Diagnostik bei MDS

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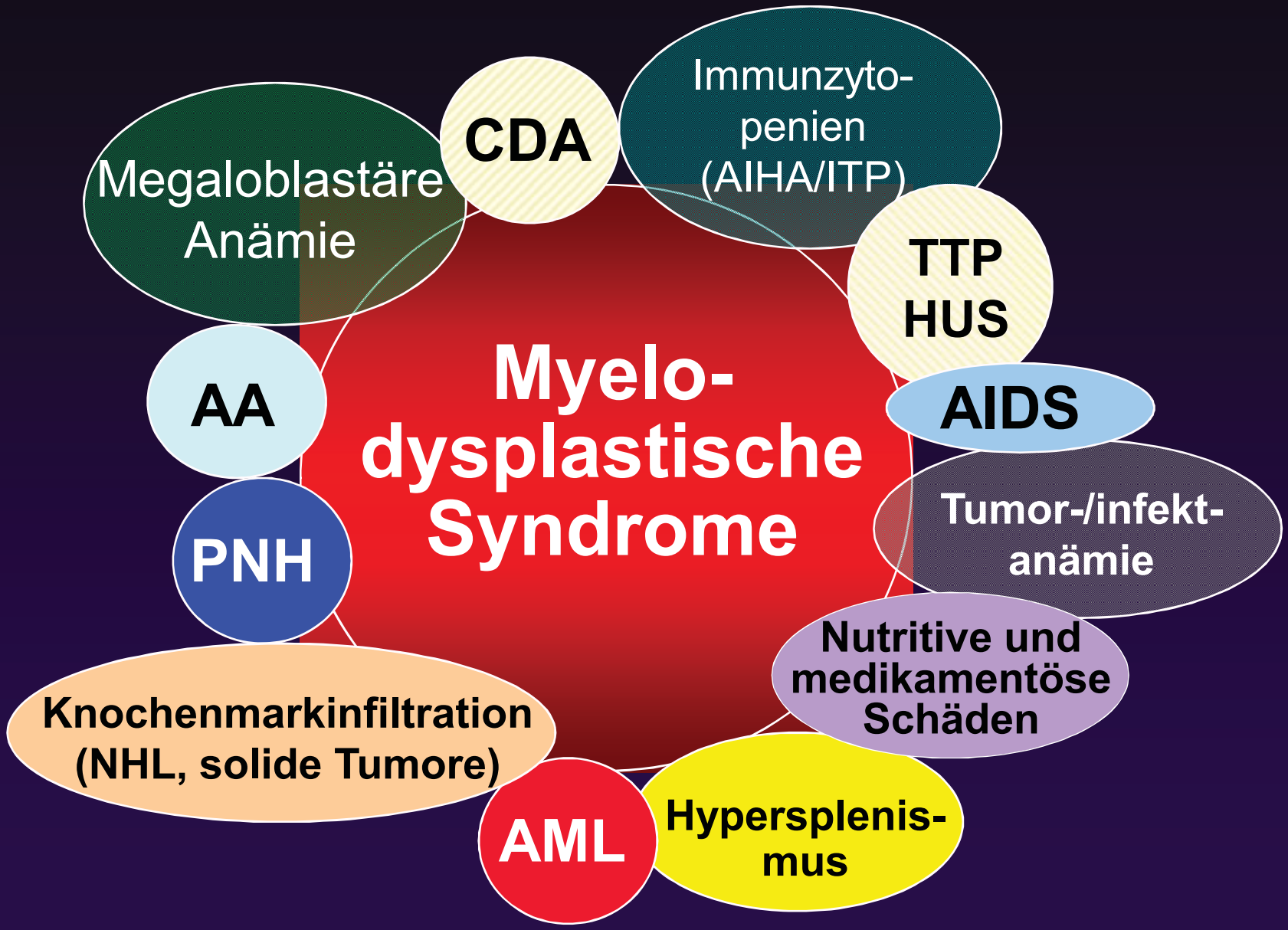
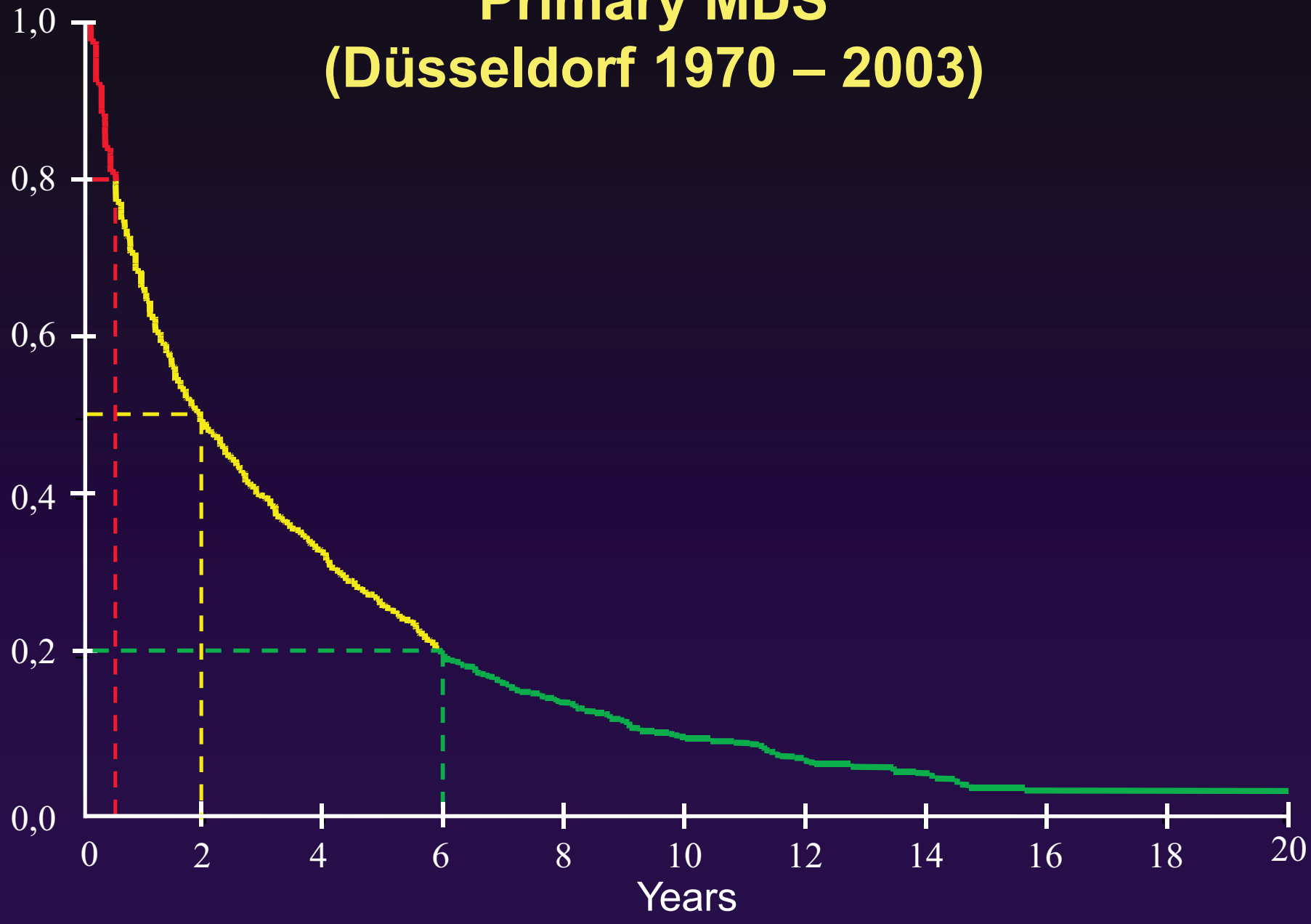
Differentialdiagnosen der MDS



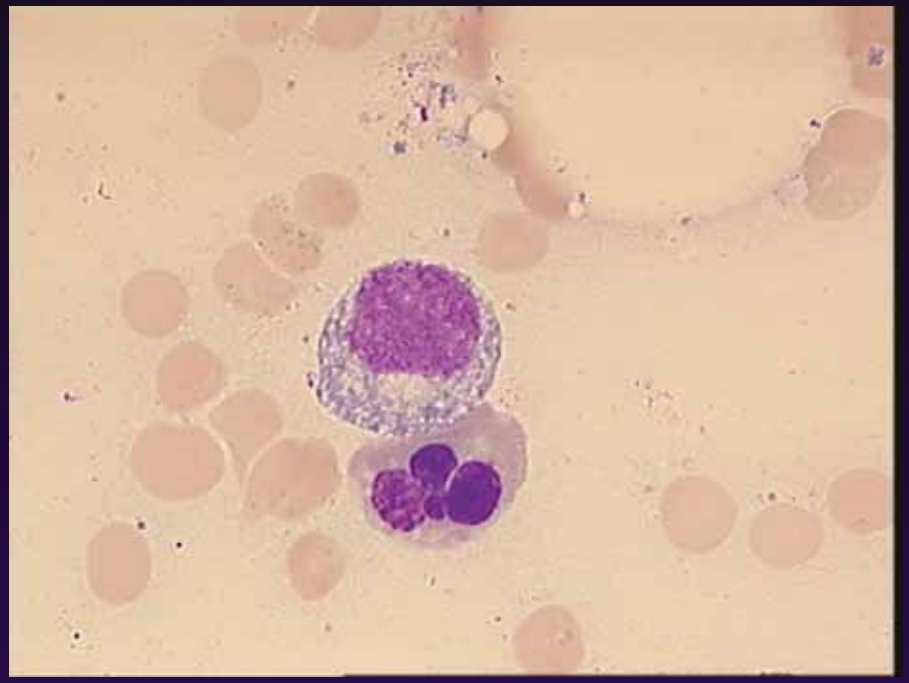
Cumulative Survival of 1806 Untreated Patients with Primary MDS (Düsseldorf 1970 – 2003)

