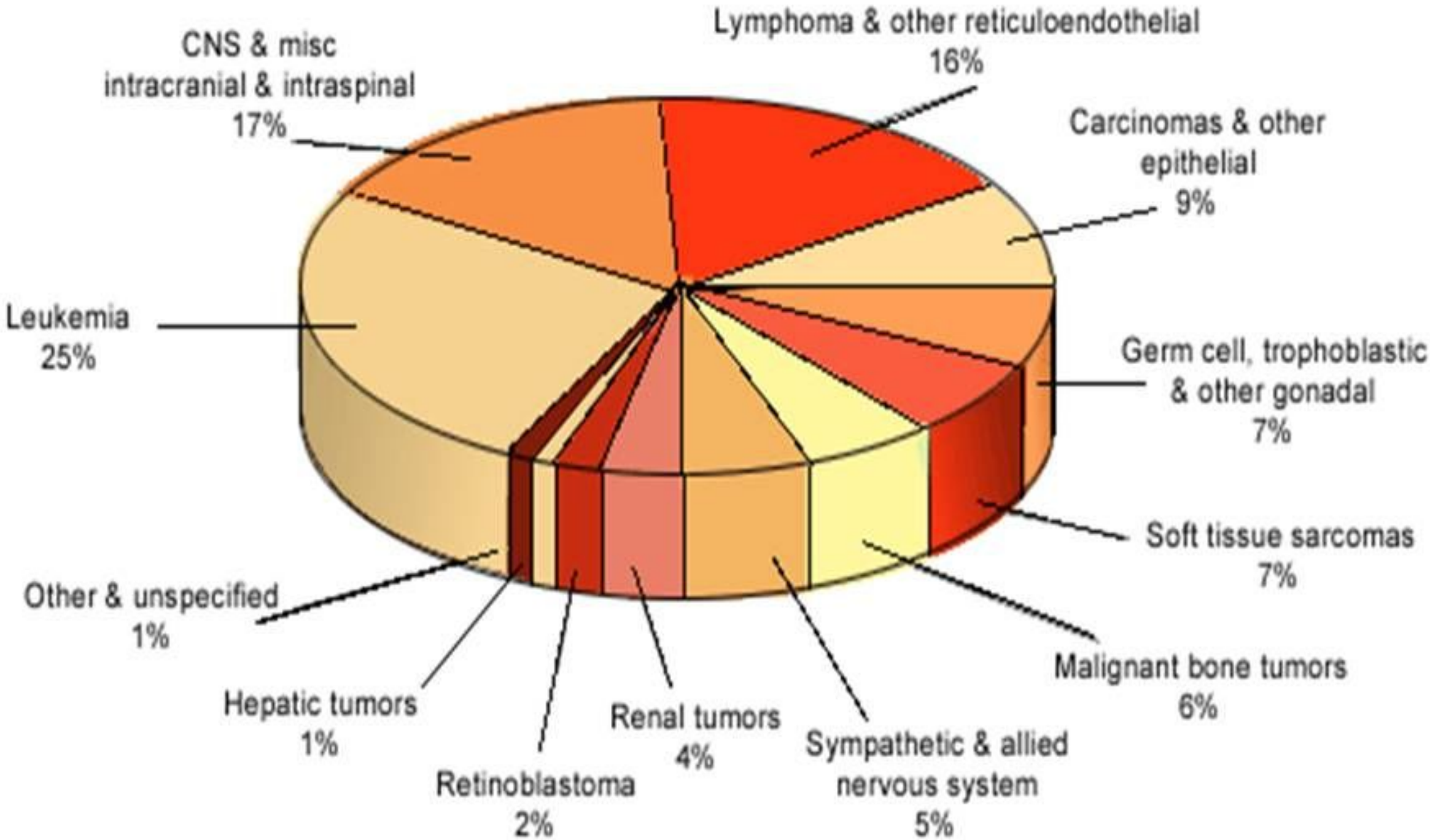
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute Lymphoblastic Leukemia

- Most Common malignancy of childhood
- Risk factors include immunodeficiency syndromes (such as Bloom syndrome, ataxia telangiectasia), Down syndrome

