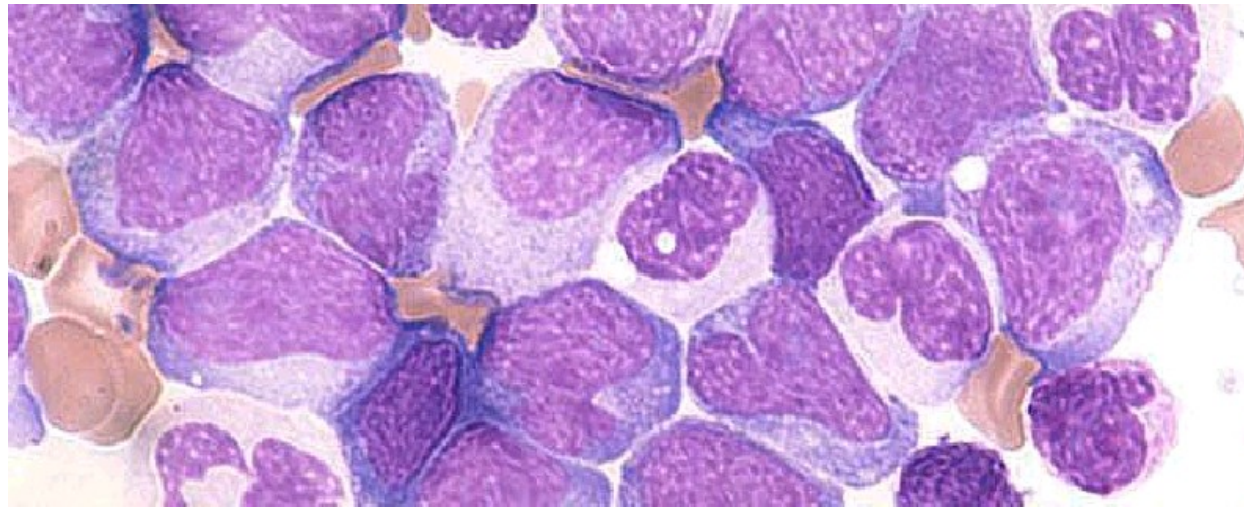


HEMATOLOGIC MALIGNANCIES



Interní hematologická a onkologická klinika
FN Brno a LF MU
Department of Internal Medicine, Hematology and Oncology,
University Hospital Brno
and Masaryk University, School of Medicine

MUNI
MED



CELL
the Czech leukemia
study group for life

 CEITEC

Hematologic malignancies

Origin – hematopoietic cells

According to blood lineage

- lymphoid malignancies**
- myeloid malignancies**

Diseases

- Leukemias**
- Lymphomas a lymphproliferative diseases**
- Myeloproliferative diseases,
myelodysplastic syndromes**

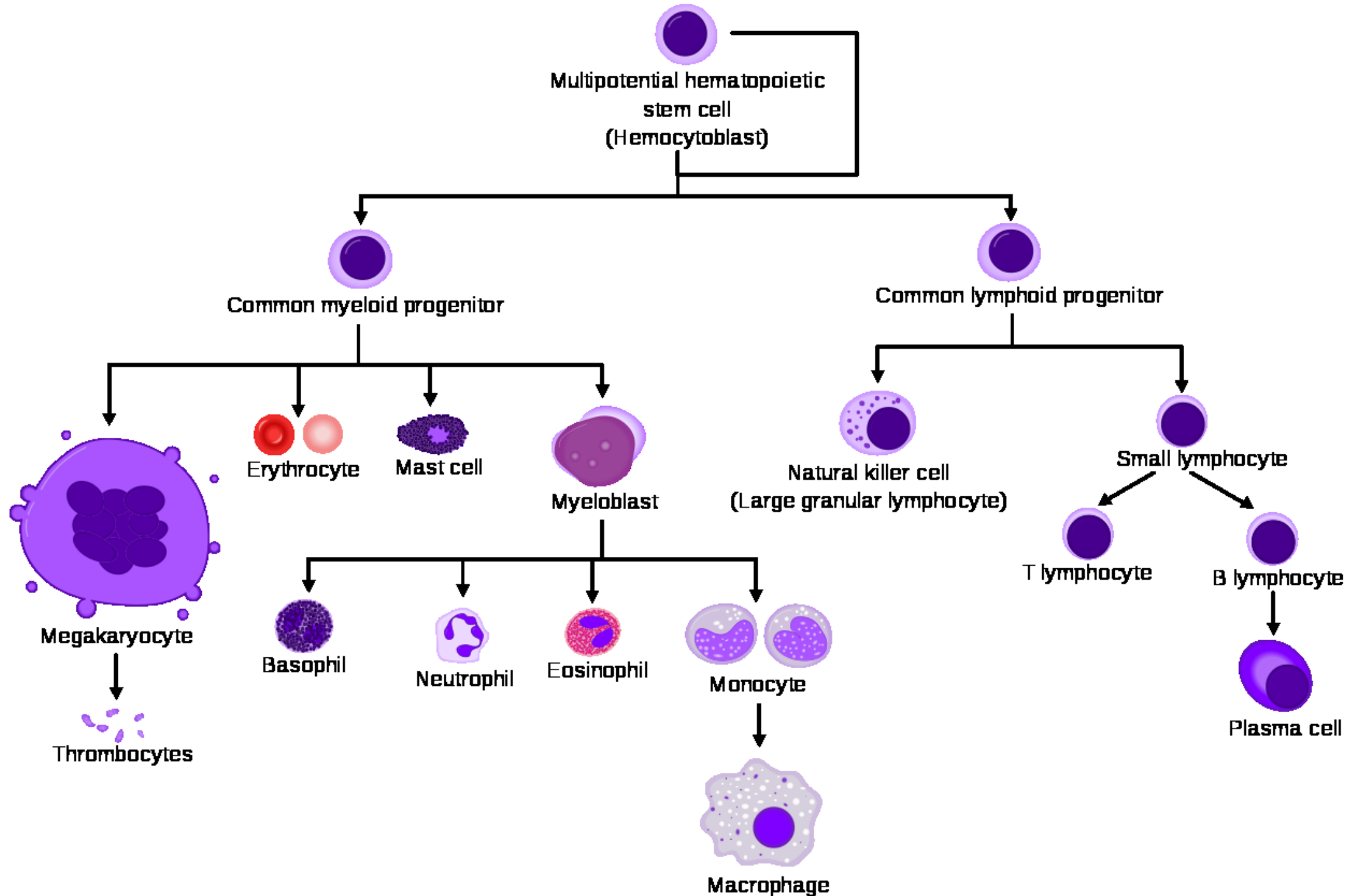


Figure S.2: Relative Frequencies of New Cancers Diagnosed Among Minnesota Females 1992-1996

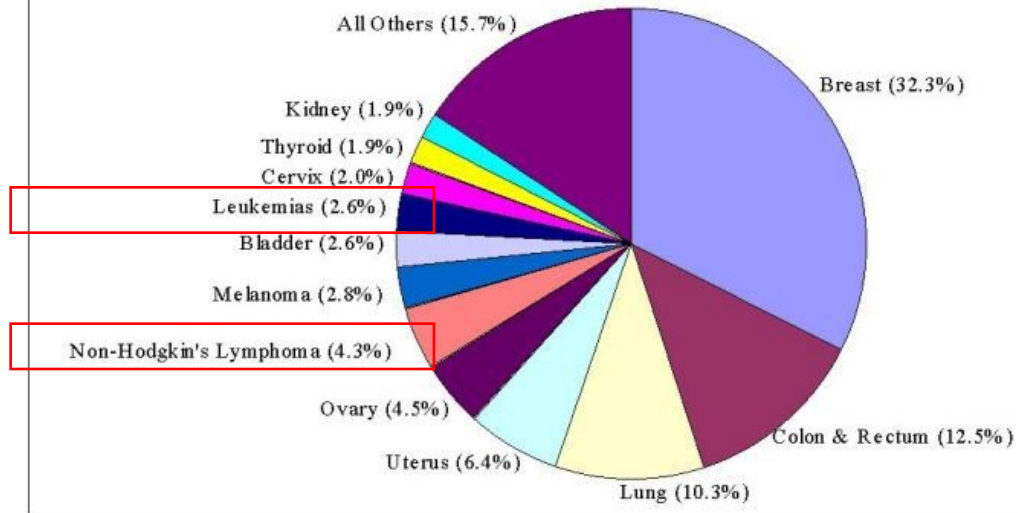
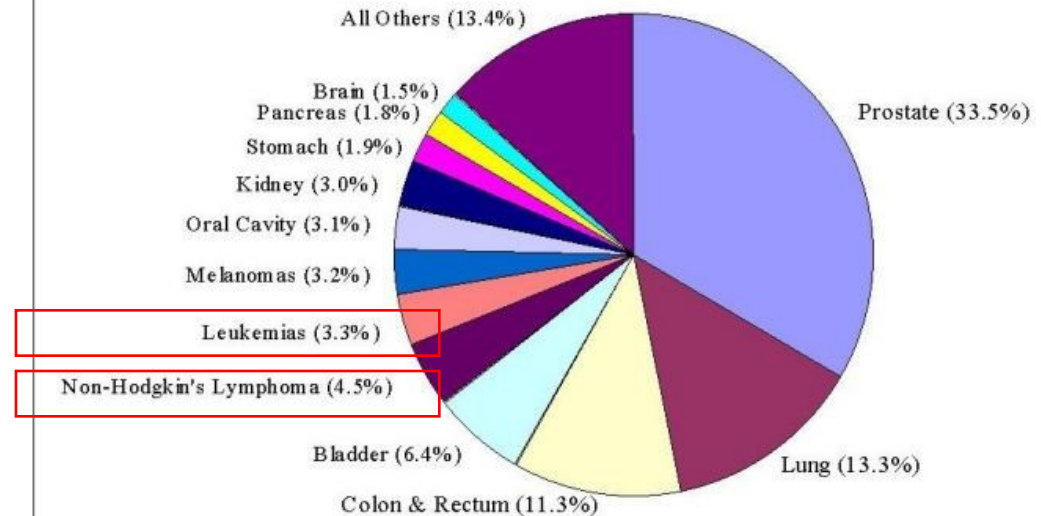


Figure S.1: Relative Frequencies of New Cancers Diagnosed Among Minnesota Males 1992-1996



Hematologic malignancies

CLONAL

disorders resulting from a mutation of DNA within a pluripotent marrow stem cell or very early progenitor cell.

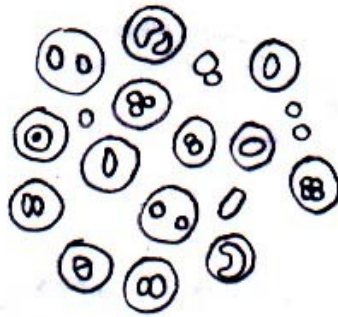
CLONAL POPULATION OF CELLS - cells with growth and/or proliferation advantage over against normal bone marrow cells.

Mutation of DNA can result in the expression of fusion genes that encode fusion proteins that are oncogenic or in the underexpression of genes that encode molecules critical to control of cell growth or programmed cell death.

Symptoms

- **Similar**
- **Often non-specific**
- **Bone marrow involvement (leukemia, myeloproliferative neoplasms)**
- **Lymphoid tissue involvement (lymphoma)**

Leukemia



John Hughes Bennett: Two Cases of Disease and Enlargement of the Spleen, in which death took place from presence of purulent matter in the blood, 1845

Heilkunde.

Weißes Blut.

In den älteren Schriftstellern finden sich hier und da Beobachtungen über Blut, das seine Farbe so vollkommen verloren hatte, daß es der Milch, dem Ehylus, Schleime (pituita) oder Eiter verglichen wurde. (Haller, Elem. physiol. 1760. Tom. II. p. 14–16.) Die Mittheilung des folgenden Krankheitsfalles wird diese scheinbar fabelhafte Angabe bestätigen.

Krankheitsgeschichte. (Auszug aus dem auf der Abtheilung geführten Journal.) Marie Straide, Köchin, 50 Jahre alt, wurde am 1. März d. J. in die Charité aufgenommen. Nach ihrer Aussage hatte sie vor einem Jahre bei

sten von Neuem zunahm, ohne jedoch je mit Brustschmerzen verbunden zu seyn. In den letzten 8 Tagen waren endlich wieder sehr zahlreiche, zum Theil blutige Durchfälle aufgetreten. Bei der Aufnahme leichtes Erbrechen der unteren Extremitäten; Leib voll, aufgetrieben, fluctirend, bedeutende Vergrößerung und wässrige Schmerzhaftigkeit der Milz; häufiger, anhaltender Husten mit reichlichen geballten Sputis, Koffelgeräusche auf der Brust; Appetit und Zunge gut; Puls 78 Schläge machend; Harn sparsam; große Erschöpfung. (Inf. Colombo c. linot. Cascarill. et Tinet. theb.). — In den nächsten Tagen bessert das Befinden sich der Durchfall nimmt ab, es stellt sich endlich Stuhlverstopfung ein (Inf. Rhei c. Mell. Tarax.). Neue Diarrhöe (Emuls. comm. c. Aq. Amygd. amar.).

II. Weißes Blut (Leukämie).

Es giebt gewisse Wahrheiten, welche sich in der Wissenschaft nur sehr langsam und schrittweise Geltung verschaffen. So scheint es meinen Mittheilungen über weißes Blut (d. h. eine Vermehrung der farblosen Blutkörperchen in dem Maasse, daß die rothe Farbe des Blutes dadurch in eine röthlich-, gelblich- oder grünlichweisse verwandelt wird) und dem Zusammenhang desselben mit chronischen Milzanschwellungen zu ergehen. Bei der ersten Veröffentlichung des von mir beobachteten Falls (Froriep's N. Notiz. 1845. No. 780.) hob ich schon diesen Zusammenhang hervor und zeigte den Unterschied dieser Blutveränderung von der sogenannten pyämischen. Trotzdem übergeht Bischoff (Müller's Archiv 1846. Jahrb. p. 135.) in seinem Referat den ersteren ganz und bemerkt nur, daß eine chemische Untersuchung nicht angestellt sei und daß der Fall mit anderen, unter dieser Bezeichnung aufbewahrten Fällen nur die Aehnlichkeit des äußeren Ansehens



Rudolf Virchow: Weisses Blut. Frorieps Notizen, 36, s. 152 – 156, 1845

What leukemias are?

- **Very different diseases**
- **Historical name: accumulation of white blood cells**
- **Not every accumulation of white blood cells is leukemia**
 - **Leukemoid reaction**
 - **Lymphoma leukemization**
- **Acute or Chronic**
- **Myeloid or Lymphoid**

Common features of leukemia

- **White blood cells accumulation**
 - precursor cells (myelo-, lympho-) – blasts
 - acute leukemia
 - myeloid lineage cells – CML
 - mature lymphocytes (CLL)
- **Leukocytosis (CML, CLL, AL)**
- **Normal WBC or leukopenia (AL)**
- **In almost all cases pathology in differential white blood count**
- **In all cases bone marrow involvement**

LEUKEMIAS

Do you know differences between acute and chronic leukemias?

Briefly:

Acute leukemia - there is defect of proliferation, proliferation of young bone marrow cells (blasts) is increased!

Chronic leukemia - there is defect of apoptosis (programmed cell death), apoptosis of mature cells is decreased, mature cells are accumulated in the body!

CAVE: CL can switch to AL (CML in blast crisis, CLL in Richter's syndrome)

LEUKEMIA INCIDENCE

12,7/100 000 M 9,8/100 000 F

Slightly increasing incidence compared with 90's (except of CML)

Europe:

**40% CLL, 25% AML, 15% CML, 11% ALL,
2% HCL, 7% other**

Myelodysplastic syndromes

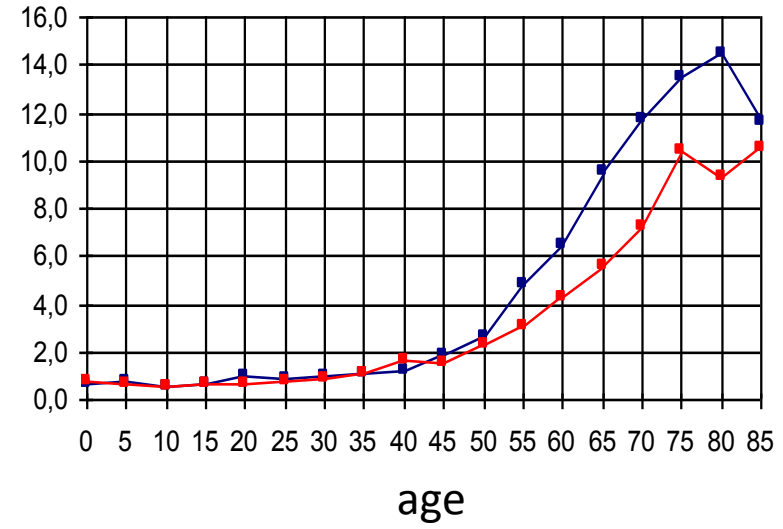
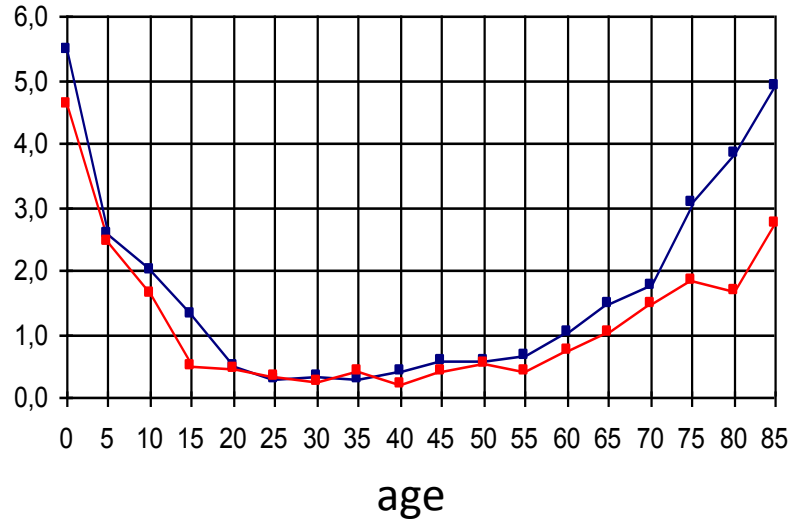
1 - 2/100 000 (older 10-20/100 000)

ALL

cases / 100 000

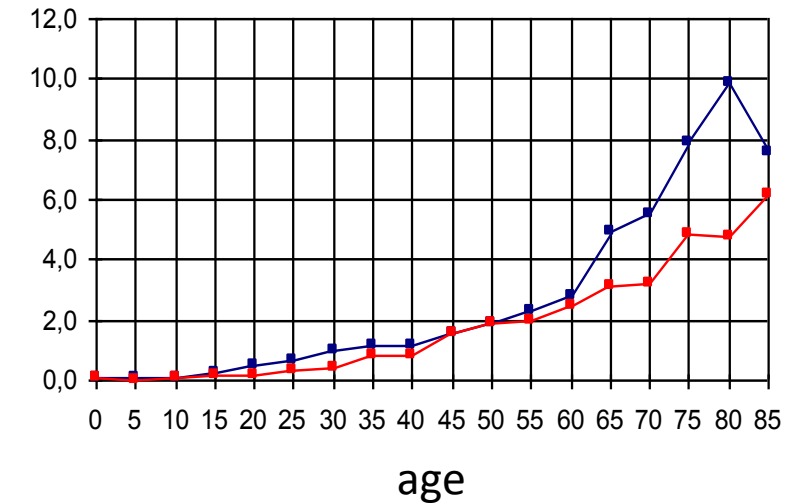
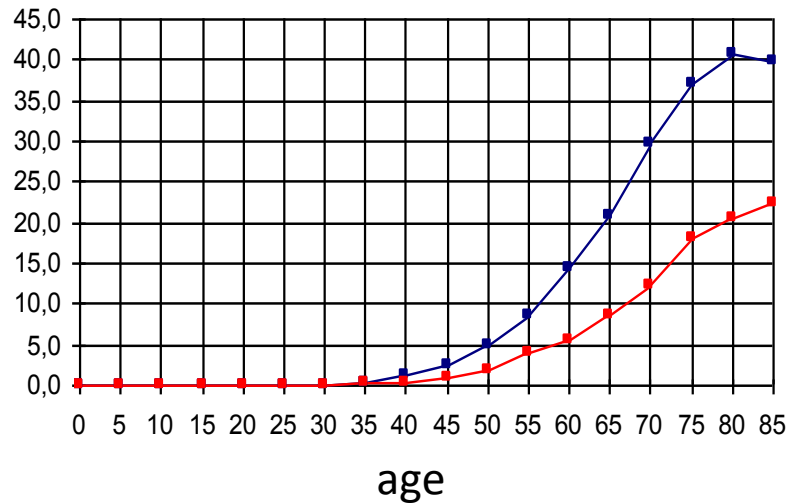
AML

—■— M
—■— F

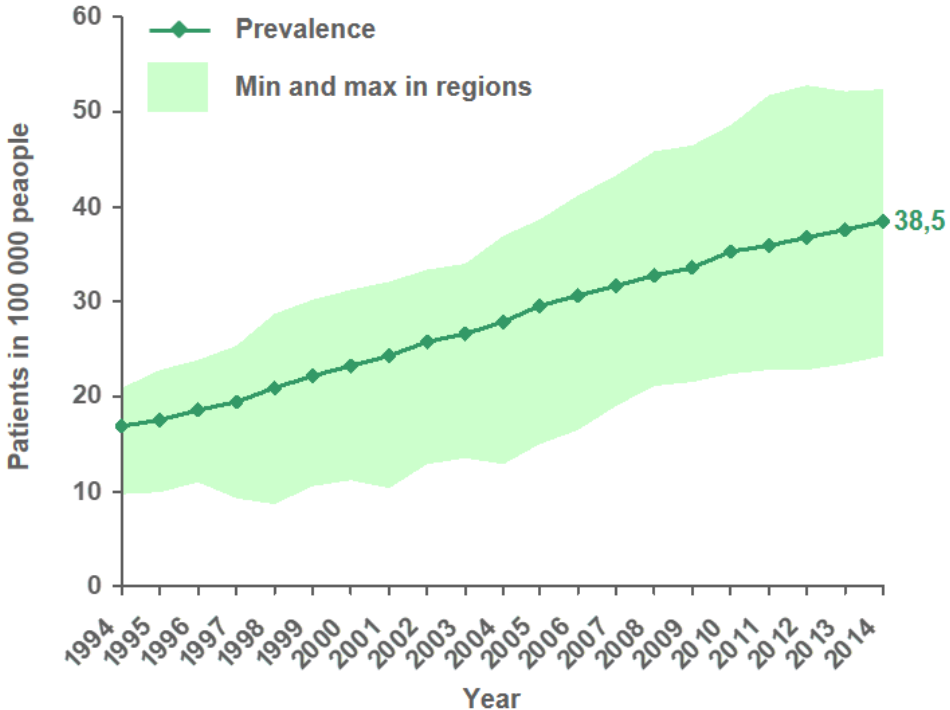
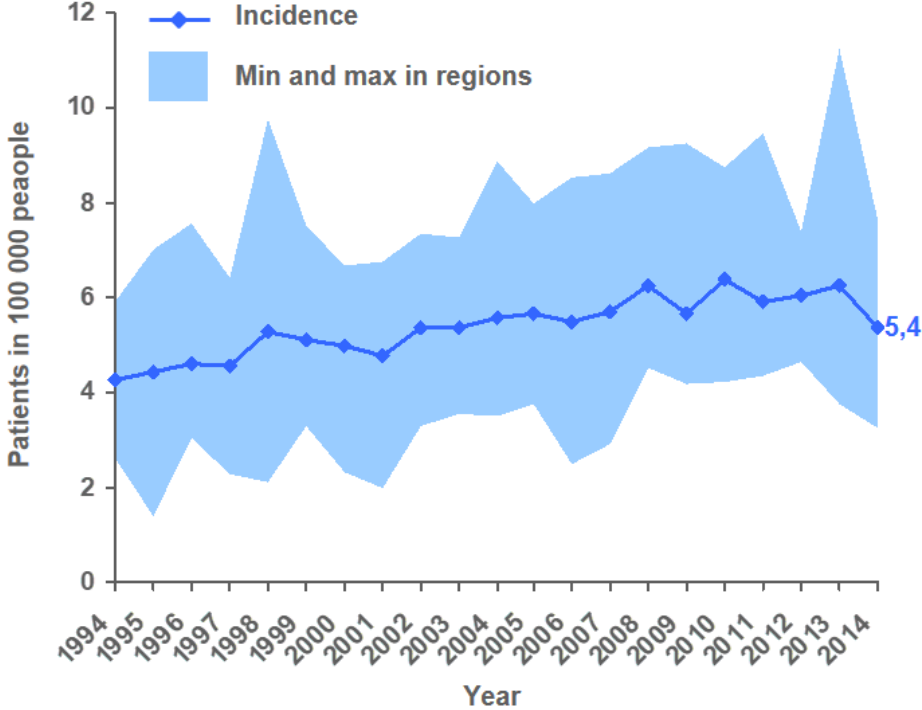


CLL

CML



LEUKEMIA INCIDENCE AND PREVALENCE - CLL as example



Clinical symptoms of malignant diseases of blood and bone marrow

| Symptoms affecting patients | Frequency |
|-------------------------------|-------------------------|
| infection, fever | 36 % (all) |
| bleeding | 33 % (APL, AML) |
| thrombosis, DIC | 10 % (APL, ET, PV) |
| lymph nodes enlargement | 57 % (ALL, CLL) |
| splenomegaly | 56 % (CML, CLL, PV, MF) |
| hepatomegaly | 47 % (CML, AML) |
| mediastinal tumor | 14 % (ALL, CLL) |
| CNS involvemnet | 7 % (ALL, AML M5) |
| involvement of another organs | 9 % (all) |

CAVE: All symptoms of hematologic diseases are non-specific!

Bleeding in
acute leukemia





Bleeding in acute leukemia



AML – gum
hyperplasia



AML – gum
hyperplasia





PLL – skin
involvement



ALL – skin involvement



Mastocytosis
- *urticaria*
pigmentosa

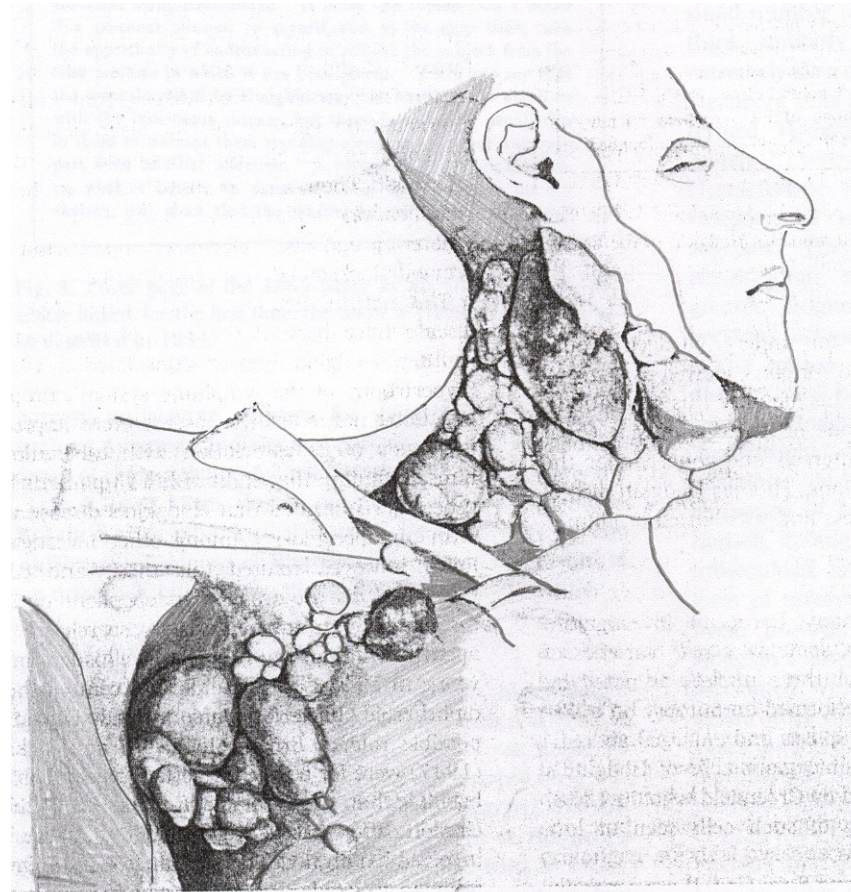
ON SOME
MORBID APPEARANCES
OF
THE ABSORBENT GLANDS
AND
SPLEEN.

BY DR. HODGKIN.

PRESENTED
BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1833.

The morbid alterations of structure which I am about to describe are probably familiar to many





CLL
- lymph nodes



CLL -
splenomegaly



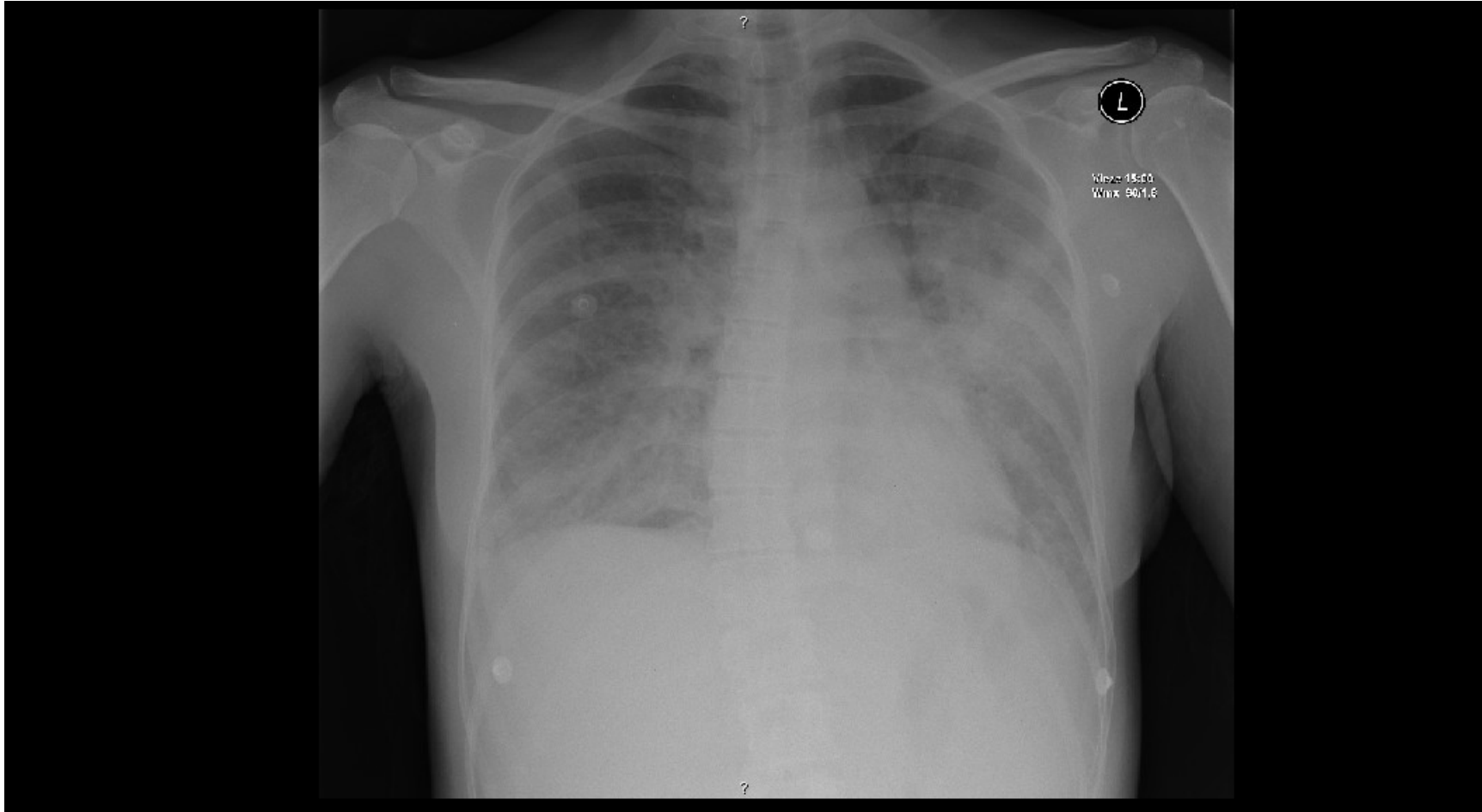


Myelofibrosis
- massive
splenomegaly



Lekocytes
- leukapheresis
bag

Lung infiltration in acute leukemia



Time from first symptoms to final diagnosis

TABLE II. Time from the First Symptoms (Analysis Only Performed Among Patients that Presented Symptoms) and from the First Medical Visit to a Definitive Diagnosis

| | ALL | AML | APL | CLL | CML | HCL | Acute leukemias | Chronic leukemias | Total |
|----------------------|---|------------------|------------|------------|------------|--------------|-----------------|-------------------|------------|
| | Time from the first symptoms to a definitive diagnosis ^a | | | | | | | | |
| No. of analyzed pts. | 90 | 305 | 59 | 125 | 68 | 22 | 454 | 215 | 669 |
| Days—median (range) | 25 (3-194) | 22 (0-226) | 14 (3-90) | 27 (3-274) | 21 (1-256) | 34.5 (4-370) | 21 (0-226) | 27 (1-370) | 22 (0-370) |
| Days—25-75% interval | 14-43 | 12-36 | 8-22 | 14-52 | 11.5-48 | 14-77 | 12-35 | 13-60 | 12-42 |
| | Time from the first medical visit to a definitive diagnosis | | | | | | | | |
| No. of analyzed pts. | 106 | 366 ^b | 74 | 293 | 123 | 41 | 546 | 457 | 1003 |
| Days—median (range) | 9 (0-108) | 7 (0-171) | 5.5 (0-71) | 12 (0-343) | 6 (0-119) | 20 (0-355) | 7 (0-171) | 10 (0-355) | 8 (0-355) |
| Days—25-75% interval | 3-16 | 3-16 | 2-12 | 4-22 | 2-16 | 8-36 | 3-15 | 3-23 | 3-19 |

LEUKEMIAS – PREDISPOSING FACTORS

Increased risk of leukemia is in:

Genetic syndromes – M. Down, FA, ataxia telangiectasia, inherited germline mutations (*ETV6, RUNX1, DDX41...*)

Drugs (chemotherapy, alkylating agents)

Radiation (can cause all leukemias except CLL)

Socioeconomic factors

(increased incidence of childhood ALL in industrial countries, probably due to later contact of children with allergens or banal childhood infections)

Viruses (EBV, HTLV I, HIV)

Benzene, toluene, etc.

LEUKEMIAS – ETIOLOGY

Somatic molecular lesions involving:

Cell proliferation

Cell division

Cell maturation

Apoptosis

Cell self-renewal

LEUKEMIAS – ETIOLOGY

The most important somatic molecular changes in leukemia and myeloproliferative neoplasms:

BCR-ABL

TP53

PML-RAR α

JAK2

LEUKEMIAS AND MYELOPROLIFERATIVE DISEASES

Blood and bone marrow features

**What can we found in periperal blood
(WBC, RBC, platelets)?**

- acute leukemia
- chronic leukemia
- myeloproliferative diseases

What can we found in bone marrow?

- acute leukemia
- chronic leukemia
- myeloproliferative diseases

Laboratory diagnostics

Peripheral blood count with differential WBC

Bone marrow

**Flow cytometry (analysis of CD antigens)
(ALL, CLL, HCL)**

Cytogenetic analysis (CML, AL, MDS, CLL)

Molecular genetic analysis (CML, APL, AL, CLL)

Cytology a cytochemistry

Histology (necessary in myeloproliferative diseases)

Do you know differences between trephine biopsy and sternal puncture?

