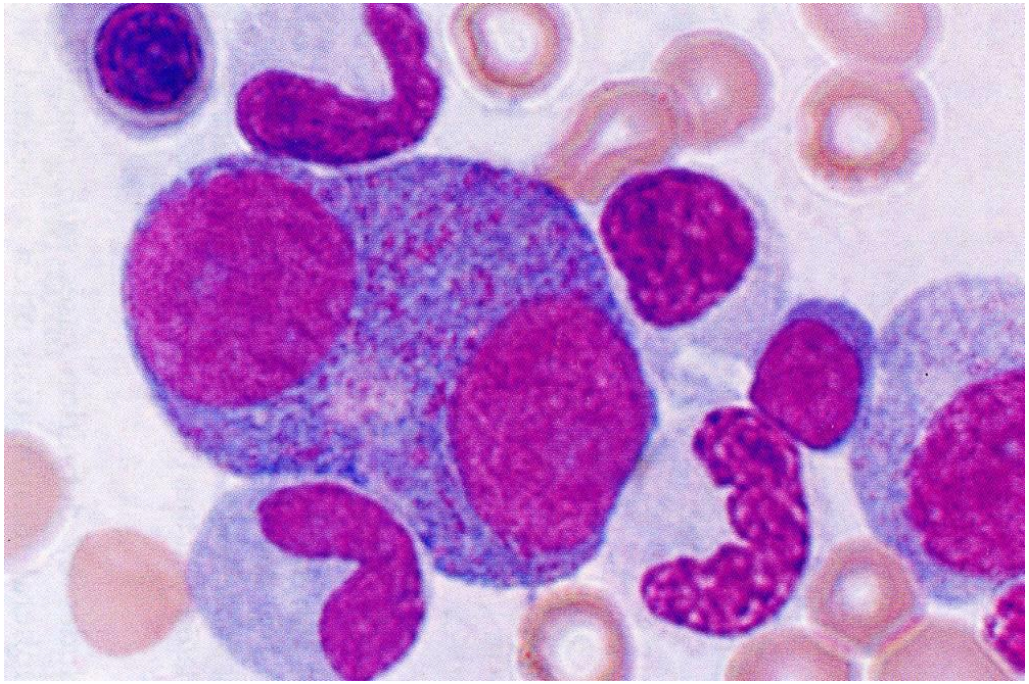
Sindromi mielodisplastiche



Castoldi G. Atlas of blood cells. 2003; p 285-98.

WHO classification of myeloid neoplasms and acute leukemia

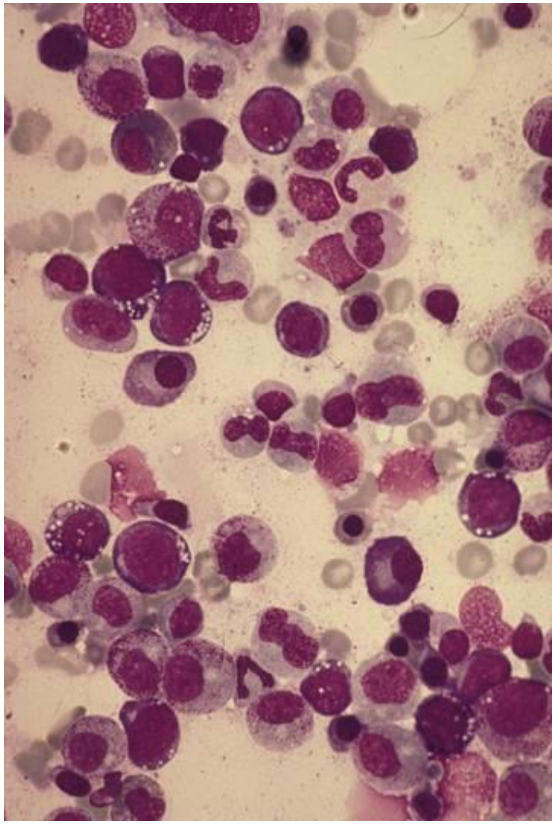
1. Myeloproliferative neoplasms (MPN)
2. Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
3. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
4. **Myelodysplastic syndromes (MDS)**
5. Acute myeloid leukemia (AML) and related neoplasms
6. Blastic plasmacytoid dendritic cell neoplasm
7. Acute leukemias of ambiguous lineage
8. B-lymphoblastic leukemia/lymphoma
9. T-lymphoblastic leukemia/lymphoma

Arber DA et al. Blood. 2016; 127(20):2391-2405

MDS: definizione

Gruppo eterogeneo di disordini clonali della cellula staminale, contrassegnati da citopenia periferica e nella maggior parte dei casi da un midollo ipercellulato con evidenti alterazioni maturative (displasia).

Le MDS presentano un aumentato rischio di evoluzione in LAM.



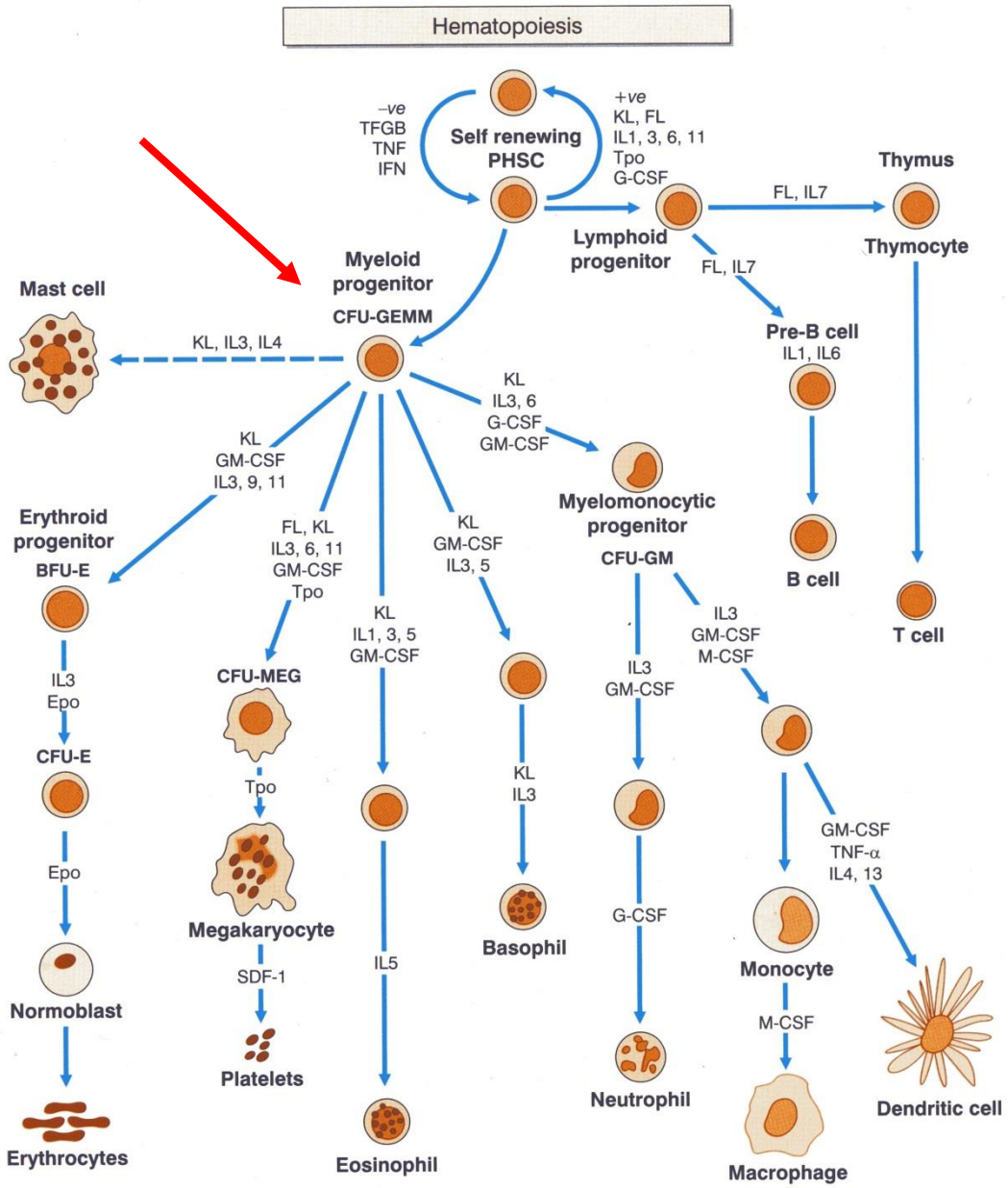
	MDS	AML	MPD
Differentiation	Impaired ←←	Impaired	Normal
Proliferation/survival	Impaired →→	Preserved	Increased

Arrows indicate where a second hit could result in progression to AML.

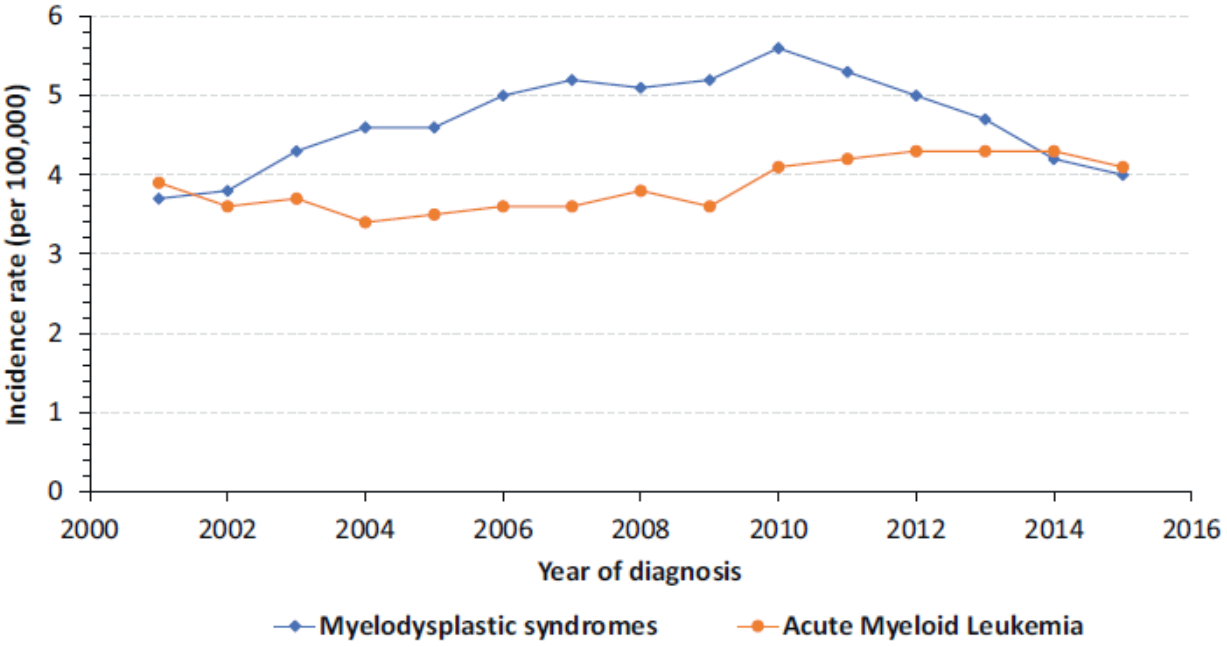
Nimer SD. Blood 2008;111:4841.

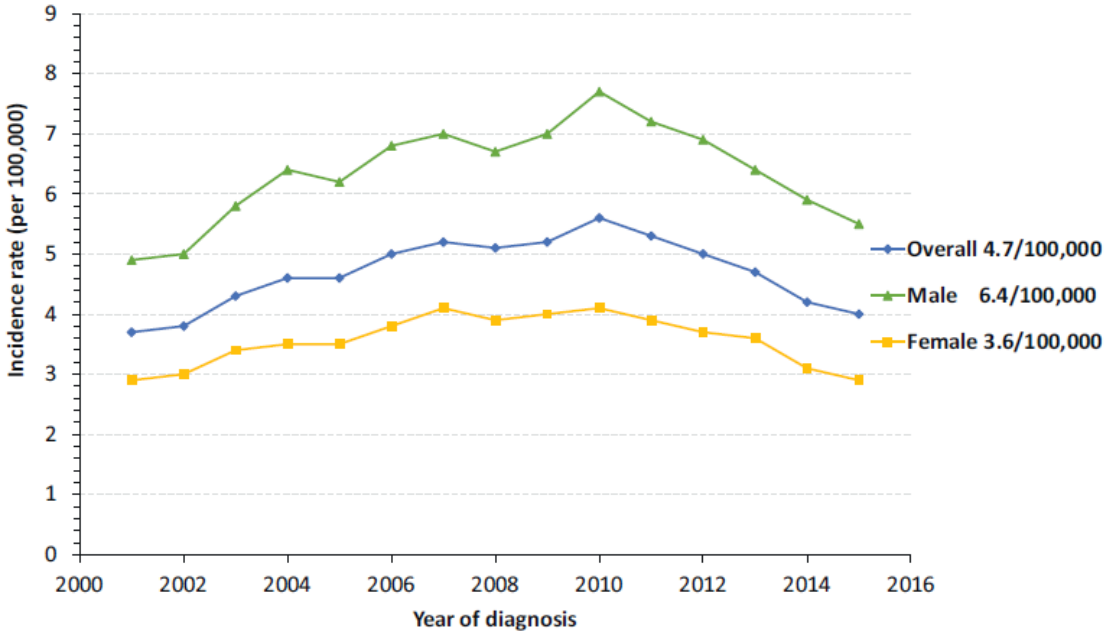
Castoldi G. Atlas of blood cells. 2003; p 285-98.

MDS: definizione



MDS: incidenza

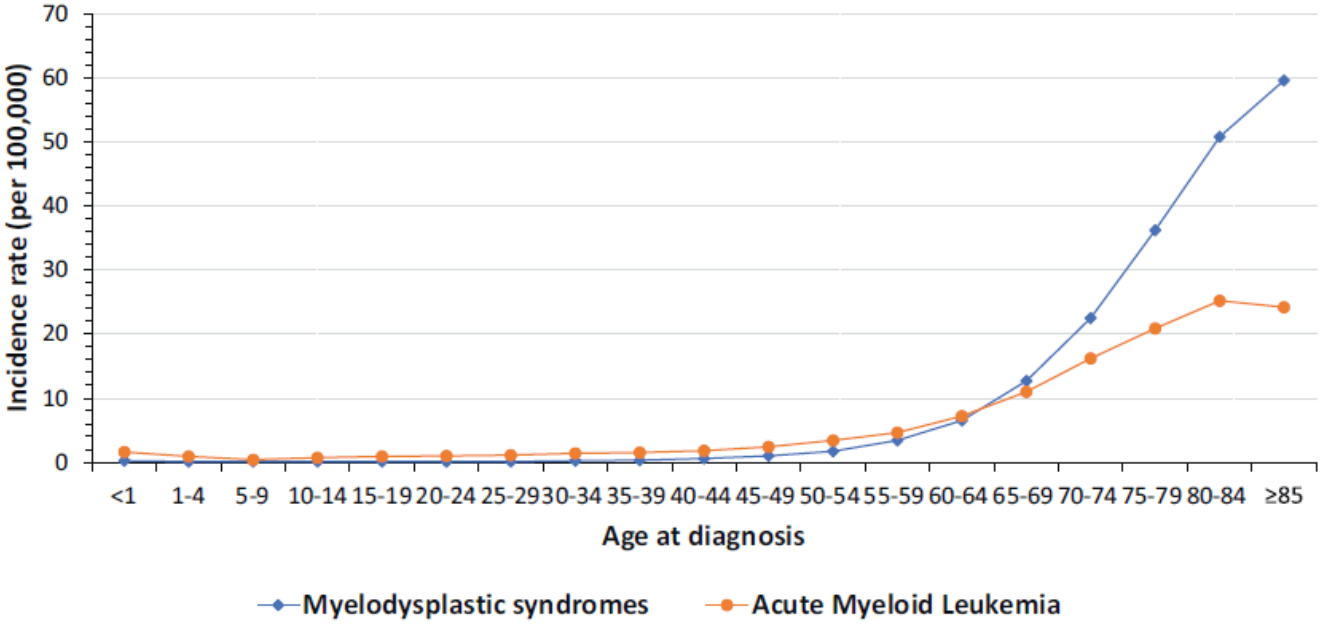


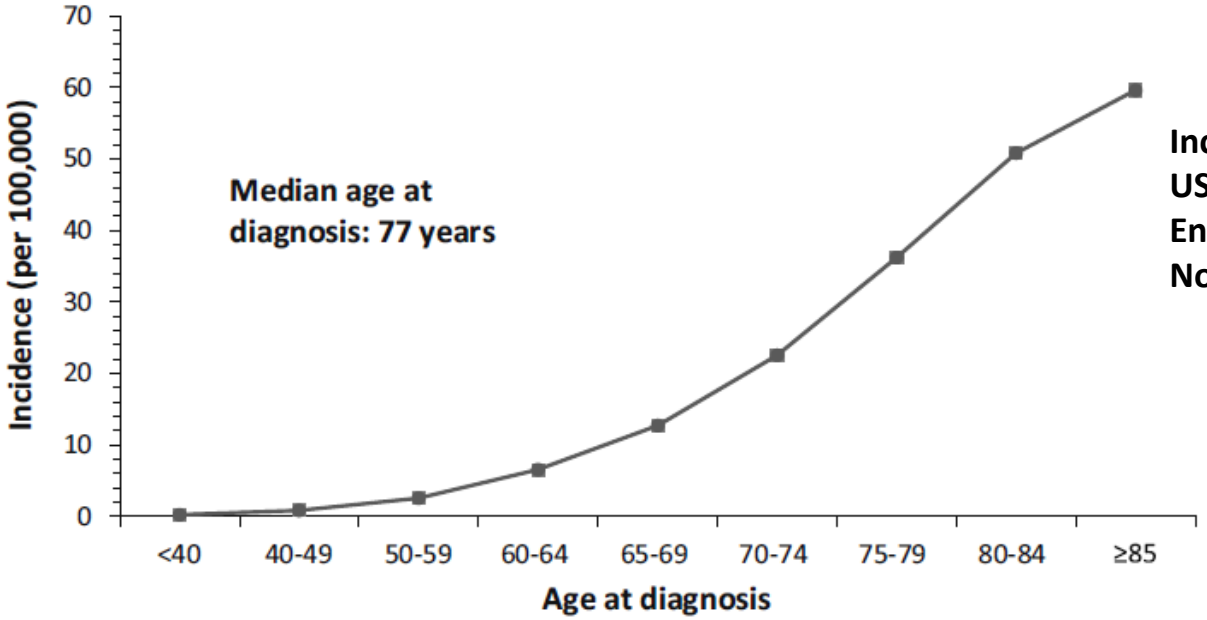


Incidence of MDS or AML in the USA(Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).

Zeidan et al. Blood Reviews 2018

MDS incidenza

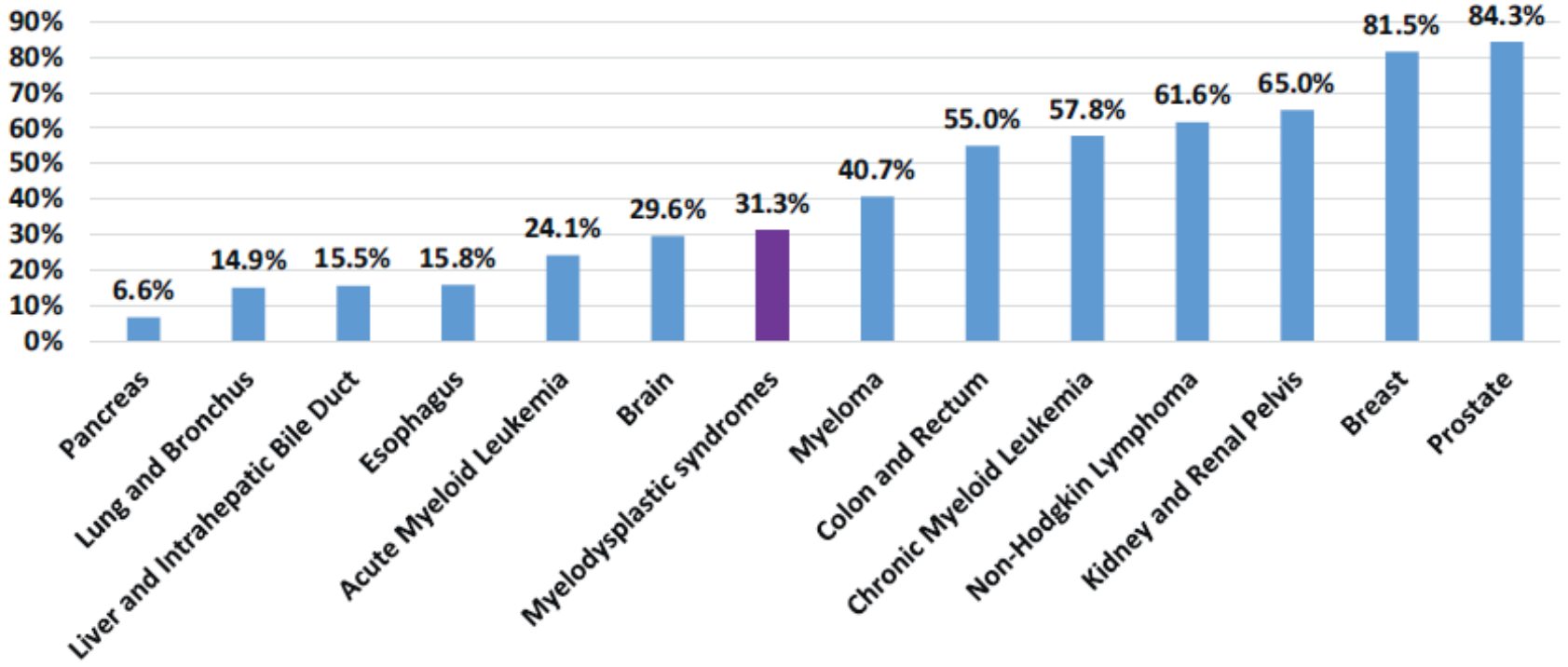




Incidence of MDS or AML in the USA(Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).

Zeidan et al. Blood Reviews 2018

Sopravvivenza a 5 anni



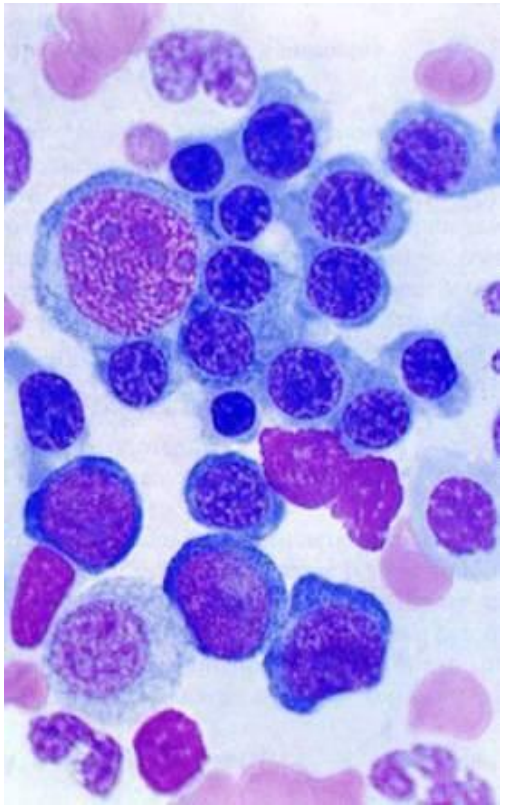
Five-year overall survival of cancer patients in the United States (Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).

Zeidan et al. Blood Reviews 2018

Eziologia

- La causa delle MDS è di solito sconosciuta.

- In alcuni casi una MDS può svilupparsi dopo l'esposizione a radiazioni, ad alcuni tossici ambientali quali il benzene o dopo trattamenti con alchilanti o inibitori delle topoisomerasi II per una precedente neoplasia



Castoldi G. Atlas of blood cells. 2003; p 285-98.

MDS

- **<u>The cause is known in only 15% of cases</u>**
- **Inherited predisposition**
  - is evident in a third of **paediatric** cases, including in children with Down's syndrome, Fanconi's anaemia, and neurofibromatosis.
  - In **adults**, inherited predisposition is less common but should be investigated in young adults or in families with other cases of MDS, AML, or AA.
- **Environmental factors** include previous use of chemotherapy, especially of alkylating agents and purine analogues, radiotherapy, and tobacco smoking.
- Recognised **occupational factors** include exposure to benzene and its derivatives,[7] and an excess of cases is reported in agricultural and industrial workers.

