Current Therapeutic and Biologic Advances in MDS

A Symposium of The MDS Foundation – ASH 2014

Impact of Comorbidity on Quality of Life and Clinical Outcomes in MDS

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ASH - 2014 – San Francisco - USA

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Disclosures:

Honoraria: Celgene

Pathogenesis of MDS

- Clonal Hematopoiesis
- Stem Cell-Derived (Permanent) Clones
- Dysplasia and Apoptosis
- Step-wise Process → secondary AML
- Role of the Microenvironment
- Treatment-Related Factors (e.g. Iron)
- Role of Age and Organ-Function
- Role of Co-Morbidities
- Role of other Patient-related Factors

Pathogenesis of MDS

Valent et al., Leuk Res 2007;31:727
Valent, Leuk Res 2008;32:1333

Normal Hematopoietic Stem Cell

First hits - mutagenic event/s ?

Clonal expansion of a premalignant progenitor cell population leading to ineffective (impaired) erythropoiesis / hematopoiesis

Disease manifestation may depend on EPO production (kidney function↓? androgens↓?)

EPO production adequate and sufficient to prevent anemia

Inadequate ´EPO-response´ to ineffective erythropoiesis → anemia

EPO-responsive progenitors

Low EPO overt MDS

no MDS detected as no anemia develops – these patients have dysplasia without cytopenia = IDUS

LOW RISK MDS
often responsive to EPO therapy (15-25% of patients)

EPO-response lost +/- blasts ↑

Disease progression/clonal expansion

HIGH RISK MDS
(cytopenia found invariably)

Further oncogenic hits that lead to maturation arrest and proliferation

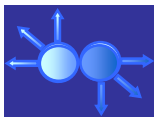
SECONDARY ACUTE MYELOID LEUKEMIA

EPO as co-factor IDUS+ICUS=MDS

Normal Hematopoiesis in the elderly

Low EPO in elderly → anemia / AOE

ICUS-A



WHO 2008 Classification of MDS*

(www.who.int/bookorders/)

- Refractory Cytopenias with Unilineage Dysplasia (RCUD)
  - Refractory Anemia (RA)
  - Refractory Neutropenia (RN)
  - Refractory Thrombocytopenia (RT)
- Refractory Anemia with Ring Sideroblasts (RARS) (≥15%)
- Refractory Cytopenia with Multilineage Dysplasia (RCMD)
- Refractory Anemia with Excess Blasts-1 (RAEB-1) (<10%)
- Refractory Anemia with Excess Blasts-2 (RAEB-2) (≥10%)
- Myelodysplastic Syndrome - Unclassified (MDS-U)
- MDS associated with isolated del(5q) [the only cytogenetic variant]
- [Childhood Myelodysplastic Syndrome (separate subchapter, separate authors)]

*WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, 2008, Chapter 5, Pages 88-107
Authors: Brunning RD, Orazi A, Germing U, Le Beau MM, Porwit A, Baumann I, Vardiman JW, Hellstrom-Lindberg E

Classification of MDS According to Etiology

1) Primary (*de novo*) MDS
   - No Mutagenic Event in CH
   - No Previous CT or SCT
   - No Previous Radiation
2) Secondary MDS
   - Mutagenic Event known
   - Even if many Years ago
   - Often with Complex Biology
   - Often with Complex Karyotype

Classification of MDS According to Age

1) Childhood MDS (also by WHO)

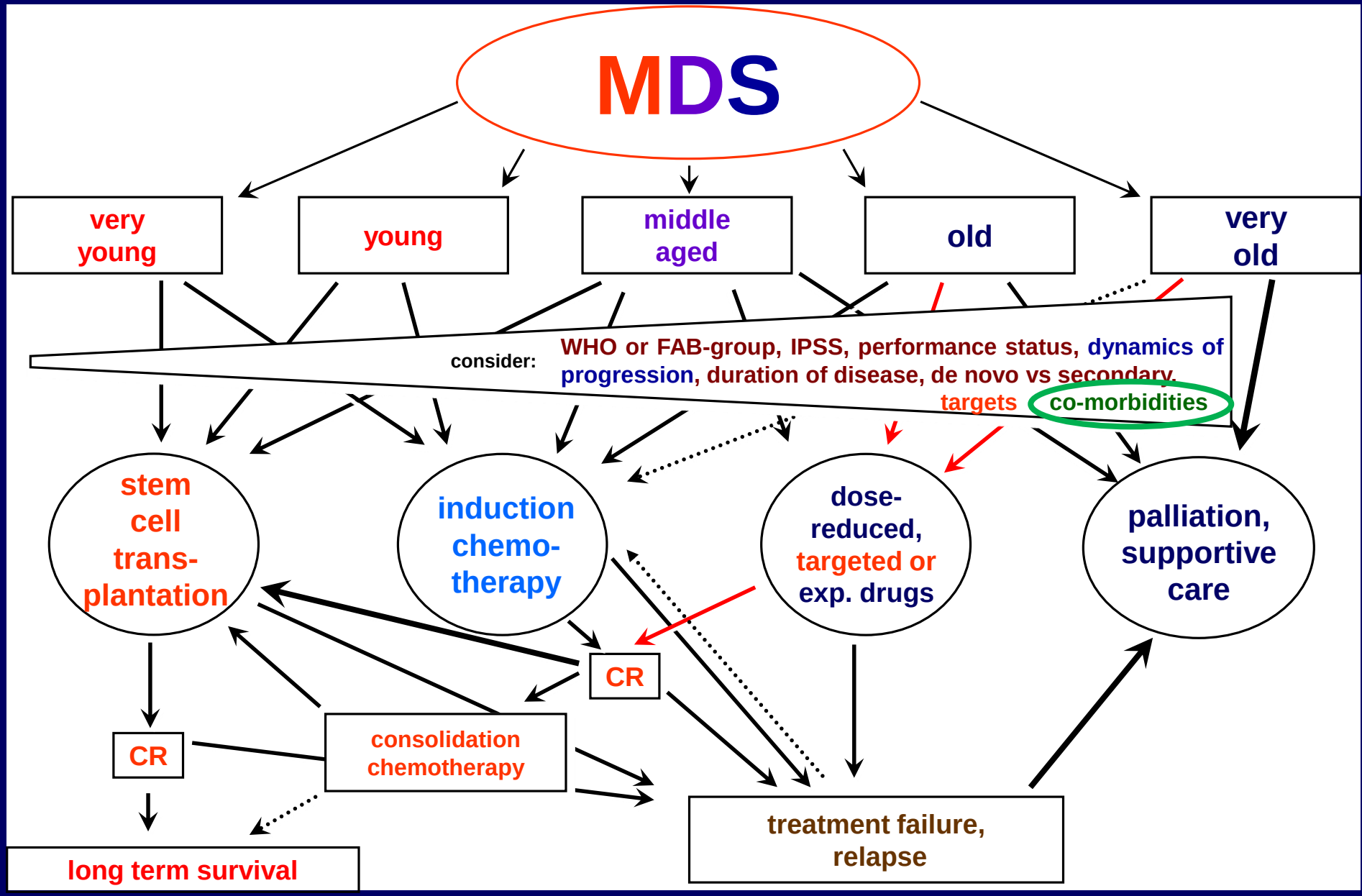
2) MDS in Younger Adults

- Often Fit and Transplantable
- Few or no Comorbidities
- EPO Production usually normal

3) MDS in The Elderly (≈ > 70 yrs)

- Often "Not So Fit"
- Comorbidities often present
- EPO Production often impaired
- Often Complex Disease Biology

