

# ***LYMPHOMAS***

## ***Non-Hodgkin's lymphoma II.***

***Diagnosis - Staging – Treatment –  
Examples***

# Pacientka KH 1950

- žena, 2010 – postupně rostoucí uzlina na krku – 2-3 měsíce**
- Praktický lékař 2 linie ATB**
  - Objevení se celkových příznaků – únava, noční pocení**
  - Rychlé zhoršení – nárůst, polykací obtíže**



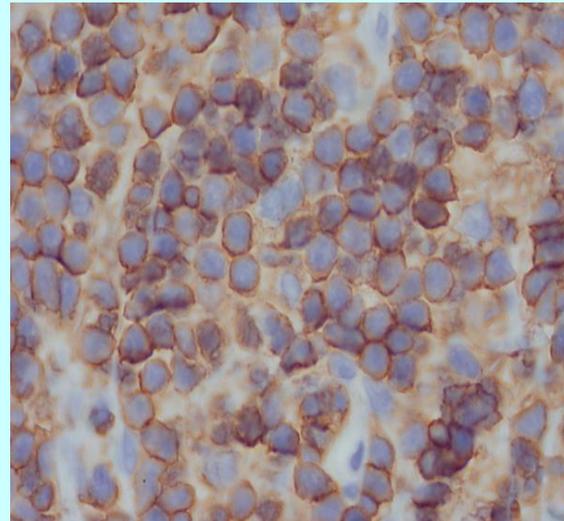
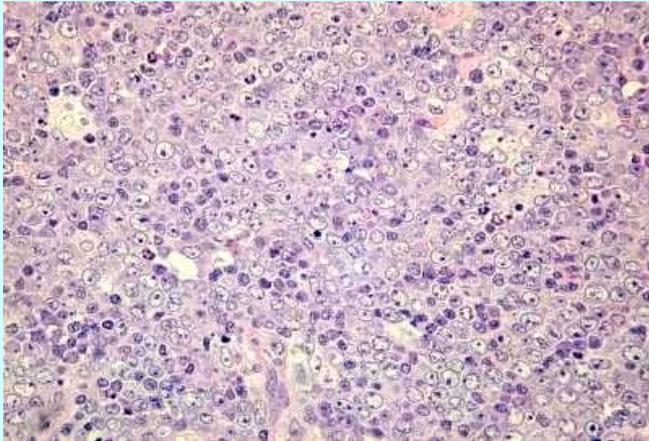
# *What do we need for lymphoma diagnosis?*

- **Biopsy sample allways needed! The more the better!**
- **Any lesion suspected of malignancy should be removed or biopsied**
- **Non-invasive or „minimally invasive diagnostics – often takes much, much longer.**
- **Fine needle aspiration today is obsolete and should not be used**

# *Lymphomas - what are we looking at?*

- **Morphology: large v. small cells, nodular v. diffuse growth**
- **Immunohistochemistry, immunocytochemistry: characteristic combination of markers for particular tumor**
- **Clinical characteristics**
- **Cytogenetics, molecular biology: minimal residual disease markers**
- **Gene expression profiling: Targets for smart drugs**

# Patient KH 1950- dg DLBCL at 62y



# *Staging: Determination of the extend of disease*

## **Allways:**

- **History, physical examination, WBC, biochemistry (LDH!!)**
- **Whole body CT or**
- **PET-CT: currently recommended for all FDG avid lymphomas: HL, DLBCL, FL..)**
- **Bone marrow biopsy: not mandatory for Hodgkin's and DLBCL**

## *Staging II*

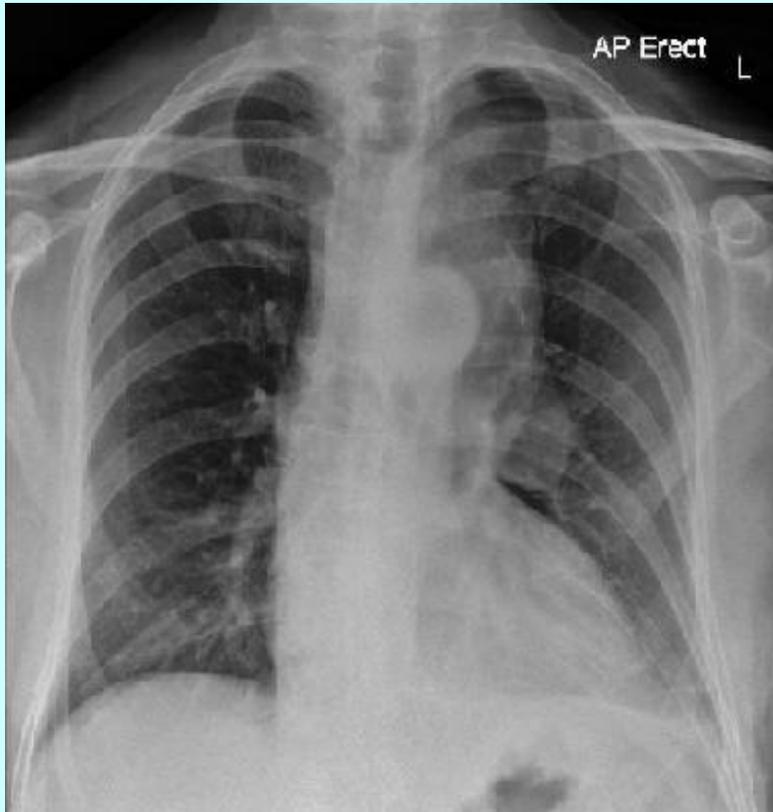
**Only based on clinical situation:**

- **Endoscopy**
- **Central nervous system evaluation (MRI, CSF examination)**
- **Other organ biopsies (liver...)**

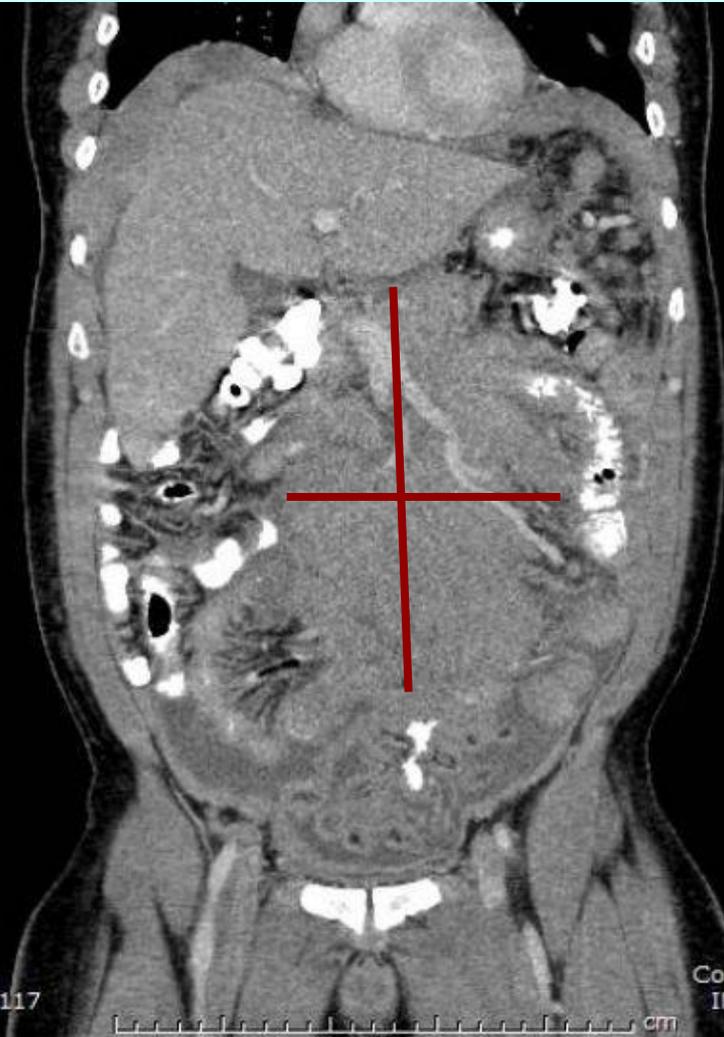
**Evaluation of patient „fitness“ – ability to receive therapy:**

- **ECG, echocardiography, spirometry, thyroid gland hormones...**

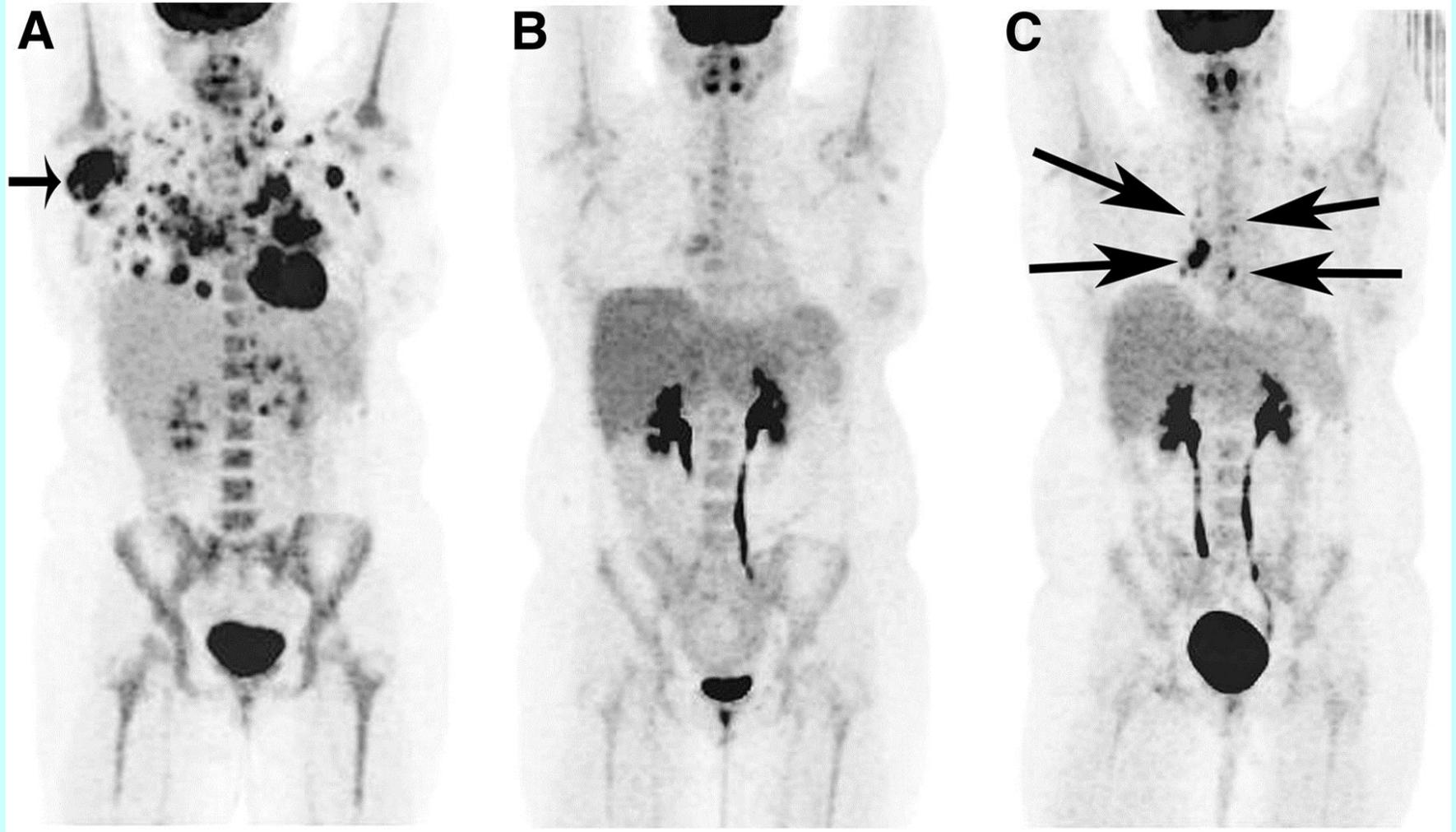
# *Lymphoma diagnosis based on chest X-ray*



