PATHOLOGY OF BRAIN TUMORS

Presented By : Dr Amit Thapa

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Epidemiology

incidence

Primary cerebral malignancy-

4 to 10/Lac general population

1.6% of all primary tumors

2.3% of all cancer related deaths

Francis Ali-Osman, 2005

2nd most common cancer in children

20% of all cancers in children <15 yrs

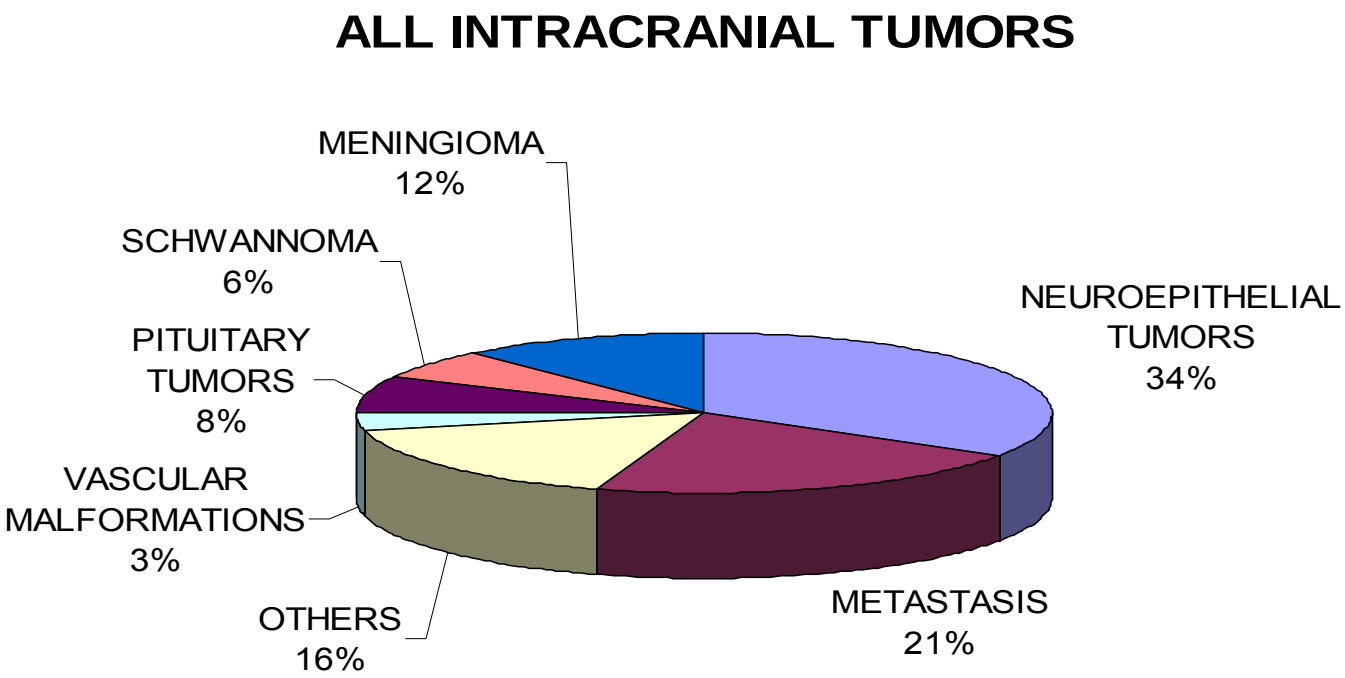
Epidemiological
incidence of individual tumor

Classification	Incidence / 100,000 population / yr
Metastatic	6
Astrocytoma	1.5
Glioblastoma	3
Meningioma	3
Primary CNS lymphoma	
Immunocompetent	0.3
Overall	0.8-6.8
Medulloblastoma	0.5
Germ cell tumor	0.2
Pinealoma / pineoblastoma	0.1