Treatment Algorithms in Patients with MDS



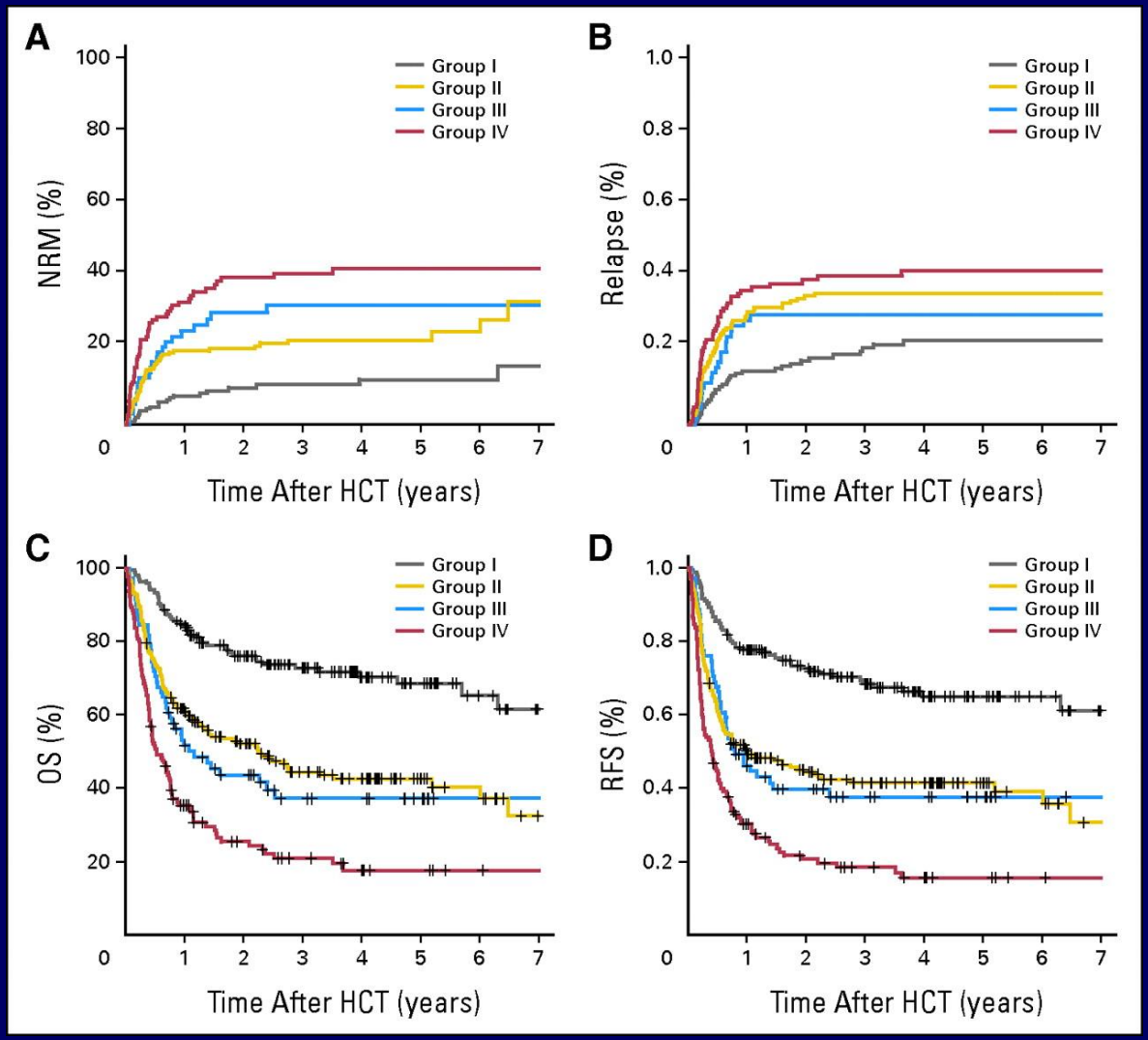
Valent et al, Wien Klin Wochenschr 2003;115:515-536

Risk stratification of patients with acute myeloid leukemia or MDS receiving allogeneic HCT

HCT-CI

OS

RFS



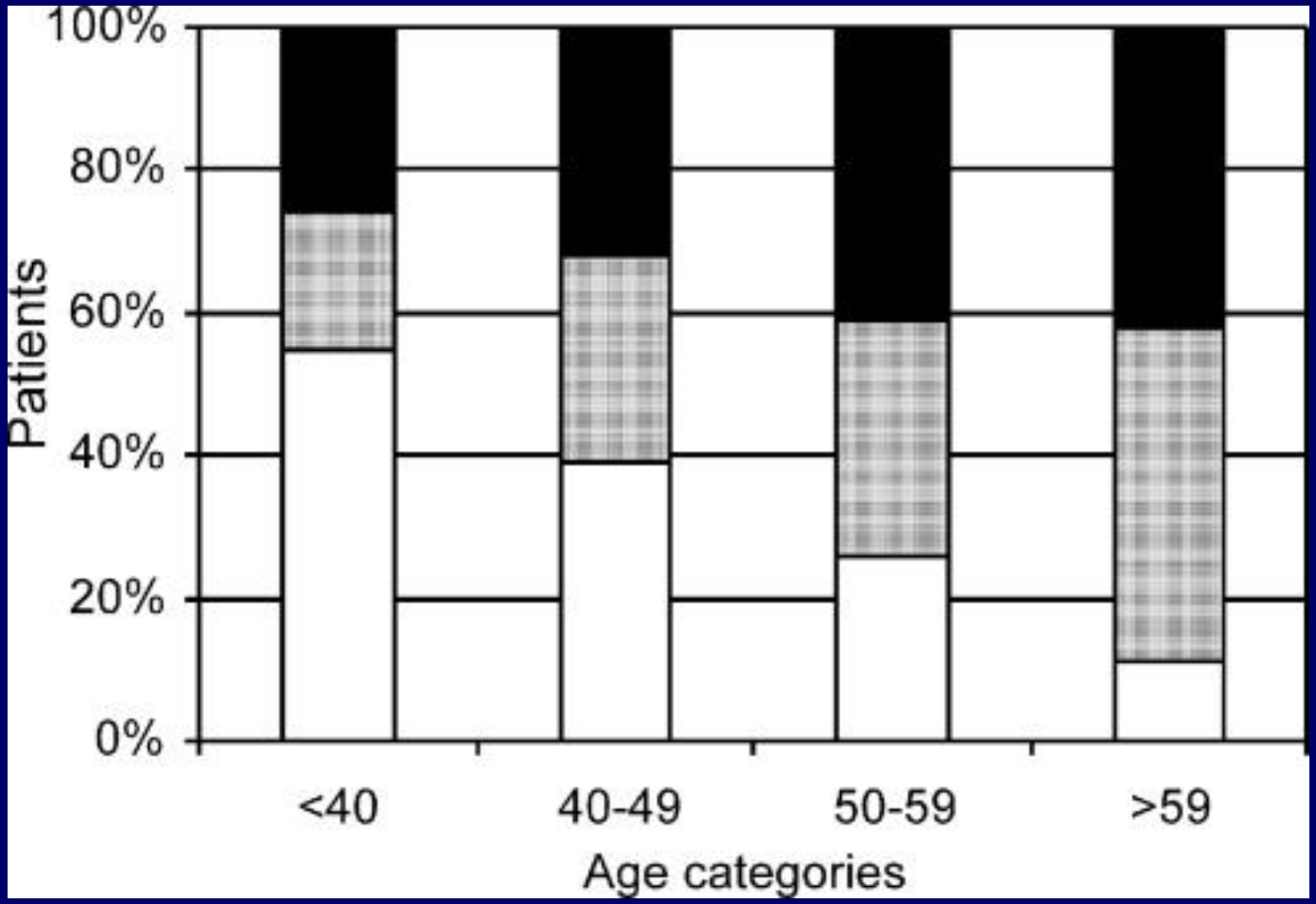
HCT, Hematopoietic (stem) cell transplantation
CI, Comorbidity index
OS, Overall survival

Sorror et al. JCO 2007;25:4246-4254

JOURNAL OF CLINICAL ONCOLOGY ASCO

NRM, nonrelapse mortality
OS, overall survival
RFS, relapse-free survival.

Age and Comorbidity



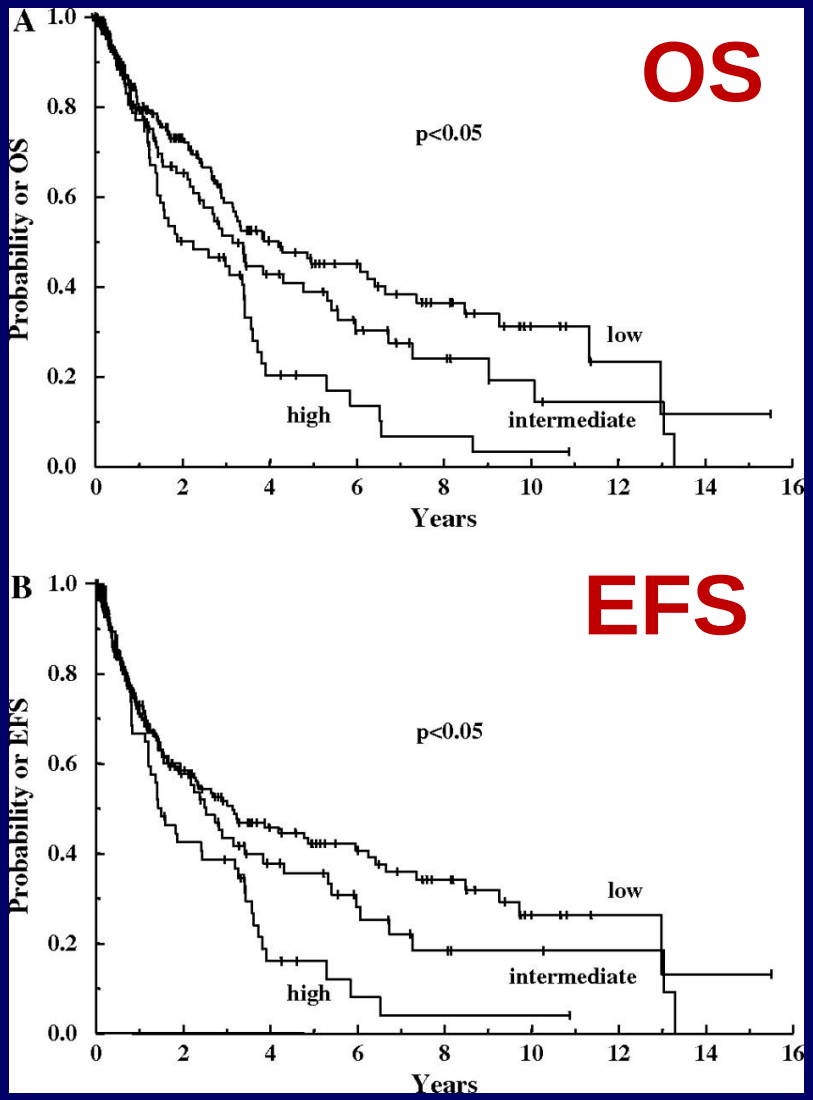
HCT-CI score 0, white area;
HCT-CI scores 1 to 2, gray area;
HCT-CI scores more than or equal to 3, black area.