# *Large lymphoma mass in the abdomen*



# *Positron emission tomography*

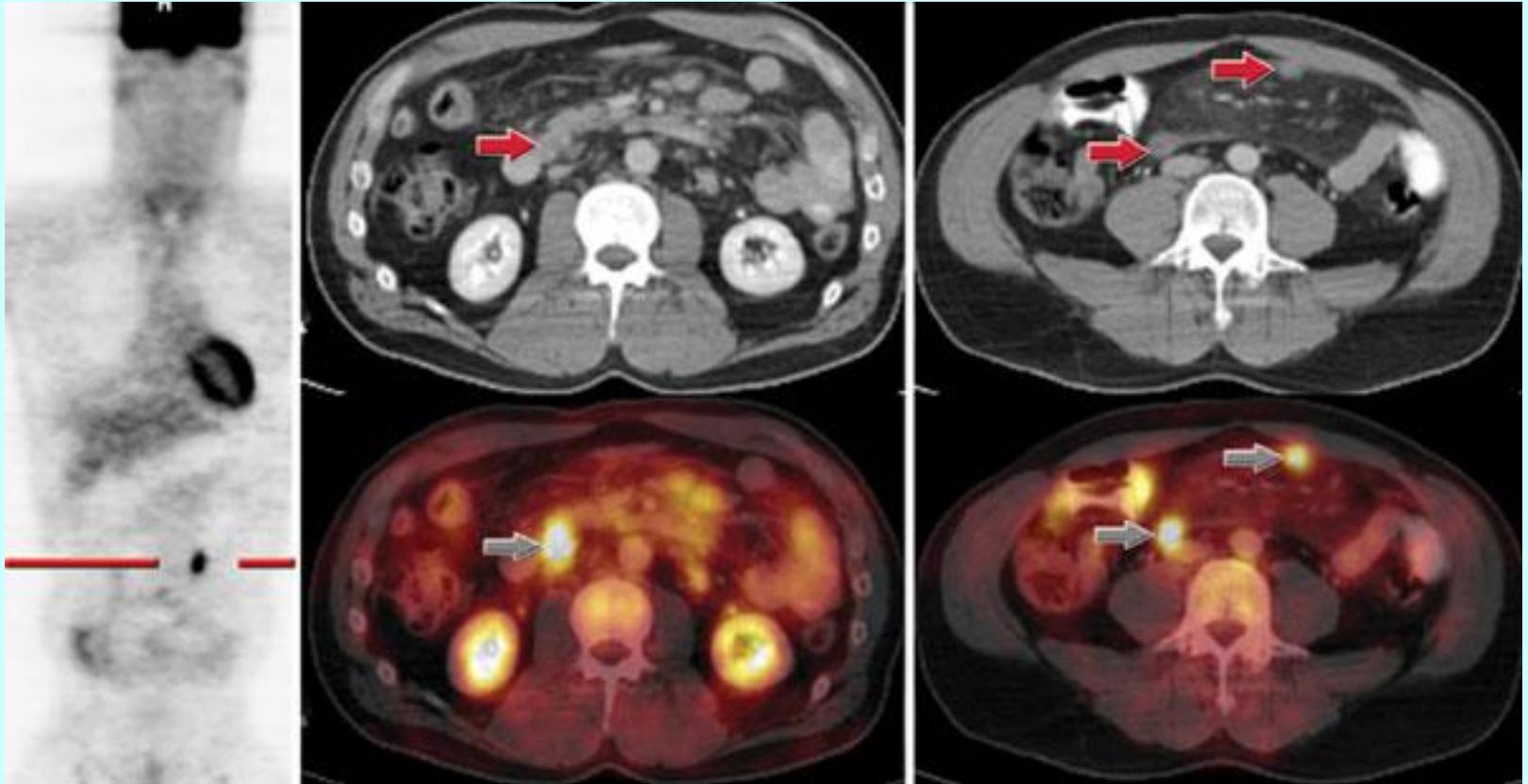


**Before treatment**

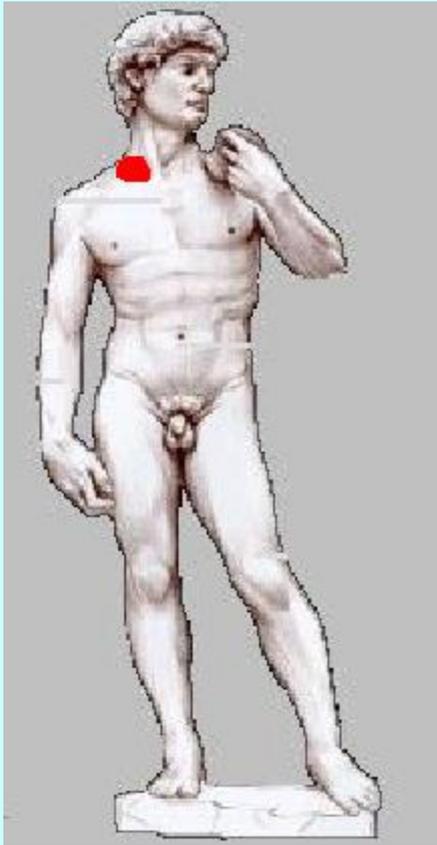
**After treatment**

**Relapse**

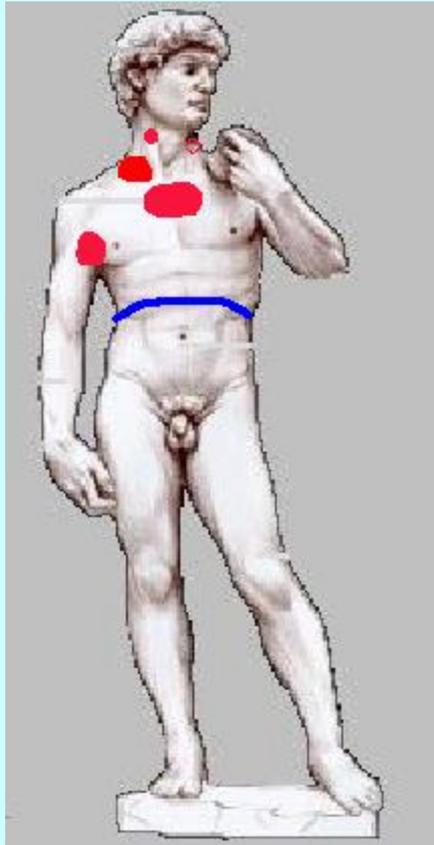
# *PET-CT scans: merged images I*



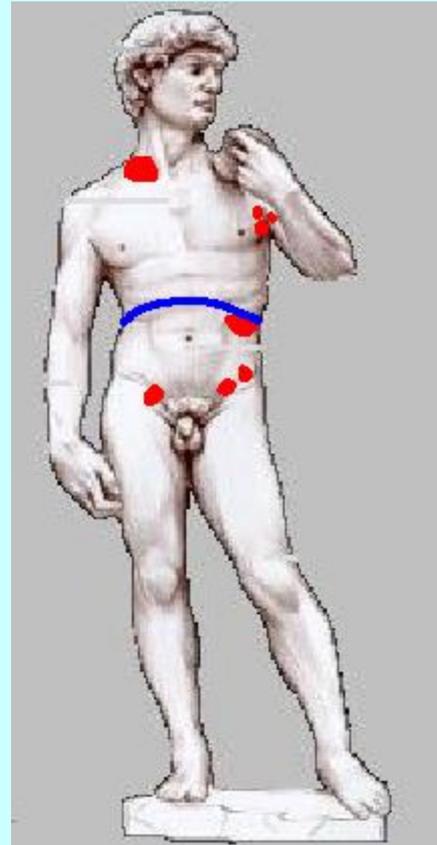
# *Staging according to Ann Arbor classification (originally for Hodgkin's lymphoma)*



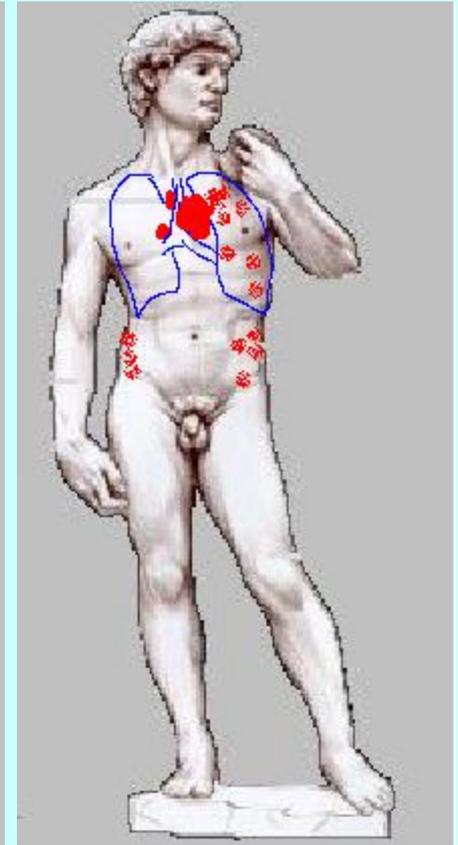
**Stage I**



**Stage II**



**Stage III**



**Stage IV**

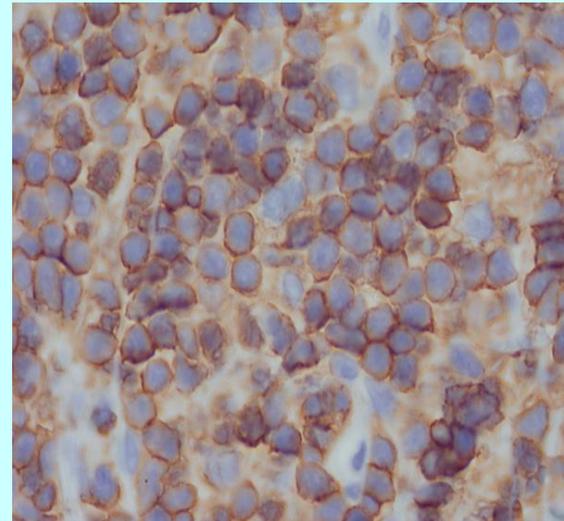
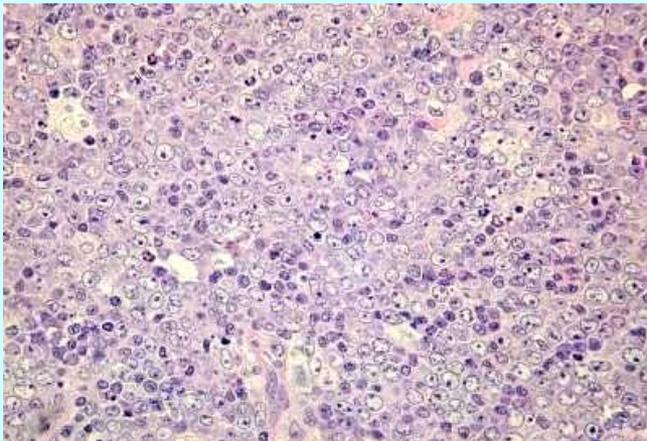
# *More refined prognostic tools - prognostic indexes: International prognostic index (IPI) for aggressive lymphomas*

<b>Rizikové faktory</b>	<b>Míra rizika</b>	<b>Statistická významnost</b>	<b>Jednotlivé rizikové skupiny</b>	
<b>IPI</b>			<b>IPI</b>	
Věk >60 let	1,96	p <0,001	Nízké riziko	0-1 faktor
LDH > norma	1,85	p <0,001	Středně nízké riziko	2 faktory
Performance status > 1	1,80	p <0,001	Středně vysoké riziko	3 faktory
Klinické stadium III nebo IV	1,47	p <0,001	Vysoké riziko	4-5 faktorů
Postižení >1 extranodálního orgánu	1,48	p <0,001		
<b>aaIPI (&lt;60 let)</b>			<b>aaIPI (&lt;60 let)</b>	
Klinické stadium III nebo IV	2,17	p <0,001	Nízké riziko	0 faktorů
LDH > norma	1,95	p <0,001	Středně nízké riziko	1 faktor
Performance status > 1	1,81	p <0,001	Středně vysoké riziko	2 faktory
			Vysoké riziko	3 faktory

# Pacient KH 1950- dg DLBCL at 62y



- DLBCL**
- 62 let**
- KS IIB**
- Bulky onemocnění**
- Vyšší LDH**
- HBsAg+**
- HIV neg**
- Normální funkce orgánů**



# *Treatment of lymphoma*

# *Treatment modalities*

- **Chemotherapy**
- **Immunotherapy – monoclonal antibodies**
  - **Cold**
  - **Radioactive**
  - **Immunotoxins**
- **Radiotherapy**
- **Autologous stem cell transplant**
- **Allogeneic stem cell transplant**
- **New treatments, small molecules**

# *Chemotherapy*

- **First-line or salvage treatment**
- **Curative or palliative**
- **Usually combined**

**Most frequent first-line for non-Hodgkin's lymphoma:**

- **CHOP: cyklofosfamid, adriamycin, vincristin, prednison**

**Režimy záchranné léčby:**

- **Založené většinou na platině a etoposidu**

*U vyléčitelných nádorů by naším cílem mělo být  
vyléčit pacienta na první pokus*

# *Chemotherapy - salvage and palliative treatment*

➤ **Salvage treatment: with curative intent**

**Both HL and NHL: based mostly on cisplatin, etoposid, Ara-C**

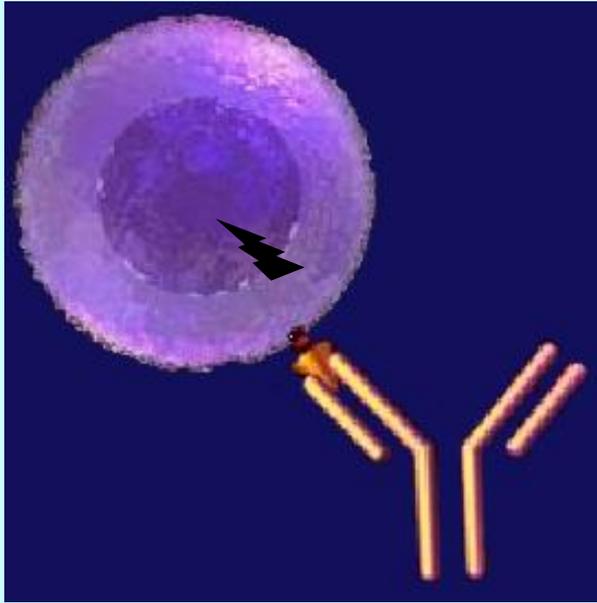
➤ **ESHAP: etoposide, methylprednisolon, Ara-C, cisplatin**

➤ **Palliative treatment: may be monotherapy or mild combination treatment, usually oral (chlorambucil, cyclophosphamide, steroids**

