The Central Nervous System: Tumors
The peripheral nervous system

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Tumor of the CNS

- **Gliomas**
- **Chorioid plexus tumors** (papillomas and carcinomas)
- **Neuronal and mixed (glio)neuronal tumors**
- **Embryonal tumors (poorly differentiated)**
- **Pineal tumors**
- **Meningeal tumors**
- **Other primary tumors of CNS**
- **Secondary (metastatic tumors –** lung, breast,…)

CNS tumors

- **Clinicopathological features:**
- **CNS tumors do not metastasise to other organs**
  - (only infiltration of adjacent tissues and spreading through
  - CSF pathways)
- **Local effects**
  - Signs related to the site of the tumor
  - e.g. epilepsy with a temporal lobe tumor, paraplegias in spinal cord tumor
- **Mass effects**
  - Signs and symptoms of space occupying lesions
  - Vasogenic oedema around CNS tumor
  - Herniation
  - Hydrocephalus in posterior fossa tumor

Gliomas

- **Astrocytomas (AC)**
  - Diffuse astrocytomas (grade II) – LG AC (static, with slow progression)

Variants: gemistocytic

  - Anaplastic astrocytomas (III)
  - Glioblastoma multiforme (grade (IV)
  - Pilocytic astrocytoma (I)
  - Pleomorphic xanthoastrocytoma (II)
  - Anaplastic pleomorphic xanthoastrocytoma (III)

- **Oligodendrogliomas**
  - Oligondendroglioma (II)
  - Anaplastic oligodendroglioma (III)

- **Mixed gliomas** (provisional entities according WHO 2016)
  - Mixed oligoastrocytoma (II)
  - Anaplastic mixed oligoastrocytoma (III)

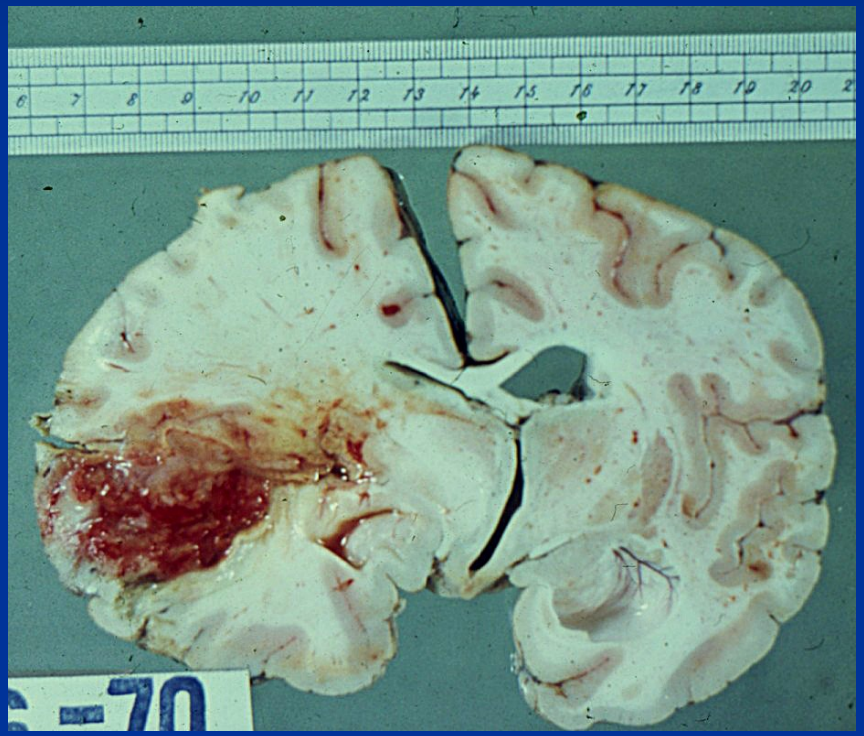
- **Ependymal tumors**
  - Ependymoma (II)
  - Anaplastic ependymoma (III)
  - Myxopapillary ependymoma (I)
  - Subependymoma (I)

High grade (HG) astrocytomas (AC)

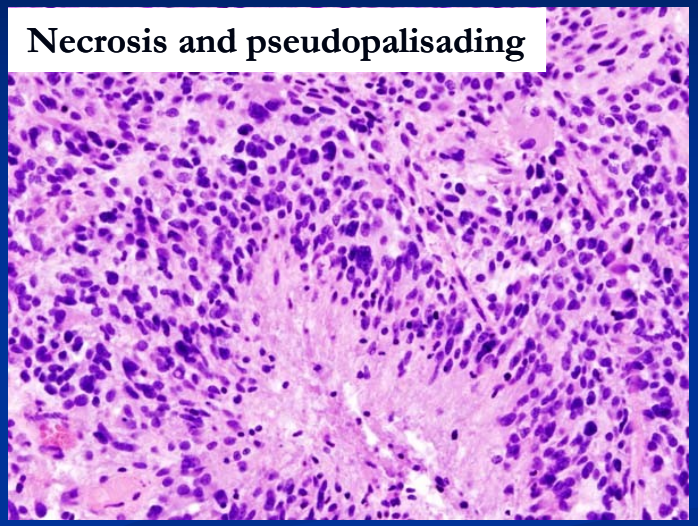
- **Anaplastic astrocytoma (III)**
  - Increased cellularity
  - Increased degree of anaplasia, nuclear pleomorphism, increased proliferative aktivity

- **Glioblastoma (IV)**
  - Necrosis and pseudopalisading
  - Vascular endothelial proliferation
  - Primary (in older) and secondary (in younger with history of LG AC)
  - Very poor prognosis

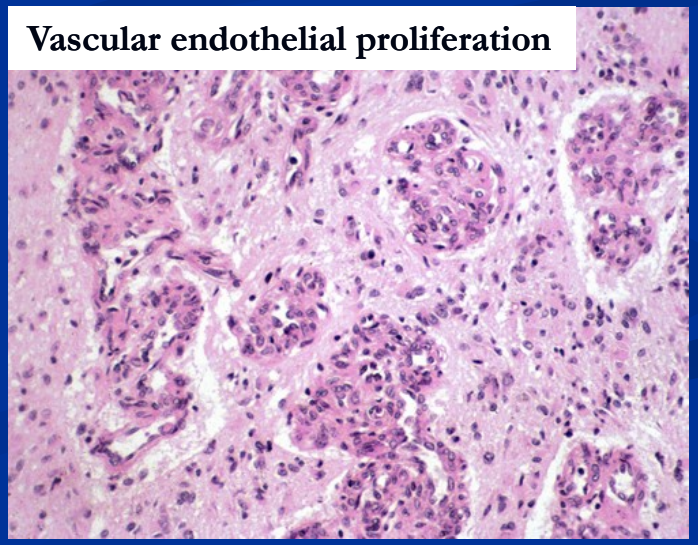
Glioblastoma



Necrosis and pseudopalisading



Vascular endothelial proliferation

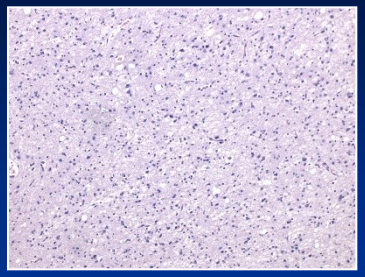


WHO 2016: integrated diagnosis

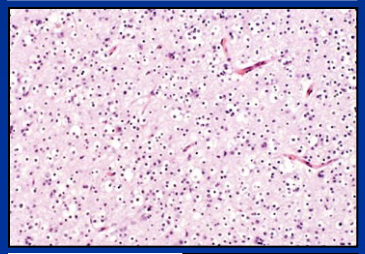
- Histopathological diagnosis/typing
- Histopathological grading/WHO grade
- **Molecular information**

