

TUMOREN des KINDESALTERS



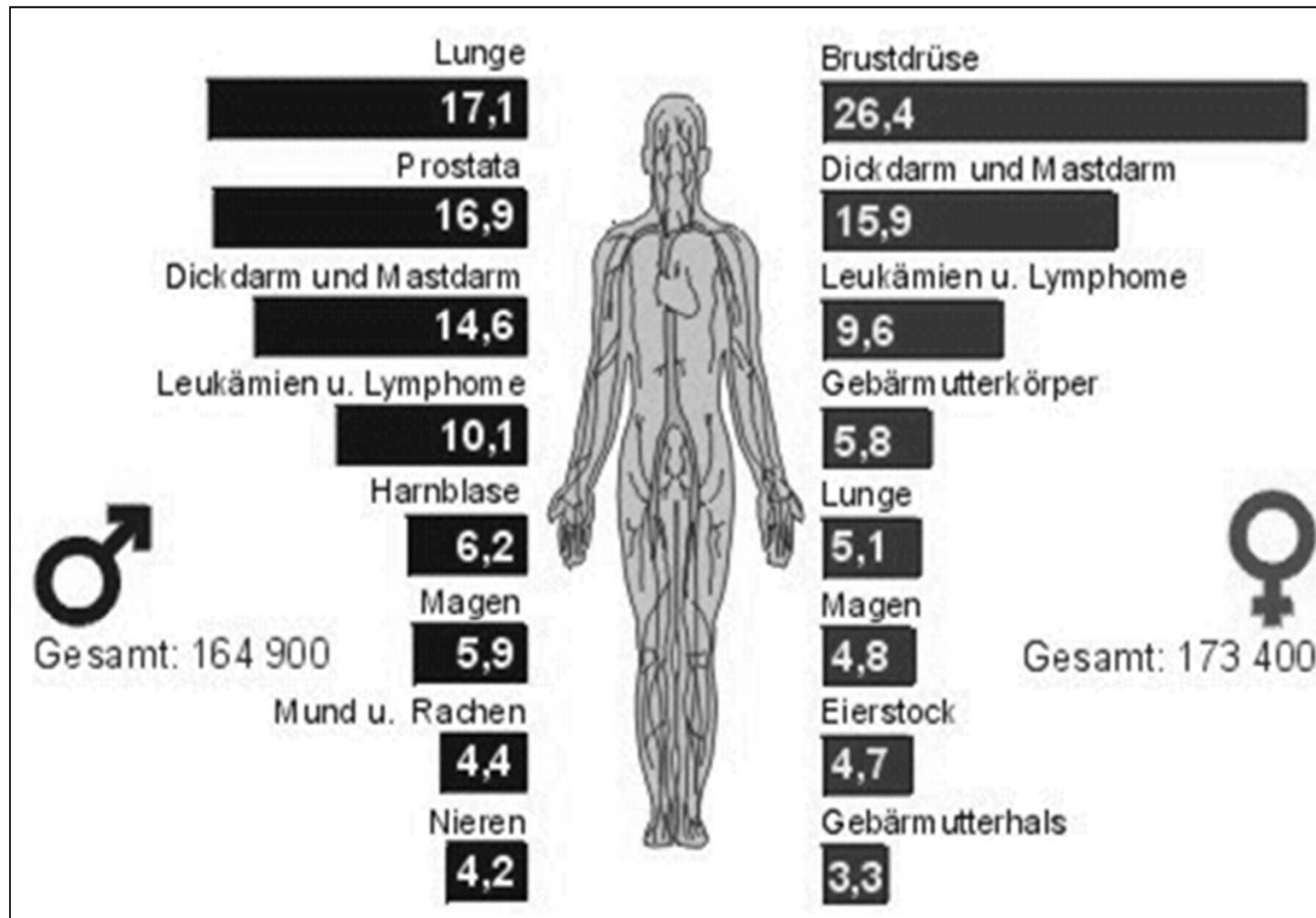
**Prof. Dr. Andras Kiss
med. habil., Ph.D., D.Sc.**

**Semmelweis Universität,
Budapest
II. Institut für Pathologie**

2017, Herbstsemester

Krebserkrankungen in Deutschland - Erwachsene

Prozentuale Anteile der häufigsten Krebsformen bezogen auf
Neuerkrankungen 1997



Krebs bei Kindern und Jugendlichen

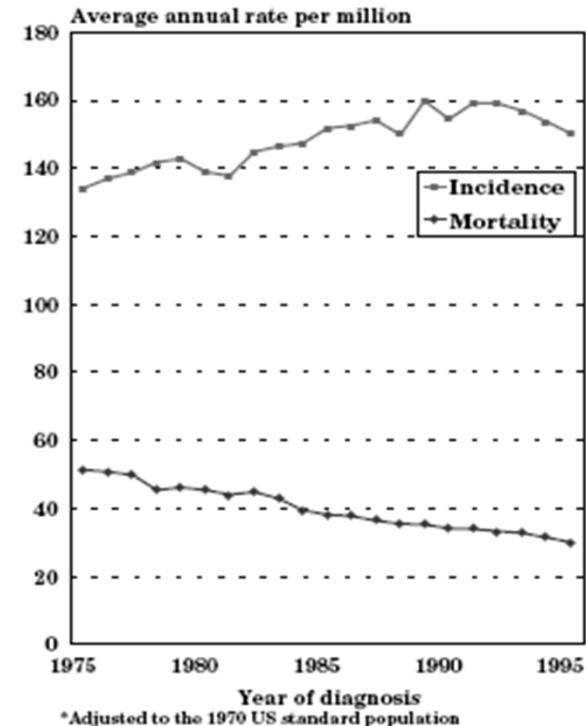
Solide Tumoren

ZNS-Tumoren	19 %
Astrozytom	8 %
Ependymom	2 %
Sonstige	9 %
Neuroblastom	9 %
Nephroblastom (Wilms-Tumor)	6 %
Weichteilsarkome	6 %
Rhabdomyosarkom	4 %
Sonstige	3 %

Tendenzen

- ★ Inzidenz ist relativ stabil
- ★ Mortalität ist abnehmend

Figure 1: Trends in age-adjusted* SEER incidence & U.S. mortality rates for all childhood cancers age<20, all races, both sexes, 1975-95

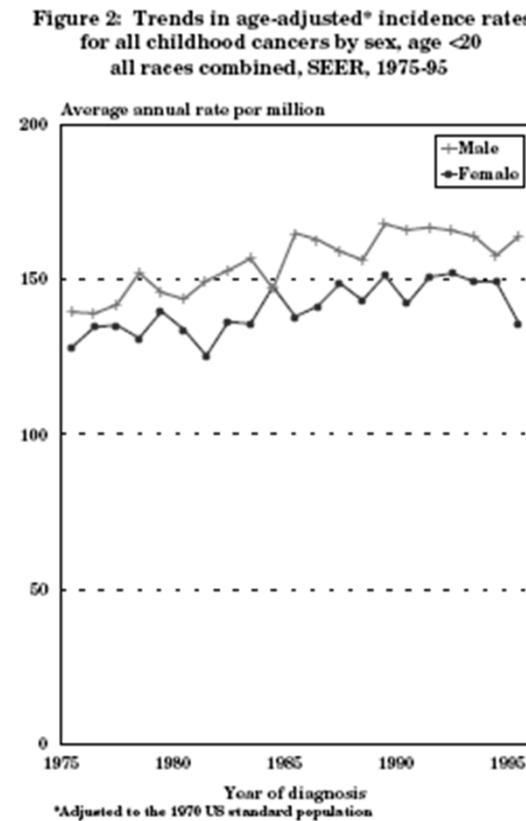


Krebsinzidenz

Hodgkin Lymphom

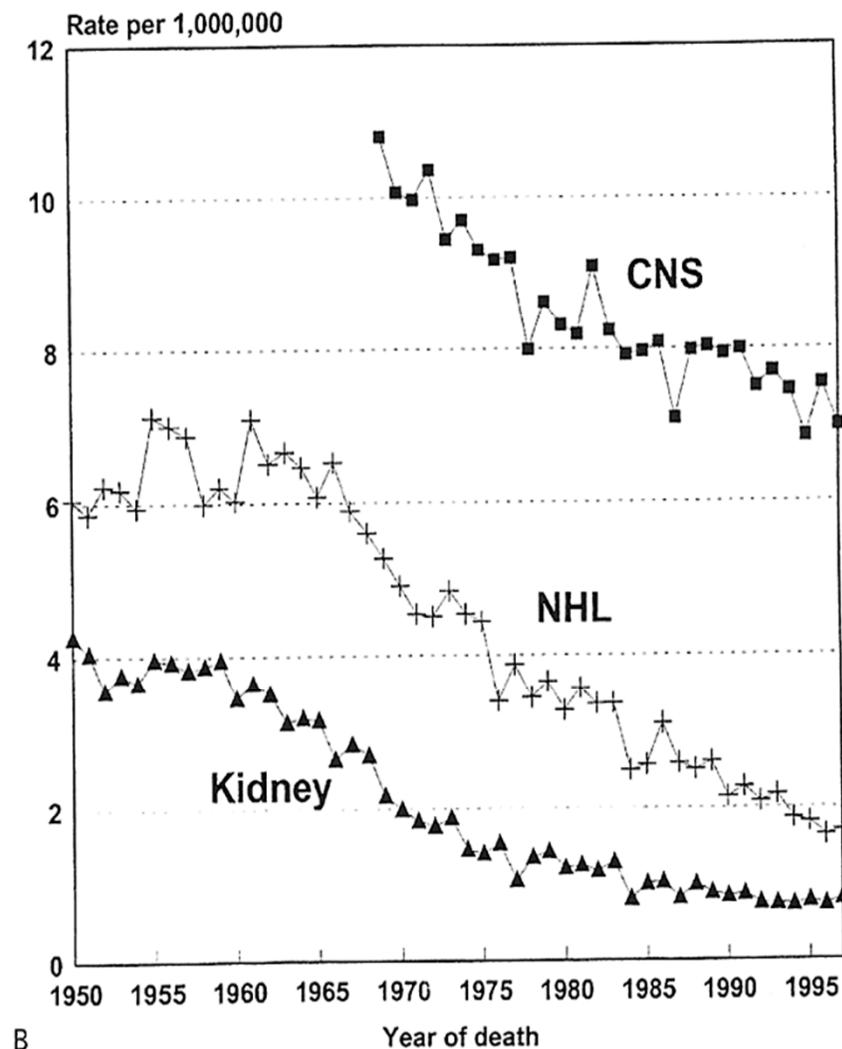
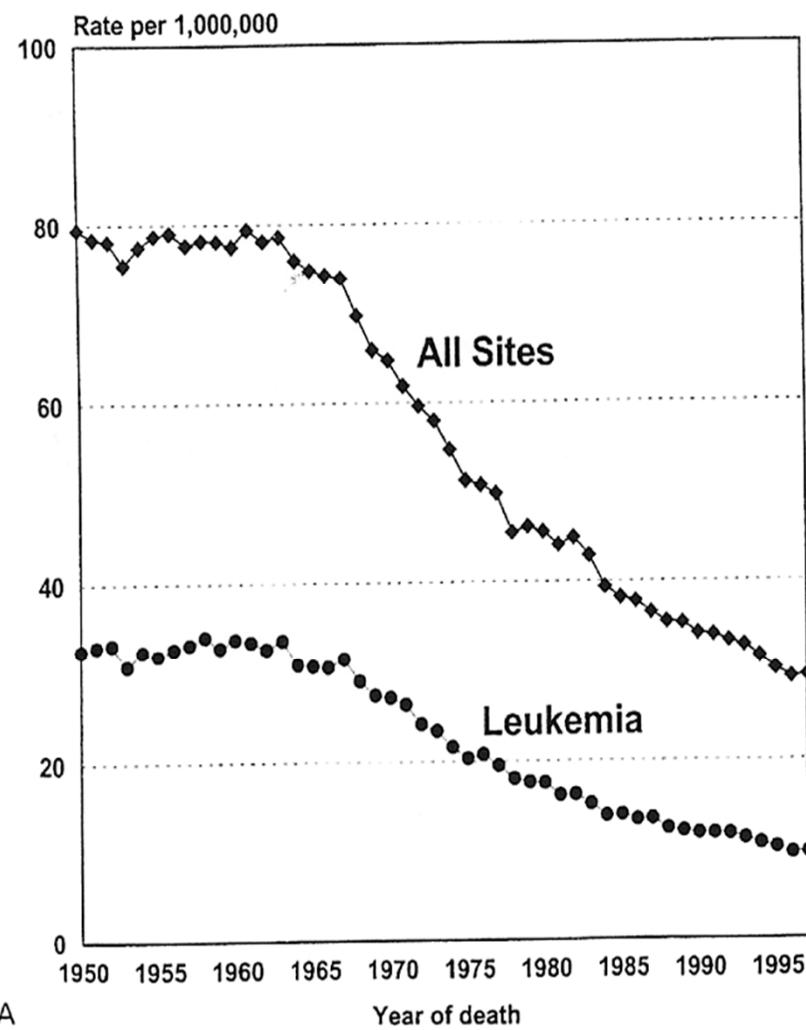
Alter < 15 Jahre
Jungen > Mädchen

Alter > 15 Jahre
Mädchen > Jungen



- ★ Generell höher in Manner als in Frauen
- ★ Einige histologische Subtypen zeigen Geschlechtspradispositon
- ★ Alter kann die Geschlechtshaufigkeit auch beeinflussen

Mortalitatrate der Kindheitstumoren



Alters-spezifische Tumormortalität

Figure XIV.6: Trends in age-specific cancer mortality rates by type, age <5, all races, both sexes United States, 1975-95

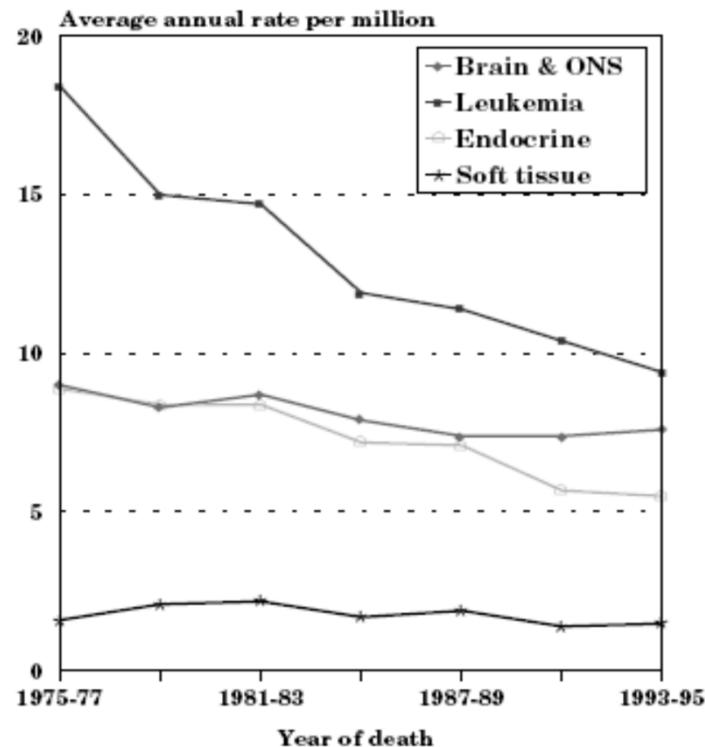
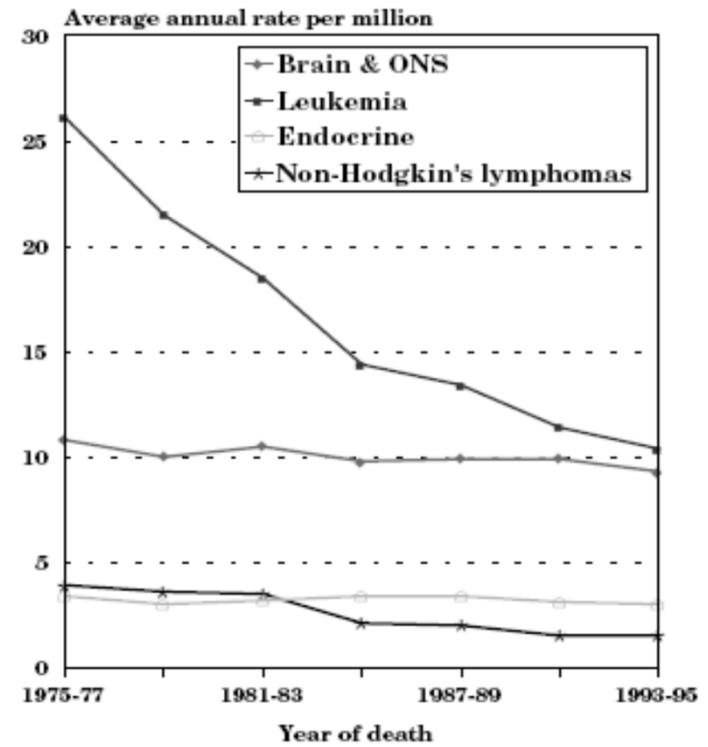


Figure XIV.7: Trends in age-specific cancer mortality rates by type, age 5-9, all races, both sexes United States, 1975-95



Alters-spezifische Tumormortalität

Figure XIV.8: Trends in age-specific cancer mortality rates by type, age 10-14, all races both sexes, United States, 1975-95

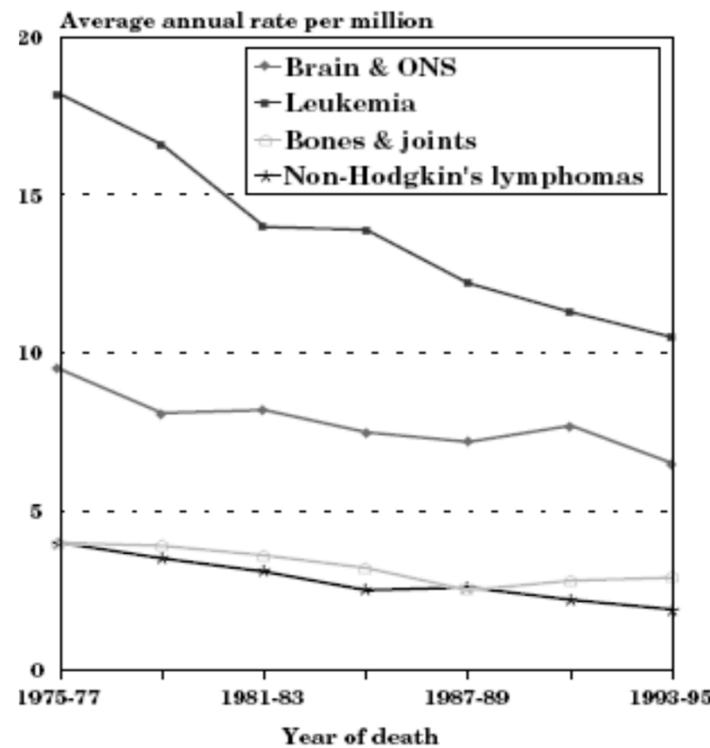
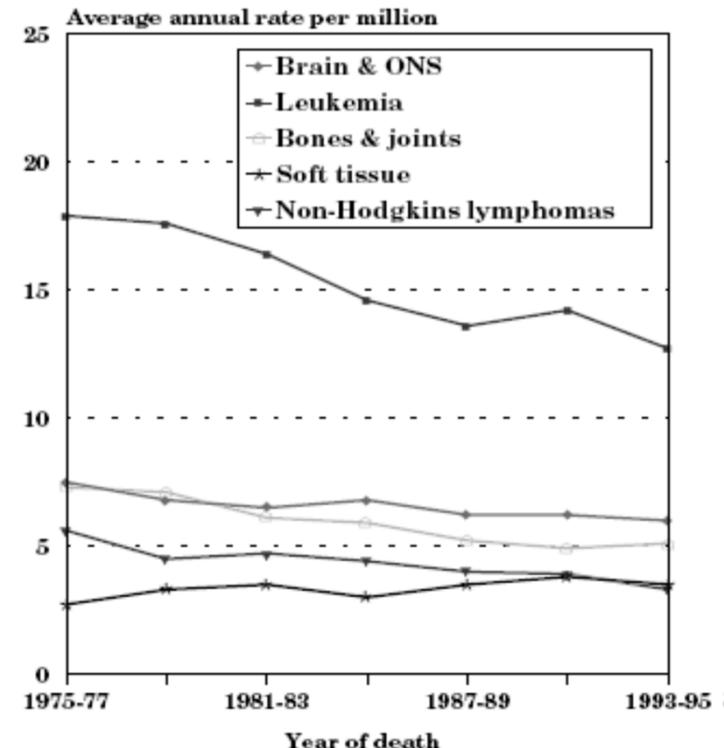
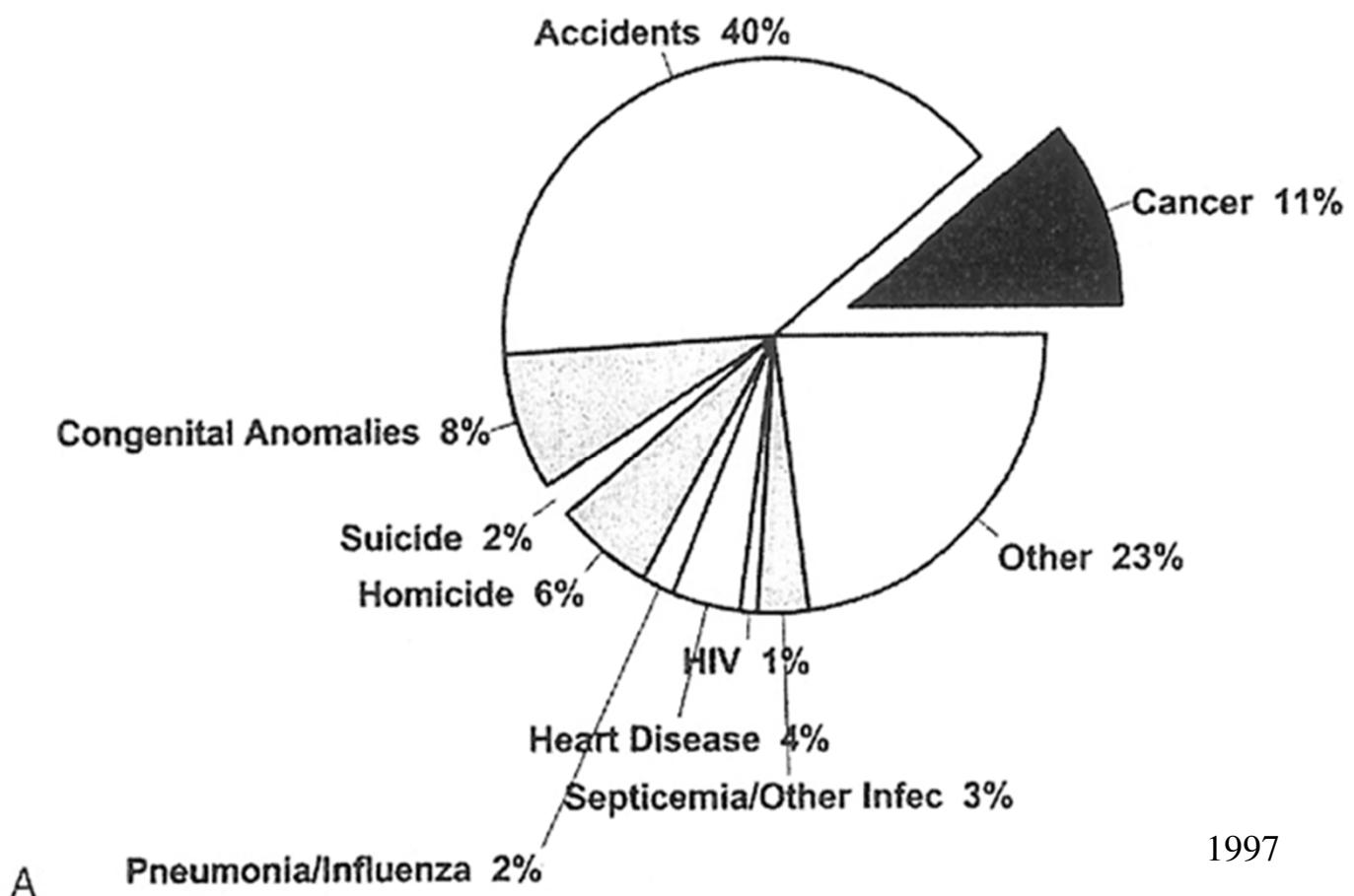


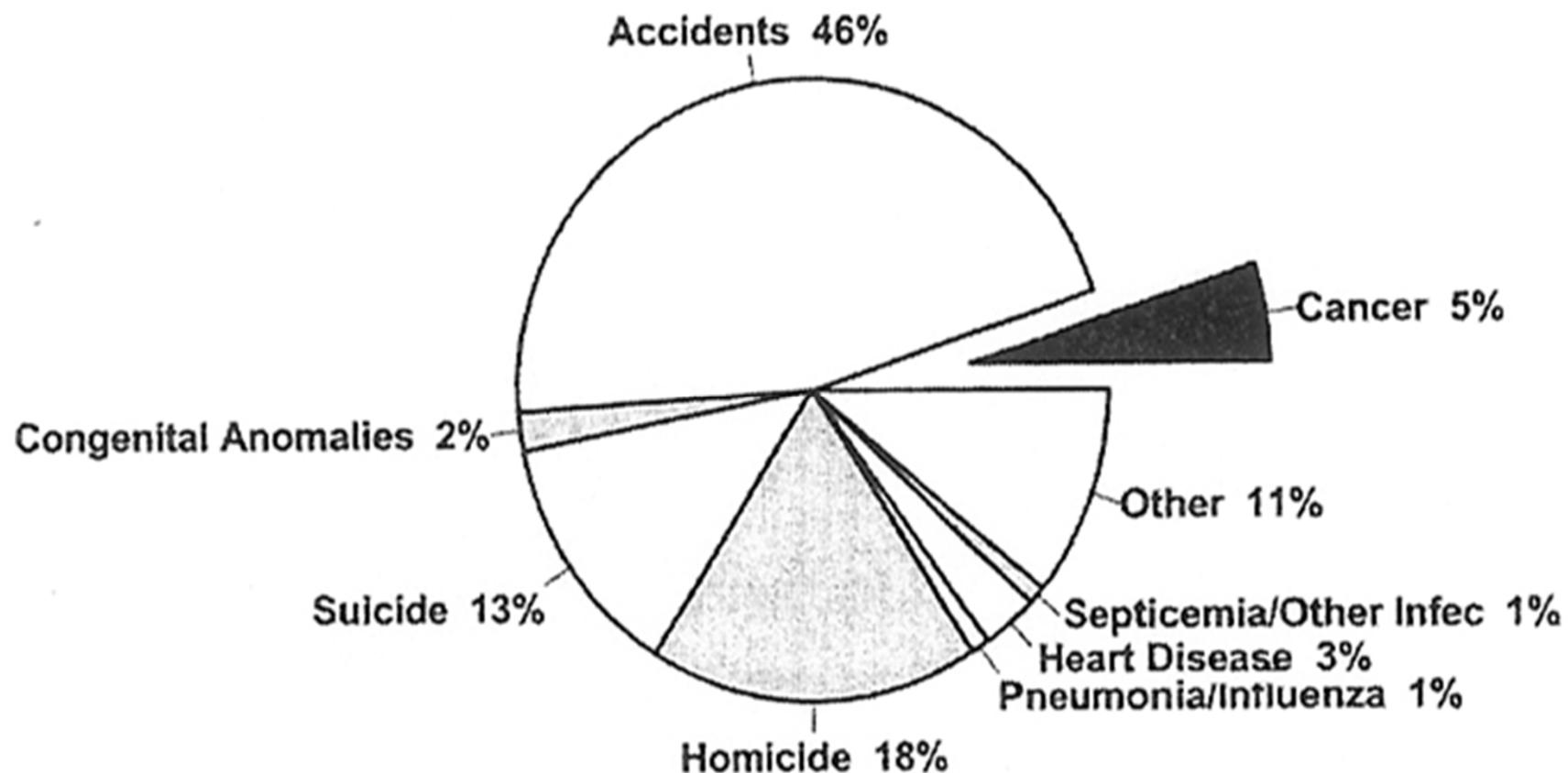
Figure XIV.9: Trends in age-specific cancer mortality rates by type, age 15-19, all races both sexes, United States, 1975-95



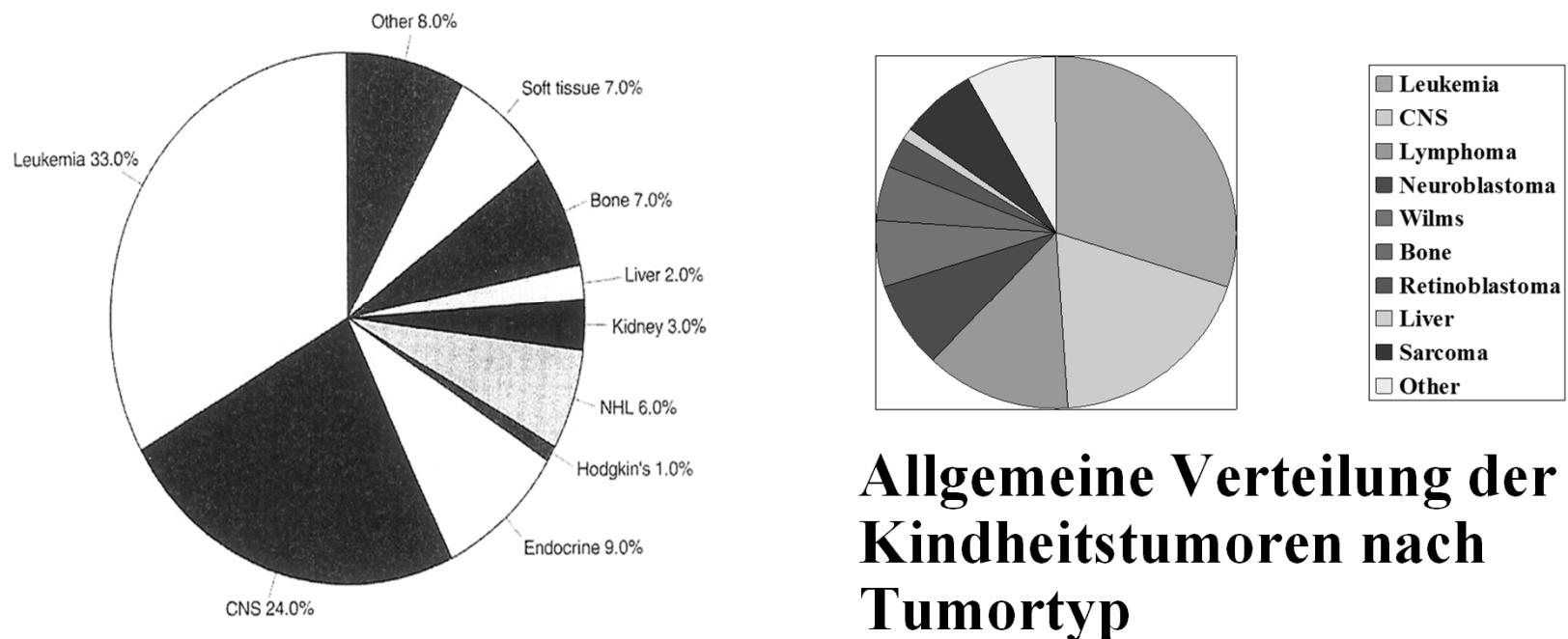
Leitende Todesursachen bei Kinder < 14 J in der USA



Leitende Todesursachen bei Jugendlicher (17-20 Jahre) in der USA

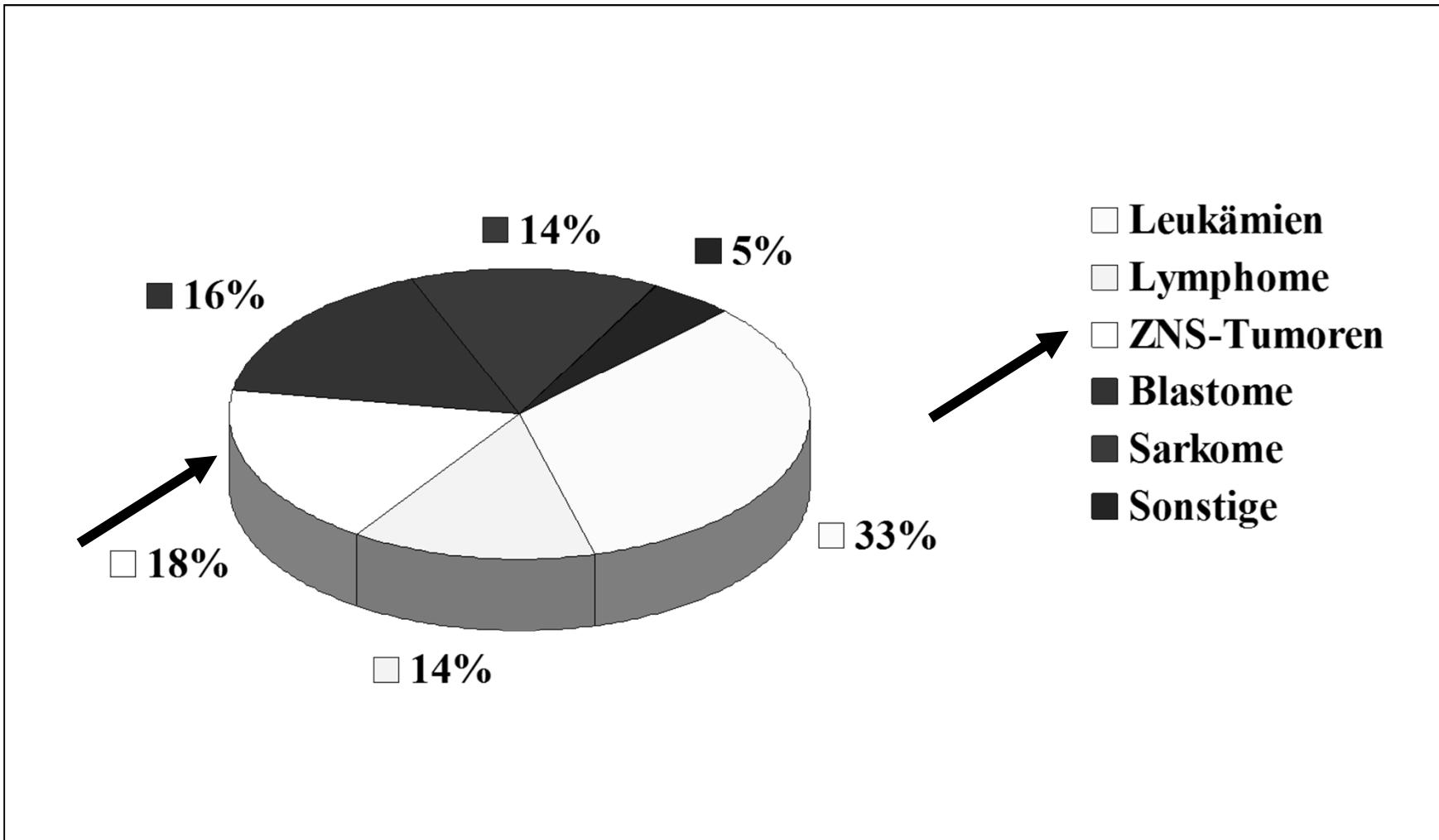


Verteilung der Kindheitstumoren



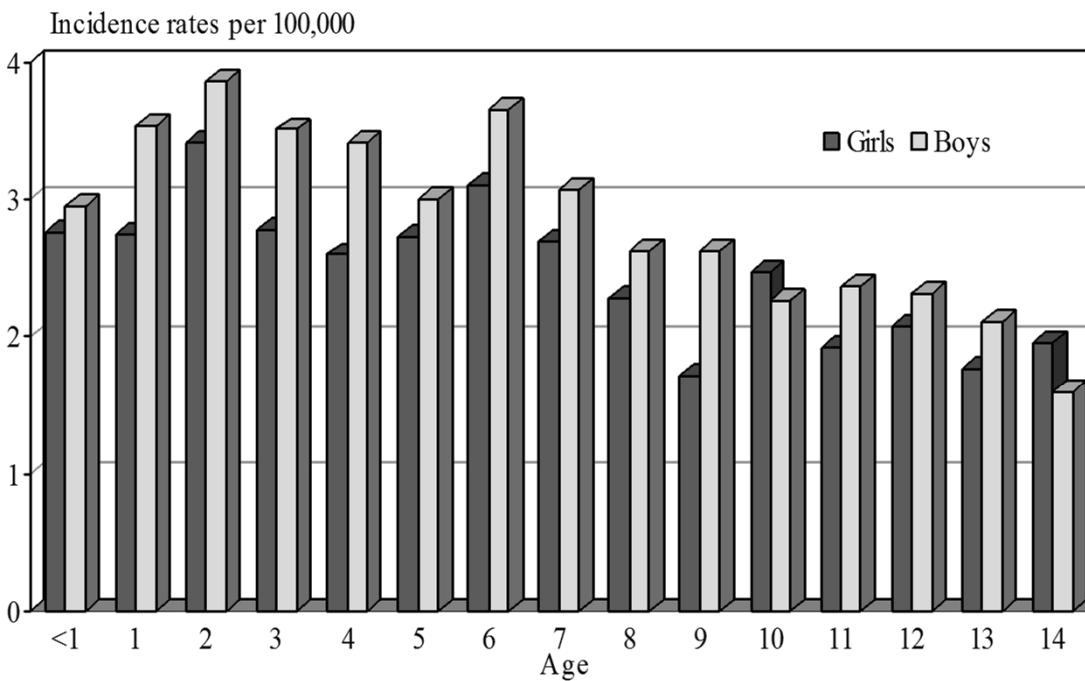
**Allgemeine Verteilung der
Kindheitstumoren nach
Tumortyp**

Krebs bei Kindern und Jugendlichen



Krebs bei Kindern und Jugendlichen

Inzidenz pro 100.000 - ZNS-Tumoren



Histologie Verteilung nach ALTER

< 5 Jahre vs. > 15 Jahre

Figure XIII.2: Distribution of cancer types, age <5
all races, both sexes, SEER, 1986-95

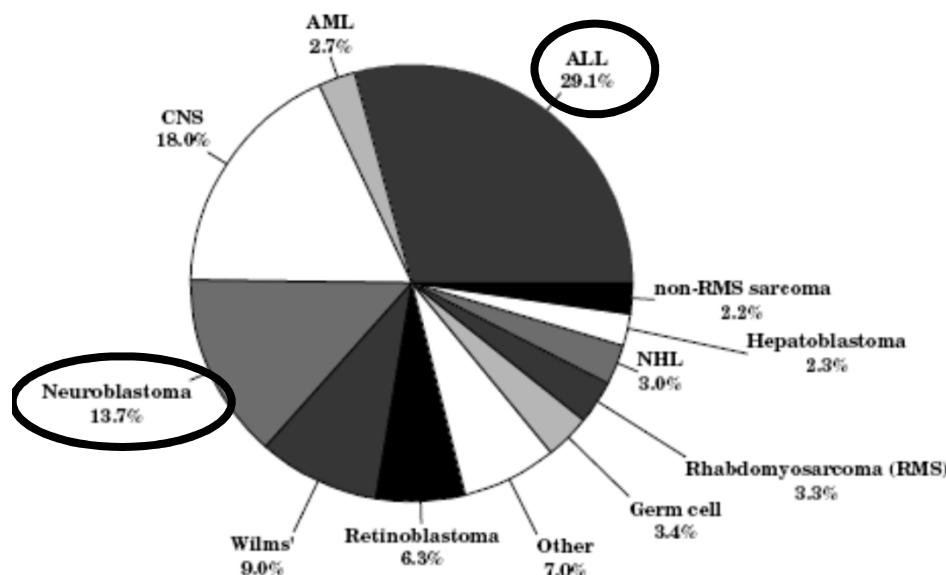
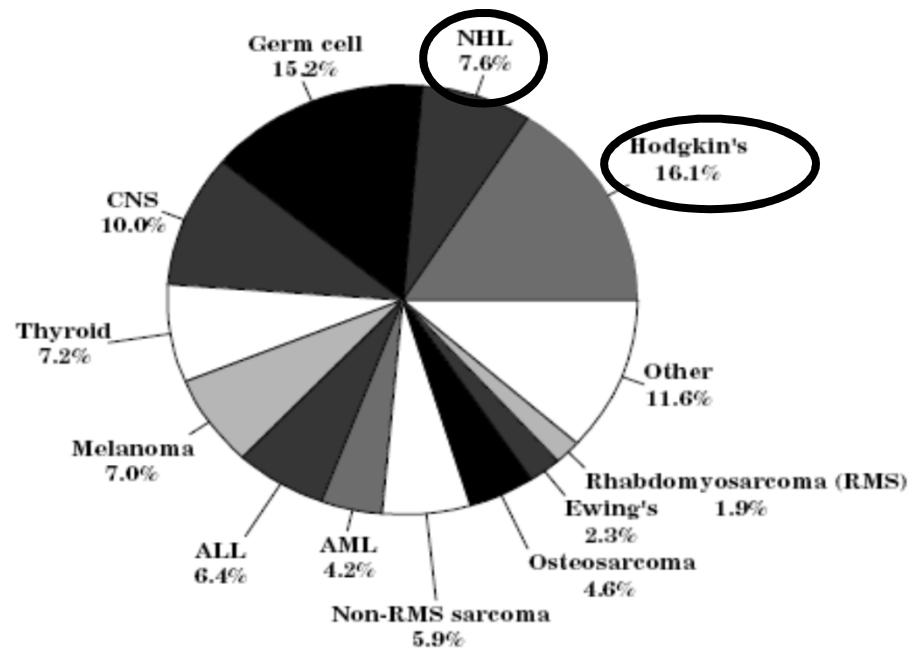
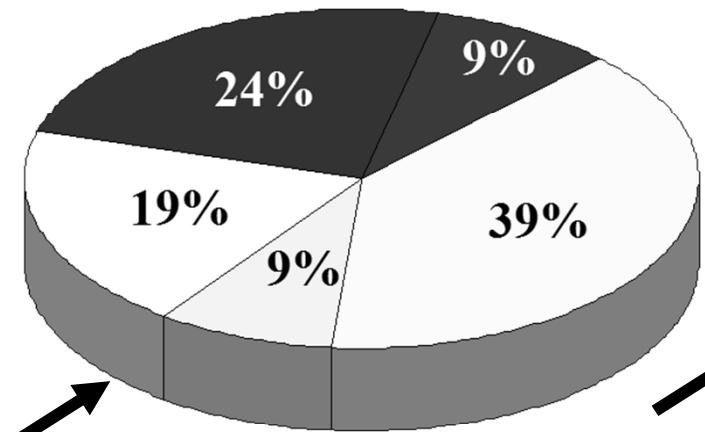


Figure XIII.1: Distribution of cancer types, age 15-19
all races, both sexes, SEER, 1986-95