Parkin, 1997

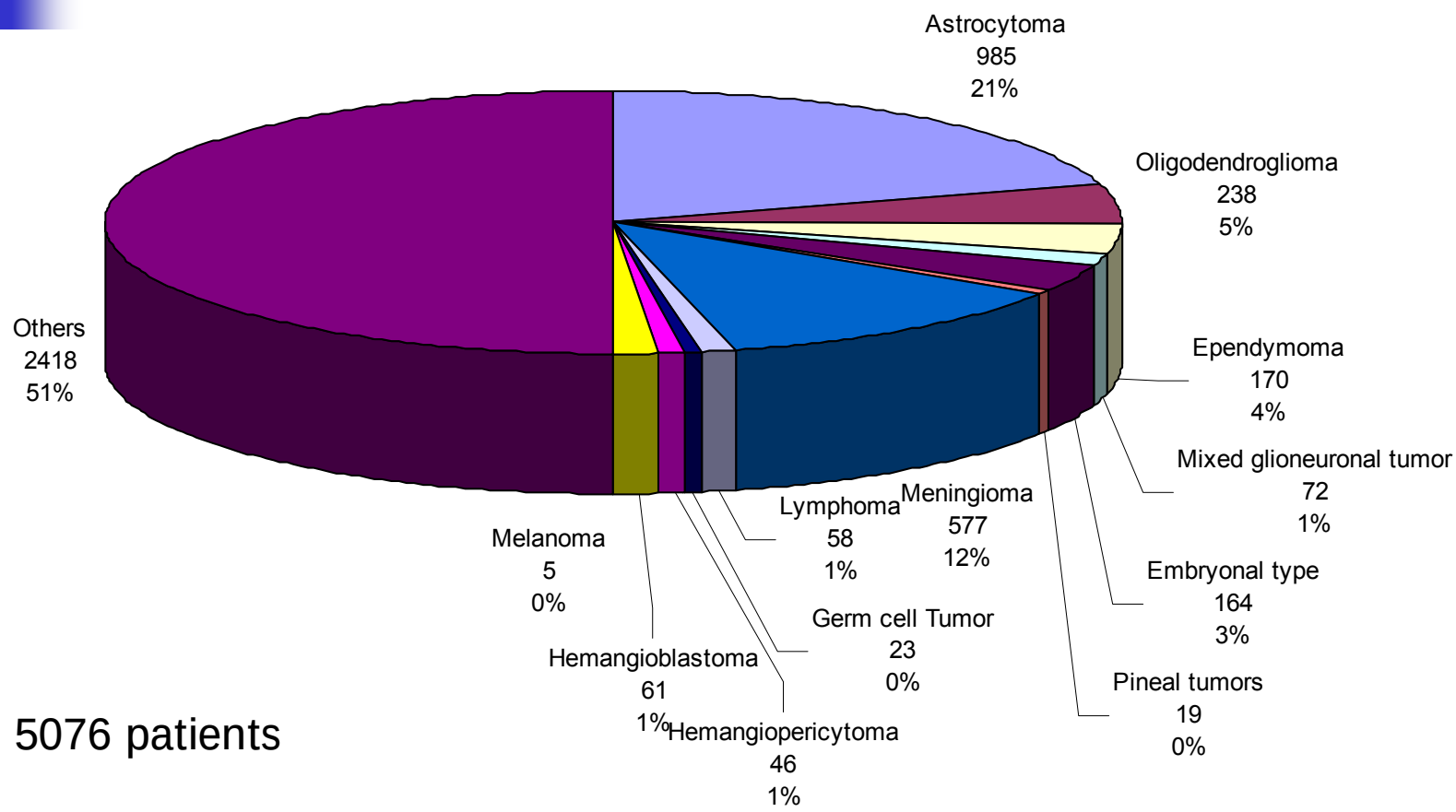
Epidemiology

comparative incidence



Epidemiology

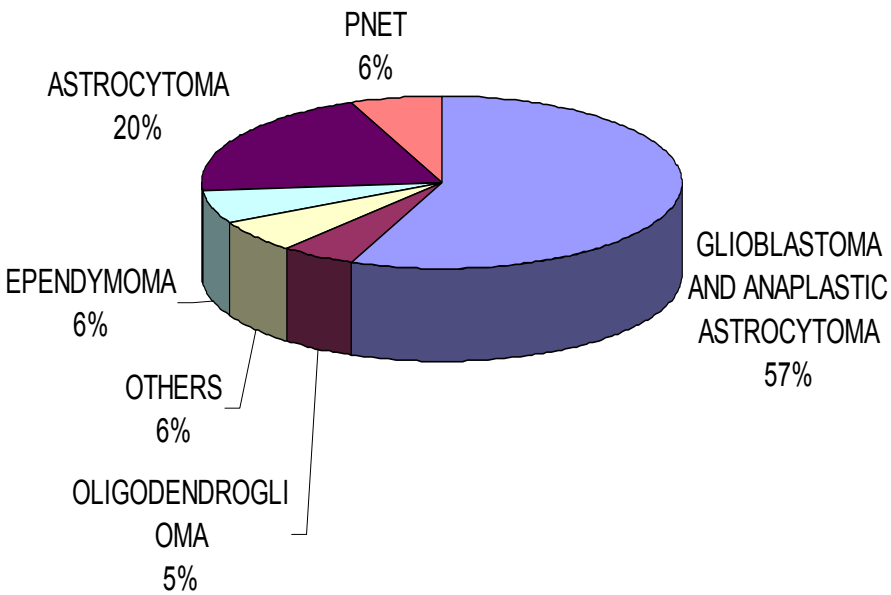
Relative incidence at AIIMS (2002-2007)