AML

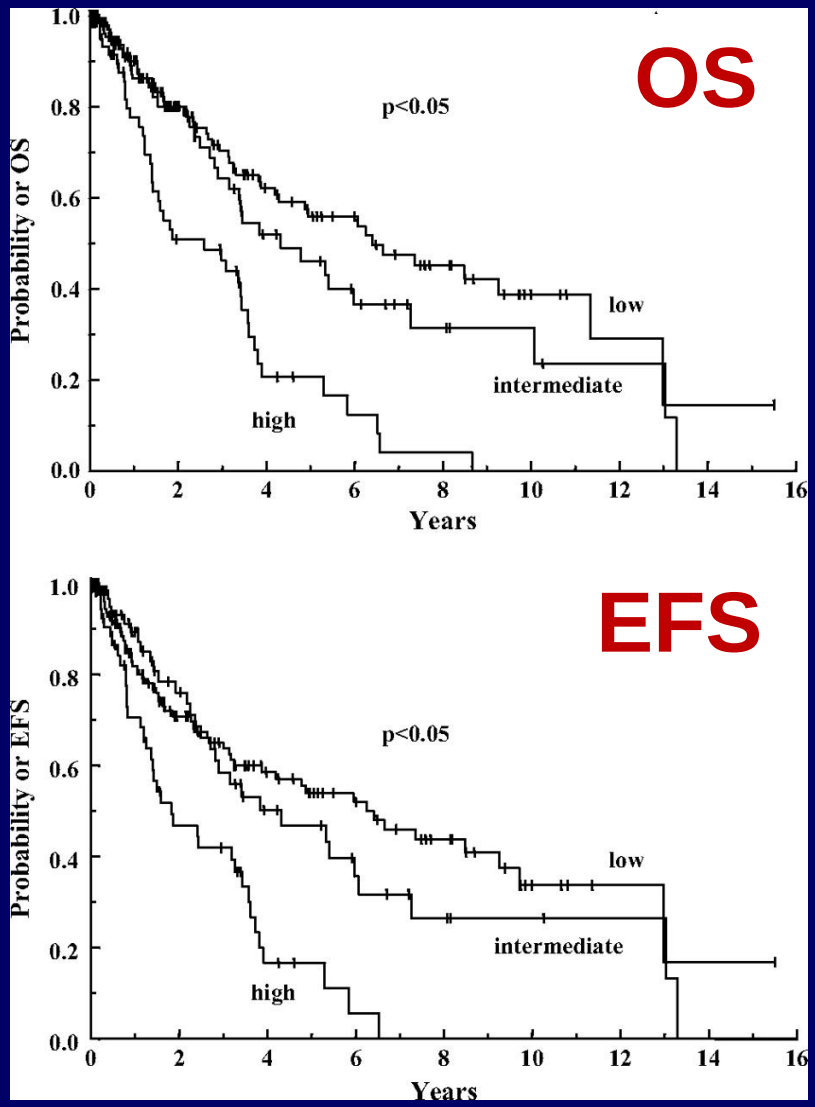
Sorror et al., Blood 2007;110:4606-4613

OS and event-free survival (EFS) according to HCT-CI groups

All MDS Patients

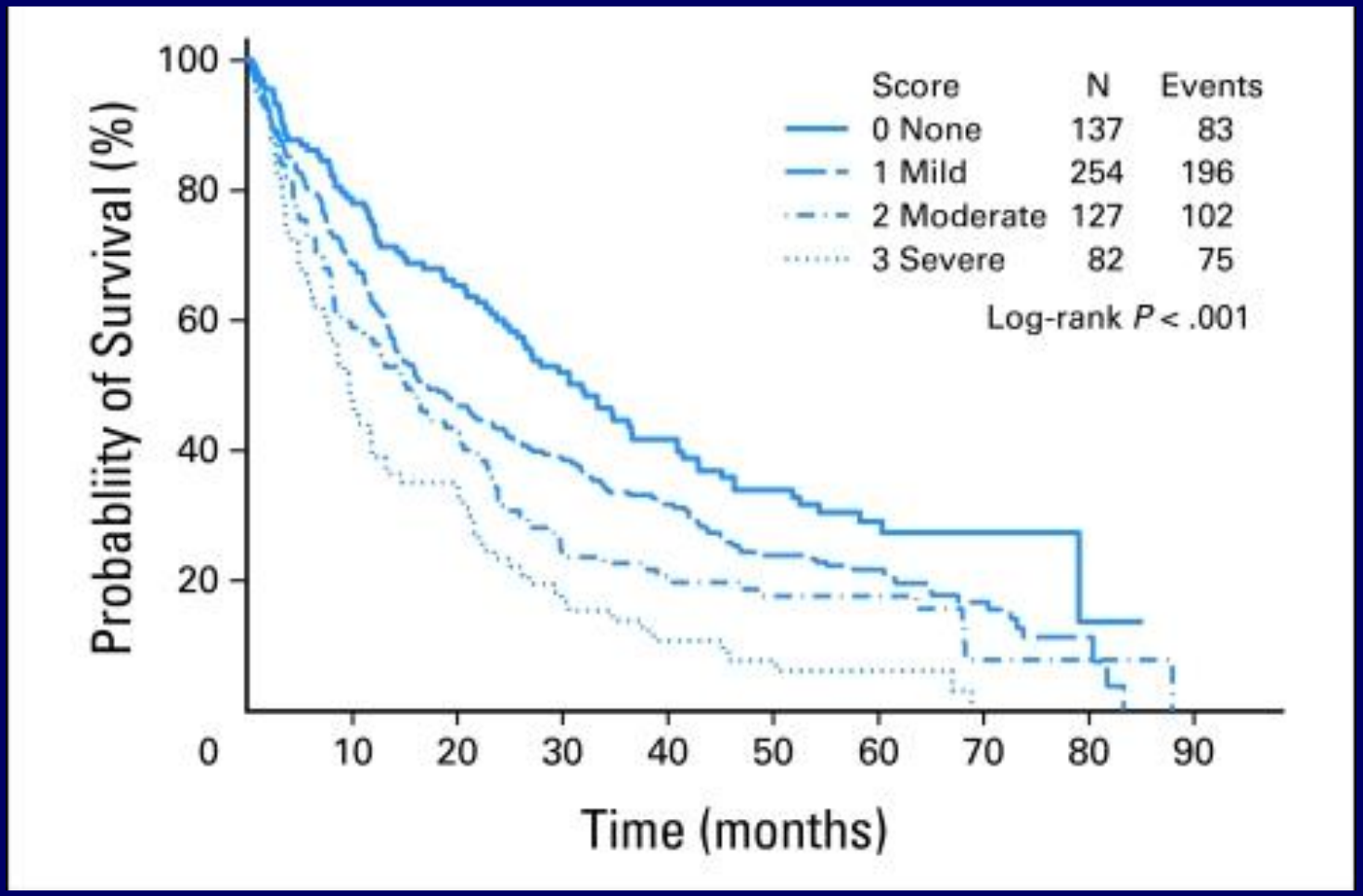


IPSS Low + Int-1 MDS Patients



Sperr et al, Ann Oncol 2010; 21:114-119

Impact of Comorbidities (ACE-27) on Survival in Patients with MDS



Adult Comorbidity Evaluation-27 (ACE-27) comorbidity score

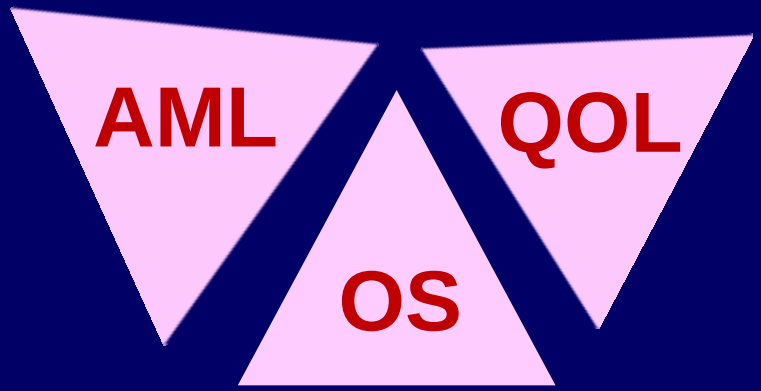
Naqvi et al, J Clin Oncol 2011;29:2240-2246.