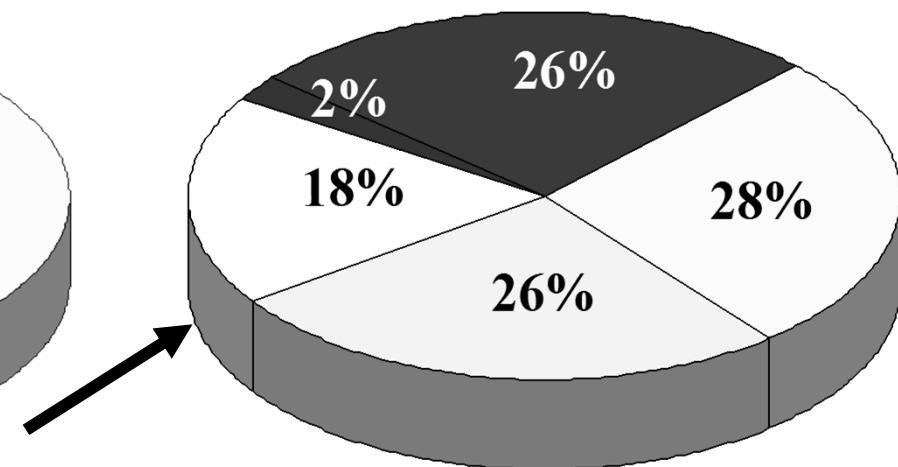


Krebs bei Kindern und Jugendlichen

Alter 0 - 9 J



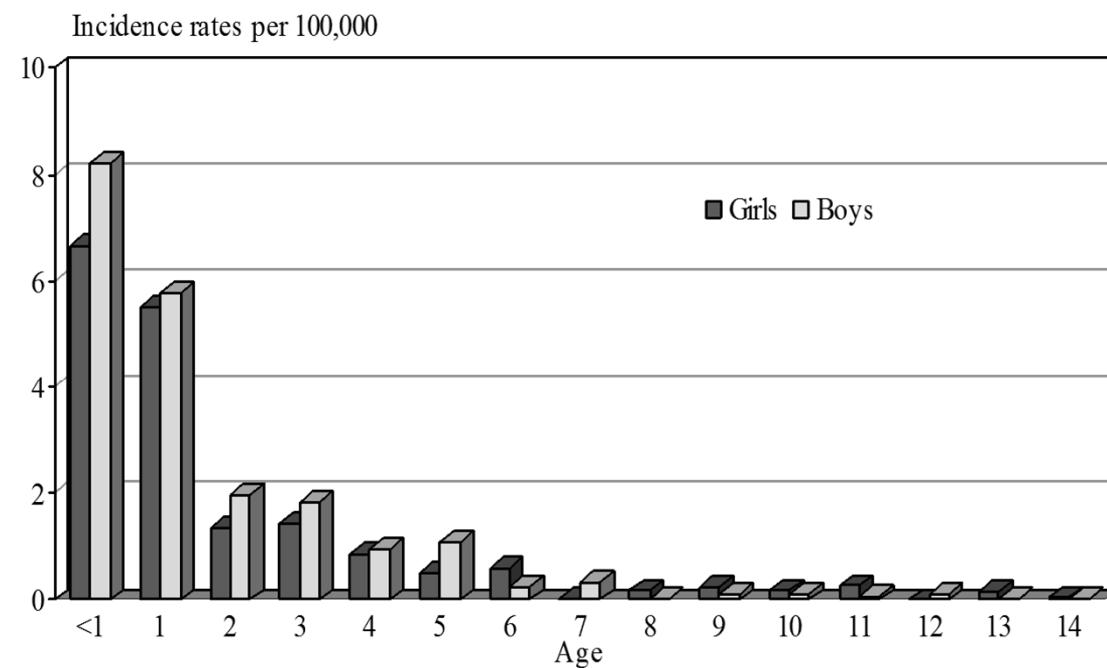
Alter 10 - 19 J



Hämatome Lymphome ZNS-Tumoren Bösartige Sarkome

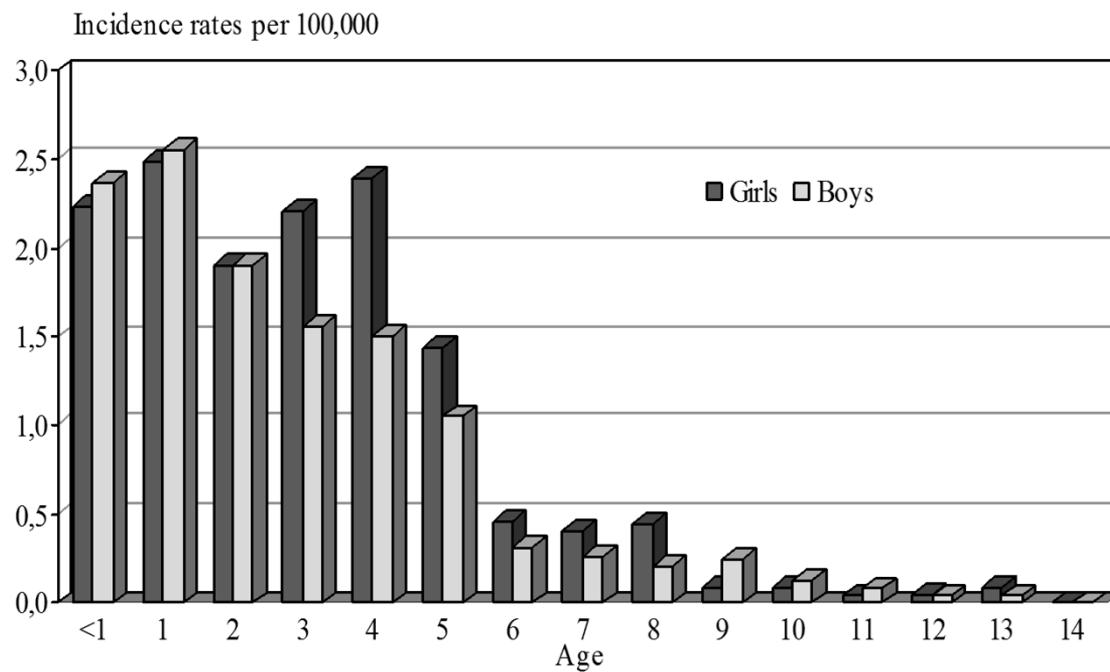
Krebs bei Kindern und Jugendlichen

Inzidenz pro 100.000 - Neuroblastom



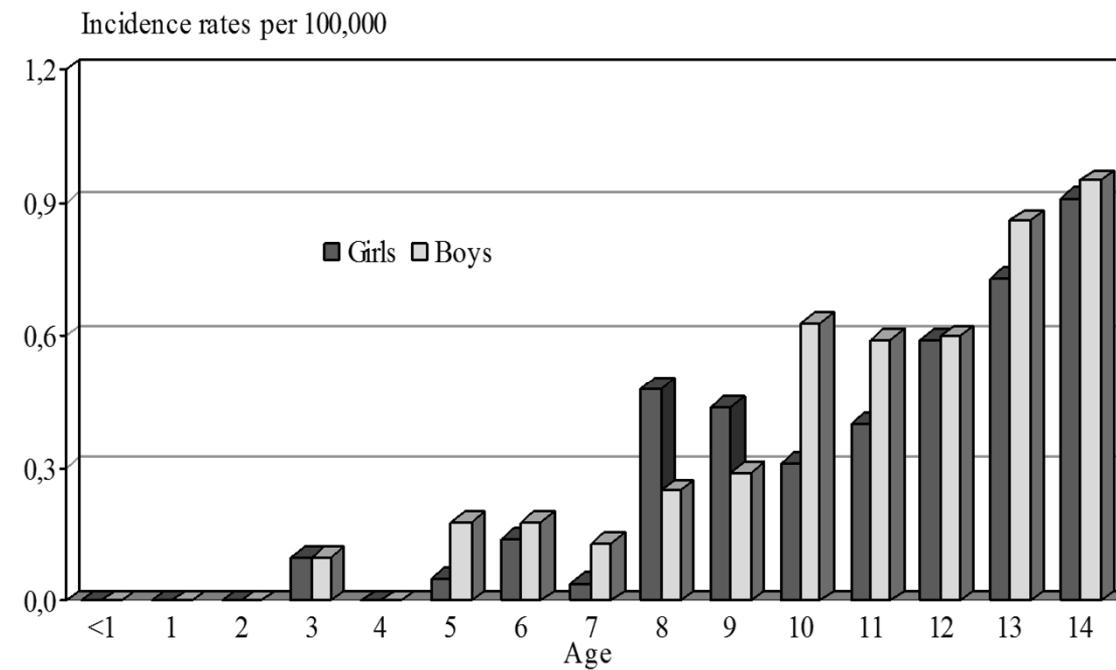
Krebs bei Kindern und Jugendlichen

Inzidenz pro 100.000 - Nephroblastom



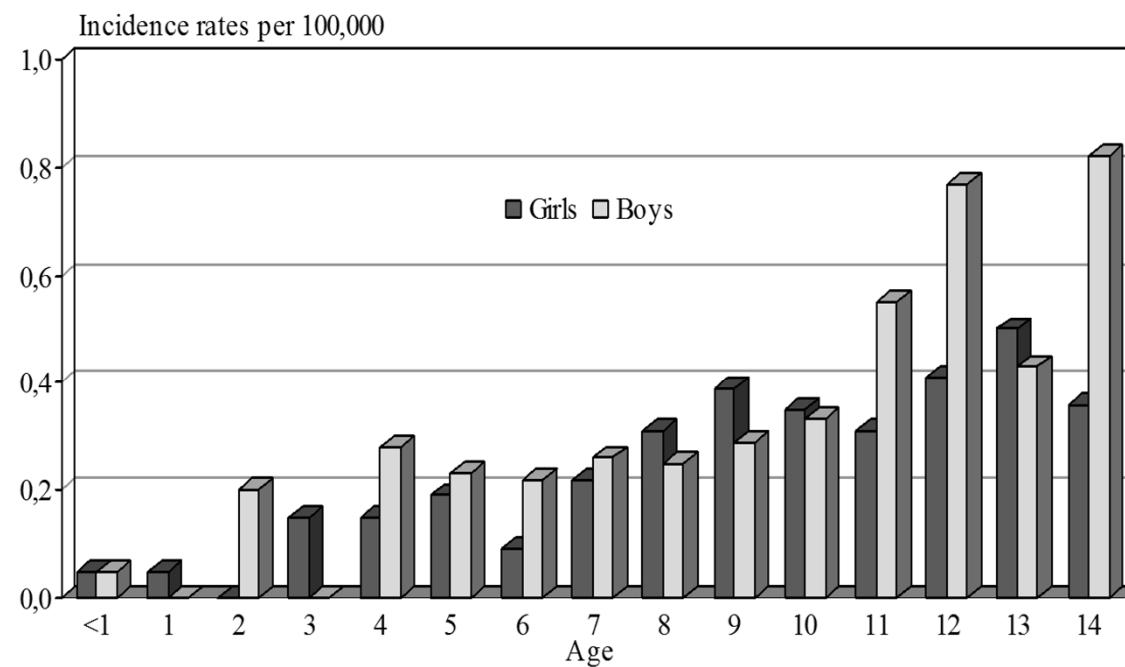
Krebs bei Kindern und Jugendlichen

Inzidenz pro 100.000 - Osteosarkom



Krebs bei Kindern und Jugendlichen

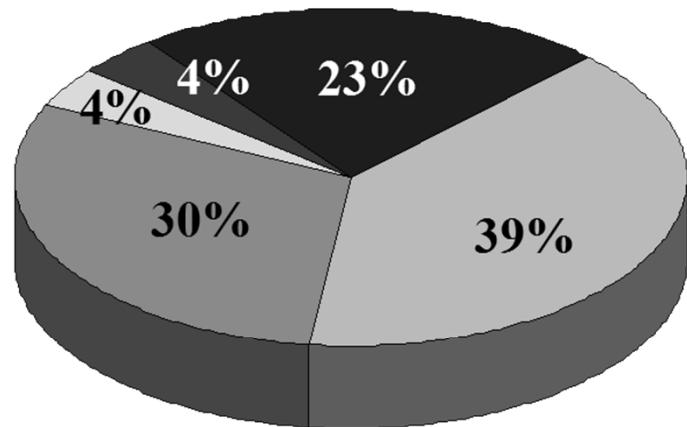
Inzidenz pro 100.000 - Ewing-Sarkom



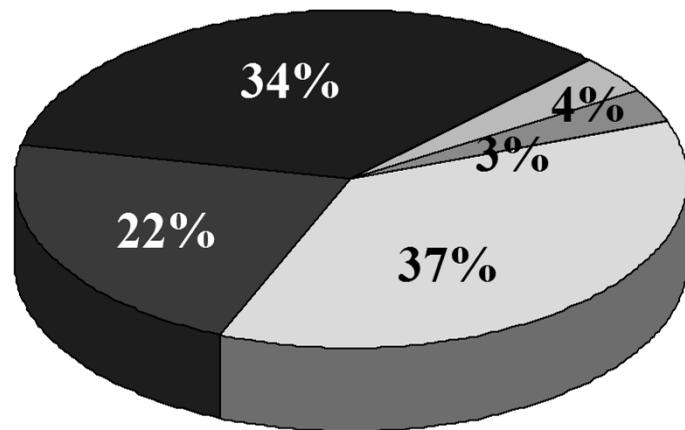
Krebs bei Kindern und Jugendlichen

Blastome und Sarkome

Alter 0 - 9 J



Alter 10 - 19 J



■ Neuroblastom ■ Nephroblastom ■ Osteosarkom ■ DWS ■ WIS

Alters-spezifische Anzahl der Neuerkrankungen der Kindheitstumoren

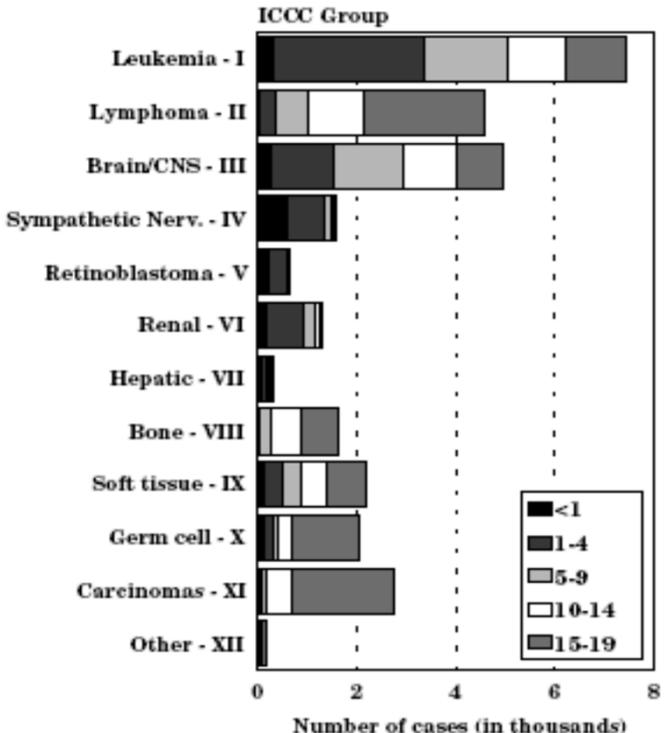
★ Häufigster Tumortyp

- < 15 yrs – Leukemie
- > 15 yrs – Lymphom

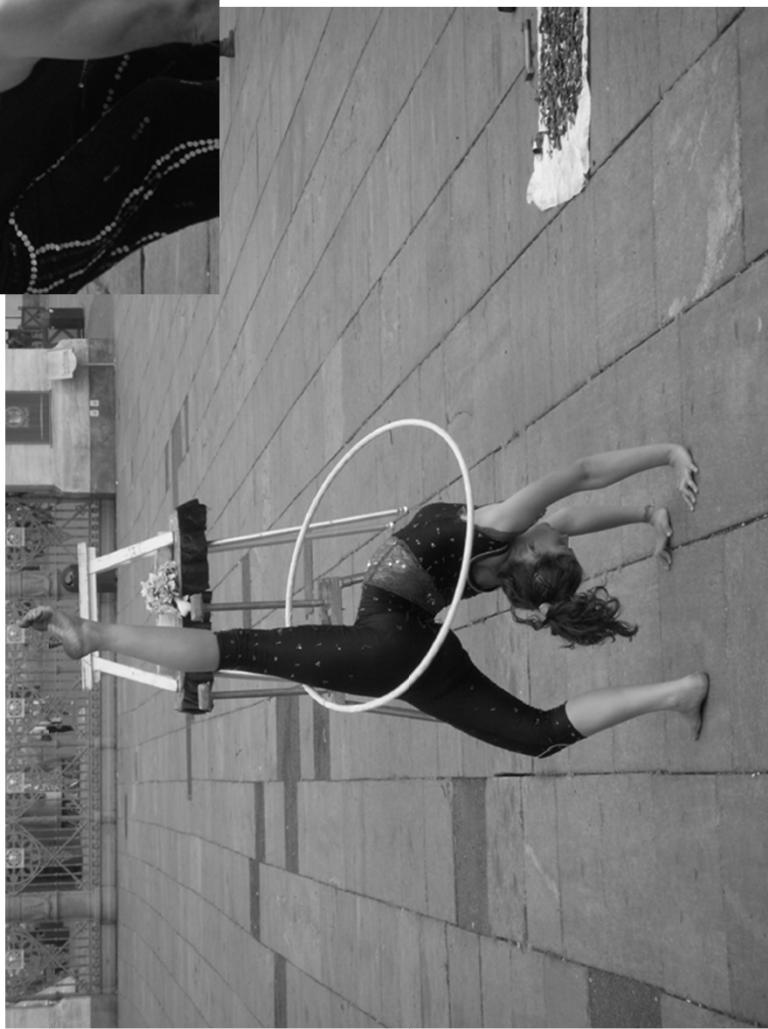
★ 2. häufigster Tumor

- < 10 yrs – ZNS Tumoren
- 10-14 yrs – Lymphom
- > 15 yrs – Leukemie

Figure 4: Number of cases of all childhood cancers by ICCC and age group, all races both sexes, SEER, 1975-95



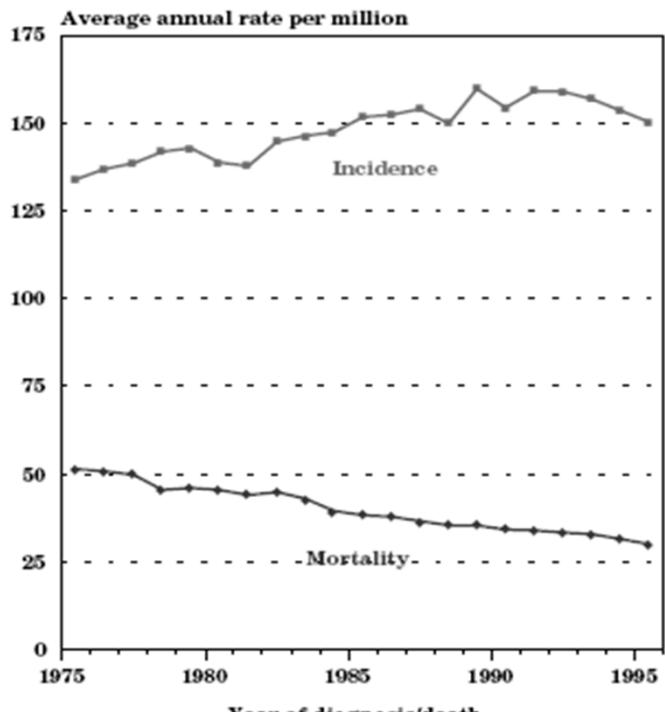




gegenteiliges Überleben-Erscheinung ...

★ Total Mortalität ist sinkend !

Figure XIV.1: Trends in childhood cancer age-adjusted* rates, all races, both sexes, age <20
SEER incidence & US mortality, 1975-95



*Adjusted to the 1970 US standard population

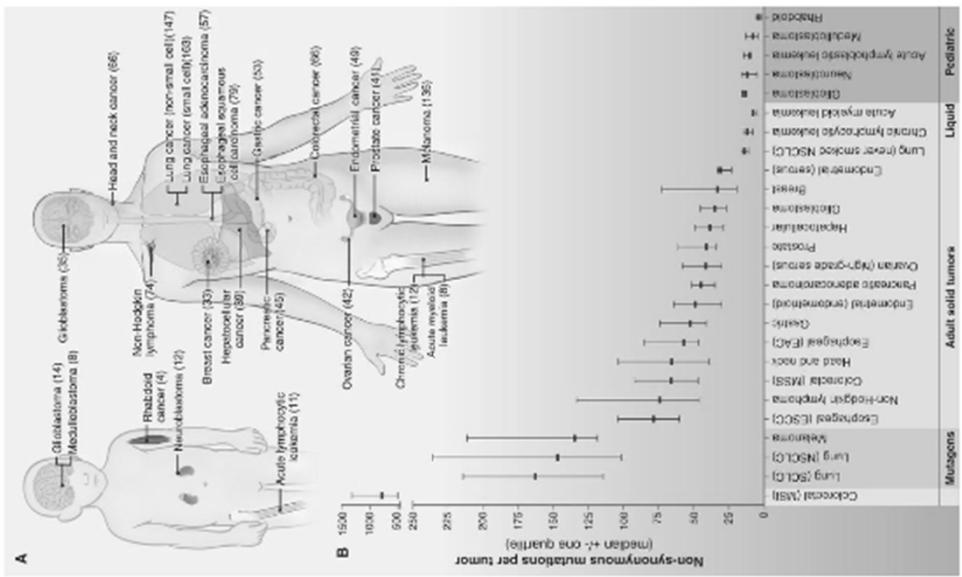


Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

(A) The genomes of a diverse group of adult (right) and pediatric (left) cancers have been analyzed. Numbers in parentheses indicate the median number of nonsynonymous mutations per tumor. **(B)** The median number of nonsynonymous mutations per tumor in a variety of tumor types. Horizontal bars indicate the 25 and 75% quartiles. MSI, microsatellite instability; SCLC, small cell lung cancers; NSCLC, non-small cell lung cancers; ESCC, esophageal squamous cell carcinomas; MSS, microsatellite stable; EAC, esophageal adenocarcinomas. The published data on which this figure is based are provided in table S1C.

Pediatrische Tumoren

1	Akute lymphoide Leukemie	32.9	H
2	Astrocytom	17.9	N
3	Neuroblastom	10.2	N
4	Non-Hodgkin Lymphom	9.1	H
5	Wilms' tumor	8.3	M
6	Hodgkin's lymphom	7.3	H
7	PNET	6.8	N
8	Acute myeloide Leukemie	5.8	H
9	Rhabdomyosarkom	4.7	M
10	Retinoblastom	3.9	N
11	Osteosarcom	3.4	M
12	Ewing Sarcom	3.3	N

n/10⁶ Kinder – USA;
Neurogenische: 32,1%; Haematologische: 55,1%
Mesenchymale: 16,4%

Hereditare Tumor / Syndrome

★ Fam	RBL	RBL	RB1
★ Fam Wilms tumor		WT	WT1
★ Beckwith-Wiedemann sy		WT, HB, RMS	b11p15
★ Li-Fraumeni sy		L, SRC, CN	p53
★ Ataxia teleangiectasia		NHL, CN	ATM
★ NF1		SRC, GL	NF1
★ MEN1/2		AC-endocr	MEN1,2
★ Fam. Polyposis Coli		HB	APC
★ Basal cell nevus sy		MeBL	
★ Bloom sy		L	RECQL



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Neurogene Tumoren

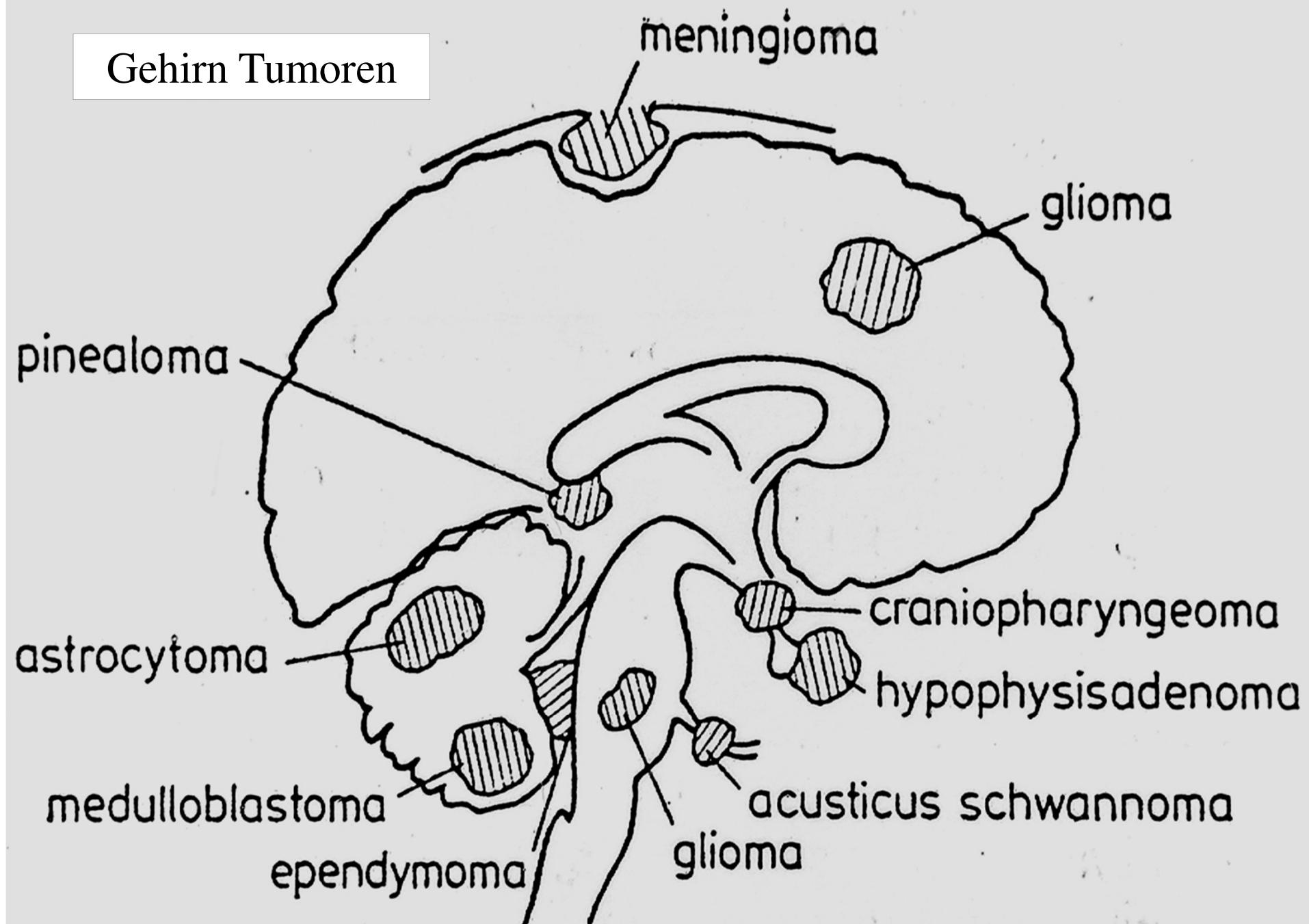
Peripheres Nervensystem

- ★ Neuroblastom
- ★ Ewing Sarkom
- ★ PNET

ZNS

- ★ Astrozytische Tumoren
- ★ Retinoblastom
- ★ ZNS PNET

Gehirn Tumoren



Pediatrische Neurochirurgische Neuropathologie

- ★ Gehirntumoren sind an 2. Platz nach Leukemien in Kinder
- ★ Gehirntumoren sind die häufigste solide Tuomoren der Kinder
- ★ 70% of pediatric Gehirntumoren sind in fossa posterior
 - Pilozytisches Astrozytoma
 - Medulloblastom
 - Ependymom

ZNS Tumoren: pediatrische vs. adulte

★ Erwachsene: 70% of tumors are supratentorial

- Meningiom
- Pituitary Adenom
- High grade Astrozytom
 - Anaplastische Astrozytom (grade III)
 - Glioblastoma multiforme (grade IV Astrozytom)

★ Pediatriche: 70% sind in fossa posterior

- pilozytisches Astrozytom (cerebellares Astrozytom)
- Medulloblastom

Klinische Erscheinung

★ Klinische Symptomatik hängt von :

- Alter, Lokalisation, und Tumor Typ und grade

★ Symptome können die folgenden sein:

- Erhöhter intrakranialer Druck
 - Sekunder wegen der Obstruktion der CSF in der Aqueduct
 - Hydrocephalus (Infante), Kopfschmerzen, Papillenödem, Erbrechen
- Krämpfe/ Epilepsie
- fokale neurologische Defiziten
- Hormonale Veränderungen (pituitares Adenom)
- Sichtfeld (Sehen) Veränderungen (Diplopie, Feld Defekten)
 - Pituitares Adenom – Druck auf Chiasma opticum

CNS Tumoren: Lokalization

* Extra-axial

- Meningiom

* Zerebrale Hemisphere

- Grade II-III Astrozytom, GBM

* Durch (crossing) corpus callosum - GBM

* optic nerve – pilozytisches Astrozytom (NF-1)

* Sella - Pituitares Adenom

* Peri-III Ventrikel - Pilozytishes Astrozytom, GBM

ZNS Tumoren: Lokalization

★ posterior fossa (in Kinder)

- pilozytisches Astrozytom
- Medulloblastom

★ Hirnstamm (pons)

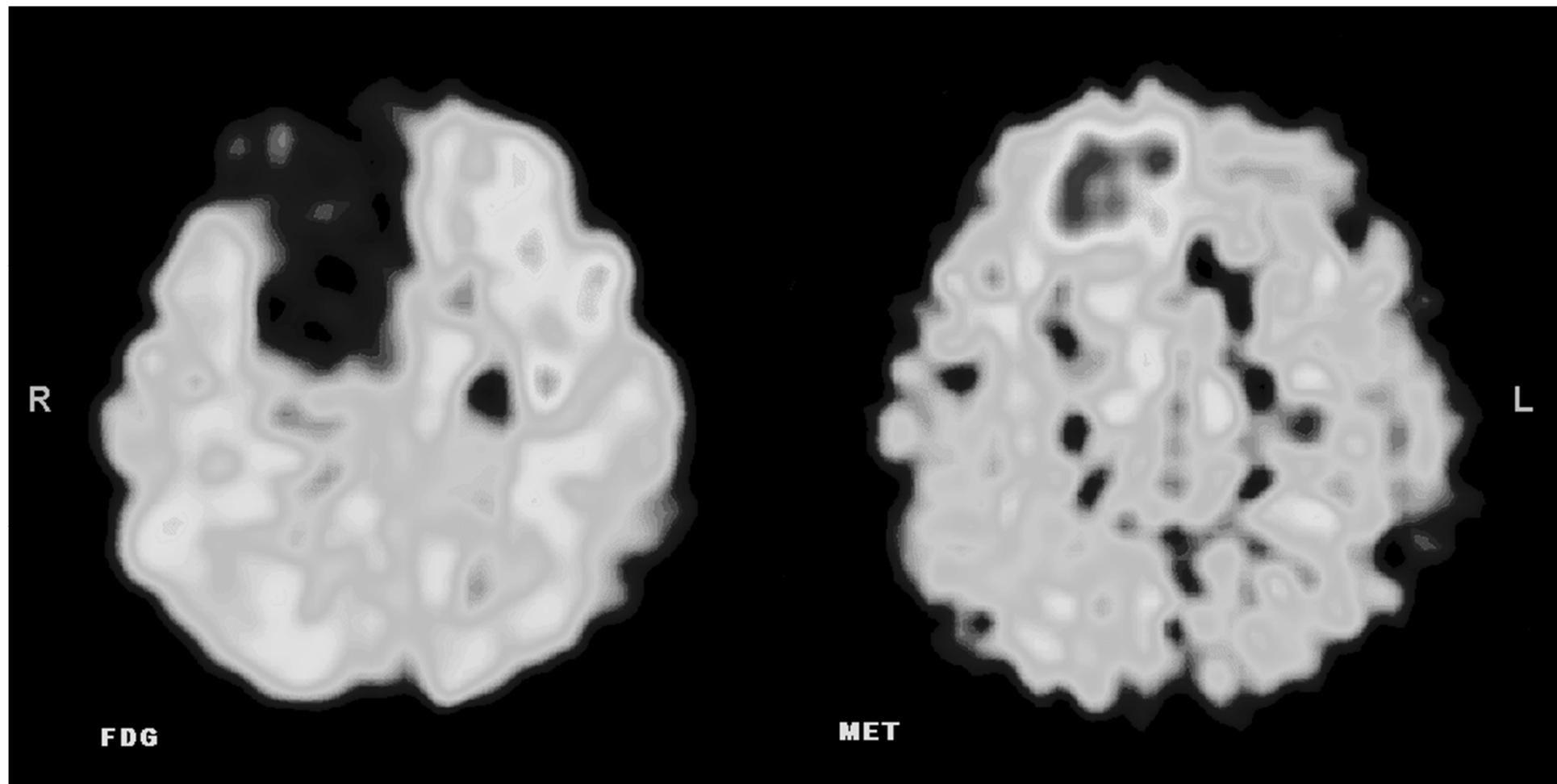
- pontin Gliom (Astrozytom)

★ Rückenmark

- low-grade Astrozytom (Grade I and II)

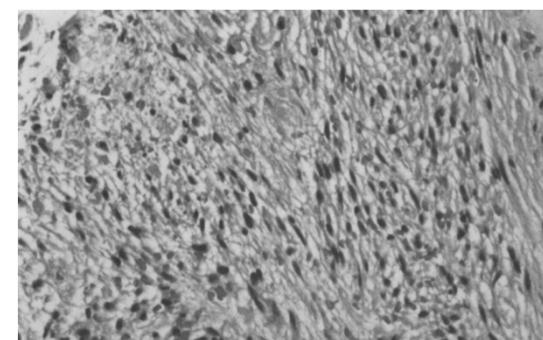
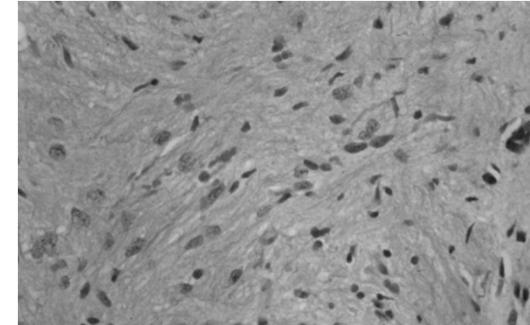
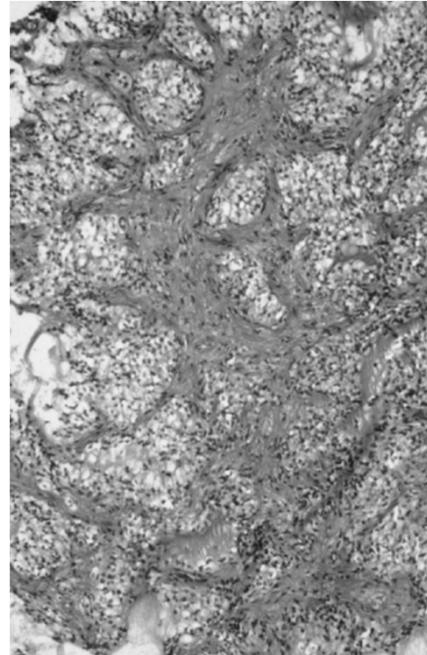
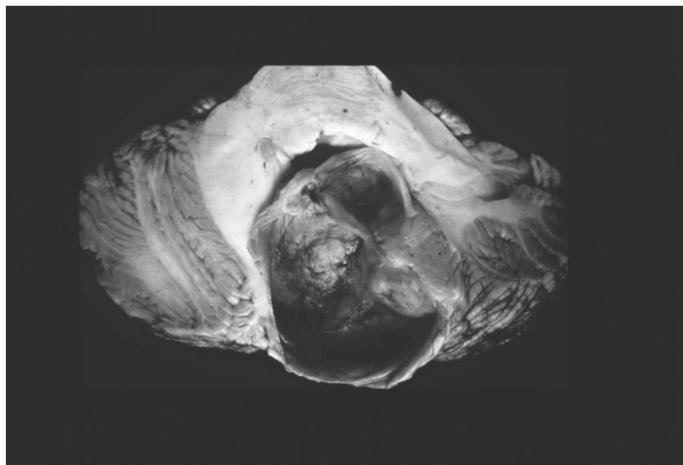
Pilozytisches Astrozytom

- Am häufigsten in Kinder
- Grade I Astrozytom
- Zerebellum (posterior fossa), optisches Nerv
 - Thalamus, Rückenmark, zerebral
- Diskrete, gut umgeschriebene Masse
- Häufig mit assoziiertem zystischem Gebiet
- Kontrast Material Verstärkung
- Histologisches Bild:
 - Biphasisch: piloide Zelle und mikrozystische Gebiete
 - Rosenthal Fibers
 - Keine Mitose



Astrozytom (WHO grade II)

Pilozytisches Astrozytom



Tumor der Zerebellum, häufig mit Zysten,
biphasisch, Rosenthal Fiber, piloide
Zelle

Gliale pediatrische Tumoren

Astrozytom (AC)

Protoplasmatisch – Gutartig

Fibrillar

Pilocytisch

Gemistozytisch

AC anaplastische Foci

Glioblastoma multiforme – bösartigste
variant

Lokalization:

Cerebellum (cystisch)

Juvenile pilocytische AC (III. Ventrikel)

Differenziertes ponts AC

Rückenmark AC

Riesen zell AC (sclerosis tuberosa)

AC – Grading

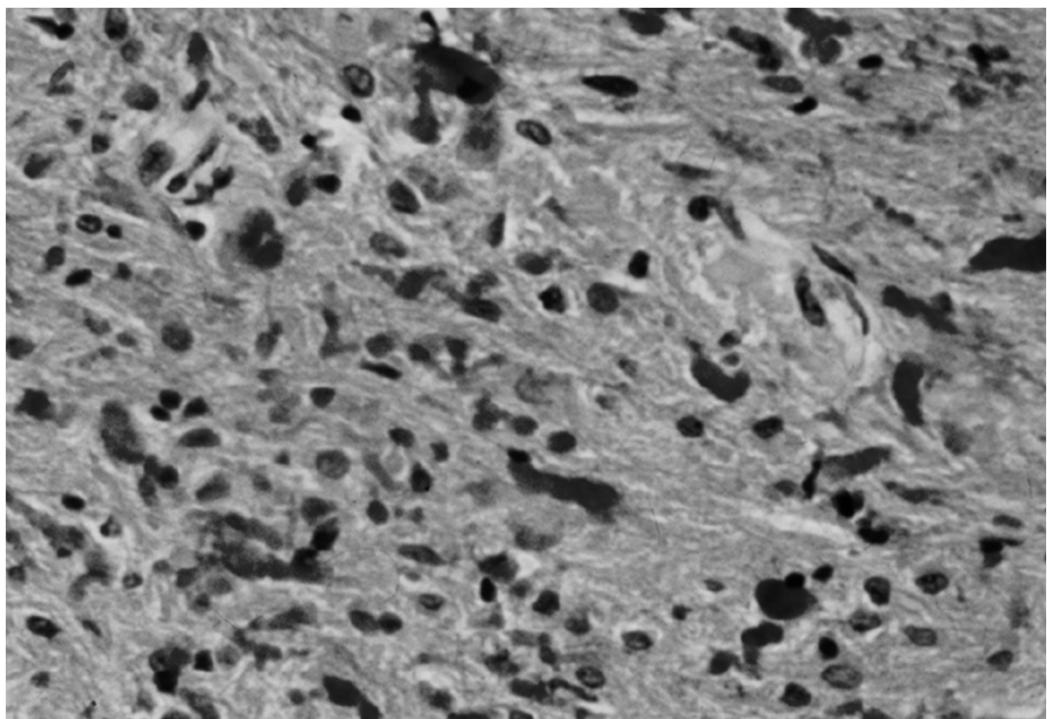
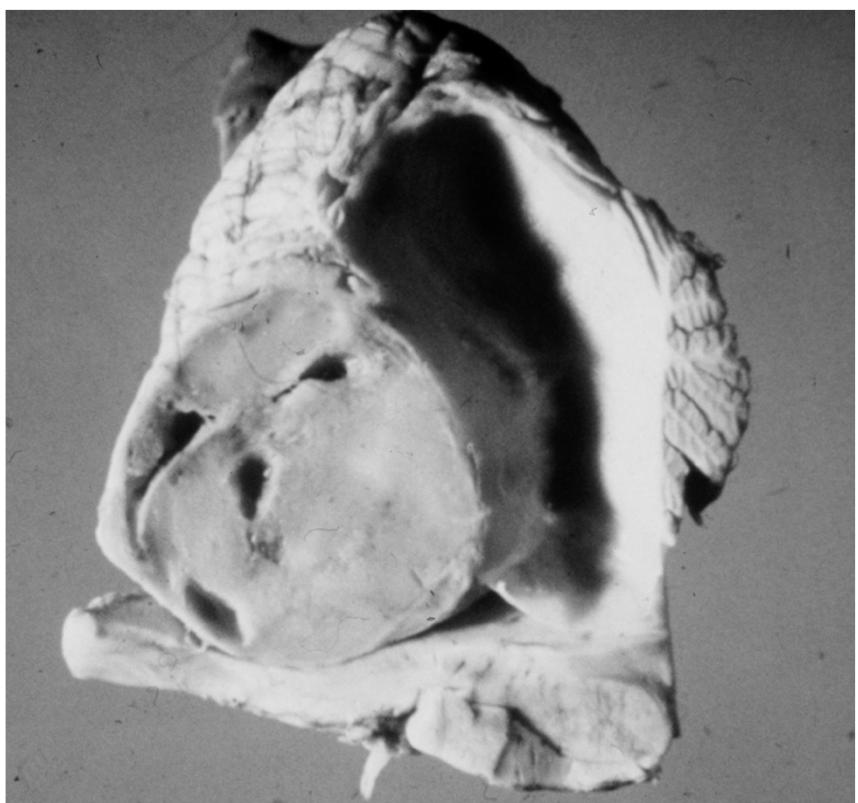
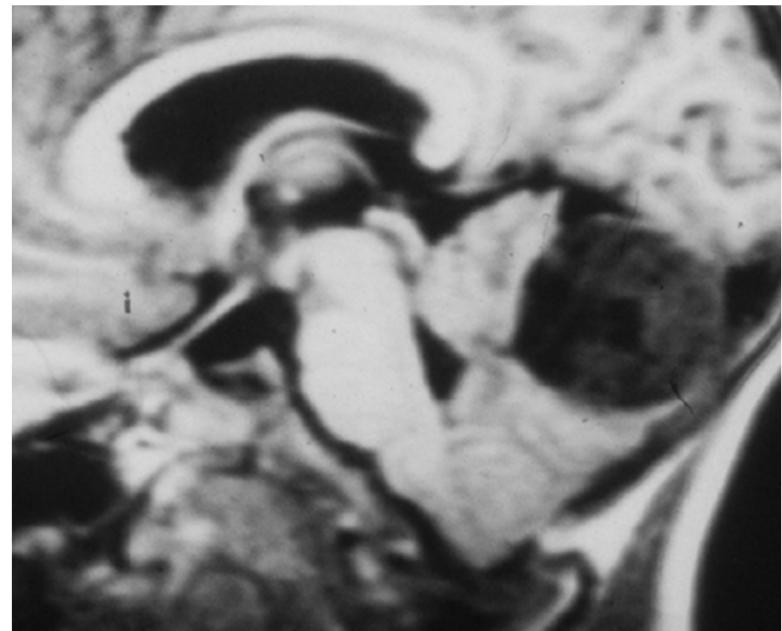
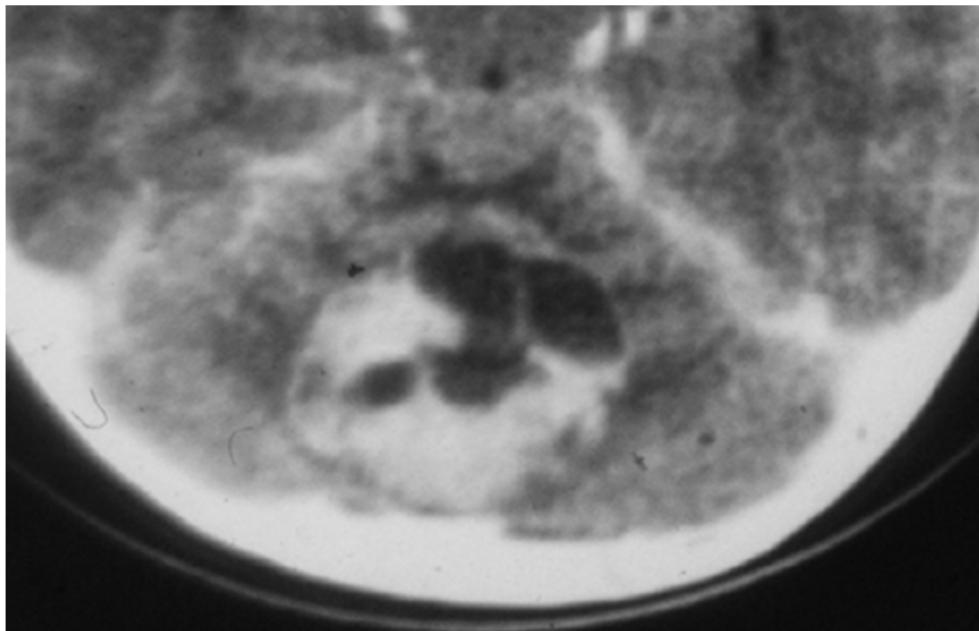
Nuclear atypia, mitosis,
endothelial
proliferation, necrosis

