Nový stratifikační model pro MGUS/SMM.

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XIII. Workshop pro mnohočetný myelom
Mikulov 10.- 11.4.2015

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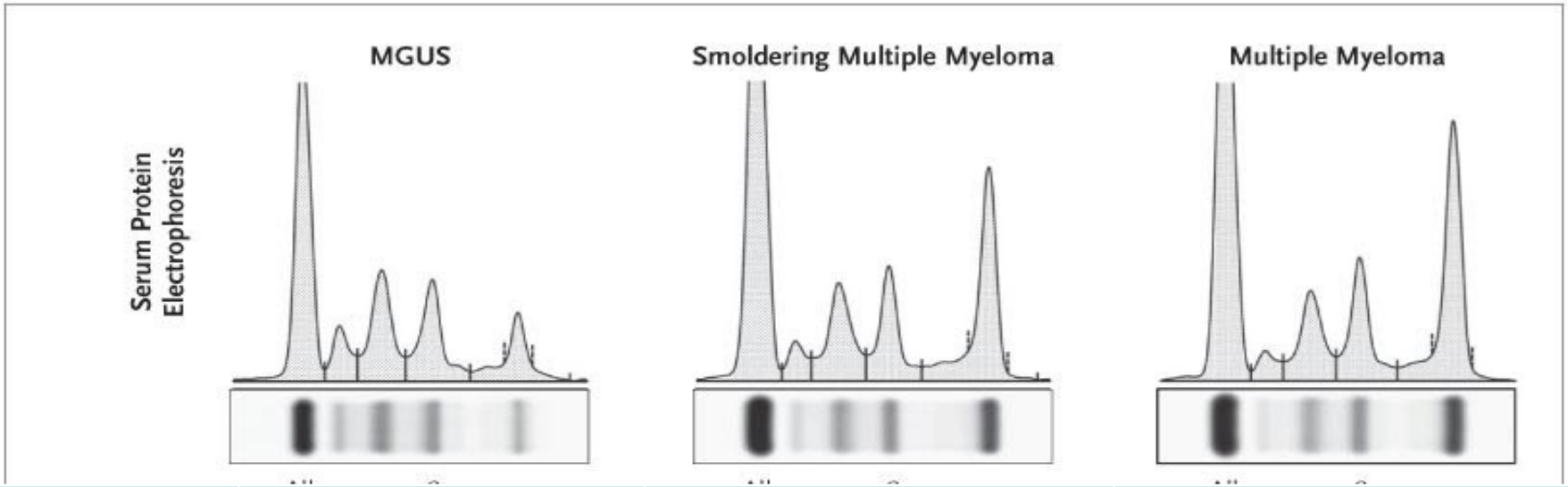
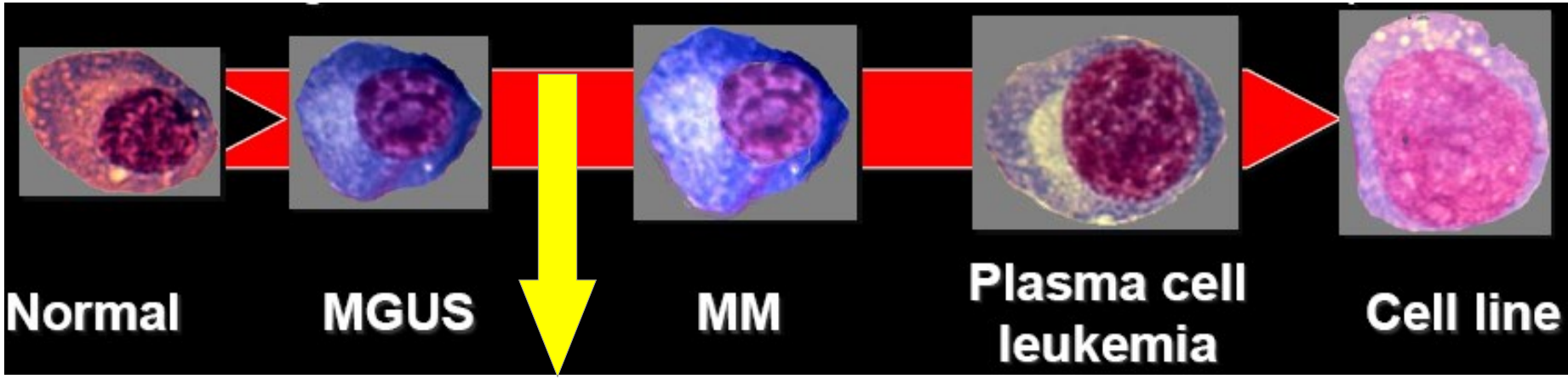
Diagnosis of monoclonal gammopathies



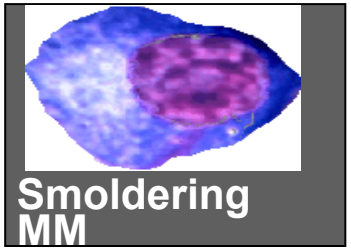
Feature	MGUS	SMM	MM
BMPC, %	< 10	≥ 10	≥ 10
Serum M-protein, g/dL	< 3	≥ 3	≥ 3
Clinical manifestation	Absent	Absent	Present

IMWG. Br J Haematol. 2003; 121(5):749-757.

