

# MNOHOČETNÝ MYELOM – CO NOVÉHO V POSLEDNÍM PŮLSTOLETÍ Z POHLEDU FNO ?

V. Ščudla, J. Bačovský, M. Vytřasová, J. Minařík

## Postupný rozvoj

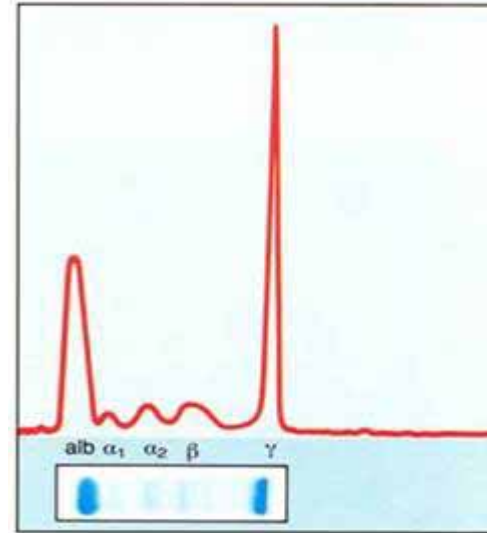
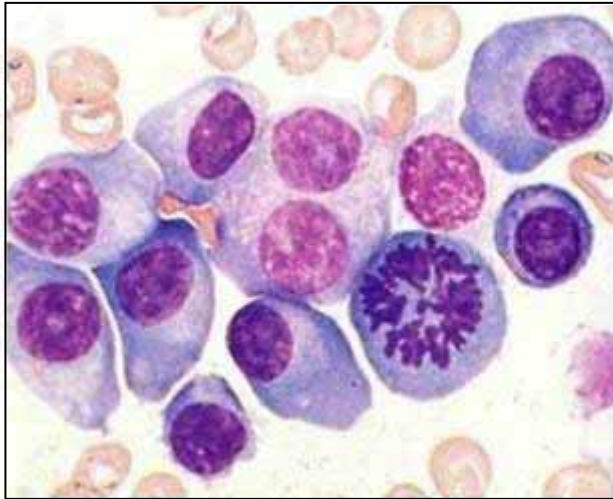
- diagnostických metod
- prognostických ukazatelů
- stážovacích systémů
- léčebných postupů

- *I. interní klinika < 1988*
- *III. interní klinika > 1988*
- *HOK*

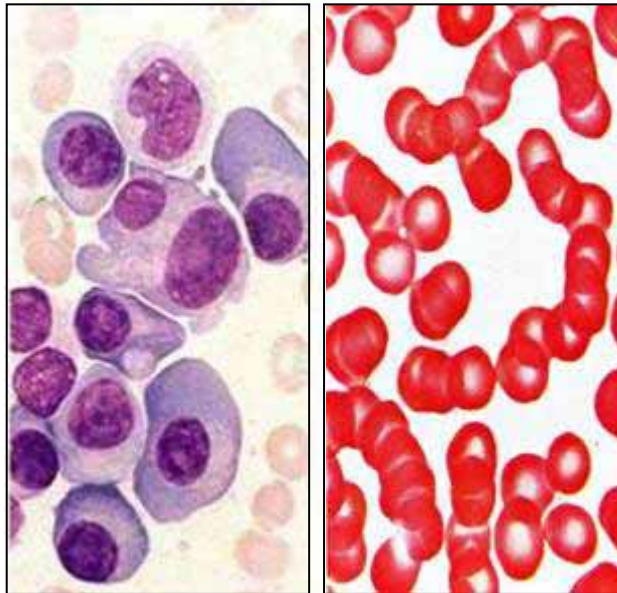
- *Ústav patologie*
- *Odd. klin. imunologie*
- *OKB*
- *Radiologická klinika*
- *KNM*
- *Onkologická klinika*



# MNOHOČETNÝ MYELOM



C  
R  
A  
B  
I



**MM – klonální, nekontrolovaná proliferace a akumulace neoplasticky transformovaných el. B-buněčné linie/plazmocytů (CD<sub>138</sub>+) provázená produkcí M-proteinu („paraprotein“) prokazatelného v séru nebo v moči a projevy orgánové dysfunkce „CRABI“**

**MM**

**NEOBYČEJNÁ HETEROGENITA**

Klinický  
obraz

Léčebná  
odezva  
KR-PR-NR

Trvání OR  
stabilní -  
„plateau“ fáze

Prognóza  
nemoci  
„EFS-OS“

**ODLIŠNÉ BIOLOGICKÉ VLASTNOSTI NÁDOR.  
TKÁNĚ – MIKRO/MAKROPROSTŘEDÍ**

**TERAPEUTICKÝ „TERČ“**

My.bb.

„Mikroprostředí“ KD

„Interakce“ My.bb vs organismus

Migrace

EC-matrix

OSB/OSK

cytokiny

Imunol.funkce

Proliferace/Apo

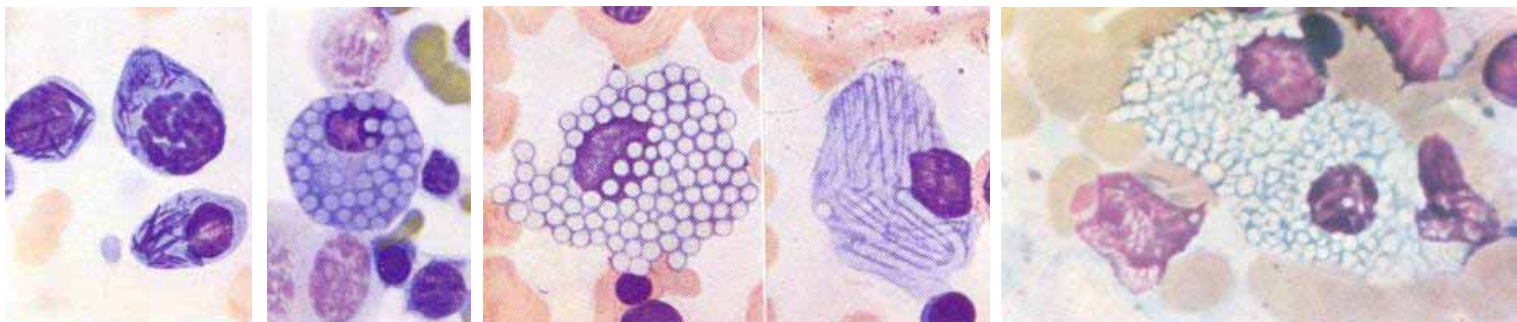
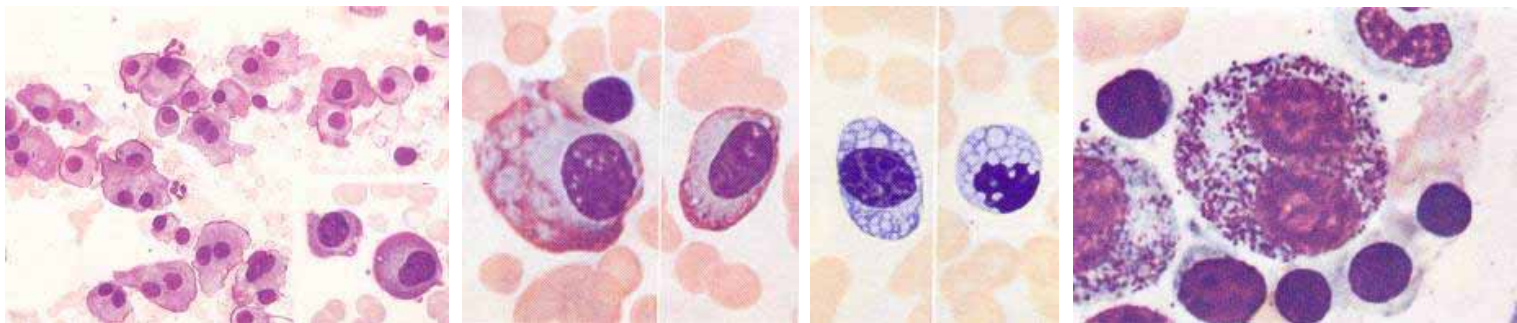
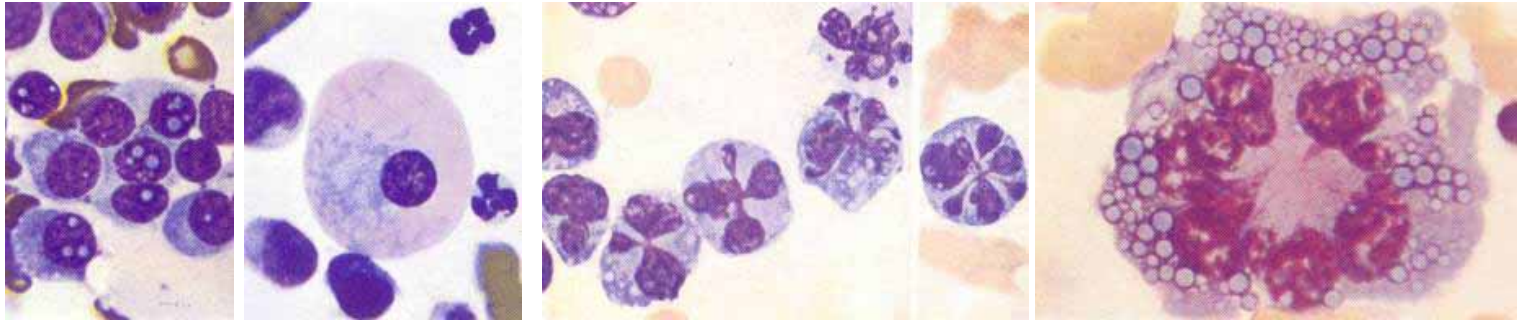
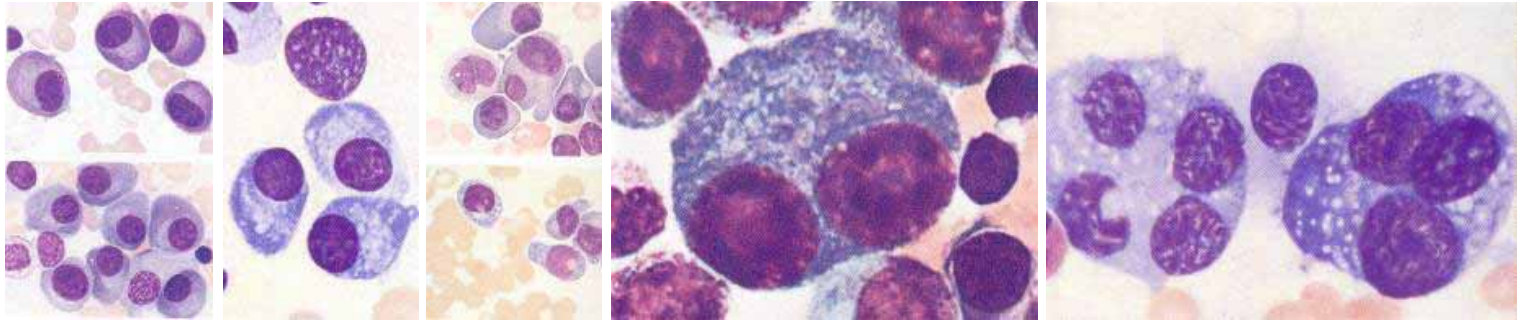
Rezistence

Bb.stromatu

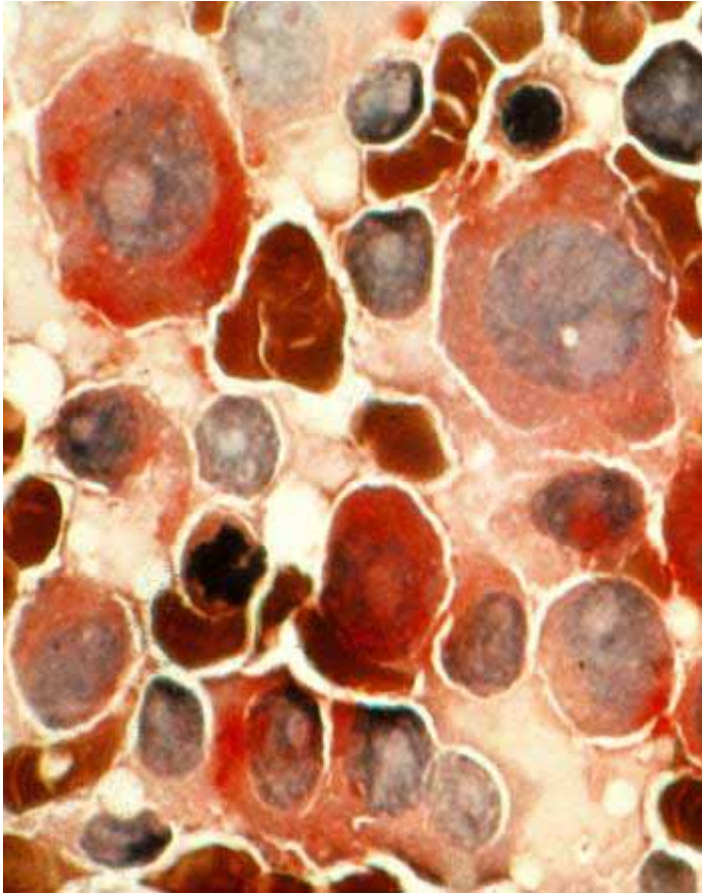
CAM

.....

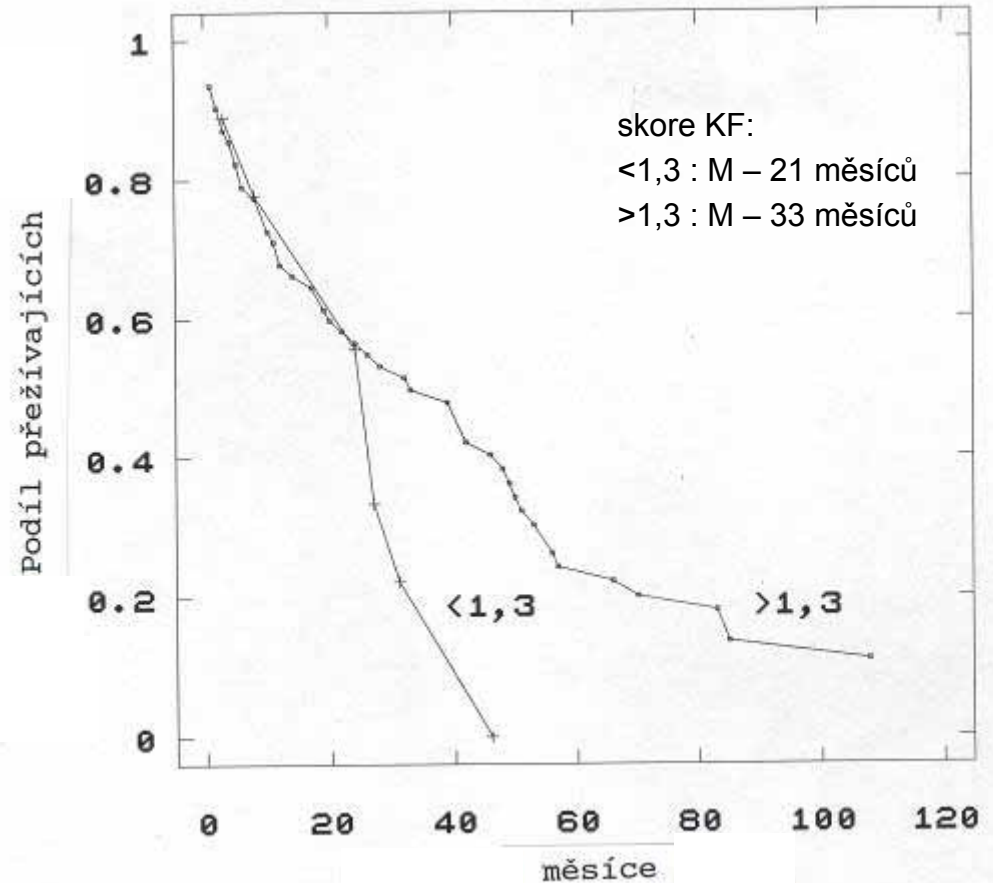
# MM – MORFOLOGIE



# MM – VZTAH SKORE KF K PROGNÓZE (OS)








*B. Wiedermann, A. Špidlová, 1979*



*J. Bačovský et al., 1992*

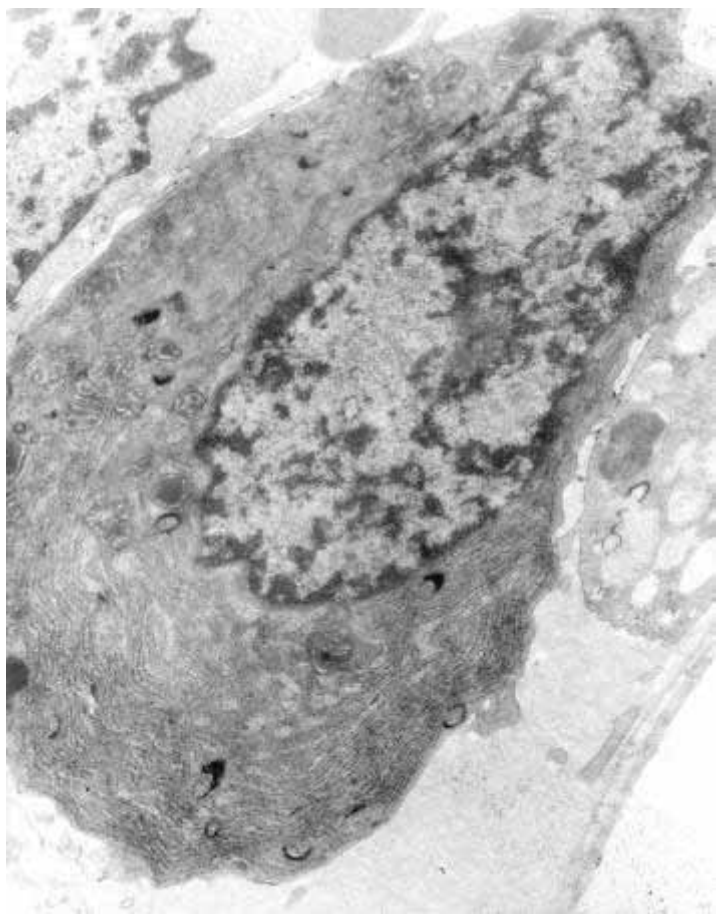
# MM – HODNOCENÍ NCA S POMOCÍ ELMÍ

DEGREE OF NUCLEO-CYTOPLASMIC ASYNCHRONY (NPA), Graham 1974 (modified by Kod'ousek & Kamarád 1979)	
 <p style="text-align: right; font-size: 2em; font-weight: bold;">0</p>	<p><u>NORMAL PLASMA CELLS</u> with synchronous maturation of the nucleus and cytoplasm.  <u>N</u>-coarsely condensed chromatin clumps on the nuclear membrane                      no nucleolus  <u>C</u>-mature appearance, with parallel arrangement of rough endoplasmic reticulum (RER)</p>
 <p style="text-align: right; font-size: 2em; font-weight: bold;">1</p>	<p><u>SLIGHT ASYNCHRONY</u>  <u>N</u>-disperse, small aggregates of chromatin, occasional medium-size nucleoli  <u>C</u>-mature</p>
 <p style="text-align: right; font-size: 2em; font-weight: bold;">2a</p>	<p><u>MODERATE ASYNCHRONY</u>  <u>N</u>-small residual aggregates of chromatin, conspicuous nucleolus  <u>C</u>-mature (see NPA-1)</p>
 <p style="text-align: right; font-size: 2em; font-weight: bold;">2b</p>	<p><u>MODERATE ASYNCHRONY</u>  <u>N</u>-similar to NPA-1  <u>C</u>-marked dilatation of tubules the RER</p>
 <p style="text-align: right; font-size: 2em; font-weight: bold;">3</p>	<p><u>MARKED ASYNCHRONY</u>  <u>N</u>-diffusely spread chromatin without clumping, large nucleolus  <u>C</u>-dilatation of RER</p>