Phenotype of gliomas

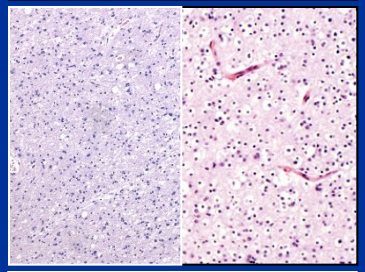
Astrocytic



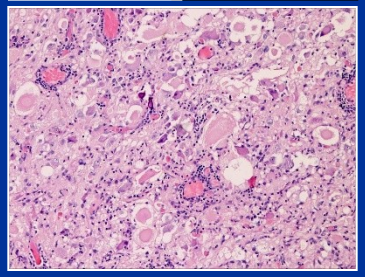
Oligodendrocytic



Oligoastrocytic

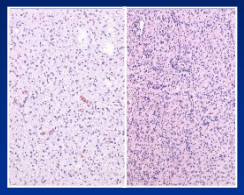


Glioneuronal

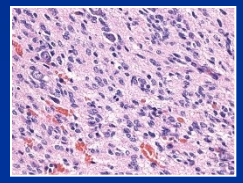


Grading of gliomas

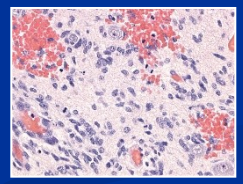
Cellularity



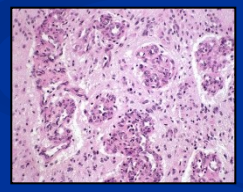
Cytonuclear atypia



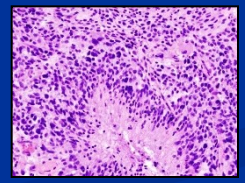
Mitoses



Microvascular proliferates

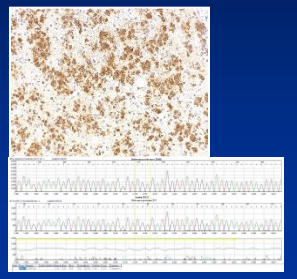


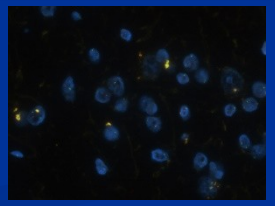
Necroses



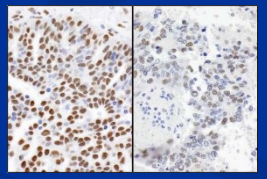
Genotype of gliomas

Mutations IDH1, IDH2

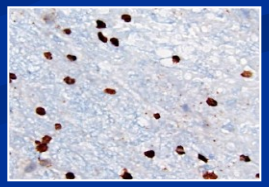




Codeletion 1p/19q



Mutation ATRX



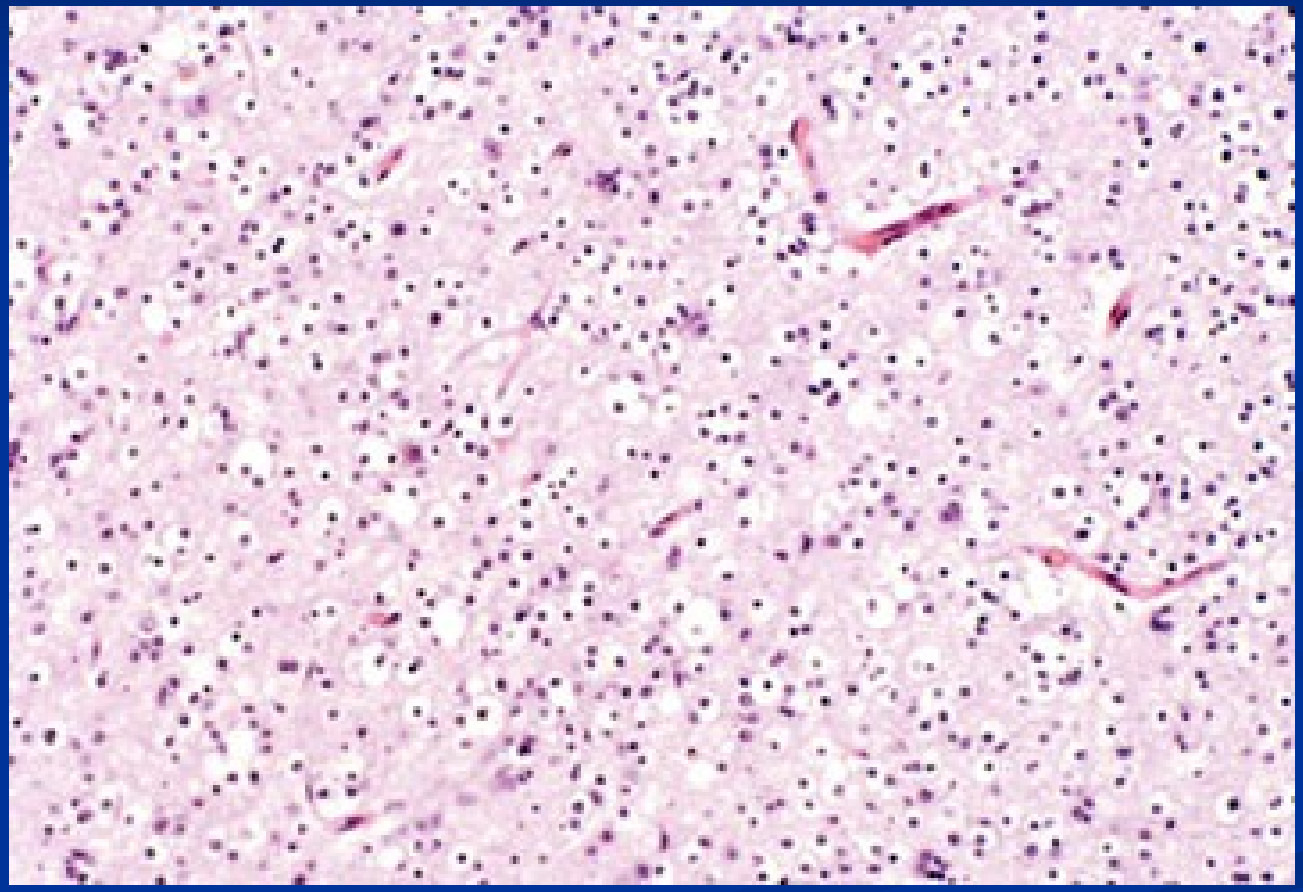
Mutation H3K27M

Oligodendroglioma (II)

- White matter of cerebral hemispheres (most frequently frontal lobes)
- Well circumscribed, gelatinous, gray masses, with cysts, hemorrhage, calcification
- Sheets of regular cells, clear halo of cytoplasm
- Delicate network of anastomosing capillaries
- Perineuronal satellitosis
- LOH for 1p and 9q/IDH mutated
- Better prognosis than AC

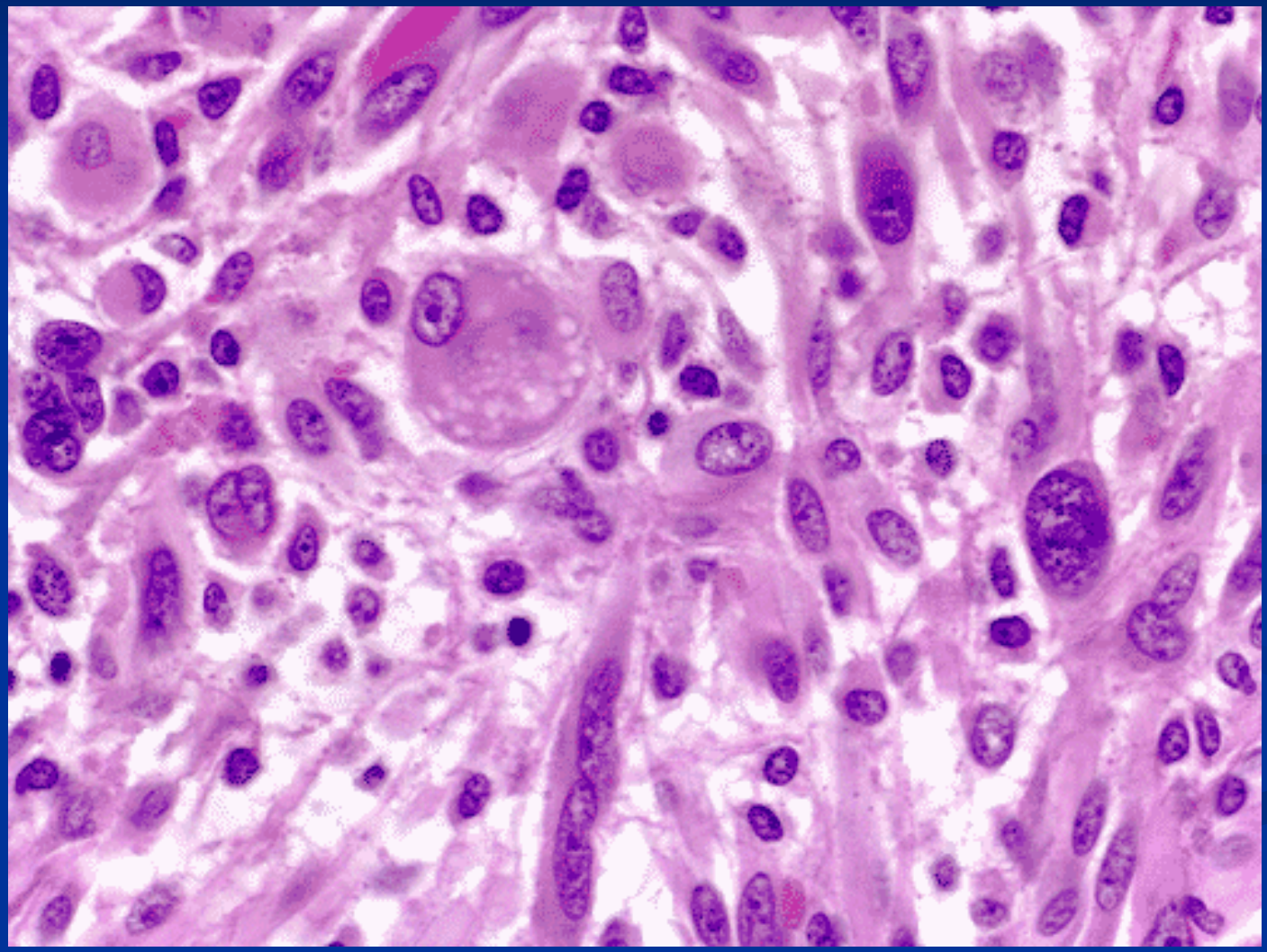
+ anaplastic oligodendroglioma (III): hypercellularity, nuclear anaplasia, mitotic activity, necrosis

Oligodendroglioma



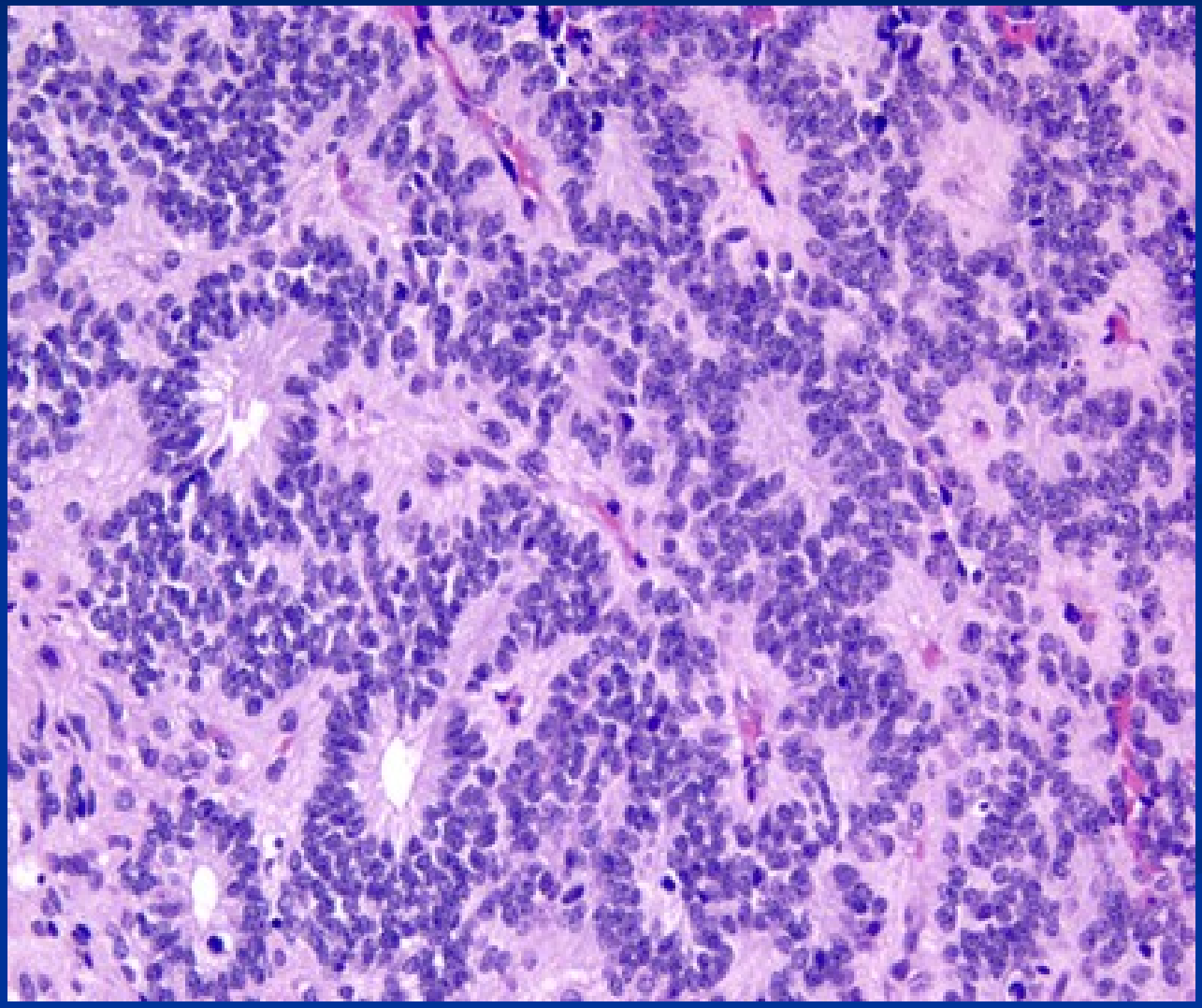
- **Pilocytic astrocytoma (I)**
- Often cystic, also solid
- Usually circumscribed, arising from optic nerve to conus medullaris
- Bipolar cells („hair cells“) + Rosenthal fibers and eosinophilic granular bodies
- Often biphasic (fibrillary areas + loose microcystic pattern)
- Usually first two decades
- **Pleomorphic xantoastrocytoma (II); anaplastic (III)**
- Temporal lobe of children and young adults
- Neoplastic occasionally bizarre astrocytes, also lipidized
- Necrosis and mitotic activity indicate higher grade