Distribution of Childhood Cancer 1 -19 y



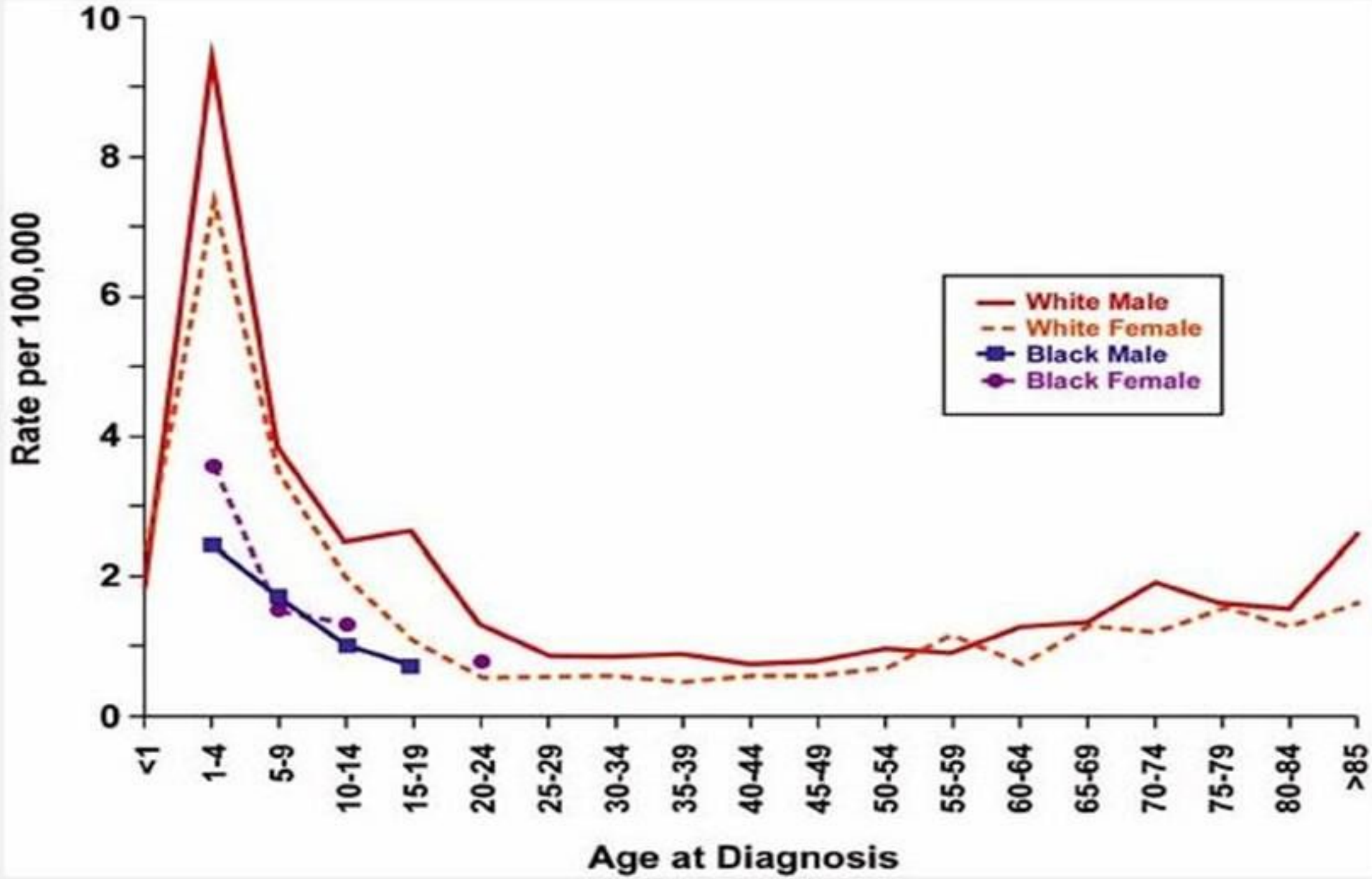


Figure 80.2. Age-specific incidence rates of ALL according to race ar
to insufficient data.

Acute Leukemia

Age predominance

ALL - children (peak incidence 4 yrs)