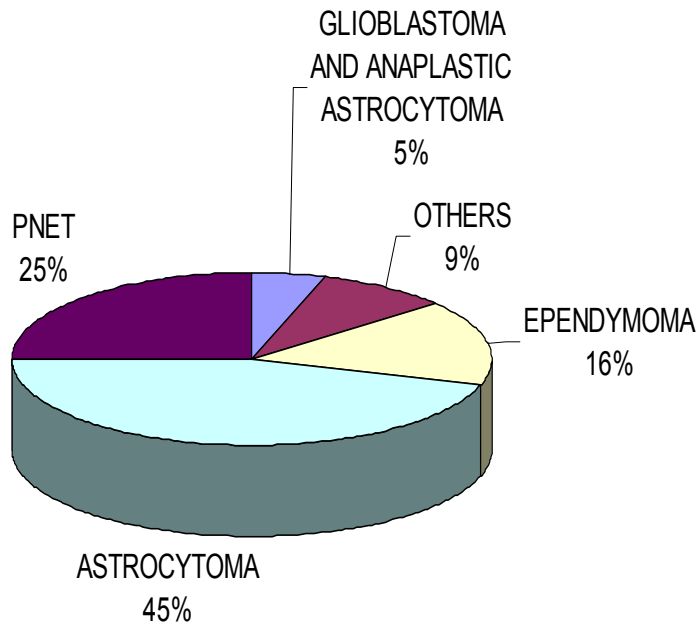
n= 5076 patients

Epidemiology
comparative incidence

INTRACRANIAL NEUROEPITHELIAL TUMORS, ALL AGES

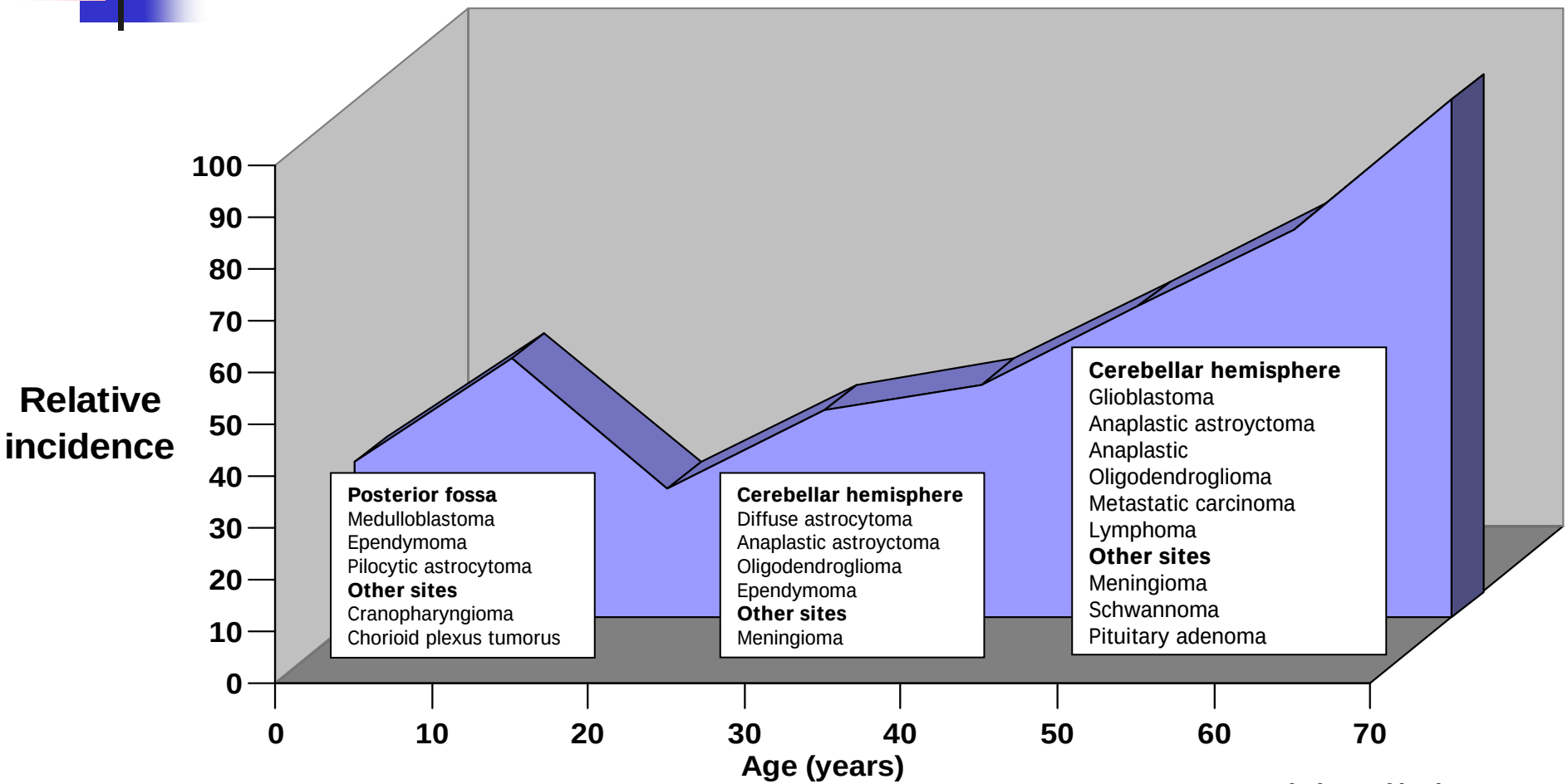


PRIMARY NEUROEPITHELIAL TUMORS OF CHILDHOOD



Epidemiological profile...

