HEMATOLOGIC MALIGNANCIES

BIOLOGY

- Failure of terminal differentiation
- Failure of differentiated cells to undergo apoptosis
- Failure to control growth
- Neoplastic “stem cell”

FAILURE OF TERMINAL DIFFERENTIATION

- **Result: accumulation of rapidly dividing immature cells**
- **Example: acute leukemias, aggressive lymphomas**

FAILURE TO UNDERGO APOPTOSIS

- **Result: accumulation of relatively well-differentiated, slow-growing cells**
- **Example: chronic lymphocytic leukemia, indolent lymphomas**

THE NEOPLASTIC STEM CELL

- Propagation of malignant clone may depend on a subset of cells with stem cell-like properties
- Some neoplastic stem cells retain the ability to differentiate into more than one cell type (eg, myeloproliferative/myelodysplastic disorders)
- Eradication of neoplastic stem cell essential to cure disease?
- Neoplastic stem cells may be slow-growing and resistant to treatment

MYELOID NEOPLASIA

- Myeloproliferative disorders
  - Polycythemia vera
  - Essential thrombocytosis
  - Myelofibrosis/myeloid metaplasia
  - Chronic myelogenous leukemia
- Myelodysplasia
- Acute myelogenous leukemia

ACUTE LEUKEMIA

Information used in classification

- Clinical setting
- Morphology
- Histochemistry
- Surface markers
- Cytogenetics
- Molecular genetics

ACUTE LEUKEMIA

Adverse prognostic features

- Old age, poor performance status
- Therapy-induced
- Prior myelodysplastic/myeloproliferative disorder
- High tumor burden
- Cytogenetics: Ph[1] chromosome, deletion of 5 or 7, multiple cytogenetic abnormalities
- Molecular: FLT3 internal tandem duplication

ACUTE MYELOGENOUS LEUKEMIA

- Affected cell: myeloid stem cell or committed progenitor cell
- Differentiation: arrested at early stage, with absent or decreased maturation
- Kinetics: marrow replacement by immature cells, decreased normal hematopoiesis
- Marrow: usually markedly hyercellular with preponderance of blast forms
  - Hypocellular variants occur
- Peripheral blood: variable decrease in all cell lines with or without circulating immature cells

ACUTE MYELOGENOUS LEUKEMIA

Epidemiology

- 90% of adult acute leukemia: 2.2 deaths/100,000/yr
- Incidence rises with age
- Risk factors: exposure to ionizing radiation, alkylating agents and other mutagens (implicated in10-15% of all cases), certain organic solvents (benzene)
- Precursor diseases: myelodysplastic & myeloproliferative disorders, myeloma, aplastic anemia, Down syndrome, Klinefelter syndrome, Fanconi syndrome, Bloom syndrome

ACUTE MYELOGENOUS LEUKEMIAS

FAB (French-American-British) classification

- M0 (minimal differentiation)
- M1 (myeloid blasts)
- M2 (some differentiation)
- M3 (promyelocytic)
- M4 (myelomonocytic)
- M5 (monocytic)
- M6 (erythroleukemia)
- M7 (megakaryoblastic leukemia)
- Unclassifiable (evolved from MDS, other secondary leukemias)

Newer classification schemes place more emphasis on cytogenetics and less on morphology

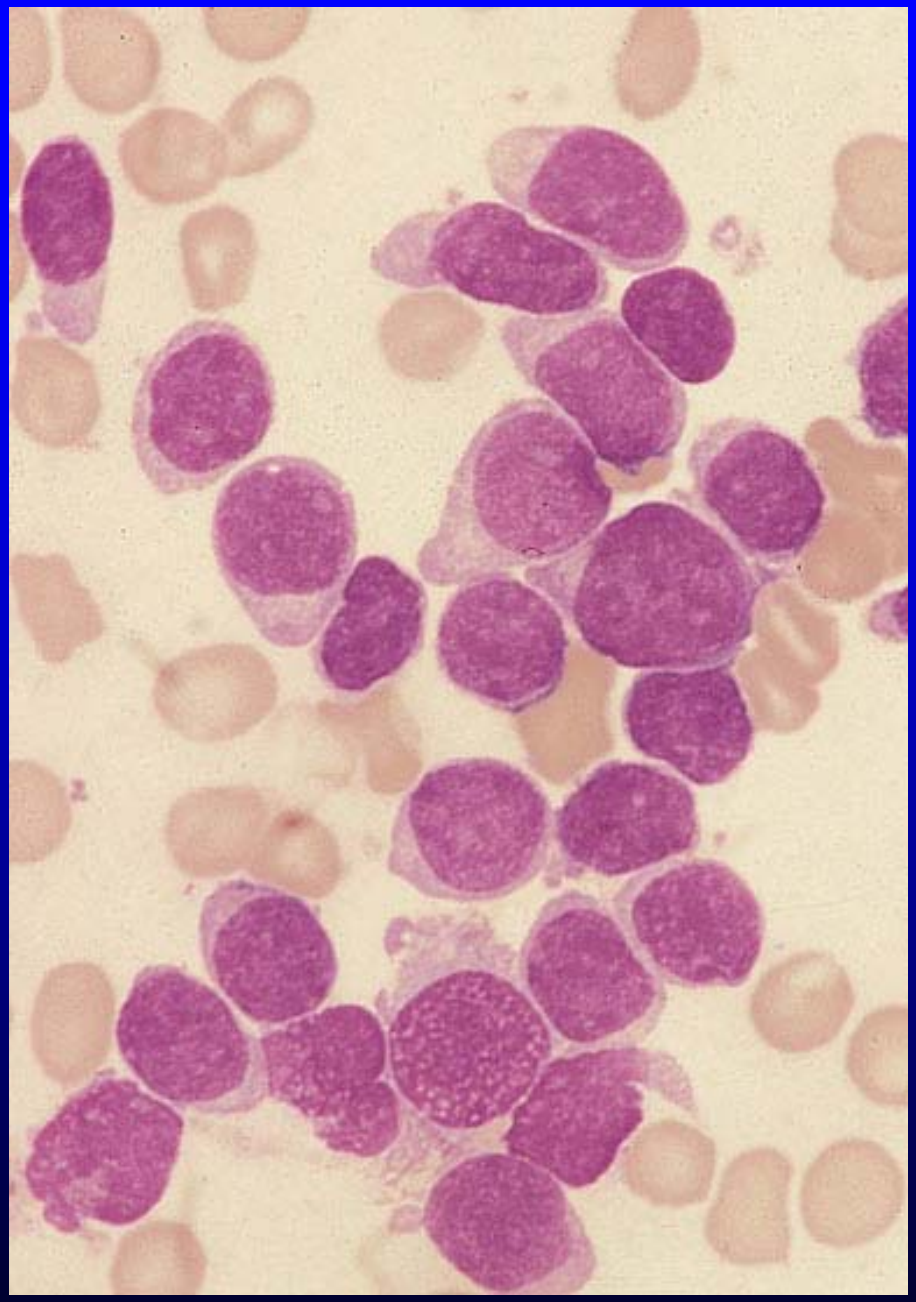
WHO classification of AML

- AML with recurrent cytogenetic abnormalities
  - t(8;21)
  - inv(16)
  - Acute promyelocytic leukemia – t(15;17) and variants
  - AML with 11q23 (MLL gene) abnormalities
- AML with multilineage dysplasia
- AML/MDS, therapy-related
- AML not otherwise categorized
  - Minimally differentiated
  - Without maturation
  - With maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic and monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma
- AML with ambiguous lineage
  - Undifferentiated AML
  - Bilineal AML
  - Biphenotypic AML