GR-1 none

GR-2 1/Na, M,E,N

GR-3 2/Na,M,E,N

GR-4 >2/Na,M,E,N

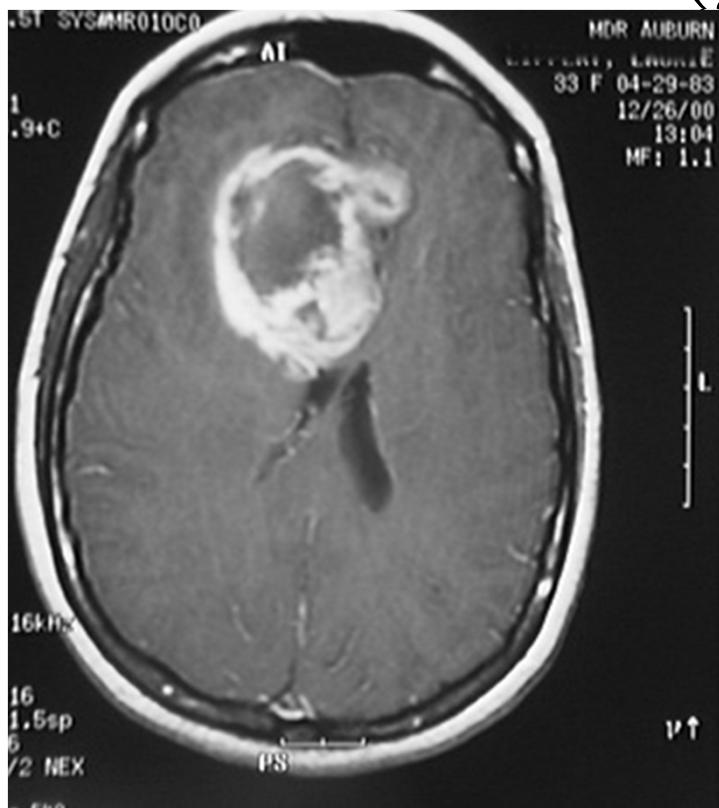


Pilozytisches Astrozytom

Astrozytom - high grade

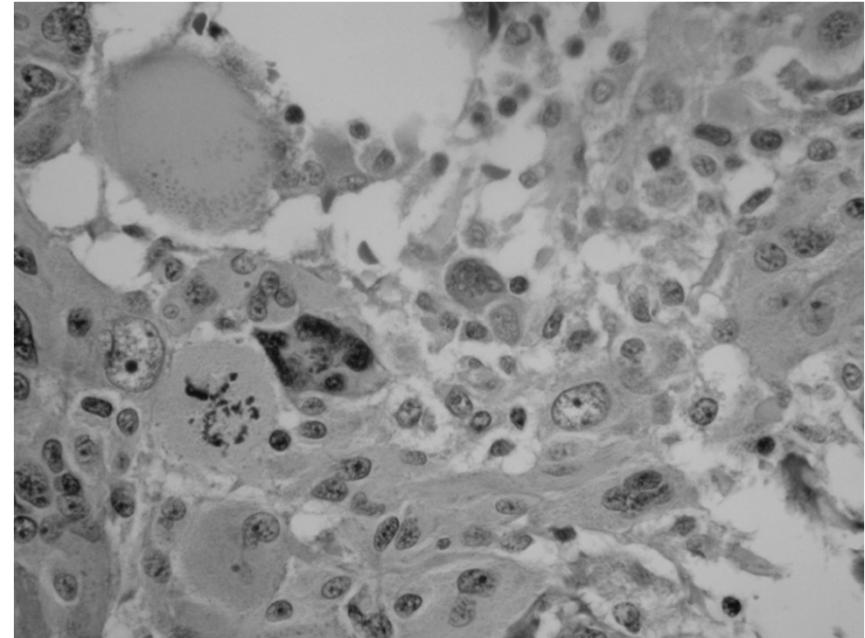
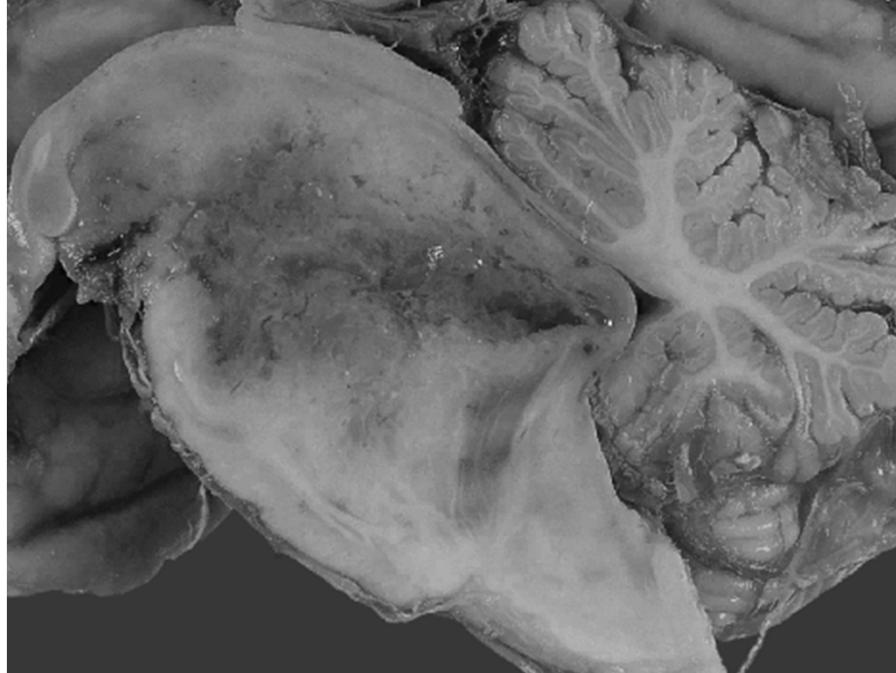
- ★ Astrozytom Grade II und III are wirklich selten in Kinder
- ★ Grade IV - Glioblastoma multiforme
- ★ Diffus infiltrirender glialer Tumor der zerebrale Hemispheren
- ★ Kontrast Material verstarkender Tumor
- ★ Histologisches Bild:
 - Hyperzellular, mit ausgepratem nuklearem Pleomorphismus
 - Viele Mitose
 - Endotheliale Proliferation
 - Nekrose mit pseudopallisade Stellung

Glioblastom (grade IV)



- ★ Seltener in Kinder in Vergleich zu Erwachsenen, typisches histopathologisches Bild (Nekrose mit psuedopallisade Stellung)

Pontin Gliom



Diffuse Vergösserung des Pons, meistens high grade Astrozytom (III-IV)

MEDULLOBLASTOM

Alter: 5-10 Jahre

Lokalization: Zerebellum,
IV. Ventrikel,
Vermis

5 Jahre Überleben: 50%

Undifferenziertes neurogenes
blastisches Tumorform

Merkmale:
Rozette 1/3
Pseudorozette
Perivaskulare Pseudo-rozette
Rhythmiscc pallisad
wellen
MI über 10%

Diff:

Neuronal
Astrozytar
Riesen Zell Pigmentert / papillar

Dissemination:

30% zerebrospinal,
Knochen
lymphatisch

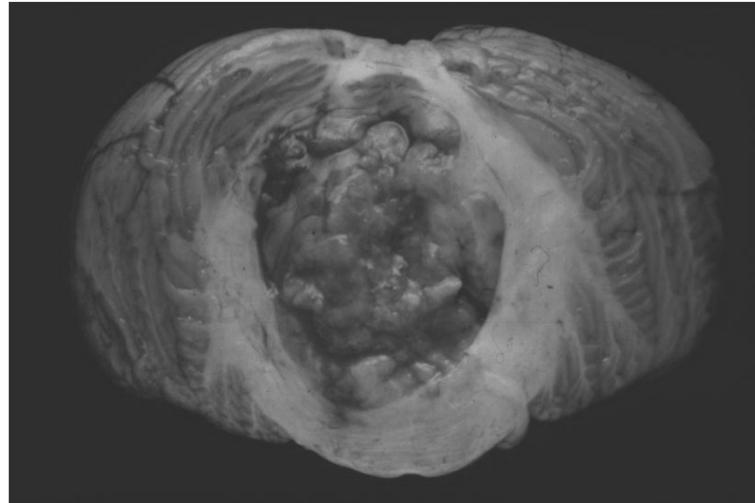
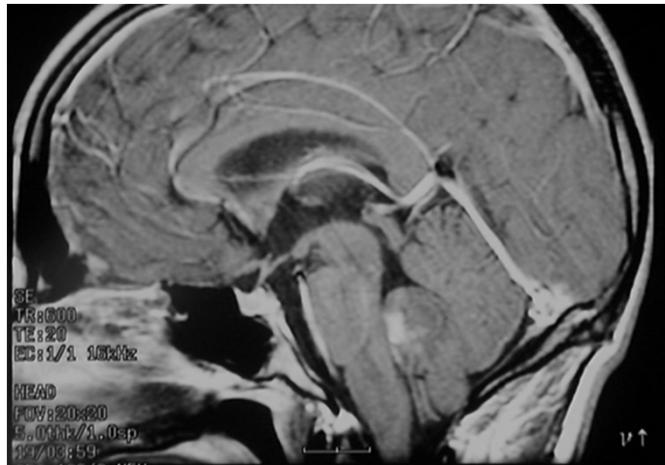
Prognose:

Chirurgisches Reziduum <25% (gut)
mesencephalon, med. oblong inf.
(schlecht)
Spinale Met. (schlecht)
CSF + Zytologie (schlecht)
<4 Jahe (gut)

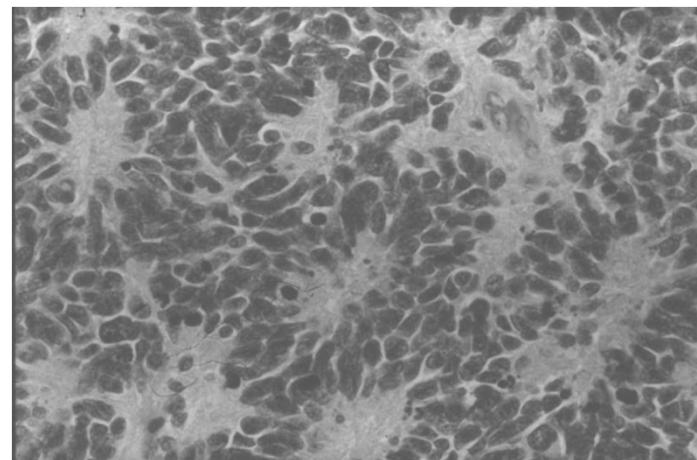
Medulloblastom

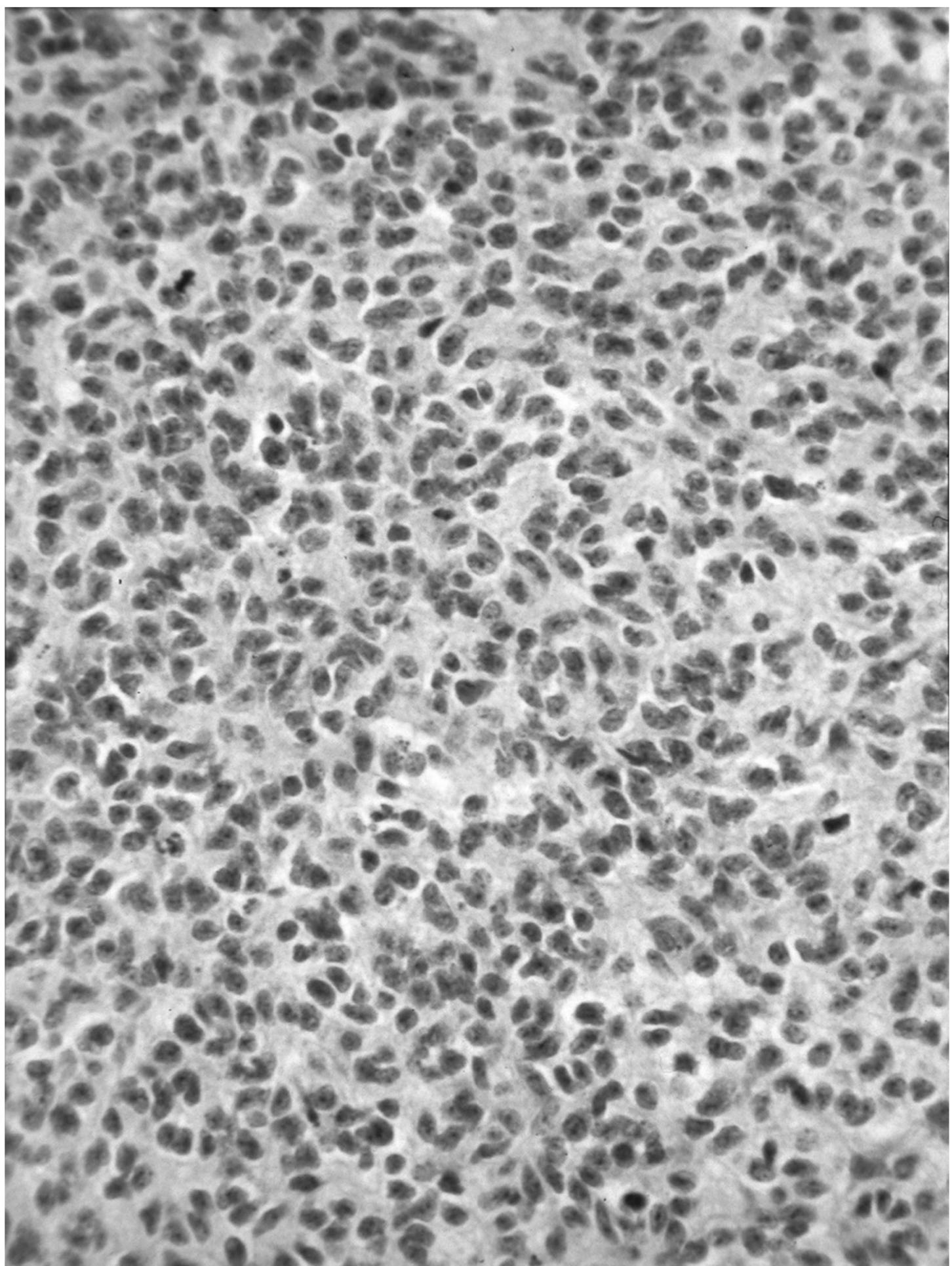
- ★ PNET der Fossa posterior in Kinder
- ★ Histologisches Bild:
 - Hyperzellulares “small blue cell tumor”
 - Viele Mitosen
 - Apoptotische (karyorrhektische) Zelle
 - Endotheliale Proliferation
 - Nekrose
 - neuronale oder gliale Differenzierung
 - Homer Wright Rosetten
 - GFAP positive Zelle

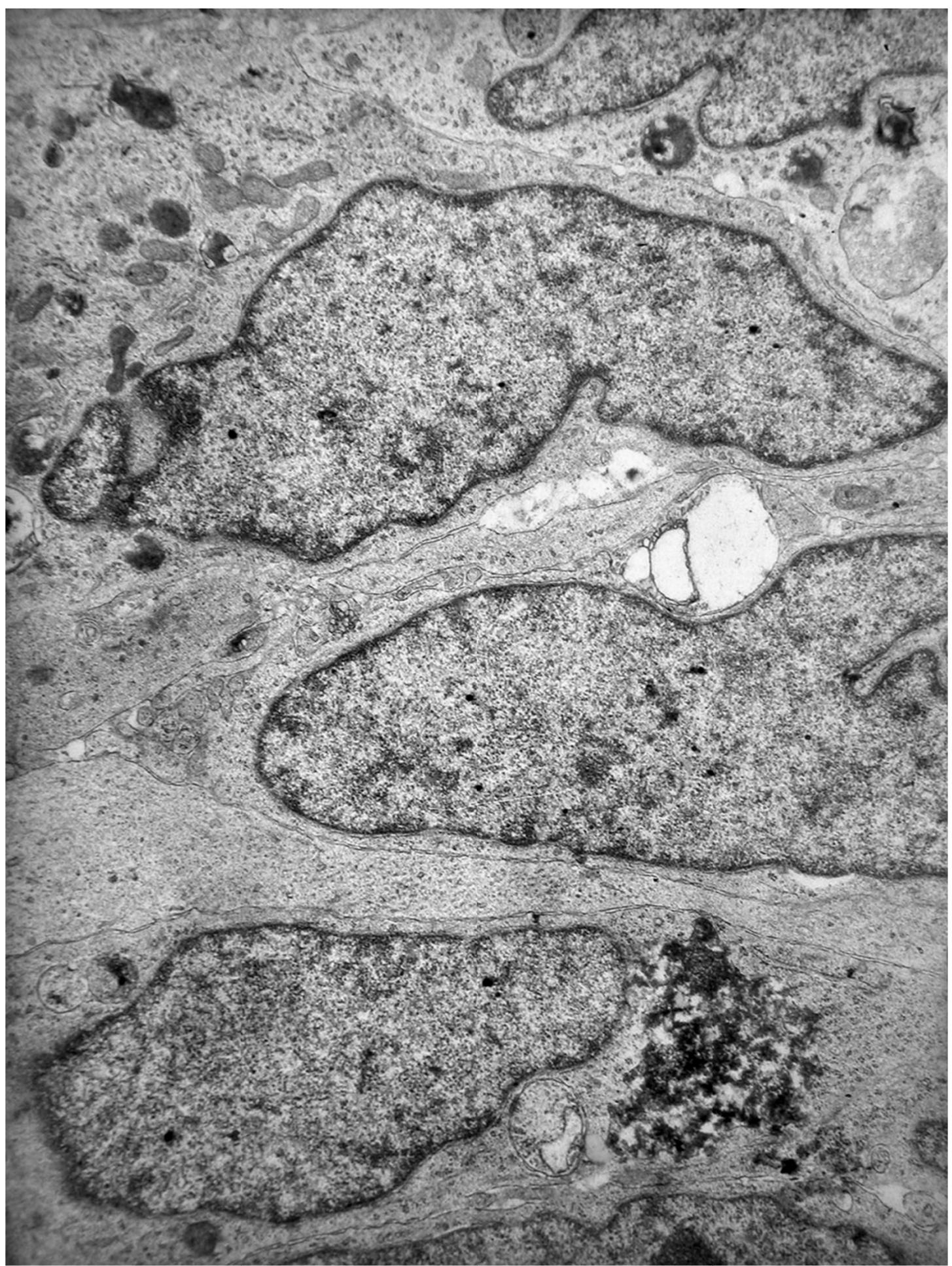
Medulloblastom



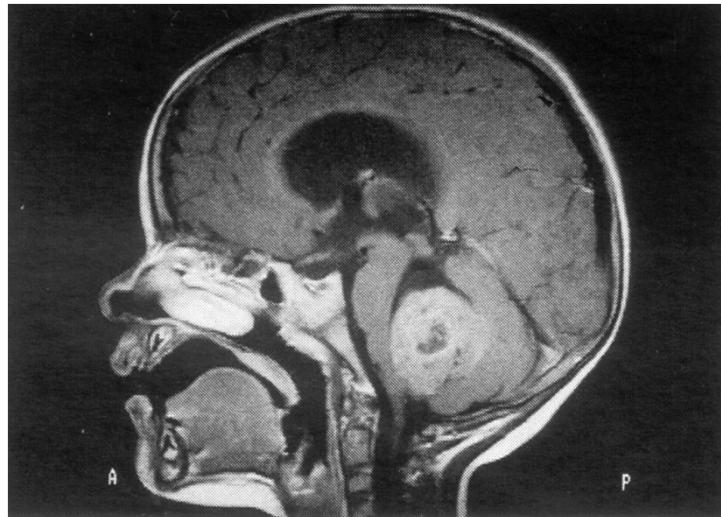
- ★ Tumoröse Masse, in der Decke der IV. Ventrikel wachsend
- ★ Homer Wright Rosette



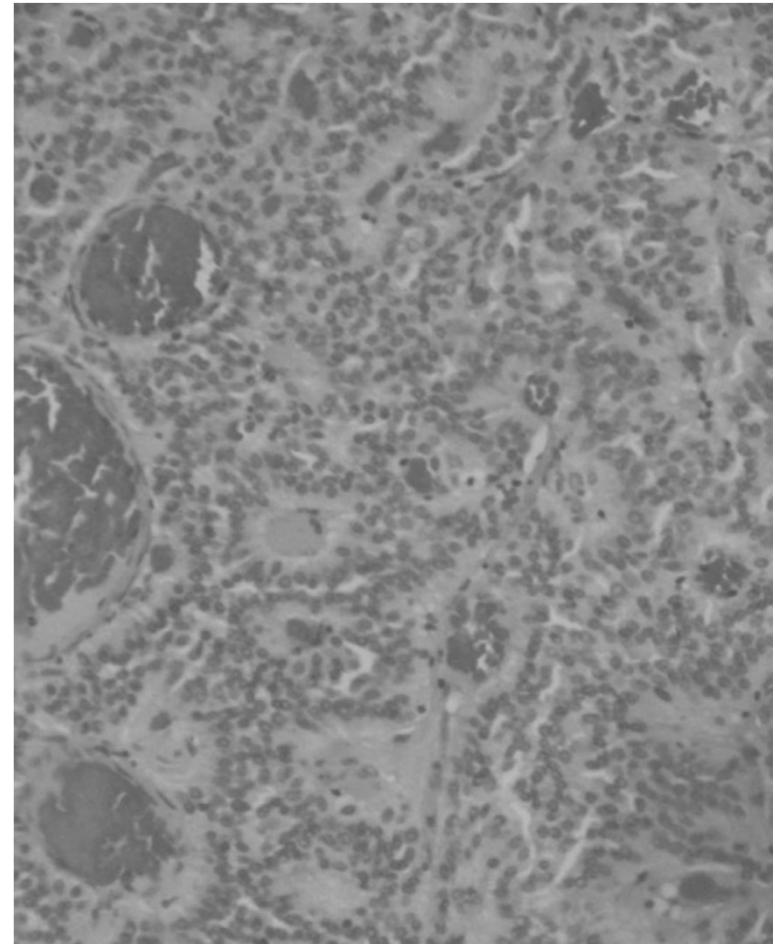




Ependymom



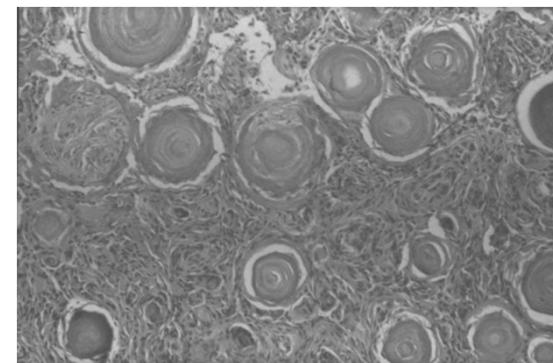
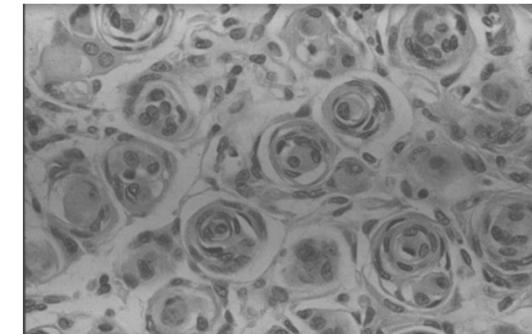
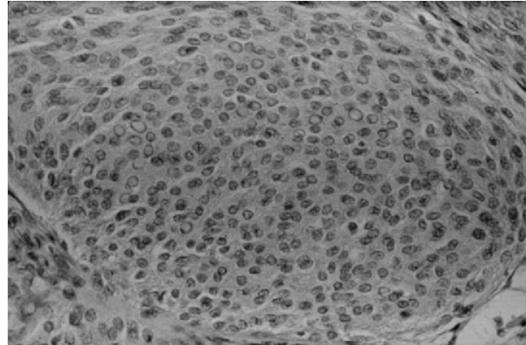
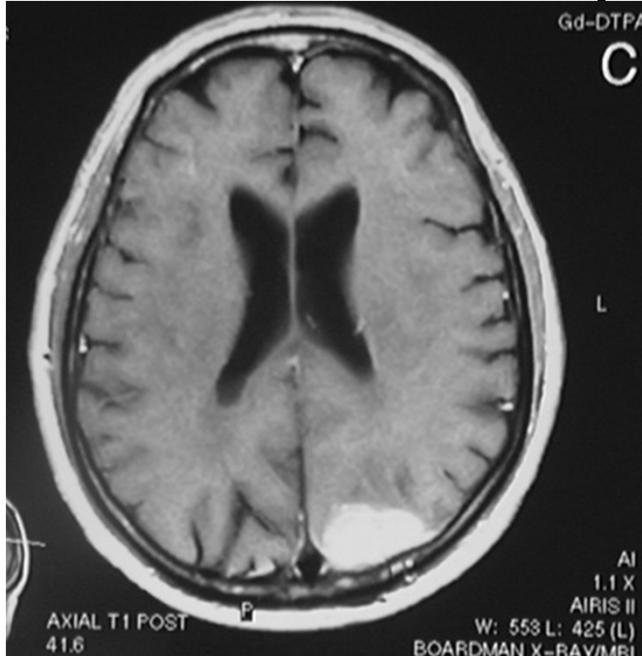
- ★ Tumoröse Masse,
entwickelt in dem Bodem
der IV. Ventrikel
- ★ Perivaskular
Pseudorosetten



Meningiom

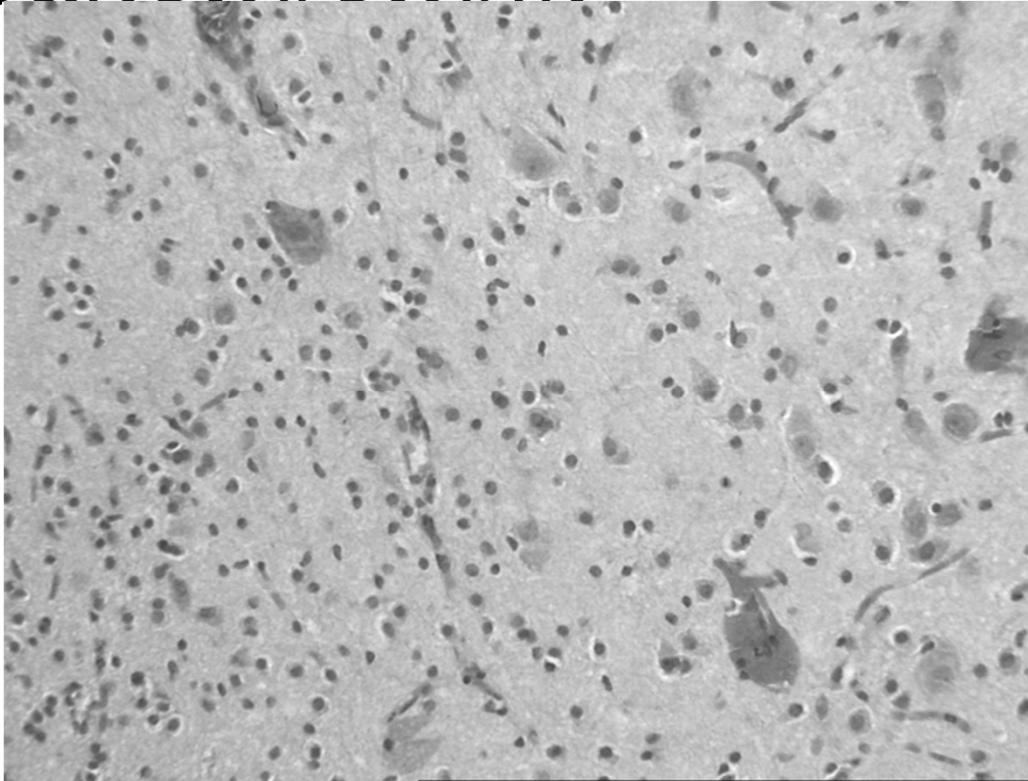
- ★ Diskrete, non-invasive Tumoren
 - Extra-axial, drückt Gehirnmaterial
 - Assoziiert mit dura mater
 - **Hyperostose odr Invasion der Schadel ist haufig**
- ★ Histologisches Bild:
 - Fibroblastische oder menigotheliale Zelle
 - menigothelialer Wirbel
 - Psammoma Körperchen
- ★ SELTEN in Kinder, machmal intraventrikular (laterale Ventrikeln)

Meningiom



Extra-axiale Tumoren, meningotheiliale Zelle, Wirbel und Psammoma Körperchen

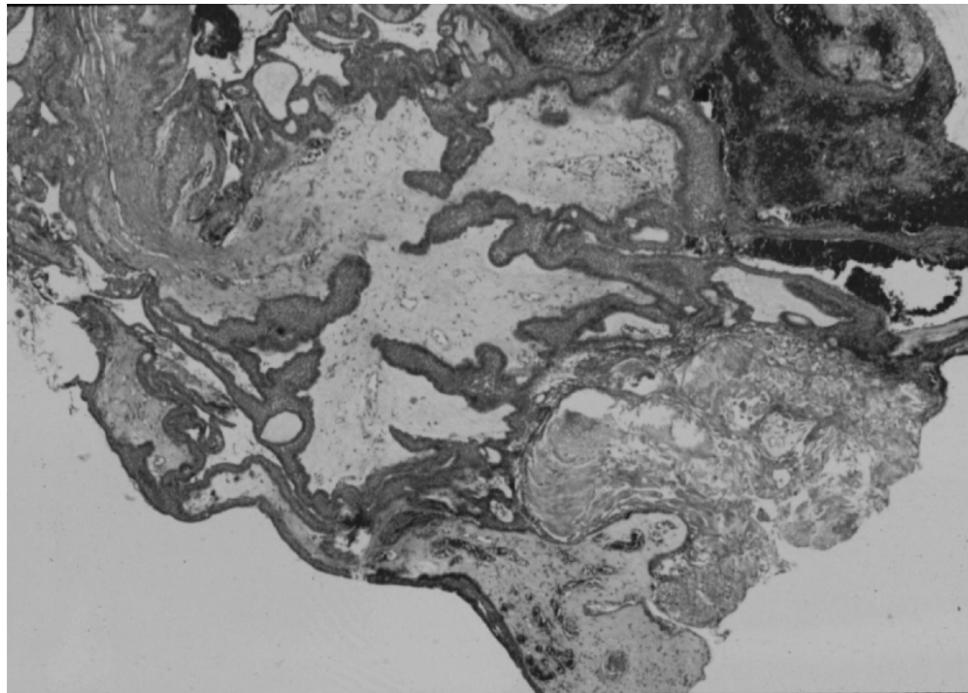
Gangliogliom



Zerebrum, zervikomedullar, häufig mit zystische Komponenten

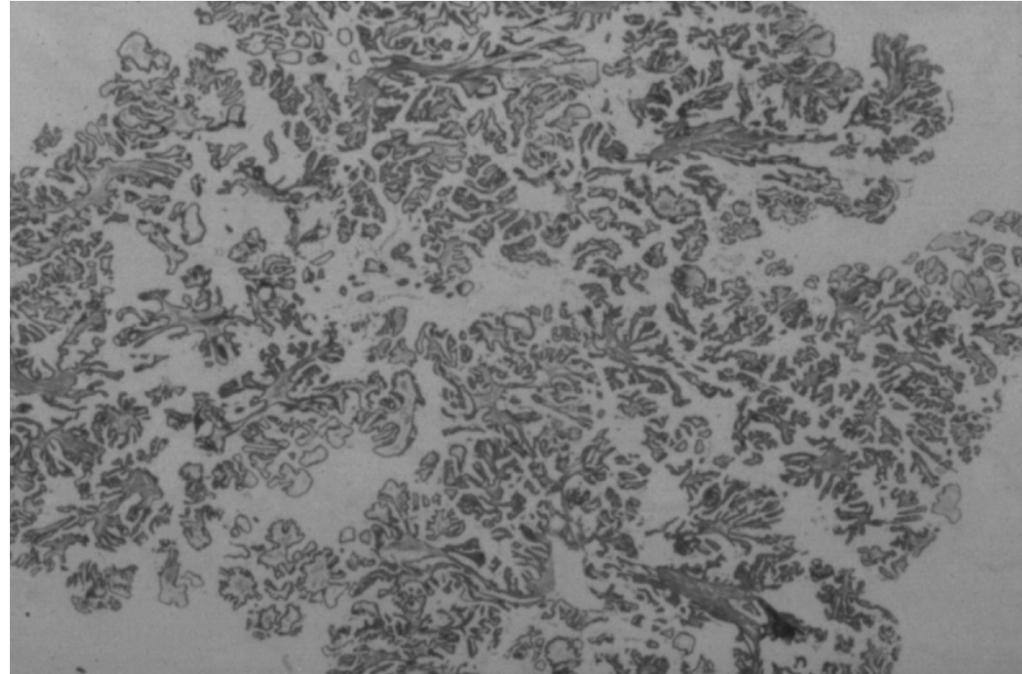
Erhöhte Nummer der Neuronen (manchmal binukelar) und erhöhte Nummer der
gliale Zelle (typisch astrozytar)

Kraniopharyngiom



- ★ Heterogene, zystische Masse in suprasellare Region
- ★ Basaloid Schicht, stellate Reticulum, “wet” Keratin, häufig kalzifiziert

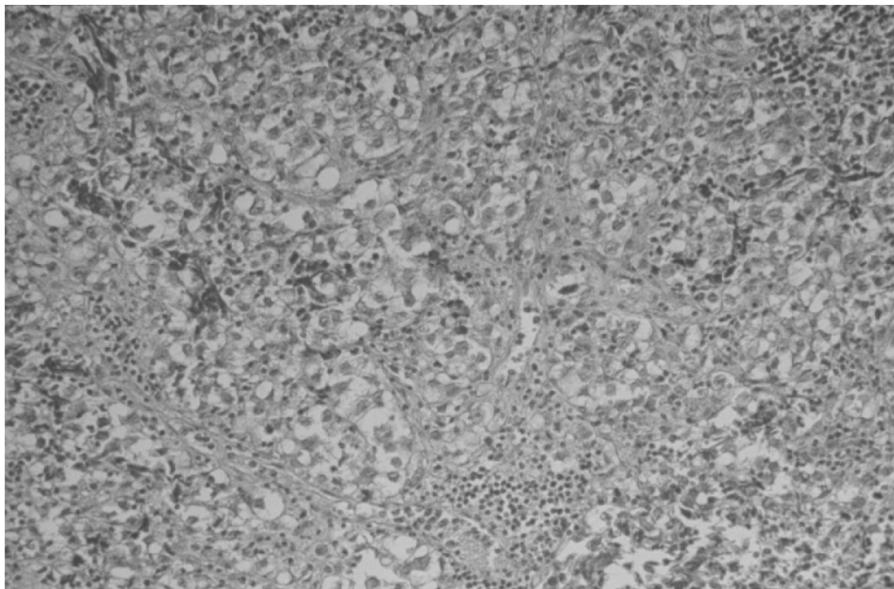
Choroid plexus Papillom



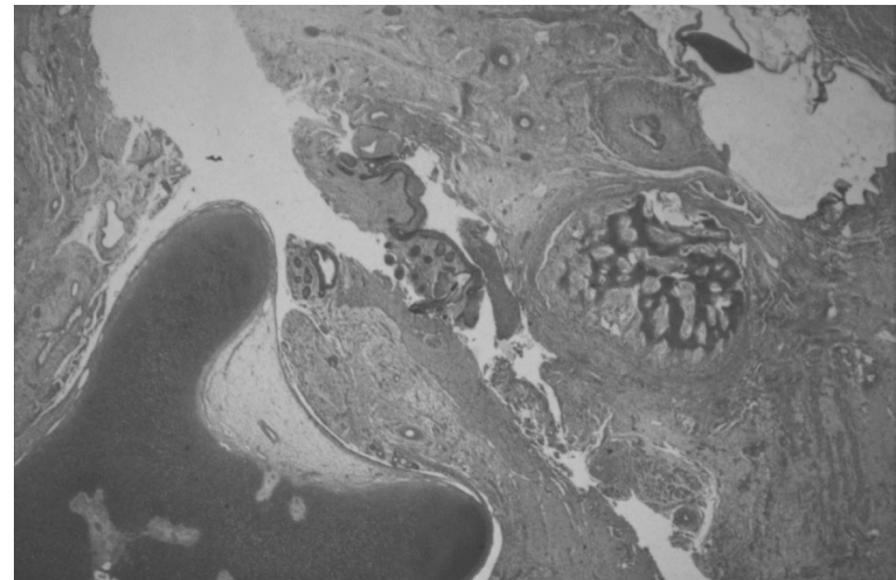
★ Laterale Ventrikel in Kinder (IV. Ventrikel in Erwachsenen)

Keimzell Tumoren

Germinom



Teratom



- ★ Pineal - 99% männlich, die Mehrheit ist Germinom
- ★ Suprasellar – häufig gemischt mit Keimzell Tumoren,
50% weiblich
- ★ Teratomen sind selten

RETINOBLASTOM

Anfang: 1-3 Jahre

Familiar (au. dominant) / sporadisch

Genetik:

RB1 supressor Gen chr13q14
105 kD nukleares Phosphoprotein
Inaktivierung LOH, Keimzell
Mutation+2nd hit

Assoziiert mit:

Kong. kardiovaskulare Deff.
Black-Sulzberg Syndrom
Infantile kortikale Hyperostose
Dentinogenesis imperfecta
Inkontinentia pigmenti
Familiar kong. Katharakt

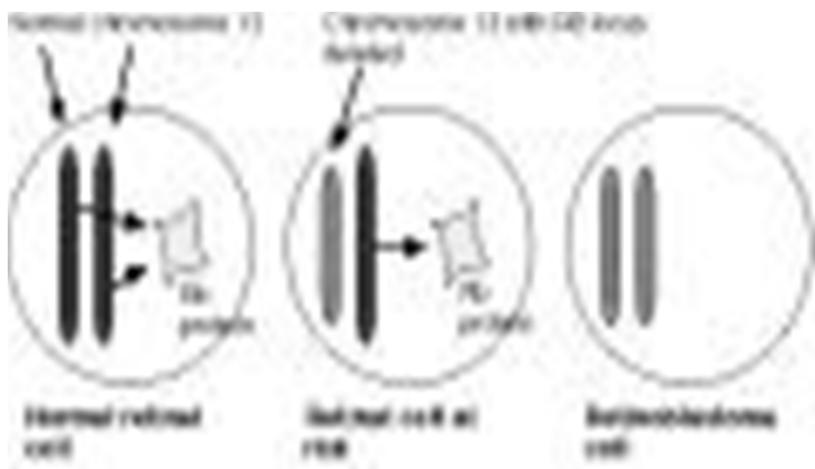
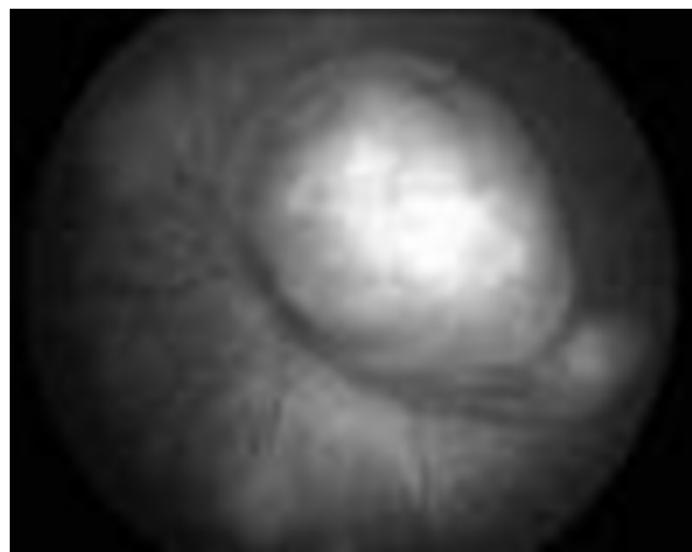
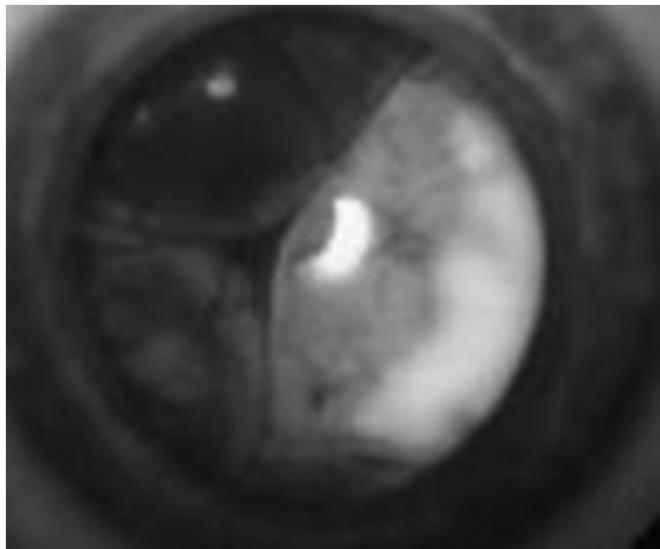
Morfologie:

Retina „small round cell tumor „, (40% bilateral)
Inneres granulares Layer
Neuronales layer - Ganglion layer
Ausseres granularer layer
Exophytisch
Endophytisch
(Vitrogen)
Rozette
Flexner-Wintersteiner Rozette
Fleurette

Markers:

NSE
Synaptophysin
Chromogranin A
S-100
GFAP+/-

Rb. Retinoblastoma Gen



Retinoblastom

“Autosomal dominant einzell Gen Krankheit ”

**RB1 chr 13q14: 105 kD nukleares Protein: E2F-DP1 inhib.
Onkosuppressor, rezessiv, LOH!!!!!!**

Gen Defekten:

Keimzell Mutation/Deletion (hereditär) 2x

Sporadische Mutation/Deletion/Hypermethylation + keimzell

Pathologie:

• Retinoblastom, p53 neg, CD99 neg.

