

ACUTE MYELOID LEUKEMIA

What is an Acute Myeloid ? Leukemia

Accumulation of early myeloid progenitors (blast cells) in bone marrow and blood

Definition requests presence of 20% or more blasts in BM

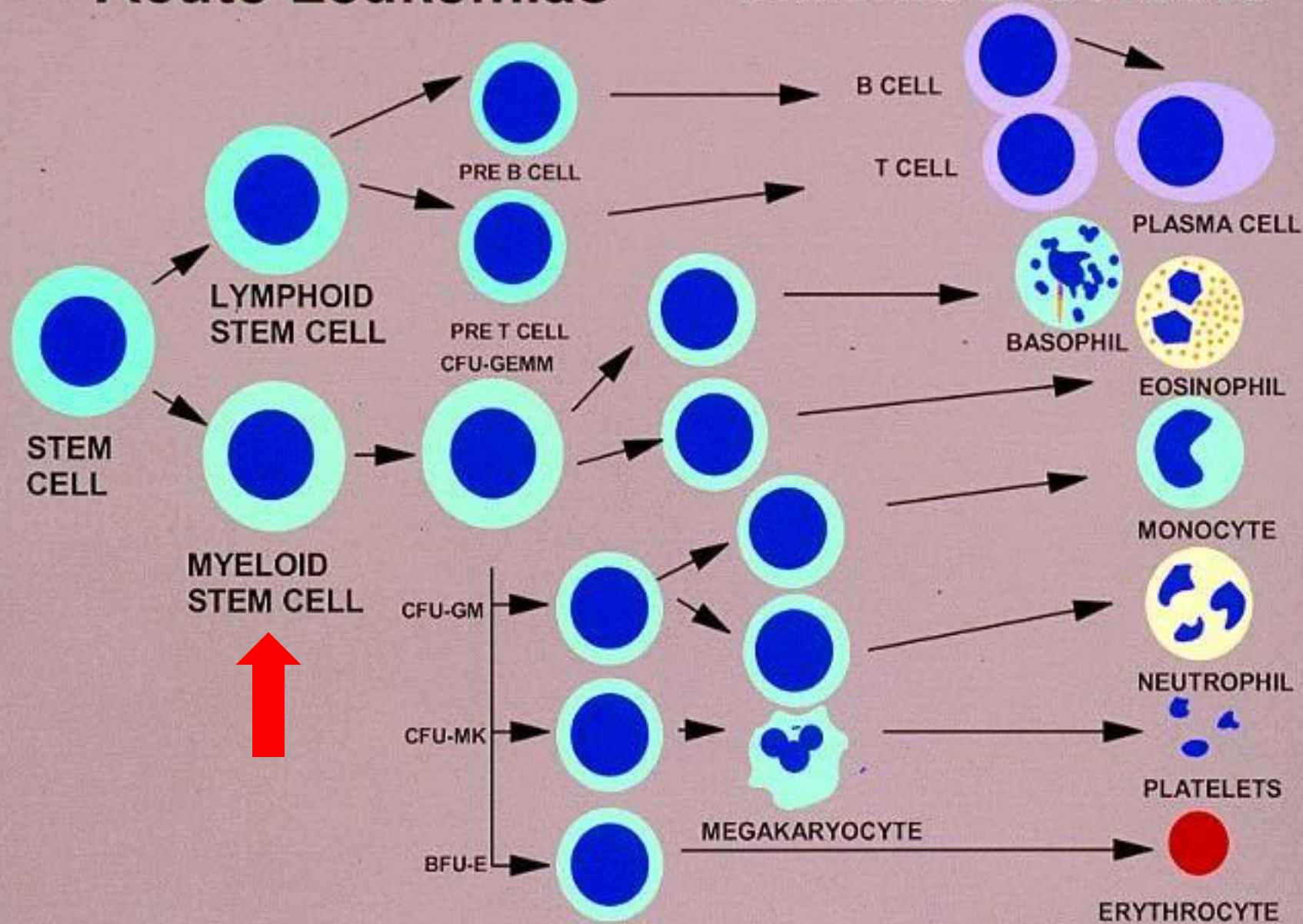
Normally- less than 5%

ETIOLOGY

- Environment: irradiation, chemotherapeutic agents, organic solvents - benzene etc.
- Genetic diseases: neurofibromatosis, Wiscott-Aldrich synd., defective DNA repair - Fanconi, Down synd.
- Acquired disorders: Aplastic Anemia, PNH
- **MOST OF THE CASES APPEAR WITH NO APPARENT RISK FACTORS!!!**

Acute Leukemias

Chronic Disorders



AML

Aggressive disease with an acute onset

Can occur **De Novo**

or

following a known leukomogemic trigger
:(radiation, chemotherapy, diseases)

