Malignant Solid Tumors of Childhood

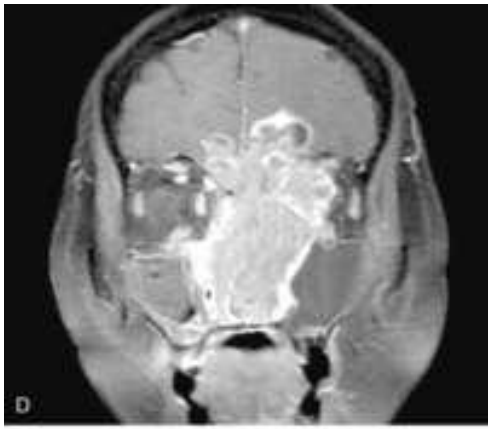
Peter Hauser

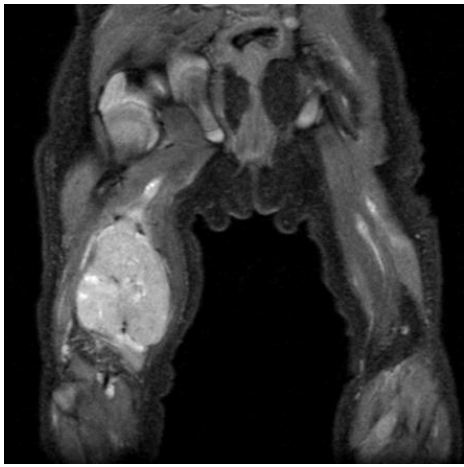
Type of tumors

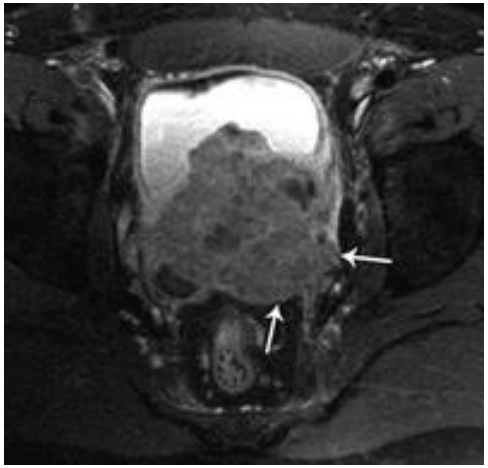
Localization	Typical pediatric tumor type	Typical age (Year)
CNS	Medulloblastoma/PNET astrocytoma, ependymoma, ATRT ,CPC	9 (0-25) 0-2
Liver	Hepatoblastoma	0-2
Kidney	Wilms tumor rhabdoid tumor	2-4 0-2
Suprarenal gland	Neuroblastoma	0-4
Bone	Osteosarcoma Ewing sarcoma	10-18
Soft tissue	Rhabdomyosarcoma	2-8
Eye	Retinoblastoma	0-2

Histology is not organspecific

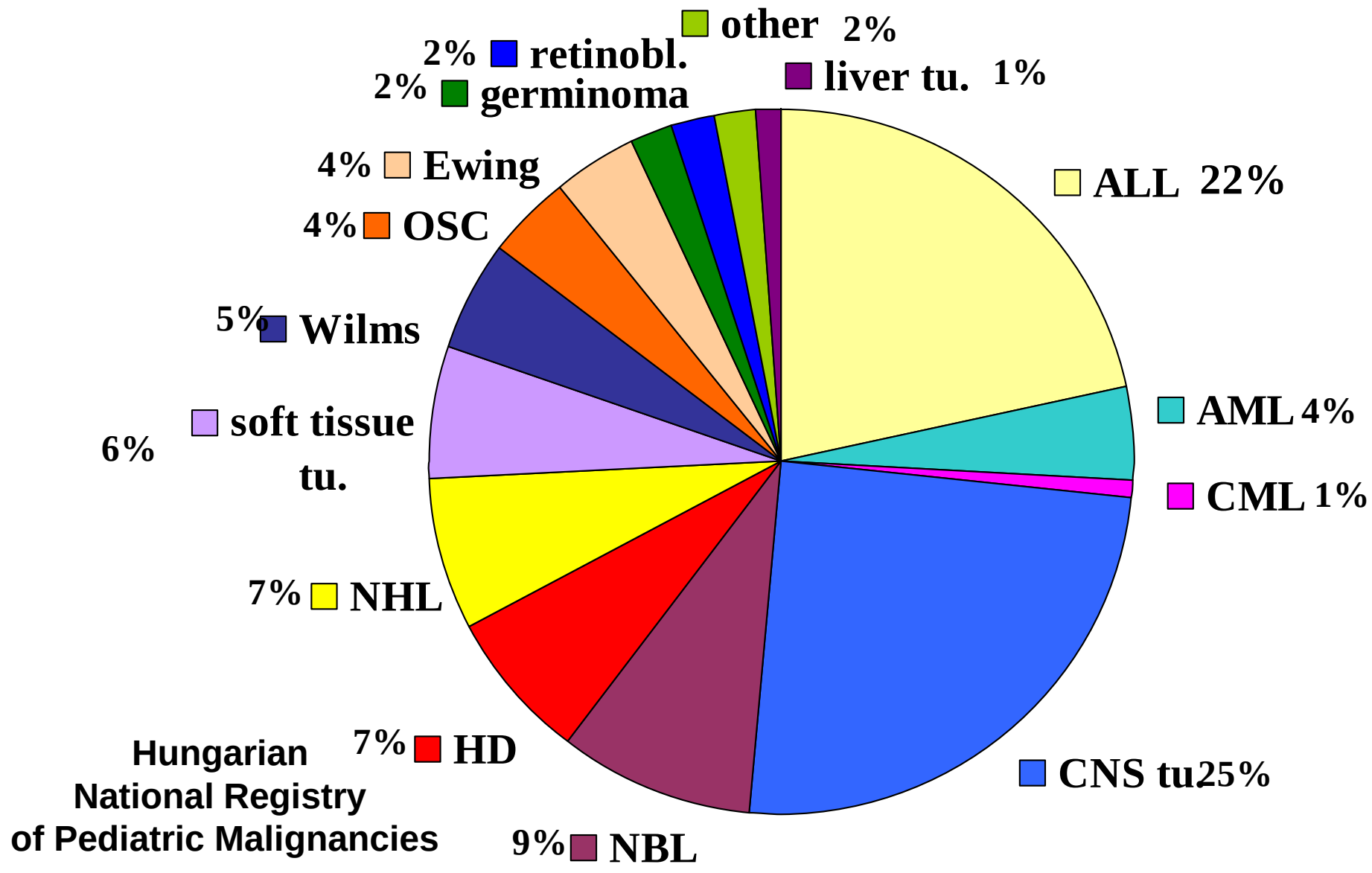
- Rhabdomyosarcoma
  - Head and neck
  - Parameningeal
  - Orbita
  - Nasal sinus
  - Genito-urinary tract
  - extremity
  - Intrathoracal
  - Retroperitoneal
  - pelvic







Distribution of Pediatric Malignancies in Hungary (2007)



Rate of inheritance in pediatric malignancies (%)

- Adrenocortical cc. 50-80
- Optic glioma 45
- Retinoblastoma 40
- Phaeochromocytoma 25
- Wilms tumor 3-5
- CNS tu 1-3
- Leukaemias 2-5

Genetic diseases- pediatric malignancies

- Ret protooncogen (MEN2): thyroid gland medullary cc
  - (screening of the family – compulsary preventive thyeroidectomia!)
- APC gene: medulloblastoma (adulthood: colon cc!!!)
- Rb gene : retinoblastoma
- Down syndrome: AML
- NF1 (neurofibromatosis): CNS tumors
- p53 mutation: Li Fraumeni syndrome
- WT1 gene (11p13): Wilms-tumor
  - WAGR- sy: Wilms tu, aniridia, genital abnorm. ment.ret.)
  - Denys-Drash sy (nephropathy, Wilms tu, intersex)
  - Beckwith Wideman sy (Wilms tu, hemihypertrophia)

Why occuring pediatric tumors?

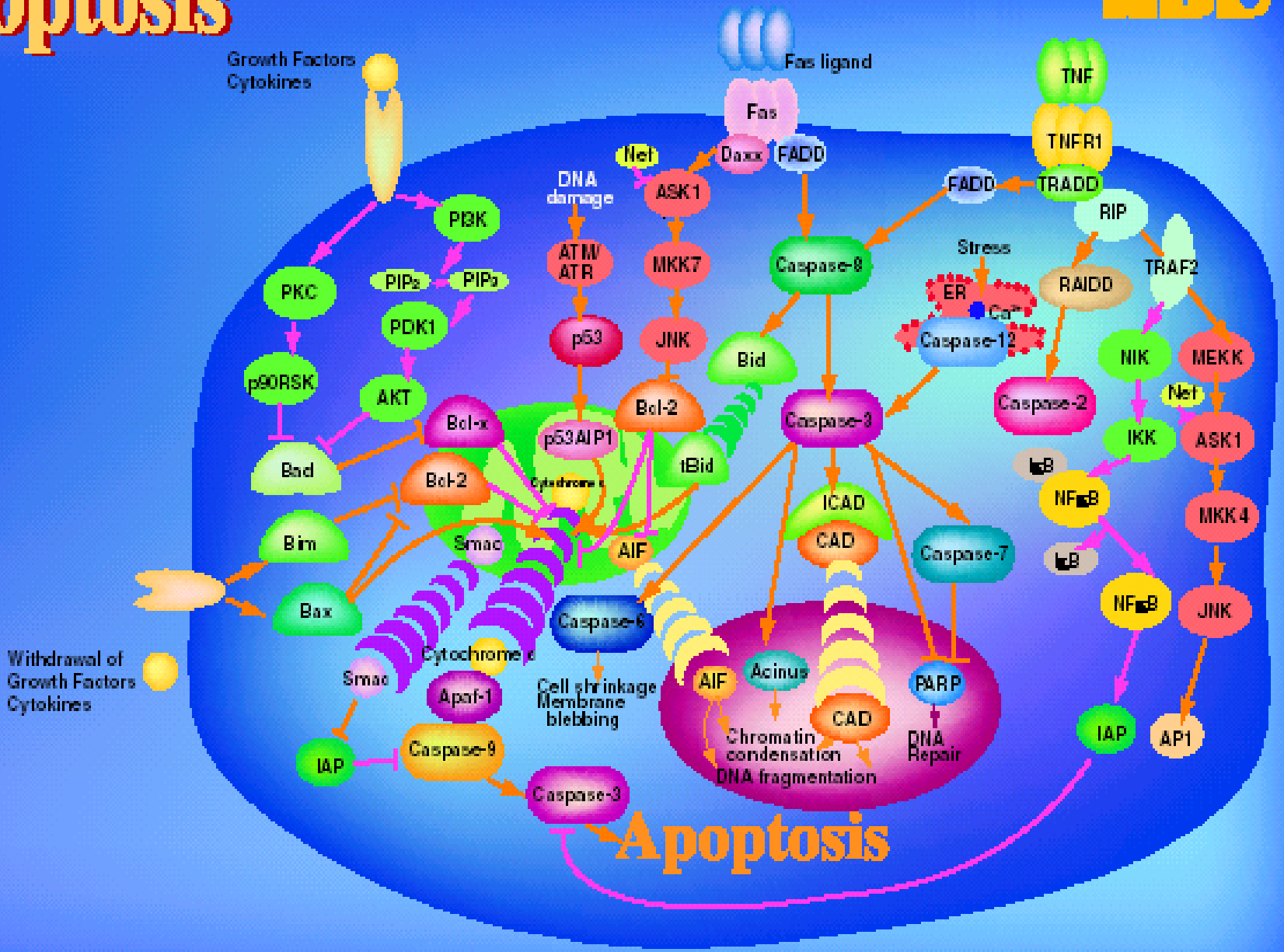
The question is to be answered….

- Not due to a wrong habbits (smoking, drinking, eating etc) nor enviromental factors

- lack of apoptosis?
- lack of cellular migration in intrauterine period?
- Improper regulation of cellular signalling pathways?
- Improper effect in the microenviroment of the cells?