age wise distribution



Common tumors according to age distribution

Tumors of childhood

1. Cerebral hemispheres
Diffuse astrocytoma
Pilocytic astrocytoma
Anaplastic astrocytoma
GBM
PXA
PNET
Ganglion cell tumors
Ependymoma
Oligodendroglial tumors
Atypical teratoid/rhabdoid

2. Latral ventricles
Ependymoma
CPP
Astrocytoma
SEGA
PNET

3. Third ventricle
Ependymoma
Astrocytoma
CPP

4. Pineal region
Pineal cell tumors
Germ cell tumors
Glial tumors

5. Sellar region
Craniopharyngioma
Germ cell tumors
Pilocytic astrocytoma
Hamartoma

6. Brain Stem
Diffuse astrocytoma
Pilocytic astrocytoma
Anaplastic astrocytoma
GBM

7. Fourth ventricle
Ependymoma
Medulloblastoma
Pilocytic astrocytoma
CPP

8. Cerebellum
Medulloblastoma
Pilocytic astrocytoma
Atypical teratoid/rhabdoid

9. CPA
Ependymoma
CPP
Astrocytoma

Tumors of adulthood

1. Cerebral hemispheres
Diffuse astrocytoma
Anaplastic astrocytoma
GBM
Meningioma
Ependymoma
PXA
Oligodendroglioma
Mixed glioma
Gliomatosis cerebri
Ganglion cell tumors
Primary lymphoma

