN LYMPHOMA: highly curable disease (80-85%)

- **IF RT:** involved field radiotherapy
- **BEACOPP ESCALATED**
  - bleomycin, etoposid, adriamycin, cyklofosfamid, vinkristin, prokarbazin prednison
- **ABVD**
  - adriamycin, bleomycin, vinblastin, dacarbazin



B-NONHODGKIN LYMPHOMA

- 90% of NHLs
- Expression of CD19+, CD20+
- Anti-CD20 based therapy

- B-cell receptor (BCR) signaling pathway
  - ibrutinib
  - idelalisib

- Microenvironment
  - lenalidomid

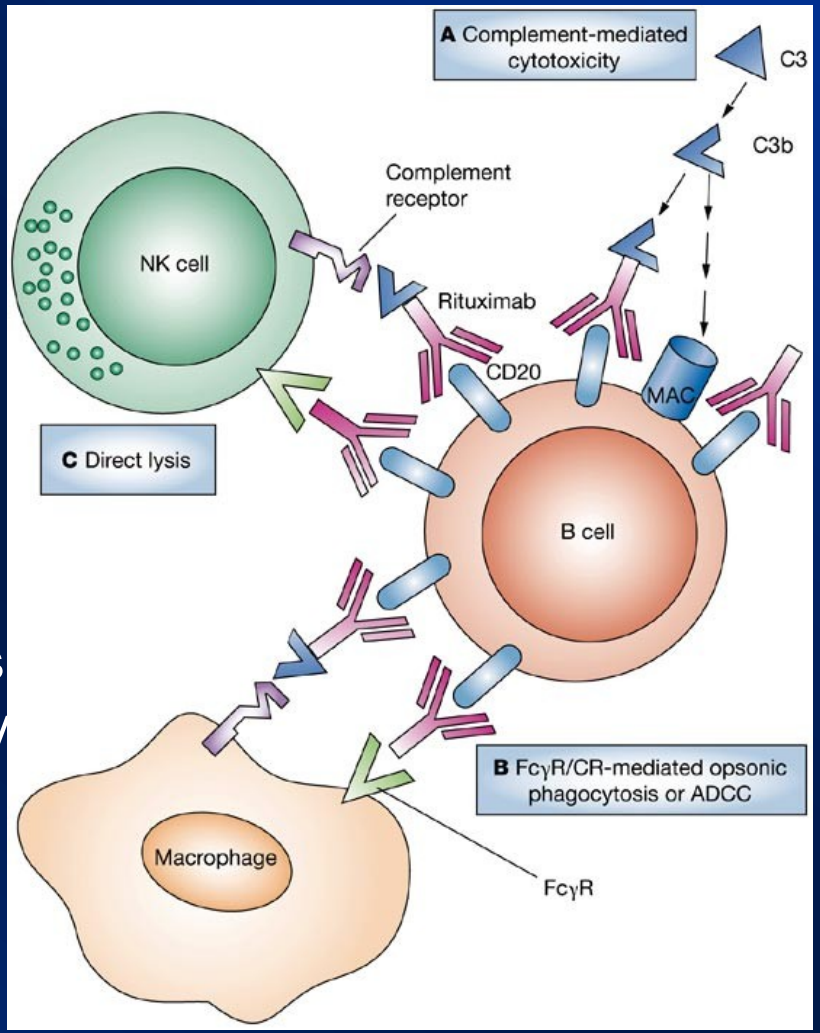
- **Aggressive B-NHL**
  - DLBCL
  - Burkitt

- **Indolent B-NHL**
  - Follicular lympoma
  - Marginal zone lymphoma
  - Mantle cell lymphoma

Anti CD20 **monoclonal antibody** **R**ituximab – Mabthera®, Rituxan®

- Chimeric humanized IgG1
- CD20 receptor on surface of nearly all B-lymphoid cells
- including malignant lymphocytes
- R is standard component of treatment of B-lymphomas
- Favourable efficacy/toxicity ratio

- Mechanism of action
  - CDC (complement dependent cytolysis
  - ADCC (antibody dependent cytotoxicity
  - Apoptosis induction
  - Direct antiproliferative effect



BCR (B-CELL RECEPTOR) SIGNALING

Active BCR signaling

-Antigen driven
-BCR immobile clusters
- activation of NF-κB, PI3, MAPk
-NF-κB activated by BTK
-ABC-DLBCL