Apoptosis

MBL



MEDICAL & BIOLOGICAL LABORATORIES CO., LTD.
5-10 Marunouchi 3 chome, Naka-ku, Nagoya 460-0002, JAPAN
TEL : +81-52-971-2081 FAX : +81-52-971-2337
URL : http://www.mbl.co.jp e-mail: info@mbl.co.jp

MBL International Corporation
200 Dexter Avenue, Watertown, MA 02472, U.S.A.
TEL: 1-800-200-5459, (617) 926-6964 FAX: (617) 926-6954
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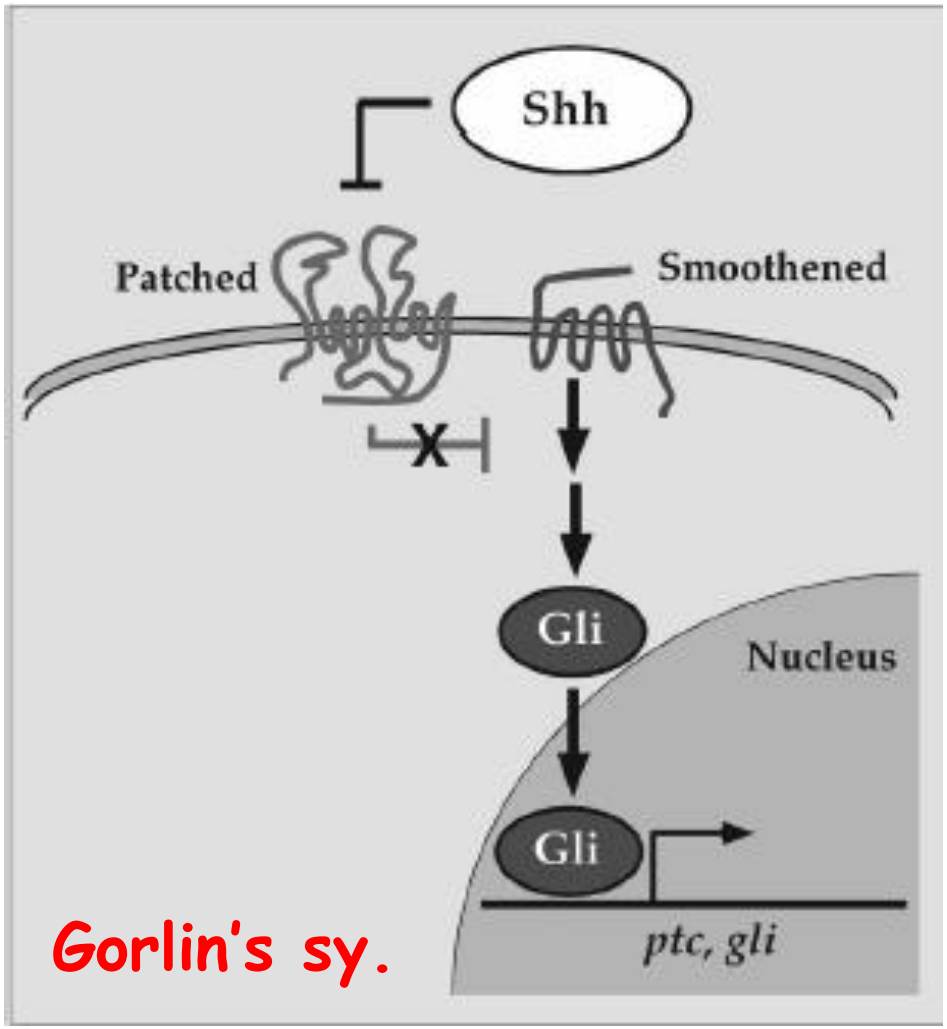
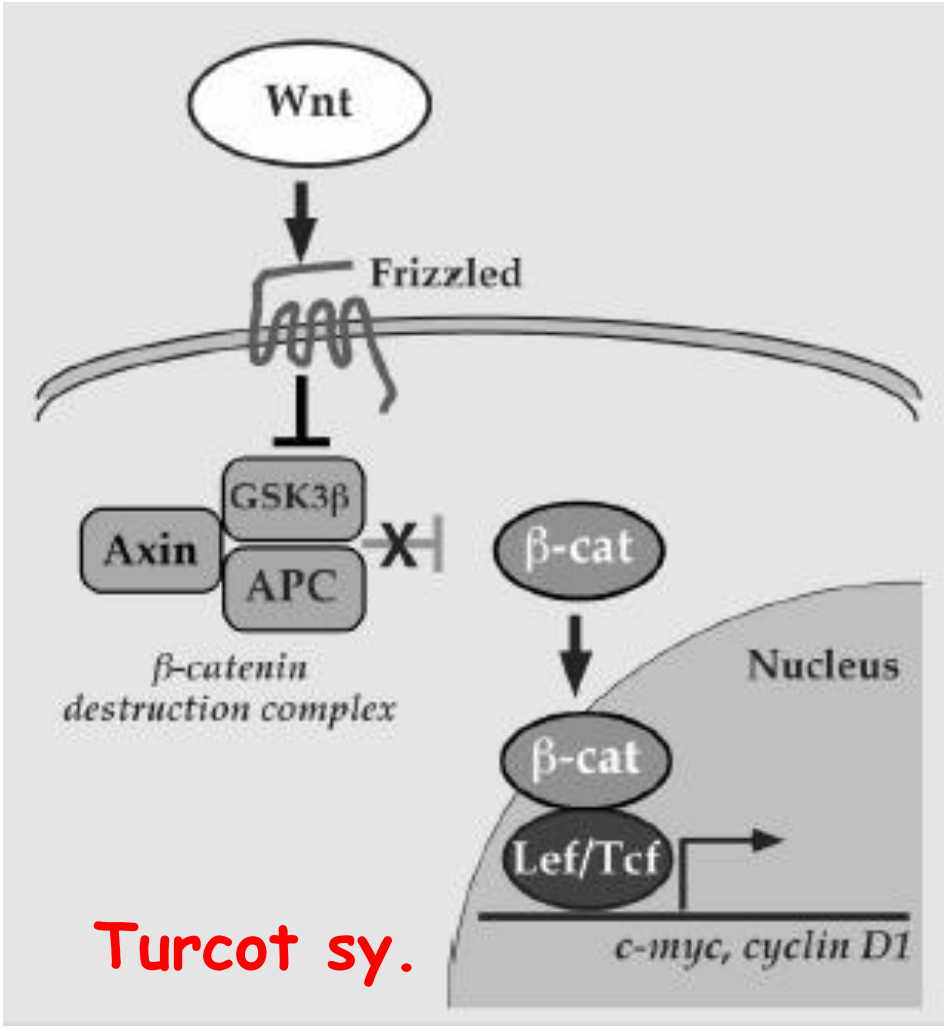
Role of signaltransduction pathway in development of medulloblastoma





Robert Wechsler-Reya and Matthew P. Scott:Annu. Rev. Neurosci., 24: 385–428, 2001.

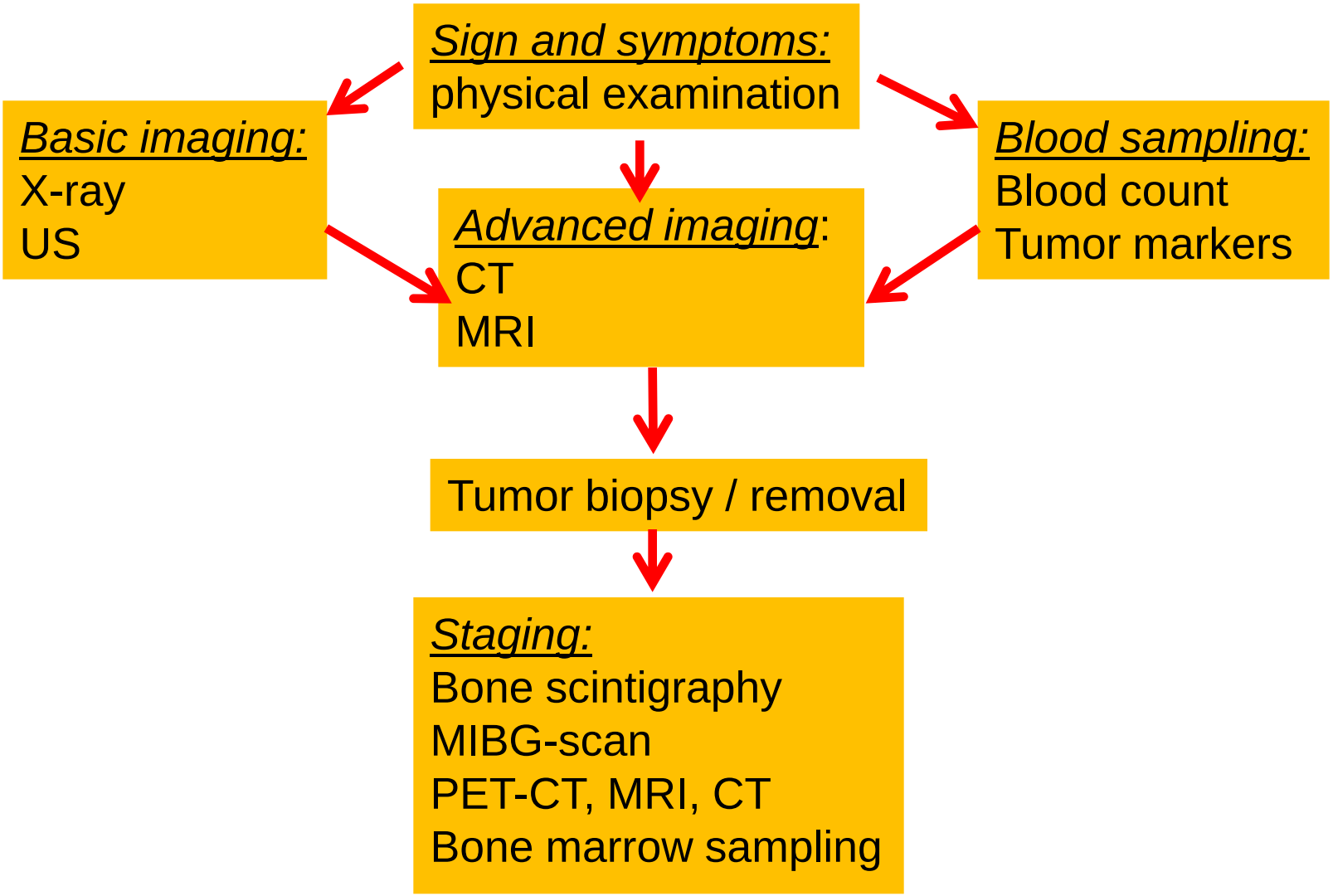
Signs and symptoms

- pallor
- anemia
- Cutaneous bleeding
- Severe long term infection
- pain
- Bone pain
- swelling
- Palpable mass
- Hepato-, splenomegaly
- Increased lymph node
- Behavioral changes
- Impairing learning capacity
- headache
- Visual impairement
- Nausea vomiting
- vertigo
- ataxia
- Brain nerve palsy

Activity at presence of symptoms:

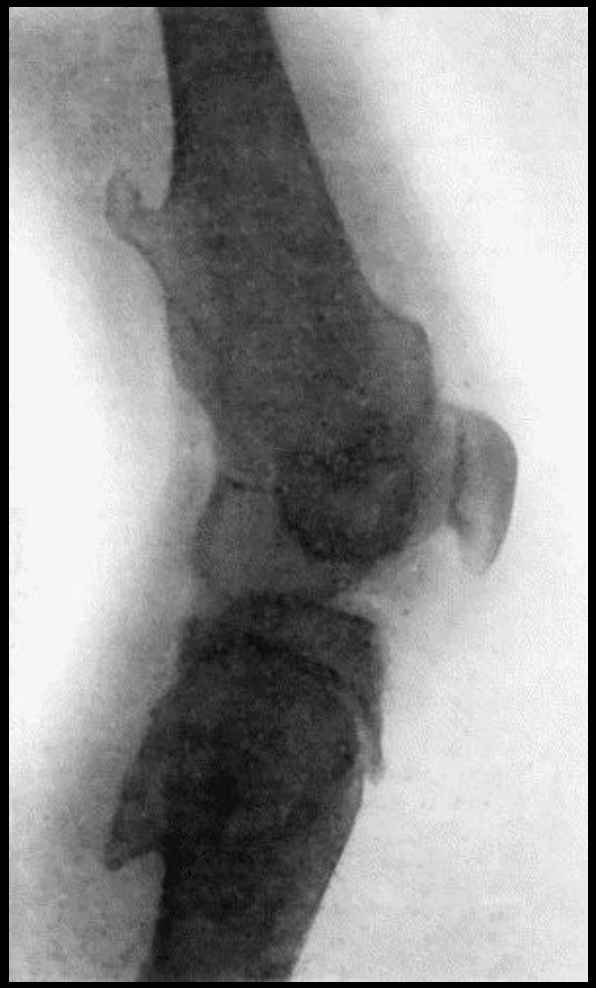
Think of possible presence of a malignant disease!