Three different End Points in MDS: Survival, AML-Evolution, QOL

Disease-related Factors:
Karyotype and Molecular Lesions
Blast Cell Count, Blood Counts
Histologic BM Patterns e.g. Fibrosis
Flow Patterns, EMI, Splenomegaly

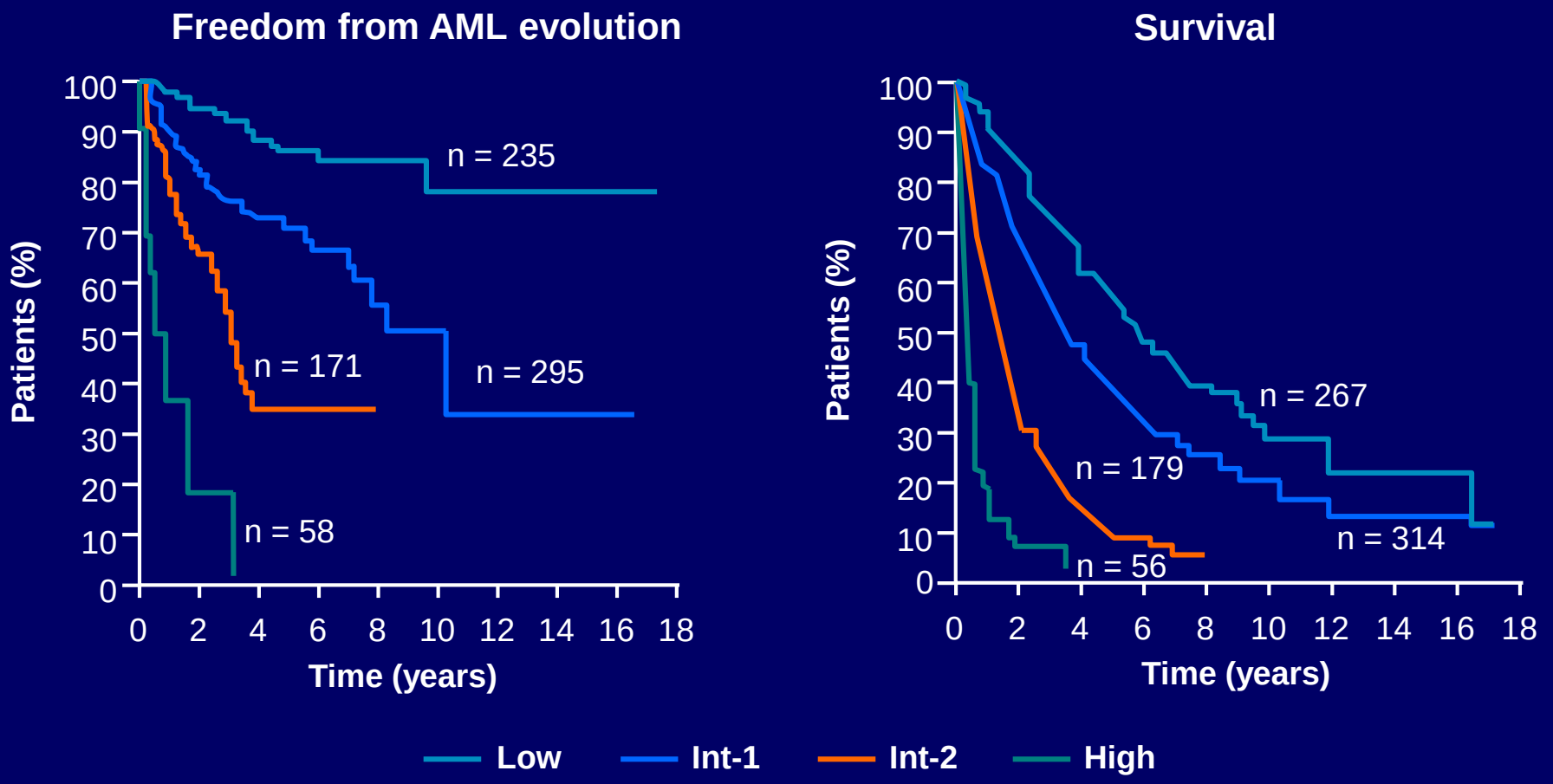
MDS

Patient-related Factors:
Age, Mutagenic Events, ECOG
Gender, Germline Patterns, SNP
Social Factors, Psychology
CoMorbidities



Overall Outcome

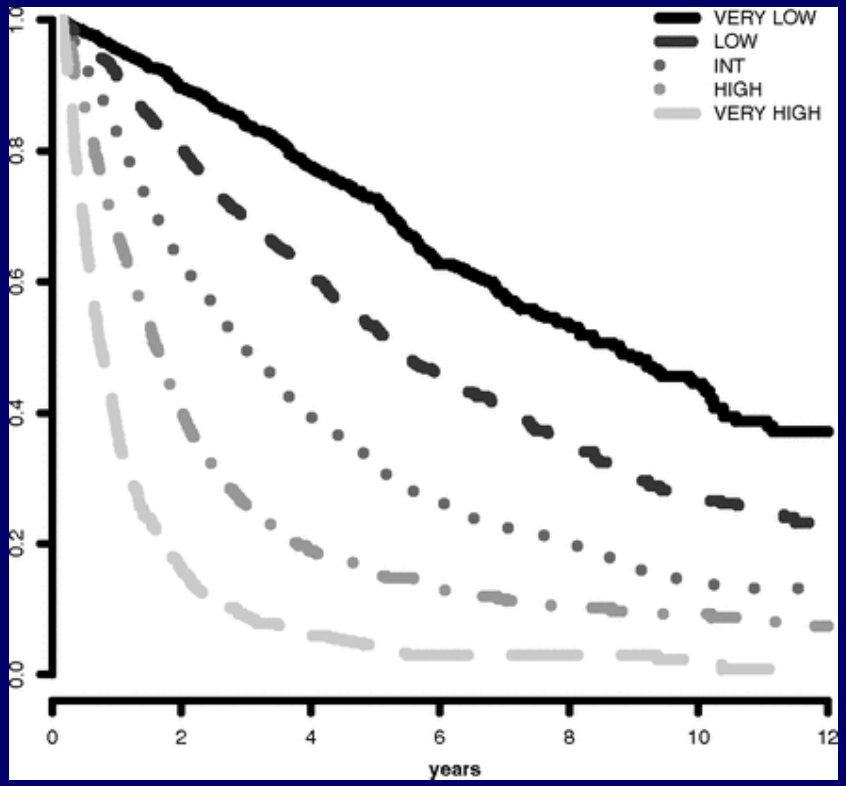
International Prognostic Scoring System (IPSS) - Classification