2. Lateral ventricles
SEGA
Ependymoma
Subependymoma
CPP
Oligodendroglioma
Central neurocytoma
Meningioma

3. Third ventricles
Ependymoma
Subependymoma
CPP
Central neurocytoma

4. Pineal region
Pineal tumors
Germ cell tumors

5. Sellar region
Pituitary adenoma
Craniopharyngioma

6. Brain Stem
Diffuse astrocytoma
Anaplastic astrocytoma
GBM

7. Fourth ventricles
Ependymoma
Subependymoma
CPP
Meningioma

8. Cerebellum
Medulloblastoma
Hemangioblastoma
Pilocytic astrocytoma

9. CPA
Schwannoma
Meningioma
Epidermoid tumors

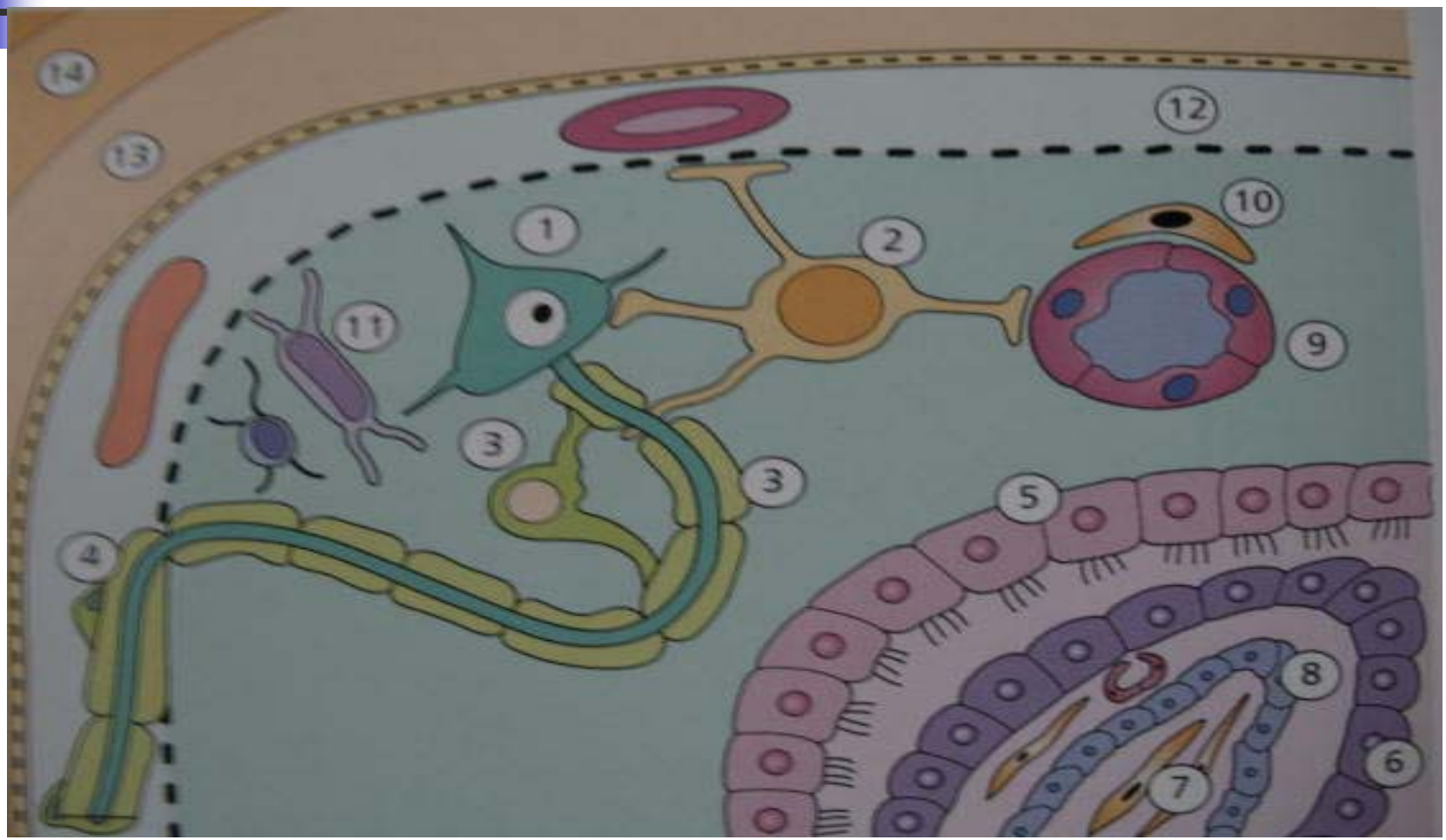
Epidemiology
Gender

•Males are more likely to be diagnosed with brain tumors than females-(1.5:1)

•Meningiomas and pituitary adenomas are slightly more common in women than in men.

Pathophysiology of brain tumors...

Pathogenesis



Pathology of brain tumors
- Dr Amit Thapa

Pathophysiology of brain tumors...
Pathogenesis

Cells of origin for most brain tumors – debatable

Molecular enquiries-

most likely cells of origin are multipotential stem cells

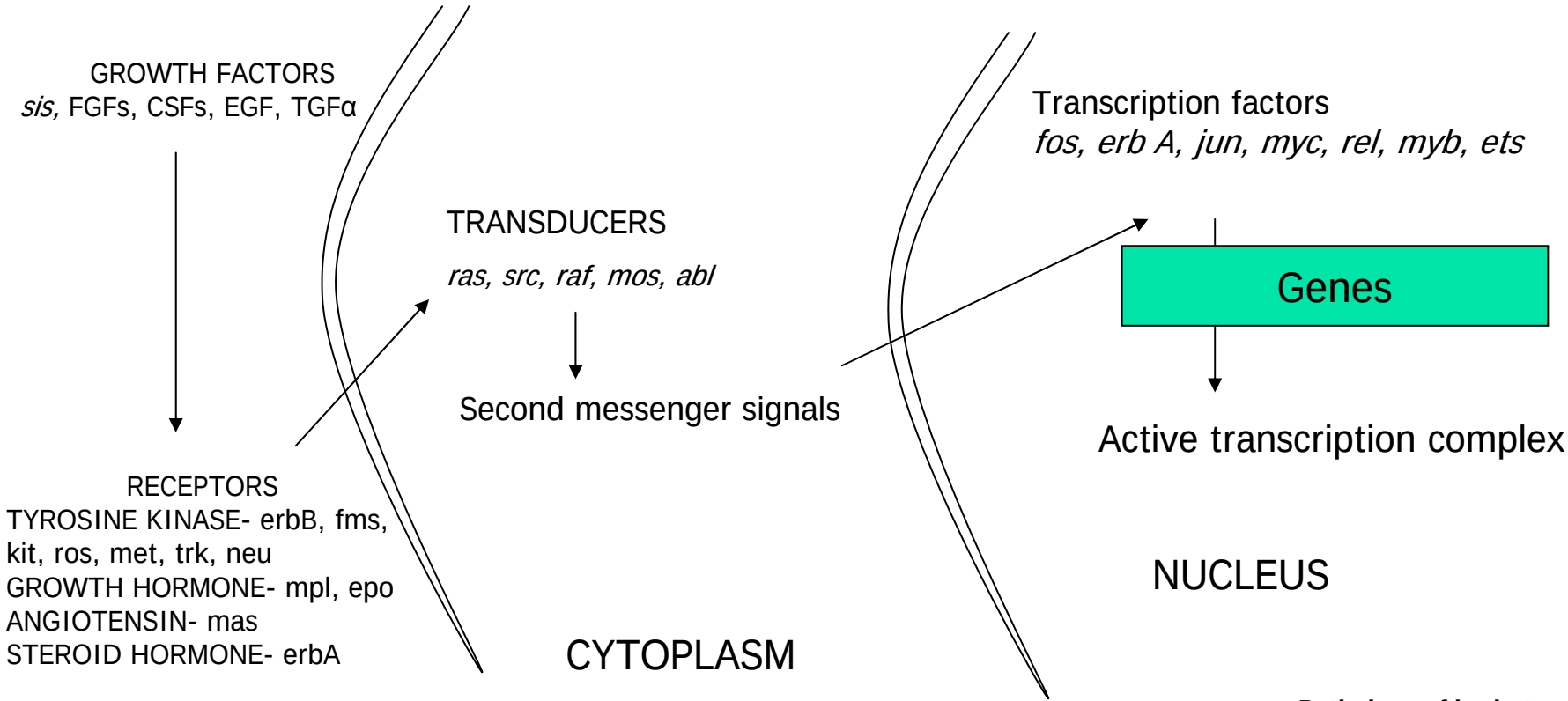
reside in both the developing and adult brain.