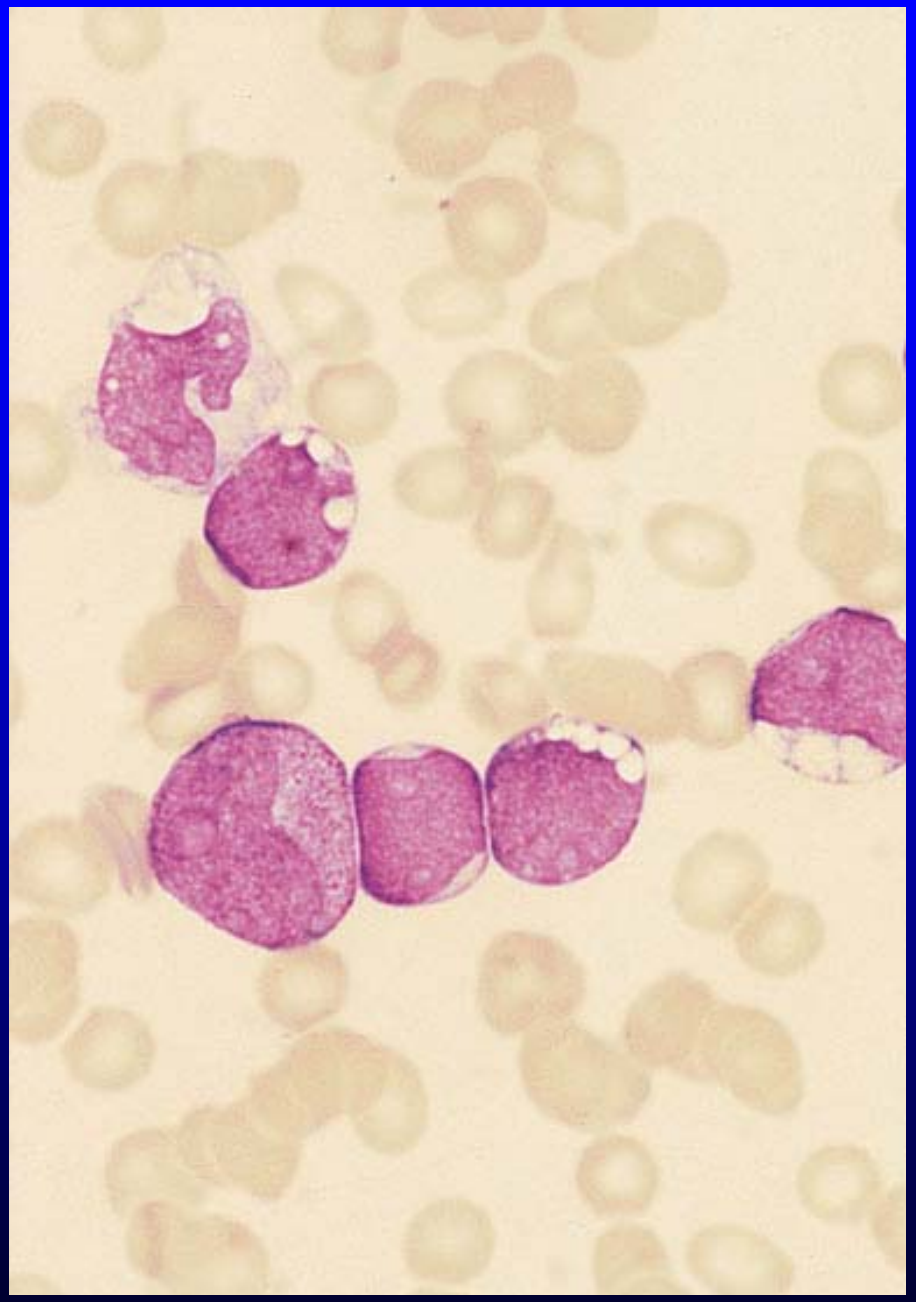
ACUTE PROMYELOCYTIC LEUKEMIA

(APML; FAB M3)

- t (15;17)
- Translocation involves retinoic acid receptor gene
- High incidence of DIC/fibrinolysis
- All-trans retinoic acid induces remission in high proportion of cases
- Favorable prognosis



M0



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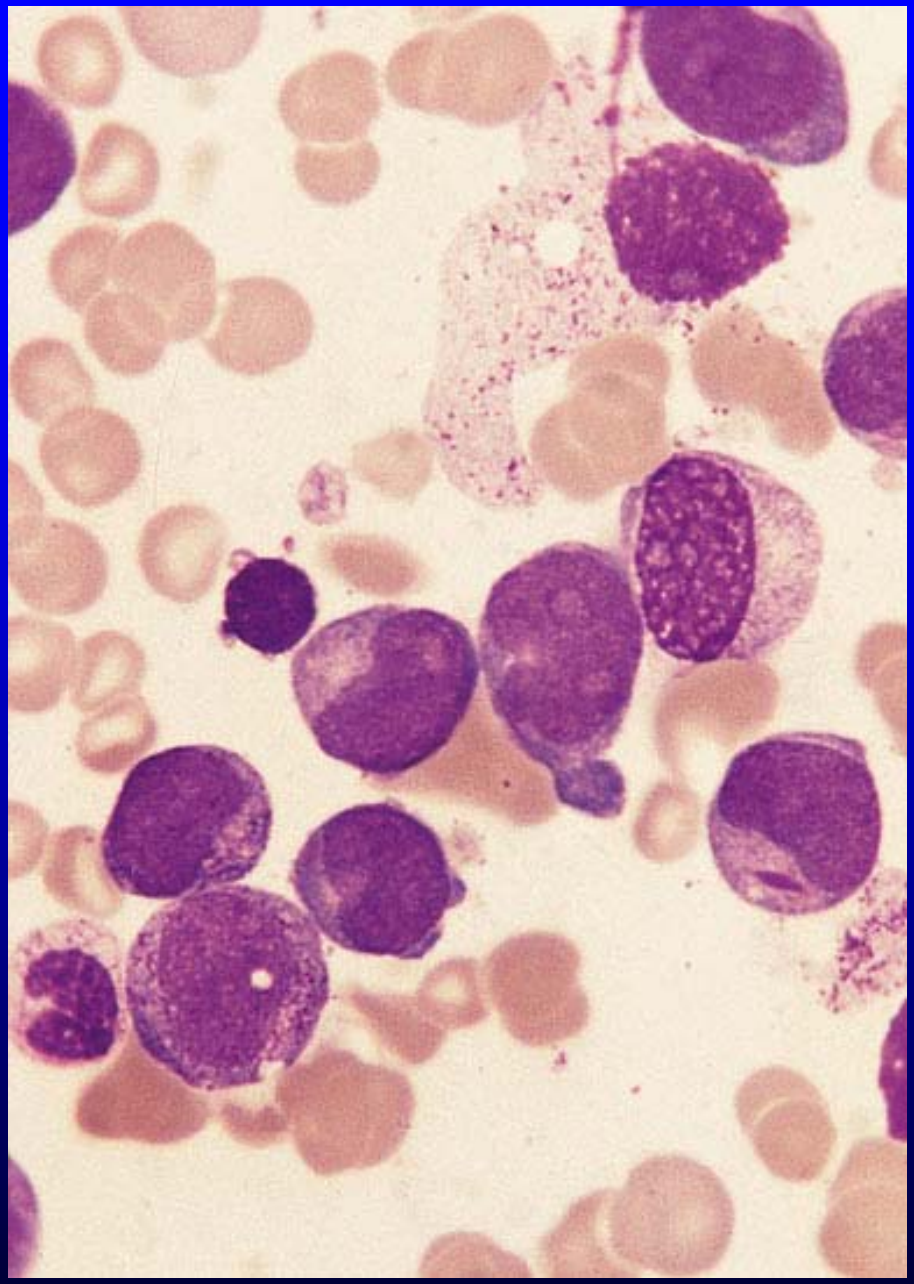