AML - adults (median age 50 yrs), represents ~10 -20% of childhood leukemias

Acute Leukemia

Hematopoietic Precursors

↓

Malignant Transformation

↓

Proliferation and Accumulation

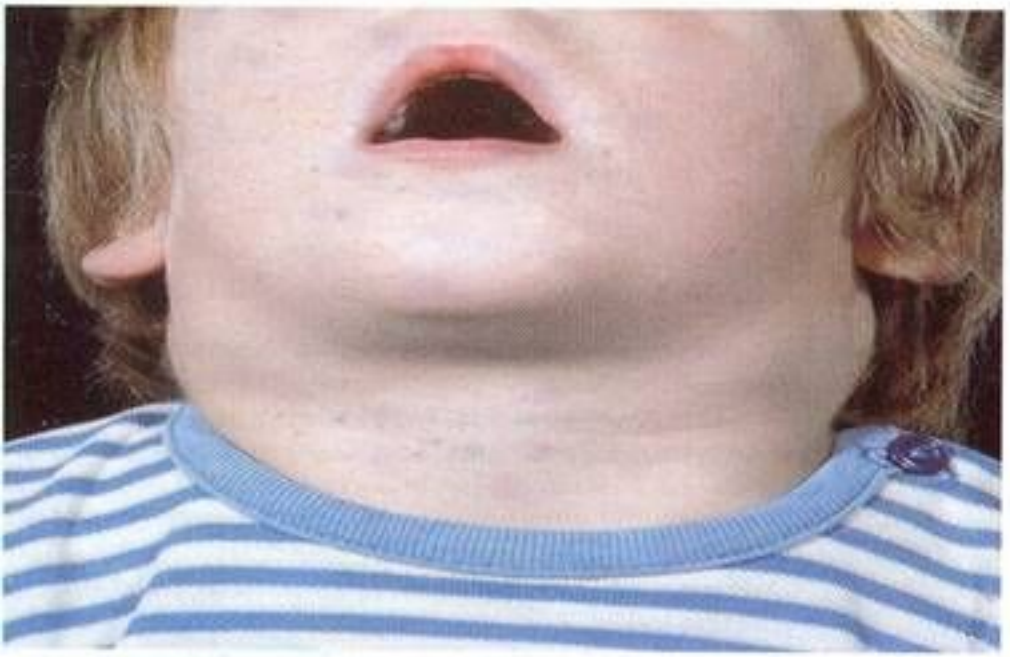
↓

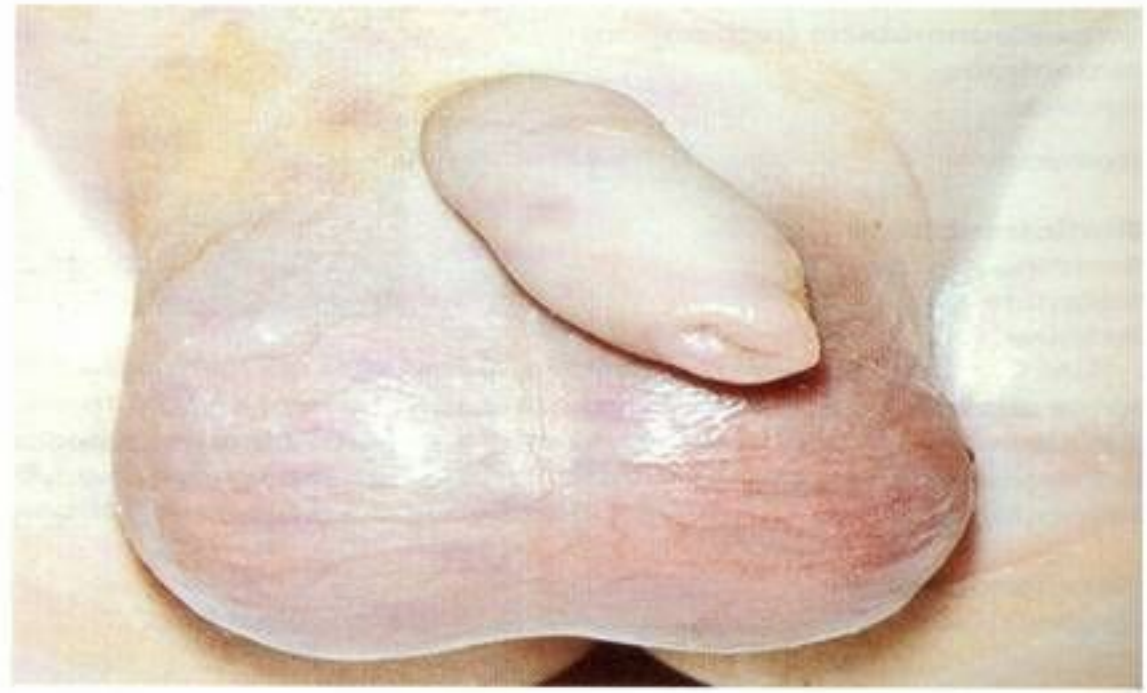
Signs and symptoms

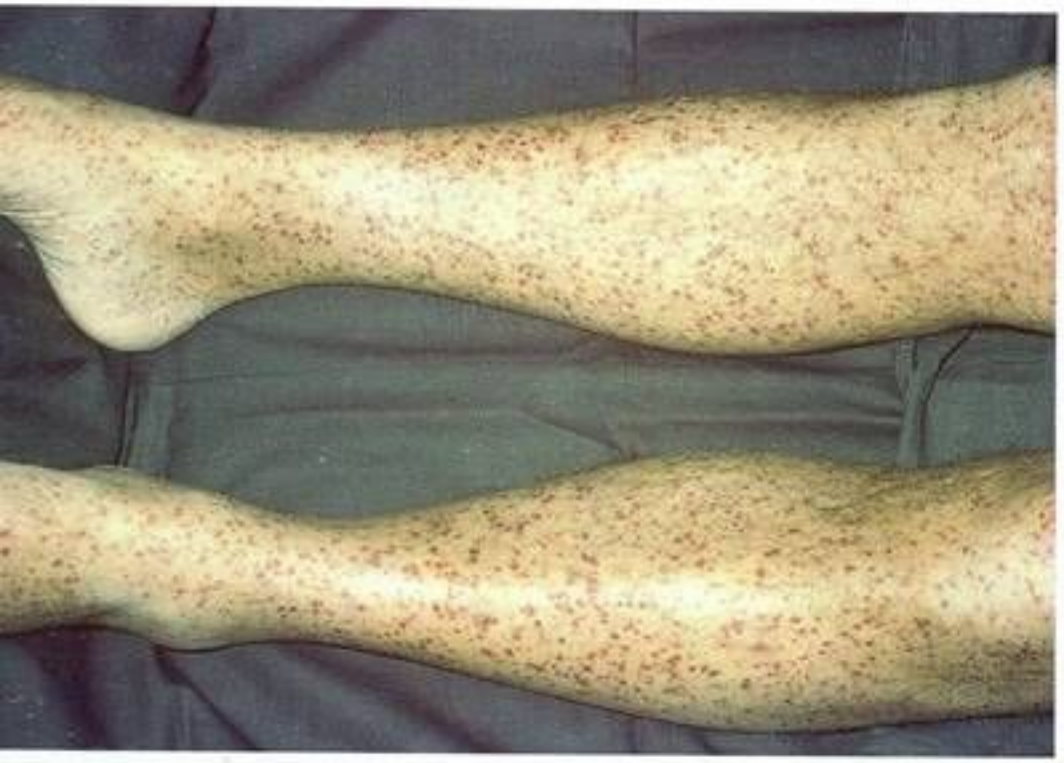
Acute Leukemia - Clinical Features

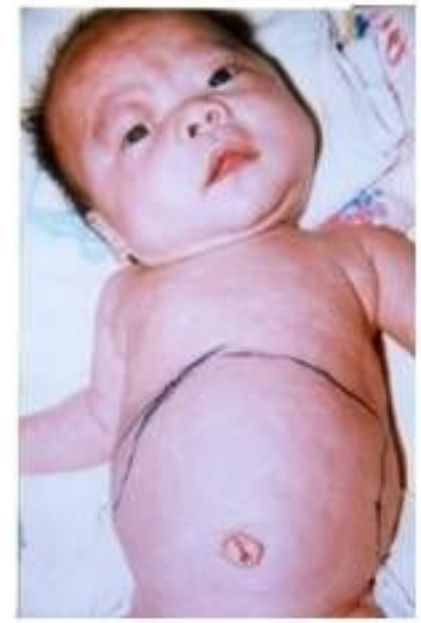
- **Loss of normal marrow function**
  - Pallor (anemia), fatigue, fever, infection, petechiae, bruising, bleeding
- **Infiltration of organs**
  - Hepatomegaly, splenomegaly, bone pain (periosteum, marrow), lymphadenopathy, testicular enlargement, SVC syndrome