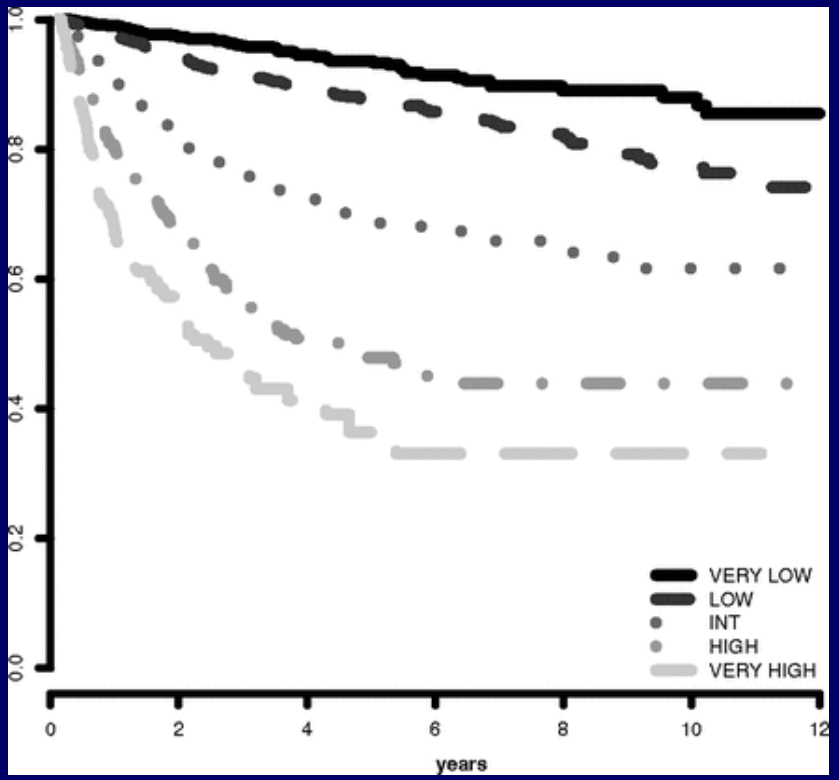
Greenberg et al. Blood. 1997;89:2079

The revised IPSS = IPSS-R
Survival and AML-free Survival

Survival Probability

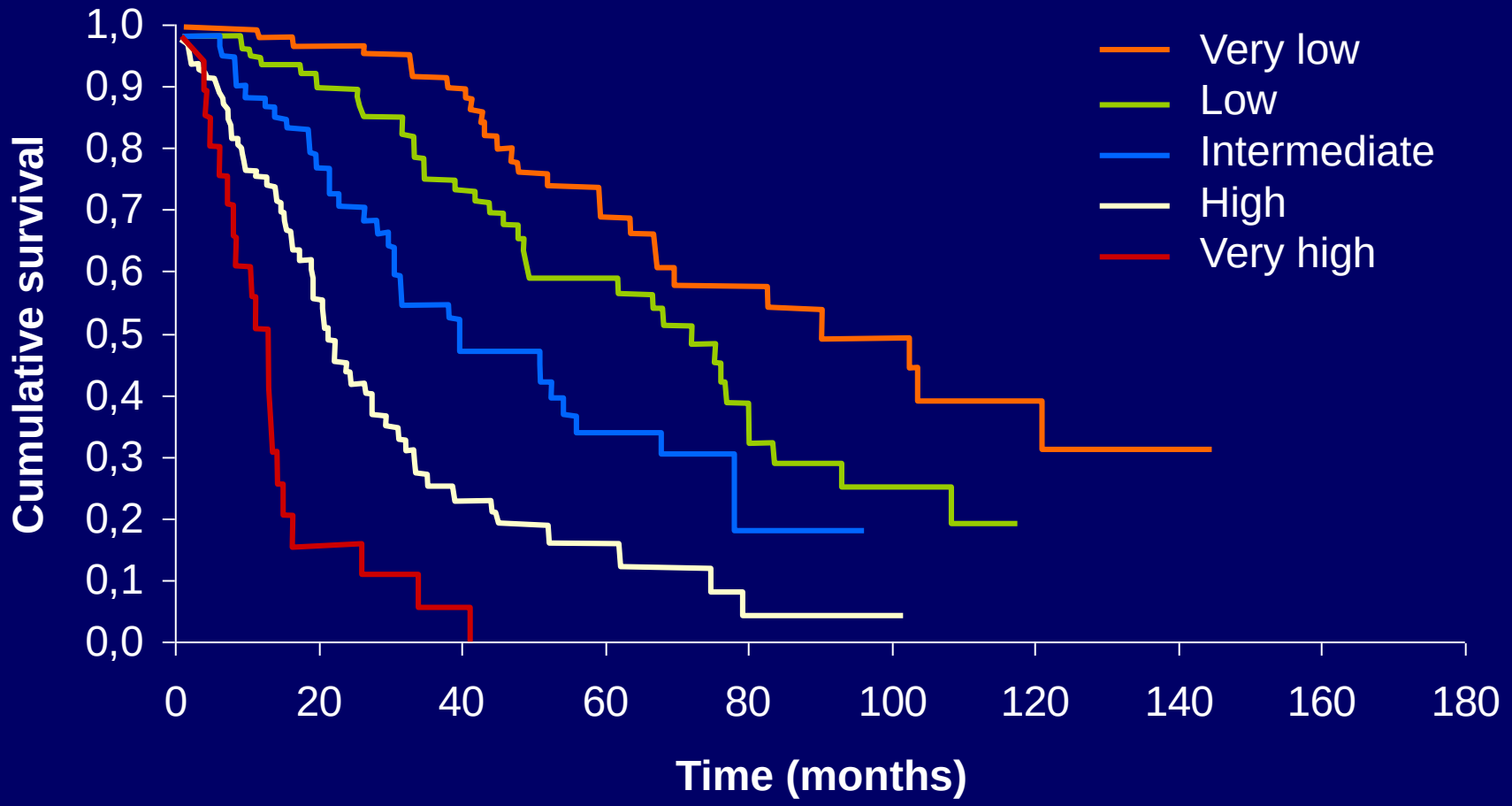


AML-Evolution Probability



Greenberg et al, Blood 2012;120:2454-2465

WHO-based Prognostic Scoring System = The WPSS: Cumulative Survival



Malcovati L, et al. Blood. 2005;106:232a

The Problem in MDS: What Therapy in what Patients ?

The available Scoring Systems are still not always optimal !

Not optimized for Endpoints

We need better Score-Models that include recommendations:

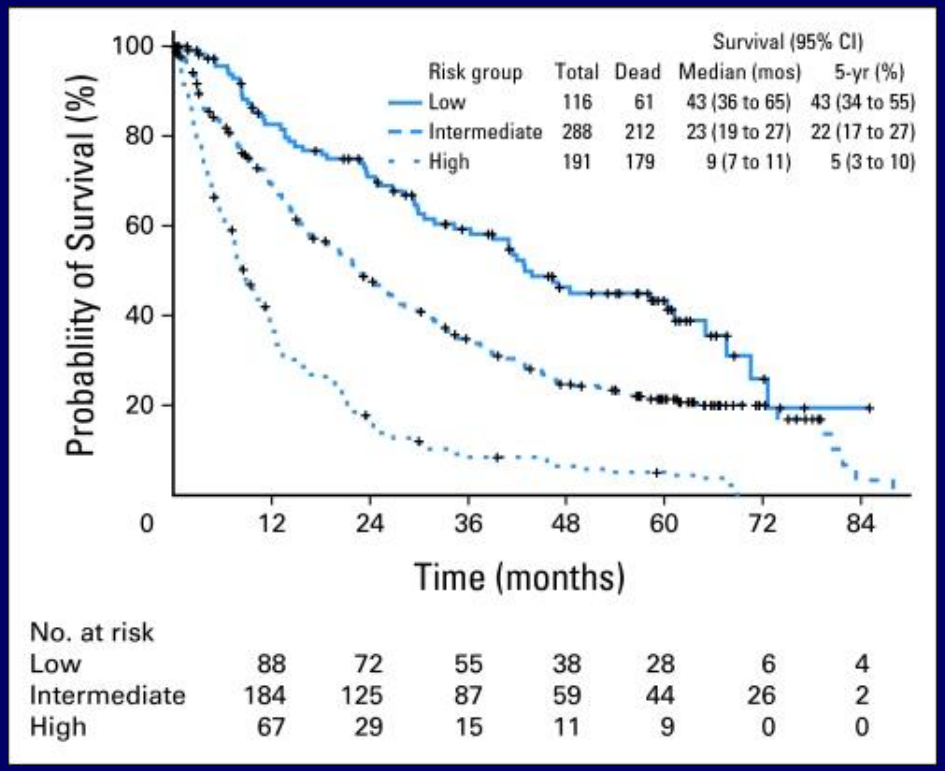
GO-GO, SLOW-GO, NO-GO !

Impact of Comorbidities (ACE-27) on Survival in Patients with MDS

Multivariate Survival Model and Score

Variable	Coefficient	Score*
Age, years		
>65	0.582	2
Comorbidity (ACE-27)		
Mild or moderate	0.301	1
Severe	0.782	3
IPSS		
INT-2	0.512	2
HIGH	0.769	3

*Score points were obtained by dividing estimated coefficients by 0.3.



LOW = 0-1
INT = 2-4
HIGH = 5-8

Naqvi et al, J Clin Oncol 2011;29:2240-2246.

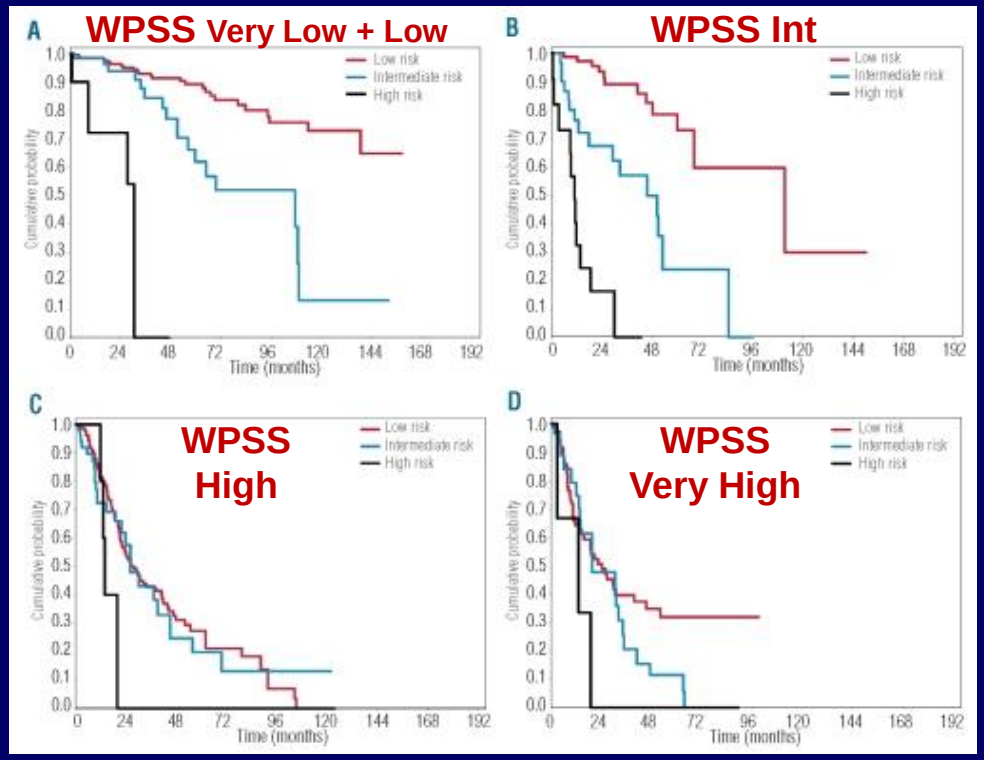
The MDS-specific comorbidity index (MDS-CI) Italian – German Collaboration

Comorbidity	HR obtained through a multivariable Cox's survival analysis with NLD as an outcome	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	3.57 (P<0.001)	2
Moderate-to-severe hepatic disease	2.55 (P=0.01)	1
Severe pulmonary disease	2.44 (P=0.005)	1
Renal disease	1.97 (P=0.04)	1
Solid tumor	2.61 (P<0.001)	1

MDS-CI risk	Sum of individual variable scores	Proportion of patients in the learning cohort belonging to the risk group (%)
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	>2	50/840 (6%)

NLD: non-leukemic death.

