Lymphomas – lymphoproliferative disorders (I)

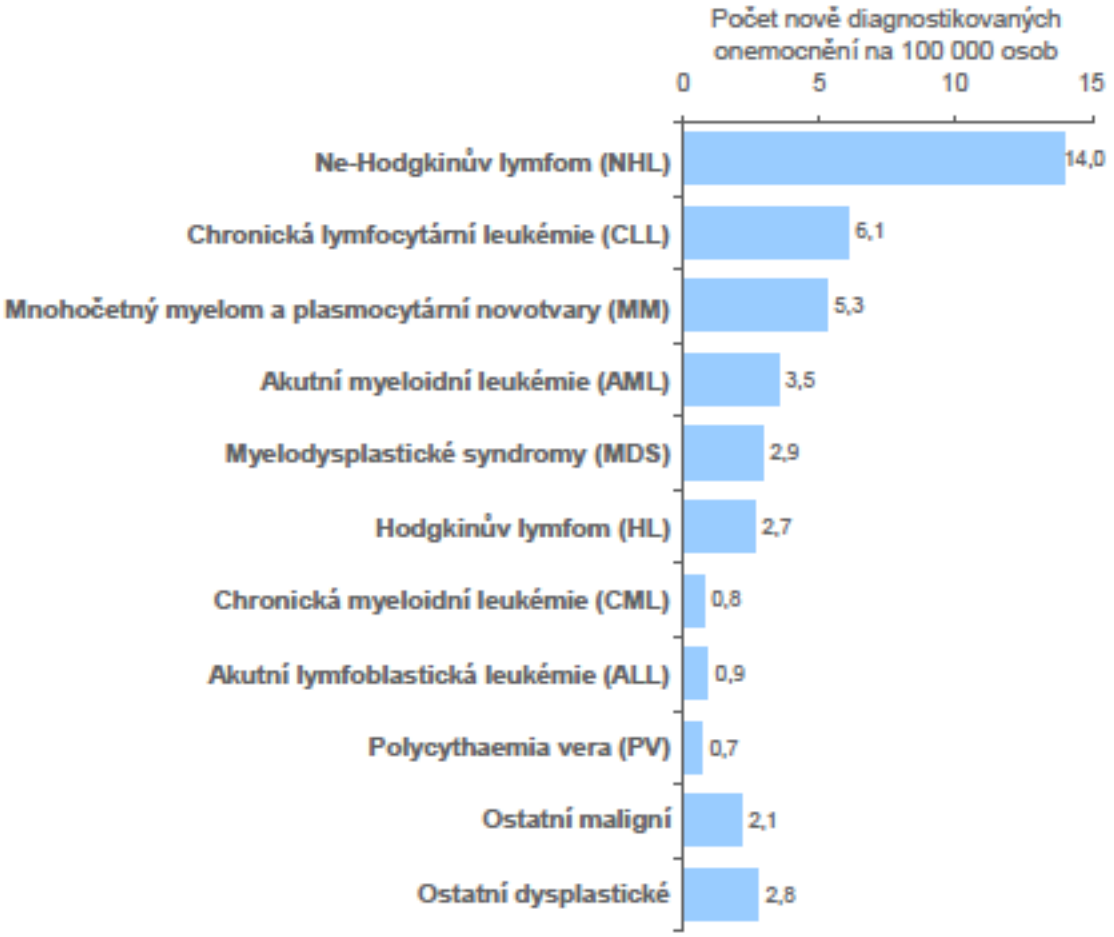
Outline

- Epidemiology
- Etiology, pathogenesis
- Pathological and clinical classification
- Diagnostics and natural history
- Staging
- Therapy

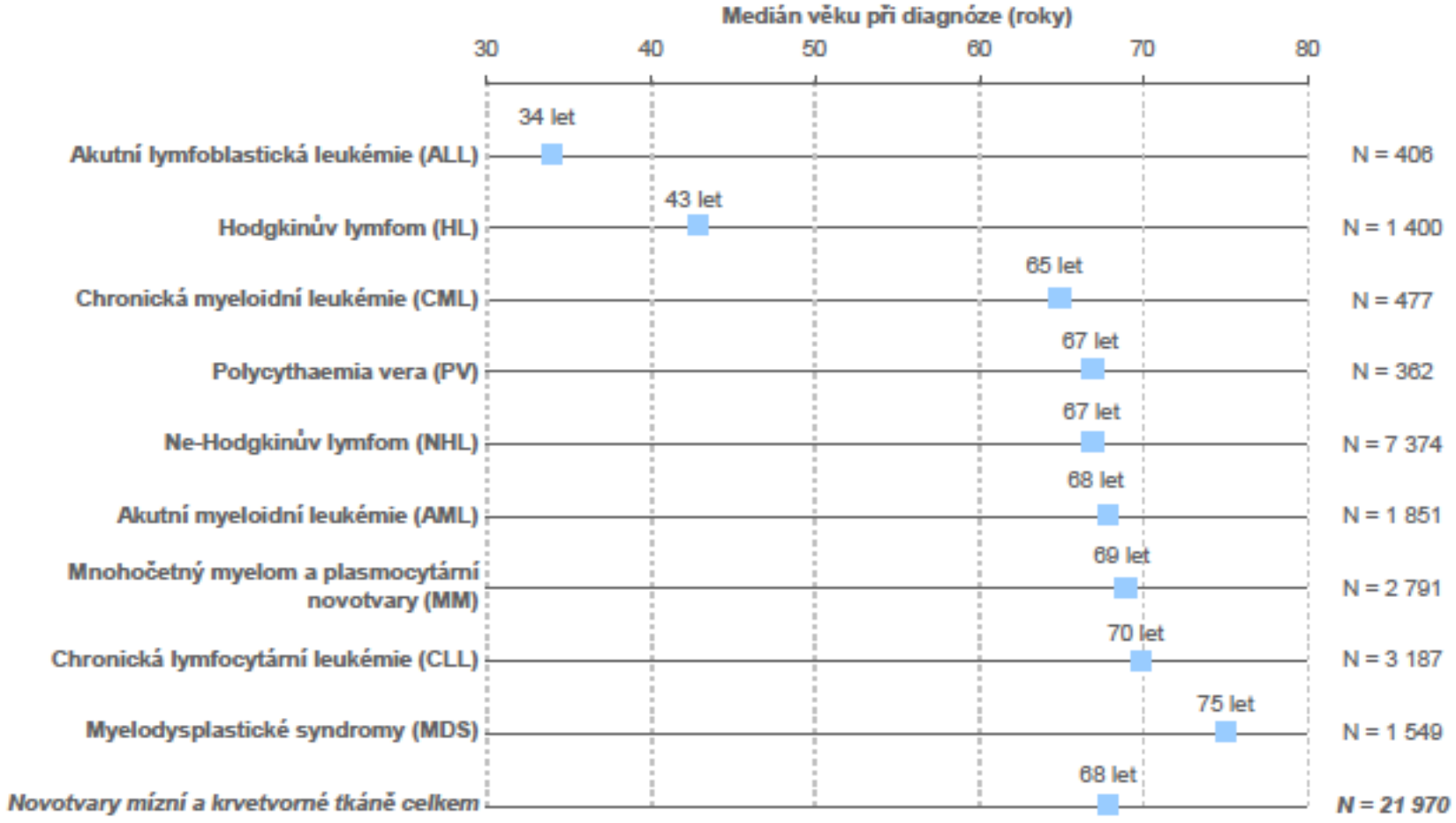
Which one of these statements is correct?