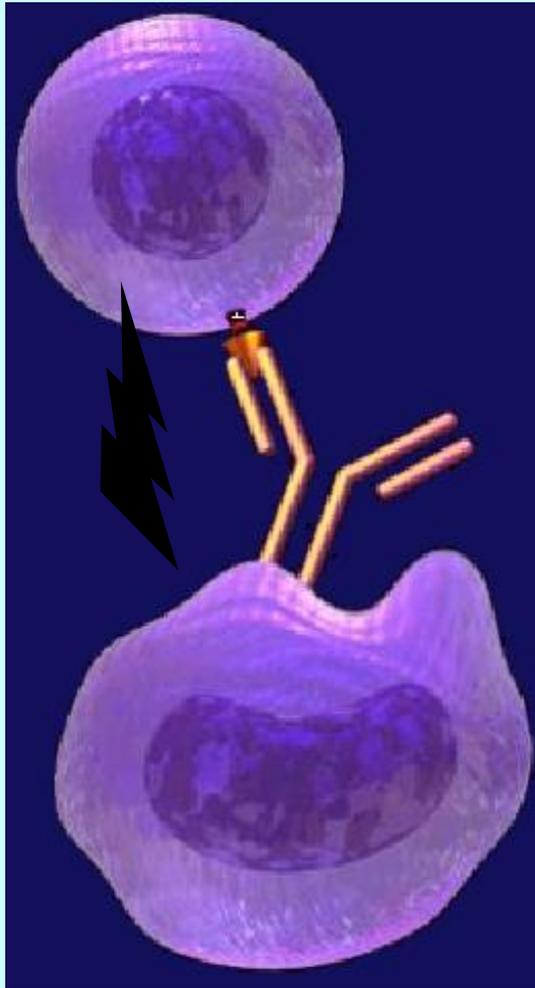
# *Immunotherapy*

- **Passive (antibodies)**
- „Cold“ – „hot“ - immunotoxins
  - Rituximab (Rituxan, Mabthera)
  - <sup>90</sup>Y Ibritumomab tiuxetan (Zevalin)
  - Brentuximab vedotin (Adcetris)
- Alone or with chemotherapy
- **Active immunotherapy – vaccination: not very successfull so far**

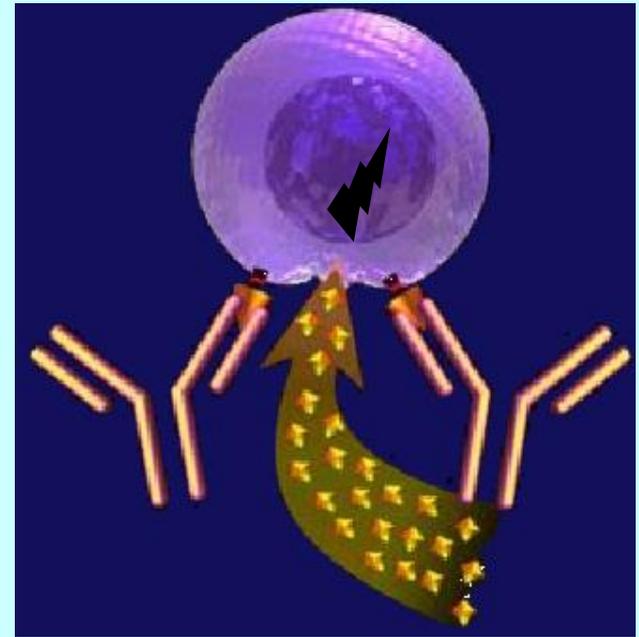
# *Cold antibodies - mechanisms*



**Direct cytotoxicity**

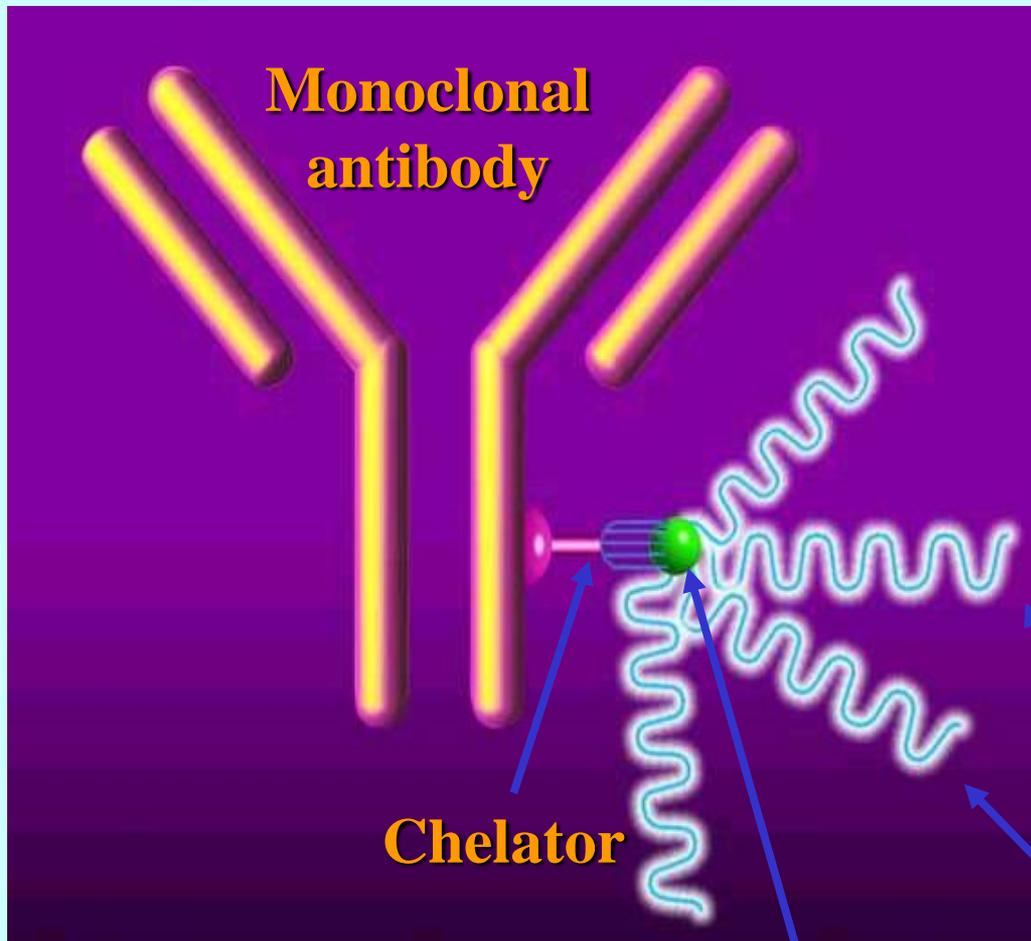


**Antibody-dependent  
Cellular cytotoxicity**



**Complement dependent  
Cytotoxicity**

# ***Zevalin® (<sup>90</sup>Y-Ibritumomab Tiuxetan)*** ***radioimmunoconjugate***



## ◆ **Ibritumomab**

- Mouse monoclonal antibody

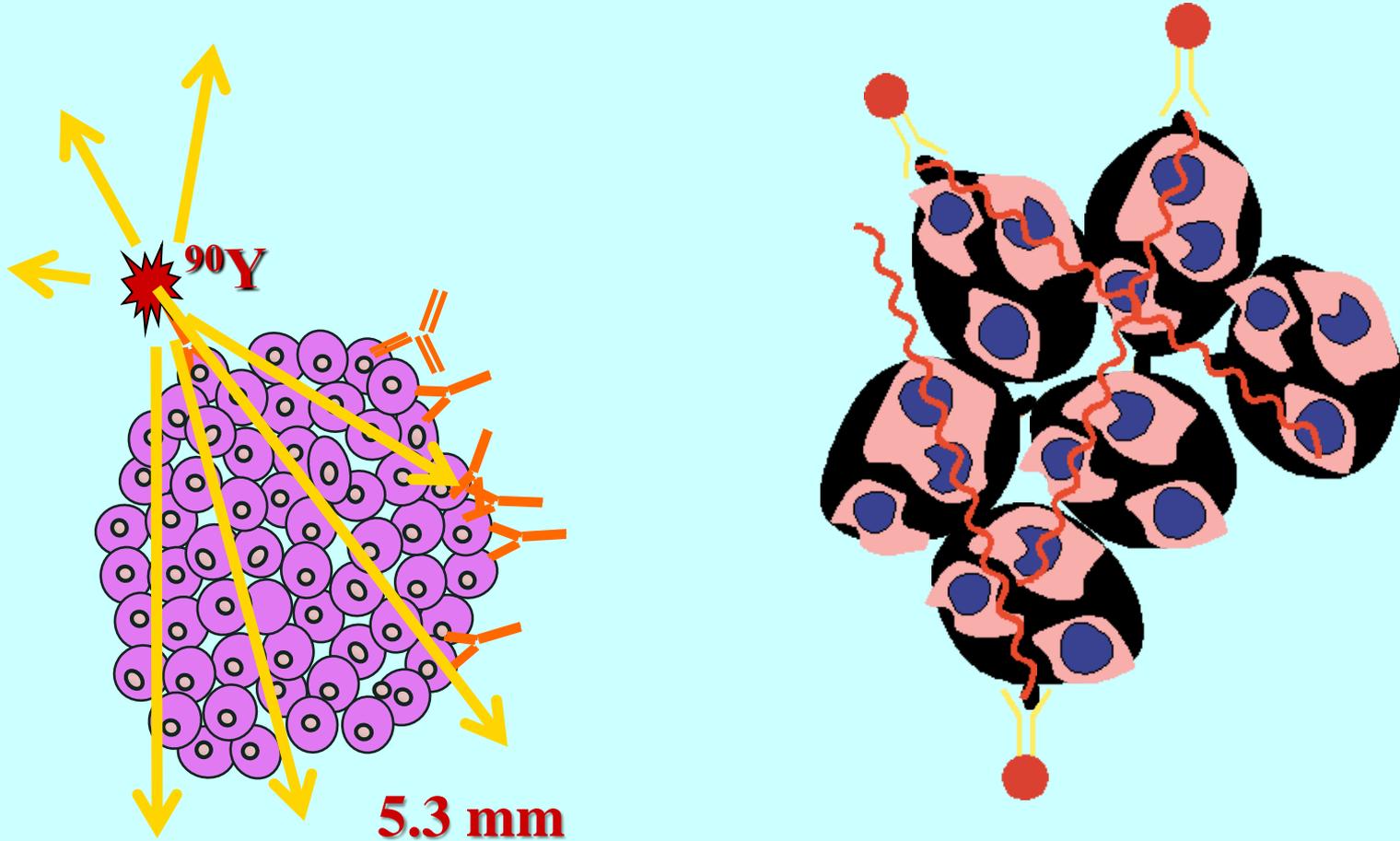
## ◆ **Tiuxetan (MX-DTPA)**

- Conjugates with antibody, enables stable retention of radiolabel <sup>90</sup>Yttrium

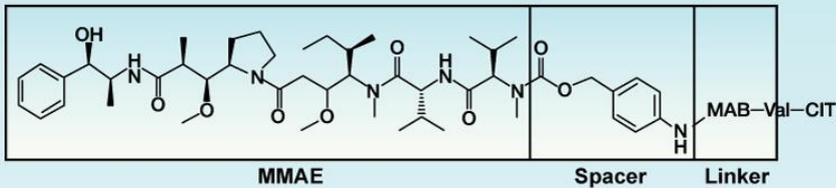
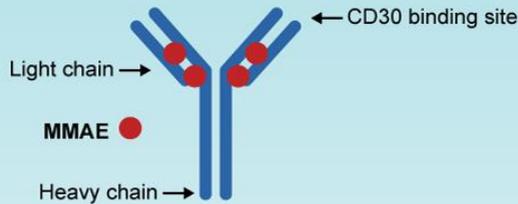
**Beta radiation**