MDS-CI in various WPSS groups (OS)



Della Porta et al, Haematologica 2011;96:441-449

New Score for Optimal Prediction of Survival in Patients with MDS

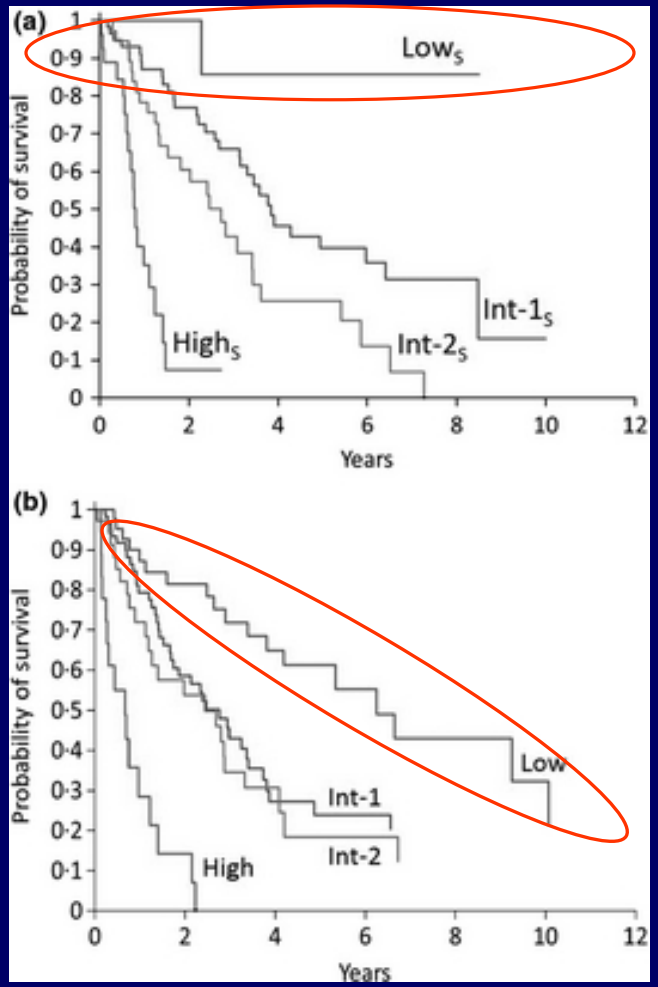
Score:

1) IPSS points
2) Ferritin <900 = 0
   ≥900 = 1
3) Age < 70 = 0
   70-79 = 0.5
   ≥80 = 1.5
4) HCT-CI
   Low/Med = 0
   High = 0.5

LOWs = 0 **INT-1s = 0.5-1.0**
INT-2s = 1.5-2.0 **HIGHs = >2**

PSSs

IPSS



Sperr et al, Eur J Clin Invest 2013;43:1120-1128

Therapy Options in MDS

Wait and Watch

Best Supportive Treatment
(Tf, EPO sc, AB, ..)

Non-Intensive Antineoplastic Therapy &
Less Intensive Therapy (Azacytidine)

Intensive Antineoplastic Drug Therapy

Stem Cell Transplantation

Experimental Treatment

PROPOSED STRATIFICATION MODEL

1) Estimate Survival Compared to the Natural Survival in Age-Matched Healthy Controls

   = Score A optimized for Survival Prediction

2) Estimate Risk of AML Development (largely independent of Patient-Related Factors)

   = Score B optimized for AML Prediction

3) Determine Therapy-Options based on Patient-Related Factors (Age, ECOG, etc), MDS type and Score A plus Score B combined assessment

4) Final Proposal: NO-GO, SLOW-GO, GO-GO

PROPOSED MODEL: EXAMPLES

Example #1

Age 59, ECOG = 0, Score A Low & Score B High

= GO GO (CT + SCT)

Example #2

Age 67, ECOG = 2, Score A High & Score B Low

= NO GO (best supportive care)

Example #3

Age 70, ECOG = 1, Score A Int & Score B High

= SLOW GO (for example azacytidine)

Dynamic Scoring and Risk Assessment in the Follow-Up (FU) in Patients with MDS

- **Dynamic Scores and Variables:**
  - **WPSS, other novel Scores**
  - **LDH in the FU as robust prognostic Variable**
  - **Cytopenias and Karyotype (IPSS Variables)**

- **Age increases in the FU !**
- **Comorbidities may worsen**
- **Some Comorbidities may improve or even resolve**
- **Physicians follow and address Comorbidities**

General Approach to MDS Patients suffering from Co-Morbidities

- Risk Assessment and Prognostication:

  a) Survival b) AML Evolution
- Optimal Management of Co-existing Disorders
- Elimination of all Risk Factors (e.g. Iron Overload)
- Age- and Comorbidity-Adjusted Support:

  a) Hemoglobin >8 g/dL; >10 g/dL (O_2 demand)

  b) Platelets depending on Comorbidities

  c) Antibiotics and G-CSF (consider Comorbidities)
- Overall Treatment Plan Adjusted to Age and various Comorbidities (cardiac and others)

Clinical Impact of Iron Overload and Iron Chelation in MDS

- Natural Course: Survival, AML Development ?
- SCT: Pre-Transplant Ferritin Levels → Prognosis
- Comorbidity: DM, Cardiac Function (CT/SCT possible?)
- Comorbidity → Quality of Life (QOL)

- Sufficient Iron Chelation can be achieved in MDS
- New Chelating Agents; these are oral Drugs (QOL)
- **Important Question may be: Life Expectancy →**

  needs a Score System optimized for predicting survival: IPSS, Age, Comorbidity, Ferritin

Previous Guidelines

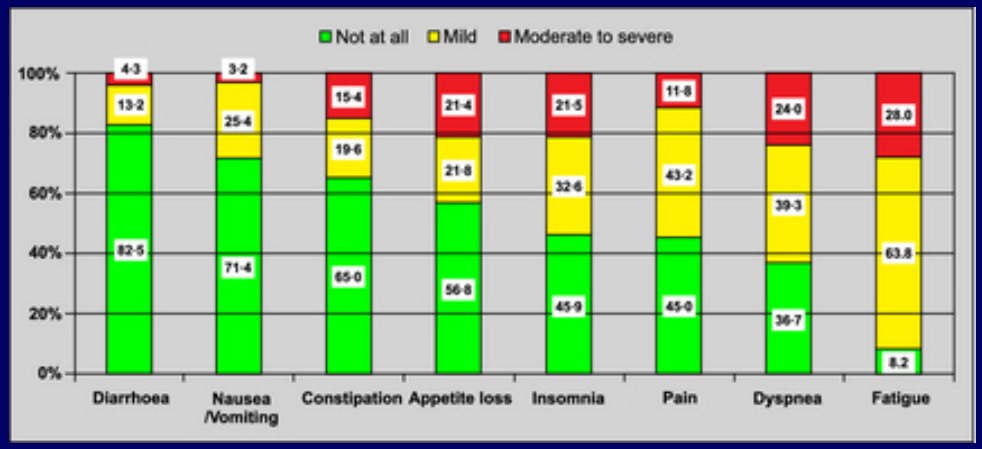
- Italian Society for Hematology Guidelines (2002)
  indication: > 50 red cell units (RCU) + > 6 months LE
  deferoxamine s.c.
- United Kingdom (U.K.) MDS guidelines (2003)
  indication: > 5 g iron (>25 RCU) + long term transfusion pts
  deferoxamine s.c.
- Nagasaki Consensus Meeting guidelines (2005)
  indication: stable disease, ferritin > 1,000 > 2,000 µg/L, pre-SCT pts
- National Comprehensive Cancer Network (NCCN) Guidelines (2007)
  indication: > 20-30 RCU + ongoing transfusions, ferritin > 2,500 µg/L
  co-morbidity (additional risk factors for organopathy)
  deferoxamine s.c. or deferasirox p.o.
- Florence Consensus Meeting guidelines (2007/2008)
  indication: ferritin > 1,000 and/or 2 RCU per months for > 1 year,
  LE > 1 year, ferritin as follow up parameter (every 3 months), pre-SCT
  deferoxamine s.c. or deferasirox p.o. or deferiprone p.o. (no response to other therapies)

Gattermann, Leuk Res 2007;31(S3):10-15

How to measure QOL ?

- ´Semi-Objective´ Parameters: ECOG …
- Questionaire-based evaluation …
- Validated QLQ Scores: EORTC QLQ-C30
- Only a few standardized and validated forms and approaches are available
- QOL may change over time and depends on many factors and overall situation in each case
- QOL may also change with social, private, economic and other factors/conditions