Sternal puncture - we can collect only marrow blood. SP fits for diagnostics of leukemias.

VÝSLEDEK VYŠETŘENÍ Z HEMATOLOGIE

Pacient: [REDACTED]

Datum a čas odběru: [REDACTED]

| Vyšetření | Hodn. Výsl. | Jedn. | Meze/koment. |
|----------------------|-------------|---------------------------|-----------------------------|
| Leukocyty | <.> | 8.75 x10 ⁹ /l | (4 - 10) |
| Erytrocyty | <.> | 3.80 x10 ¹² /l | (3.8 - 5.4) |
| Hemoglobin | <L> | 115.0 g/l | (120 - 160) |
| Hematokrit | <L> | 0.320 l/l | (0.35 - 0.46) |
| Střední objem ERY | <L> | 83.6 fL | (84 - 96) |
| Trombocyty | <.> | 163.0 x10 ⁹ /l | (150 - 350) |
| Stř. množství HGB v | <.> | 30.2 pg | (28 - 34) |
| Prům. koncentrace HG | <.> | 362.0 g/l | (320 - 370) |
| Šíře distribuce ERY | <.> | 13.5 % | (10 - 15.2) |
| Střední objem trombo | <L> | 7.05 fl | (7.8 - 11) |
| Trombocytový hematok | <L> | 1.15 ml/l | (1.21 - 3.5) |
| Šíře distribuce trom | <.> | 17.00 % | (15.5 - 17.1) |
| Neutrofily % | <L> | 19.80 % | (50 - 70) |
| Lymfocyty % | <.> | 22.40 % | (20 - 40) |
| Monocyty % | <H> | 57.00 % | (2 - 12) |
| Eosinofily % | <.> | 0.28 % | (0 - 5) |
| Basofily % | <.> | 0.60 % | (0 - 1) |
| Neutrofily (absolutn | <L> | 1.73 x10 ⁹ /l | (2 - 7) |
| Lymfocyty (absolutní | <.> | 1.96 x10 ⁹ /l | (0.8 - 4) |
| Monocyty (absolutní | <H> | 4.99 x10 ⁹ /l | (0.08 - 1.2) |
| Eosinofily (absolutn | <.> | 0.02 x10 ⁹ /l | (0 - 0.5) |
| Basofily (absolutní | <.> | 0.05 x10 ⁹ /l | (0.01 - 0.1) |
| Neutrofily mikroskop | <L> | 20.0 % | (50 - 70) |
| Tyče mikroskopicky | <.> | 0.0 % | (0 - 4) |
| Lymfocyty mikroskopi | <.> | 23.0 % | (20 - 40) |
| Monocyty mikroskopic | <.> | 2.0 % | (2 - 12) |
| Eosinofily mikroskop | <.> | 0.0 % | (0 - 5) |
| Basofily mikroskopic | <.> | 0.0 % | (0 - 1) |
| Metamyelocyty mikros | <H> | 1.0 % | (0 - 0) |
| Myelocyty mikroskopi | <.> | 0.0 % | (0 - 0) |
| Promyelocyty mikrosk | <.> | 0.0 % | (0 - 0) |
| BLASTY mikroskopicky | <H> | 54.0 % | (0 - 0) |
| Prolymfocyty mikrosk | <.> | 0.0 % | (0 - 0) |
| Plazmatické buňky | <.> | 0.0 % | (0 - 0) |
| Nedif.buňky | <.> | 0.0 % | (0 - 0) |
| Nedif.blasty | <.> | 0.0 % | (0 - 0) |
| Normoblasty mikrosko | < > | 5.0 /100 bb | |
| Hodnocení morfologie | < > | | |
| Hodnocení morfologie | < > | | hypersegmentace neutrofilů, |
| Morfologie ERY | < > | | : |
| Morfologie PLT | < > | | mírná anizo PLT, |
| KOMENTAR | < > | | Změna oproti předešlému. |
| Neznamé vyšetření | < > | | NRBC/100WBC :0.00 |



Laboratory diagnostics

Biochemical analysis of blood (elevated LD in myeloproliferative diseases)

Coagulation – DIC, thrombophilia, bleeding
fibrinogen, aPTT, PT, AT III, DD, EGT

Other

(Chest X ray, abdominal sonography, ECG, heart sonography, serology – CMV...)

- we have to exclude focal infections and to evaluate function of heart, kidneys, liver and lungs (chemotherapy is nephrotoxic, hepatotoxic or cardiotoxic)

CLASSIFICATION OF LEUKEMIA

FAB (1982)

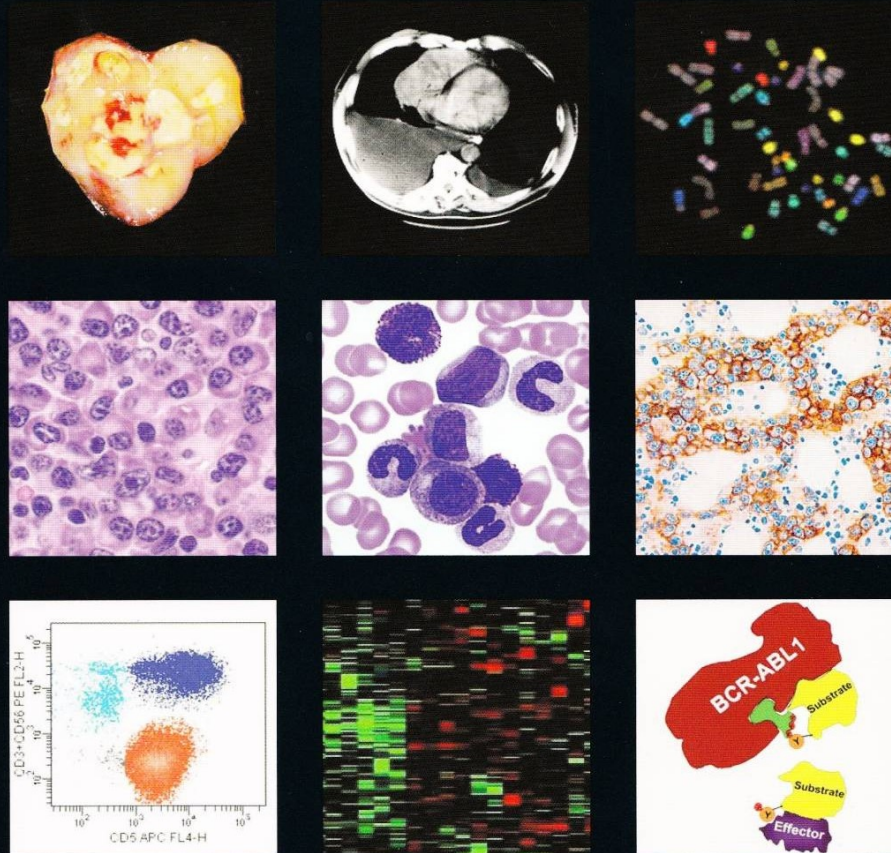
Classification according to morphology of malignant cells

WHO (1999-)

Classification according to morphology, cytogenetic features, flow cytometry, and molecular genetic features

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



CHRONIC LYMPHOCYtic LEUKEMIA (CLL)

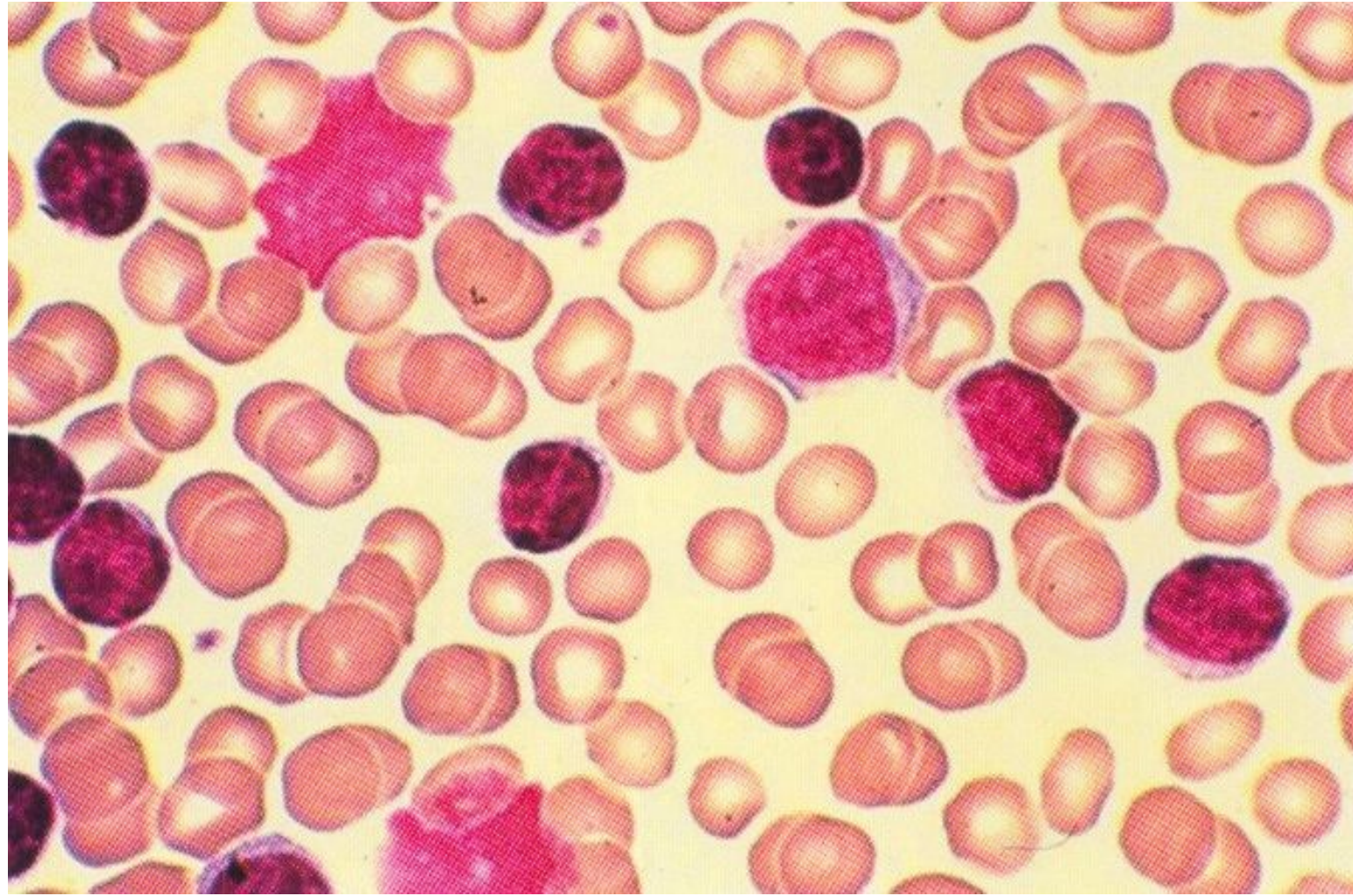
The most common leukemia of Caucasians. CLL is a disorder characterized by the accumulation of small mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues.

Laboratory and clinical features:

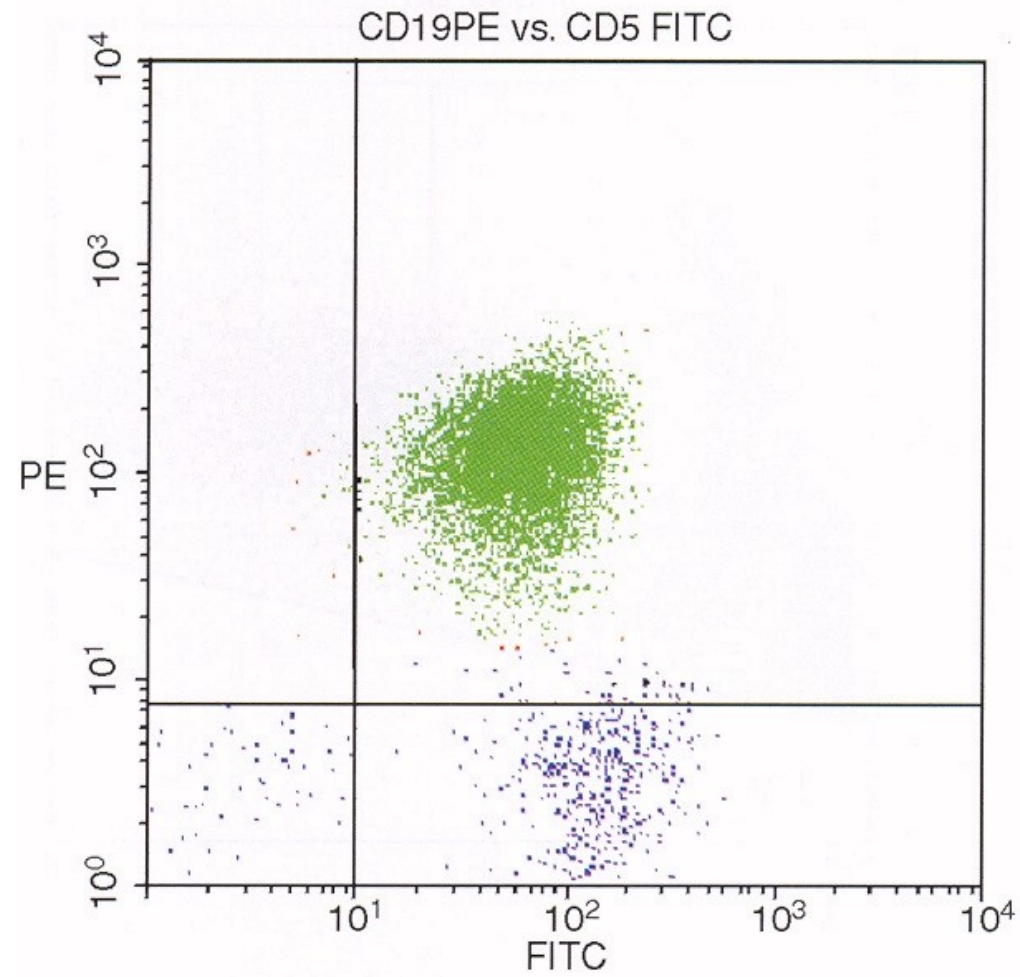
**leukocytosis (absolute lymphocytosis),
lymphadenopathy, splenomegaly, hepatomegaly, anemia,
thrombocytopena, often autoimmune diseases
(hemolysis).**

Prognosis – different (better in CLL mutated genes for IgH or/and in CLL with del 13q14.

Median survival of CLL patients is 11+ years.



Diagnostics based on flow cytometry: CD5+19+20dim+23+FMC7-79b-200+sIg+/-

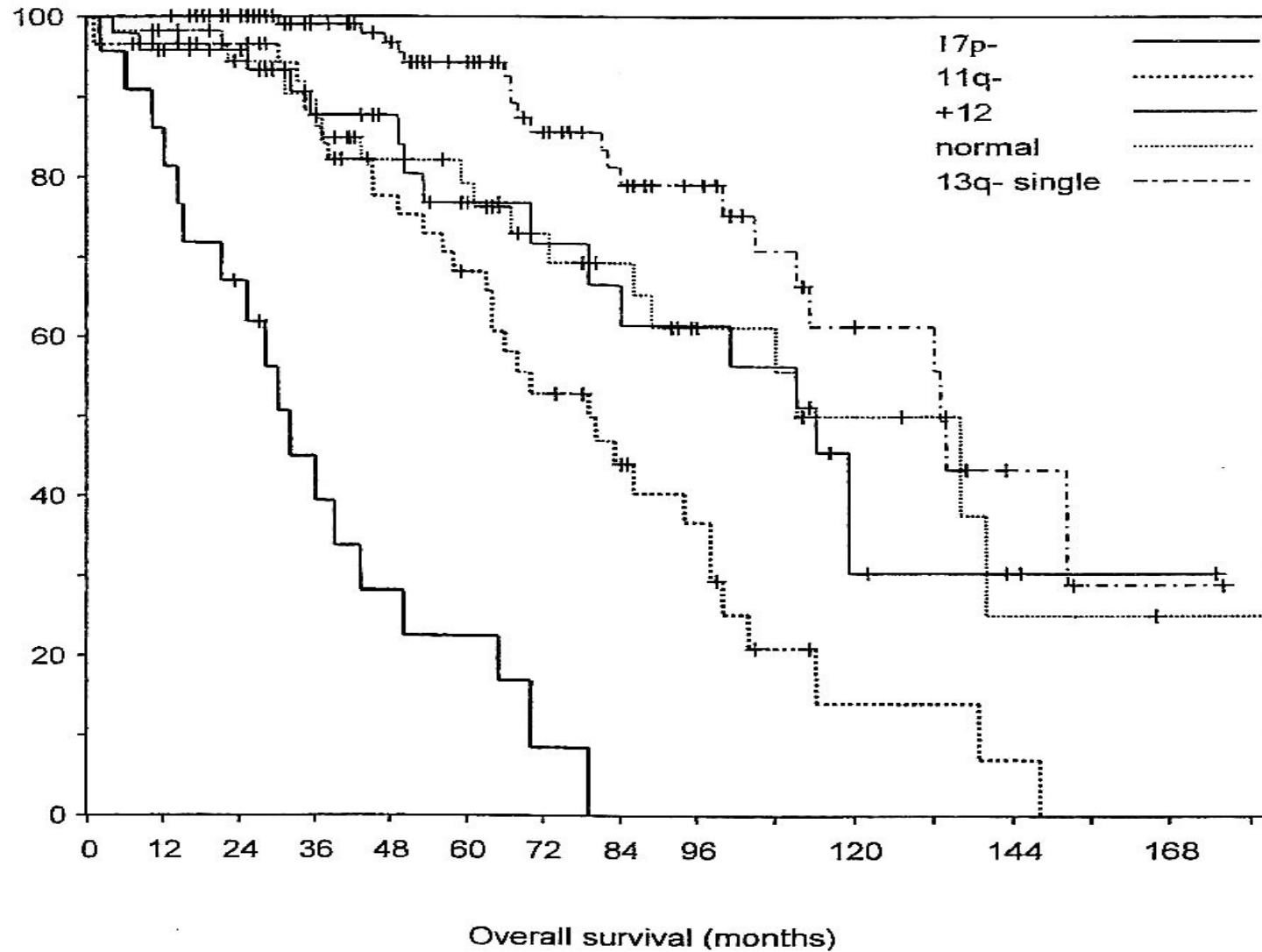


CLL staging

Treatment in stage Rai III or IV patients only (Binet C)

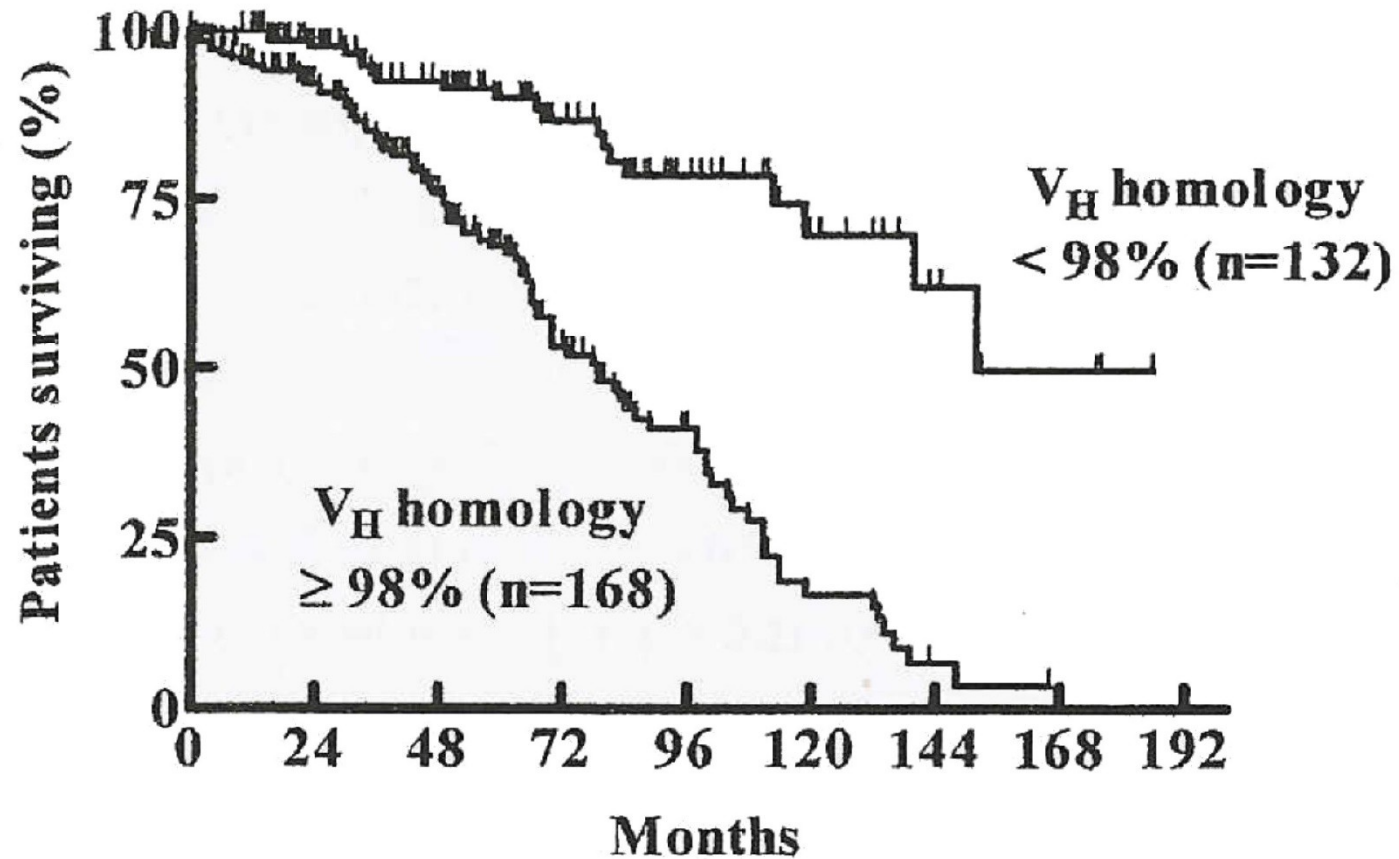
| Clinical stage (Rai) | Risk | Median survival |
|--|--------------|------------------------|
| 0 (lymphocytosis) | Low | >150 months |
| I (lymphocytosis + lymphadenopathy) | Intermediate | 101 |
| II (lymphocytosis + splenomegaly) | Intermediate | 71 |
| III (lymphocytosis + anemia Hb < 110 g/l) | High | 19 |
| IV (lymphocytosis + thrombocytopenia < 100x10 ⁹ /L) | High | 19 |
| Clinical stage (Binet) | | |
| A (involvement <3 regions) | Low | Not reached |
| B (involvement ≥ 3 regions) | Intermediate | 84 |
| C (anemia and thrombocytopenia) | High | 24 |

CLL prognosis based on cytogenetics



CLL prognosis based on IgHV mutational status

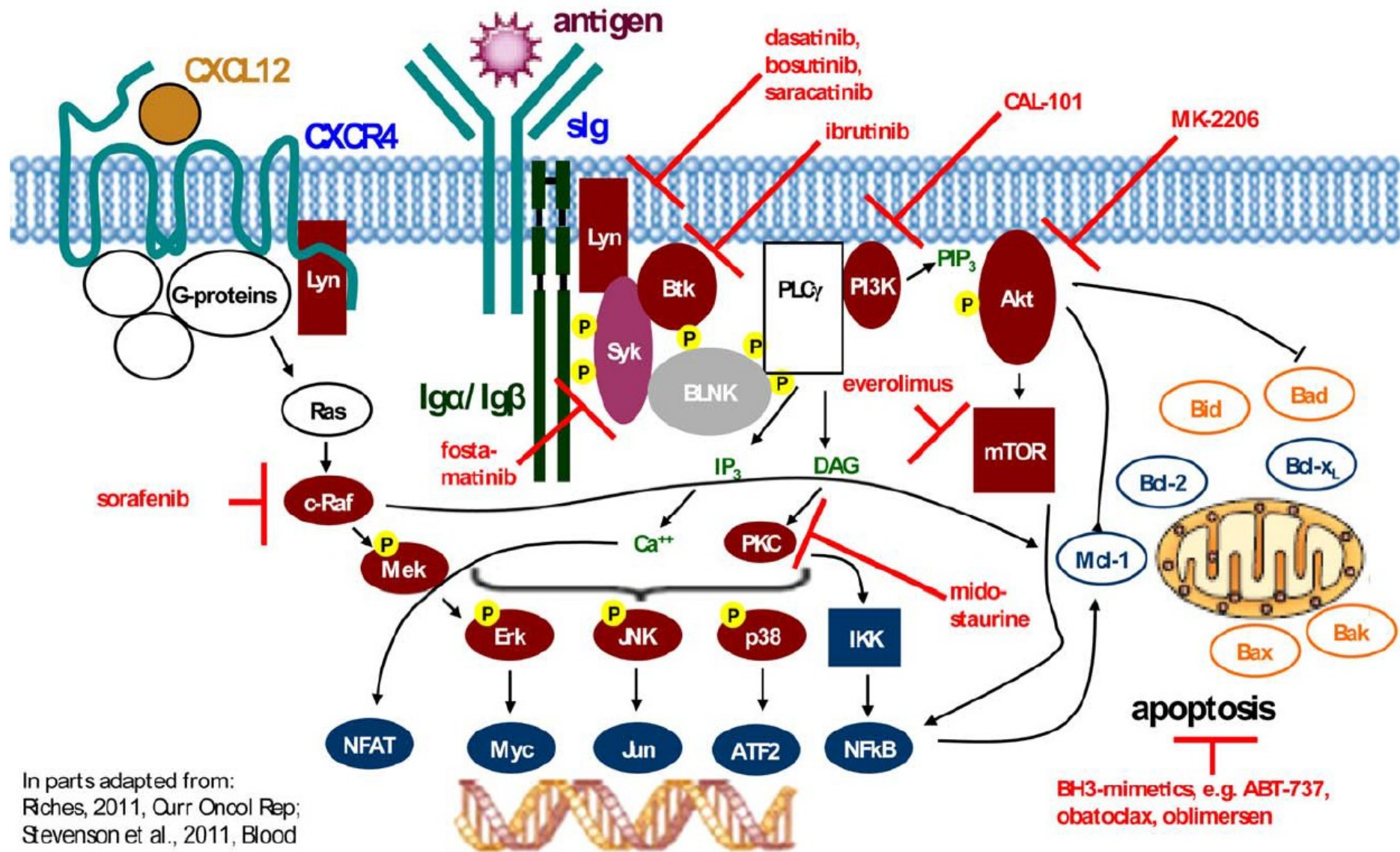
A



CLL THERAPY

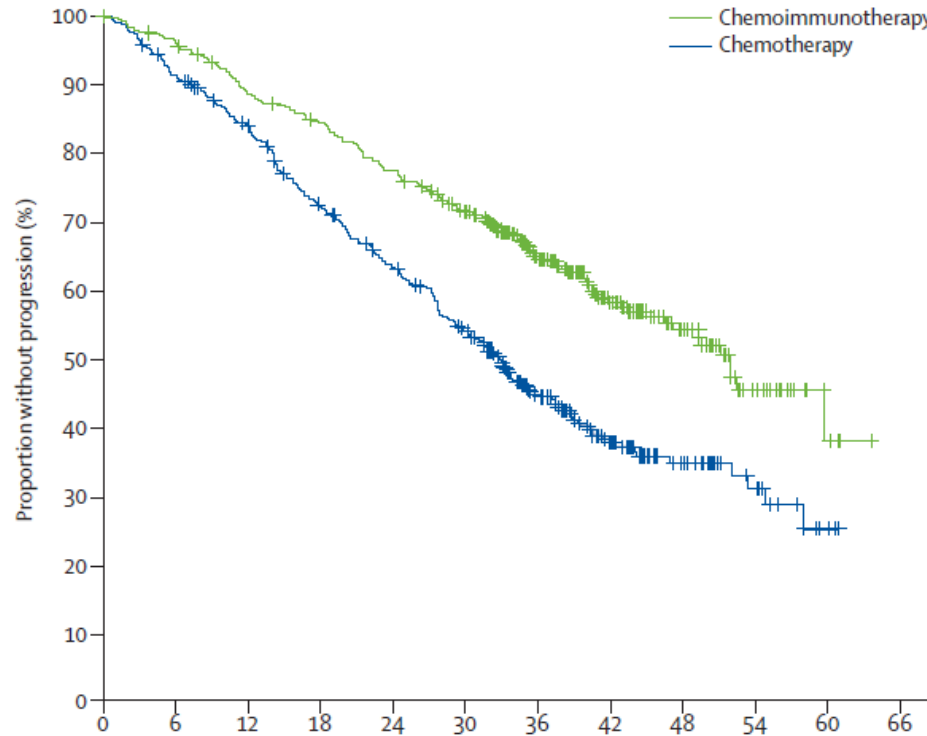
Treatment for advanced stages only:

- **fludarabine+cyclophosphamide+rituximab**
 - **bendamustine+rituximab**
- **chlorambucil + anti CD20 antibody (rituximab, obinutuzumab)**
 - **ibrutinib, idelalisib (BCR inhibitors)**
 - **venetoclax (Bcl2 inhibitor)**
 - **(allogeneic transplant)**



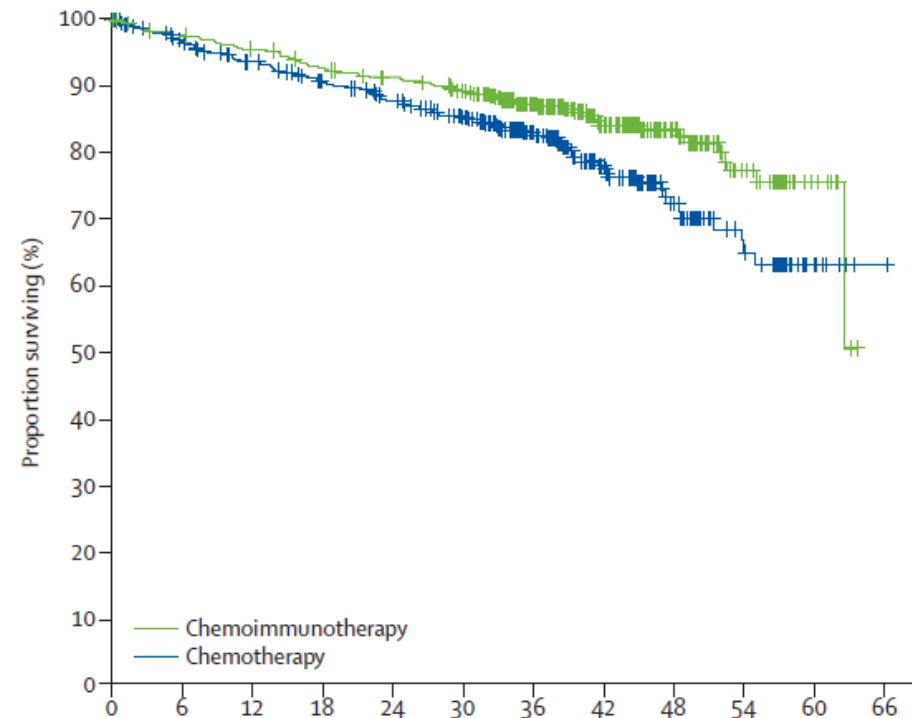
In parts adapted from:
 Riches, 2011, Curr Oncol Rep;
 Stevenson et al., 2011, Blood

CLL – FCR regimen treatment outcome

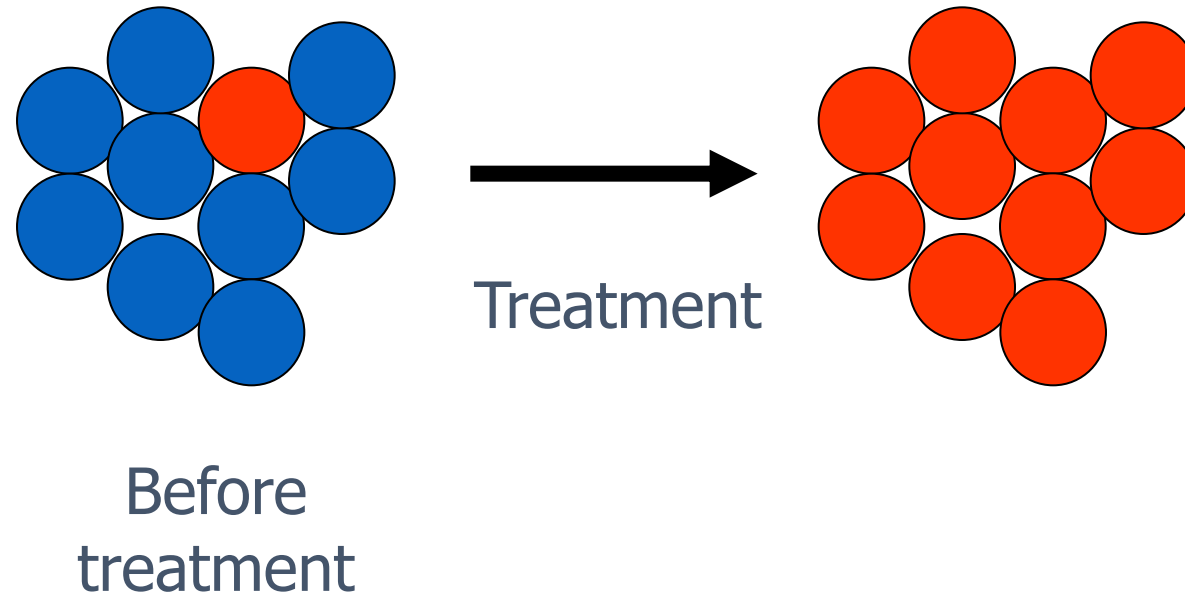


**PFS at 3 years
45% vs. 65%
p < 0,0001**

**OS at 3 years
83% vs. 87%
p = 0,012**

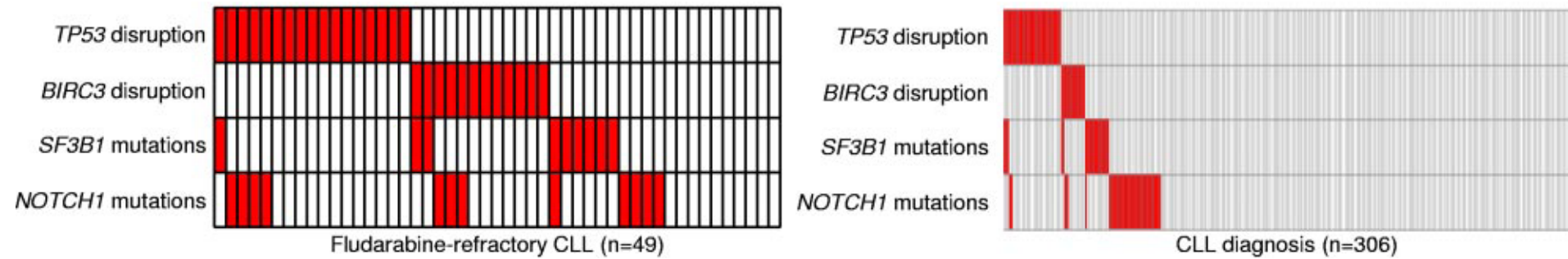


Clonal evolution in CLL – *TP53*



Unfavorable *SFB3*, *NOTCH1*, *BIRC3* mutations

D



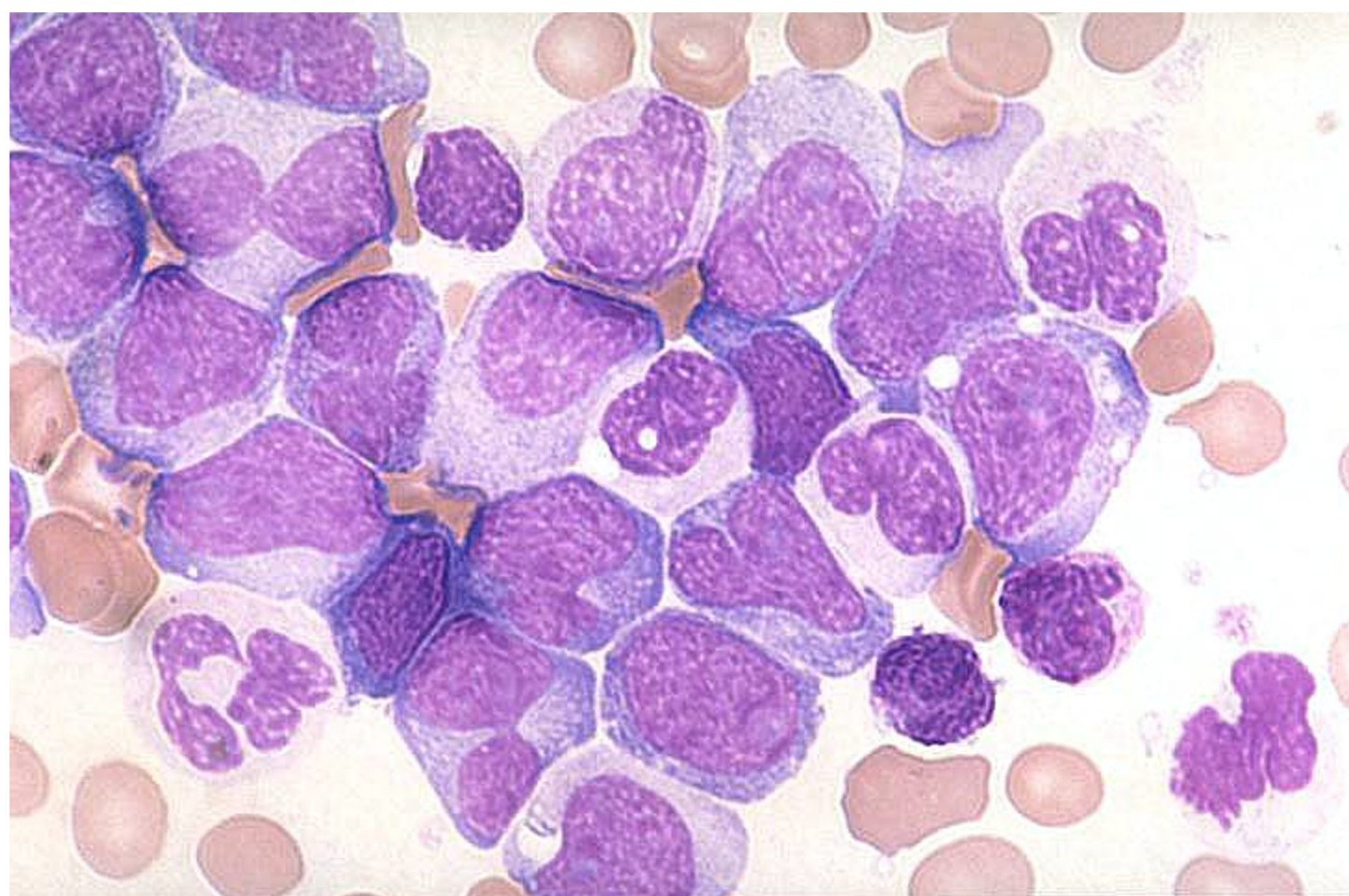
CHRONIC MYELOID LEUKEMIA (CML)