Diagnostic work-up in suspicion of pediatric cancer



Bone pain

Bone cyst aneurysmal



Exostosis

X-ray of bone tumors

Osteosarcoma

Ewing sarcoma

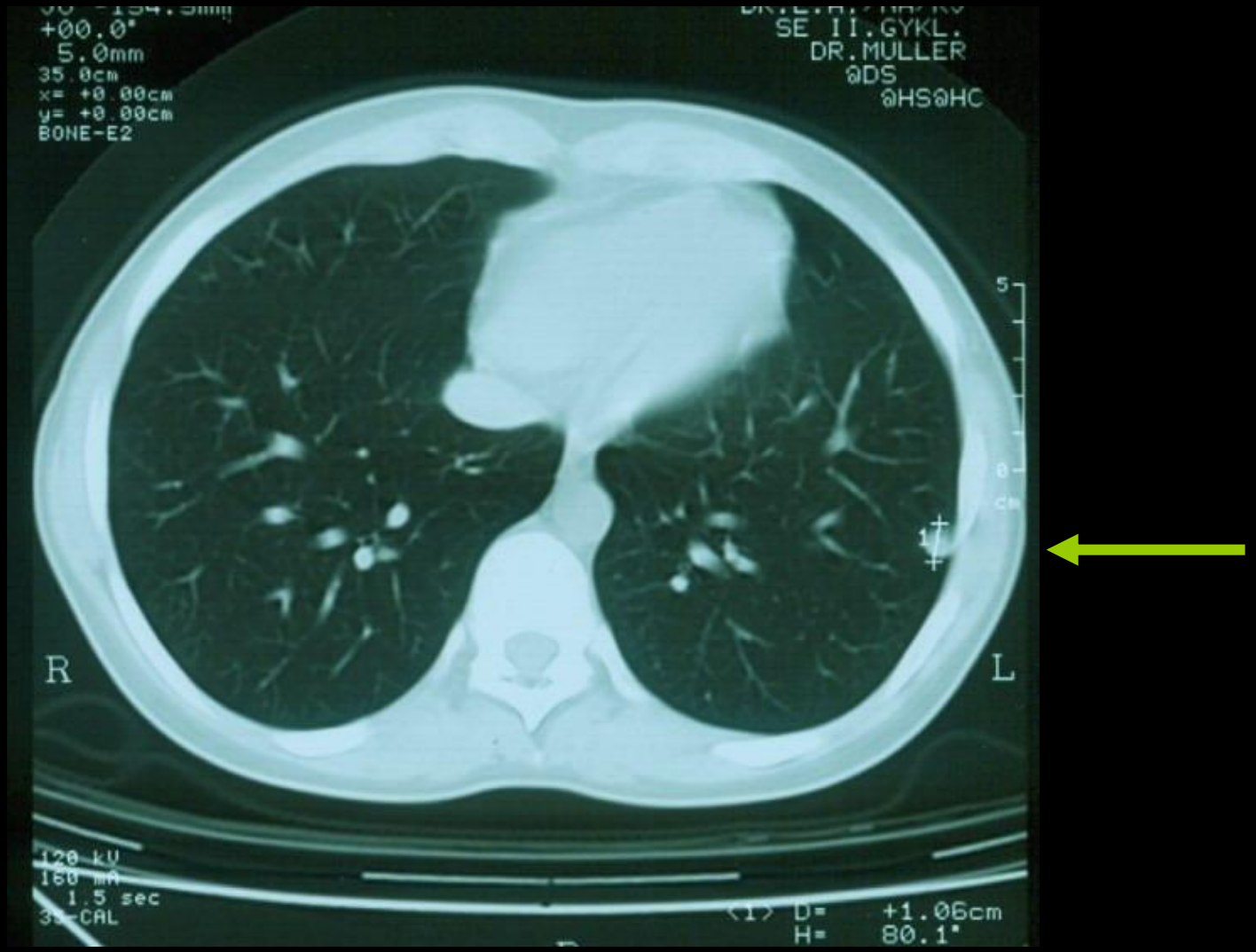
MRI of left femur

T1 weighted

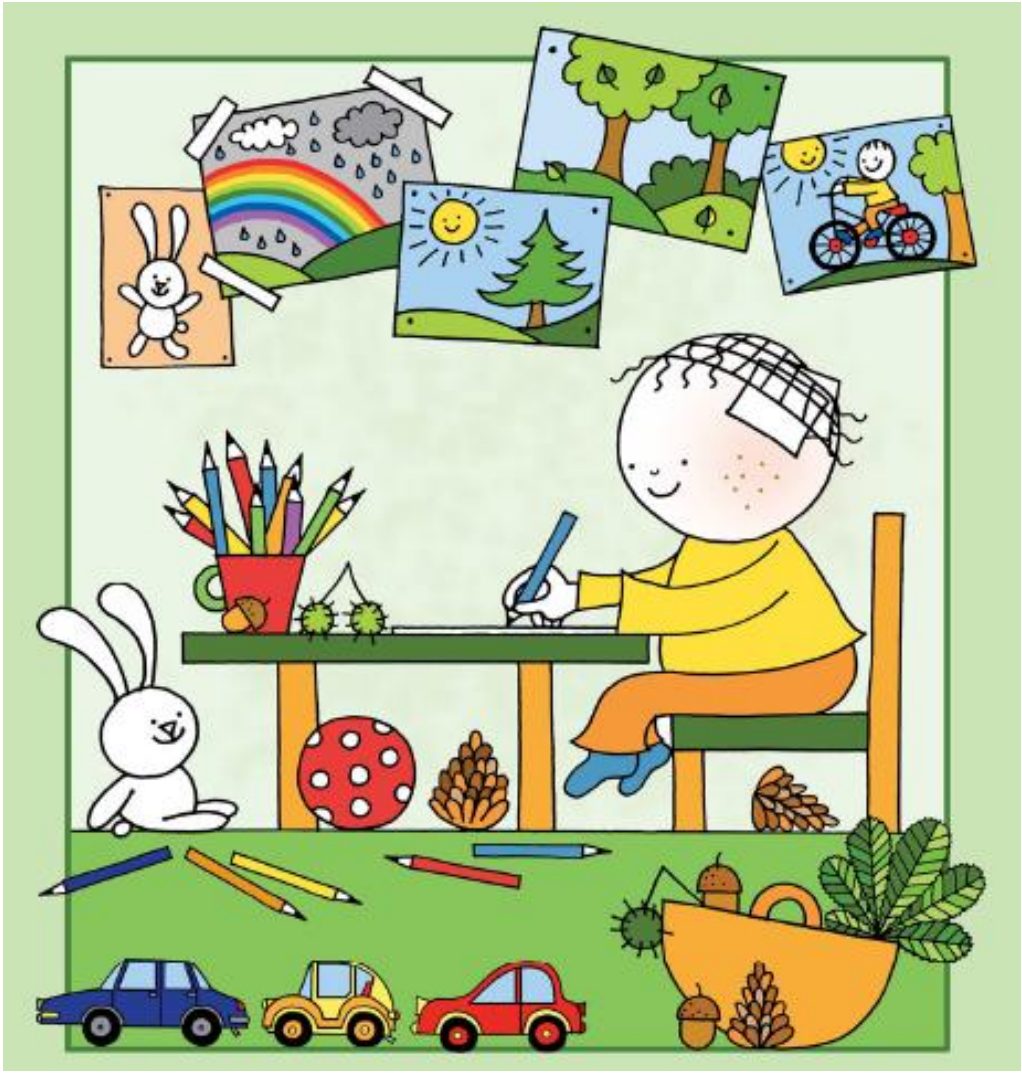
contrast

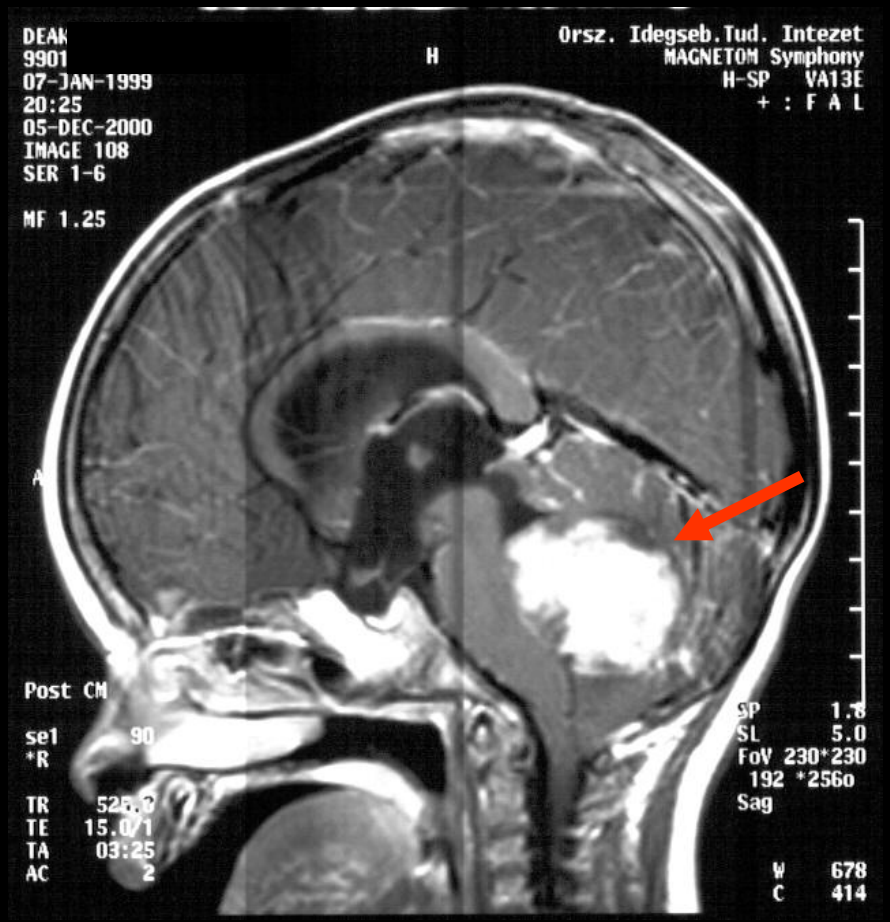
99mTc bone scintigraphy

Chest CT


+00.0°
5.0mm
35.0cm
x= +0.00cm
y= +0.00cm
BONE-E2
SE II.GYKL.
DR.MULLER
@DS
@HS@HC
R
L
120 kV
160 mA
1.5 sec
CAL
<1> D= +1.06cm
H= 80.1°

Brain tumor





Medulloblastoma

Possible Signs of brain tumor

headche

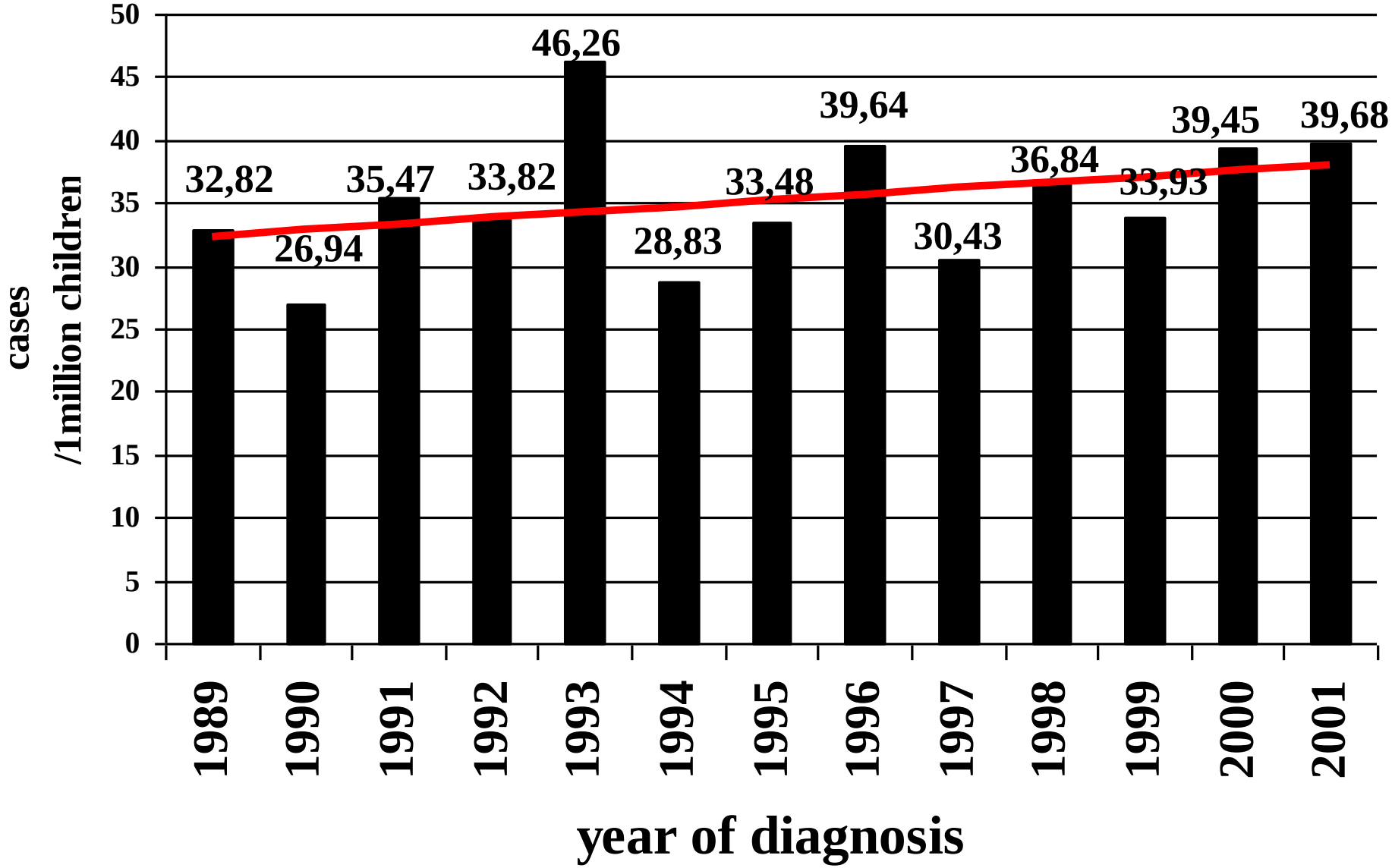
+

neurologic sign

And/or

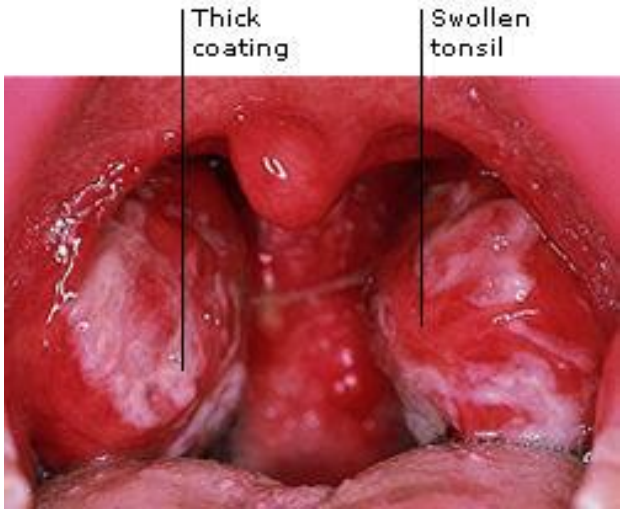
Signs of increased intracranial pressure