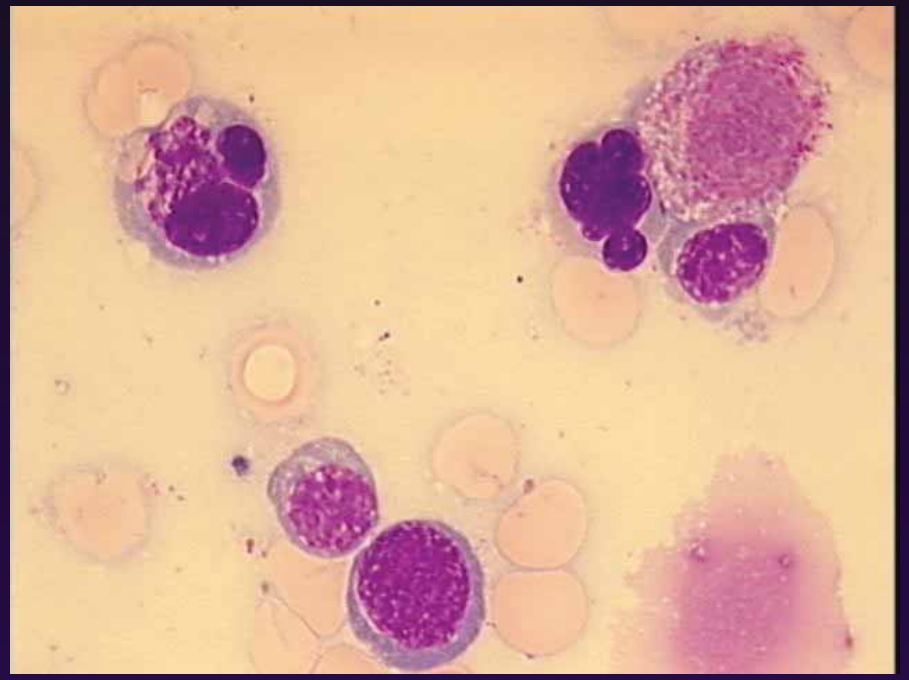


Dysplasiekriterien

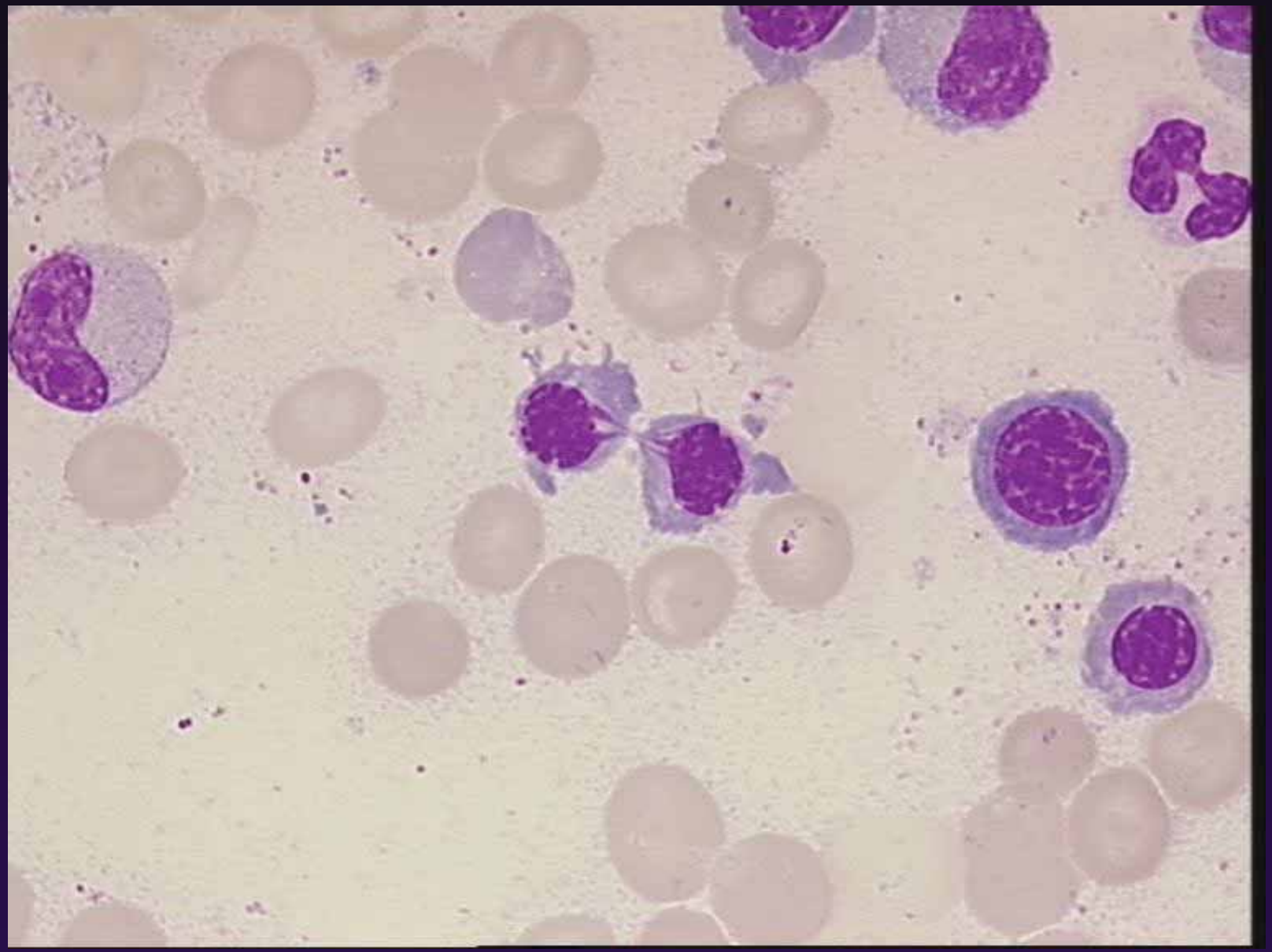
- Erythropoiese
  - Kernanomalien
  - Ringsideroblasten
- Megakaryopoiese
  - Mikromegakaryozyten
  - mononukleäre Megakaryozyten
- Granulopoiese
  - Pseudopelger Zellen
  - Hypogranulierte Zellen
  - vermehrte Blasten