Panel: Causes of myelodysplastic syndromes

Antineoplastic agents

Alkylating agents

- Busulfan
- Carboplatin
- Carmustine
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Dacarbazine
- Lomustine
- Melphalan

Topoisomerase II inhibitors

- Daunorubicin
- Doxorubicin
- Etoposide
- Mitoxantrone
- Razoxane

Purine analogues

- Fludarabine and others

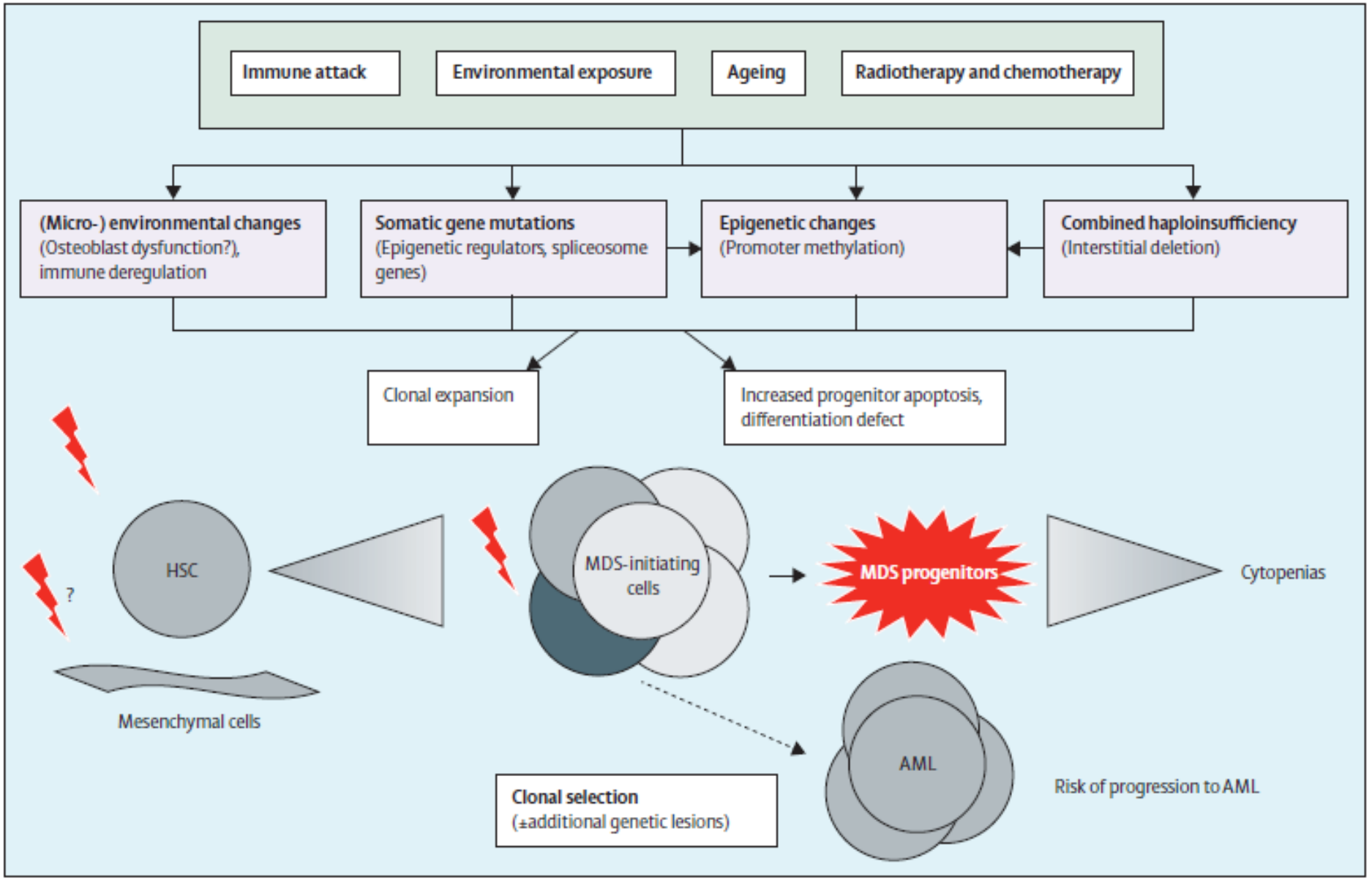
Radiotherapy

Environmental factors

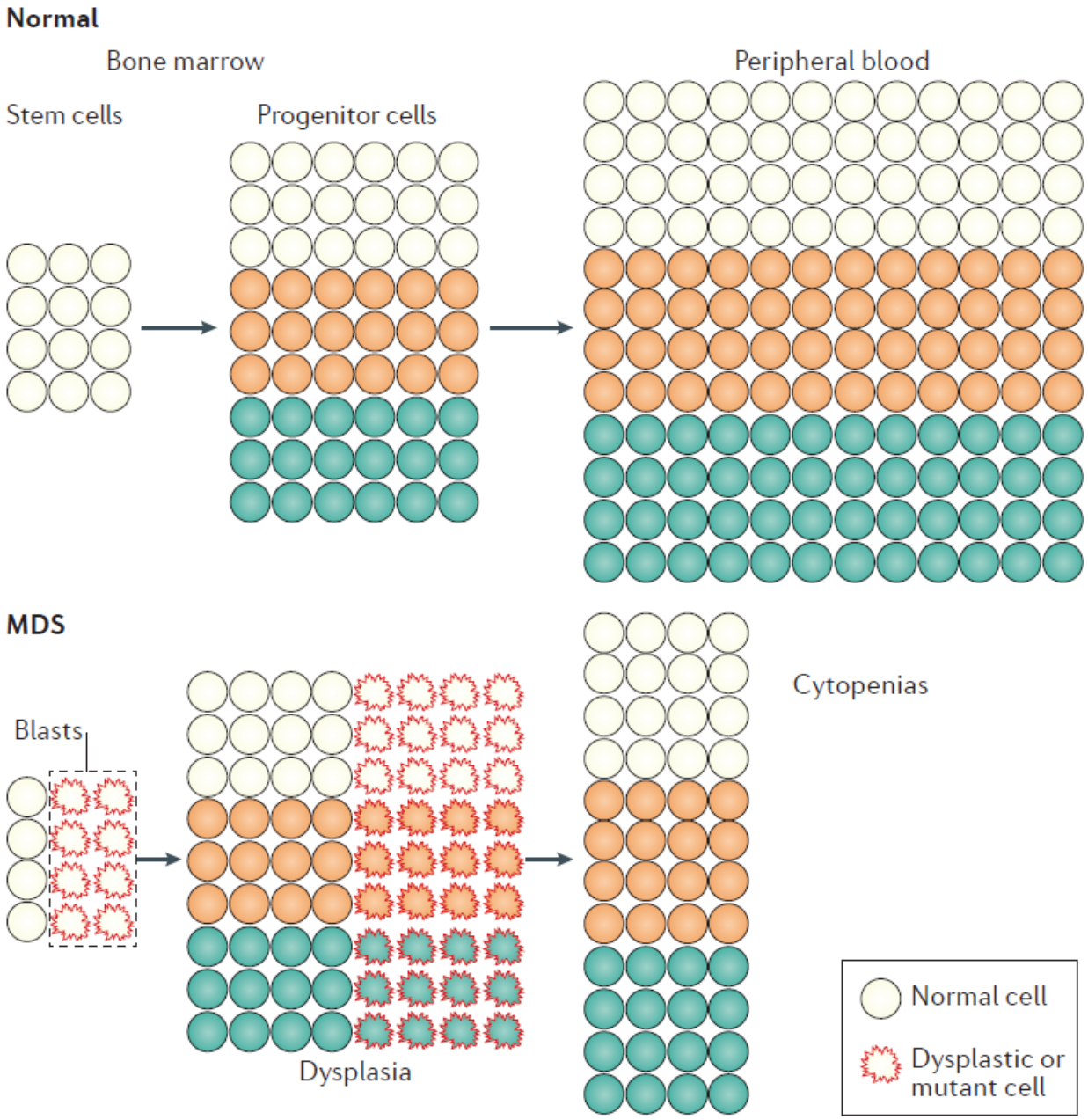
- Tobacco
- Ionising radiation
- Benzene exposure (and industrial hydrocarbons)
- Agricultural compounds (pesticides, herbicides, fertilisers)

Ades et al. Lancet 2014; 383: 2239–52

Pathogenesis of MDS



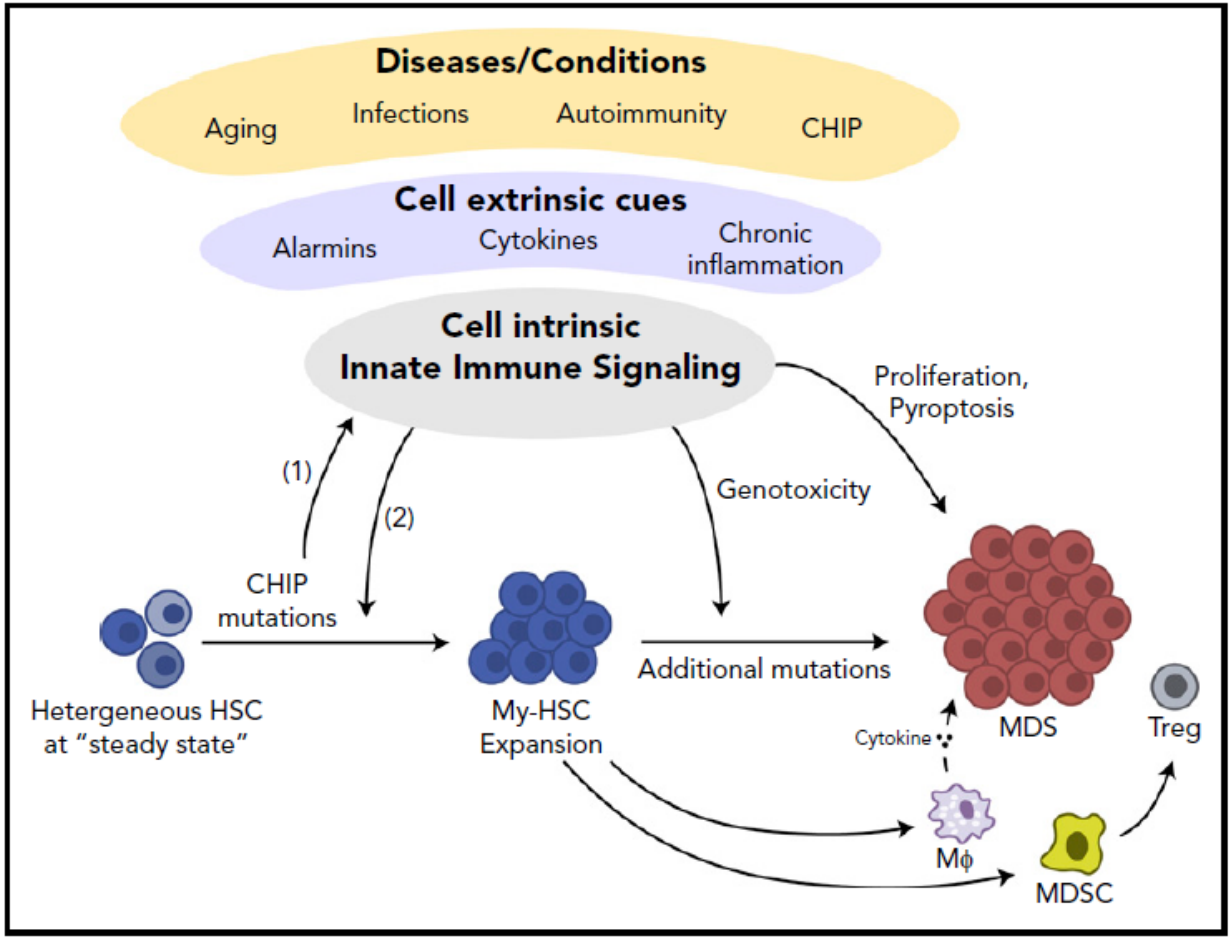
Ades et al. Lancet 2014; 383: 2239–52



Sperling et al. Nature Reviews Cancer 2017

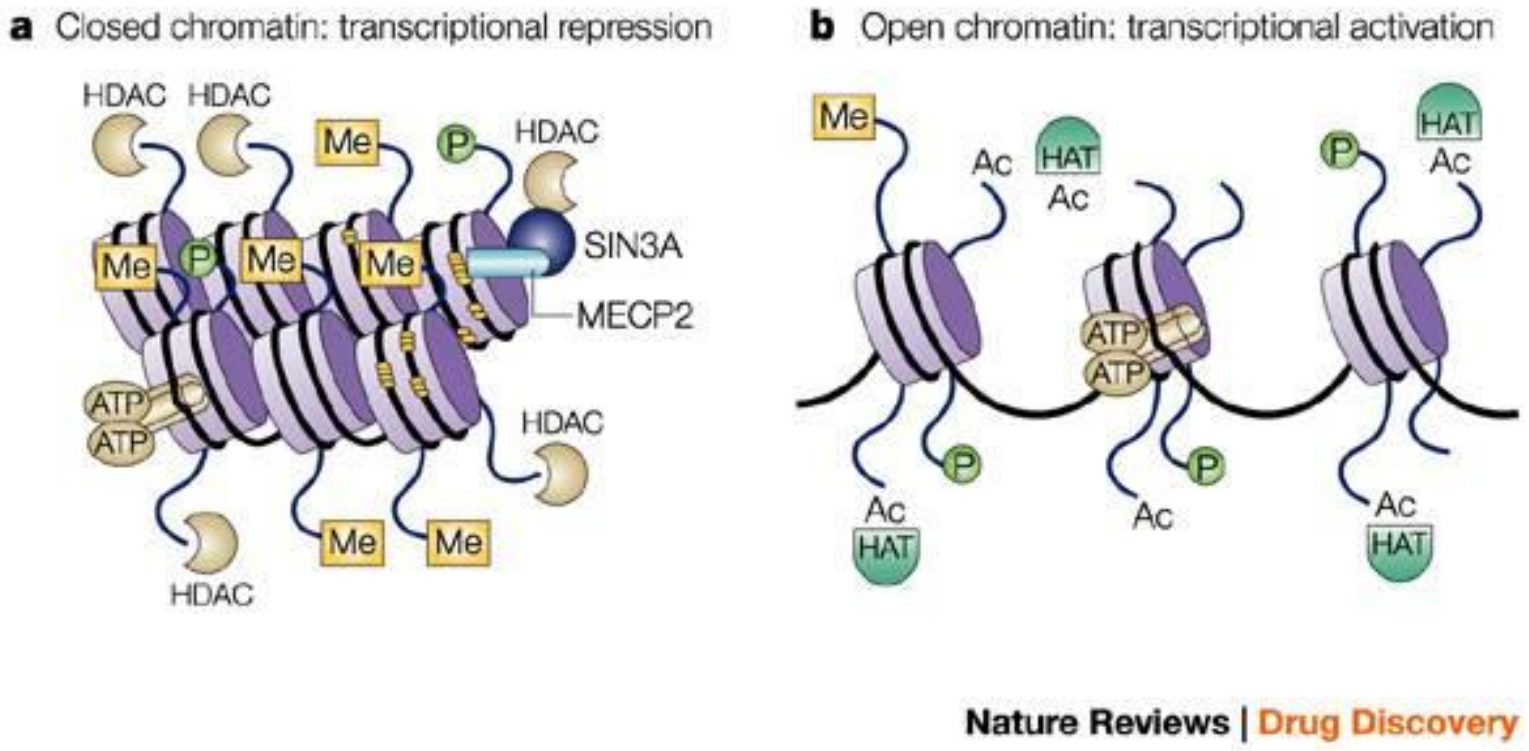
Sperling et al. Nature Reviews Cancer 2017

Figure 2. Model of innate immune signaling dysregulation in the pathogenesis of MDS. Certain diseases and conditions, such as aging, autoimmune disorders, chronic infections, and/or clonal hematopoiesis of indeterminate potential (CHIP), can induce innate immune signaling dysregulation in HSCs in part by creating an inflammatory BM microenvironment characterized by increased alarmins and/or cytokines. Development of MDS may occur by at least 2 independent mechanisms. (1) CHIP-associated mutations (ie, DNMT3a or TET2) occur in HSCs by innate immune independent mechanisms and drive the expansion of myeloid-biased HSC leading to altered innate immune signaling and development of MDS. (2) Prolonged innate immune signaling caused by clonally expanded myeloid-biased HSCs directly increases the risk of acquiring mutations (ie, CHIP mutations) contributing to MDS. Innate immune signaling dysregulation at the MDS stage occurs through cell-intrinsic (ie, increased cell death via pyroptosis) and cell-extrinsic mechanisms (ie, cytokines and alarmins stimulation from macrophage and myeloid derived suppressor cells [MDSCs]). As a result of altered innate immune signaling, MDSCs also promote regulatory T cell (Treg) activation to limit T-cell surveillance.



Barreyro et al. Blood. 2018;132(15):1553-1560

Epigenetic changes



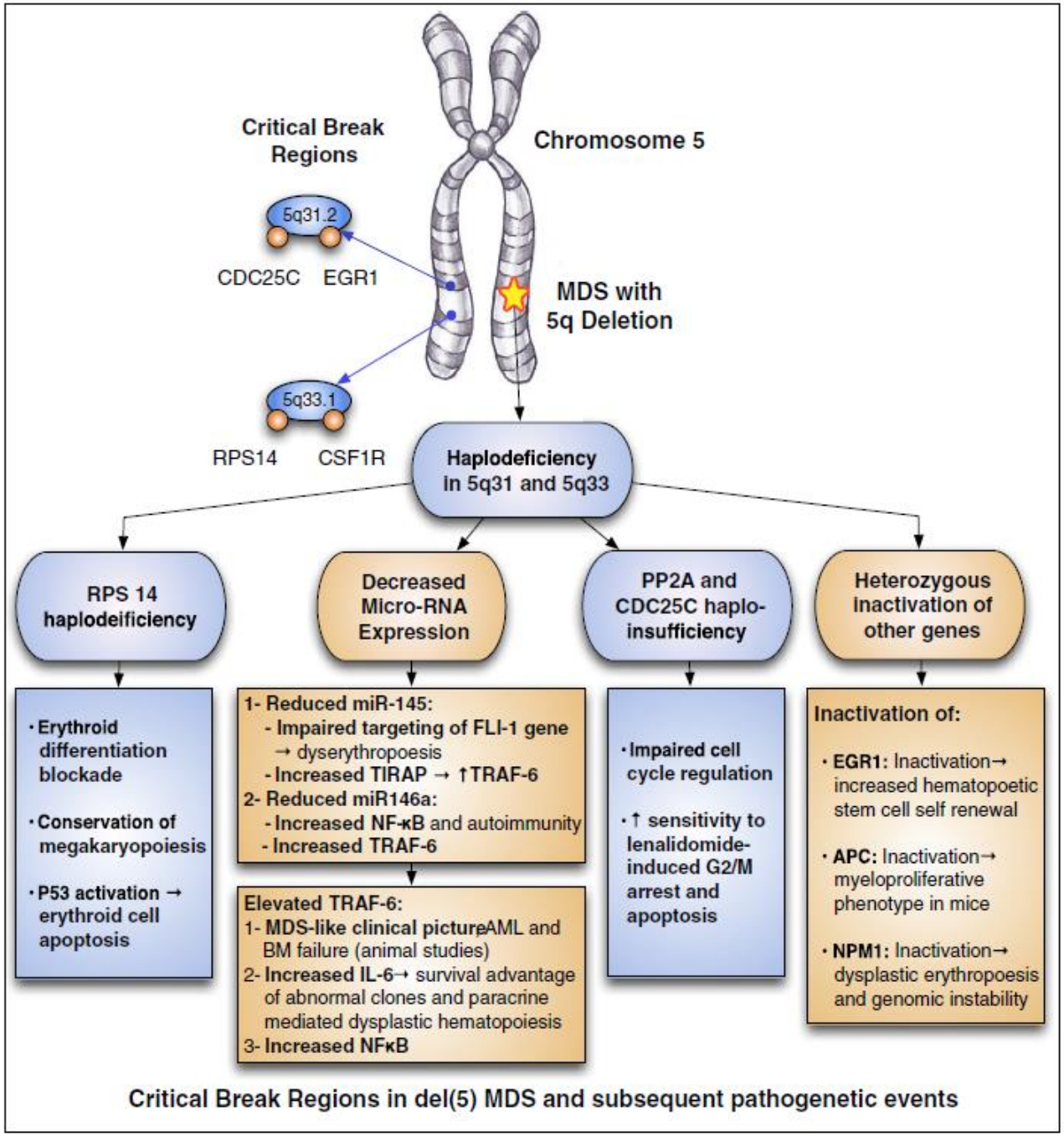
Nucleosomes consist of DNA (black line) wrapped around histone octomers (purple).

Post-translational modification of histone tails by methylation (Me), phosphorylation (P) or acetylation (Ac) can alter the higher-order nucleosome structure.

Nucleosome structure can be regulated by ATP-dependent chromatin remodellers (yellow cylinders), and the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Methyl-binding proteins, such as the methyl-CpG-binding protein (MECP2), target methylated DNA (yellow) and recruit HDACs.

a. DNA methylation and histone deacetylation induce a closed-chromatin configuration and transcriptional repression.

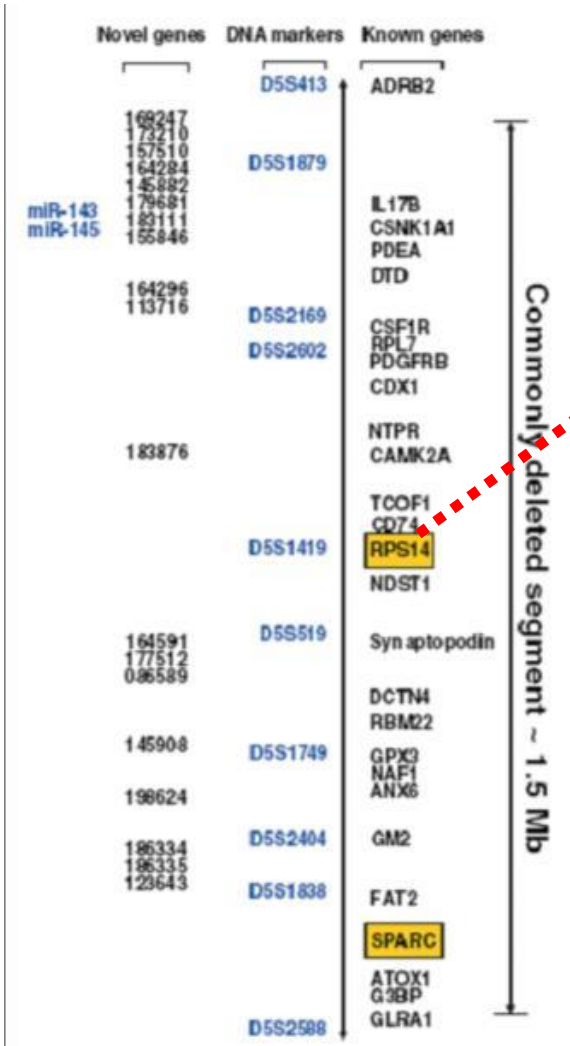
b. DNA demethylation and histone acetylation relaxes chromatin, and allows transcriptional activation.

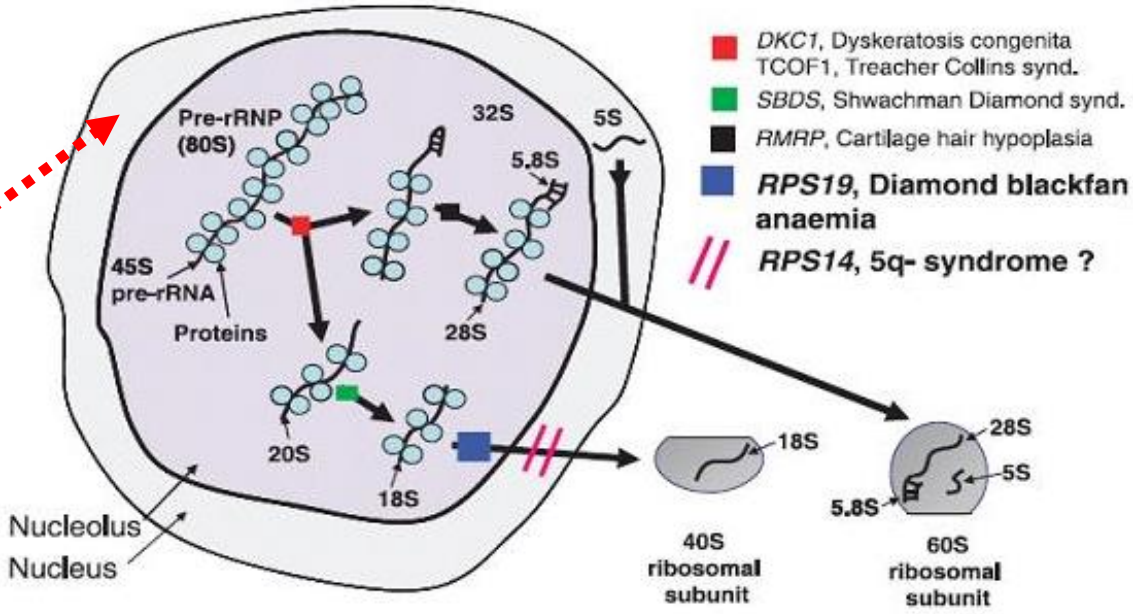


Critical Break Regions in del(5) MDS and subsequent pathogenetic events

Ann Hematol (2014) 93:723–733

Ribosomal biogenesis and BM falilure syndromes

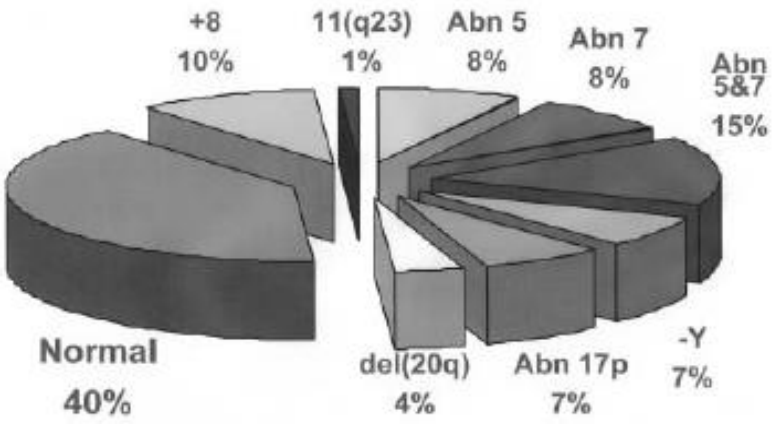




Mohamedali and Mufti, BJH 2008;144:157

Citogenetica

- La citogenetica ha un ruolo decisivo nella diagnosi e nella definizione della prognosi
- Anomalie citogenetiche sono riscontrabili del 40-70% delle MDS de novo e nel 95% delle forme secondarie a chemioterapia (therapy-related)
-