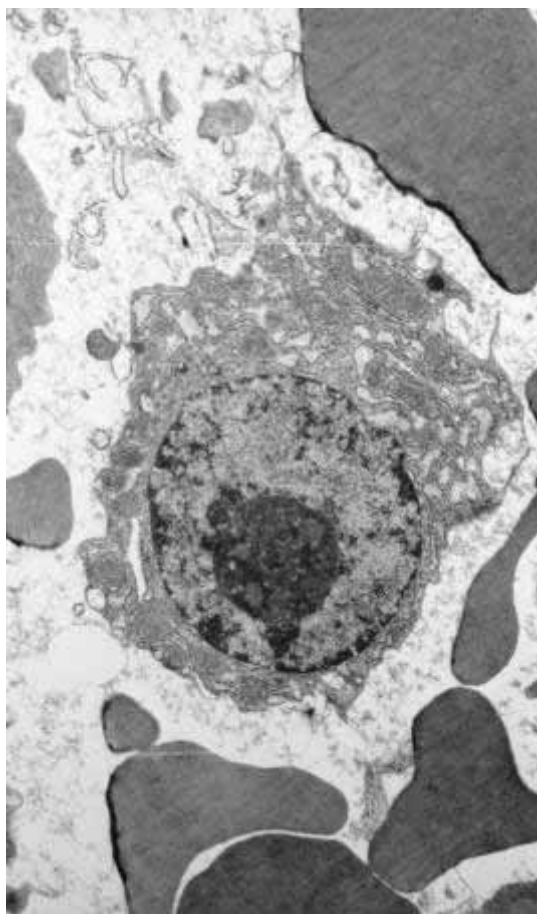
*R.Kod'ousek, V. Kamarád et al., 1979*

# MM – STUPEŇ JÁDRO-PLAZMOVÉ ASYNCHRONIE (NPA)

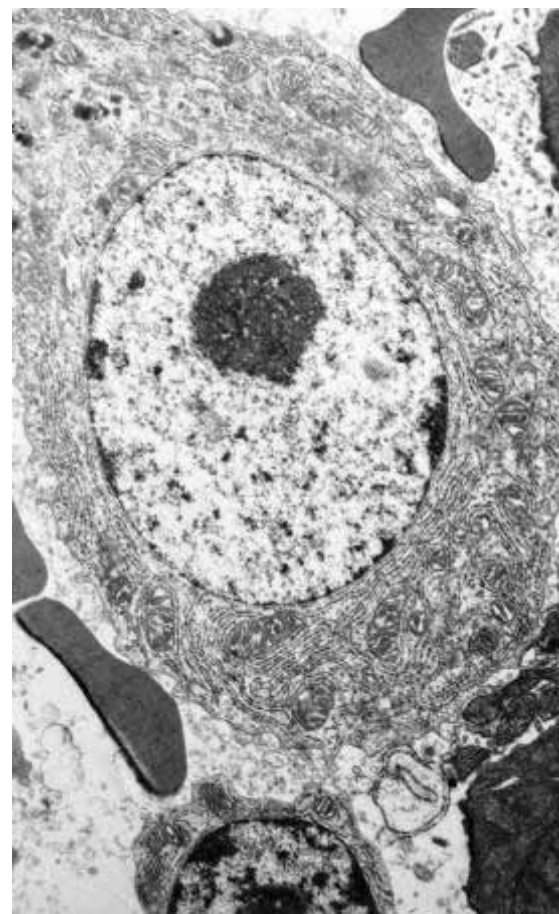
NPA-1



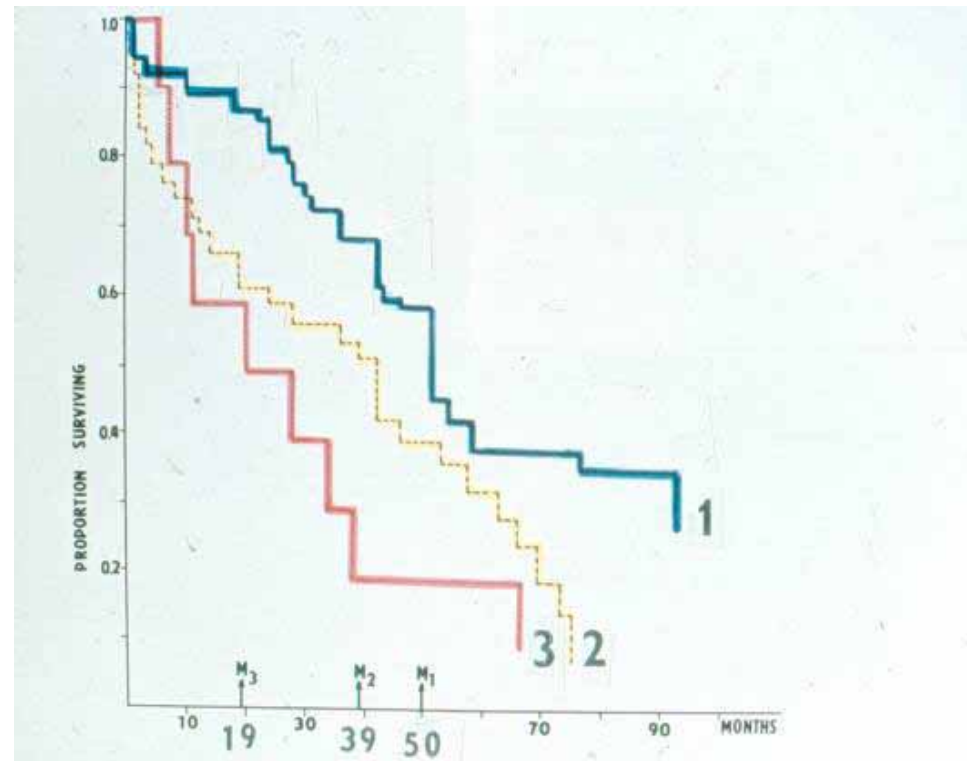
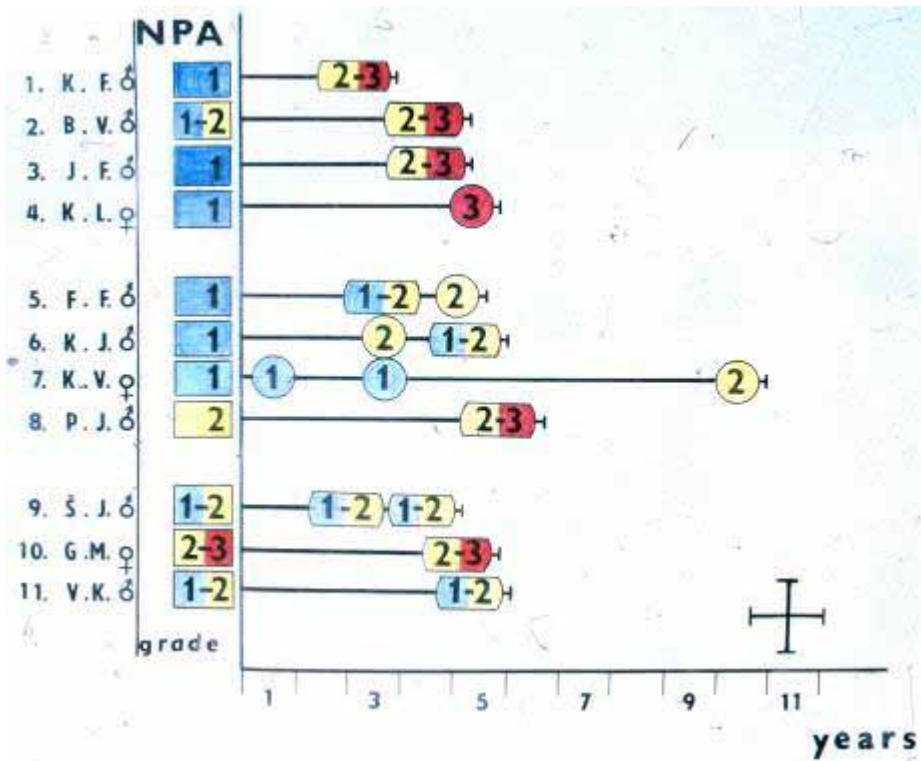
NPA-2



NPA-3



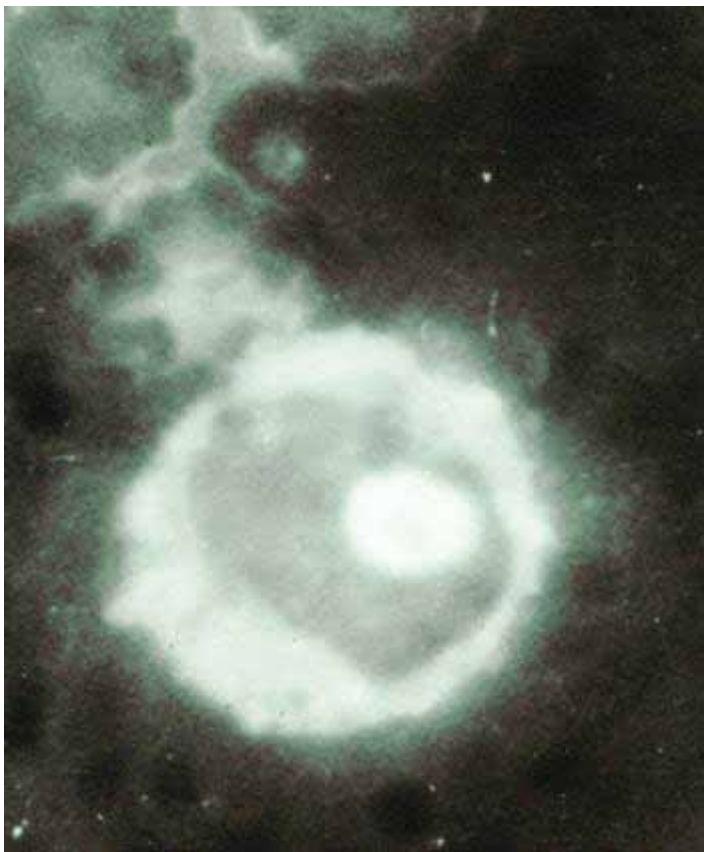
# MM – VZTAH NPA K PROGNÓZE



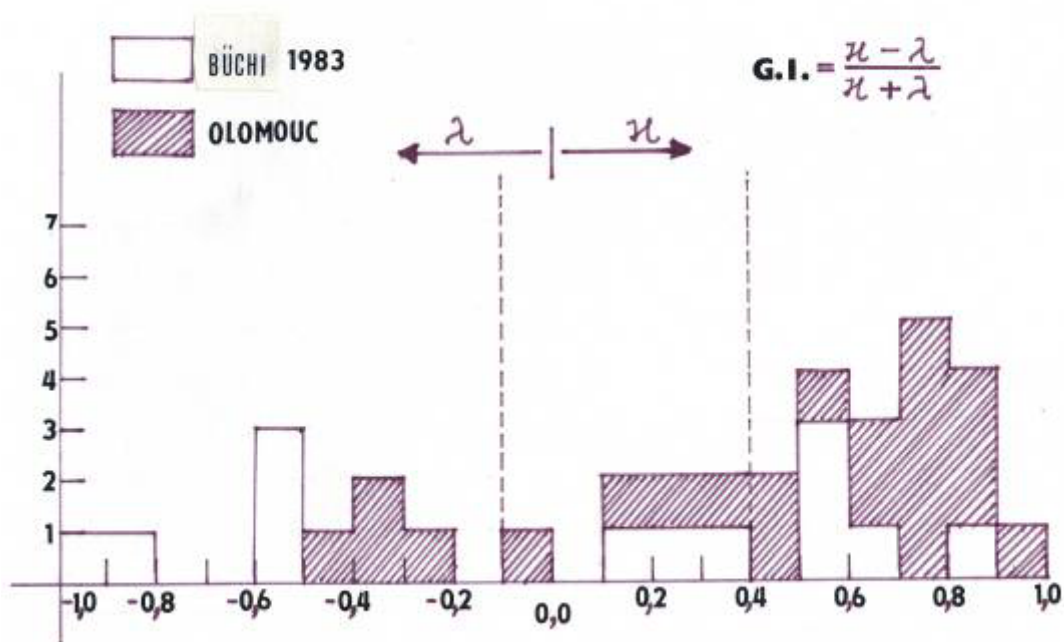
V. Ščudla, J. Dušek et al., 1984



# MM – GARETTŮV INDEX

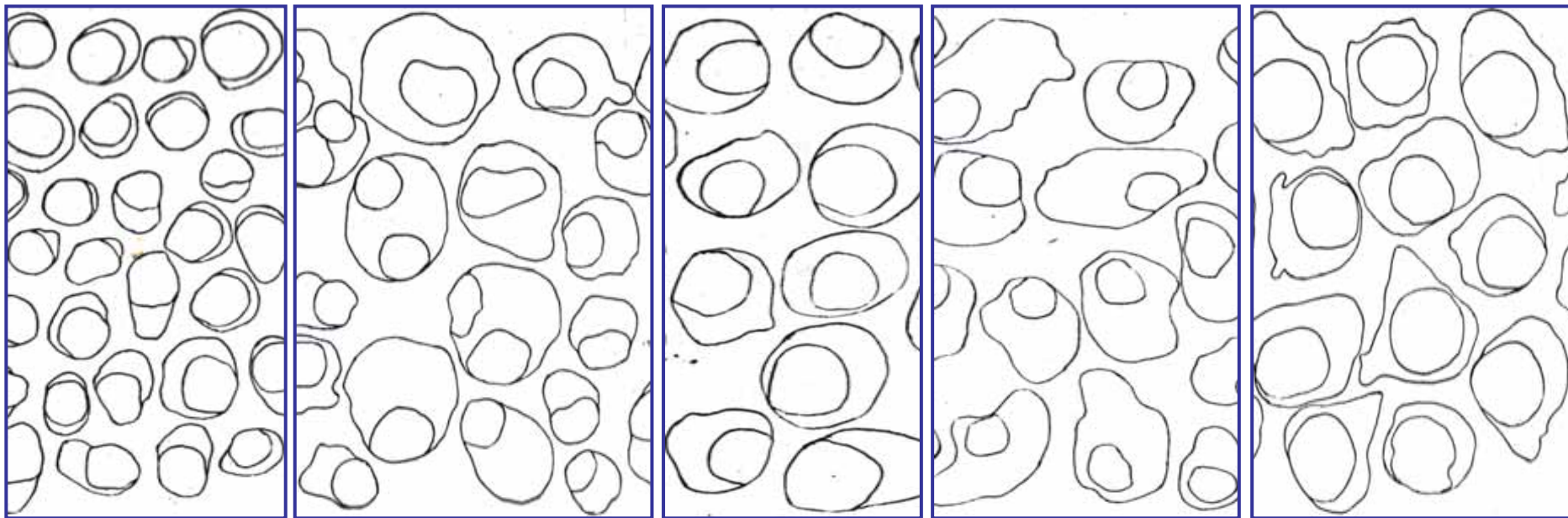


FREKVENČNÍ DIAGRAM HODNOT G.I. U 30 NEMOCNÝCH S MNOHOČETNÝM NYELOMEM



*L. Hanzlíková et al., 1988*

# PLANIMETRIE MYELOMOVÝCH BUNĚK



MM-lymfoplasmocyt.  
typ, vysoký N/C index

MM-nápadná anisocytóza,  
dvě linie – „LP“ a „obří“  
My.bb.