Tonic BCR signaling

- Antigen independent
- essential for B-cell survival

-BCR freely mobile
- namely PI3 pathway
- Burkitt lymphoma

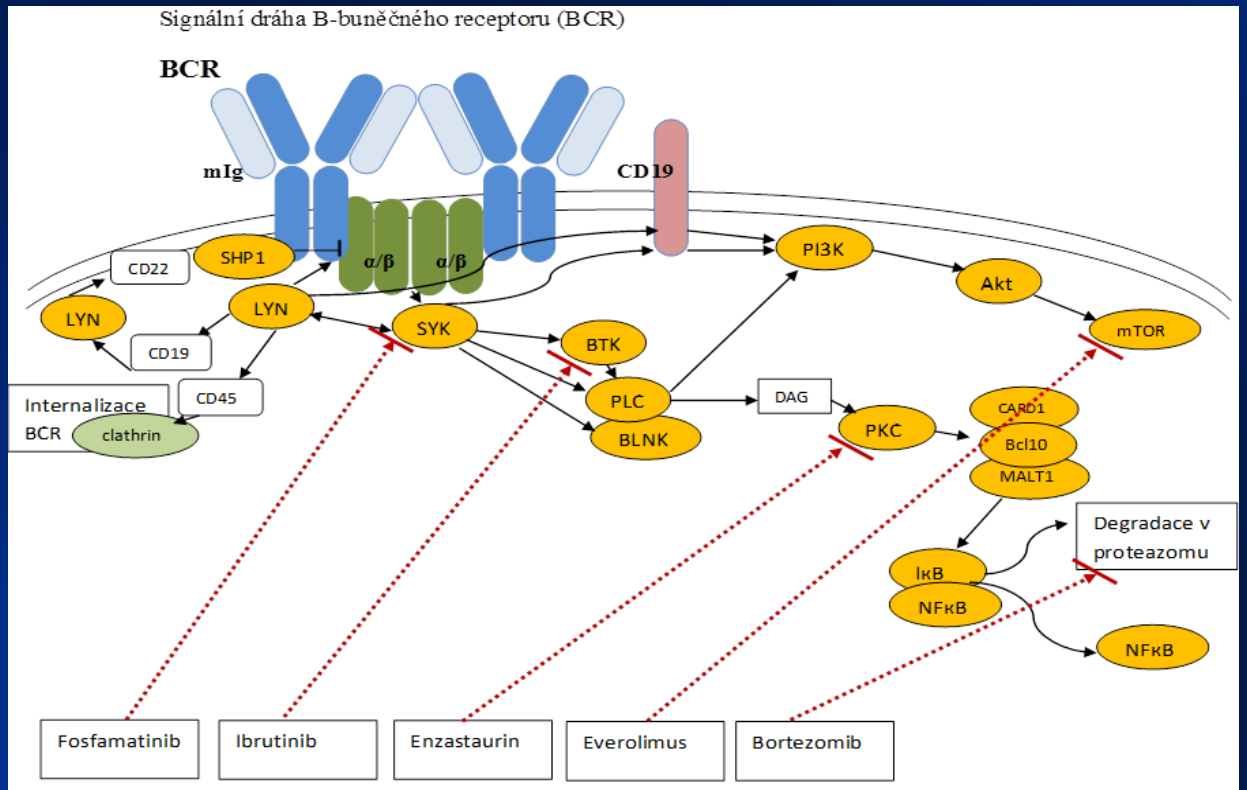
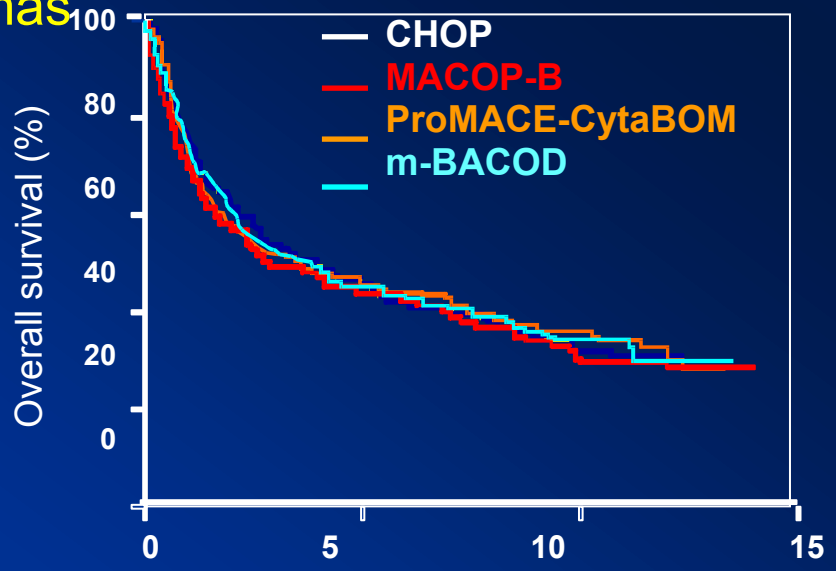
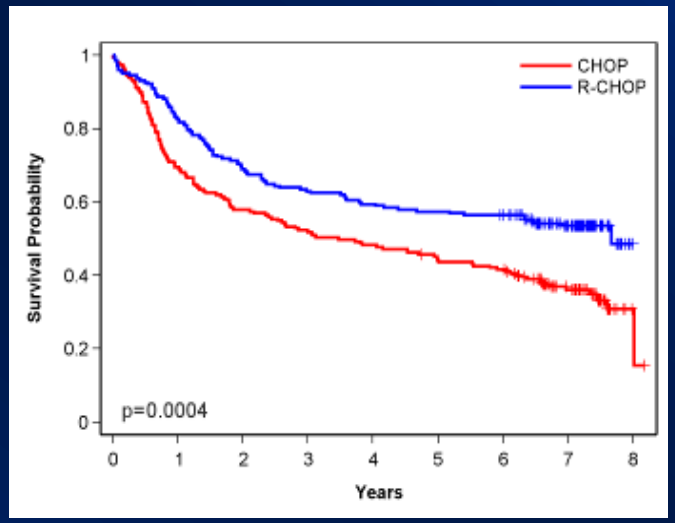


Schéma upraveno dle Gold 2010 a Roschewski 2012.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

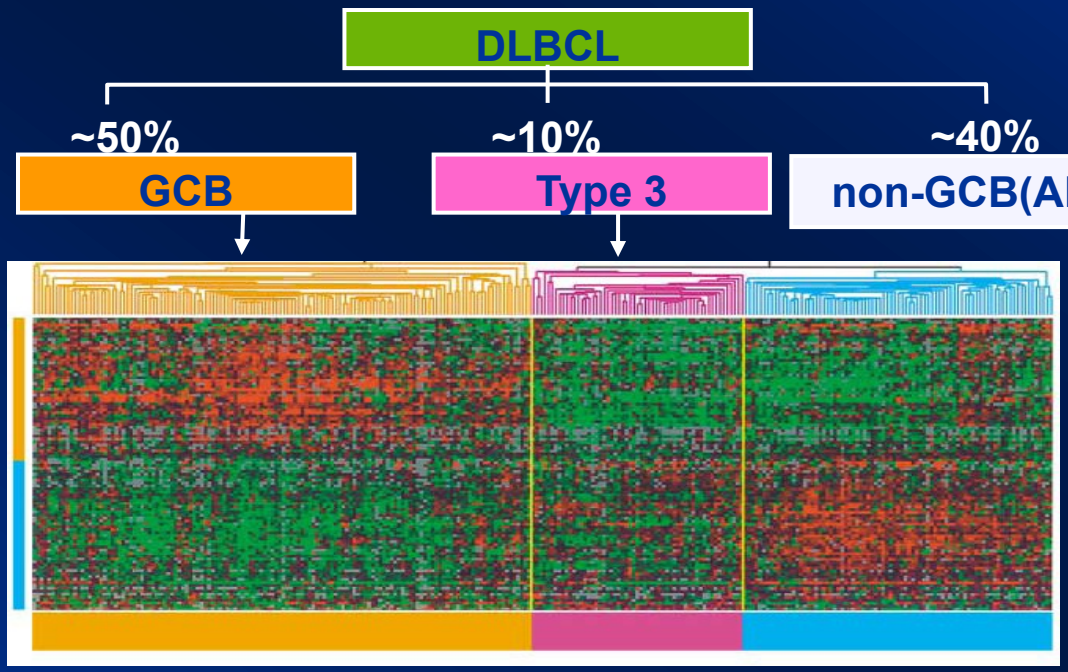
- An aggressive subtype of NHL (~ 35-40% of NHLs)
- Median age at diagnosis around 60yrs
- Clinically and biologically heterogeneous disease
- Recently identified at least 2 distinct subtypes („GCB“ vs. „ABC“)
- Clinical course usually with aggressive, rapid progression
- 50% long term cure with current standard therapy (R-CHOP)
- CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) developed empirically ~ 40 years ago, R-CHOP is current global standard
- Doxorubicin & Cyclophosphamide essential drugs in high grade lymphomas





Patients over 60 (LNH98-5) 2002

DLBCL – MOLECULAR CLASSIFICATION



GCB (germinal center) phenotype:

Bcl2, c-myc

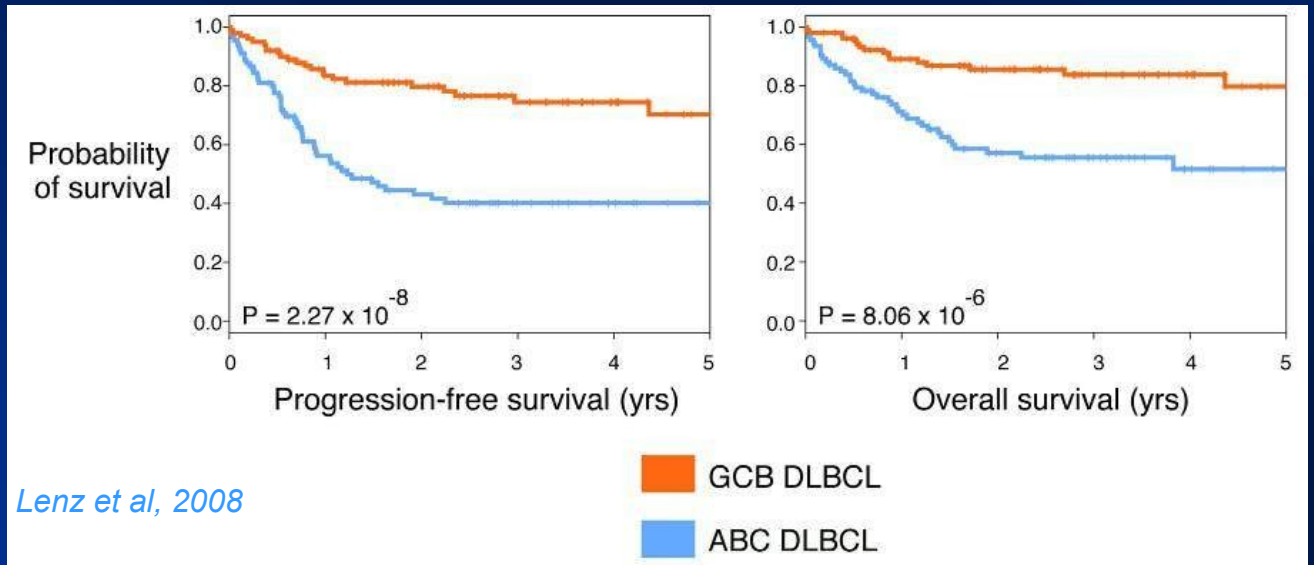
Rare mutation in BCR subunits

ABC(= activated B-cell) phenotype

CARD11, BCL10, MALT1, NF-κB

mutation in BCR subunits

1. *Alizadeh et al, Nature 2000*
2. *Davis et al, Exp Med 2001*
3. *Rosenwald et al, NEJM 2002*
4. *Hans et al, Blood 2004*
5. *Ngo et al, Nature 2006*
6. *Lenz et al, J Clin Oncol 2007*



Lenz et al, 2008

DIFFUSE LARGE B-CELL LYMPHOMA

- Morphological variants:
  - centroblastic, immunoblastic, anaplastic

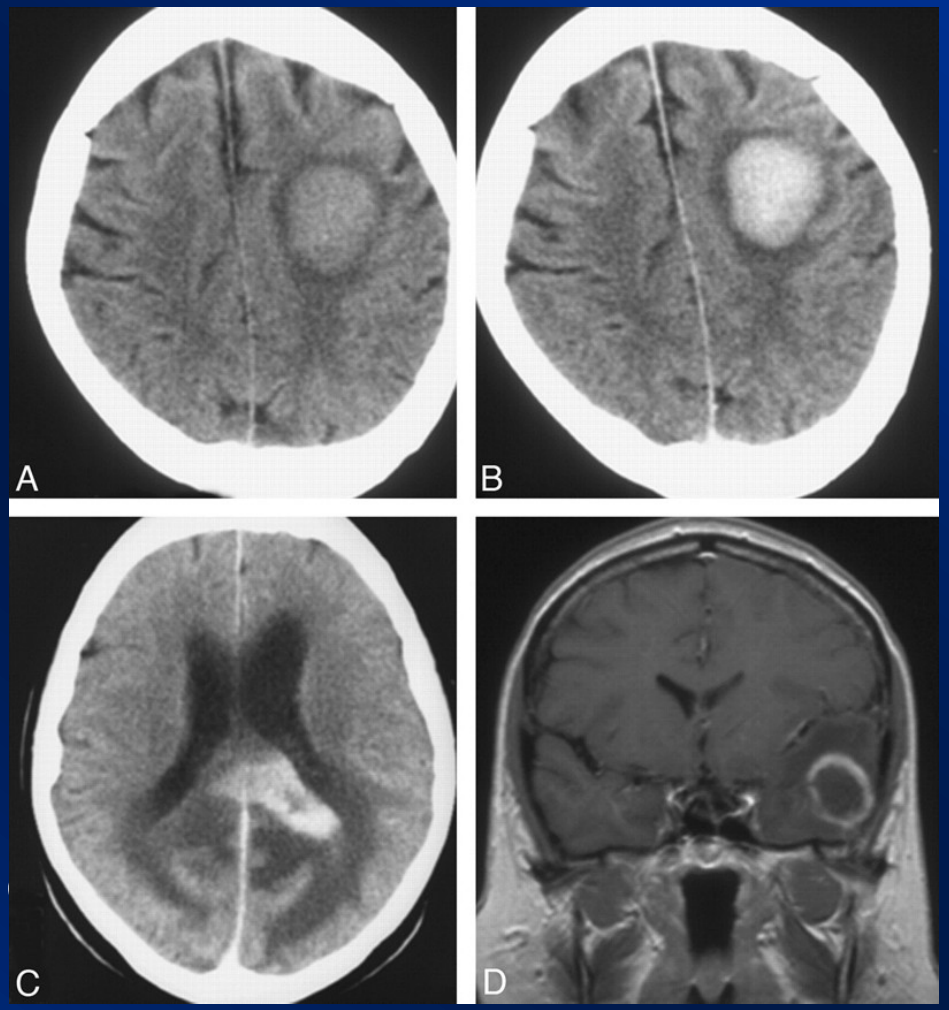
- DLBCL subtypes according to WHO 2008
  - DLBCL, NOS
  - Primary mediastinal DLBCL
  - Plasmablastic lymphoma
  - EBV associated DLBCL in elderly
  - Primary DLBCL of CNS
  - T-cell histiocyte rich
  - Primary cutaneous leg-type
  - ALK+ anaplastic DLBCL
  - DLBCL associated with chronic inflamation
  - Intravascular DLBCL
  - Primary effusion lymphoma
  - HHV8 associated DLBCL
  - DLBCL myc+bcl2+

Borderline DLBCL: DLBCL/BL

Gray zone lymphoma: DLBCL/Hodgkin

PRIMARY CNS LYMPHOMA

- Rare type of aggressive lymphoma
  - about 4% of CNS tumours
  - about 1% of all lymphoma
- Localization:
  - common in hemispheras (38%)
  - Thalamus/basal gangliae (16%)
  - c.calosum (14%)
- Median age 60-65 ys
- PCNSL (5-year OS 30-50%)
- Histologically: DLBCL in 95%



PRIMARY CNS LYMPHOMA

- **Symptoms:** neurological deficits, epi-paroxysms, amention, lethargy

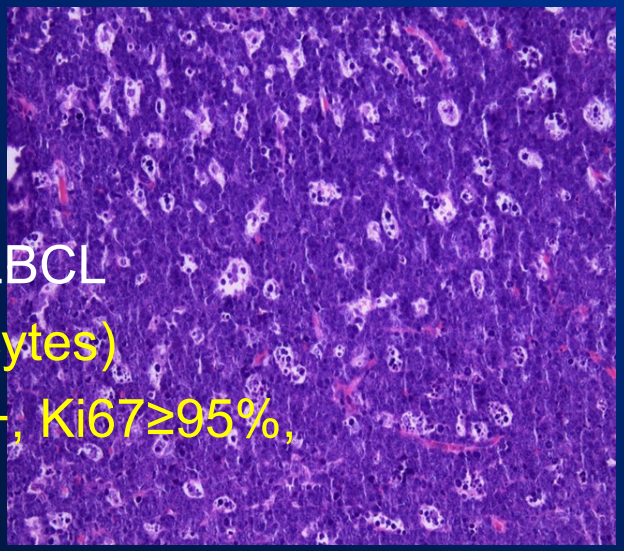
- **Diagnosis:** MRI (typical pattern) + stereotactic biopsy

- **!Corticosteroids!** give in antiedematic setting **NOT BEFORE BIOPSY,** corticoids can completely destroy lymphoma tissue for histological evaluation!!!!