MDS and mutations

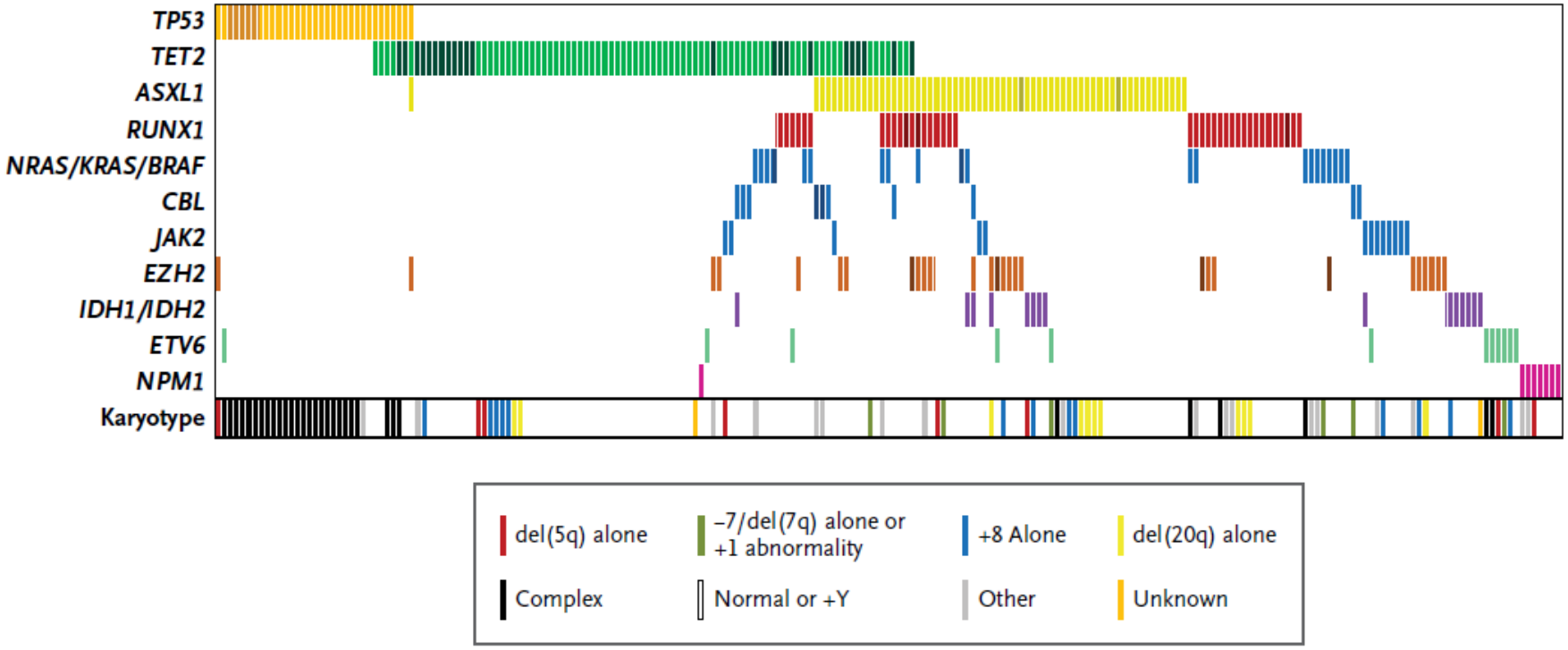
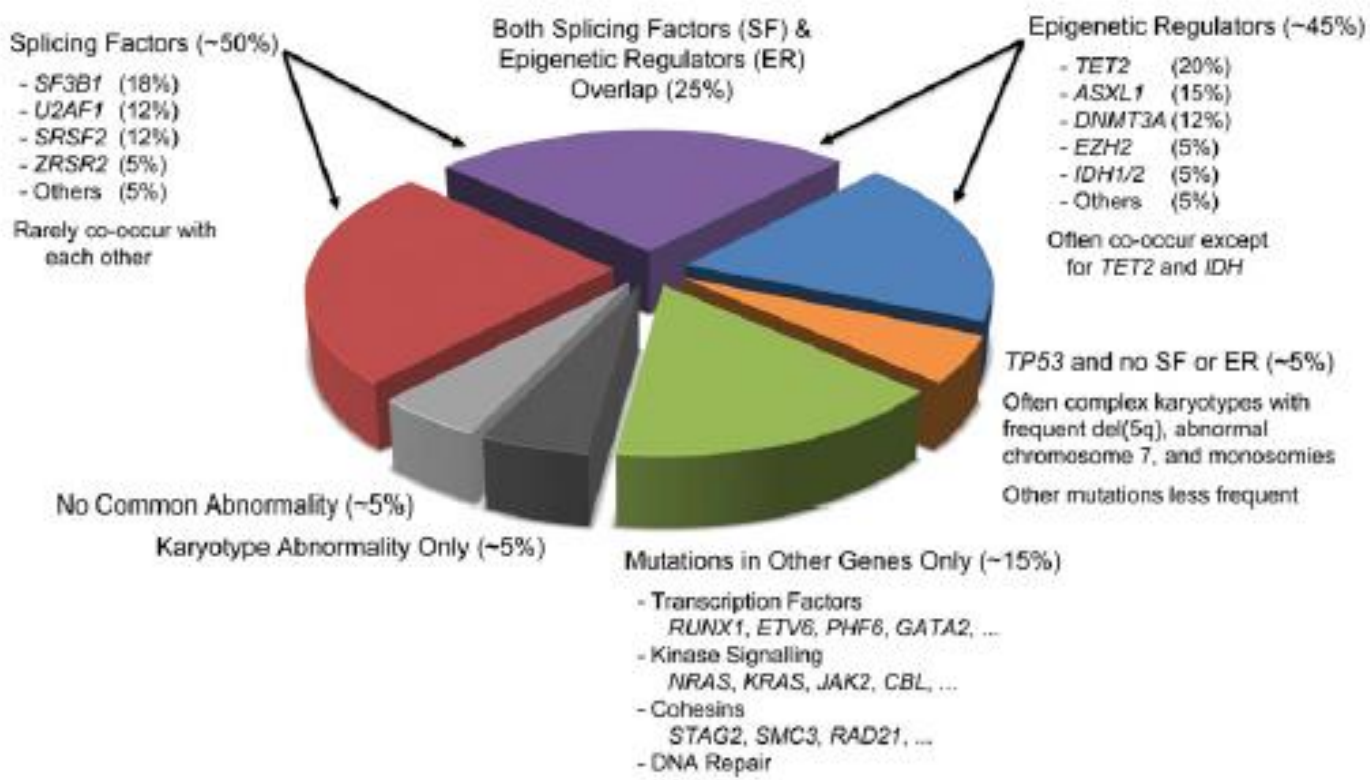


Figure 1. Mutations and Cytogenetic Abnormalities in 223 Samples with at Least One Mutation.

Mutations in the 11 most frequently mutated gene groups are shown by colored bars. Each column represents 1 of the 223 samples with a mutation in one or more of the genes listed. Darker bars indicate samples with two or more distinct mutations in that gene group. The karyotype of each of the 223 samples is also shown.

N Engl J Med 2011;364:2496-506.

Distribution of recurrent mutations and karyotypic abnormalities in MDS.



Bejar & Steensma. Blood. 2014;124(18):2793-2803

Clonal cells from nearly 50% of MDS patients harbor a splicing factor (SF) mutation, and a similar fraction carry >1 mutated epigenetic regulator (ER).

Approximately 25% of patients have mutations of genes in both groups. Patients with TP53 mutations often have fewer cooperating mutations and instead have a high rate of chromosomal abnormalities, including frequent complex karyotypes.

Many other genes can be comutated with SF and ER genes, but such mutations also occur in the absence of SF or ER lesions in 15% of patients.

Only approximately 10% of patients lack mutations in any of the common recurrently mutated genes.

	Frequency of mutations (%)	Gene function	Prognosis
SF3B1	15–30%	Spliceosome	Favourable?
TET2	15–25%	DNA hydroxymethylation	Neutral
ASXL1	10–20%	Histone modifications	Unfavourable
RUNX1	5–15%	Transcription factor	Unfavourable
TP53	5–10%	Transcription factor	Unfavourable
DNMT3A	5–10%	DNA methylation	Unfavourable?
NRAS, KRAS	5–10%	Signal transduction	Unfavourable (low-risk syndromes)
SRSF2	5–10%	Spliceosome	Unfavourable
U2AF1	5–10%	Spliceosome	Unfavourable (low-risk syndromes)
BCOR-L1	5–6%	Transcription repressor	Unfavourable
ZRSR2	5%	Spliceosome	Neutral?
EZH2	3–7%	Histone modifications	Unfavourable
ETV6	3%	Transcription factor	Unfavourable
JAK2	3–4%	Signal transduction	Favourable?
IDH1, IDH2	4–5%	DNA hydroxymethylation and histone modifications	Unfavourable
UTX	1–2%	Histone modifications	Unfavourable?

***Table 1*: Recurrent somatic gene mutations in myelodysplastic syndromes**

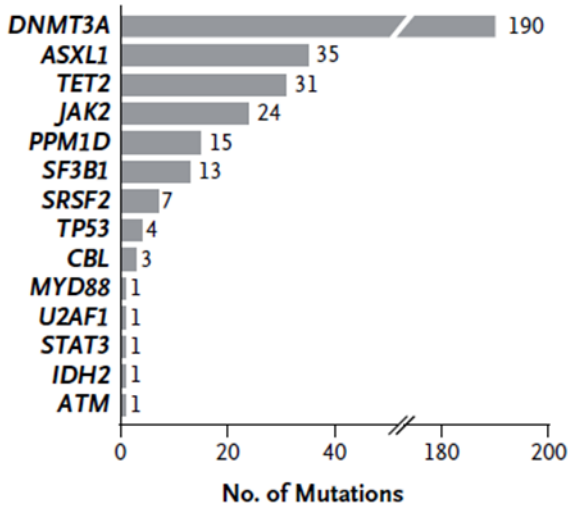
***Ades et al. Lancet* 2014; 383: 2239–52**

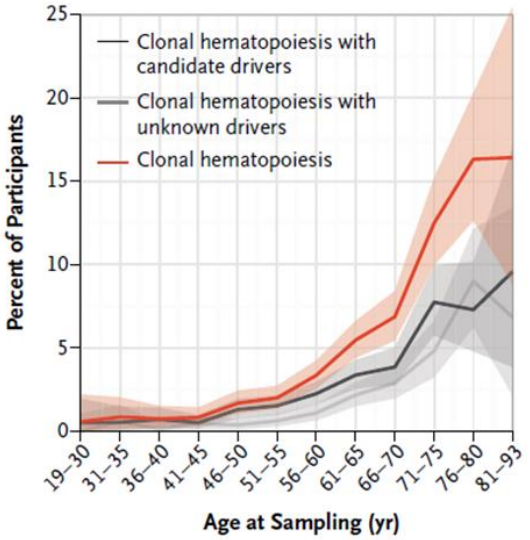
Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

- whole-exome sequencing of DNA in PB cells from **12,380** persons, unselected for cancer or hematologic phenotypes from Swedish national patient registers.

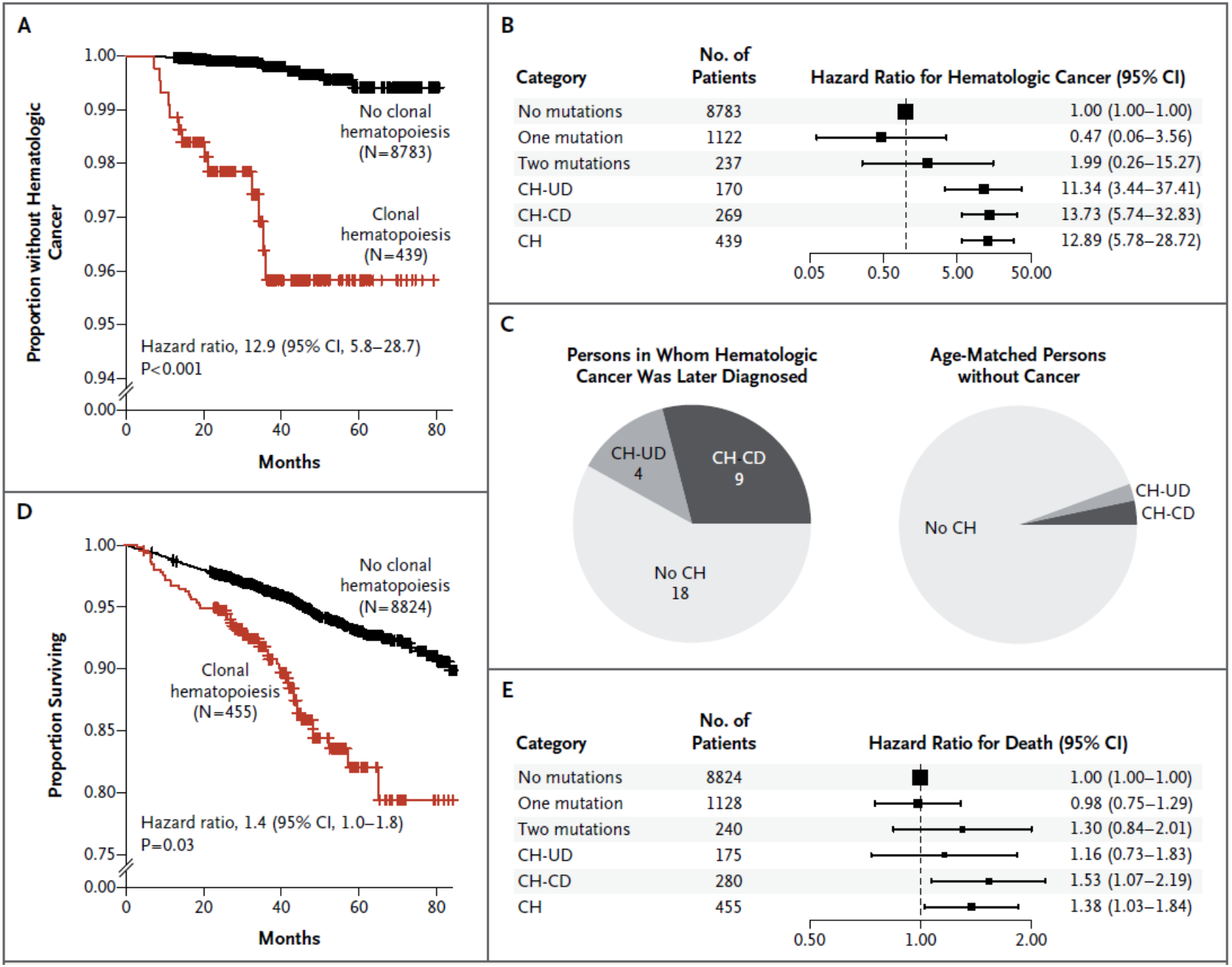
- Clonal hematopoiesis with somatic mutations was observed **in 10% of persons older than 65 years of age** but in only 1% of those younger than 50 years of age.

- **Clonal hematopoiesis was a strong risk factor for subsequent hematologic cancer** (HR, 12.9; 95% confidence interval, 5.8 to 28.7).





Genovese et al, N Engl J Med 2014;371:2477-87.



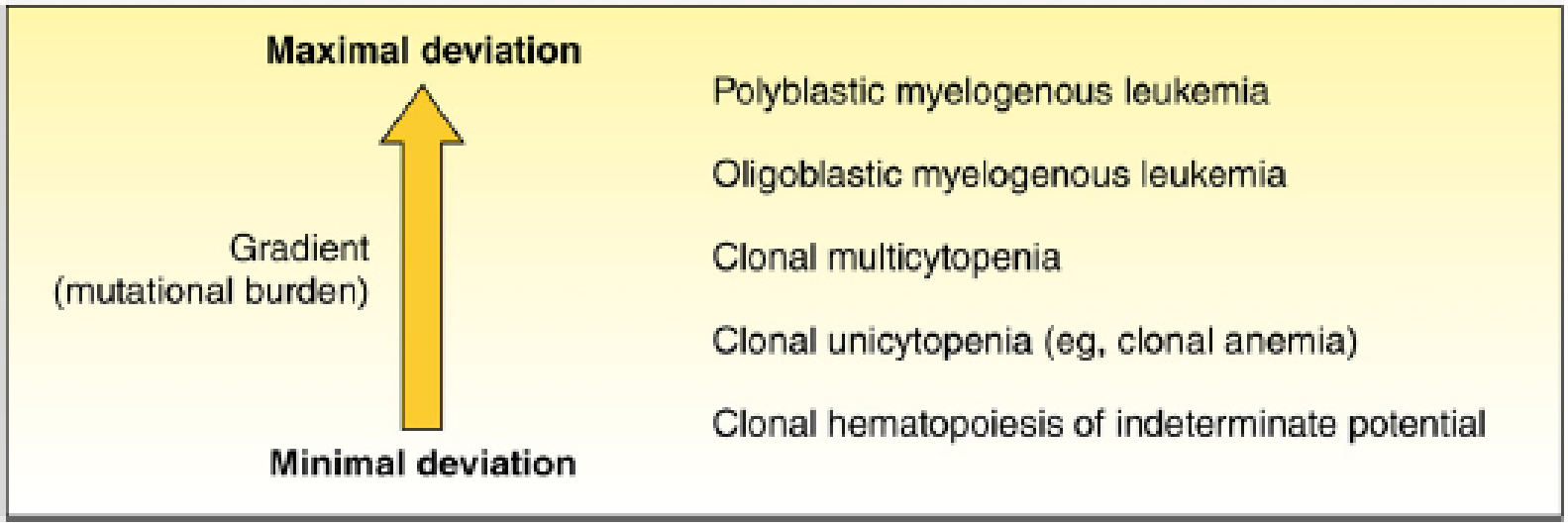
Genovese et al, N Engl J Med 2014;371:2477-87.

Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes

Clonal **H**ematopoiesis of **I**ndeterminate **P**otential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele frequency of at least 2% (e.g., *DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, U2AF1, CREBBP, CUX1, SRSF2, MLL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1*)
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

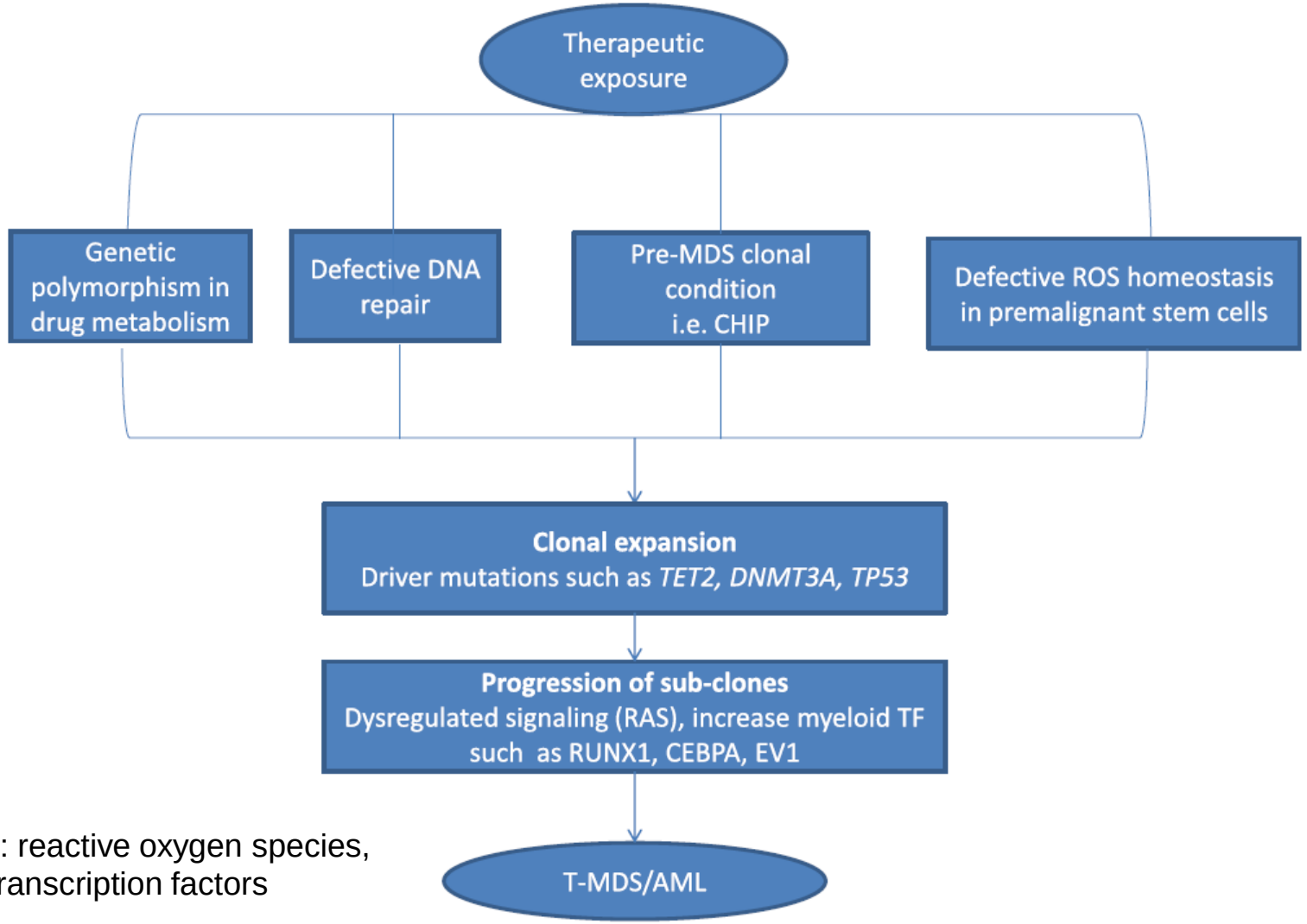
Steensma et al, Blood 2015;126:9



A schematic relationship among the disorders that fall under the rubric of myelodysplastic neoplasms. Myelodysplastic disorders are less deviated forms of acute myelogenous leukemia.[7] Here, deviation is considered in terms of loss of regulated processes of proliferation, differentiation, and maturation compared with normal polyclonal hematopoiesis. Mutational burden considers qualitative as well as quantitative oncogenetic contributions to neoplasia. Professional illustration by Patrick Lane, ScEYEnce Studios.

Lichtman MA Blood 2015:126:1

Model for development of t-MN

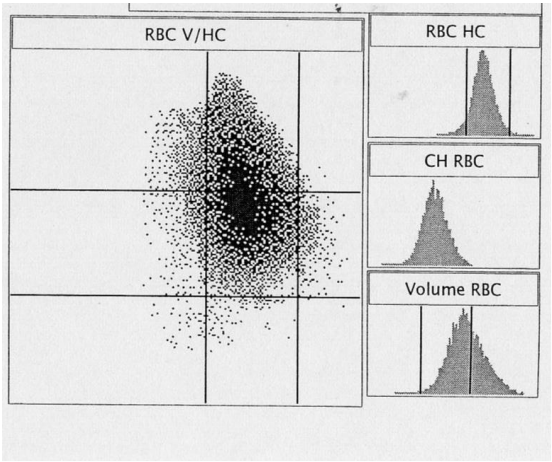


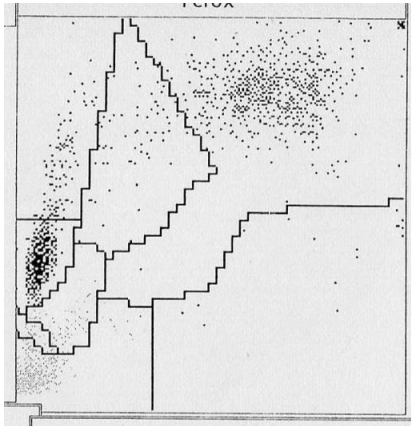
ROS: reactive oxygen species,
TF: transcription factors

A. Abou Zahr et al. / Blood Reviews 31 (2017) 119–128

TEST	RISULT	PAT	NORMALI	UNITA'
WBC		2.41	(5.2 - 12.4)	x10.e3 /uL
RBC		2.35	(4.2 - 6.1)	x10.e6 /uL
HGB		9.0	(12 - 18)	g/dL
HCT		27.3	(37 - 50)	%
MCV		116.3	(80 - 99)	fL
MCH		38.5	(27 - 31)	pg
MCHC	33.1		(33 - 37)	g/dL
CHCM	33.4		(33 - 37)	g/dL
RDW		18.8	(11.5 - 14.5)	%
HDW		3.35	(2.2 - 3.2)	g/dL
PLT		61	(130 - 400)	x10.e3 /uL
MPV	9.5		(7.2 - 11.1)	fL
%NEUT		38.9	(40 - 74)	%
%LYMPH		51.2	(19 - 48)	%
%MONO		3.1	(3.4 - 9)	%
%EOS	0.8		(0 - 7)	%
%BASO	0.6		(0 - 1.5)	%
%LUC		5.4	(0 - 4)	%
#NEUT		0.94	(1.9 - 8)	x10.e3 /uL
#LYMPH	1.24		(0.9 - 5.2)	x10.e3 /uL
#MONO		0.08	(0.16 - 1)	x10.e3 /uL
#EOS	0.02		(0 - 0.8)	x10.e3 /uL
#BASO	0.02		(0 - 0.2)	x10.e3 /uL
#LUC	0.13		(0 - 0.4)	x10.e3 /uL
LI		1.78	(1.90 - 3)	
MPXI	3.8		(-10 - 10)	
WBCPEROX	2.29			
WBC BASO	2.41			

ANISO	++
MACRO	+++
HYPO	+
LS	++
ATYP	+
BLASTS	+





Valutazione morfologica sangue periferico e midollare

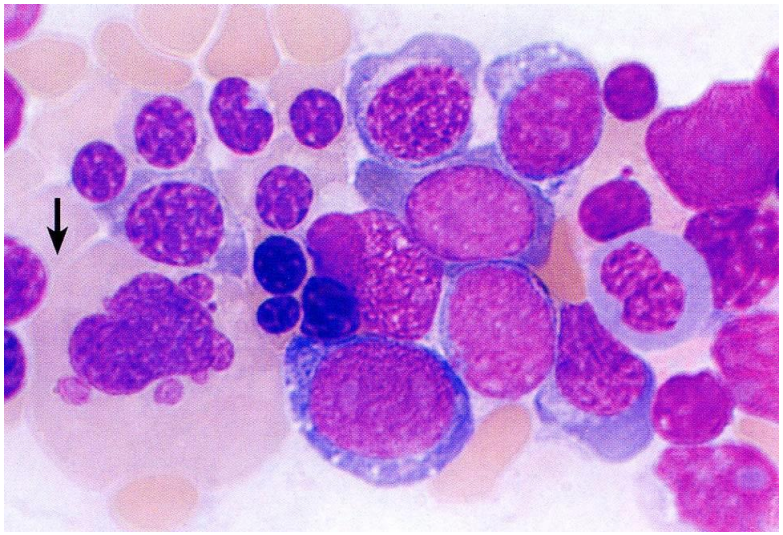
- Valutazione morfologica sangue periferico per orientamento diagnostico (diagnosi differenziale, segni di displasia, blasti etc)

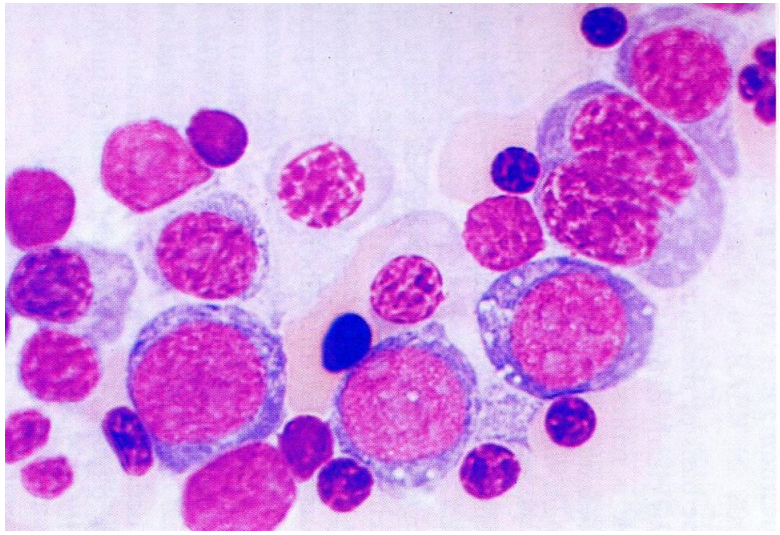
- Valutazione morfologica midollare:
  - Riscontro di segni di displasia
  - La valutazione morfologica dei blasti
    - Non raccomandata la valutazione citofluorimetrica
  - La % di blasti valutata su almeno 500 cellule (almeno 100 cellule non eritroidi)