1. Lymphoproliferative diseases are mostly diseases of young people
   0
2. 10-year survival is approximately 20%
   0
3. 10-year survival is 3 times better than 40 years ago
   0
4. 50% of lymphoproliferative disorders is preventable
   0

Incidence novotvarů mízní a krvetvorné tkáně v České republice v letech 2011–2015



Věk pacientů s novotvary mízní a krvetvorné tkáně v České republice v letech 2011–2015



Non-hodgkin‘s lymphoma, age specific incidence

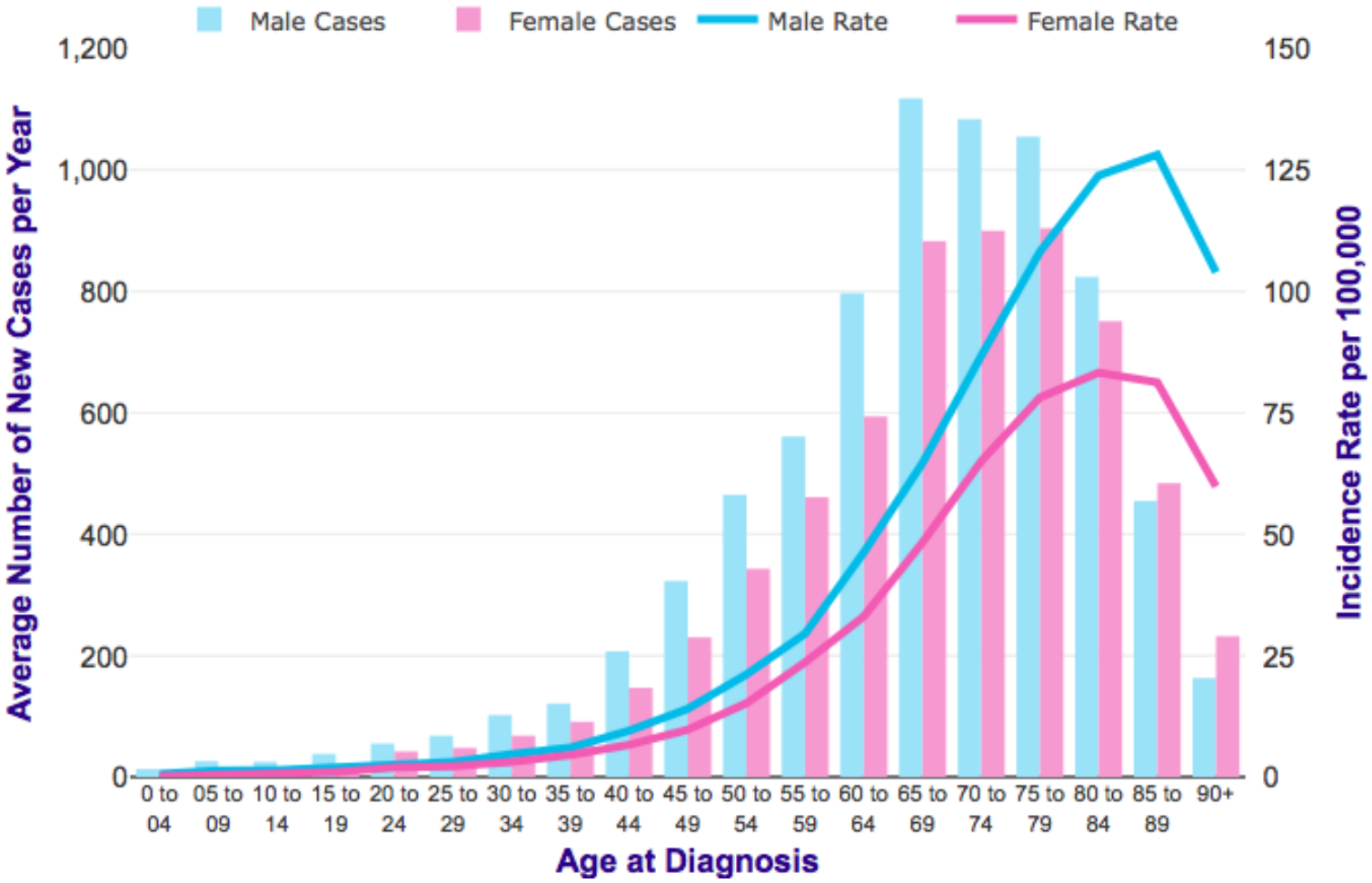
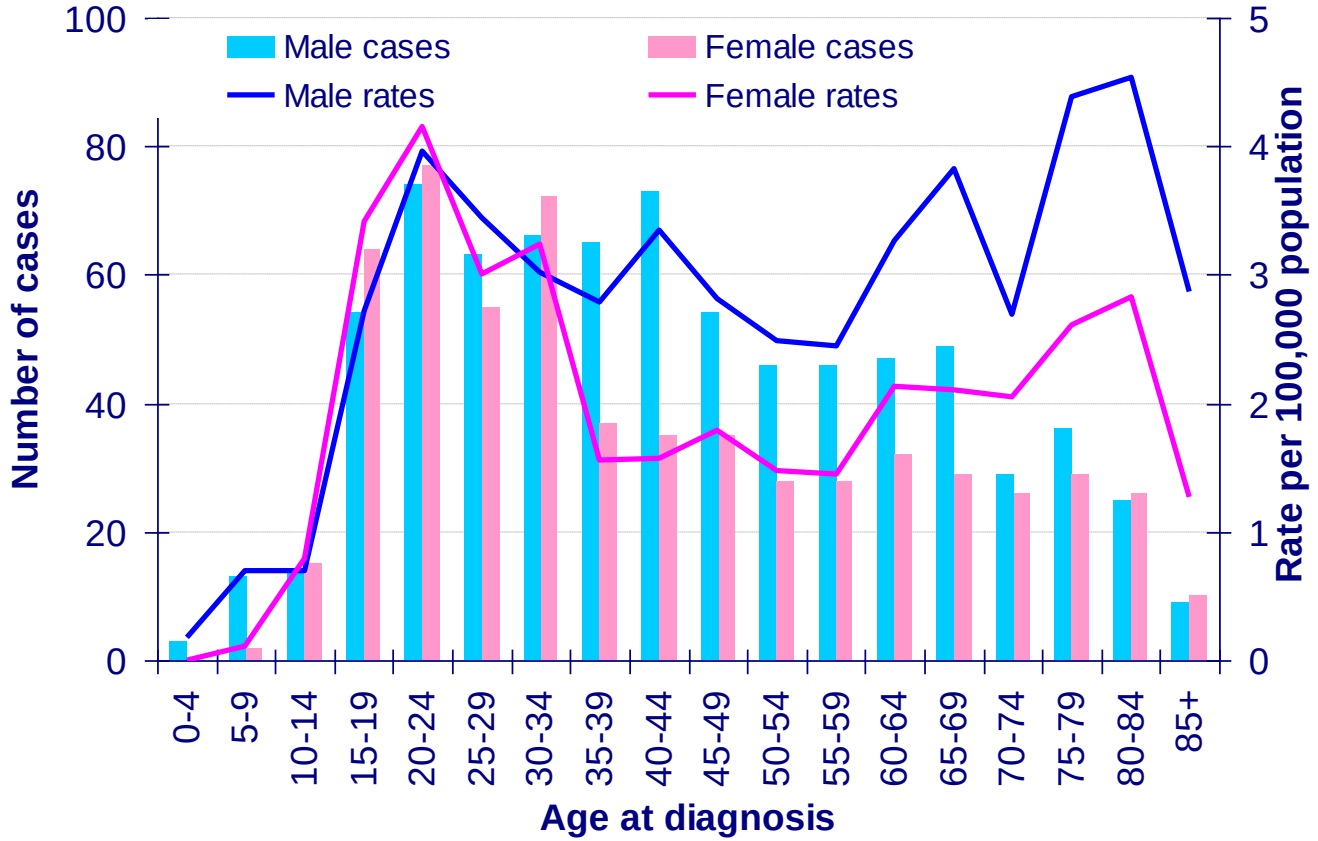