- **Treatment:** cytostatics with ability to cross blood-brain barrier and have sufficient level in CSF
  - **high-dose MTX (~3g/m2) and high-dose AraC (~2g/m2)** + whole **brain radiotherapy (36-46 Gy)**

BURKITT LYMPHOMA

- Very rapidly growing/ aggressive; high-grade B-cell lymphoma
- Rare disease in central Europe
  - Endemic (Africa, young boys, jaw or facial mass, EBV related)
  - Sporadic (any age, usually abdominal mass)
  - Epidemic (immunodeficiency associated)



- Different behavior (and therapy) compared to DLBCL
- „Starry sky“ morphology (medium-sized lymphocytes)
  Phenotype: CD10+, bcl6+, bcl2-, CD20+, sIgM+, Ki67≥95%,
  t(8;14) in 80% cases, c-myc translocation

- Abdominal symptomatology (intususception, appendicitis-like)
- BM and CNS involvement in 30% of cases
- Tumor lysis syndrome (spotaneous!)
  - hyperuricaemia, extremelly elevated LDH
- Therapy: highly intensive chemo: CR 80%, long-term survival 50%

BASIC CHARACTERISTICS OF LOW AGGRESSIVE B-NHLs (FL, MZL, SLL,..)

- Overall survival even without treatment in years to 10 ys
- Radiotherapy (IF RT) can have a curative effect in stage I or II
- Advanced stages (III/IV) are chemosensitive but generally incurable because of reccurent disease
- Chemotherapy-based (CHT) therapy is indicated in symptomatic cases or in large mass
-
- Transformation into more aggressive and resistant lymphoma in 10-60% patients during course of disease

FOLLICULAR LYMPHOMA clinical behavior

- Slow growing (sometimes vanishing) painless lymphadenopathy with relapsing course after treatment, spontaneous remissions are not exception, with or without general symptoms
- Global median overall survival >18 years,
  BUT up to 20% dies during 2 years since diagnosis
- FL is considered incurable with exception of localised (limited stages I/II ~ 10-20% FL patients)
- Cause of death – treatment toxicity and transformation (~25-60%) to more aggressive NHL

Follicular Lymphoma (and other indolent B-NHLs): principles of therapy

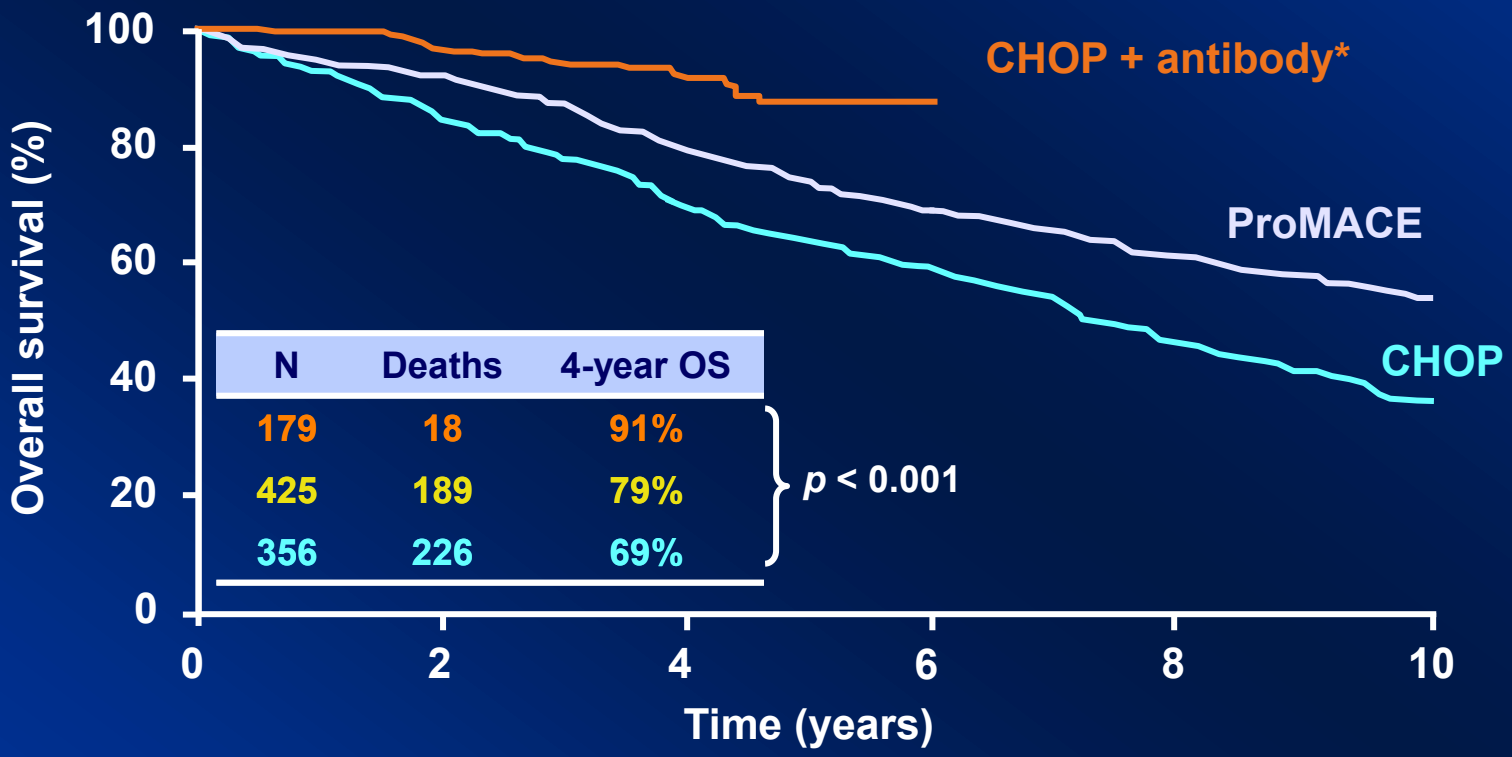
PRIMARY THERAPY (first line)

- Localised FL (stage I+II): IF RT 24Gy
- Advanced FL (stage III+IV):
  - /large tumor/: antiCD20+ chemotherapy + antiCD20 maintenance (2ys)
  - /low tumor/: watch and wait

THERAPY OF RELAPSE

- Chemotherapy antiCD20 maintenance
- High-dose chemotherapy + autologous stem cell support
- **Allogeneic bone marrow transplantation**
- Radioimmunotherapy
- Radiotherapy even very low dose (~4Gy!!!)