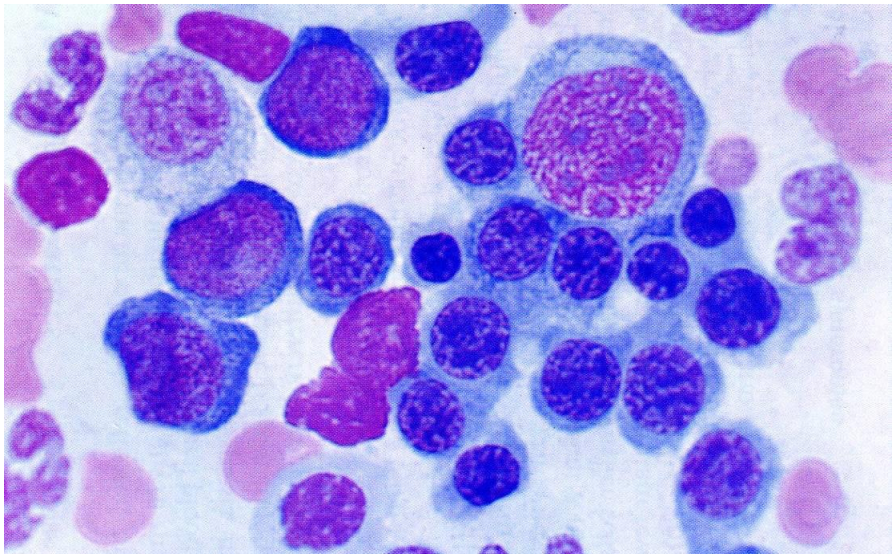
Caratteristiche morfologiche di displasia

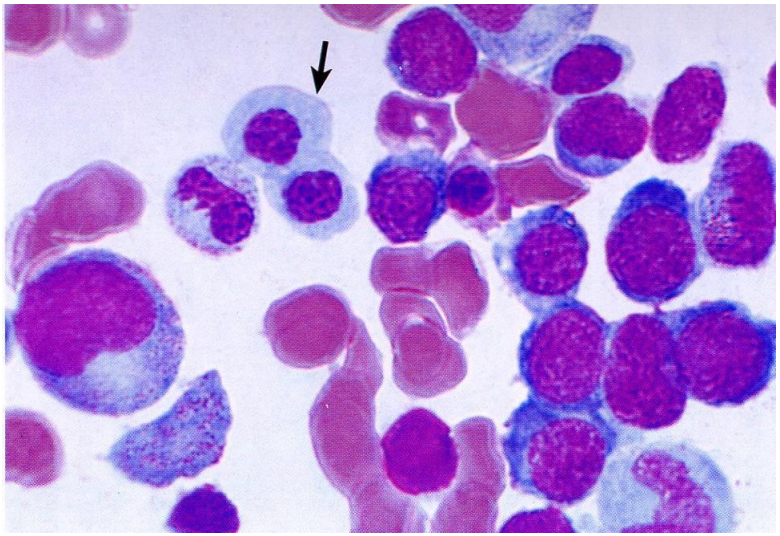
filiera	Nucleare	Citoplasmatica
eritroide	Multinuclearità, carioressi, mitosi anomale, megalobastosi	Vacuoli, difetti di emoglobinizzazione, sideroblasti ad anello
granulocitaria	Forme Pseudo-Pelger, ipersegmentazione, nuclei ad anello, forme giganti, clumping cromatinico, granulociti binucleati	Ipogranulaione, corpi di Dohle, vacuolizzazioni, difetti di mieloperossidasi
megacariocitaria	Micromegacariociti, forme mononucleate, megacariociti con nuclei dispersi	Asincronia nucleo/citoplasmatica, piastrine giganti, piastrine ipogranulate o granulate
monocitaria	Ipersegmentazione, nuclei con forme bizzarre	Aumentata basofilia citoplasmatica, granulazioni prominenti

Displasia eritroide

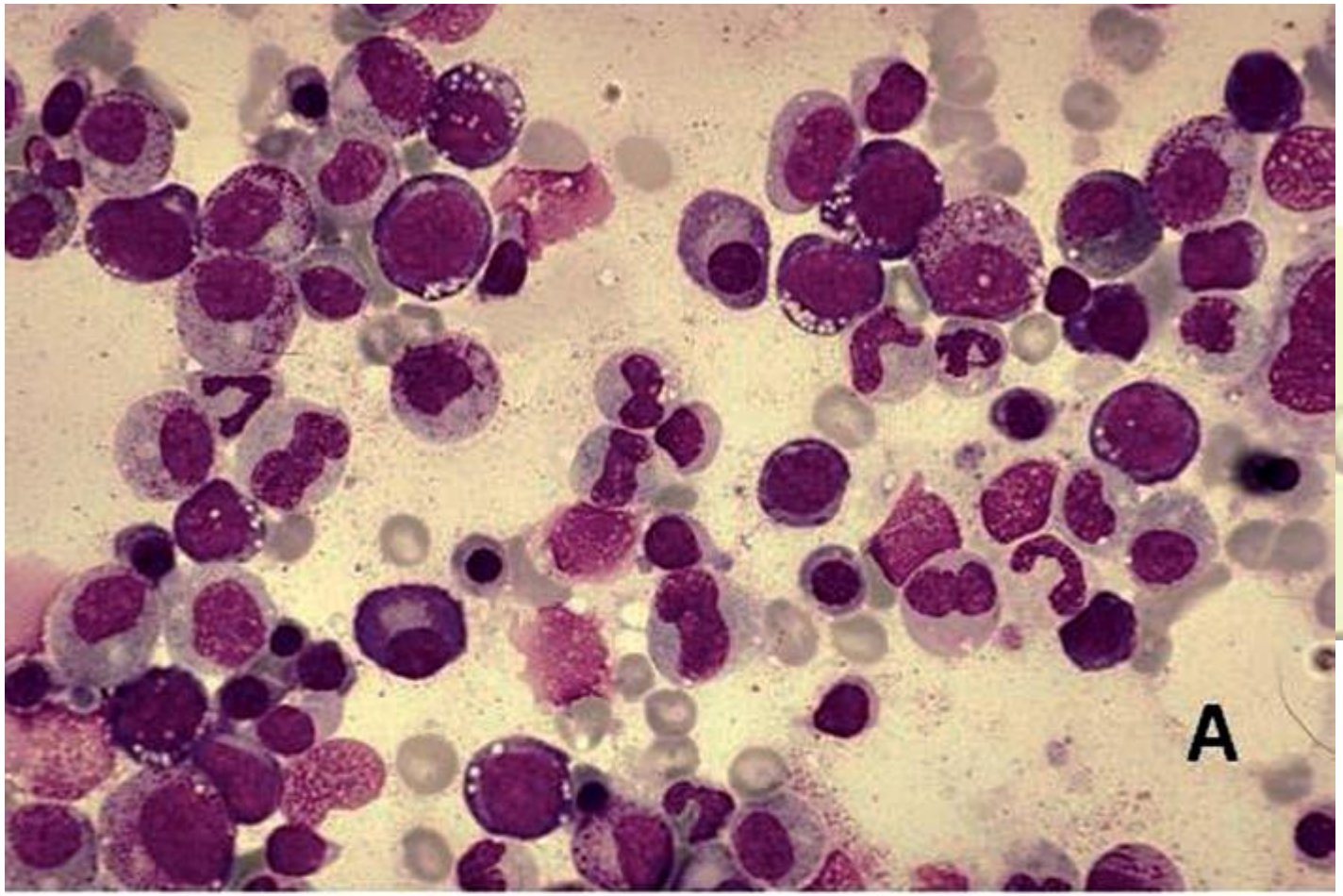


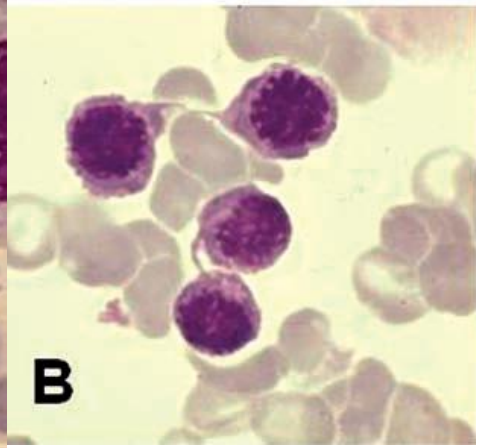






Displasia eritroide

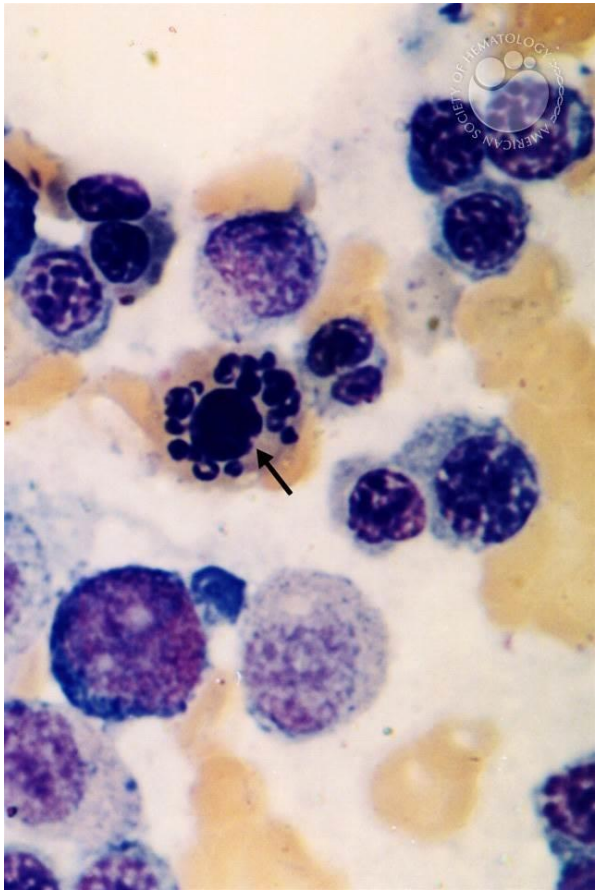


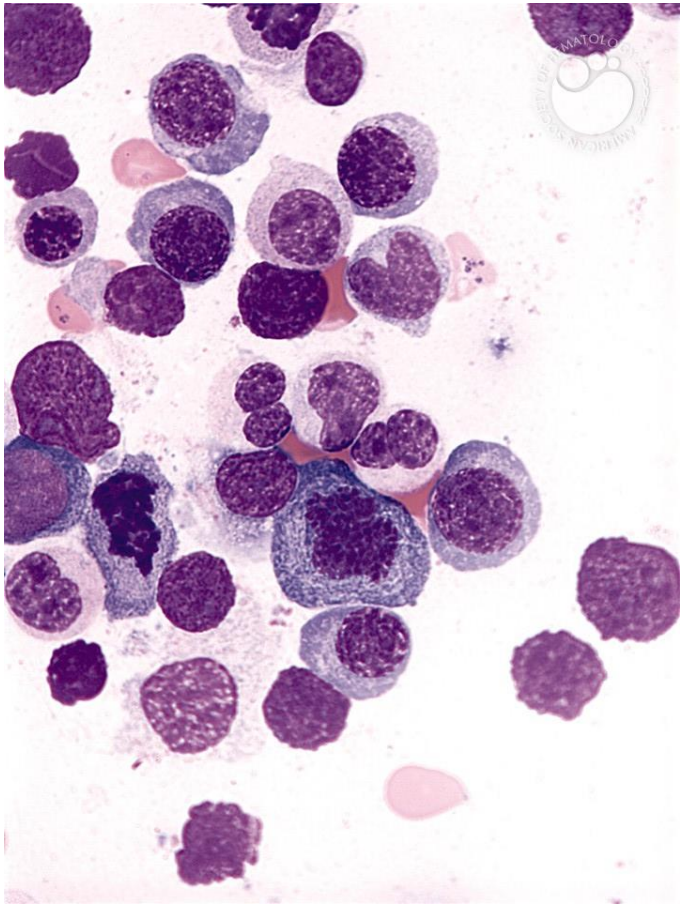


Rigolin et al seminari di Ematologia Oncologica 2009

Displasia eritroide

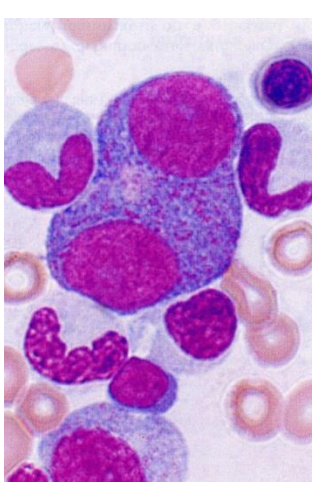
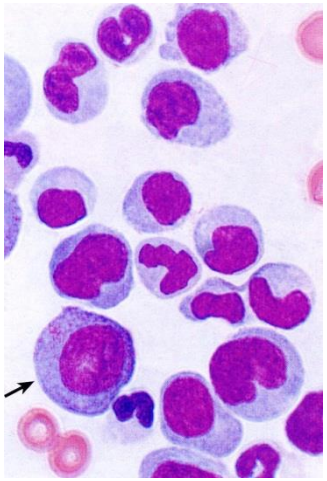
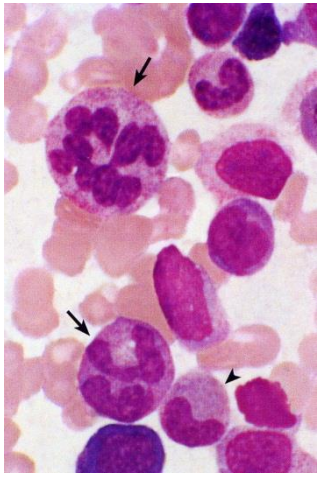
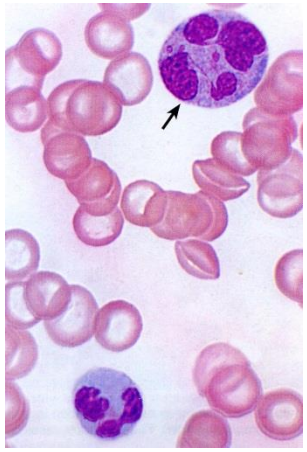
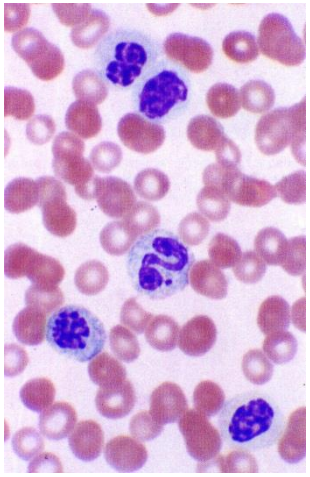
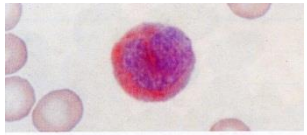
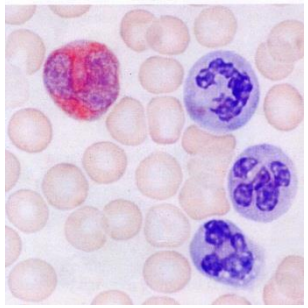
Erythroid karyorrhexis in myelodysplasia



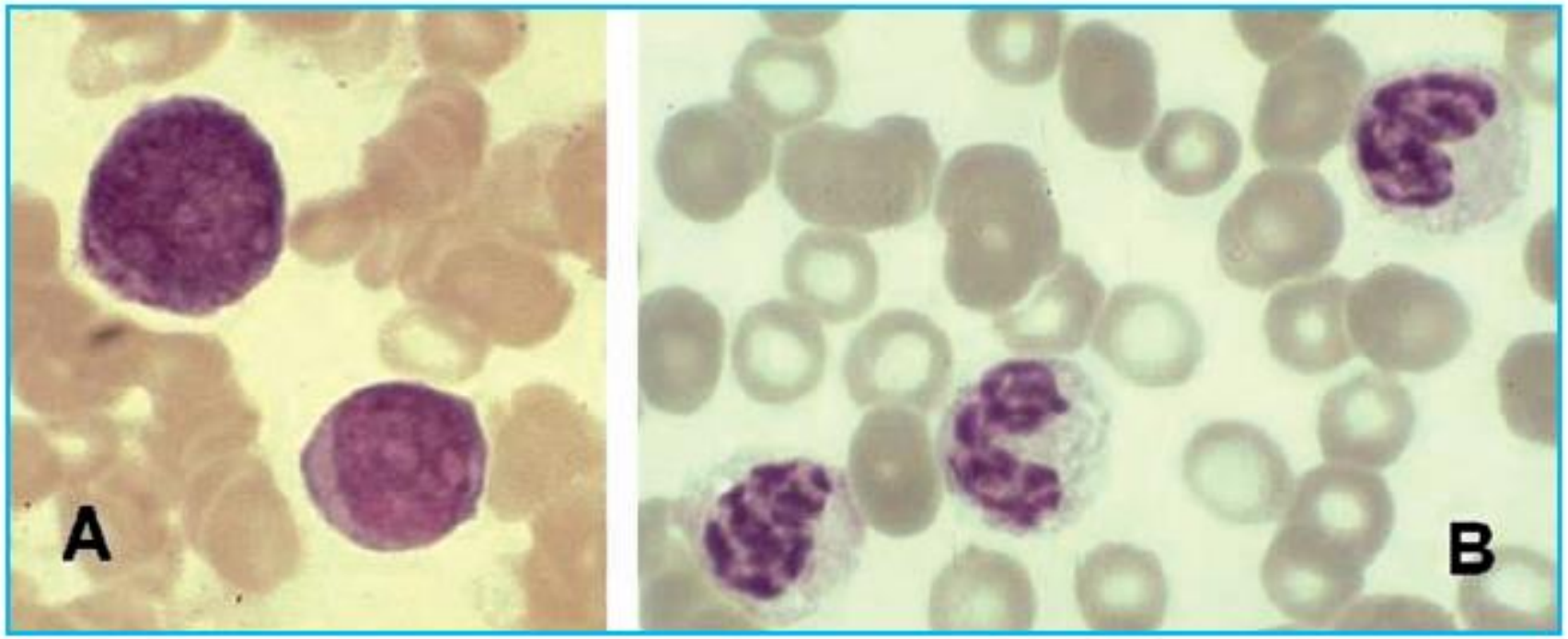


ASH image bank

disgranulopoiesi

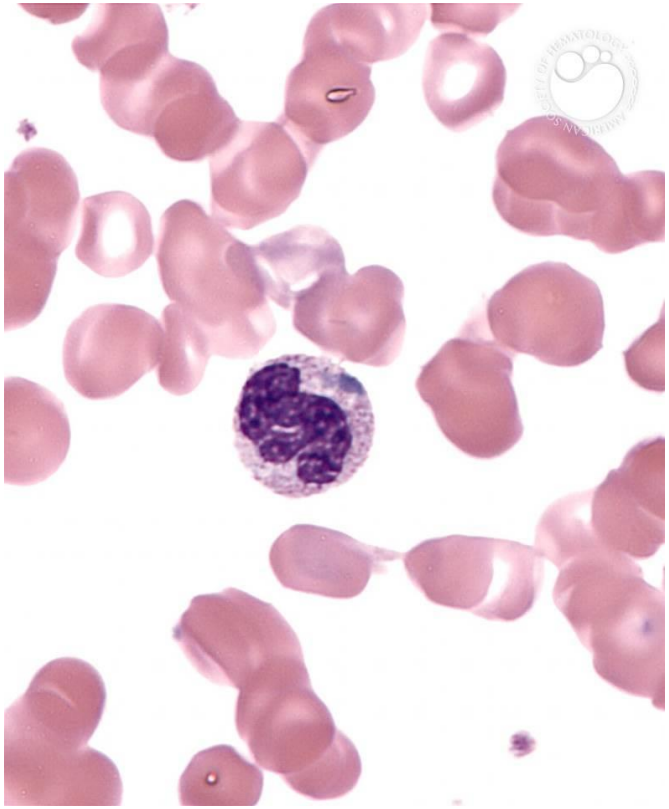








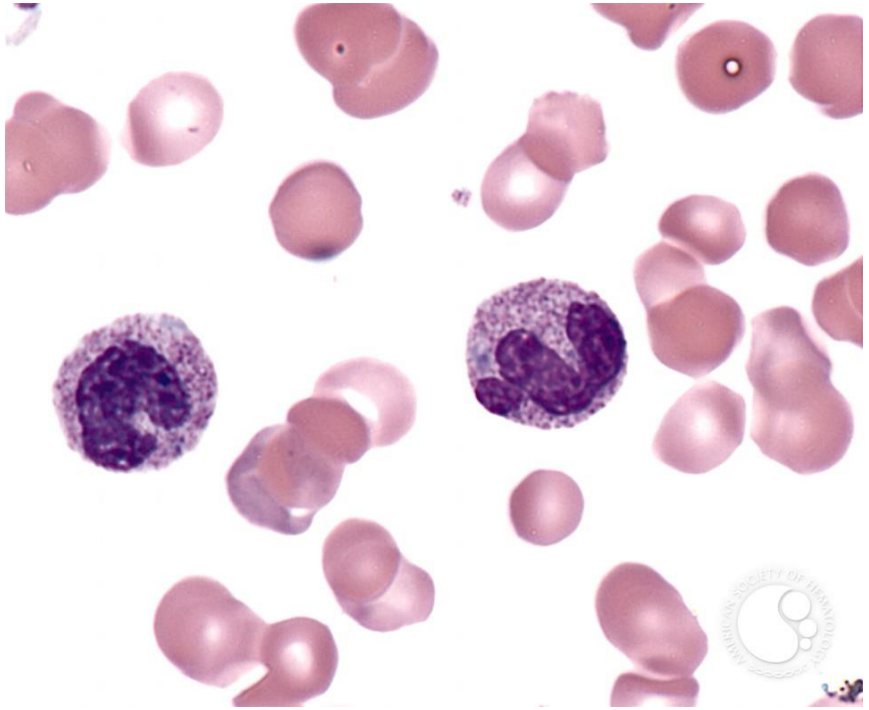
Blasti e pseudo Pelger



Rigolin et al seminari di Ematologia Oncologica 2009

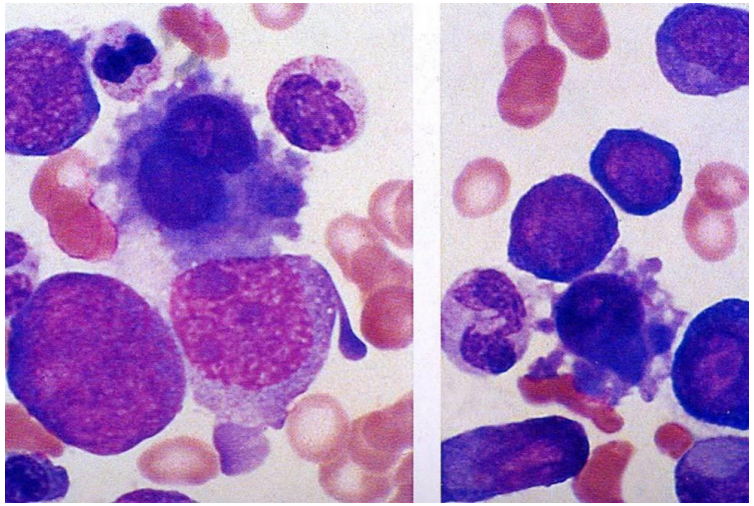
Corpi di Dohle

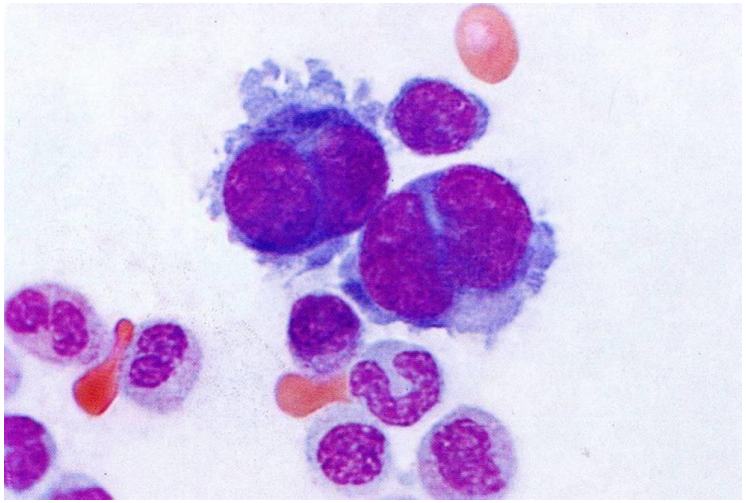


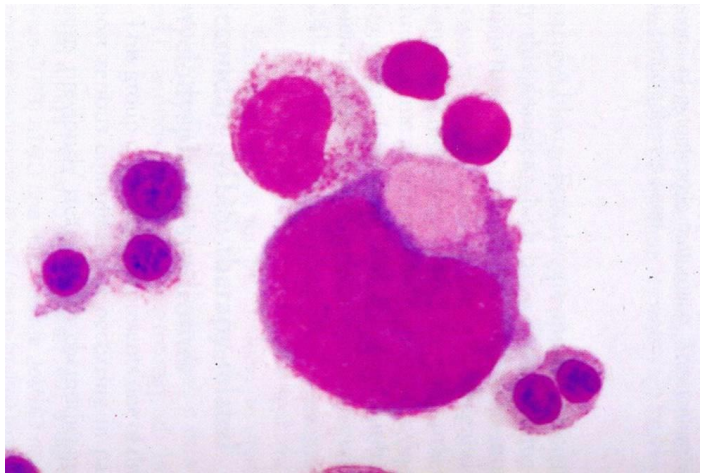


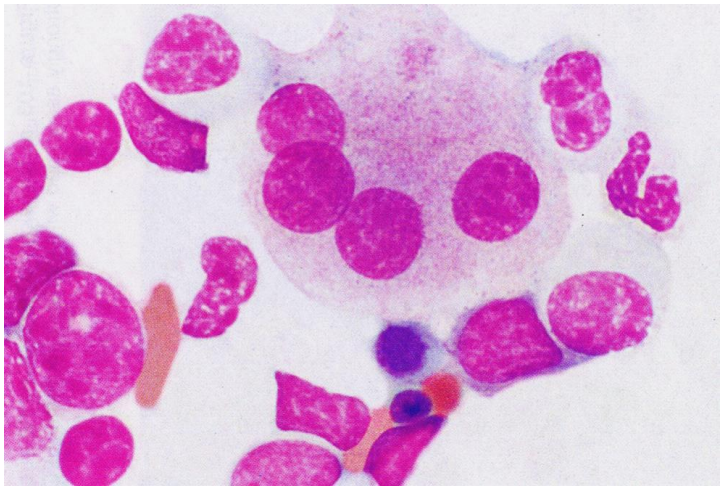
ASH image bank

Displasia megacariocitaria

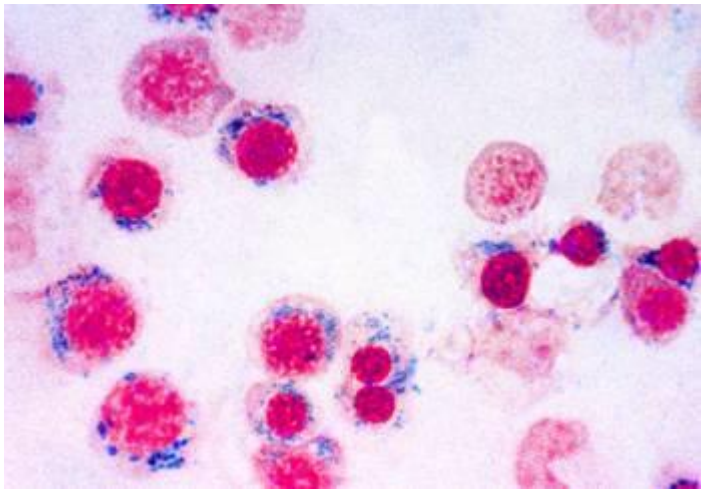








Sideroblasti



Il Working Group ha definito 3 tipi di sideroblasti:

- **Tipo 1: meno di 5 granuli di ferro nel citoplasma;**
- **Tipo 2: 5 o più granuli di ferro, ma non in una distribuzione perinucleare;**
- **Tipo 3 o sideroblasti ad anello: 5 o più granuli in posizione perinucleare, che circondano il nucleo o interessano almeno un terzo della circonferenza nucleare.**

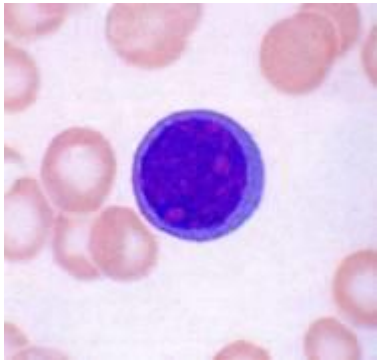
Nel conteggio dei sideroblasti ad anello, occorre valutare almeno 100 precursori eritroidi nei vari stadi maturativi.