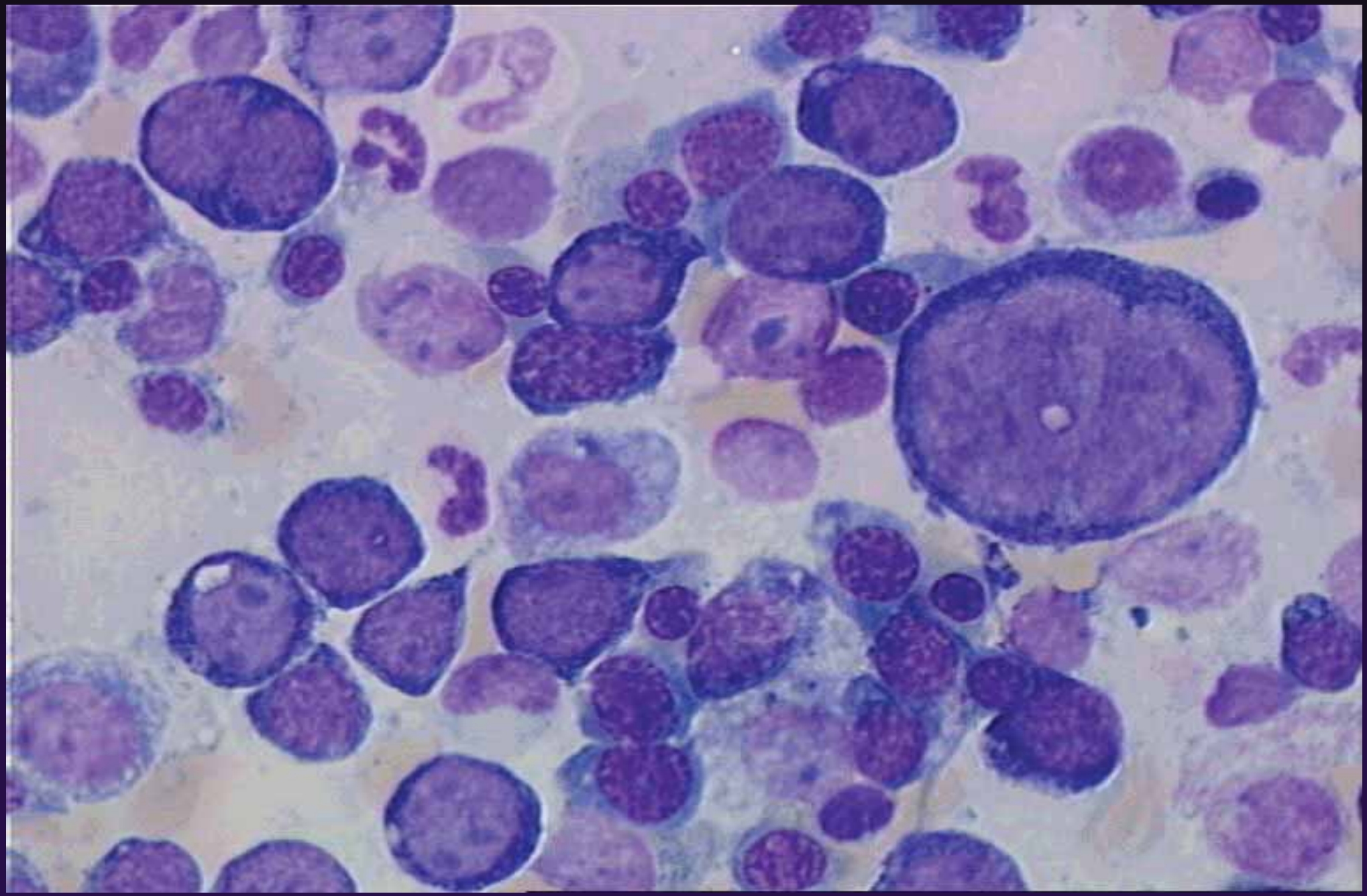
Erythroide Dysplasien bei MDS



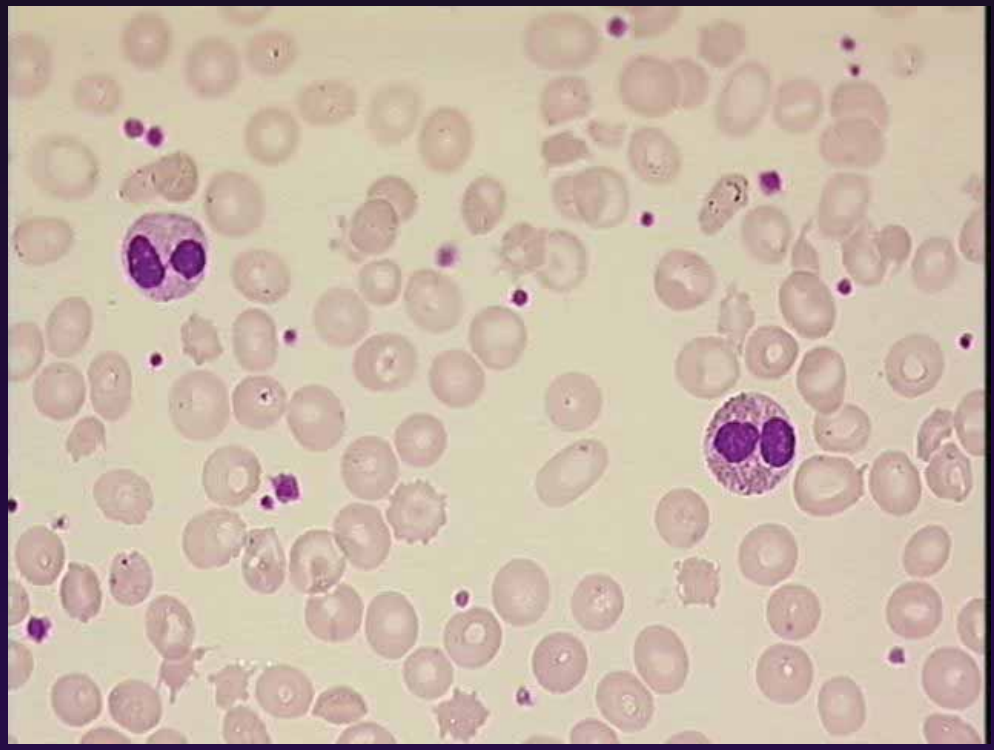


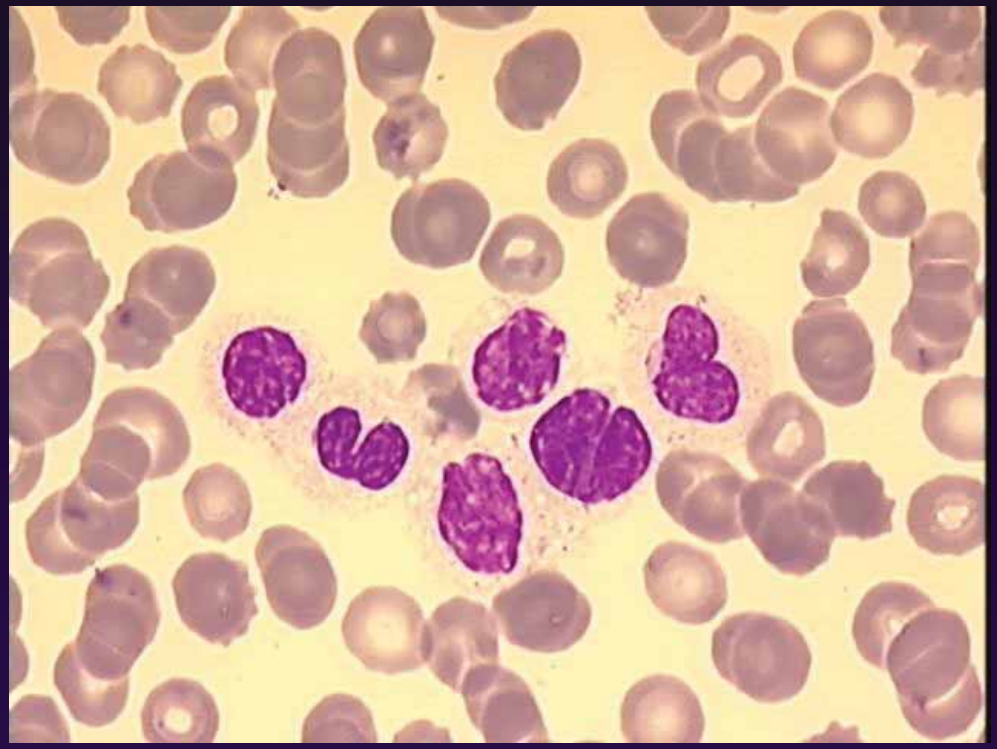
Erythroide Dysplasien bei MDS



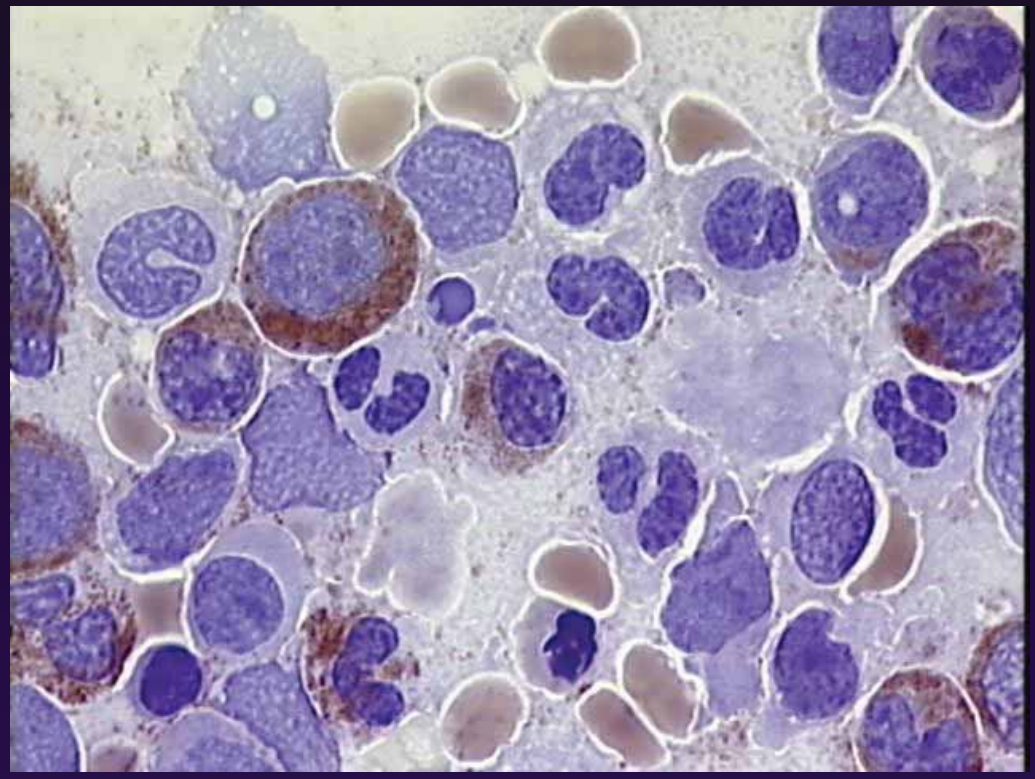


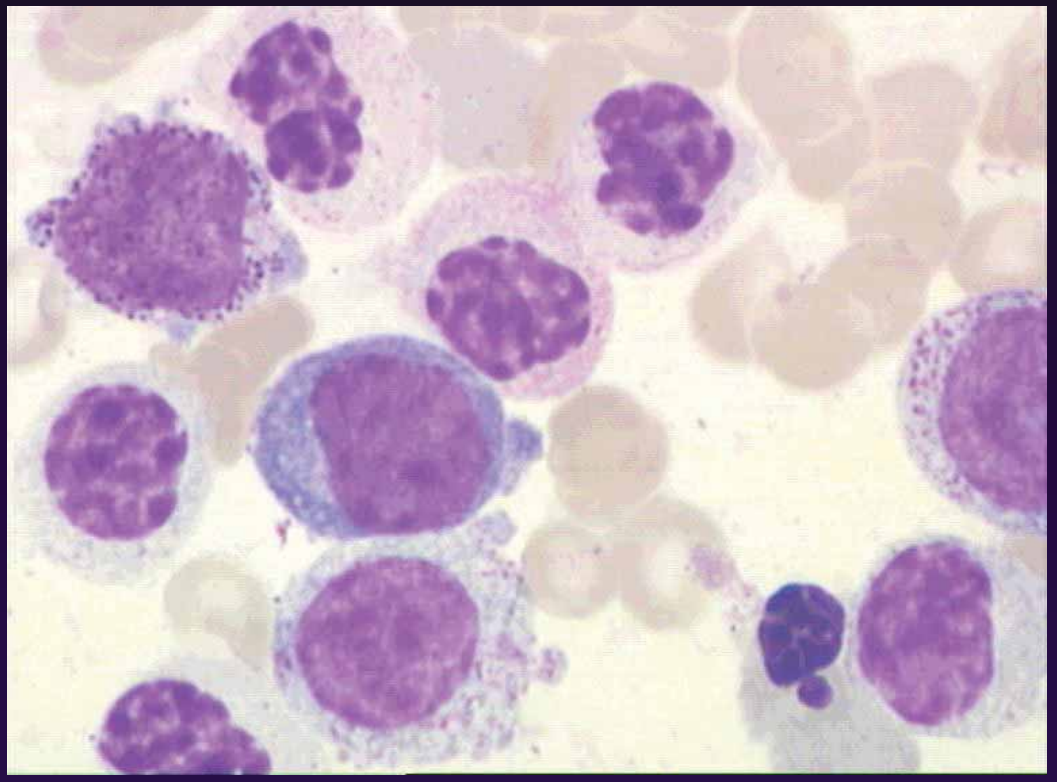
Granulozytäre Dysplasien bei MDS



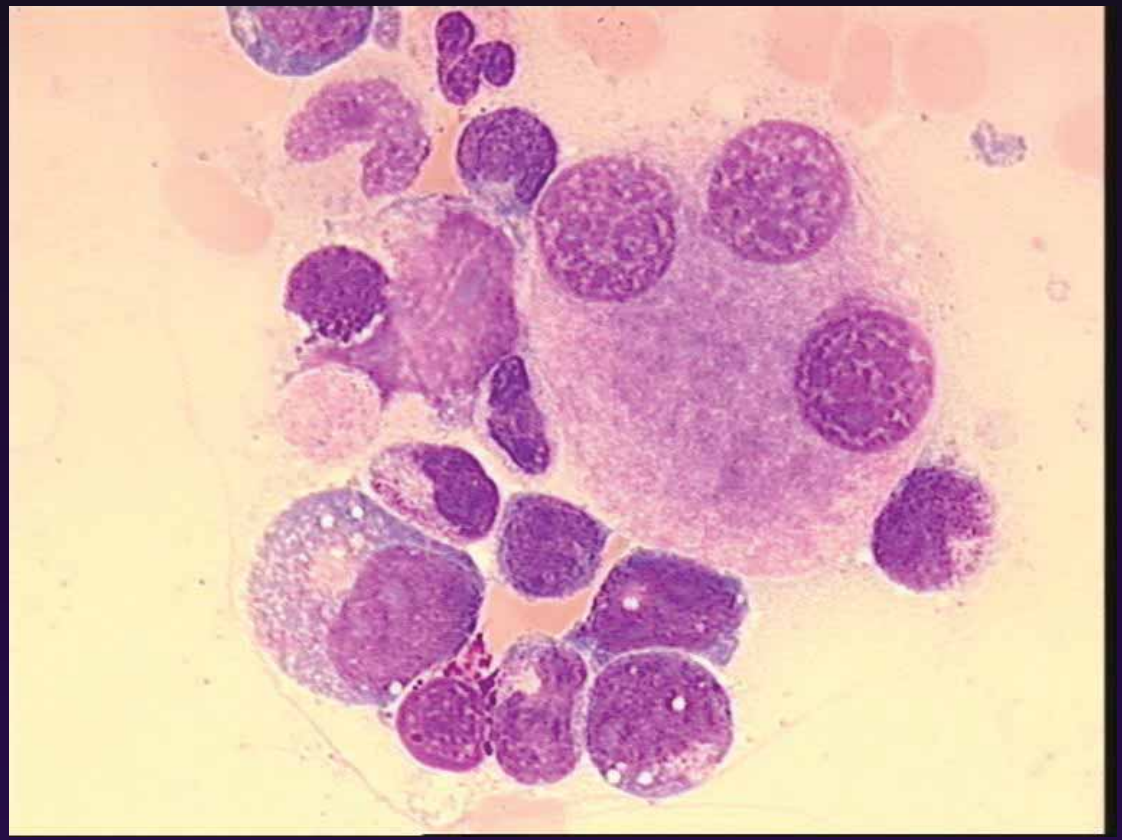


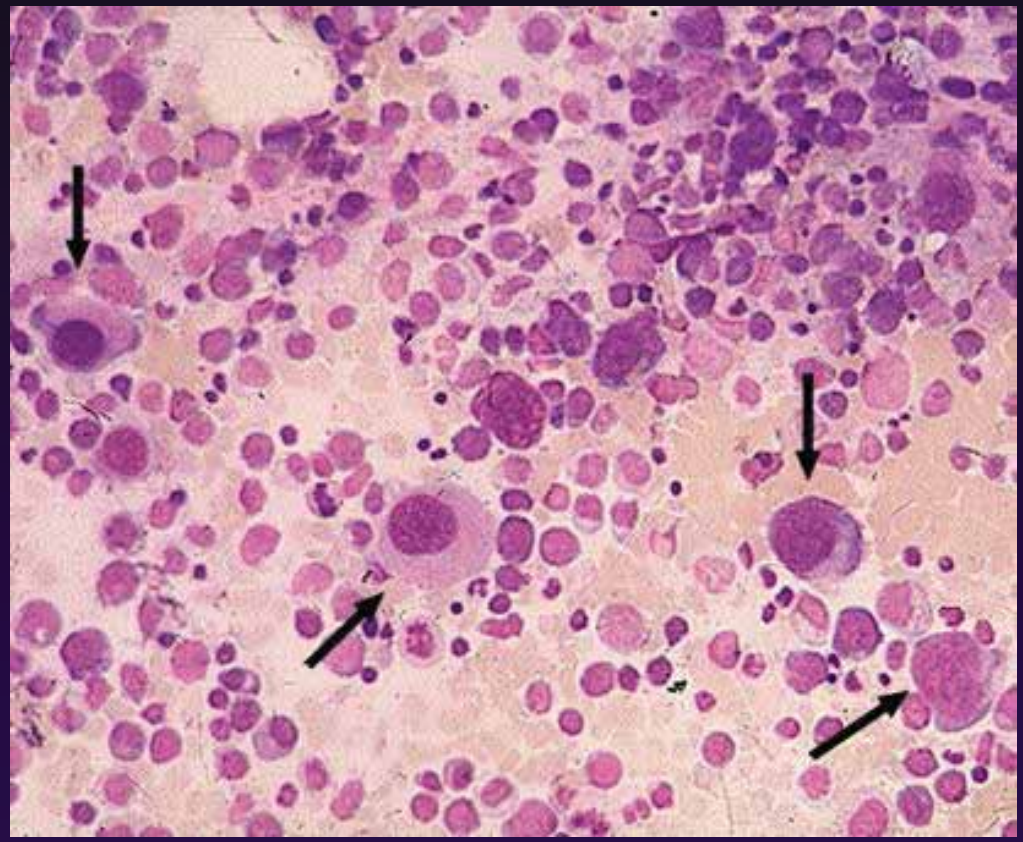
Granulozytäre Dysplasien bei MDS





Megakaryozytäre Dysplasien