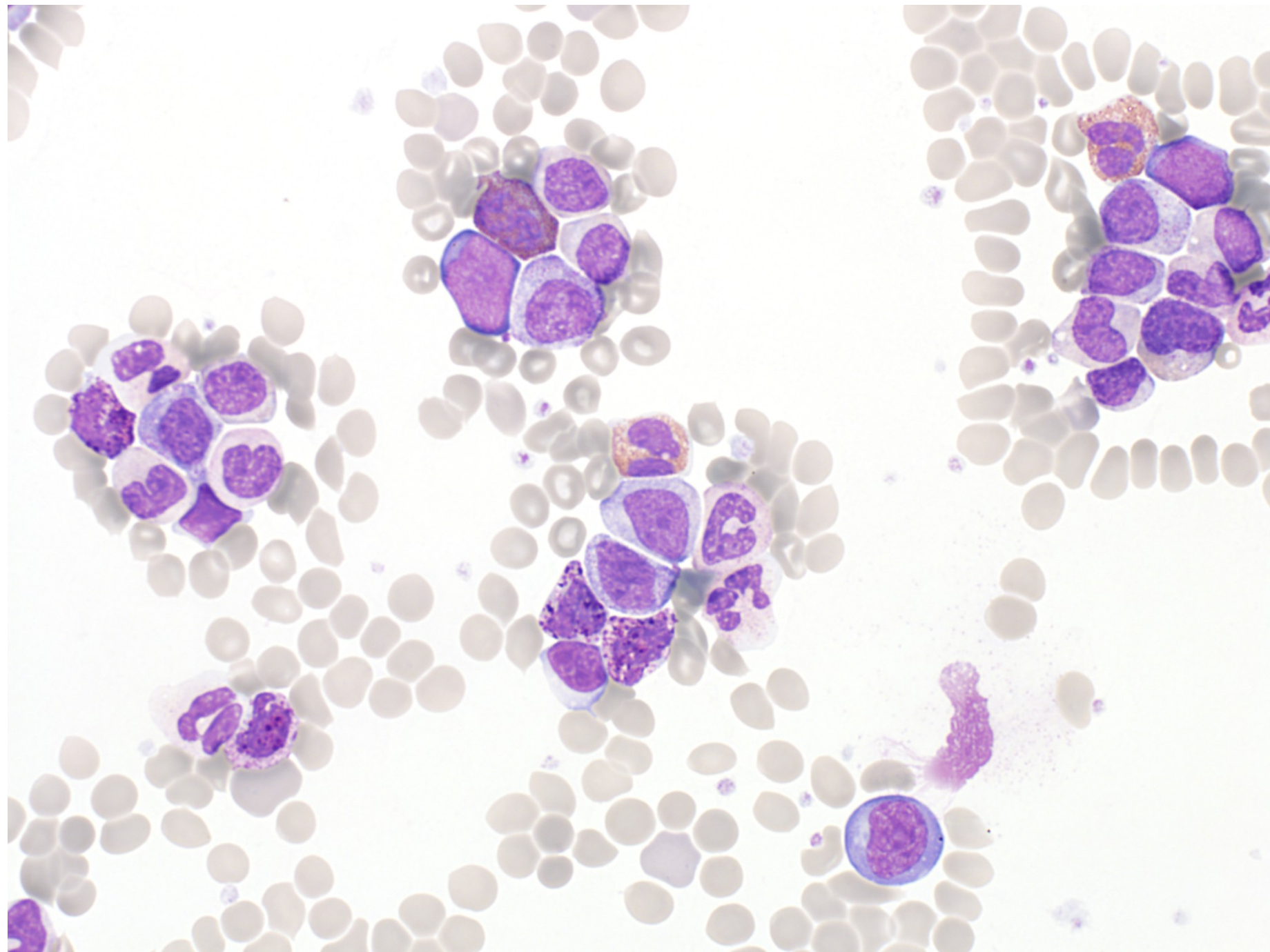
CML is a pluripotent stem cell disease that is characterized by extreme blood granulocytosis, basophilia, often thrombocytosis, anemia, and splenomegaly.

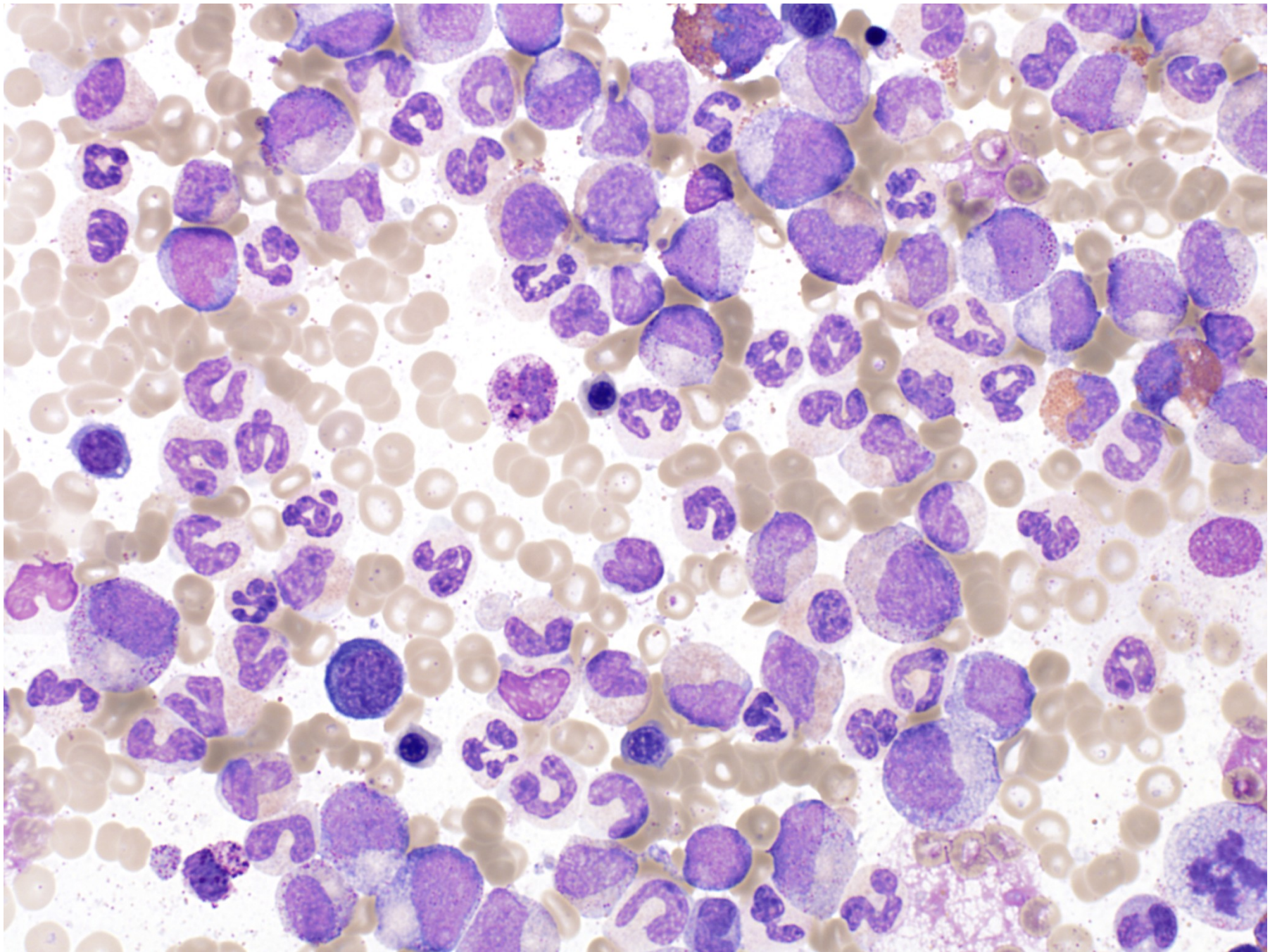
Stages of untreated CML:

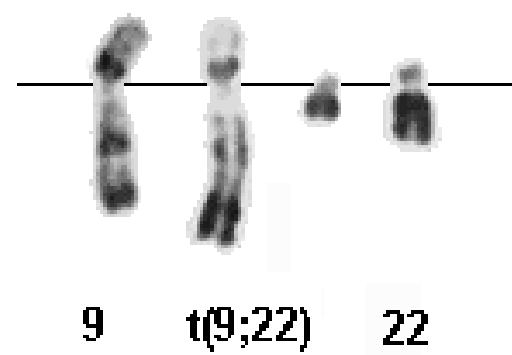
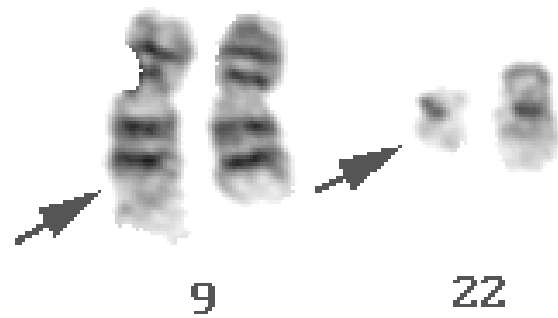
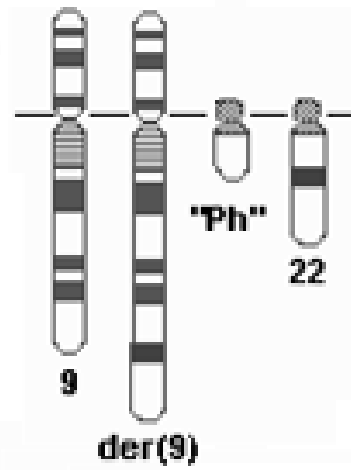
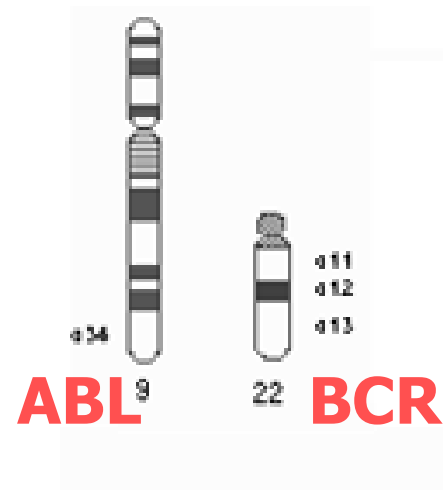
chronic phase, accelerated phase (rapid increase of WBC, worsening of thrombocytopenia, new cytogenetic features, resistance to treatment), blast crisis (resembles to acute leukemia)

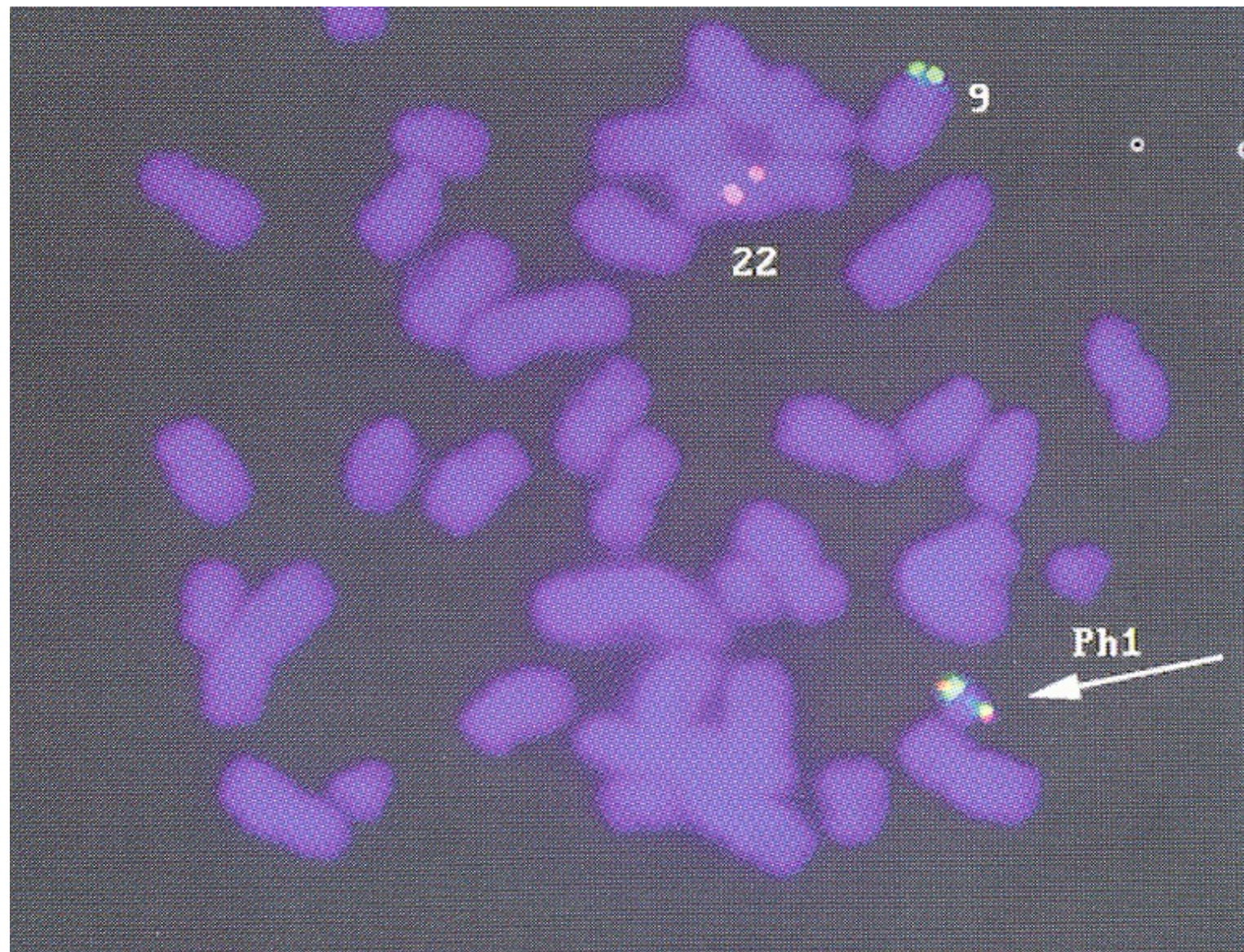
Etiologic role of chromosome discovered in Philadelphia - Ph chromosome











- **Ph chromosome arises from t(9;22)**
- **chimeric gene *BCR-ABL* arises from Ph chromosome**
- ***BCR-ABL* gene produces BCR-ABL tyrosinkinase**
- ***BCR-ABL* tyrosinkinase induces defect of apoptosis**

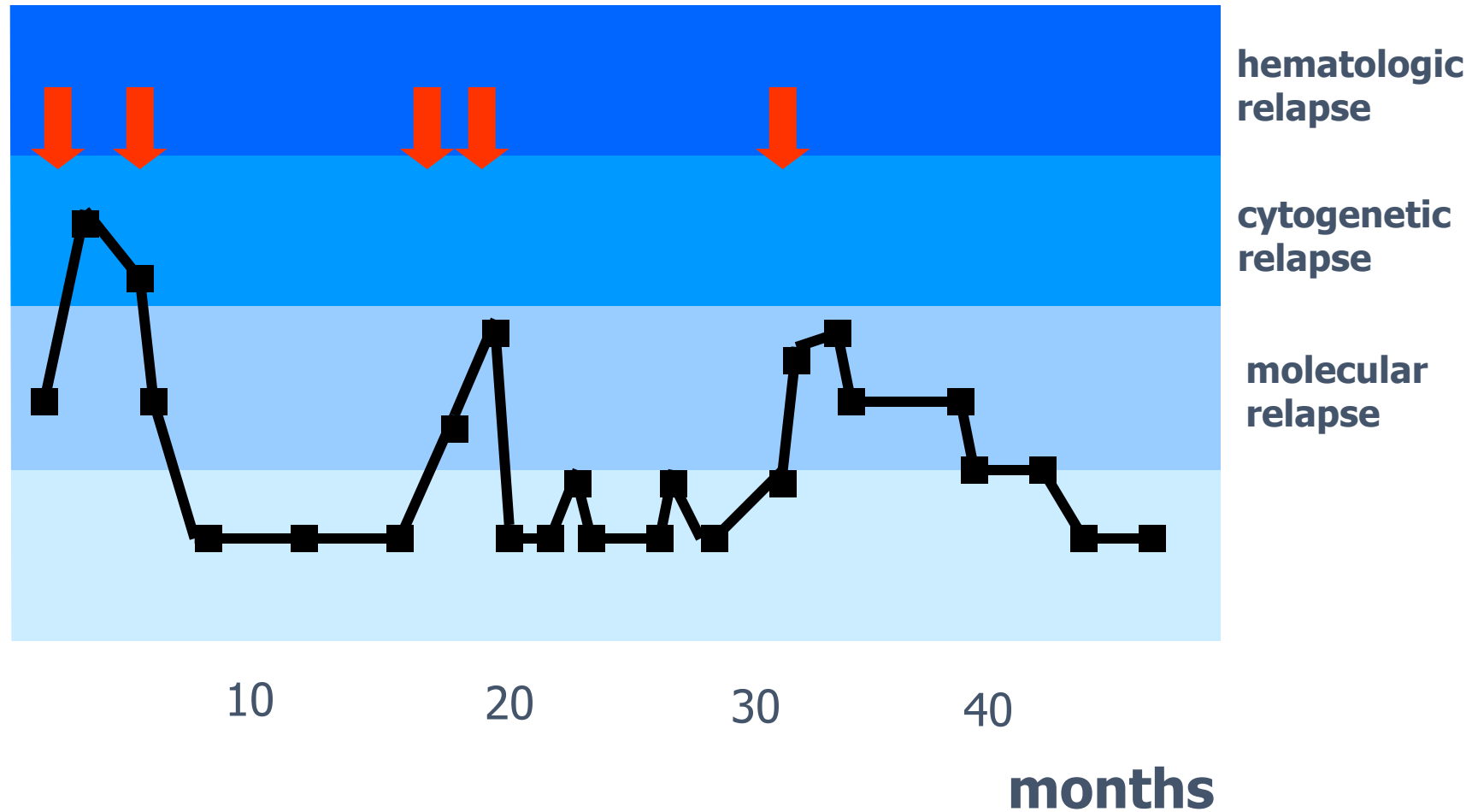
There is almost no *BCR-ABL* negative CML!

Minimal residual disease during treatment

- **Hematologic monitoring**
- **Cytogenetic monitoring**
- **Molecular genetic monitoring
(RQ-RT-PCR, digital PCR, NGS)**

Minimal residual disease during therapy

Molecular relapse is better manageable compared with cytogenetic or hematologic relapse



THERAPY

All patients treated!

- **imatinib**
- **nilotinib, dasatinib, bosutinib**
- **ponatinib**
- **interferon**
- **allogeneic transplantation**

II. Zwei Fälle von Leucaemie.

Mitgetheilt

von

Dr. **Lissauer** in Bendorf.

Der in Nr. 31. dieser Wochenschrift von Dr. Valentiner mitgetheilte Fall von Leucaemie, bei welcher zur Coupirung des Fiebers Liq. arsenic. Fowler angewandt wurde, brachte mir zwei Fälle derselben Krankheit in Erinnerung, die ich kurz nach einander im Landkrankenhaus in Cassel zu beobachten Gelegenheit hatte, von welchen bei einem Liq. arsen. Fowler. eine Zeit lang versuchsweise von gutem Erfolge war. Ich theile beide Fälle hier kurz mit, theils als einen kleinen Beitrag zur Kenntniss dieser im Ganzen immer noch selten diagnosticirten Krankheit, theils, um zur weiteren Anwendung obigen Mittels anzuregen.

N. N., 32 Jahre alt, weiblichen Geschlechts, wurde im October v. J. aufgenommen. Sie gab an, früher stets gesund, mit 17 Jahren regelmässig menstruiert gewesen zu sein, und vor ungefähr einem Jahre ein uneheliches Kind geboren zu haben, das bald nach der Geburt gestorben sei. Von ihrem Liebhaber, der ihr die Ehe versprochen, hintergangen, habe sie sich sehr geämt und viel Sorgen gemacht. Zugleich will sie seit dieser

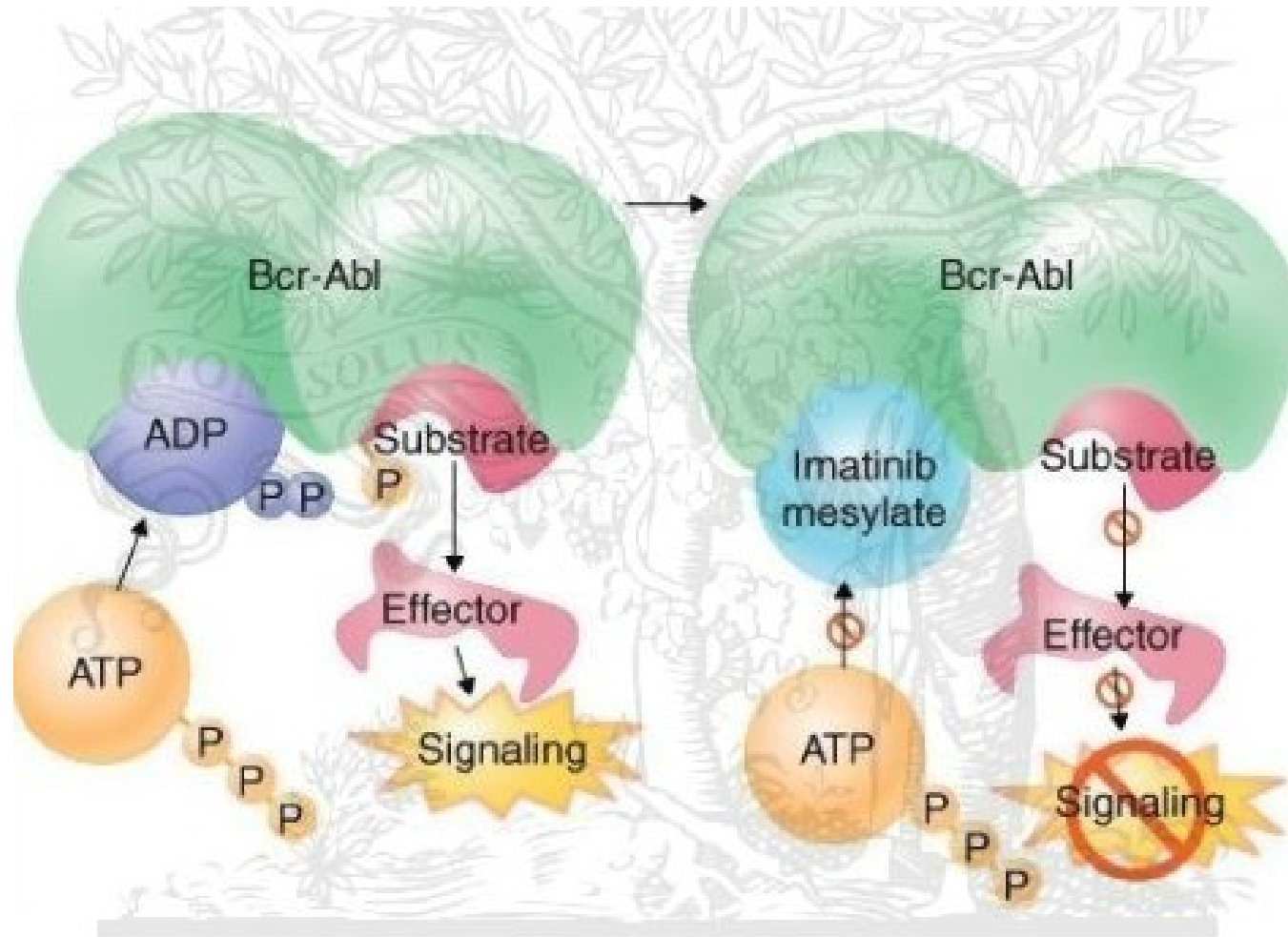
*) Malgaigne l. c. p. 1004. *Revue medic. chirurg.*, 1849, T. V., p. 246.

Asenic trioxide

Lissauer: Zwei Fälle von Leucaemie.

Berlin. Klin. Wochenschrift, 2, 1865, s. 403 - 404

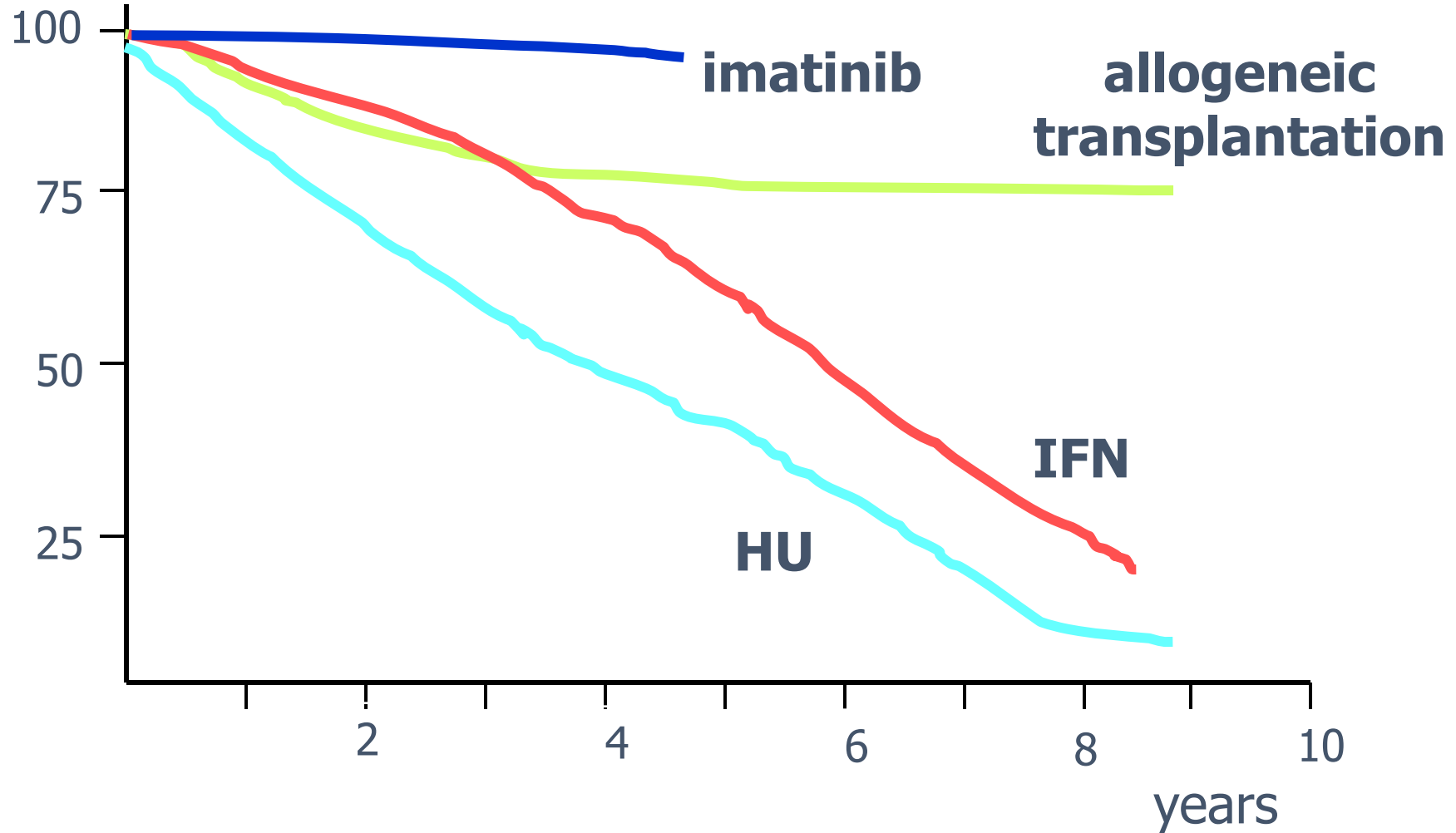
Imatinib mode of action



| CP-CML | Léčebná strategie |
|-------------------------|---|
| <u>1. linie:</u> | •Imatinib 400 mg |
| <u>2. linie:</u> | |
| IM-intolerance | •DASATINIB nebo NILOTINIB |
| IM-selhání | •DASATINIB nebo NILOTINIB •aloTKB (progrese do AP/BC, T315I) |
| IM-suboptimální odpověď | •IM stejná dávka •IM navýšení dávky •DASATINIB nebo NILOTINIB |

Prognosis of CML patients

survival (%)



ACUTE MYELOID LEUKEMIA (AML)

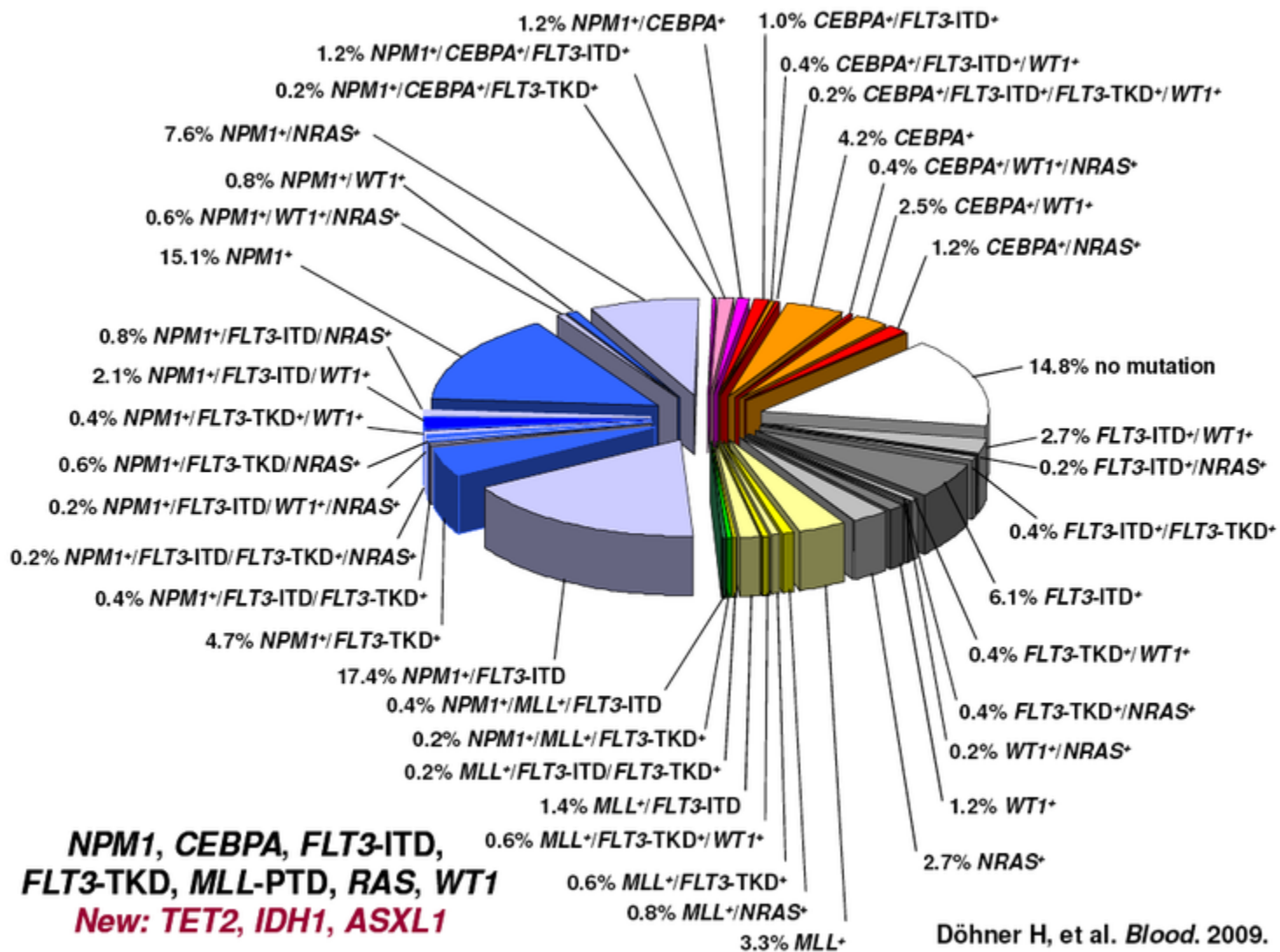
AML is clonal malignant disease that is characterized by the proliferation of abnormal (leukemic) blasts, principally in the marrow, and impaired production of normal blood cells.