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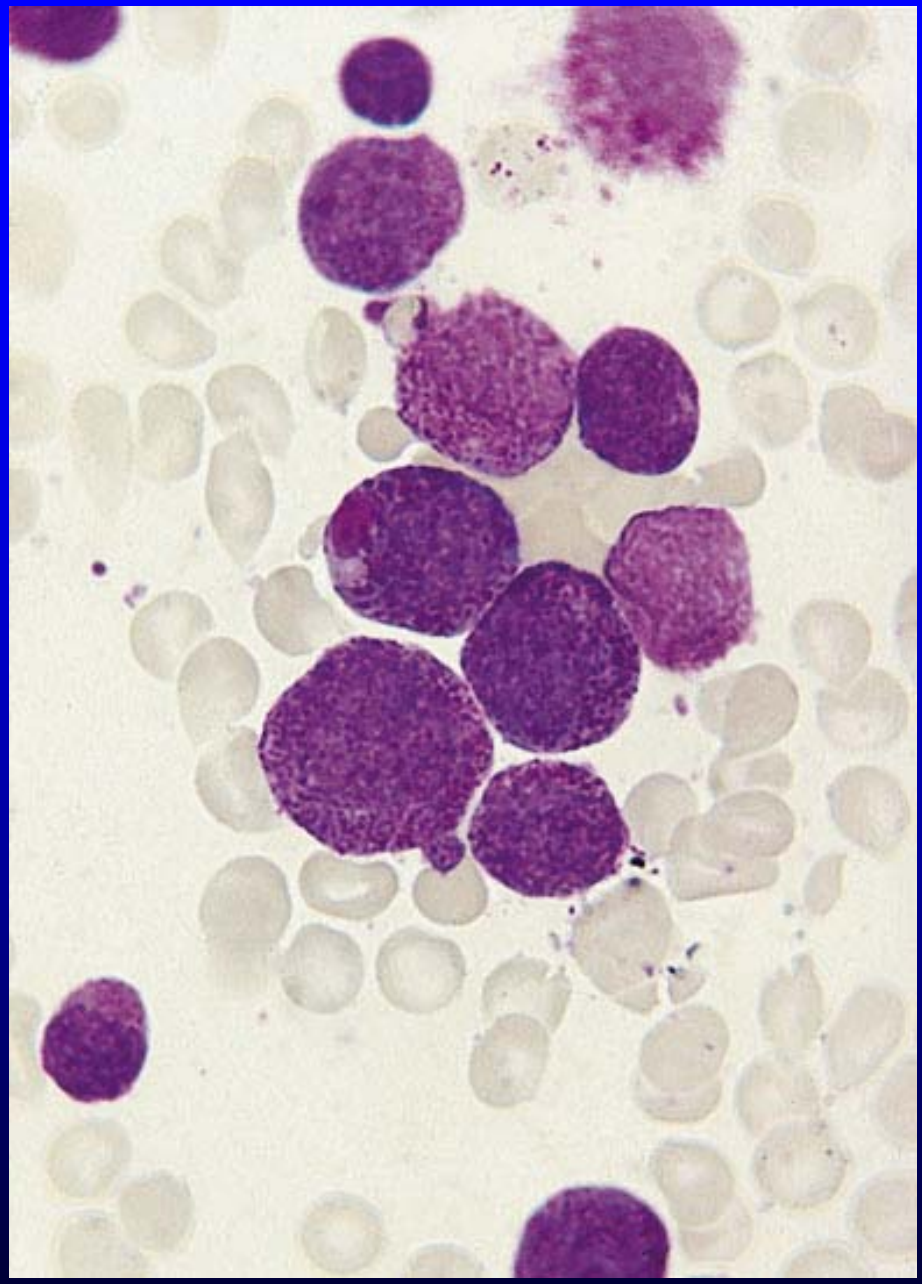

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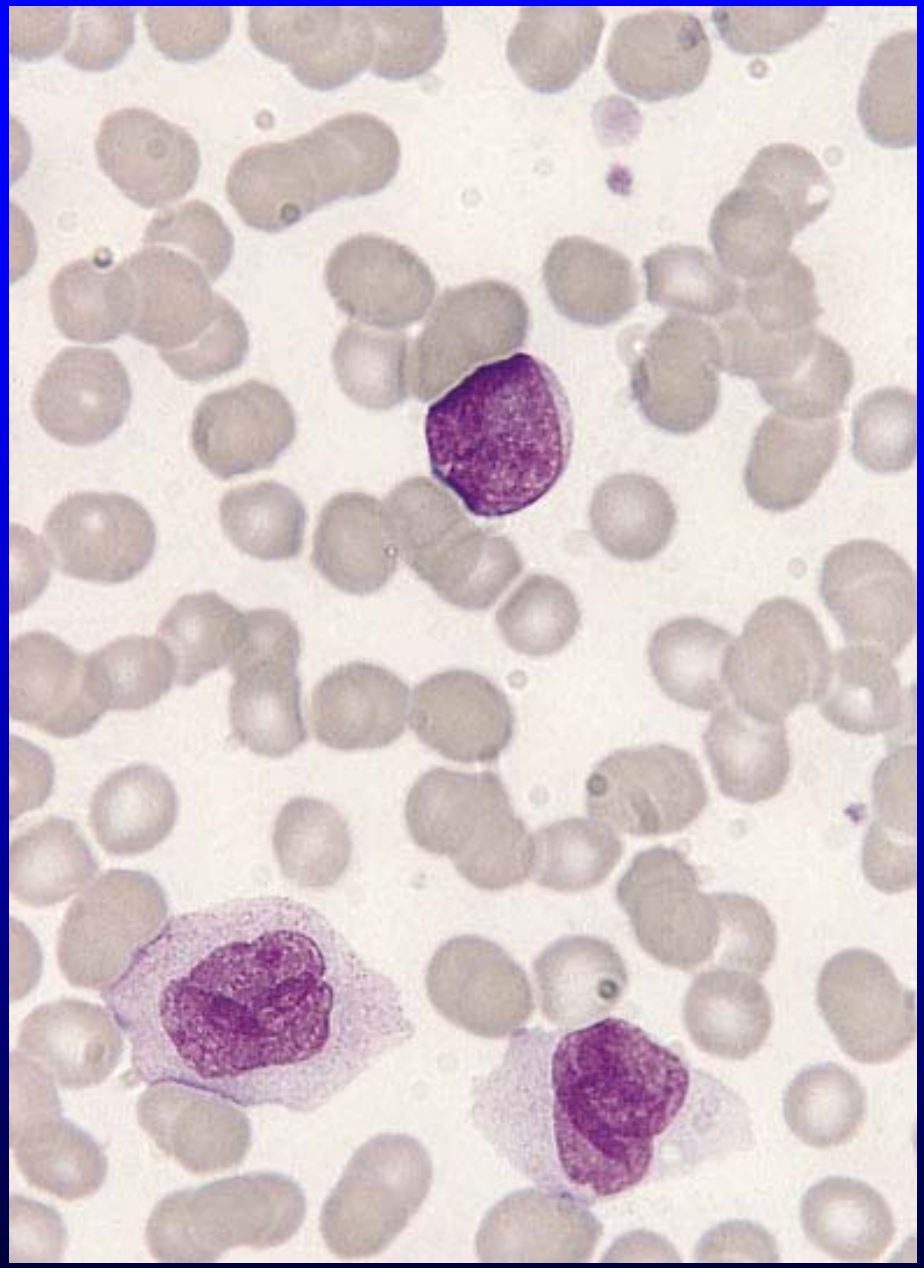