**<sup>90</sup>Y radionuclide**

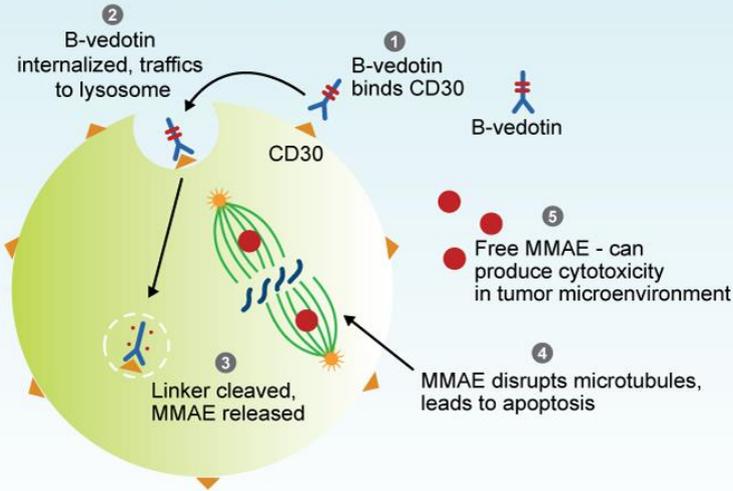
# *Crossfire effect of immunoconjugate*



### Structure of Brentuximab Vedotin (B-Vedotin)



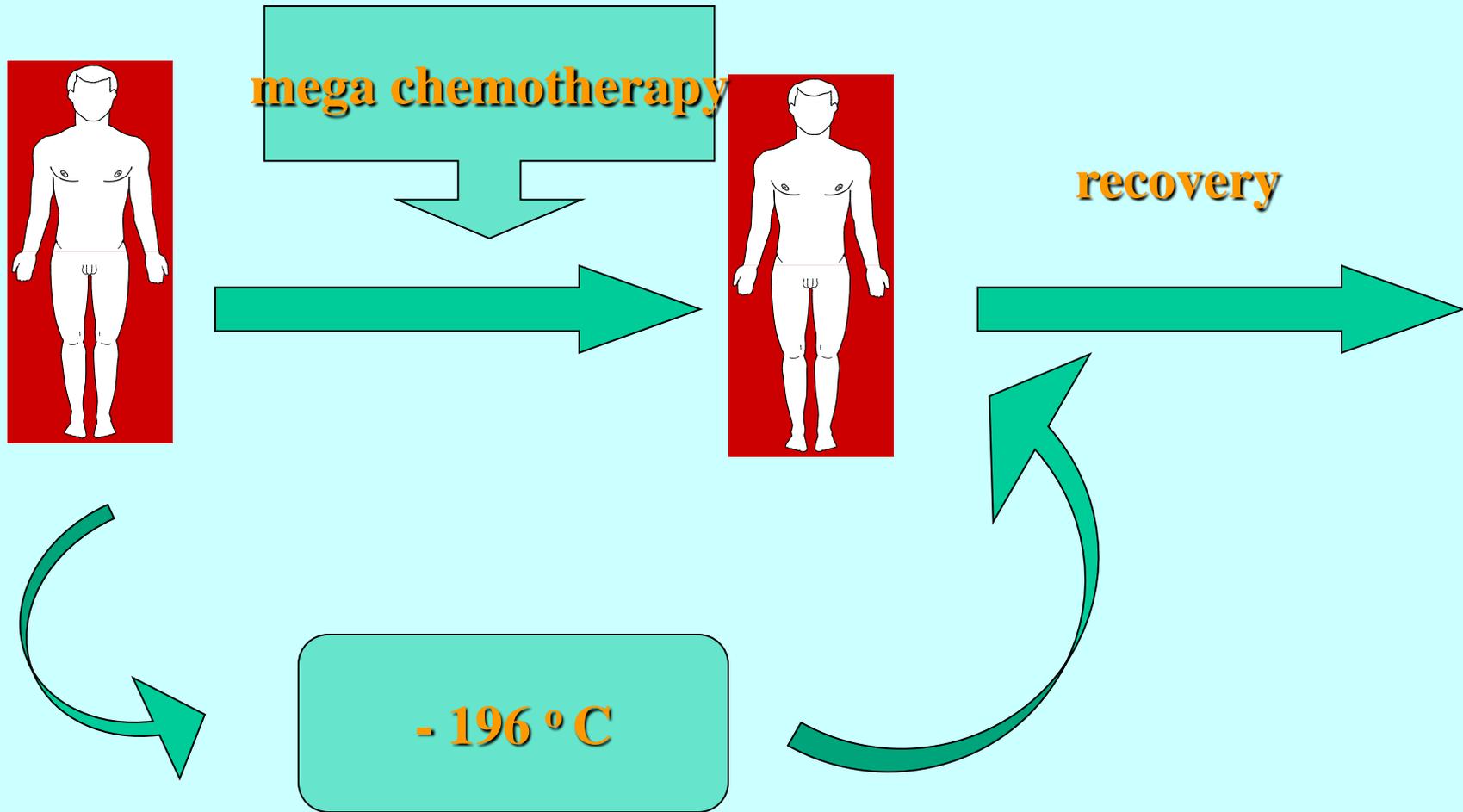
### ADC Internalization Process



ADC = antibody-drug conjugate; MAB = monoclonal antibody; MMAE = monomethyl auristatin E (microtubule-disrupting agent)

***Brentuximab vedotin (Adcetris): anti-CD30 + monomethyl auristatin E (MMAE)***

# *Autologous transplantation*



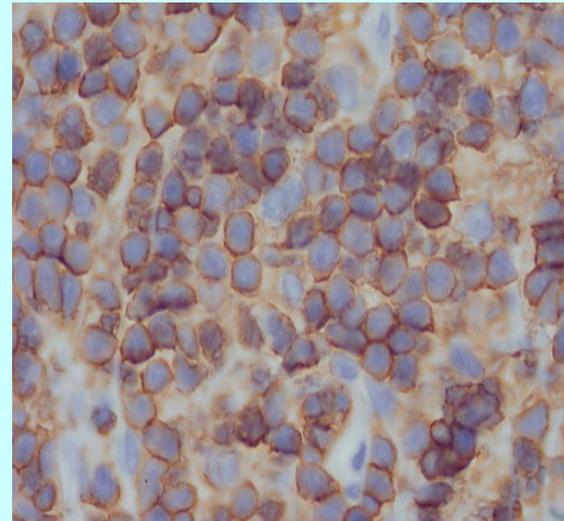
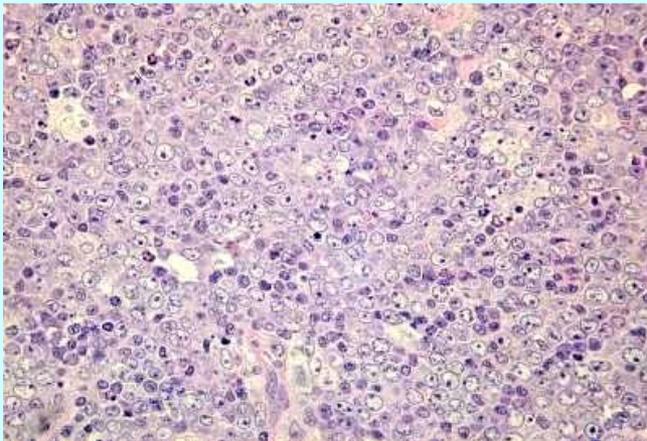
# *How to evaluate treatment response?*

- **Complete remission** – negative CT (PET-CT), bone marrow, normal laboratory, no symptoms...
- **Partial remission** – more than 50% regression
- **Stable disease** – less than PR, but no progression
- **Progression, relapse** – new lesion or increase of existing lesion 50% or more
- **Minimal residual disease** – can be found only by very sensitive methods (FACS, molecular biology...)

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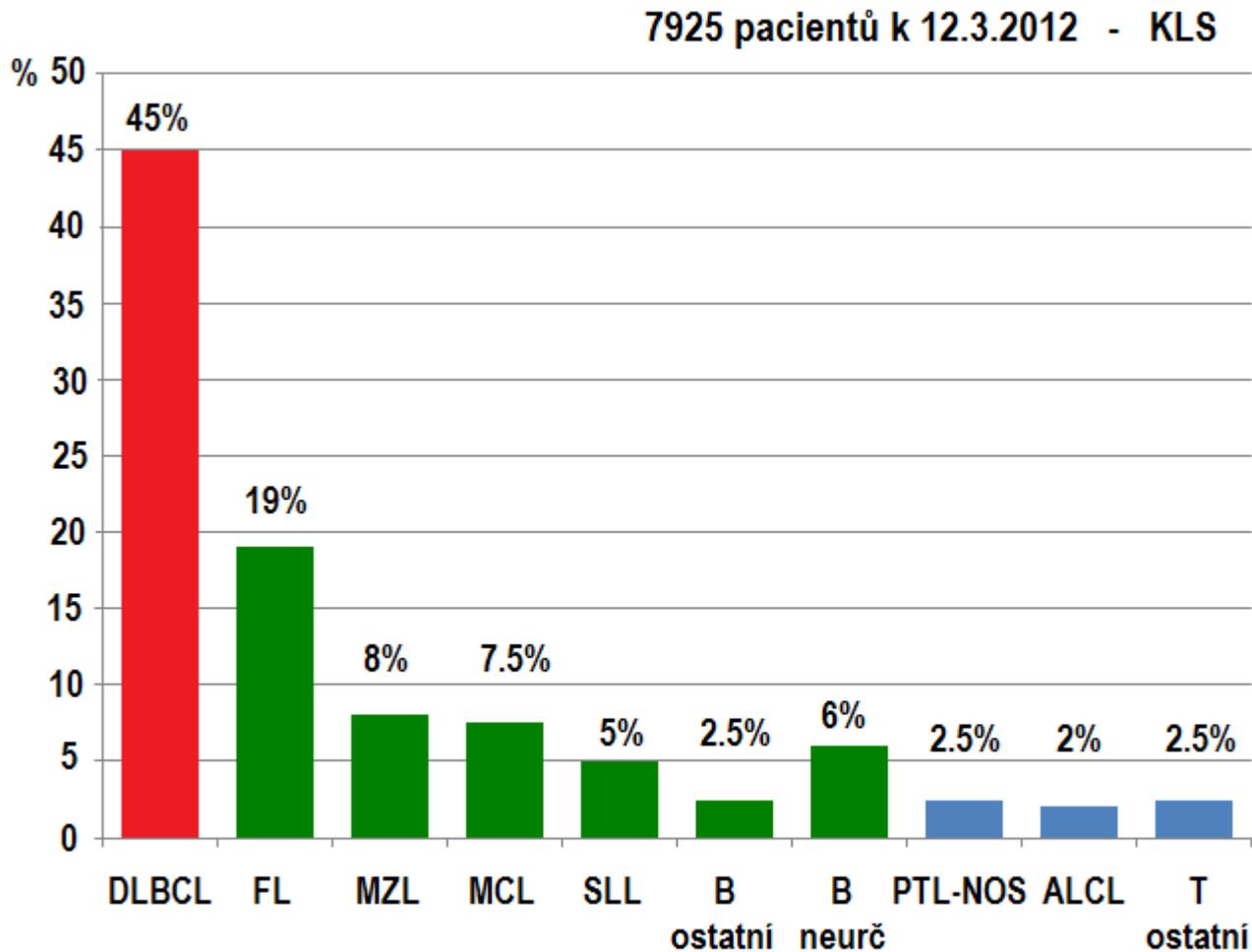
# *Léčba*

- **8x G-CHOP... Parciální remise PET pozitivní**
- **2x R-DHAP: dtto**
- **BEAM + autologní transplantace – kompletní remise PET-negativní**
- **Ozáření obou stran krku**
- **Zajištění lamivudinem (HbSAg pozitivita)**

# Pacientka KH 1950 – květen 2016



# *Non-Hodgkin's lymphomas in Czech republic (KLS, 2012)*



# *Diffuse large B-cell lymphoma (DLBCL)*

- **Aggressive, CD20 positive**
- **Not homogenous disease: GC, ABC, mediastinal B-lymphoma, primary CNS lymphoma ...**
- **Oncogenes: Bcl-2 - t(14;18), Bcl-6 – t(3;14), c-myc – t(8;14)**
- **Double and triple hit lymphomas**
- **Median age >60 years**
- **15-20% have bone marrow infiltration**
- **B-symptoms frequent**

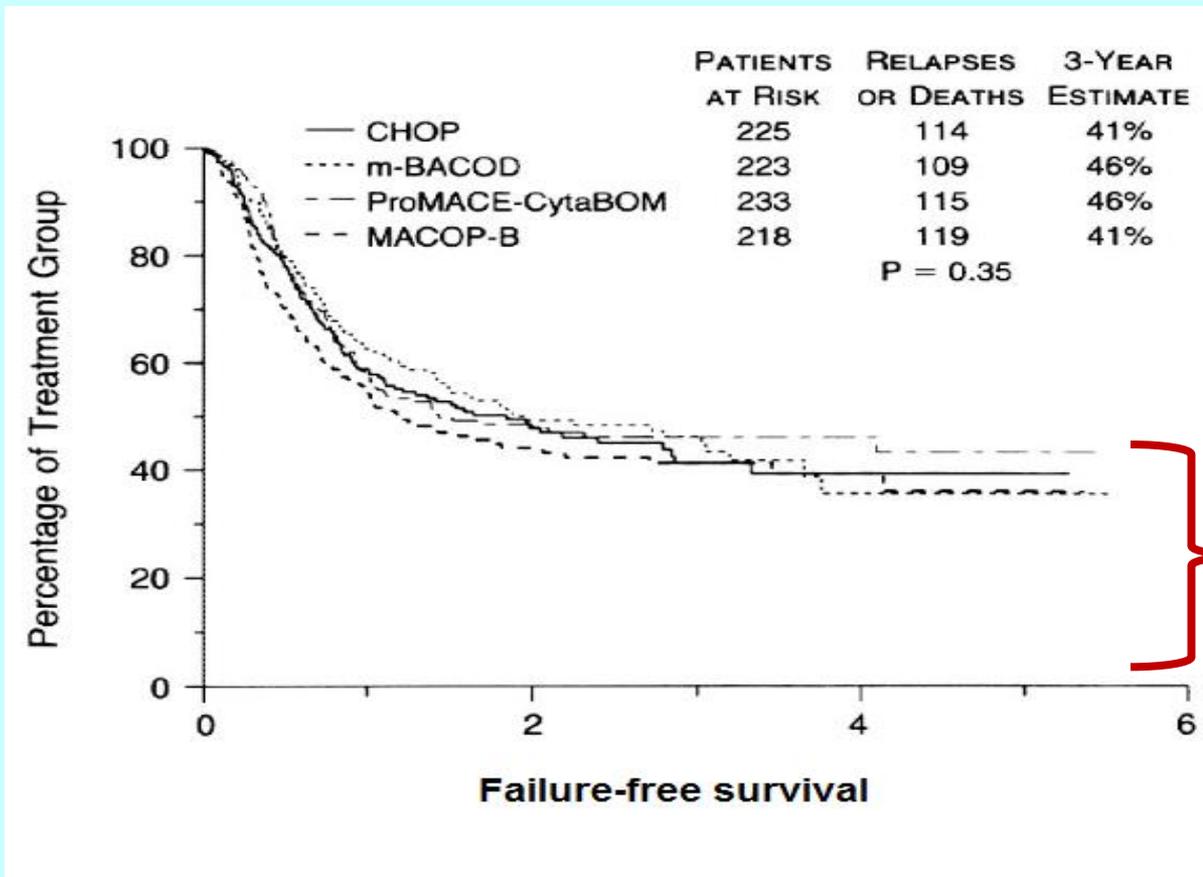
# *Natural history of aggressive lymphomas:*