Figure 1.2: Numbers of new cases and age specific incidence rates, by sex, Hodgkin's lymphoma, UK 2003



Survival

Survive non-Hodgkin lymphoma for 10 or more years, 2010-11, England and Wales

Age

Age that non-Hodgkin lymphoma survival is highest, 2009-2013, England

Improvement

Non-Hodgkin lymphoma survival in the UK has tripled in the last 40 years

Preventable cases

Non-Hodgkin lymphoma cases are preventable, UK, 2015

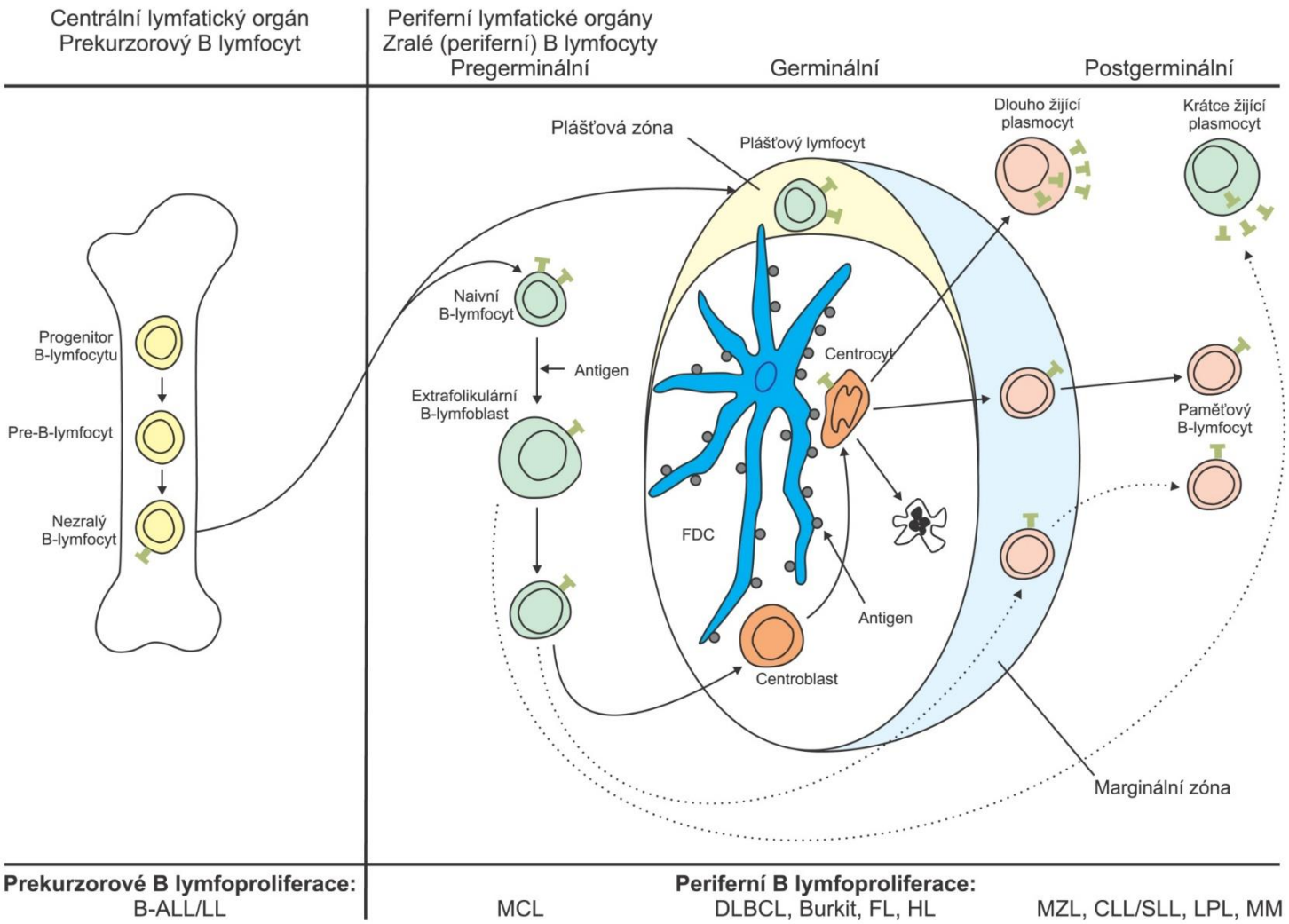
H. Pylori

Non-Hodgkin lymphoma cases caused by infections, UK, 2015

Etiology

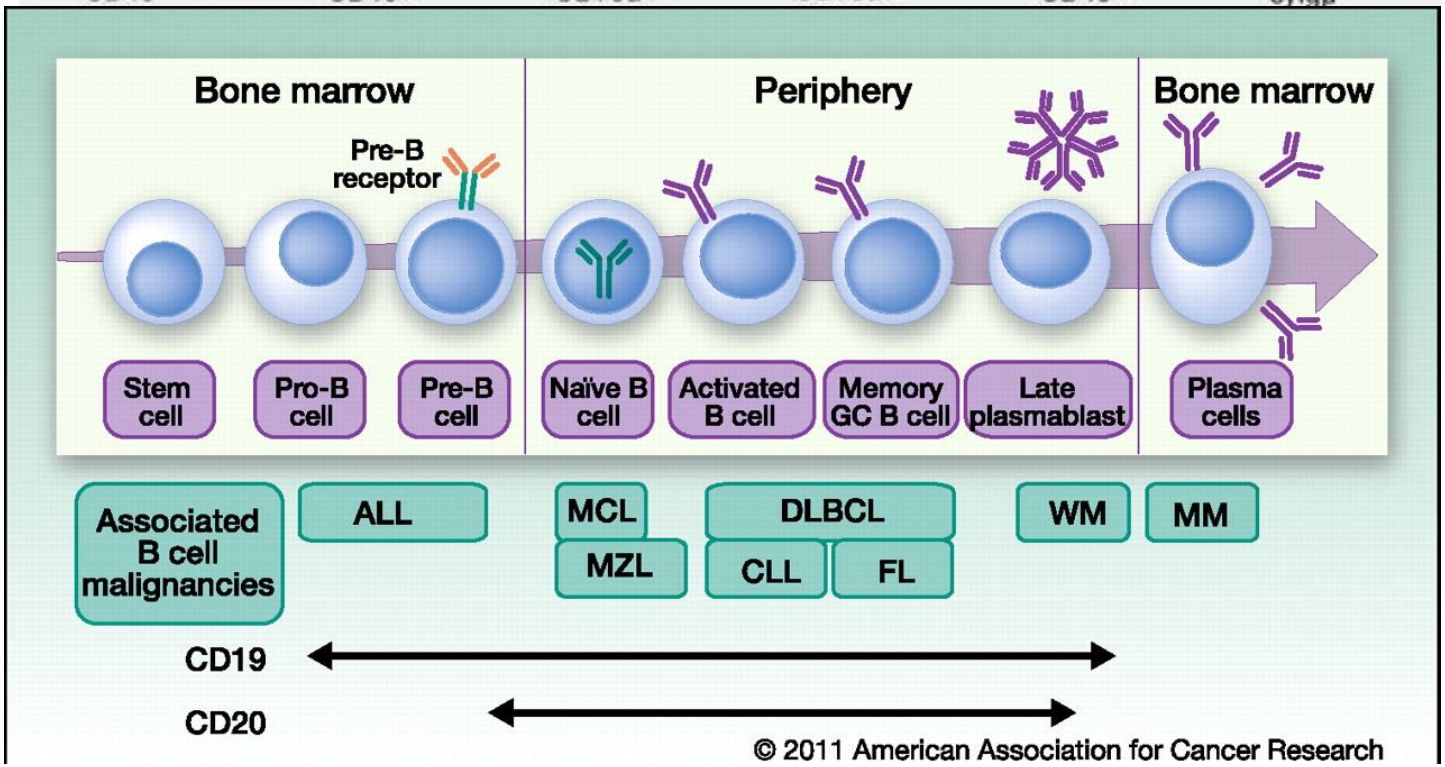
- Immunosuppression
- Infection (EBV, HTLV1, SV40?)
- Chronic antigenic stimulation (Helicobacter pylori, hepatitis C)
- External causes, cytostatics, radiation
- Genetic predisposition