Idiopathic cytopenia of unknown significance (ICUS)
Idiopathic dysplasia of unknown significance (IDUS)

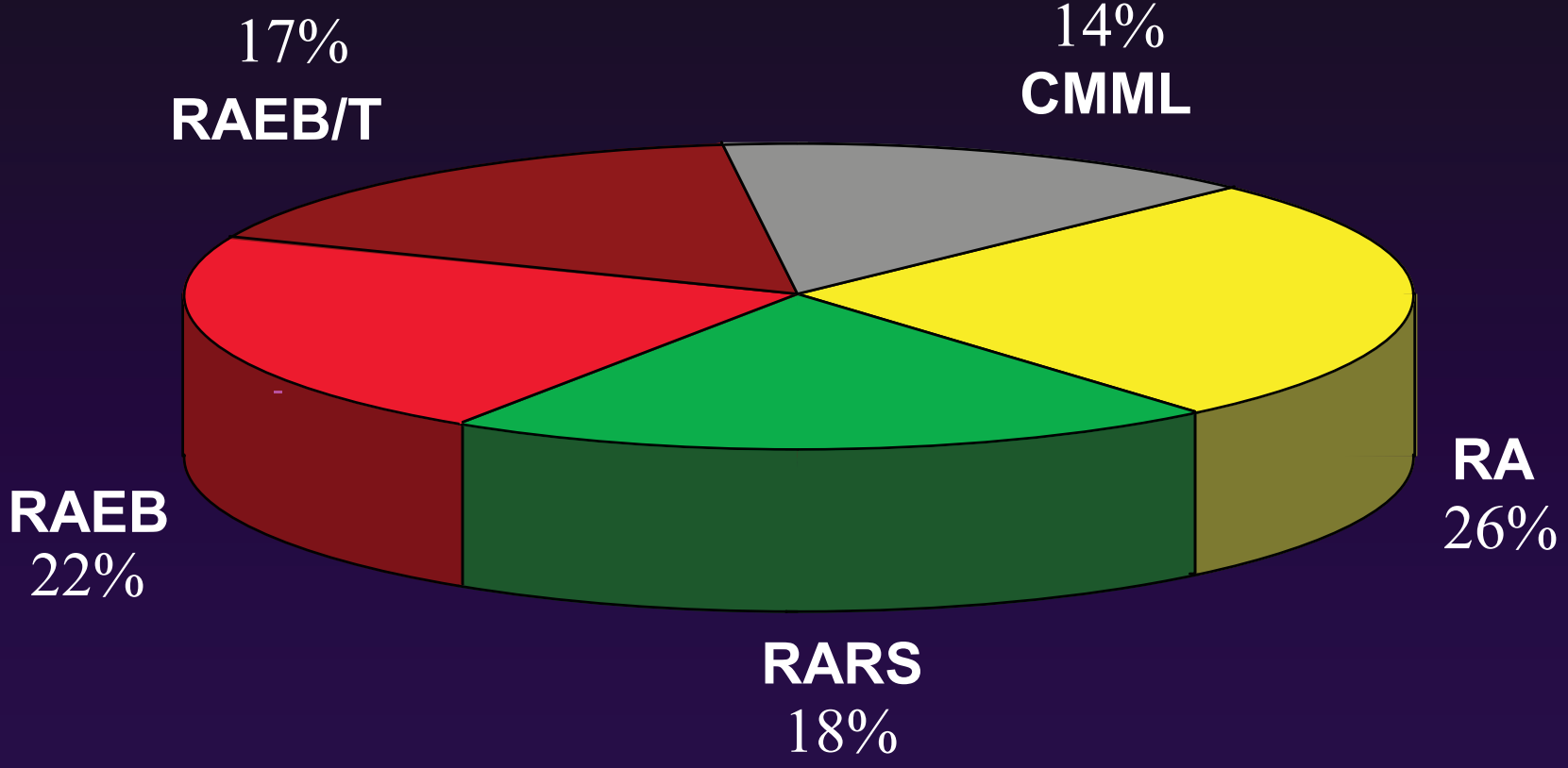
ICUS	IDUS
Hämoglobin <11.0 g/dL	Hämoglobin >11.0 g/dL
Neutrophile <1500/µL	Neutrophile >1500/µL
Thrombozyten <100.000/µL	Thrombozyten >100.000/µL
	für >6 Monate
„Keine signifikante Dysplasie“	„Signifikante Dysplasie“

Morphological classification of myelodysplastic syndromes (FAB-classification)