MM-střední velikost,  
malá anisocytóza

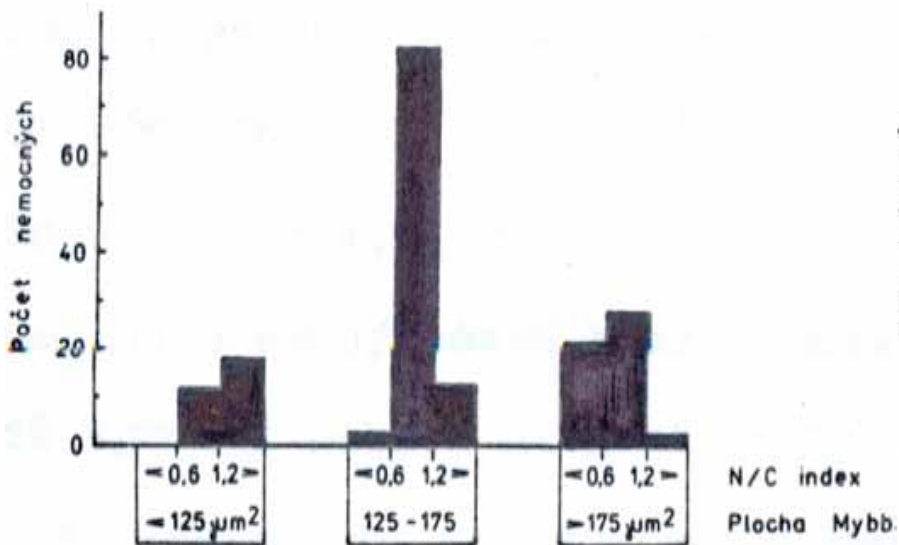
MM-velké bb. s malými  
pyknotickými jádry,  
bohatá cytoplazma

MM-obří elementy,  
velká jádra, nízký  
N/C poměr

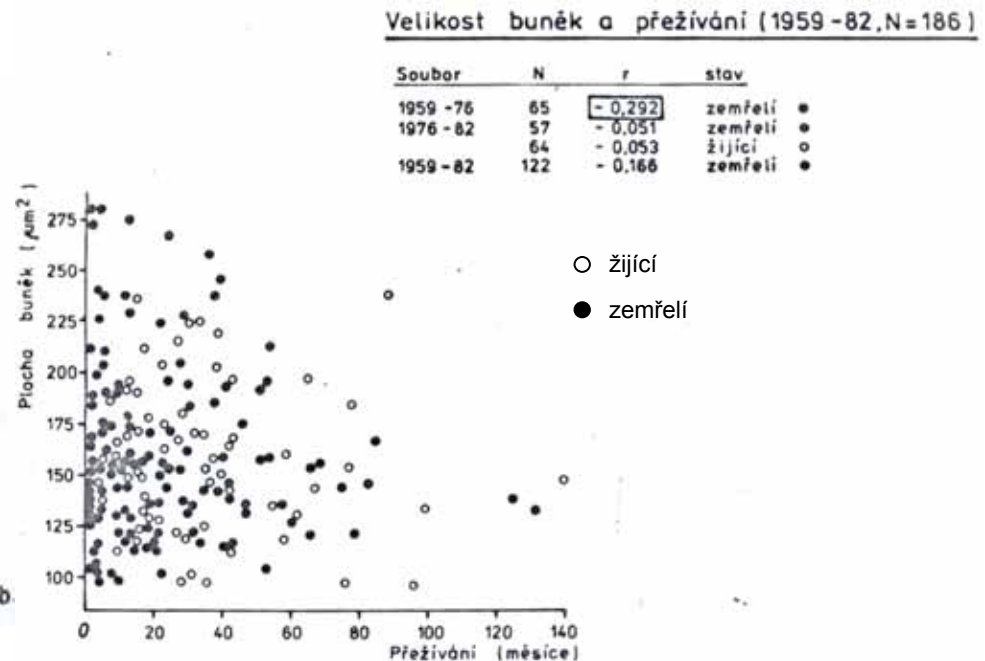
# PLANIMETRIE MYELOMOVÝCH BUNĚK

## histogram, vztah k OS

(n-208, 1959-1982)



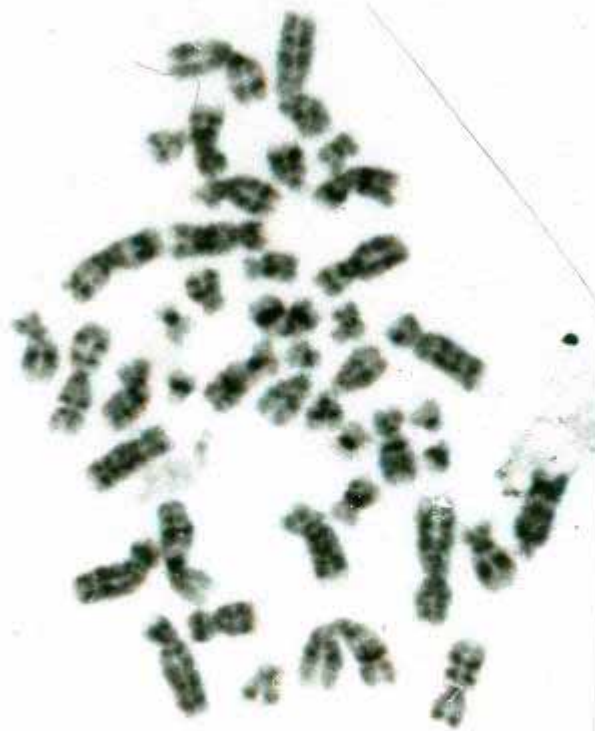
Rozložení dle NC/indexu a velikosti My.bb.  
(„malé, střední, velké“)



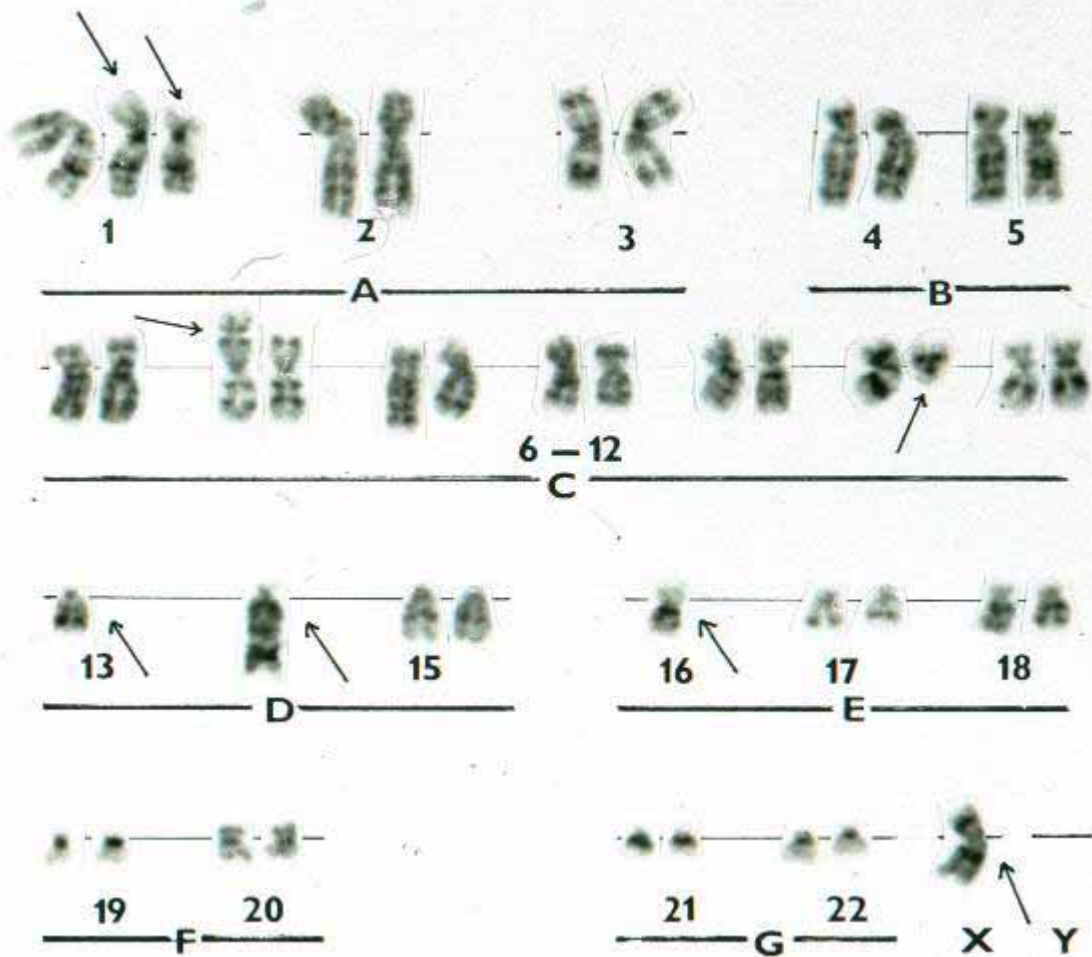
Korelační diagram (Pearson) – vztah mezi  
velikostí My.bb. a celkovým přežitím (OS)

# MM – KLASICKÁ CYTOGENETIKA

Jméno: H. J., 1949

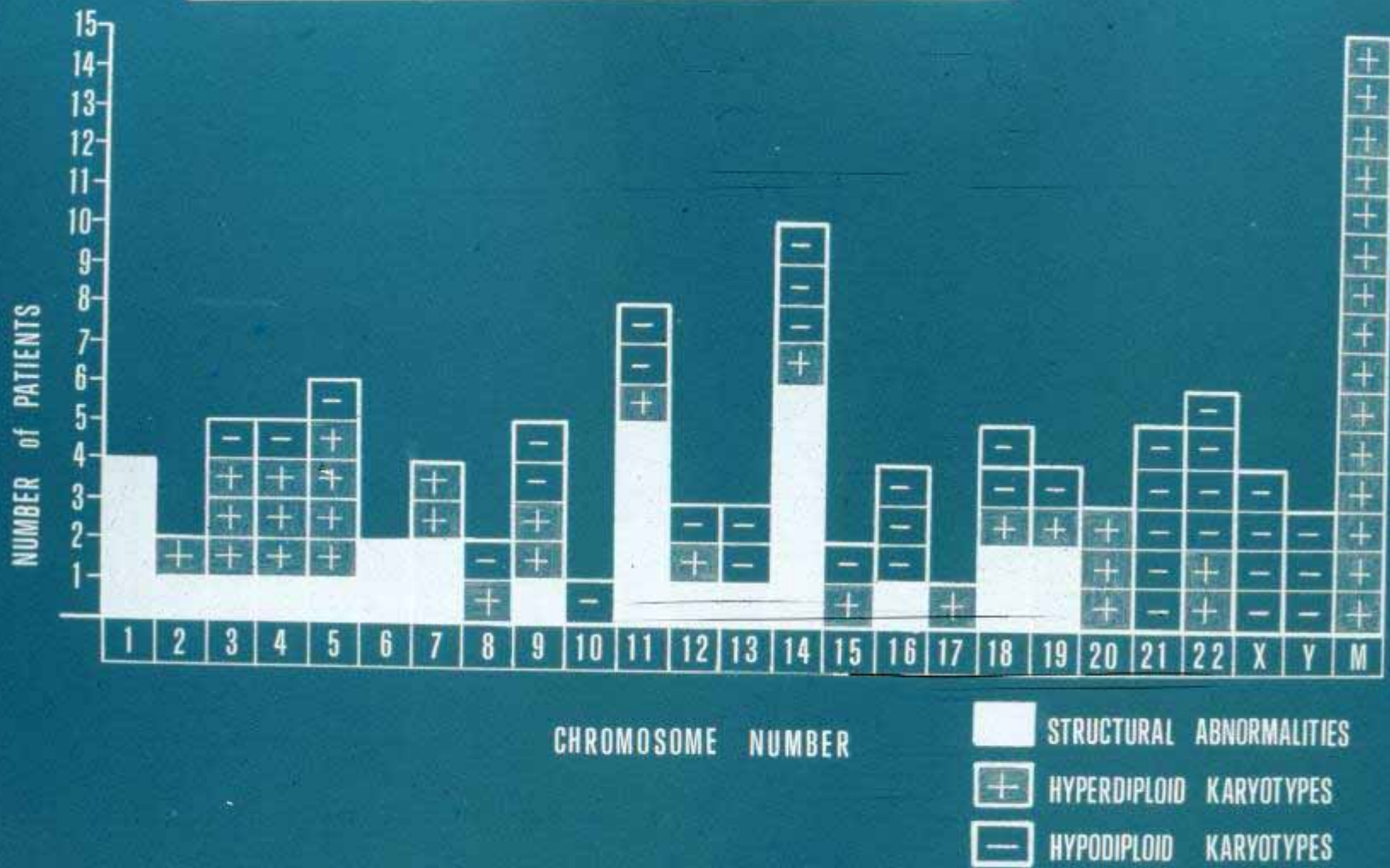


ODDĚLENÍ KLINICKÉ HEMATOLOGIE  
cytogenetická laboratoř  
FNsP OLMOUC

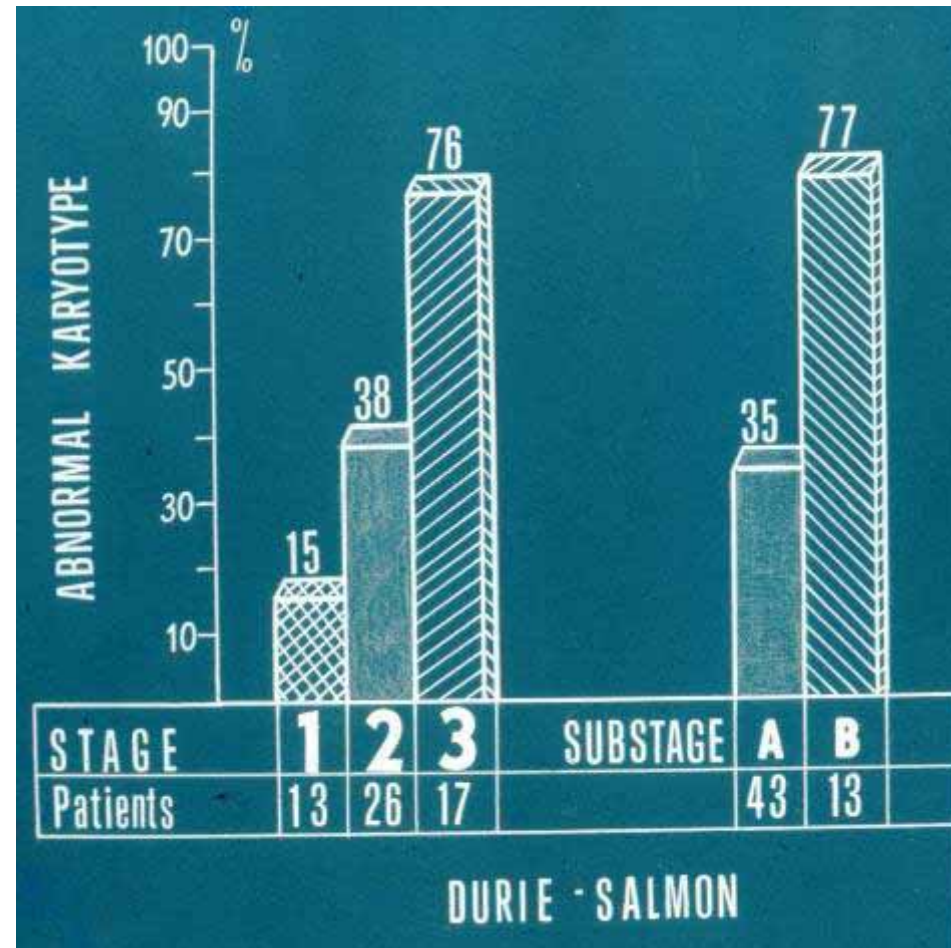
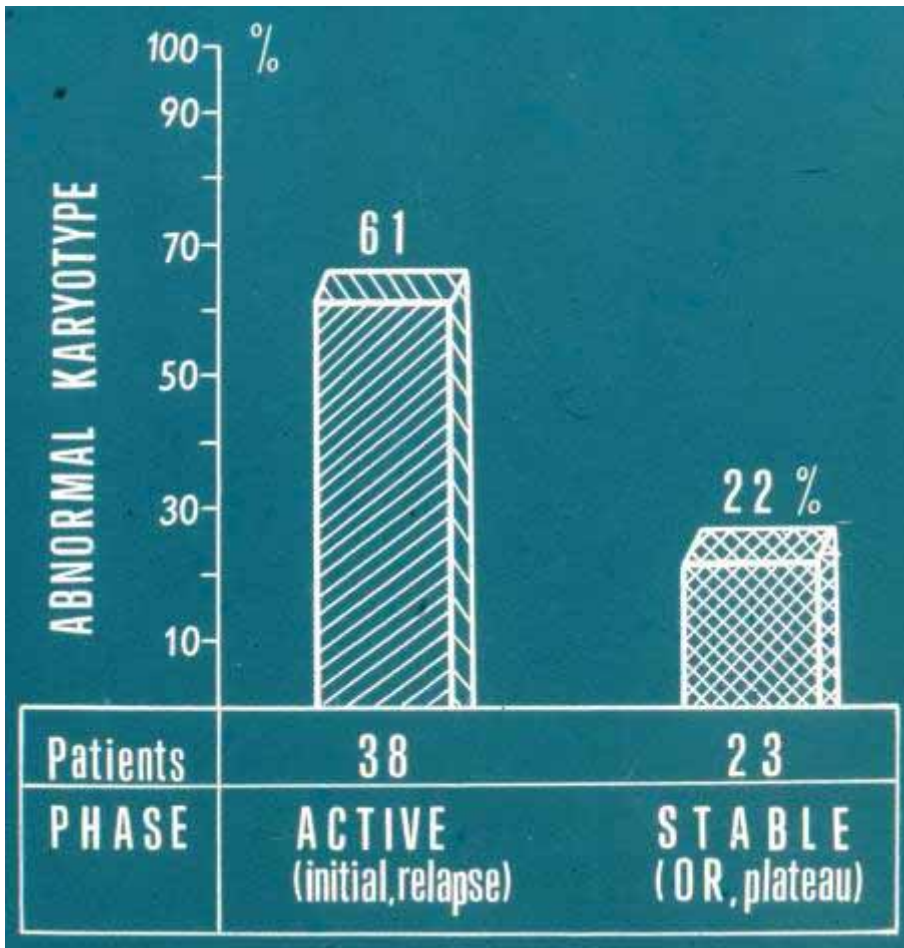