Trend of incidence of CNS tumors in Hungary

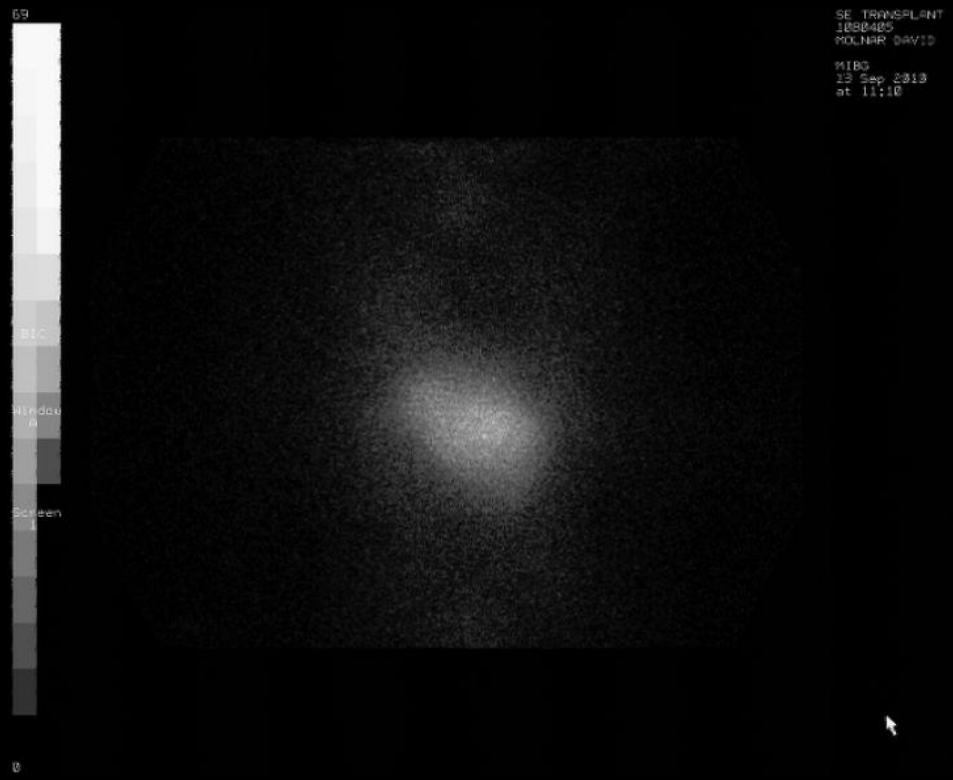


Abdominal mass


A.D.A.M.

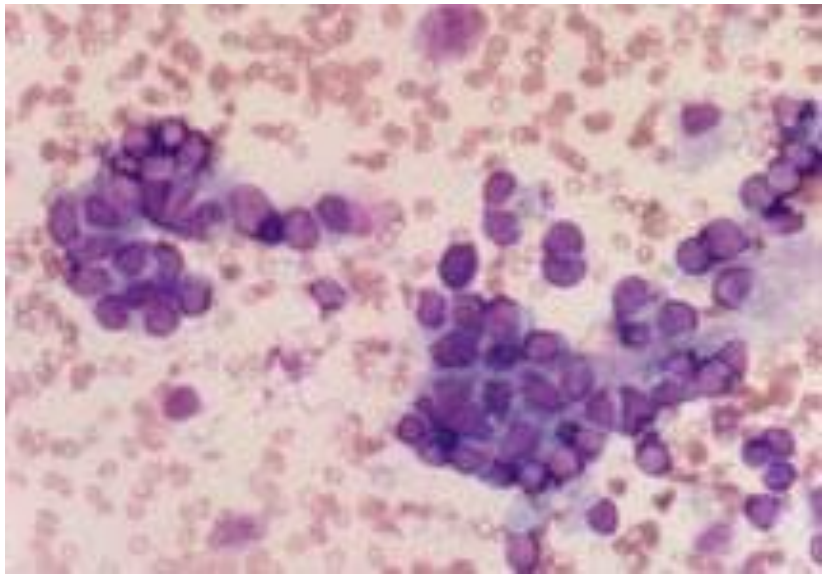

Thick coating
Swollen tonsil

MRI
neuroblastoma

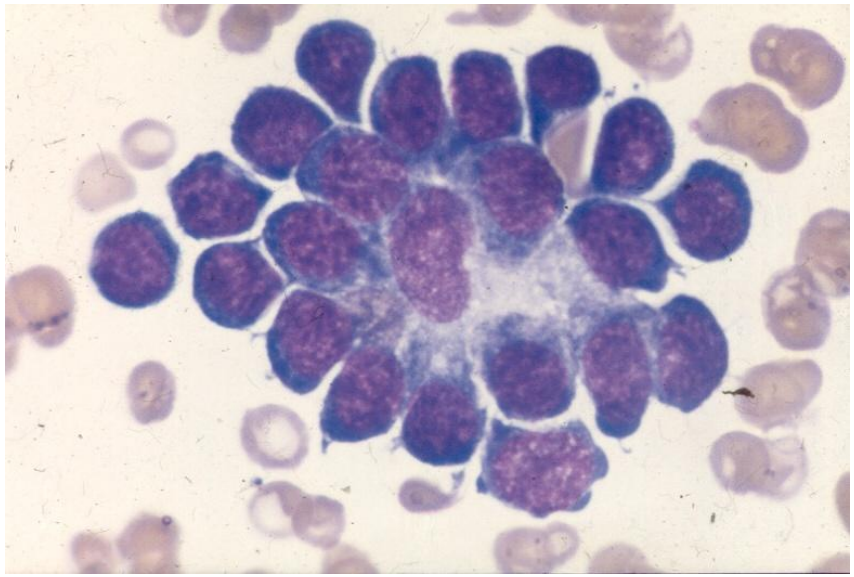


MIBG
neuroblastoma

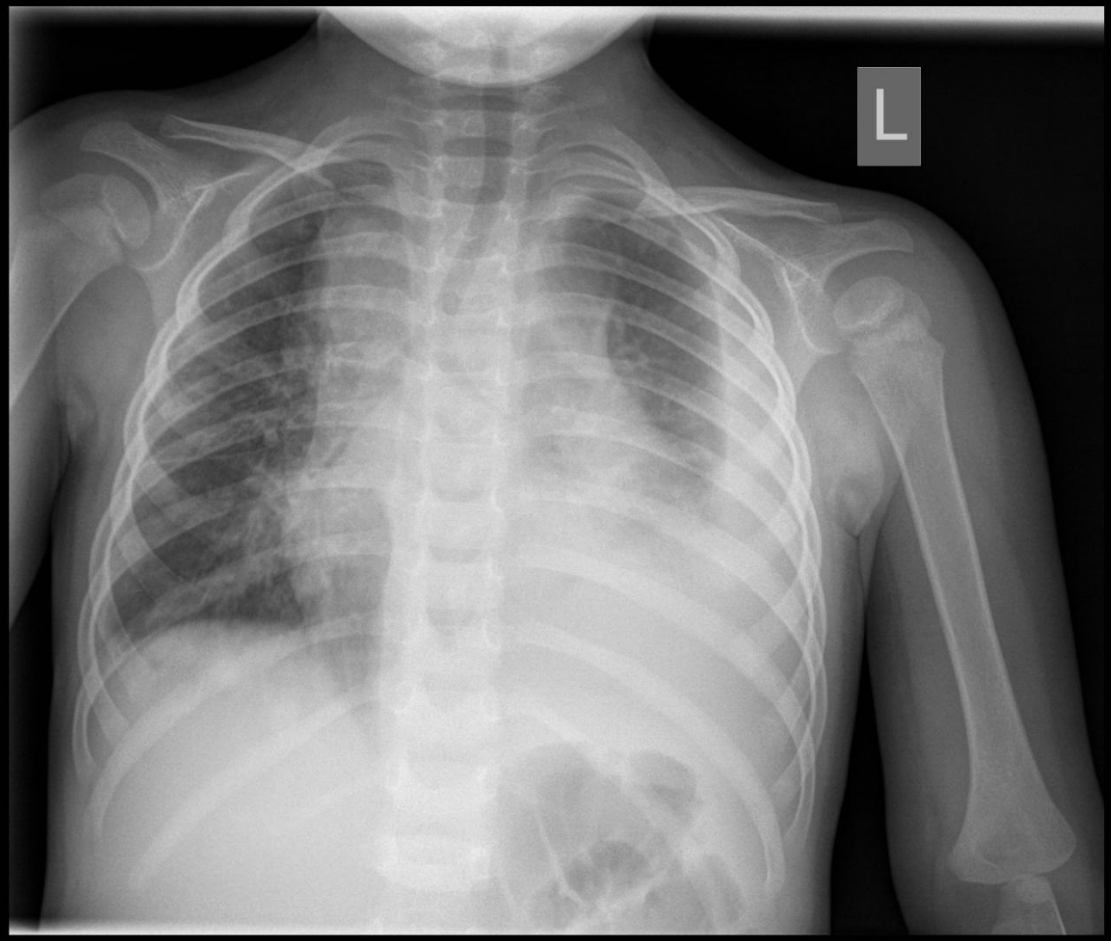
Metastasis in bone marrow



Nests of tumor cells



Homer-Wright rosette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Activity after diagnosis

treatment

- General organ check-up
- Staging
- Antitumor therapy:
  - Pre- and postoperative chemotherapy
  - Irradiation
  - Surgery
  - Prevention and treatment of side effects of therapy

rehabilitaion

- Diagnosis sharing
- Prepare parents and child for the reaction of the human enviroment
- Maintan previous life style as much as possible:
  - School, activities
- Presence of parents

Main principles of therapy 1

- Definition of aim of therapy: cure or palliative
- Usually chemosensitive tumors
  - (sarcomas, embryonal tumors)
- Higher tolerability, intact organs
- More agressive therapy than in adults
- Complex therapy (surgery-irradiation-chemoth)
- Co-administration of several drugs
- Length of therapy: ½ -1 year