Pathogenesis I – development of normal B cell



Maturation curve

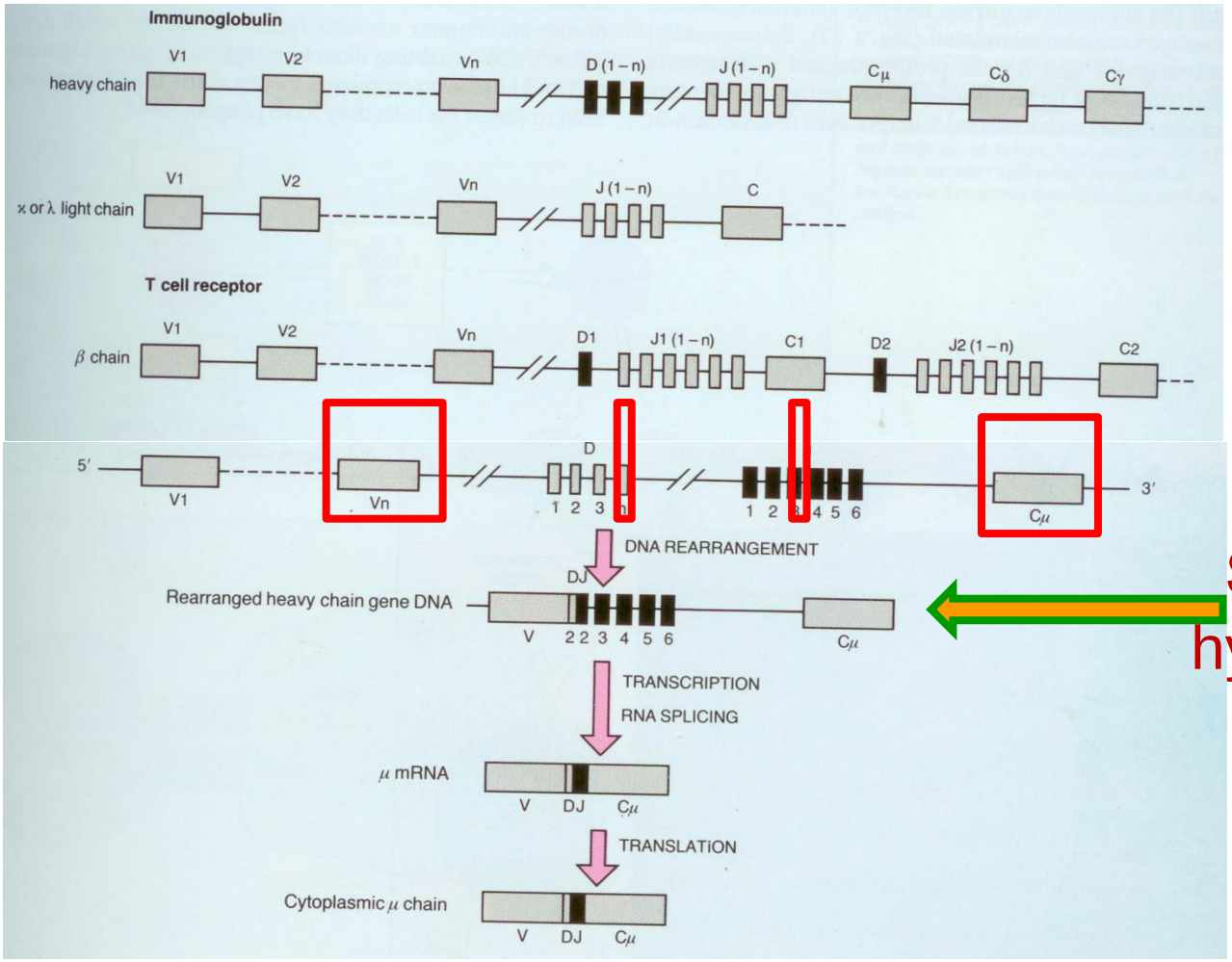
Pro-B-Cell	Pro-B-I-Cell	Pro-B-II-Cell	Immature-B-Cell	Mature-B-Cell	Plasma-Cell
CD34+	CD34+	$CD20^{het}$	CD20+	CD20+	CD38+
TdT+	TdT+	CD22+	CD22+	$CD22^{high}$	CD19+
CD22+	CD22+	CD38+	CD38+	CD19+	CD138+
$CD38^{high}$	CD38+	CD19+	CD19+	CD79a+	CD45+
$CD45^{low}$	CD19+	CD79a+	CD79a+	$CD45^{high}$	cylgμ



WHO classification of lymphoproliferation

	B	T
Precursor lymphomas	B-ALL/B-LBL	T-ALL/T-LBL
Peripheral lymphomas	All other B-NHL	All other T-NHL
	Hodgkin‘s lymphoma	

Pathogenesis II – What can go wrong?