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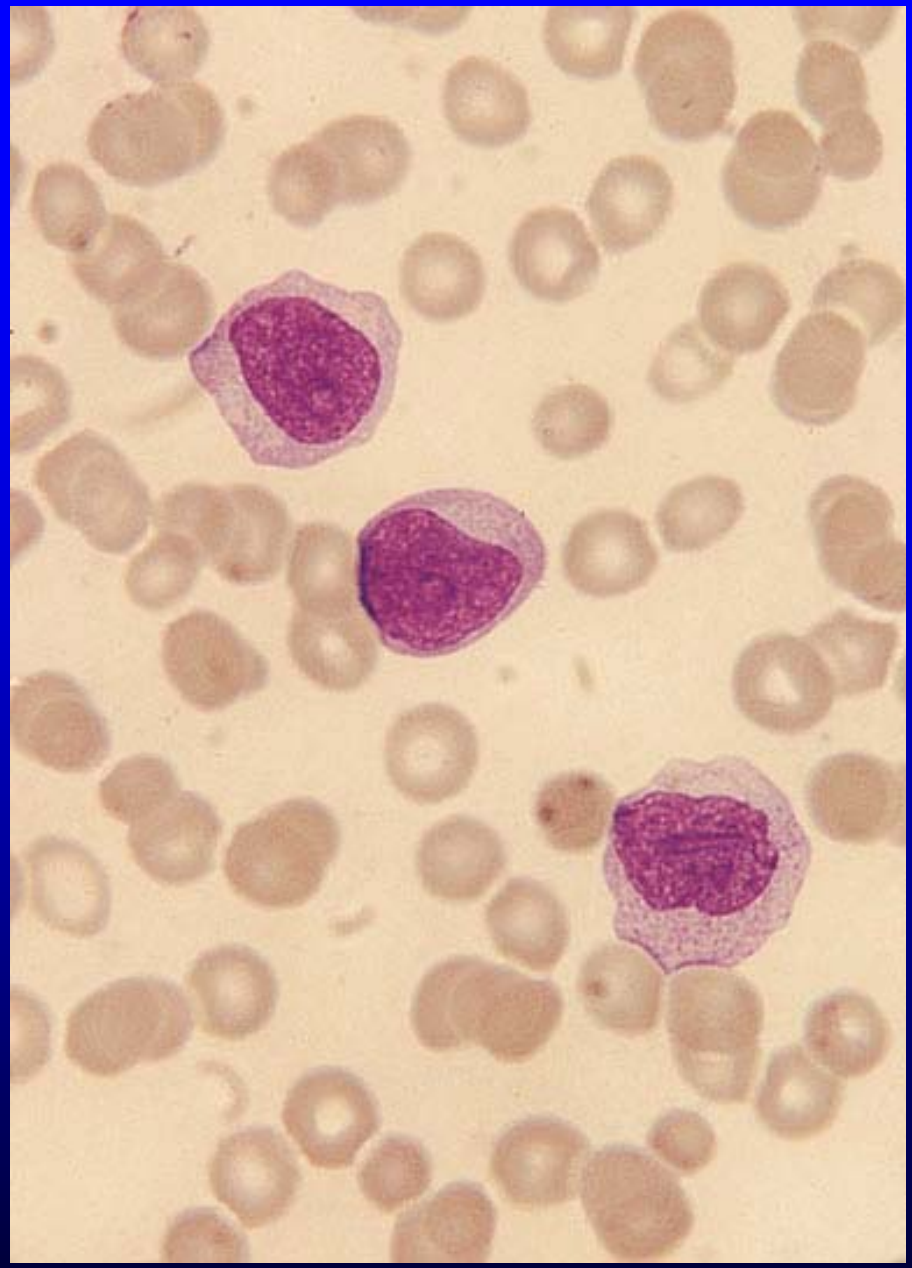

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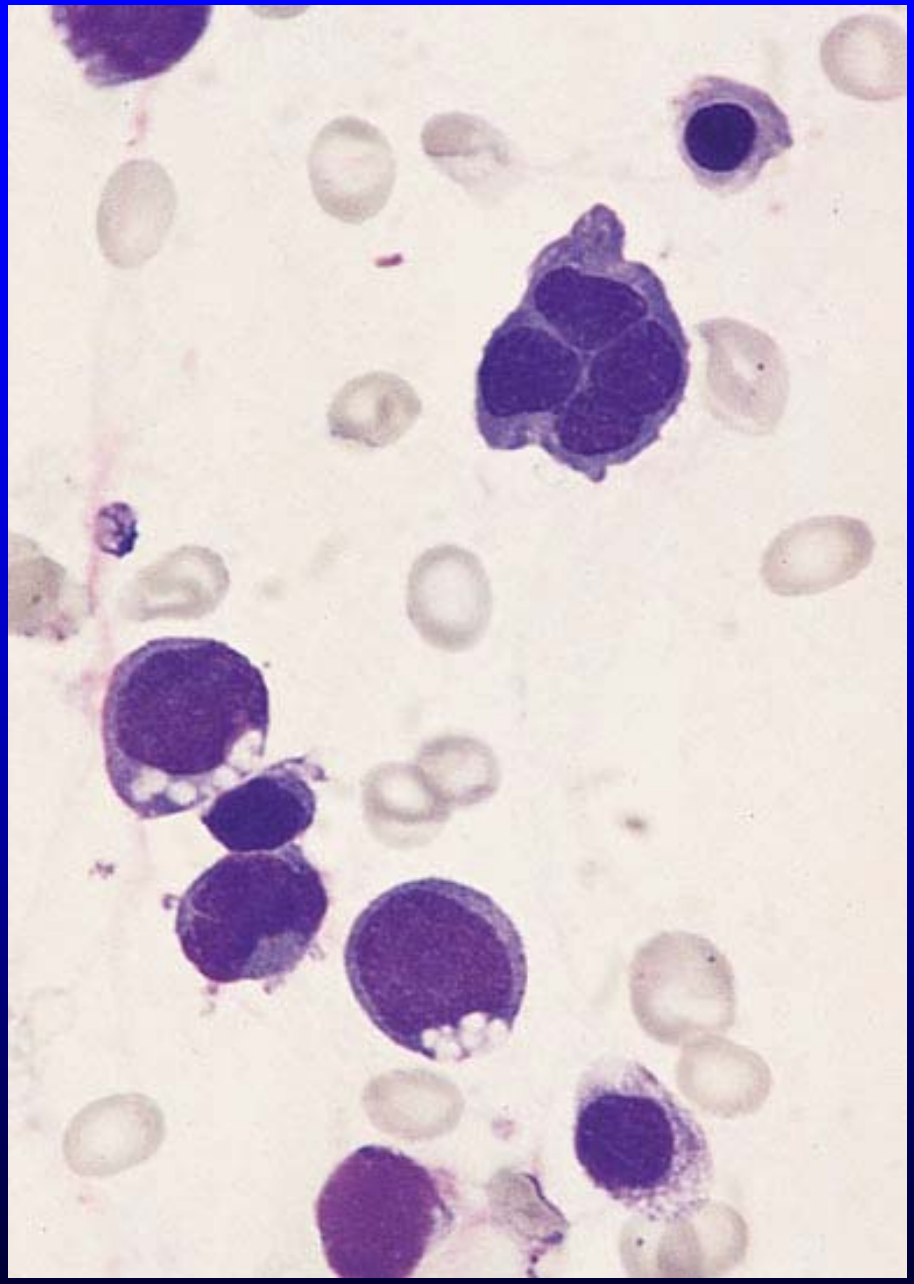