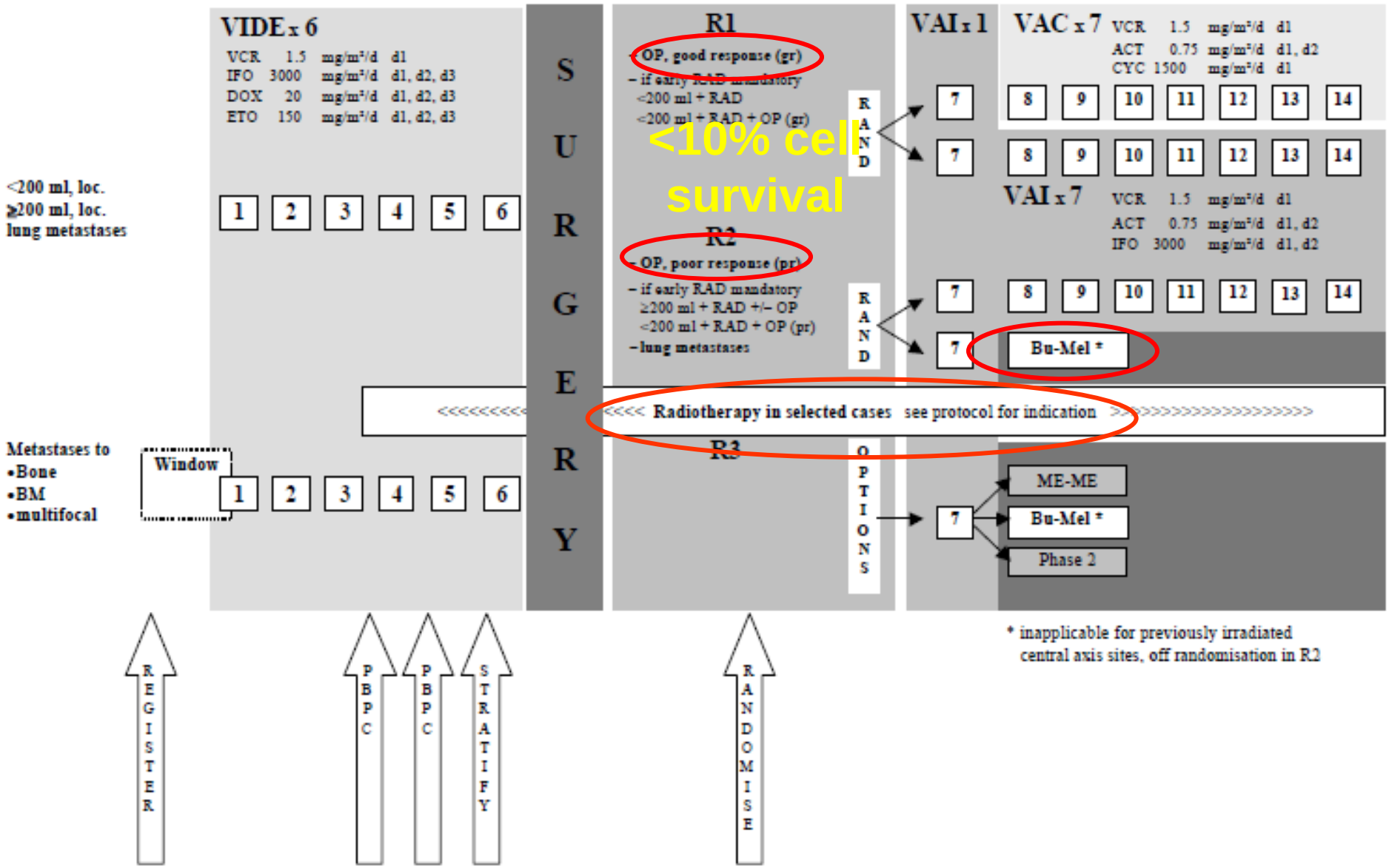
Main principles of therapy 2

- Surgical goal at primary diagnosis:
  - not the primary complete removal (Quality of life!)
- In certain situation therapy without histology:
  - Wilms–tumor (based on MR or CT)
  - Hepatoblastoma (hepatic mass+0.5-3év+AFP⇑)
  - Corpus pineale tumor+AFP/βhCG⇑= germ cell tu
  - (Diffuse) brain stem glioma (dangers of sampling)
  - retinoblastoma

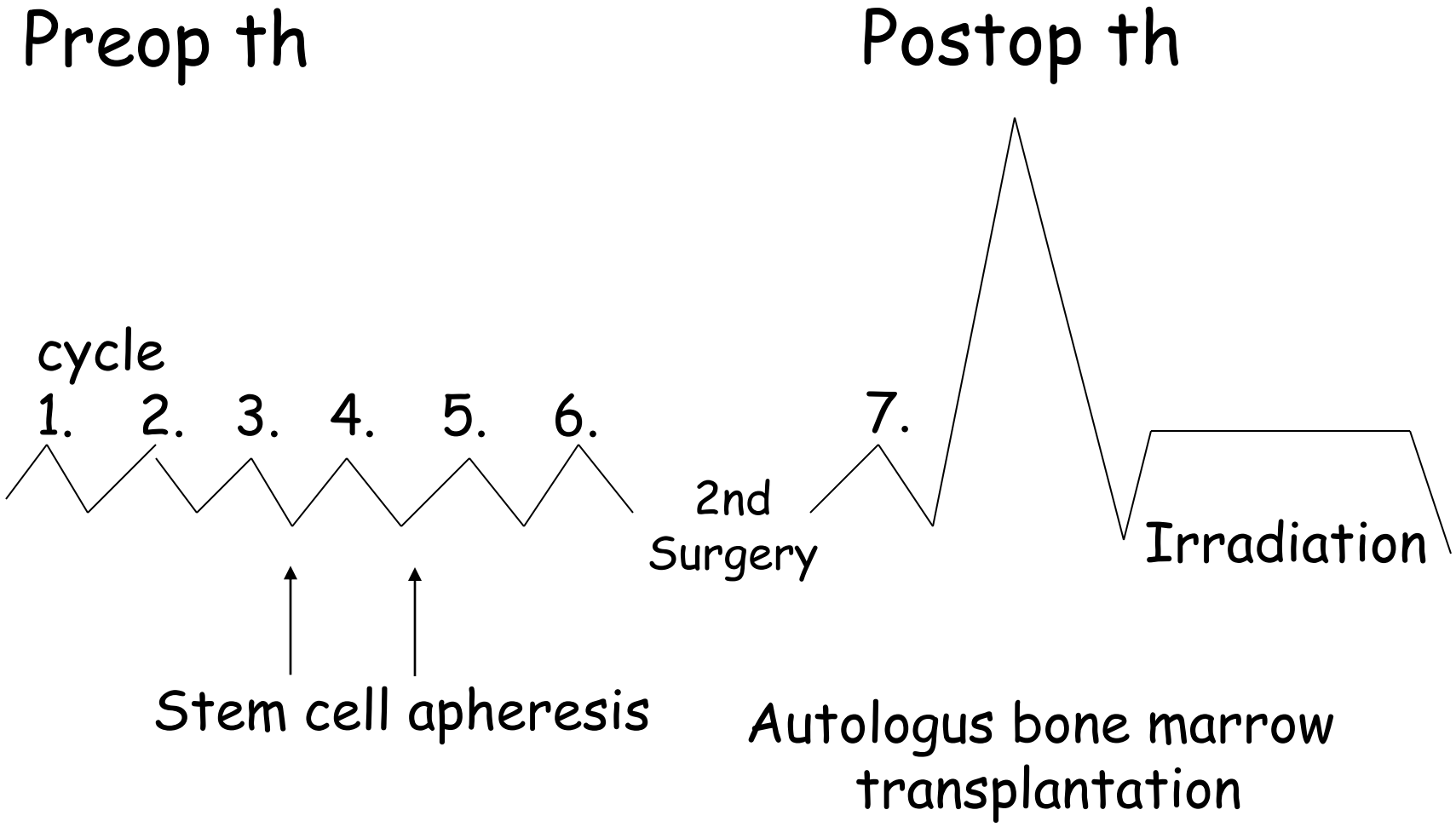
Main principles of therapy 3

- Preoperatív (neoadjuvans) chemotherapy:
  - shrinkage of the tumor
  - avoid mutilating surgery
- „Second look resection” – biological answer!!!!!
- Postoperative chemotherapy:
  - to kill invisible micrometastasis from circulating tumor cell after surgery
- Irradiation: to avoid long term side effects
  - (bone growth, brain development)

EURO-E.W.I.N.G. 99

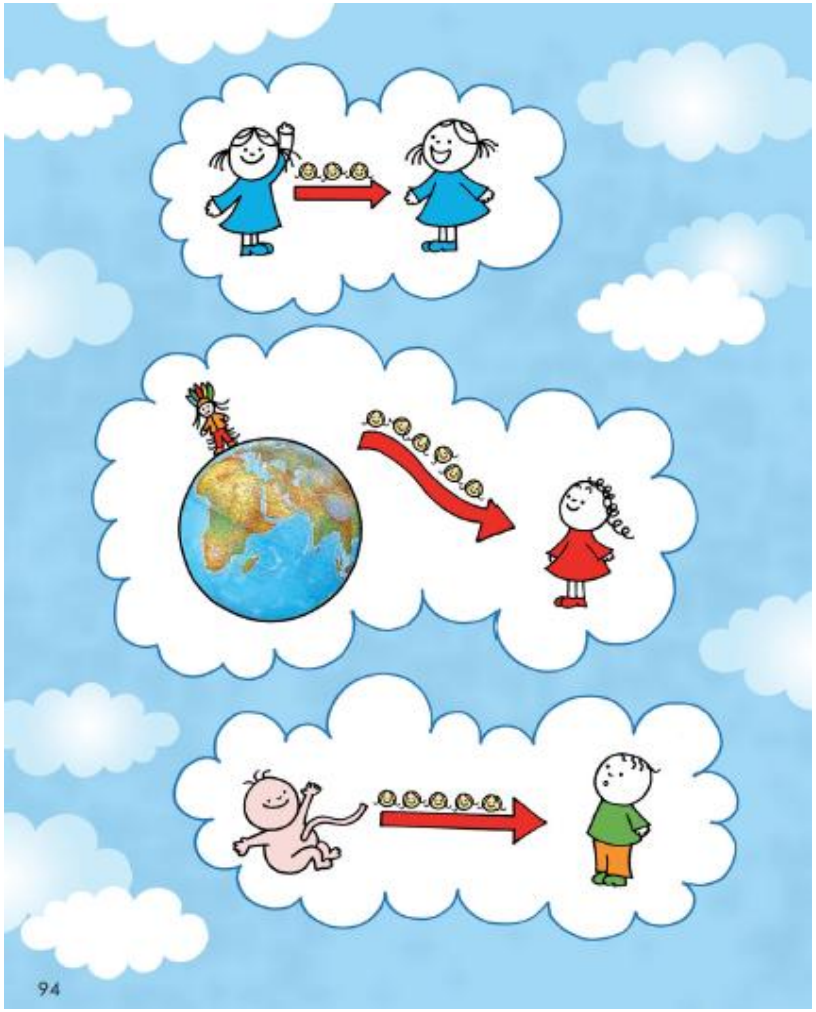


Schema of therapy



Type of bone marrow transplantation

- allogeneic
- autologus
- syngen



Stem cell recources

- Bone marrow
- Peripherial blood
- Umbilical blood

CD34+ stem cell selection

Indication for hematologic stem cell transplantation:

- Hematologic diseases
- Congenital immundeficiencies
- Storage and metabolic disease
- **Malignant solid tumors**
- Autoimmun diseases

Indication of autologus hematologic stem cell transplantation in solid tumors

- chemosensitive tumor
- disseminated disease, residual tumor
- medulloblastoma, Ewing sarcoma, neuroblastoma

Stem cell transplantation

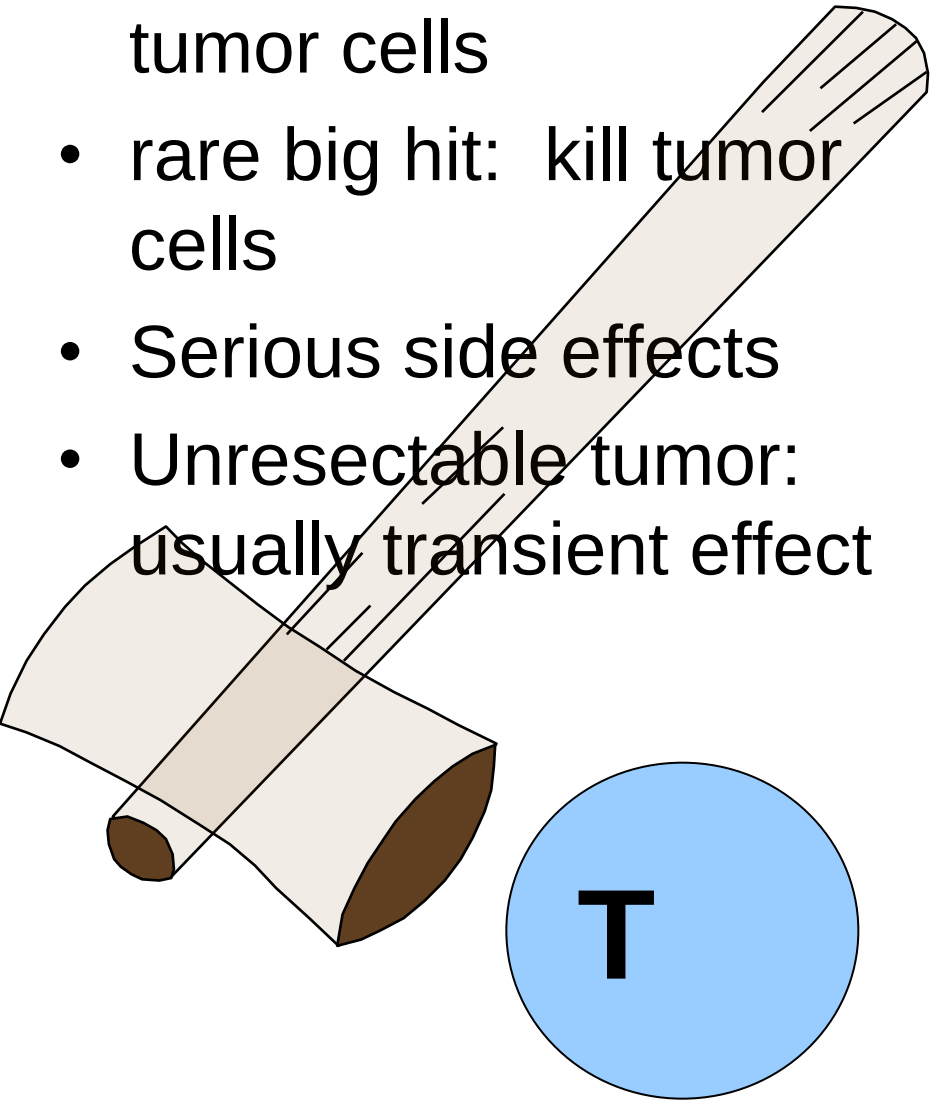
Inefficient primary therapy

- CURATIVE th:
  - Second line drugs
  - Different target
  - Radical surgery
  - Clinical trials (Phase 2-3.)
- PALLIATIVE care