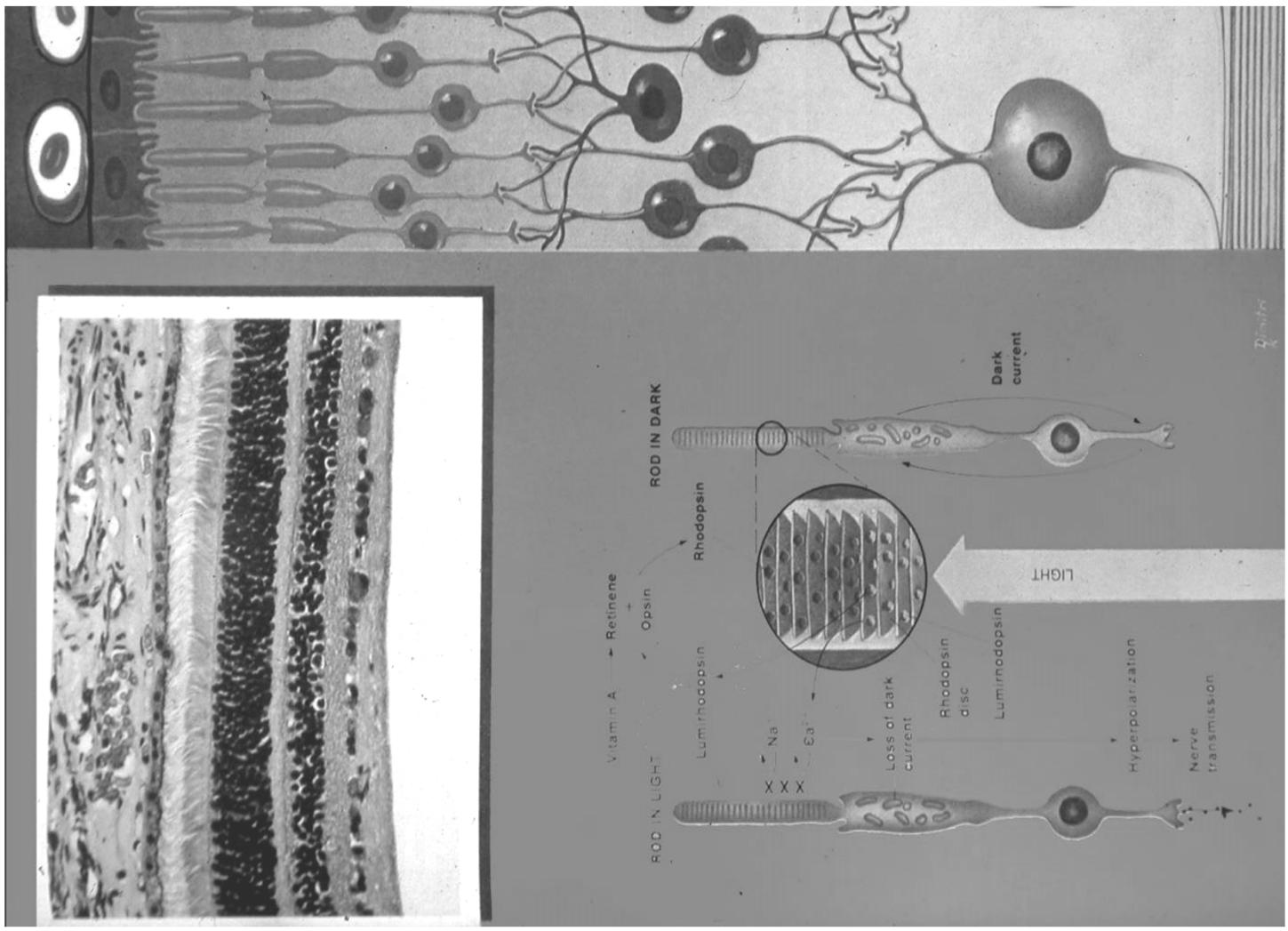
Bilateral (trilateral: Pinealom)

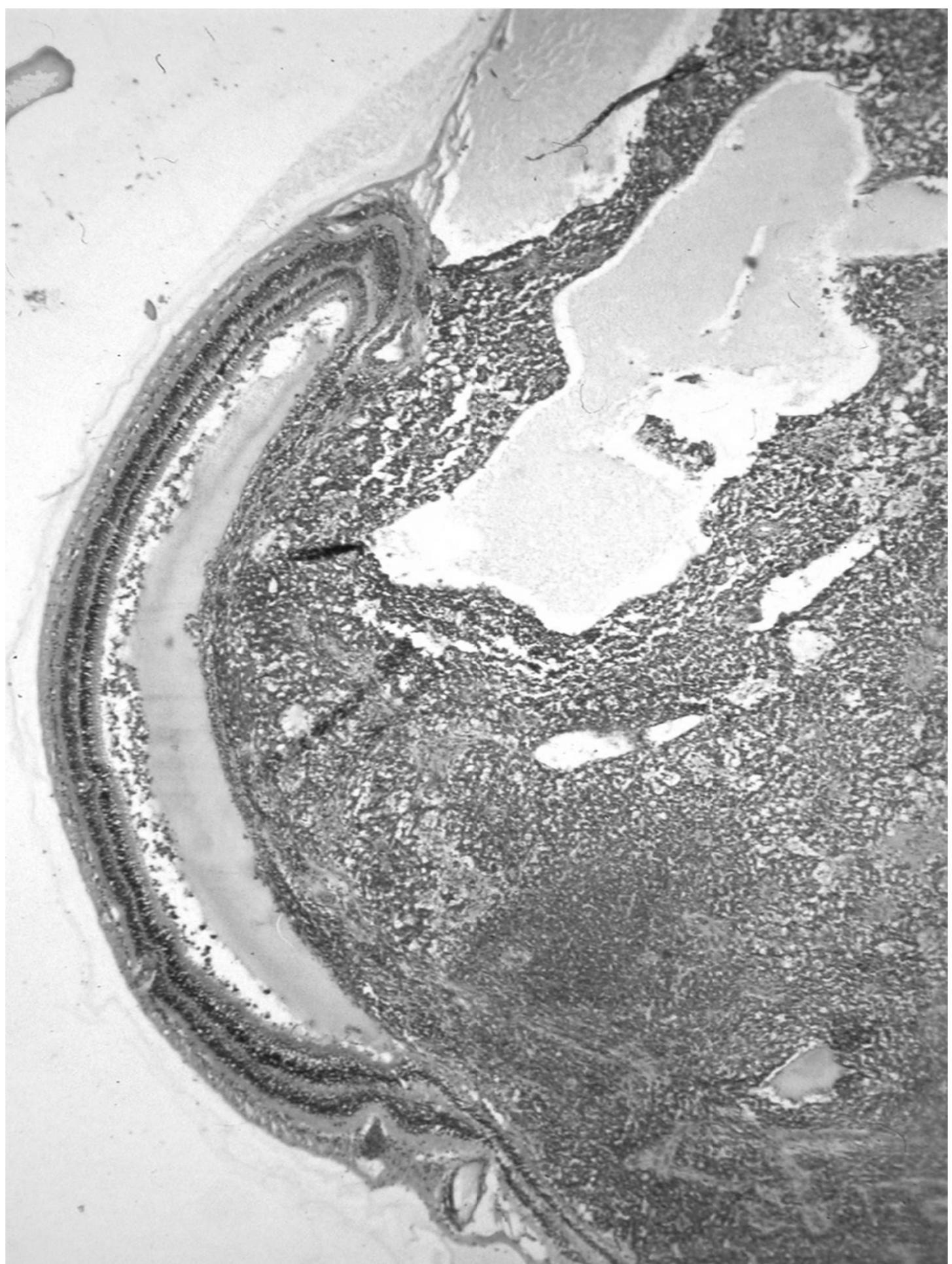
unilateral multifokal

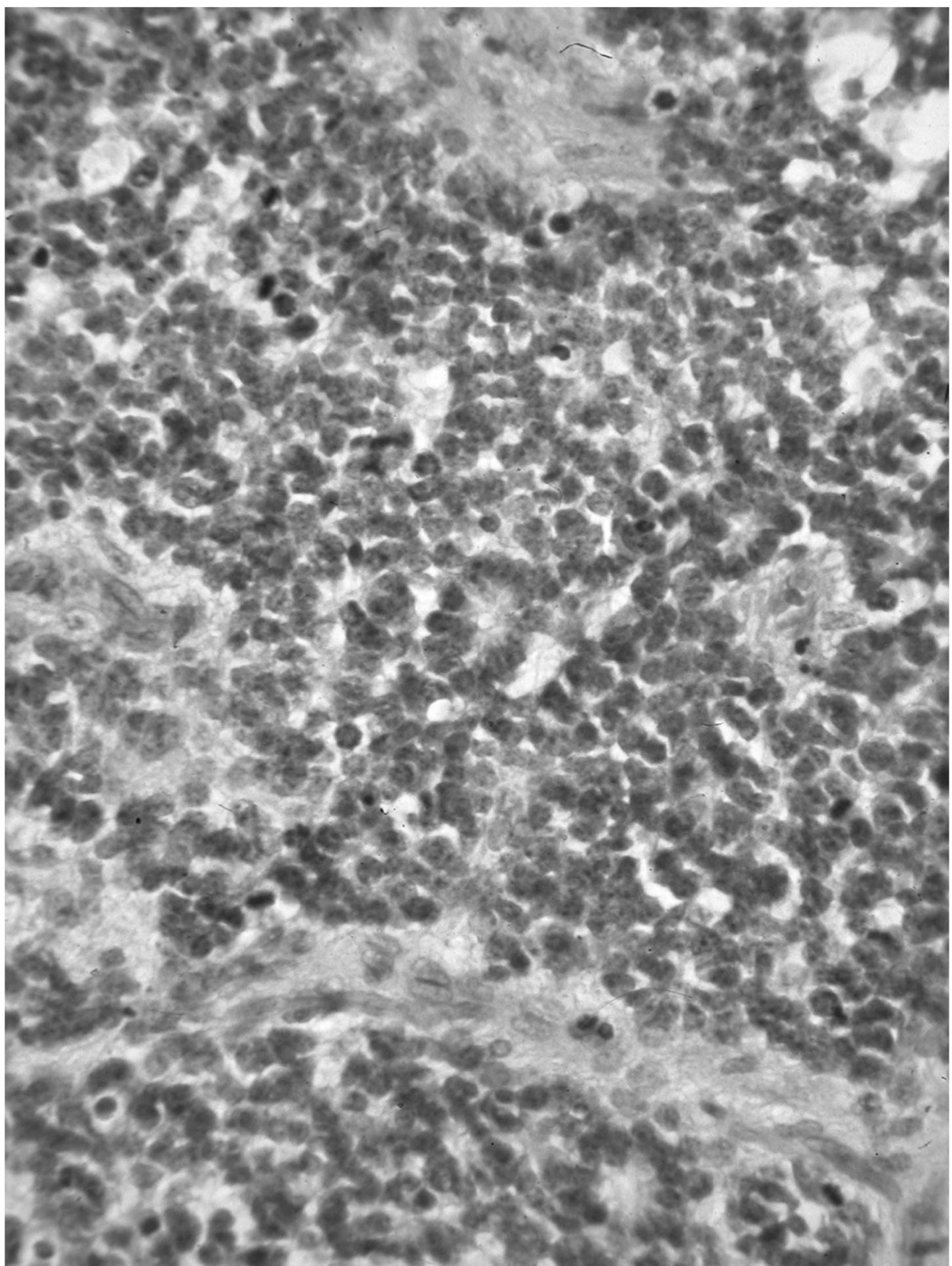
unilateral

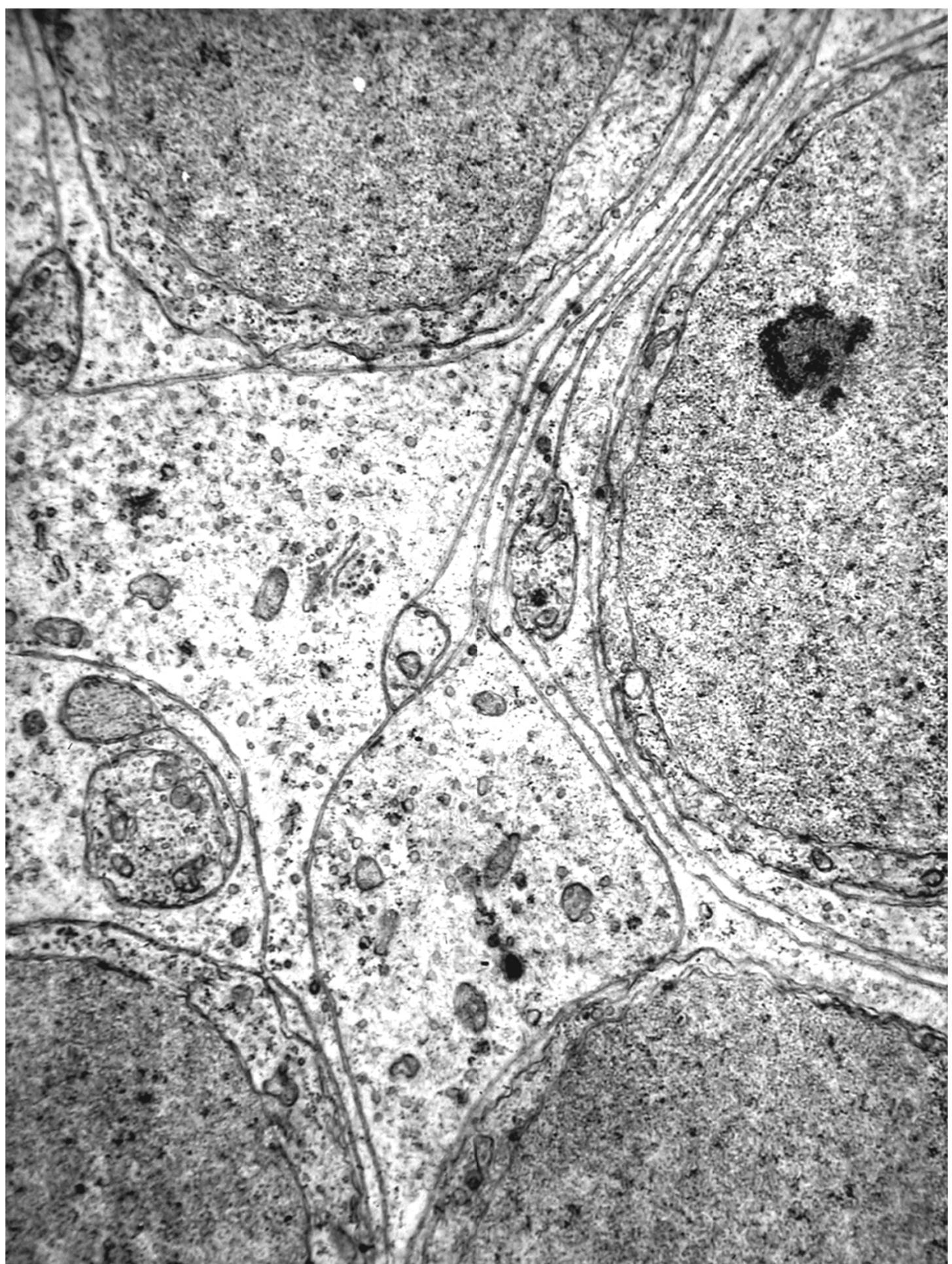
• Retinom

• Retina Degeneration











NEUROBLASTOM

In situ häufig unter 3 Monate (2,5%)

Assoziiert mit:

- Neurofibromatose
- Beckwith-Wiedemann Syndrom
- Hirschsprung Krkht.

Merkmale:

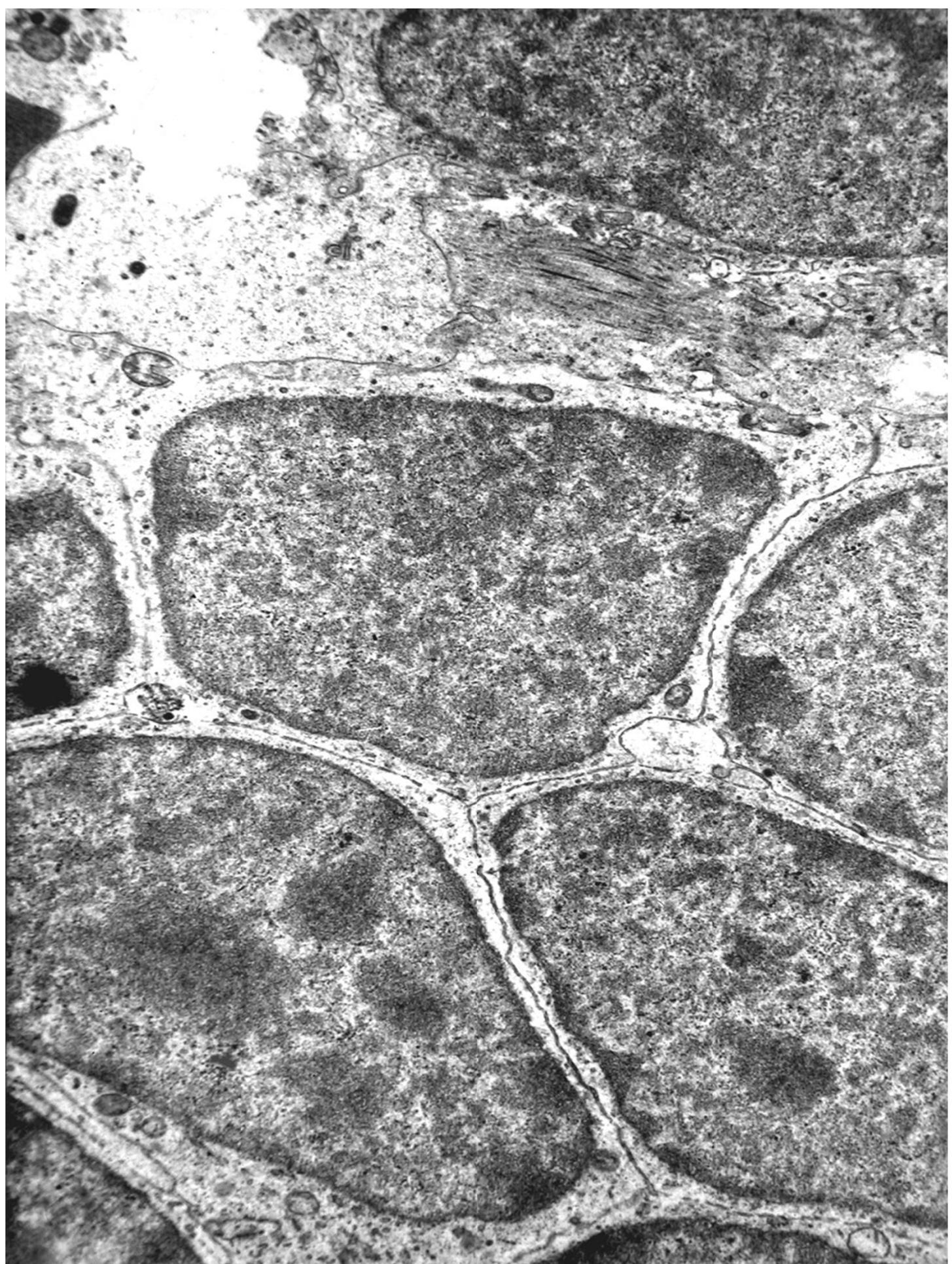
- NBL
- Fibrovaskulares Stroma
- Kalzification
- Blutung
- Nekrose
- Rozette
- Diff Ganglion Zelle +/-
- Schwann Zell diff. +/-
- PAS -

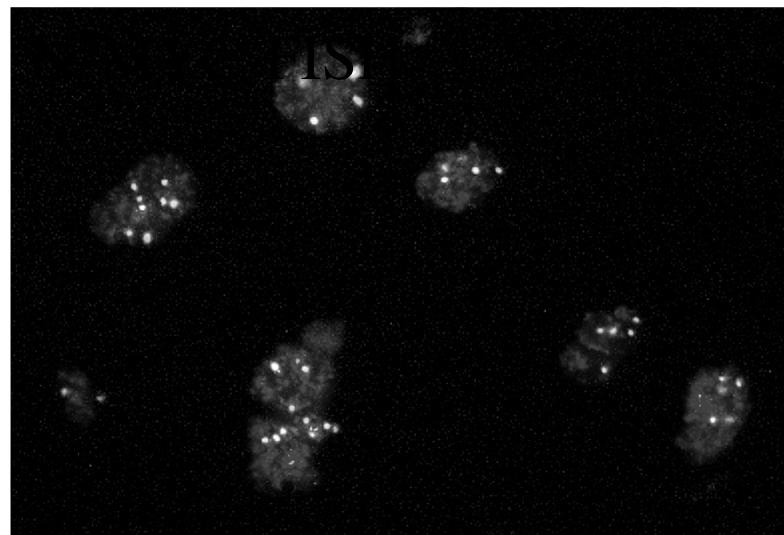
Forme:

- Monomorph, NBL stroma-arm
Differenziert
- Nicht-differenziert
- NBL stroma reich
Nodular
gut differenziert
gemischt

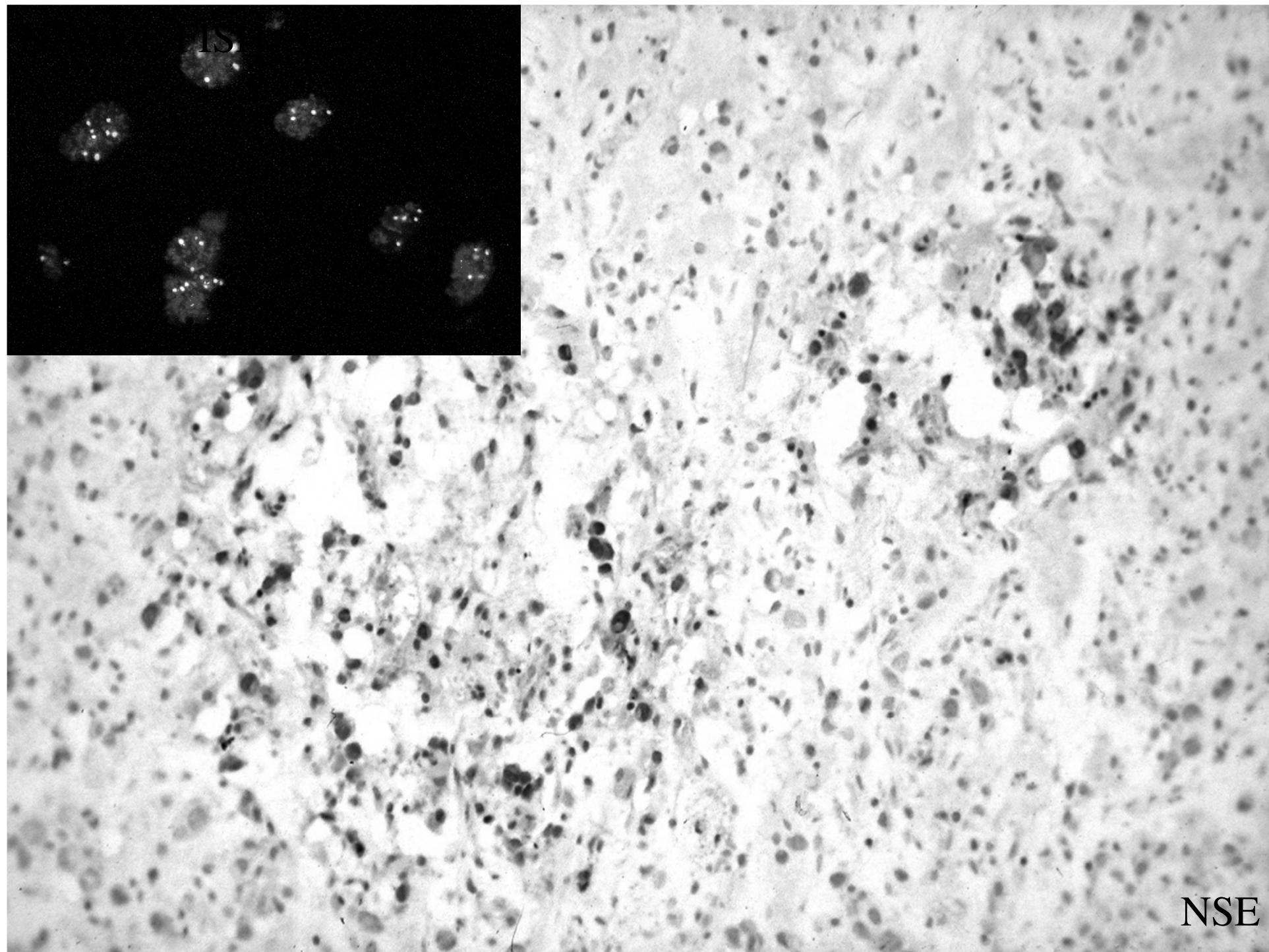
Prognose:

- N-myc Amplifikation (schlecht)
- *TRK (NGFR) (gut)*
- Mitose/kariorhexis Rate (schlecht)
- Alter ist höher (schlecht)
- Hohes stage (schlecht)
- VMA/HVA <1,5 (schlecht)
- NSE > 100 ng/ml (schlecht)
- LDH > 1000 IU/ml (schlecht)
- *Hyperdiploid DNS (gut)*





IS



NSE

n-myc Gen-Amplifikation - Schwab und Mitarbeiter:

THE LANCET Oncology, 4:472, 2003

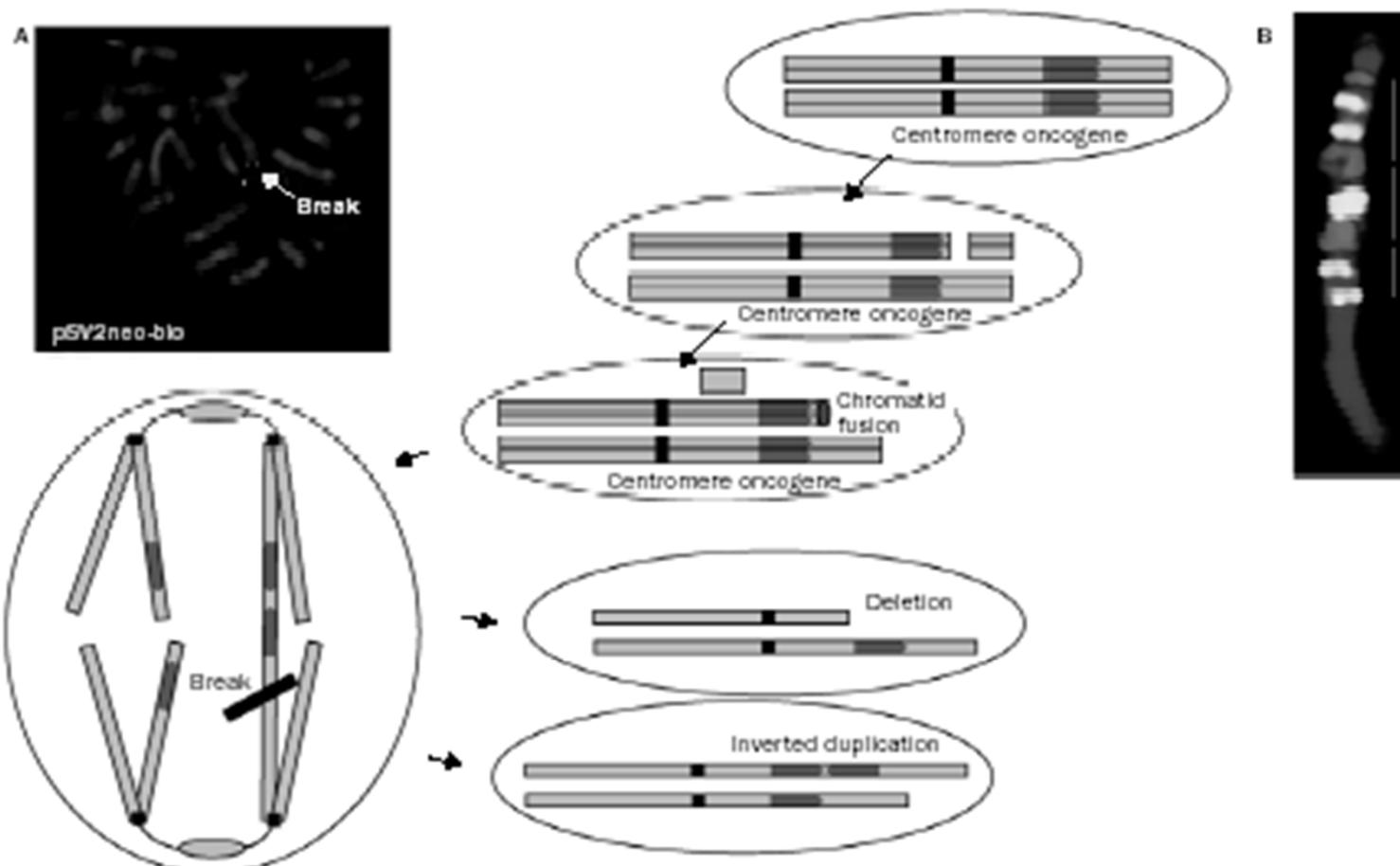


Figure 3. (a) Breakage-fusion-bridge cycles as a general mechanism for gene amplification, but probably not for MYCN-amplification. (b) Cytogenetic evidence for the generation of inverted amplification repeats by breakage-fusion-bridge cycles. Gene copy increase by breakage-fusion-bridge cycles rarely exceeds five to eight copies of rather large inverted DNA regions but amplified MYCN is present in neuroblastomas in up to 300 copies. White bars indicate the dimension of an amplified DNA unit.

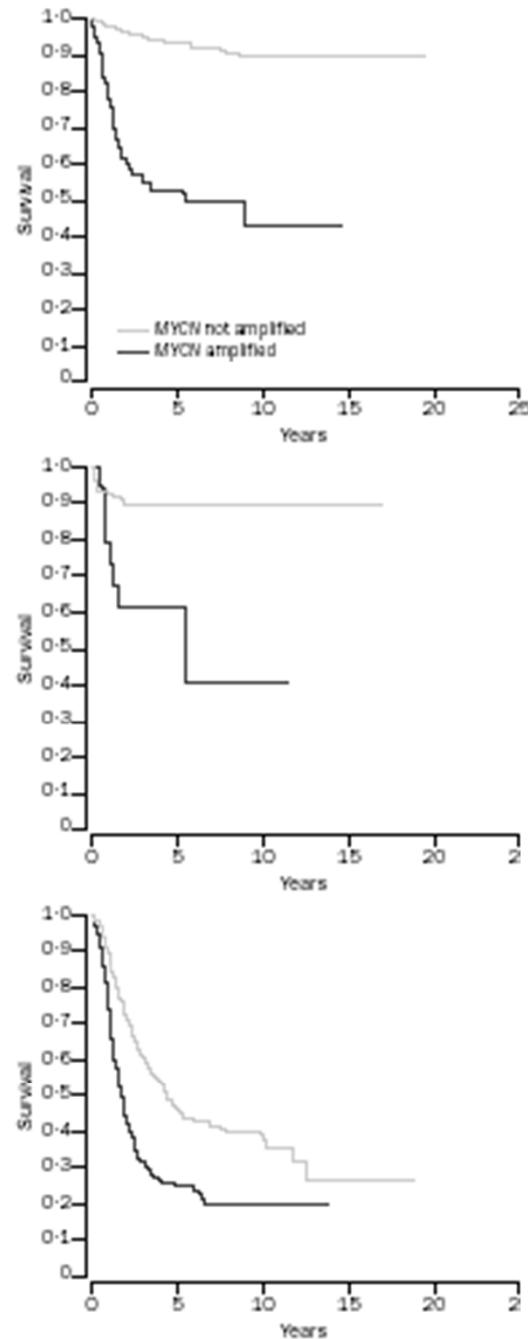


Figure 4. Stage-related overall survival by MYCN amplification in 17 patients with neuroblastoma. (a) Stage 1-3 disease. (b) Stage 4S disease. (c) Stage 4 disease. $p=0.01$ for all curves.

Neuroblastom - n-myc Gen-Amplifikation

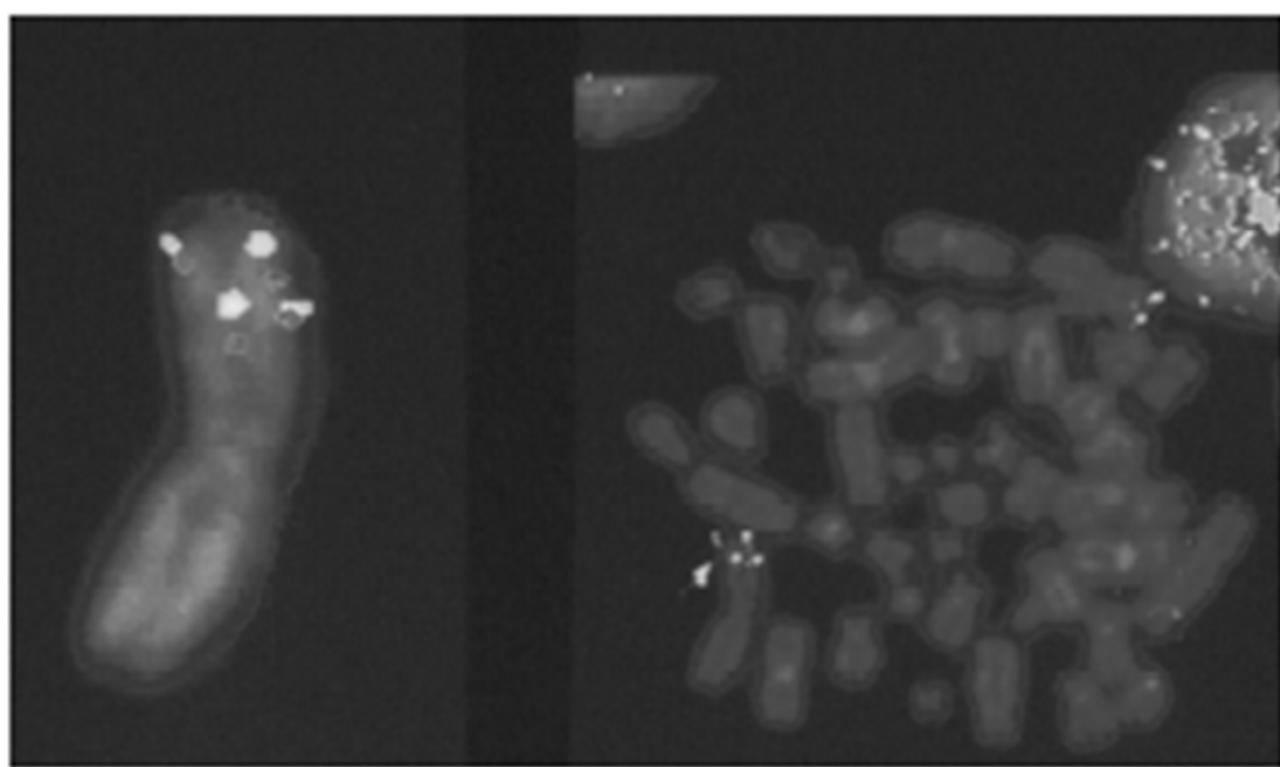
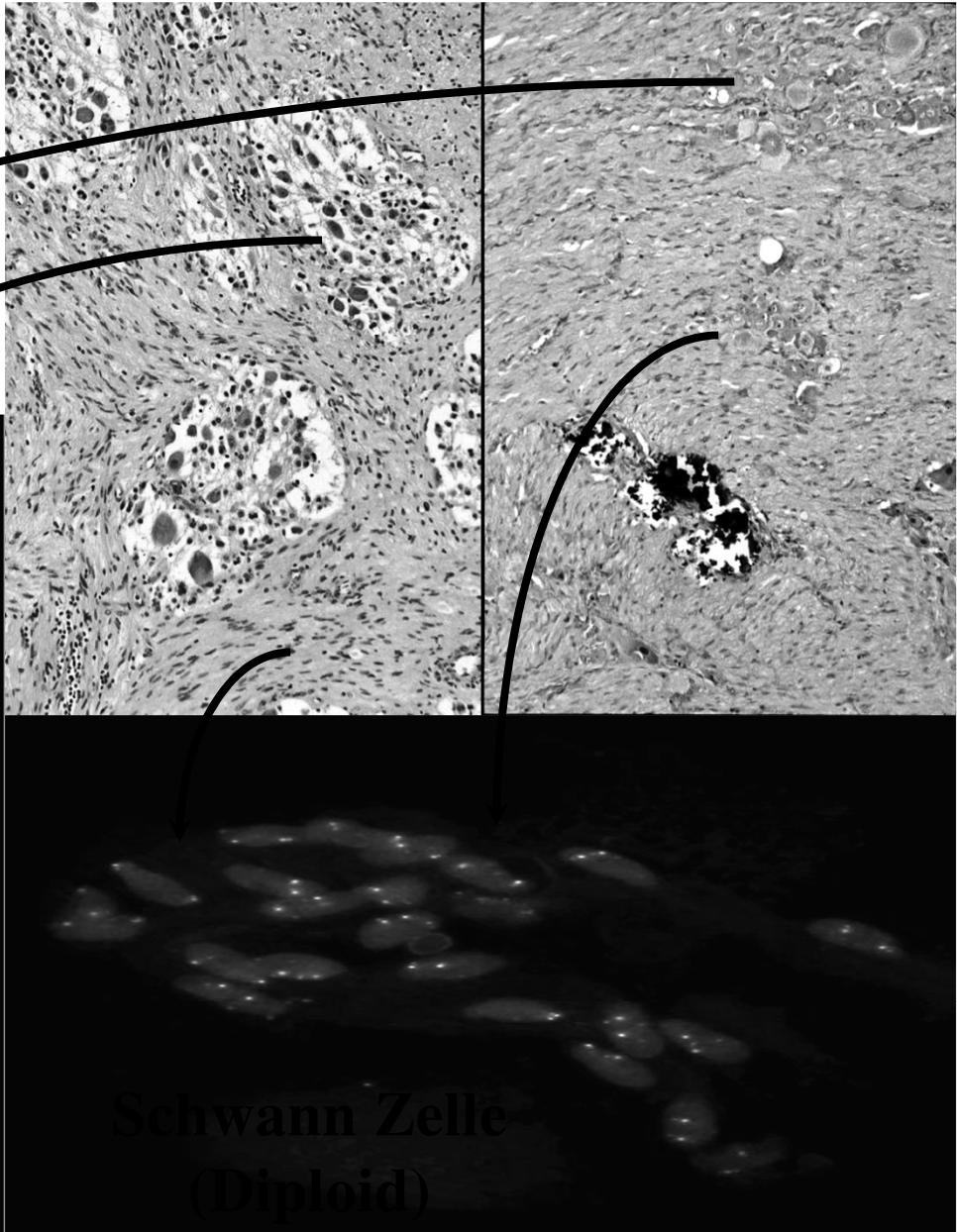
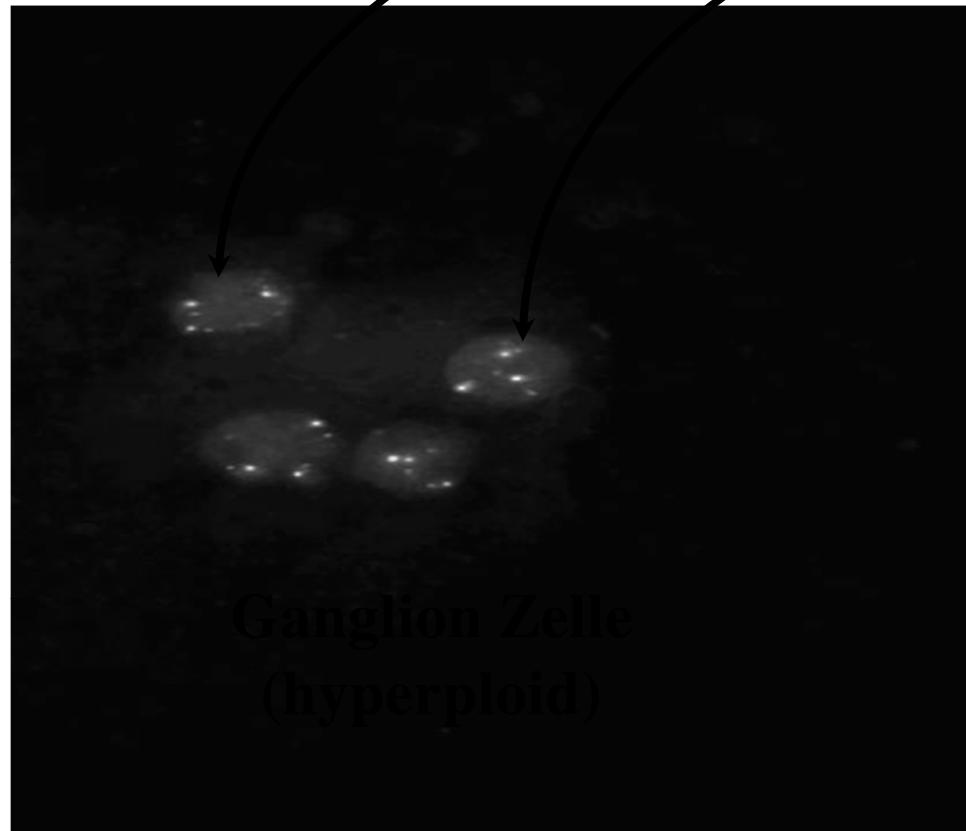


Figure 5. Duplication of 2p24. FISH analysis identifies non-inverted tandem duplication at the MYCN locus 2p24. MYCN is shown in green and an anonymous cosmid probe in red.

**DNA Index in
GNB, intermixed
und GN**



**Neuroblastische/Ganglion Zelle und Schwann stromale Zelle
verschiedene zellulare Herkunft**

International Neuroblastoma Pathology Committee

Committee Members

USA: Dehner, L.P.; Joshi, V.V.; Shimada, H.

Italy: d'Amore, ESG

France: Peuchmaur, M

Japan: Hata, J.

Norway: Roald, B.

Austria: Ambros, I.M.

Morphologic classification of
Peripheral Neuroblastic Tumors

- ✓ Prognostically Significant
- ✓ Biologically Relevant

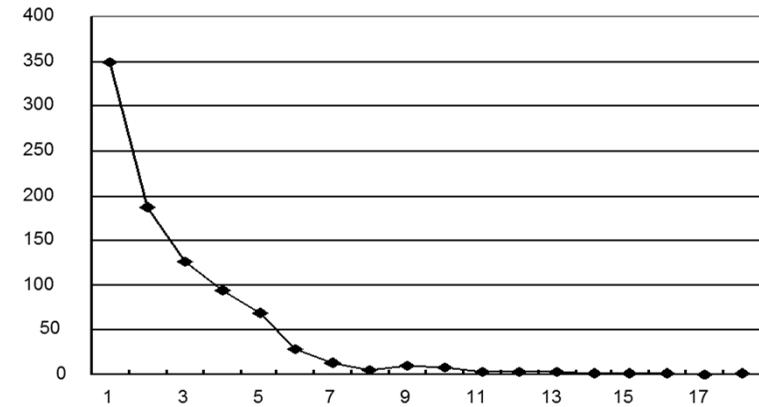


Peripheral Neuroblastic Tumors

Neural Crest Origin ➤

**Neuroblastoma
Ganglioneuroblastoma
Ganglioneuroma**

*Involution
Spontaneous Regression
Maturation
Progression*



Past: Enigmatic Tumors, Unpredictable

Current: Biologically Heterogeneous Tumors
 Molecular Properties reflecting Clinical
 Behaviors

NBL Subtypen (INPC)

	Group	Feature
Neuroblastoma, NB (stroma-poor)	undifferentiated (NUD) Poorly diff (NPD) differentiating (NDF)	No neuropil <5% differentiating NBL Neuropil, <5% dNBL Neuropil, >5% dNBL
Ganglioneuroblastoma, mixed (GNBi)	Schwann- stroma rich	MKI (mitosis/kariorexis ratio) Grade: diff SCHW stroma ratio
Ganglioneuroblastoma, noduláris/ komposit, GNBn		MKI
Ganglioneurinoma, (Schw- stroma dominant, GN)	differentiated differentiating	

4 Categories in pNTs

International Neuroblastoma Pathology Classification

Neuroblastoma

(Schwannian stroma-poor)

Undifferentiated Subtype

Poorly Differentiated Subtype

Differentiating Subtype

Ganglioneuroblastoma, Intermixed

(Schwannian stroma-rich)

Ganglioneuroma

(Schwannian stroma-dominant)

Maturing Subtype

“stroma-rich, well differentiated”
in the original Classification

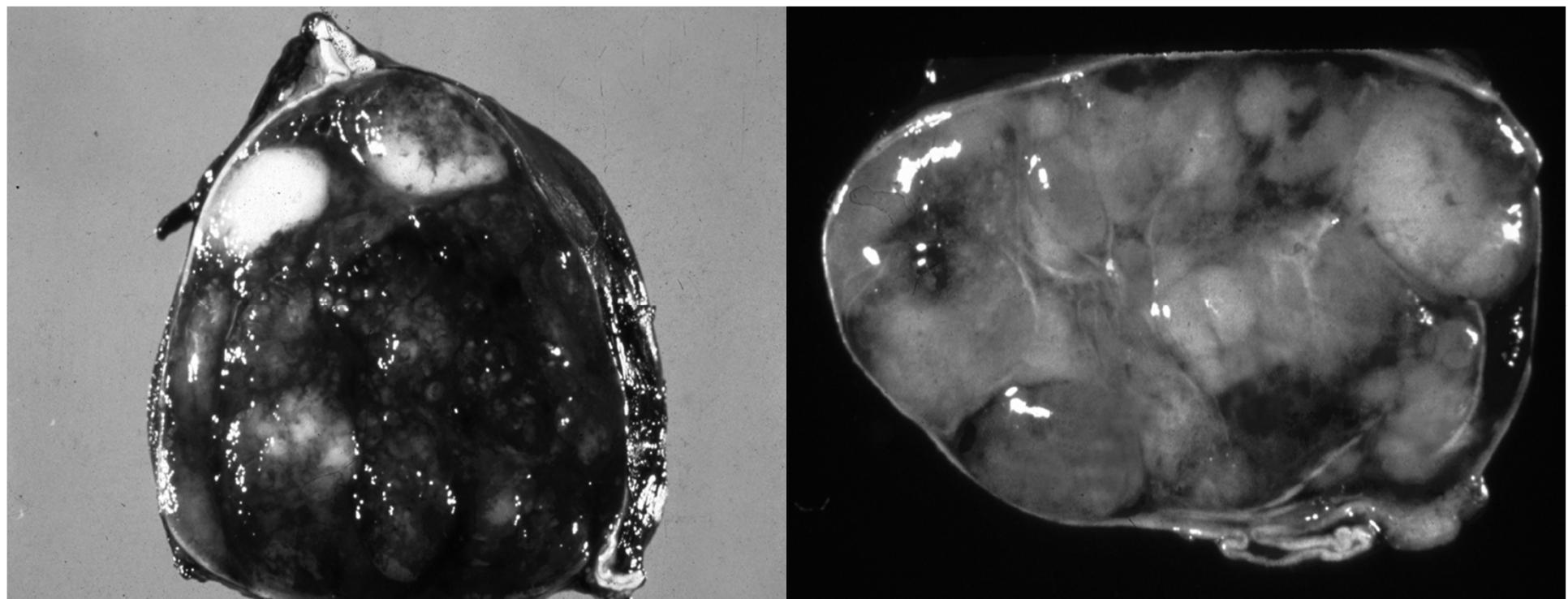
Mature Subtype

Ganglioneuroblastoma, Nodular

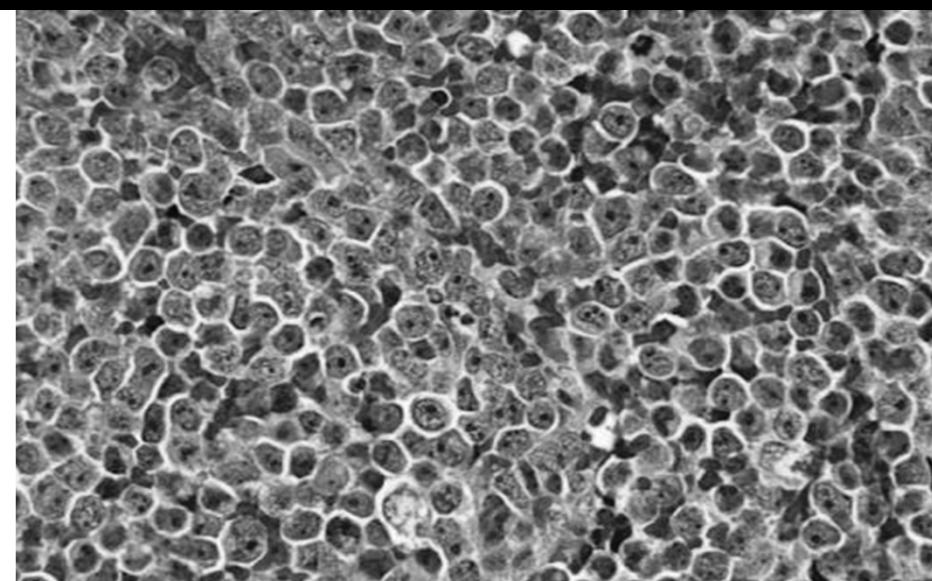
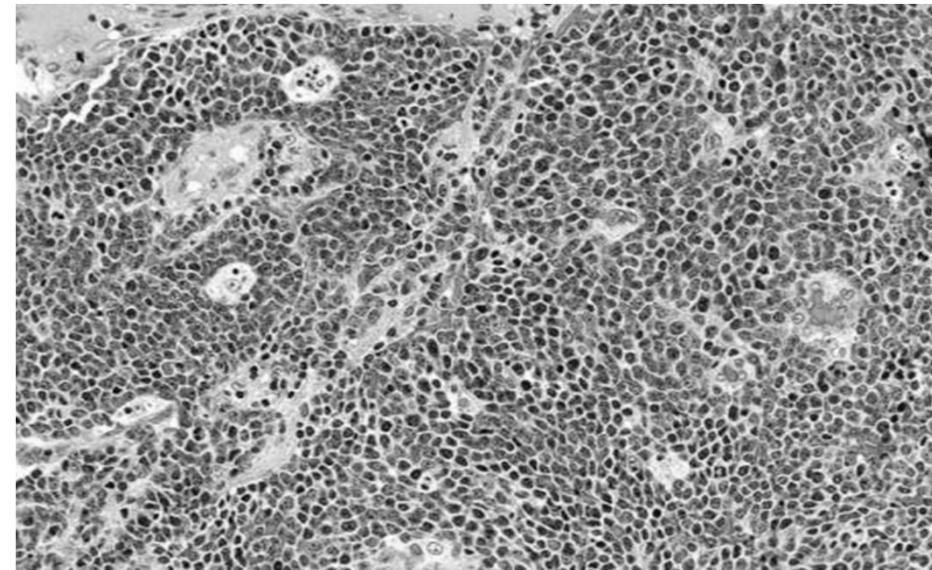
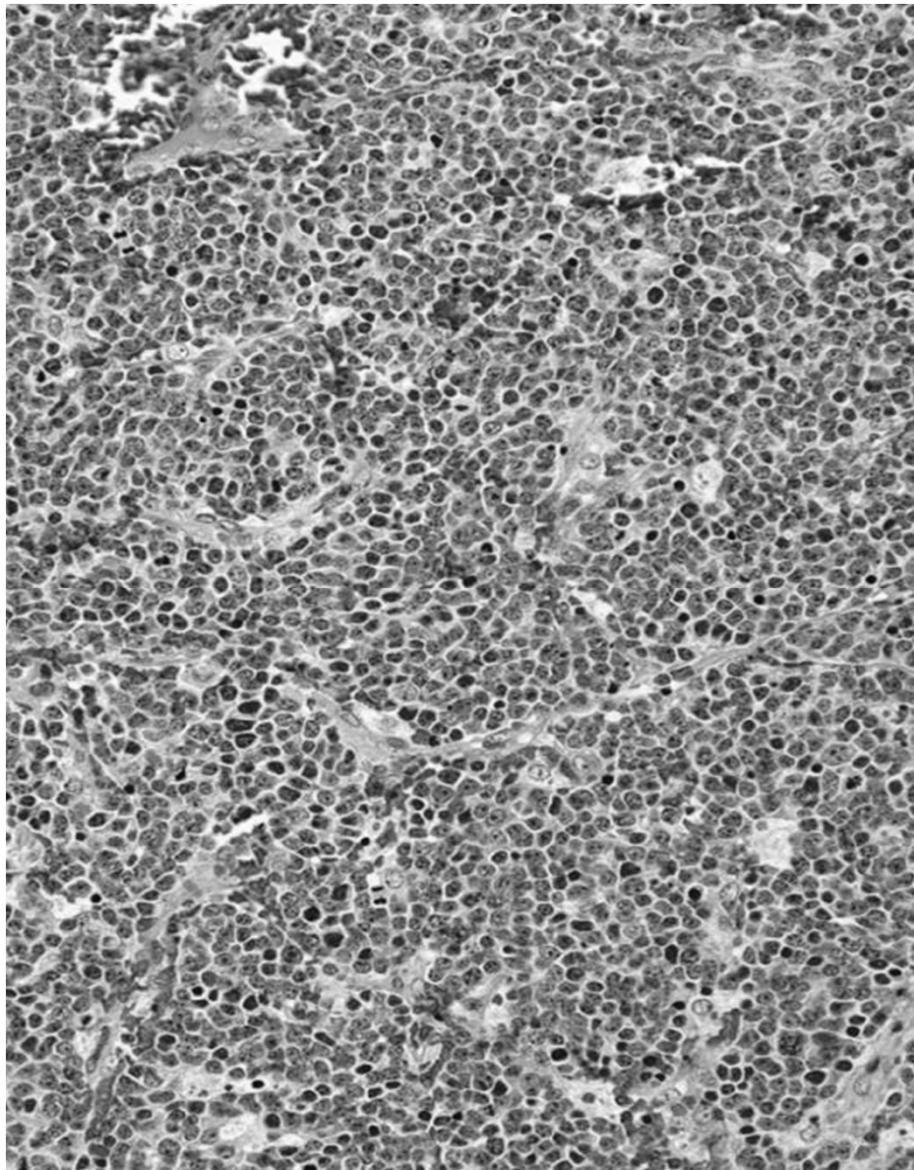
(composite, Schwannian stroma-rich/
stroma-dominant & stroma-poor)