MM: Oncology perspective



Early intervention



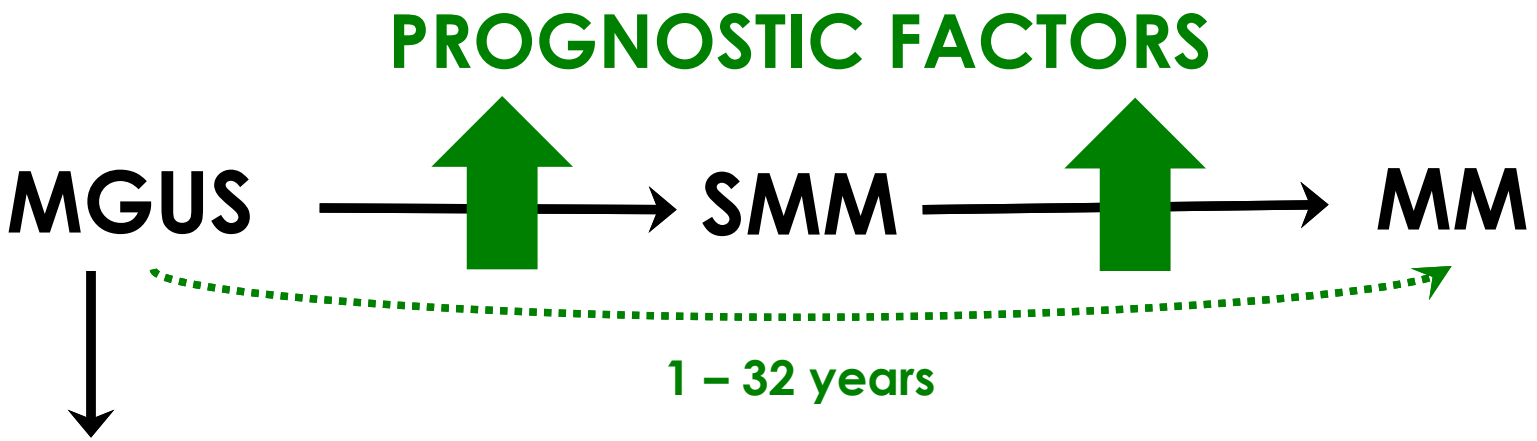
Agressive clonal selection

Cure

Chronic disease management

MM: Oncology perspective

Premalignant precursor of multiple myeloma (MM) is stable and not associated with the presence of secondary clinical manifestations (< 30 g/l serum M-Ig, < 10% bone marrow clonal PCs)



Permanently higher risk of malignant disorder development

MGUS consistently precedes MM

Landgren, O. et al. 2009. Blood 113(22): 5412-5417
Weiss, B. M. et al. 2009. Blood 113(22): 5418-5422
Kyle, R. A. et al. 2010. Leukemia 24: 1121-1127

Risk stratification model for MGUS

Risk-Stratification Models for MGUS

- 2 independent risk stratification schemes for MGUS
  - The Mayo model relies heavily on serum protein findings[1-2]
  - The PETHEMA model utilizes flow cytometry of BM aspirates[1,3]

Study Group	Mayo[1-2]	PETHEMA[1,3]
Risk Factors	• Serum M-protein > 1.5g/dL • FLC (κ/λ) ratio < 0.26 or > 1.65 • Non- IgG MGUS	• ≥ 95% aPCs • Nor DNA aneuploidy
Risk Group (# factors)	• Low: 1 • Medium: 2 • High: 3	• Low: 0 • Medium: 1 • High: 2

BM: bone marrow; aPCs: neoplastic plasma cells ; FLC: free light chain; Ig: immunoglobulin;

1. Kyle RA, Therneau TM, Rajkumar SV ,et al. A long- term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002; 346(8):564-569.

2. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood 2005;106(3):812-817.

3. Perez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertaiin significance and smouldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007;110(7):2586-2592.