- **Fast presentation (weeks, months...)**
- **Often B-symptoms**
- **Immediate therapy allways needed**
- **Curable, but...**
- **Treatment failure allways means poor prognosis**

# *How to approach DLBCL at diagnosis*

- **!! Always chemoimmunotherapy (R-CHOP) – even in stage I disease!! (DLBCL is CD20+)**
- **Radiotherapy only in bulky disease (>10 cm) or according to PET**
- **Patient who does not achieve PET-.negative complete remission after first-line treatment, continues salvage treatment immediately**

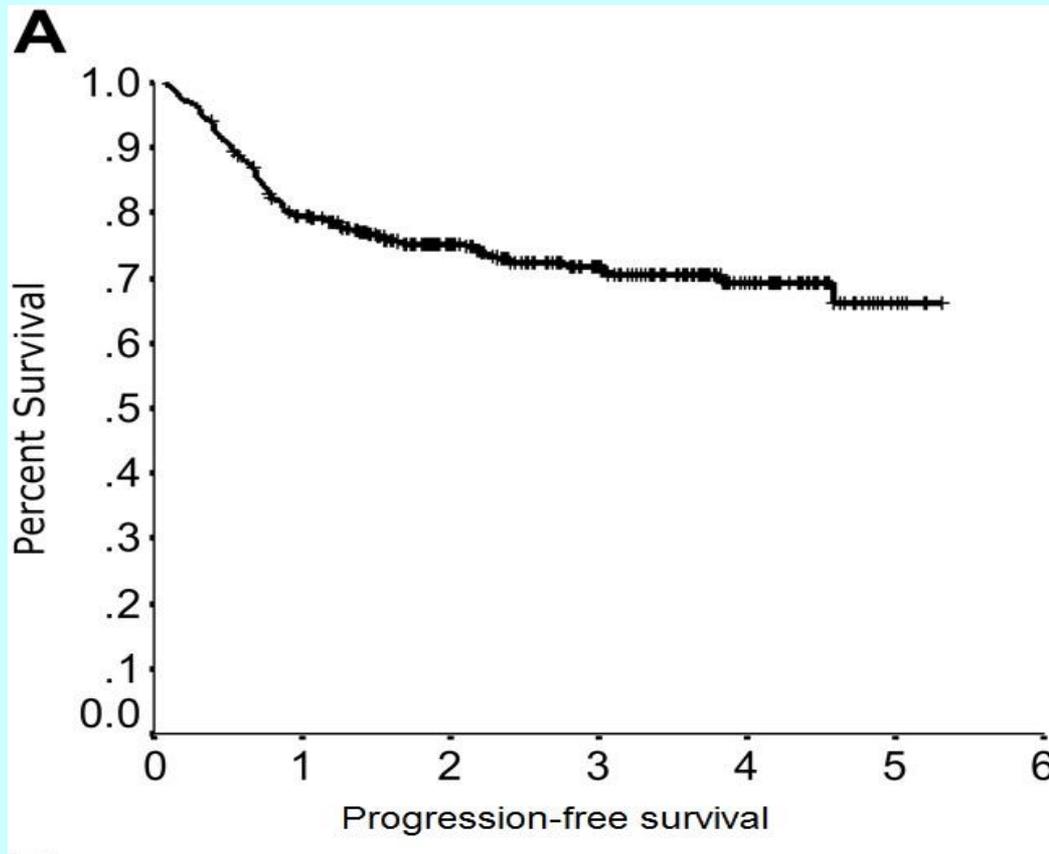
# *DLBCL: fate of patients before rituximab*



**30-40%  
cured**

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**50-60%  
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# *DLBCL prognosis - R-IPI:*