Secondary AML

Leukemia

Malignant Transformation



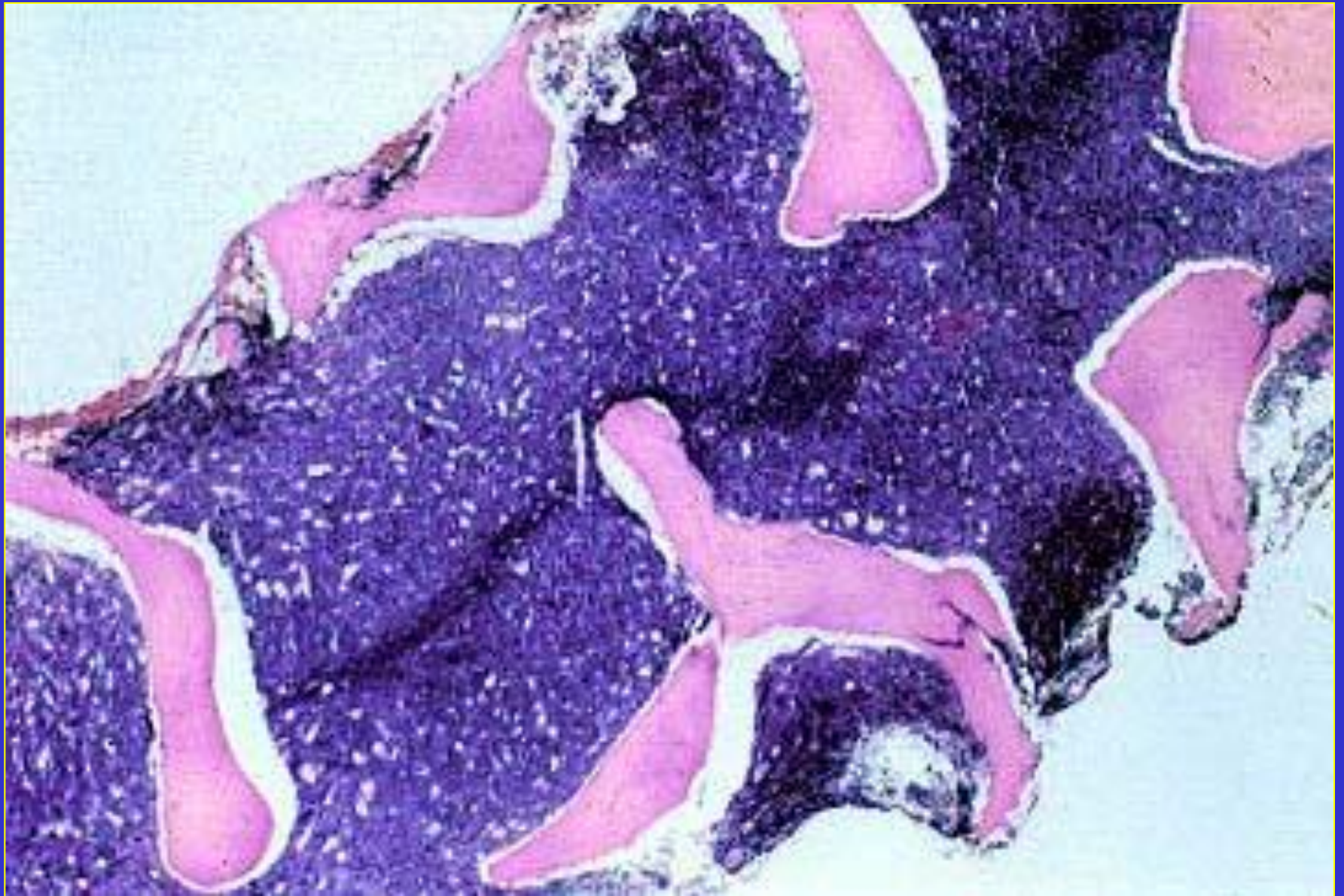
Proliferation and Accumulation



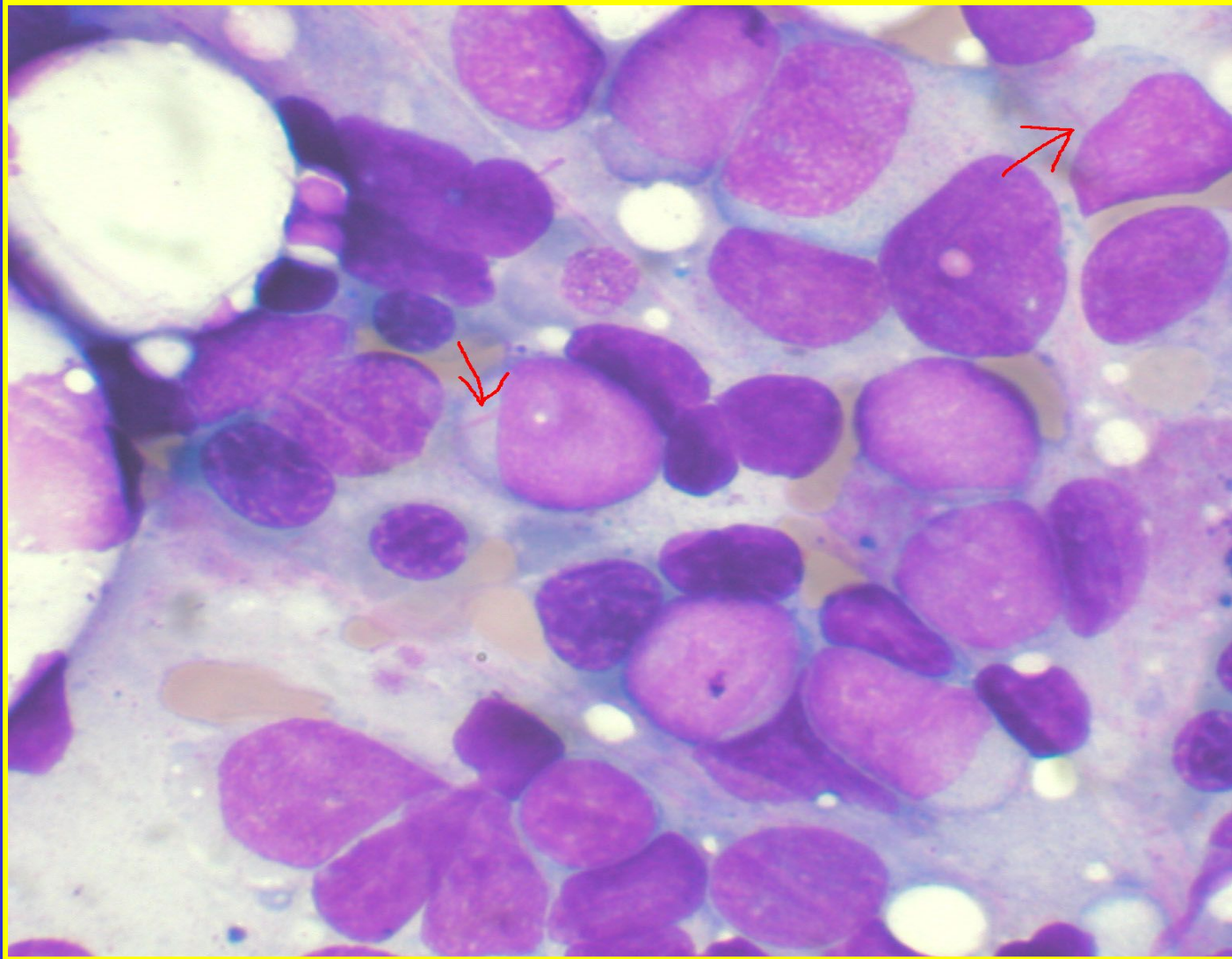
Peripheral blood

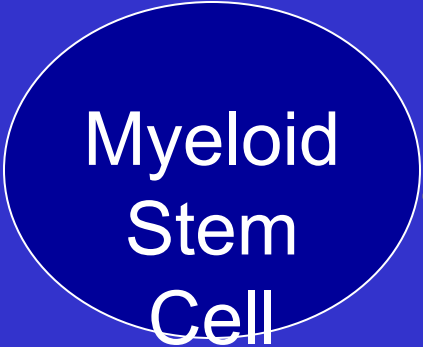
Visceromegalias

BM - Acute Leukemia (low power)