Neuroblastoma (Schwannian Stroma-Poor)

Undifferentiated Subtype
Poorly Differentiated Subtype
Differentiating Subtype



**Neuroblastoma (Schwannian stroma-poor)
Undifferentiated Subtype**



Neuroblastoma (Schwannian stroma-poor) Undifferentiated Subtype

Light Microscopy

Septal Demarcation

Frequent Findings:

High MKI

Prominent Nucleoli

Starry Sky

Electron Microscopy

Neurosecretory

Granules (+)

Primitive Neurites (+)

Immunohistochemistry

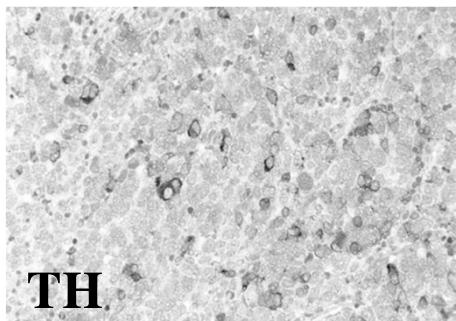
Limited Neuronal Markers

PGP 9.5 (+)

TH (+/-)

Vimentin (+/-)

MIC2 (-) or (+)



TH

Molecular Markers

MYCN

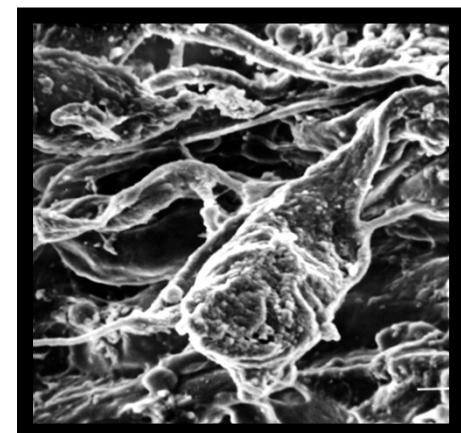
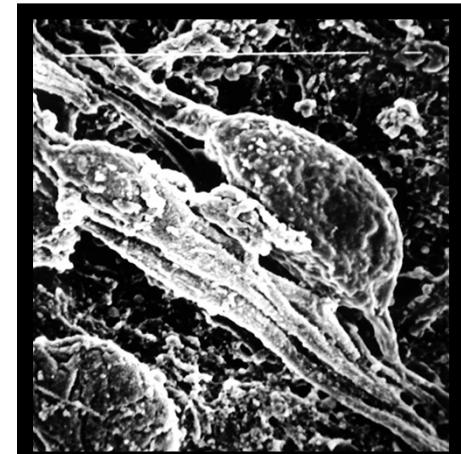
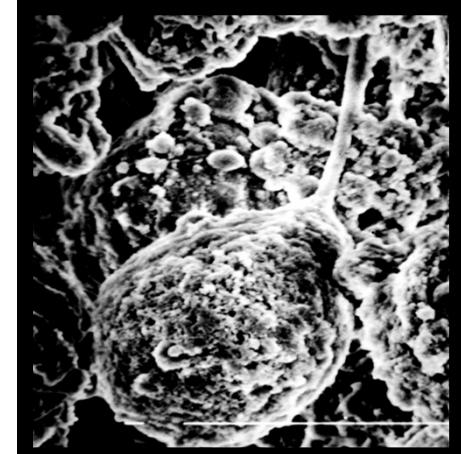
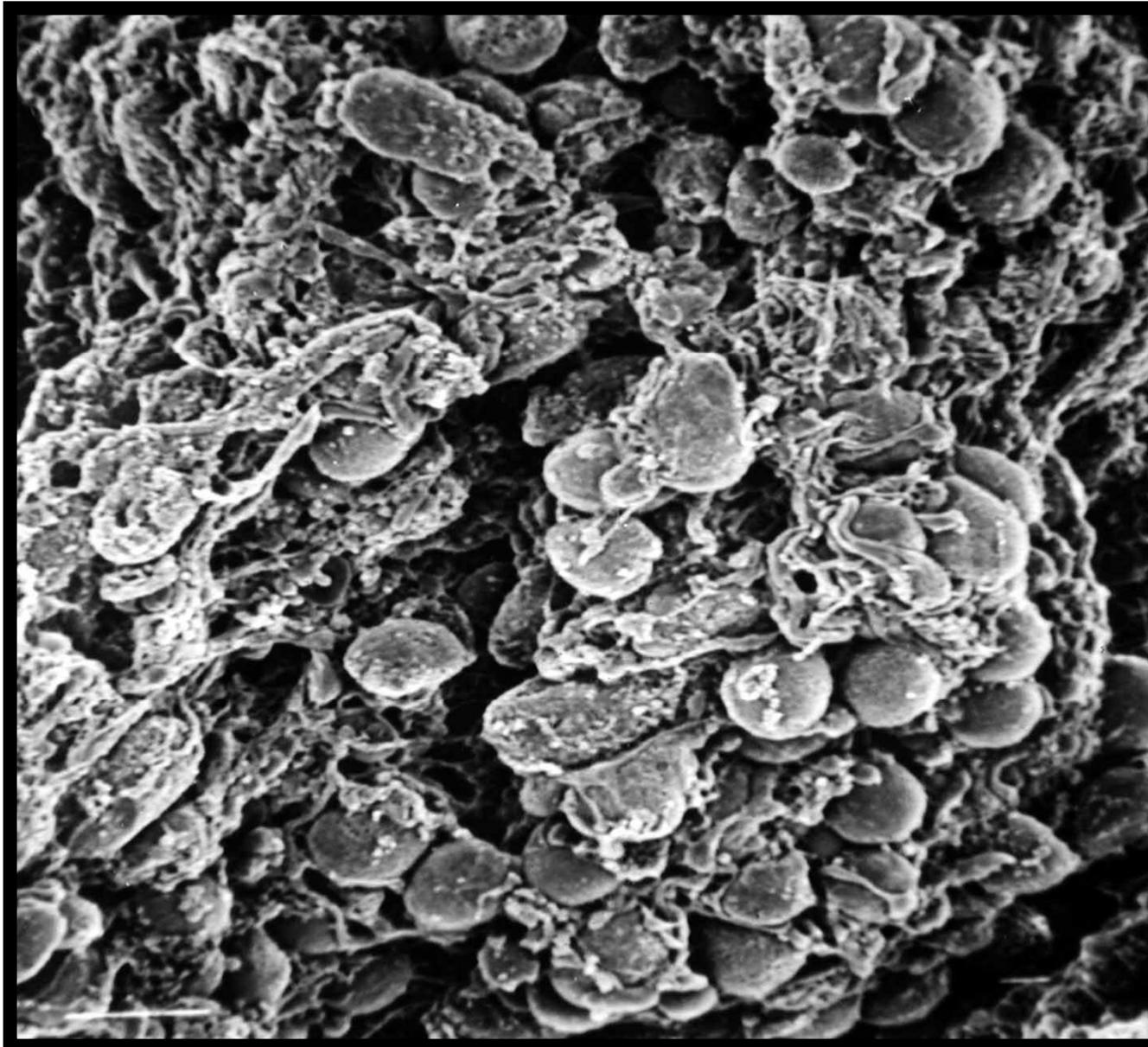
frequently amplified

trkA

low expression

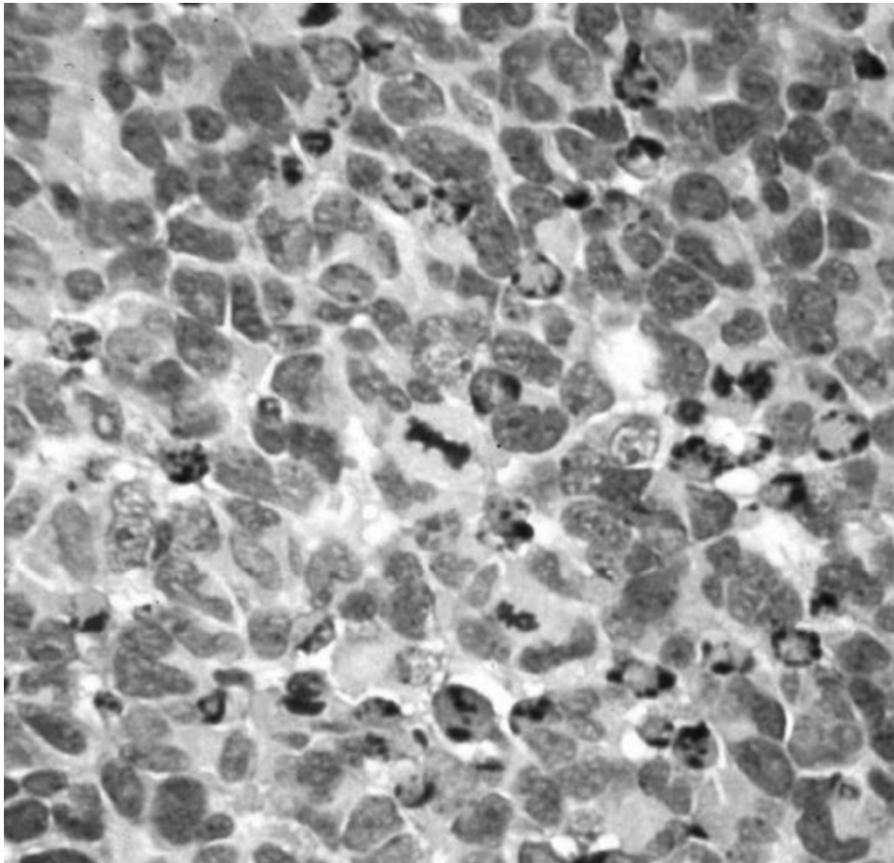
EWS translocation (-)

Neuroblastoma, SEM



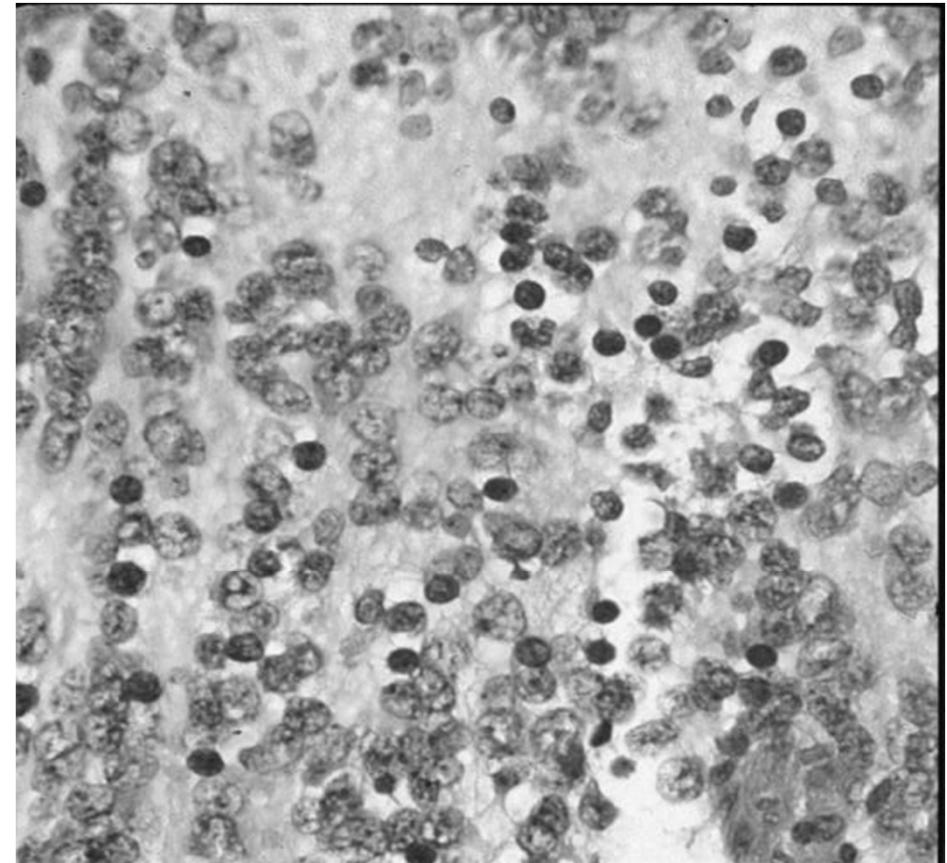
MKI Counting

Mitotic & Karyorrhectic Nuclei

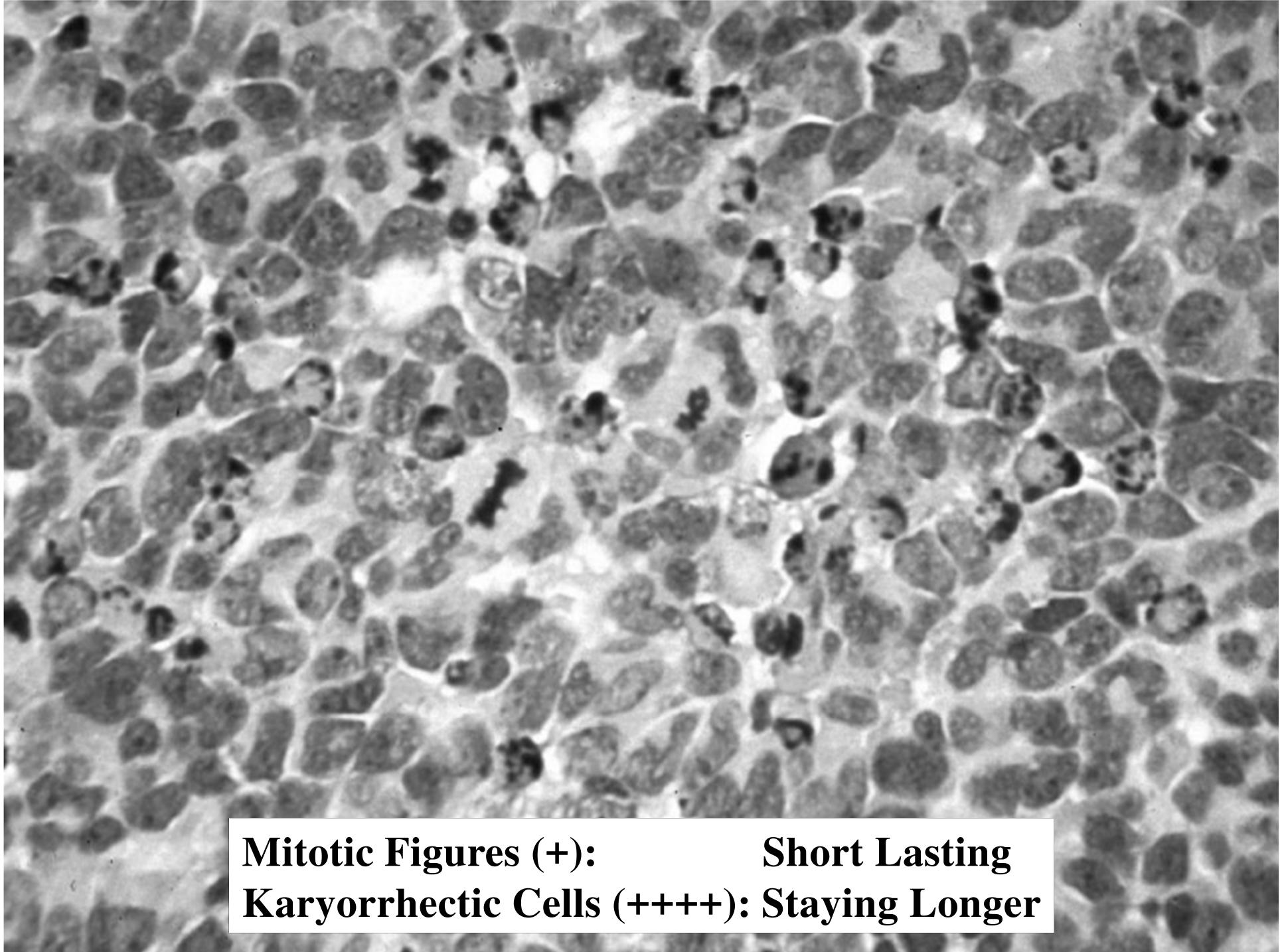


Karyorrhexis:
Agonizing Cellular Death
due to Genomic Instability

Simply Hyperchromatic Nuclei



Pyknosis:
Quiet cellular death
due to Senescence

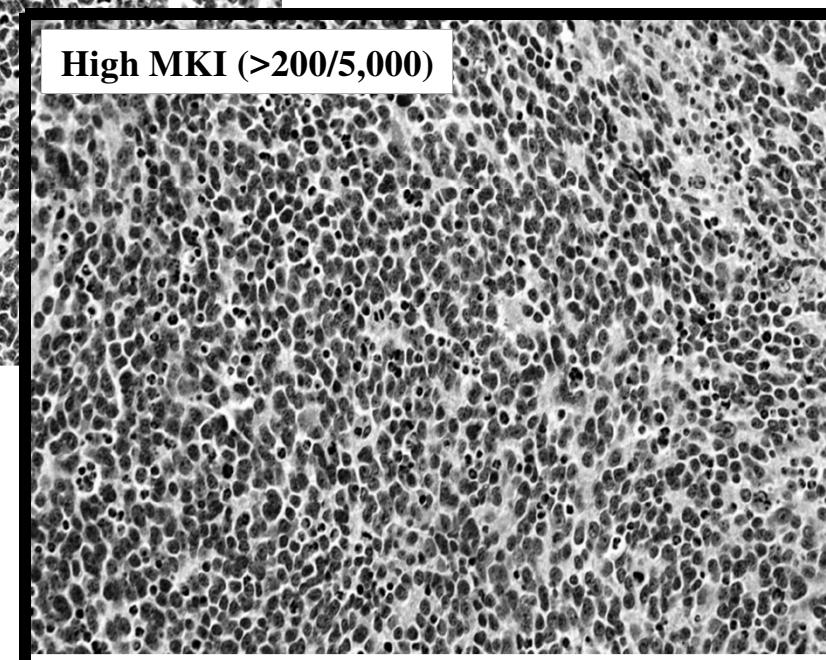
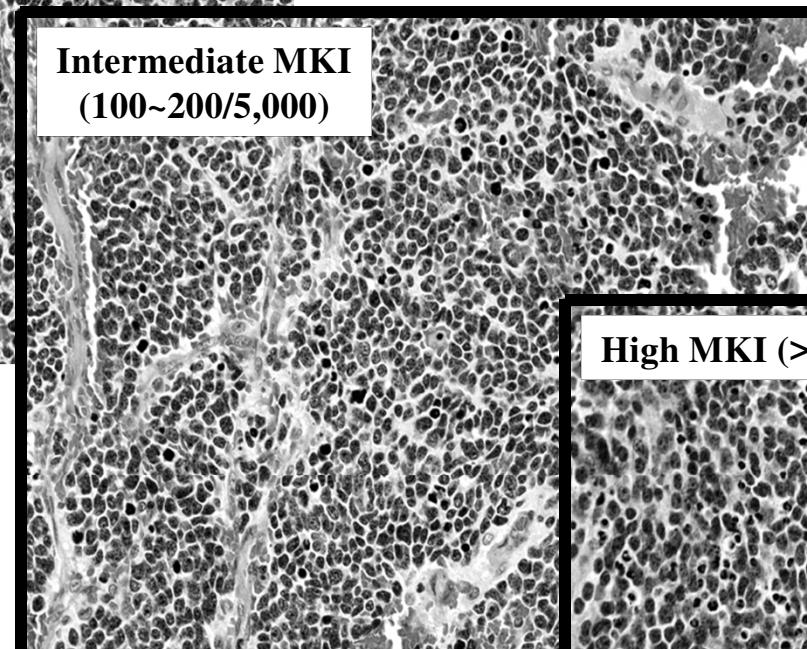
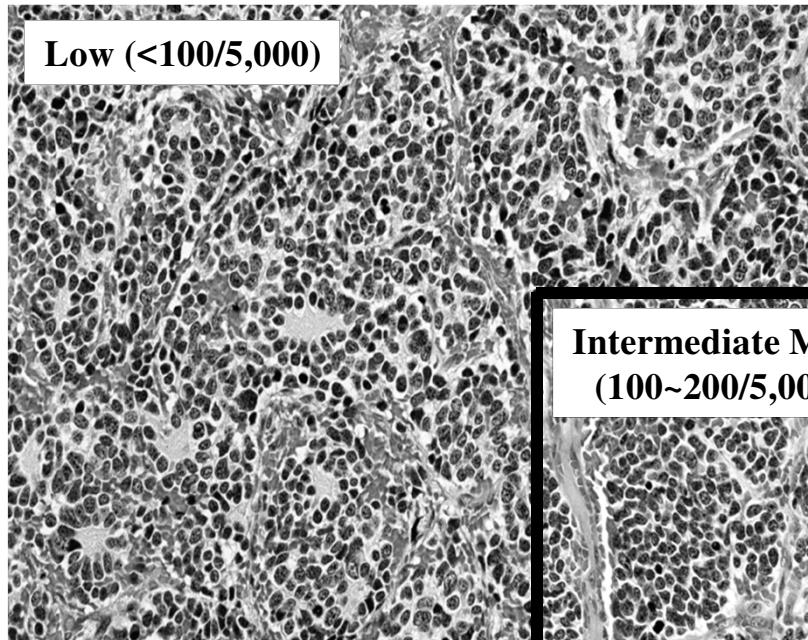


Mitotic Figures (+): Short Lasting
Karyorrhectic Cells (+++): Staying Longer

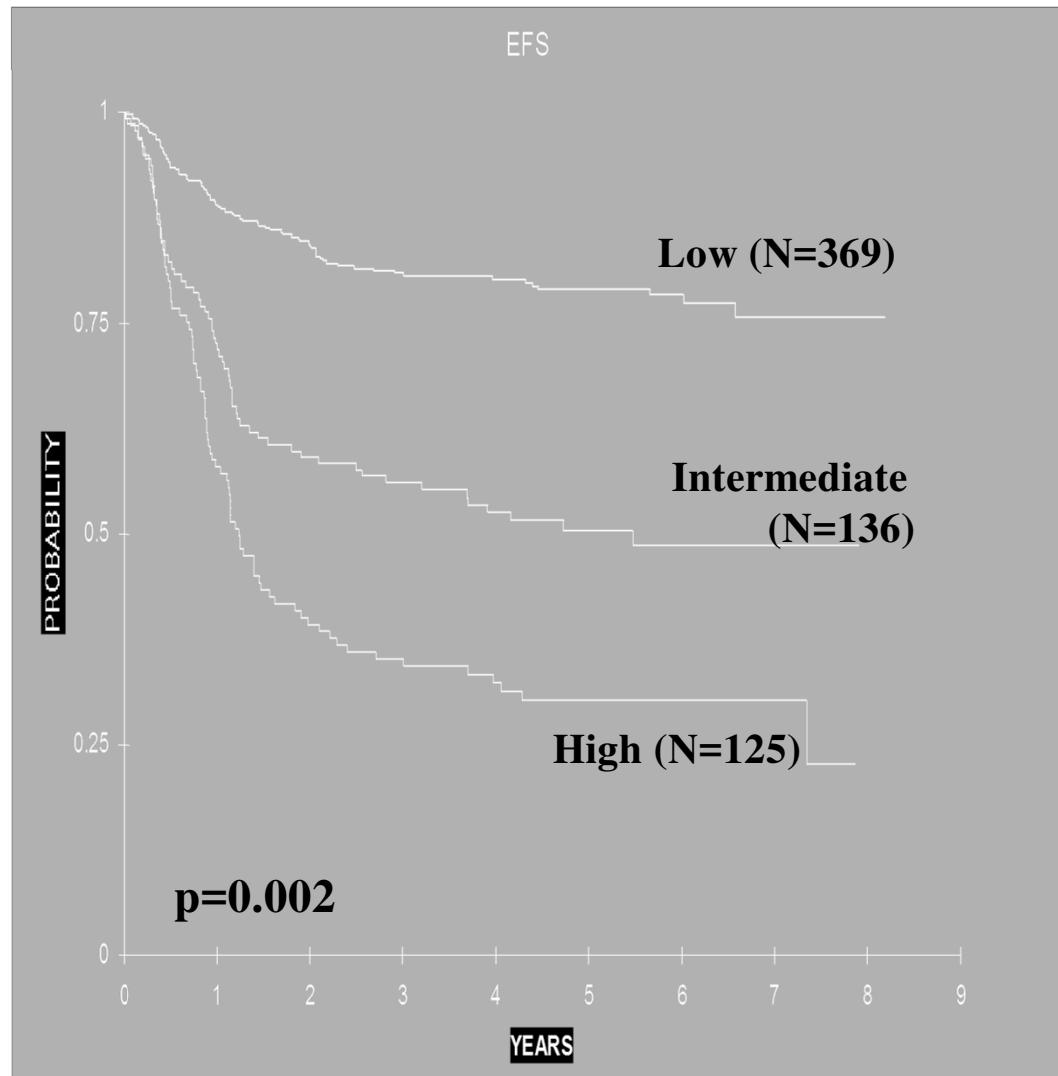
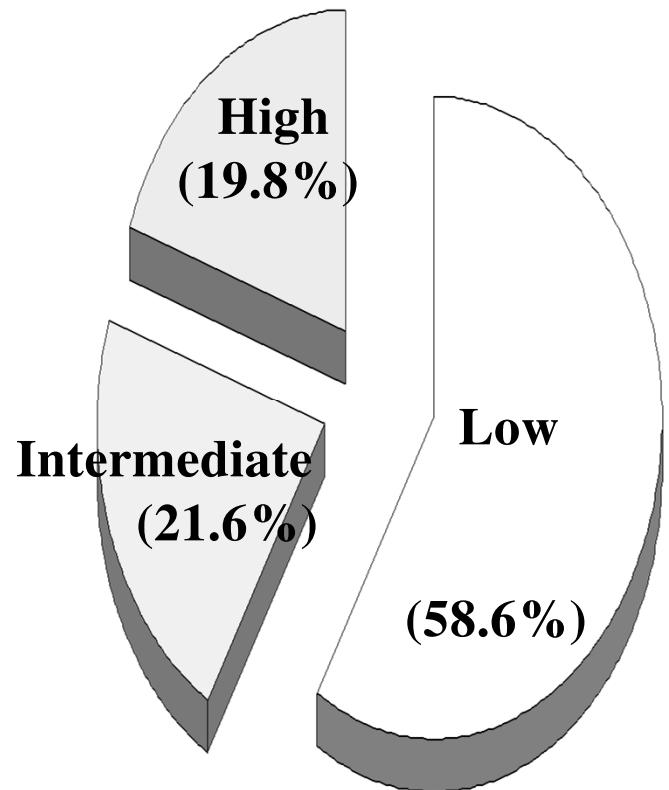
Determination of MKI

Sum of

- Mitosis: Cellular Proliferation
- Karyorrhexis: Cellular Death



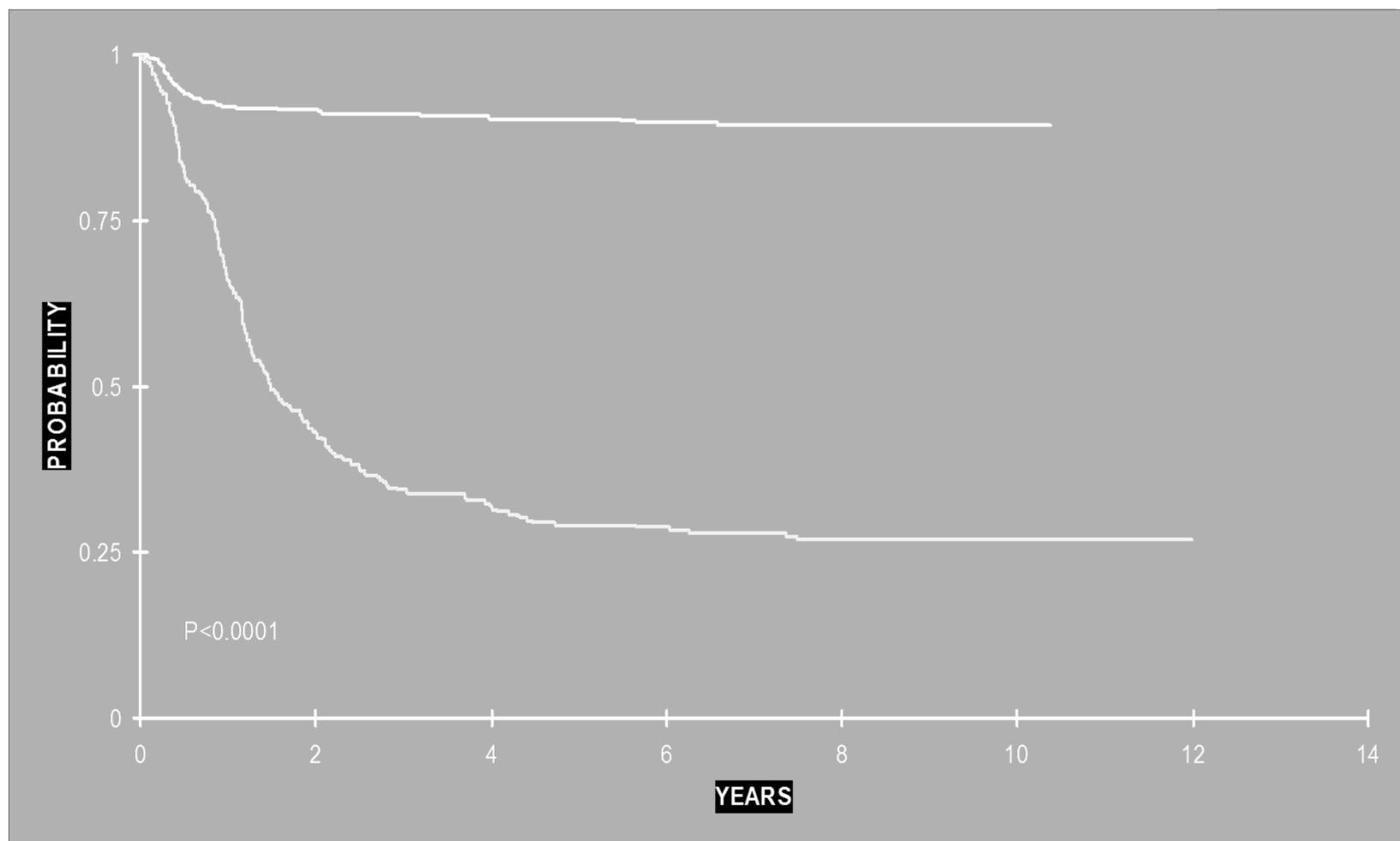
*Prognostic Effects
by MKI
in Neuroblastoma Tumors (CCG-3881/-3891 Study)*



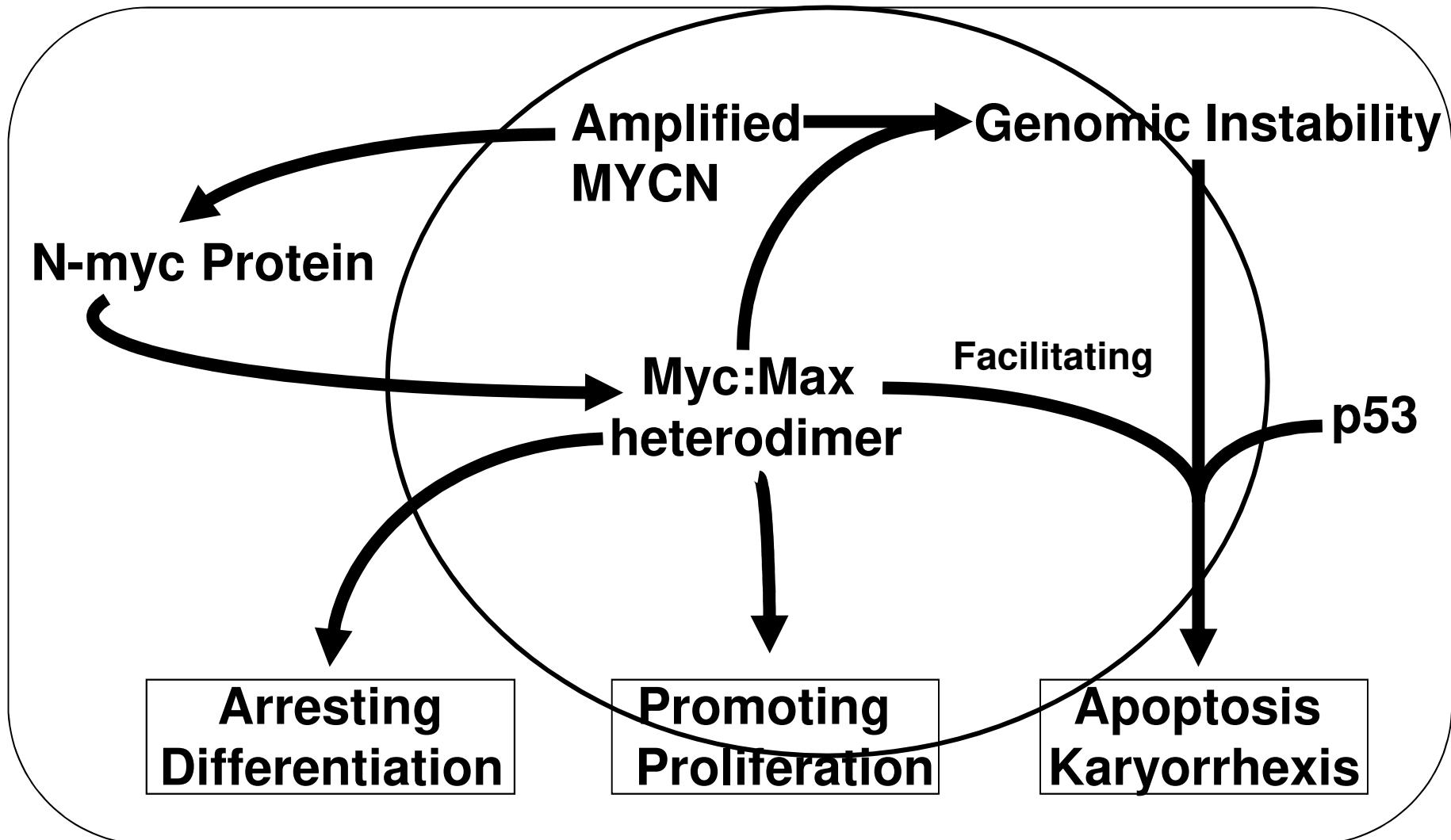
International Neuroblastoma Pathology Classification (Shimada System)

CCG -3881/-3891 Study

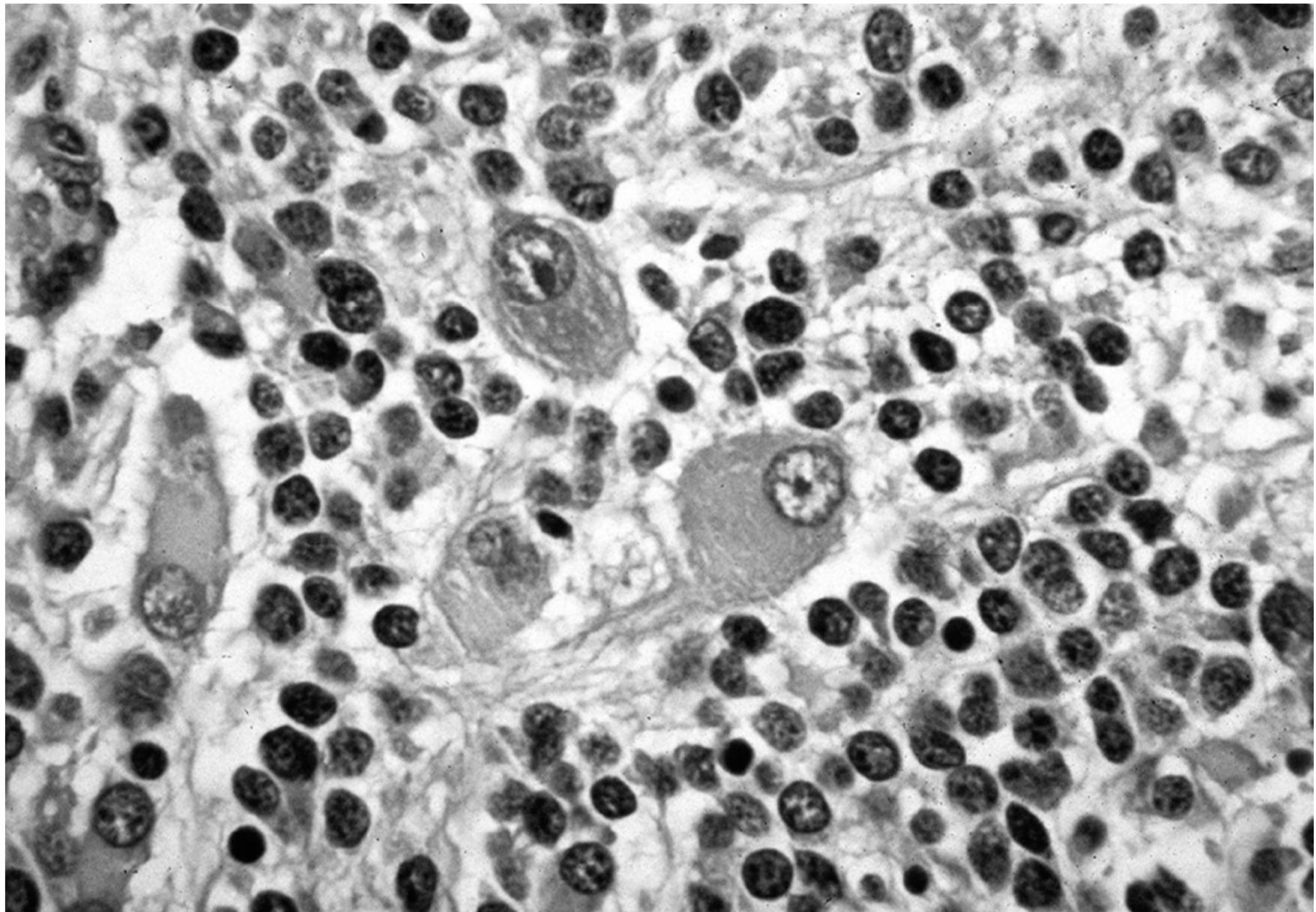
EFS



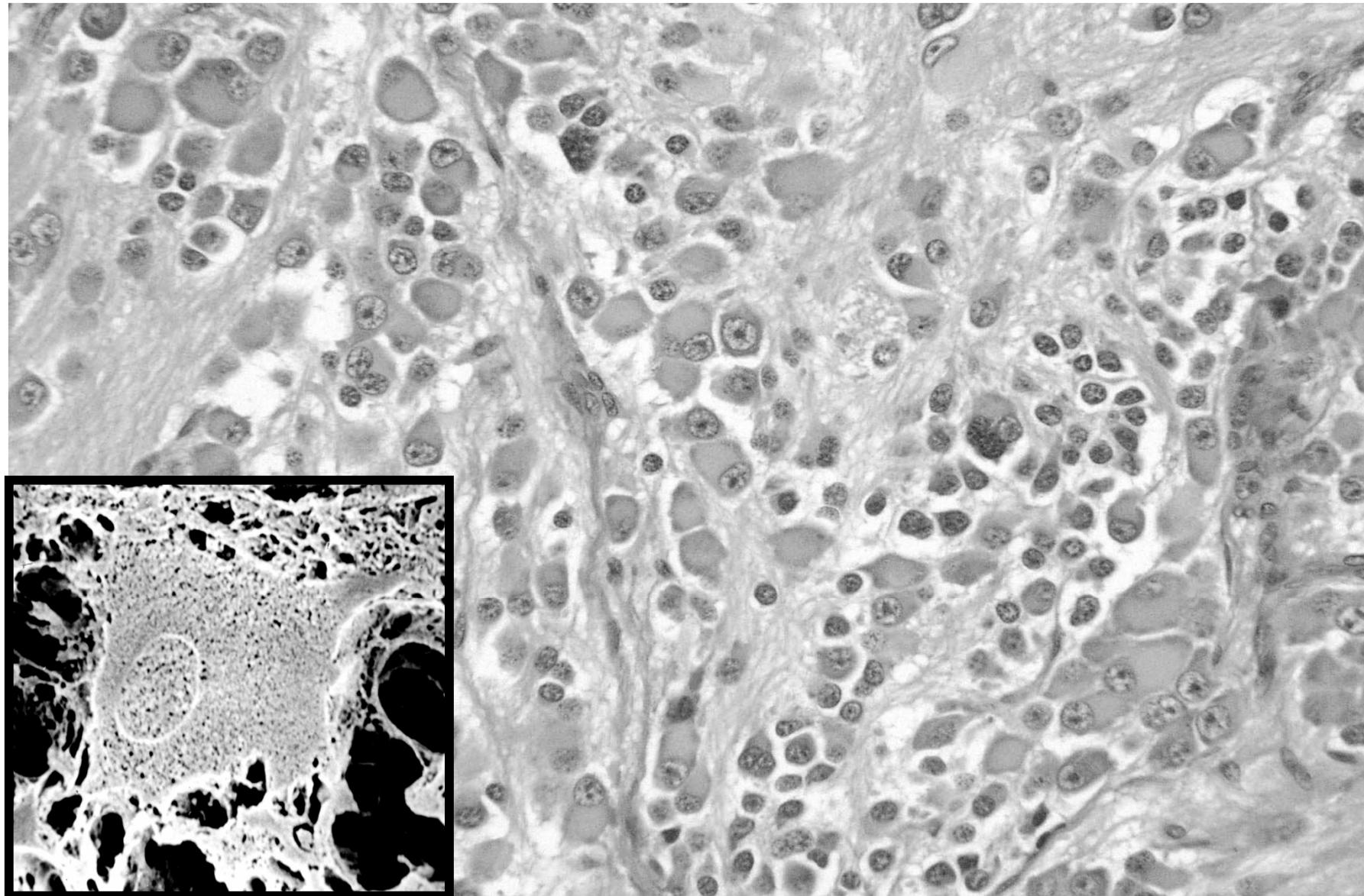
MYCN amplification in Neuroblastic Tumors