Risk stratification models for MGUS

Mayo Clinic [1,2]		
No. of risk factors	No. of patients	Risk of progression at 20 years (%)
1	420	**21**
2	226	**37**
3	53	**58**

PETHEMA Study Group[3]		
No. of risk factors	No. of patients	Risk of progression at 5 years (%)
0	28	**2**
1	22	**10**
2	33	**46**

Risk factors:

- non IgG MGUS
- M-protein > 1.5 g/dL
- FLC ratio < 0.26 or > 1.65

Risk factors:

- ≥ 95% aPC
- nor DNA aneuploidy

1. Rajkumar SV,Blood. 2005 Aug 1; 106(3):812-7
2. Dispenzieri A, Blood. 2008 Jan 15; 111(2):785-9
3. Perez-Persona E,Blood. 2007;110(7):2586–2592

MGUS

Searching
for predictive model

MGUS CZ

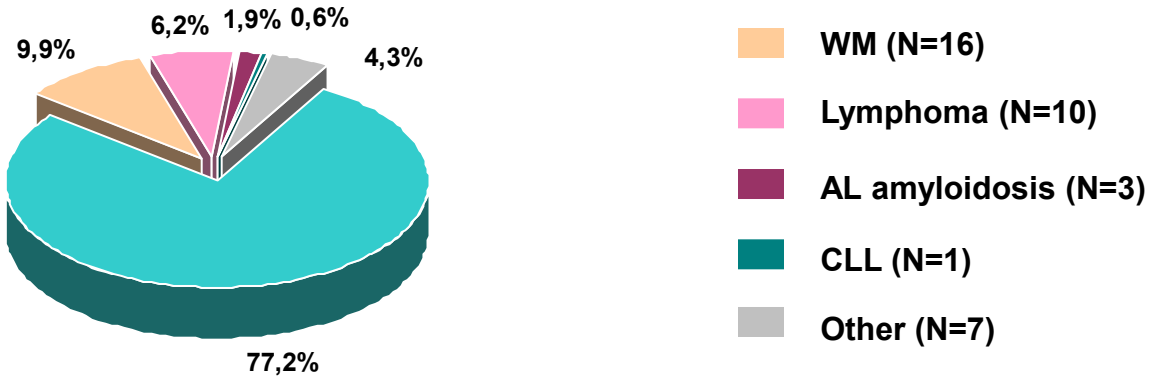
Statistical analysis of 1887 persons with MGUS from RMG registry of Czech Myeloma Group

11/2013

Progression to tumor

Base: patients with progression to tumor

Type of tumor (N=162)



Type of tumor	N=162
MM	125 (77.2%)
WM	16 (9.9%)
Lymphoma	10 (6.2%)
AL amyloidosis	3 (1.9%)
CLL	1 (0.6%)
Other	7 (4.3%)

The key predictors factors of progression

N (%)	Without progression	Progression to tumor	p[1]
Total (N=1887)	**N=1725**	**N=162**	
Age (at diagnosis)			
60-69 vs. younger than 50	47/561 (7.7%)	1.78 (1.04-3.05)	0.036
older than 69 vs. younger than 50	52/571 (8.3%)	2.55 (1.49-4.36)	**0.001**
MIG in serum			
normal	1529 (94.0%)	97 (6.0%)	**<0.001**
abnormal (>15g/l)	172 (74.8%)	58 (25.2%)	
Bone marrow infiltration			
normal	1049 (92.5%)	85 (7.5%)	**<0.001**
abnormal (> 5%)	128 (78.0%)	36 (22.0%)	
Immunoparesis			
One Ig lower vs. other	41/319 (11.4%)	2.06 (1.43-2.99)	**<0.001**
Both Ig lower vs. other	22/97 (18.5%)	3.06 (1.94-4.85)	**<0.001**
Any Ig lower vs. other	63/416 (13.2%)	2.78 (1.99-3.90)	**<0.001**
FLC index			
normal	831 (97.0%)	26 (3.0%)	**<0.001**
abnormal (<0.26 or >1.65)	575 (87.7%)	81 (12.3%)	
Hemoglobin normal	1455 (92.5%)	118 (7.5%)	0.014
abnormal (<120g/l)	265 (88.0%)	36 (12.0%)	
LDH			
normal	1021 (94.5%)	59 (5.5%)	**<0.001**
abnormal (>3.75ukat/l)	564 (88.0%)	77 (12.0%)	
Type of paraprotein			
normal	1198 (91.7%)	109 (8.3%)	0.594
abnormal (non IgG)	520 (90.9%)	52 (9.1%)	

[1] ***Tested by ML Chi-square test***

Validation
of known clinical models

Mayo model

Distribution of MGUS persons according to risk groups based on the Mayo Clinic model confirmed predictive power of Mayo Clinic model based on our data although isotype of M- protein was not found as independent predictor .

Mayo model

No. of risk factors	Overall rate of progression N (%)	HR (95% CI)	p	Kaplan-Meier's estimate of risk of progression % (95% CI) at: 2 years	10 years
0 (N=571)	**13** (2.3%)	*reference*		**1.2** (0.5-2.6)	**4.9** (2.5-9.5)
1 (N=593)	**41** (6.9%)	**2.59** (1.39-4.84)	**0.003**	**1.7** (0.9-3.2)	**16.3** (11.1-23.7)
2 (N=296)	**42** (14.2%)	**4.79** (2.56-8.93)	**<0.001**	**4.8** (2.8-8.1)	**24.6** (17.6-33.8)
3 (N=26)	**9** (34.6%)	**12.97** (5.52 -30.48)	**<0.001**	**15.8** (6.2 - 36.8)	**54.9** (27.8-85.7)

MIG in serum≥1.5 g/dL, Kappa/lambda ratio <0.26 or >1.65, M-protein type: none IgG

Modified PETHEMA model

Immunoparesis instead of DNA aneuploidy was used together with the presence of abnormal plasma cells (aPCs) to validate the modified PETHEMA model. We confirmed predictive power of this model based on our data.