- **CNS manifestations**
  - Headache, nausea, nerve palsy

ALL









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FAB Classification for ALL

(French-American-British Classification)

- > 25% blasts in bone marrow (differs from WHO classification)

3 groups, L1 – L3 based on morphology

- L1 small blasts, scanty cytoplasm
- L2 medium sized blasts, more cytoplasm
- L3 large blasts, often darker blue cytoplasm, vacuoles in nucleus/cytoplasm

ALL

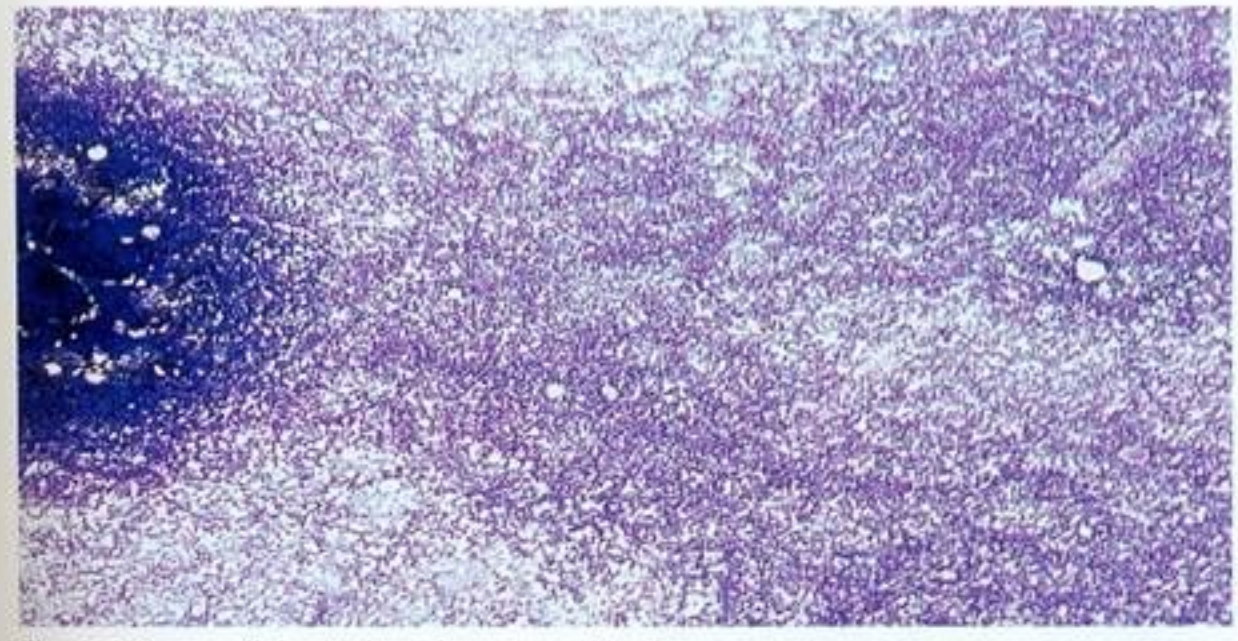


Fig. 125 Hypercellular leukaemic marrow film (*low power*).