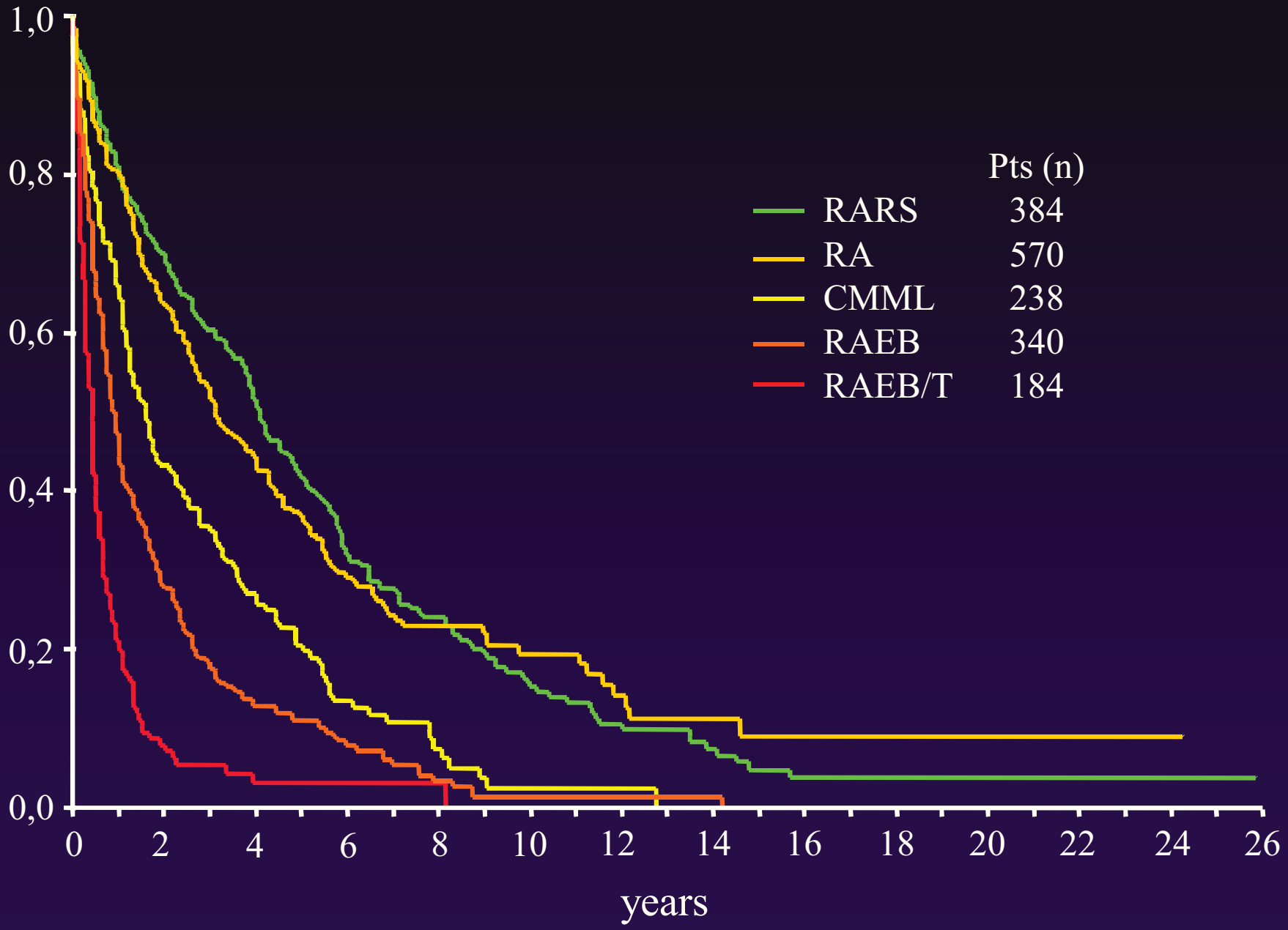
Subtype	Blast percentage		additional features
	Blood	Bone marrow	
Refractory Anemia (RA)	≤ 1%	< 5%	
Refractory Anemia w ringed sideroblasts (RARS)	≤ 1%	< 5%	> 15% ringed sideroblasts in bone marrow
Refractory anemia w blast excess (RAEB)	< 5%	5-20%	
Chronic myelomonocytic leukemia (CMML)	< 5%	5-20%	peripheral monocytosis (> 103/µl)
RAEB in transformation (RAEB/T)	≥ 5%	21-30%	optional Auer-rods

DÜSSELDORF BONE MARROW REGISTRY

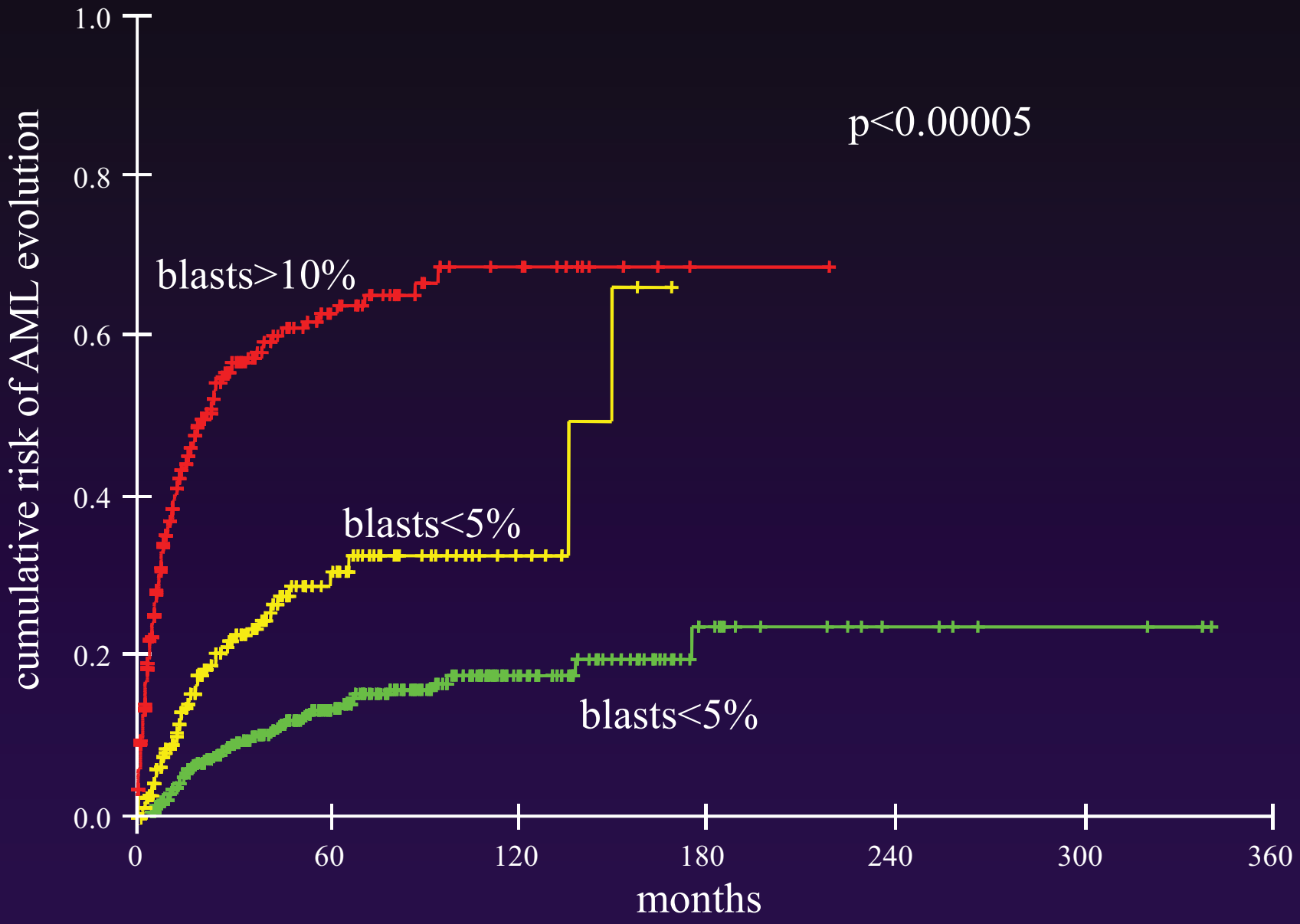
Morphological subtypes of 1698 MDS patients