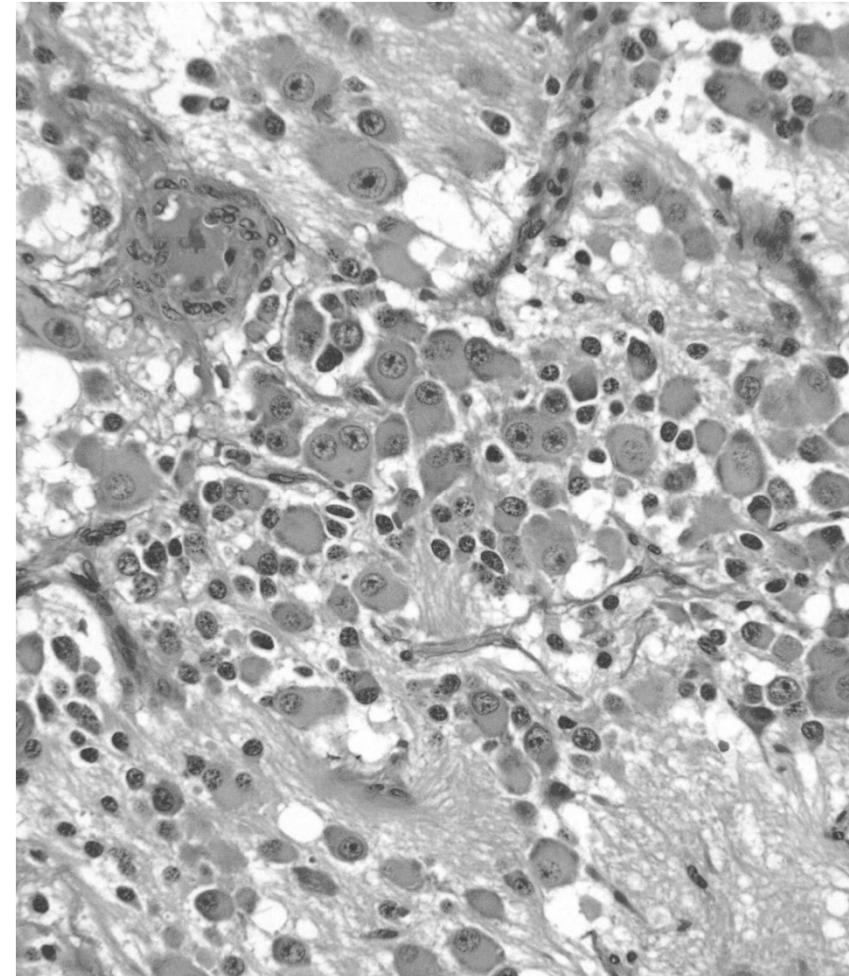
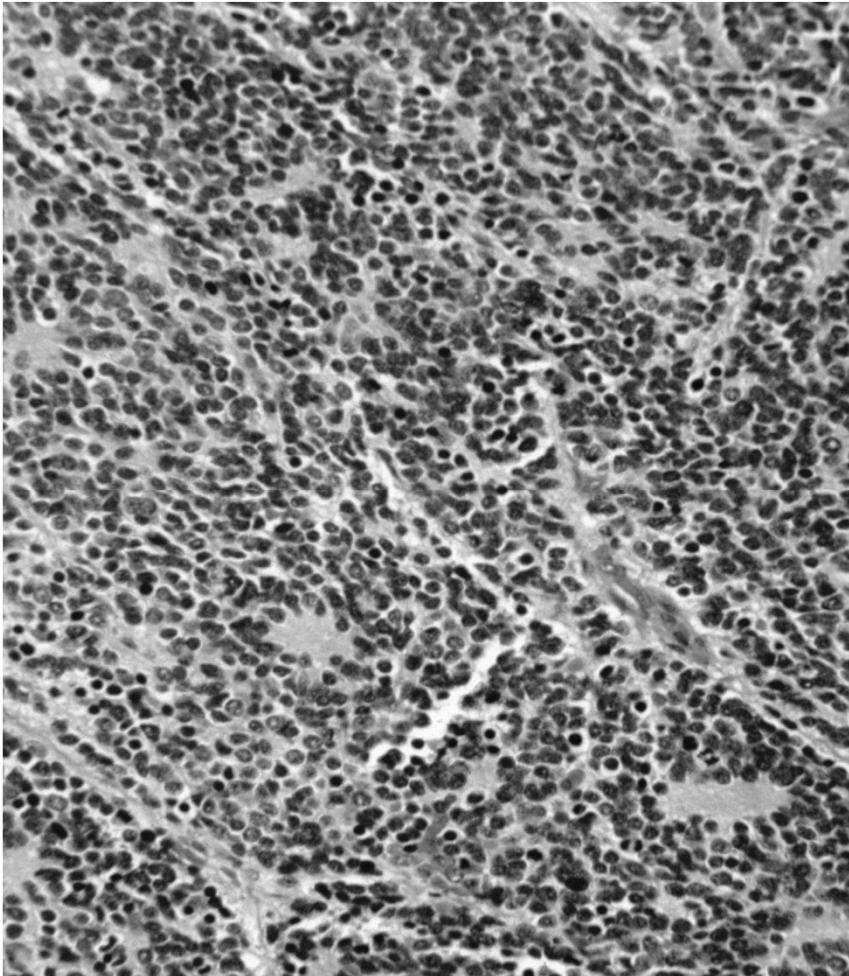
Differentiating Neuroblasts



Neuroblastoma (Schwannian stroma-poor) Differentiating Subtype

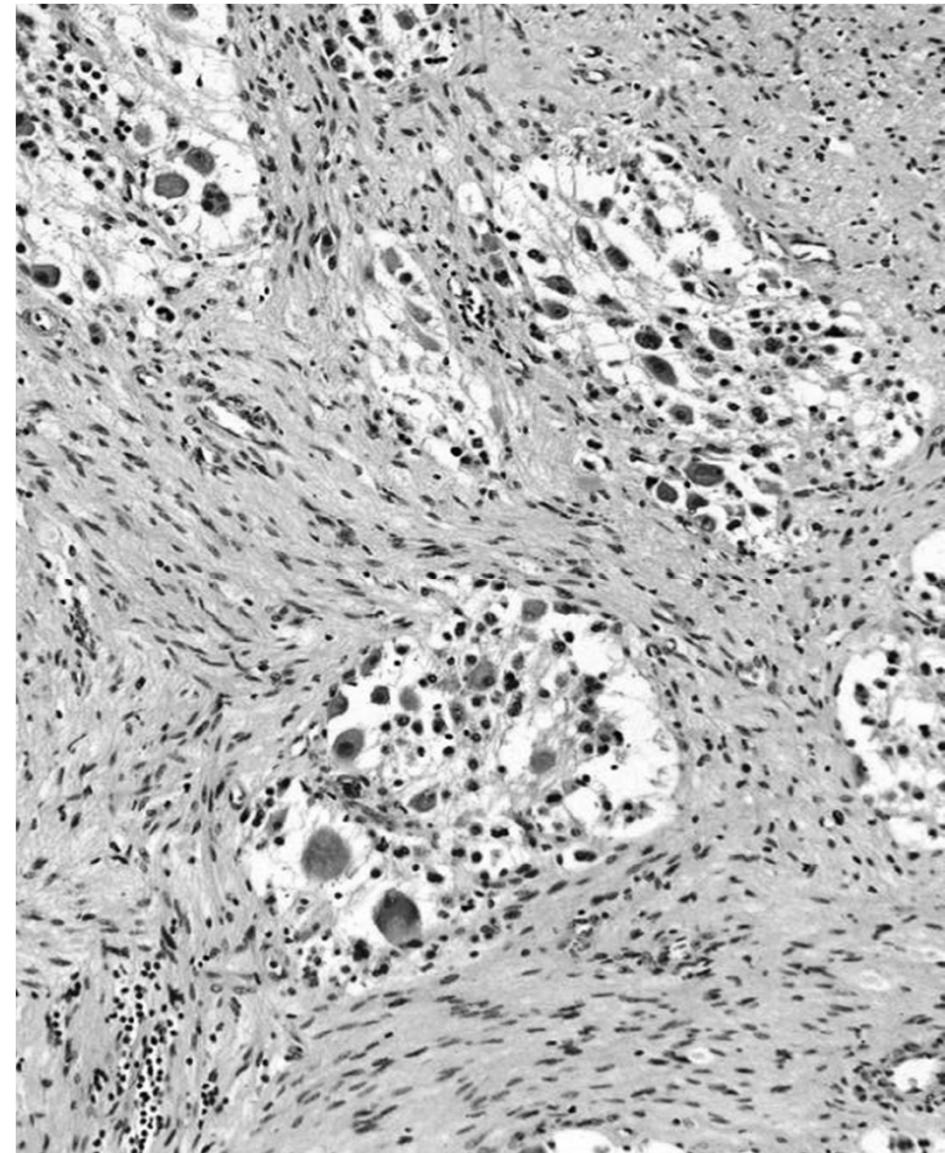
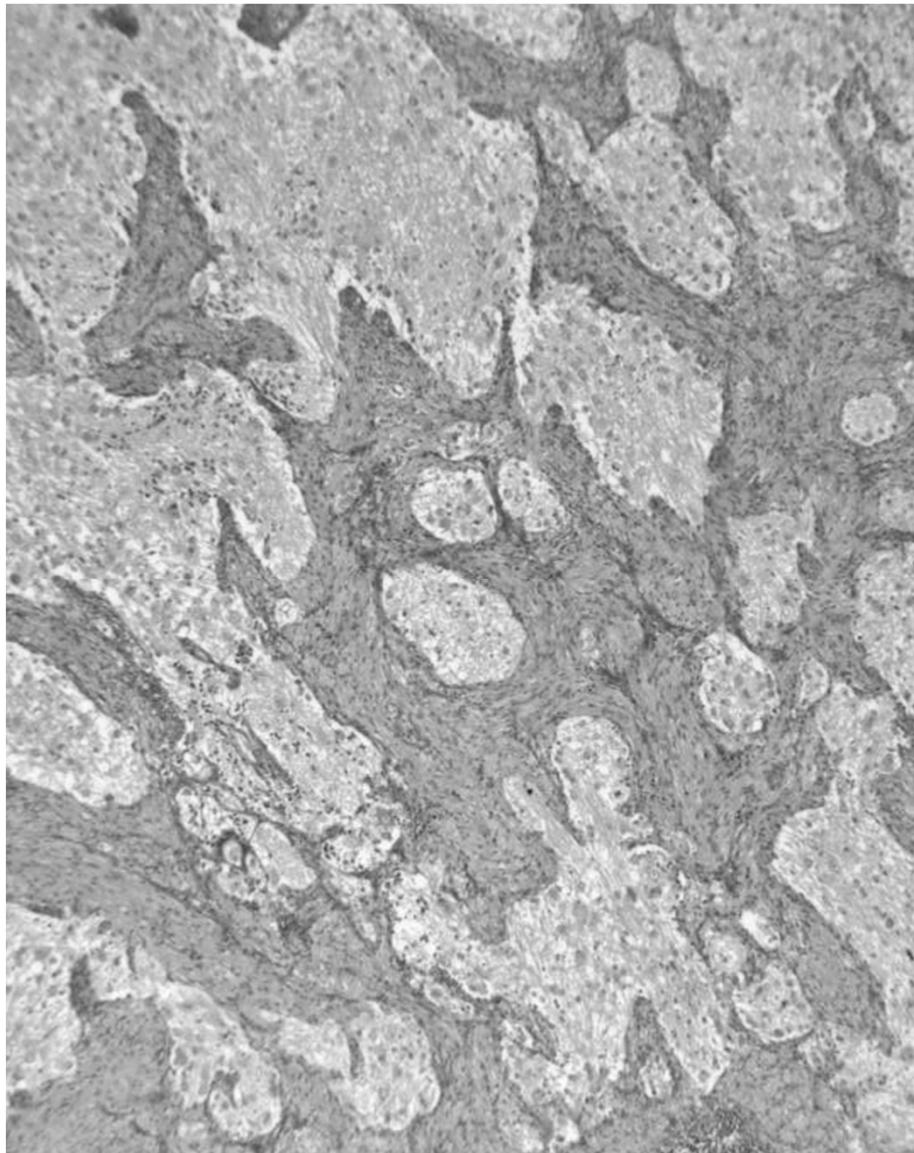


Poorly Diff. Subtype to Differentiating Subtype



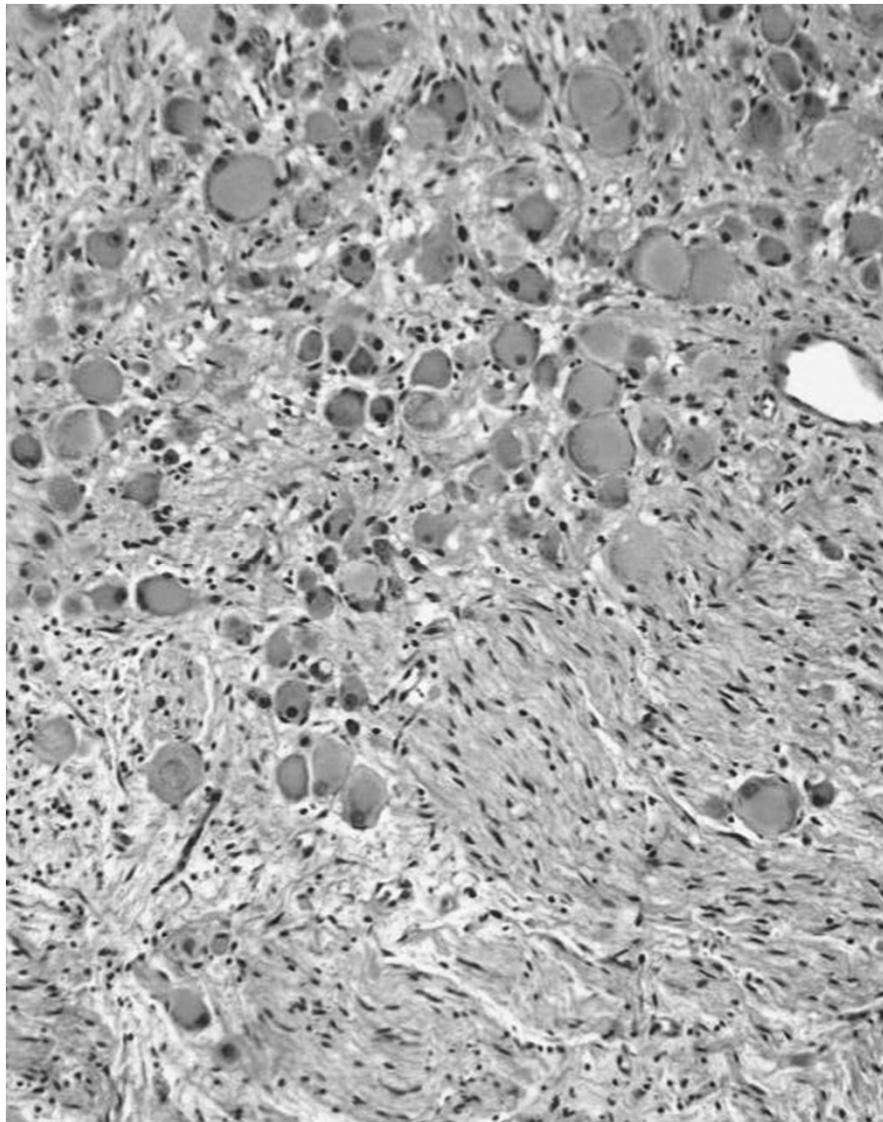
**Neuroblastische Differenzierung
Zelltod**

Ganglioneuroblastoma, Intermixed (Schwannian stroma-rich)

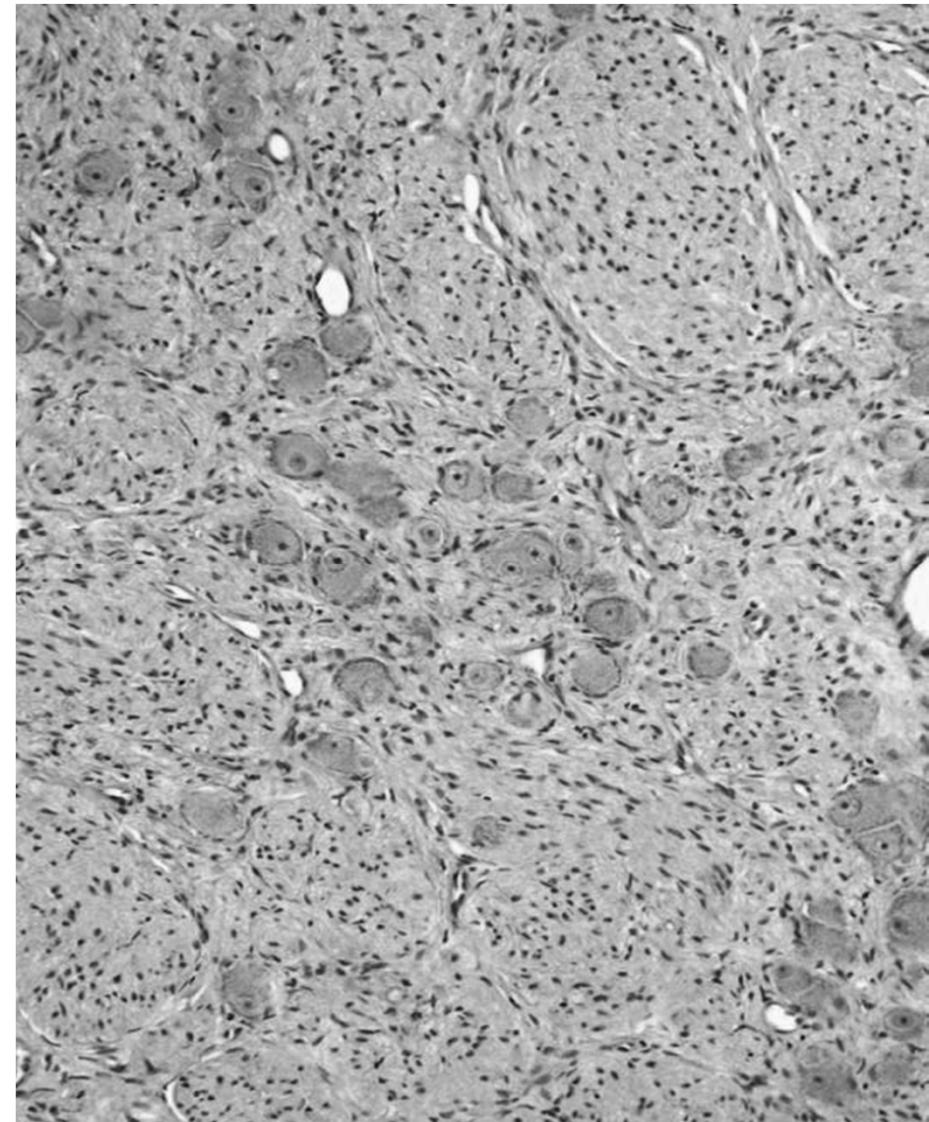


Ganglioneuroma (Schwannian stroma-dominant)

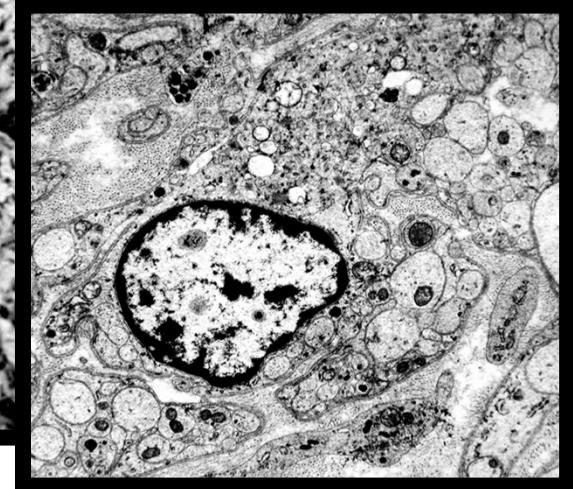
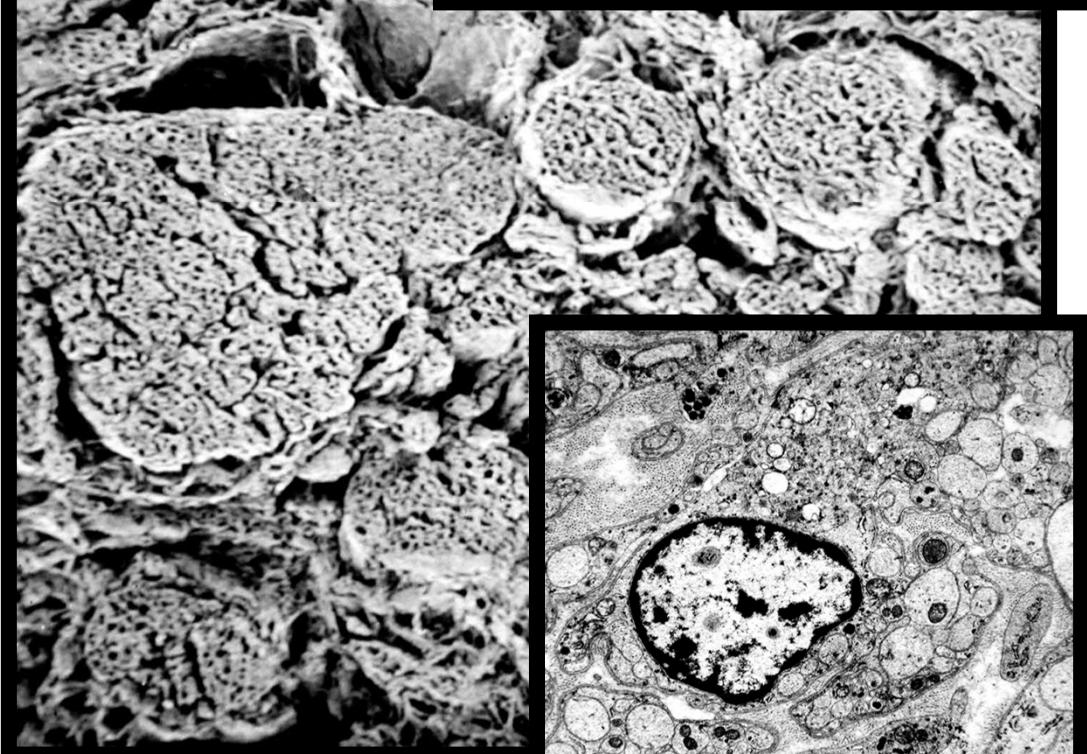
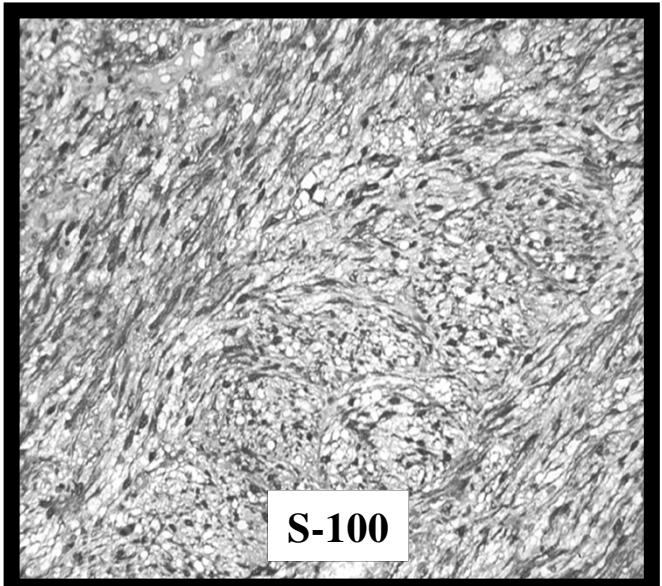
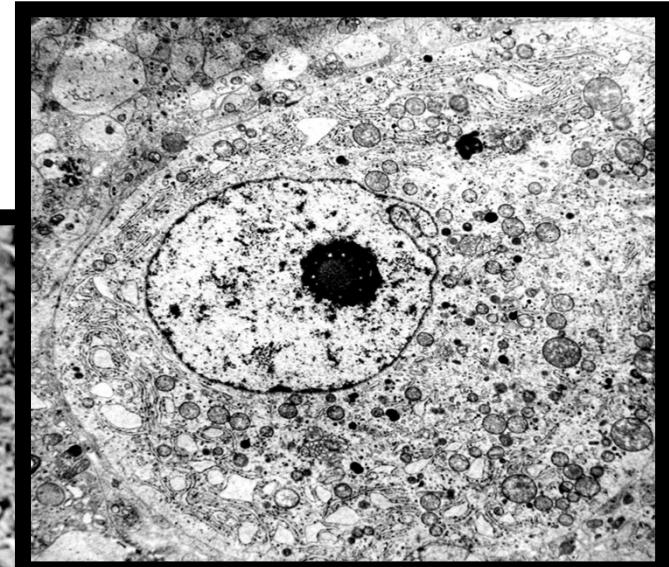
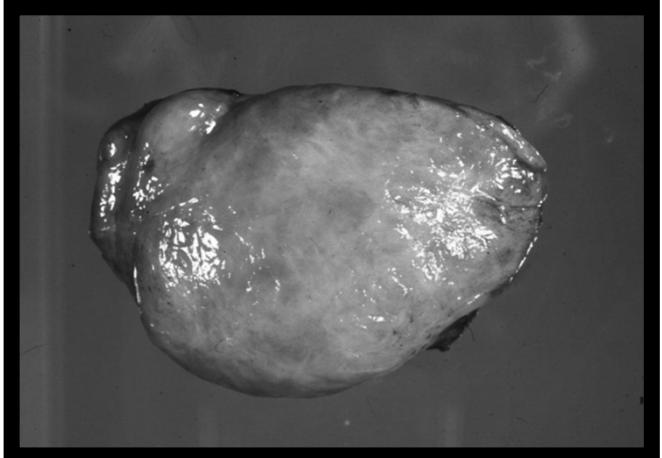
Maturing Subtype



Mature Subtype



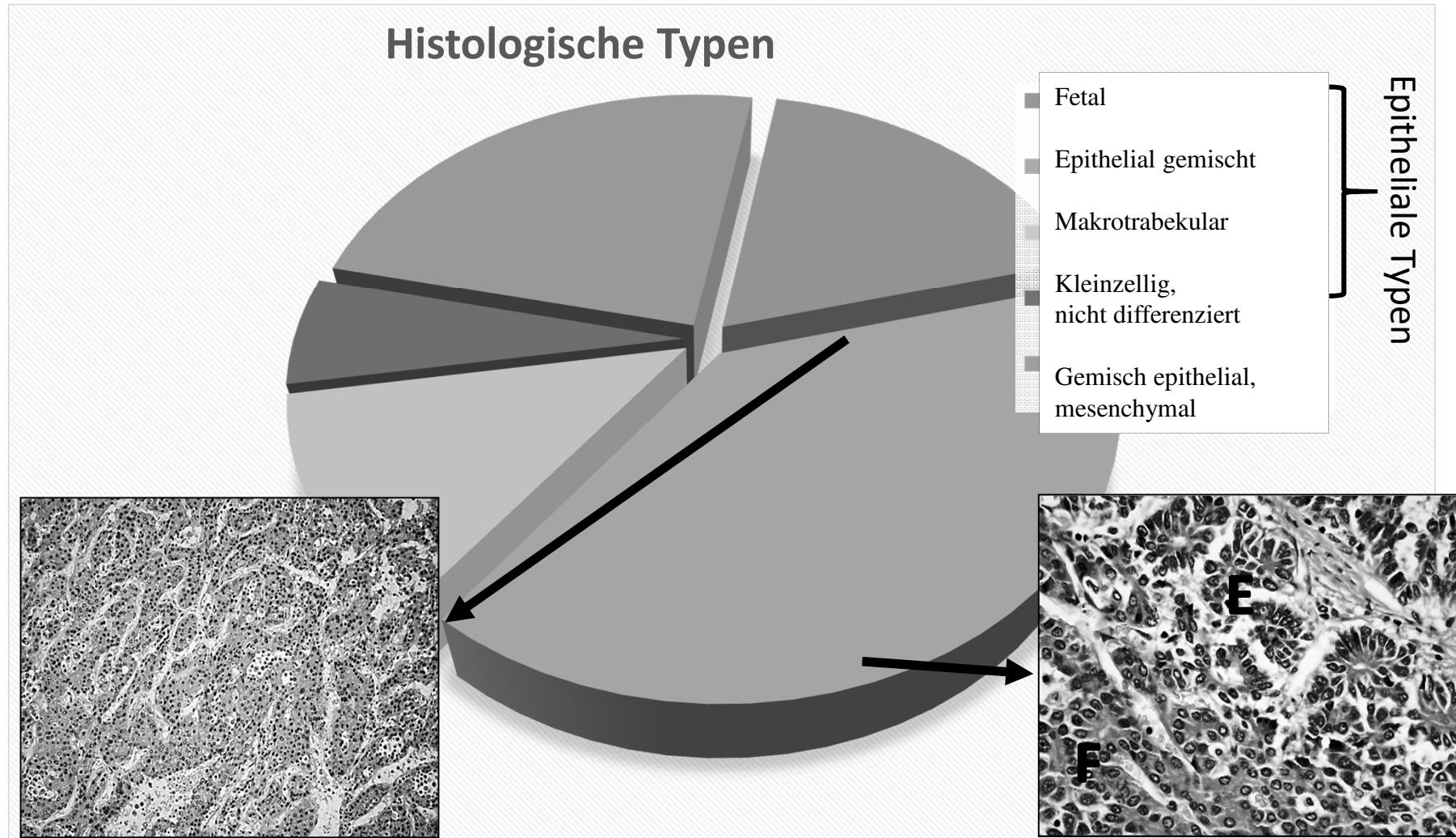
Ganglioneuroma



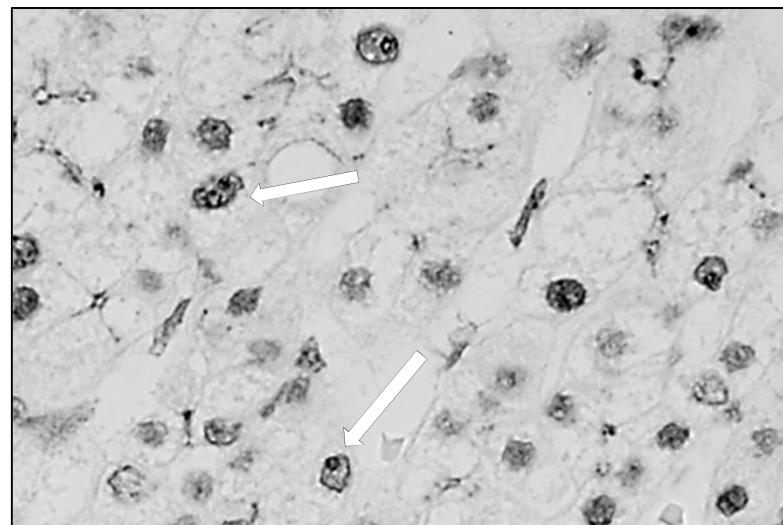
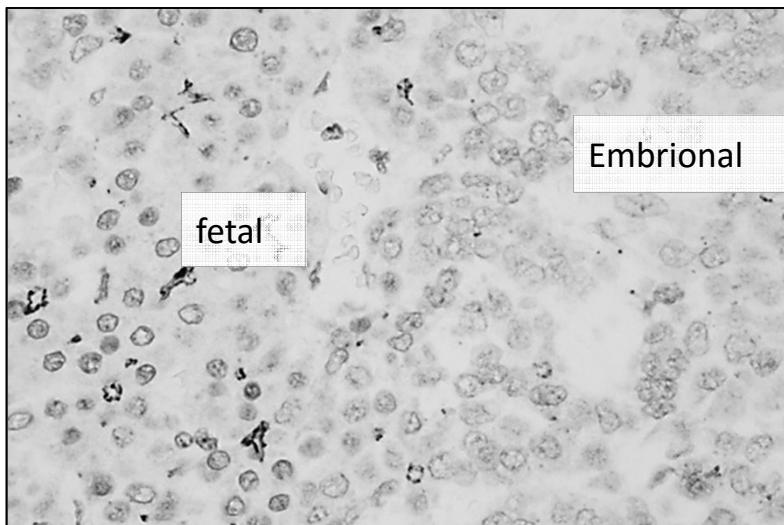
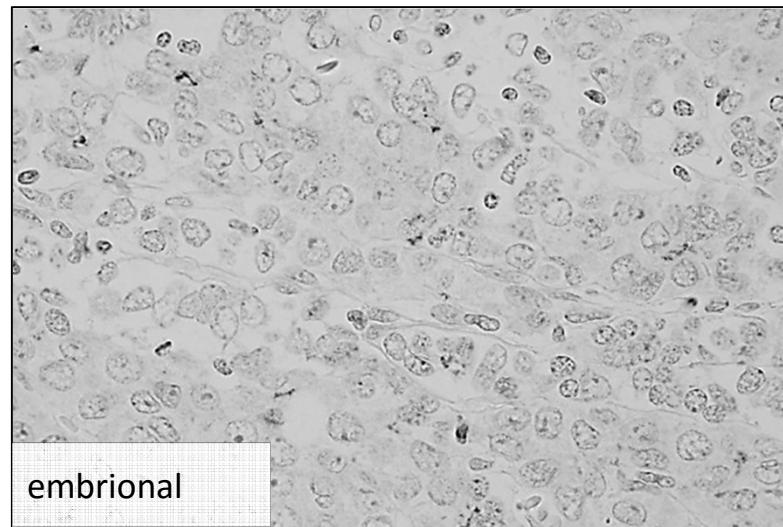
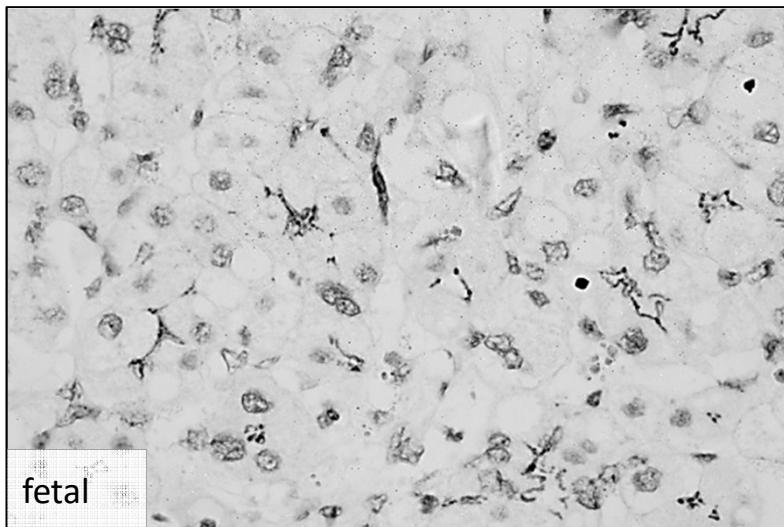
Hepatoblastom (HB)

- HB ist in 80% unifokal, abdominales Terime, Fieber, Gewichtsabnehmen, Appetitlosigkeit, pubertas precox
- Normochrome, normocytare Anemie, Thrombozytoses¹
- Tumormarker: AFP (< 100 ng/ml: schlechte Prognose), delta-like protein -1²
- 5 Jahre Überleben ist über 70% ³
- Differenzierung der epithelialen Komponenten ist wichtig für Überleben (fetal/embrional)

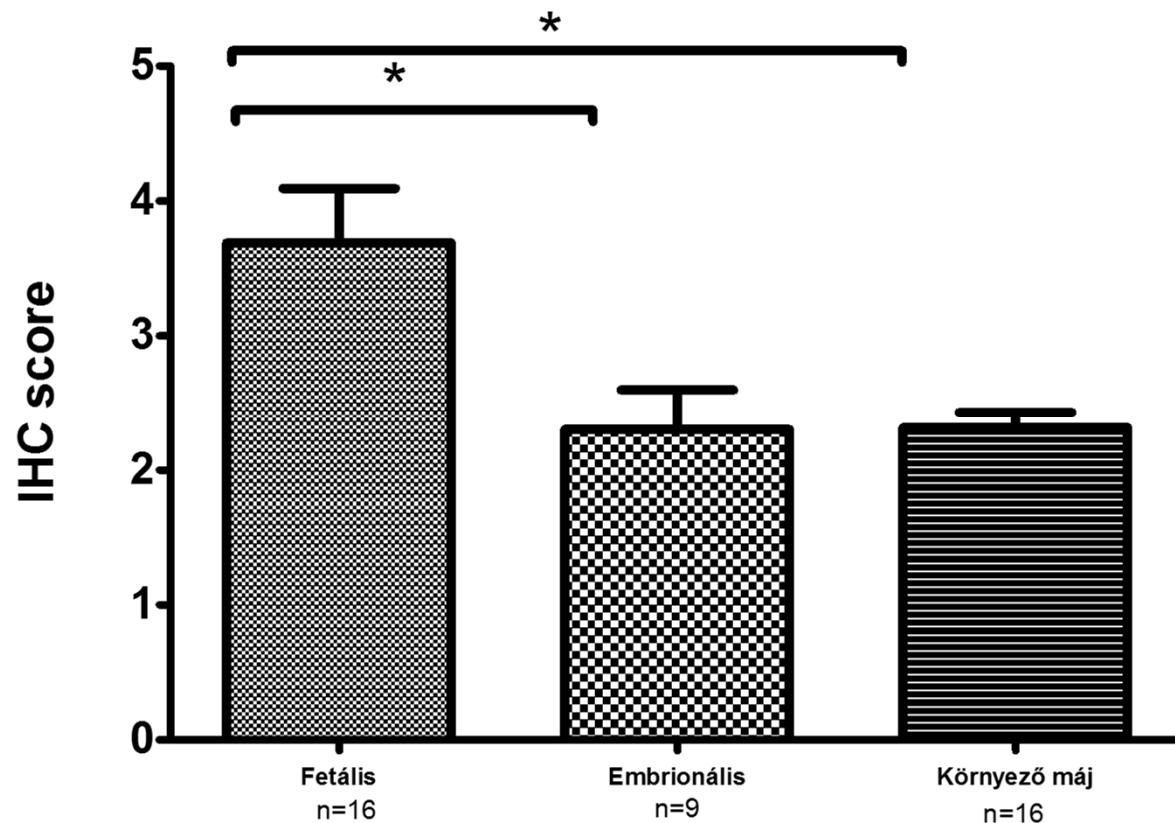
Hepatoblastom (HB)



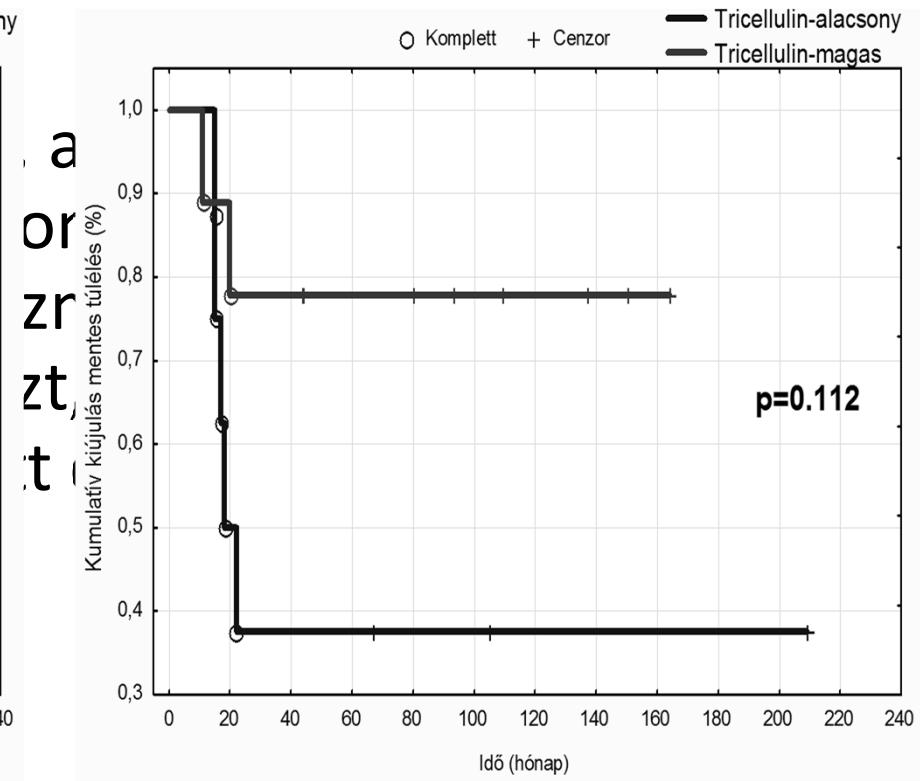
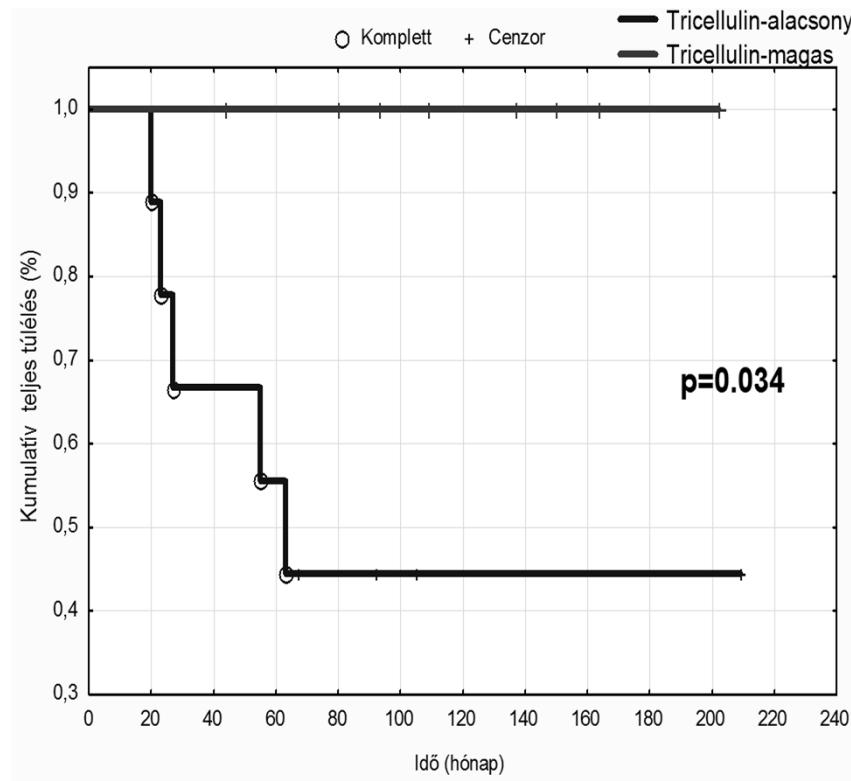
Tricellulin expression in HB