Am J Pathol 2001; 159: 779-86
Genes Dev 2001; 15: 1311-33

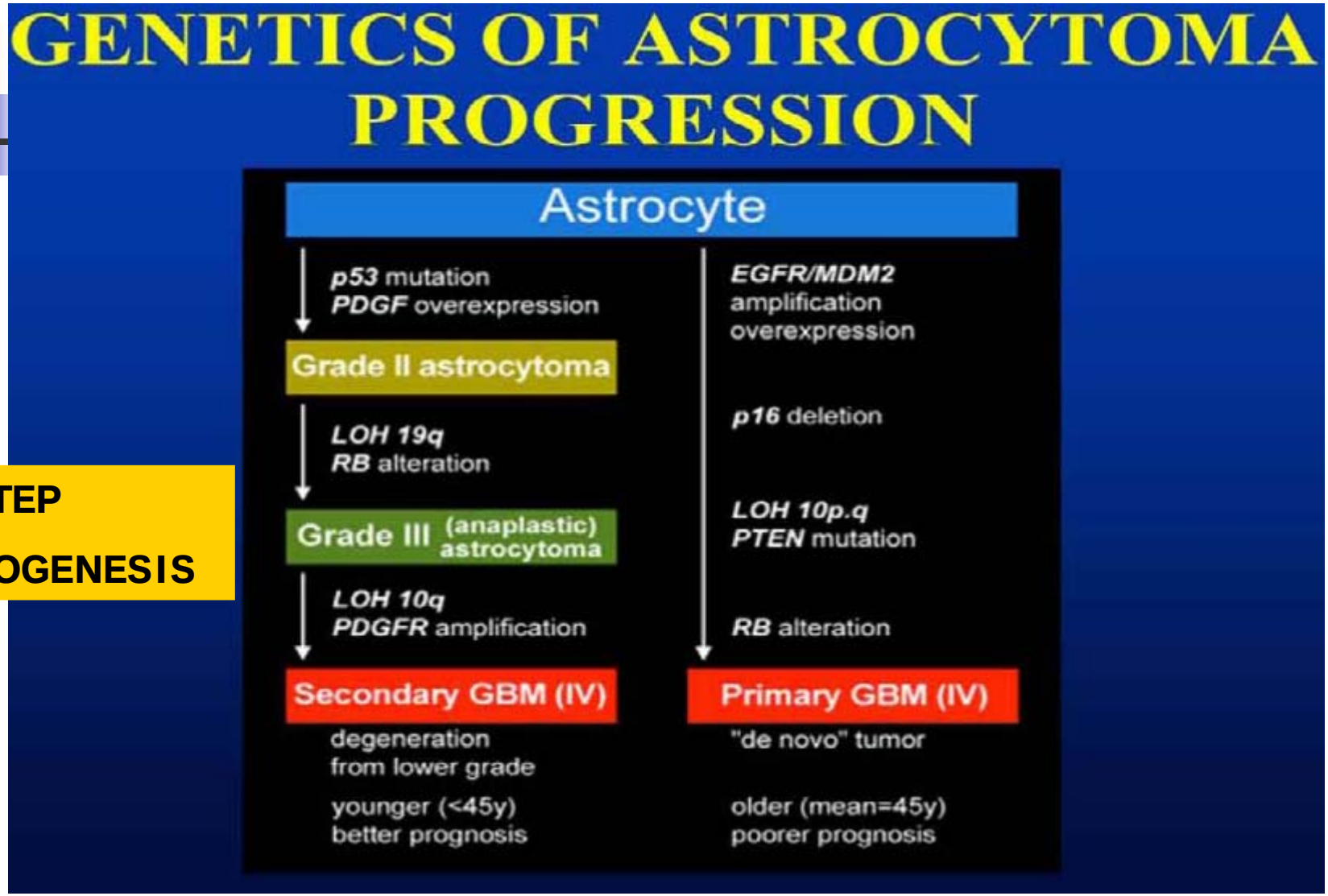
Pathophysiology of brain tumors...
ONCOGENES AND CNS

ONCOGENES

TUMOR SUPRESSOR GENES



Pathophysiology of brain tumors...