La percentuale di sideroblasti ad anello ai fini della classificazione rimane il 15% come per la classificazione FAB e WHO.

Haematologica 2008; 93:1712-1717.

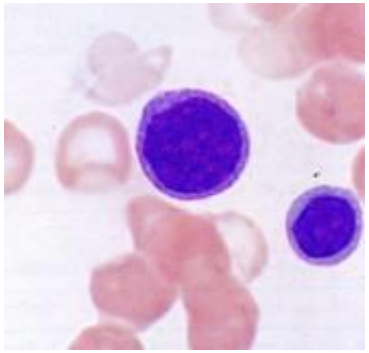
blasti e promielociti nelle MDS

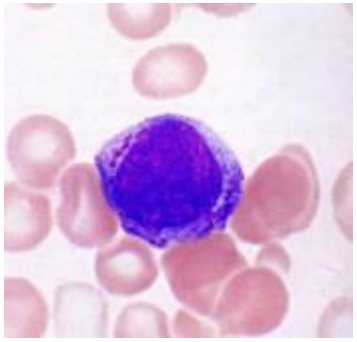
Aspetti cellulari	Blasto non granulato	Blasto granulato	Promielocito normale	Promielocito displastico
Nucleo	Centrale di forma variabile	Centrale di forma variabile	Ovale, rotondo, indentato Centrale od eccentrico	Ovale, rotondo, indentato in posizione eccentrica
Cromatina	fine	fine	Fine od intermedia	Fine o grossolana
Nucleolo	1-2	1.2	Ben riconoscibile	Ben visibile
Zona Golgi	Non evidente	Non evidente	Ben visibile	Presente ma poco sviluppata
Granuli	Non visibili	Presenti (talora corpi di Auer)	Azzurrofili uniformemente dispersi	irregolare presenza e distribuzione
Citoplasmaa	basofilo	basofilo	basofilo	Basofilia ridotta ed irregolare

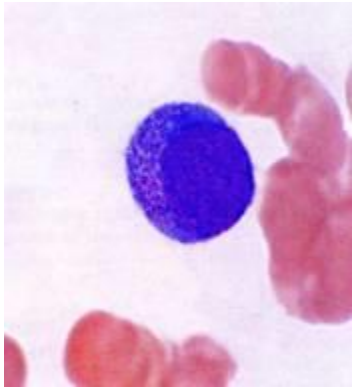


Blasto non granulato

Blasti granulati







promielocito

Haematologica 2008; 93:1712-1717.

Criteri diagnostici minimi nelle MDS

A. **Prerequisiti**
   1. **Citopenia costante in una o più delle seguenti filiere: Hb <11 g/dL, ANC < 1500 uL o piastrine <100,000 uL**
   2. **Esclusione di tutti gli altri disordini come causa della citopenia/displasia**

B. **Criteri decisivi correlati alla MDS**
   1. **Displasia in almeno il 10% di tutte le cellule o >15% di sideroblasti ad anello**
   2. **5–19% di cellule blastiche nello striscio midollare**
   3. **Anomalie cromosomiche tipiche (citogenetica o FISH)**

C. **Co-criteri (per i pazienti che soddisfano i criteri A ma non quelli B)**
   1. **Anomalo fenotipo mediante citometria a flusso**
   2. **Anomalie molecolari (gene chip profiling, o mutazioni puntiformi (RAS, etc)**
   3. **Anomalie colturali dei progenitori midollari e/o circolanti (CFU-assay)**

- **La diagnosi di MDS può essere formulata quando entrambi i prerequisiti ed almeno un criterio decisivo sono soddisfatti.**

- **Se nessun criterio decisivo è soddisfatto, ma è molto probabile che il paziente sia affetto da una neopasia mieloide clonale, i co-criteri devono essere applicati e possono aiutare nel raggiungimento della diagnosi di MDS o di una condizione definita 'fortemente sospetta di MDS'.**

Valent P Leuk Res 2007; 31: 727

Diagnosis of MDS requires:

(A) Persistent blood cytopenia(s) as defined by local laboratory ranges (with consideration of patient factors, such as ethnic background, altitude of residence, etc), without another reversible cause, such as nutritional deficiency or the effect of a drug, and

(B1) Increased myeloblasts (5%-19%), or

(B2) Extensive dysplasia (>10% of marrow cells in at least 1 lineage: erythroid, granulocytic, or megakaryocytic), or

(B3) Karyotypic evidence of clonality with a typical MDS-associated alteration, such as del(5q) or monosomy 7 (excluding nonspecific alterations, such as trisomy 8, loss of the Y chromosome, isolated del(20q), or trisomy 15[53])

Supplemental "co-criteria" include

(C1) Abnormal findings on histologic or immunochemical studies of marrow biopsy that could be consistent with MDS, such as abnormally localized immature precursors, clusters of CD34-positive blast cells, or >10% dysplastic micromegakaryocytes detected by immunohistochemistry

(C2) Abnormal immunophenotype of marrow cells by flow cytometry with multiple MDS-associated phenotypic aberrancies

(C3) Evidence of a clonal population of myeloid cells by molecular genetic testing, which is the subject of this article

If (A) is present, but not (B1-B3), then the case might be termed "idiopathic cytopenias of undetermined significance" (ICUS): a term that is agnostic about clonality

C1-C3 alone are generally not yet considered specific enough by themselves to be confident about the diagnosis of MDS, but can help confirm the diagnosis if other criteria are present

Steensma DP, Blood. 2018;132:1657-63

Citopenia idiopatica di incerto (indeterminato) significato (ICUS)

Definizione

Citopenia in una o più delle seguenti filiere (per più di 6 mesi):

Hb < 11 g/dL; neutrofili <1500 uL; piastrine <100,000 uL

Esclusa una MDS

Escluse tutte le altre possibili cause di citopenia

Indagini iniziali richieste per la diagnosi di ICUS

Anamnesi dettagliata (farmaci, tossici, mutageni, etc.)

Attento esame clinico comprendente indagini radiologiche ed ecografia splenica

Emocromo con conteggio differenziale al microscopio e completa valutazione biochimica clinica

Biopsia osteomidollare ed immunistochimica

Aspirato midollare e colorazione per il ferro.

Citometria a flusso midollare e sangue periferico

Analisi cromosomica con FISH (pannello standard minimo: 5q31, CEP7, 7q31, CEP8, 20q,CEPY, p53)

Analisi molecolare se appropriato

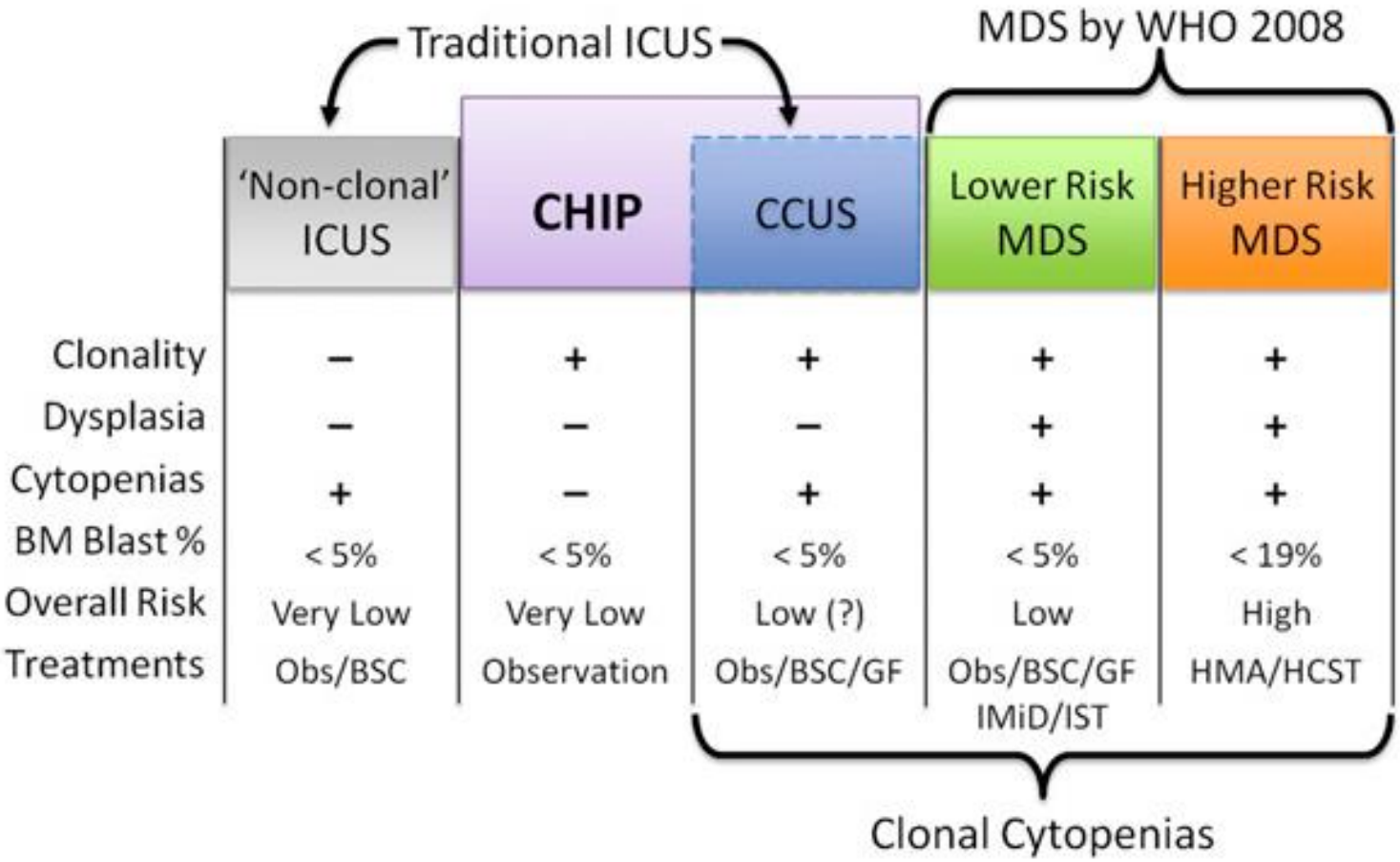
Esclusione di infezioni virali (HCV, HIV, CMV, EBV, altre)

Indagini raccomandate nel follow-up

Emocromo con formula e biochimica clinica ad intervalli di 1–6 mesi

In caso di evidente sospetto di MDS: esame midollare

Clonal hematopoiesis of undetermined potetial (CHIP)

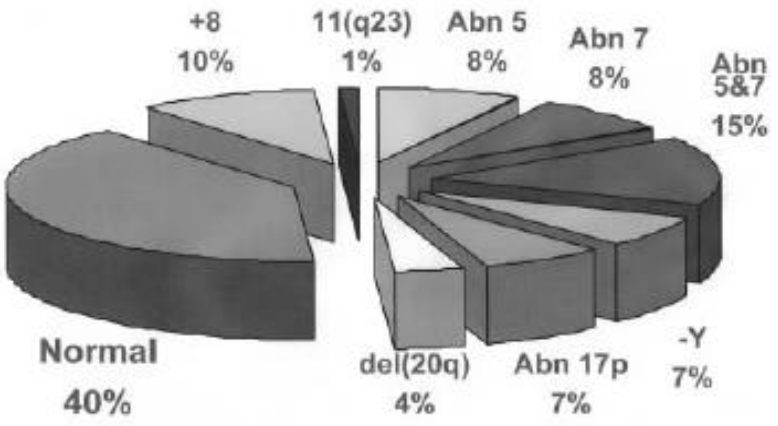


ICUS: idiopatic cytopenia of undetermined significance
CCUS: clonal cytopenia of undetermined signficance

Steensma et al, Blood 2015;126:9

Citogenetica

- La citogenetica ha un ruolo decisivo nella diagnosi e nella definizione della prognosi
- Anomalie citogenetiche sono riscontrabili del 40-70% delle MDS de novo e nel 95% delle forme secondarie a chemioterapia (therapy-related)

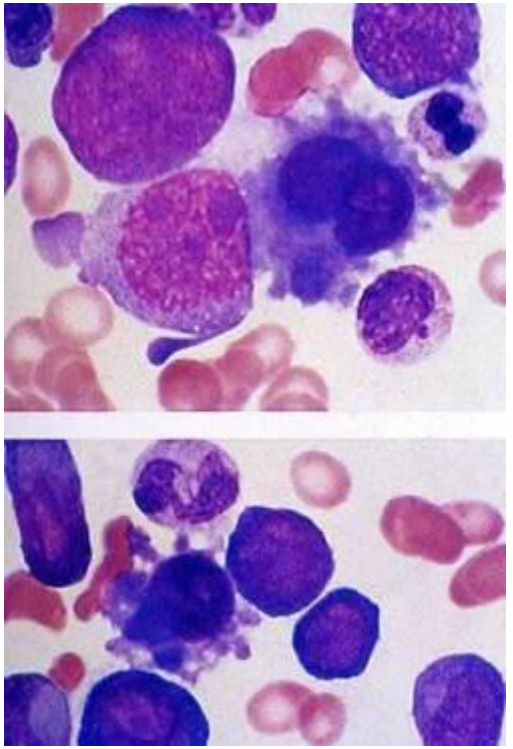


Anomalie cromosomiche e MDS

Table 6. Recurring chromosomal abnormalities considered as presumptive evidence of MDS in the setting of persistent cytopenia of undetermined origin, but in the absence of definitive morphologic features of MDS

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

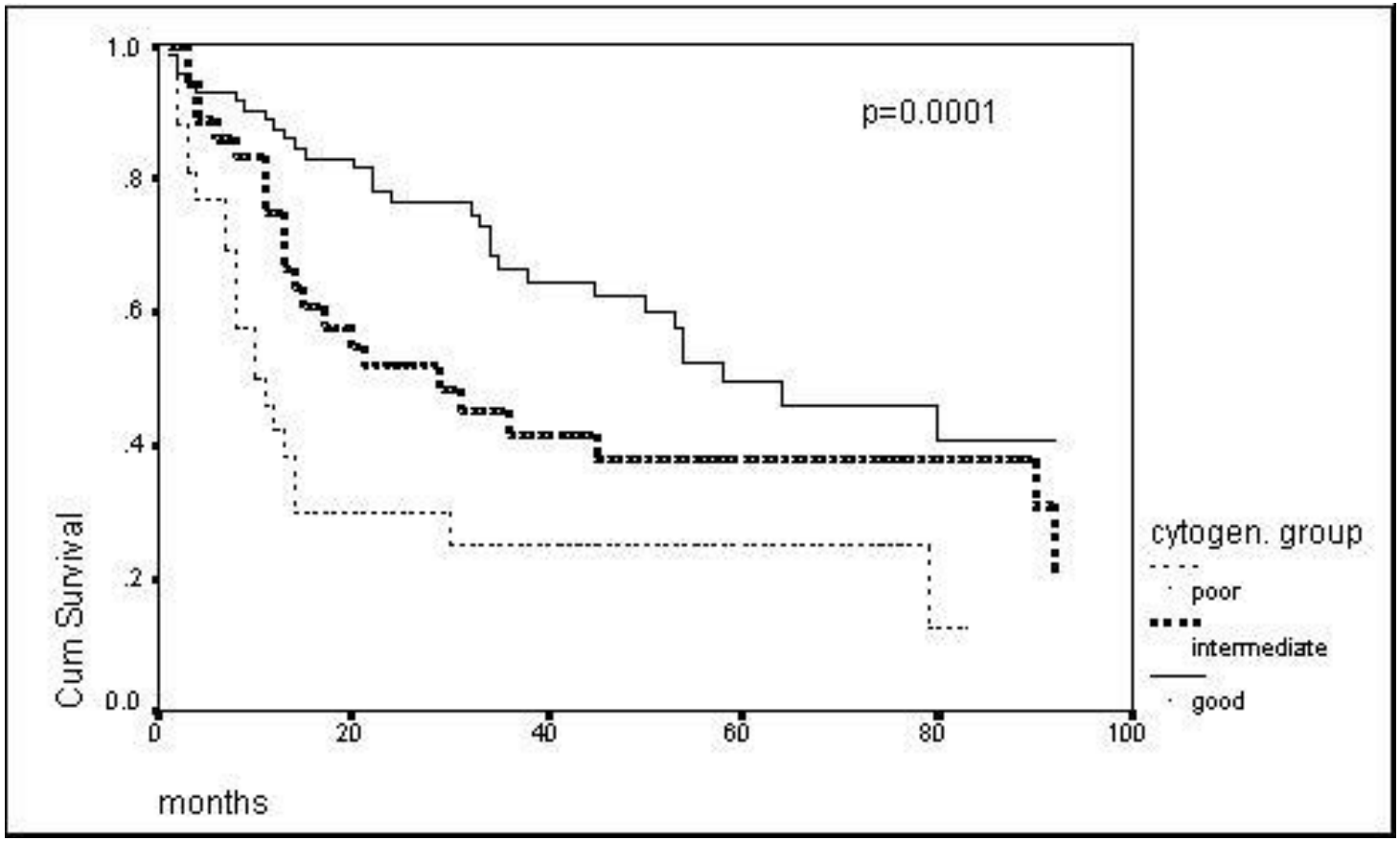
Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.



Vardiman JW et al Blood 2009;114:937

Castoldi G. Atlas of blood cells. 2003; p 285-98.

Citogenetica e sopravvivenza



Karyotype

- **Good:** normal, -Y, del(5q), del(20q)
- **Intermediate:** other abnormalities
- **Poor:** complex (>= 3 abnorm) or chrom 7 abnorm

Recurrent cytogenetic abnormalities in MDS

Chromosomal abnormality	Key genes deleted*	IPSS-R risk category[6]	Clinical features
Normal	NA	Good	NA
del(5q)	*CSNK1A1*, *RPS14*, *EGR1*, *APC*, *DDX41*, *HSPA9*, *NPM1*, *TIFAB*, *DIAPH1*, *miR-145* and *miR-146a*[130–140]	Good	Sensitive to lenalidomide[196]
Monosomy 7 or del(7q)	*EZH2*, *MLL3* and *CUX1* (REFS 148–150)	Poor	Monosomy 7 may have a worse prognosis than del(7q)[197]
Trisomy 8	Unknown	Intermediate	High response rate to immunosuppression[190]
Trisomy 19	Unknown	Intermediate	Unknown
del(20q)	*MYBL2*, *TP53RK* and *TP53TG5* (REF. 198)	Good	Often associated with mutations in splicing factors[198]
del(17p)	*TP53* (REF. 109)	N/A	Poor response to alloHSCT[35].
Complex‡ and monosomal§	*TP53* (REF. 109)	Poor to very poor	Associated with *TP53* mutation[35]
del(11q)	*MLL* and *ATM*[199]	Very good	Unknown
Y chromosome loss (–Y)	Unknown	Very good	May not be pathogenic, but instead may be lost during normal ageing[200]

alloHSCT, allogeneic haematopoietic stem cell transplantation; *APC*, adenomatous polyposis coli; *ATM*, ataxia telangiectasia mutated; del, deletion; *CSNK1A1*, casein kinase 1 α1; *CUX1*, cut like homeobox 1; *DDX41*, DEAD-box helicase 41; *DIAPH1*, Diaphanous-related formin 1; *EGR1*, early growth response 1; *EZH2*, enhancer of zeste 2; *HSPA9*, heat shock protein family A (HSP70) member 9; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; miR, microRNA; *MLL*, mixed lineage leukaemia; *MYBL2*, v-myb avian myeloblastosis viral oncogene homologue-like 2; NA, not applicable; N/A, not included in the IPSS-R; *RPS14*, ribosomal protein S14; *TP53RK*, TP53 regulating kinase; *TP53TG5*, TP53-target gene 5; *TIFAB*, TRAF-interacting protein with forkhead-associated domain B.*Other genes have been implicated in some studies; ‡complex: ≥3 abnormalities; §monosomal: >2 monosomies.

Sperling et al. Nature Reviews Cancer 2017

	Proportion of patients (%)	Karyotype	Median survival (years)	Time to 25% AML evolution (years)
Very good	4%	–Y, del(11q)	5·4	NR
Good	72%	Normal, del(5q), del(12p), del(20q), double including del(5q)	4·8	9·4
Intermediate	13%	del(7q), +8, +19, i(17q), any other single or double independent clones	2·7	2·5
Poor	4%	–7, inv(3)/t(3q)/del(3q), double including –7/del(7q); complex: 3 abnormalities	1·5	1·7
Very poor	7%	Complex >3 abnormalities	0·7	0·7

AML=acute myeloid leukaemia. NR=not reached.

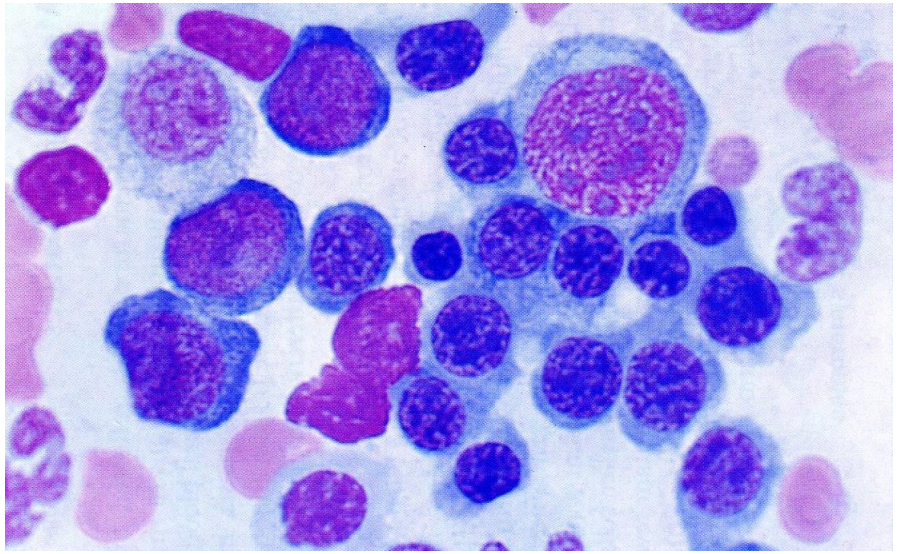
Table 2: **Cytogenetic findings in patients with myelodysplastic syndromes, by their prognostic value[8,68]**

Ades et al. Lancet 2014; 383: 2239–52

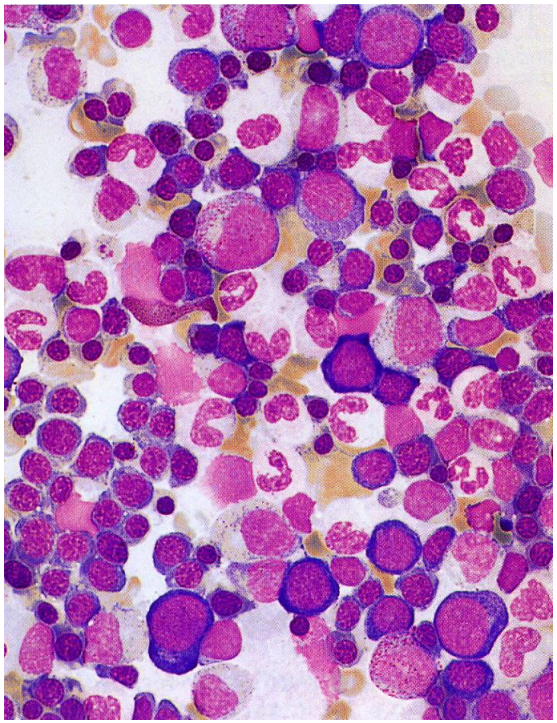
	Blood findings	Bone-marrow findings
Myelodysplastic syndrome		
Refractory cytopenia with unilineage dysplasia (refractory anaemia; refractory neutropenia; refractory thrombocytopenia)	One or two cytopenias; no or rare blasts (<1%)	One lineage dysplasia ≥10% of cells in one myeloid lineage; <5% blasts; <15% of erythroid precursors ring sideroblasts
Refractory anaemia with ring sideroblasts	Anaemia; no blasts	≥15% of erythroid precursors ring sideroblasts; erythroid dysplasia only; <5% blasts
Refractory cytopenia with multilineage dysplasia	Cytopenia(s); no or rare blasts (<1%); no auer rods; $<1\times10^9$ cells per L monocytes	Dysplasia in ≥10% of cells in at least two myeloid lineages (neutrophil, erythroid precursors, or megakaryocytes); <5% blasts in marrow; no auer rods; with or without 15% ring sideroblasts
Refractory anaemia with excess blasts 1	Cytopenia(s); <5% blasts; no auer rods; $<1\times10^9$/L monocytes	Dysplasia in one or several lineages; 5–9% blasts; no auer rods
Refractory anaemia with excess blasts 2	Cytopenia(s); 5–19% blasts; with or without auer rods; $<1\times10^9$/L monocytes	Dysplasia in one or several lineages ; 10–19% blasts; with or without auer rods
Myelodysplastic syndrome unclassified	Cytopenias; <1% blasts	Unequivocal dysplasia in <10% of cells in one or more myeloid lineages accompanied by a cytogenetic abnormality is presumptive evidence for diagnosis; <5% blasts
MDS associated with isolated del(5q)	Anaemia; normal or increased platelet count in most cases; no or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei; <5% blasts; isolated del(5q) cytogenetic abnormality; no auer rods
Myelodysplastic–myeloproliferative neoplasms		
Chronic myelomonocytic leukaemia 1	Persistent peripheral blood monocytosis ($>1\times10^9$/L); no Philadelphia chromosome or *BCR-ABL1* fusion gene; <5% blasts	Dysplasia in one or more cell lines; <10% blasts
Chronic myelomonocytic leukaemia 2	Persistent peripheral blood monocytosis ($>1\times10^9$/L); no Philadelphia chromosome or *BCR-ABL1* fusion gene; <19% blasts	Dysplasia in one or more cell lines; 10–19% blasts
Myelodysplastic or myeloproliferative disease, unclassifiable	Morphological features of myelodysplastic syndrome; prominent myeloproliferative features (platelets $>600\times10^9$ cells per L, leucocytes $>13\times10^9$/L, splenomegaly); no Philadelphia chromosome or *BCR-ABL1* fusion gene; no del(5q), t(3;3)(q21;q26), inv3(q21;q26); no underlying myeloproliferative disease	..
Provisional entity: refractory anaemia with ring sideroblasts and thrombocytosis	Similar to refractory anaemia with ring sideroblasts; platelet $>600\times10^9$ cells per L	Similar to refractory anaemia with ring sideroblasts; without del(5q)
Therapy-related neoplasm		
Acute myeloid leukaemia or myelodysplastic syndrome in individuals exposed to cytotoxic agents	..	..