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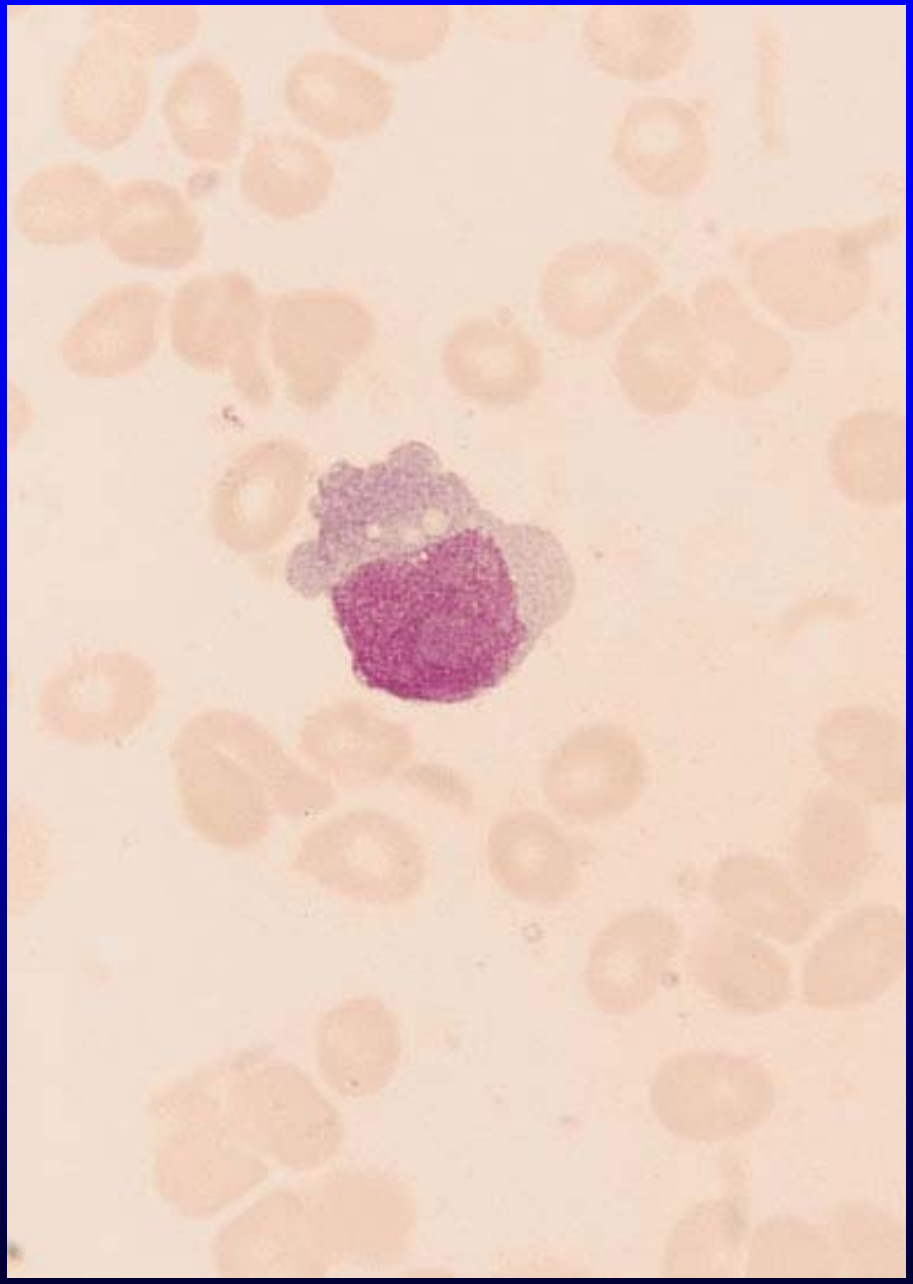
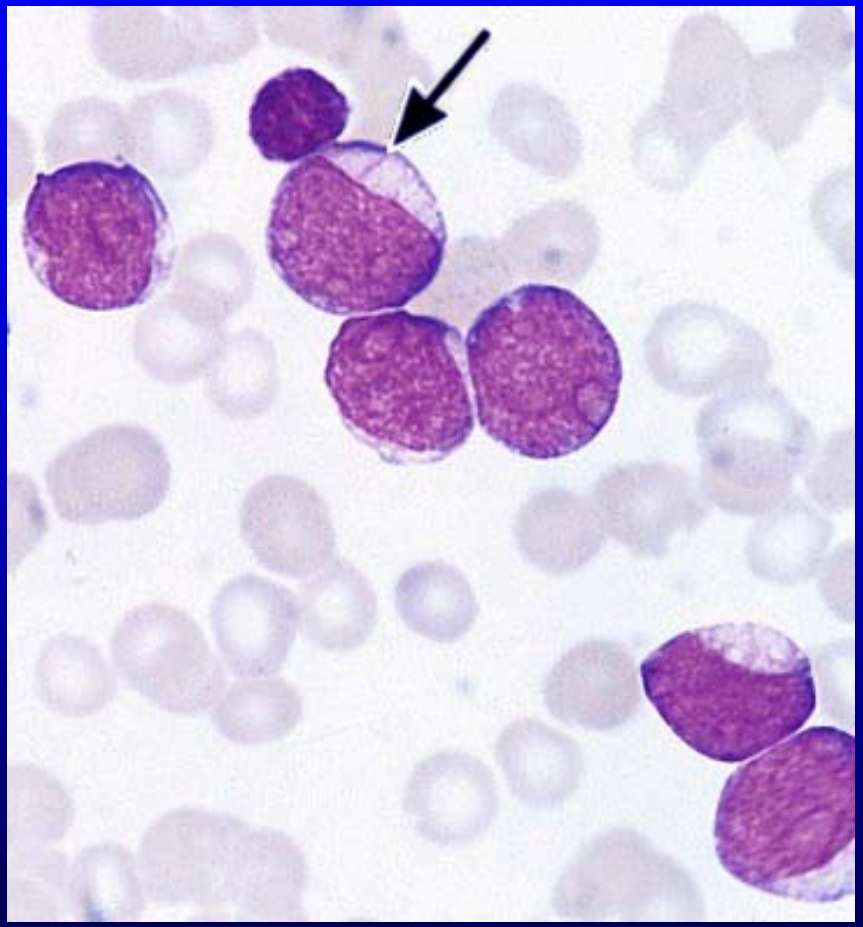