Anti-CD20 antibody therapies have changed the course of FL



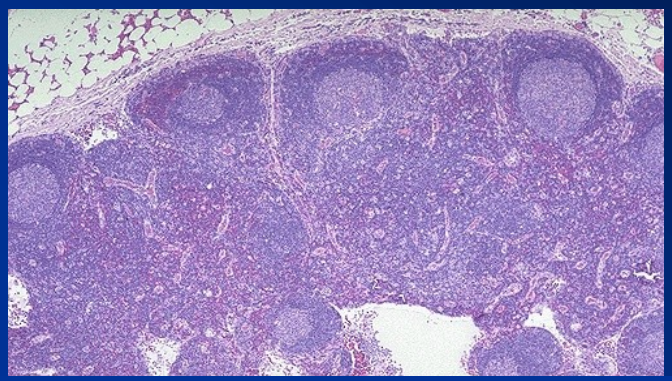
ProMACE: prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide

*SWOG 9911: CHOP + ^{131}I-tositumomab;
SWOG 9800: CHOP + MabThera
OS = overall survival

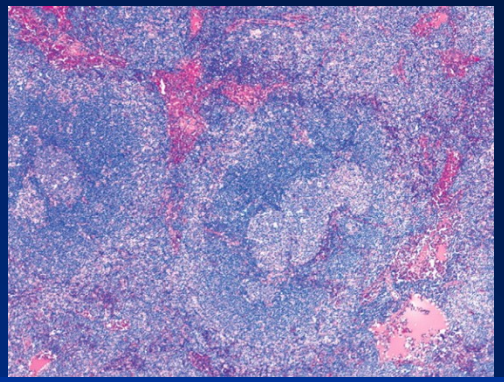
1. Fisher RI, *et al. J Clin Oncol* 2005; 23:8447–8452.

MARGINAL ZONE LYMPHOMAS (MZLs)

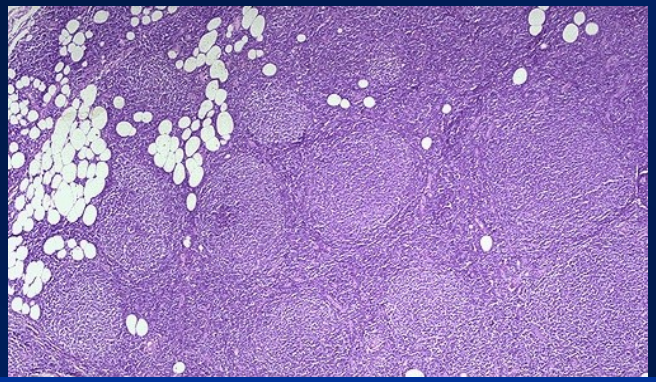
- **Indolent B-NHLs**
- **Nodal** – very similar to FL
- **Splenic** with/without vilous lymphocytes
  - Splenomegaly leading symptom
  - Treatment options: splenectomy
    rituximab monotherapy
- **Extranodal (MALT)**



LYMPHADENITIS



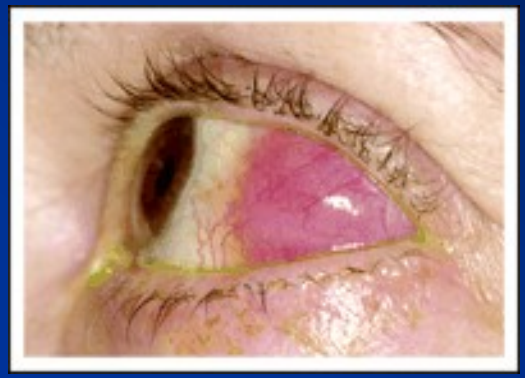
MZL

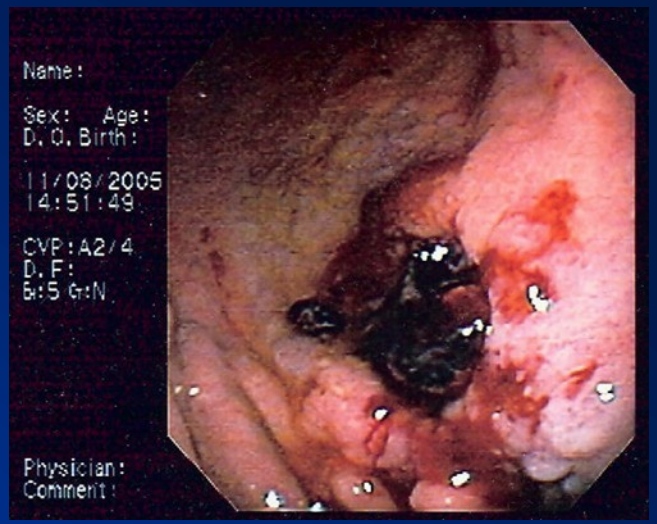


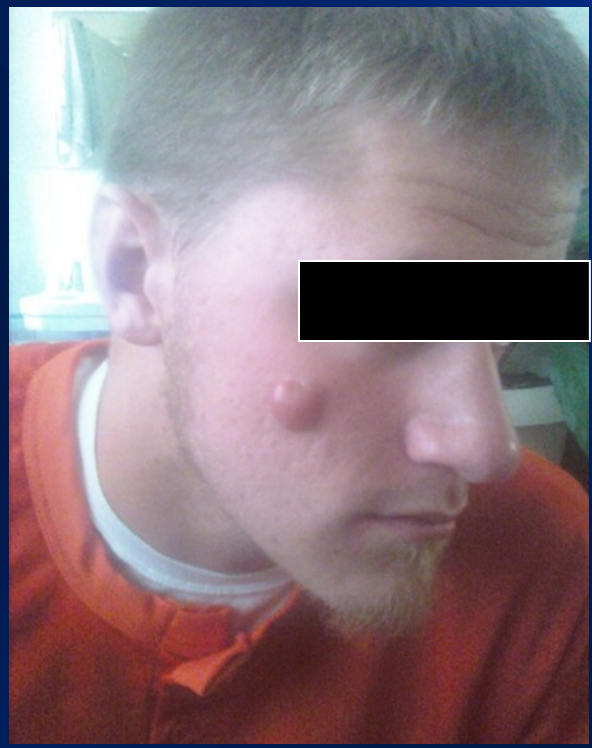
FOLLICULAR LYMPHOMA

MALT: MUCOSA ASSOCIATED LYMPHATIC TISSUE LYMPHOMA

- Subtype of MZL
- Etiology: antigen stimulation (H.pylori, Borellia, Chlamydia, HCV…)
- MALT-lymphoma of stomach
  - symptoms: „gastric ulceration“ (reccurent or non-healing)
  - Helicibacter pylori
- MALT lymphoma of conjunctiva
  - chlamydia
- MALT lymphoma
  - Borelia infection







MALT lymphomas: treatment principles

- Limited stage (I and II)
  - Antibiotics, curative radiotherapy (30Gy)
- Generalized stage (III and IV)
  - treatment like in FL (RCOP/RCHOP)