Morphology AML





Myeloid
Stem
Cell

Pathophysiology

Radiation

Chemotherapy

Viruses

chromosomal damage

t(8;21),M2
t(15;17) M3
Inv 16;M4e

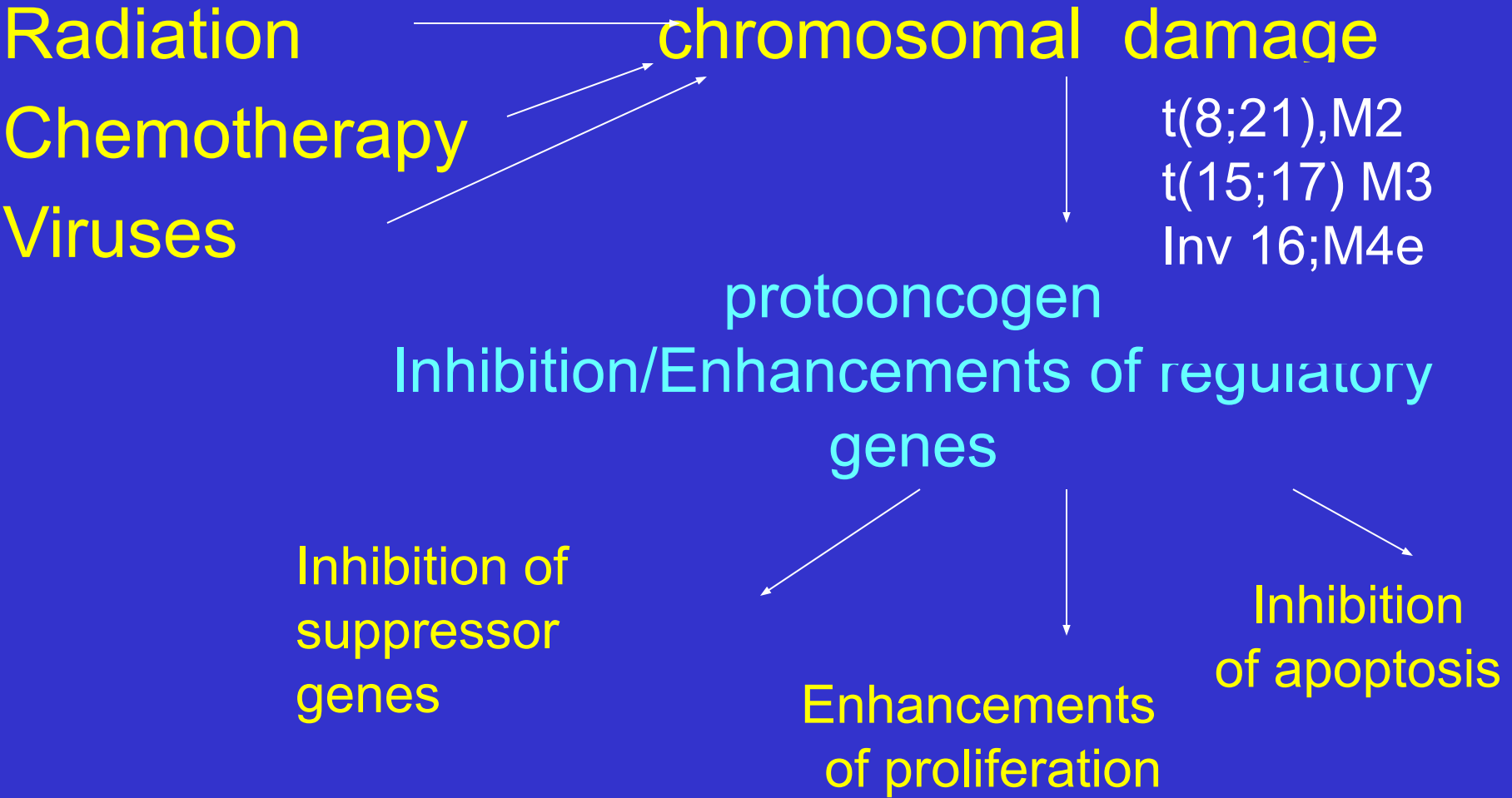
protooncogen

Inhibition/Enhancements of regulatory genes

Inhibition of suppressor genes

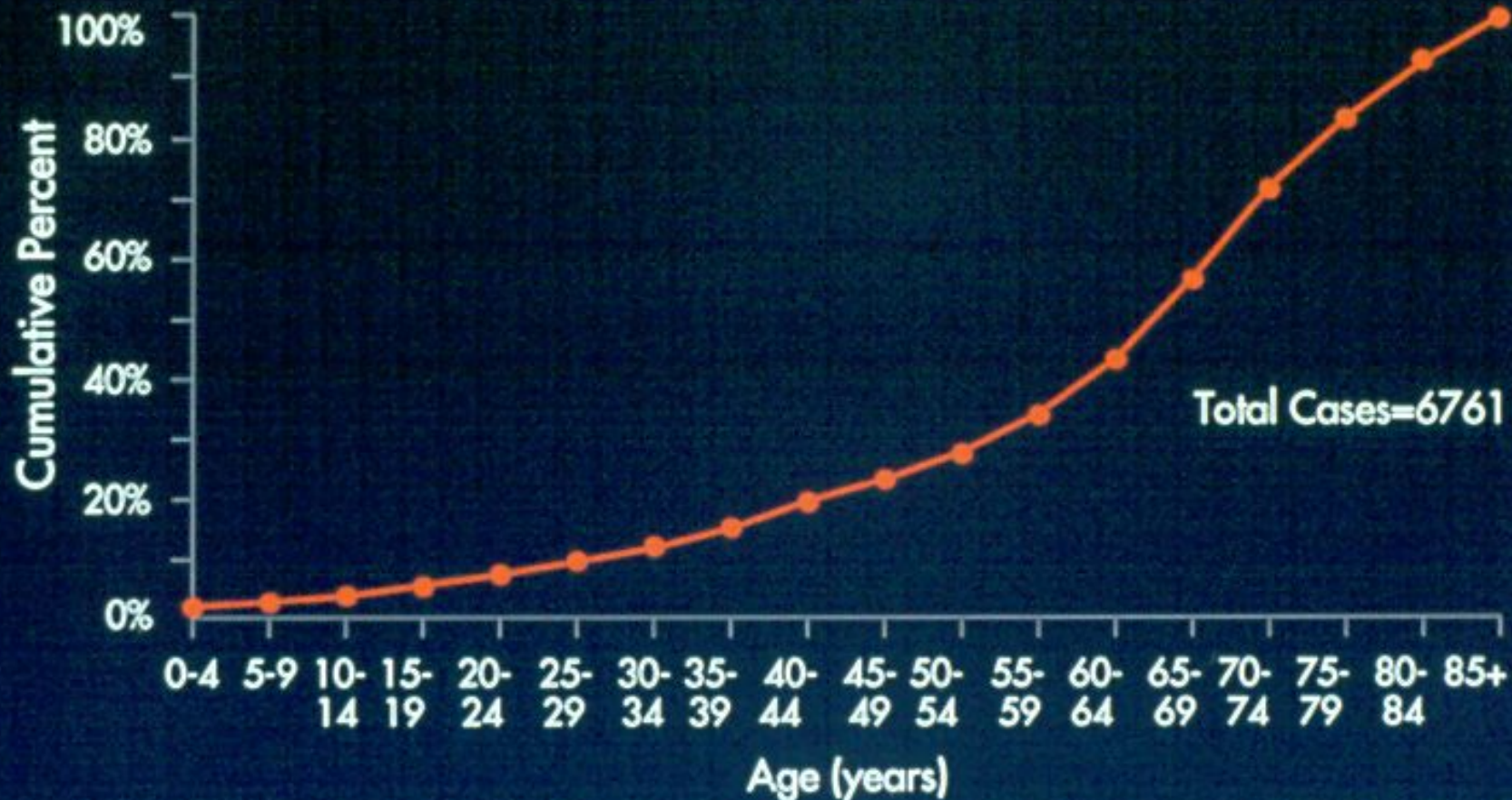
Enhancements of proliferation

Inhibition of apoptosis



Epidemiology

Acute Myeloid Leukemia Annual Occurrence by Five-Year Age Interval 1988 - 1992



Predisposing factors

Environmental Benzen, herbicies

Chemotherapy :AK ; NU;PRC

Radiation

Acquired diseases Meyloproliferative(CML;PV..)

Aplastic anemia

Genetic Congenital abnormality

: *to repair DNA*

Down syndrome

Ashkenazi Jews >> orientals

Relatives(1st degree x3)

Clinical symptoms of Acute Leukemia

Bone marrow expansion

Bone pain

Bone marrow failure

Leucopenia

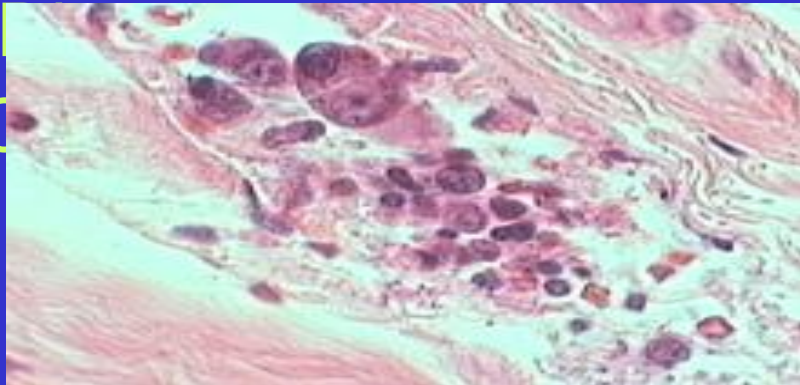
infections

Thrombopenia bleeding

Anemia

Leucostasis

>50,000 blasts



Clinical symptoms

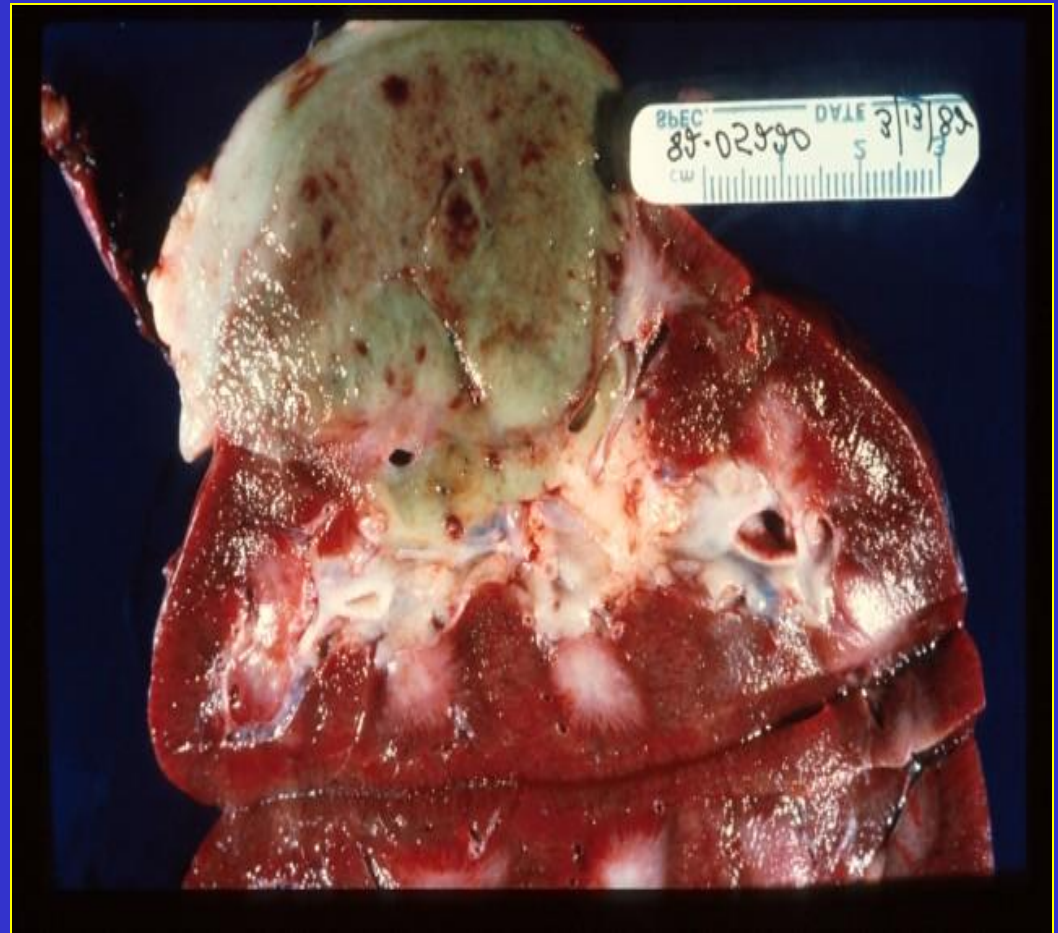
Extramedullary
(Chloroma)