Metronomic therapy

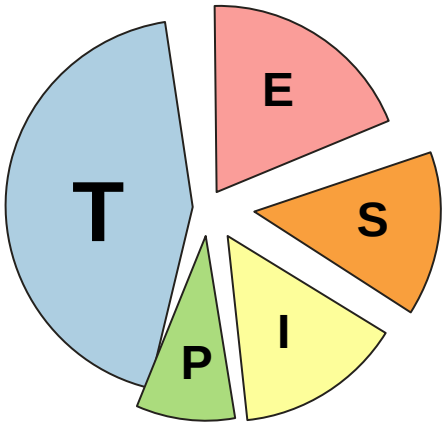
Classic chemoth

- Tumor contains only tumor cells
- rare big hit: kill tumor cells
- Serious side effects
- Unresectable tumor: usually transient effect



Metronomic th

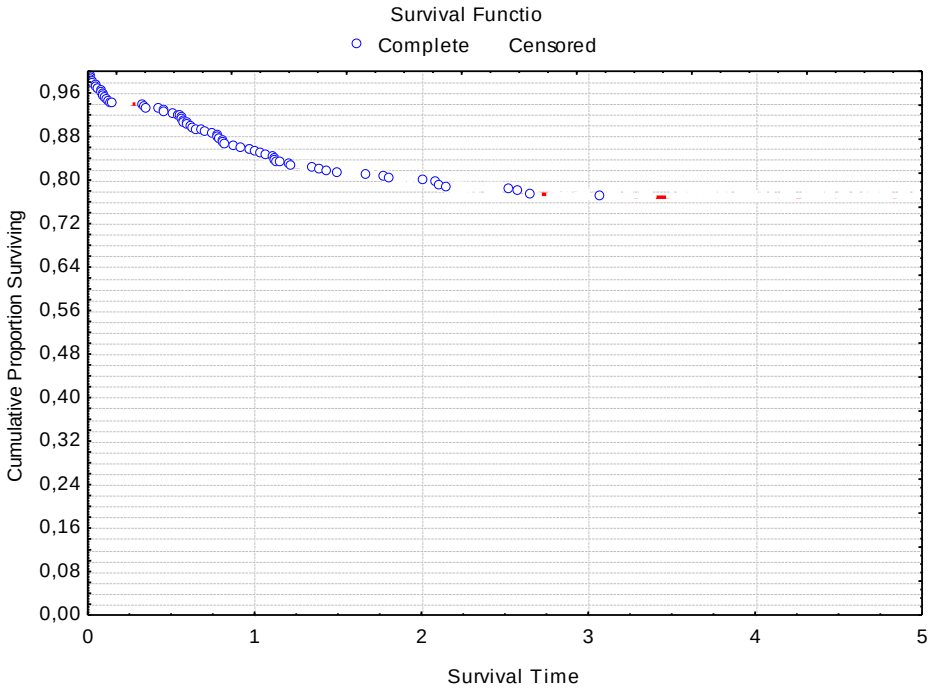
- Tumor contain: tumorcells, immunocells, stromal cells, vessels and endothels)
- To inhibit expansion of vessels
- Continuous weak antitumor effect
- Slight side effects – good quality of life



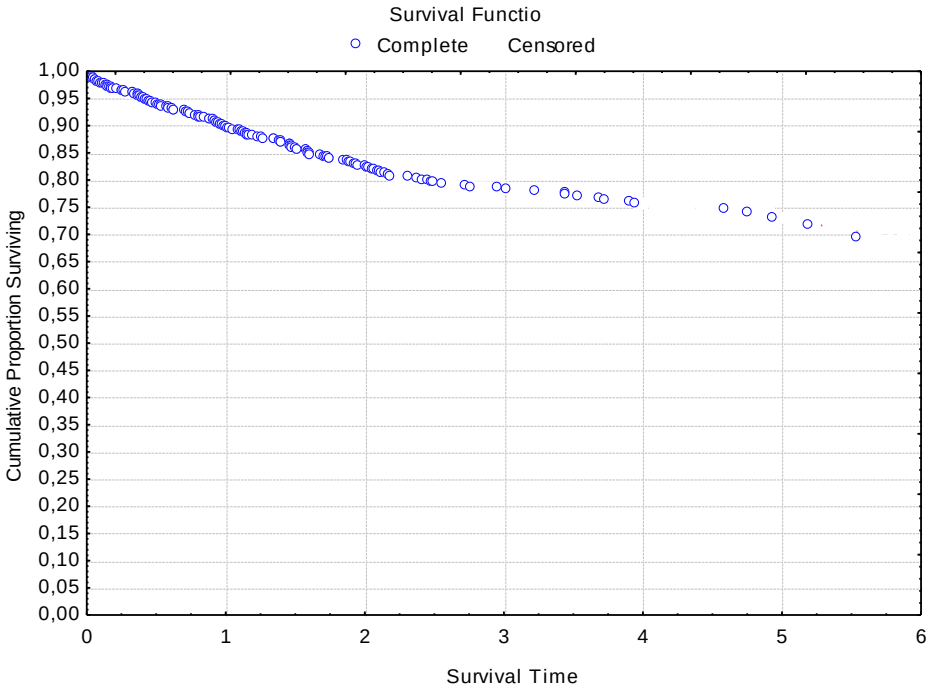
Palliative care

- pallium = mantle (lat.)
- Goal: mantain sufficient quality of life =
  no aggressive treatment
- Tools:
  - pain mangement
  - psychological support (child and family)
  - well tolerable antitumor treatment
  - irradiation

Overall survival (OS) of pediatric malignancies in Hungary



OS leukemias



OS solid tumors

Courtesy Jakab Zsuzsa, Hungarian Tumor Registry

Acute side effects of chemotherapy

- Nausea, vomiting
- Hair loss

- Life threatening – immediate hospitalization:
  - Granulocytopenia – sepsis
  - Thrombocytopenia – bleeding
  - Anemia

Organ system	Chronic health condition
Neurological	Paralysis
	Seizure
	Fatigue
	Chronic pain
	Spasticity
	Ataxia
	Dysarthria
Ocular	Diplopia
	Cataracts
	Visual loss
Auditory	Tinnitis
	Hearing loss
Neurocognitive	Learning deficits
	Executive function (planning and organization)
	Sustained attention
	Memory
	Processing speed
	Visual–motor integration
	Diminished IQ
	Behavioral change
Neuropsychiatric	Social withdrawal
	Depression
	Anxiety
	Posttraumatic stress
Endocrine	Gonadal dysfunction, gonadotropin deficiency, infertility
	Metabolic syndromes, obesity
	Growth hormone deficiency
	Precious puberty
	Hyperprolactinemia
	Central hypothyroidism
	Central adrenal insufficiency

Long term side effects of treatment of pediatric CNS tumors 1

Secondary tumors:

Meningeoma
Glioma
Sarcoma

Thyroid cancer

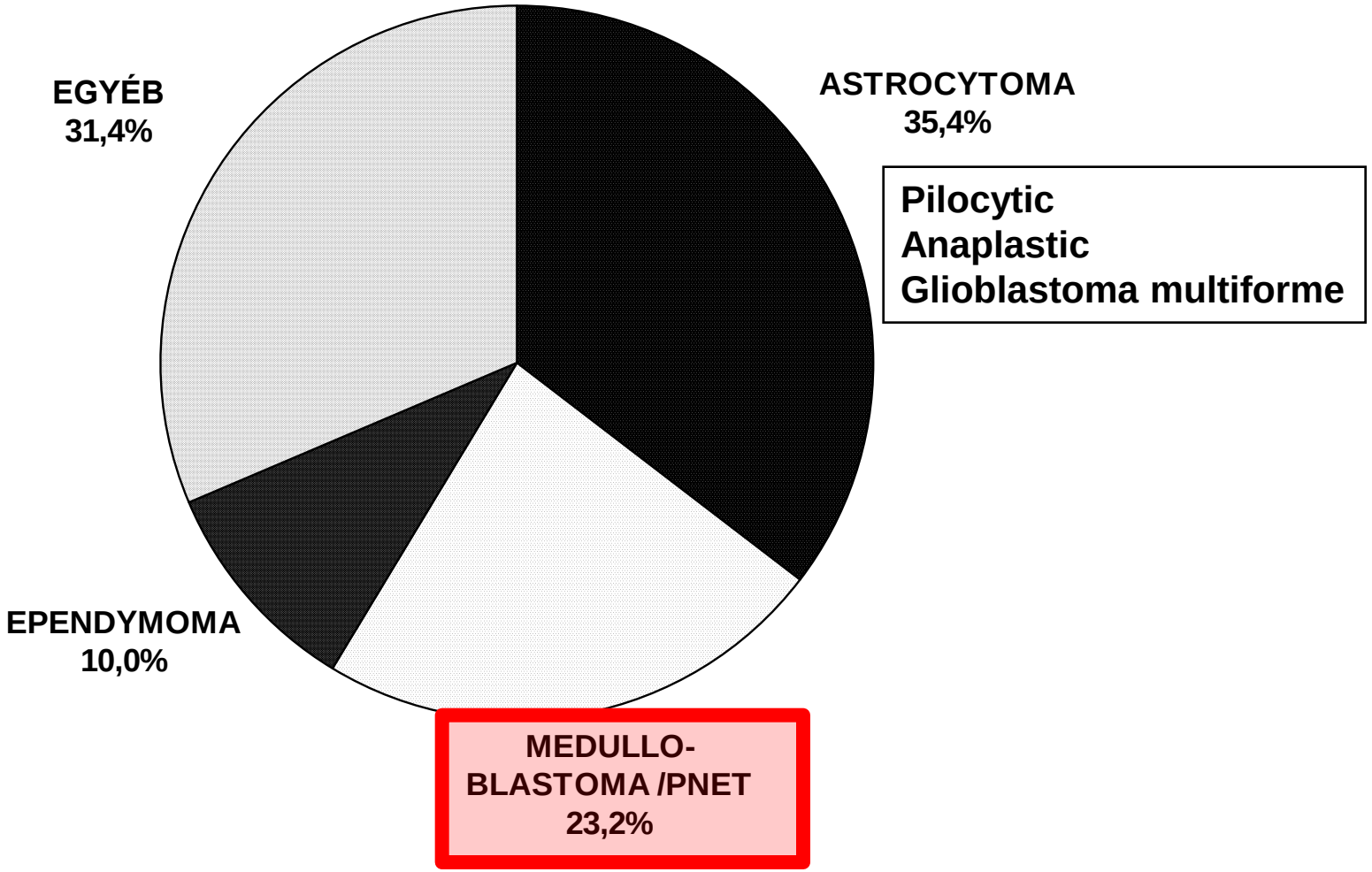
Pulmonary	Pulmonary fibrosis
	Interstitial pneumonitis
	Restrictive lung disease
	Obstructive lung disease
Gastrointestinal	Dysphagia
	Esophageal stricture
	Bowel obstruction
	Chronic enterocolitis
	Fistula
	Strictures
	Hepatic dysfunction
Cardiac	Congestive heart failure
	Cardiomyopathy
	Pericarditis
	Pericardial fibrosis
	Valvular disease
	Myocardial infarction
	Arrhythmia
	Atherosclerotic heart disease
Renal	Impaired function
Dental	Tooth/root agenesis
	Root thinning/shortening
	Enamel dysplasia

Long term side effects of treatment of pediatric CNS tumors 2

Future directions

- Genetic based reclassification – individual therapy
- Immuno therapy – dendritic cells
- Tumor specific monoclonal antibodies
- Enzyme inhibitors (TKI)

Subtypes of Brain tumor (WHO 2000)