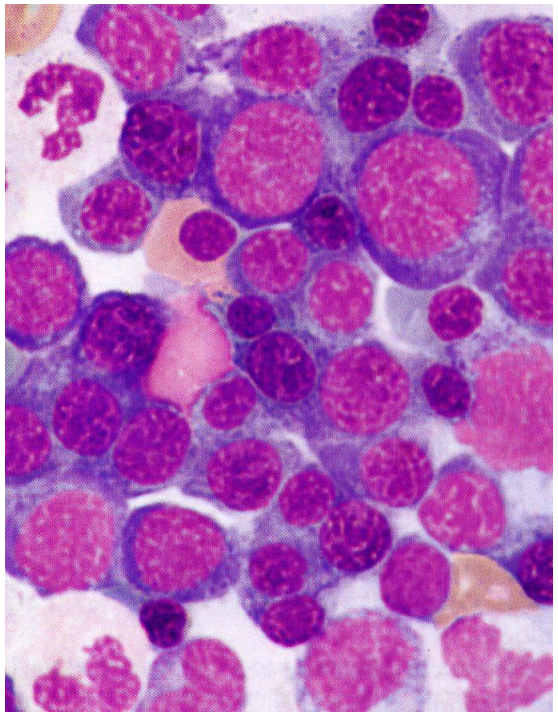
Table 3: **WHO 2008 classification**[6]

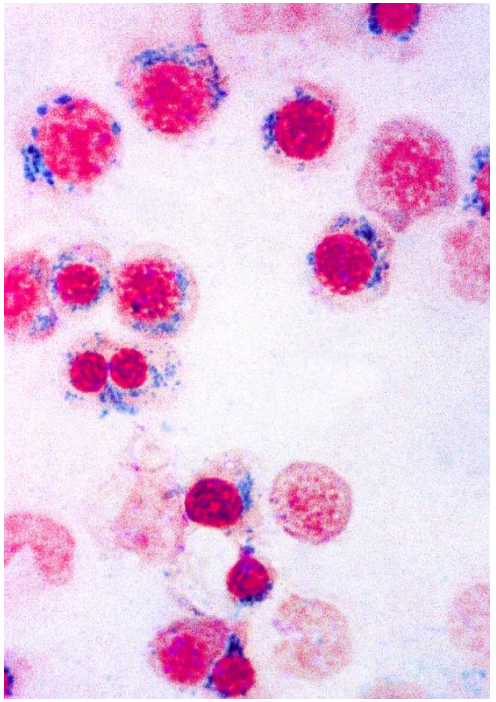
RA



RARS







Diagnostic criteria for MDS/MPN with ring sideroblasts and thrombocytosis

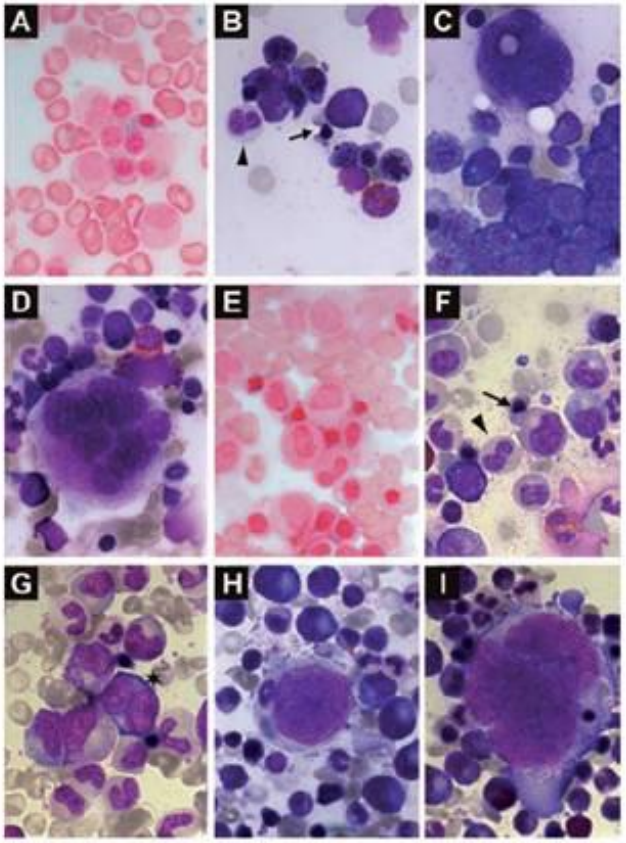


Figure 2. Bone marrow morphology demonstrating both dysplastic and proliferative features in a *JAK* V617F negative patient (n. 511; A-D) and a patient with the mutation (n. 510; E-I). Ringed sideroblastosis (A,E) associated with immaturity, megaloblastoid changes and abnormal nuclear budding (arrows) and binuclearity (asterix) of erythroblasts (B,C,F,G). Dysgranulopoiesis with numerous hypogranular (arrowheads) myeloid cells (B,F,G; Pappenheim's stain). Evidence of both small megakaryocytes with round nuclei and mature cytoplasm (C,H) and large multinucleated forms (D, I). A, E, Perls' stain; B-D, F-I, Pappenheim's stain; ×1000.

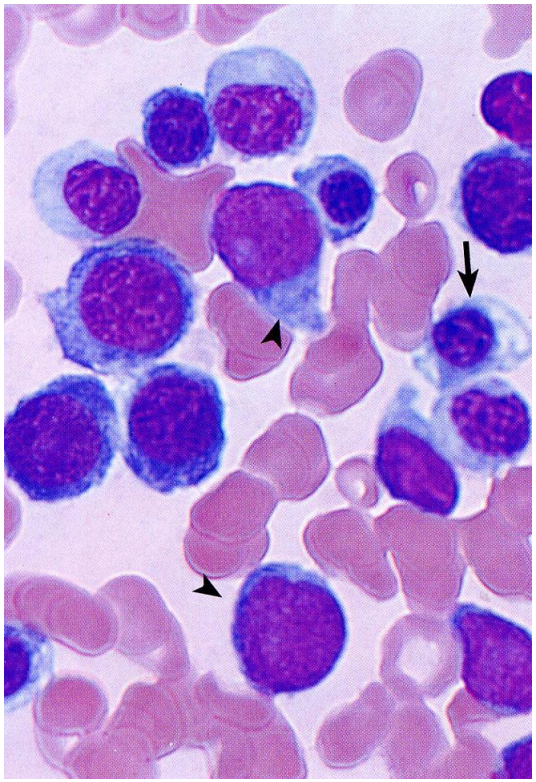
- **Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, >=15% ring sideroblasts*, <1% blasts in PB and <5% blasts in the BM**
- **Persistent thrombocytosis with platelet count >=450 x 10^9/L**
- **Presence of a SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†**
- **No BCR-ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB, or FGFR1; or PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡**
- **No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN**

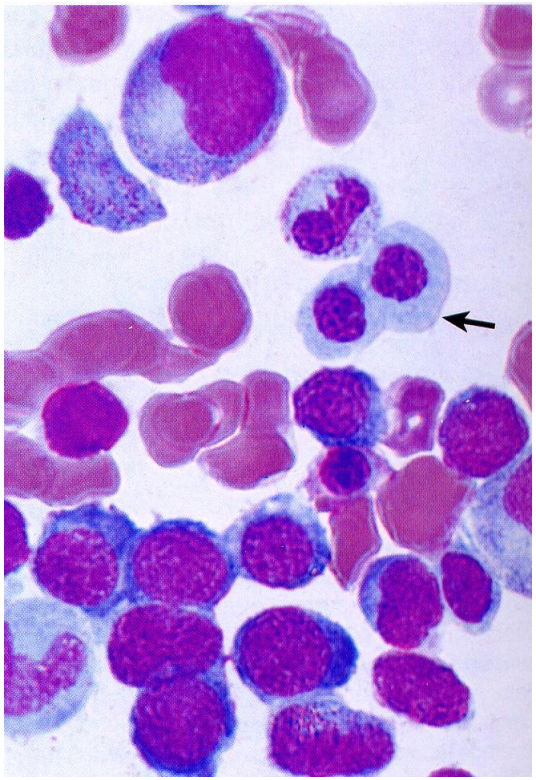
***At least 15% ring sideroblasts required even if SF3B1 mutation is detected.**
†A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of SF3B1 mutation together with a mutation in JAK2 V617F, CALR, or MPL genes.
‡In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del (5q)-no or minimal absolute basophilia; basophils usually ,2% of leukocytes.

Schmitt-Graeff AH, Haematologica. 2008; 93:34

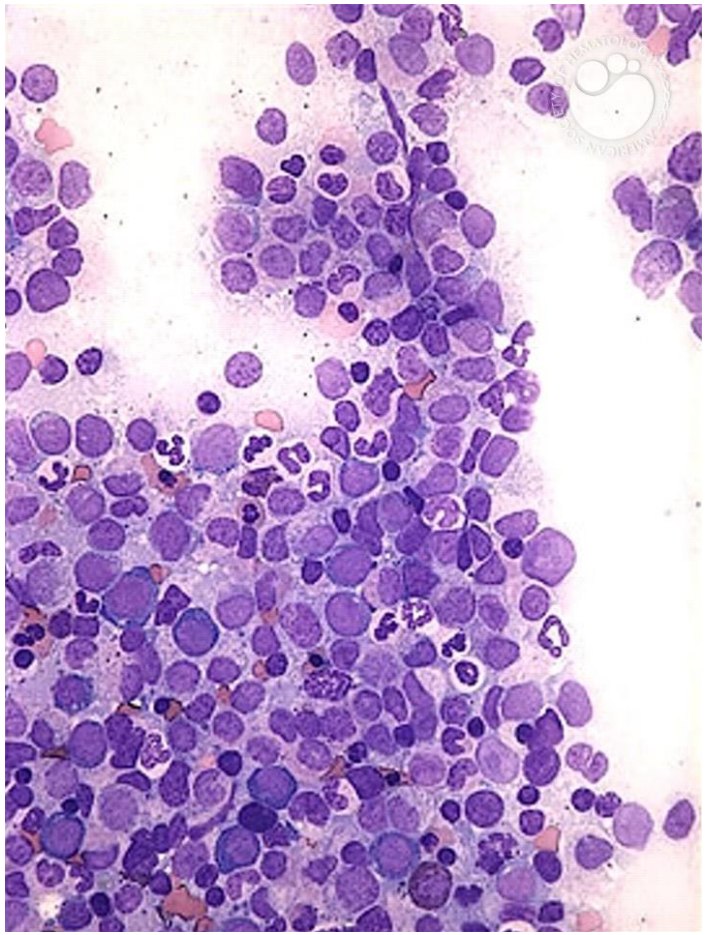
Blood. 2016;127(20):2391-2405

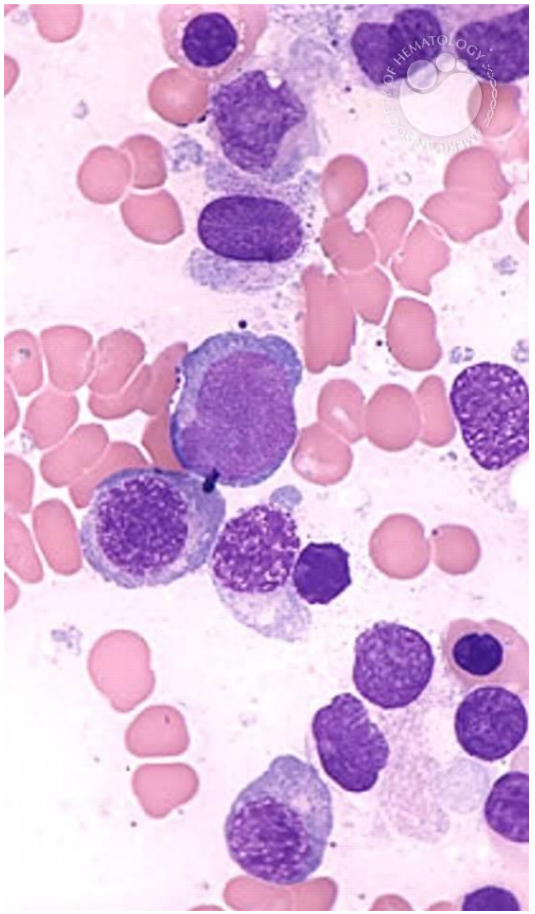
RAEB-1





RAEB 2

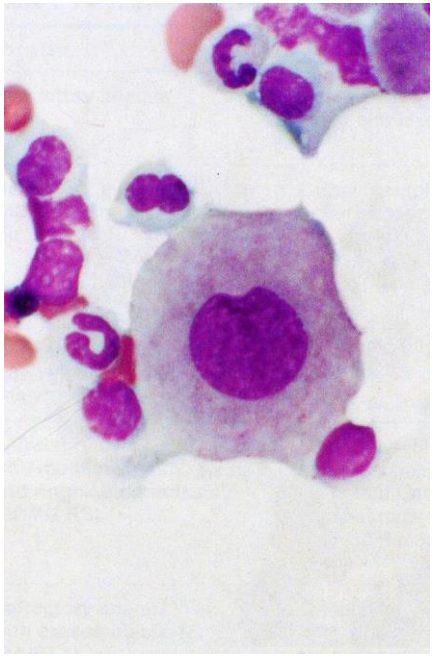


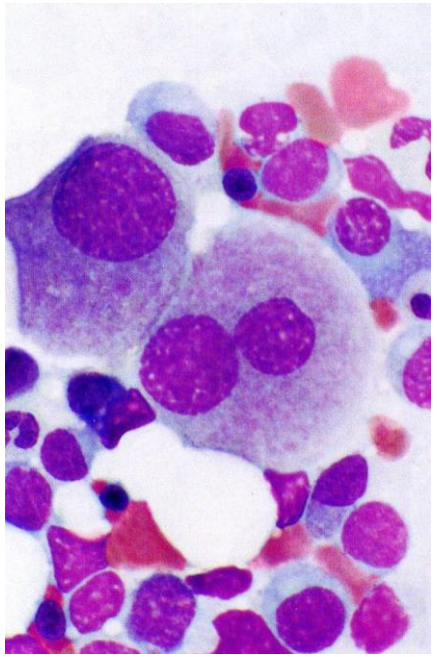


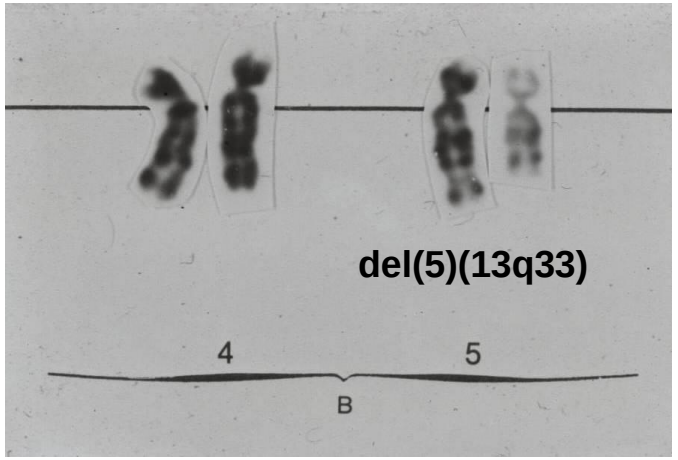
ASH image bank

Sindrome da 5q-

- Presentazione clinica
  - Età avanzata
  - Sesso femminile (F:M 7:3)
  - Basso rischio di progressione in LAM
  - Buona prognosi
- Quadro ematologico
  - Anemia macrocitica
  - Modesta leucopenia
  - Normale/elevato numero di piastrine
  - ipoplasia eritroide midollare
  - Megacariociti monolobati
  - Delezione intestiziale braccio lungo del cromosoma 5 come singola anomalia
  - Blasti < 5%







2016 WHO classification of myeloid neoplasms and acute leukemia

Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood

Blood. 2016;127(20):2391-2405

Table 15. PB and BM findings and cytogenetics of MDS

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

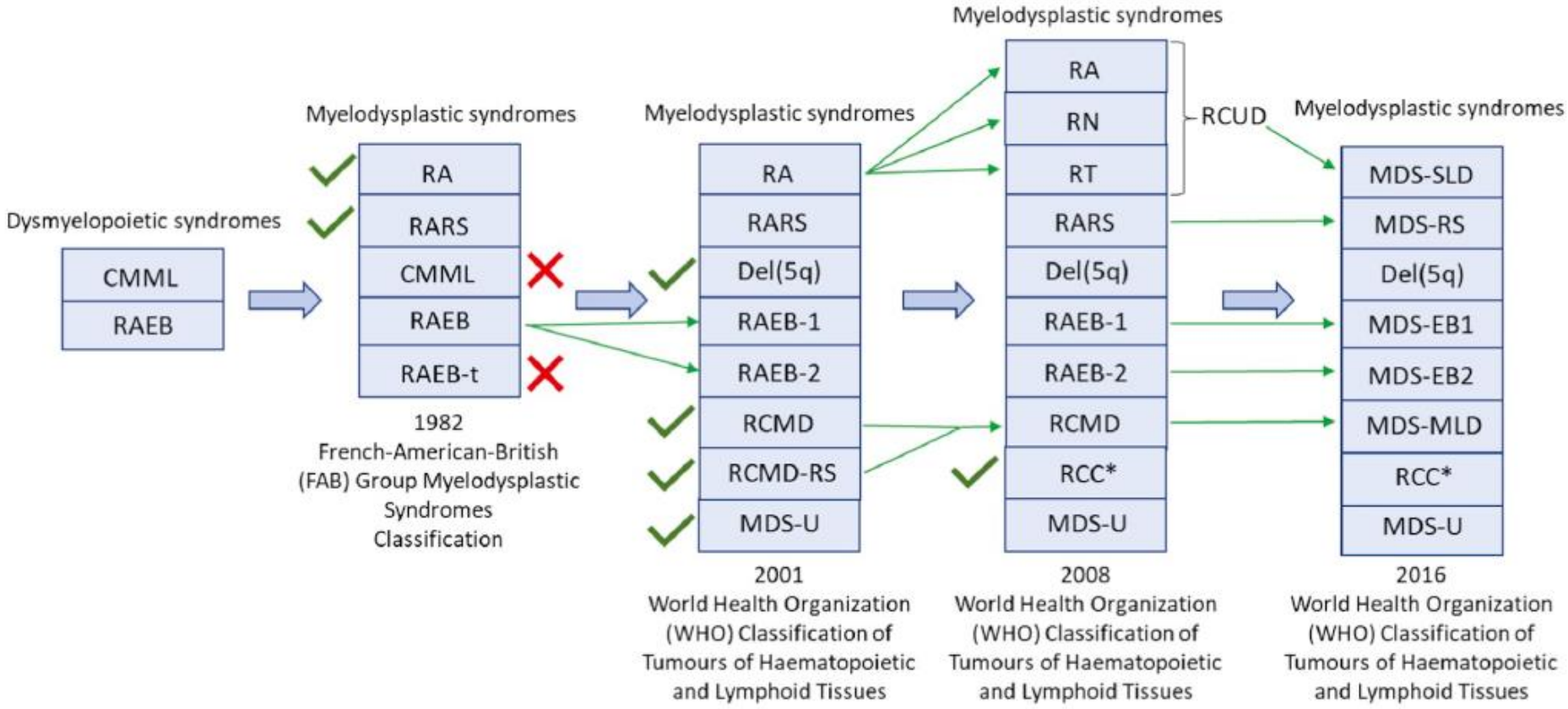
†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Blood. 2016;127(20):2391-2405

Evolution of MDS classification systems



Zeidan et al. Blood Reviews 2018

MDS: clinical findings

- Clinical features are non-specific and mainly result from cytopenias.
- **Anaemia**, is symptomatic in many pts, leading to fatigue, poor quality of life, and destabilisation of underlying cardiovascular disease.

- **Thrombocytopenia** is commonly associated with platelet dysfunction, potentially leading to bleeding symptoms even in moderate thrombocytopenia.

- **Infections** (especially with gram-neg bacilli, gram-pos cocci, and fungi) can occur with only moderate neutropenia due to neutrophil function defects.

- Many patients have **immune disorders**, including relapsing polychondritis, vasculitis, and seronegative polyarthritis.
  - The two disorders tend to be diagnosed almost simultaneously, which suggests a pathophysiological relation.

Ades et al. Lancet 2014; 383: 2239–52

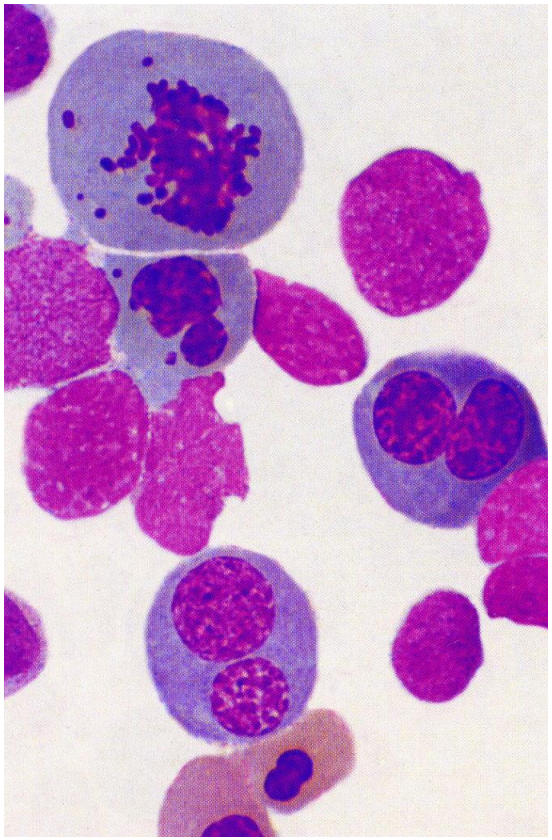
MDS: Differential diagnosis

- All other causes of cytopenias must be carefully excluded;
  - vitamin defi ciencies
  - autoimmune disease,
  - Liver disease,
  - hypersplenism,
  - viral infections,
  - drug intake,
  - exposure to environmental toxins,
  - aplastic anaemia,
  - Acute leukemias
  - Large granular lymphocytic leukemia
  - Hairy cell leukemia
  - Myelofibrosis
  - Paroxysmal nocturnal haemoglobinuria,
  - bone-marrow infiltration by malignancy,
  - rare forms of hereditary anaemias (such as congenital dyserythropoetic anaemias).

therapy related MDS

- **Rischio attuariale 0.25-1% per anno da 2 a 5-7 anni dalla fine della chemioterapia**

- **Rischio dose dipendente e aumenta esponenzialmente dopo i 40 anni**

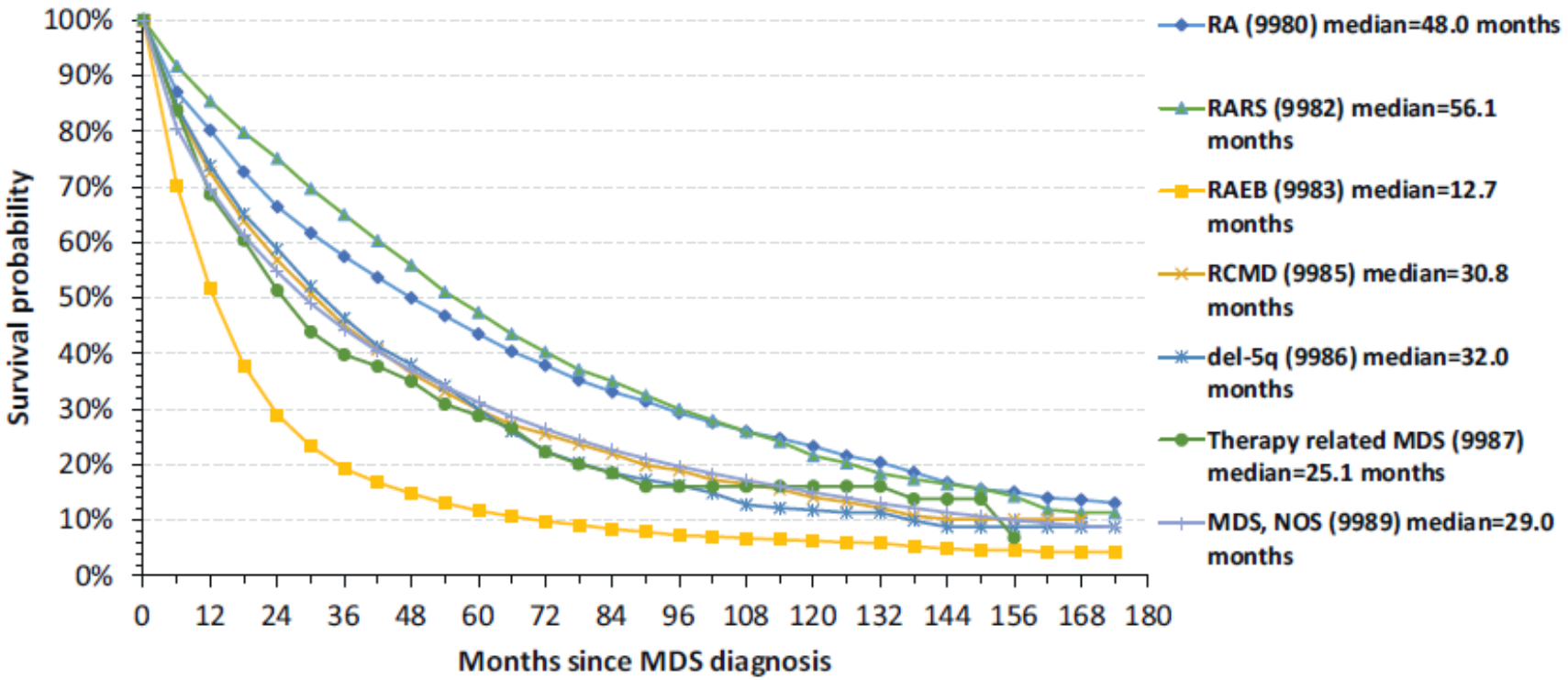


Genomic differences between t-MDS/AML and de novo (d)-MDS/AML.