Skin

CNS

Gingiva

Kidney



Extramedullary: Gingival hypertrophy



Clinical symptoms

DIC

Bleeding

Thrombosis

Metabolic

Hyperuricemia

Tumor lysis syndrome

↑ K, ↑ phosphor, Ca↓

↑ Uric Acid

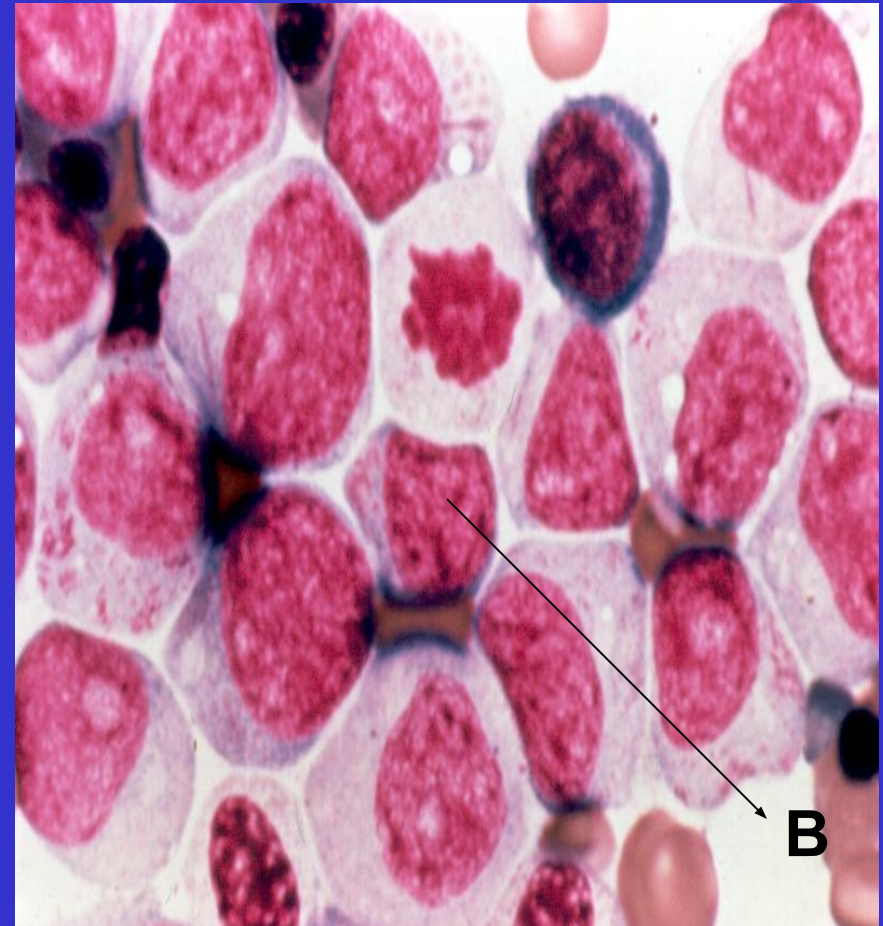
Diagnosis

(blasts in bone marrow/peripheral blood 20% <

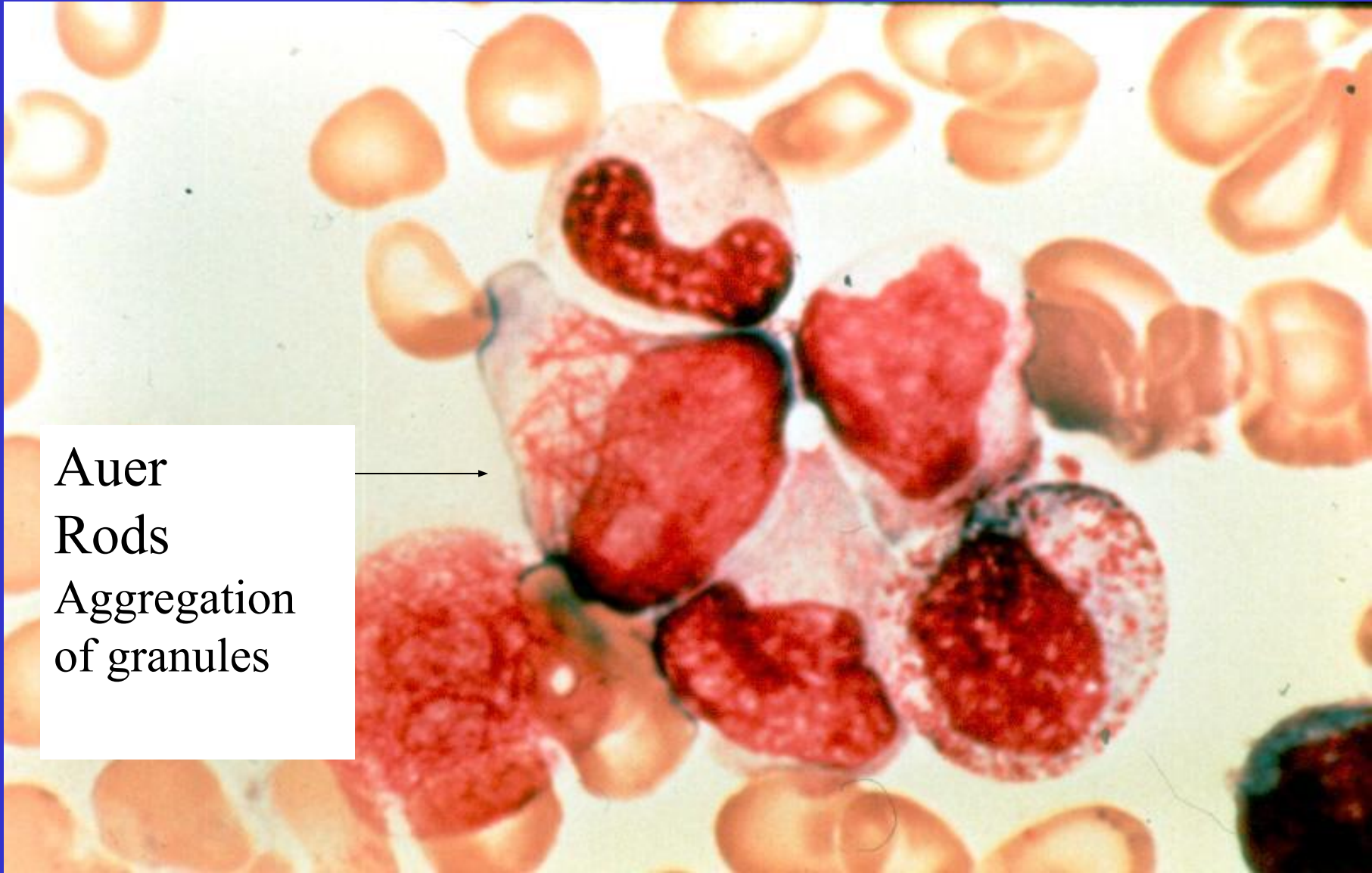
Normal bone marrow



AML ;blasts

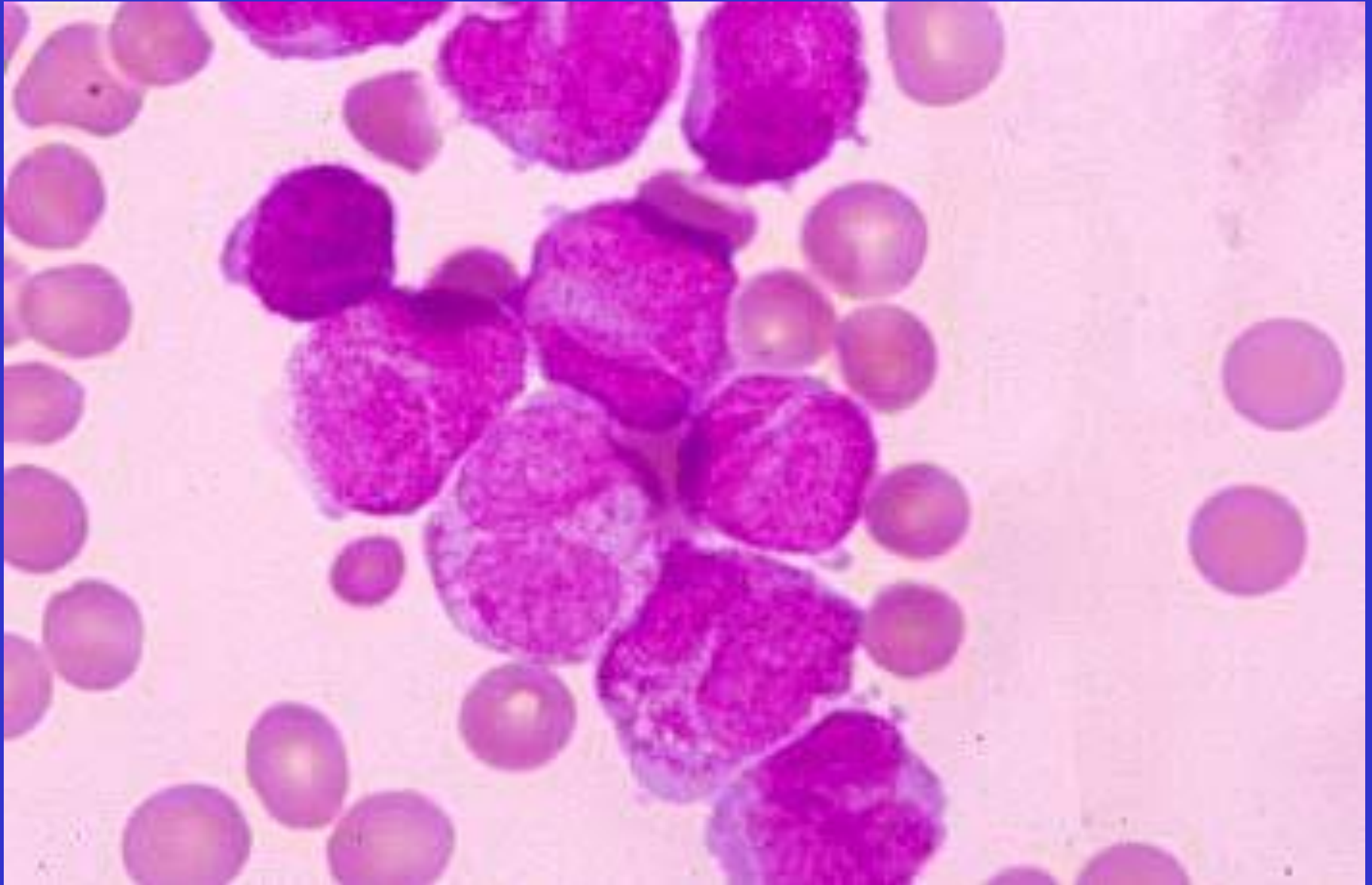


Acute leukemia - AUER Rods (FAB;AML M3)