M7



Auer rod in AML

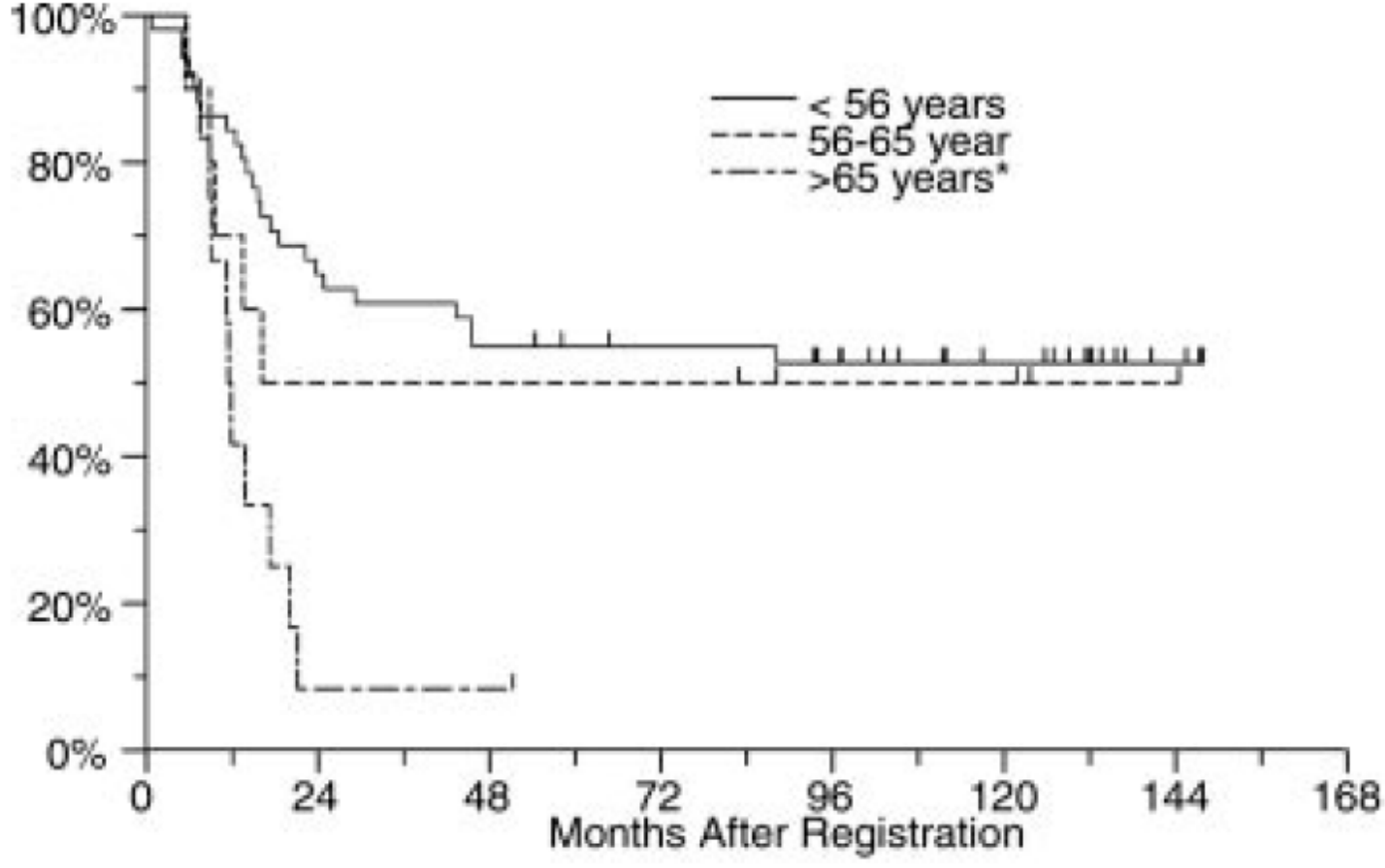
ACUTE LEUKEMIA

Treatment

- Remission induction: aggressive combination chemotherapy (typically anthracycline + cytarabine)
- Post-remission consolidation: high-dose cytarabine x several cycles
- Allogeneic bone marrow transplant in selected patients

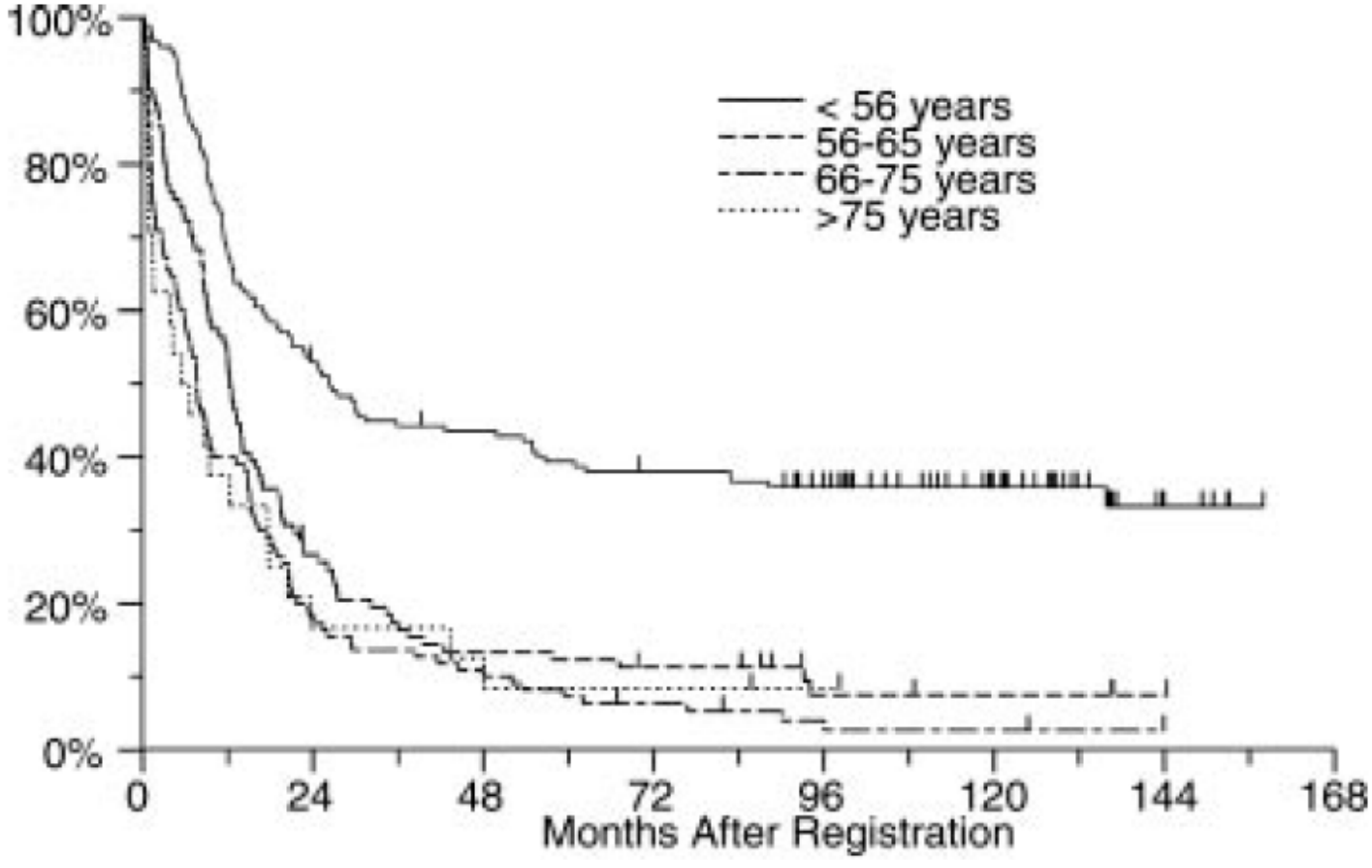
- Cure rates 75%+ in childhood ALL; as high as 50% in "good risk" adults, up to 60% in BMT recipients
- Overall cure rates still low in adults