Pleomorphic xantoastrocytoma



- **Ependymoma (II)**
  - Next to ependyma-lined ventricular system, 4th ventricle
  - First 2 decades affected
  - Solid or papillary masses; complete extirpation due to localization impossible
  - Small „blue“ cells, granular chromatin, dense fibrillary background, perivascular pseudorosettes and rosettes
- **Anaplastic ependymoma (III)**
- **Subependymoma (I)**
  - benign, slowly growing, intraventricular
- **Myxopapillary ependymoma (I)**
  - Filum terminale of spinal cord

Ependymoma



Neuronal and mixed (glio)neuronal tumors

- **Gangliogliomas (I-II)**

- **Dysembryoblastic neuroepithelial tumor (DNET)**
  - In temporal lobe
  - Associated with epilepsy
  - Usually grade I; gangliogliomas may be gr. II/III

- **Dysplastic gangliocytoma of the cerebellum (I)**

- **Central neurocytoma (II)**
  - LG neuronal neoplasms
  - Within vetricular system

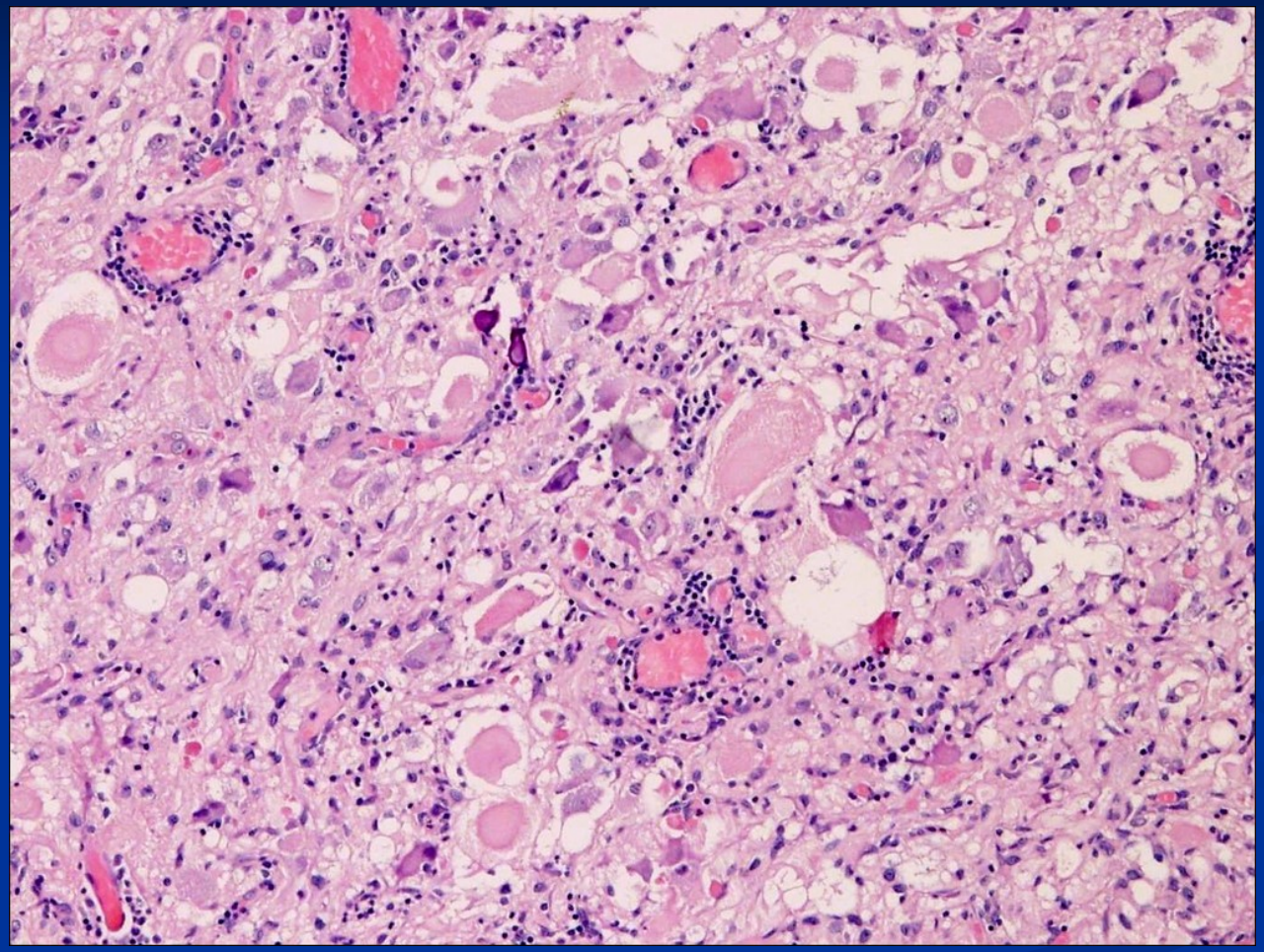
Spectrum of long-term epilepsy associated tumors

- **Usually low grade, well differentiated, with low proliferating activity and low malignant potential, superficially localized** (cortical or subcortical; frontal and temporal localization)**, mixed neuronal-glial tumors, expression of stem cell marker CD34**

- **Mixed neuronal-glial tumors :**
  - Ganglioglioma (GI, rare GII-GIII)
  - Dysembryoplastic neuroepithelial tumor (DNET, GI)
- **Others:**
  - Pilocytic astrocytoma (GI)
  - Diffuse astrocytoma (GII)
  - Oligodendroglioma (GII)
  - Pleomorphic xanthoastrocytoma (GII)
  - Subependymal giant cell astrocytoma (GI ; associated with tuberous sclerosis)
  - Angiocentric glioma (GI)

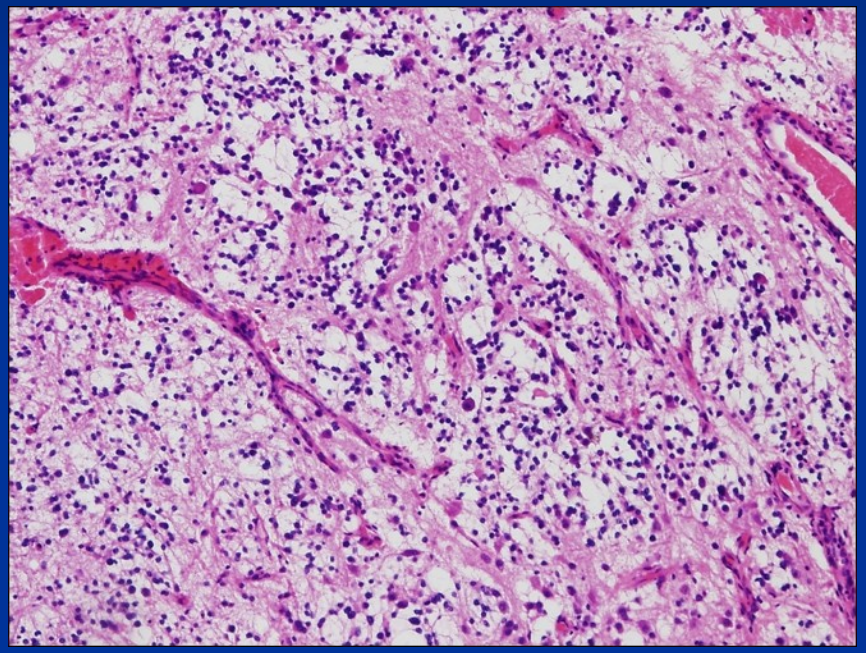
WHO 2007

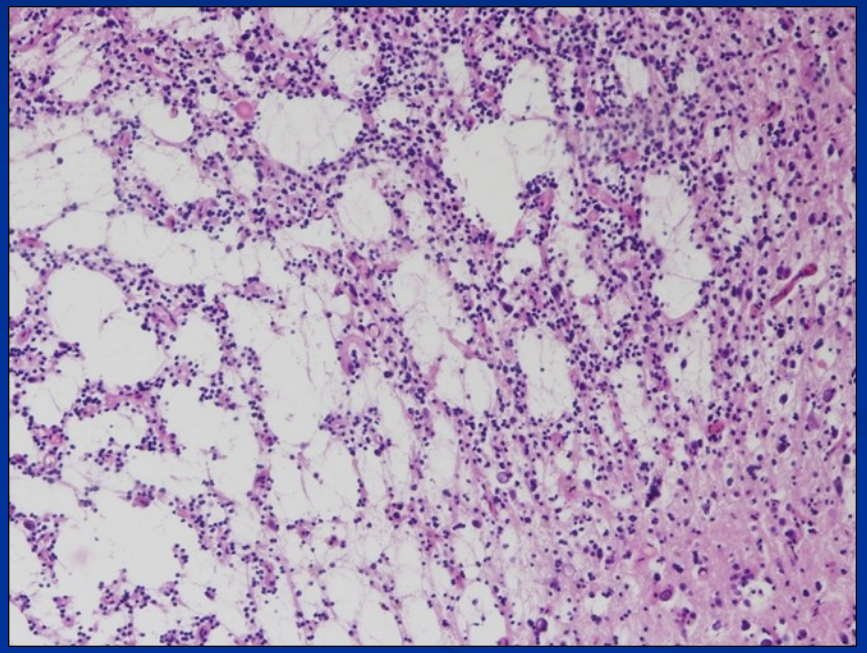
Gangliоglioma



- well differentiated, slowly growing neuroepithelial tumor
- neoplastic ganglion cells + neoplastic glial cells
- WHO GI; higher grades very rare; >70 % in temporal lobe