Somatická hypermutace

Patogenesis III – it went wrong: genetic abnormalities

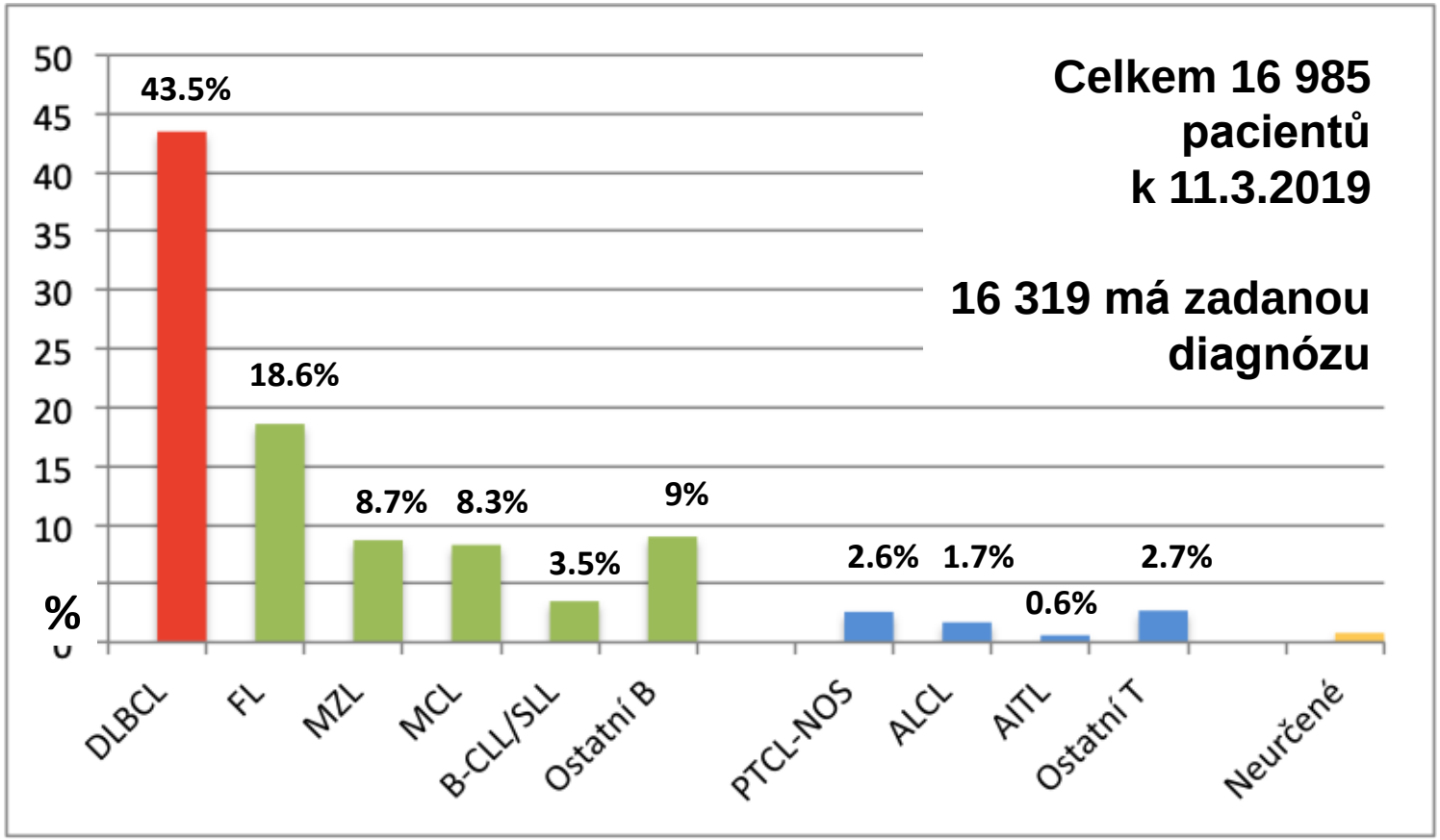
Cytogenetic abnormality	Histology	Antigen rearrangement	Oncogene expression	% of cases
B-cell lymphoma				
t(14;18)(q32;q21)	FL	IgH	*bcl-2*	≈ 90%
	DLBCL	IgH	*bcl-2*	15%–30%
t(11;14)(q13;q32)	Mantle cell	IgH	*bcl-1*	> 95%
t(1;14)(p22;q32)	MALT lymphoma	IgH	*bcl-10*	≈ 5%
t(11;18)(q21;q21)	MALT lymphoma		*API2* on chromosome II *MALT-1* on chromosome 18	≈ 30%
t(9;14)(p13;q32)	Lymphoplasmacytic lymphoma	IgH	*PAX-5*	
8q24 translocations	Burkitt lymphoma and variants		*c-myc*	≈ 99%
t(8;14)(q24;q32)		IgH		
t(2;8)(p11-12;q24)		Ig-κ		
t(8;22)(q24;q11)		Ig-λ		
(3;22)(q27;q11)	Diffuse (large cell, small cleaved cell)	Ig-κ	*bcl-6* (*LAZ3*)	
(3;14)/(q27;q32)	DLBCL	IgH	*bcl-6*	≈ 35%
T-cell lymphoma				
14q11 abnormalities				
inv 14(q11;q32)	Variable	TCR-α	*tcl-1*	
t(10;14)(q24;q11)	Variable	TCR-α	*hox-11* (*tcl-3*)	
i(7q)(q10)	Hepatosplenic	TCR-α	*ALK*	
2p23 translocations				
t(2;5)(p23;q35)	ALCL	TCR-α	*Npm*	
t(1;2)(p21;p23)	ALCL	TCR-α	*TPM3*	
t(2;3)(p23;p20)	ALCL	TCR-α	*TFG*	
t(2;22)(p23;q11)	ALCL	TCR-α	*CLTCL*	
inv(2)(p23;q35)	ALCL	TCR-α	*ATIC*	

WHO classification (B neoplasms) 2016

- 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*
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha 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*
- 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 CNS
- Primary cutaneous DLBCL, leg type
- EBV positive 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 positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8 positive 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*

Swerdlow S H et al, Blood 2016 127:2375-2390;

NHL entities in the Czech Lymphoma Study Group Registry



CLSG KLS
Czech Lymphoma Study Group
Kooperativní Lymfomová Skupina

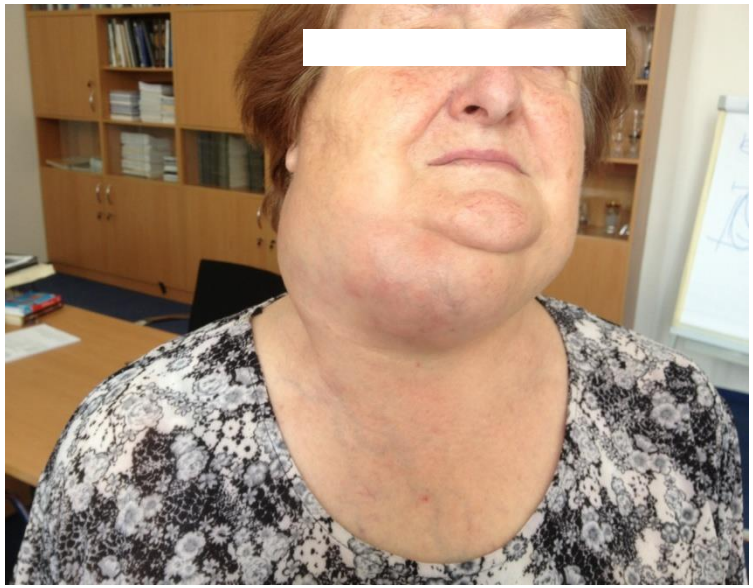
Clinical (not WHO!) lymphoma classification

- Aggressive
- Indolent

DLBCL (aggressive lymphoma) and FL (indolent lymphoma) makes up approximately 60% of patients with NHL

Patient KH 1950

- Female, 2012 – 4-5 months slowly growing neck lymph node
- Practical physician – 2 lines of antibiotics
- Systemic symptoms – fatigue, night sweats
- Then rapid growth, local symptoms (swallowing difficulties)



What will be the diagnostic procedure?

1. Blood analysis
   - 0
2. Chest X-ray
   - 0
3. Ultrasonography
   - 0
4. PET/CT
   - 0
5. biopsy
   - 0
6. Radical tumor removal after peroperative biopsy
   - 0

When to perform lymph node biopsy?