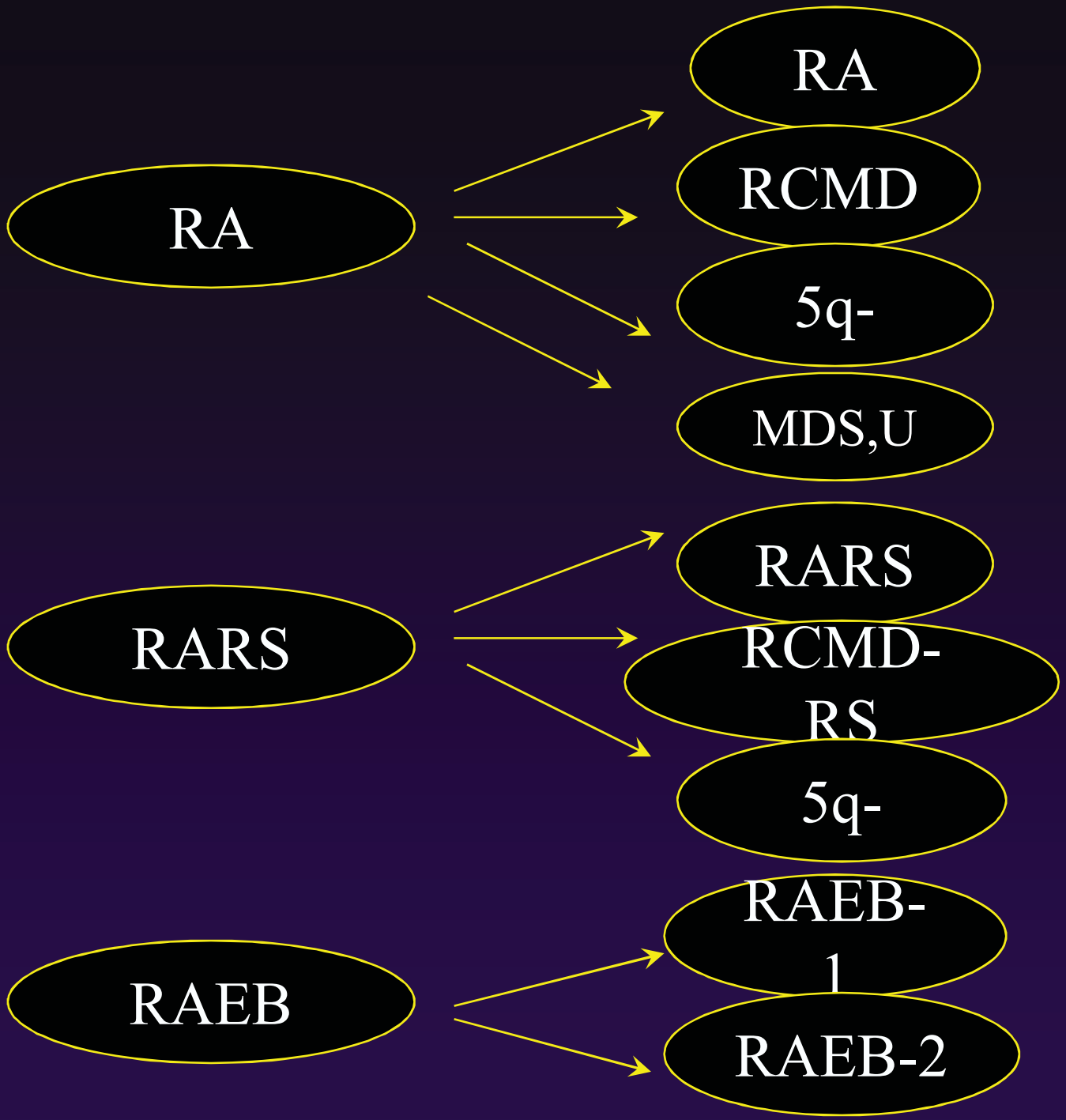


Prognostic Value of the FAB Classification



Risk AML


p<0.00005
blasts>10%
blasts<5%
blasts<5%
cumulative risk of AML evolution
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
months


RA
RA
RCMD
5q-
MDS,U
RARS
RARS
RCMD-RS
5q-
RAEB
RAEB-1
RAEB-2

WHO Klassifikation der MDS (2008)

Subtyp	Blut	Knochenmark
Refractory Cytopenia *with Unilineage Dysplasia* **A, T, N**	*Anämie* *≤1% Blasten*	*Einliniendysplasie* *<5% Blasten* *<15% Ringsideroblasten*
Refractory Anemia with Ringsideroblasts ***(RARS)***	*Anämiae* *≤1% Blasten*	*Nur Dyserythropoiesie* *<5% Blasten* *>15% Ringsideroblasten*
Refractory Cytopenia with multilineage Dysplasia with or without ring sid. ***(RCMD)***	*Zytopenie* *≤1% Blasten* *Keine Auerstäbch.* *<1000 /ml Monozyten*	*Dysplasie in >10% Zelllinien* *<5% Blasten,* *Keine Auerstäbchen*
MDS with isolated del(5q)	*Anämie* *normale oder erhöhte Thrombos*	*<5% Blasten , keine Auerstäbchen* *Megakaryocyten mit hypolobulierten Kernen*
MDS, unclassifiable	*Zytopenie*	*Dysplasie (nicht erythroid)*

WHO Klassifikation der MDS (2008)

Subtyp	Blut	Knochenmark
Refractory Anemia with excess blasts I (***RAEB I***)	*Zytopenie* *<5% Blasten* *keine Auerstäbchen* *<1000 /µl Monocyten*	*Einlinien- oder Multilinen-Dysplasie* *keine Auerstäbchen* *5-9 % Blasten*
Refractory Anemia with excess blasts I I (***RAEB II***)	*Zytopenie* *<19% Blasten* *Auerstäbchen möglich*	*Einlinien- oder Multilinen-Dysplasie* *10-19 % Blasten* *Auerstäbchen möglich*

WHO classification 2008

„MDS unclassifiable“

Category	peripheral Blasts	med. Blasts
MDS unclassifiable	≤1%	<5%

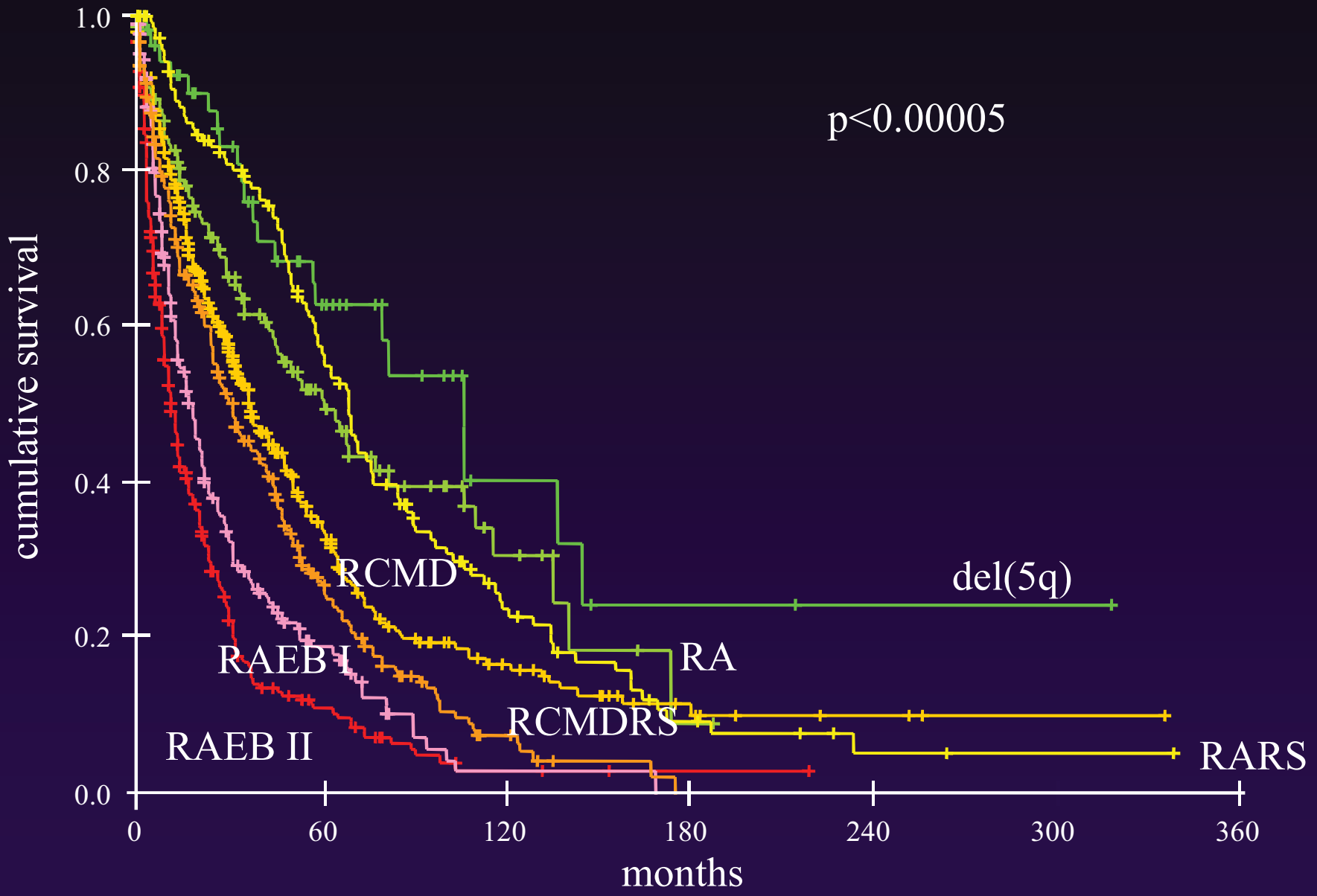
a) RCUD with Pancytopenia (U-pan)
b) RCUD or RCMD with 1% peripheral blasts (U-pB)
c) <10% dysplastic cells, but typical cytogenetic aberrations (U-nodys)

Bruning et al, Blue book 2008

Diagnostic categorization in MDS

- easy:	*RAEB (increased blasts)* *RCMD (RS) (multilineage Dysplasia)* *RARS (Ring sideroblasts)*
- intermediate:	*MDS with del(5q) (typical morphology)* *CMML (monocytic proliferation)*
- difficult:	*RCUD* *1) no multilineage Dysplasia* *2) only about 20% have Ring sideroblasts* *3) abnormal Karyotype very rare* *→ Diagnosis of exclusion, diagnosis can be confirmed during the course of the disease*