Modified PETHEMA model

No. of risk factors	Overall rate of progression N (%)	HR (95% CI)	p	Kaplan-Meier's estimate of risk of progression % (95% CI) at: 2 years	10 years
0 (N=245)	**8** (3.3%)	*reference*		**1.6** (0.5-4.9)	**11.7** (4.8-26.9)
1 (N=80)	**11** (13.8%)	**3.98** (1.60-9.91)	**0.003**	**8.1** (3.7-17.3)	**78.3** (40.1-98.9)
2 (N=11)	**2** (18.2%)	**14.23** (2.86-70.76)	**0.001**	**28.0** (7.2-76.2)	-

Immunoparesis: Any, CD56+ aPC: ≥95%

CMG model

Based on the 5 parameters with independent predictive value in the univariate analysis we proposed a new CMG model:

1, immunoparesis

2, serum M-protein quantity ≥ 1.5 g/dL

3, BMPC > 5%

4, abnormal sFLC ratio

5, serum level of hemoglobin < 12.0 g/dL

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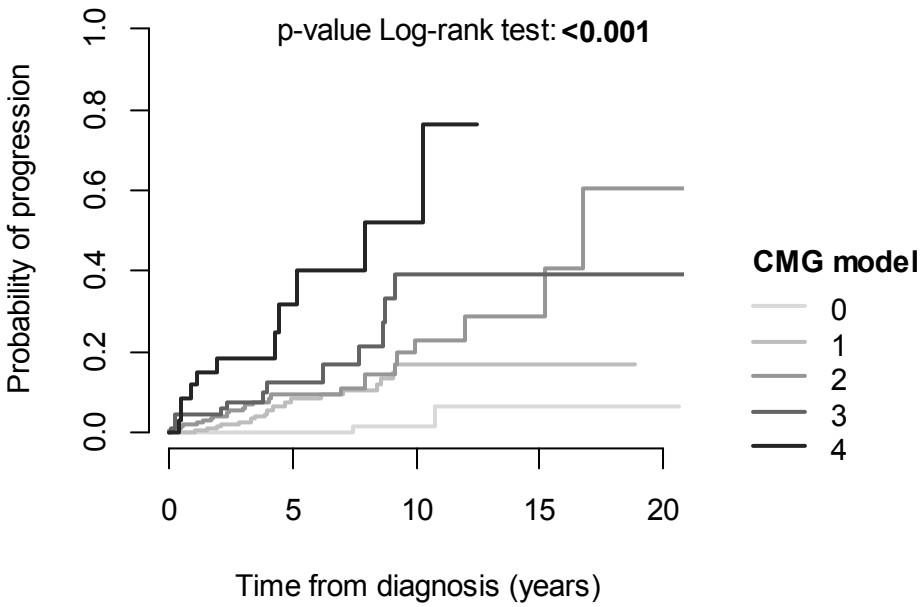
CMG model

No. of risk factors	Overall rate of progression N (%)	HR (95% CI)	p	Kaplan-Meier's estimate of risk of progression % (95% CI) at: 2 years	10 years
0 (N=311)	2 (0.6%)	*reference*		0.0 (-)	**1.6** (0.2-11.1)
1 (N=307)	21 (6.8%)	**9.59** (2.25-40.90)	**0.002**	**1.6** (0.6-4.1)	**16.9** (10.6-26.3)
2 (N=210)	25 (11.9%)	**15.80** (3.74-66.80)	**<0.001**	**4.3** (2.1-8.3)	**22.9** (13.9-36.5)
3 (N=93)	13 (14.0%)	**22.76** (5.13-101.02)	**<0.001**	**4.5** (1.7-11.5)	**39.4** (22.2-63.0)
4-5 (N=35)	11 (31.4%)	**63.17** (13.99-285.36)	**<0.001**	**18.2** (8.6-36.3)	**52.3** (28.3-80.8)

MIG in serum≥1.5 g/dL, Kappa/lambda ratio <0.26 or >1.65, BM infiltration - cytology>5%, Hemoglobin<12.0 g/dL, Immunoparesis: Any