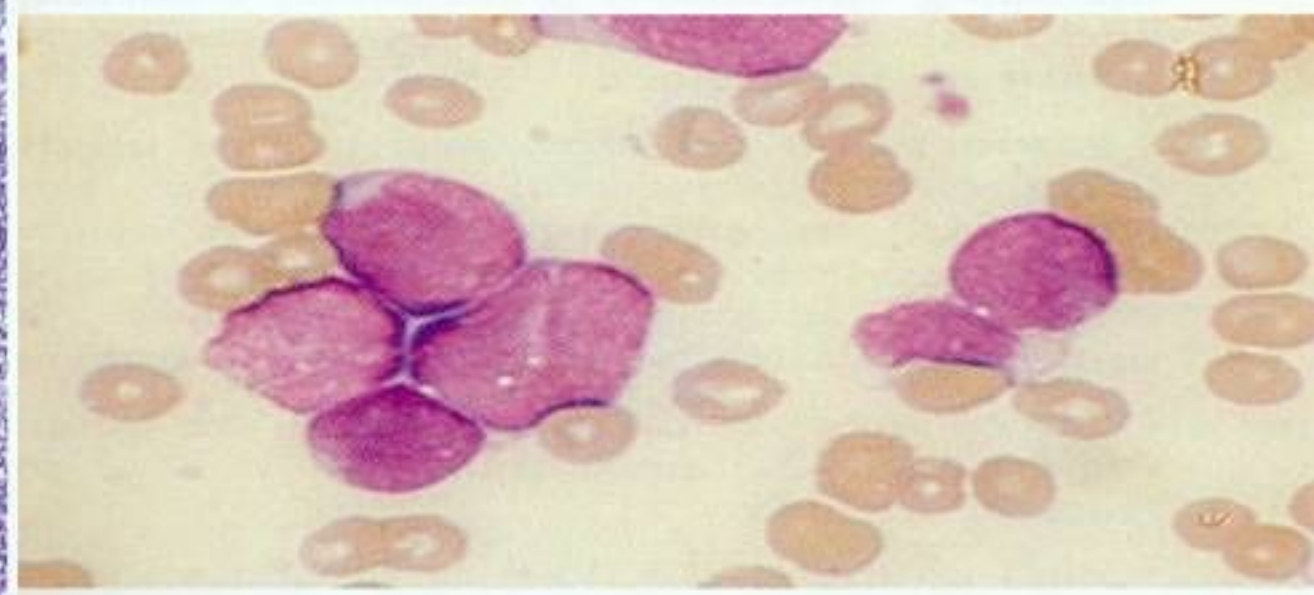


Fig. 133 ALL FAB Type L_2.

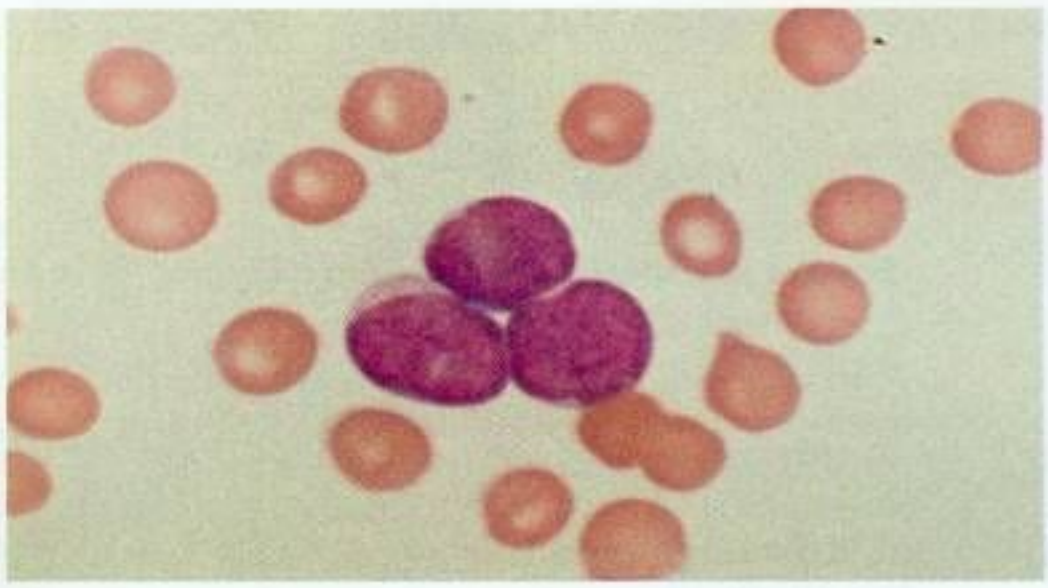


Fig. 132 ALL FAB Type L_1.

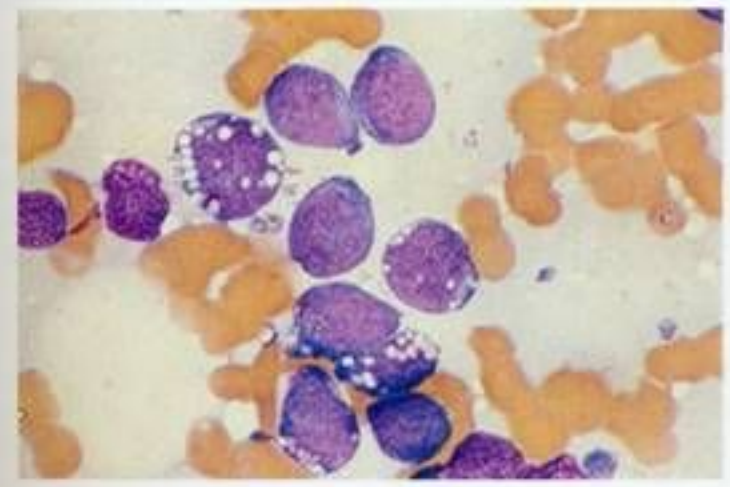


Fig. 134 ALL FAB Type L_3.