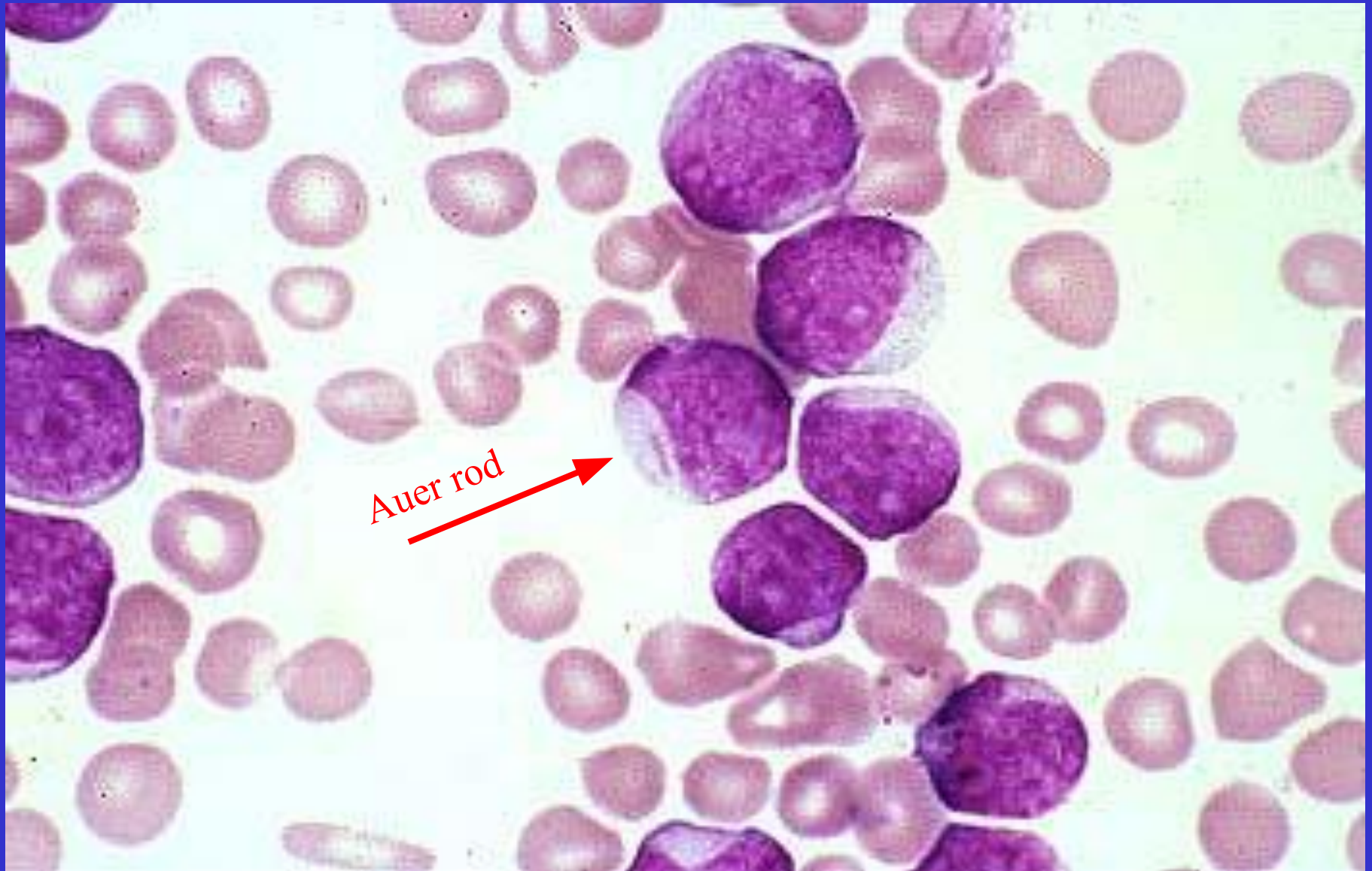


Auer
Rods
Aggregation
of granules

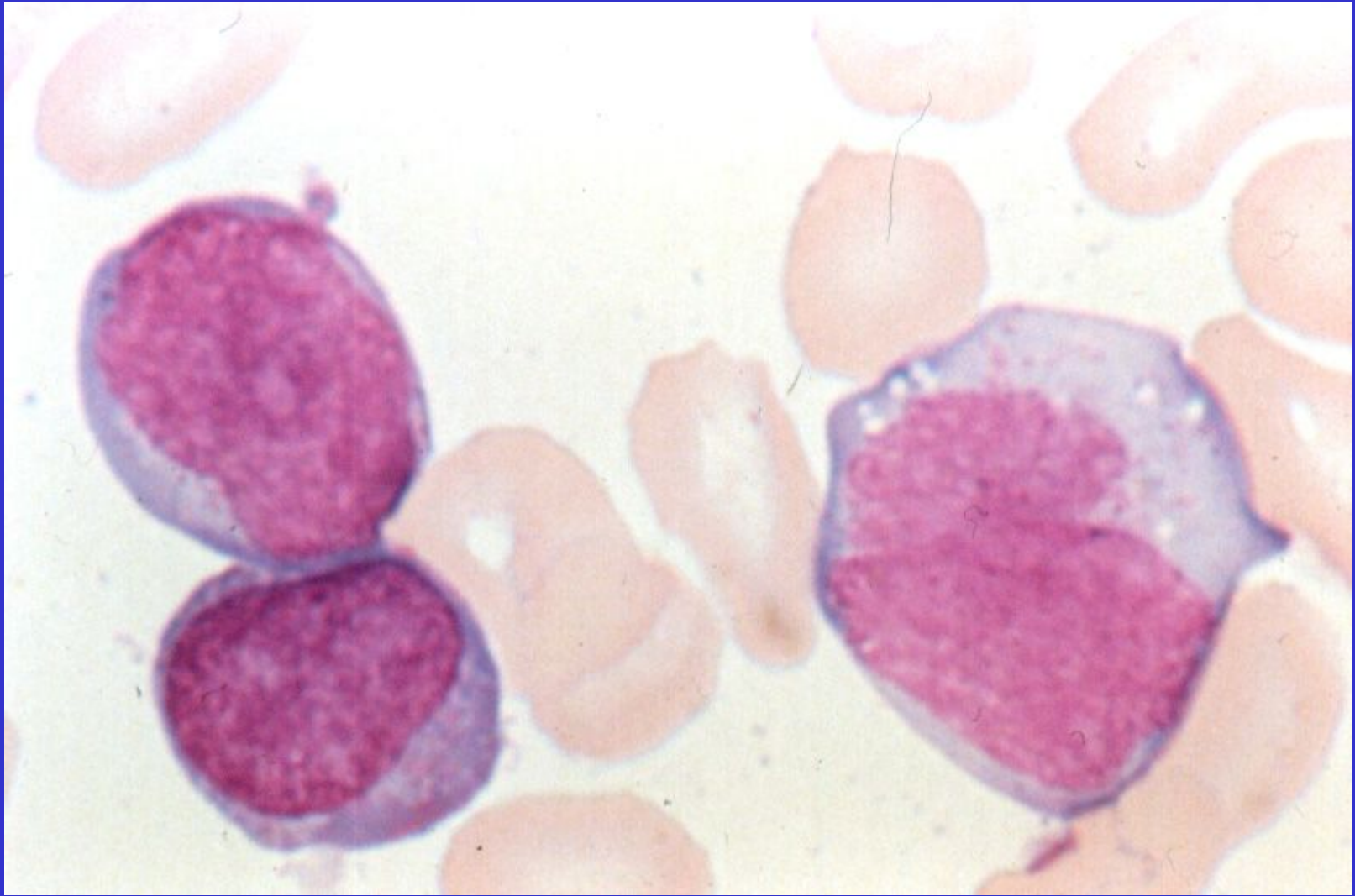
Acute promyelocytic leukemia - AML M3



Myeloblasts - AML



AML M2 blasts



French American British (FAB) classification

Based on morphology and staining-
(cytochemistry)

Divides patients into 7 AML subtypes-

A morphological rather than biological-
classification

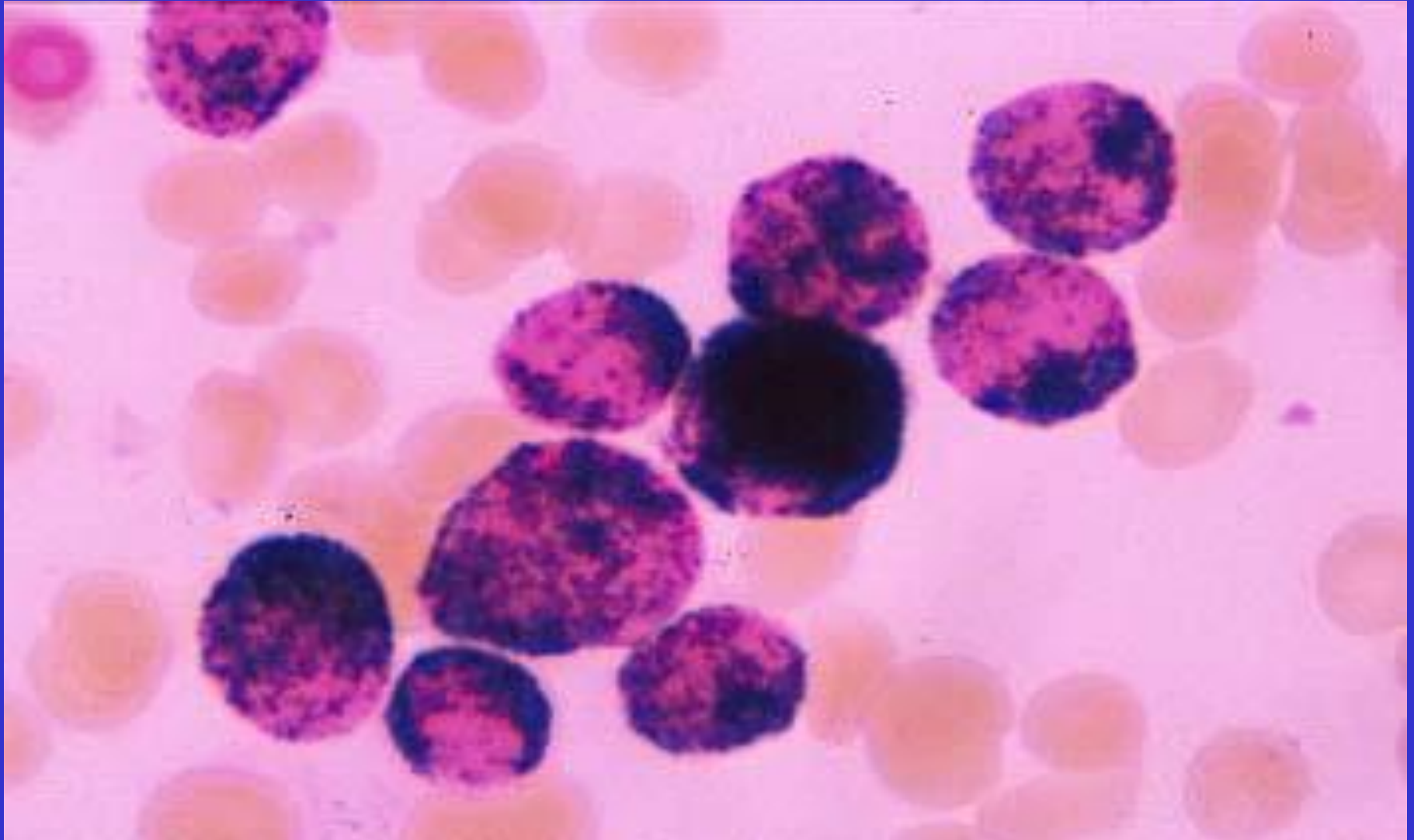
Correlation between morphological and-
biological characteristics may exist , but not
always