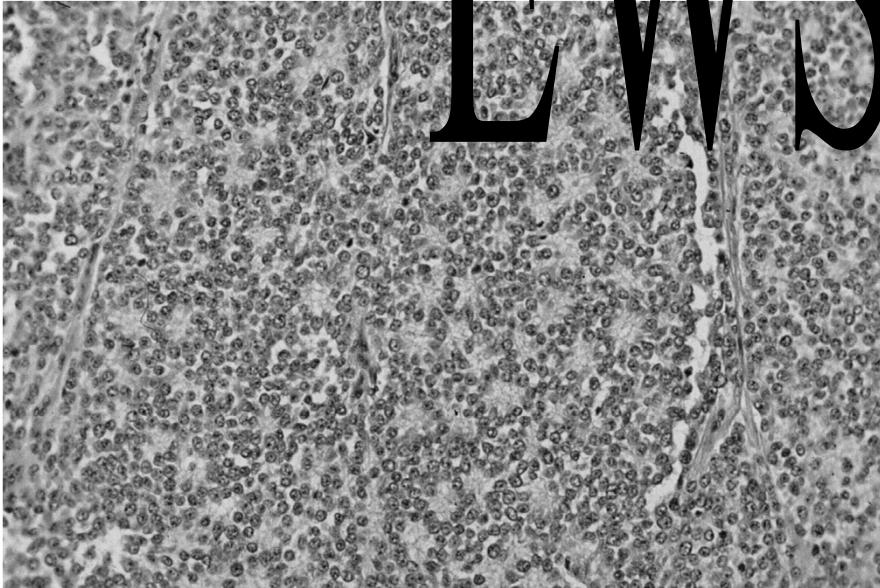


Tricellulin expression in HB

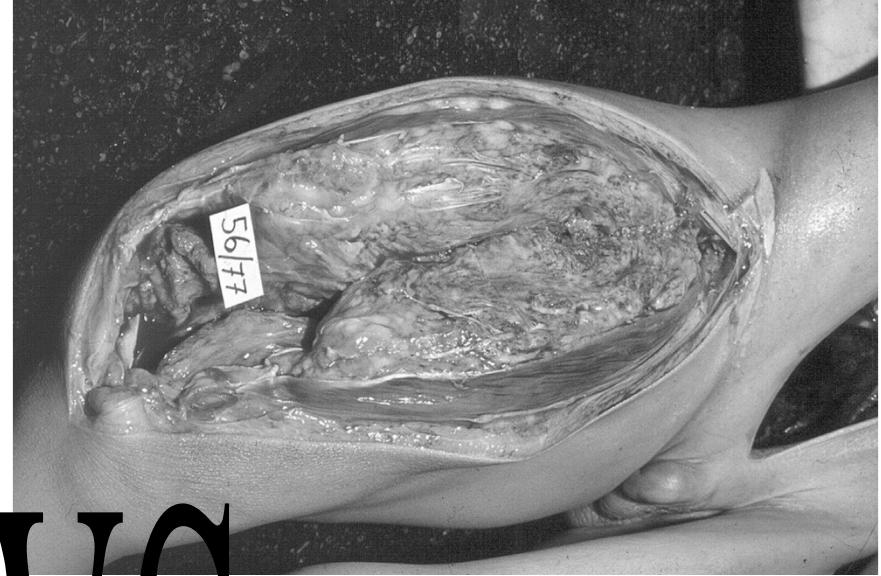


Tricellulin und Überleben





EWS



Ewing Sarcom

EWING SARKOM-PNET

Genetische Markers

tumor-specifisches neues Transkription Faktor (ETS)

- chr22q12EWS-chr11q24FLI-1 EWSFLI-1
- chr22q12EWS-chr21ERG EWSERG
- chr22q12EWS-chr7ETV1 EWSETV-1
- chr22q12EWS-chr17E1AF EWSE1AF

Funktion

- TGFBRII inhib. (Tumorsuppressor Gen)
- IGFRI inhib. (Apoptose)
- PLC inhib. (Signal modulator)

Marker: MIC2/CD99 (T Zell-CAM)

Schlechte Prognose

- p16/INK4A Mutation/Deletion
- p53 Mutation

ZNS-PNET GENETIK

E-kadherin Signal (WNT)
APC Mutation
β-katenin Mutation
(IHC: nukleares Katenin)

EGF Signal Transduktionsweg
ERBB4 -JMdel

IGF-I Signal Transduktionsweg
IGF-IR Amplifikation
(IHC: IGFR+)

EWING SARKOM/PNET

M/W Rate = 3/1

Lokalization:

- Femur
- Pelvis

Genetik:

- Tr 11/22
- EWS chr22q12, CD99/MIC2, p30/32
- Fusionsprotein: FL1-EWS

Morphologie:

- SRCT fibrillares Stroma
- Granulares Zytoplasma
- Glassy Kerne
- Mitose +/-

Merkmale:

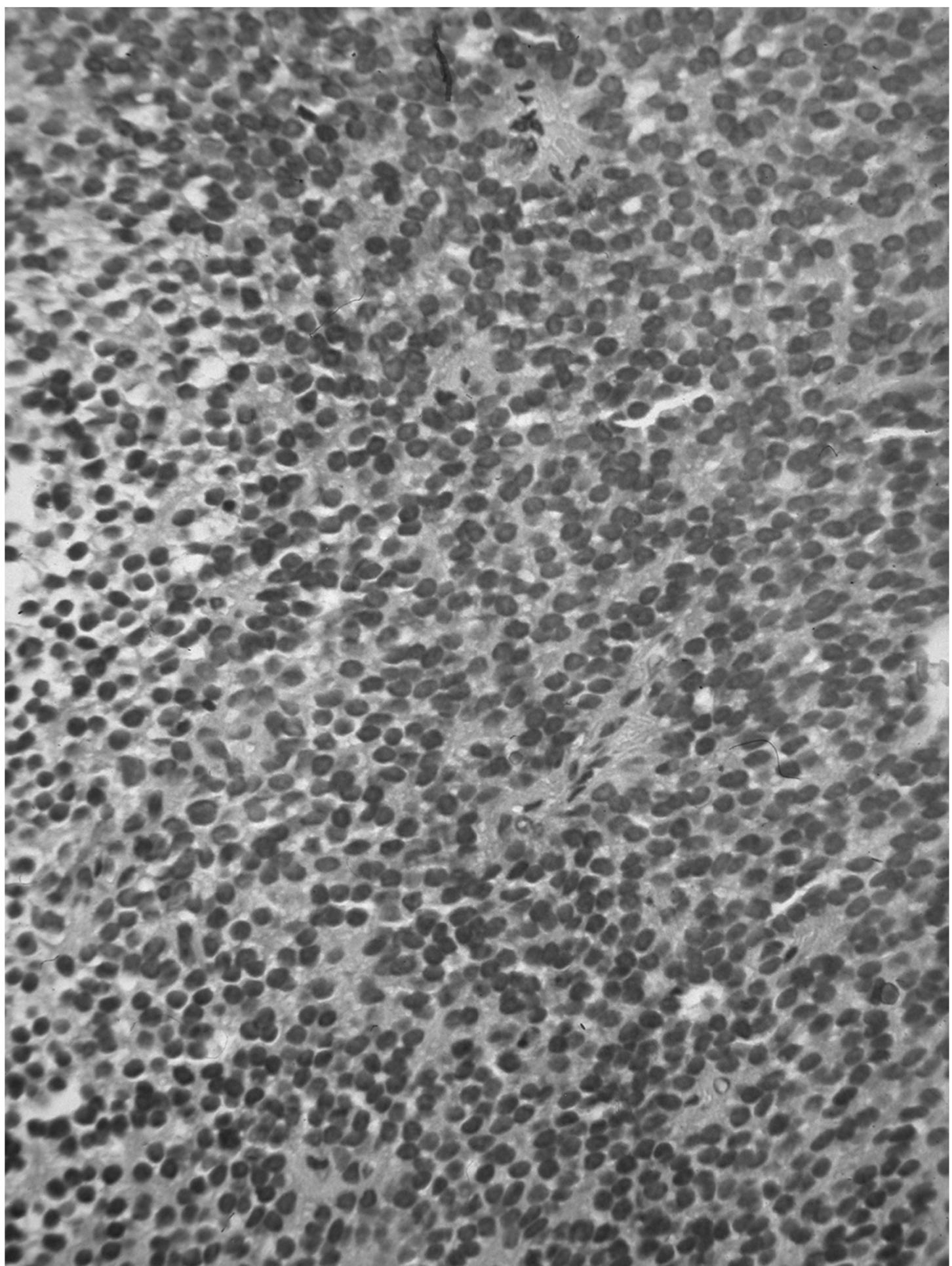
- Glykogen
- TEM: Lysosom, Desmosoma-like
- Neurogenische Merke

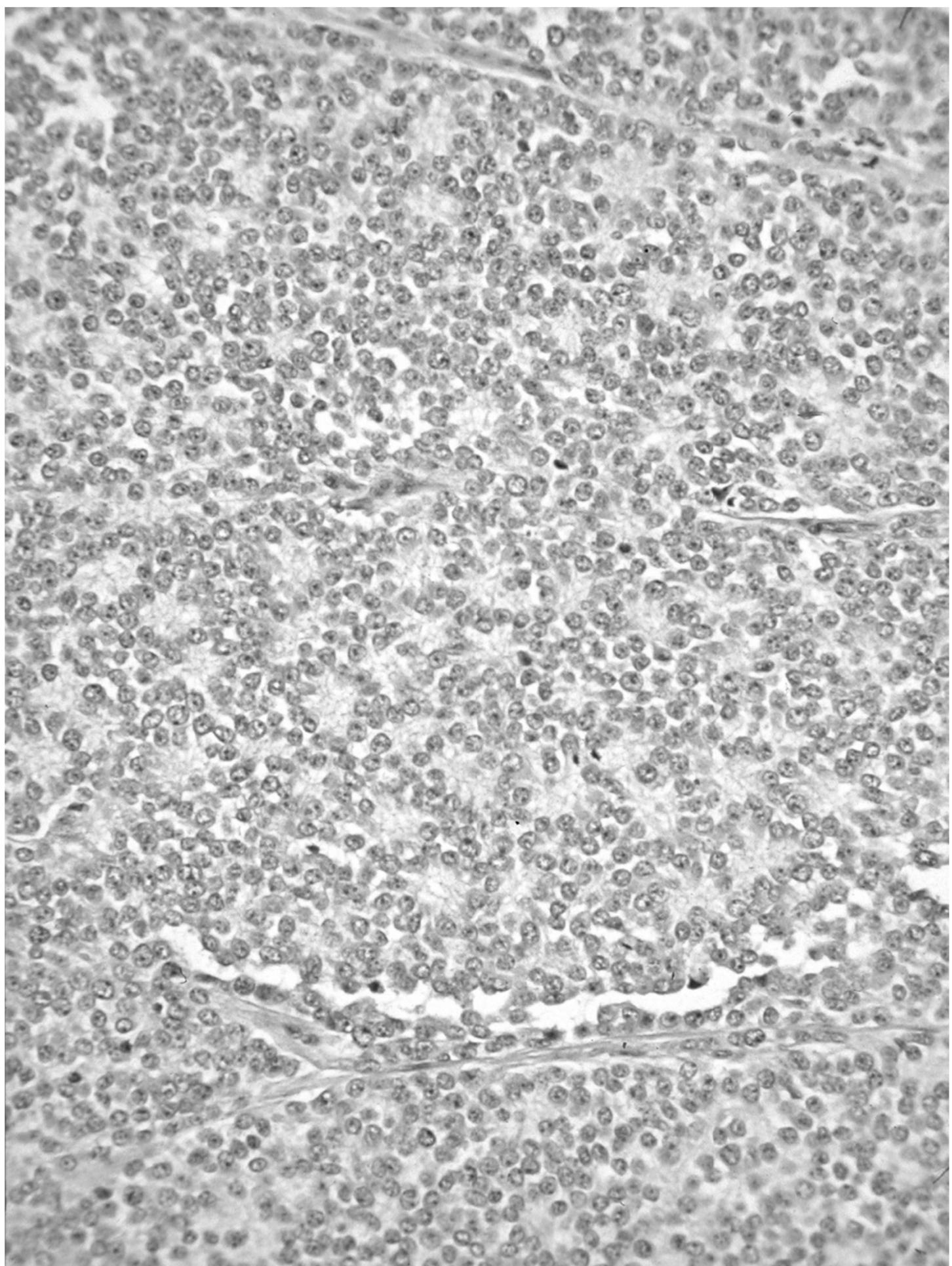
Schicksal:

- Staging --- schlecht
- Metastasen (Lunge, Knochenmark)

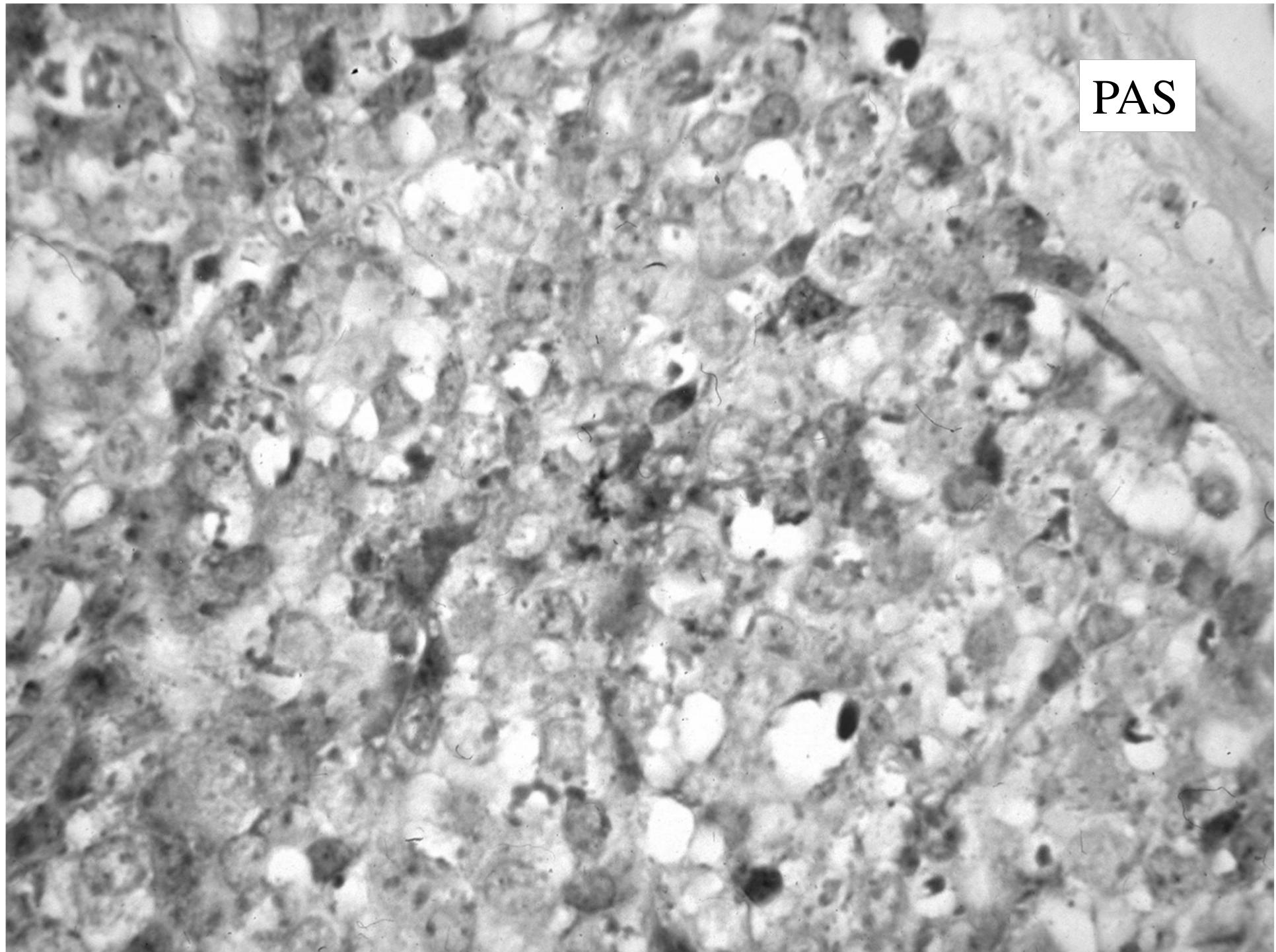
Prognose:

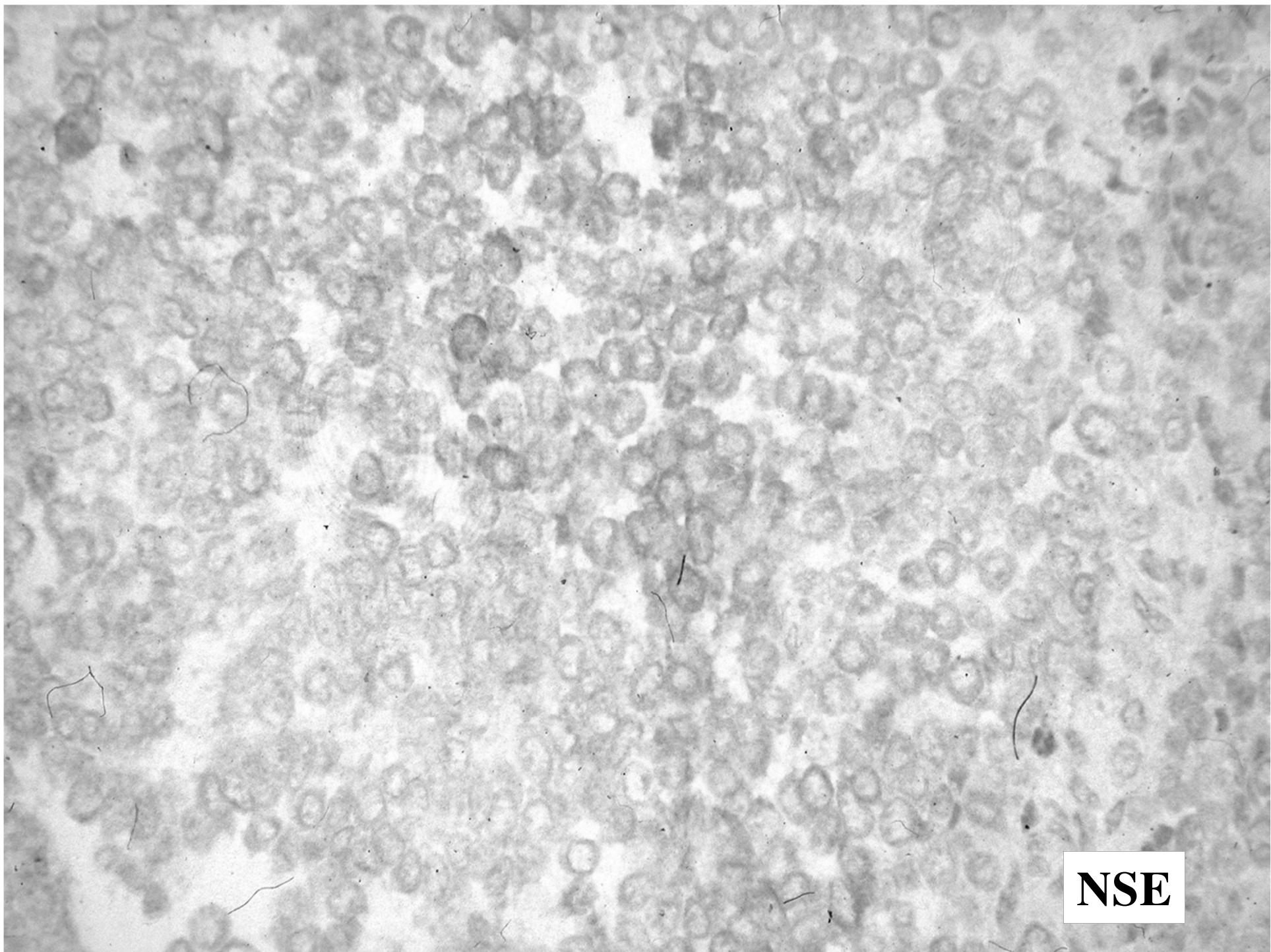
- Primär Tumor gut lokalisiert
- T Stage
- Metastasen (LND, viszeral)
- Soft tissue (Weichteil) Infiltration
- LDL hoch (schlecht)





PAS





NSE

EWING SARKOM-PNET

Familie

- **Klassisches Ewing Sarkom (osseal)**
- **Extraosseales Ewing Sarkom**
- **Askin Tumor (thoracopulmonares PNET)**
- **Esthesioneuroblastom**

EWING SARKOM

DIFFERENTIAL-DIAGNOSE

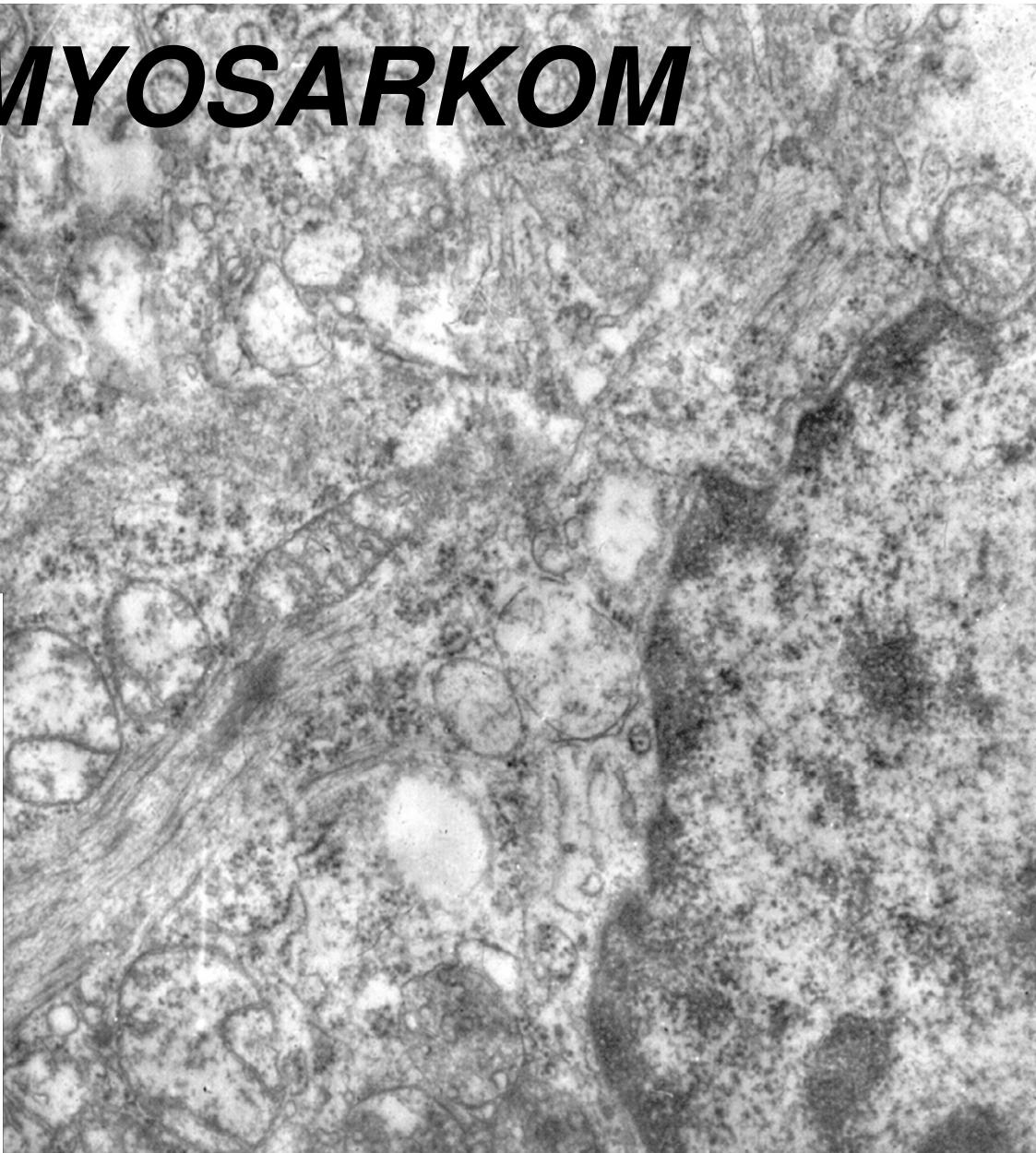
	vim	CD99	B2M	MB2	CD57	syn
EWS	+	+	-	-	-	-
PNET	+	+	±	+	+	+
NBL	-	-	+	+	+	+

Desmoplastischer „small round cell „, Tumor (peritoneales Serosa- derived primitiver Tumor)

- Molekulares Marker: chr11p13-chr22q12 Translokation
 - Marker-gen: EWS-WT1 Fusionen
- Folge: WT1-regulierte Gendefekten

RHABDOMYOSARKOM

- embriональные
 - botryoid
- alveolares
- pleiomorphes



RHABDOMYOSARKOM

Alter: 4 Jahre

Assoziiert mit:

Li-Fraumeni Sy (p53 Mutation)
Neurofibromatose I.

Genetik:

MyoD1, chr11p15, Transkription
Faktor,
Aktivierung (Mutation)
(alveolar/embryonal)
Alveolar
tr 2-13, tr 2-8, 2-5
chr2q15 PAX3 Gen
chr13q14FKHR Gen
FUSION PROTEIN +

Del RB1

p53 Mutation

h-ras Amplifikation

c-myc Amplifikation

Lokalization:

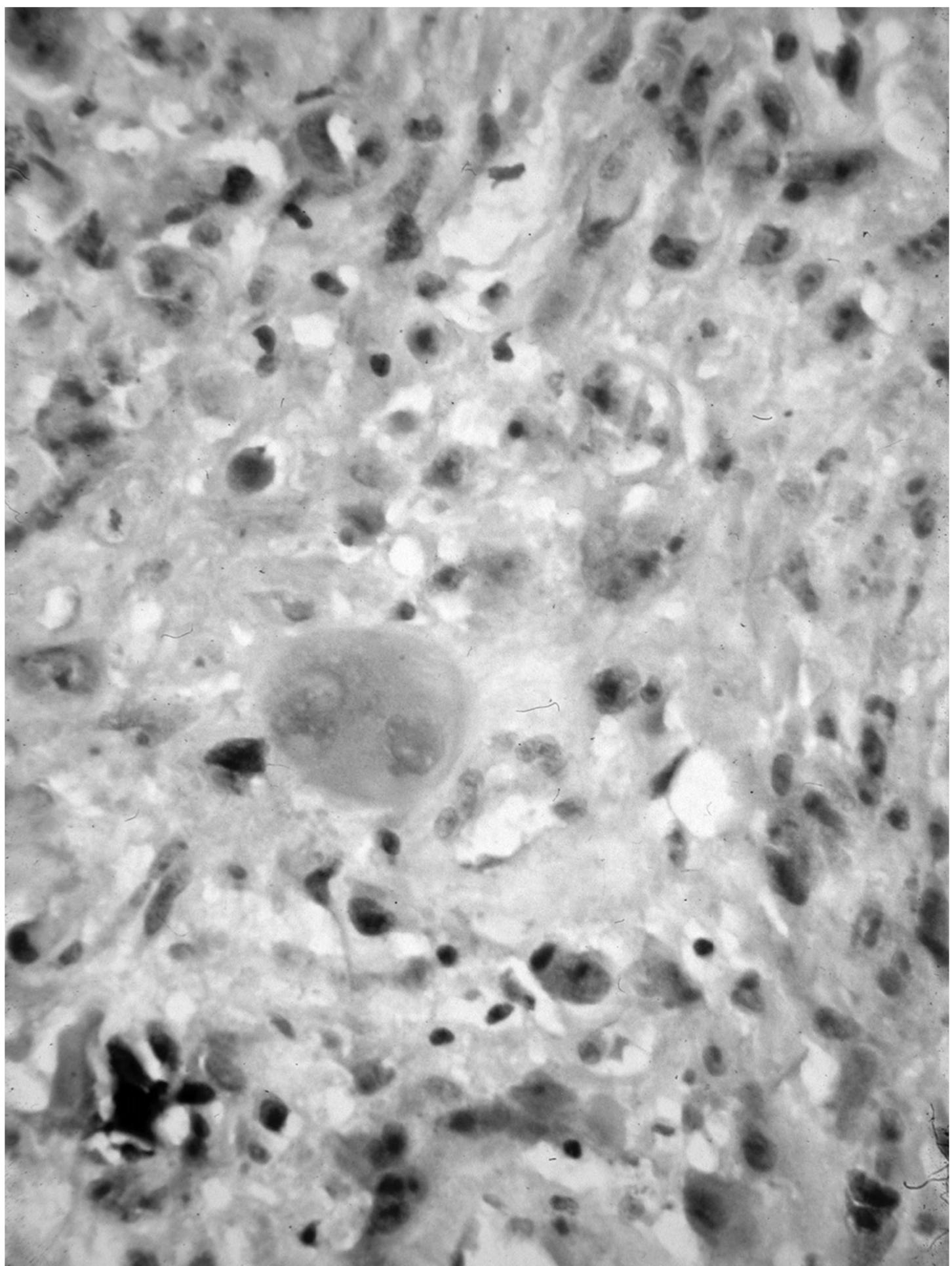
- Kopf/Hals (meningeal, parameningeal, infratemporal, Ohren, Nase)
- abdominal
- Körper, Extremitäten

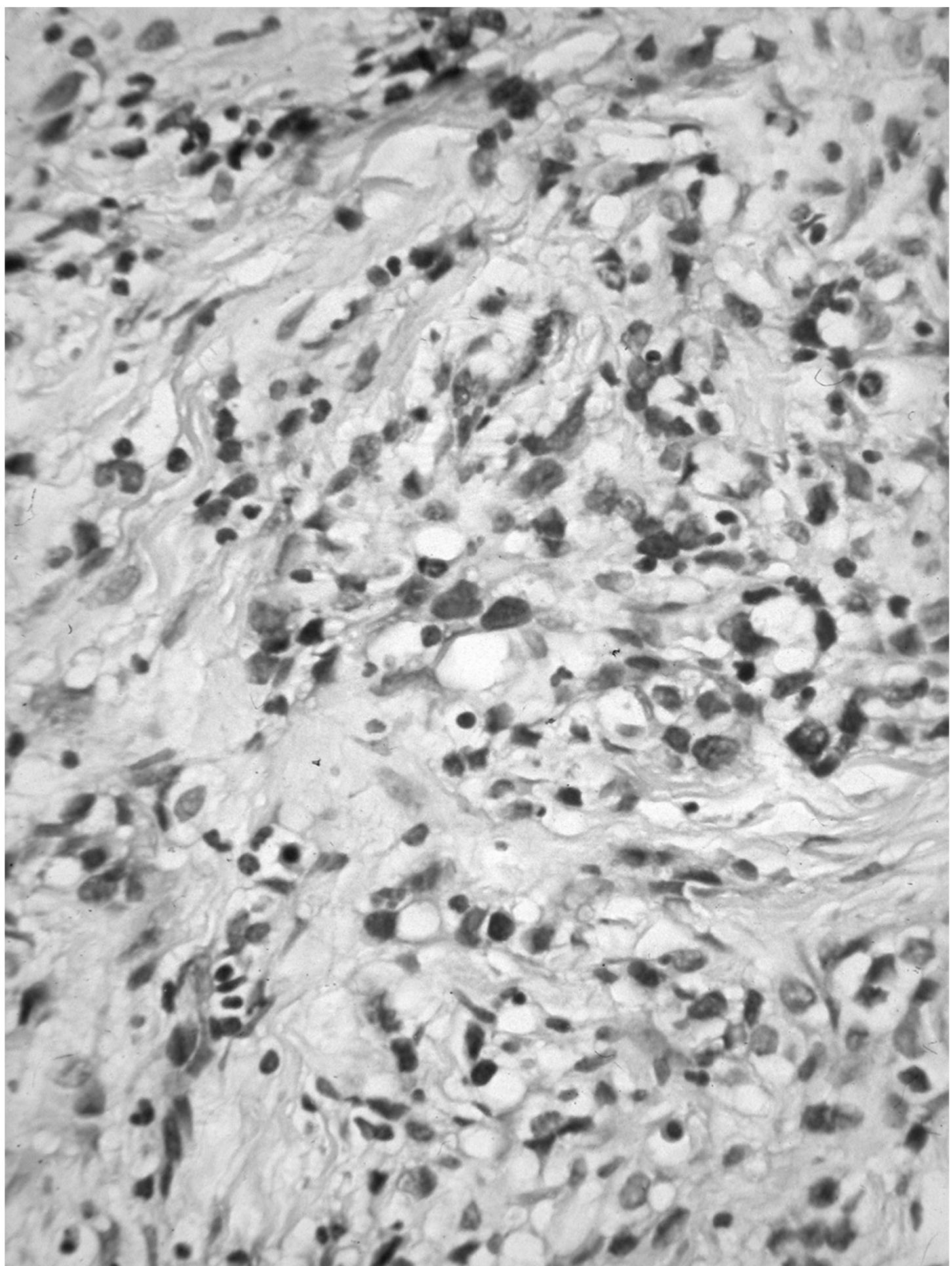
Morphologie:

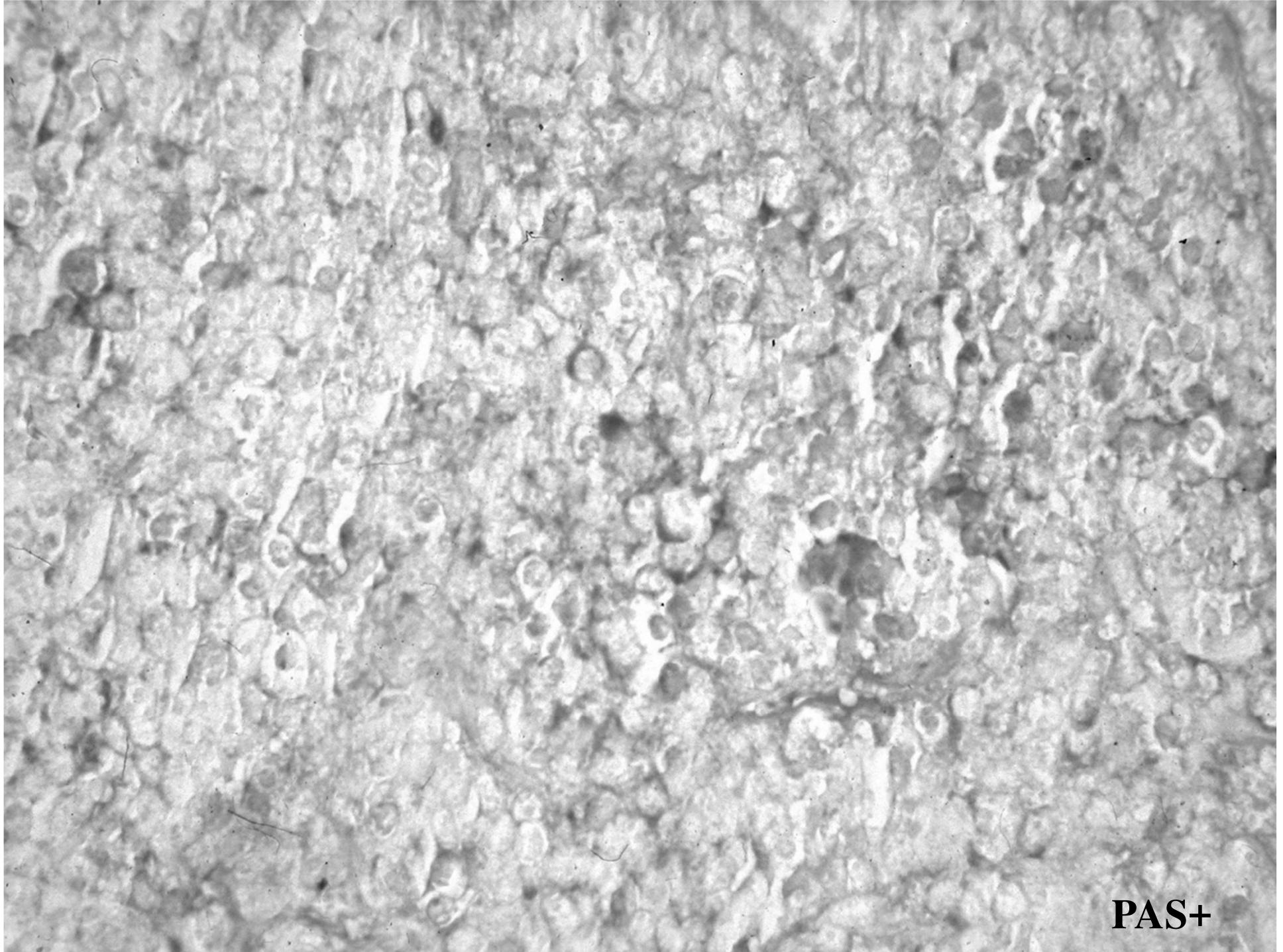
- Embryonales
 - Botrioid
- Alveolares
- Spindle-zellig
- Undiff. Rund-zellig
- Rhabdoid (differenziert)

Markers:

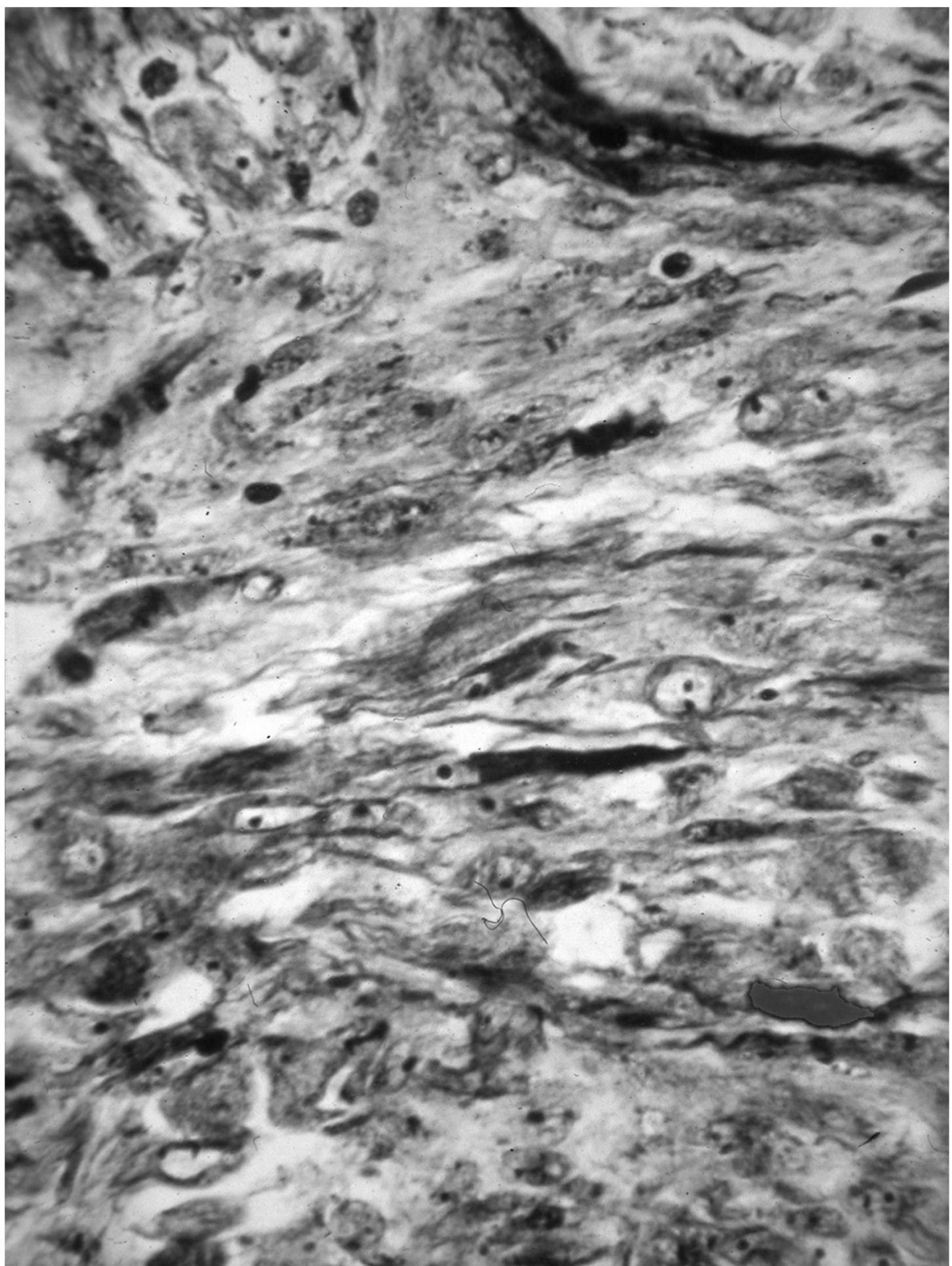
- Vimentin, lmwCK, coll-IV, Lam, N-CAM
- Desmin- MHC, sarkomeric Aktin
- **Troponin – embryonales**
- **MyoD1 – alveolares, embryonales**
- Dystrophin