SURVIVAL ACCORDING TO AGE IN PATIENTS WITH FAVORABLE CYTOGENETICS TREATED FOR AML (Excluding APML)



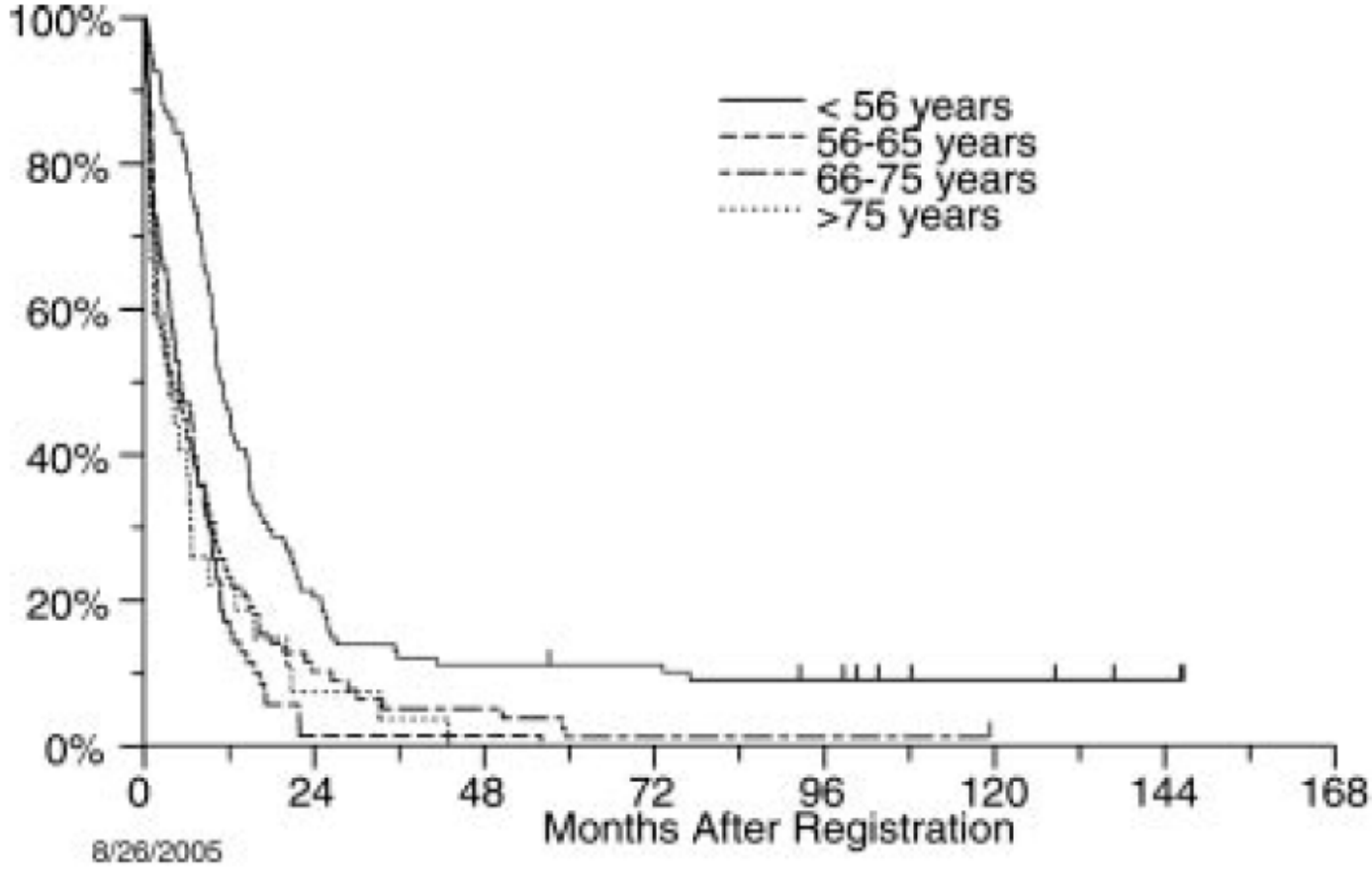
Blood 2006;107:3481

SURVIVAL ACCORDING TO AGE IN PATIENTS WITH INTERMEDIATE CYTOGENETICS TREATED FOR AML



Blood 2006;107:3481

SURVIVAL ACCORDING TO AGE IN PATIENTS WITH UNFAVORABLE CYTOGENETICS TREATED FOR AML



Blood 2006;107:3481

IMPACT OF NPM AND FLT3 ITD MUTATIONS ON RELAPSE RATE AND SURVIVAL IN NORMAL KARYOTYPE AML

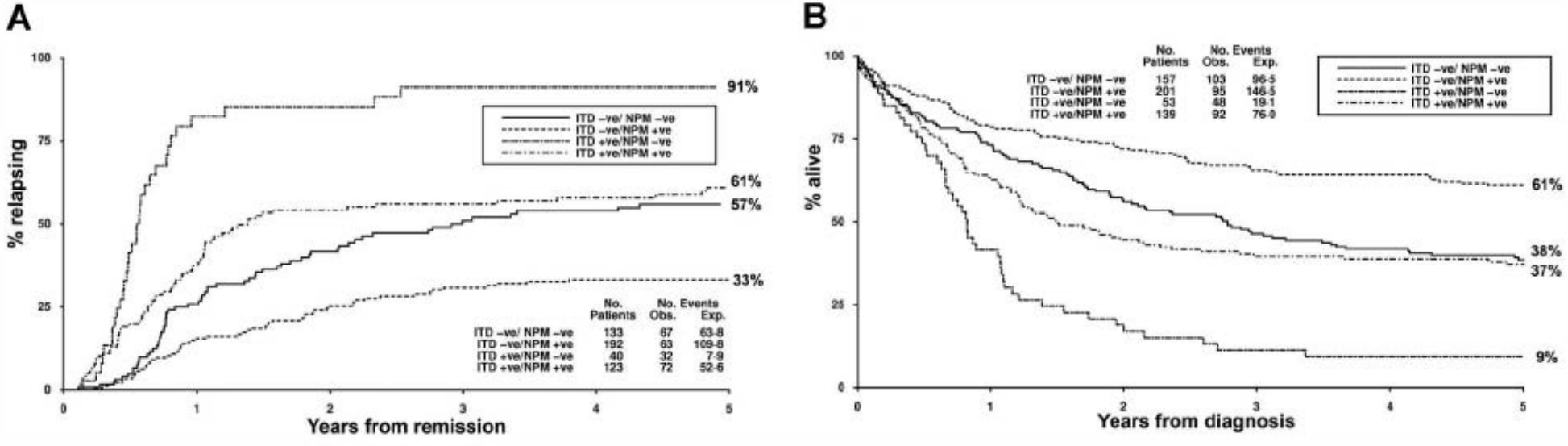
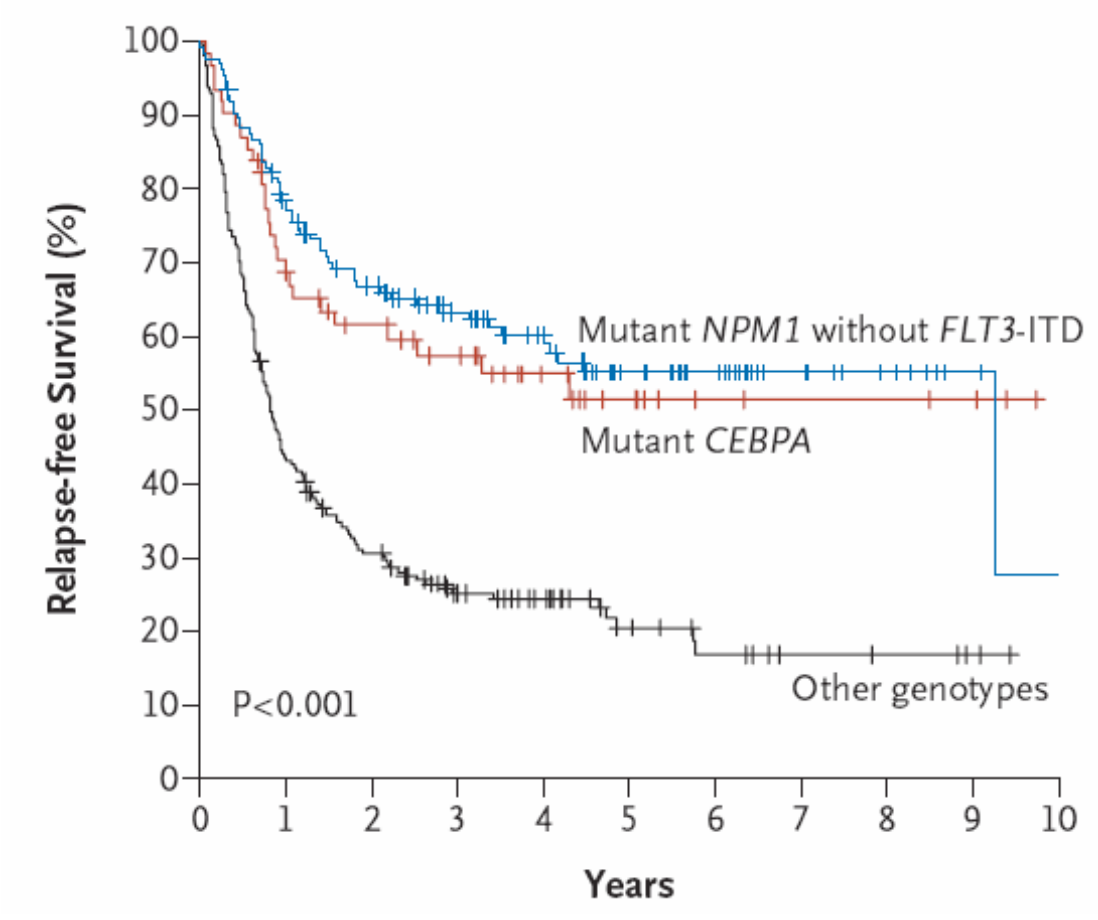