**0 risk factors**

**10% patients**

**94% PFS at 4 years**

**1-2 risk factors**

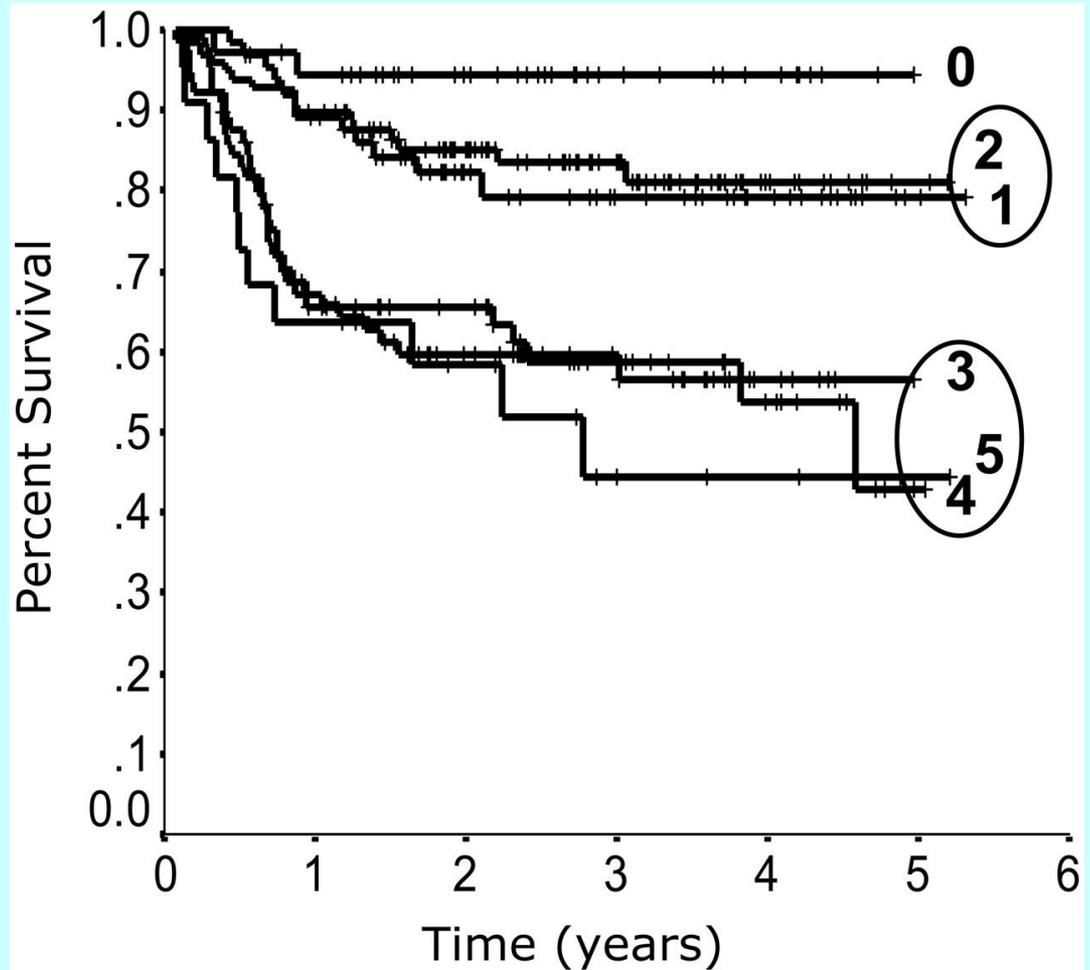
**45% patients**

**80% PFS at 4 years**

**3-5 risk factors**

**45% patients**

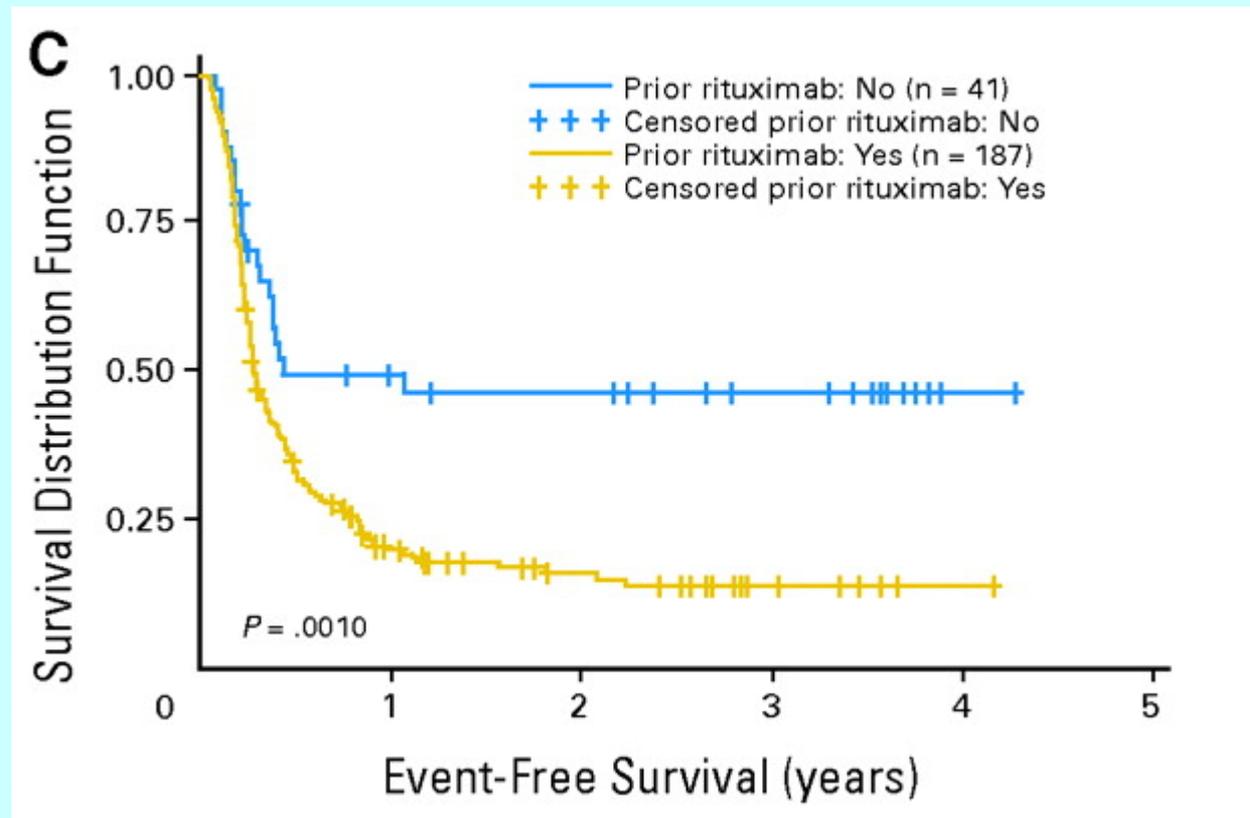
**53% PFS at 4 years**



# *Approach to DLBCL at relapse*

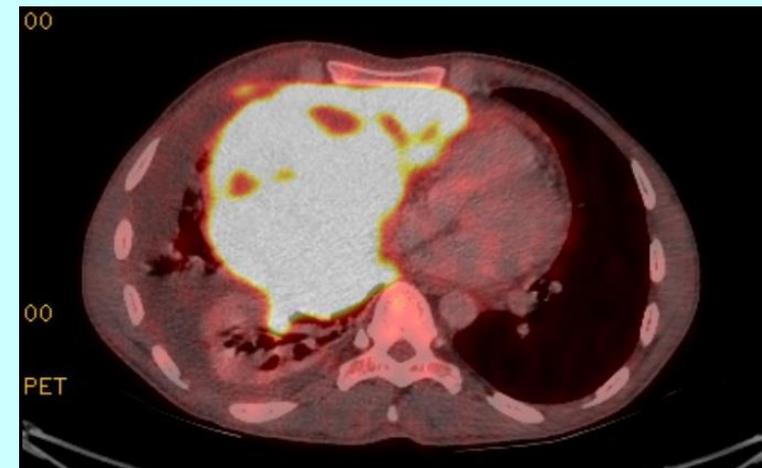
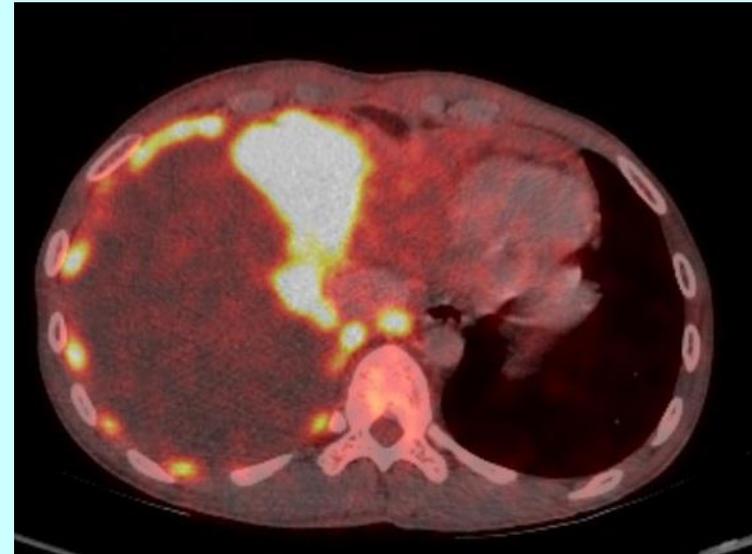
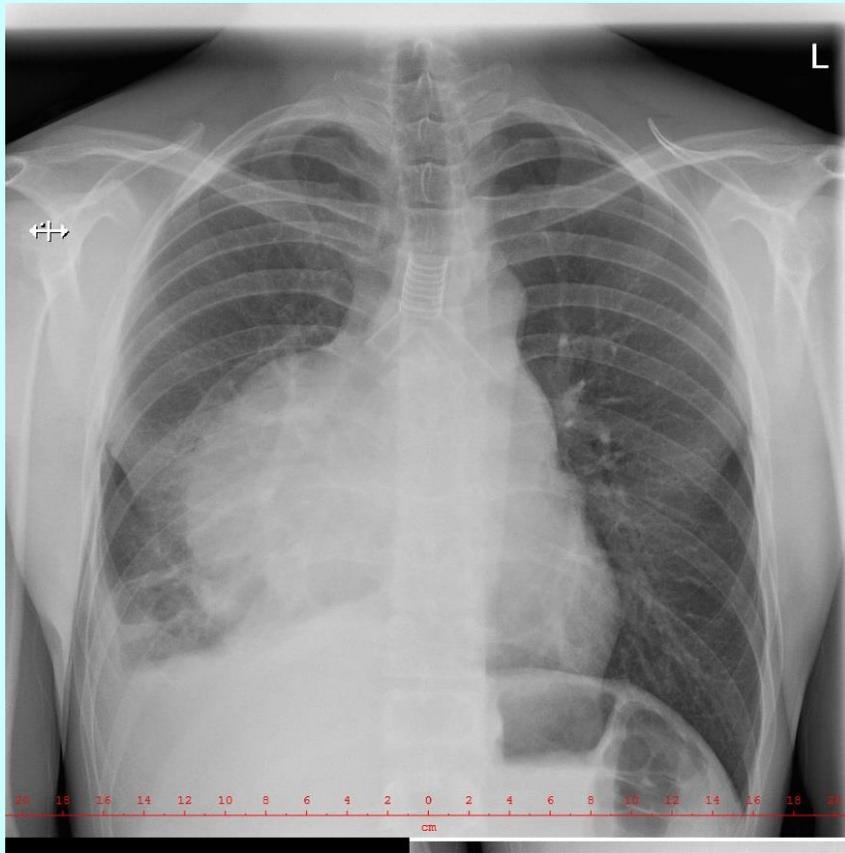
- **Curative v. Palliative treatment**
- **Salvage regimens: R + cisplatin, carboplatin, etoposide, steroids**
- **Autologous transplant if possible (in patients responding to salvage treatment, up to 65-70 years)**

# *Salvage therapy in DLBCL: platinum-based regimen + ASCT (with rituximab)*



**Relapse < 12 months after treatment**

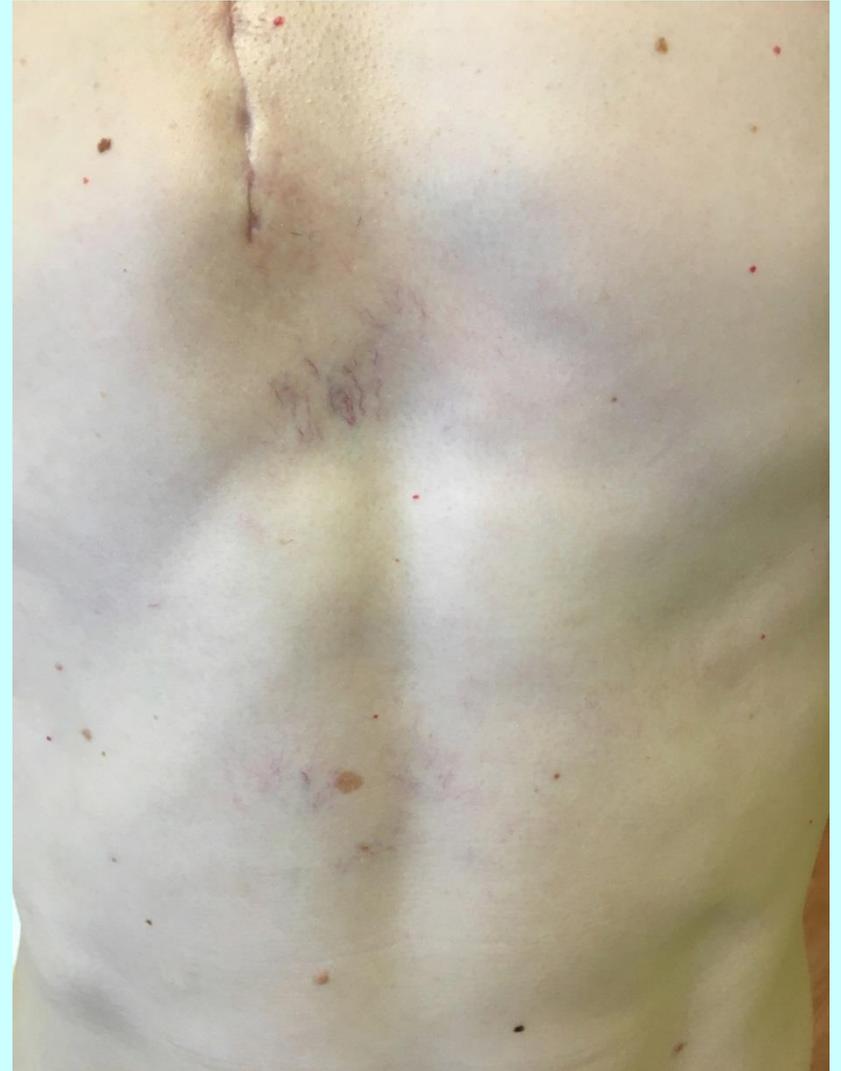
# *K-M, 1985, muž, primární mediastinální B-lymfom*



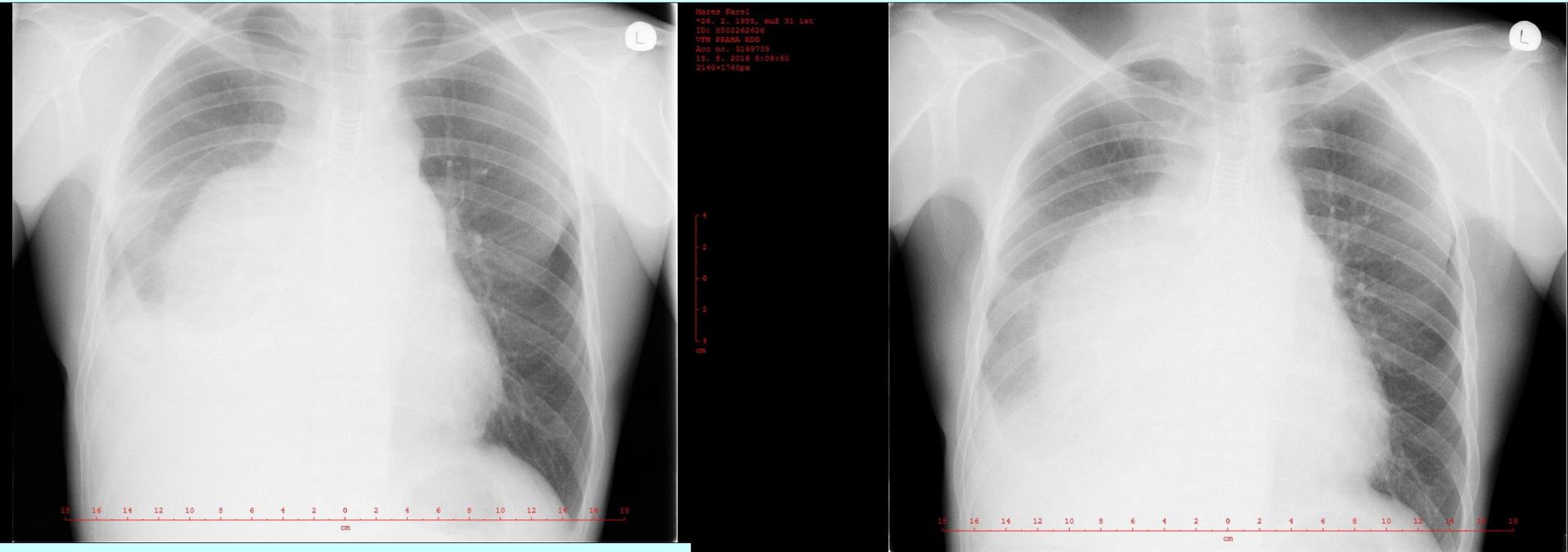
## *K-M, 1985, muž, primární mediastinální B-lymfom (2)*

- **Léčba úvodní: 6x R-CHOP s kurativním záměrem**
- **Při dosažení PET-negativity či jen reziduální PET-pozitivity po léčbě: radioterapie mediastinálního rezidua**
- **Při persistenci nemoci na pleuře – záchranná léčba (R-ESHAP + ASCT) plus záření mediastina**

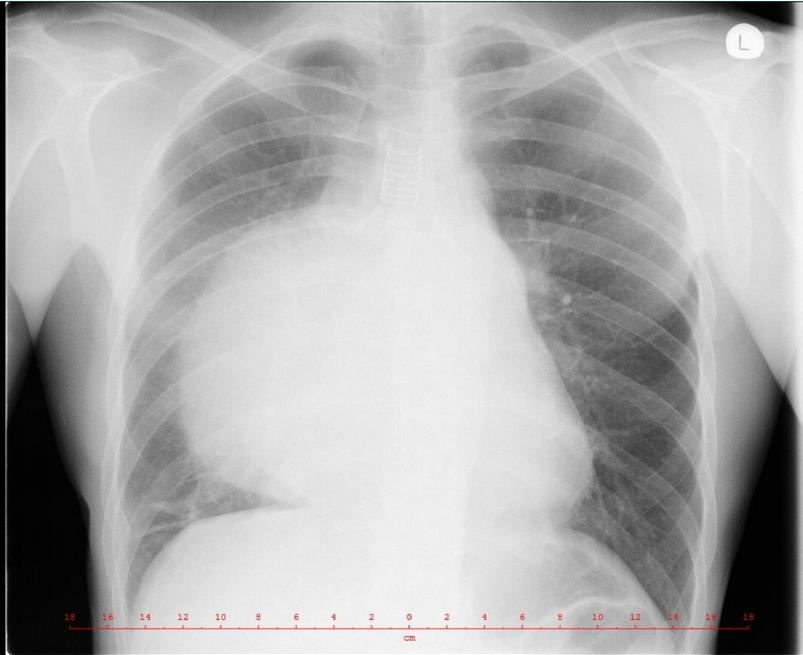
***K-M, 1985, muž, primární  
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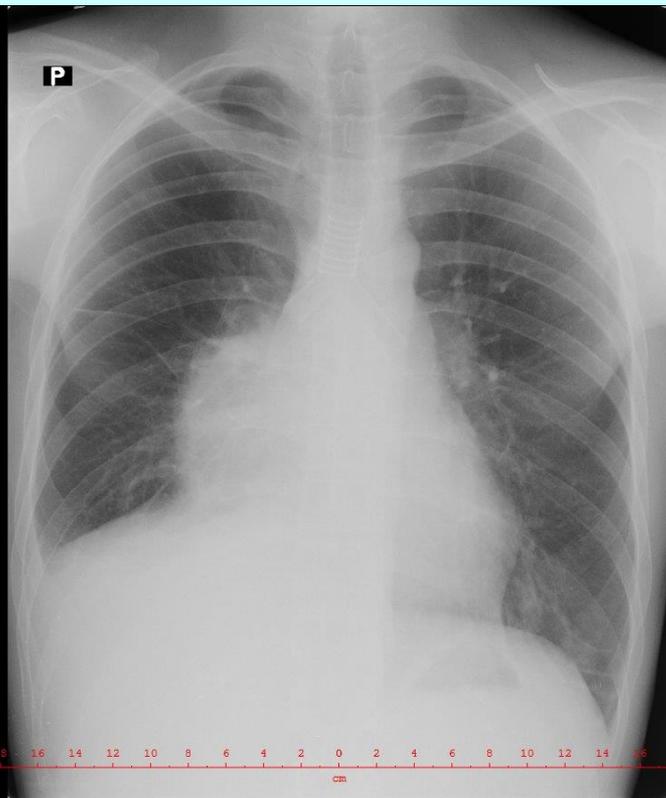
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# *K-M, 1985, muž, primární mediastinální B-lymfom (5)*