Time to progression into MM for CMG model

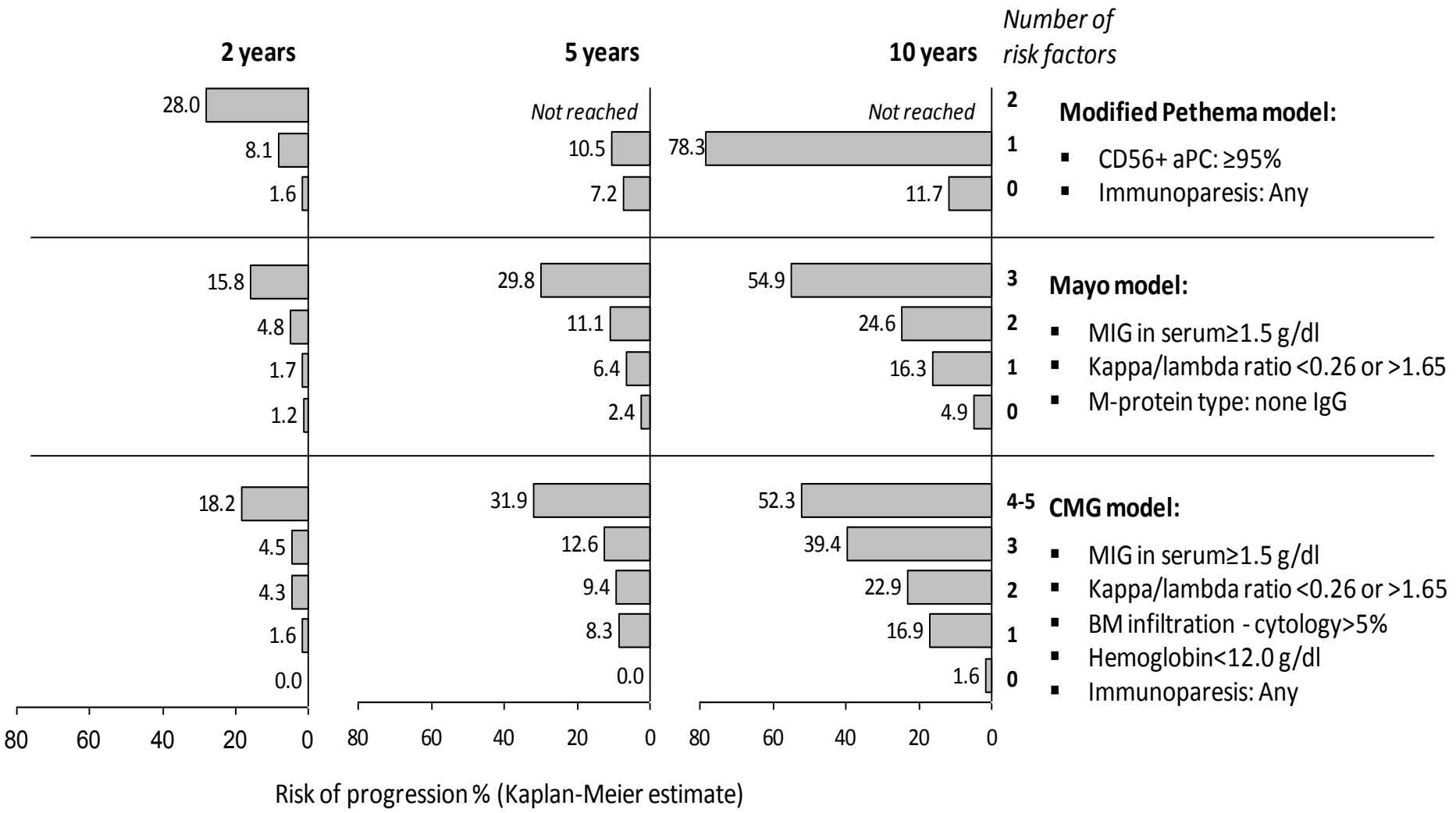


	CMG model (N=956)				
	0 (N=311)	**1 (N=307)**	**2 (N=210)**	**3 (N=93)**	**4-5 (N=35)**
Number of PG	2	21	25	13	11
Median (95% CI)	n.r.	n.r.	16.7 (13.9-19.5)	n.r.	8.0 (3.9-12.0)
Risk at: 1 year % (95% CI)	0.0 (-)	0.0 (-)	2.0 (0.7-5.2)	4.5 (1.7-11.5)	11.8 (4.6-28.4)
Risk at: 2 years % (95% CI)	0.0 (-)	1.6 (0.6-4.1)	4.3 (2.1-8.3)	4.5 (1.7-11.5)	18.2 (8.6-36.3)
Risk at: 3 years % (95% CI)	0.0 (-)	2.5 (1.1-5.4)	5.5 (3.0-10.1)	7.8 (3.5-16.7)	18.2 (8.6-36.3)
Risk at: 5 years % (95% CI)	0.0 (-)	8.3 (5.0-13.6)	9.4 (5.7-15.2)	12.6 (6.2-24.5)	31.9 (16.1-56.8)
Risk at: 10 years % (95% CI)	1.6 (0.2-11.1)	16.9 (10.6-26.3)	22.9 (13.9-36.5)	39.4 (22.2-63.0)	52.3 (28.3-80.8)