QOL in MDS: Pre-treatment Symptom Prevalence assessed by QLQ

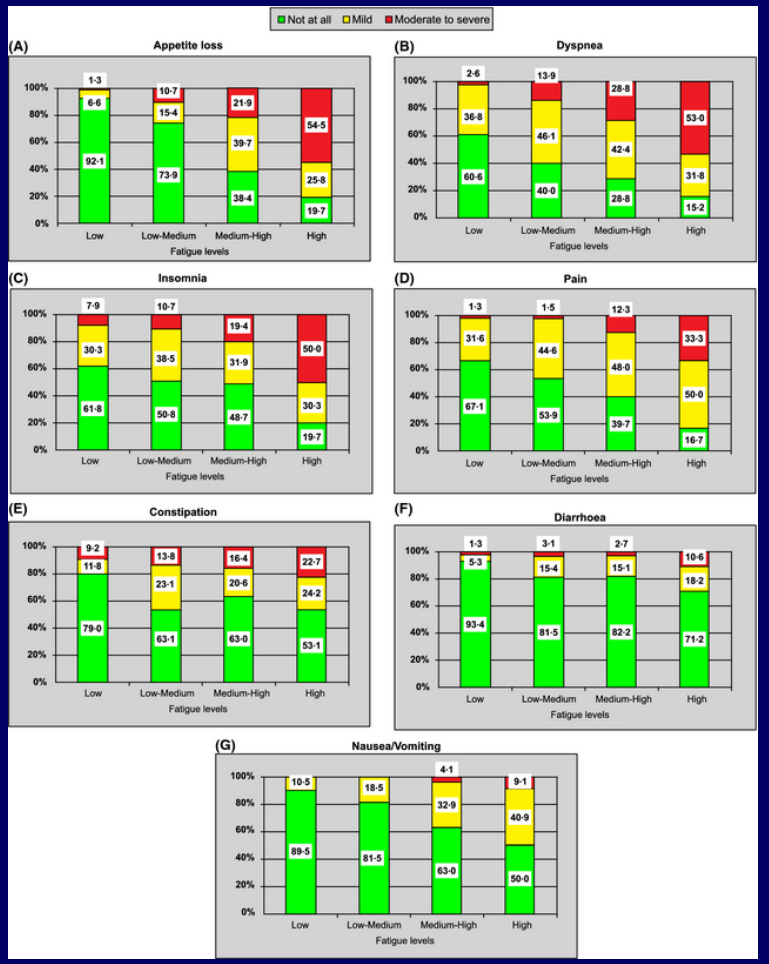


EORTC QLQ-C30

Fatigue is a Relevant and Frequent Symptom in MDS and impairs QOL

Efficace et al, Br J Haematol 2014, in press

Correlation between Fatigue and other Symptoms



QOL is always relative & subjective

- **QOL may change over time and depends on many factors and the overall situation in each case**
- **QOL may also change with social, private, economic and other factors/conditions**
- **QOL may depend on the living place and on technical or environmental factors**

CAN WE ALWAYS MEASURE QOL:

- IN A CLINICALLY RELEVANT WAY ?

- IN A PATIENT-RELEVANT MANNER ?

QOL is always relative & subjective

Myelodysplastic Syndromes

THANK YOU FOR YOUR ATTENTION !

Peter Valent & MDS Study Group Vienna & MDS Platform of the Austrian Society for Hematology and Oncology

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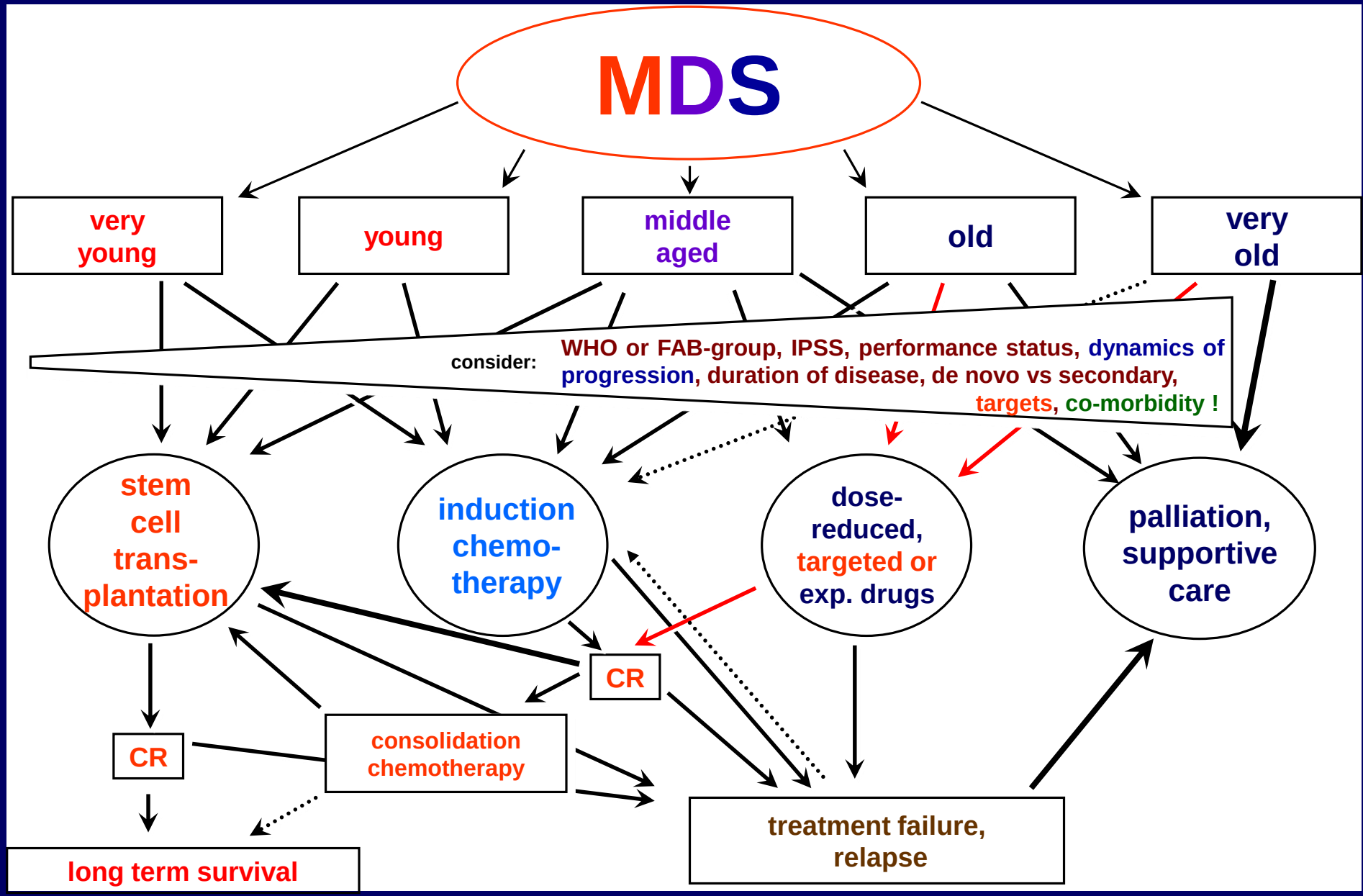
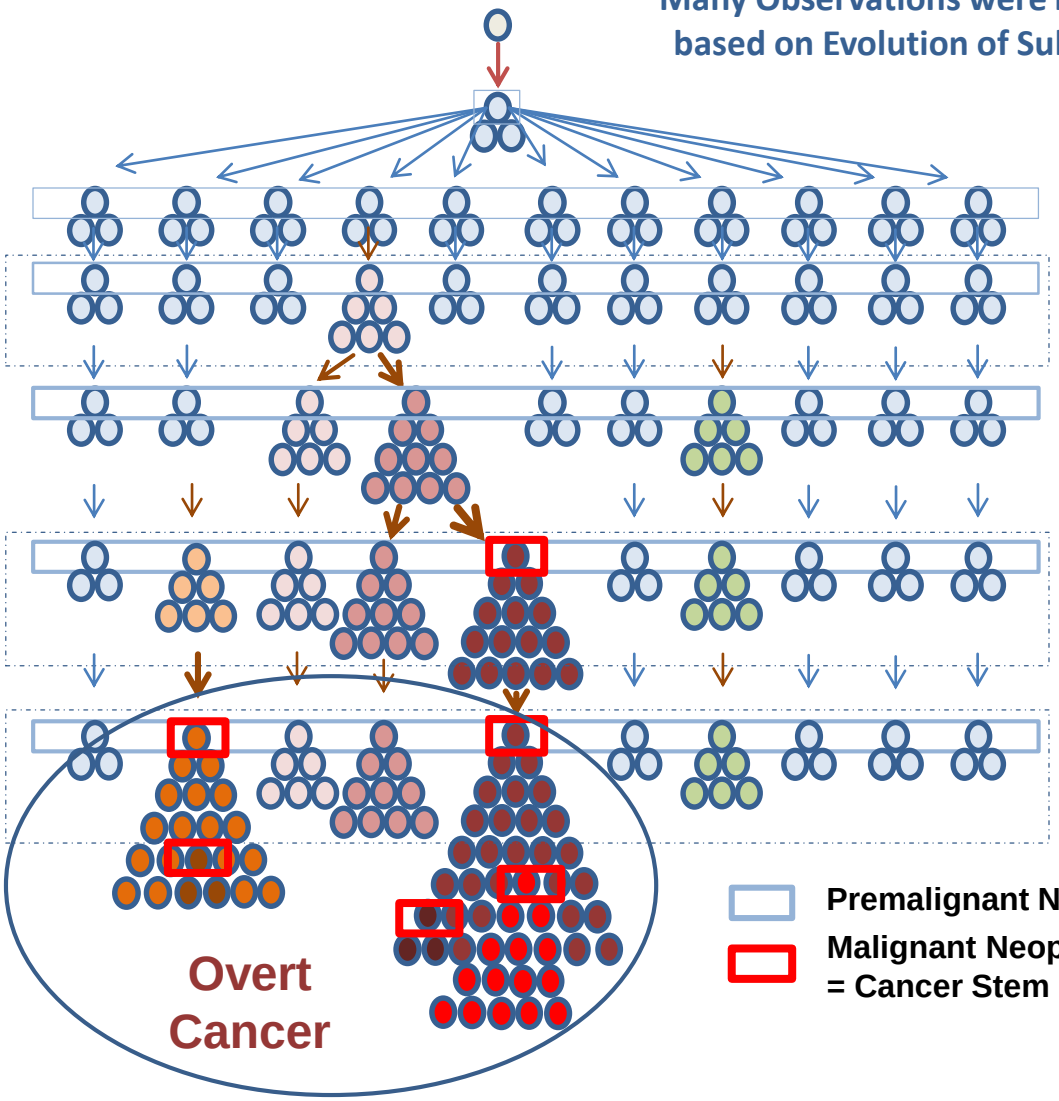
Treatment Algorithms in Patients with MDS



HIERARCHY AND SUBCLONE FORMATION FROM NEOPLASTIC STEM CELLS DURING EVOLUTION OF CANCER AND LEUKEMIA*

*Many Observations were made in the Paradigmatic CML Model, based on Evolution of Subclones carrying *BCR/ABL* Mutations



- Long Latency Periods (Decades) in early Phases of LSC Evolution
- Premalignant Neoplastic Stem Cells versus Malignant SC = CSC/LSC
- Extensive Subclone Formation
- Each Subclone contains its own Stem Cell Compartment
- Phenotypic, Biochemical and Functional Heterogeneity
- Different Mechanisms of Drug Resistance in Subclones

Premalignant Neoplastic Stem Cells

Malignant Neoplastic Stem Cells
= Cancer Stem Cells = LSC

HIERARCHY AND SUBCLONE FORMATION FROM NEOPLASTIC STEM CELLS DURING EVOLUTION OF CANCER AND LEUKEMIA*

MDS ?