Mutation [70]	t-MN (%)	d-MN (%)
tP53	39 in t-MDS 35.7 in t-AML	17 in d-MDS, p0.04 12.8 in d-AML, p0.002
PTPN11	11.9 in t-AML	2.1 in d-AML, p0.0075
FLT3	7.1 in t-AML	21.7 in d-AML, p0.03
NPM1	2.5 in t-AML	16.4 in d-AML, p0.01
Cytogenetic differences		
-5/del5q [68]	40 in t-MDS/AML	10-20 in d-MDS/AML
−7/del(7q) [69]	55 in t-MDS	5 in d MDS (as sole abnormality)
Translocations of 11q23 [122]	25 in t-MDS	5.1 in d-MDS
T (11,16) [123]	2 in t-MDS	0
Complex karyotype [68,69,123]	39-90 in t-MDS	20 in d-MDS

A. Abou Zahr et al. / Blood Reviews 31 (2017) 119–128

Survival MDS by subtype in the USA



(Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).

Zeidan et al Blood Reviews 2018

International prognostic Scoring System

	0 points	0·5 points	1·0 point	1·5 points	2·0 points
Bone-marrow blasts (%)	<5%	5–10%	..	11–20%	21–30%
Number of cytopenias*	0–1	2–3	..	..	..
Cytogenetics	Good: normal, Y, del(5q), del(20q)	Intermediate: other abnormalities	Poor: complex ≥3 abnormalities, chromosome 7 abnormalities	..	..

*Platelet count <100 × 10^9/L; haemoglobin <100 g/L; absolute neutrophil count <1·8 × 10^9/L.

Table 4: The international pronostic scoring sytem (IPSS)[7] score values

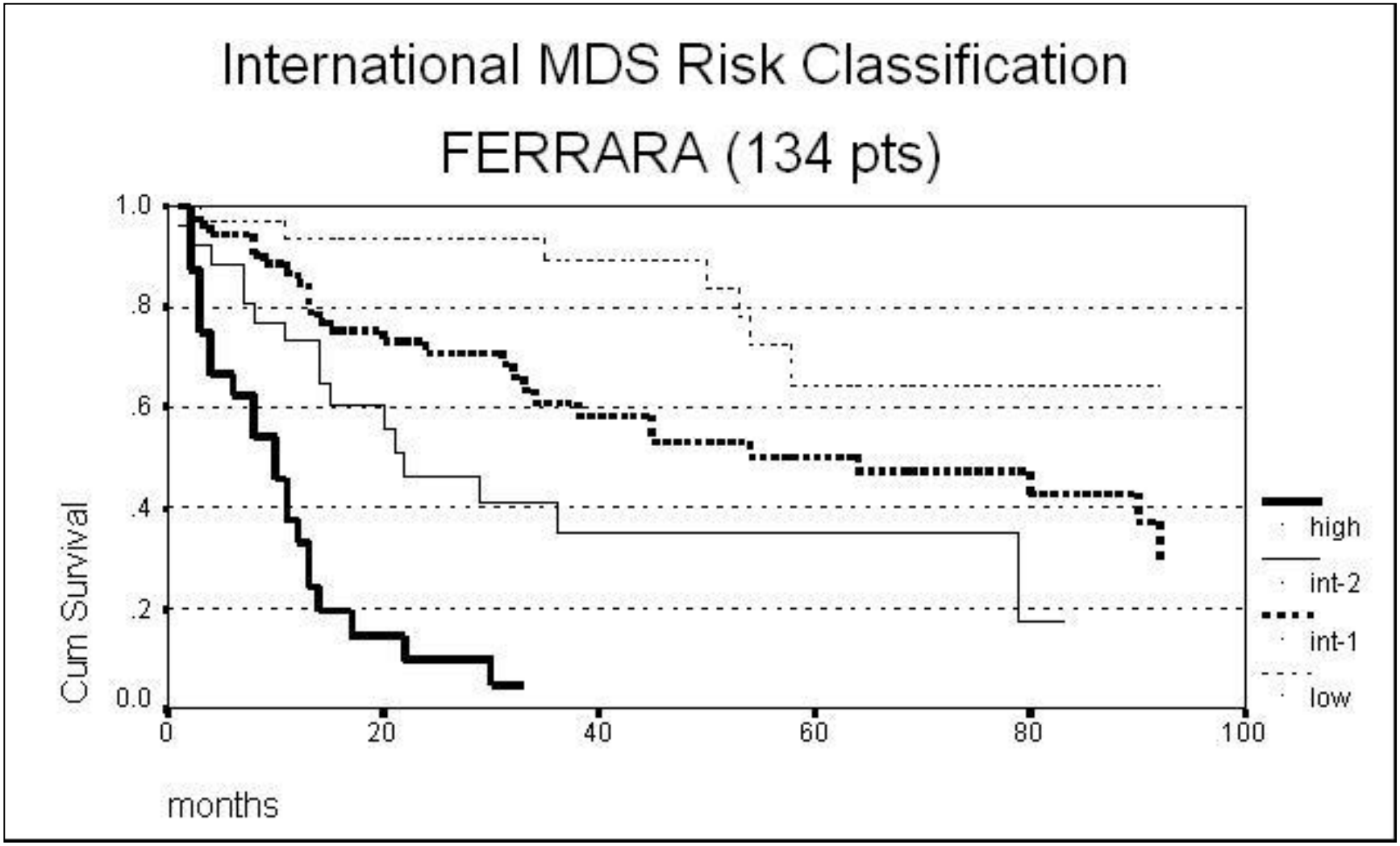
	Low	Intermediate 1	Intermediate 2	High
Risk score	0	0·5–1·0	1·5–2·0	≥2·5
Proportion of patients (%)	33%	38%	22%	7%
Median survival (years)	5·7	3·5	1·2	0·4
Time to 25% AML evolution (years)	9·4	3·3	1·1	0·2

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia.

Table 5: IPSS prognostic risk category clinical outcomes

Greenberg et al, Blood, 1997;89:2079

IPSS e sopravvivenza



Revised International Prognostic Scoring System for Myelodysplastic Syndromes

	0 points	0·5 points	1·0 point	1·5 points	2·0 points	3·0 points	4·0 points
Cytogenetics*	Very good	--	Good	--	Intermediate	Poor	Very poor
Bone-marrow blasts (%)	≤2%	--	>2 to <5%	--	5–10%	>10%	--
Haemoglobin (g/L)	≥100	--	80 to <100	<80	--	--	--
Platelet count (x10⁹/L)	≥100	50 to <100	<50	--	--	--	--
Absolute neutrophil count (x10⁹/L)	≥0·8	<0·8	--	--	--	--	--

*As in table 2.

Table 6: Revised international prognostic scoring system prognostic score values

	Very low	Low	Intermediate	High	Very high
Risk score	≤1·5	>1·5–3·0	>3·0–4·5	>4·5–6·0	>6·0
Proportion of patients (%)	19%	38%	20%	13%	10%
Median survival (years)	8·8	5·3	3·0	1·6	0·8
Time to 25% evolution to AML (years)	NR	10·8	3·2	1·4	0·73

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia. NR=not reached.

Table 7: Revised IPSS prognostic risk category clinical outcomes

Greenberg PL et al. Blood. 2012;120(12): 454-2465

Comparison between MDS risk assessment tools

IPSS

Metric		Score
Blasts		
	<5%	0
	5-10%	0.5
	11-20%	1.5
	21-30%	2
Cytogenetics[b]		
	Good	0
	Intermediate	0.5
	Poor	2
Cytopenias	Hgb <10 g/dL, PLT <100/µL, ANC <1.5/µL	
	0-1	0
	2-3	0.5
Risk Group		
	Low	0
	INT-1	0.5-1
	INT-2	1.5-2
	High	≥2.5

IPSS-R

Metric		Score
Blasts		
	≤2%	0
	>2-<5%	0.5
	5-10%	1.5
	>10%	2
Cytogenetics[c]		
	Very good	0
	Good	0.5
	Intermediate	2
	Poor	3
	Very poor	4
Cytopenias		
	Hgb 8-<10 g/dL	1
	Hgb <8 g/dL	1.5
	ANC <0.8/µL	0.5
	PLT 50-100/µL	0.5
	PLT <50/µL	1
Risk Group		
	Very low	≤1.5
	Low	1.5-3
	Intermediate	3.5-4.5
	High	5-6
	Very high	>6

WPSS

Metric		Score
WHO classification		
	RA, RARS, del(5q)	0
	RCMD, RCUD-RS	1
	RAEB-1	2
	RAEB-2	3
Cytogenetics[b]		
	Good	0
	Intermediate	1
	Poor	2
Transfusion requirement		
	Yes	1
Risk Group		
	Very low	0
	Low	1
	Intermediate	2
	High	3-4
	Very high	5-6

MDAPSS

Metric		Score
Blasts		
	5-10%	1
	11-29%	2
Cytogenetics		
	Chromosome 7 abnormality	3
	Complex karyotype[a]	3
Cytopenias		
	PLT <30/µL	3
	PLT 30-49/µL	2
	PLT 50-199/µL	1
	WBC >20/µL	2
	Hgb <12 g/dL	2
Prior transfusion		
	Yes	1
Age (years)		
	≥65	2
	60-64	1
Risk Group		
	Low	0-4
	INT-1	5-6
	INT-2	7-8
	High	≥9

WPSS: WHO Classification–Based Prognostic Scoring System for MDS
MDAPSS: MD Anderson Global Prognostic Scoring System

Zeidan et al. Blood Reviews 2018

Comorbidities in MDS

Comorbidity	Definition	Prevalence	
Cardiac	Arrhythmia*	7%	
	Heart valve disease**	2%	25%
	Coronary artery disease *** or myocardial infarction	8%	
	Congestive heart failure or ejection fraction ≤50%	19%	
Cerebrovascular	Transient ischemic attack and/or ischemic or hemorrhagic cerebrovascular accident	5%	
Mild to moderate pulmonary	DLCO and/or FEV1 66%-80% or dyspnea on moderate or slight activity	3%	
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requires oxygen	2%	
Mild hepatic ****	Chronic hepatitis, persistent bilirubin > ULN to 1.5 x ULN or AST/ALT > ULN to 2.5 x ULN	14%	
Moderate to severe hepatic ****	Cirrhosis, fibrosis, persistent bilirubin > 1.5 x ULN or AST/ALT > 2.5 x ULN	3%	
Renal	Persistent creatinine > 2 mg/dL, renal dialysis, or renal transplant	4%	
Solid tumor	Malignancy at any time point in the patient's history, excluding non-melanoma skin cancer	10%	
Rheumatological	One or more of the following conditions: systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, polymyalgia rheumatica	2%	
Gastrointestinal	One or more of the following conditions: Crohn's disease, ulcerative colitis, or peptic ulcer requiring treatment	6%	
Diabetes	Diabetes requiring treatment with insulin or oral hypoglycemics	11%	
Endocrine	One or more of the following conditions: thyroid disorders, adrenal disorders, parathyroid gland disorders, pituitary gland disorders, or hypogonadism	5%	
Obesity	Body mass index >35 kg/m^2	2%	
Psychiatric	Depression or anxiety requiring psychiatric counseling or treatment	2%	

*DLCO indicates diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase. *Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias; **Except mitral valve prolapse; ***One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft; ****HCV infection was documented in 7% of patients.*

Della Porta Haematologica 2011;96:441

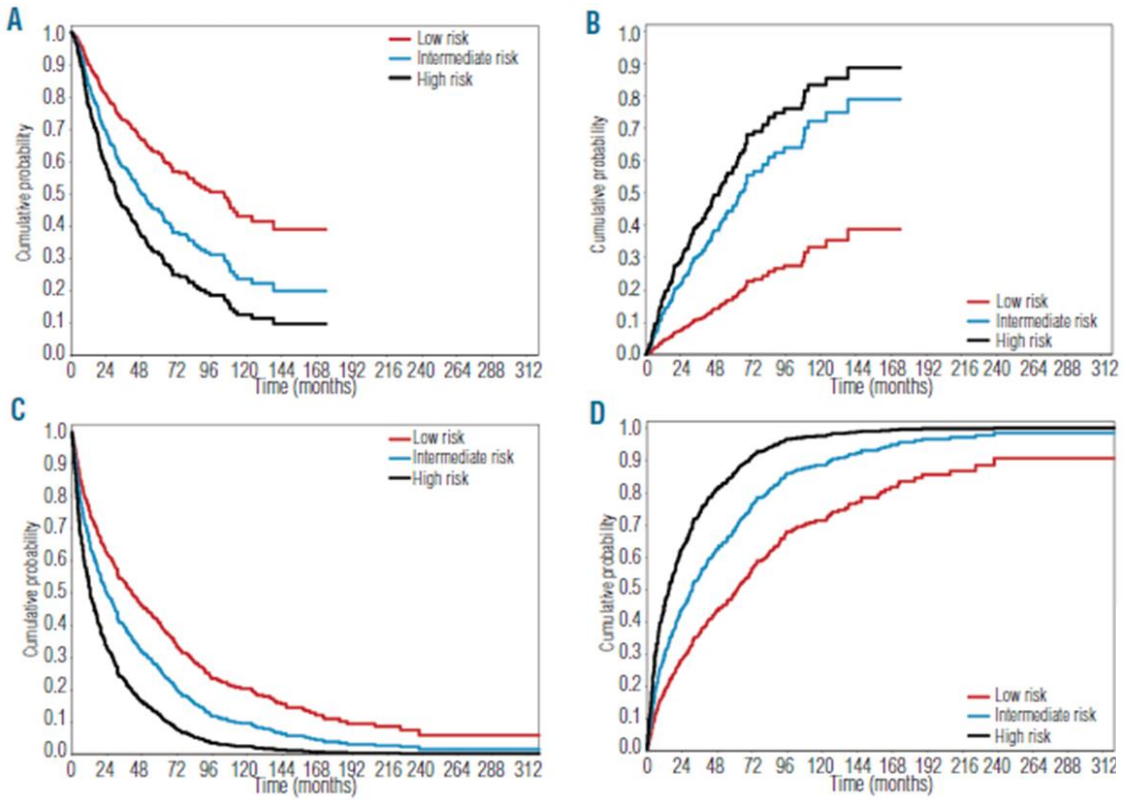


Figure 1. Relationship between MDS-CI category, risk of non-leukemic death and overall survival in the learning and validation cohorts of MDS patients. (A-B) Italian learning cohort; (A) Probability of overall survival according to time-dependent MDS-CI risk. (B) Probability of non-leukemic death according to time-dependent MDS-CI risk. (C-D); German validation cohort. (C) Probability of overall survival according to time-dependent MDS-CI risk. (D) Probability of non-leukemic death according to time-dependent MDS-CI risk.

MDS comorbidity score

Della Porta Haematologica 2011;96:441

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

terapia

- Terapia di supporto
  - Trasfusioni, antibiotici, etc
- Fattori di crescita: Epo, G-CSF
- Chemioterapia
- Trapianto di cellule staminali
  - Allogenico
- Terapia immunosoppressiva: ciclosporina, globulina antilinfocitaria (cariotipo normale / trisoma 8)
- Farmaci immunomodulanti: lenalidomide (del5q)
- Agenti ipometilanti: 5 azacitidina, decitabina
- Inibitori delle istone deacetilasi: acido valproico, fenilbutirrato, tricostatin A
- Inibitori farnesil transferasi (RAS): tipifarnib
- Inibitori di FLT3: sunitinib
- Agenti differenzianti: retinoidi, 1,25-diidrossivitamina D3, arsenico triossido, etc

Table 1. Prognostic risk factors relevant for HSCT eligibility and for outcome after HSCT

Prognostic risk factor	Tools to measure risk factors in patients with MDS	Outcome after	
		Nontransplant interventions, including supportive care	HSCT
Patient related			
Age (chronological)	Calendar, IPSS-R[20]	Age influences prognostic impact of disease-related factors[20]	Impact age influenced by other patient-related factors[15]
Performance status (functional ability)	Karnofsky status ≥ 80%		Better survival after HSCT[15]
Frailty (reduced physical fitness)	Specific tools have to be tested in HSCT[117]		Fit patients better outcome[12,16-18]
Comorbidities	HSCT-specific CI (HCT-CI)[14]		Low CI better outcome[13]
Disease related			
Percentage of marrow blasts	IPSS(-R), WPSS, WHO[20,21]	Related to prognosis[20,21]	Only impact if <5% marrow blasts[22]
Cytogenetic risk groups	IPSS(-R), WPSS, CPSS[20,21,44]	5 prognostic groups[19]	Only very-poor-risk[29] and monosomal karyotype[30]
Severity of cytopenias	IPSS(-R), WPSS[41,42]	IPSS-R better prediction of prognosis compared with IPSS[42]	Only very-poor-risk group of IPSS-R prognostic
Marrow fibrosis	WHO criteria[51]	Severity fibrosis prognostic[51]	Severity fibrosis prognostic[52]
Transfusions burden	WPSS[41,63]	WPSS[41]	WPSS[64]
FCM	ELN FCM score[25,27]	ELN FCM score[24]	Not validated yet[27]
Molecular mutations	No specific tools yet[34]	Mutations in RUNX1, U2AF1, ASXL1, TP53, and others: poor prognosis[34]	Mutations in TP53, EZH2, ETV6 poor prognostic[23,35]
Disease status (after nontransplant treatment interventions)			
ESA failure	High Epo levels, high transfusion intensity[6,68]	High Epo levels, high transfusion intensity[6,68]	No direct impact reported
Lenalidomide failure	Absence of 5q−[5]	Absence of 5q−[5]	No direct impact reported
HMA failure	HMA-therapy–specific risk score[71]	HMA-therapy–specific risk score,[71] complex karyotype[118] TET2 and TP53 mutations[72,73]	Best available treatment after HMA failure,[76] but response status prognostic factor
ICT	MDS-specific risk score[4]	MDS-specific risk score[4]	Best available treatment available after failure of first-line ICT,[70] but response status and remission duration prognostic factor[31]

De Witte et al. Blood. 2017;129(13):1753-1762

Current Treatment Algorithm in Myelodysplastic Syndromes

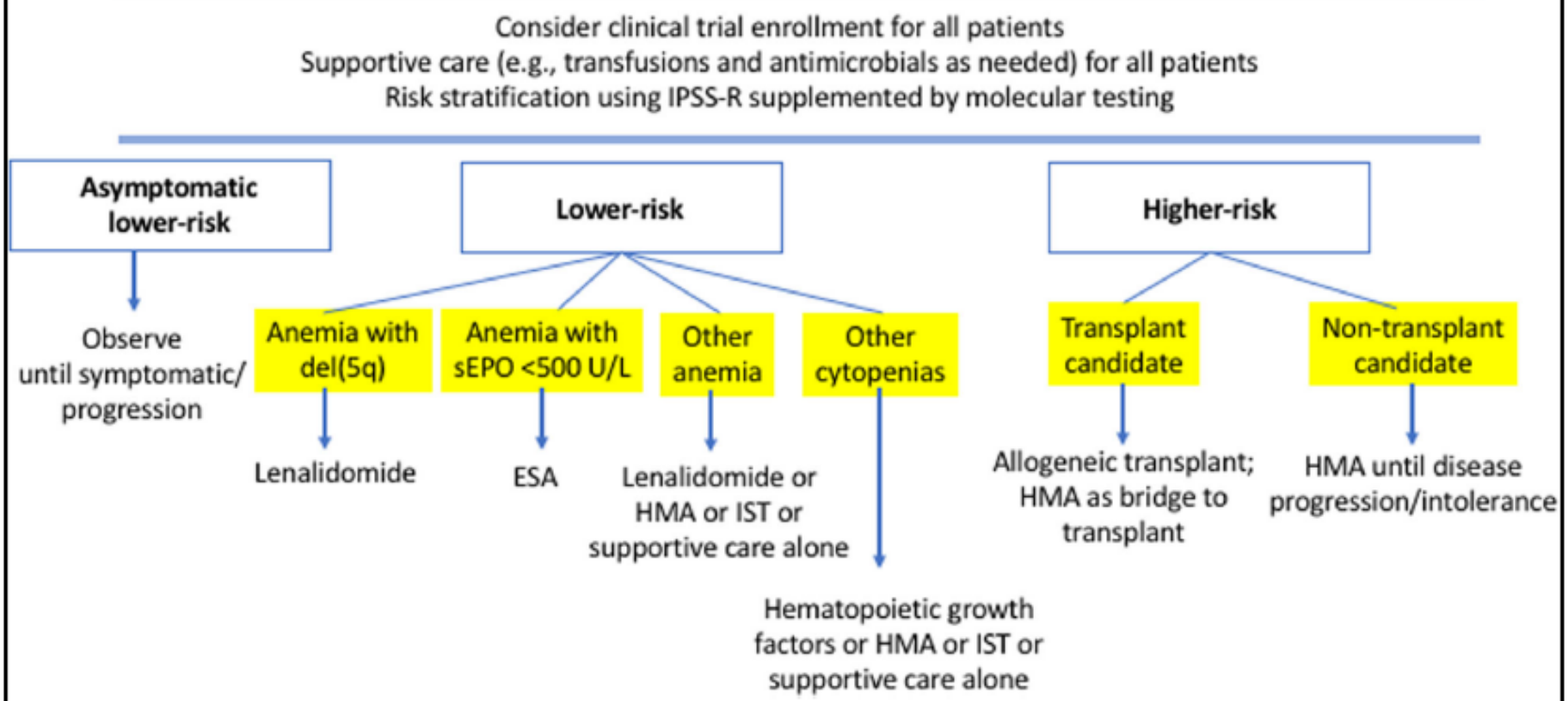
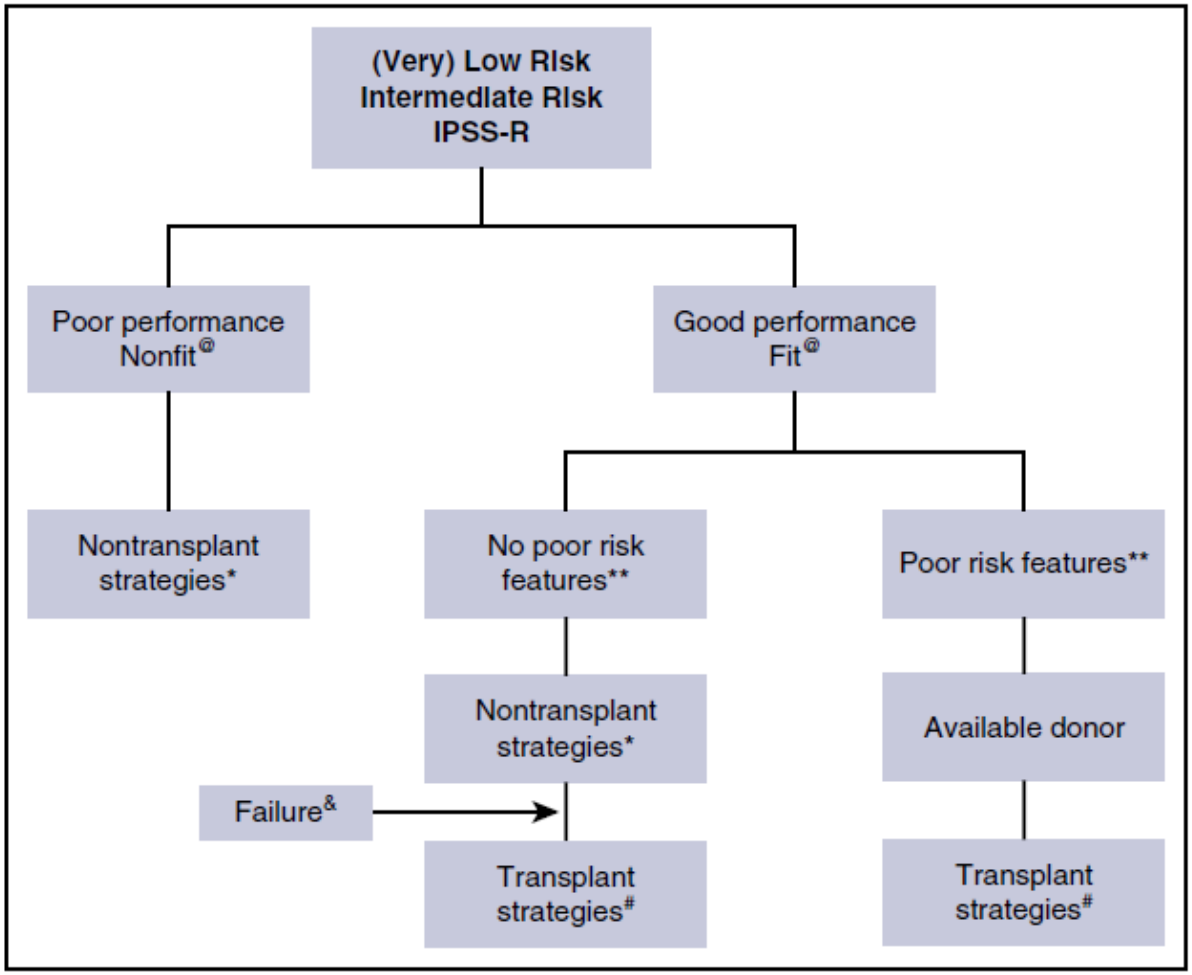


Fig. 1 MDS treatment algorithm as described in the text. Clinical trials should be considered for all patients, but is recognized that many patients will not have access to trials or will not be eligible for available trials or will not want to go on trials, especially those requiring travel to a major center. In fact only a very small proportion of patients with MDS are currently enrolled on prospective interventional trials. However, increased trial enrollment is an important goal given the continued poor outcomes with MDS. EPO erythropoietin, ESA erythropoiesis-stimulating agent, HMA DNA hypomethylating agent, IST immunosuppressive therapy (anti-thymocyte globulin, cyclosporine, or tacrolimus)

Steensma Blood Cancer Journal (2018) 8:47

Figure 1. Therapeutic algorithm for adult patients with MDS and (very) low-risk or intermediate IPSS-R risk scores. @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies (for details of various nontransplant interventions [transfusions, ESAs, lenalidomide, and cytoreductive therapy], see "Timing of transplantation." Nontransplant interventions may include >1 line of nontransplant intervention, eg, treatment with ESAs, followed by lenalidomide in patients with 5q−). ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias [neutrophil counts, $<0.3 \times 10^9$/L; platelet counts, $<30 \times 10^9$/L], high transfusion intensity ≥2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of donor selection, type of conditioning and posttransplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity and good Karnofsky status). @ indicates donor availability (the improved outcome of HSCT with haploidentical donors utilizing posttransplant cyclophosphamide increases the donor availability).