AML - WHO classification

- AML with recurrent cytogenetic translocations - M2 with t(8;21), M3 with t(15;17) and variants, M4eo with (inv16), AML with 11q23 abnormalities
- AML with multilineage dysplasia ± MDS
- AML or MDS therapy related (alkylating agents, epidiphylotoxin, other)
- FAB subtypes without other features
- Acute biphenotypic leukemia

Cytochemistry

Myeloblasts - myeloperoxidase positive



Diagnosis

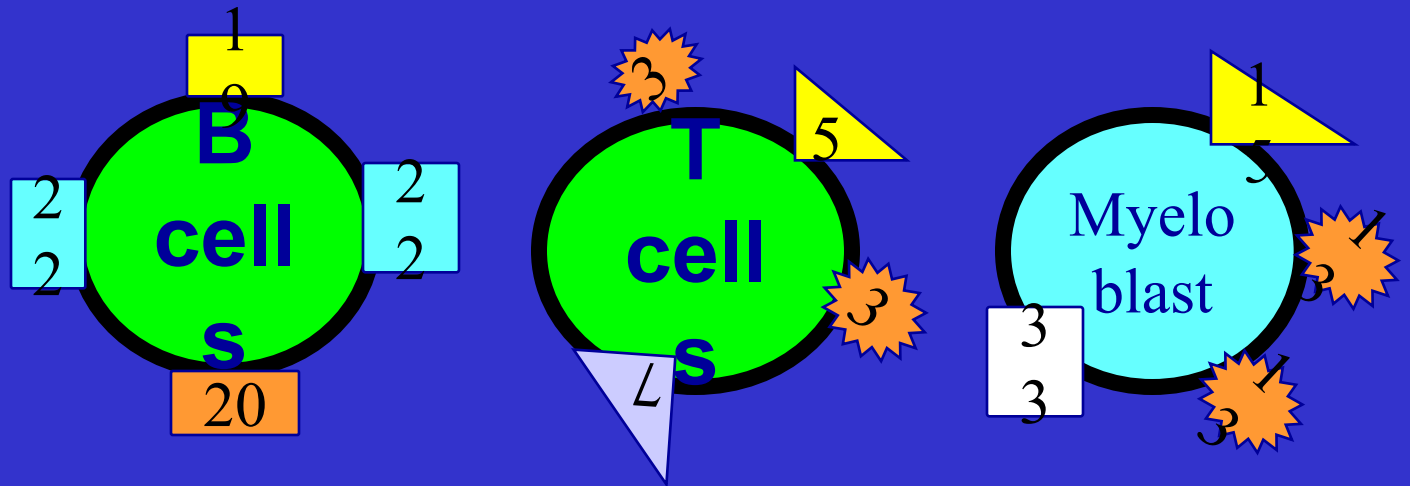
Diagnosis : >20% blasts in BM

: Cytochemical stains

- ALL TdT +, MPO

O

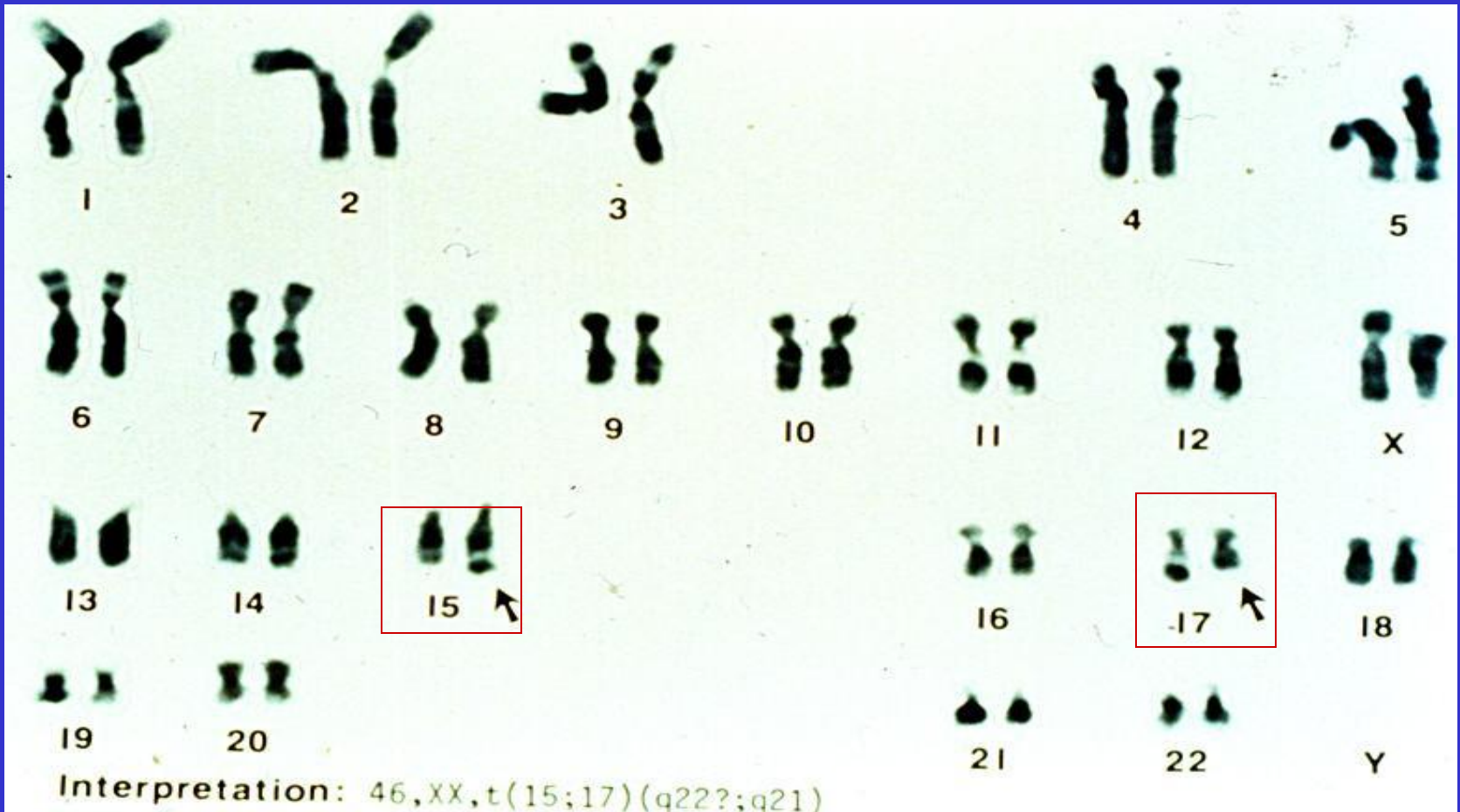
FACS



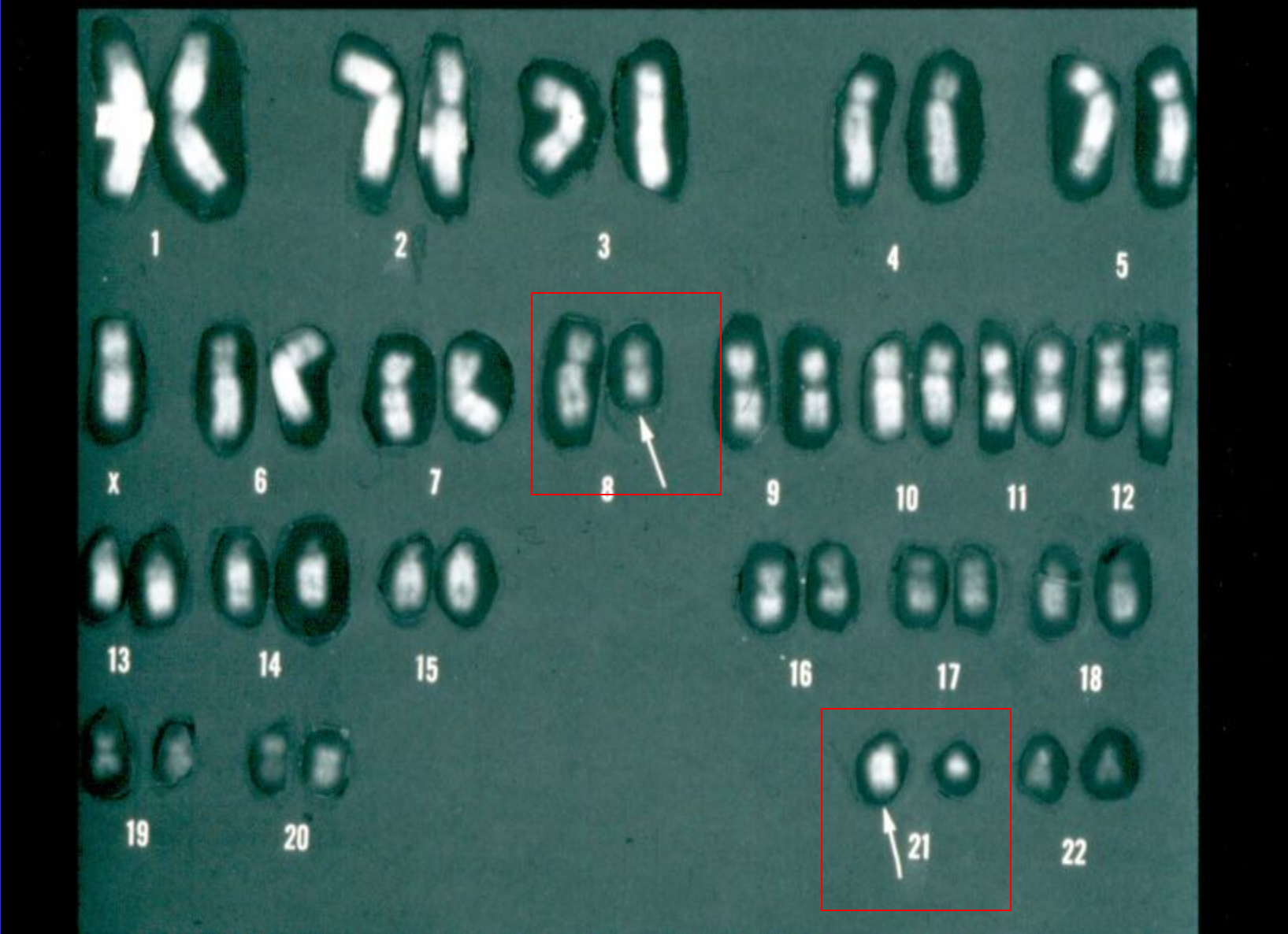
Classified into subgroups based on cell surface markers and cytogenetics