1. Lymph node larger than 2 cm, persisting >2 months without evidence of infection in drained region

   0
2. Larger than 3 cm, persisting more than 3 months

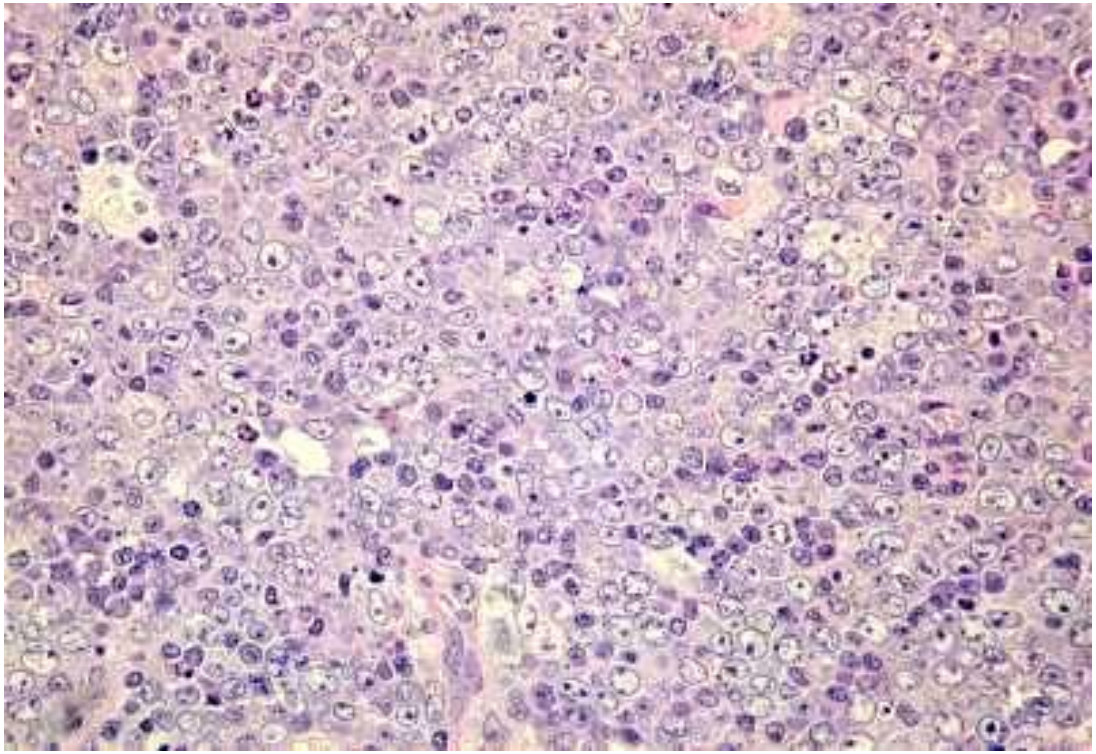
   0
3. Twice as big after one month of observation

   0
4. Ineffectivity of antibiotics

   0
5. When the disease is as large as in this patient

   0

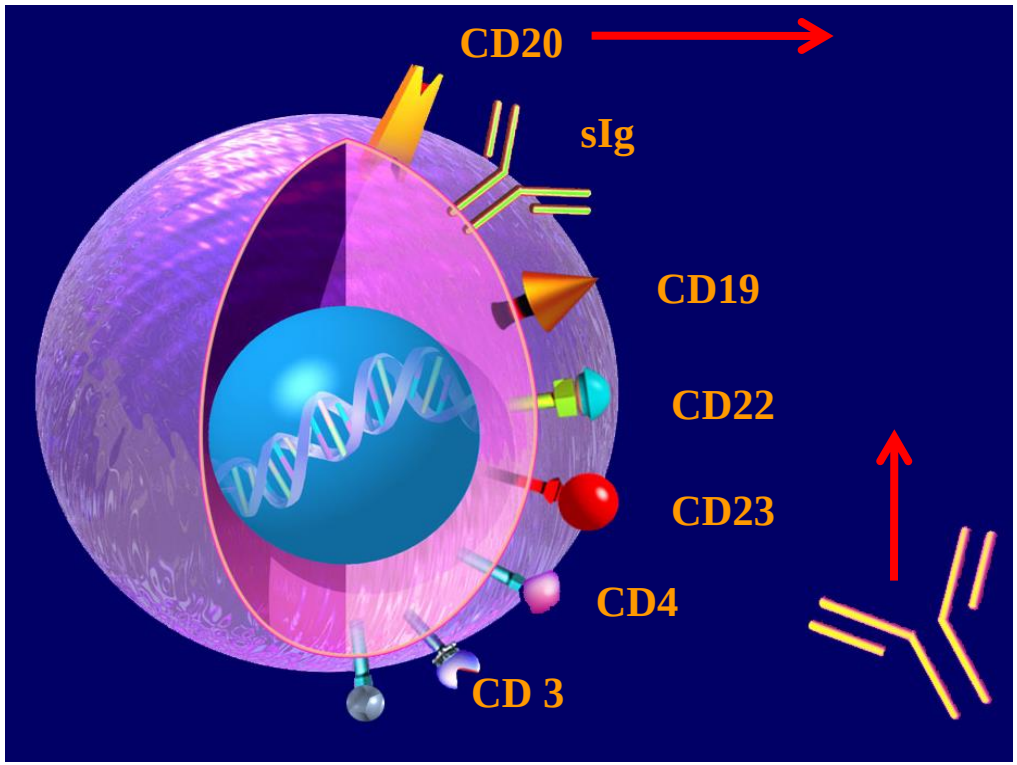
Morphology – hematoxylin-eosin

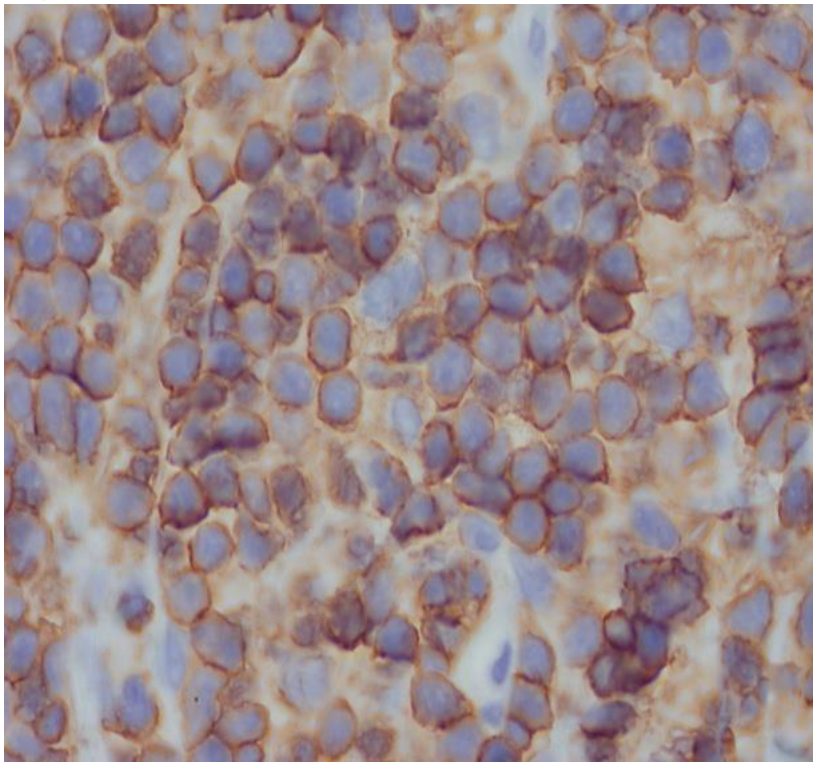


Diffuse large cell tumor – tumor cells most probable lymphocytes

What else??