Signs and symptoms of AML include pallor, fatigue, weakness, palpitations, bleeding, fever, and dyspnea.

In bone marrow, there is more than 20% of blast cells.
(less than 20% - myelodysplastic syndrome)

Median survival of untreated patients is 6 weeks.

AML – heterogenous disease



Acute myeloid leukemia (AML) and related neoplasms

AML with recurrent genetic abnormalities

AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*

AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*

APL with *PML-RARA*

AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*

AML with t(6;9)(p23;q34.1);*DEK-NUP214*

AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*

AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*

Provisional entity: AML with BCR-ABL1

AML with mutated *NPM1*

AML with biallelic mutations of *CEBPA*

Provisional entity: AML with mutated RUNX1

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, NOS

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

Acute monoblastic/monocytic leukemia

Pure erythroid leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

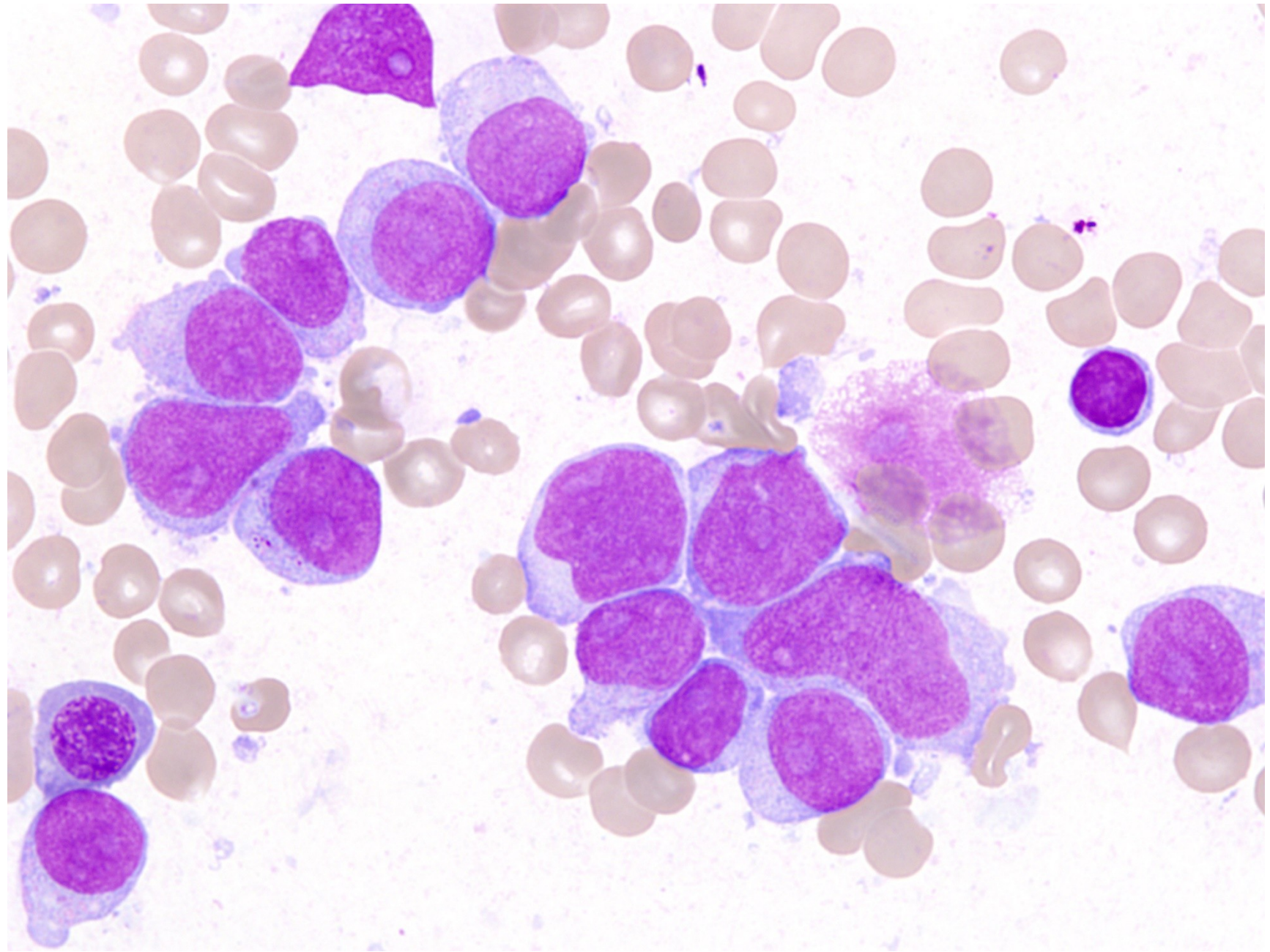
Acute panmyelosis with myelofibrosis

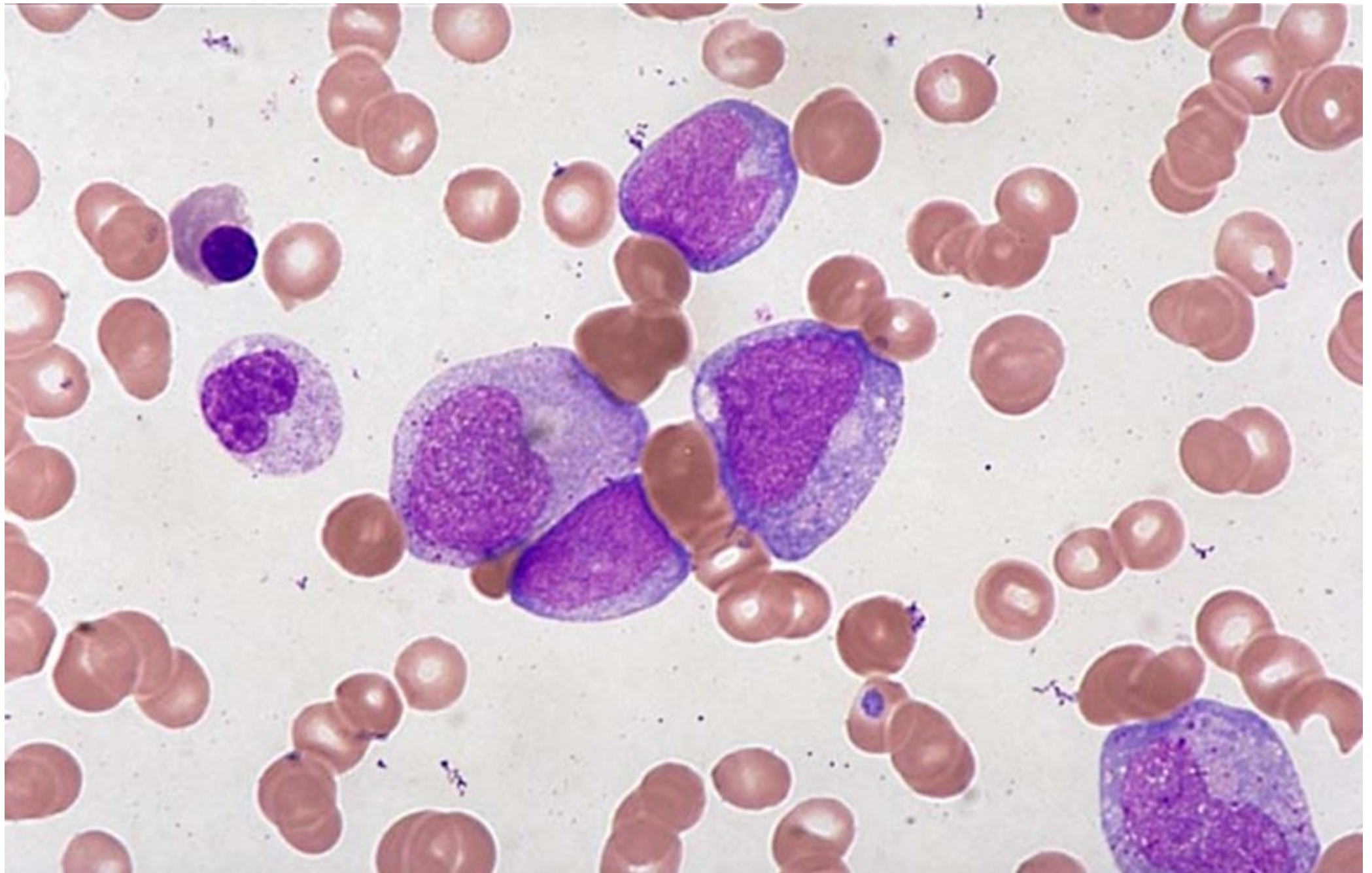
Myeloid sarcoma

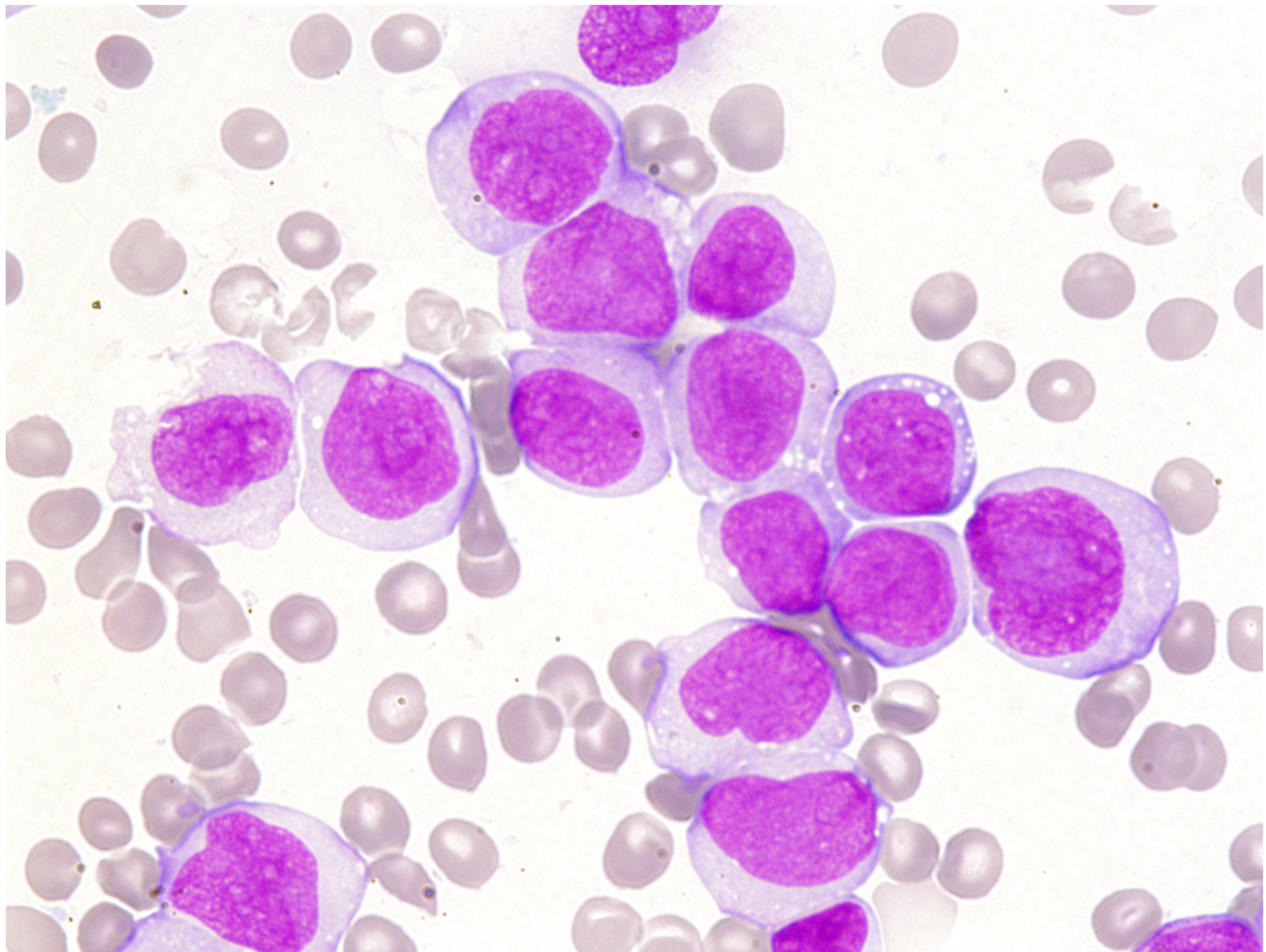
Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis (TAM)

Myeloid leukemia associated with Down syndrome

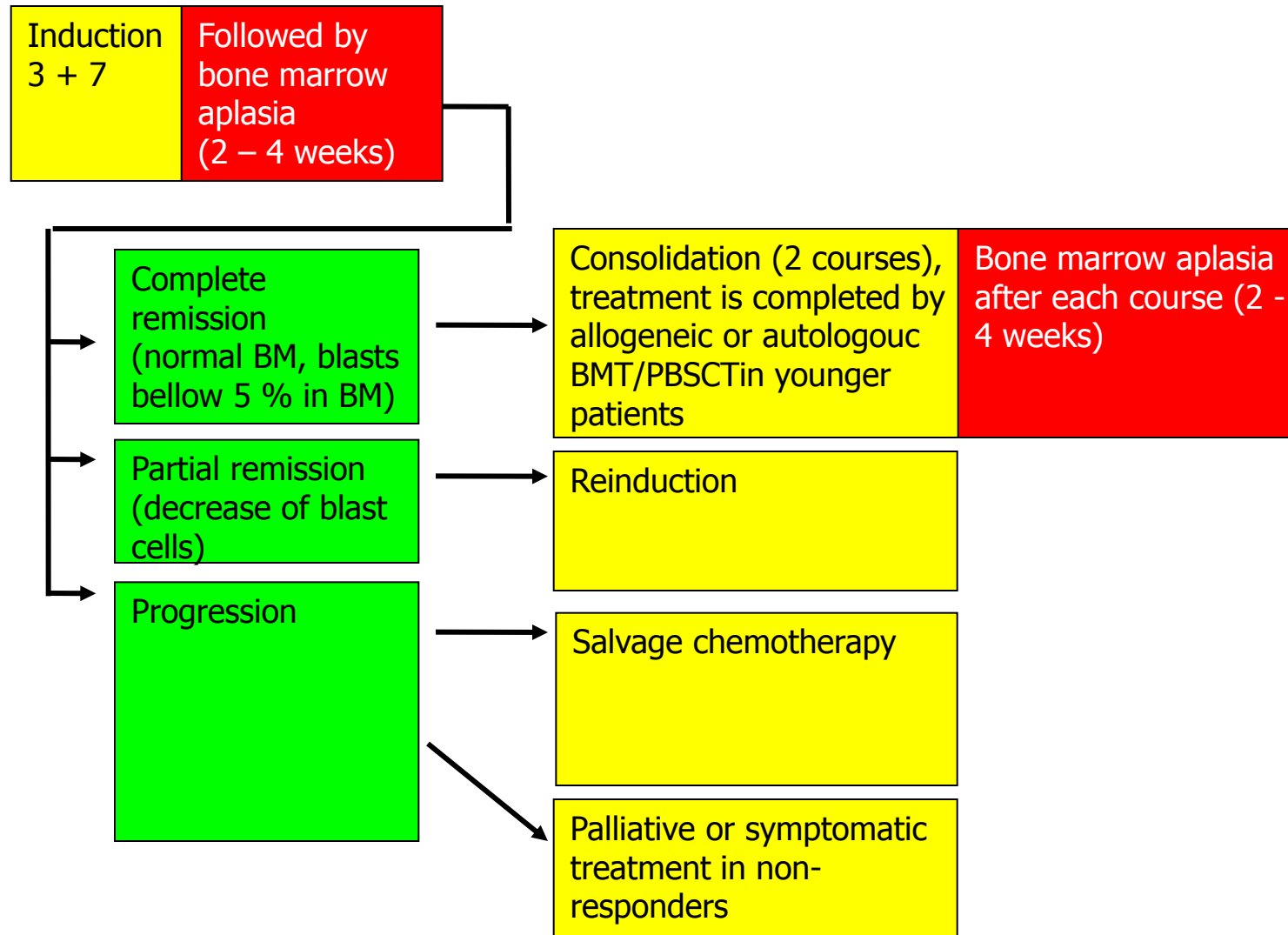






Treatment of AML

Treatment of choice of AML are courses of chemotherapy, the most potent drugs are cytosinarabioside and anthracyclines.



Treatment of AML

Novel drugs for AML:

Midostaurin

Venetoclax

Gilteritinib

Acute promyelocytic leukemia (APL, AML M3)

APL is variant of AML (constitutes about 5-10% of AML in central Europe, about 25% of AML southern Europe, and 50 % of AML in eastern Asia).

There are prominent hemorrhagic complications (DIC, melena, hematuria, pulmonary bleeding, CNS bleeding)

Prognosis of APL was very poor 30 years ago (almost all patients died).

Nowadays, DFS is 80%.

Acute promyelocytic leukemia (APL, AML M3)

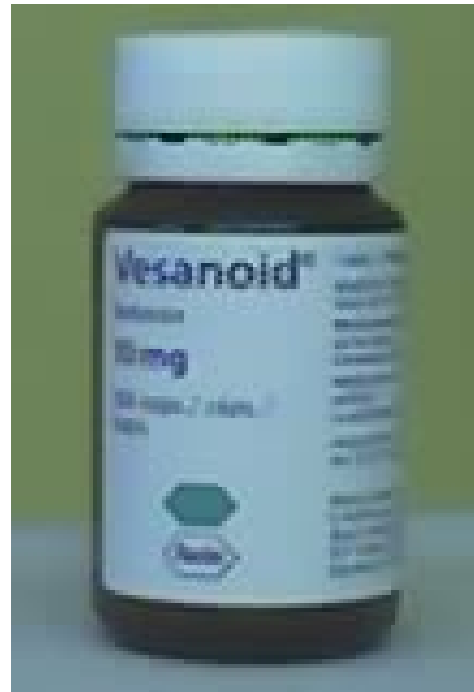
Promyelocytes are granular cells. In granula are coagulopathy-inducing factors (tissue factor...).

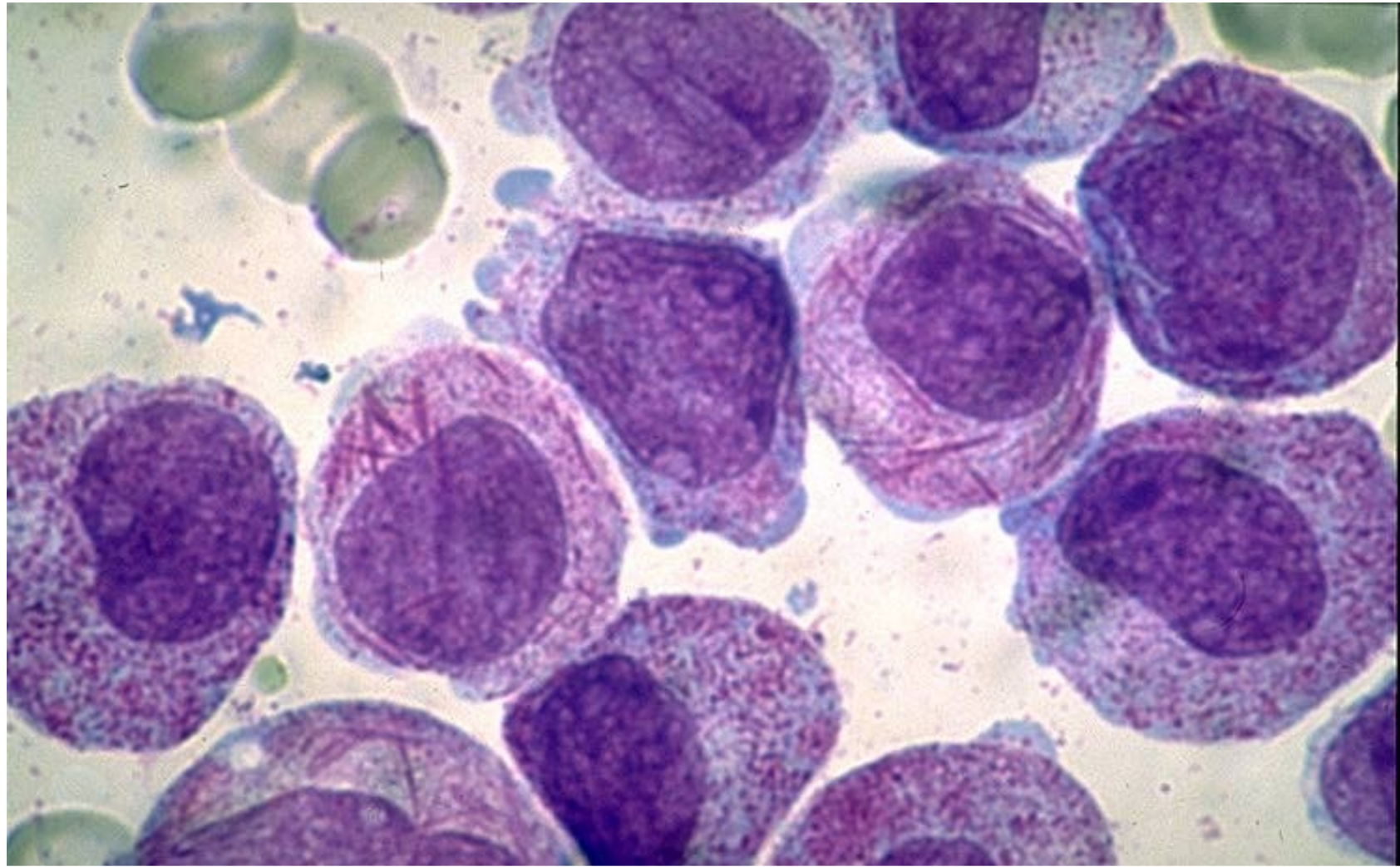
Majority of APL is characterized by t(15;17).
A translocation between chromosome 17 and 15 results in chimeric fusion gene *PML-RARα*.

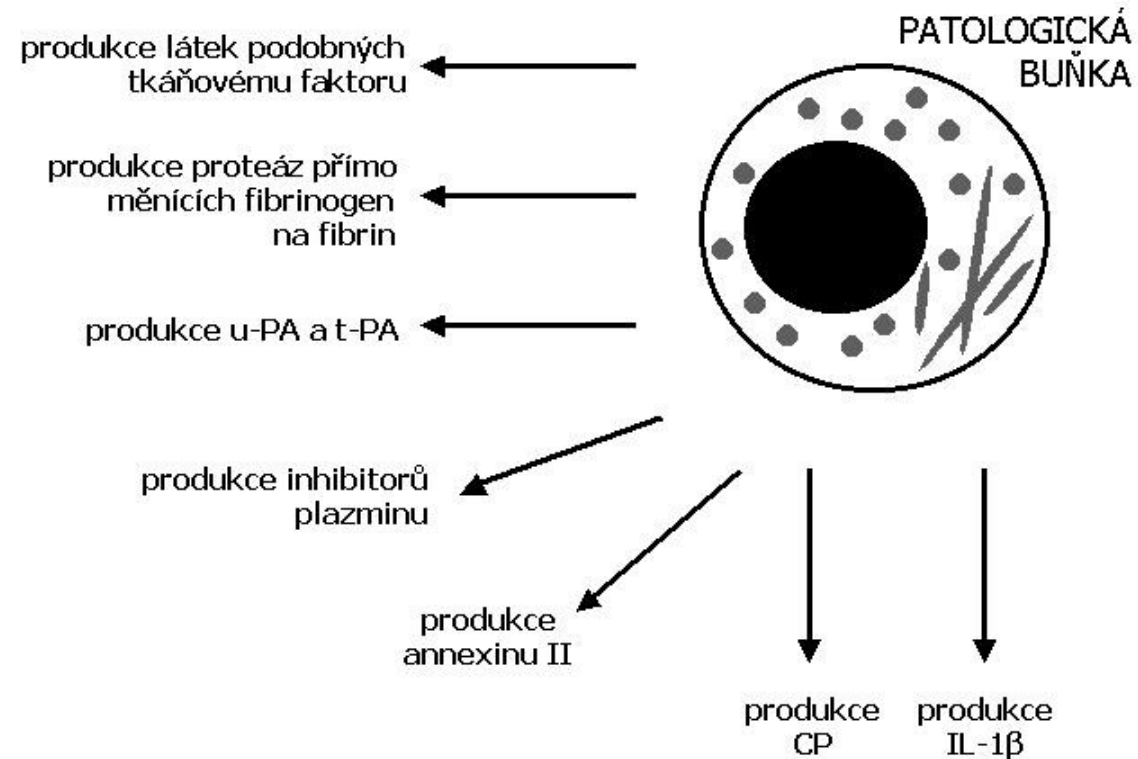
PML-RARα gene produces PML-RARα abnormal receptor for retinoids. (Retinoids are necessary for normal bone marrow cells differentiation). In cells with t(15;17) normal differentiation is stopped.

We can restore differentiation by means of ATRA + ATO or chemo.

Chemotherapy or arsenic trioxide + ATRA is treatment of choice for APL!



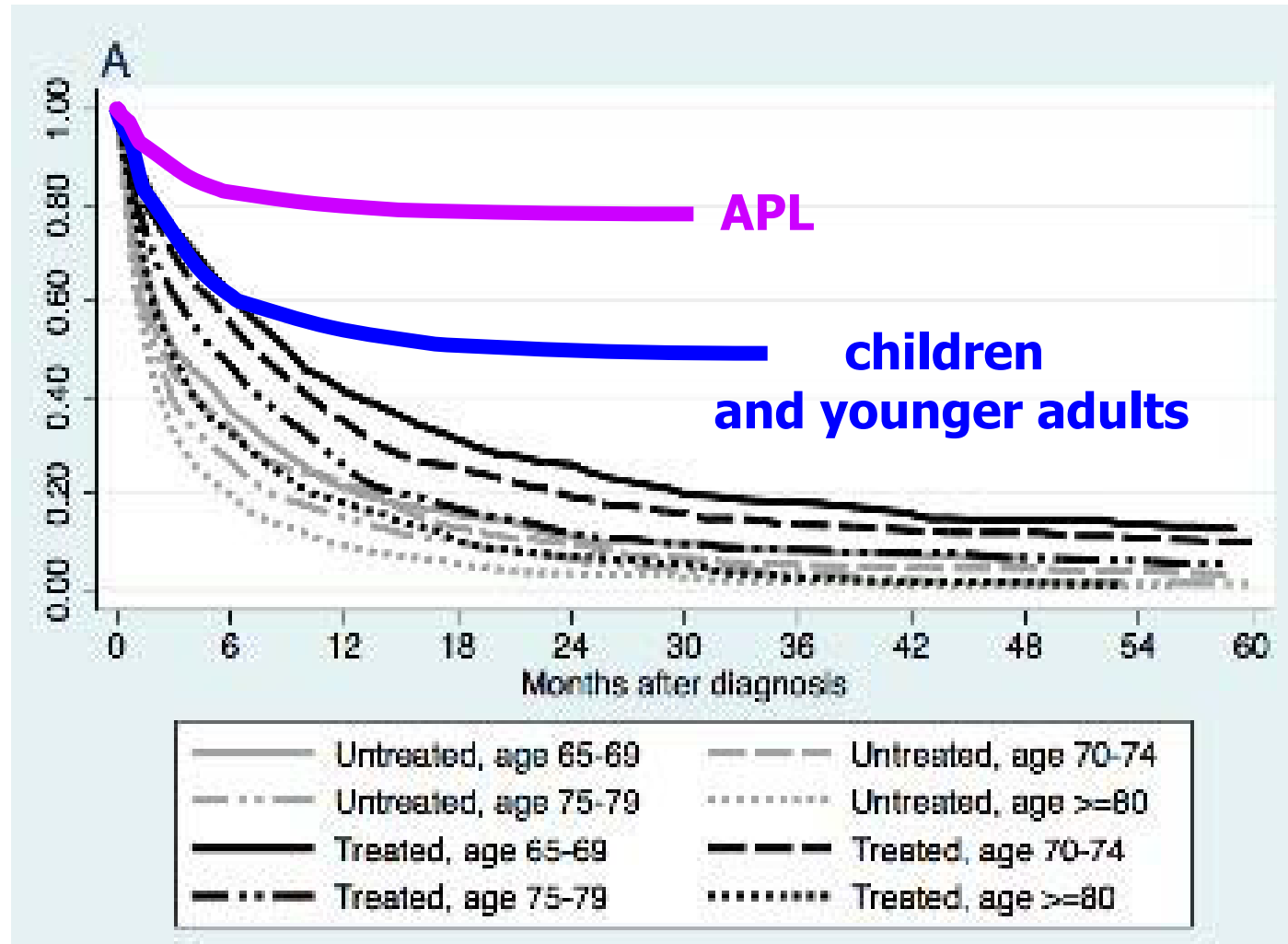




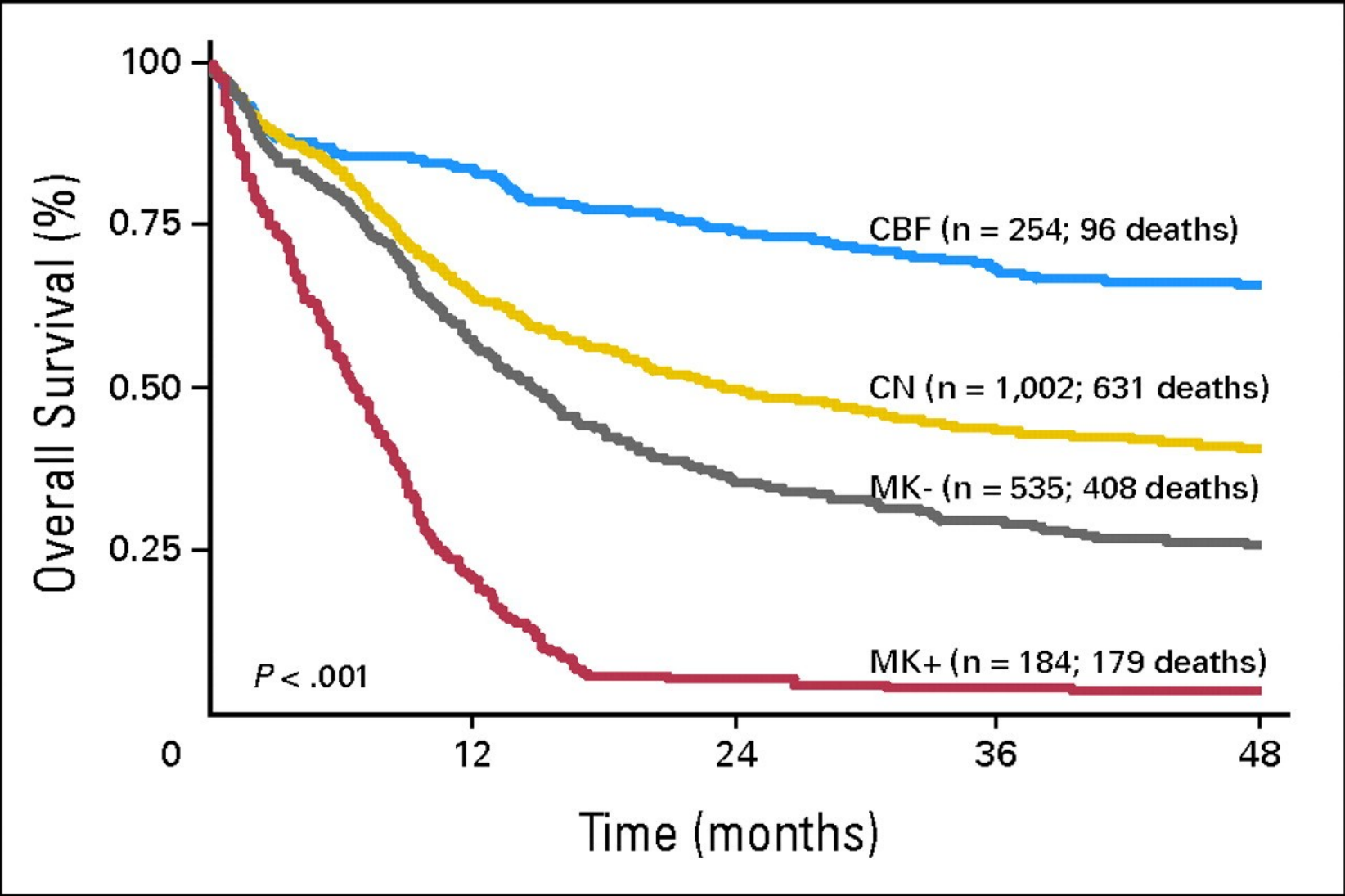
Bleeding diathesis in APL:

CP – *cancer procoagulant*, IL-1 β – interleukin 1 β , t-PA – tissue plasminogen activator, u-PA – urokinase.

Survival of AML patients



Survival of AML patients



good risk
standard risk
poor risk

t(8;21)
inv(16)

normal
karyotype

komplex.
karyotype
- 7

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

The most common leukemia in childhood.

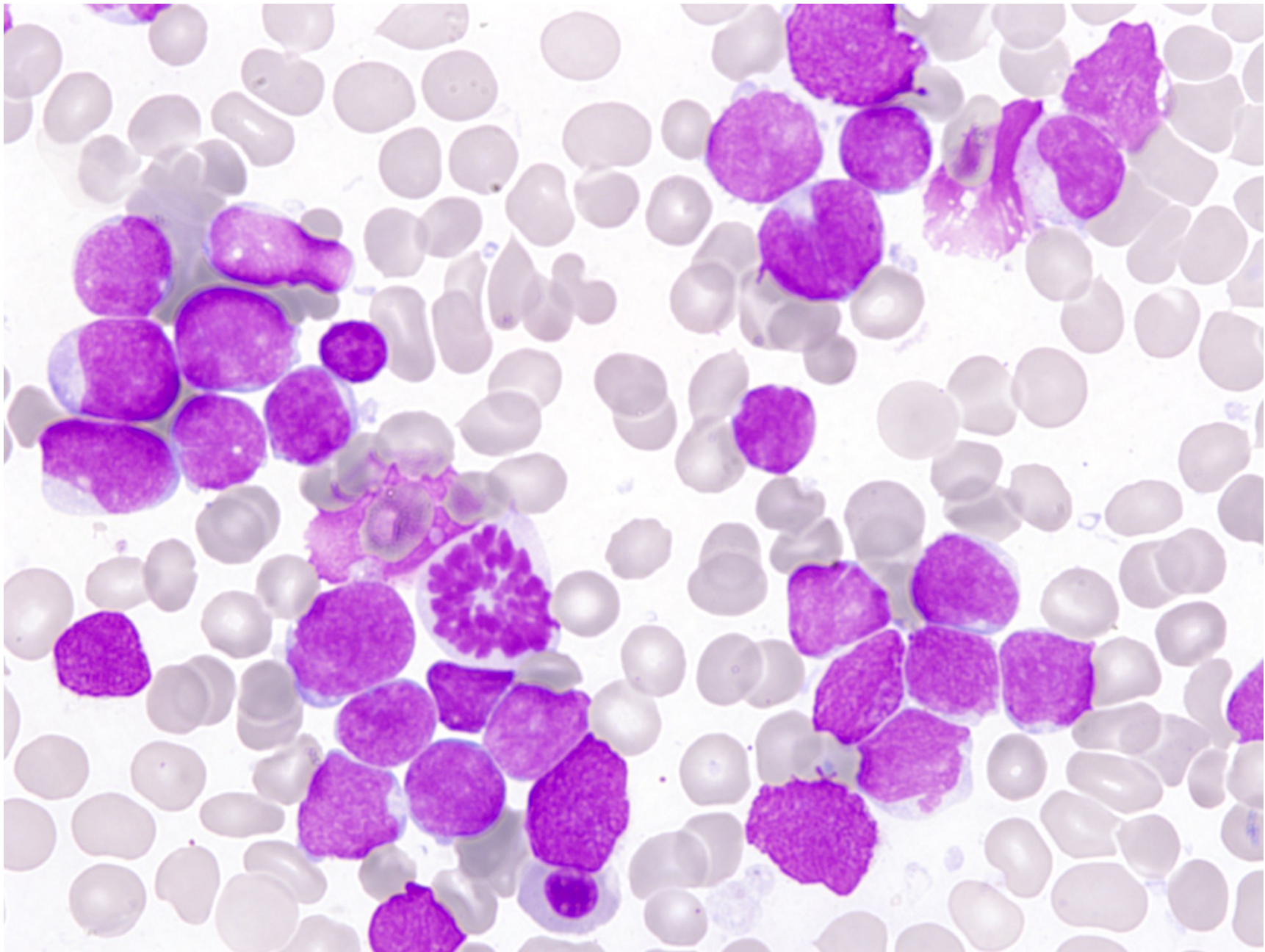
In children - very good prognosis.