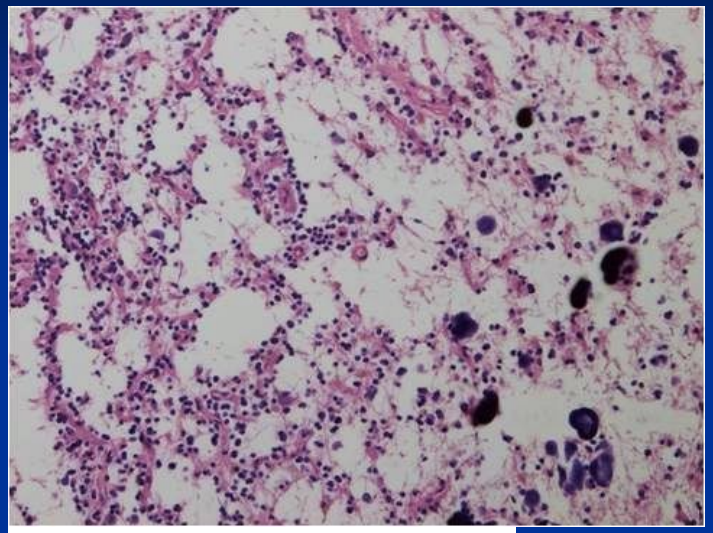
DNET



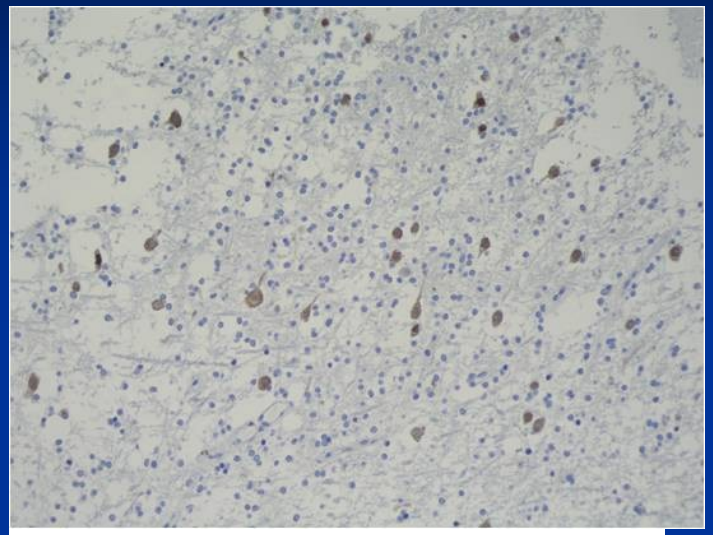


- WHO GI, benign, usually supratentorial glial-neuronal neoplasms
- in children and young adults
- cortical location
- complex columnar and multinodular architecture, „specific glioneuronal elements“ (bundles of axons lined by oligodendroglia-like cells+floating neurons)