Immunohistochemistry, flow cytometry





Diffuse large B-cell lymphoma (DLBCL)
= aggressive lymphoma

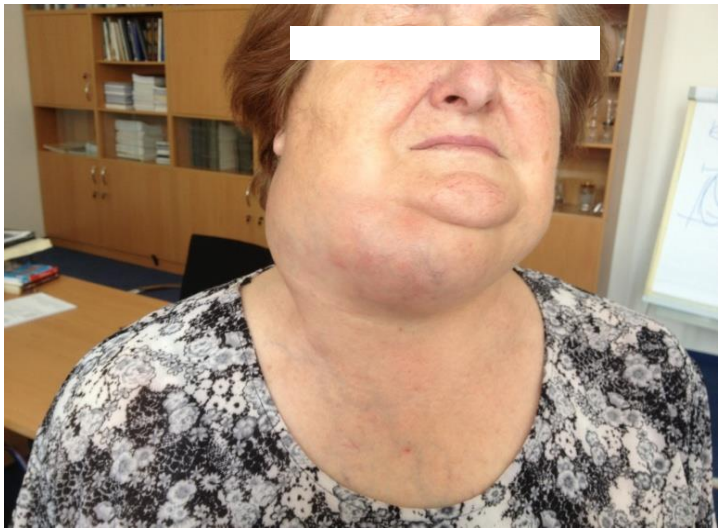
Aggressive lymphomas

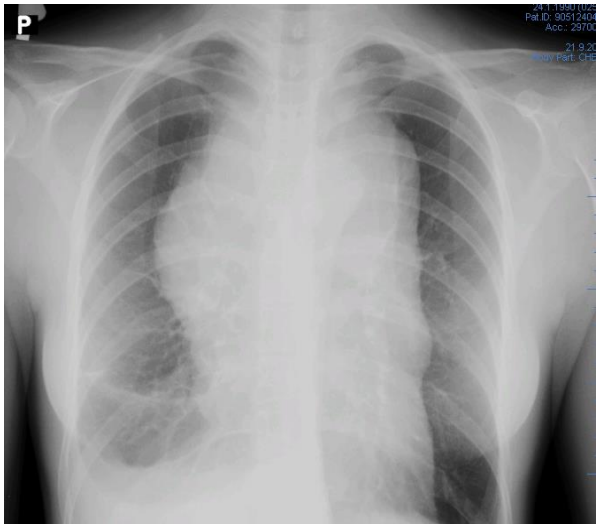
- Short history: weeks to moths
- Even in advanced stage curable
- Treatment is needed immediately after diagnosis: chemotherapy, immunotherapy ± radiotherapy
- Usually good response to treatment

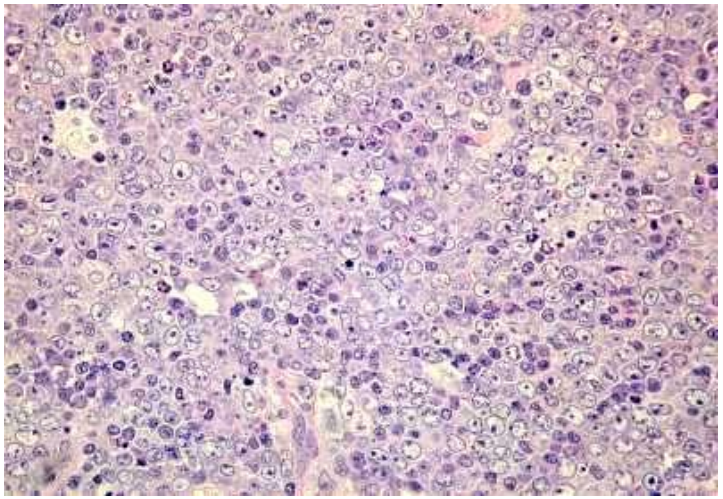
BUT:

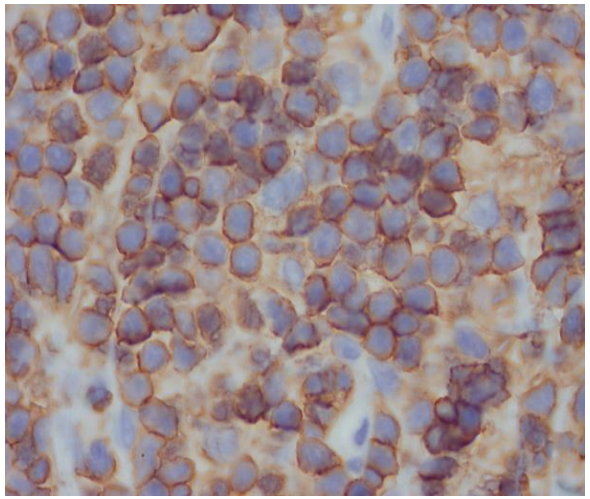
- Relapse allways means poor prognosis

Patient KH, 62 years









- Age >60 years - bad
- Clinical stage II - good
- LDH > normal – bad
- Extranodal involvement: none – good
- Performance status: good

- (B-lymphoma = CD20 positive)

What is the probability of this patient to be alive in 5 years?