In adults - poorer prognosis.

ALL is a neoplastic disease resulting from somatic mutation in a single lymphoid progenitor cell.

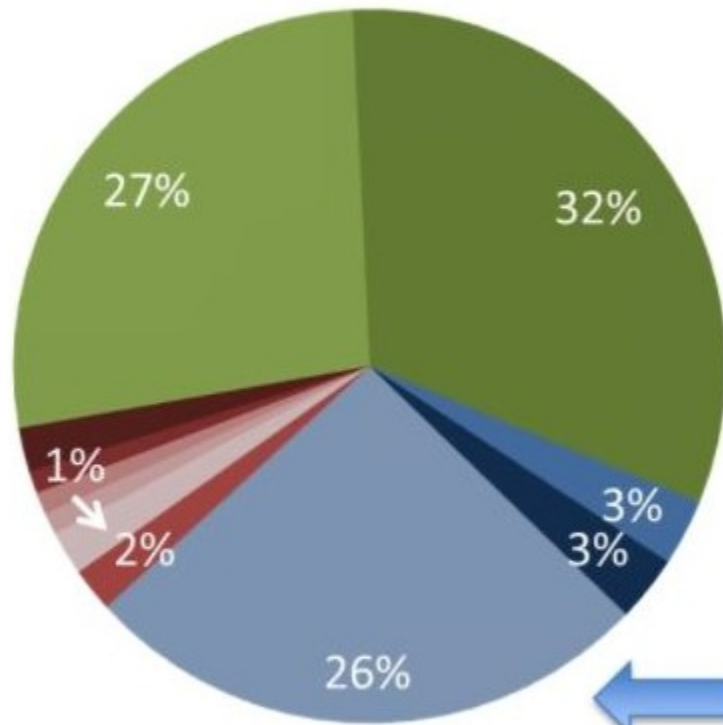
B precursor ALL vs. T precursor ALL

BM - more than 20% of lymphoblasts (usually 80 - 100%).

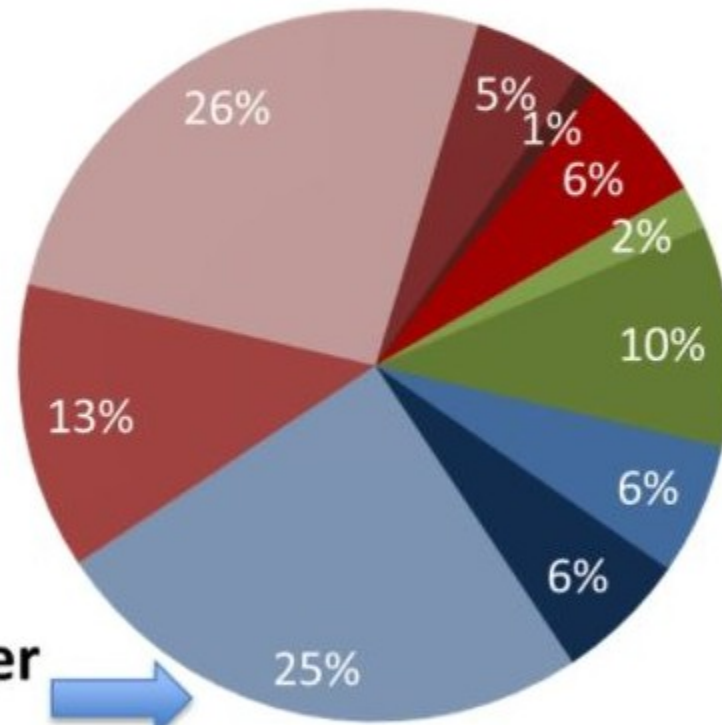


Age specific frequency of genetic subgroups in ALL

**Children & adolescents
(1-24 years)**



**Adults
(25-59 years)**



**B-other
ALL**

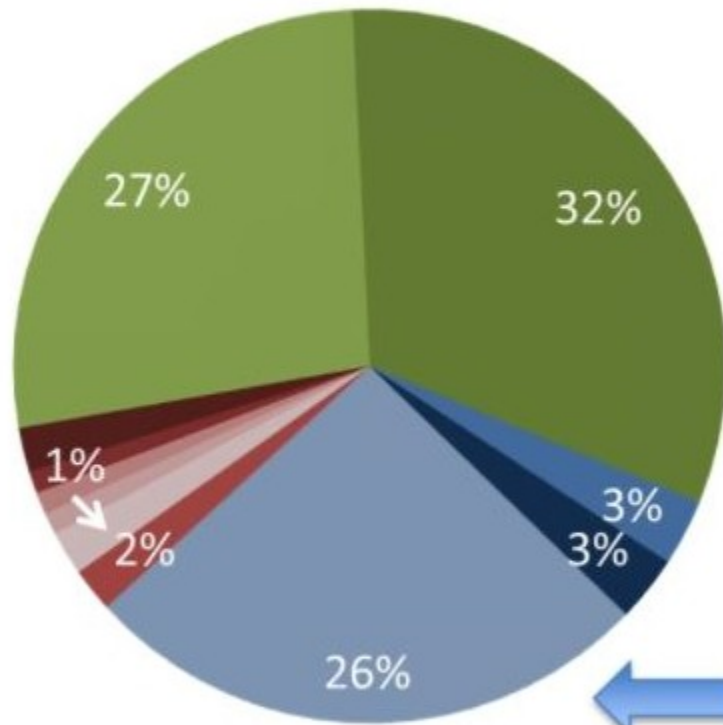
- t(12;21)/ETV6-RUNX1
- IGH translocations
- t(9;22)/BCR-ABL1
- Low hypodiploidy

- High hyperdiploidy
- B-other
- t(17;19)/TCF3-HLF
- iAMP21

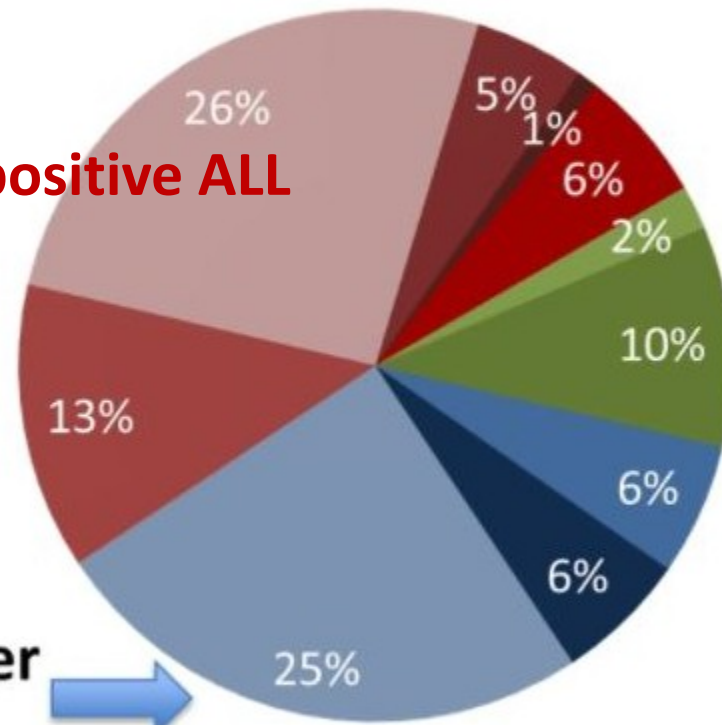
- t(1;19)/TCF3-PBX1
- MLL translocations
- Near haploidy
- Complex karyotype

Age specific frequency of genetic subgroups in ALL

**Children & adolescents
(1-24 years)**



**Adults
(25-59 years)**



Ph positive ALL

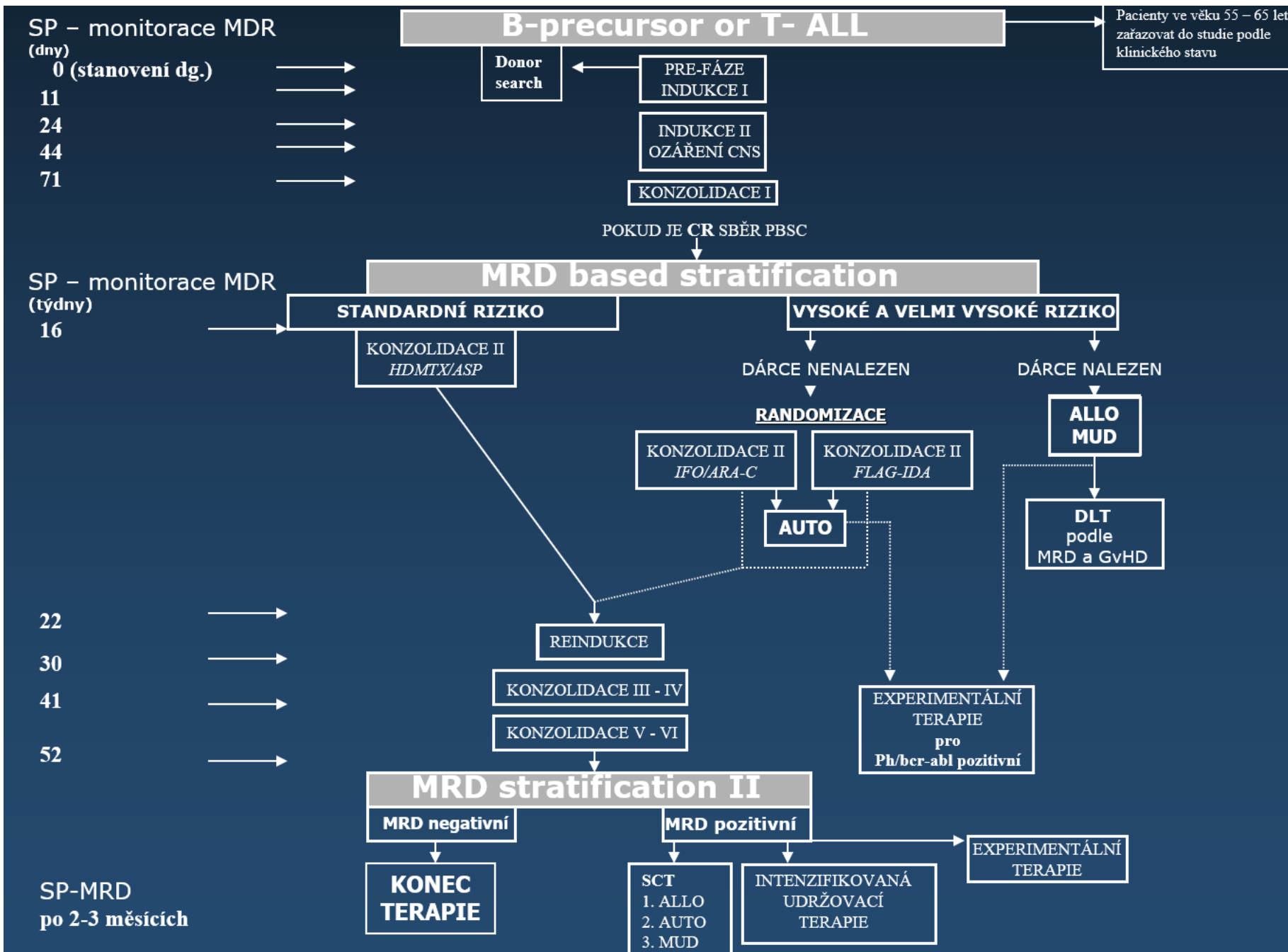
**B-other
ALL**

- t(12;21)/ETV6-RUNX1
- IGH translocations
- t(9;22)/BCR-ABL1
- Low hypodiploidy

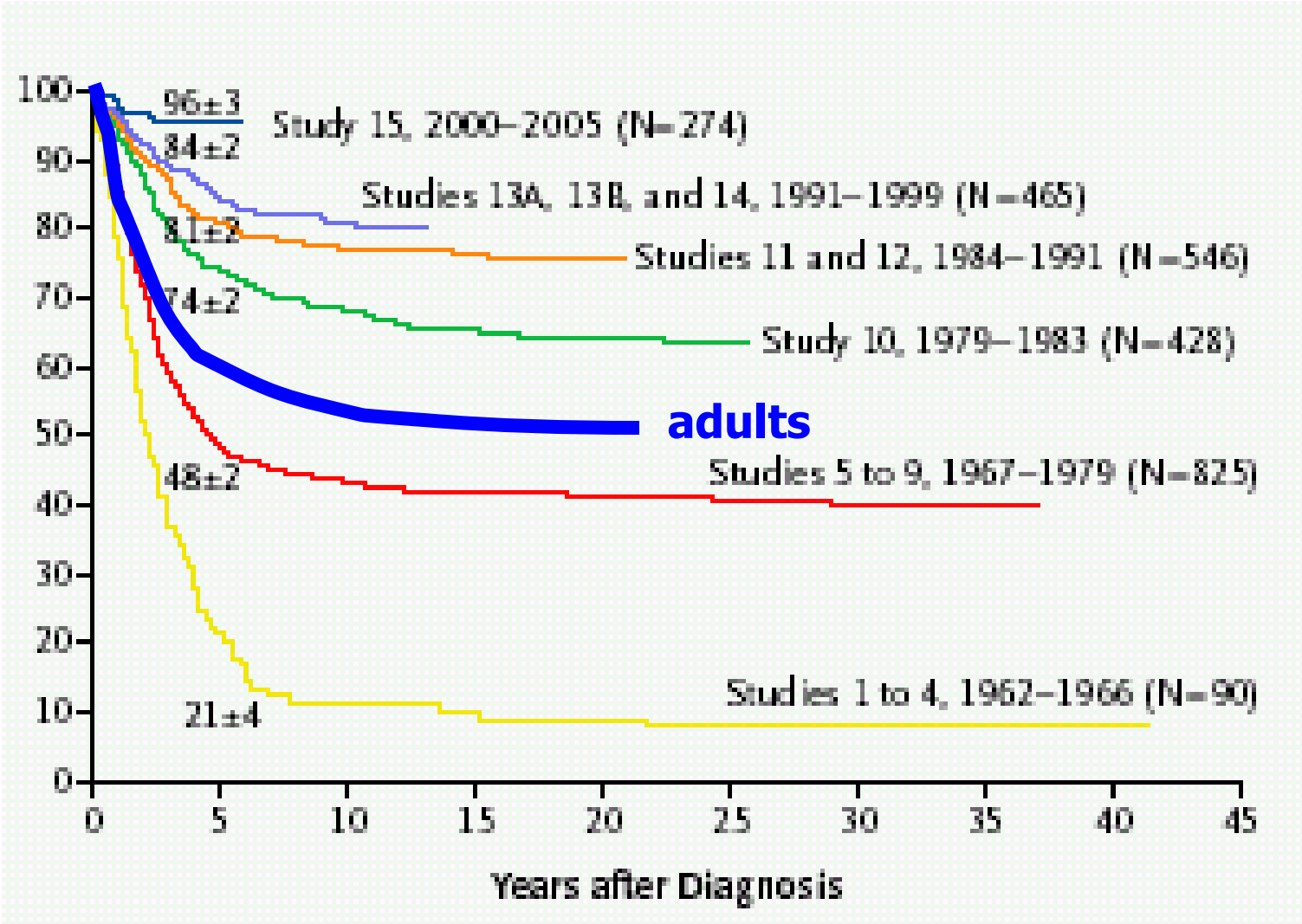
- High hyperdiploidy
- B-other
- t(17;19)/TCF3-HLF
- iAMP21

- t(1;19)/TCF3-PBX1
- MLL translocations
- Near haploidy
- Complex karyotype

ALL – therapy overview



Childhood ALL survival



MYELOYDYSPLASTIC SYNDROMES

Heterogeneous group of malignant diseases with different prognosis – dysplasia of myeloid lineage.

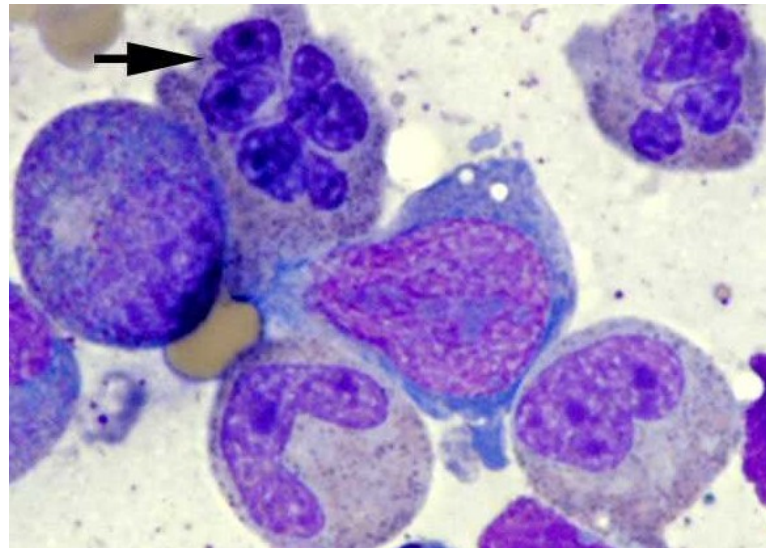
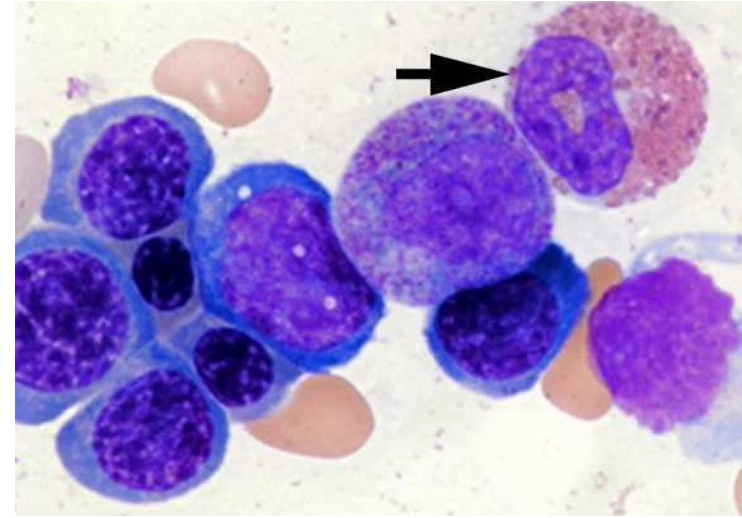
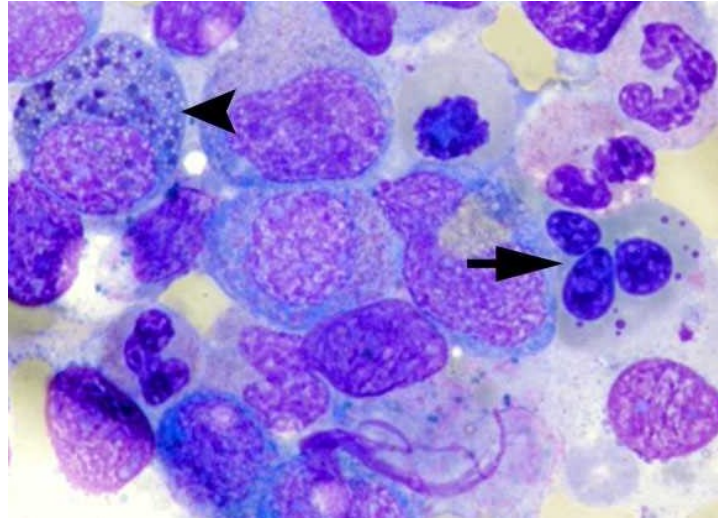
In BM - blasts below 20 % and dysplastic features (hypogranular cells, cells with atypical shape of nucleus, hypergranular cells, cells with abnormal plasma)

The only curative option is BMT/PBSCT in high risk patients.

Patients asymptomatic or without donor - only symptomatic treatment or watch and wait strategy.

MYELODYSPLASTIC SYNDROMES

- dysplastic features



MDS – classification I

| MDS type | Dysplasia | Cytopenia | Ring sideroblasts | Blasts in peripheral blood | Blasts in bone marrow | Cytogenetics |
|---|-----------|-----------|-------------------|----------------------------|-----------------------|---|
| MDS with single lineage dysplasia (MDS-SLD) | 1 | 1 or 2 | <15%, < 5% | < 1%, no Auer rods | <5%, no Auer rods | Any except of del(5q) |
| MDS with mixed lineage dysplasia (MDS-MLD) | 2 or 3 | 1 - 3 | <15%, < 5% | < 1%, no Auer rods | <5%, no Auer rods | Any except of del(5q) |
| MDS with ring sideroblasts (MDS-RS) | | | | | | |
| MDS-SLD-RS | 1 | 1 or 2 | ≥ 15%, ≥ 5%* | < 1%, no Auer rods | <5%, no Auer rods | Any except of del(5q) |
| MDS-MLD-RS | 2 or 3 | 1 - 3 | ≥ 15%, ≥ 5%* | < 1%, no Auer rods | <5%, no Auer rods | Any except of del(5q) |
| MDS with isolated del(5q) | 1-3 | 1-2 | No or few | < 1%, no Auer rods | <5%, no Auer rods | del(5q) or 1 more except of -7 or del(7q) |

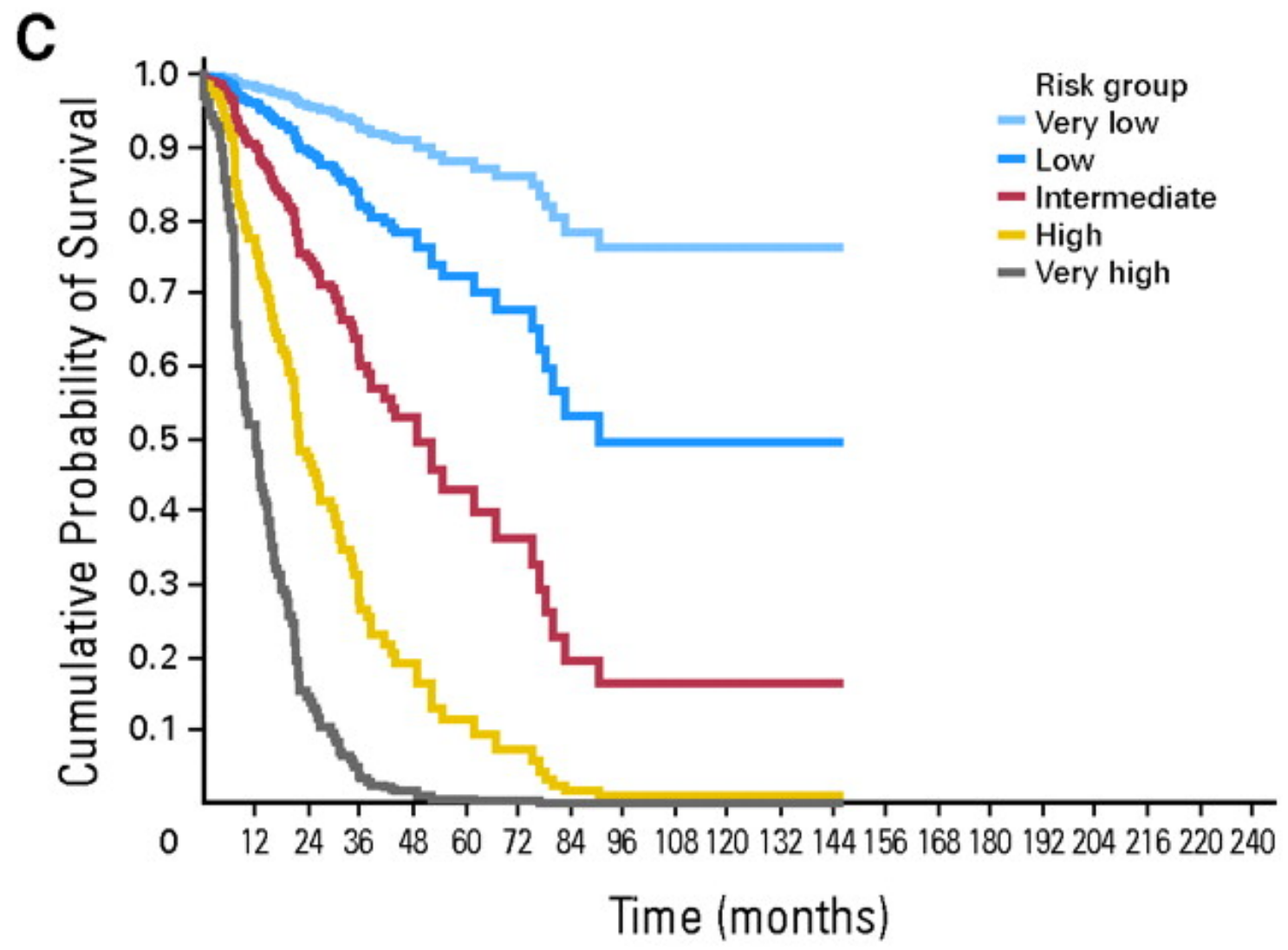
MDS – classification II

| MDS type | Dysplasia | Cytopenia | Ring sideroblasts | Blasts in peripheral blood | Blasts in bone marrow | Cytogenetics |
|---|-----------|-----------|-------------------|----------------------------|-----------------------|---------------------|
| MDS with excess of blasts (MDS-EB) | | | | | | |
| MDS-EB-1 | 0-3 | 1-3 | No or few | 2-4%, no Auer rods | 5-9%, no Auer rods | Any |
| MDS-EB-2 | 0-3 | 1-3 | No or few | 5-19%, or Auer rods | 10-19%, or Auer rods | Any |
| MDS unclassifiable (MDS-U) | | | | | | |
| With 1% of blasts in PB | 1-3 | 1-3 | No or few | 1%, no Auer rods | < 5%, no Auer rods | Any |
| With 1 lineage dysplasia and pancytopenia | 1 | 3 | No or few | < 1%, no Auer rods | < 5%, no Auer rods | Any |
| With cytogenetic abnormality | 0 | 1-3 | < 15% | < 1%, no Auer rods | < 5%, no Auer rods | MDS typical feature |
| Refractory cytopenia in childhood | 1-3 | 1-3 | No | < 2% | < 5% | Any |

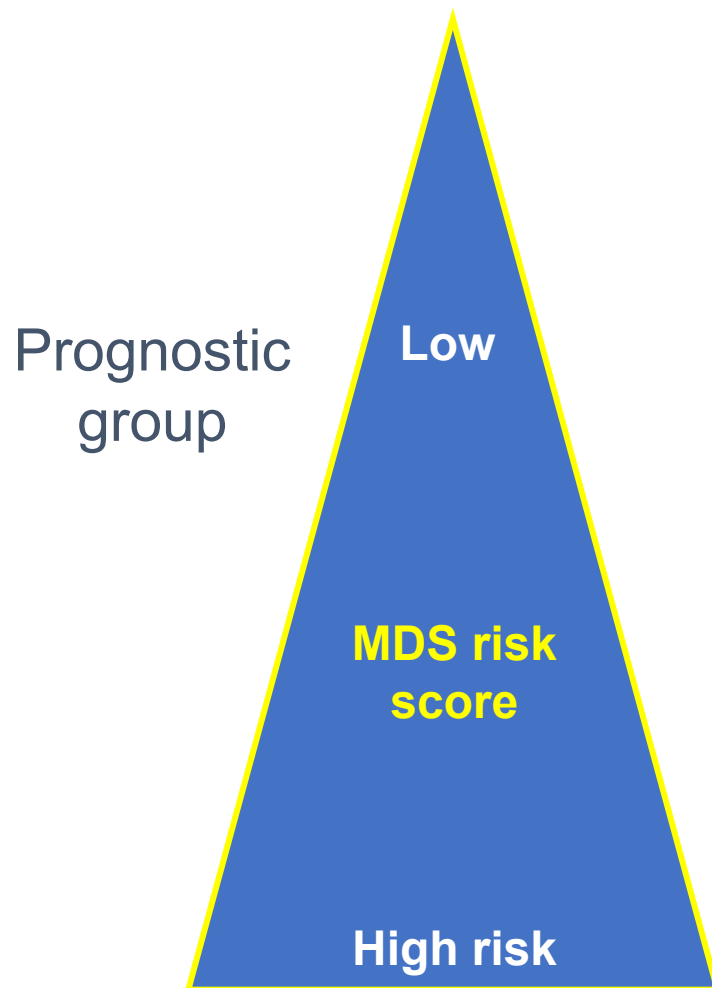
MDS - prognosis

| | Score | | | | |
|------------------------|-------|--------------|------|-------|-------|
| Prognostic marker | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Bone marrow blasts (%) | <5 | 5–10 | | 11–20 | 21–30 |
| Karyotype | Good | Intermediate | Poor | | |
| Cytopenia | 0/1 | 2/3 | | | |

| Score | IPSS subgroup | Median survival (years) |
|---------|---------------|-------------------------|
| 0 | Low | 5.7 |
| 0.5–1.0 | Int-1 | 3.5 |
| 1.5–2.0 | Int-2 | 1.2 |
| > 2.5 | High | 0.4 |

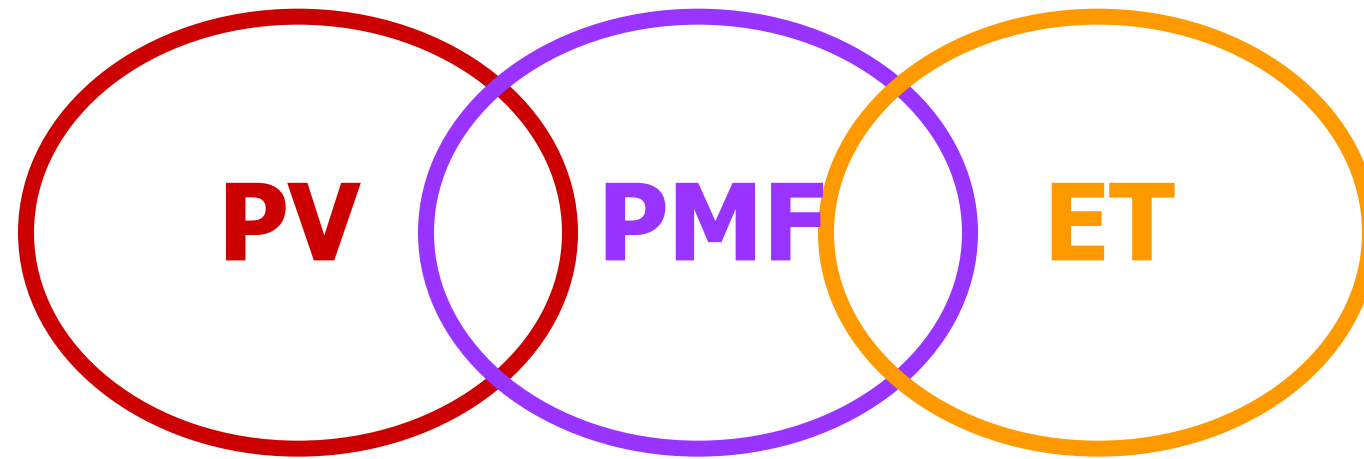


MDS THERAPY



- Supportive care, transfusions, prophylaxis of iron overload
- Erythropoietin
- Immunosuppressive therapy
- Low-dose chemotherapy
- Epigenetic therapy (5-azacytidine)
- Allogeneic SCT, clinical trial

MYELOPROLIFERATIVE NEOPLASMS



MYELOPROLIFERATIVE NEOPLASMS

Proliferation of myeloid lineage

(granulocytic, erythroid, megakaryocytic)

MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative neoplasms (MPN)

Chronic myeloid leukemia (CML), *BCR-ABL1*⁺

Chronic neutrophilic leukemia (CNL)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

PMF, prefibrotic/early stage

PMF, overt fibrotic stage

Essential thrombocythemia (ET)

Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of

PDGFRA, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*

Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement

Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement

Myeloid/lymphoid neoplasms with *FGFR1* rearrangement

Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2

POLYCYTHEMIA

Polycythemia is characterized by an increase of the total red cell volume.

Primary form (PV, clonal neoplastic disorder)

Secondary forms due to appropriate or inappropriate increases in levels of EPO (hemoglobins with high affinity to oxygen, high altitudes, pulmonary and heart diseases, tumours producing EPO)

PV is characterised by increases not only of the number of red cells but also of the granulocytes and platelets and splenomegaly.