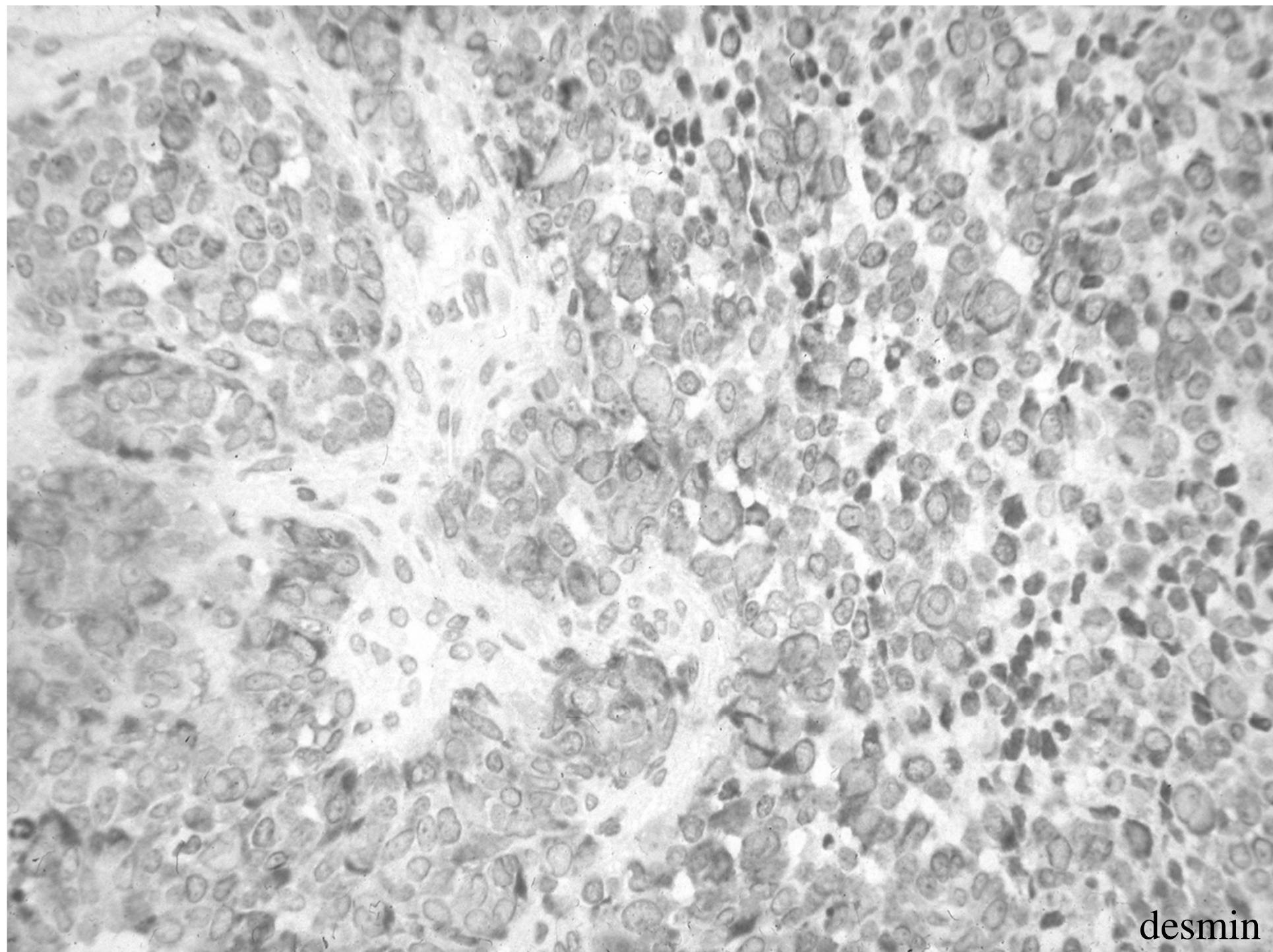




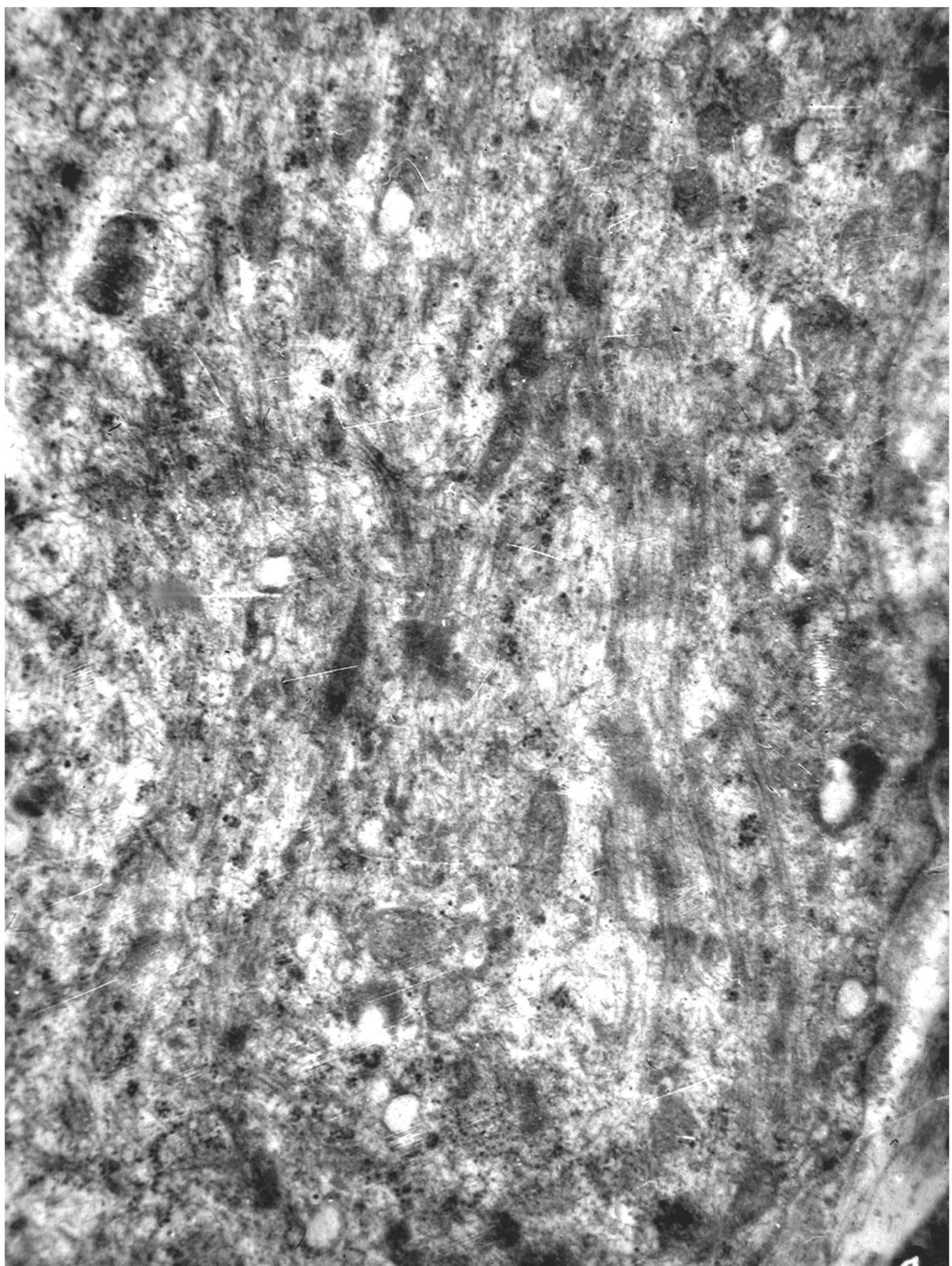


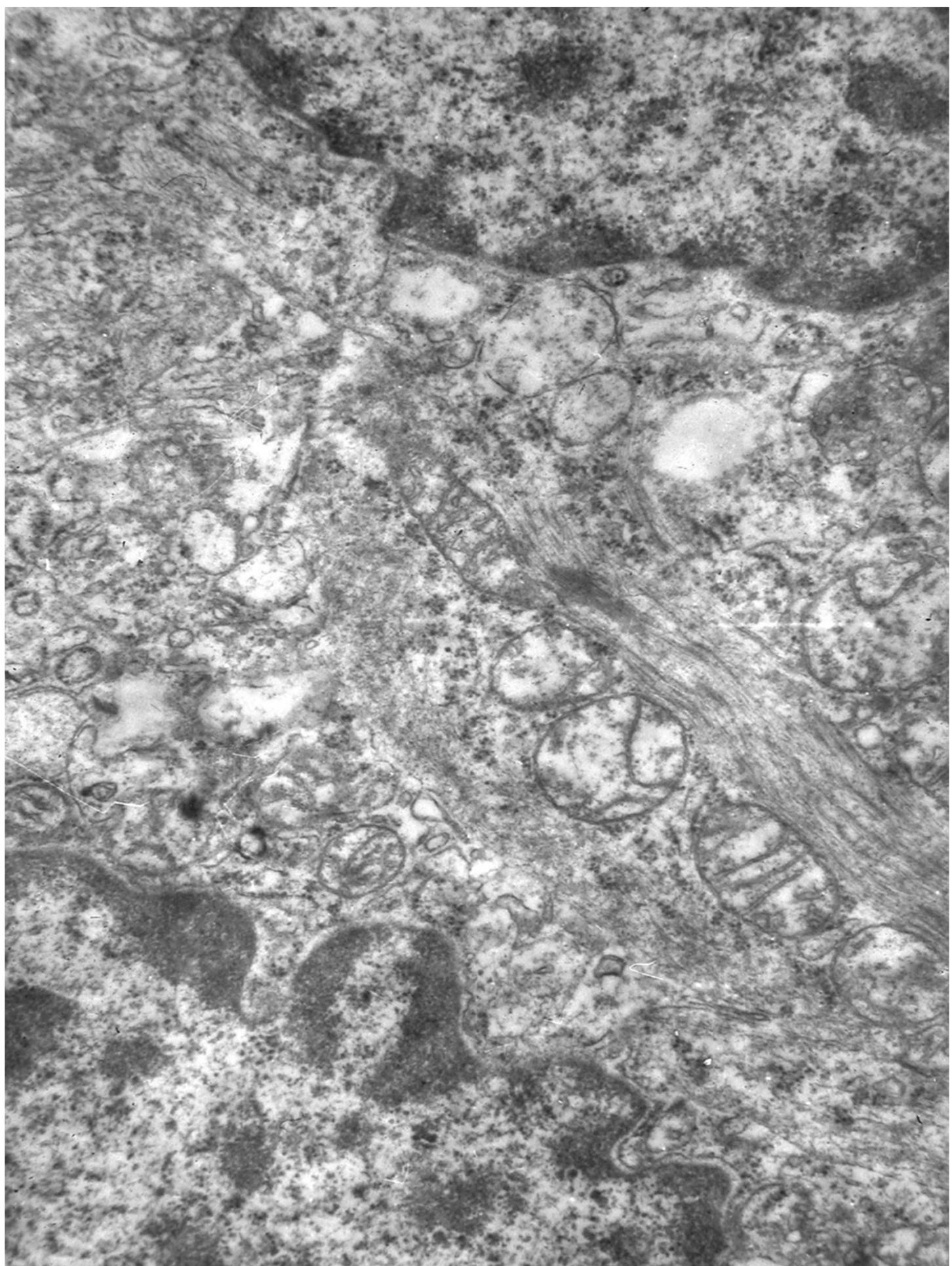
PAS+





desmin





RMS molekulare Genetik

Alveolares

* chr2q35-13q14

PAX3-FKHR Fusion GEn

* chr1-13q14

PAX7-FKHR Fusion Gen

MyoD

Myogenin

IGFBP5

* FGFR4

* AchR γ

2N/4N DNS

Embryonales

* chr11p15.5

WT1?or INS (imprinting)

MyoD

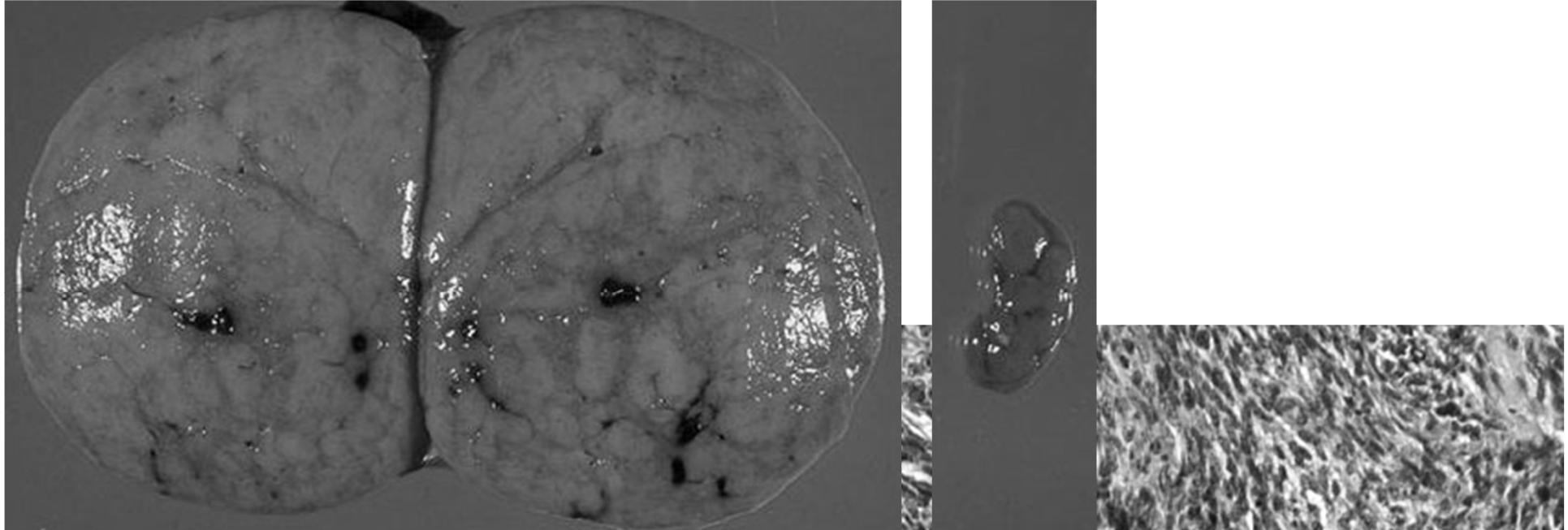
troponin

IGF2

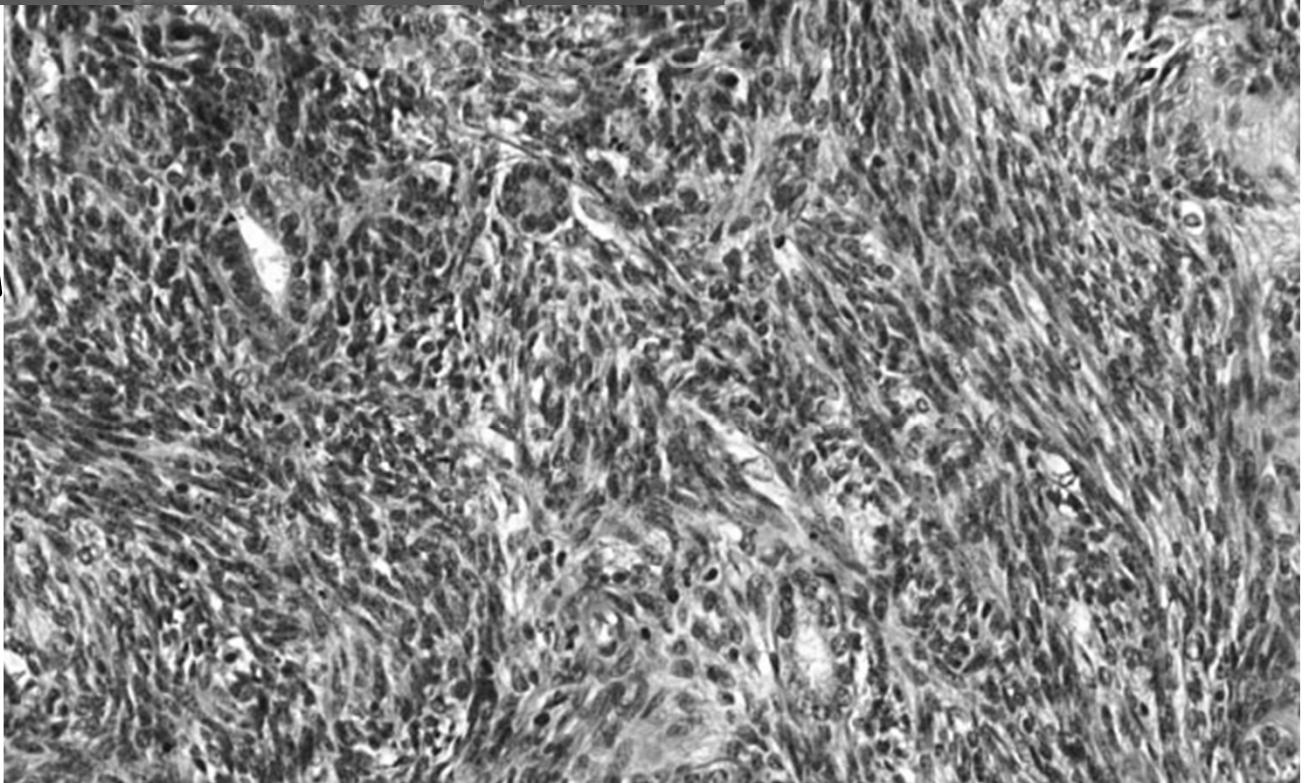
* FGFR4

* AchR γ

hyperdiploid DNS



**Nephroblastom
(Wilms Tumor)**



WILMS TUMOR (NEPHROBLASTOM)

Alter: 2-4 Jahre

WAGR Syndrom

- Wilms
 - Aniridia
 - Genitourinare Malformation
 - Mentale Retardation
- ## **Danys-Drasch Syndrom**
- Pseudohermaphroditismus
 - GN/Neophrose

1% fam, 10% bilateral (synchron,
metachron)

Genetick

- Fam
- WT1, chr11q13 PAX3 Gen,
Transkription Faktor
- Mutation, LOH, Deletion
- Sporadisch
- WT2, Chr11p15, Hras1 und IGF2
Homolog

Morphologie:

- Klassischer Wilms BLS, STR, EPITH mit fokale Anaplasie
- Klarzelliges Sarkom
 - Epitheloid
 - Myxoid
 - Zystisch
- Rhabdoid Wilms (monomorph)

Prognose:

- Grading
 1. Keine Anaplasie
 2. Fokale Anaplasie
 3. Sarkom
 4. Rhabdoid
- Histologie: (W<Wa<S<Rh)
- LND involvement
- <2 y gute Prognose
- Viszerale Metastase (schlecht)

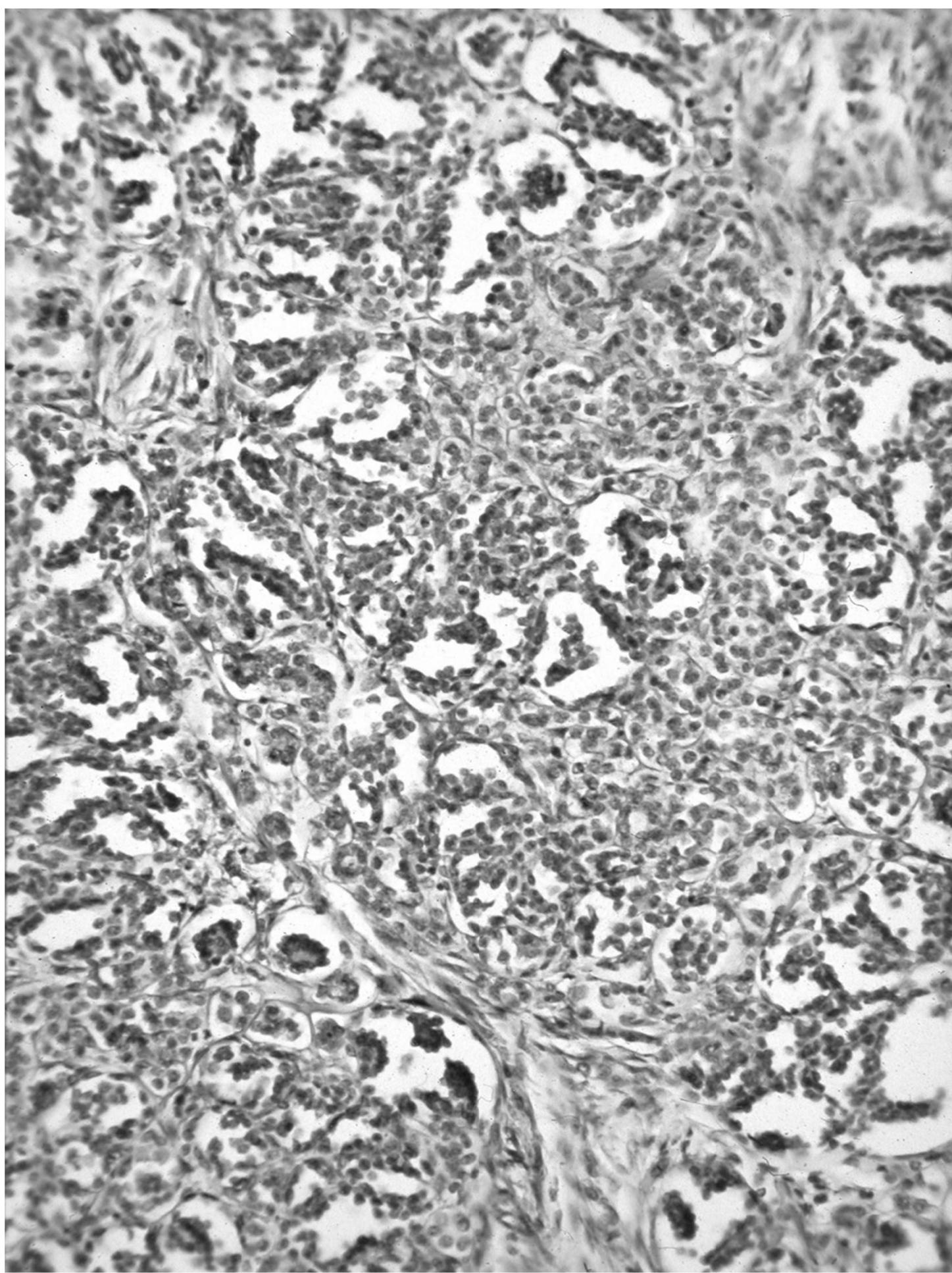
NEPHROBLASTOM-WILMS TUMOR

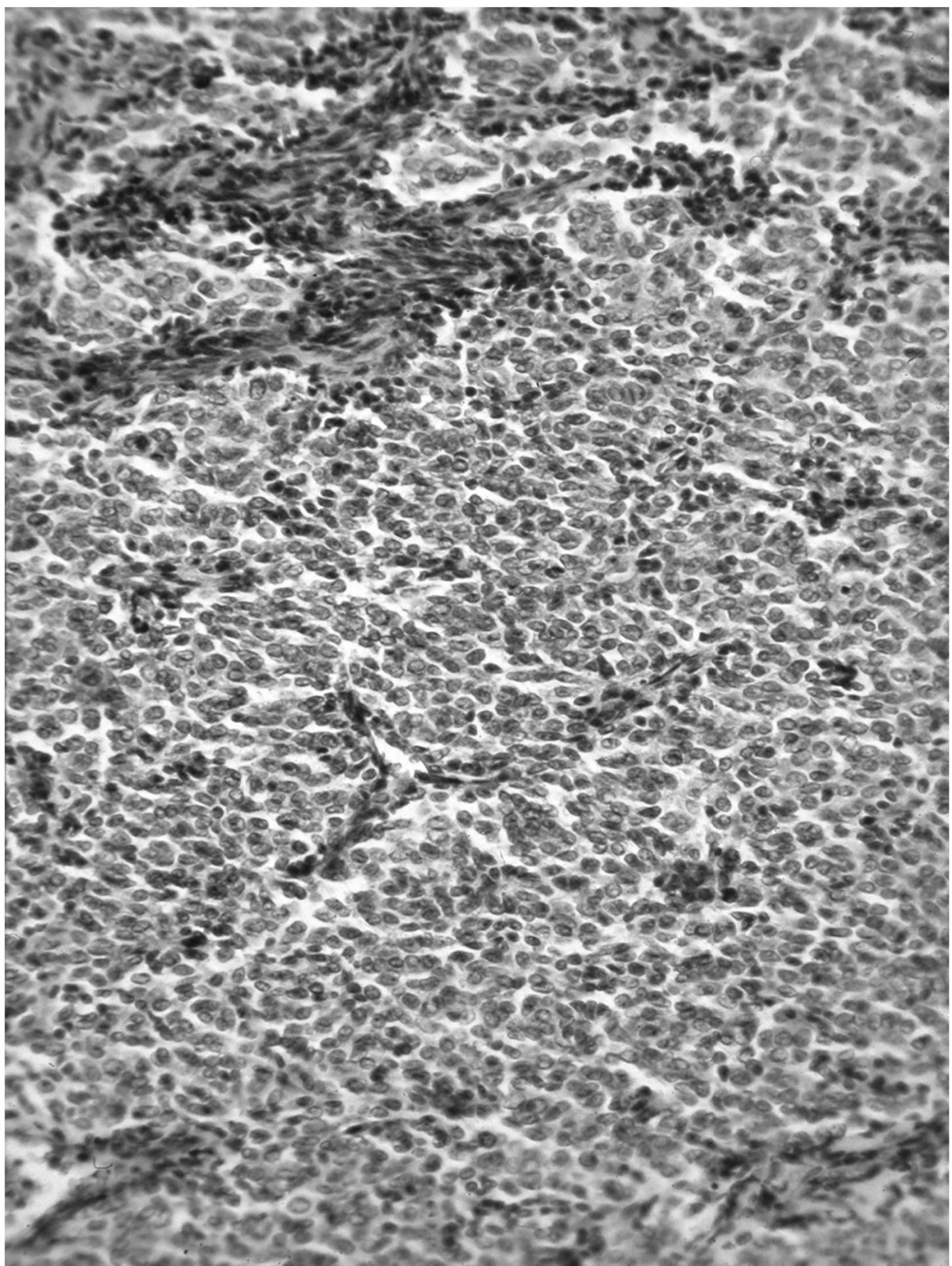
***Triphasisch**

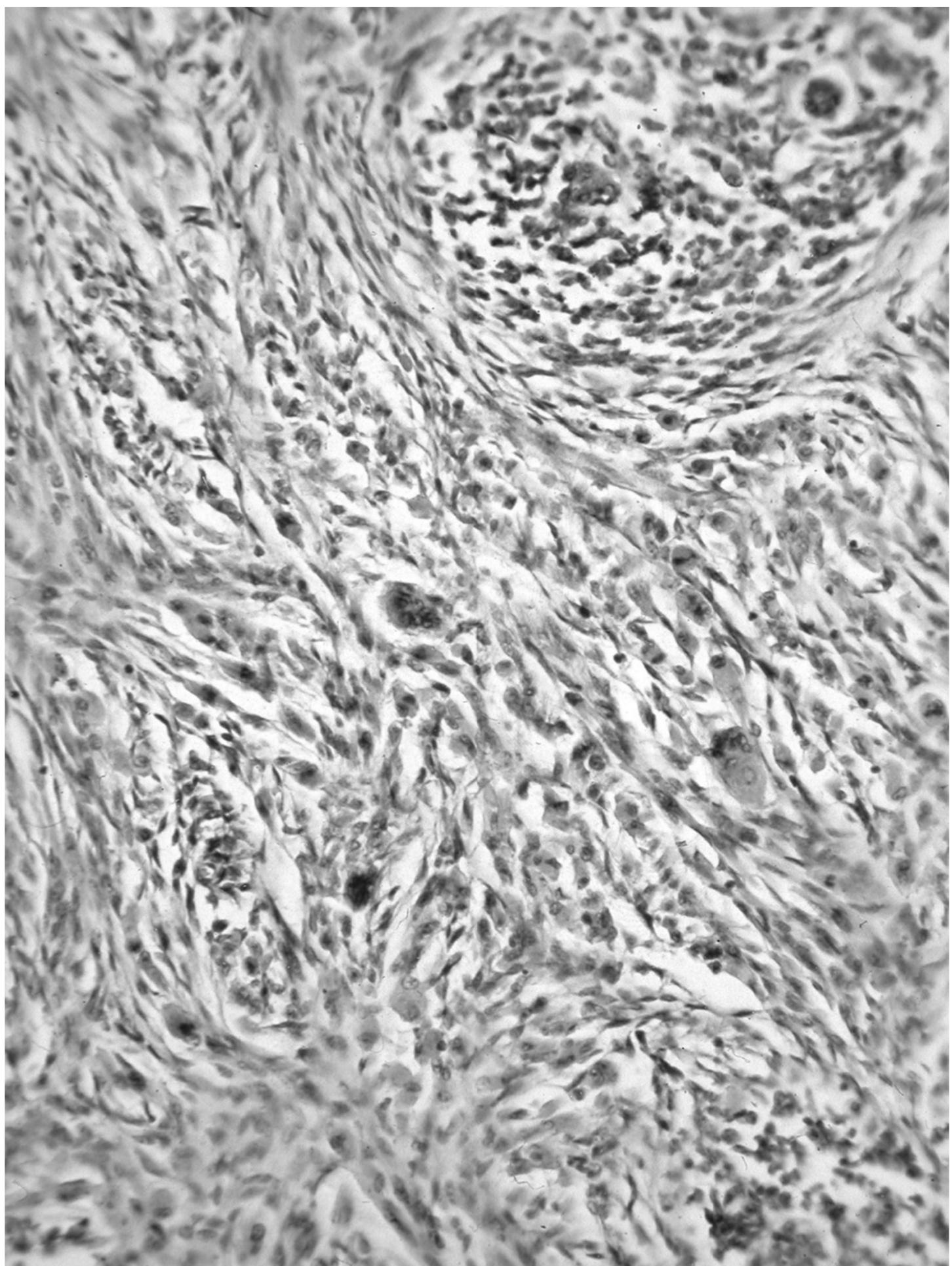
***Stromal predominant**

***Blastema-predominant**

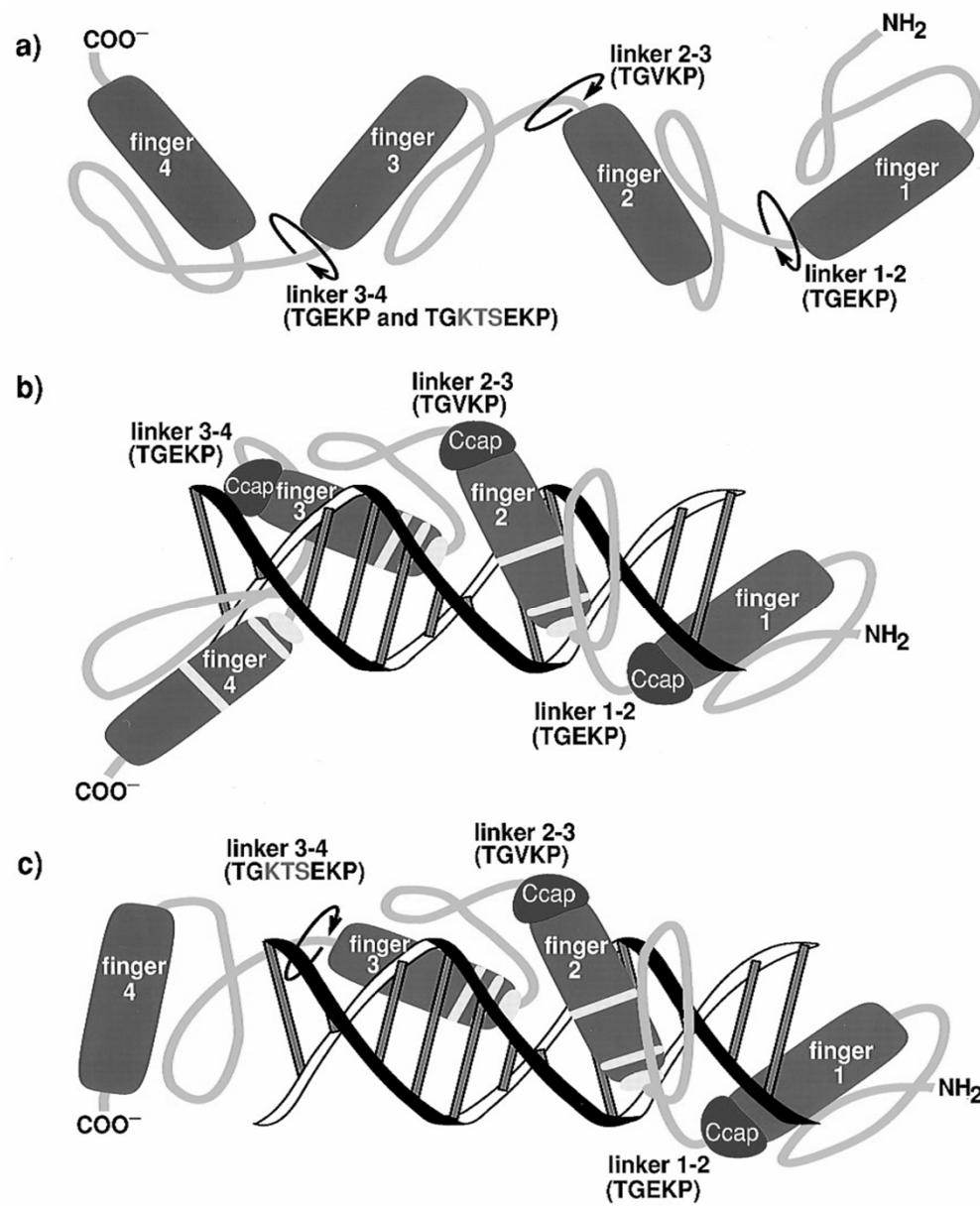
***Rhabdoid**



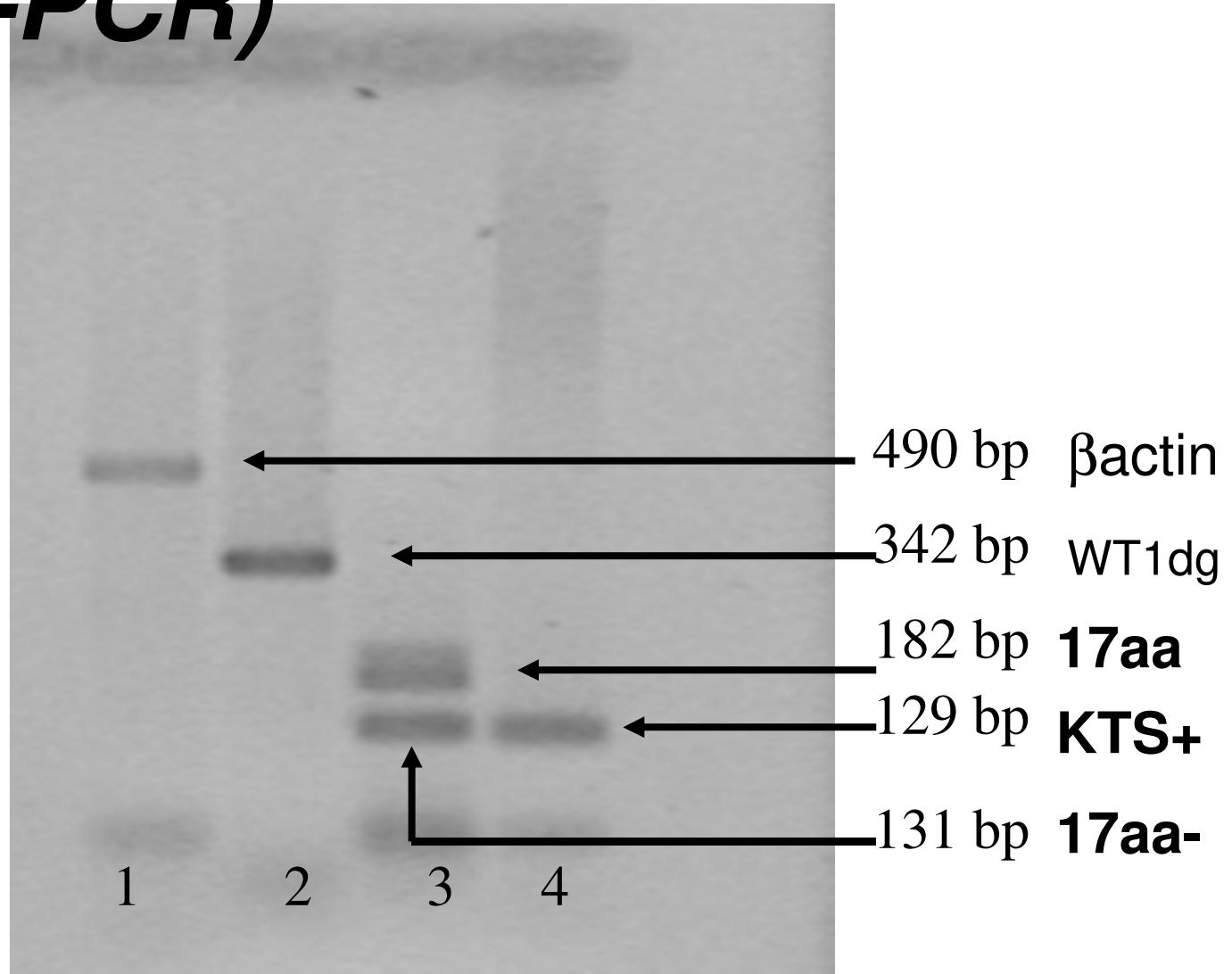




WT1 Proteine

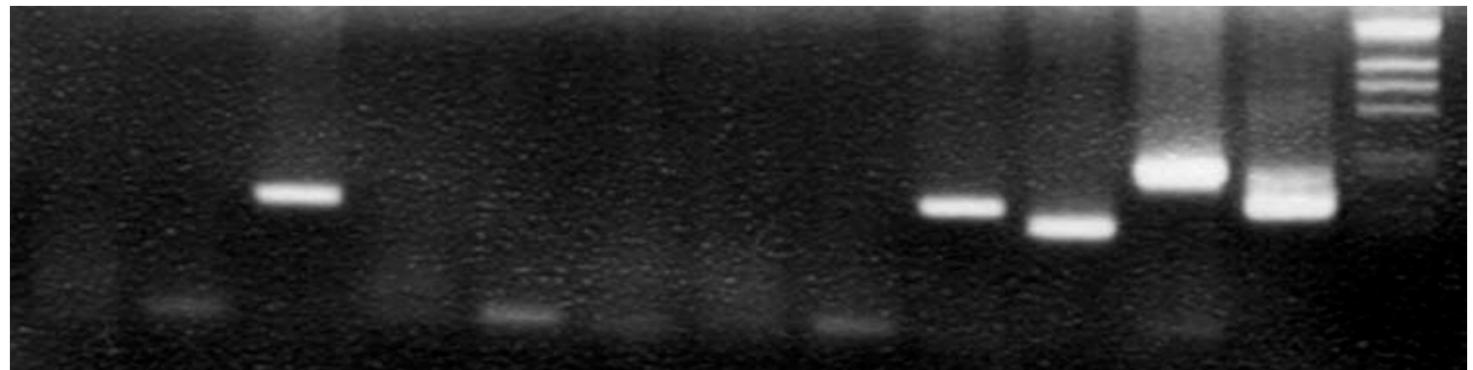


WT1 mRNA splice Varianten (nRT-PCR)



***Detektierung der HPV Viren in menschlichem Wilms'
Tumor (E6-RT-PCR)***
negative Kontrolle: donor Niere (3353/97)

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. Ms

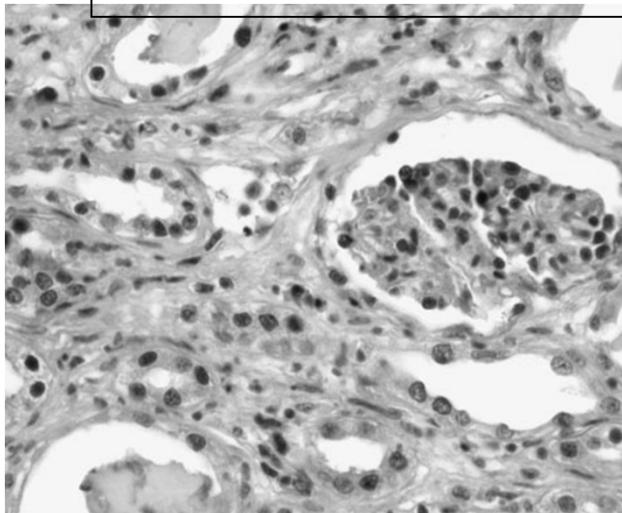


1. 48/95 HPV16
2. 48/95 HPV18
3. 48/95 HPV33
4. 3353/97 HPV16
5. 3353/97 HPV18
6. 3353/97 HPV33

7. 7530/96 HPV16
8. 7530/96 HPV18
9. 7530/96 HPV33
10. HPV16 + control
11. HPV18 + control
12. HPV33 + control

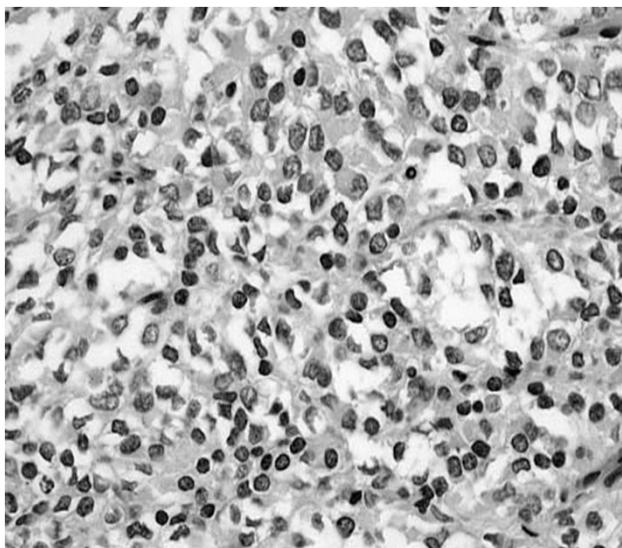
Nachweis für HPV33 in menschlichem Wilms' Tumor

IHC

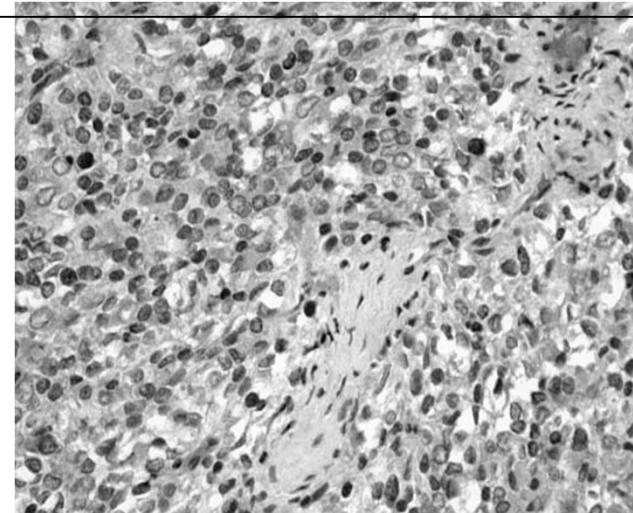


E7 Protein

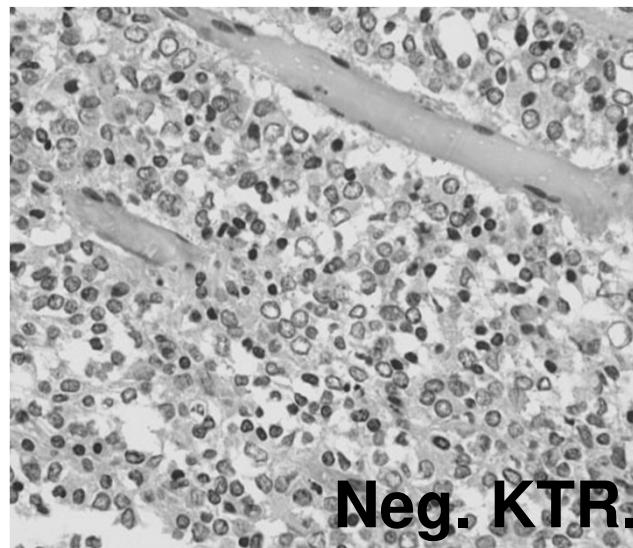
ISH



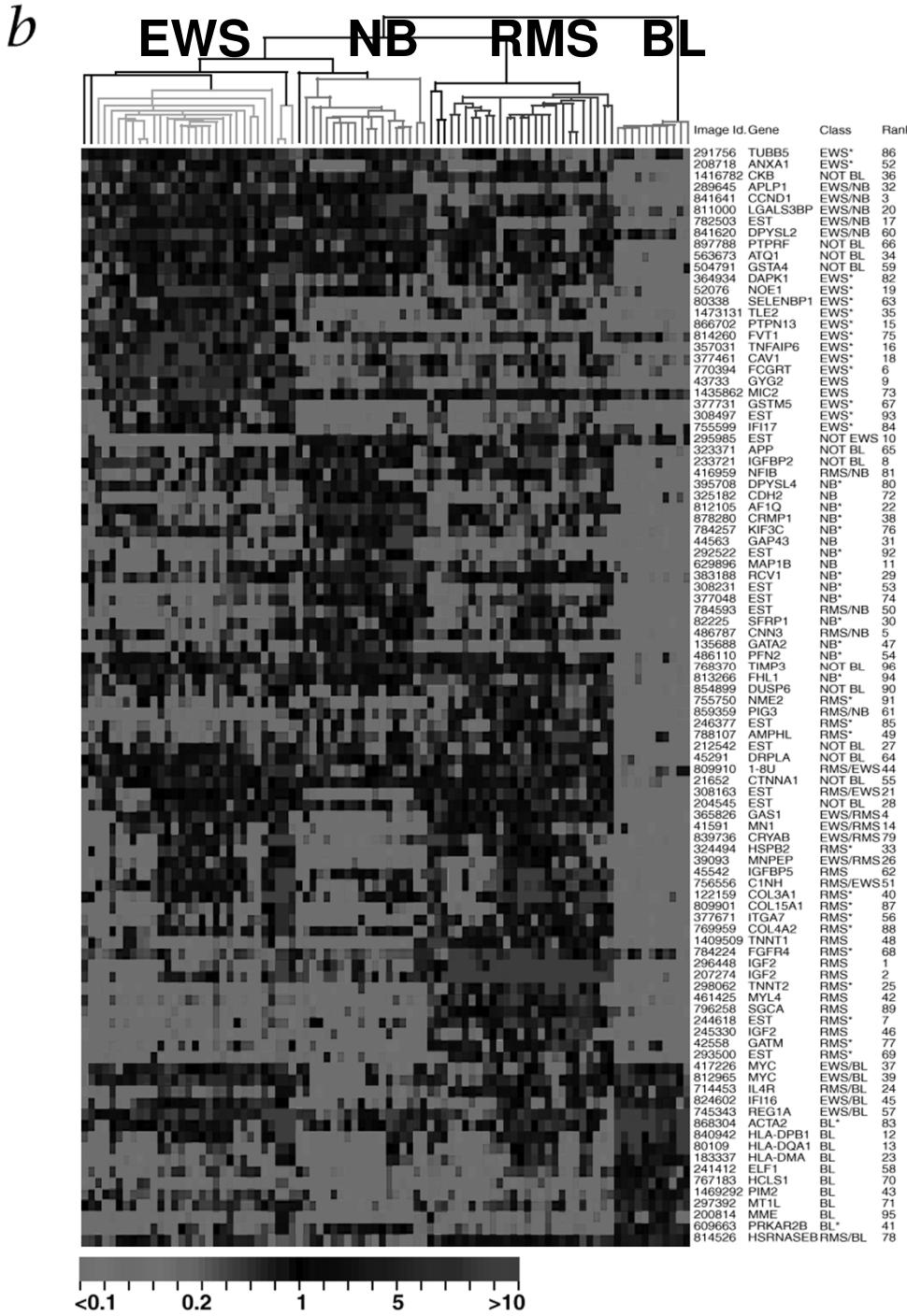
E6 DNS



Neg. KTR.



**6000 Gen
DNS-chip**



Cluster Analyse

**96 discriminating
Gene**

**Neural network
(Neural Netz)**

Khan et al.
Nat Med 2001, June

Gen Expression Profil

gemeinsam
spezifisch

EWS	NB	RMS	B-NHL
TUBB5n	DPYSL4	NME2	ACTA2
ANXA1n	CDH2	AMPHL	HLA-DPB1
DAPK1	AFIQ	HSBP2	HLA-DQA1
SELENBP1	CRMP1	IGFBP5m	HLA-DMA
TIE2	KIF3C	COL3A1	ELF1
DTPN13	GAP43	COL15A1	HCLS1
FNT1	MAP1B	COL4A2	PIM2
TNFIP6	RCV1	ITGA7m	MT1L
CAV1	SFRP1	TNNT1,2	MME
FCGRT	GATA2	FGFR4m	PRKAR2B
GYG2	PFN2	IGF2m	
NOE1n	FHL1	MYL4m	
GSTM5n		SGCA	
IFI17		GATM,	
	APLP1 APLP1		
	CCND1 CCND1		
	DPYSL2 DPYSL2		
		NF1B NF1B	
		CNN3 CNN3	
		PIG3 PIG3	
			HSRNASEB HSRNASEB
			MYC
			IL4R
			IFI16
			REG1A
	MYC IL4R		
	IFI16 REG1A		
	REG1A 1-8U		
MIC2,	1-8U GAS1		
	GAS1 MN1		
	MN1 CRYAB		
	CRYAB MNPEP		
	MNPEP C1NH		
	C1NH	1-8U GAS1,	MIC2
		MN1 CRYAB	
		CRYAB MNPEP	
		MNPEP C1NH	

Khan et al.
Nat Med 2001, June