1. 25% 0
2. 50% 0
3. 75% 0
4. 100% 0

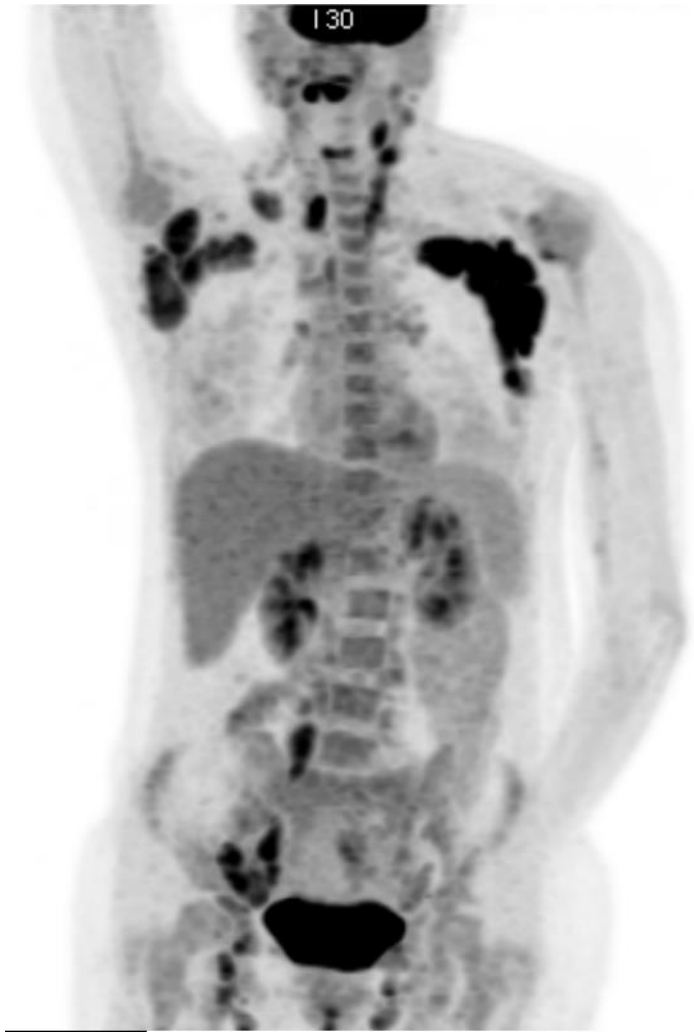
Indolent lymphomas

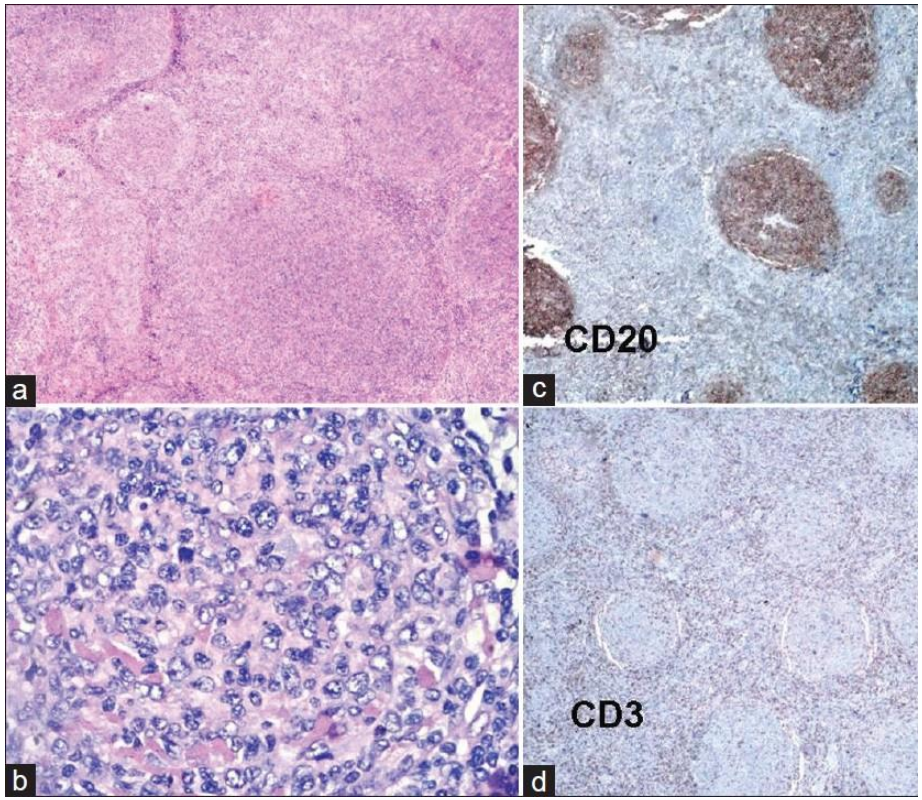
- Long history: months to years
- Mostly advanced disease – incurable

BUT:

- Not necessary to treat immediately after diagnosis
- Usually good response to treatment, frequent relapses
- Relapse (even repeated) does not mean necessarily poor prognosis
- Risk of transformation – change to histologically high grade lymphoma – repeated biopsies

Patient AT 1950 (53 years)– dg. 2003





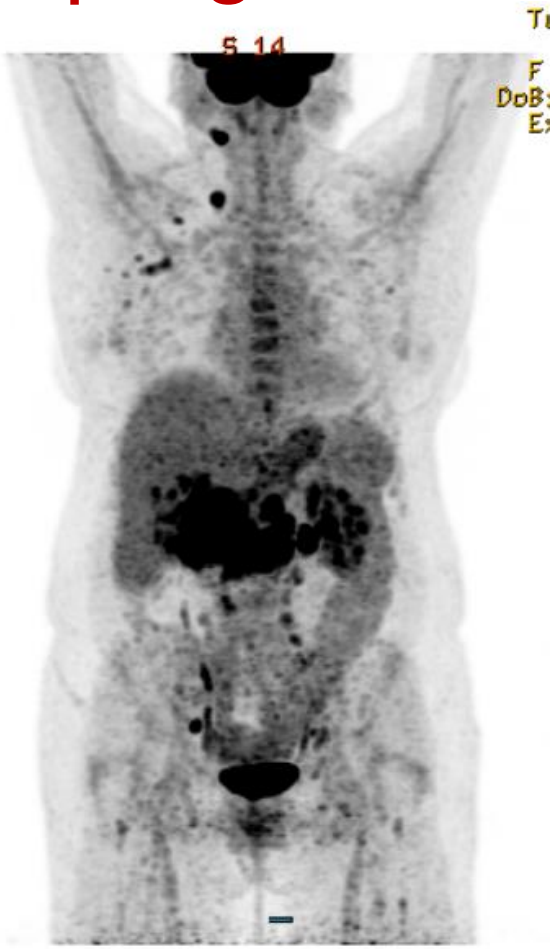
Patient AT, 1950

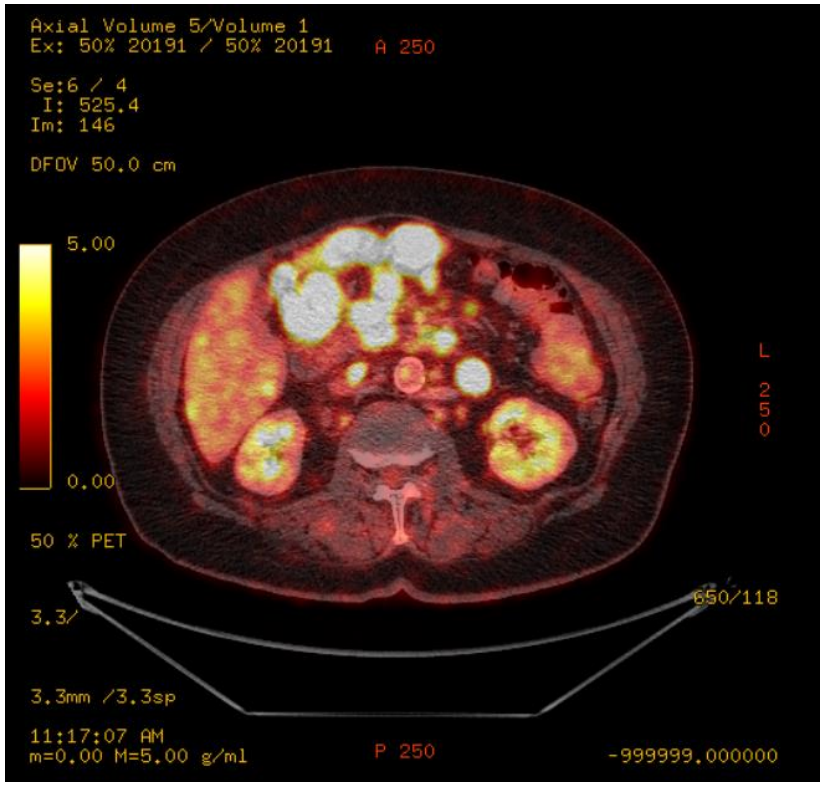
- Follicular lymphoma, clinical stage III (advanced disease)
- Treatment: 8x CHOP (chemotherapy withou antiCD20 immunotherapy)
- Progression 2005, two lymph nodes in right axilla
- Not treated, just watch and wait

How long will this patient be without treatment?

1. One year
   0
2. Five years
   0
3. Ten years
   0
4. Fifteen years
   0
5. Twenty years
   0

October 2016 – massive mesenteric progression – chemoimmunotherapy R-COP





Patient A-T, 1950

- May 2017 – PET-CT negative after 8 cycles of therapy
- May 2019 – finished the anti-CD20 maintenance therapy
- In ongoing complete remission

What is the take-home message for me?

1. Lymphomas are very rare, I don‘t know why I should learn anything about them

   0

2. I will think about them especially in older patients

   
   3

3. Most lymphoma patient have quite good prognosis

   
   4

4. After relapse/progression, prognosis is allways poor

   
   2

5. Nothing

   0


Thank you for your attention