MULTISTEP CARCINOGENESIS

Pathophysiology of brain tumors...
FAMILIAL SYNDROMES

Disorder	Gene	Location	Protein function	Tumour types associated with disorder	Involved in sporadic CNS tumo
Li fraumeni	*TP53* (only 70%)	17p13.1	Transcription factor, apoptosis induction, etc	Many including astrocytomas	Mainly astrocytic
Neurofibromatosis type 1	*NF1*	17q11.2	GTPase activating protein homology	Astrocytomas (brain stem optic nerve) ependymomas, PNETs and meningiomas (pheochromocytoma), etc	Unknown
Neurofibromatosis type 2	*NF2*	22q12.2	Ezrin/moesin/radixin-like	Vestibular schwannomas, meningiomas, spinal schwannomas	Meningiomas, schwannomas
Familial adenomatous polyposis coli (or Turcot syndrome A)	*APC*	5q21–q22	Regulates β-catenin	Medulloblastoma	Unknown
Hereditary non-polyposis colorectal cancer (or Turcot syndrome B)	*MLH1*	3p21.3	Microsatellite instability (MIN+)	Glioblastoma (unknown if all germline mutations are associated with glioblastoma)	Unknown; astrocytic tumours th are MIN+ occur but are uncom
	MSH2	2p22–p21			
	MLH3	14q24			
	PMS1	2q31–q33			
	PMS2	7p22			
Basal cell naevus syndrome/Gorlin's syndrome	*PTCH*	9q22.3	Receptor for SHH inhibits SMO	Medulloblastoma	Medulloblastoma
Cowden disease (multiple hamartoma syndrome, Lhermitte-Duclos, etc)	*PTEN*	10q22–q23	Dual specificity phosphatase and Tensin homology	Astrocytomas reported but tumours in other organs more common—thyroid, breast, female genito-urinary tract	Glioblastomas
Melanoma-astrocytoma syndrome	*CDKN2A/p14ARF*	9p21	Cell cycle control (G1-S)/p53 level control	Astrocytomas	Astrocytic

Pathophysiology of brain tumors...
ETIOGENESIS

VIRUSES

- RNA virus- oncorna family

  Rous sarcoma virus, ASV, MSV, SSV

- DNA virus- Papovaviruses, Adenoviruses

  (Bovine papilloma virus, Human JC virus, SV40)

NO CONCLUSIVE PROOF OF VIRAL INDUCTION OF HUMAN BRAIN TUMORS

Pathophysiology of brain tumors...
ETIOGENESIS

RADIATION- Fibrosarcoma, meningiomas, GBM (?)

- True incidence unknown
- Criteria

1. Tumor must occur within ports of radiation therapy
2. Adequate latent period must have elapsed
3. No other predisposing factors- NF, MEN
4. Definitive tumor diagnosis
5. Rarely occur spontaneously in control

Pathophysiology of brain tumors...
ETIOGENESIS

CHEMICAL AGENTS

- Methylcholanthrene pellets- 1939
- Polycyclic hydrocarbons (PCHs)-

  gliomas (7-14 months),

  depending upon location
- Alkylating agents- most commonly used agent

  gliomas (oligodendrogliomas)

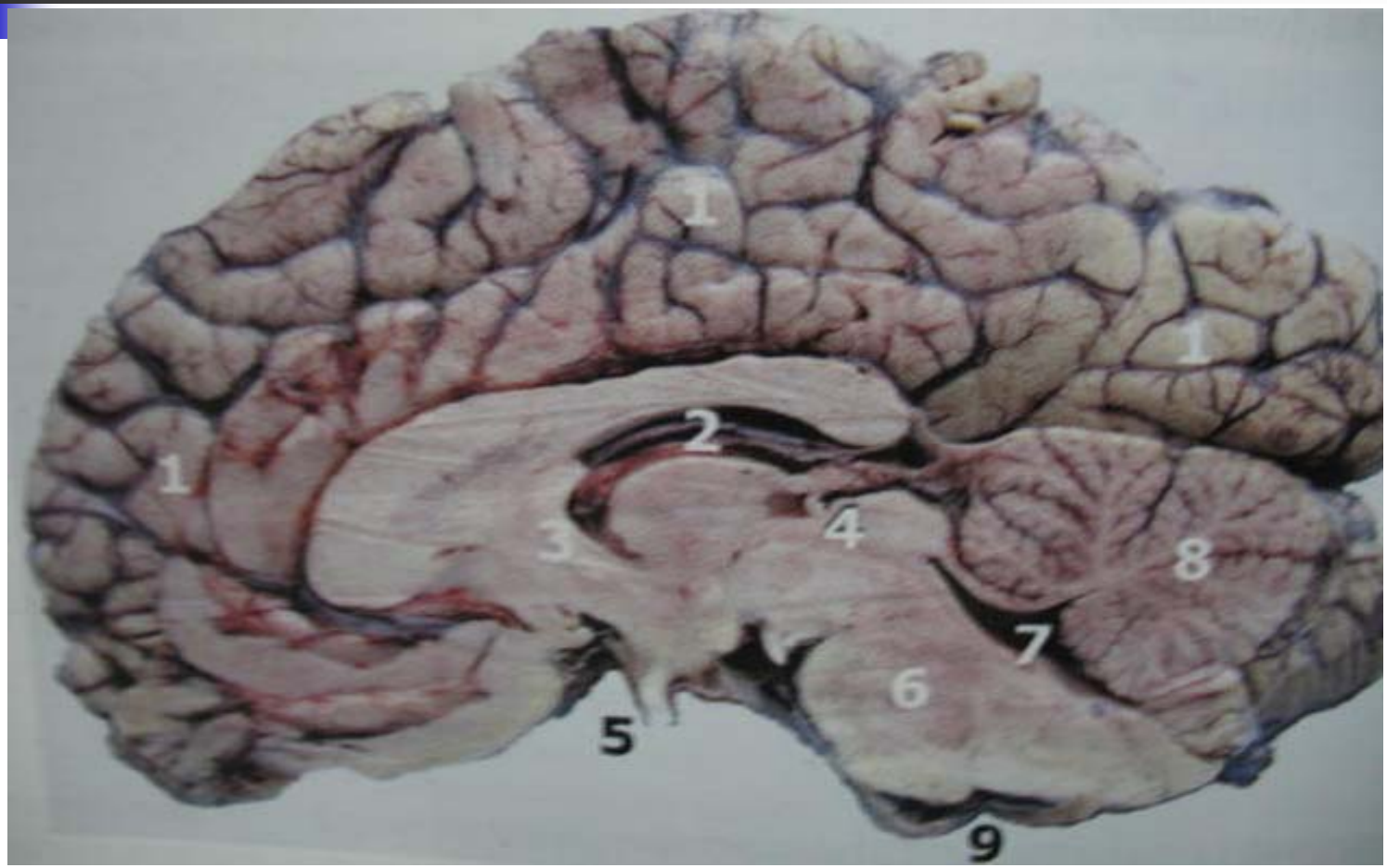
Pathophysiology of brain tumors...
IMMUNOLOGY OF BRAIN TUMORS