WHO classification 2001

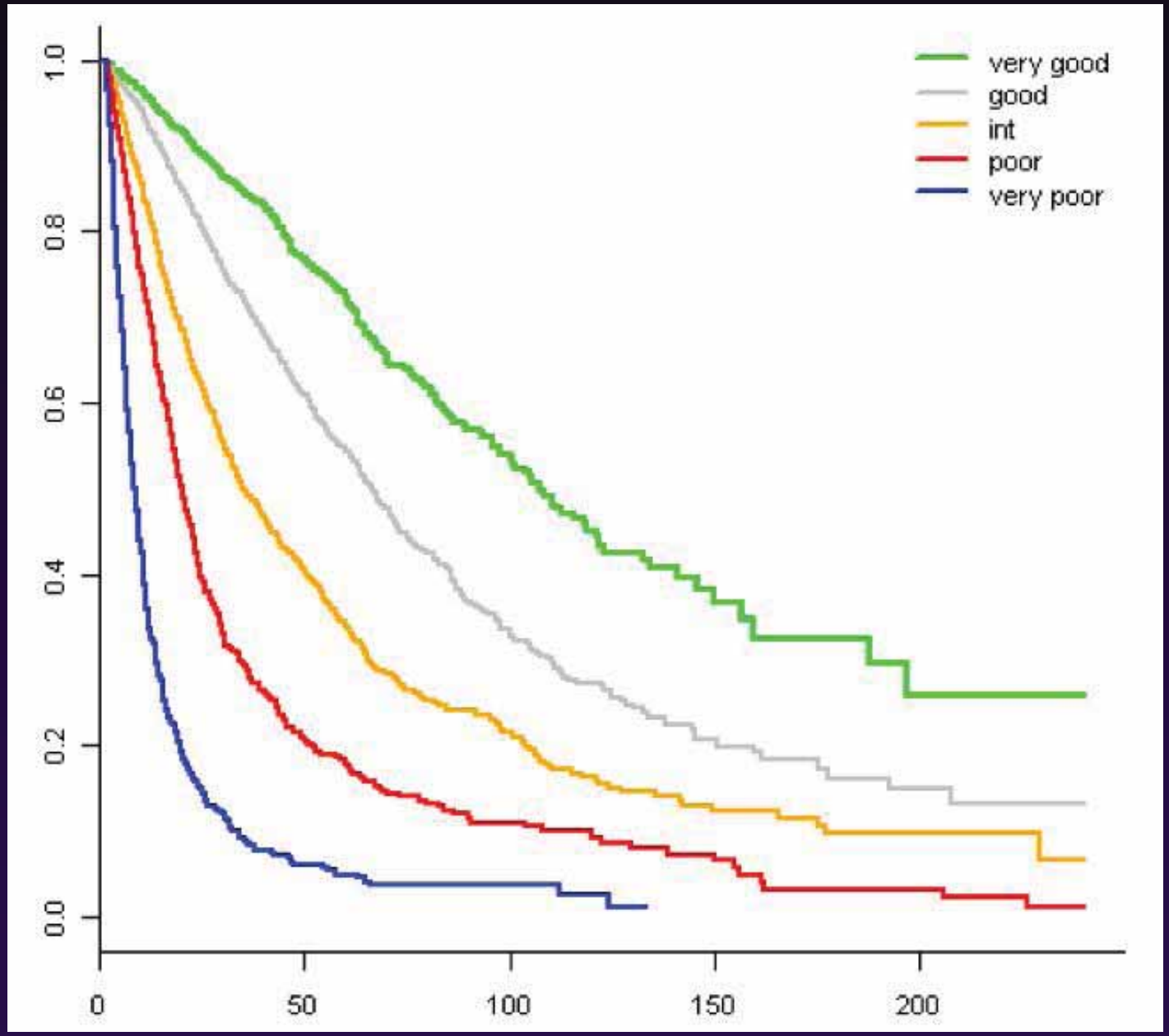


International Risk Score - revised

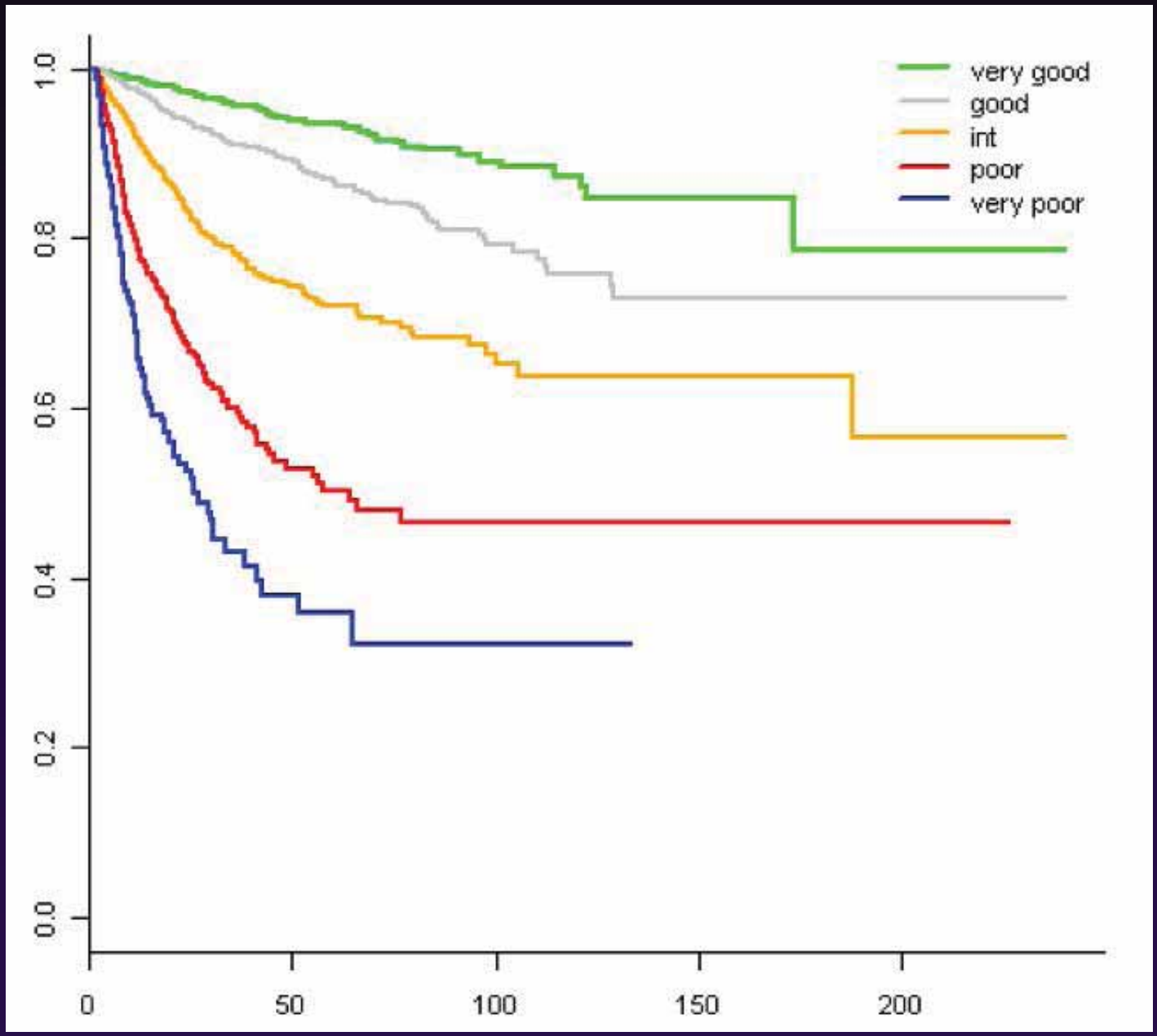
	Punkte						
	0	0,5	1	1,5	2	3	4
KM – Blasten	≤ 2		2 – 5		5 – 10	> 10	
Zytogenetik	Very Good		Good		Int	Poor	Very Poor
Hämoglobin	≥ 10		8 – 10	< 8			
Neutrophile	≥ 0,8	< 0,8					
Thrombozyten	≥ 100	50 – 100	< 50				

Greenberg et al, Blood, 2012

IPSS – revised: Gesamtüberleben

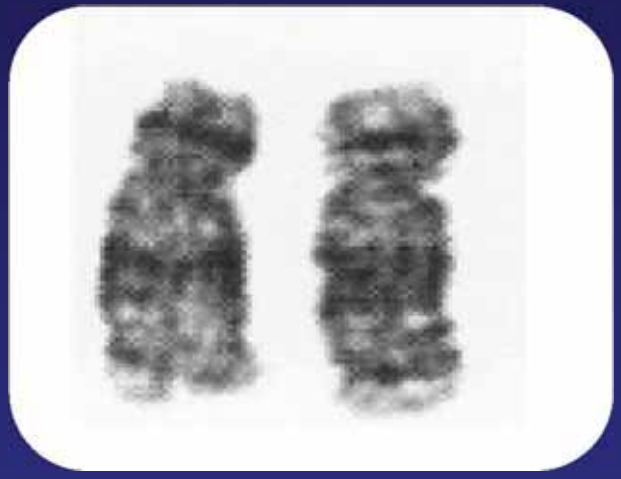


IPSS – revised: Leukämiefreiheit



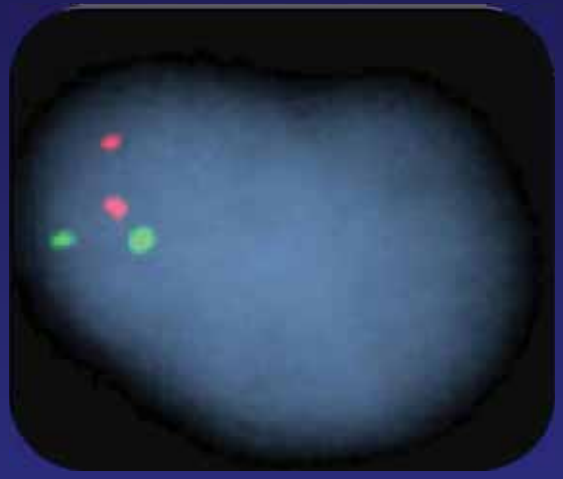
Diagnostik der MDS am Beispiel del(5q) : Methoden

Standard Zytogenetik (MC)[1]



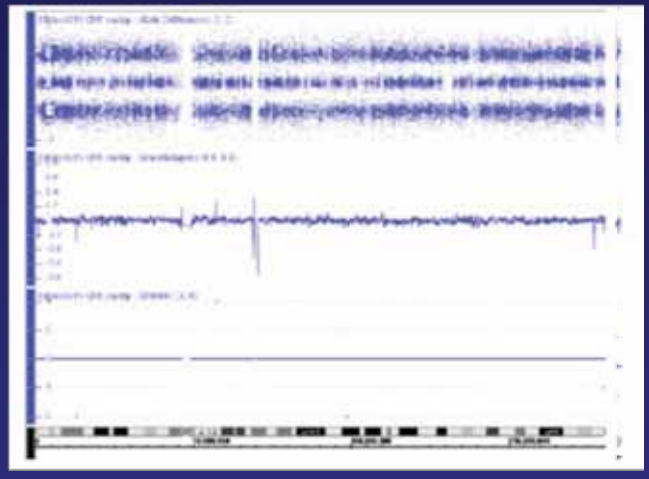
- Standardanalyseverfahren
- 25 Metaphasen sollten analysiert werden[2]

Fluorescence *in situ* hybridisation (FISH)[1]



- Zusatznutzen bei nicht ausreichenden Metaphasen
- 6% zusätzliche del(5q) Ausbeute bei 657 Patienten[1]

SNP array (SNP-A) karyotyping[3]