POLYCYTHEMIA VERA

Diagnosis

Peripheral blood count

Histology of bone marrow

Total erythrocyte volume

Erythropoietin level

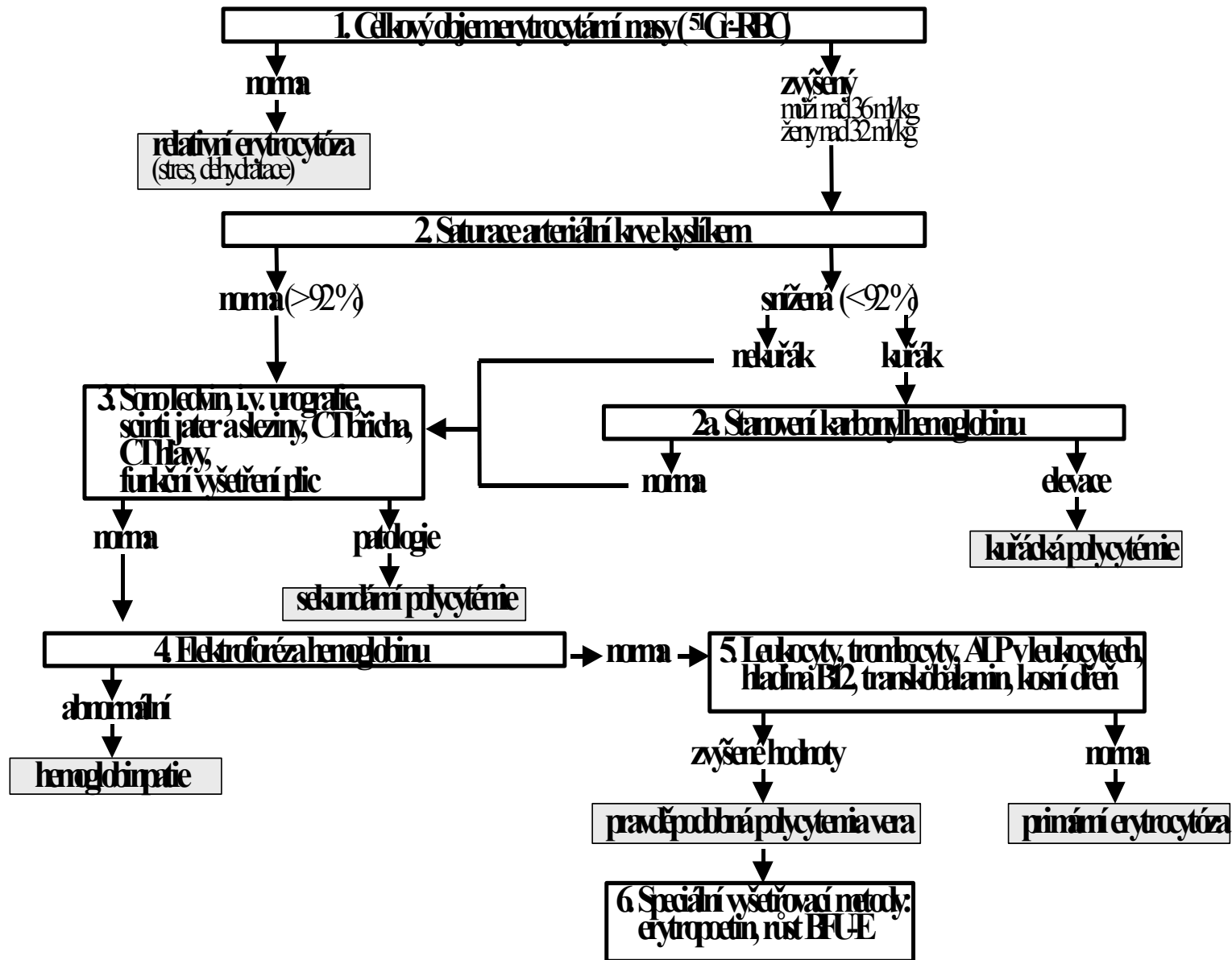
JAK2 V617F mutation

We have to exclude all secondary polycythemias

Secondary polycythemias are more frequent than PV

Complications - bleeding, thrombosis, leukemia, bone marrow fibrosis

POLYCYTHEMIA VERA – differential diagnosis







POLYCYTHEMIA VERA

Therapy

Phlebotomy

Antiaggregant therapy of anticoagulation therapy

Interferon alpha

Hydroxyurea

Ruxolitinib (JAK2 inhibitor)

ESSENTIAL THROMBOCYTHEMIA

Clonal proliferation of megakaryocytes in bone marrow and increased peripheral blood platelet count.

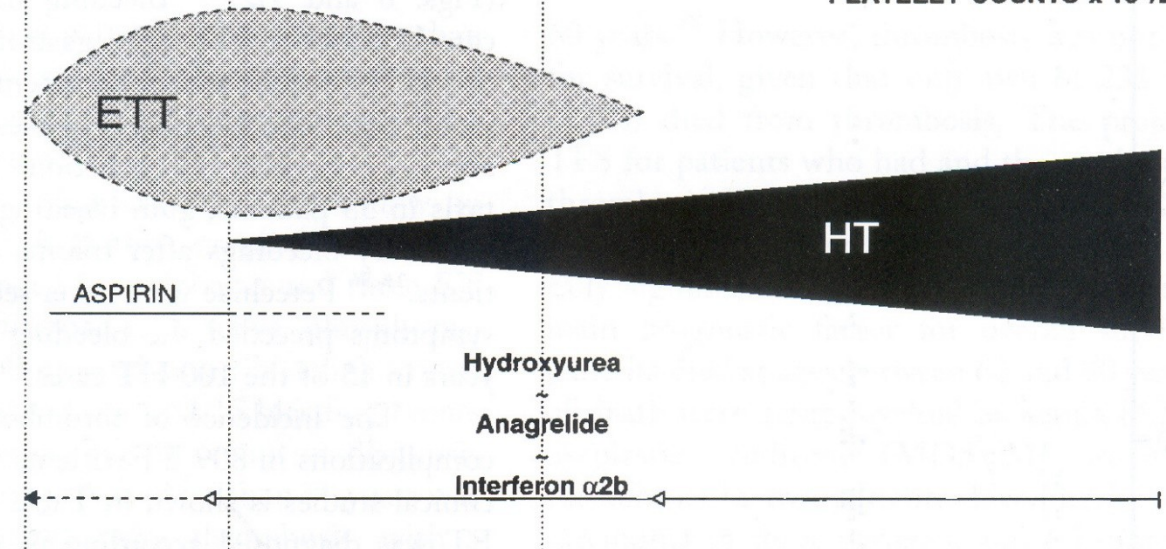
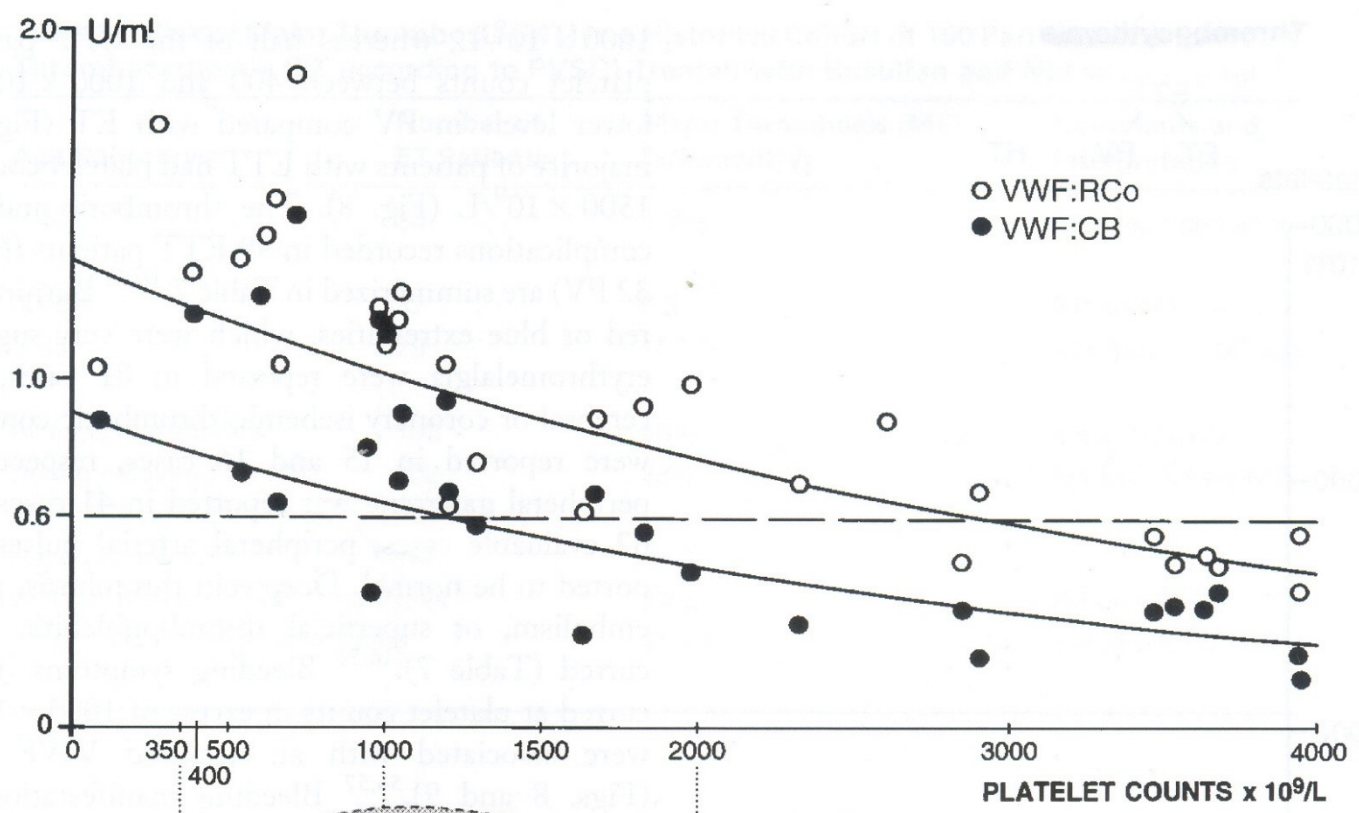
***JAK2 V617F* mutation, calreticulin mutation**

Differential diagnosis:

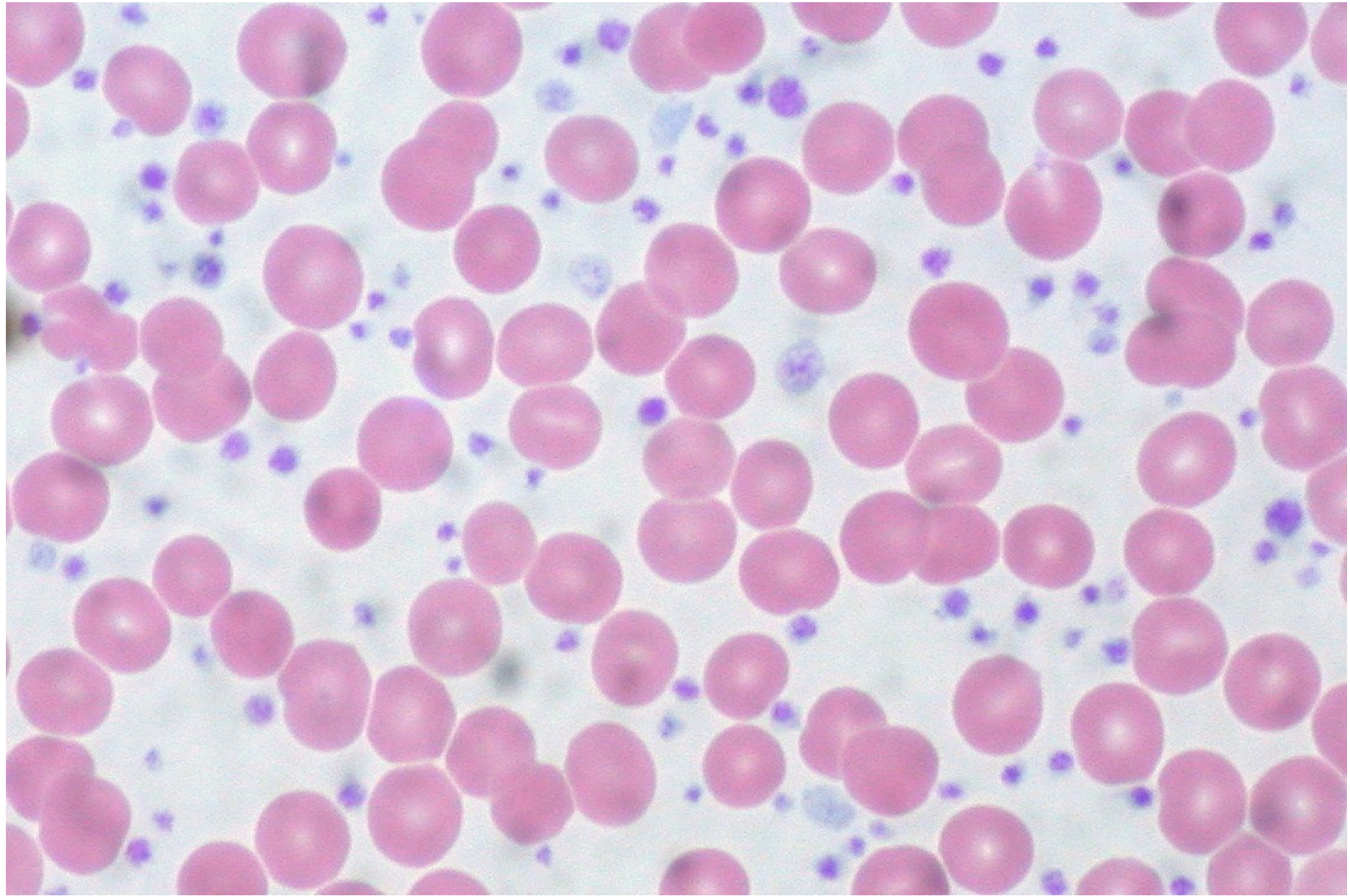
Secondary thrombocytemias (sideropenia, chronic infection, splenectomy, malignancies, bleeding, hemolysis).

Myeloproliferative disorders, MDS

Complications - bleeding, thrombosis, leukemia, bone marrow fibrosis



ETT: ERYTHROMELALGIC THROMBOTIC THROMBOCYTHEMIA
 HT: HEMORRHAGIC THROMBOCYTHEMIA



ESSENTIAL THROMBOCYTHEMIA

Therapy

Antiaggregant therapy of anticoagulation therapy

Interferon alpha

Anagrelide

Hydroxyurea

PRIMARY MYELOFIBROSIS

Clonal disorder characterized by transformation of normal bone marrow to fibrotic and non-functional bone marrow.

JAK2 V617F, CALR mutation, MPL mutation

Hyperplastic stage - increased precursors of platelets in BM, increased WBC, RBC and PLT.

Late stage – fibrosis (extramedullary hematopoiesis leading to massive splenomegaly).

Prognosis – median shorter than in PV or ET.

PRIMARY MYELOFIBROSIS

Therapy

Interferon alpha

Anagrelide

Hydroxyurea

JAK2 inhibitors (ruxolitinib)

Supportive care

Allogeneic transplantation

Lymphoma

LYMPHOMA

Lymphoid tissue involvement (lymph nodes, other lymphoid tissue)

- **Mature B cell neoplasms**
- **Mature T cell and natural killer (NK) cell neoplasms**
- **Precursor lymphoid neoplasms**
- **Hodgkin lymphoma**
- **Immunodeficiency-associated lymphoproliferative disorders**

LYMPHOMA - symptoms

Local expansion symptoms

Systemic symptoms

Weight loss

Subfebrilia, fever

(>3 weeks)

Pruritus

Night sweat

Fatigue

LYMPHOMA - symptoms

Local expansion symptoms

Lymphadenopathy peripheral

Lymphadenopathy mediastinal

(cough, feeling of pressure in the chest, upper vena cava syndrome)

Lymphadenopathy abdominal

(hydronephrosis, abdominal discomfort)

Splenomegaly

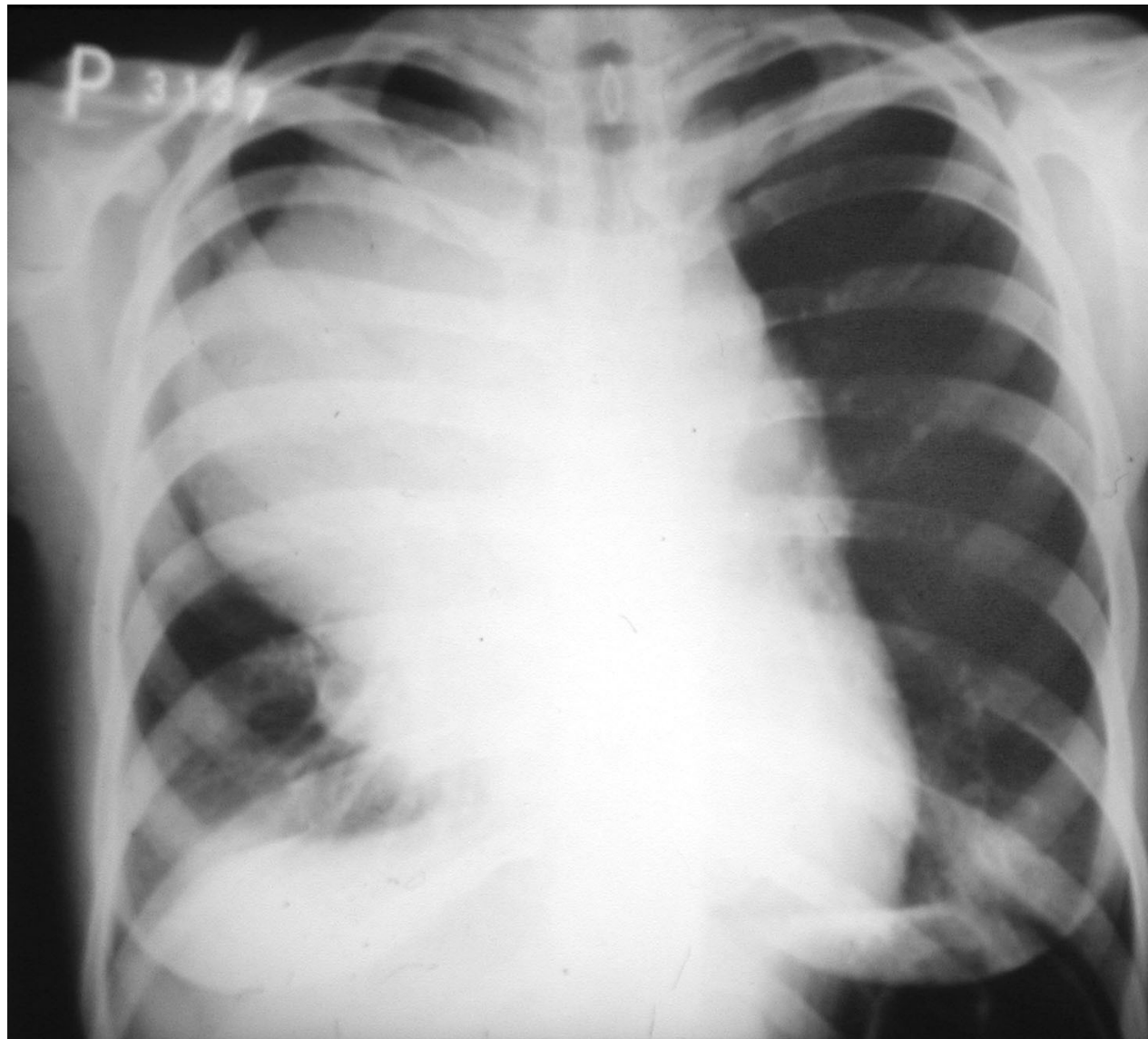
(abdominal discomfort, quick feeling of satiety)

Bone marrow involvement

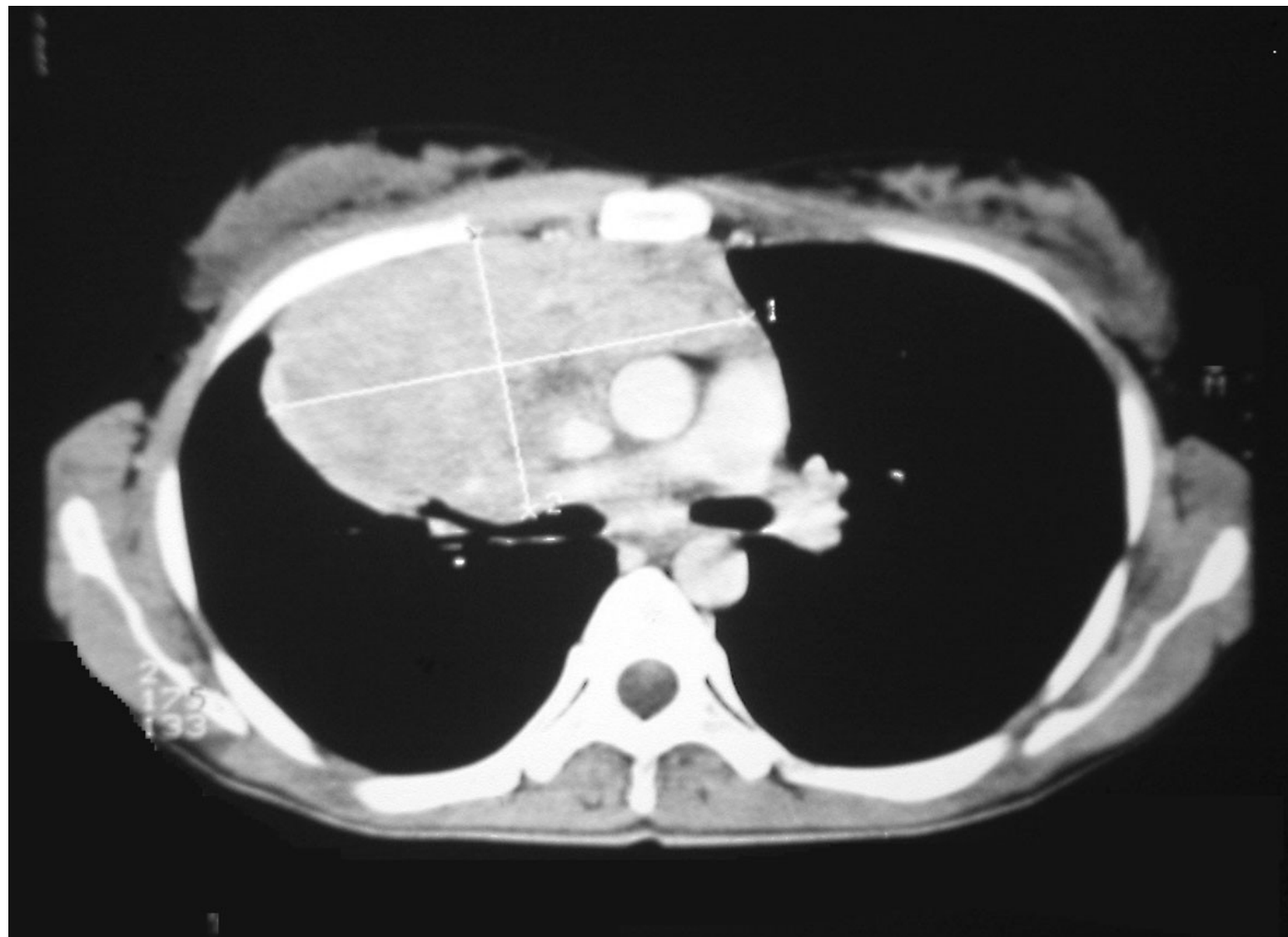
(cytopenia)

Osteolytic bone lesions

LYMPHOMA - symptoms

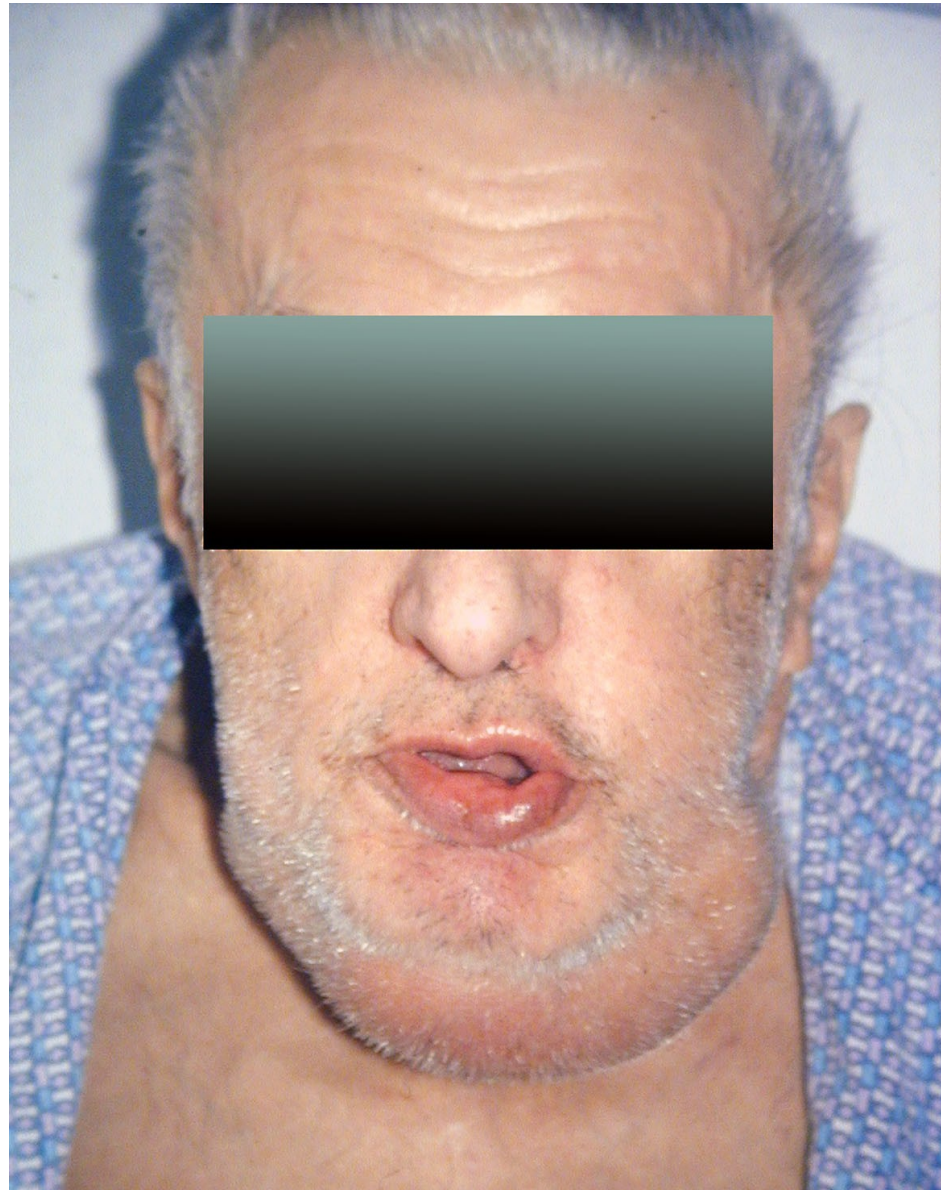


LYMPHOMA - symptoms

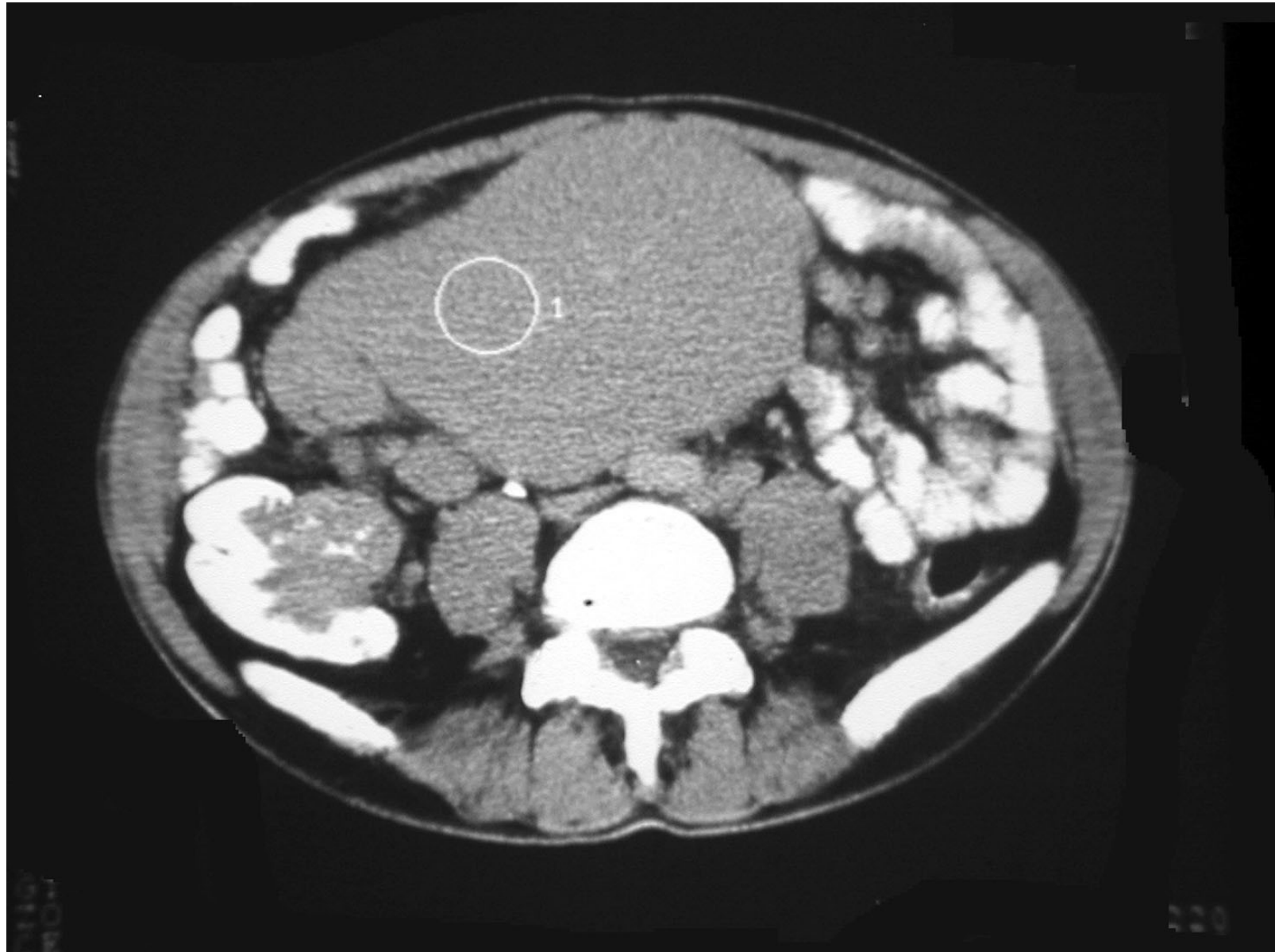




LYMPHOMA - symptoms



LYMPHOMA - symptoms



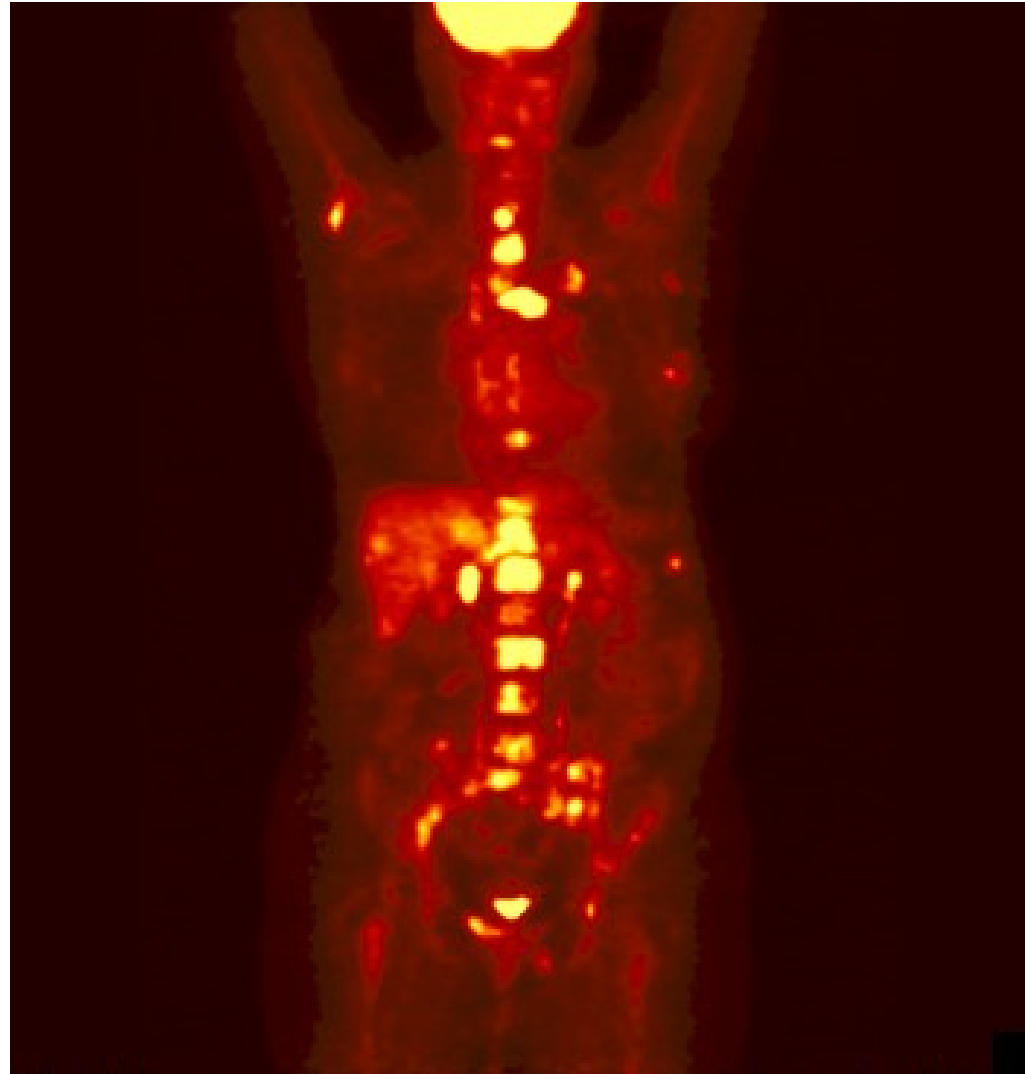
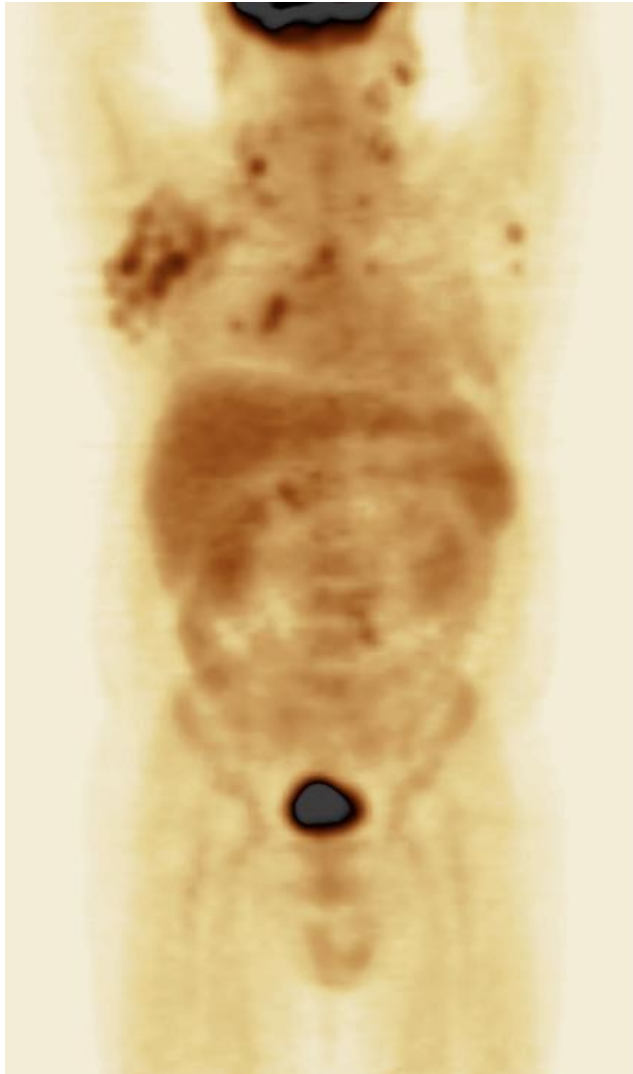
LYMPHOMA - symptoms



LYMPHOMA - symptoms



LYMPHOMA - symptoms



NON-HODGKIN LYMPHOMA

- **Mature B cell neoplasms**
 - **Mature T cell and natural killer (NK) cell neoplasms**
-
- **Lymph node involvement**
 - **Extranodal lymphoma**

Indolent NHL

slow growth - remission possible, cure unlikely
= start of treatment only with symptoms