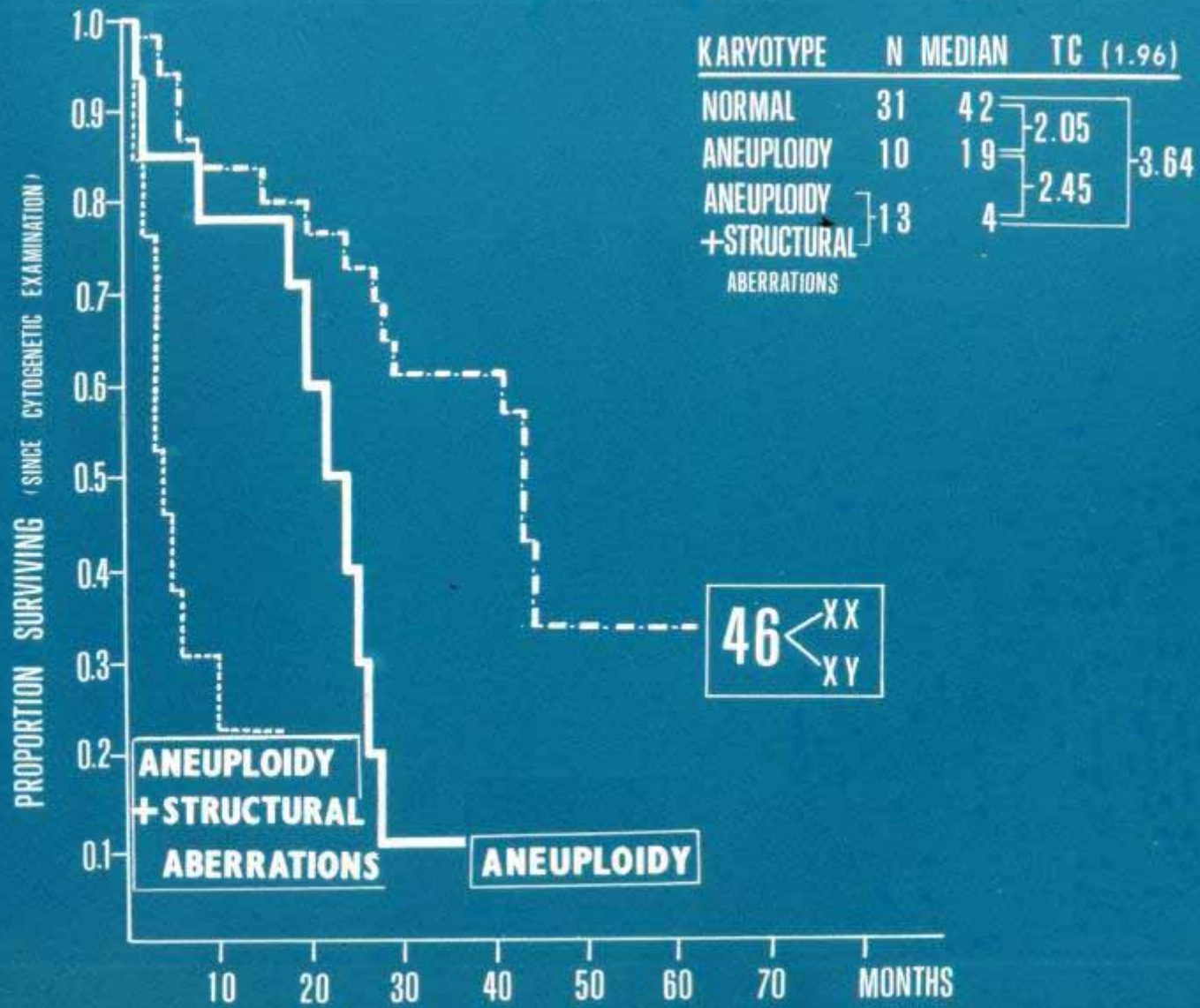
Datum vyš.: 23.2.1968

# MM - FREQUENCY of ANOMALOUS CHROMOSOMES in 56 PATIENTS

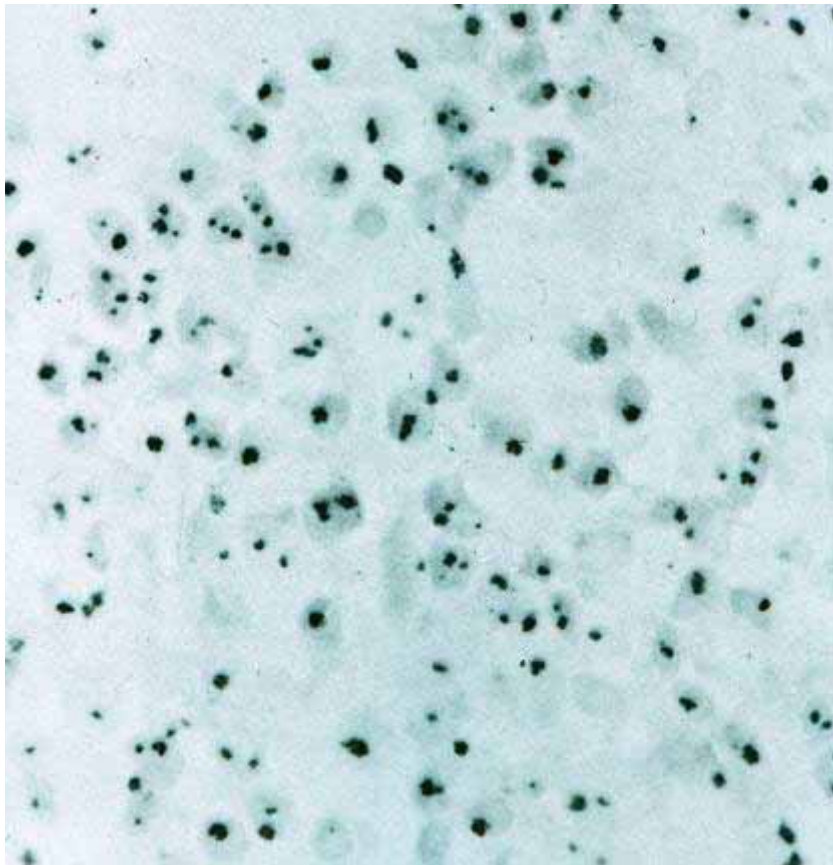


# MM – VZTAH CHROMOZOMÁLNÍCH ZMĚN KE STÁDIU A AKTIVITĚ NEMOCI

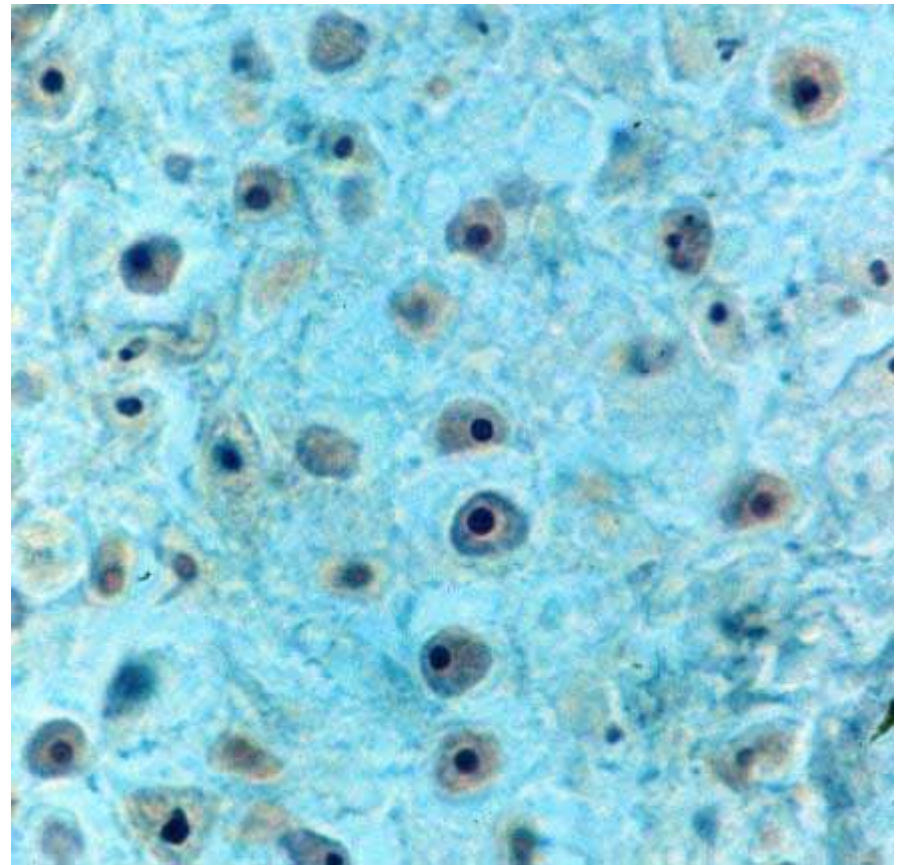




# Ag – NOR – My. bb.



- Ag - NOR My. bb. (typ I – III)
- Počet NOR / 1 buňku
- Velikost NOR



metoda dle Platona a Crockera ( $\text{AgNO}_3$ )  
(obraz metabol.aktivity jadérka), bb.růstu,  
„marker“ proliferace)



# MM – MOLEKULÁRNÍ CYTOGENETIKA (I)

## Mnohobarevná FISH – M-FISH

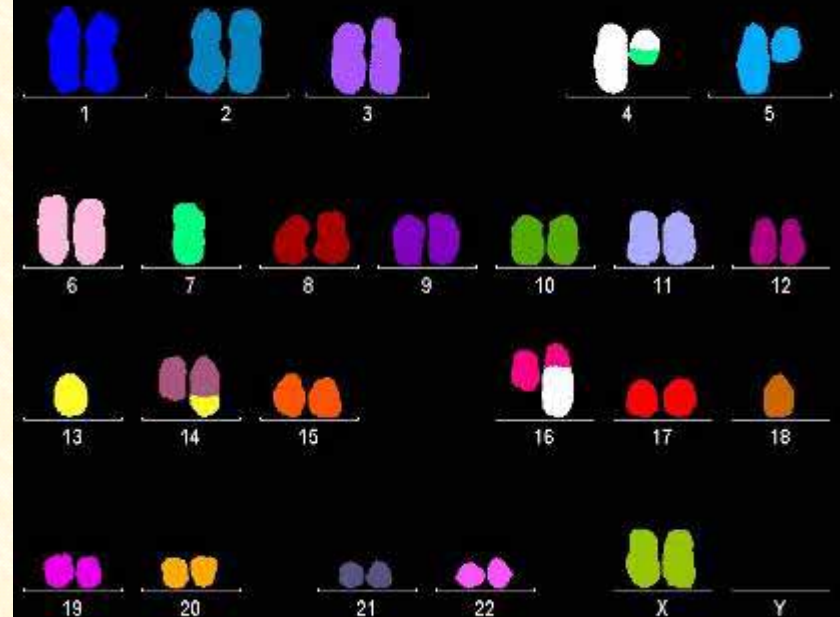
### Kombinacní barvení

5 fluorochromu  
a jejich  
kombinace

- DEAC
- FITC
- SO
- TR
- Cy5

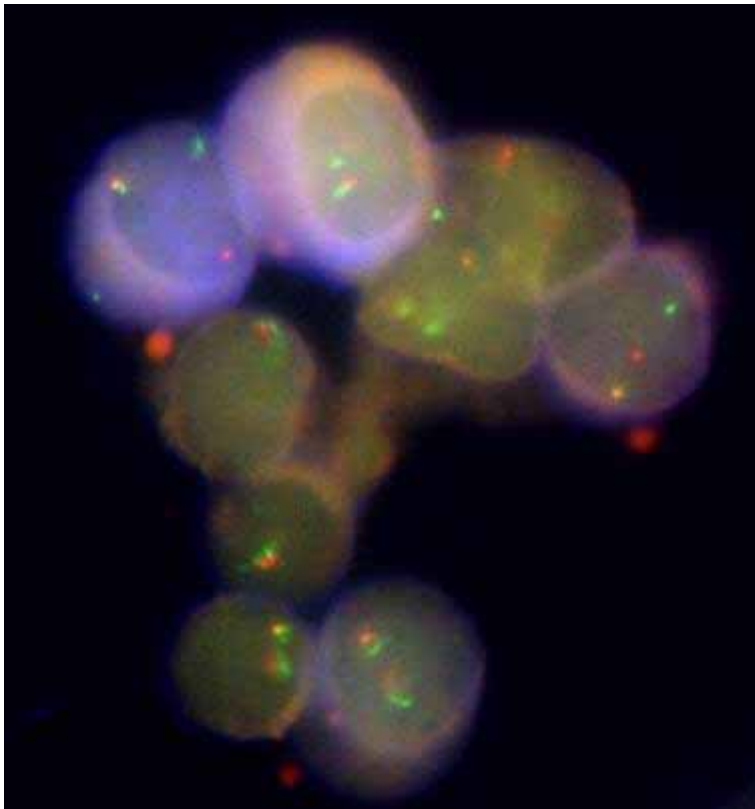
#	DEAC Ex 426nm/ Em 480nm	FITC Ex 495nm/ Em 521nm	SO Ex 559nm/ Em 588nm	TR Ex 595nm/ Em 615nm	Cy <sup>TM</sup> 5 Ex 649nm/ Em 670nm
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
X					
Y					

## Mnohobarevná FISH – M-FISH



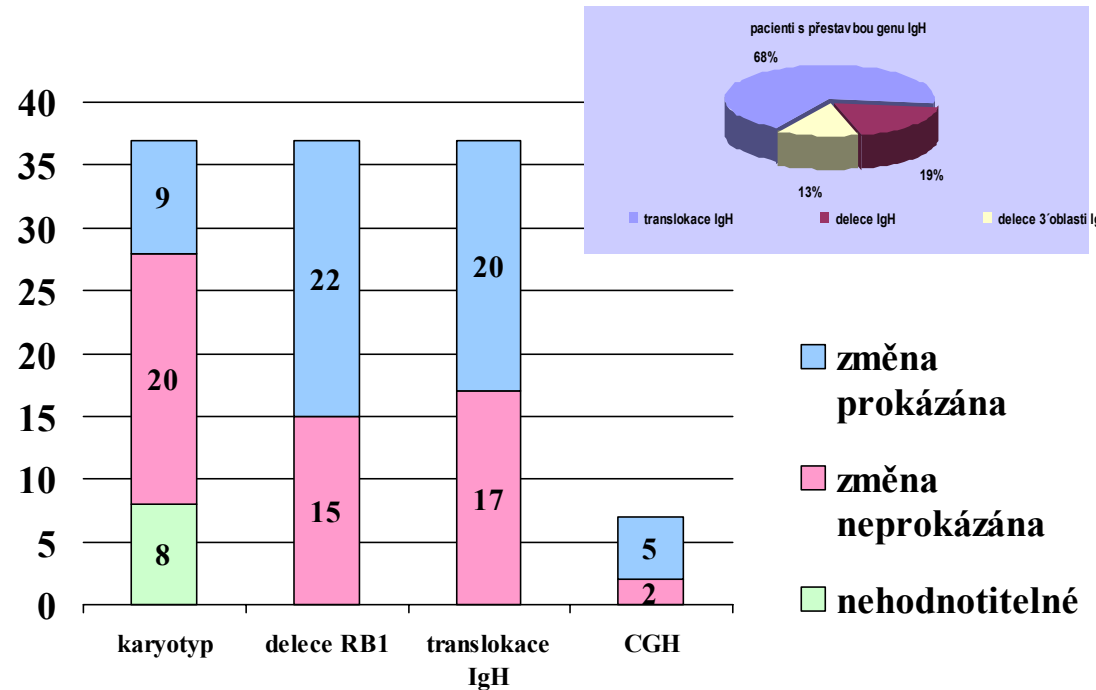
*M. Jarošová, M Holzerová et al., 2003*

# MM – MOLEKULÁRNÍ CYTOGENETIKA (II)



LSI IgH Dual Color (14q32)Vysis

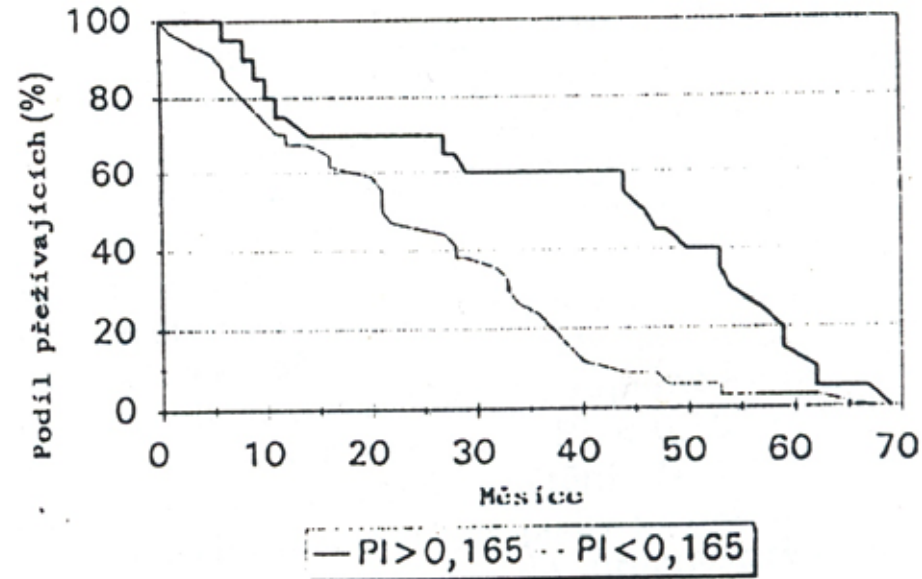
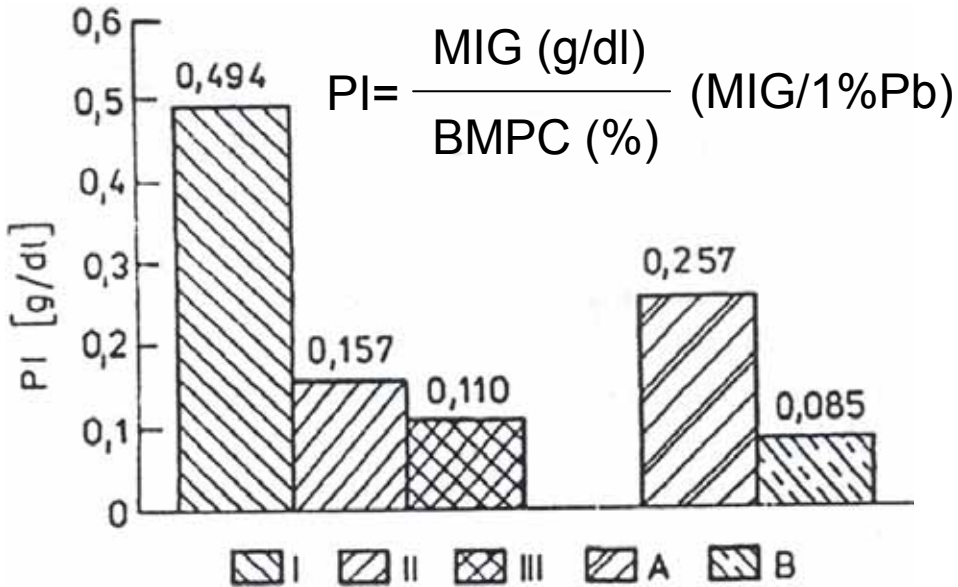
## Výsledky vyšetření pacientů s MM (n-37)