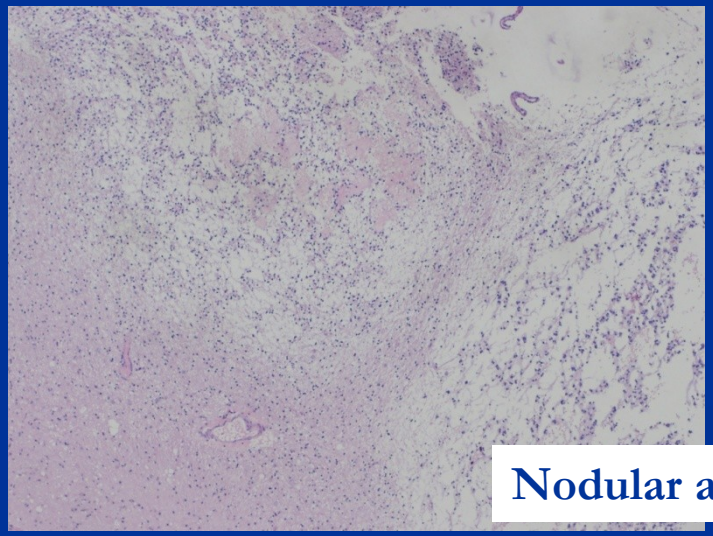
DNET

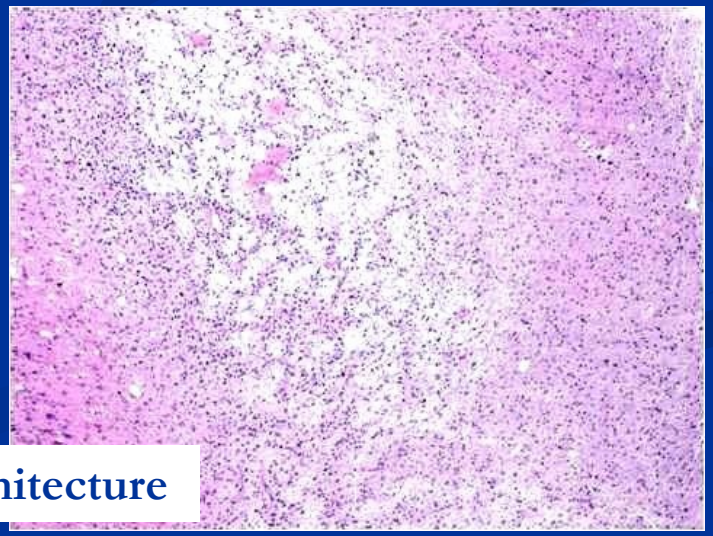


Calcification in DNET



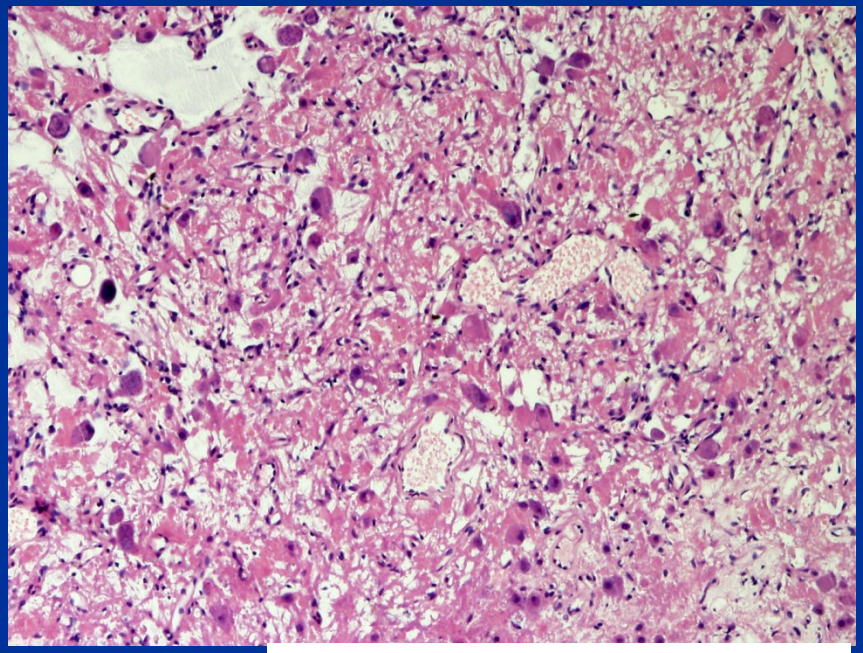
NeuN immunohistochemistry



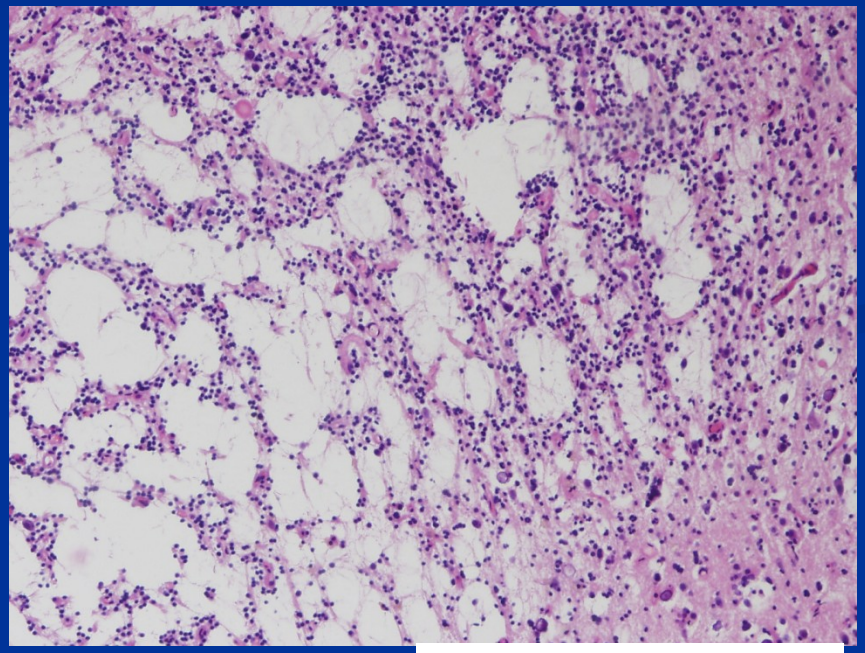


Nodular architecture

Composite glioneuronal tumour:
DNET and ganglioglioma component

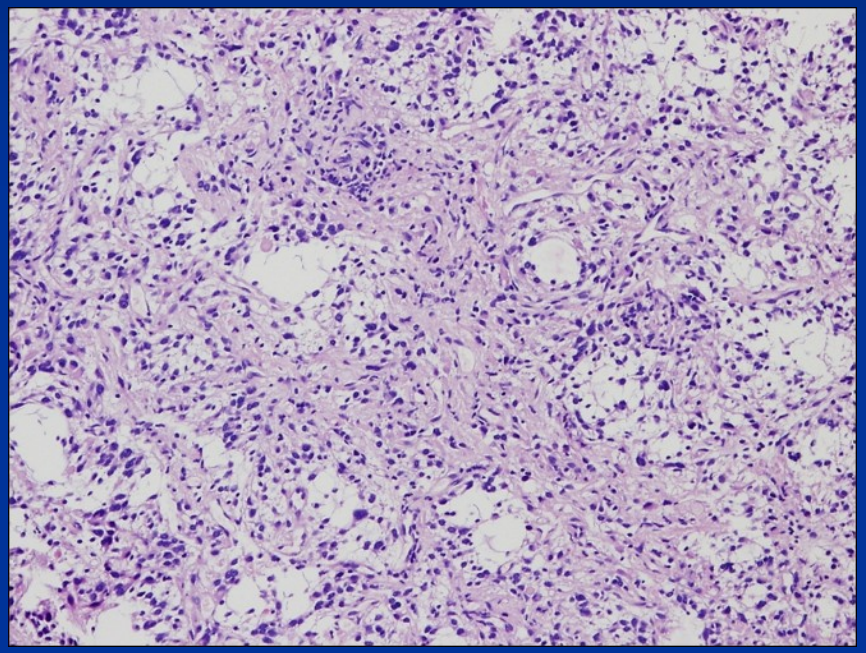


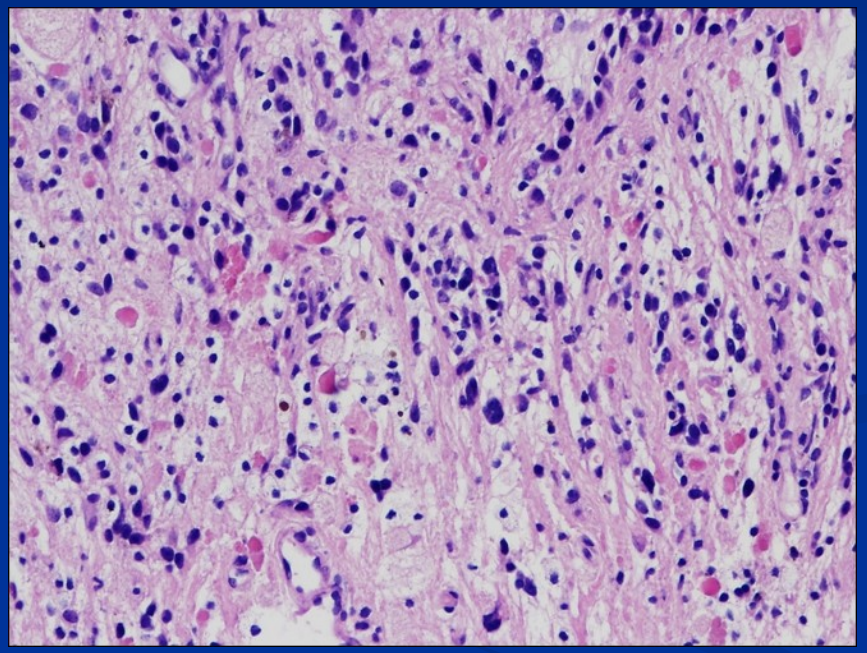
Ganglioglioma component



DNET component

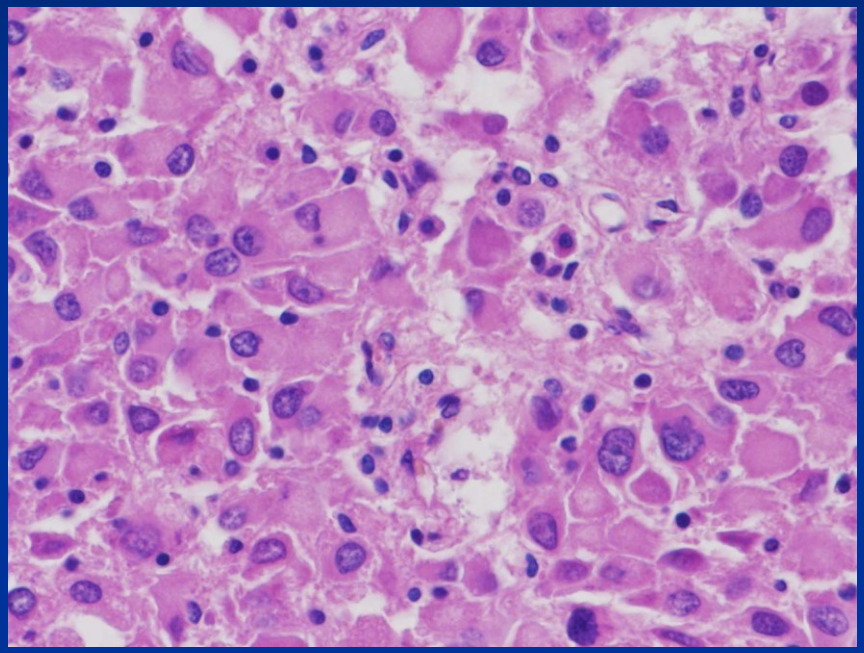
Pilocytic astrocytoma



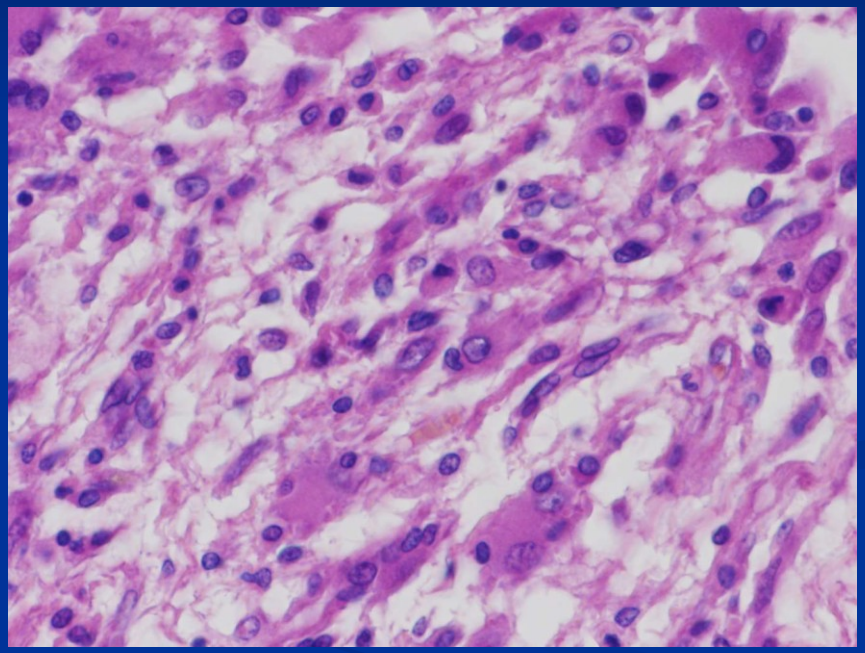


- WHO GI, relatively circumscribed, slowly growing, often cystic
- histologically biphasic pattern (compacted bipolar cells and loose-textured multipolar cells + Rosenthal fibers and eosinophilic granular bodies)

Subependymal giant cell xanthoastrocytoma

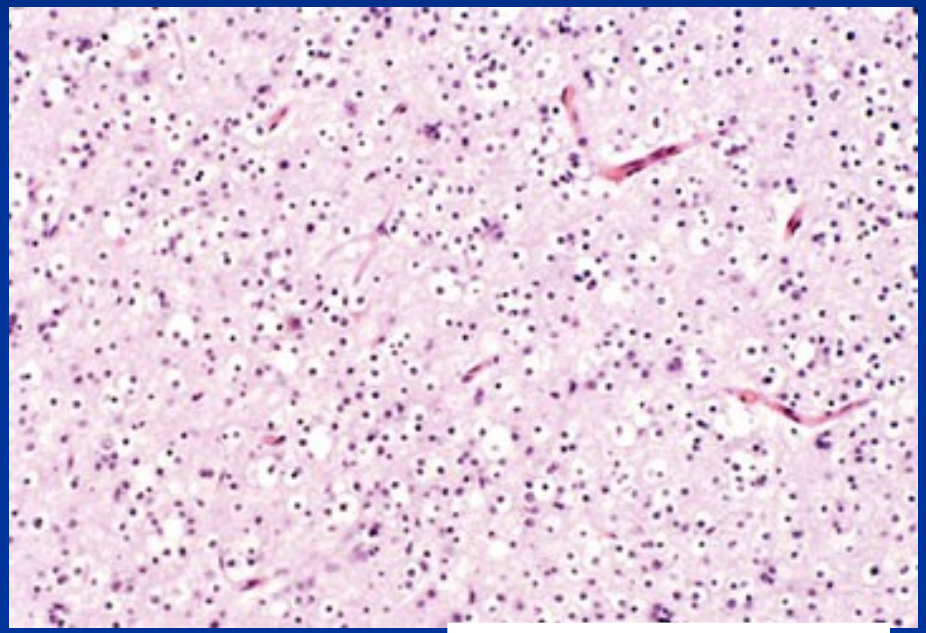


Pleomorphic eosinophilic tumour cells



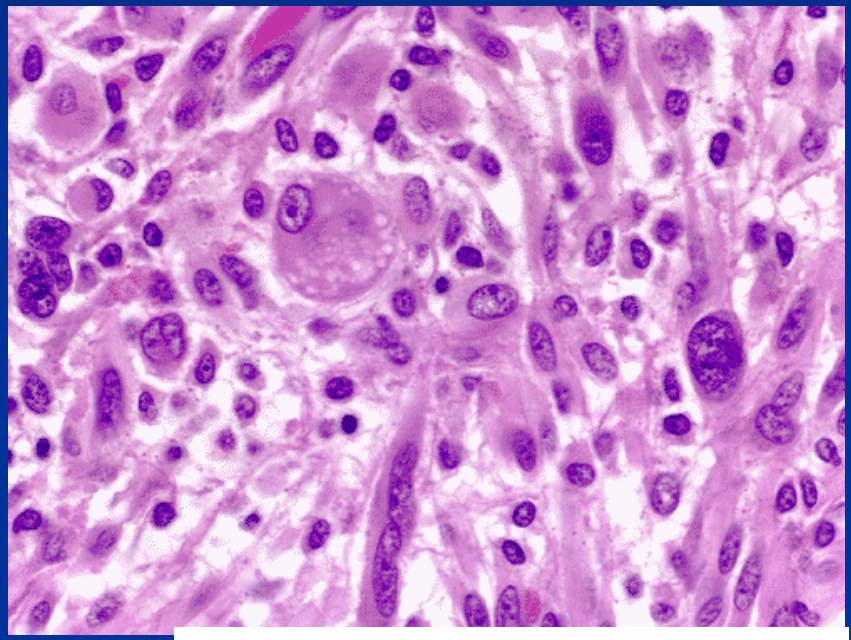
Elongated tumour cells forming streams

- WHO GI; tuberous sclerosis complex
- benign, slowly growing, arising in the wall of the lateral ventricles, composed of the large ganglioid astrocytes



Oligodendroglioma

- WHO GII, a diffusely infiltrating
- WD glioma
- cerebral hemispheres
- deletions 1p and 19q



Pleomorphic xantoastrocytoma

- WHO GII
- superficial localisations in cerebral hemispheres + involvement of meninges
- pleomorphic lipidized cells

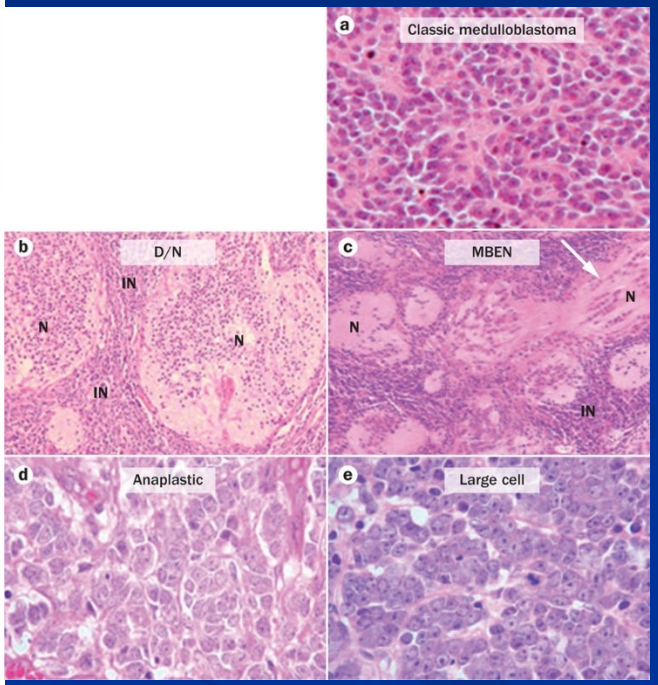
Medulloblastoma (gr. IV)