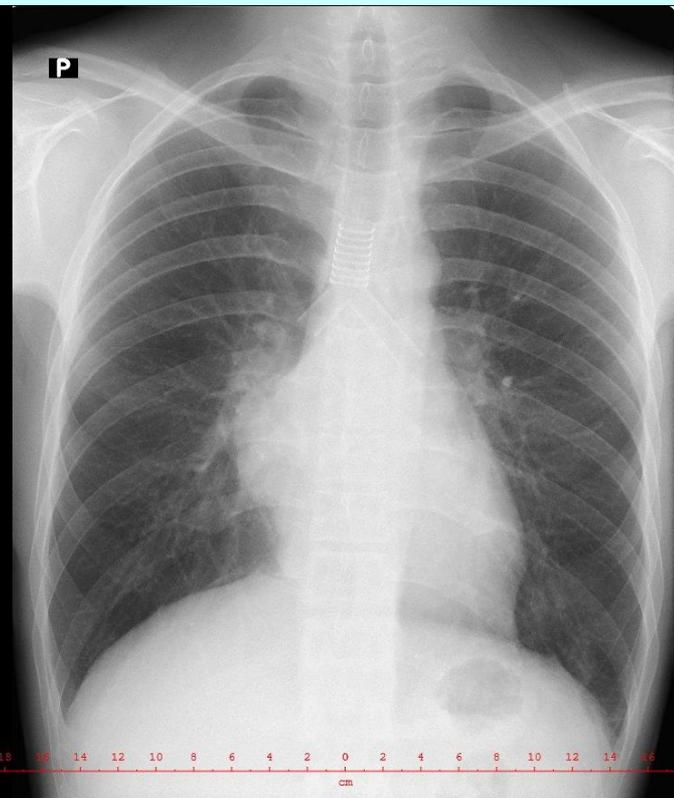


# *K-M, 1985, muž, primární mediastinální B-lymfom (6)*



Mares Karel  
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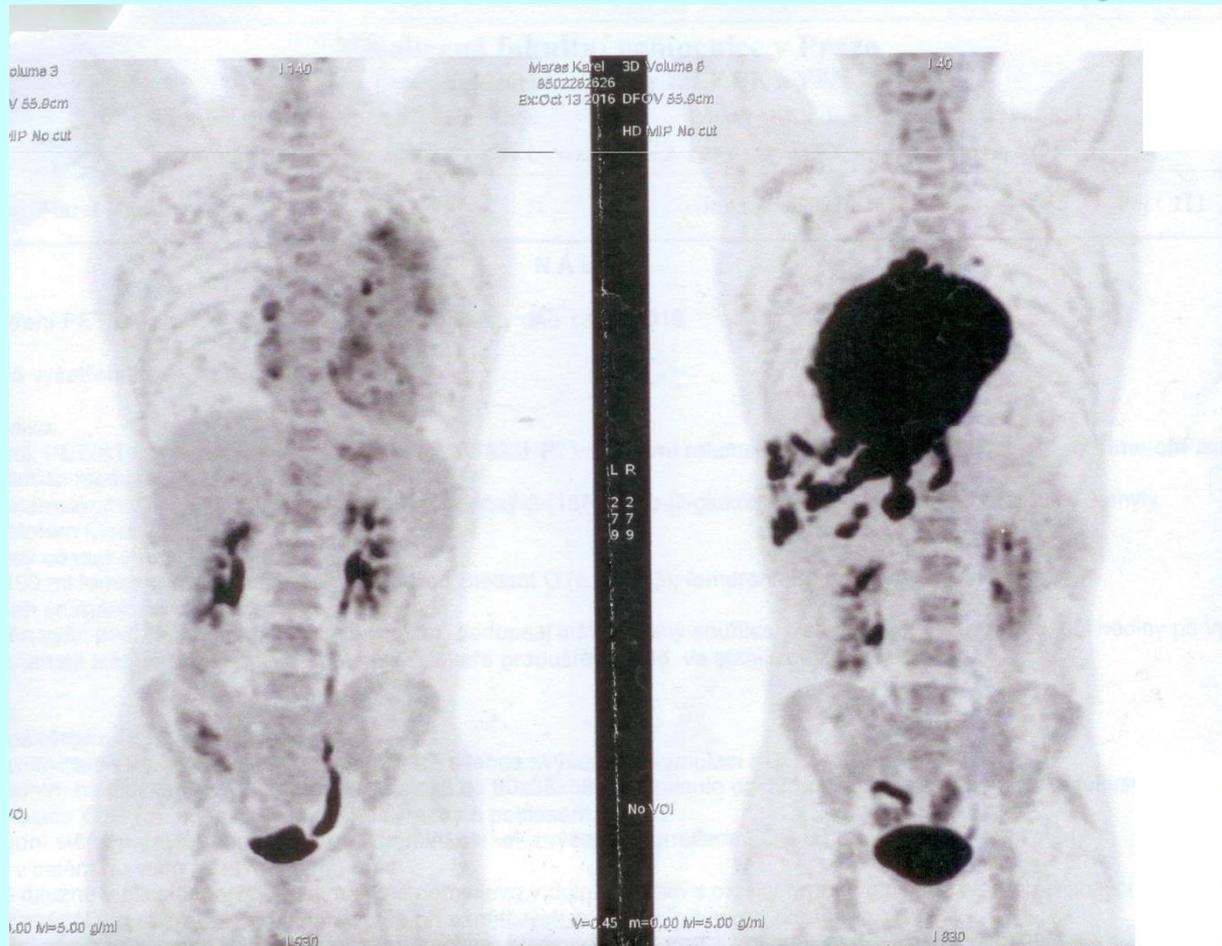
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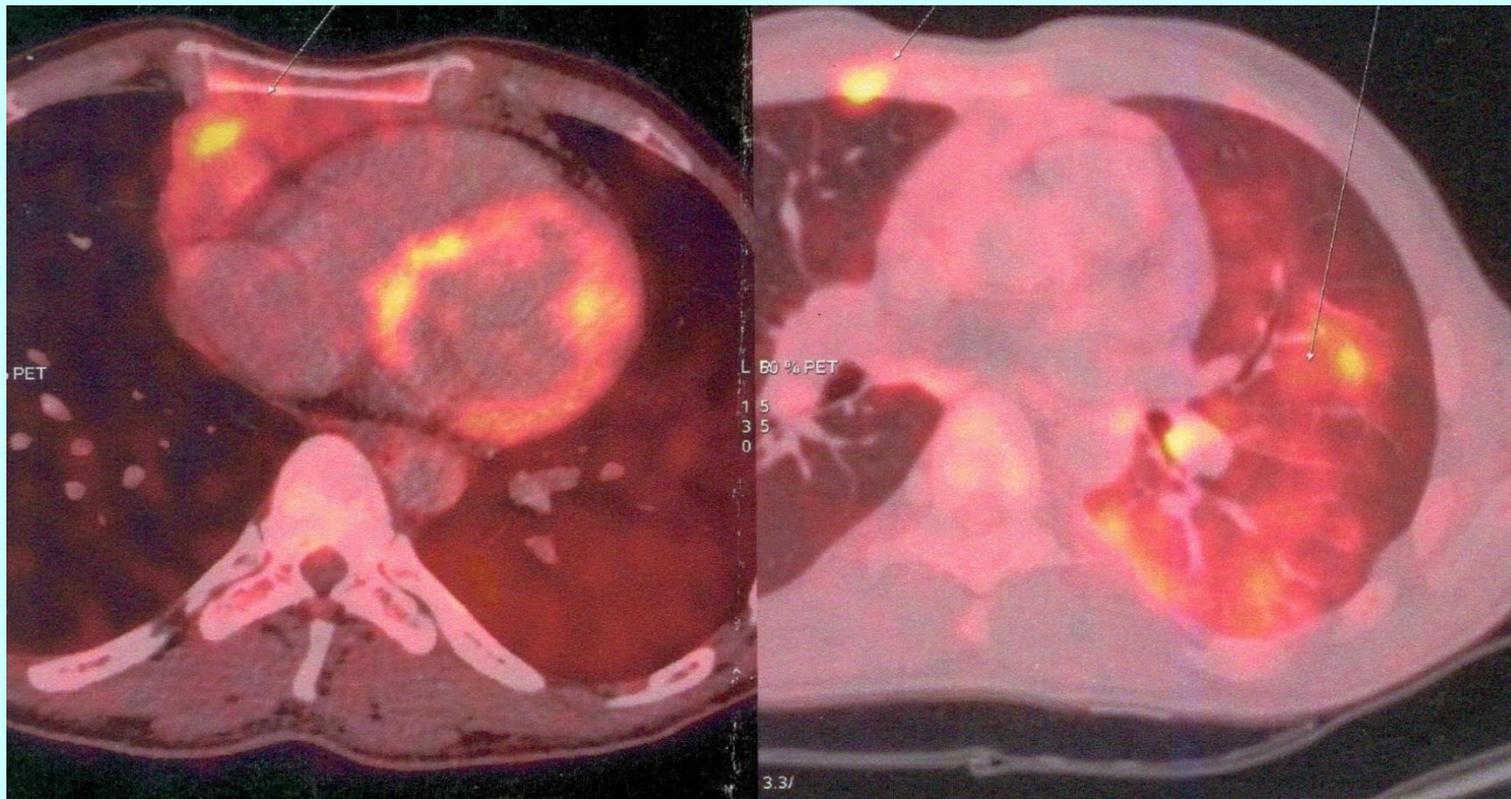
# *K-M, 1985, muž, primární mediastinální B-lymfom (7)*