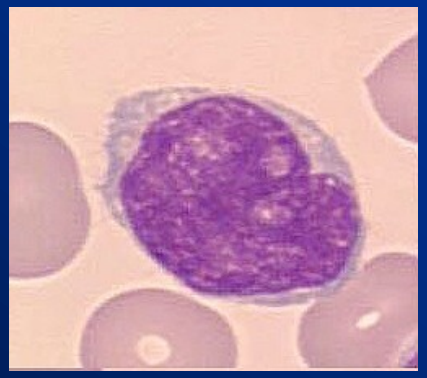
REMARKS:

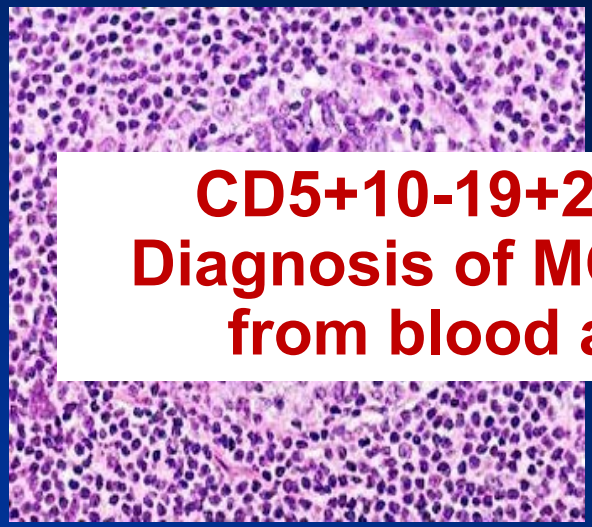
Multiple biopsy of mucosa (even normally looking)

Helicobacter pylori must be ALWAYS examined

MANTLE CELL LYMPHOMA

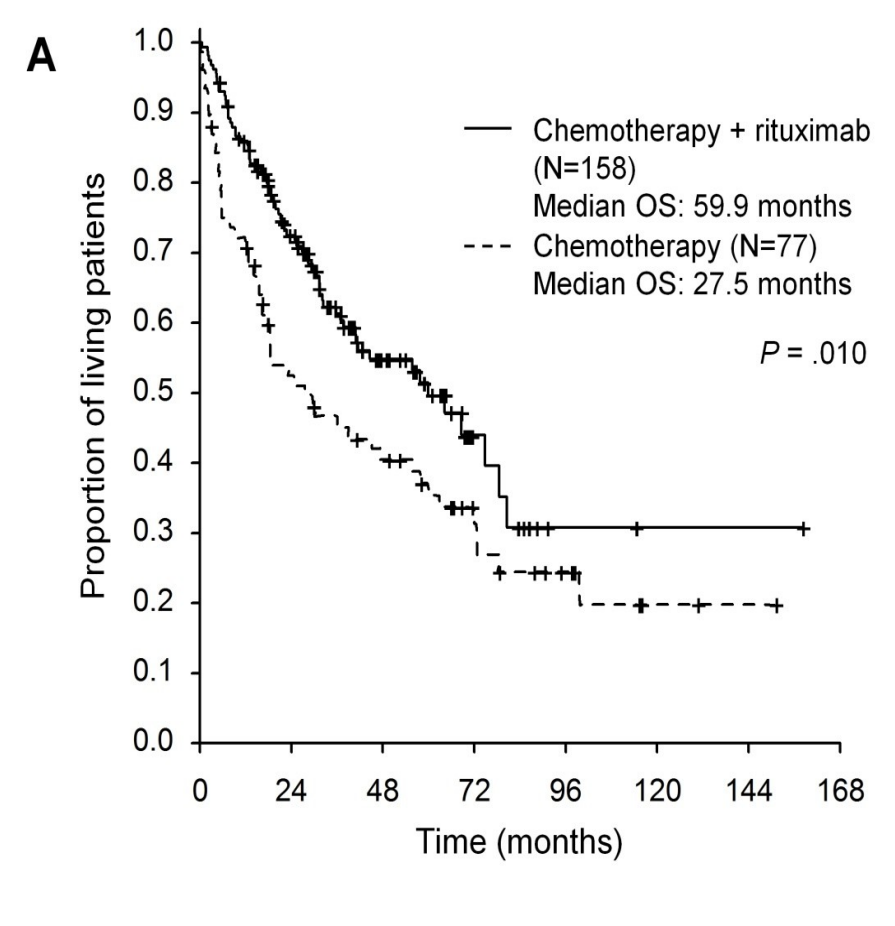
- Mantle cell lymphoma = lymphoma from „mantle cells“ of lymphatic follicle
- 6-8 % of all Nonhodgkins´s lymphomas
- B-NHL (CD20+)
- Typically in older men
- Frequent extranodal involvement (>80%cases)
  - Blood, bone marrow
  - Gut (multiple lymphomatpus polyposis)





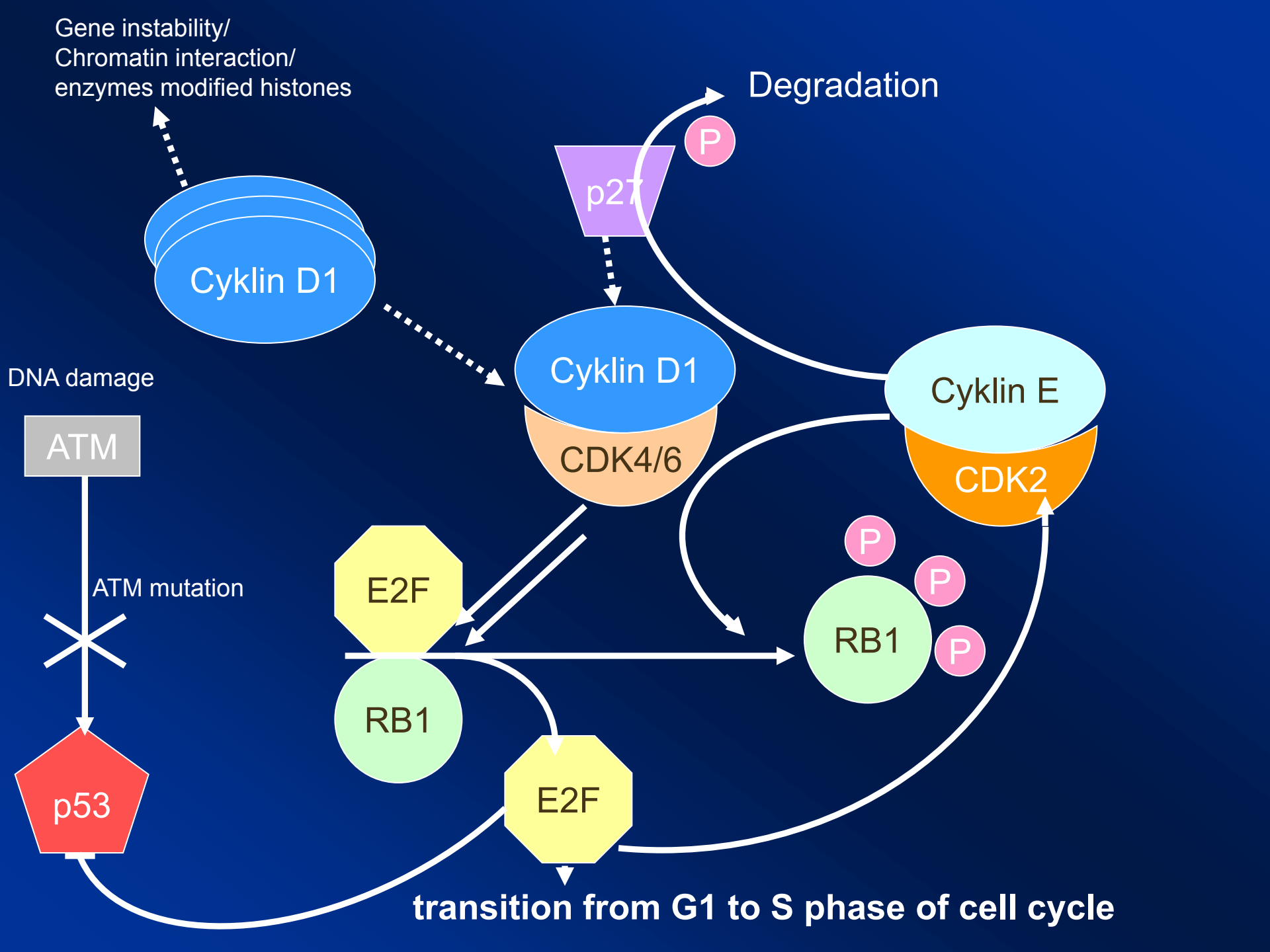
CD5+10-19+20+23-79b+sIgDM+sλ+
Diagnosis of MCL can be made by flow from blood and/or bone marrow!