Diagnosis : Karyotype, cytogenetics

chromosomal abnormalities: M3

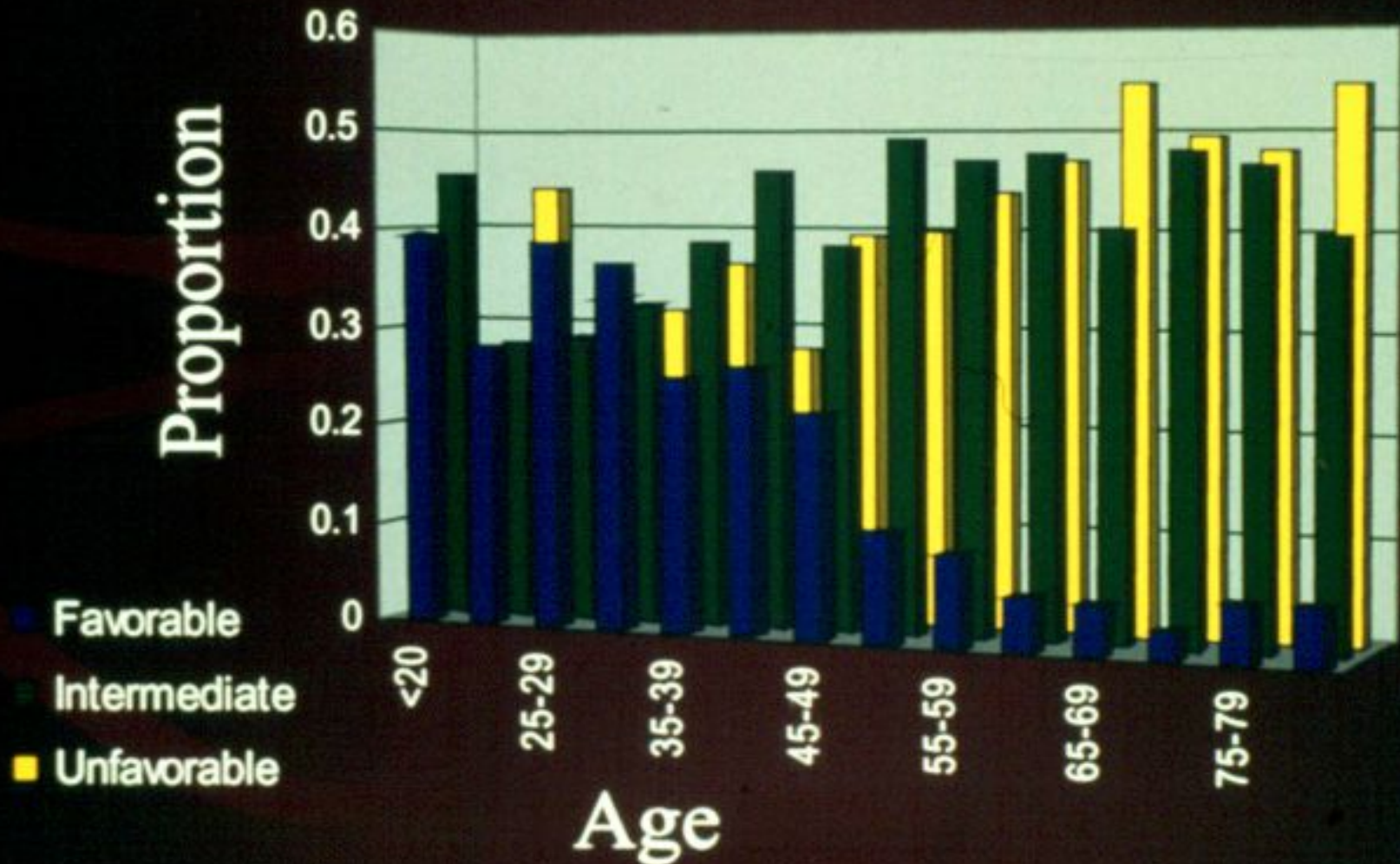


AML M2



Chromosomal abnormalities (cytogenetics)

Frequency of Cytogenetic Findings by Age



Prognosis Risk factors

Cytogenetics

Flt-3 mutation

Age

White blood cell count at presentation

FAB classification

De-novo /secondary

Response to first course of chemotherapy

Cytogenetic Classification

SWOG

MRC ; As for SWOG,

except:-

Favorable

t(15;17)
Inv(16)
t(8;21)-

t(8;21) — \pm other
abnormality

Intermediate

+8
normal
karyotype

11q23
del(9q), del(7q) — alone
Complex karyotypes (> 3 abn,
but
 < 5 abn)

Unfavorable

-5/del(5q), -7/del(7q),
inv(3q), 11q23, 20q,
21q, del(9q), t(6;9)
t(9;22), 17p,
Complex (> 3 abn)

All abnormalities of unknown
prognostic significance

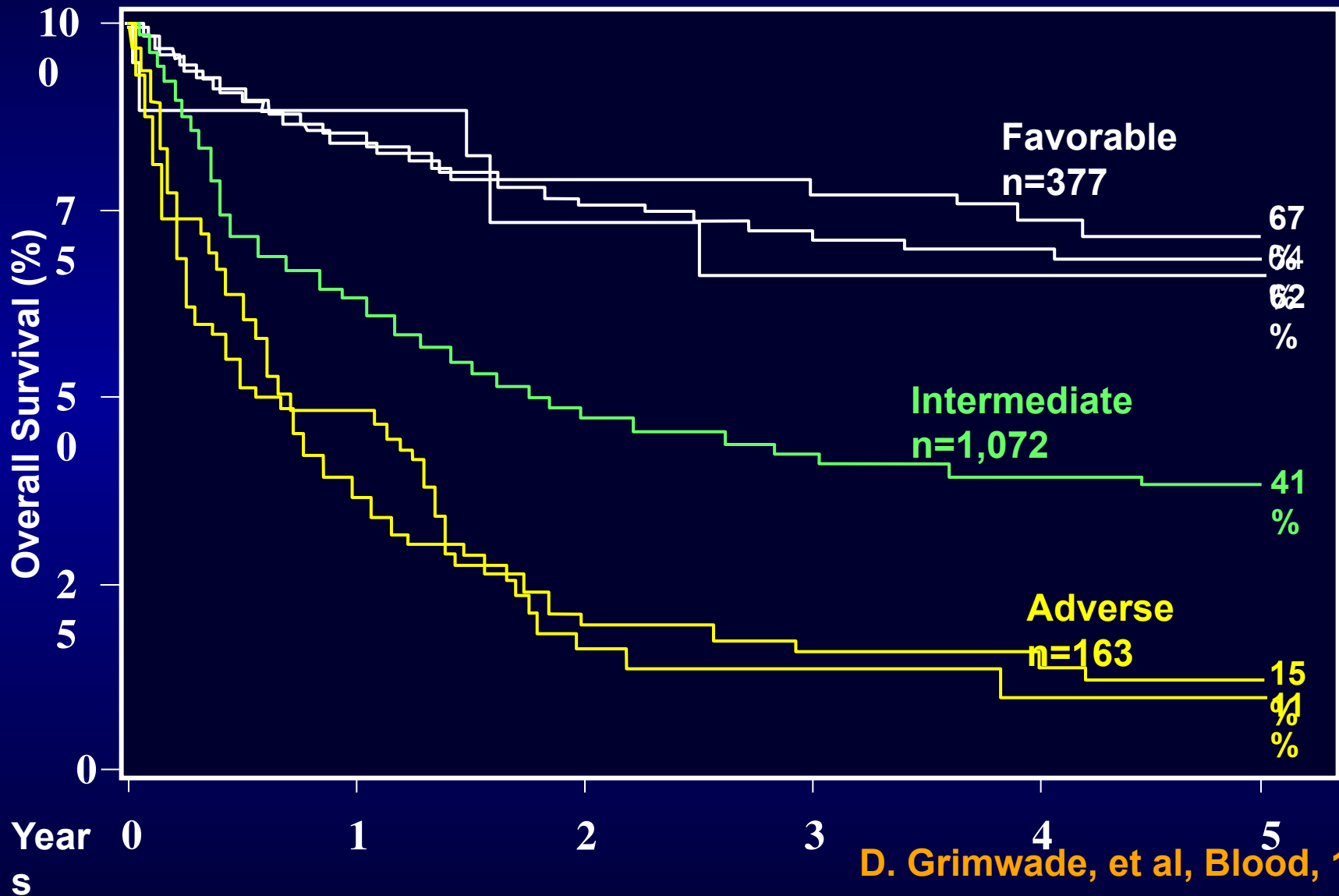
Complex karyotypes (> 5
abn)