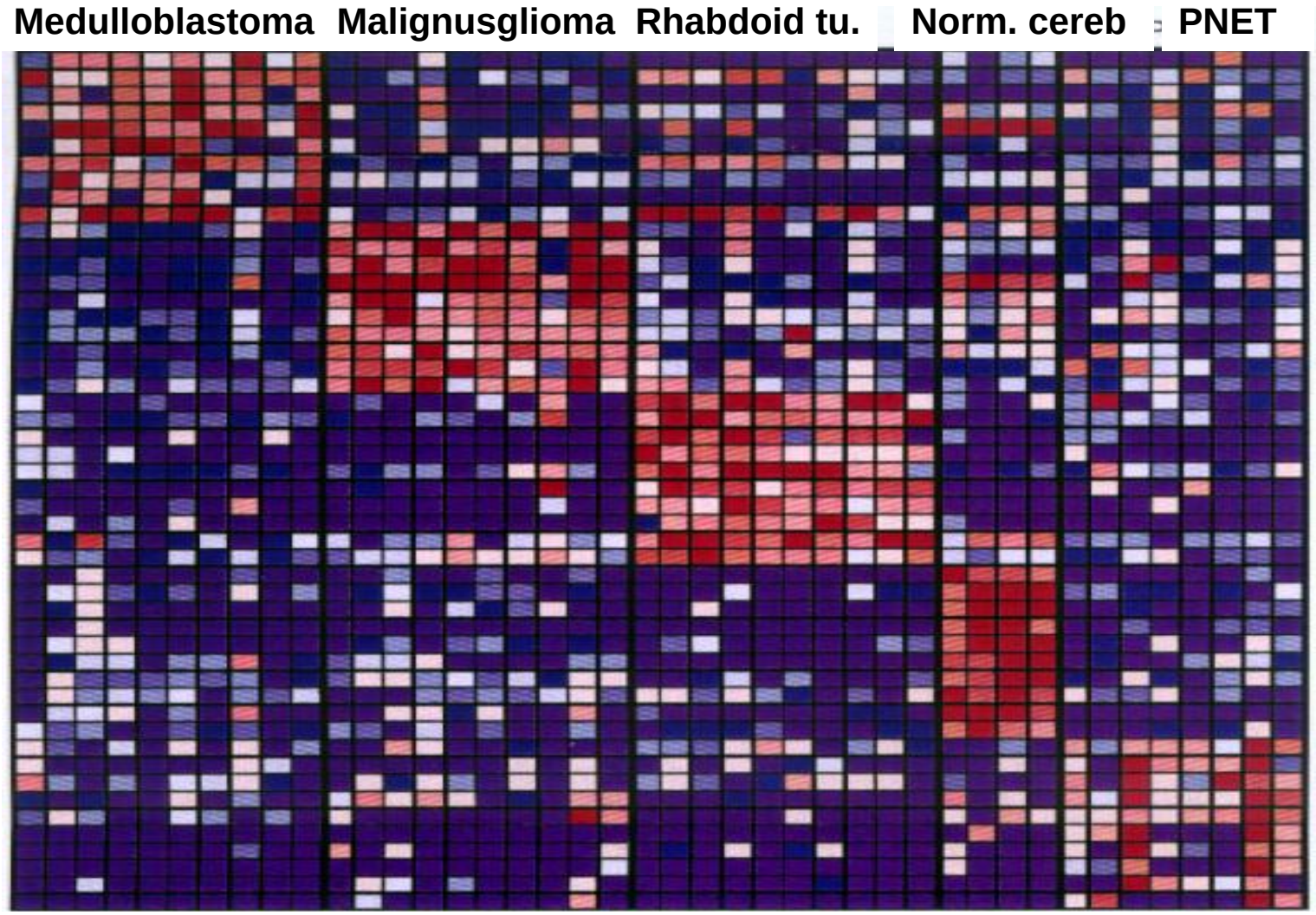
Hauser et al. Med and Ped Oncol (2003);41:590-591

Pediatric embryonal brain tumors
(WHO, 2007)

1. Medulloblastoma
2. Atypical teratoid, rhabdoid tumor (AT/RT)
3. CNS PNET:
    - CNS ganglioneuroblastoma
    - CNS neuroblastoma
    - ependymoblastoma
    - medulloepithelioma

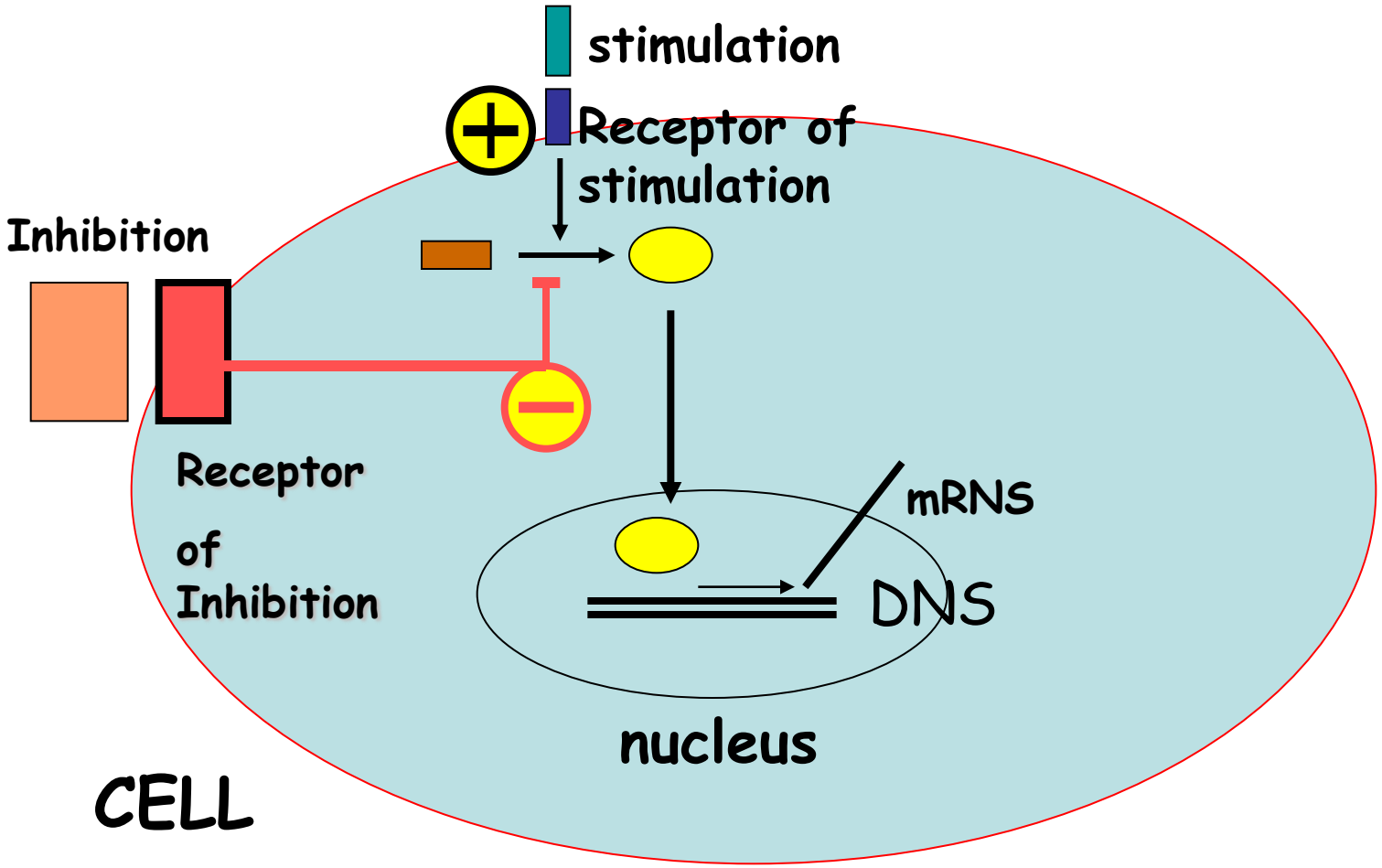
→ ETANTR

Genexpression profile of brain tumors

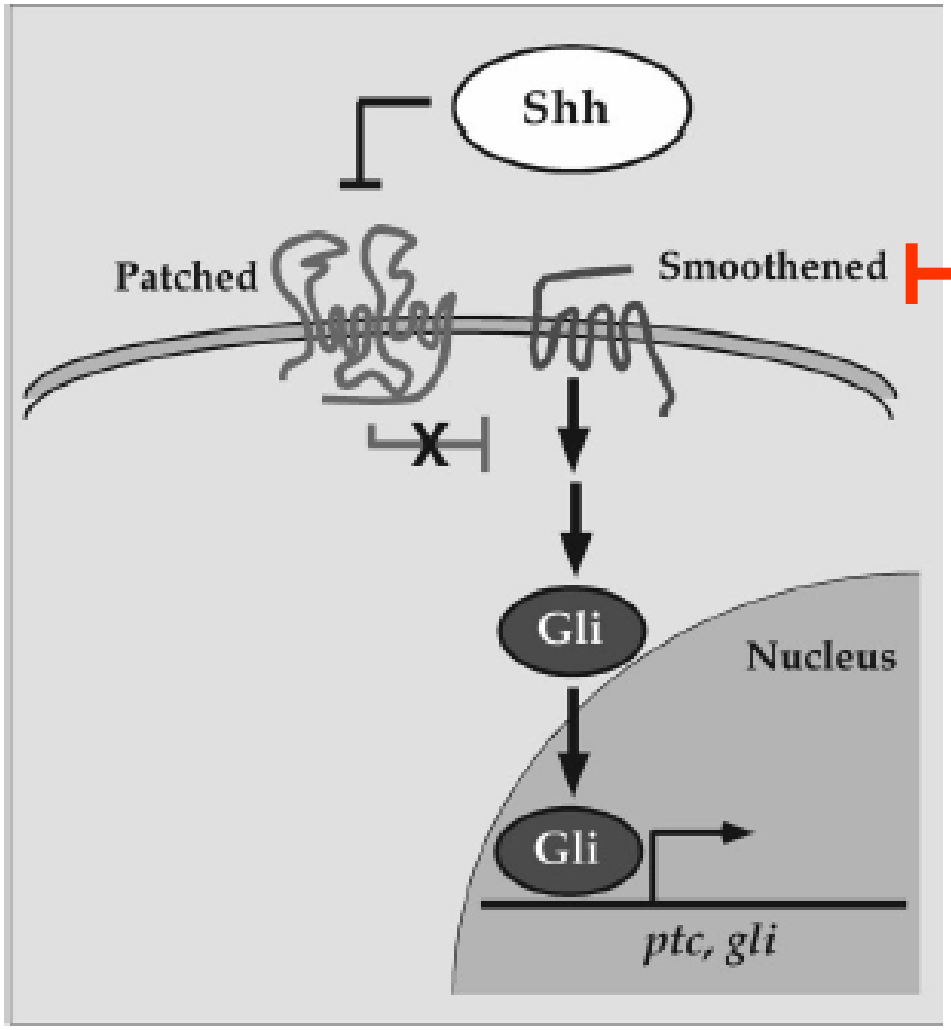


Pomeroy et al.: Nature, 415(6870): 436-442, 2002.