Comparison of current models

No. of risk factors	Overall rate of progression N (%)	HR (95% CI)	p	Kaplan-Meier's estimate of risk of progression % (95% CI) at: 2 years	10 years
Modified Pethema model[1]					
0 (N=245)	8 (3.3%)	*reference*		1.6 (0.5-4.9)	11.7 (4.8-26.9)
1 (N=80)	11 (13.8%)	3.98 (1.60-9.91)	**0.003**	8.1 (3.7-17.3)	78.3 (40.1-98.9)
2 (N=11)	2 (18.2%)	14.23 (2.86-70.76)	**0.001**	28.0 (7.2-76.2)	-
Mayo model[2]					
0 (N=571)	13 (2.3%)	*reference*		1.2 (0.5-2.6)	4.9 (2.5-9.5)
1 (N=593)	41 (6.9%)	2.59 (1.39-4.84)	**0.003**	1.7 (0.9-3.2)	16.3 (11.1-23.7)
2 (N=296)	42 (14.2%)	4.79 (2.56-8.93)	**<0.001**	4.8 (2.8-8.1)	24.6 (17.6-33.8)
3 (N=26)	9 (34.6%)	12.97 (5.52-30.48)	**<0.001**	15.8 (6.2-36.8)	54.9 (27.8-85.7)
CMG model[3]					
0 (N=311)	2 (0.6%)	*reference*		0.0 (-)	1.6 (0.2-11.1)
1 (N=307)	21 (6.8%)	9.59 (2.25-40.90)	**0.002**	1.6 (0.6-4.1)	16.9 (10.6-26.3)
2 (N=210)	25 (11.9%)	15.80 (3.74-66.80)	**<0.001**	4.3 (2.1-8.3)	22.9 (13.9-36.5)
3 (N=93)	13 (14.0%)	22.76 (5.13-101.02)	**<0.001**	4.5 (1.7-11.5)	39.4 (22.2-63.0)
4-5 (N=35)	11 (31.4%)	63.17 (13.99-285.36)	**<0.001**	18.2 (8.6-36.3)	52.3 (28.3-80.8)

Risk of progression in 2, 5 and 10 years for modified Pethema, Mayo and CMG model



Conclusion

- We confirmed validity of previously considered clinical models for the risk of progression from MGUS to MM by the Mayo Clinic group and the Spanish PETHEMA group (model used for SMM).

- The created CMG model for the risk of progression from MGUS to MM or related malignancies was established with an advantage **for better identification of MGUS persons at low risk** (87% of persons with risk of progression below 10% in 5 years) as well as few persons at the highest risk of progression.

SMM

Searching
for predictive model

SMM CZ

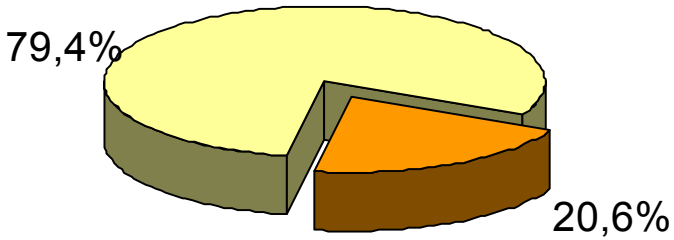
Statistical analysis of 287 patients with SMM from RMG registry of Czech Myeloma Group

11/2013

SMM CMG: Basic characteristics

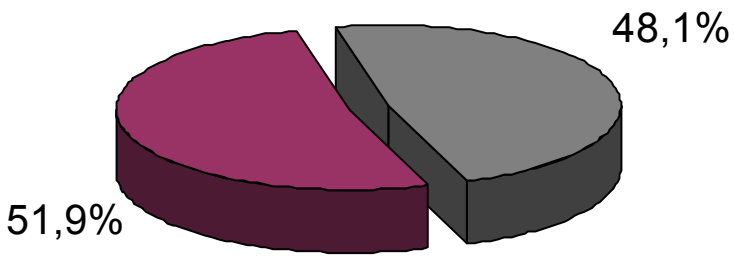
N=287

Development from MGUS



- **Development from MGUS (N=59)**
- **New dg. SMM (N=228)**

Progression



- **Progression into MM (N=149)**
- **No progression (N=138)**

In univariate analysis factors significantly associated with progression were as follows:

Risk factor	Hazard ratio (95% CI)	p
Serum free light chain ratio (iFLC/uFLC) ratio > 30	**2.49** (1.49-4.17)	**<0.001**
Plasma cell infiltration in bone marrow cytology ≥ 15%	**2.19** (1.36-3.54)	**<0.001**
Immunoparesis: Any	**2.01** (1.36-2.96)	**<0.001**
M - protein concentration ≥ 2.3 g/dL	**2.00** (1.44-2.79)	**<0.001**
Beta2 microglobulin (g/dL): ≥ 2vs. <2	**1.87** (1.29-2.70)	**0.001**
Thrombocyte count ≤ 250 x 10^9/l	**1.70** (1.17-2.44)	**0.005**

In multivariate analysis, 3 factors showed independent predictive value:

- ✓ Immunoparesis
- ✓ Serum M-protein quantity ≥ 2.3 g/dL
- ✓ iFLC/uFLC > 30)

Based on the 3 parameters with independent predictive value we proposed a new **CMG model.**

CMG model

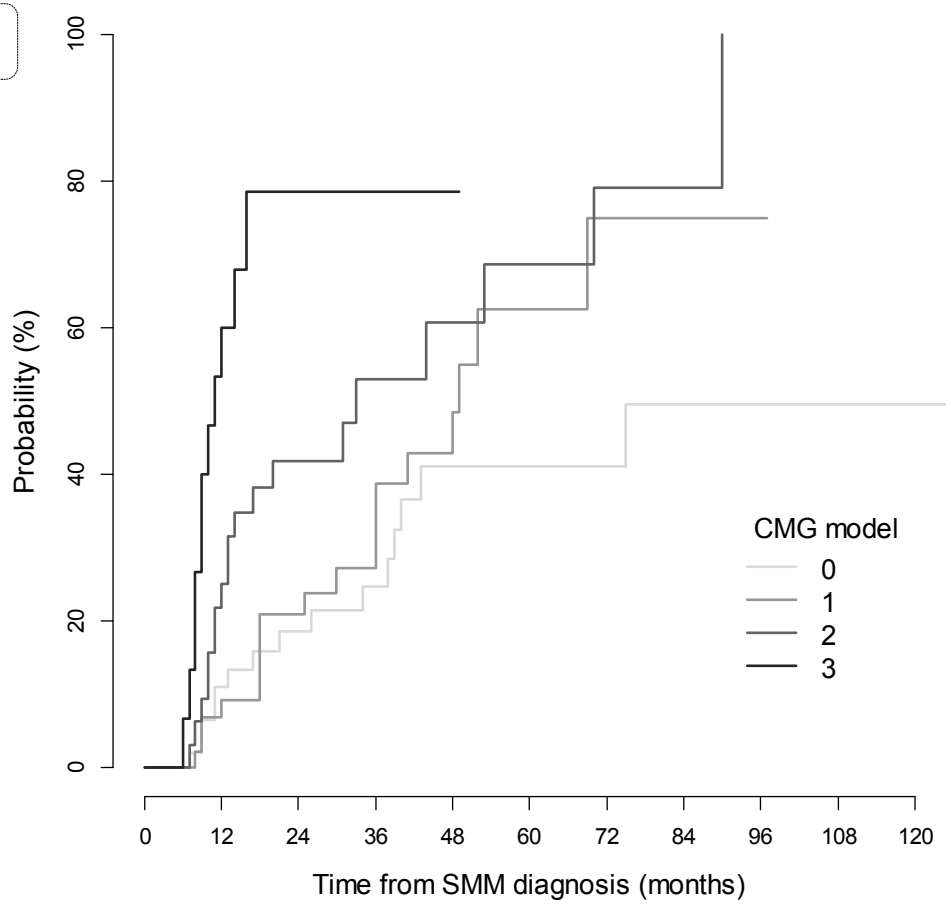
	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Model[1]				
Immunoparesis: Any	2.01 (1.36-2.96)	**<0.001**	1.81 (1.04-3.13)	**0.035**
iFLC/uFLC>30	2.49 (1.49-4.17)	**<0.001**	2.36 (1.37-4.04)	**0.002**
Serum M-protein quantity (g/l)≥23	2.00 (1.44-2.79)	**<0.001**	1.55 (0.91-2.64)	0.109

Model:	Risk groups	N (without PG/ PG into MM)	HR (95% CI)	p
Model (N=139)	**0 (N=48)**	32/16	*reference*	
	1 (N=44)	26/18	**1.46** (0.73-2.91)	0.283
	2 (N=32)	13/19	**2.53** (1.28-5.01)	**0.008**
	3 (N=15)	4/11	**6.77** (3.01-15.22)	**<0.001**