Unknown

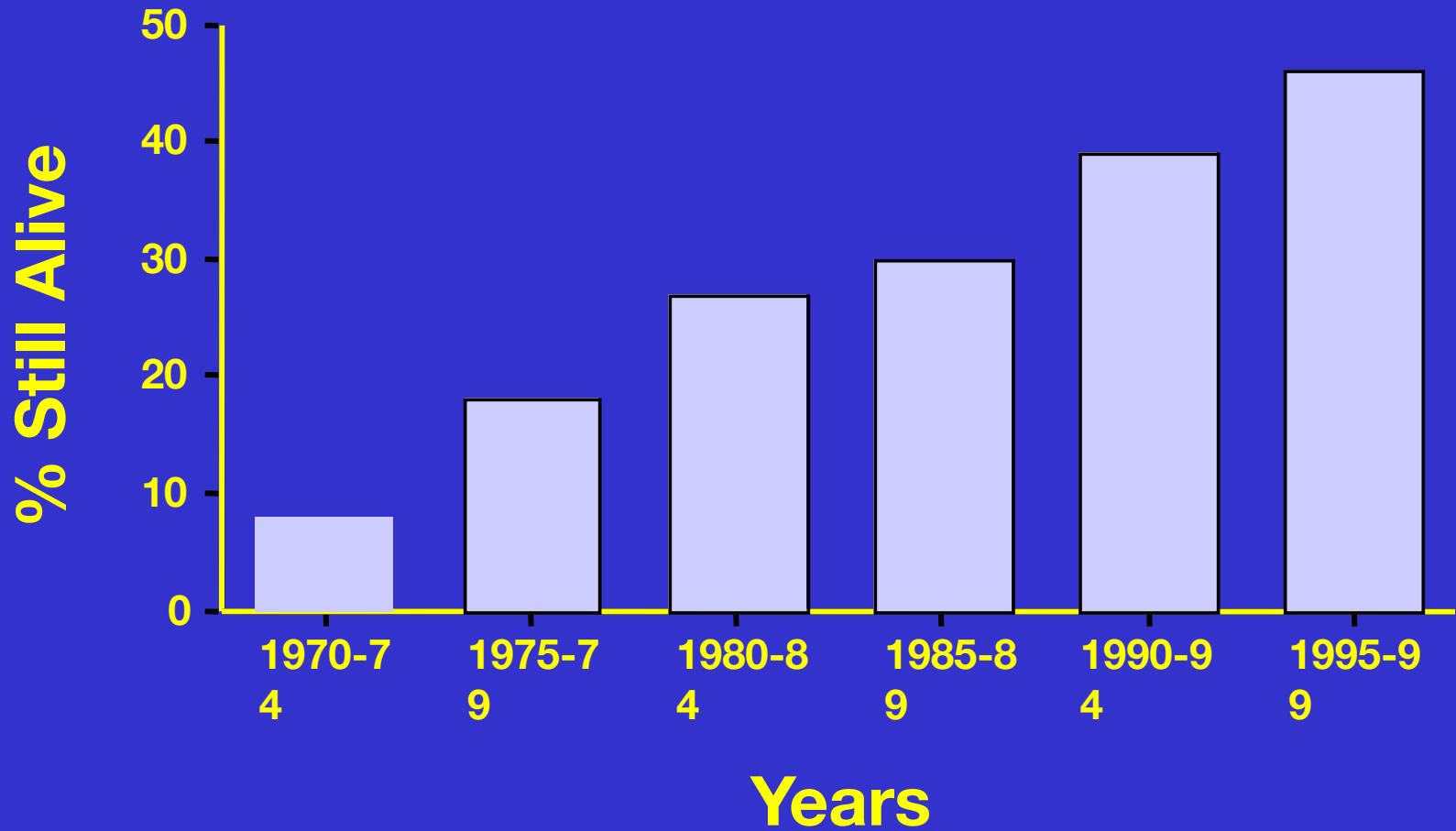
All other clonal chromosomal
aberrations with less than 3

abn

Cytogenetic and prognosis



Treatment



Treatment of acute leukemia (I)

: Supportive care

Hydration

Allopurinol to prevent hyperuricemia

Cytapheresis

Blood products

: Patient workup

History for occupational exposure or exposure

Bone marrow aspiration and biopsy

Bone marrow sample for cytogenetic, FACS, PCR

Treatment in the Younger AML Patient <60yrs

**Course I of chemotherapy
INDUCTION**

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graph TD; A[Course I of chemotherapy INDUCTION] --> B[Intensive Chemotherapy]; A --> C[Allogeneic Stem Cell Transplantation]; A --> D[Autologous Stem Cell Transplantation];
```

**Intensive
Chemotherapy**

**Allogeneic
Stem Cell
Transplantation**

**Autologous
Stem Cell
Transplantation**

Outcome at 5 years

Allo

Chemotherapy

Relapse

20-30%

40-60%

Overall survival

50%

50%

TRM

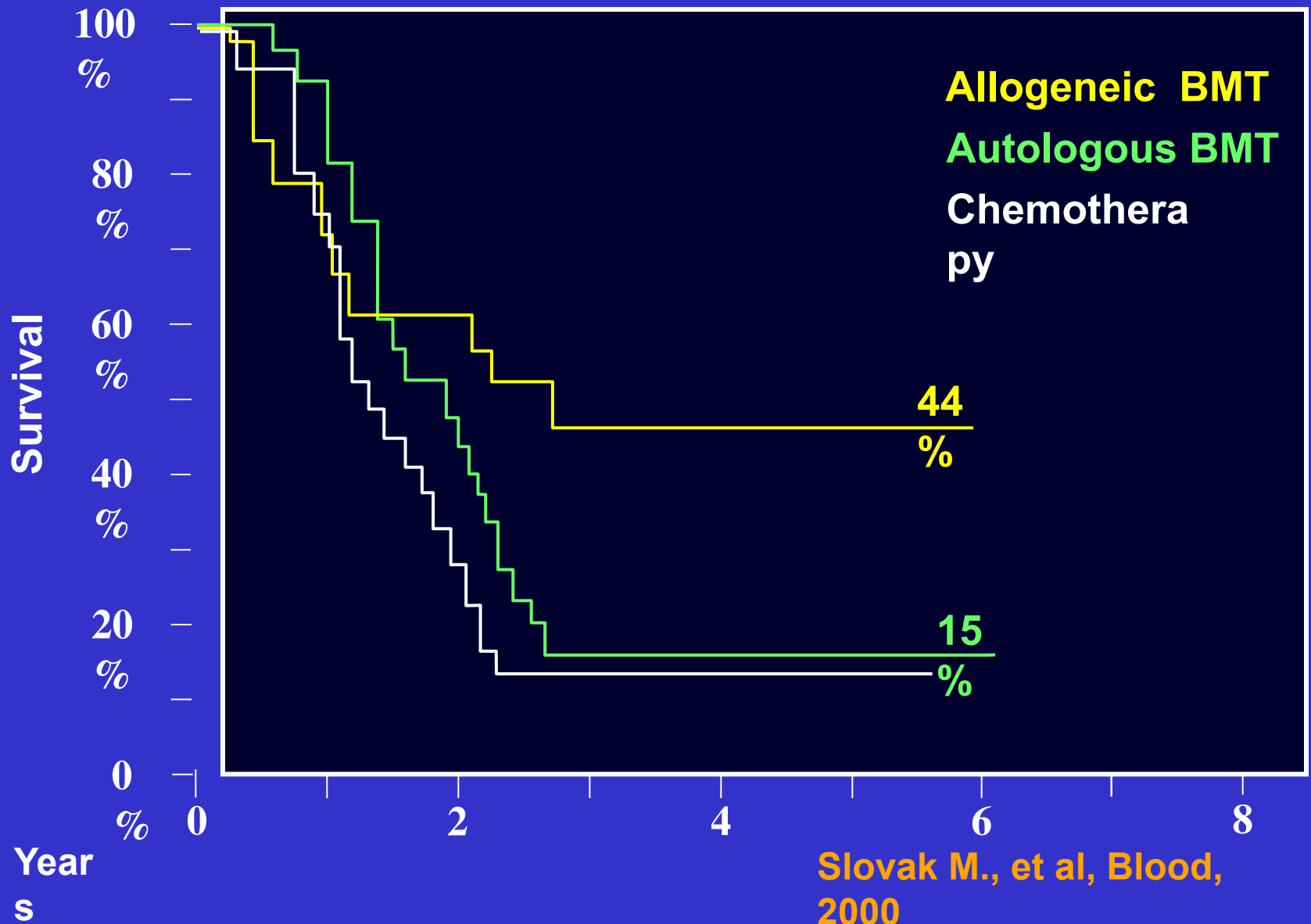
20-30%

5%

So how to choose which therapy
?to a specific patient

use the prognostic factors
to estimate
relapse rate and survival

Unfavorable Cytogenetics



?What is the best treatment

Who should have a
matched related Allo
? SCT

Patients with poor risk
and standard risk younger than
35/40 years in CR1

Patients in CR2 or beyond

Who should have an
?Auto SCT

Favourable/standard risk
patients who relapsed,
responded again to
chemotherapy and have no
matched donor

? Patients in CR1

AML in Elderly patients(>60 years)

The majority of the patients are older than 60

Lower remission rate

Higher treatment-related morbidity & mortality

Very poor outcome

higher frequency of poor risk cytogenetics & resistance to chemotherapy

Future directions

Identify new prognostic factors

New therapies : Modulation of drug resistance

:Biological, specific treatments

Monoclonal antibodies

ATRA in APL, t (15;17)

Summary

The majority of patients still die of their disease
(significantly poor outcome in elderly patients)

:Further improvement is needed

Better ability to predict patients outcome

Tailoring treatment to patient's risk factors

Improving therapy & supportive care

New strategies for elderly patients

Suggested Reading

Hoffbrand Hematology

Williams Hematology

Harrison's Text book of Internal Medicine