Acute Leukemia

- **Classified by a number of criteria:**
  - WHO/FAB classification
  - Cytochemistry (Terminal deoxy Transferase = TdT, Myeloperoxidase = MPO, Sudan Black = SB, Esterase, others)
  - Immunophenotype (flow cytometry)
  - Cytogenetics (ploidy, translocation, duplicate)
  - Molecular biology (gene fusion, proteins)
  - Others

Acute Leukemia - Laboratory Features 1

- **CBC findings**
  - Leukocytosis
    - Not always present
    - Presence of "atypical" cells or blasts
  - Cytopenias (usually more than 1 cell line)
    - Anemia – usually normochromic, normocytic
    - Thrombocytopenia
    - Neutropenia
    - Pancytopenia

Acute Leukemia - Laboratory Features 2

- **Chemistry**
  - Elevated LDH
    - Non-specific indicator of cell turnover
    - Not always elevated
  - Elevated uric acid
    - Product of nucleic acid metabolism
    - Can interfere with kidney function
  - Elevated creatinine
    - Can be the result of increased uric acid
    - Can interfere with therapy

Differential Diagnosis of Lymphoblastic Leukemia/Lymphoma

- Benign proliferation in BM
  - Hematogone hyperplasia
  - Polyclonal B-cell Lymphocytosis
- Neoplastic proliferation:
  - Minimally differentiated AML and Acute megakaryoblastic leukemia

  -Burkitt and blastic mantle cell lymphomas

  -Metastatic tumors

Acute Leukemia Differential 1

- **Non malignant conditions**
  - Leukemoid reaction
  - Acute infectious lymphocytosis
  - Autoimmune disease (JRA, Lupus, ITP, Evans)
  - Infections (EBV, CMV)
  - Aplastic anemia
  - Histiocytoses (HLH, LCH)
  - Marrow/tissue infiltrative diseases/fibrosis (Gaucher)
  - Vascular obstruction/anomalies (KM, cirrhosis)

Acute Leukemia Differential 2

- **Pre malignant conditions**
  - Myelodysplasia
  - Myeloproliferative disorders
- **Other Malignancies**
  - Chronic Myelogenous leukemia
  - Neuroblastoma
  - Rhabdomyosarcoma

PERIPHERAL BLOOD (PB)

- **CBC (Complete blood count)**
  - Anemia.
  - Thrombocytopenia.
  - Variable white blood cell count (WBC)
    - **50% of patients have WBC<10x10^9/L(low)**
    - **30% of patients have WBC between 10-50x10^9/L**
    - **20% of patients have WBC>50x10^9/L**
  - Asymptomatic eosinophilia (rare)
  - Blast

BONE MARROW ASPIRATE & BIOPSY

- Aspiration smears: hypercellular marrow, usually extensive replacement by lymphoblasts.

- Bone marrow biopsy:
  extensive replacement by lymphoblasts..

- Aspiration and/or biopsy can be sent for send for flow cytometry and /or cytogenetics.

IMMUNOPHENOTYPE of ALL

- Children
  - ≈ 85% B lymphoblastic
  - ≈ 15% T lymphoblastic
- Adults
  - ≈ 75% B lymphoblastic
  - ≈ 25% T lymphoblastic

Normal expression of antigens

- B-cell markers: CD19, CD20, CD22, CD79a

- T-cell markers: CD2, CD3, CD4, CD5, CD7, CD8

- Myeloid markers: CD117, CD33, CD13

- Monocytic markers: bright CD11b, CD11c, CD14, CD64, and HLA-DR

PROGNOSIS

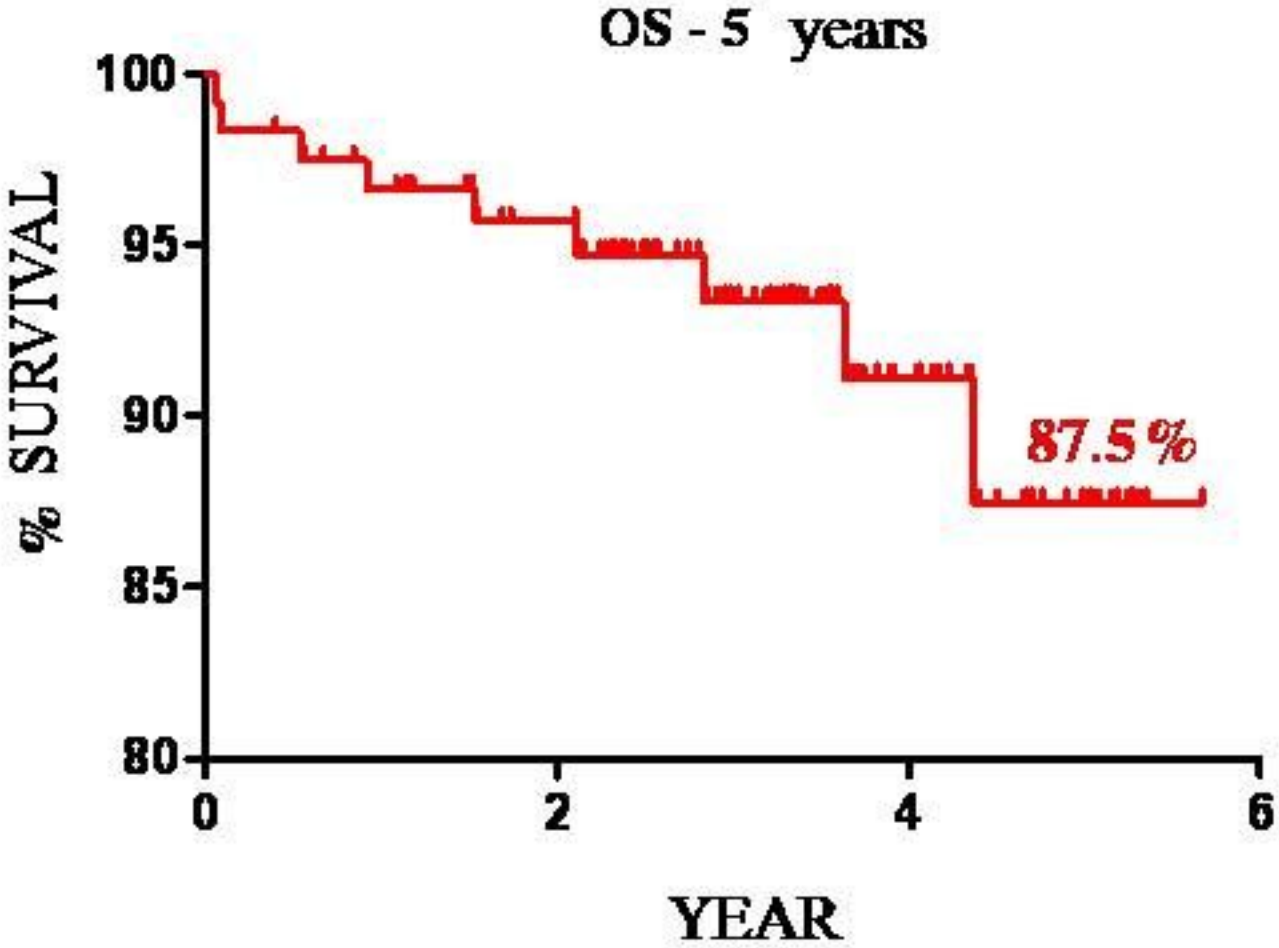
Determinants	Favorable	Unfavorable
White blood cell counts	<10 × 10^9/L	>200 × 10^9/L
Age	3–7 y	<1 y, >10 y
Gender	Female	Male
Ethnicity	White	Black
Node, liver, spleen enlargement	Absent	Massive
Testicular enlargement	Absent	Present
Central nervous system leukemia	Absent	Overt (blasts + pleocytosis)
FAB morphologic features	L1	L2
Ploidy	Hyperdiploidy	Hypodiploidy <45
Cytogenetic markers	Trisomies 4, 10, and/or 17	t(9;22) (BCR-ABL)
	t(12;21) (*TEL-AML1*)	t(4;11) (*MLL-AF4*)
Time to remission	<14 d	>28 d
Minimal residual disease	$<10^{-4}$	$>10^{-3}$