- 20 % of brain tumors in children
- In the midline of cerebellum; 4th ventricle, hydrocephalus
- Well circumscribed, grey
- hypercellular, „small blue cells“, neuroblastic rosettes (Homer Wright rosettes)
- High proliferation, mitoses
- Expression of neuronal markers (synaptophysin, NF; GFAP+ cells, vimentin)
- Dissemination through the CSF
- 4 histological subtypes; 4 molecular subtypes
- Prognosis in untreated dismal; with total excision and irradiation: 5-year survival rate as high as 75 %

Integrated diagnosis of medulloblastomas:

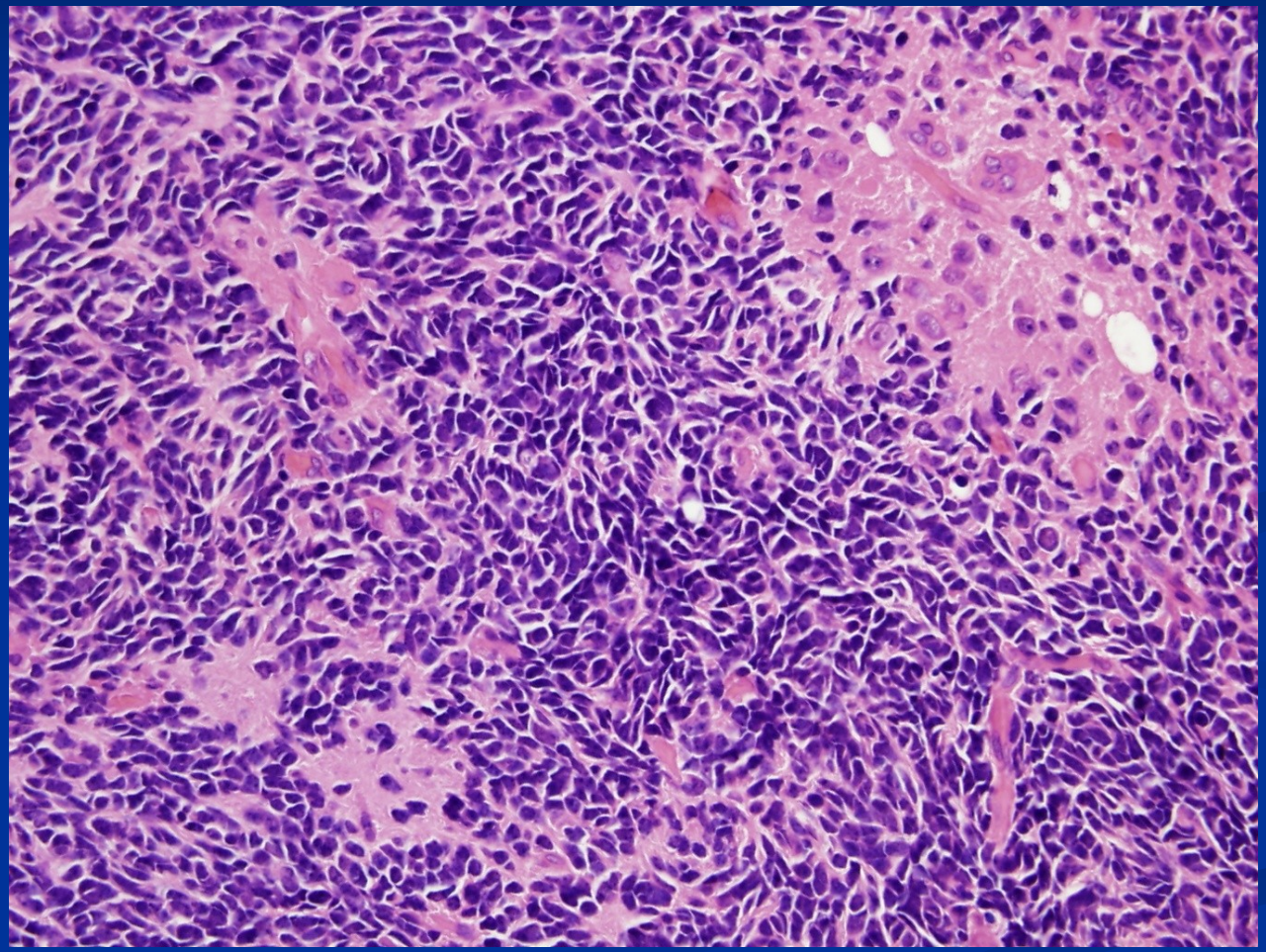
- histopathological diagnosis/typing
- genetic profiling – 4 molecular subtypes

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance



Histological subtypes of medulloblastomas

Medulloblastoma



Other embryonal tumors/ WHO gr. IV

- **Atypical teratoid/rhabdoid tumors**
  (posterior fossa, supratentorially; under 5, dismal prognosis)
- **Embryonal tumor with multilayered rosettes, C19MC altered**
- **Medulloepithelioma**
- **CNS neuroblastoma/ganglioneuroblastoma**
- **CNS embryonal tumor**

Other tumors of CNS

- **Primary CNS lymphomas (DLBCL)**

- **Germ cell tumors**
  - Midline structures, pineal region, suprasellar region
  - Teratomas; germinomas (similar to seminomas),…

- **Pineal parenchymal tumors**
  - Pinealoblastomas (high grade tumors)
  - Pineocytomas (well differentiated)
  - Gliomas in pineal region

Tumors of the meninges

- **Meningioma** (meningothelial)

  - nonmeningothelial

- **Meningeal hemangiopericytoma (so-called)**
- **Solitary fibrous tumors**

Meningioma (gr. I-III)

- Usually well defined rounded masses, adjacent to dura; encapsulated, extension into bone (reactive hyperostotic changes); less common „en plaque“ growth

- **Grade I meningiomas:**

- meningothelial
- fibroblastic
- transitional
- psammomatous
- microcystic, secretory, angiomatous,….

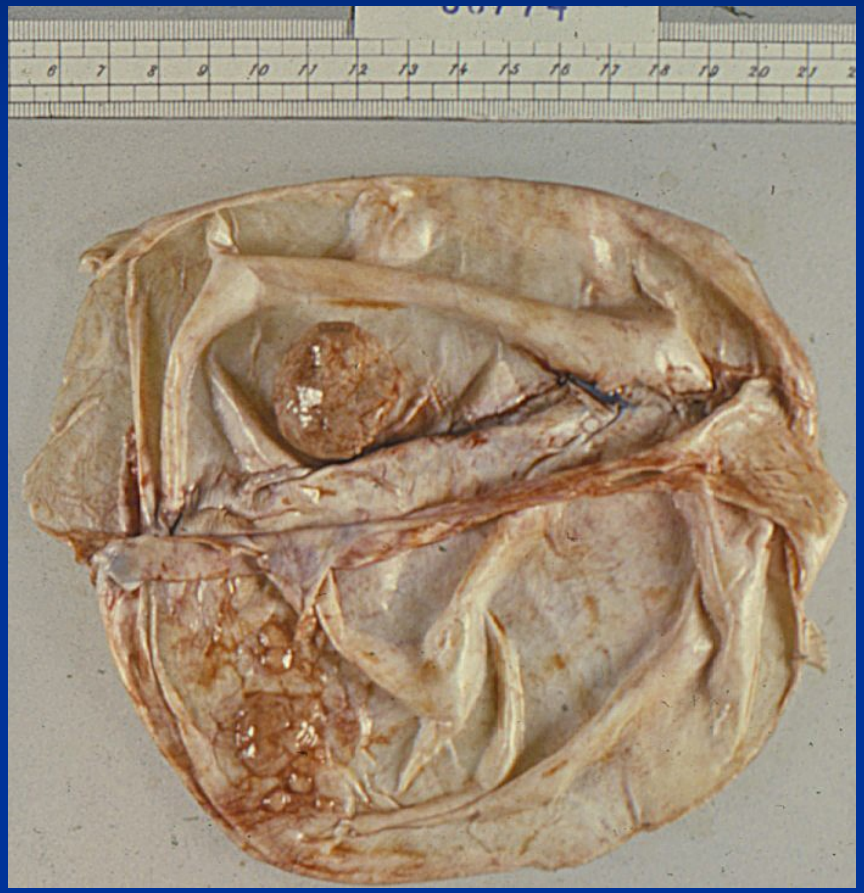
- **Grade II meningiomas:**

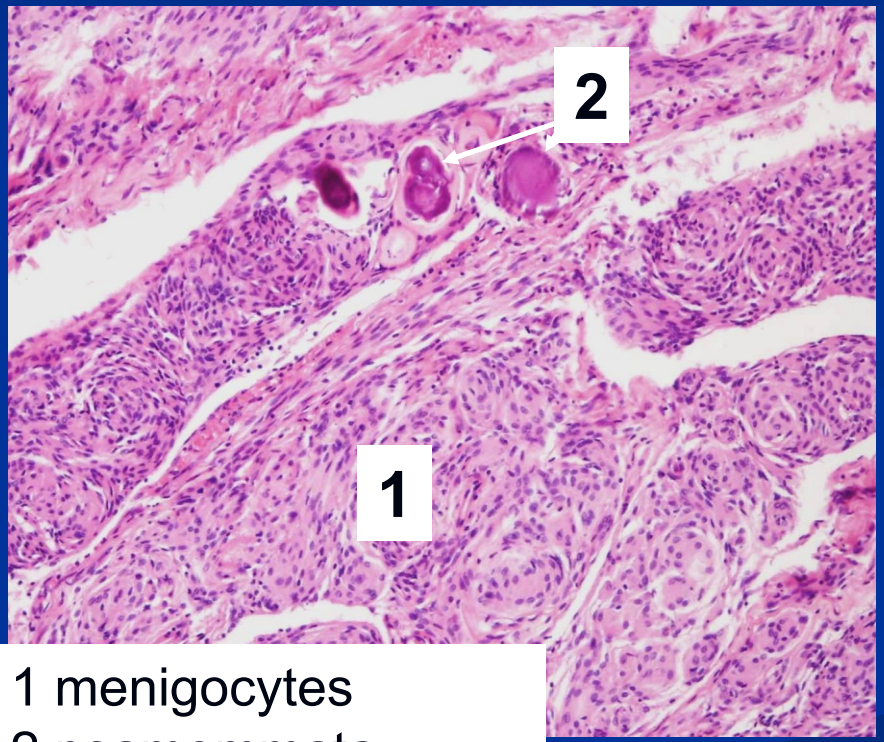
- atypical, clear cell, chordoid

- **Grade III meningiomas:**

- anaplastic (malignant), rhabdoid, papillary

Meningioma





1 menigocytes
2 psamommata

- **Craniopharyngeoma:**

- Arise from squamous cell rests (derived from Rathke pouch) in sellar region
- Benign (gr. I), partly cystic epithelial tumor