De Witte et al. Blood. 2017;129(13):1753-1762

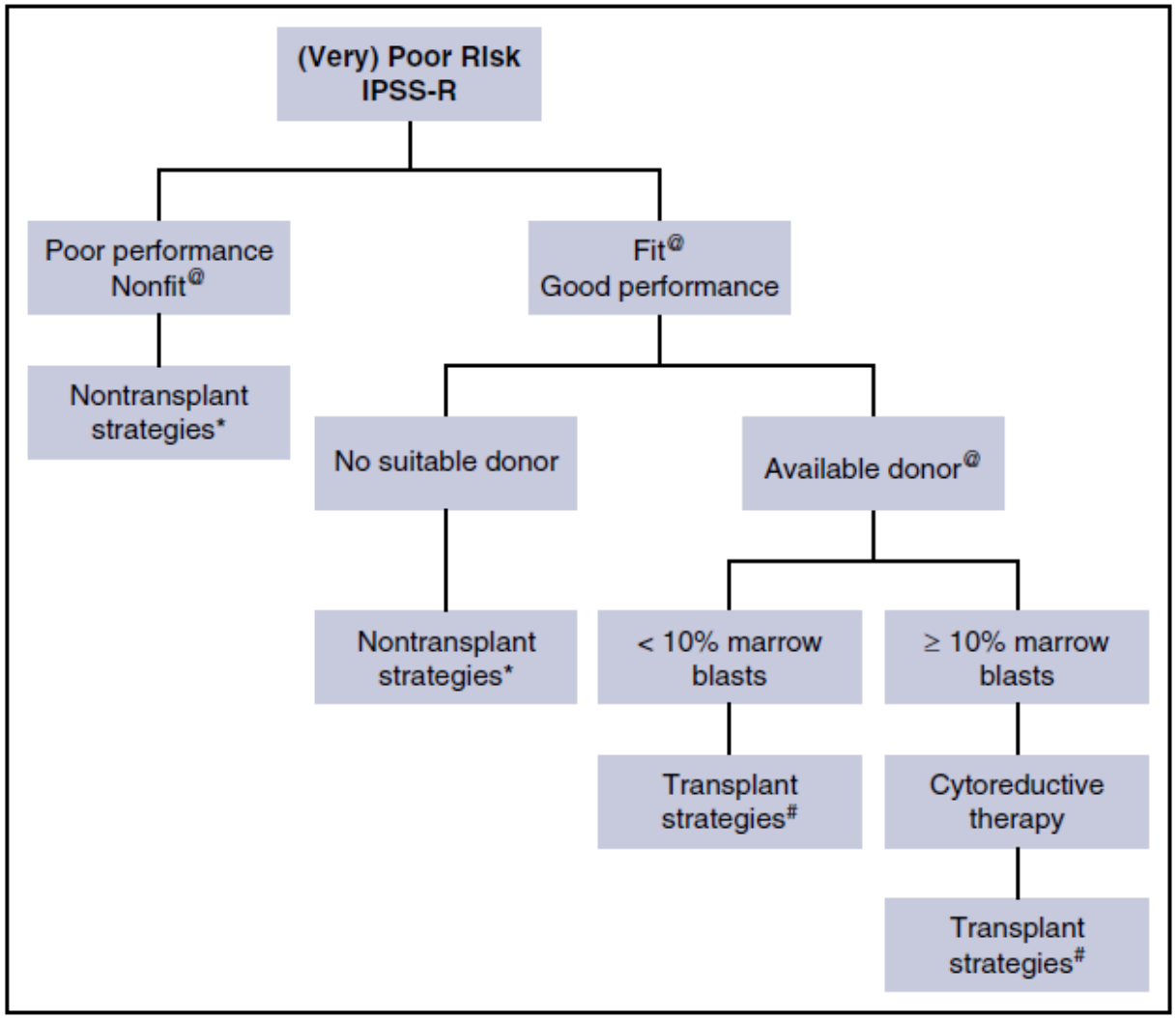
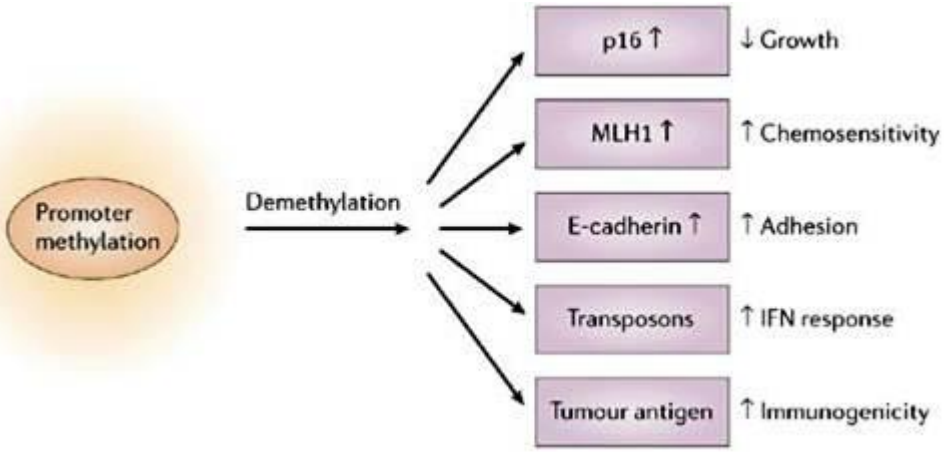


Figure 2. Therapeutic algorithm for adult patients with MDS and poor IPSS-R scores. @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies (for details of various nontransplant interventions [transfusions, ESAs, lenalidomide and cytoreductive therapy], see "Timing of transplantation." Nontransplant interventions may include >1 line of nontransplant intervention, eg, treatment with ESAs, followed by lenalidomide in patients with 5q−). ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias [neutrophil counts, $<0.3 \times 10^9$/L; platelet counts, $<30 \times 10^9$/L], high transfusion intensity ≥2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of donor selection, type of conditioning and posttransplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity and good Karnofsky status). @ indicates donor availability (the improved outcome of HSCT with haploidentical donors utilizing posttransplant cyclophosphamide increases the donor availability).

De Witte et al. Blood. 2017;129(13):1753-1762



Promoter hypermethylation and aberrant gene silencing are characteristic features of cancer. With the use of demethylating agents, genome-wide demethylation is initiated, which then leads to reactivation of methylation-silenced genes.

Nature Reviews Drug Discovery 5, 37-50 (2006)

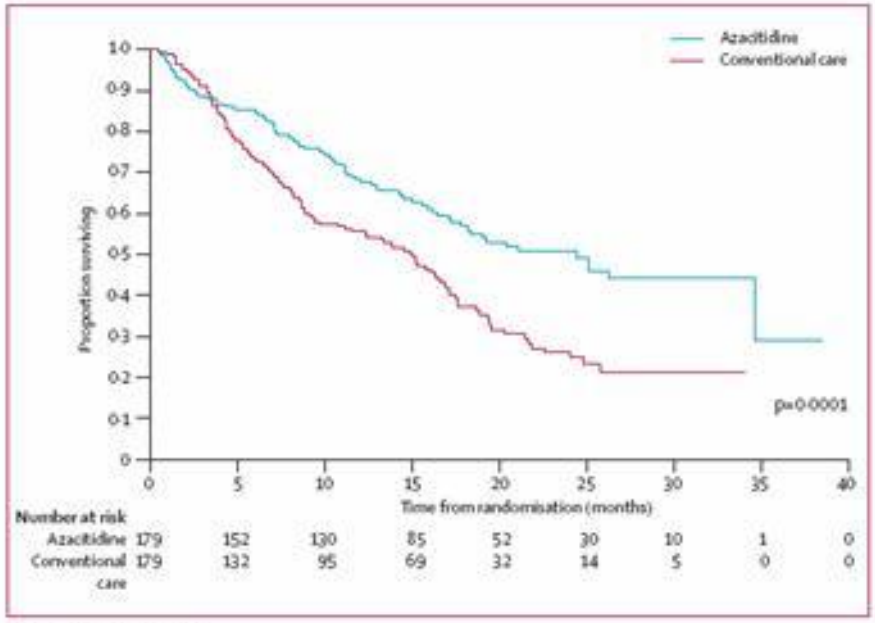
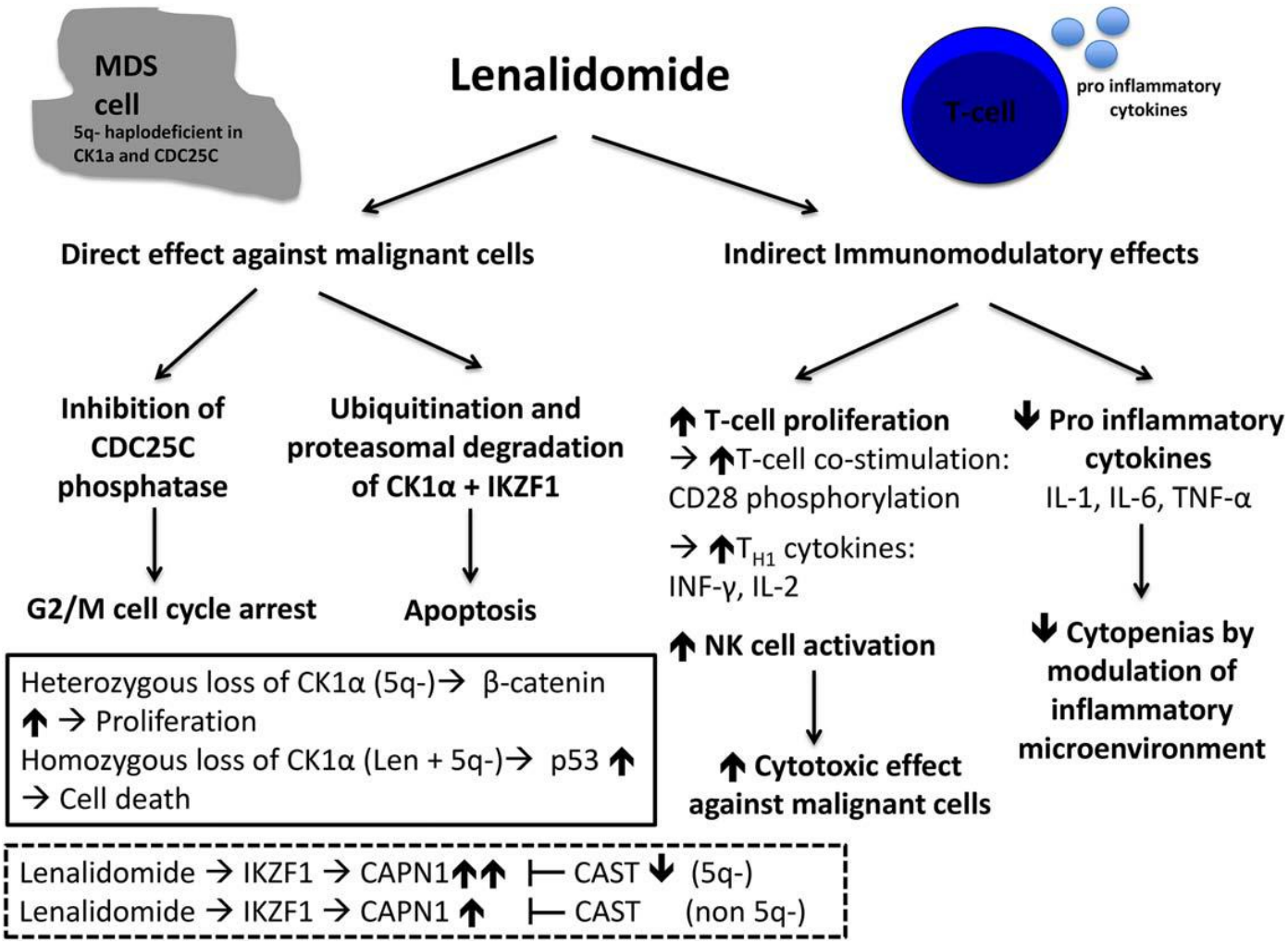


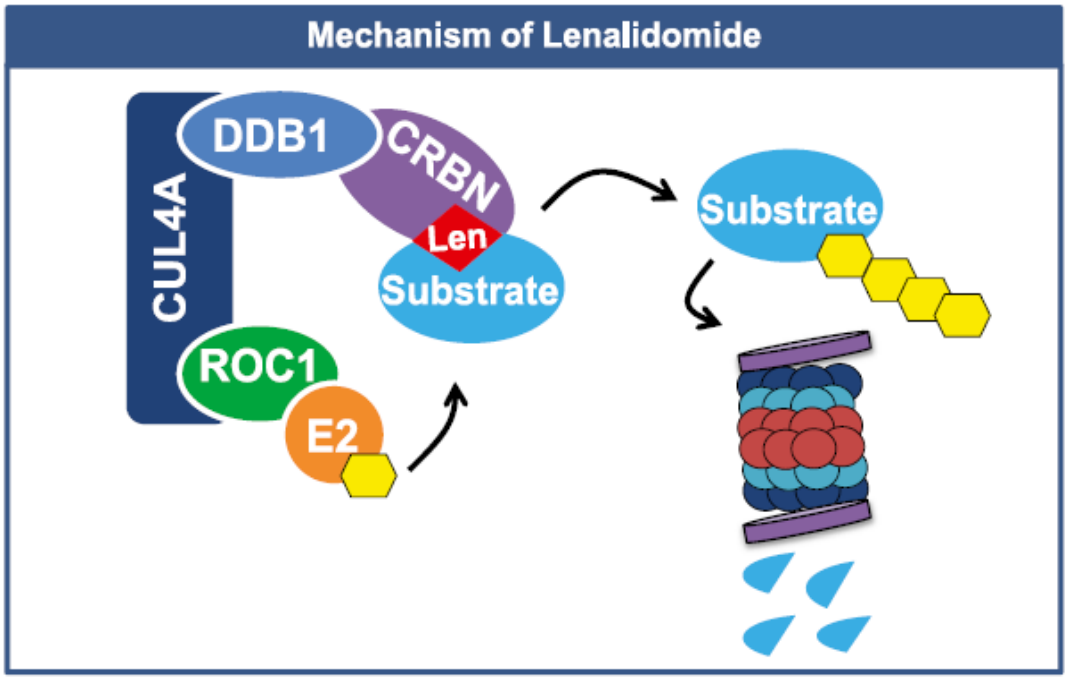
Figure 3: Overall survival

Fenaux P Lancet Oncol 2009; 10: 223–32

Mechanisms of action of lenalidomide in MDS.



Stahl & Zeidan. Cancer 2017;123:1703-1



Lenalidomide acts by a novel drug mechanism—modulation of the substrate specificity of the $CRL4_{CRBN}$ E3 ubiquitin ligase.

In multiple myeloma, lenalidomide induces the ubiquitination of IKZF1 and IKZF3 by $CRL4_{CRBN}$. Subsequent proteasomal degradation of these transcription factors kills multiple myeloma cells.

In del(5q) MDS, lenalidomide induces the degradation of CK1a, which preferentially affects del(5q) cells because they express this gene at haploinsufficient levels.

Fink and Ebert. Blood. 2015;126(21):2366-2369

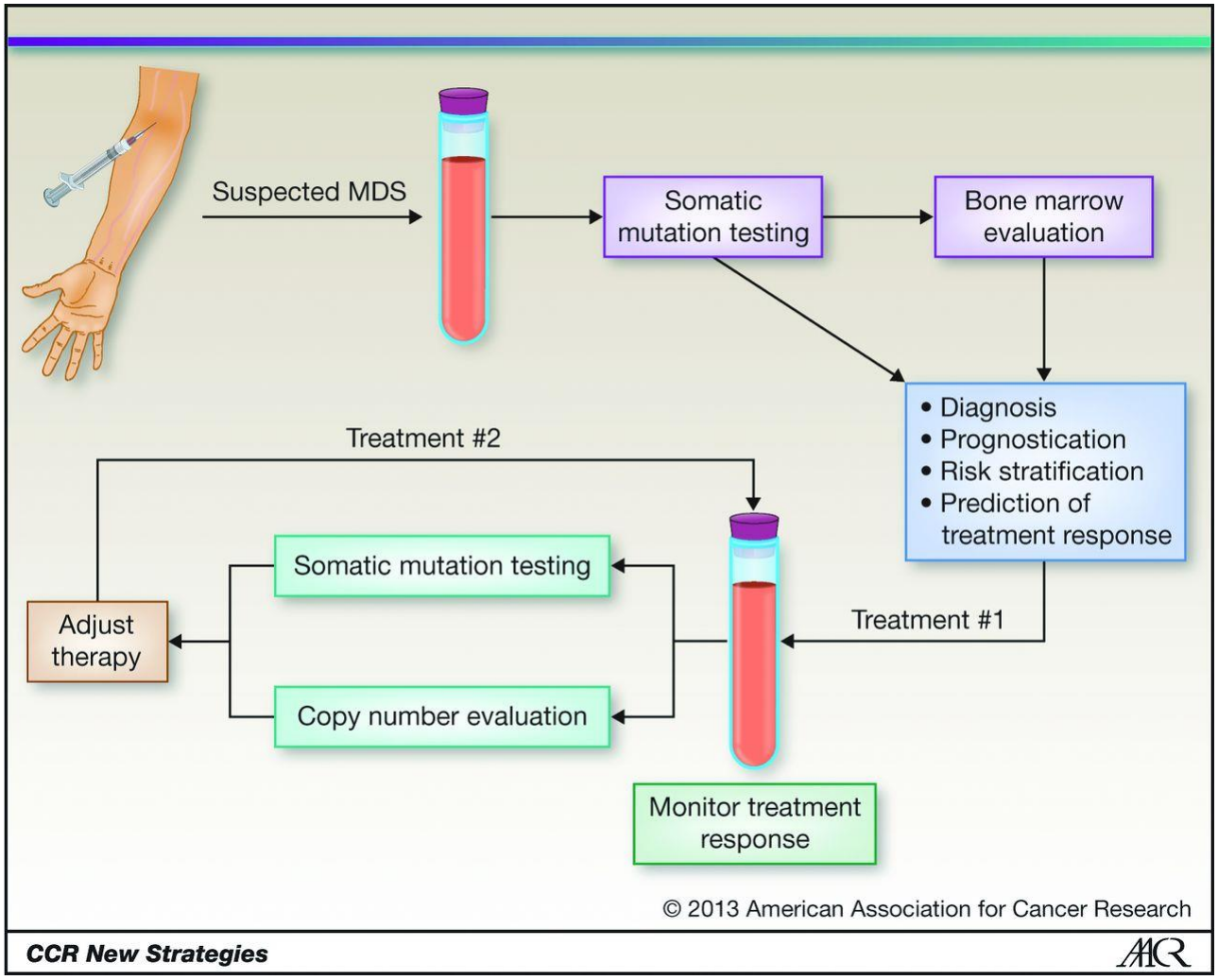
Responses to lenalidomide in 5q and non-5q MDS patients

	Non-5q−	5q−
Transfusion independence	26%	67%
Median hemoglobin rise	3.2 g/dL	5.4 g/dL
Median time to response	4.8 weeks	4.6 weeks
Complete cytogenetic response	10%	44%

Modified from List et al[45] and Raza et al[46] with permission.

Stone RM. Blood 2009;113:6296

Proposed workup of suspected MDS with incorporation of MDS-specific somatic mutation testing into clinical practice.



Tothova Z et al. Clin Cancer Res 2013;19:1637-1643

Classificazione WHO 2008 delle neoplasie mielodisplastiche mieloproliferative

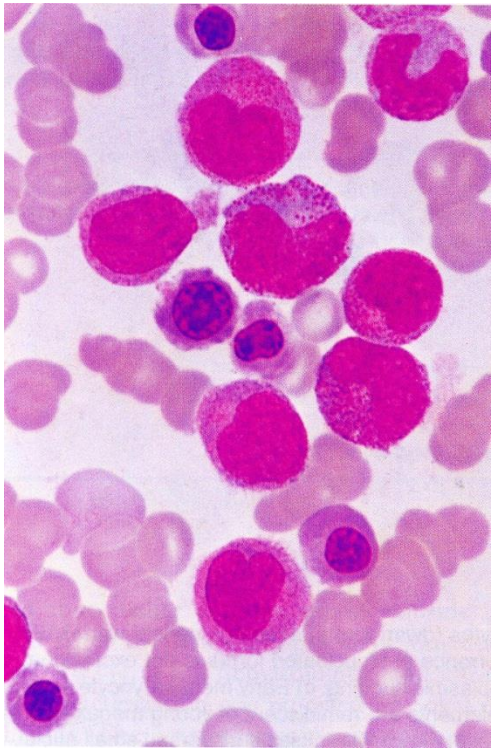
patologia	Sangue periferico	midollo
CMML	Monociti > 1 x 10^9/L No fusione BCR/ABL <20% di blasti	Displasia in una o più filiere mieloidi Blasti < 20% (i blasti includono mieloblasti, monoblasti e promonociti Non riarrangiamenti di PDGFRA e PDGFRB
Leucemia mieloide cronica atipica BCRABL negativa (aCML)	Leucocitosi, neutrofilia Displasia neutrofila Precursori neutrofili >=10% dei leucociti Blasti < 20% No fusione BCR/ABL No riarragiamenti di PDGFRA e PDGFRB	Displasia neutrofila con o senza altre filiere displastiche Blasti < 20%
Leucemia mielomonocitica giovanile	Monoliti > 1 x 10^9/L Blasti < 20% GB generalmente > 10 x 10^9/L	Blasti < 20% (i blasti includono mieloblasti, monoblasti e promonociti)
Neoplasie mielodisplastiche mieloproliferative non classificabili (MDS/MPN-U)	Caratteristiche di MDS e MPN Non precedente diagnosi di MDS o MPN Non recente terapie con fattori di crescita o citostatici No BCR/ABL o riarragiamenti di PDGFRA e PDGFRB	Caratteristiche miste di MDS e MPN Blasti < 20%
RARS-t entità provvisoria	Trombocitosi persistente > 450 x 10^9/L Anemia BCR/ABL negativa Esclusi i casi con t(3;3)(q21;q26) e inv(3)(q21q26) e isolata del 5q JAK2 mutato nel 50% dei casi (non è criterio diagnostico)	Caratteristiche morfologiche di RARS Sideroblasti ad anello >= 15% Megacariociti anomali simili a quelli osservati nelle MPN BCR/ABL negative

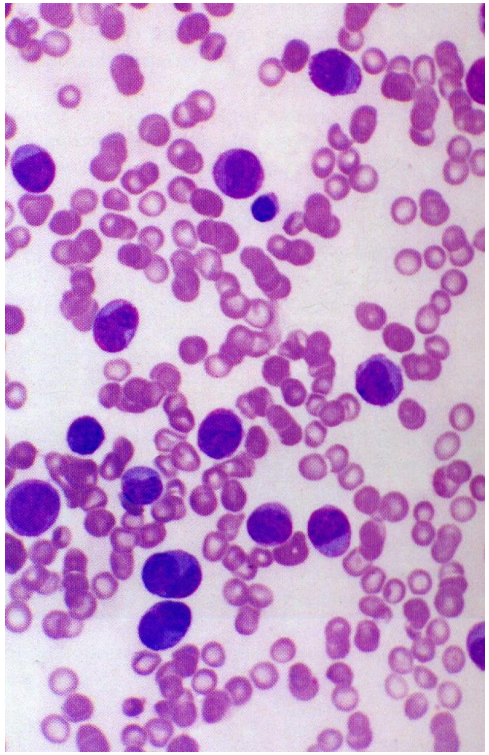
WHO 2016: MDS/MPN

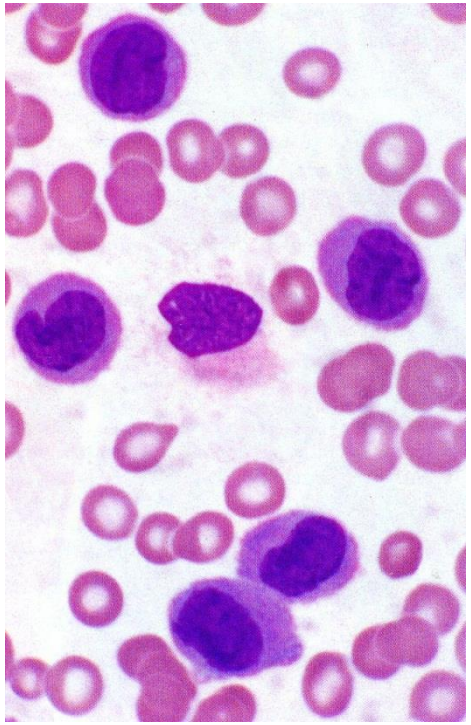
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable

Arber DA et al. Blood. 2016; 127(20):2391-2405

CMML







WHO diagnostic criteria for CMML

- Persistent PB monocytosis >1×10^9 /L (> 3 months)
- All other causes of monocytosis excluded
- No Philadelphia chromosome or *bcr/abl* fusion gene
- < 20% blasts in PB and BM
- Dysplasia or, if dysplasia is absent/minimal:
  - Demonstration of clonal cytogenetic abnormality

- CMML subcategories:
  - CMML-1: PB blasts <5%, BM Blasts <10%
  - CMML-2: PB Blasts 5–19%, BM Blasts 10–19%
  - CMML with eosinophilia (I or II): eosinophils in PB >1.5×109 /L

WHO 2016: Diagnostic criteria for CMML

CMML diagnostic criteria

- Persistent PB monocytosis ≥1 × 10^9/L, with monocytes accounting for ≥10% of the WBC count
- Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET*
- No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
- <20% blasts in the blood and BM†
- Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
- An acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells‡

or

- The monocytosis (as previously defined) has persisted for at least 3 mo and
- All other causes of monocytosis have been excluded

*Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

†Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes. Promonocytes are monocytic precursors with abundant light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count.

‡The presence of mutations in genes often associated with CMML (eg, *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in subclones. Therefore, caution would have to be used in the interpretation of these genetic results.

Arber DA et al. Blood. 2016; 127(20):2391-2405