*K. Chludová, M. Jarošová et al., 2004*

# INDEX PARAPROTEINU (San Miguel, 1989)

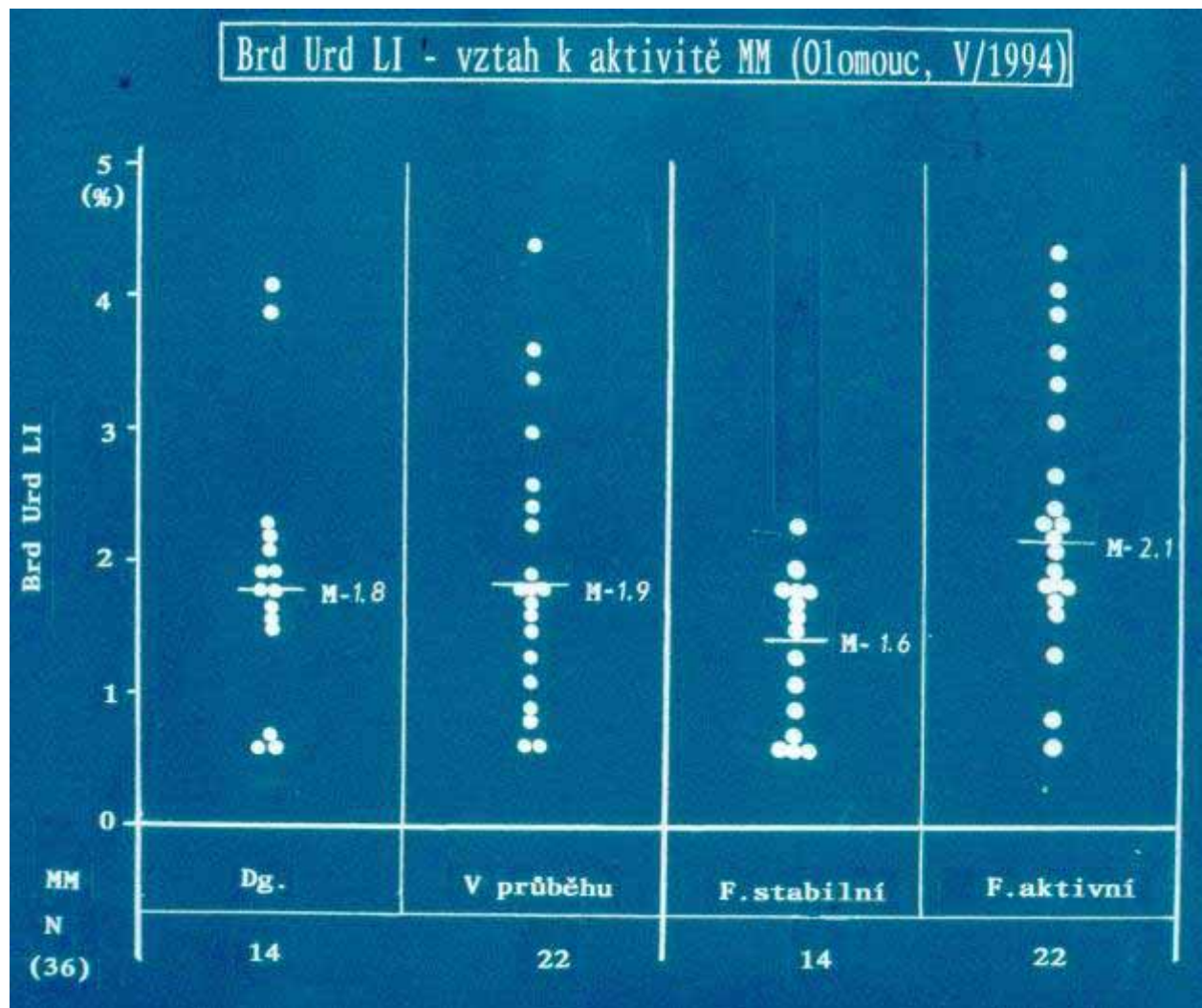
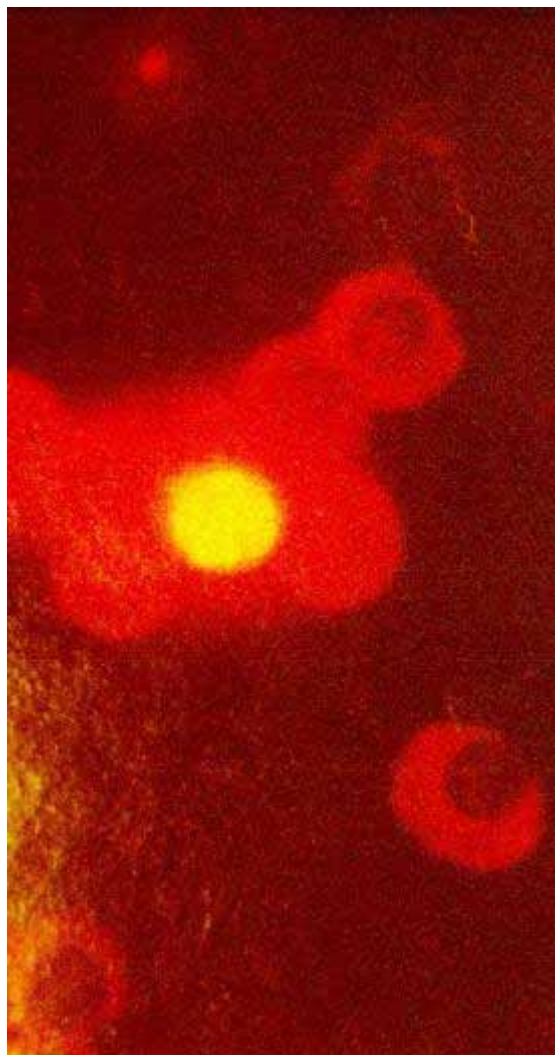
(n-54)



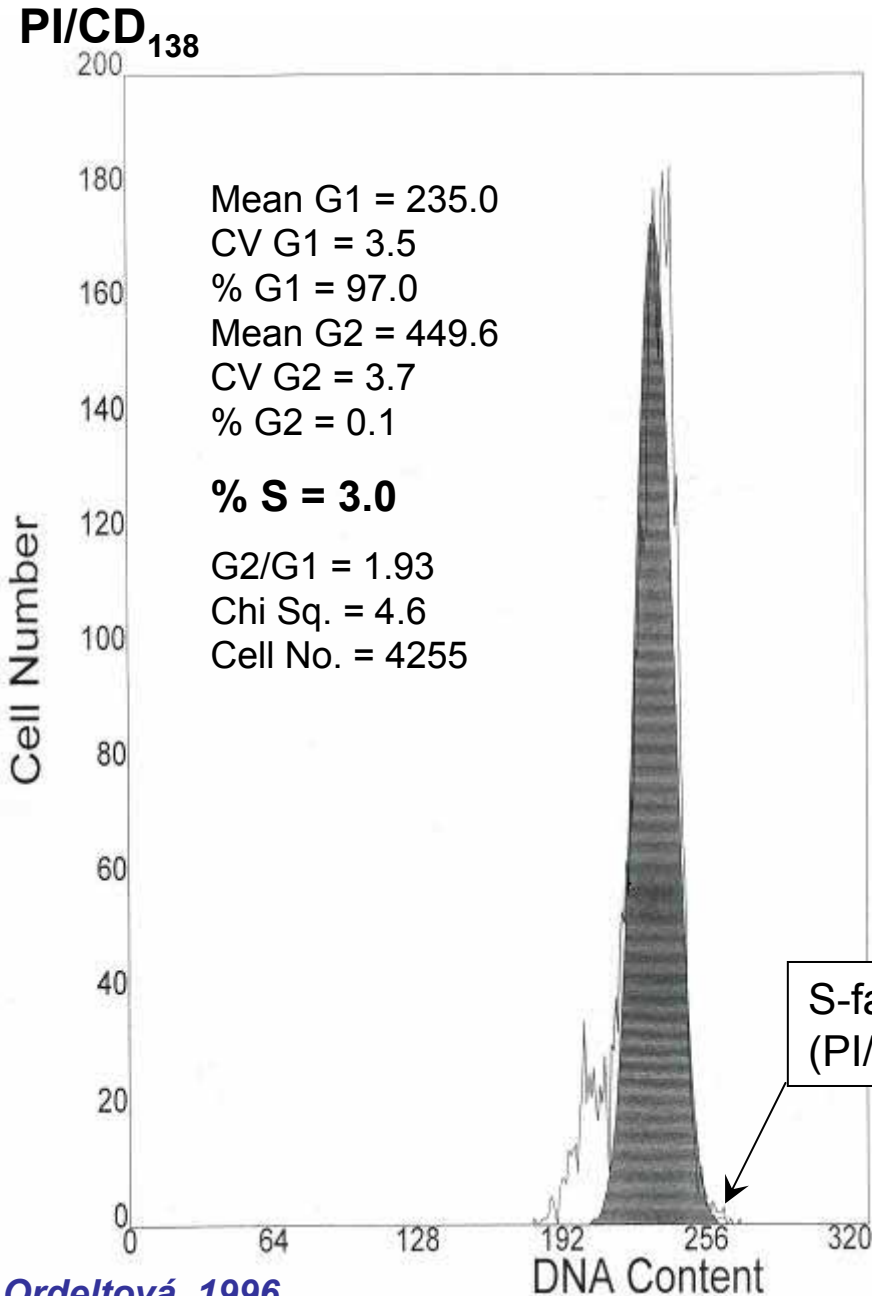
## Pos.korelace:

PI vs. S-B2M, S-kreat., S-alb., Hb, Pb (%), OS

# MM – Brd Urd LI – VZTAH K AKTIVITĚ NEMOCI

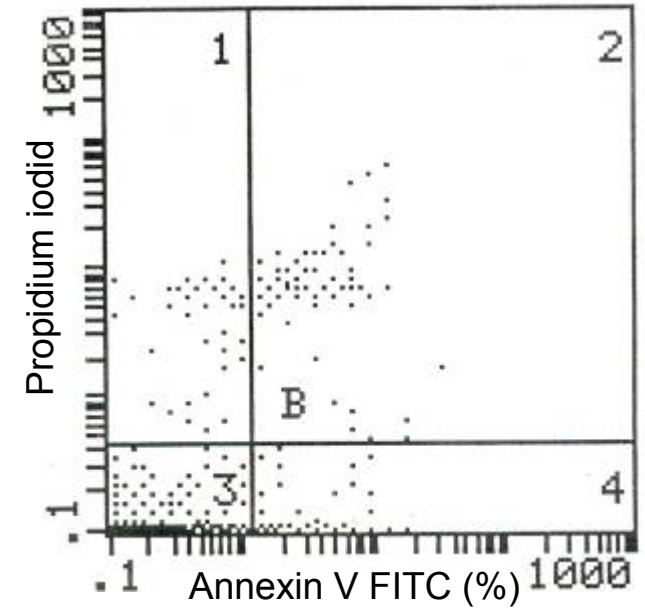


# MM – PROLIFERACE (PI/CD<sub>138</sub>) A APOTÓZY (AI/CD<sub>138</sub>)

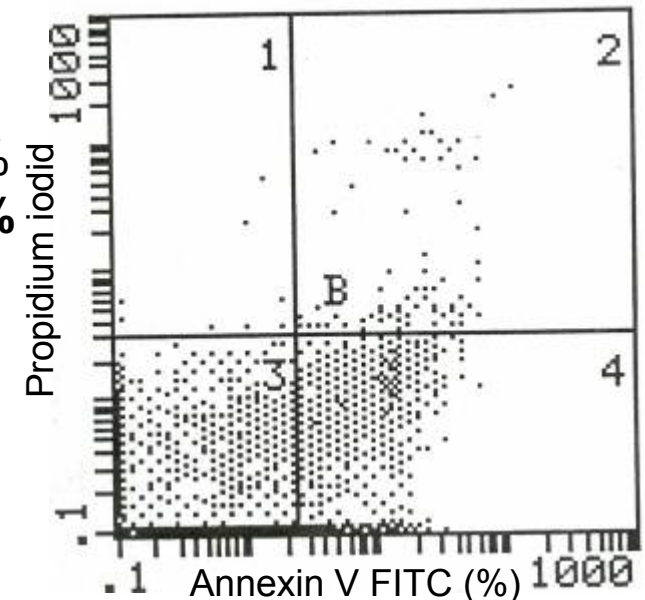


**AI/CD<sub>138</sub>**

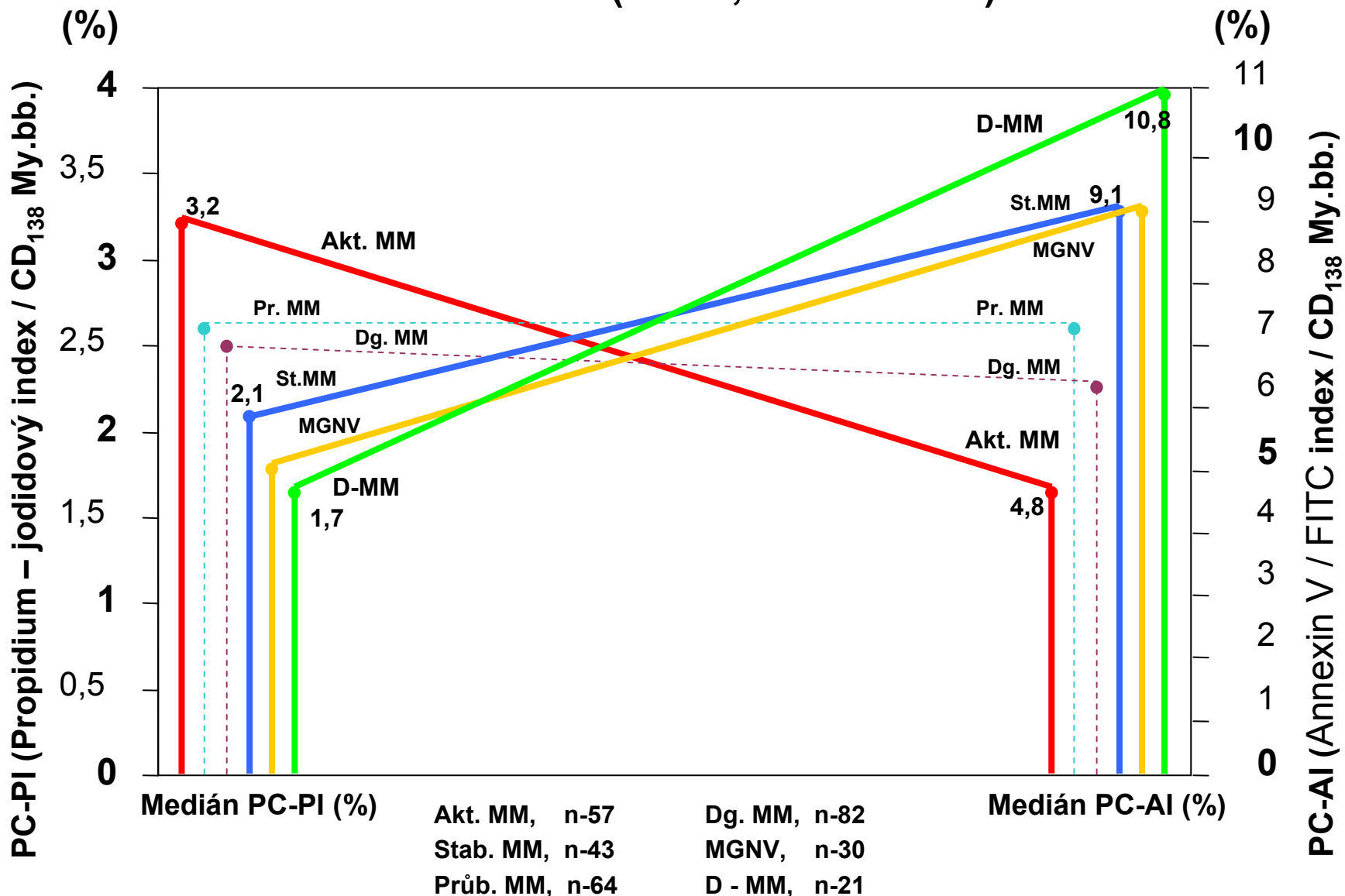
B1: 0,5%  
 B2: 1,2%  
 B3: 96,7%  
**B4: 1,7%**



B1: 0,3%  
 B2: 2,2%  
 B3: 74,1%  
**B4: 23,3%**



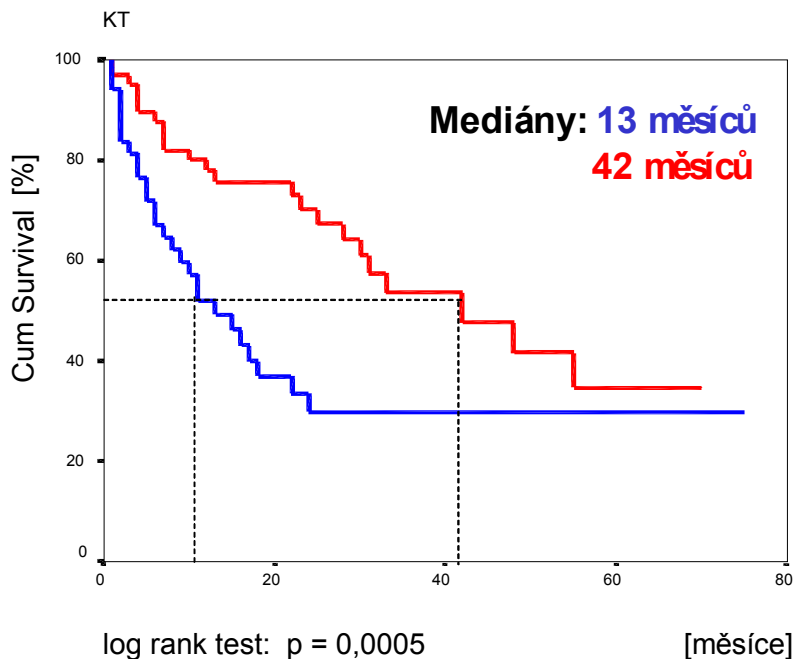
# MGNV a MM – VZÁJEMNÝ VZTAH INDEXŮ PROLIFERACE A APOPTÓZY (n-197, 2000 – 2002)