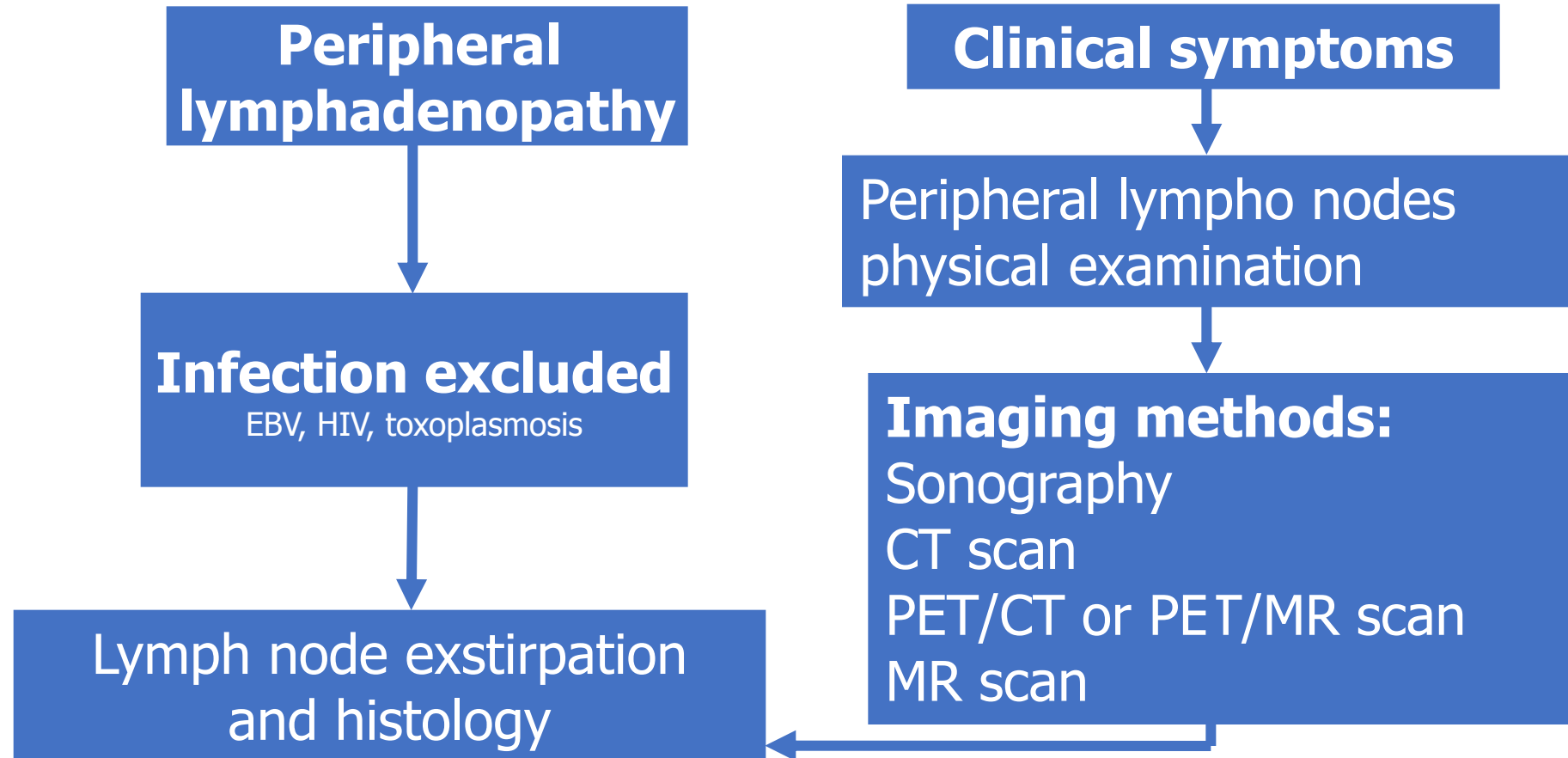
Aggressive NHL

potentially curable, treatment start as soon as possible

Very aggressive NHL

NON-HODGKIN LYMPHOMA

Diagnostics



NON-HODGKIN LYMPHOMA

Staging

CT (neck, upper arms, chest, abdomen and pelvis)

- or MRI

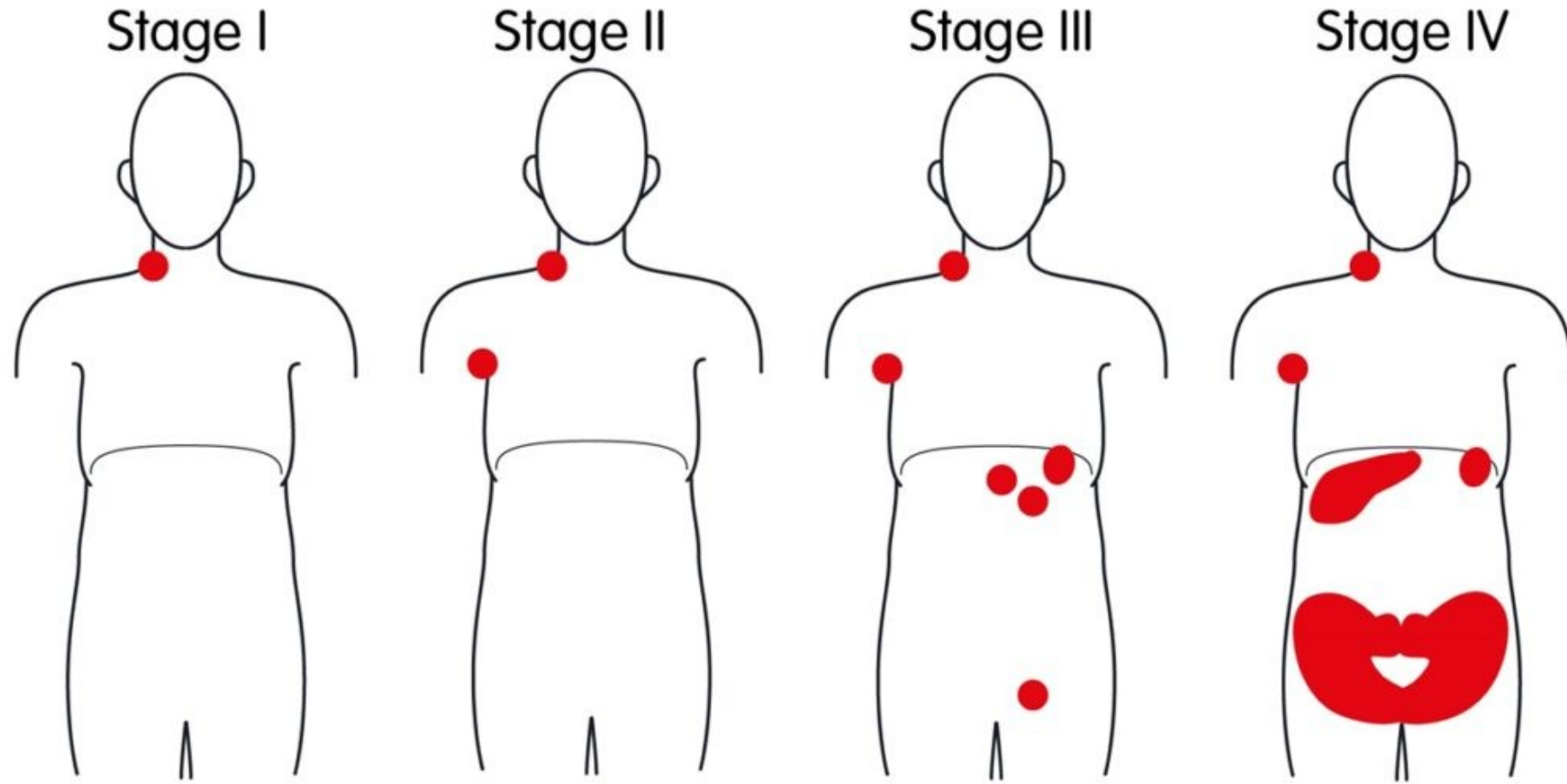
- or now PET/CT, alternatively PET/MR

Trephine biopsy and bone marrow histology

Where appropriate, a specialized examination
(gastroscopy, colonoscopy, lumbal puncture...)

NON-HODGKIN LYMPHOMA

Staging of lymphoma



A: absence of B symptoms B: fever, night sweats, weight loss

NON-HODGKIN LYMPHOMA

Prognostication

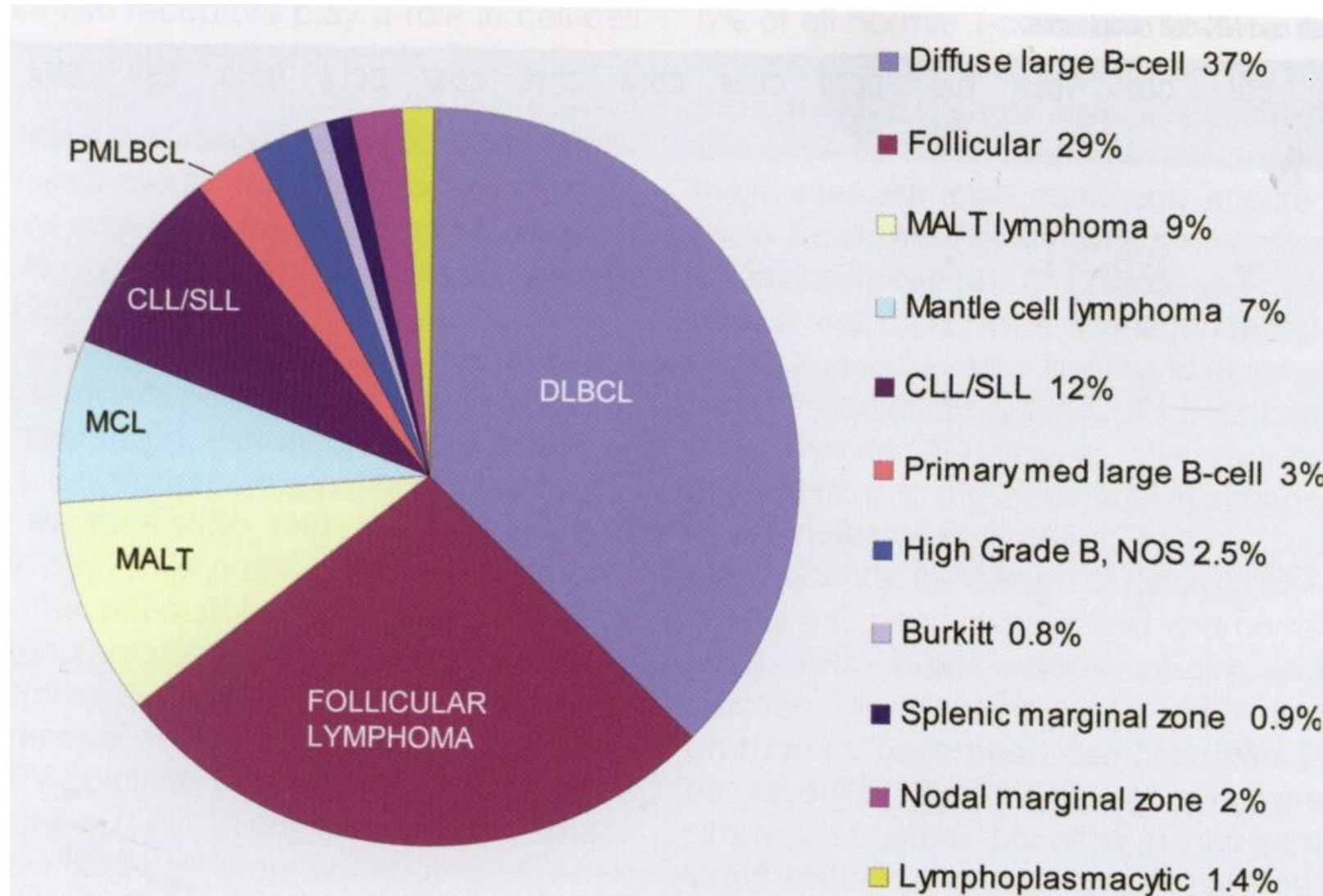
Stage I and II = **limited stage**

Stage III and IV = **advanced stage**

(several prognostic indexes for advanced stage – IPI, FLIPI...)

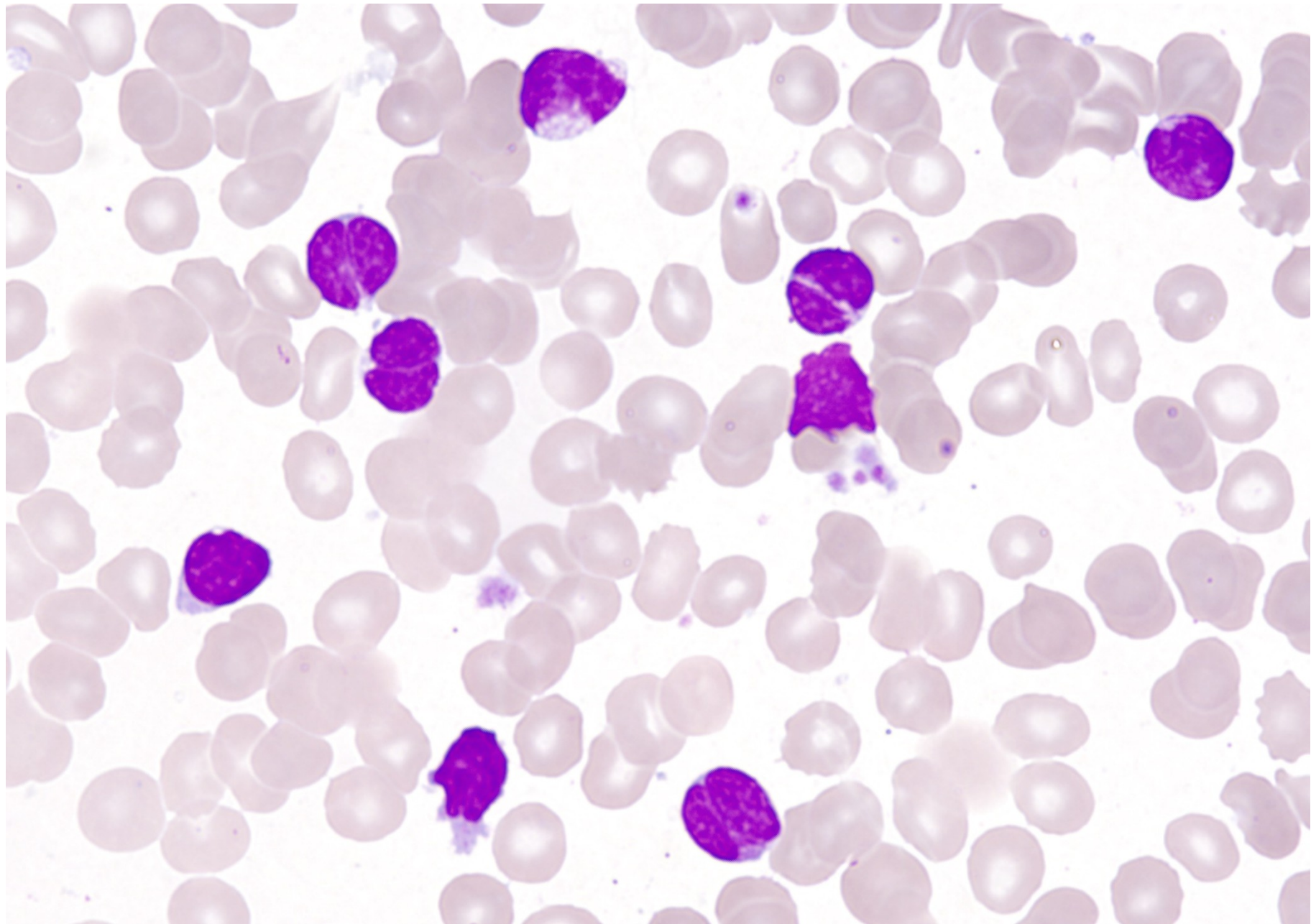
NON-HODGKIN LYMPHOMA

B-cell NHL subtypes

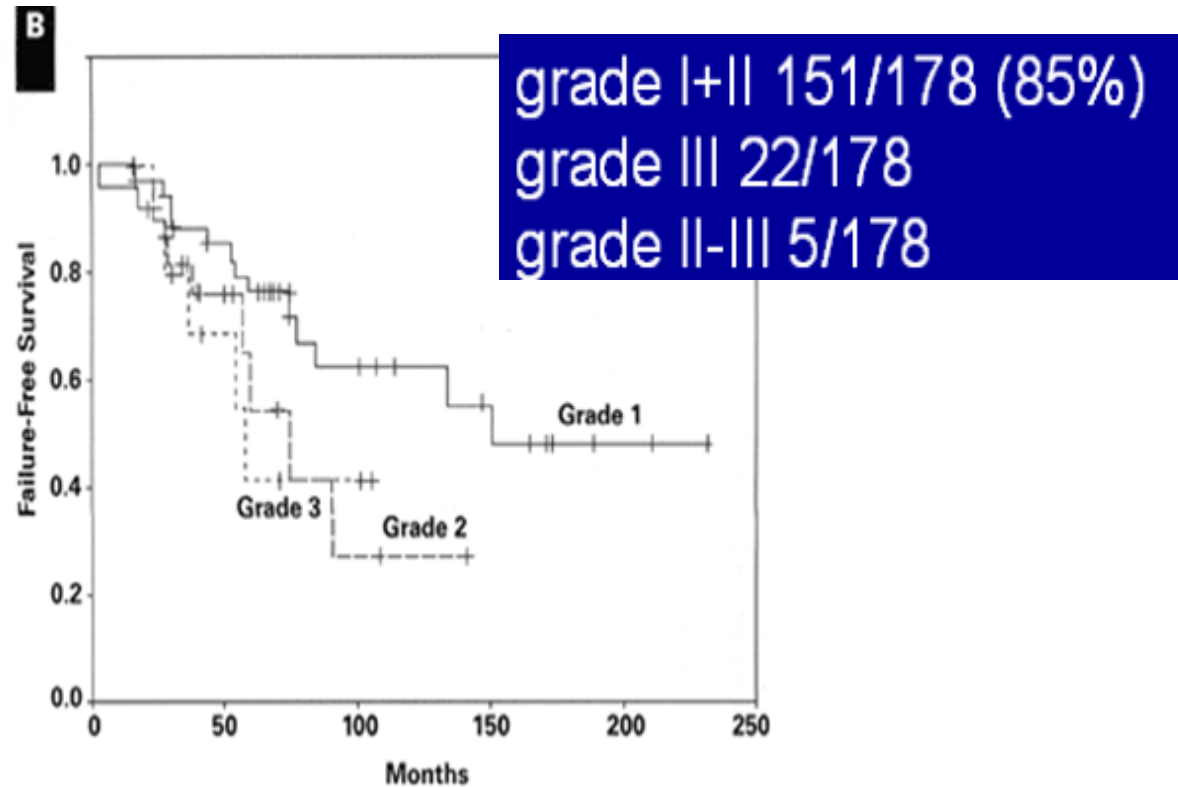
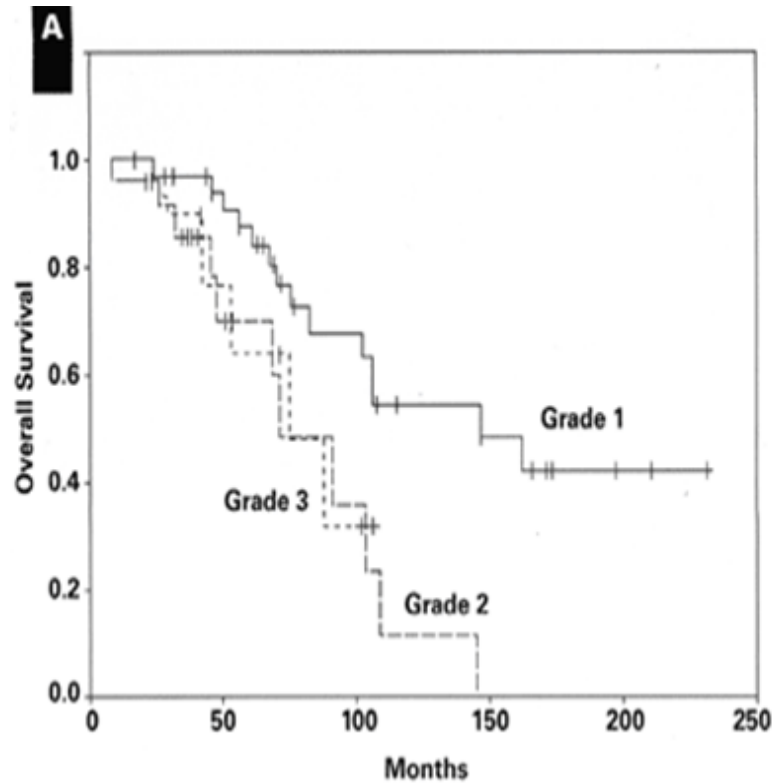


Indolent NHL - follicular lymphoma

- Survival without treatment several years in many patients
- Radiotherapy for limited stage (I.-II. st.) has curative potential
- Systemic treatment leading to remission, but no cure; repeatedly relapsed disease
- Systemic treatment in symptomatic patients only



Follicular lymphoma prognosis according to histology



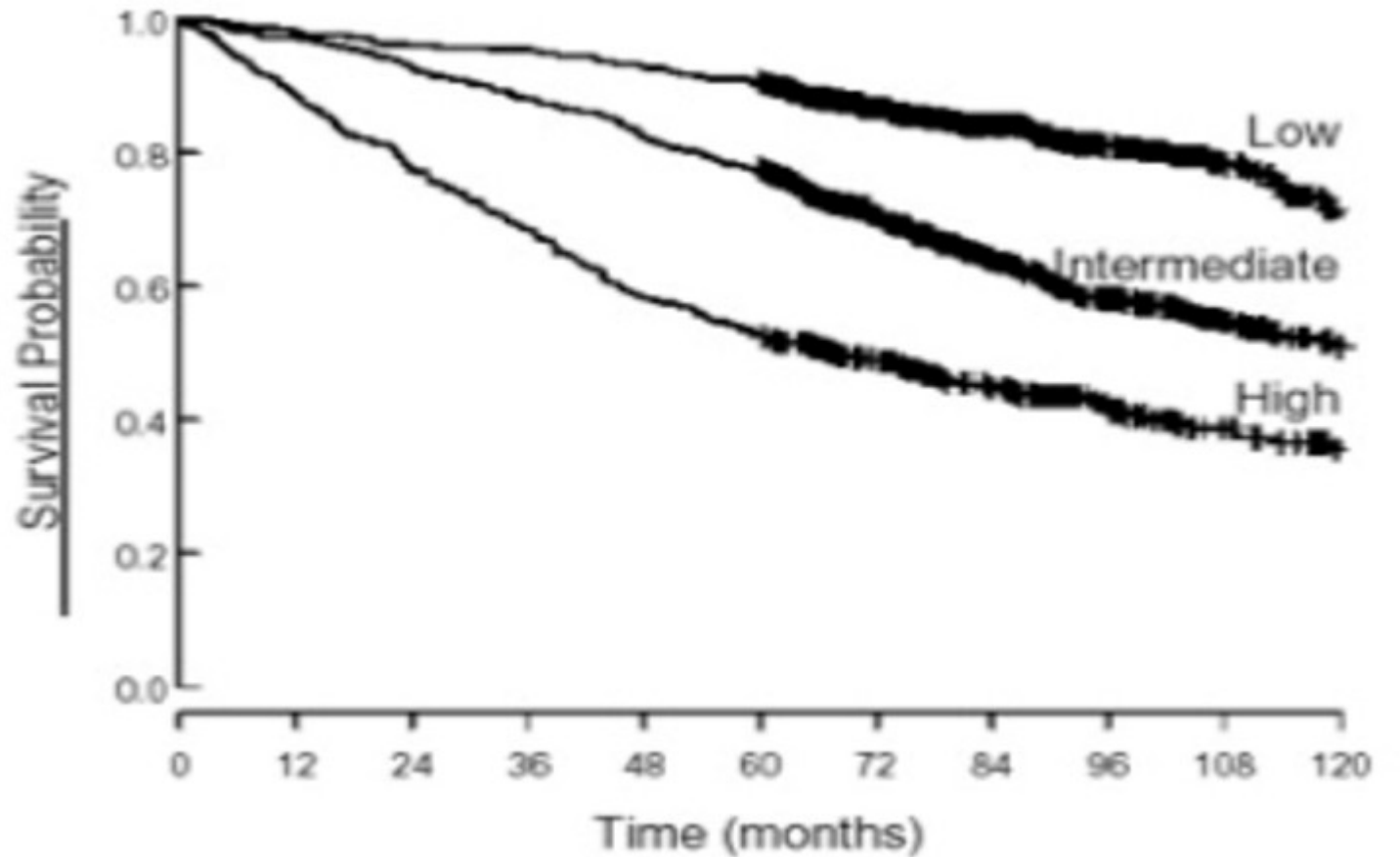
Follicular lymphoma prognostic index (FLIPI)

- Hemoglobin below 120 g/L
- Age over 60 years
- LDH above norm
- Stage II B or higher
- Involved lympho ode areas over 4

Low – FLIPI 0-1

Intermediate – FLIPI 2

High – FLIPI 3 and higher



Follicular lymphoma therapy

First-line therapy

- Limited FL (stadia I+II): IF RT 25-35Gy
- Advanced FL (stadia III+IV): anti-CD20 antibody + chemotherapy (R-CHOP regimen...)

Therapy of relapse

- Chemoimmunotherapy with anti-CD20 antibody +/- maintenance with monoclonal antibody
- High-dose therapy and autologous bone marrow transplant
- Allogeneic bone marrow transplant
- Radioimmunotherapy
- Radiotherapy (limited forms)

Indolent NHL - MALT lymphoma

- MALT – Mucosa Associated Lymphatic Tissue lymphoma
- Etiologic role of antigen stimulation, *H. pylori* infection
- Majority: MALT lymphomas of stomach
- Symptoms: non-healing stomach ulcers

MALT lymphoma therapy

Limited clinical stages (I or II)

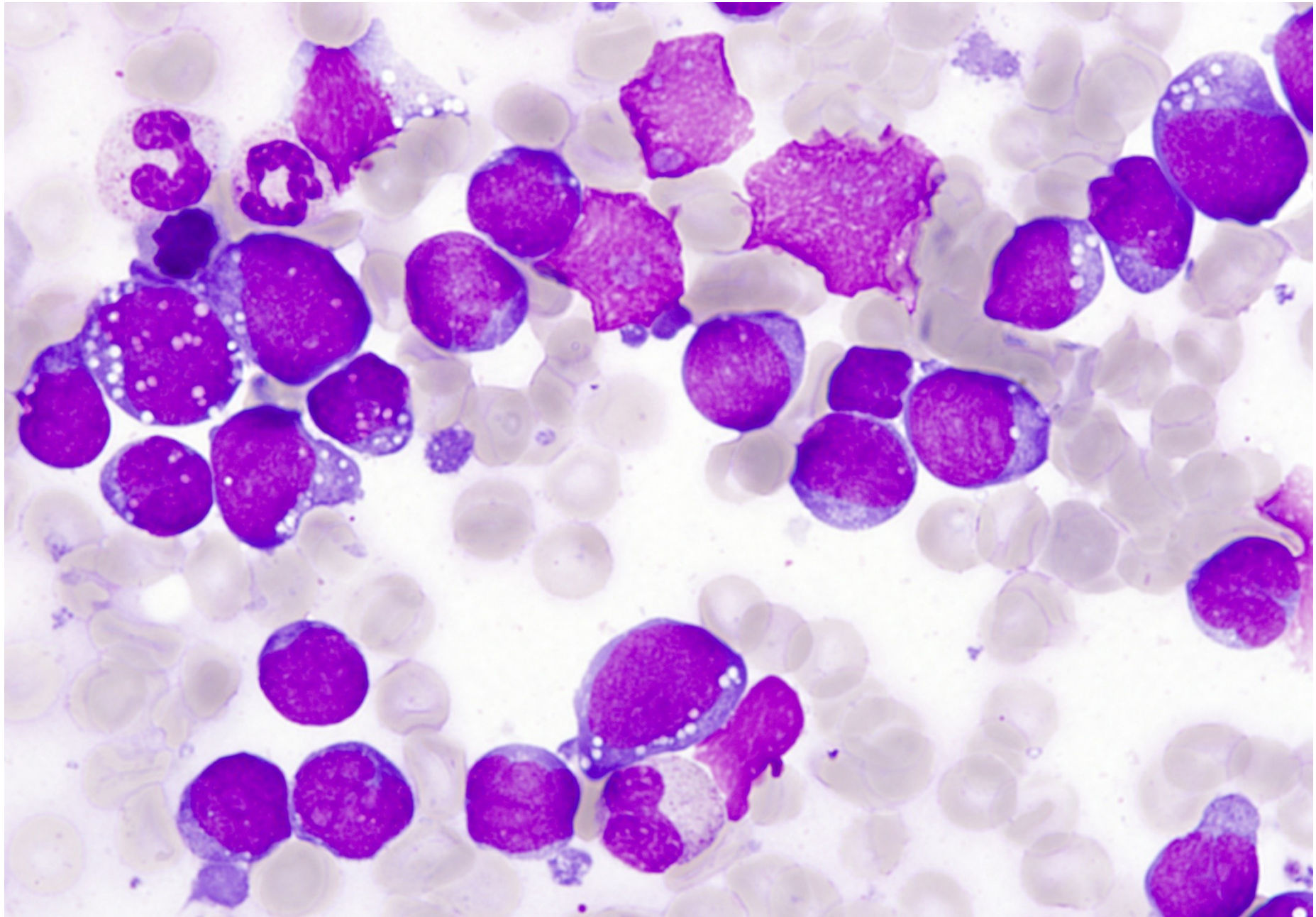
- Antibiotics, radiotherapy (surgery as alternative)

Generalized clinical stages III or IV

- Chemoimmunotherapy (as in follicular lymphoma)

Aggressive NHL – principles of therapy

- **Paliative**
 - Mantle cell lymphoma
- **Curative**
 - DLBCL
 - Burkitt lymphoma



Aggressive NHL - DLBCL

Diffuse large B-cell lymphoma

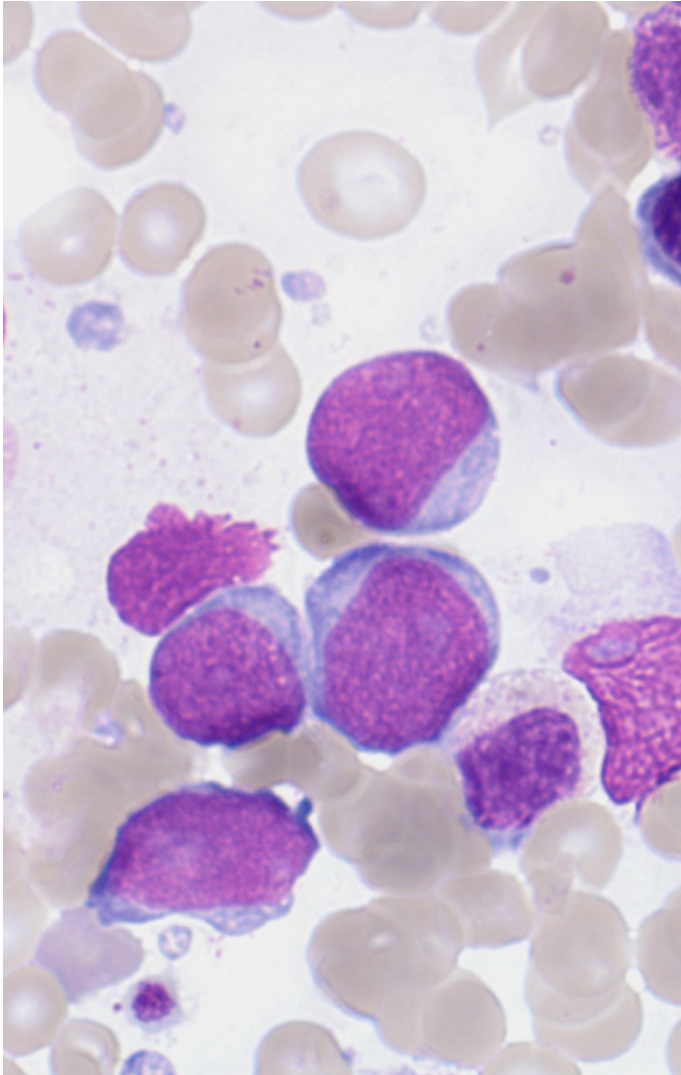
The most common lymphoma

Symptoms

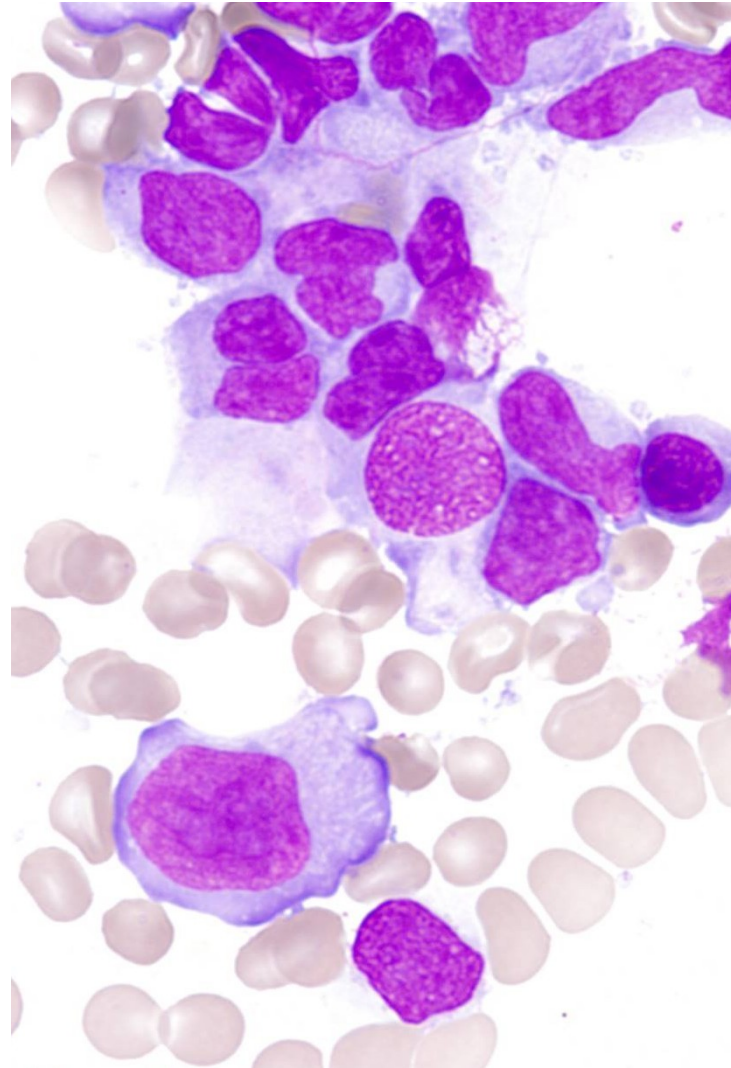
- Rapid local growth
- Large tumor mass
- Continuous generalization
- Frequent involvement of the central nervous system and bones

DLBCL – different morphological forms

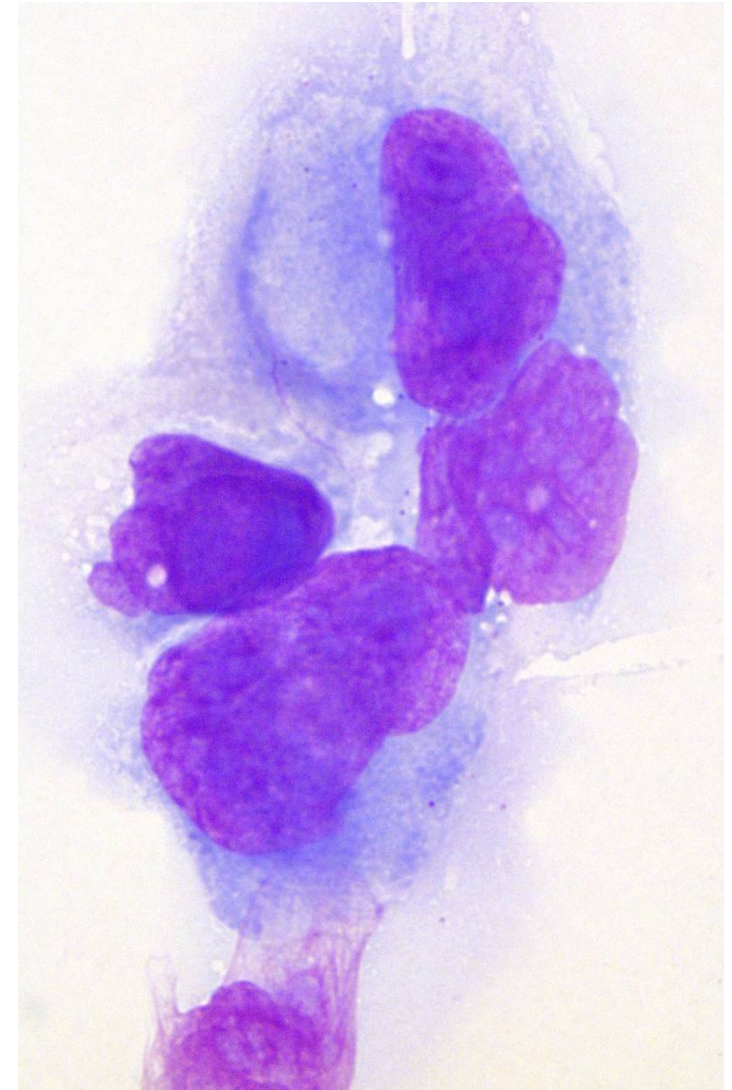
centroblastic



immunoblastic



anaplastic



DLBCL risk factors

- Age over 60 years
- Reduced physical fitness, ECOG higher than 1
- LDH level over upper limit of the norm
- Clinical stage higher than 2
- Extranodal involvement in more than 1 site

DLBCL therapy

First-line therapy

- anti-CD20 antibody + chemotherapy (R-CHOP regimen...)