- **Hemangioblastoma:**

- Sporadic or ass. with VHL sy (in younger)
- Cerebellum (medulla, spinal cord,…., supratentorial, retinal in VHL)
- Well circumscribed, cystic, with mural nodule(s)
- Capillary-size and larger thin-walled vessels with intervening neoplastic „stromal cells“ (large polygonal, vaculated, lipid-rich, PAS+)

Familial tumor syndromes with involvement of tumor suppressor gene (AD)

- **Cowden syndrome**
  - *PTEN* mutation
  - Dysplastic gangliocytoma of the cerebellum

- **Li Fraumeni syndrome**
  - Inactivation of p53
  - Medulloblastoma

- **Turcot syndrome**
  - Mutations in *APC* or mismatch repair gene
  - Medulloblastoma or glioblastoma

- **Gorlin syndrome**
  - *PTCH* mutations, upregulation of SHH
  - medulloblastoma

- **Neurofibromatosis type I**
  - AD; neurofibromas (plexiform and solitary)+gliomas of optic nerve+pigmented nodules of iris-cutaneous hyperpigmented macules *(café au lait spots)*
  - Malignant transformation of neurofibromas
  - *NF1* gene (17q11.2); neurofibromin

- **Neurofibromatosis type II**
  - AD; 8th nerve schwannomas and multiple meningiomas + gliomas, ependymomas of spinal cord + non-neoplastic lesions of Schwann cells, meningeal cells, hamartia
  - *NF2* gene (22q12); merlin

- **Tuberous sclerosis complex**
  - AD; hamartomas and benign tumors of the brain and other tissues: cortical tubers (epileptogenic), subependymal nodules, subependymal giant cell astrocytomas,…, + renal angiomyolipomas, retinal glial hamartomas, pulmonary lympangioleiomyomatosis, cardiac rhabdomyoma + cysts – cutaneous lesions (angiofibromas, subungual fibromas, hypopigmented lesions)
  - tuberin or hamartin genes mutated

- **Von Hippel Lindau Disease**
  - AD; hemangioblastomas + cysts (pancreas, liver, kidney) + renal carcinomas, pheochromocytomas
  - tumor suppressor gene – pVHL – 3p25-p26

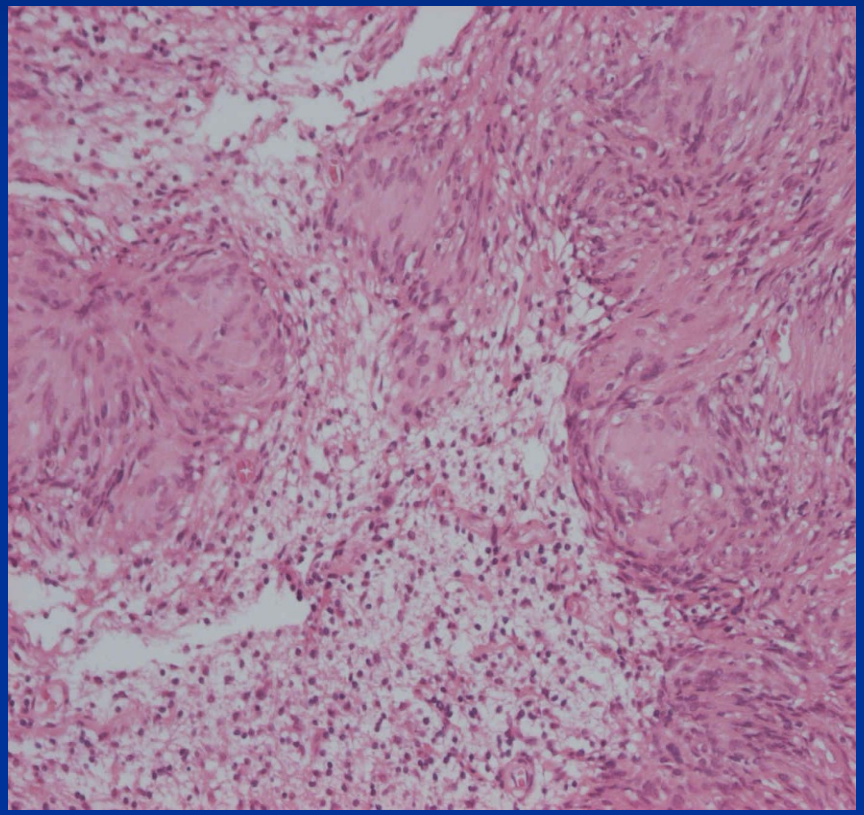
Peripheral nerve sheath tumors

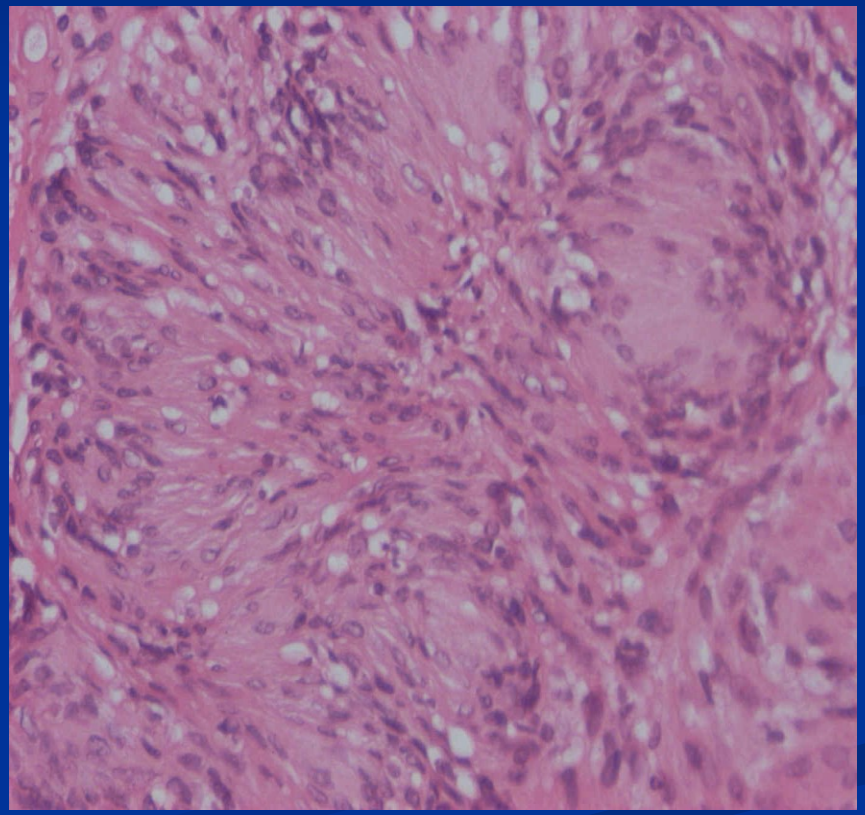
- **Schwannoma**
- benign, from neural crest-derived Schwann cell, component of NF2
- well circumscribed, encapsulated, attached to nerve; 2 patterns: Antoni A and Antoni B
- often vestibular branch of 8th nerve; sensory nerves preferentially involved (trigeminus, dorsal roots,..); extradurally – large nerve trunks

- **Malignant peripheral nerve sheath tumor**
- highly malignant, medium and large nerves affected; in NF1

- **Neurofibroma:**
- Cutaneous: localized, in dermis or subcucateously
- Plexiform: infiltrating lesion growing within and expanding a peripheral nerve; NF1; potential for malignant transofrmation; significant neurologic deficits

Schwannoma





Diseases of peripheral nerves

- Inflammatory neuropathies
- Infectious polyneuropathies
- Hereditary neuropathies
- Acquired metabolic and toxic neuropathies
- Traumatic neuropathies

Inflammatory neuropathies

- **Immune mediated neuropathies:** Guillain-Barré syndrome – GBS (acute inflammatory demyelinating polyradiculoneuropathy)
  - Weakness in distal limbs, ascending paralysis, hospital intensive care before recovering normal function (up to 20 % long term disability); in some patients followed by a subacute or chronic course
  - Inflammation and demyelination of spinal nerve roots and peripheral nerves (radiculoneuropathy)
  - Infections or prior vaccination ass. with GBS
  - T-cell mediated immune response

Infectious polyneuropathies

- **Leprosy (Hansen disease)**
  - Lepromatous leprosy: Mycobacterium leprae invading Schwann cells
  - Segmental demyelination, remyelination, loss of axons; endoneurial fibrosis and multilayered thickening of perineurial sheats
  - Symmetric polyneuropthy; pain fibers (loss of sensation)
  - Tuberculoid leprosy: cell-mediated immune response to M. leprae – granulomatous inflammation in dermis, cutaneous nerves affected

- **Diphteria** (diphteria exotoxin; selective demyelination of axons)

- **Varicella zoster virus** (varicella zoster virus; following chickenpox virus persists in neurons and sesory ganglia with potential ractivation)

Hereditary neuropathies

- Hereditary motor and sensory neuropathies (HSMN I-III,….)
- Hereditary sensory and autonomic neuropathies (HSANs)
- Familial amyloid polyneuropathies
- Peripheral neuropathy accompanying inherited metabolic disorders

HSMN

- **HSMN - Charcot-Marie-Tooth** (peripheral myelin protein 22, myelin, connexin,…
- Demyelinating neuropathy; usually AD
- Repetitive de- and remyelinations (onion bulbs – Schwann cell hyperplasia)
- Slowly progressive, progressive muscular atrophy (legs) , uscle weakness, pes cavus

- **HSMN II** (kinesin family member KIF1B)
- Axonal form – loss of myelinated axons

- **HSMN III – Dejerine-Sottas neuropathy**
- AR, genetically heterogeneous (the same genes as in HSMN I)
- Enlarged peripheral nerves, trunk and limb muscles affected

Acquired metabolic and toxic neuropathies

- **Peripheral neuropathy in adult onset diabetes mellitus** (polyol pathway and nonenzymatic glycation of proteins involved)
  - Distal symmetric sensory or sensorimotor neuropathy
  - Autonomic neuropathy
  - Focal or multifocal asymmetric neuropathy
  - Loss of small myelinated fibers, also unmyelinated fibers
  - Thickening of endoneurial arterioles
- **Metabolic and nutritional neuropathies**
  - Uremic neuropathy
  - Chronic liver disease, respiratory insuf., thyroid dysfunction
  - Thiamine deficiency (neuropathic beriberi)
  - Avitaminosis B_{12}, B_6, and E
- **Neuropathies associated with malignancy**
  - Brachial plexopathy (apex of a lung), obturator palsy (pelvic tumors), cranial verve palsies (intracranial tumors,….)
  - Paraneoplastic effect (small cell ca of lungs, plasmocytoma)
- **Toxic neuropathies**
  - Heavy metals, lead, arsenic