Prognosis of MCL (Czech Lymphoma Database)



- Prognosis is generally poor
- New drugs are needed
- Chemotherapy has limited efficacy
- Targeted therapy antiCD20
- New drugs (ibrutinib)
- t(11;14) is hallmark
- cyclinD1 overexpression

CLSG KLS
Czech Lymphoma Study Group
Kooperativní Lymfomová Skupina


Gene instability/
Chromatin interaction/
enzymes modified histones
Degradation
P
p27
Cyklin D1
Cyklin D1
CDK4/6
Cyklin E
CDK2
DNA damage
ATM
ATM mutation
E2F
RB1
P
P
P
RB1
p53
E2F
transition from G1 to S phase of cell cycle

MCL- treatment

- intensive chemotherapy is recommended if possible R-MaxiCHOP/high dose Arac/ high dose BEAM
- transplantation therapy is indicated in younger patients
- majority of MCL patients not able to receive intensive treament
- rituximab in induction and in maintenance improved MCL prognosis
- new „smart“ drugs (biological agens) focused on **BCR signaling** are promissing
  - **Ibrutinib, bortezomib, temsirolimus** +/- rituximab

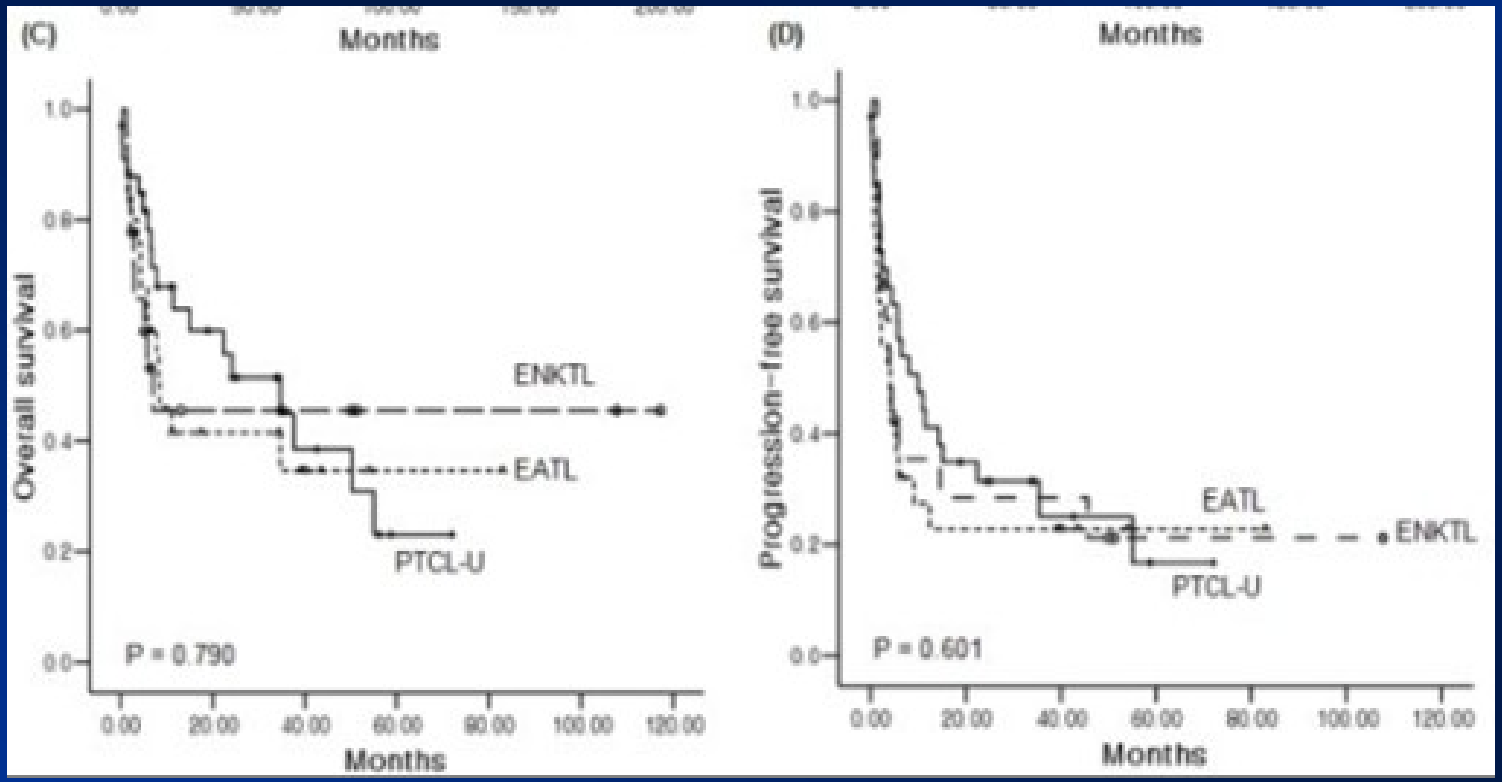
T-CELL LYMPHOMAS

- **Nodal**
  - PTCL, NOS: peripheral T-cell lymphoma not otherwise specified (25-36%)
  - ALCL: anaplastic large cell lymphoma (12-29%)
  - AITL: angioimunoblastic lymphoma (7-19%)
- **Extranodal** (tissue tropism)
  - Hepatosplenic γδ lymphoma (1.4%)
  - Enteropathy associated T-lymphoma (EATL) (5%)
  - Panniculitis-like T-cell lymphoma (0.9%)
- **Leukemic**
  - Adult T-cell leukemia, LGL-leukemia, NK-cell leukemia, T-prolymphocytic leukemia