Therapy of relapse

- Chemoimmunotherapy with anti-CD20 antibody
- High-dose therapy and autologous bone marrow transplant
- Allogeneic bone marrow transplant
- CAR T-cells

Very aggressive NHL

- **Lymphoblastic lymphoma**
 - acute lymphoblastic leukemia based protocols
- **Burkitt lymphoma**
 - aggressive therapeutic regimens

HODGKIN DISEASE

- Lymphadenopathy with or without systemic symptoms
fever, weight loss, pruritus
- Pathologic Hodgkin or RS cells
- Two peaks of incidence: young adults and elderly

HODGKIN DISEASE

- Good risk group:
Radiotherapy IF + 2 – 4 cycles of ABVD chemotherapy
- Intermediate risk group:
BEACOP chemotherapy
- Poor prognosis:
BEACOP
Nivolumab
Brentuximab vedotin (anti CD30)
Autologous/allogeneic hematopoietic cell transplantation

HODGKIN DISEASE

Prognosis

- CR rate 95 %
- Progression free survival 90 % at 3 years

Multiple myeloma

MM

Proliferation of clonal malignant plasma cells in bone marrow

**Complete monoclonal immunoglobulin molecule and/or kappa or lambda
monoclonal free light chains produced by plasma cells**

These changes lead to:

Osteolysis, osteoporosis, bone pain

Hypercalcemia

Hyperproteinemia

Renal failure

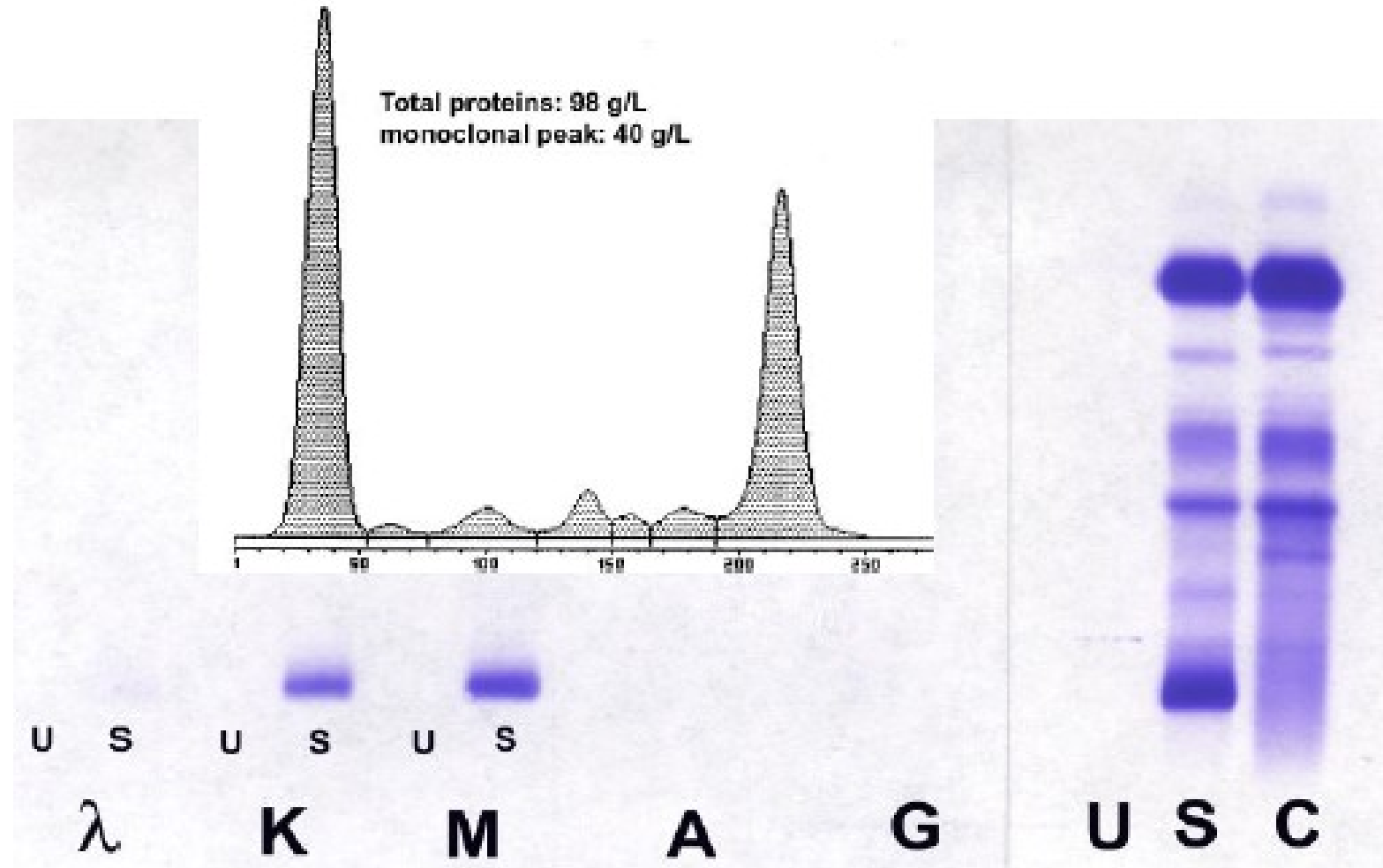
Coagulopathy

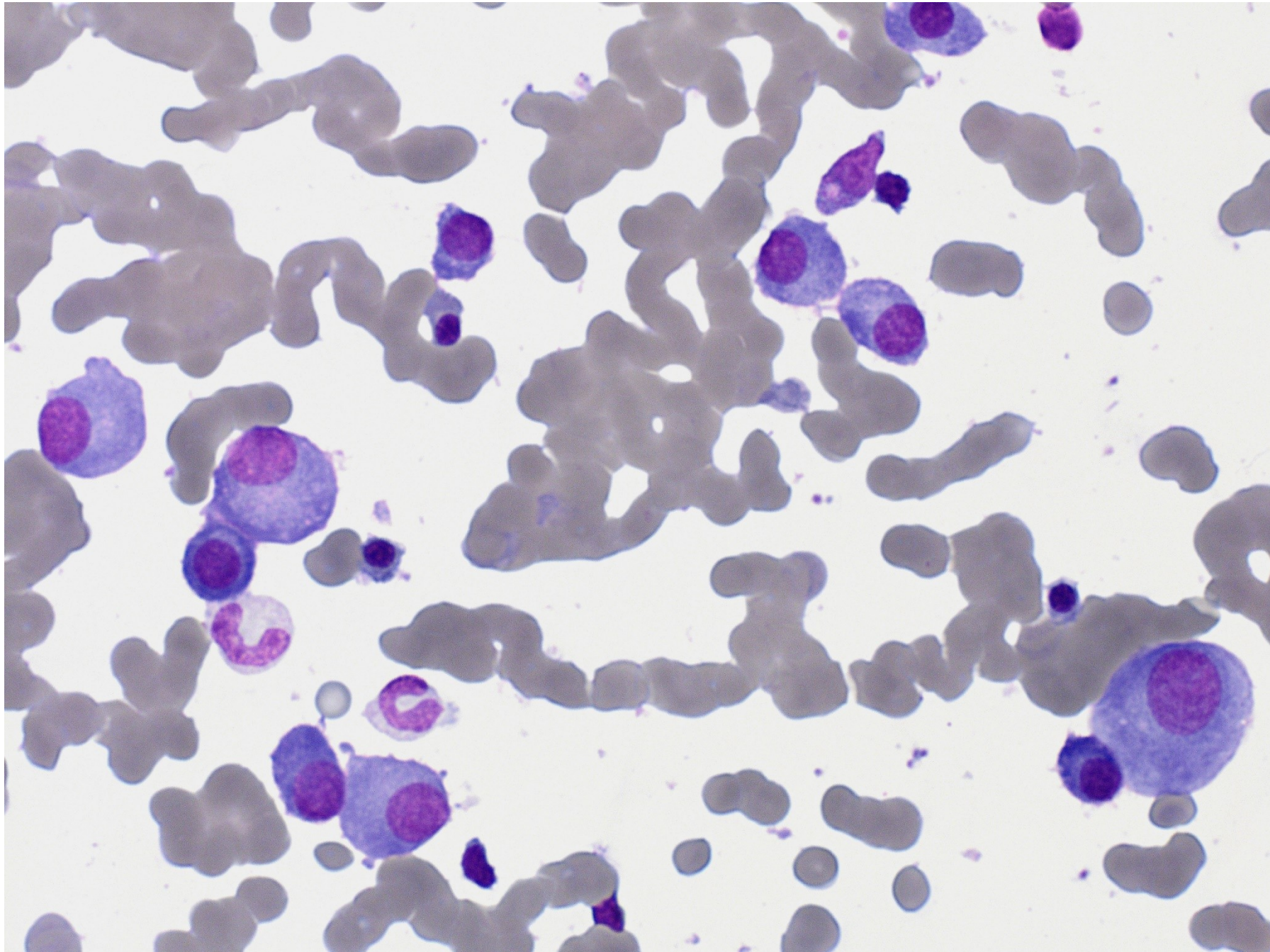
Neuropathy

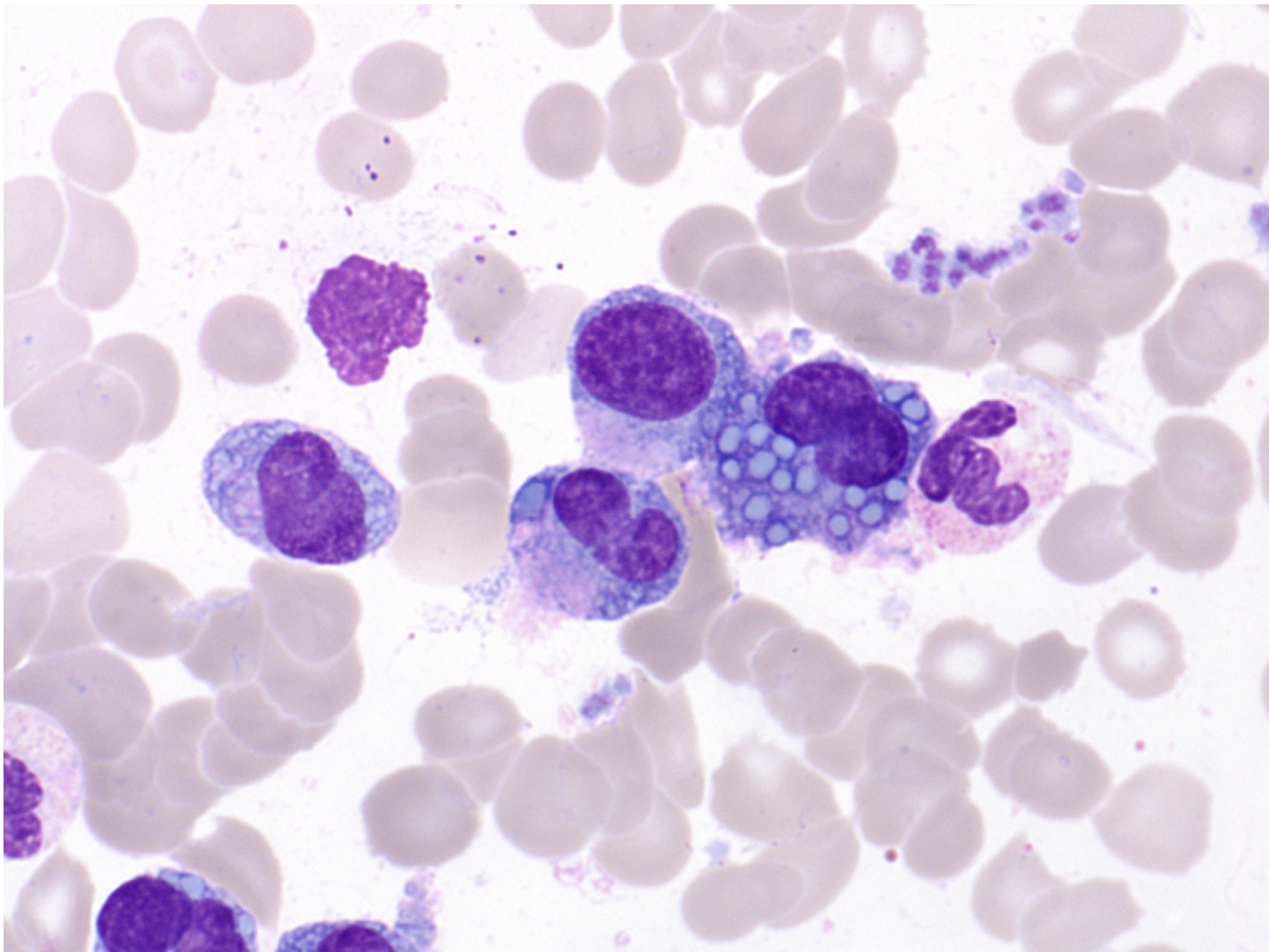
Cytopenia

Incidence 4 / 100 000

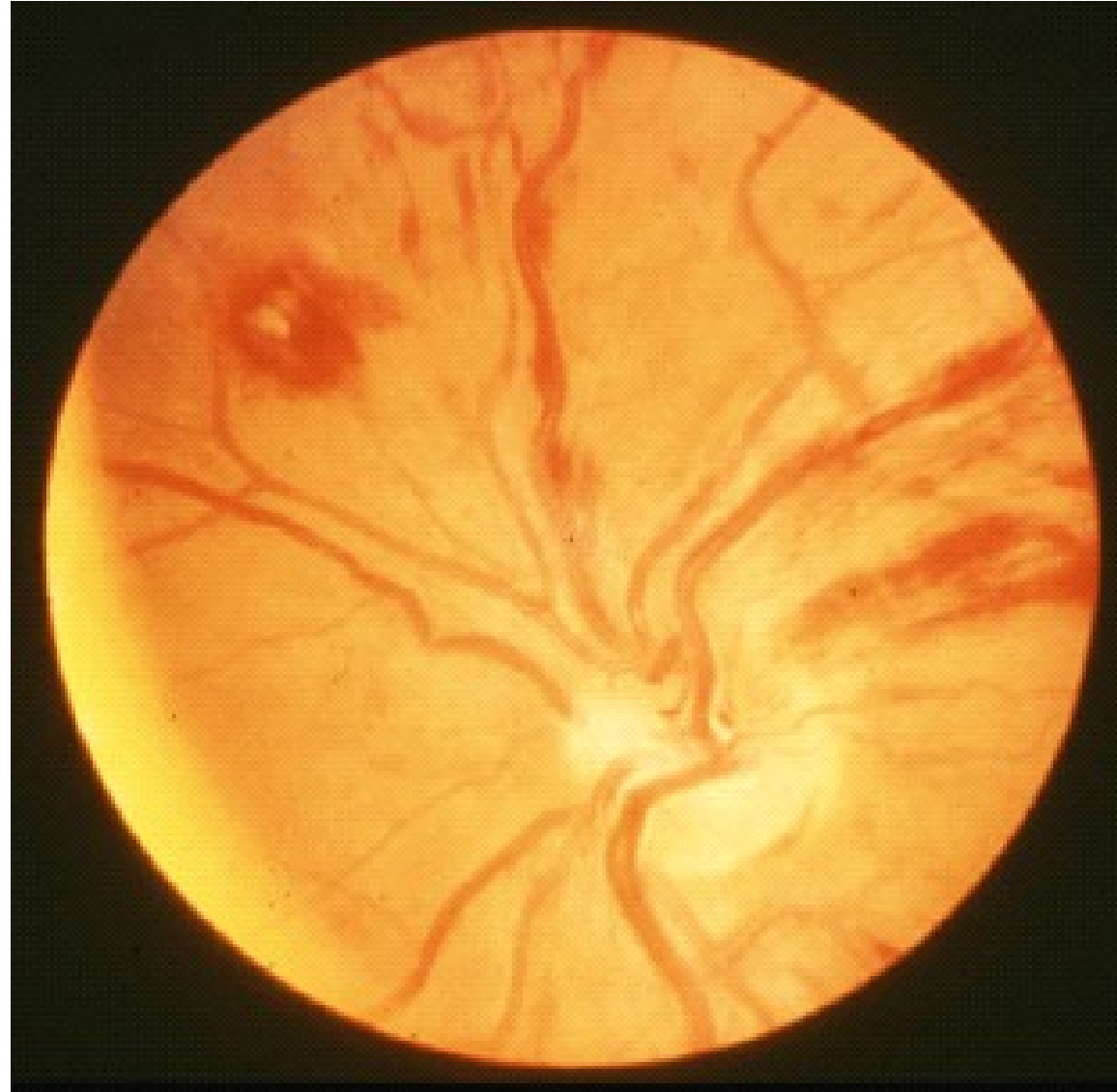
MM – immunofixation, electrophoresis, densitometry



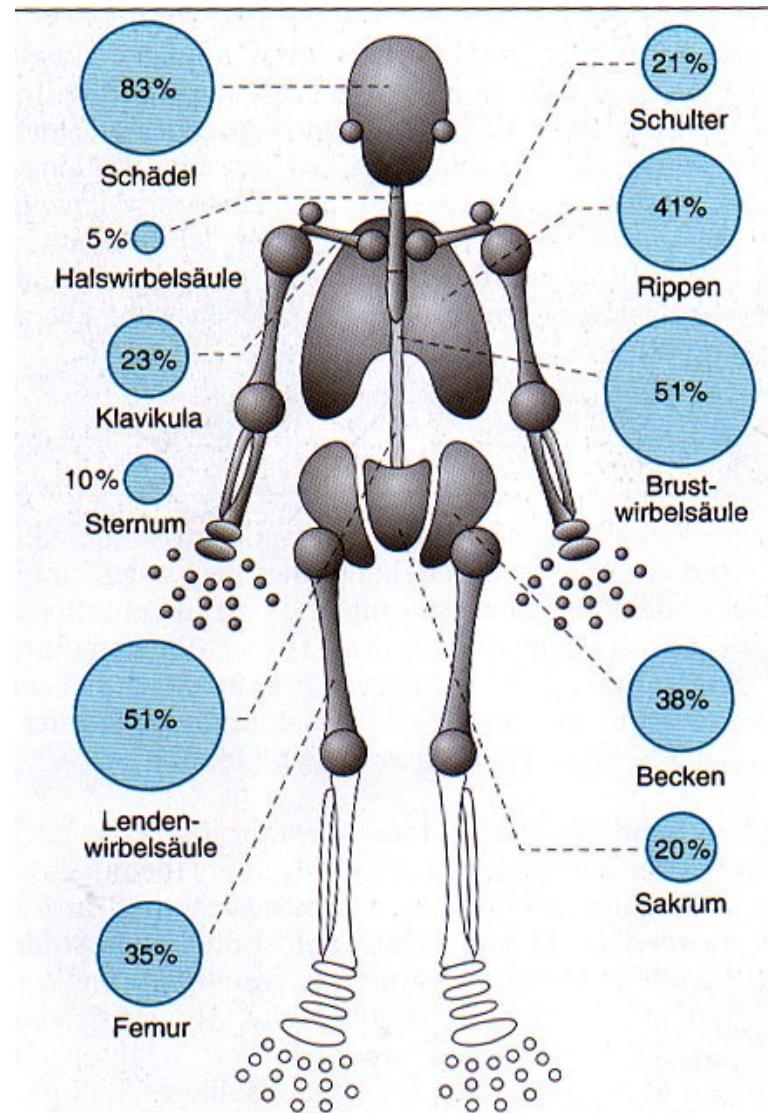
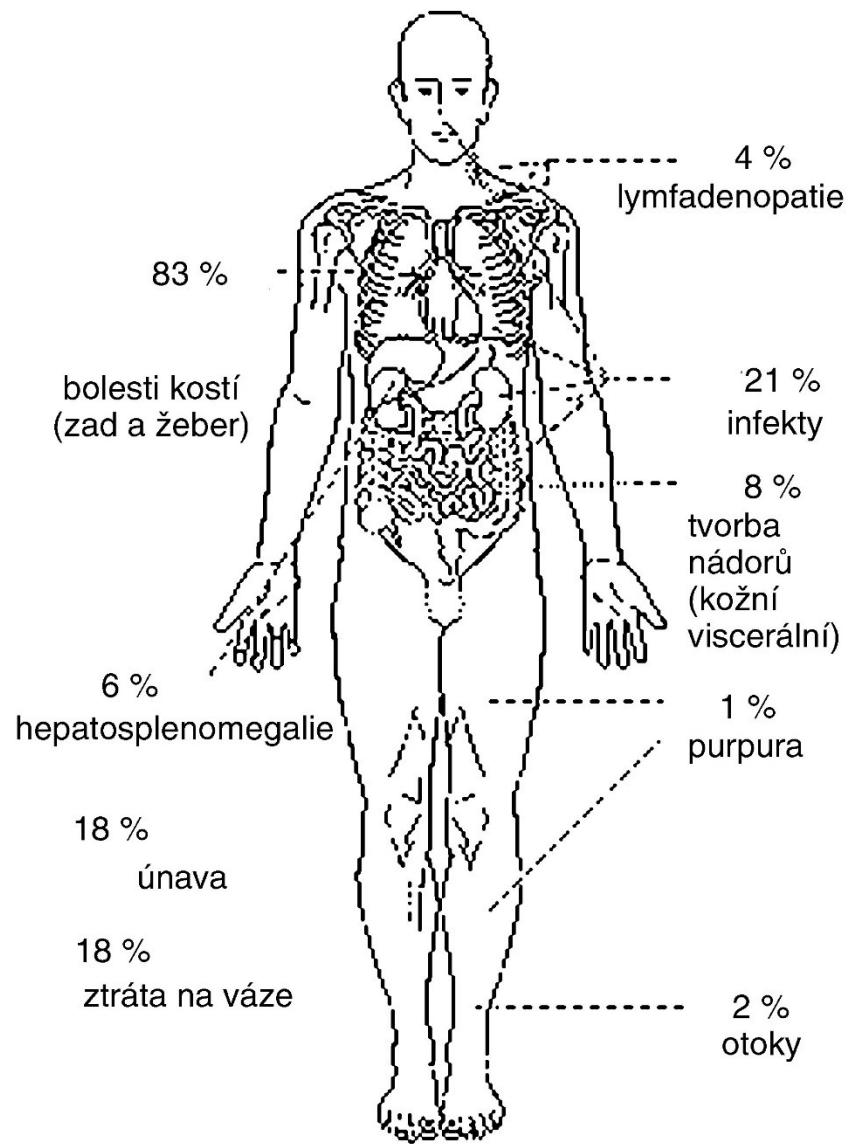




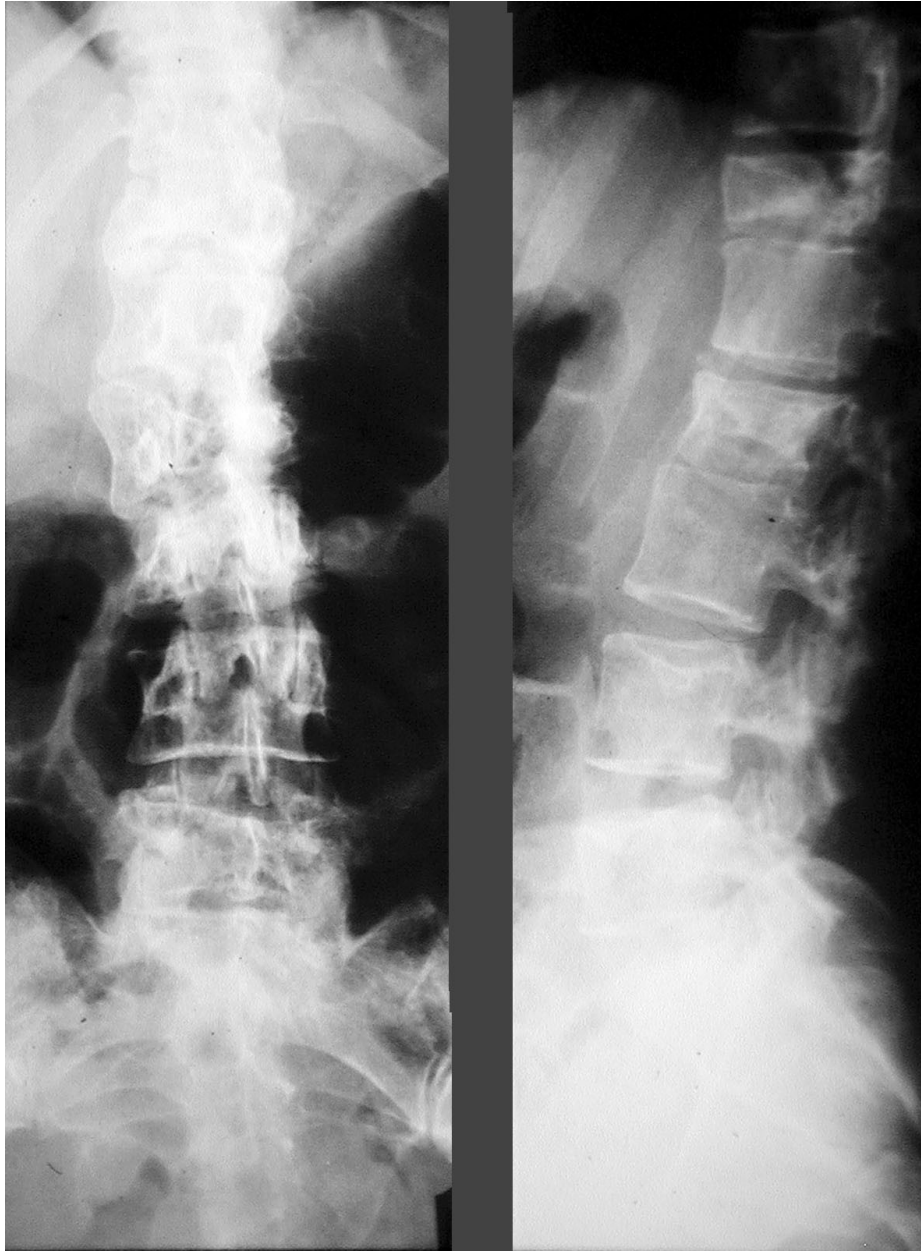
MM



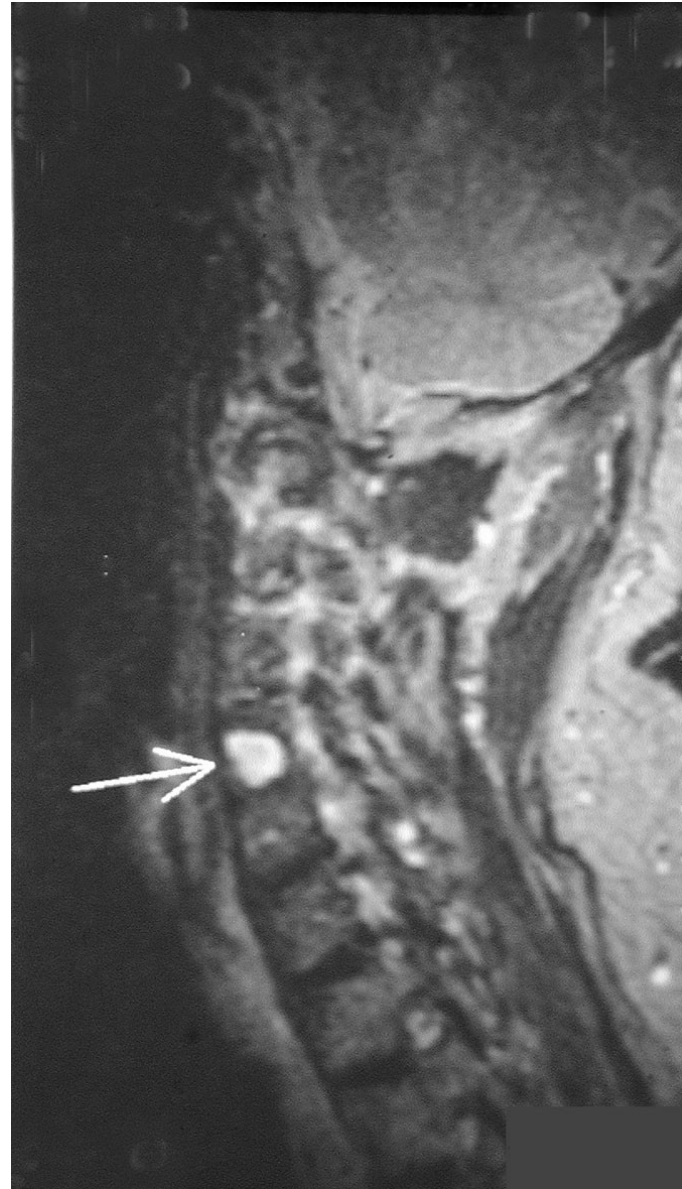
MM



MM



MM



MM



MM

Diagnostics:

Monoclonal immunoglobulin (or light chains) in peripheral blood and urine

Bone marrow histology/cytology

Imaging methods: X-ray, MR, PET/CT

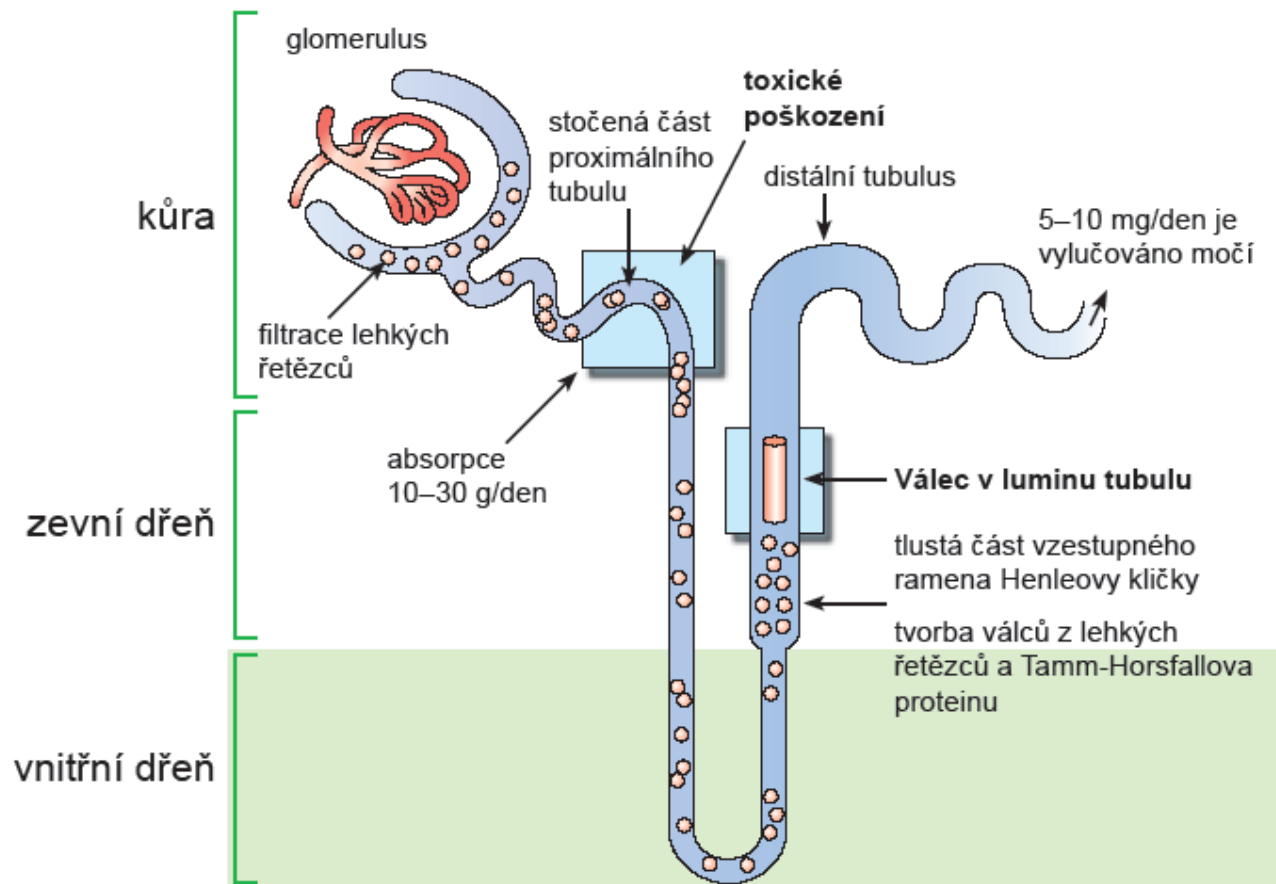
Serum immunoglobulins

Serum calcium level

Serum protein

Peripheral blood count

MM – kidney failure



MM - therapy

Indication for therapy:

Symptomatic patients: cytopenia, bone lesions, hypercalcemia, kidney failure...

Drugs:

Chemotherapy (vincristine, melphalan)

Corticosteroids (dexamethasone)

Proteasome inhibitors (bortezomib, ixazomib, carfilzomib)

IMiDs (lenalidomide, pomalidomide)

Anti-CD38 (daratumumab)

High-dose therapy + autologous hematopoietic stem cell transplantation

MM – supportive care

- Bisfosfonates
- Dialysis
- Plasmaferesis
- Radiotherapy
- Pain killers
- Prophylaxis of infection
- Tranfusions



positive mutation