[1]Risk factors
Immunoparesis any
Serum M-protein quantity≥23 g/l
iFLC/uFLC>30

Time to progression into MM for CMG model

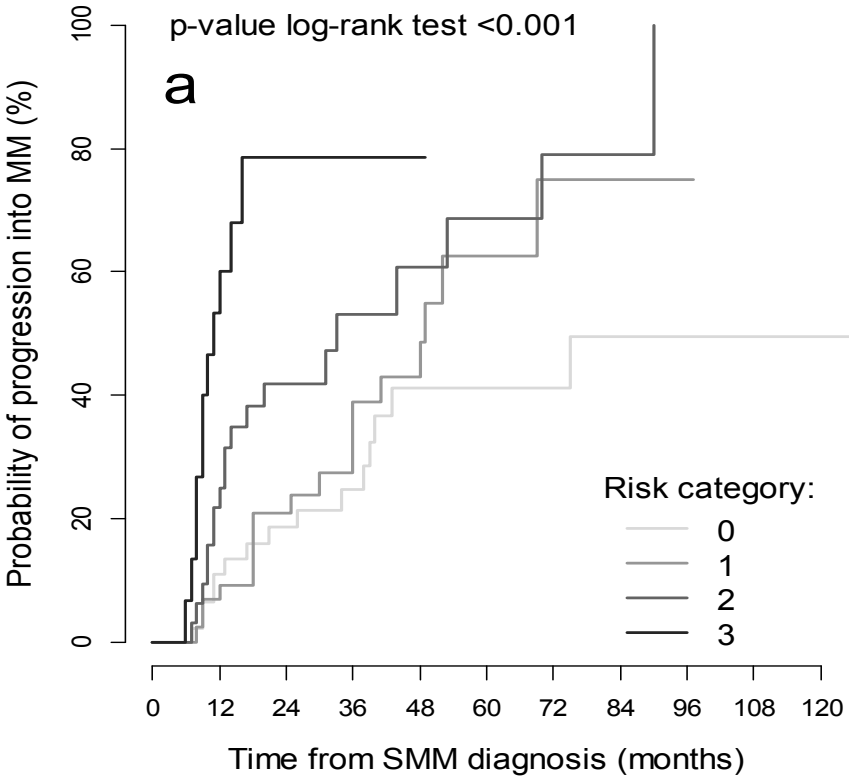
N=139

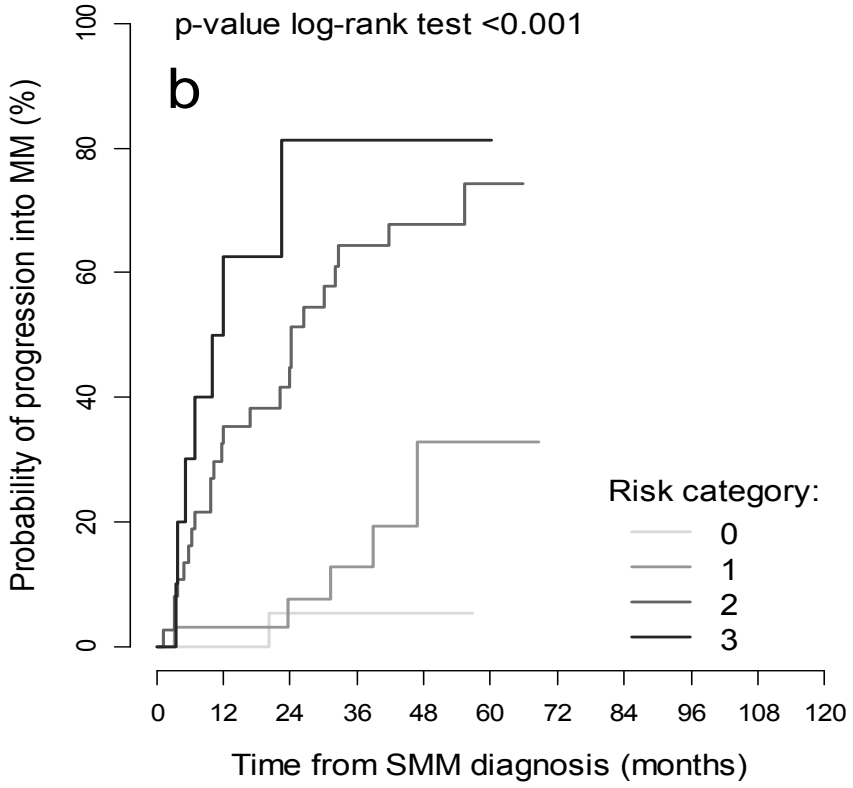


[1]Risk factors
Immunoparesis any
Serum M-protein quantity≥23 g/l
iFLC/uFLC>30

	Risk model[1]			
Cumulative progression (%)	**0 (N=48)**	**1 (N=44)**	**2 (N=32)**	**3 (N=15)**
Median (95% CI)	163.0 (32.4-293.6)	49.0 (35.5-62.5)	33.0 (7.9-58.1)	11.0 (7.2-14.8)
1 year	11.0 (4.7-24.5)	9.2 (3.6-22.7)	25.0 (13.4-43.8)	60.0 (37.2-83.5)
2 years	18.5 (9.7-33.7)	20.9 (11.0-37.8)	41.9 (26.8-61.1)	78.7 (53.1-95.7)
3 years	24.7 (13.9-41.5)	38.8 (24.2-58.1)	53.0 (35.1-73.3)	78.7 (53.1-95.7)
5 years	41.2 (25.9-61.0)	62.5 (41.9-83.0)	68.7 (46.8-88.2)	-
10 years	49.6 (30.7-72.2)	-	100.0 (-)	-

CMG risk model: CMG cohort of persons (a) and validation cohort of Heidelberg persons (b)





Conclusion

We propose and validate a **new risk model for SMM patients with prediction of 80% (78.7%; 81.3%) risk of progression to therapy requiring myeloma within 2 years** based on easily accessible clinical parameters

(CMG model).

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Thank you for your attention.