T-CELL LYMPHOMA -prognosis

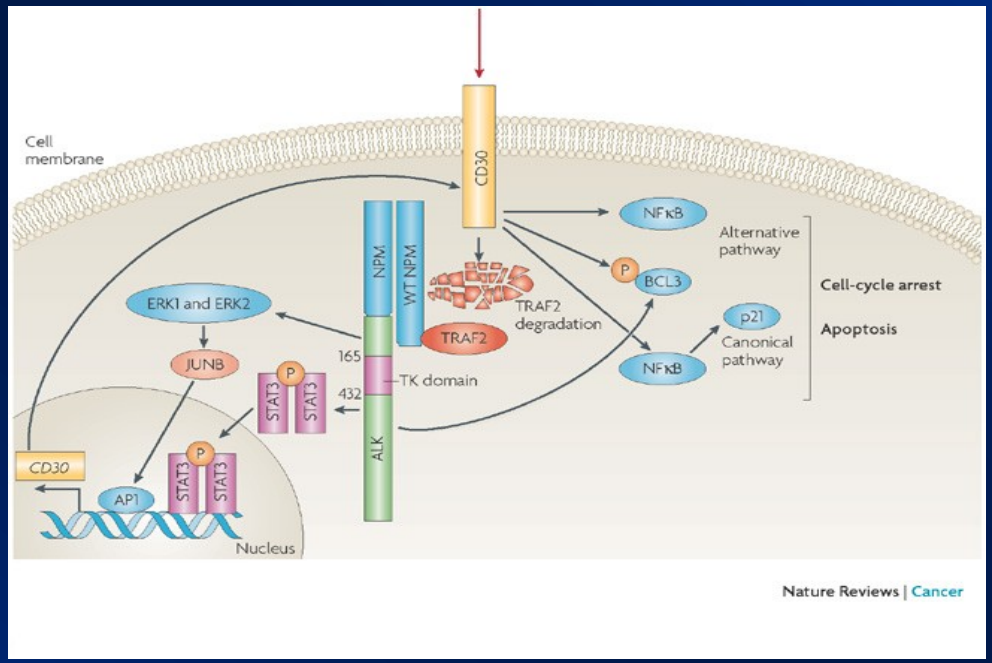
Non-cutaneous T-lymphoma have very poor prognosis

- Heterogeneity of units/ smal populations for clinical trials
- Treatment used in B-cell lymphoma (CHOP) is insufficient
- **CHOEP** (CHOP+ etoposide) better than CHOP
- CD30+ T-cell lymphoma can be treated with **brentuximab vedotin**



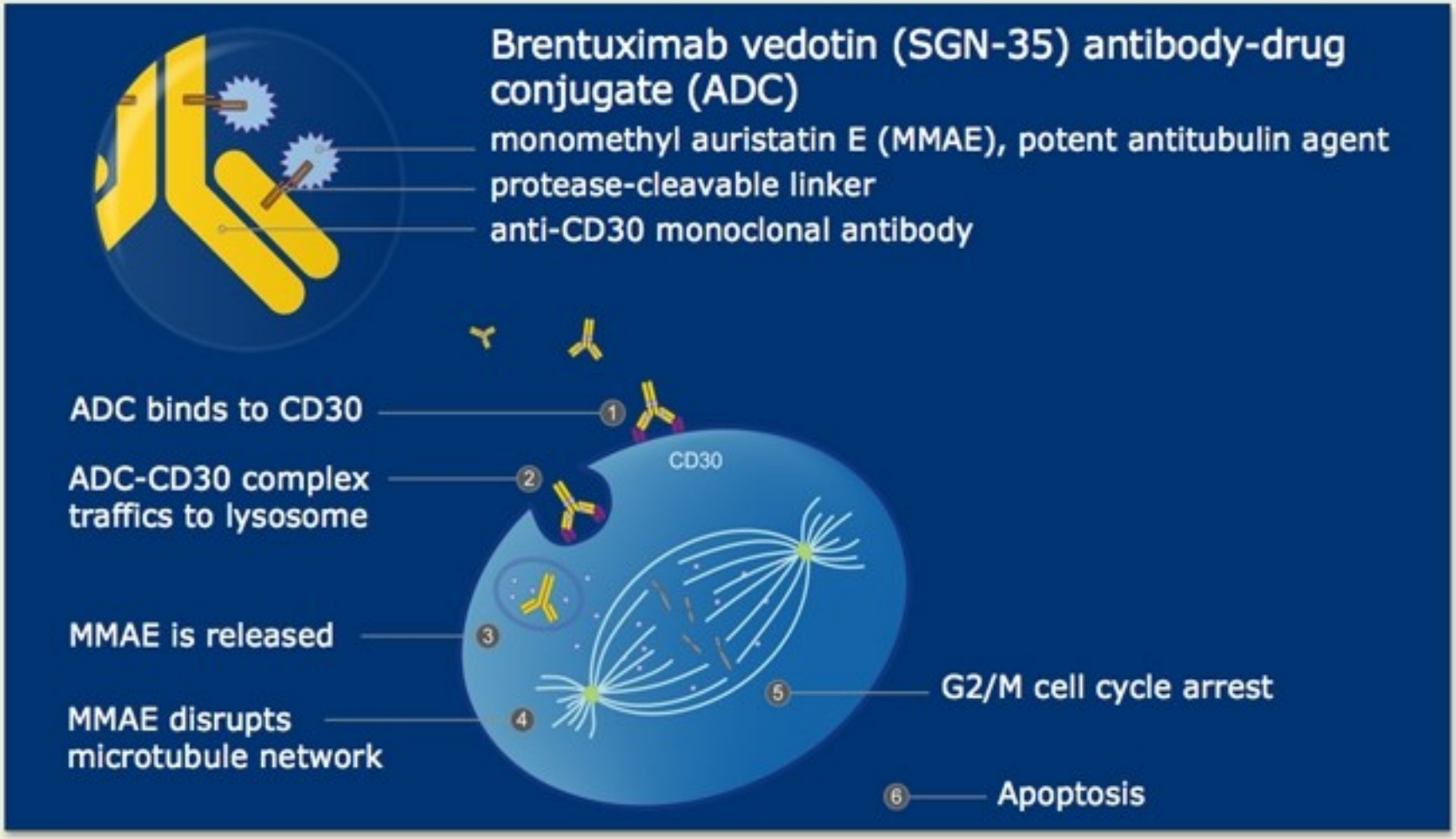
CD30 signal pathway

- CD30 is expressed:
  - on RS-cells of M.Hodgkin
  - on ALCLs
  - on primary cutaneous T-lymphomas
  - on some PTCL NOS and AITL



- Anti CD30 alone is not suficiently efficace!

Brentuximab Vedotin Mechanism of Action



With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

Long-term problems related to treatment of Hodgkin´s disease

- Typically ~10yrs or more since end of therapy
- Chemotherapy/radiotherapy
- Increased general incidence of secondary malignancies
  - More then 10-times

- Damage of gonadal functions (sterility)

- Long-term adverse events (toxicity)
  - cardiomyopathy
  - lung fibrosis
  - myelodysplastic syndrome