Figure 6. Clinical outcome in 550 patients with a normal karyotype. (A) Relapse rate. (B) Overall survival.

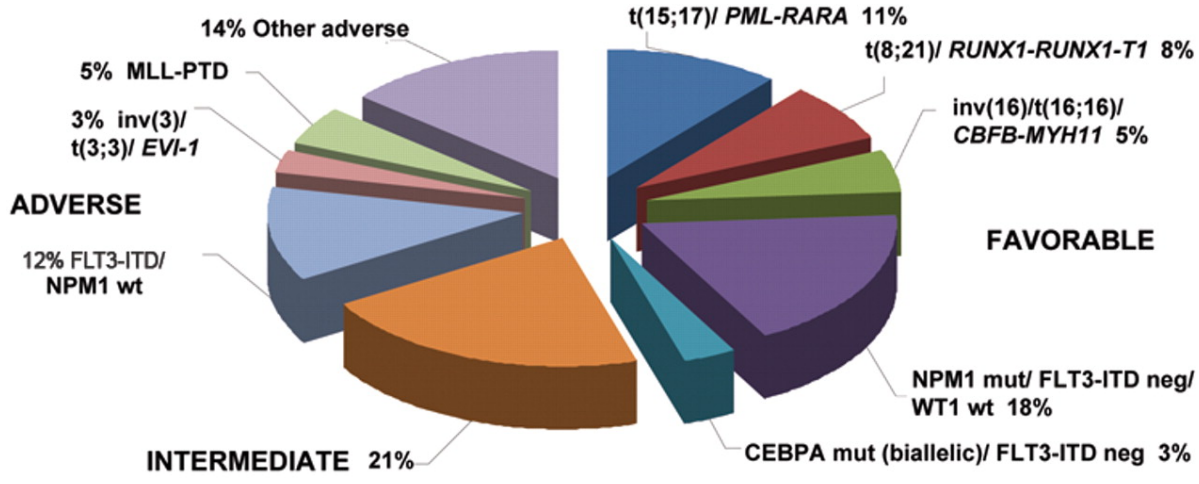
Blood 2008;111:2776

FAVORABLE IMPACT OF NPM1 AND CEBPA MUTATIONS ON SURVIVAL IN AML WITH NORMAL CYTOGENETICS



NEJM 2008; 358:1909

Frequency of prognostically relevant molecular and cytogenetic subgroups of AML arising in younger adults



Hematology 2009;385

EFFECT OF AGE AND PERFORMANCE STATUS ON EARLY MORTALITY IN TREATED AML

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Blood 2006;107:3481