**Hypotéza: inverzního - recipročního vztahu indexů proliferace a apoptózy plazmatických buněk u MGNV a MM.**

# MM – KINETICKÉ UKAZATELE A PROGNÓZA

## Propidium-jodidový index

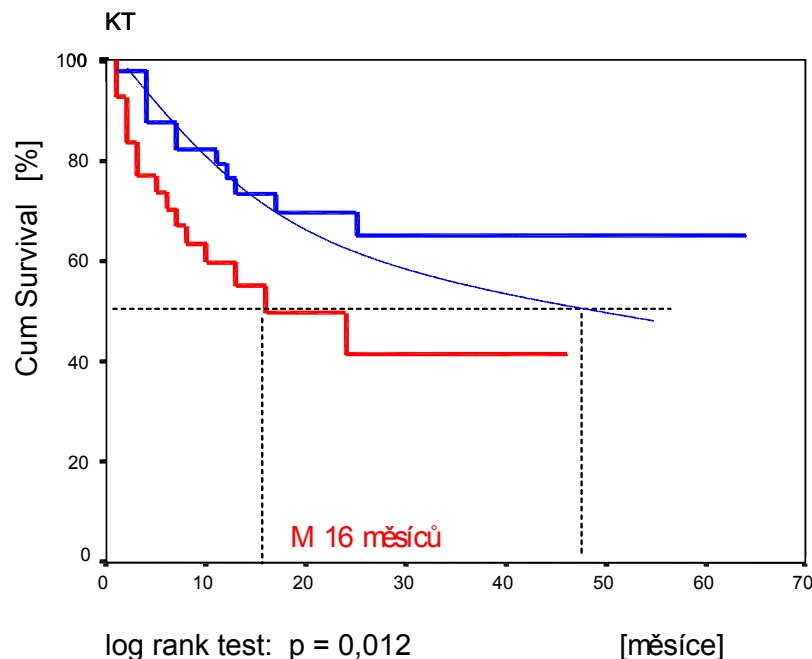


PC-PI/CD<sub>138</sub>

— < 2,8

— ≥ 2,8

## Apoptotický index



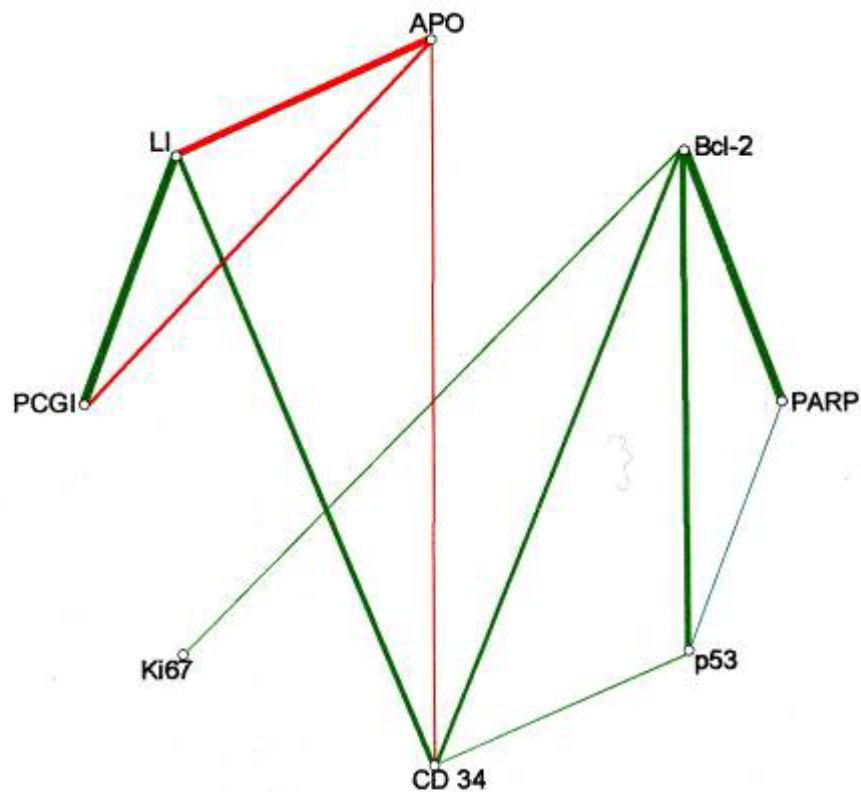
PC-AI/CD<sub>138</sub>

— ≥ 4,0

— < 4,0

# MONOKLONÁLNÍ GAMAPATIE (n-56)

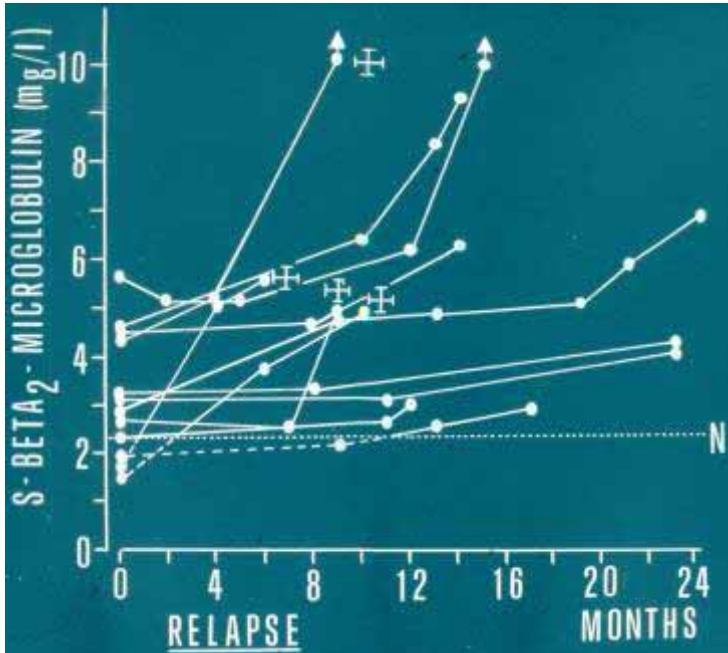
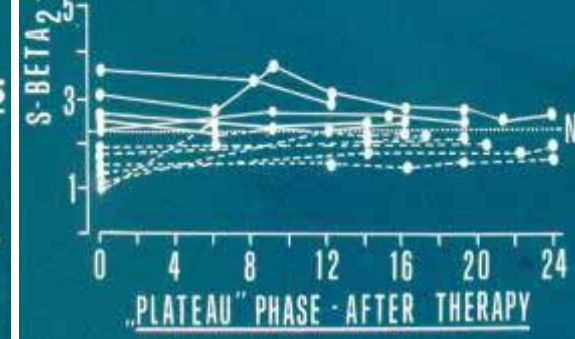
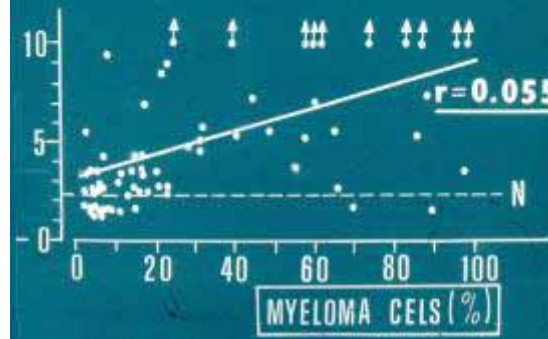
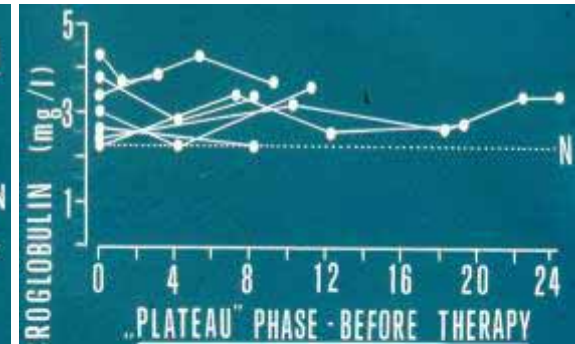
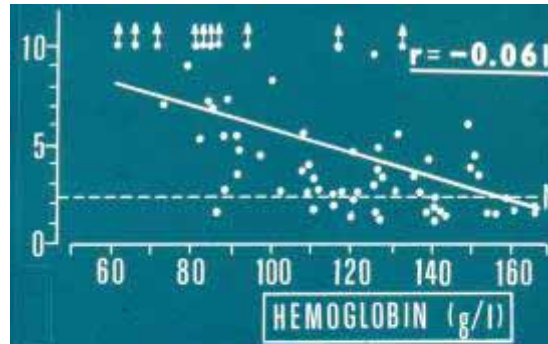
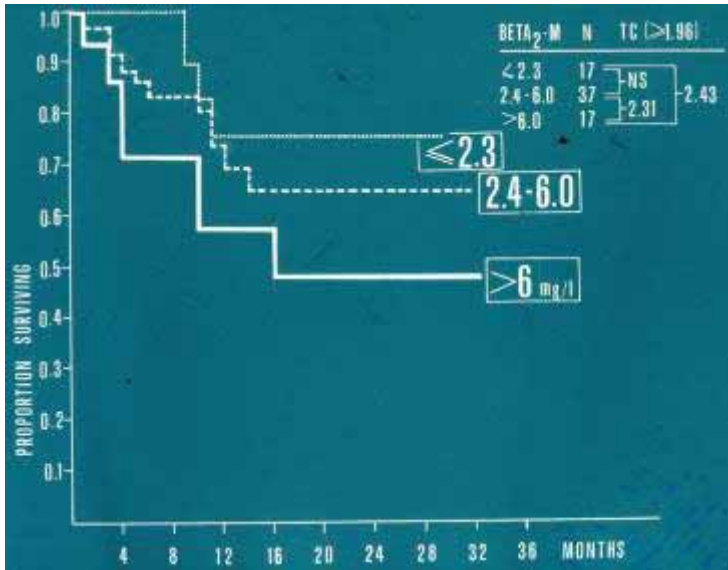
Grafické znázornění síly a typu statistické významnosti vazeb mezi sledovanými znaky



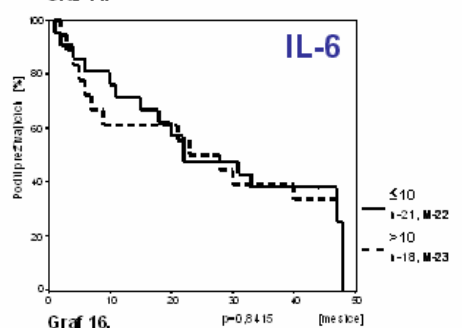
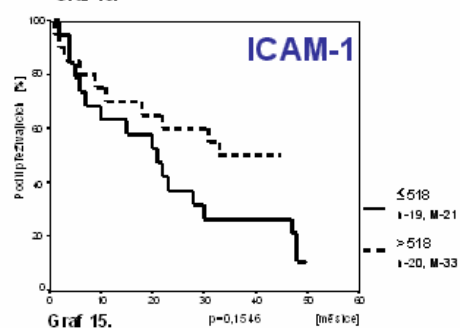
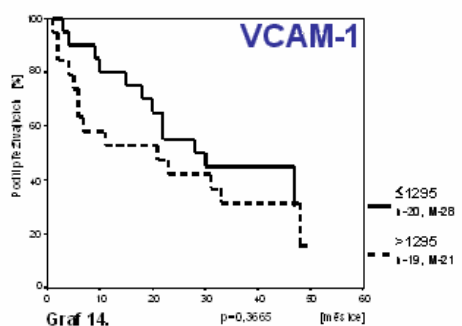
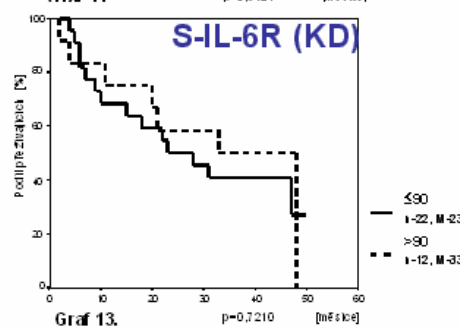
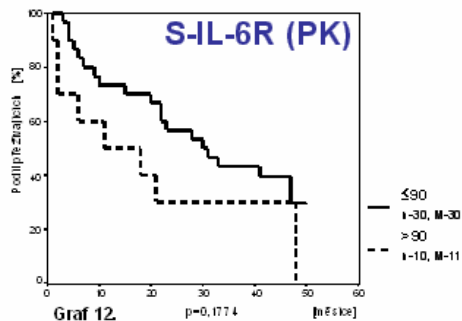
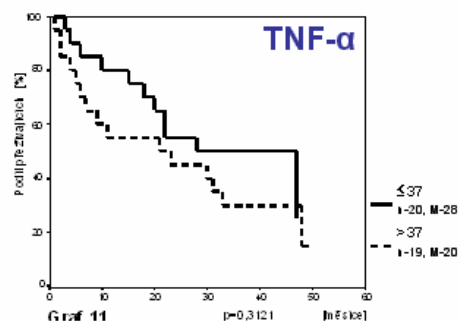
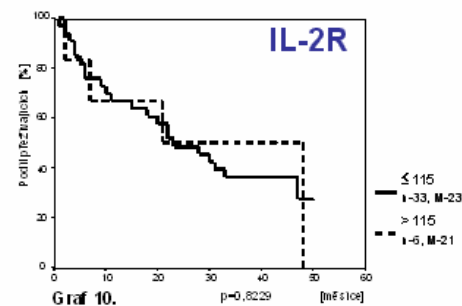
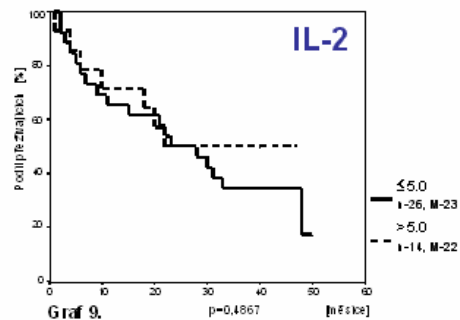
- přímá úměra
- nepřímá úměra



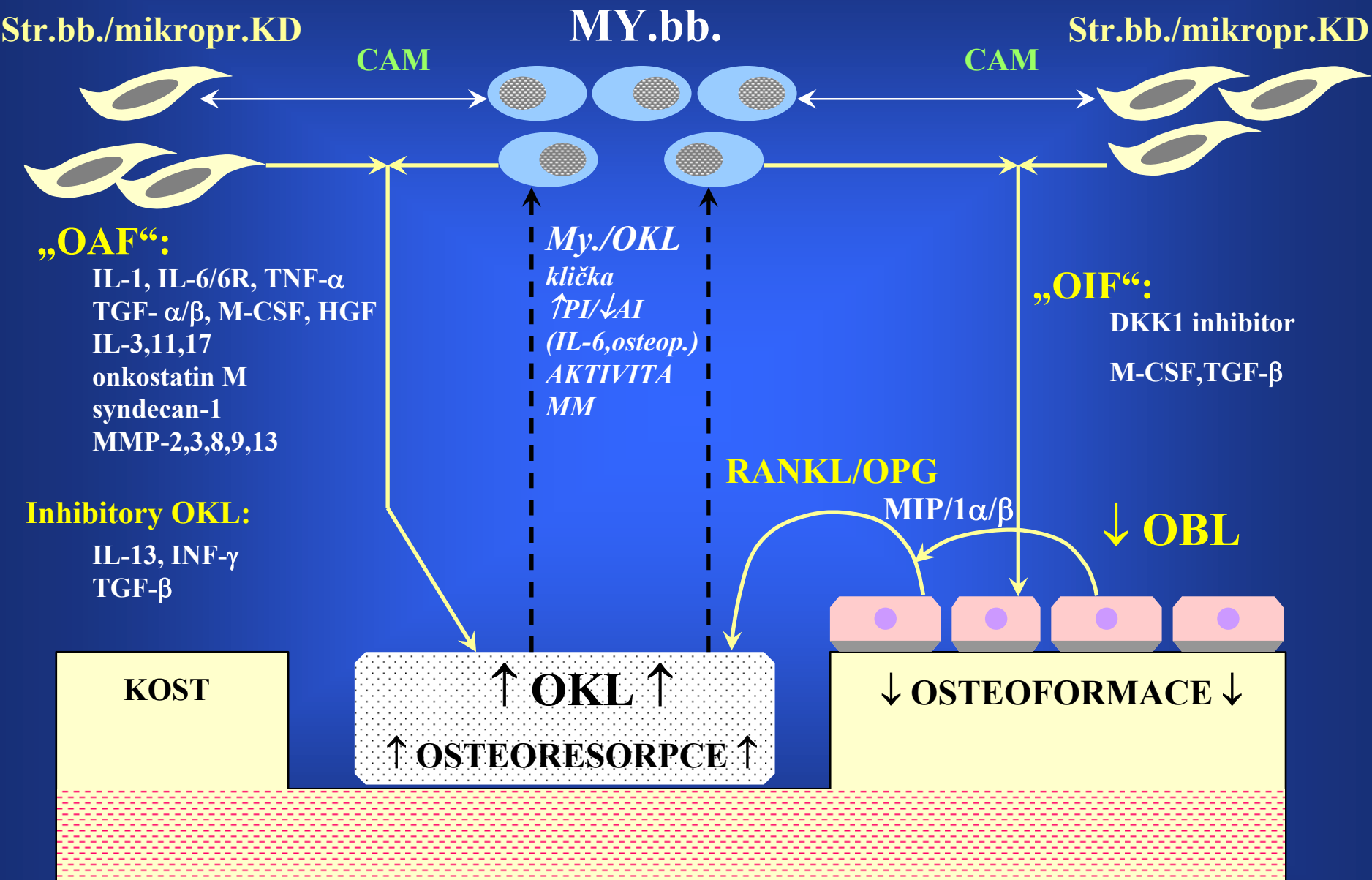
# S-Beta<sub>2</sub> microglobulin (REA)



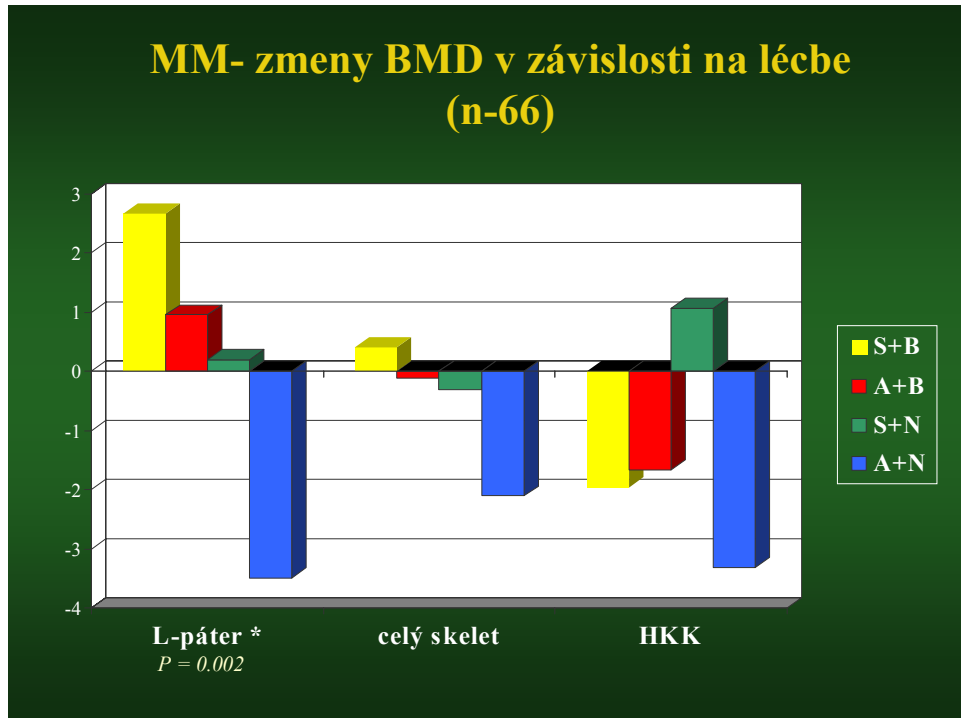
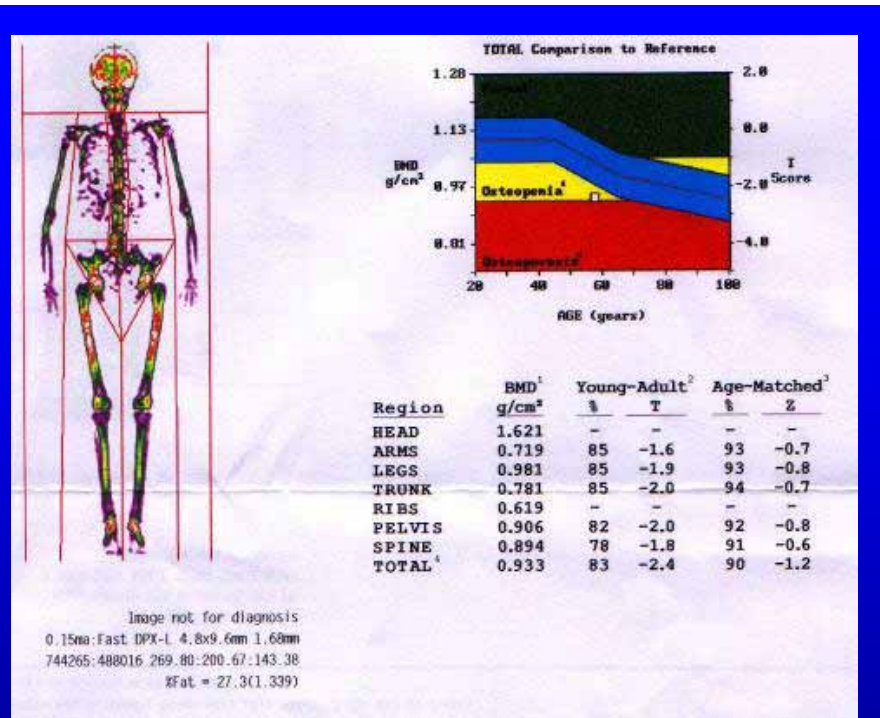
# MM – PROGNOSTICKÝ VÝZNAM (OS) SÉROVÝCH HLADIN CYTOKINŮ A CAM