Principles of Therapy

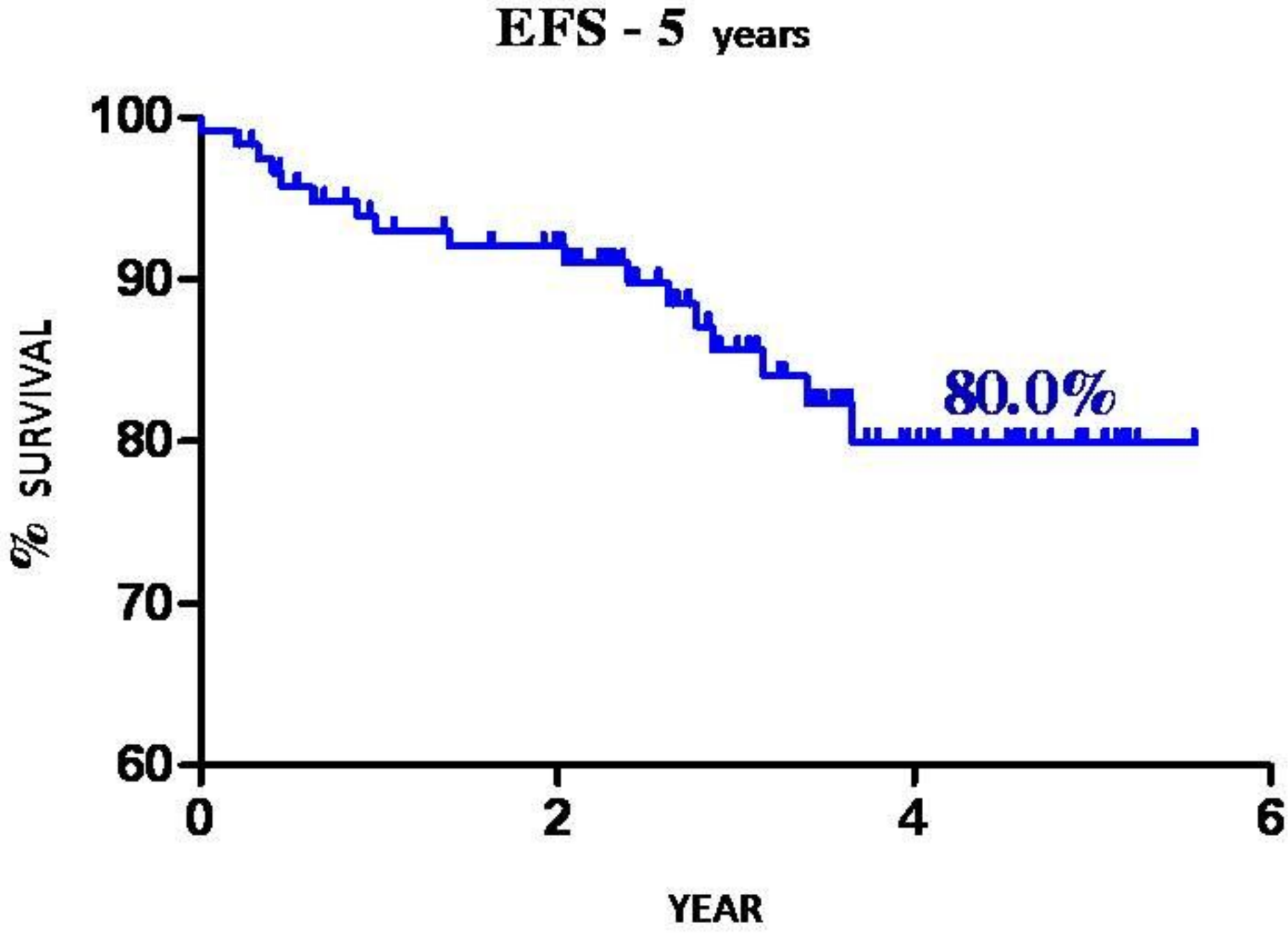
- Therapy is tailored to the type of leukemia
- Adjustments to therapy are made in accordance to response to therapy
- Management of complications occur in all phases of therapy
- Initial therapy and relapse therapy differ