**PET-CT z 9.8.16  
(vpravo),**

**Ze 13.10.2016  
(vlevo)**

# *K-M, 1985, muž, primární mediastinální B-lymfom (8)*

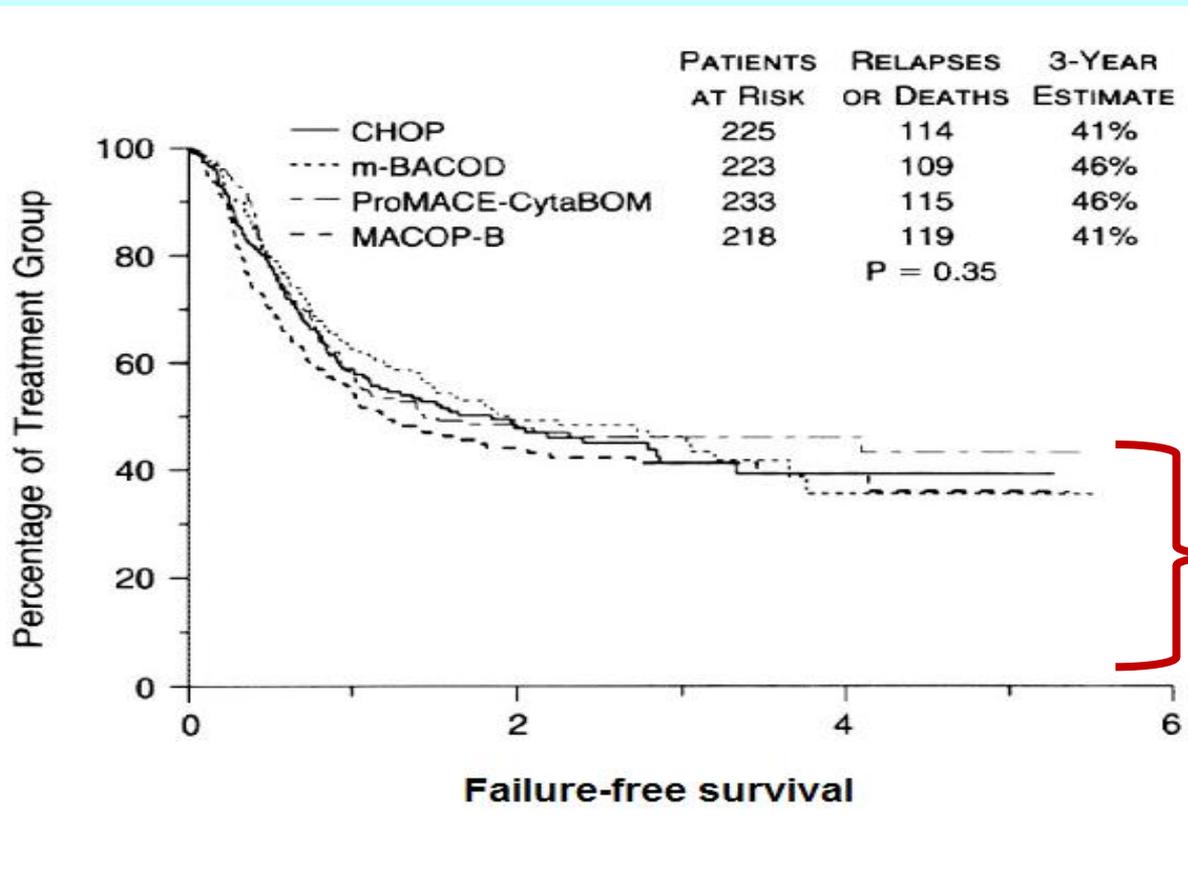


**PET-CT z 13.10.16 – levostranná atypická pneumonie**

# *How to approach DLBCL at diagnosis*

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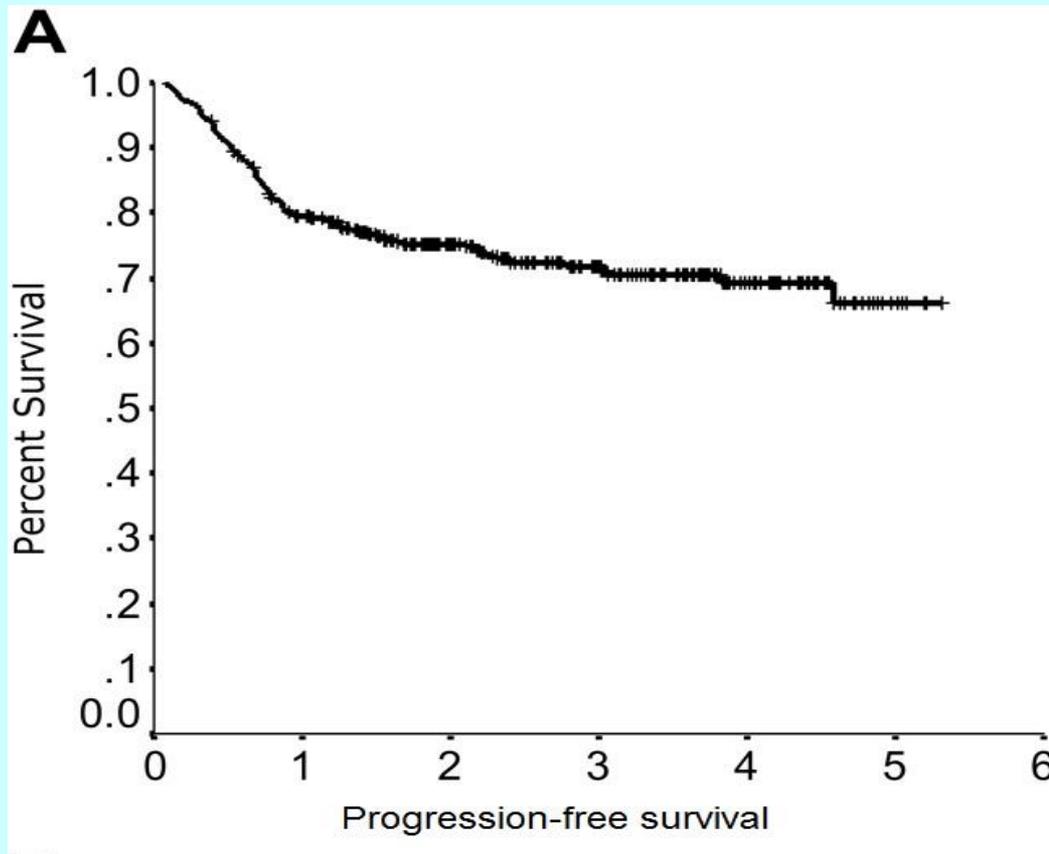
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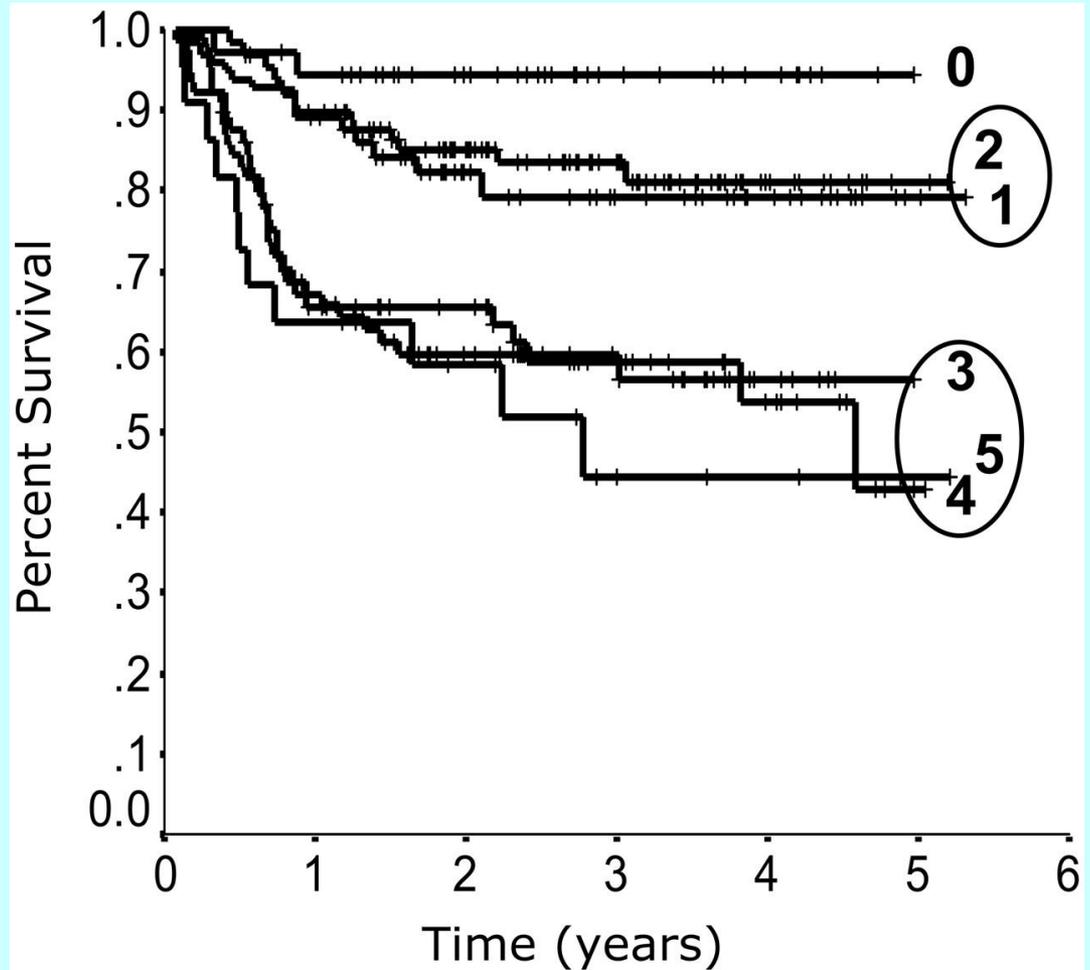
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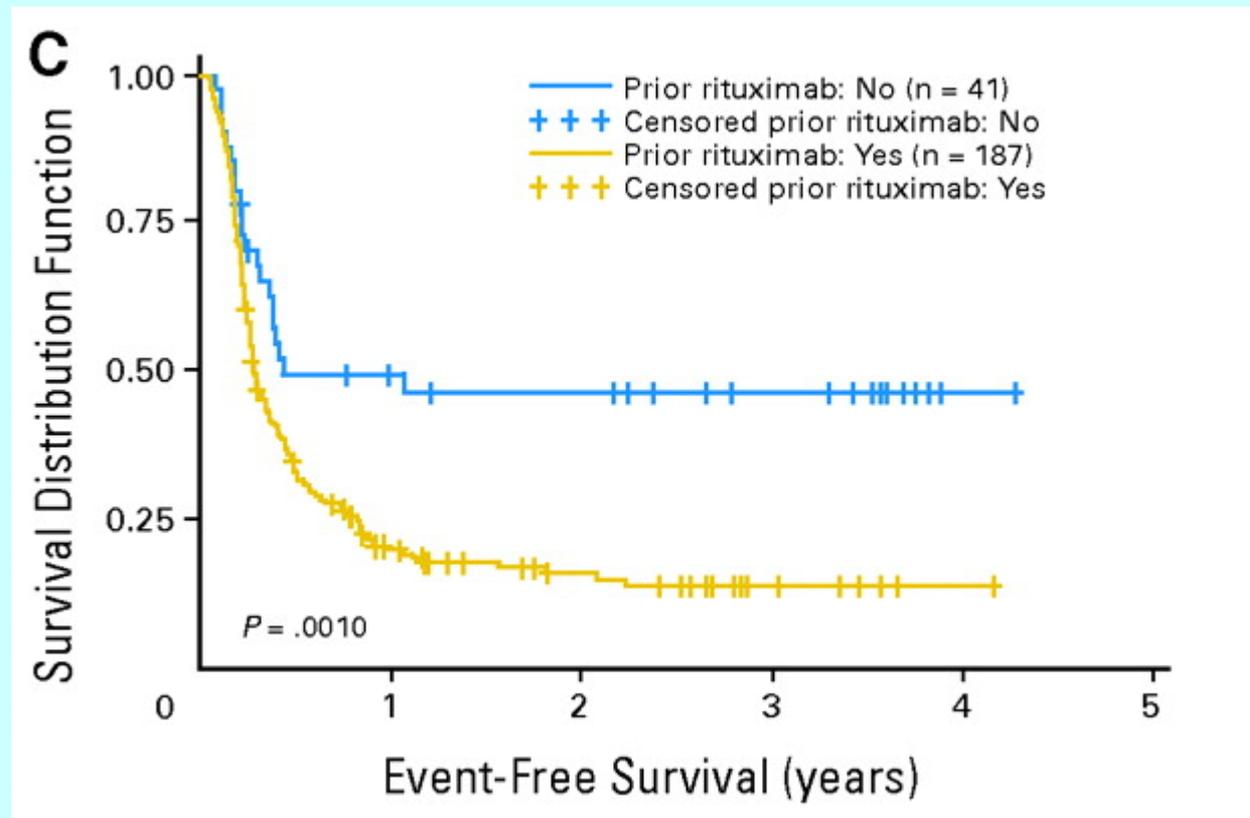
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# *Approach to DLBCL at relapse*

- **Curative v. Palliative treatment**
- **Salvage regimens: R + cisplatin, carboplatin, etoposide, steroids**
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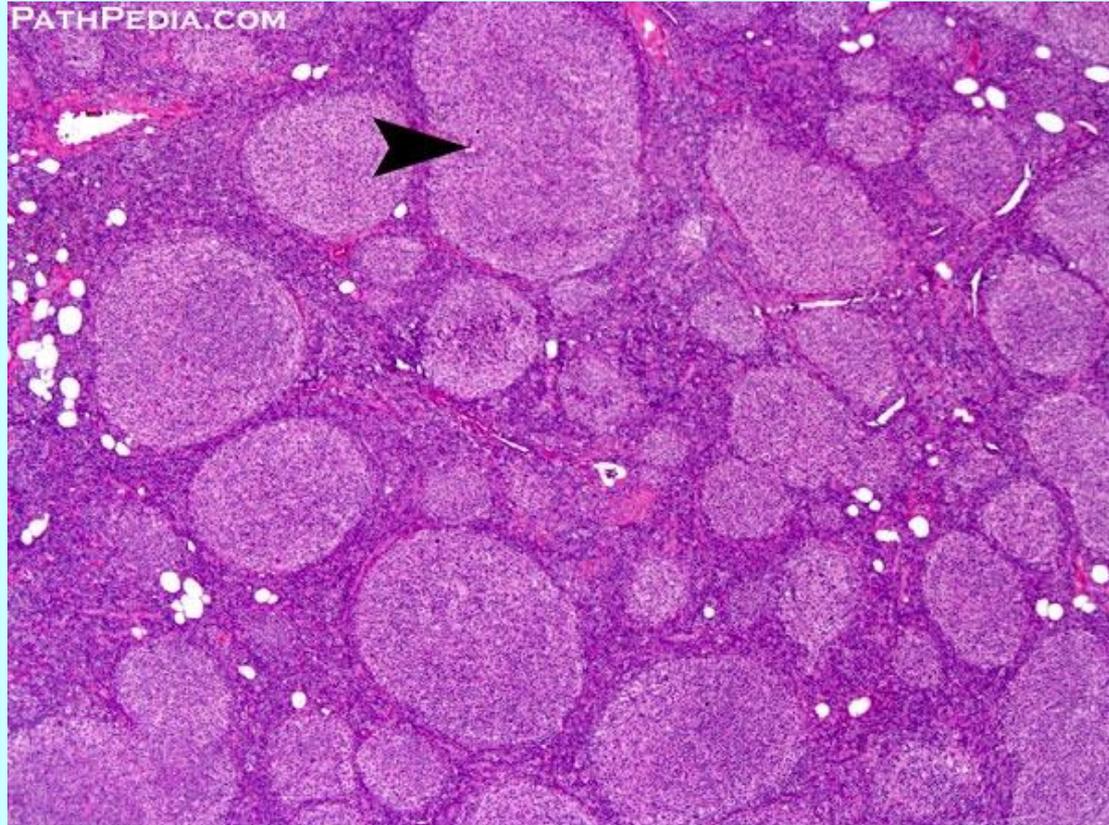


**Relapse < 12 months after treatment**

*Example of indolent  
lymphoma:*

***FOLLICULAR LYMPHOMA  
(FL)***

# *Morphology: hematoxylin-eosin*



**Follicular lymphoma**

# *Indolentní lymfomy*

- **dlouhá anamnéza: měsíce až roky**
- **většinou pokročilé onemocnění – nevléčitelné**
- **ale: není nutno vždy léčit již při diagnóze**
- **dobře zabírá na léčbu**
- **relaps (ani opakovaný) nemusí být katastrofou**
- **riziko transformace – změny do lymfomu s vyšším stupněm malignity**

# *FL - approach at diagnosis*

- **Patients with localized disease:**
  - localized radiotherapy
  - monotherapy antiCD20 (rituximab)
- **Advanced disease, no symptoms:**
  - watch and wait
  - monotherapy antiCD20 (rituximab)
- **Treatment indications (GELF, BNHL criteria):**
  - monotherapie antiCD20 (rituximab)
  - chemoimmunotherapy R-COP, R-CHOP) + rituximab maintenance

# *FL - approach at relapse (1., 2., 3....)*

- **Time to relapse x course (indolent, aggressive)**
- **!! New biopsy desirable (risk of transformation)**

## ➤ **Possible approaches:**

**Watch and wait again**

**Rituximab monotherapy**

**Radioimmunotherapy (Zevalin)**

**The same or different chemotherapy (R-COP, R-CHOP, fludarabine, bendamustin...)**

**Salvage treatment + autologous transplantation**

**Allogeneic transformation, but infrequently**

# *Follicular lymphoma - change in prognosis 1972-2002*