# MKN – PATOGENEZA



# MM – OSTEODENZITOMETRIE

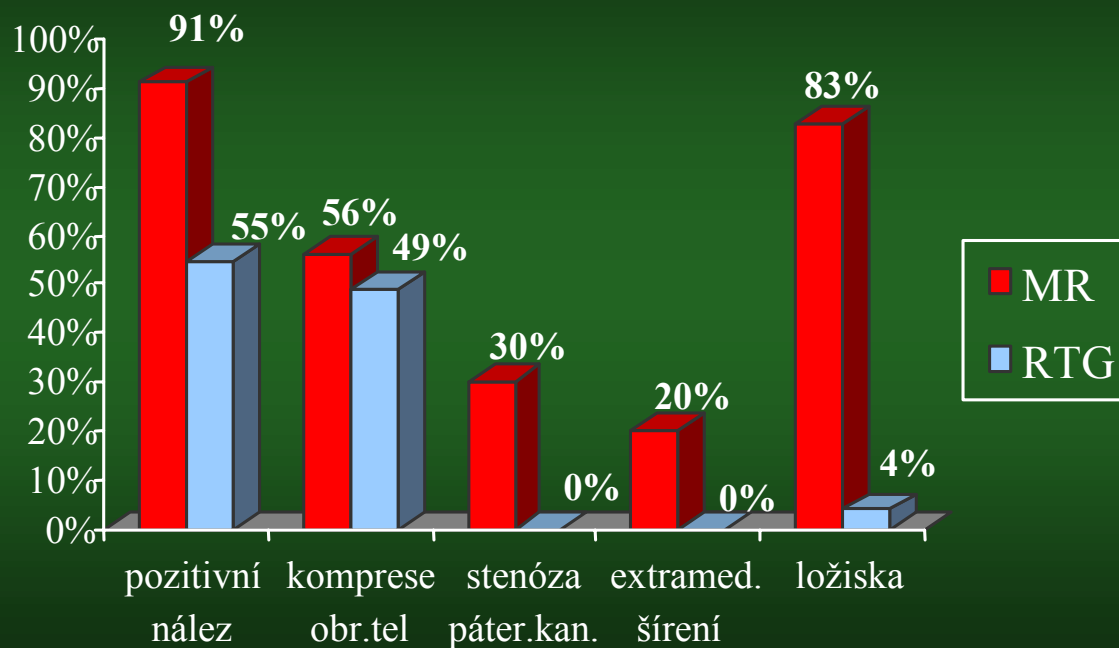


Hodnocení: BMD g/cm<sup>2</sup>  
T - skóre  
Z - skóre

# MM vs. RTG – postižení páteře



## MR vs. RTG - postižení páteře:



M. Vytrasová, V. Vavrdová et al., 2000

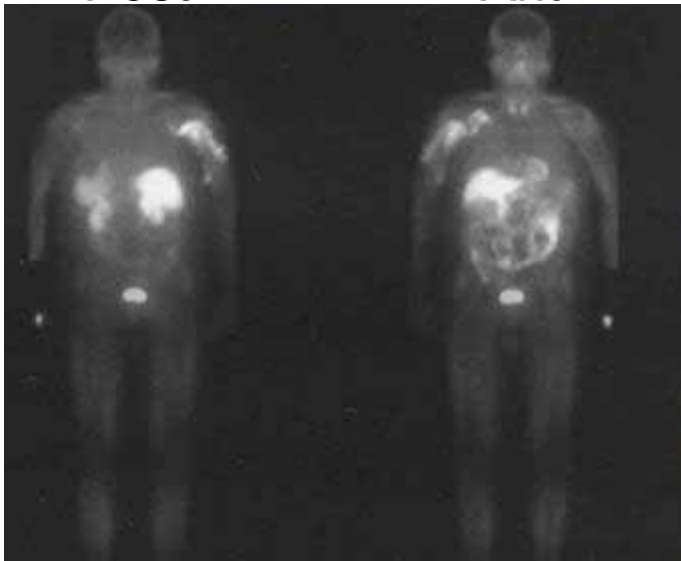
# MM – $^{99m}\text{Tc}$ – MIBI - SCINITIGRAFIE

$^{99m}\text{Tc}$ -MIBI -před léčbou



Post

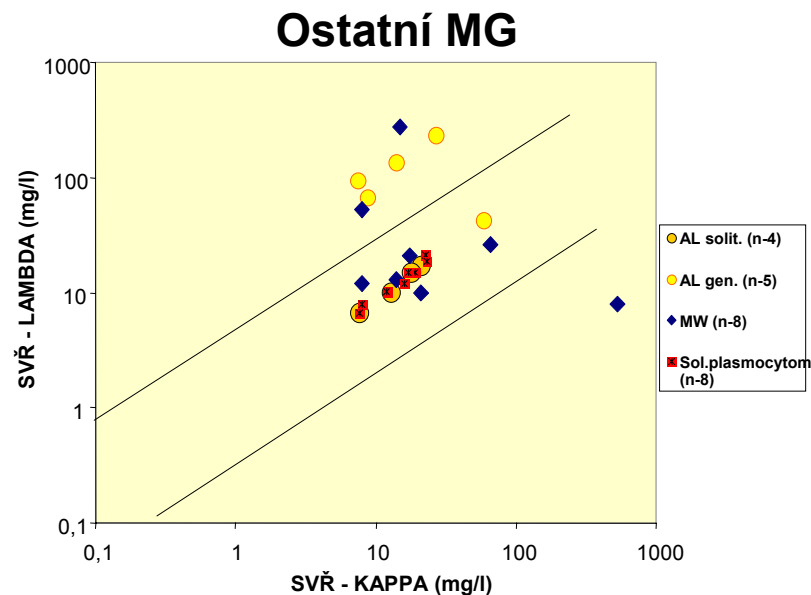
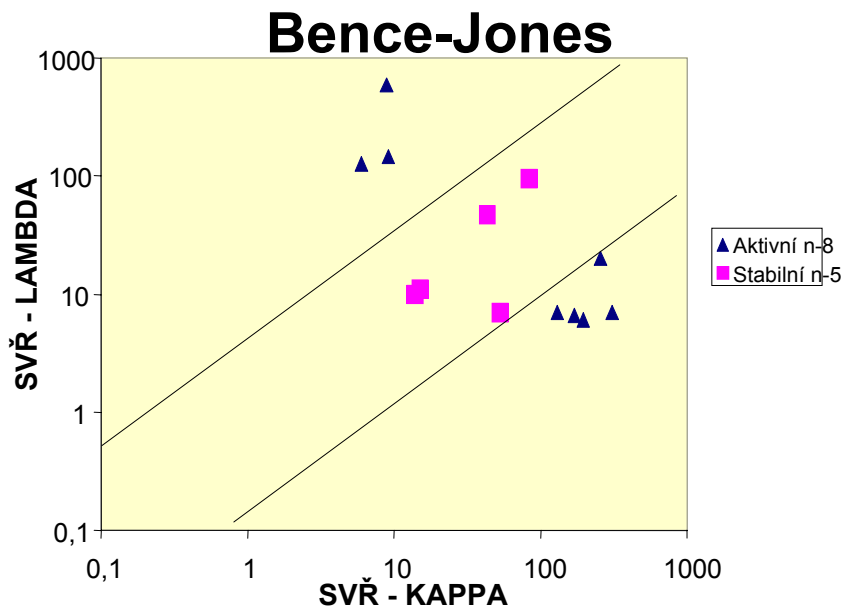
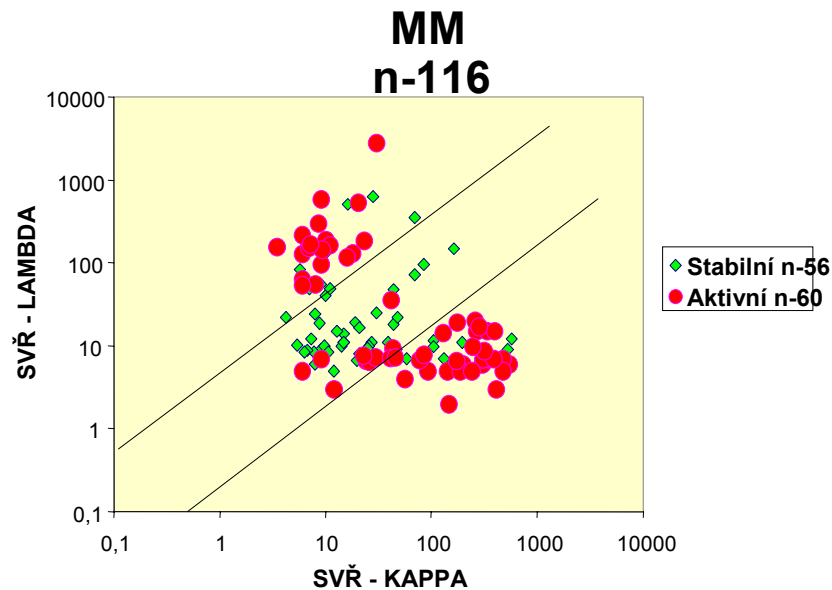
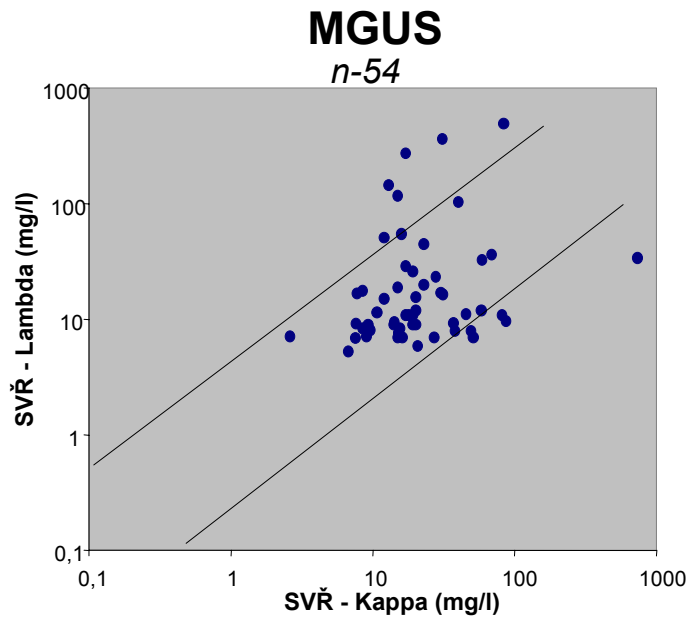
Ant



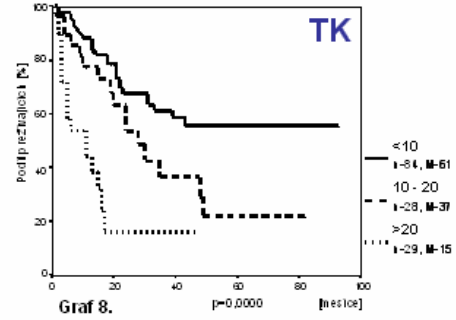
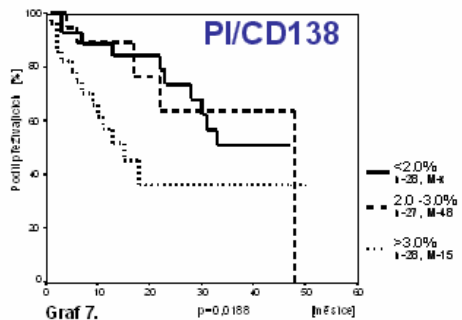
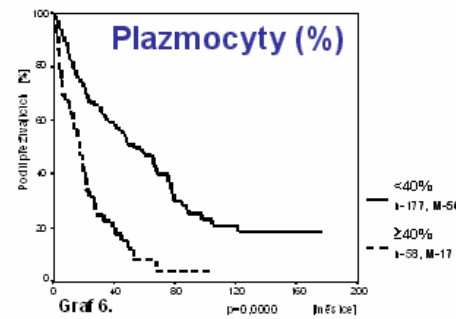
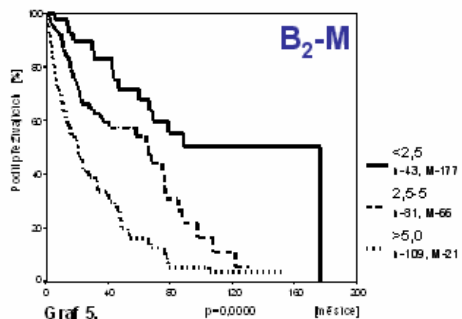
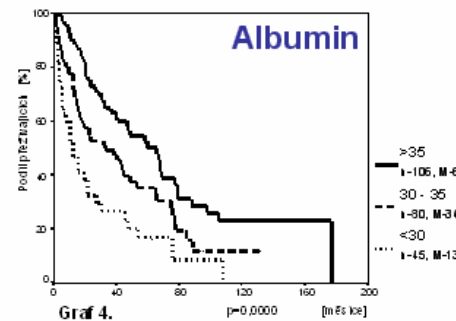
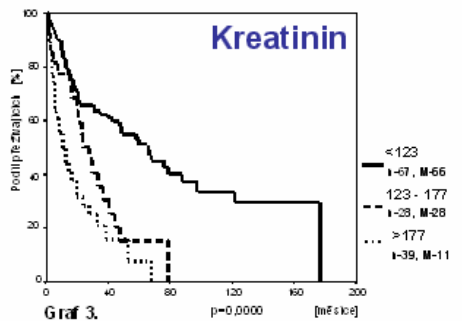
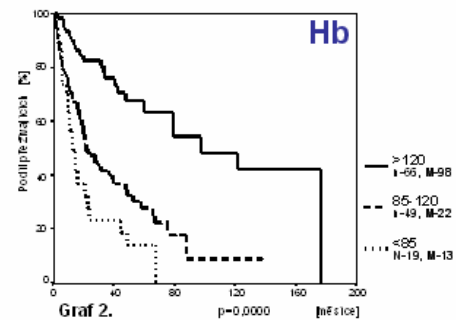
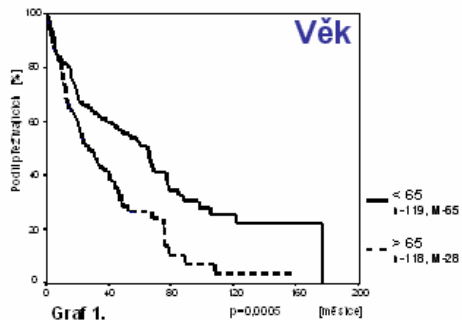
## Význam $^{99m}\text{Tc}$ - MIBI - scintigrafie u MM

- Zjištění aktivity a rozsahu lézí
- Záchyt solitárních nebo fokálních lézí zvláště u nesekrečního MM
- Dif dg. mezi MM a MGUS
- Alternativní možnost sledování aktivity a rozsahu onemocnění myelomem po APSCT
- Prediktivní význam,
- indikováno u rtg negativních bolestivých lézí

# MM – S-VLŘ U MONOKLONÁLNÍCH GAMAPATÍÍ

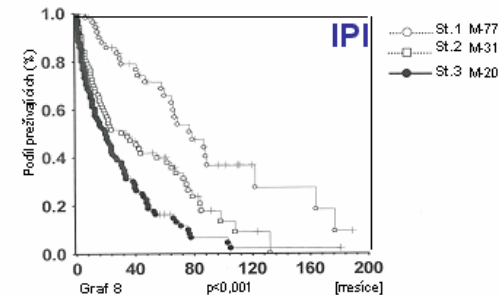
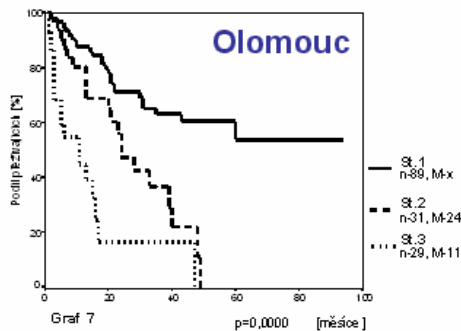
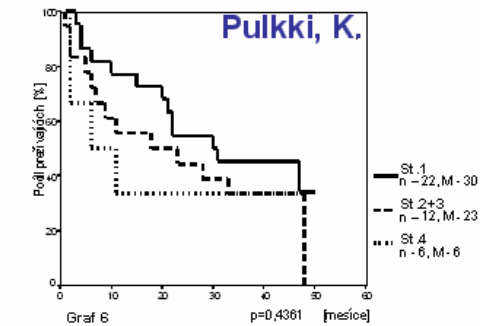
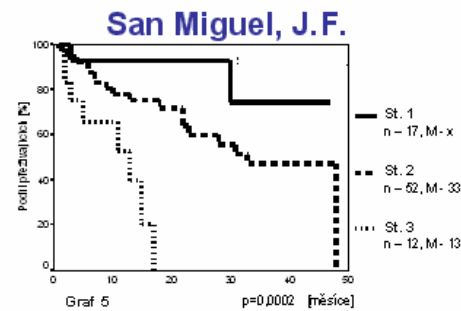
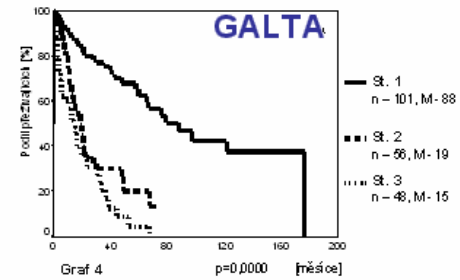
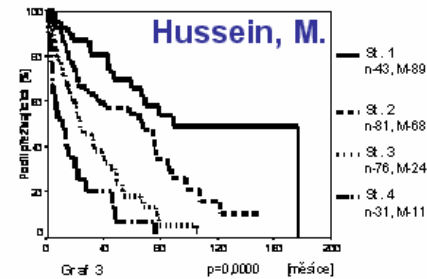
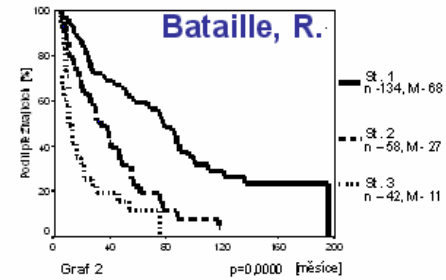
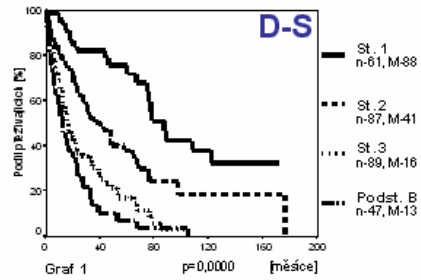