proliferation signal tranduction in a cell

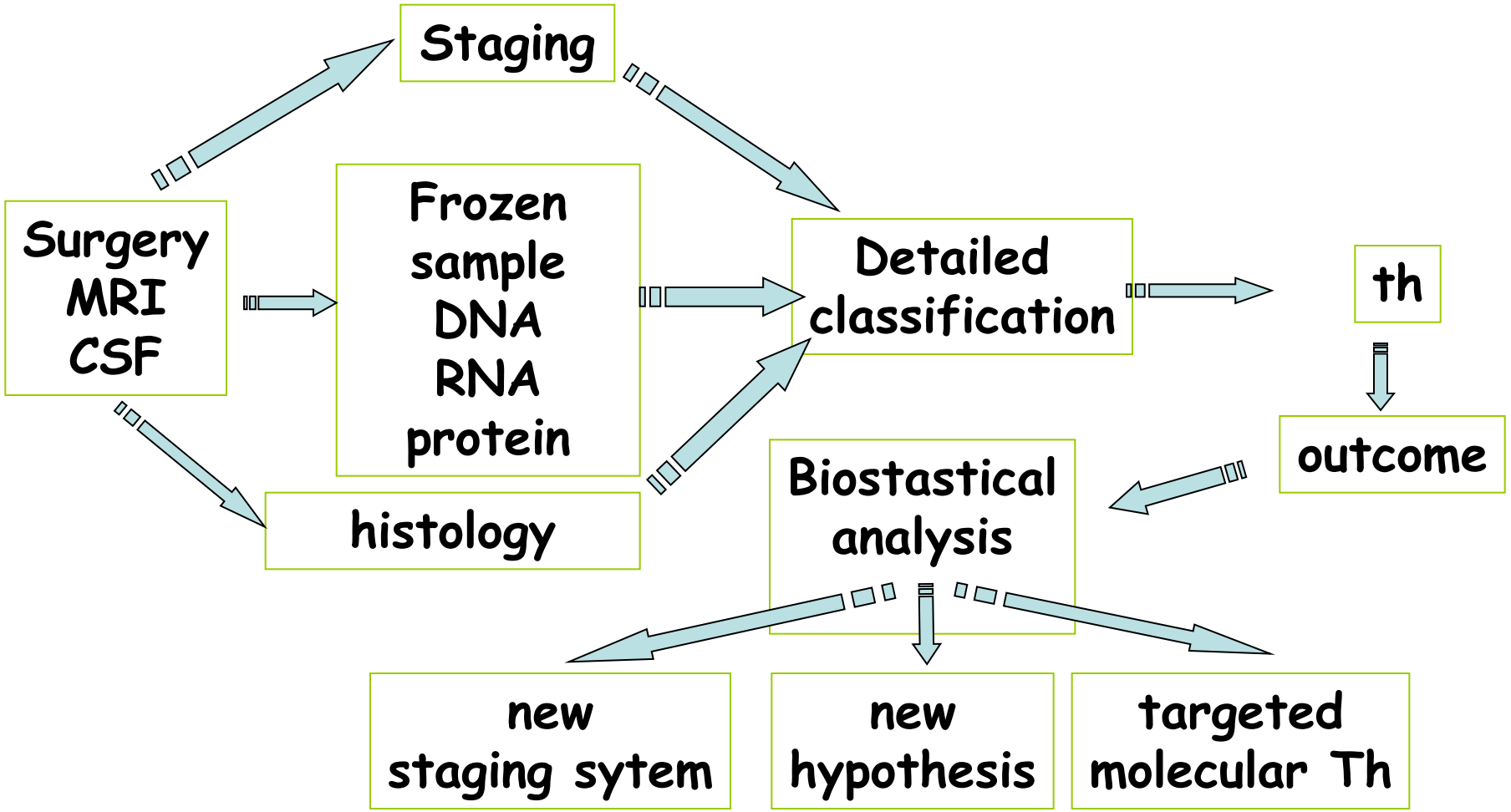


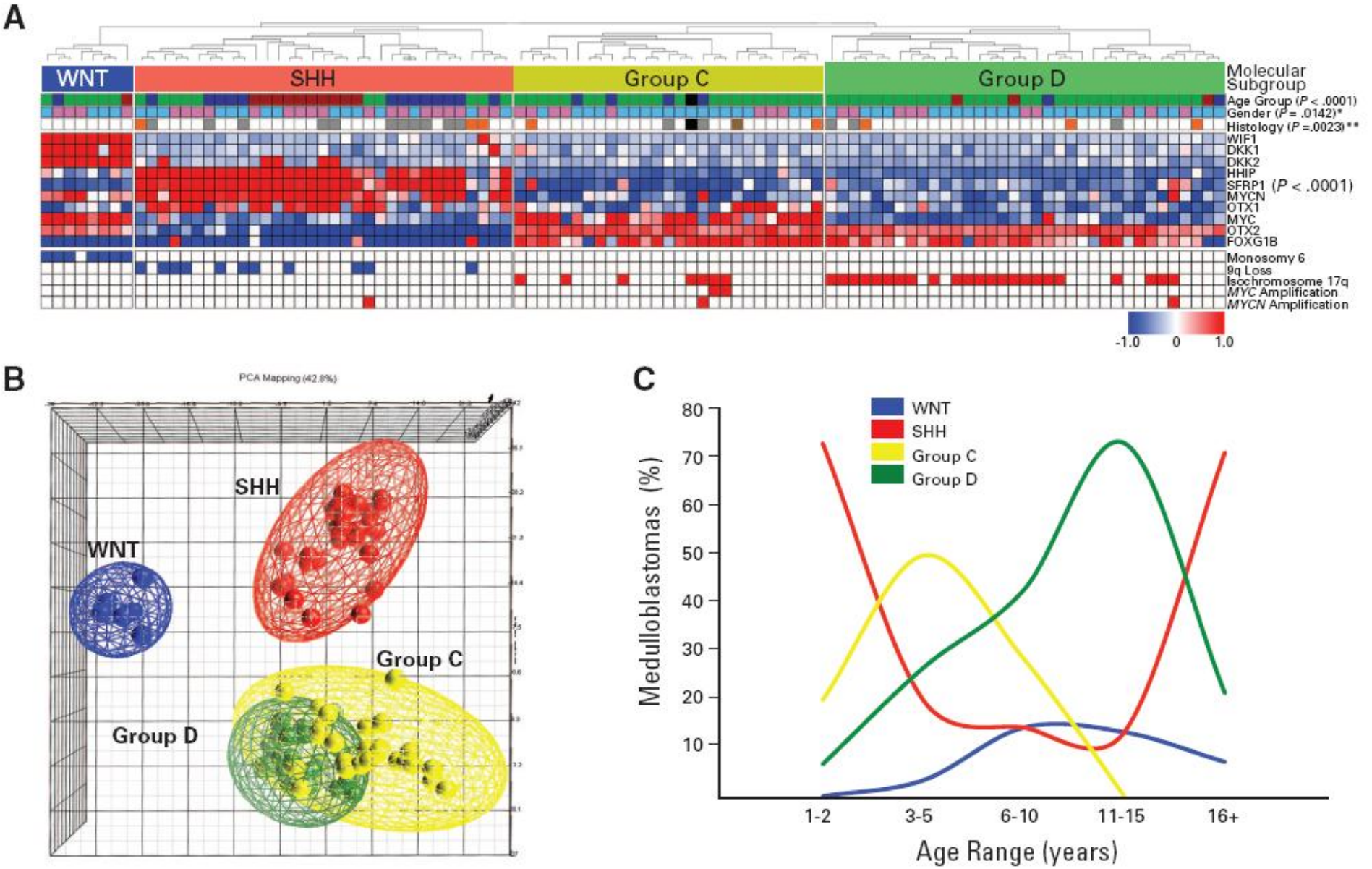
Hedgehog (Hh) pathway



Sonidegib
LDE225

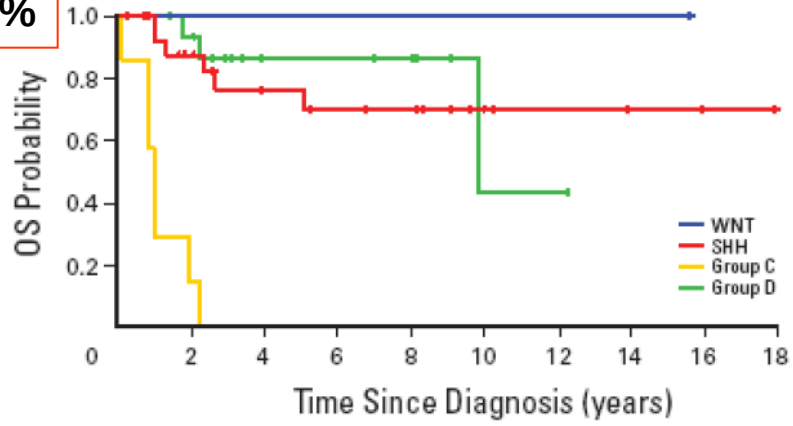
Individualized therapy of brain tumors



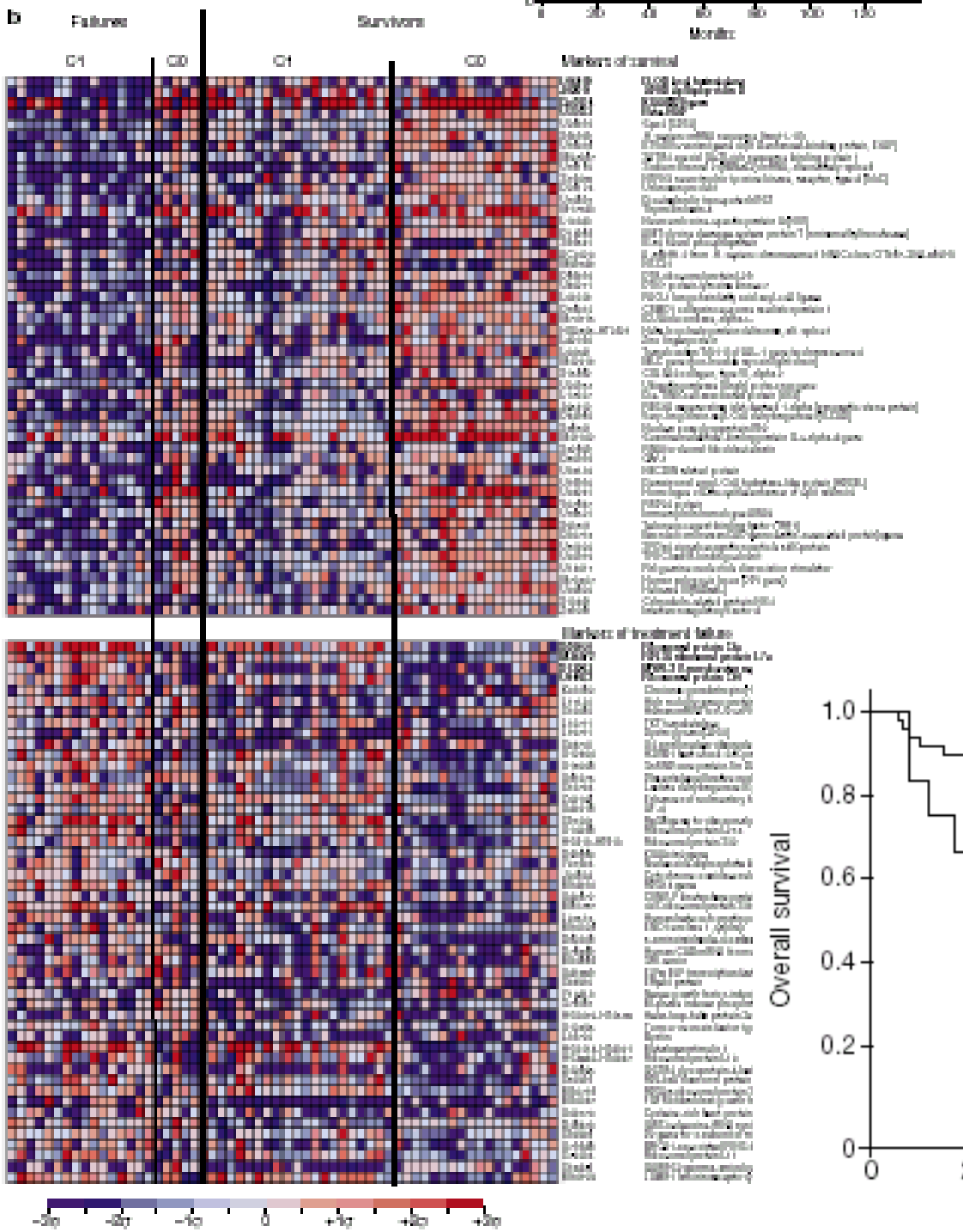

A
WNT
SHH
Group C
Group D
Molecular Subgroup
Age Group (P < .0001)
Gender (P = .0142)*
Histology (P = .0023)**
WIF1
DKK1
DKK2
HHIP
SFRP1 (P < .0001)
MYCN
OTX1
MYC
OTX2
FOXG1B
Monosomy 6
9q Loss
Isochromosome 17q
MYC Amplification
MYCN Amplification
-1.0
0
1.0
B
PCA Mapping (42.8%)
SHH
WNT
Group C
Group D
C
Medulloblastomas (%)
80
70
60
50
40
30
20
10
WNT
SHH
Group C
Group D
1-2
3-5
6-10
11-15
16+
Age Range (years)

Molecular Subgroups of Medulloblastoma

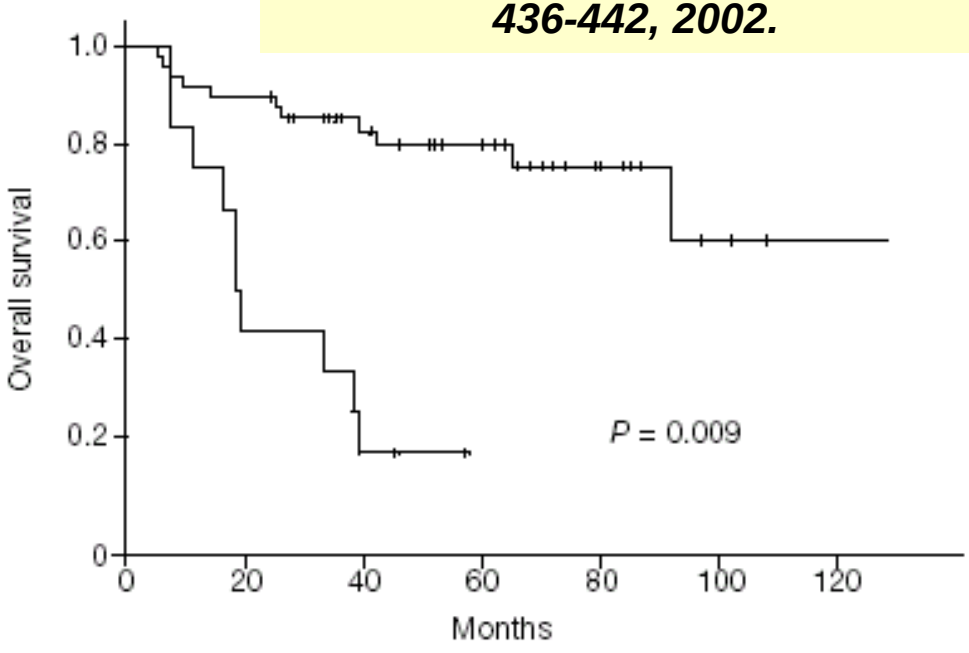
CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C
DEMOGRAPHICS				
Age Group: (infant, child, adult)				
Gender:	♂ ♂ : ♀ ♀	♂ ♂ : ♀ ♀	♂ ♂ : ♀	♂ ♂ : ♀
CLINICAL FEATURES				
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate
GENETICS	6-	3q+ 9q- 10q-	7+ 1q+ 17q+ 18q+ 11p- 8- 5q- 10q- 16q-	7+ 17q+ 18q+ 11p- X- 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification
GENE EXPRESSION	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*
Frequency:	10%	30%	25%	35%



MBL gén-expressziós profilja és a túlélés



Pomeroy et al.: Nature, 415(6870): 436-442, 2002.



Medulloblastoma lehetséges jövőbeli kezelése