FRALLE 2000 THERAPY

FRALLE 2000 THERAPY

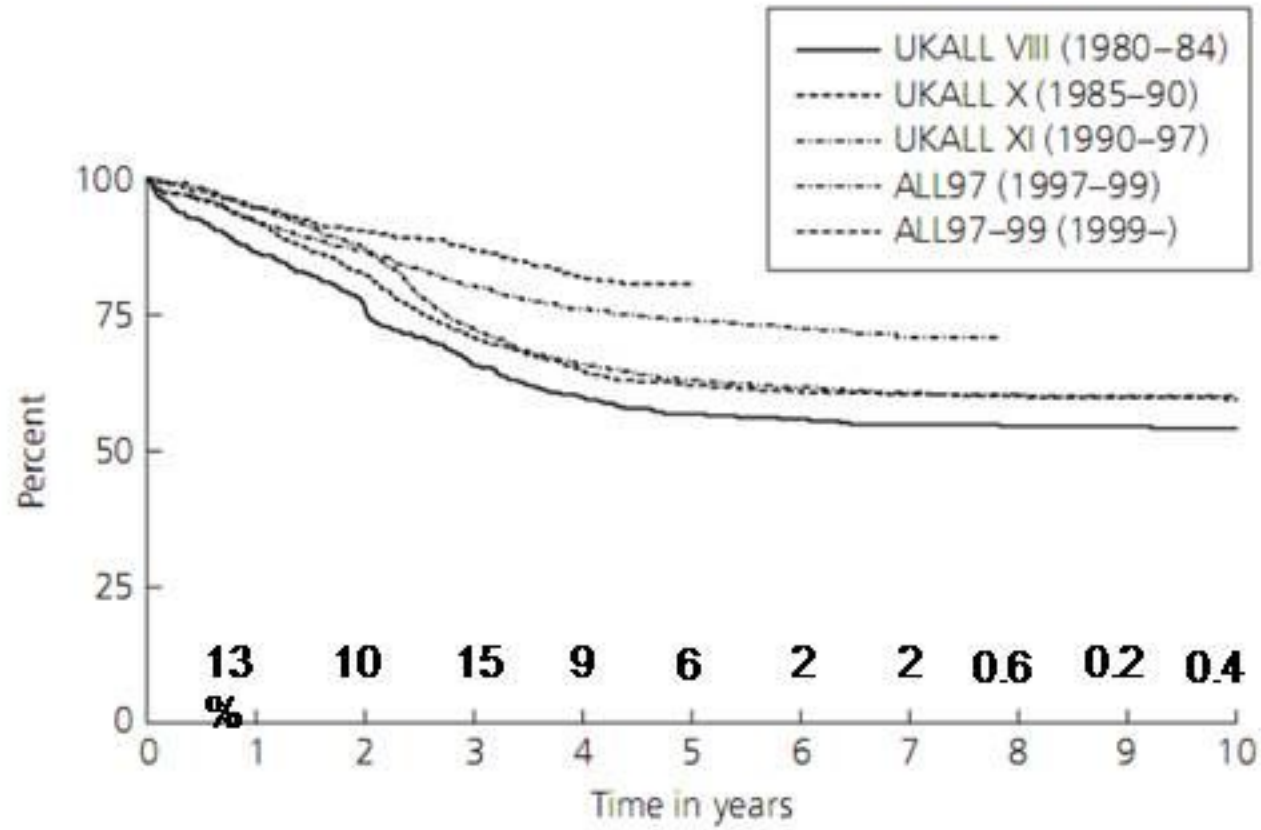


FRALLE 2000 THERAPY



TRANSPLANTATION

- Prolong survival observed in high risk patients
- Indications:
  - "VERY HIGH RISK"
  - Refractory
  - Relapse



CURE

At risk:											
UKALL VIII (1980–84)	825	714	640	543	493	468	461	453	450	449	447
UKALL X (1985–90)	1612	1487	1333	1142	1043	1001	980	971	963	954	946
UKALL XI (1990–97)	2090	1980	1828	1514	1376	1316	1287	1121	905	705	494
ALL97 (1997–99)	997	919	865	801	758	734	457	178	0	0	0
ALL97–99 (1999–)	938	889	849	614	280	0	0	0	0	0	0

Fig. 20.1 Event-free survival by trial.