# MM – PROGNOSTICKÝ VÝZNAM (OS) VYBRANÝCH UKAZATELŮ



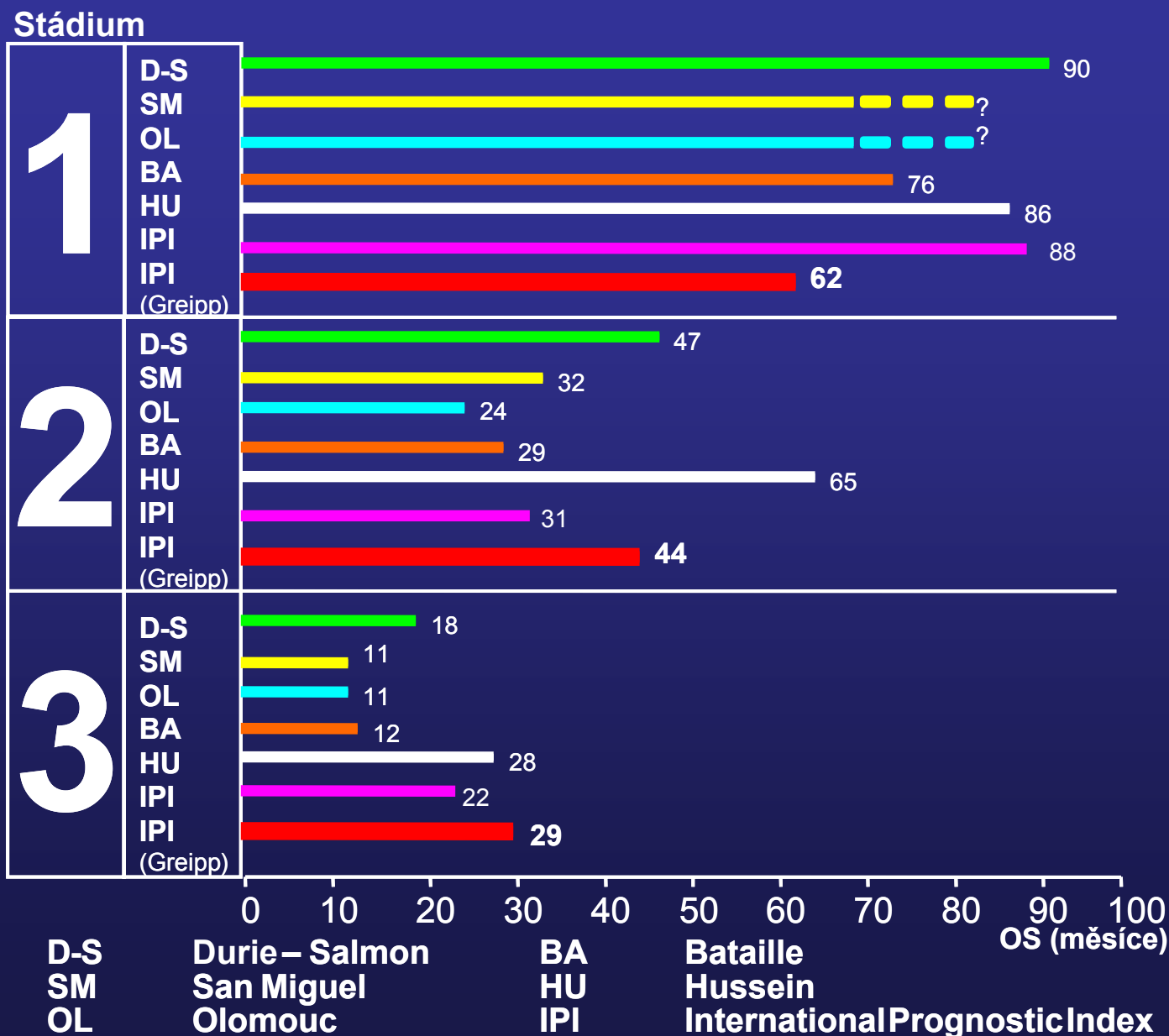


# MM – PROGNOSTICKÝ VÝZNAM STÁŽOVACÍCH SYSTÉMŮ



# MM – SROVNÁNÍ MEDIÁNŮ CELKOVÉHO PŘEŽITÍ DLE STÁDIÍ 1 - 3

(n: 60-229), KT - Olomouc 1991 - 2002



# MM – LÉČEBNÉ POSTUPY 1963-2003 VE FNO

## ☐ KONV.CHEMOTERAPIE

🔔 1963 - 1975

- MP, CP

🔔 1976 - 1995

- VMP+VMCP
- VCAP, VBAP

- VBMCP (M<sub>2</sub>-protokol)

- VAD (event. VAMP, NOP, Cy-VAD) ▶

## ☐ NOVÁ LÉČ.STRATEGIE

🔔 1996 – 2002

- HD-M + ASCT
  - INF- $\alpha$ , INF/Dex
- CIDEX, HD-Dex

## ☐ NOVÉ LÉKY

🔔 2003

- Thal-Dex
- C-Thal-Dex
- Bortezomib (Velcade)

## ☐ JINÉ

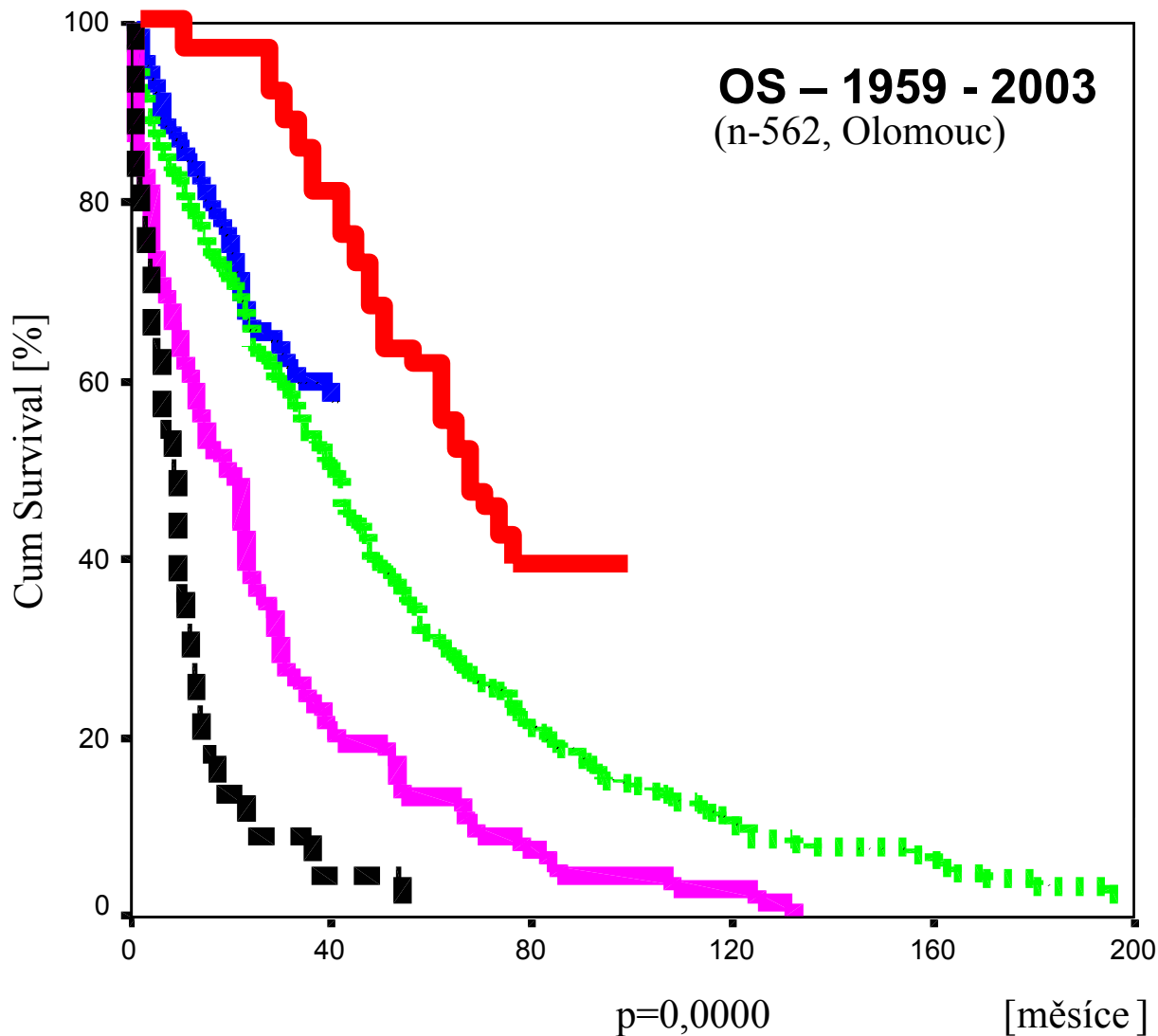
▶ Aktinoterapie

- ložisková
- „hemi-body“

▶ Chirurgická léčba

- neurochirurgie
- ortopedie

## ☐ PODPŮRNÁ LÉČBA

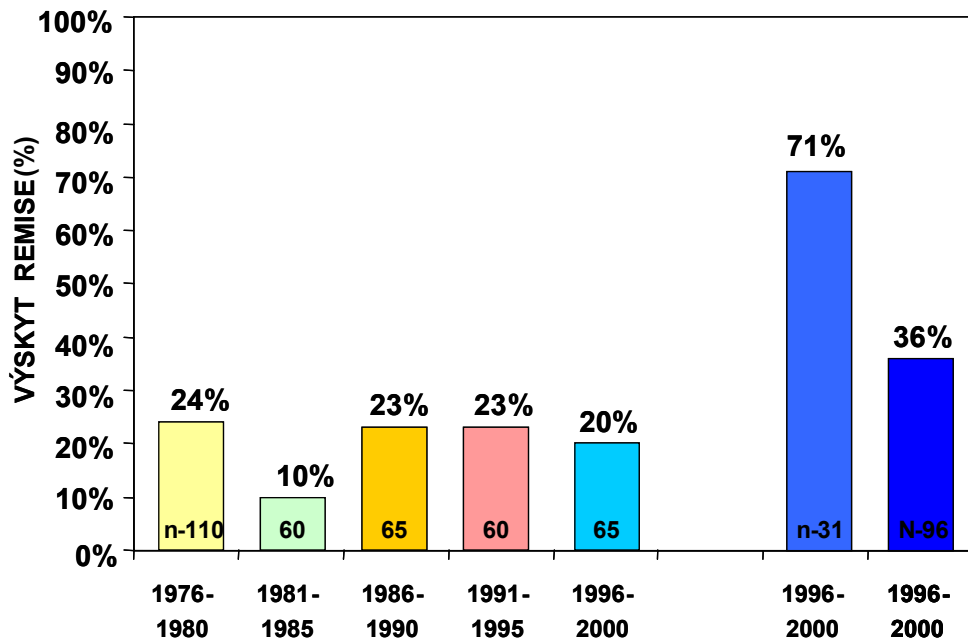


- **1995-2003**  
HD-Th+ASCT  
(n-68, M-67)
- **1996-2000**  
CT / HD-Th + ASCT  
(n-146, M-x)
- - - **1976-1995**  
CT (VMP, VMCP, VBMCP, VAD)  
(n-295, M-39)
- **1963-1975**  
MP, CP  
(n-67, M-19)
- ■ **1959-1963**  
„Symptomatic therapy“  
(n-22, M-8)

# MM – VÝSLEDKY LÉČBY (OS) 1959-2000

## Léčebná odezva

(remise: <25% M-proteinu)

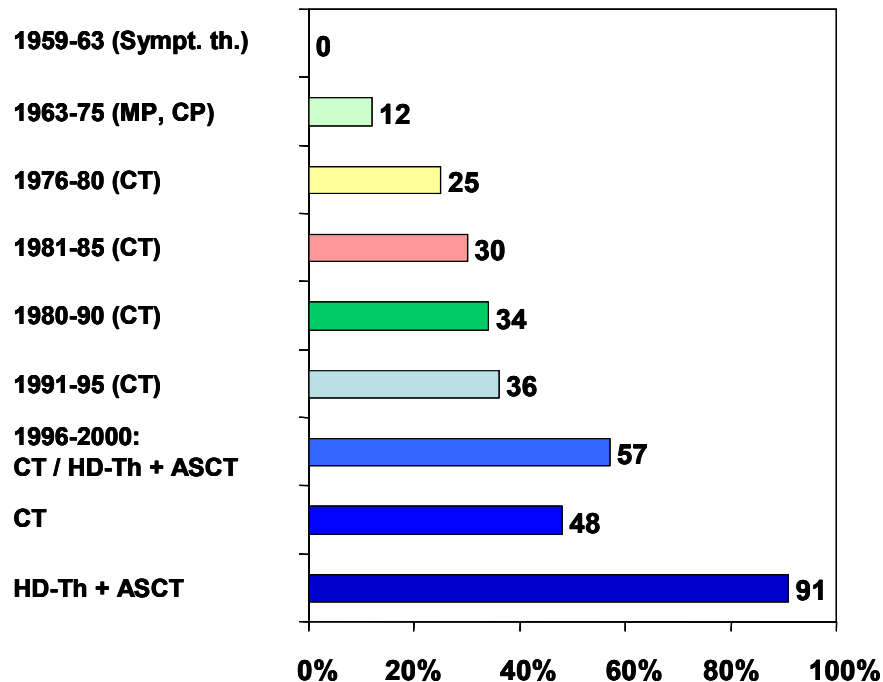


Konvenční léčba

HD-Th  
+ ASCT  
+ KT

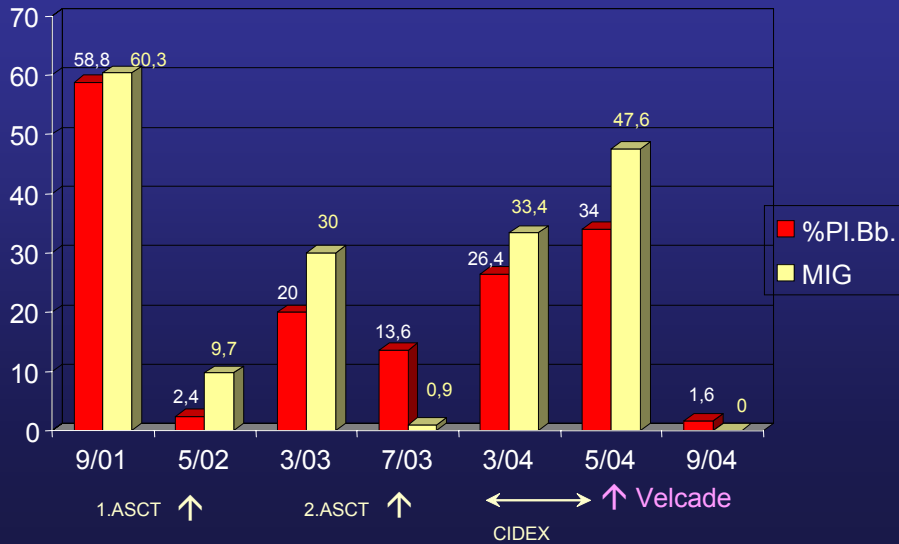
## 5 – leté přežívání

(n – 562)

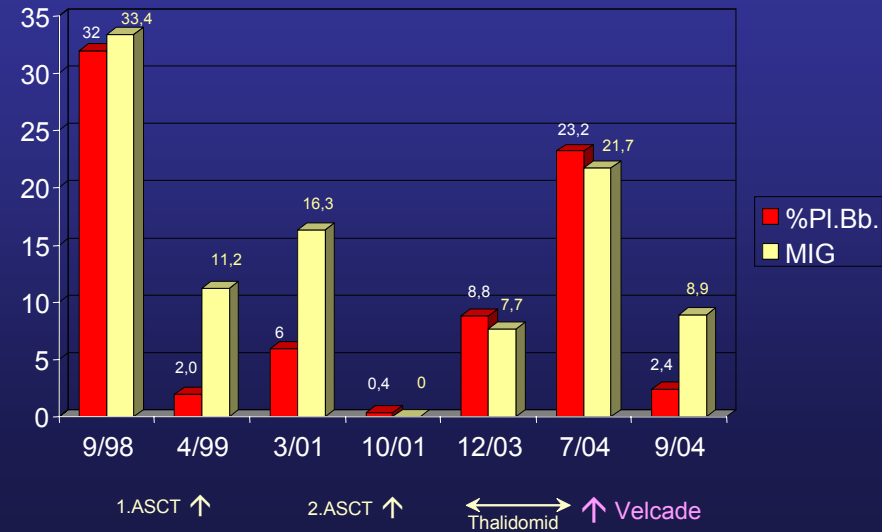


# MM – REZISTENCE: BORTEZOMIB

## VELCADE –kasuistika č.2:



## VELCADE –kasuistika č.3:



# MM – STRATIFIKACE INDUKČNÍ LÉČBY (Olomouc 2002)