Tumors of autonomic nervous system

- **Extraadrenal paragangliomas** (carotid body paragangliomas, vagal and other paragangliomas)
  - non-chromaffin paragangliomas, usually related to parasympathetic nervous system
  - Alveolar pattern, cell nests; chief cells and sustentakular cells
  - Also malignant forms

- **Extraadrenal paragangliomas** of sympathoadreal neuroendocrine system (anywhere from the pelvic floor to the neck)

- **Pheochromocytomas** (adrenal paraganglioma) (production of katecholamins, hypertension, usually benign)

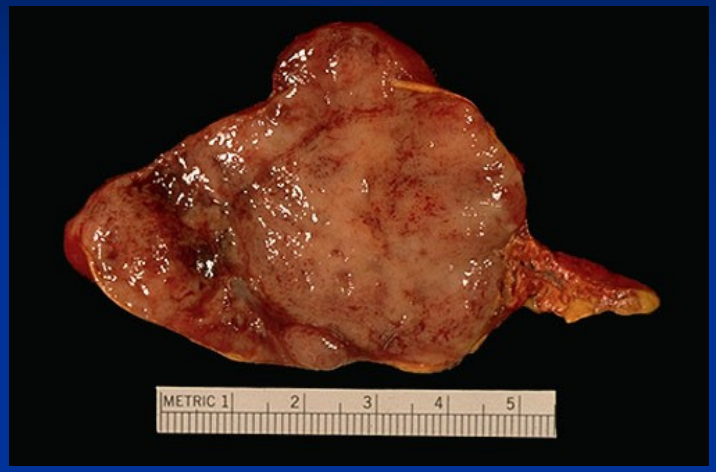
- **Gangliocytic paraganglioma** (benign, in duodenum)

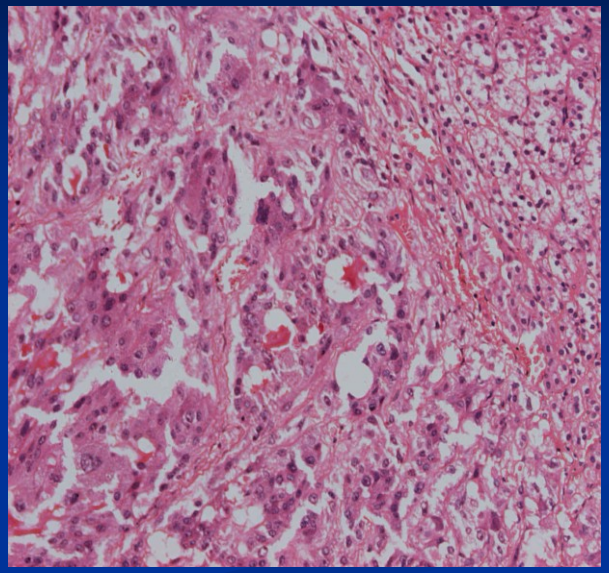
Tumors of autonomic nervous system

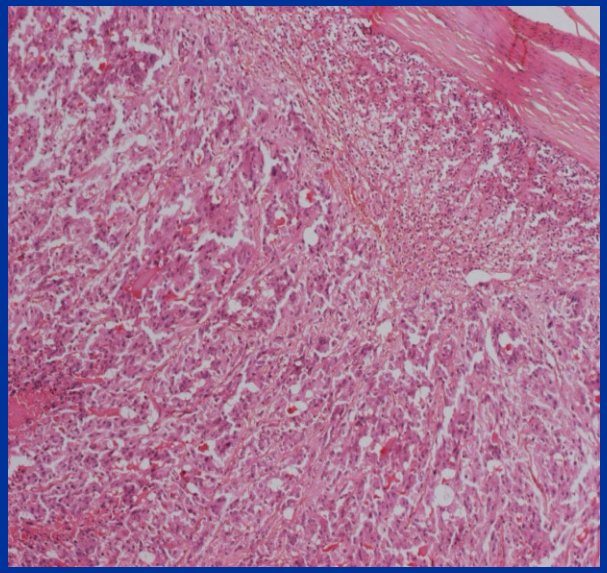
- **Neuroblastoma and ganglioneuroblastoma**
  - In children under 4 ys (85 %)
  - In adrenal gland or intra-abdominal sympathetic chain (70 %) and in thorax (at least 20 %)
  - „Small blue cell“ tumor, bulky, multinodular, hemorrhages and necrosis often, calcification, also pseudocystic, lobular or nesting pattern, fibrillary material between cells (neuritic cell processes) – neurofibrillary matrix, rosettes, chromatin: „salt-and-pepper“ appearance
  - Ganglioneuroblastoma – some cytodifferentiation or maturation with recognizable ganglion cells

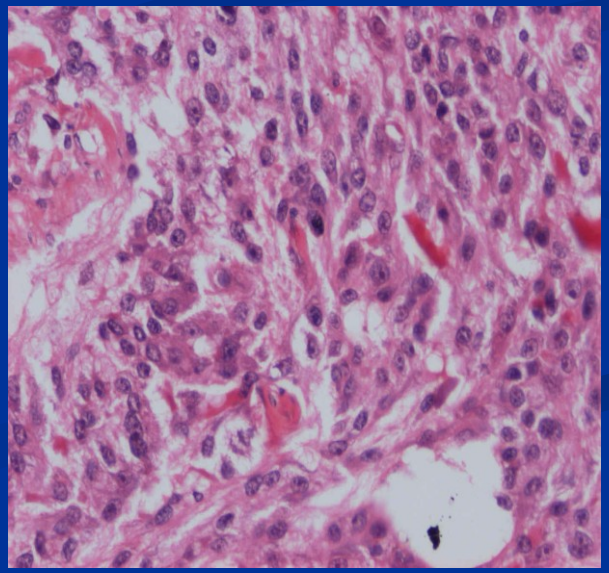
- **Ganglioneuroma**
  - In posterior mediastinum or retroperitoneum; some arising in adrenal gland
  - Patient over 10 ys
  - Well, circumscribed, with no necrosis or hemorrhages, on cut surface whorled or trabecular pattern
  - Spindle cell matrix and mature ganglion cells

Pheochromocytoma

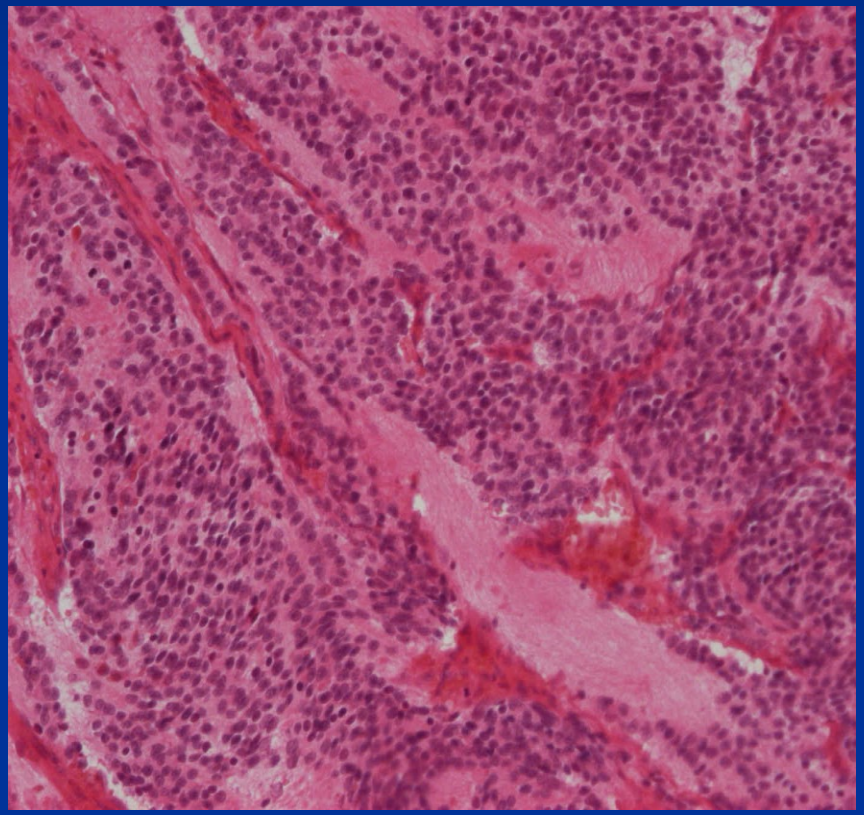


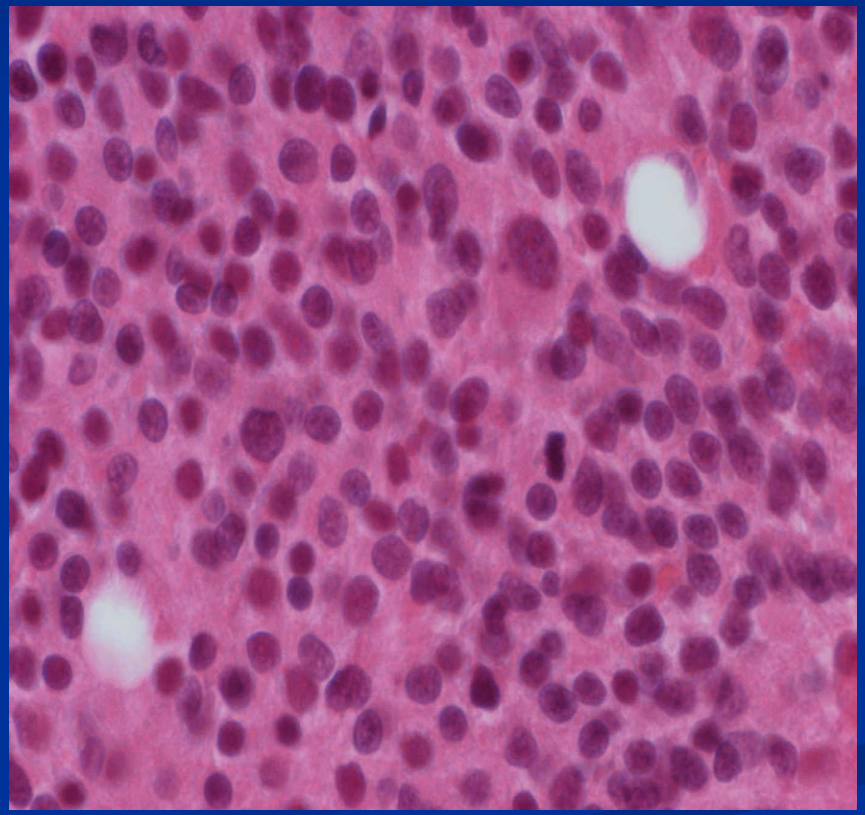






Neuroblastoma





Thank you for your attention …