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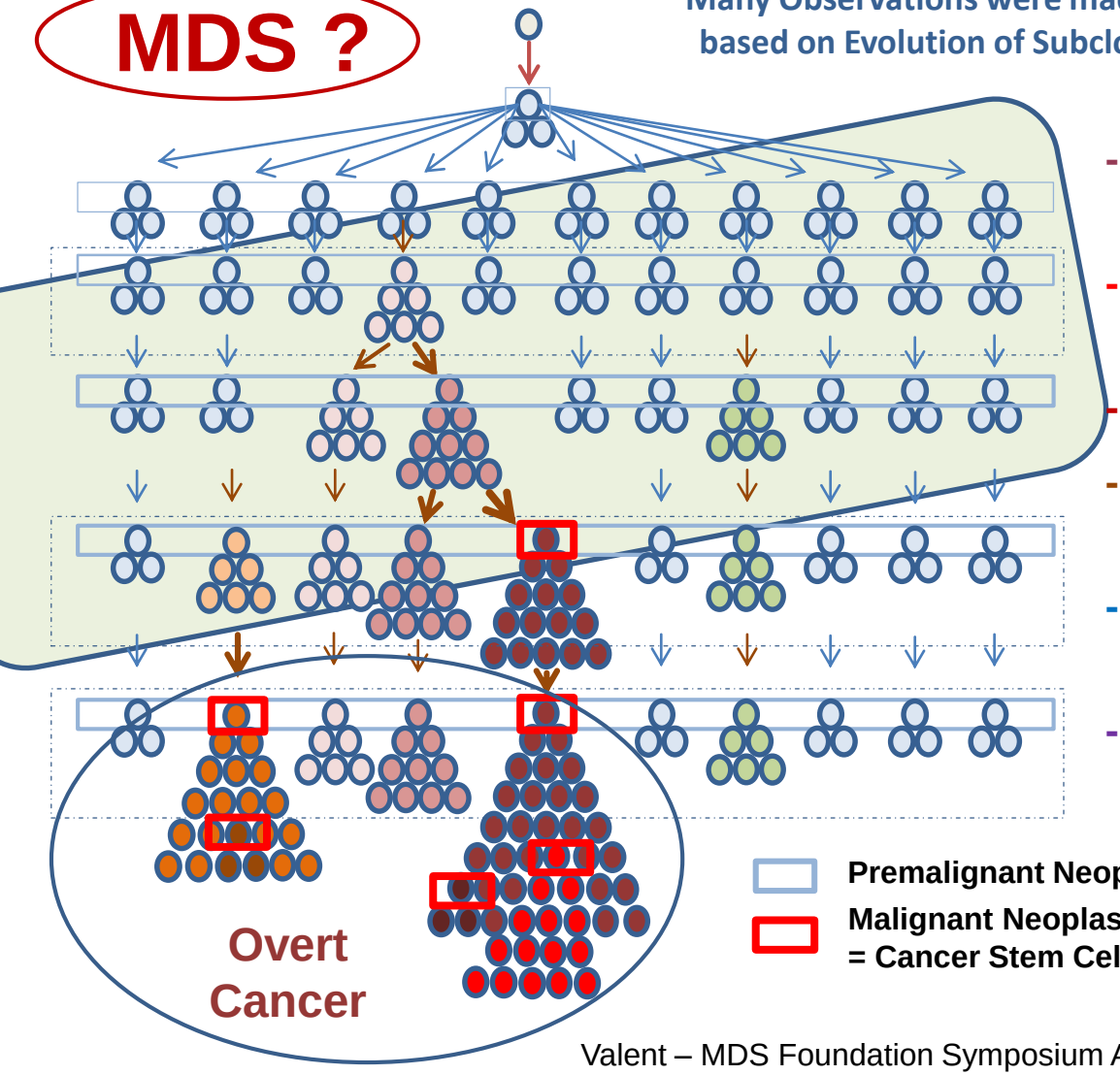

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- Different Mechanisms of Drug Resistance in Subclones

Premalignant Neoplastic Stem Cells

Malignant Neoplastic Stem Cells = Cancer Stem Cells = LSC

MDS: Minimal Diagnostic Criteria

A. Prerequisite Criteria (BOTH MUST be fulfilled)

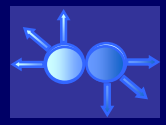
- Constant Cytopenia (one or more lines, 6 mo unless abnormal karyotype present)
- Exclusion of all other hematopoietic and non-hematopoietic diseases as primary reason for cytopenia/dysplasia (co-existing neoplasm or AML: needs BM histology)

B. MDS-related (decisive) Criteria (at least ONE)

- Dysplasia in at least 10% of: erythrocytes or/and megakaryoc. or/and neutrophils or/and >15% ring sideroblasts (iron stain)
- 5-19% blast cells in bm smears
- Typical karyotype abnormality (conventional cytogenetics or FISH)

C. Co-Criteria* (pts fulfilling A but not B & typical clinical features)

- Abnormal phenotype of bm cells by flow cytometry
- Molecular features indicative of a monoclonal disease process
- Constantly reduced bm function (e.g. low CFU levels)



*In the absence of B, Co-Criteria may lead to the prefinal diagnosis: highly suspective of MDS

Valent et al., Leuk Res 2007;31:727

MDS: Minimal Diagnostic Criteria

What if a Patient does not fulfil minimal diagnostic criteria for MDS ?

1) ICUS: Idiopathic Cytopenia of US

2) IDUS: Idiopathic Dysplasia of US

Valent et al., Leuk Res 2007;31:727
Valent & Horny, Eur J Clin Invest 2009;39:548

Definition of ICUS = Idiopathic Cytopenia of Uncertain (Undetermined) Significance

- Constant (≥ 6 m) marked cytopenia (Hb<11; ANC<1000; PLT<100000)

- MDS excluded ! - no decisive criterion / B !

- All other causes of cytopenia also excluded*

*Studies include a BM investigation (smear + histology), chromosome analysis (± FISH), various lab parameters, etc !

Valent et al., Leuk Res 2007;31:727

Definition of IDUS = Idiopathic Dysplasia of Uncertain (Undetermined) Significance

- No constant (≥ 6 m) marked cytopenia

- MDS-like features: dysplasia ± karyotype !

- All other causes of dysplasia excluded*

*Studies include a BM investigation (smear + histology), chromosome analysis (± FISH), and various lab parameters

Valent et al., Leuk Res 2007;31:727
Valent & Horny, Eur J Clin Invest 2009;39:548

Low EPO in the elderly & ICUS / IDUS

EPO as co-factor in MDS

Normal Hematopoietic Stem Cell

First hits - mutagenic event/s ?

Clonal expansion of a premalignant progenitor cell population leading to ineffective (impaired) erythropoiesis / hematopoiesis

Normal Hematopoiesis in the elderly

Disease manifestation may depend on EPO production (kidney function↓? androgens↓?)

EPO-responsive progenitors

EPO production adequate and sufficient to prevent anemia

Inadequate ´EPO-response´ to ineffective erythropoiesis → anemia

Low EPO in elderly → anemia / AOE

no MDS detected as no anemia develops – these patients have dysplasia without cytopenia = IDUS

LOW RISK MDS often responsive to EPO therapy (15-25% of patients)

ICUS

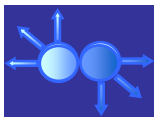
EPO-response lost +/- blasts ↑

Disease progression/clonal expansion

HIGH RISK MDS (cytopenia found invariably)

Further oncogenic hits that lead to maturation arrest and proliferation

SECONDARY ACUTE MYELOID LEUKEMIA



IDUS + ICUS = MDS

- MDS may often develop early in lifetime – usually as a clinically silent prephase = IDUS (if detected)
- In young patients with IDUS and EPO-resposive BFU-E, the EPO production may be sufficient to prevent the development of anemia
- **With age, EPO production decreases and these patients develop anemia and thus frank MDS**
- Reason for decreased EPO production in advanced age: **a) renal = ´aged kidney´** [b) androgen deficiency] studies are in progress to answer this question !
- **IDUS must not be confused with imminent AML ! How to differentiate: 1) CFU 2) 6 months !**