- SNP-A zum Nachweis von Mikrodeletionen und f UPD

UPD: uniparental disomy
SNP: single-nucleotide polymorphism

1. Mallo M, et al. Haematologica 2008;93:1001–8; 2. Steidl C, et al. Leuk Res 2005;29:987–93; 3. Makishima H, et al. Leuk Res 2010;34:447–53

The prognostic evaluation of MDS: emerging karyotyping techniques

Green: advantage **Yellow: disadvantage**

Technique	Conventional karyotyping	FISH	SNP arrays	CGH arrays
Resolution	Low	Low	High	High
Sensitivity	10%	High	20–30%	20–30%
Detection of UPD	No	No	Yes	No
Dividing cells needed	Yes	No	No	No
Distinction of individual clones	Yes	Yes	No	No
Screening for new lesions	Yes	No	Yes	Yes
Detection of balanced alterations	Yes	Yes	No	No

CGH: comparative genomic hybridisation

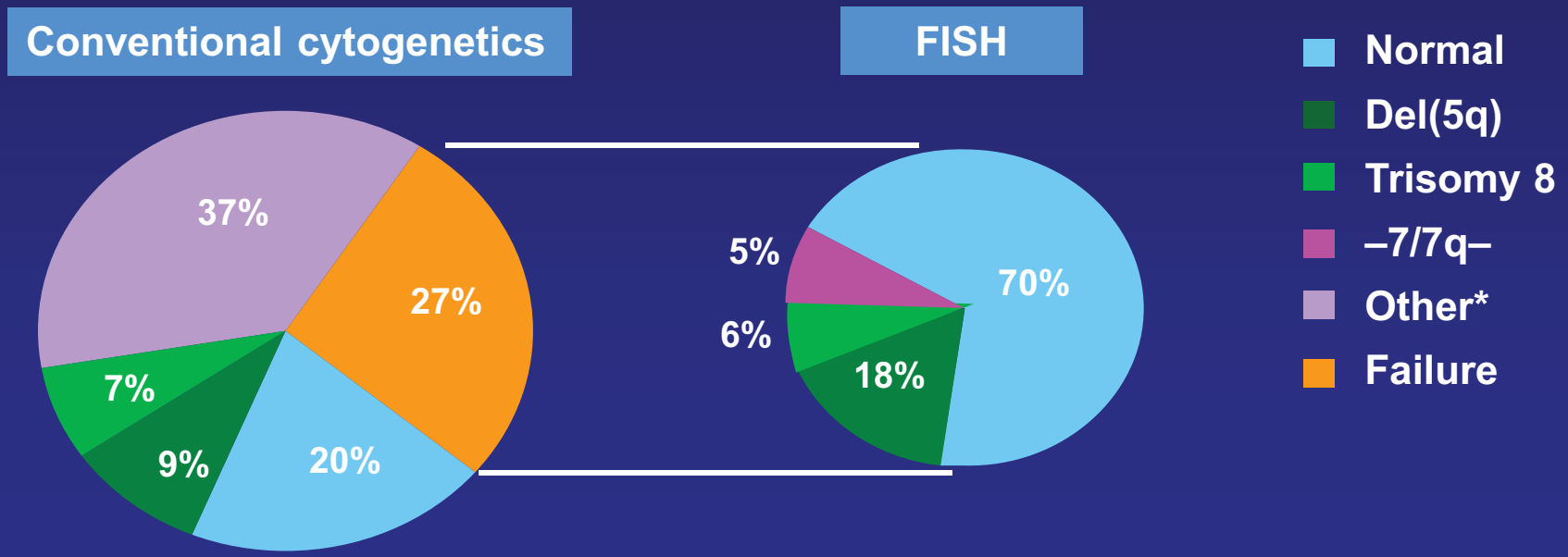
Adapted from Maciejewski JP, et al. Oral presentation at the 10th International Symposium on MDS, Patras, Greece, May 6–9 2009

Technological advances: FISH for improving diagnosis of primary MDS

Combining FISH with conventional cytogenetic analysis can improve classification of MDS

Patients and methods

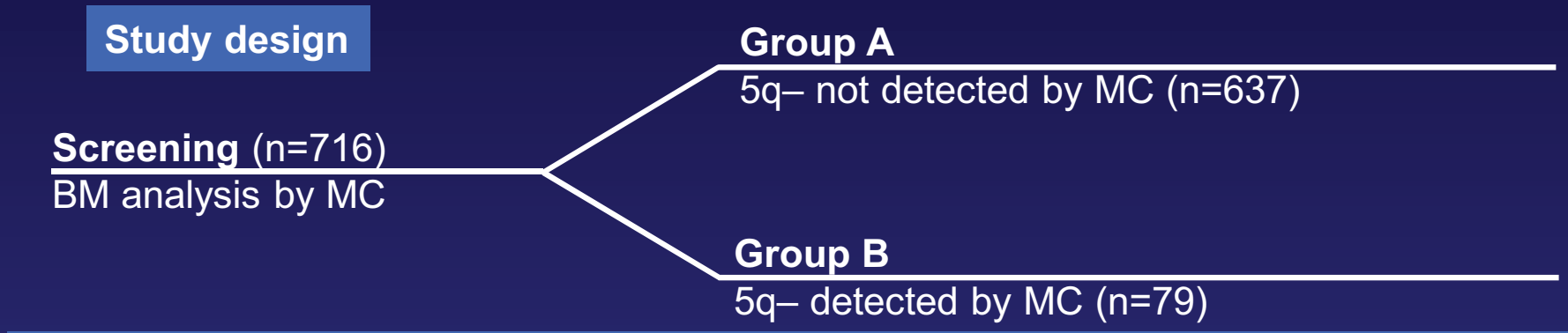
- 121 patients with suspected primary MDS
- Conventional cytogenetic analysis of BM samples
  - informative karyotype (≥20 metaphases obtained) for 90 patients
- Samples from remaining 31 patients analysed by FISH



*hypo/hyperdiploid karyotype, complex karyotype, unusual deletions and/or translocations

Luciano L, et al. Poster presentation at EHA 2010, Barcelona, Spain. Abstract 0917

FISH and del(5q)



FISH detected del(5q) in 38/637 (6%) cases in which MC had not identified 5q–

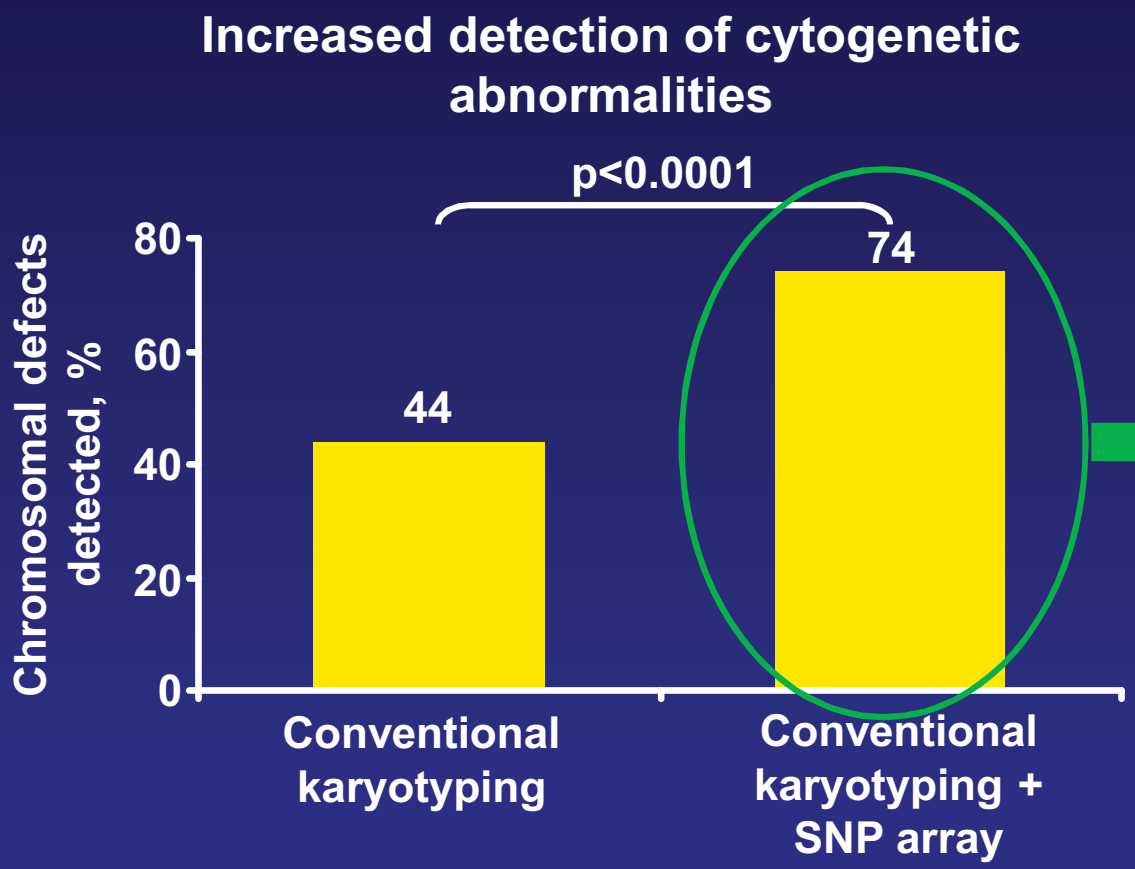
Authors' recommendation:

FISH may help in classification of cases with

- **suspected 5q– syndrome**
- **no metaphases or metaphases are not evaluable**
- **abnormal karyotype without evidence of 5q–**

Mallo M, et al. Haematologica 2008;93:1001–8

SNP arrays can detect additional ‘cryptic’ abnormalities



Novel lesions were detected with SNP in:

- **54% of normal/non-informative conventional karyotyping results**
- **62% of abnormal conventional karyotyping results**

Newly detected lesions by SNP indicated a poorer patient prognosis

Tiu RV, et al. Blood 2011;117:4552–60

Considerations with cytogenetic techniques

Metaphase cytogenetics only	→	Complement with FISH?
FISH is limited by the probes used; it is too expensive to use probes against entire genome	→	FISH must **complement**, not replace, metaphase cytogenetics
SNP-A is much more sensitive than FISH, but it can miss chromosomal translocations	→	If SNP-A becomes routinely used, it should be in conjunction with other techniques