- Tumor associated-
  - transplantation antigen, tumor specific antigen, viral antigen, fetal antigen
- Recognition → Proliferation → Effector
- Cellular immunity-

  relative suppressor dominance,

  balance between helper & suppressor
- Humoral immunity
- Is brain an immunologically privileged site ?
- Immunologic response in brain tumor
  - Host suppression
  - Cytokines, MHC antigen
  - Organ and organ related antigens
  - Cellular infiltration
  - Mechanism of suppression and blocking

Classification- cell origin and derivative



Classification of brain tumors

- Bailey and Cushing- 1926, first attempt to classify

  Bailey P, Cushing HA. A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. Philadelphia: JP Lippincott, 1926.

- Zulch and an international team (1979)

  1st WHO classification of tumors of the CNS

Classification

Primary tumors of the brain

- Tumors of Neuroepithelial tissue
- Tumors of Meninges
- Tumors of the sellar region
- Germ cell tumor
- Choroid plexus tumors
- Tumors of nerves and/or nerve sheath
- Cysts and tumor like lesions
- Other primary tumors, including skull base
- Hematopoietic neoplasms

Metastatic brain tumors and carcinomatous meningitis

WHO CLASSIFICATION OF BRAIN TUMORS, 4TH EDN, 2007

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	*9390/1**
Choroid plexus carcinoma	9390/3
Other neuroepithelial tumours	
Astroblastoma	9430/3
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	*9431/1**

Neuronal and mixed neuronal-glial tumours	
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Extraventricular neurocytoma	*9506/1**
Cerebellar liponeurocytoma	*9506/1**
Papillary glioneuronal tumour	*9509/1**
Rosette-forming glioneuronal tumour of the fourth ventricle	*9509/1**
Paraganglioma	8680/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	*9395/3**
Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

TUMOURS OF CRANIAL AND PARASPINAL NERVES

Schwannoma (neurilemoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0

WHO CLASSIFICATION OF BRAIN TUMORS, 4TH EDN, 2007 CONTD...

Perineurioma	
Perineurioma, NOS	9571/0
Malignant perineurioma	9571/3
Malignant peripheral nerve sheath tumour (MPNST)	
Epithelioid MPNST	9540/3
MPNST with mesenchymal differentiation	9540/3
Melanotic MPNST	9540/3
MPNST with glandular differentiation	9540/3

TUMOURS OF THE MENINGES

Tumours of meningothelial cells	
Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	9530/0
Secretory	9530/0
Lymphoplasmacyte-rich	9530/0
Metaplastic	9530/0
Chordoid	9538/1
Clear cell	9538/1
Atypical	9539/1
Papillary	9538/3
Rhabdoid	9538/3
Anaplastic (malignant)	9530/3
Mesenchymal tumours	
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Solitary fibrous tumour	8815/0
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteosarcoma	9180/3
Osteochondroma	9210/0
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/1
Haemangiopericytoma	9150/1
Anaplastic haemangiopericytoma	9150/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma - PNET	9364/3
Primary melanocytic lesions	
Diffuse melanocytosis	8728/0
Melanocytoma	8728/1
Malignant melanoma	8720/3
Meningeal melanomatosis	8728/3
Other neoplasms related to the meninges	
Haemangioblastoma	9161/1

LYMPHOMAS AND HAEMATOPOIETIC NEOPLASMS

Malignant lymphomas	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3

GERM CELL TUMOURS

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3

TUMOURS OF THE SELLAR REGION

Craniopharyngioma	9350/1
Adamantinomatous	9351/1
Papillary	9352/1
Granular cell tumour	9582/0
Pituicytoma	*9432/1*
Spindle cell oncocytoma of the adenohypophysis	*8291/0*

METASTATIC TUMOURS

GRADING

Histopathological grading

- Predict biological behavior of a neoplasm
- Clinical setting- influence choice of therapy

- Broder's four tiered grading- general pathology
- Kernohan and Sayre- 1952,

  graded gliomas into 1 to 4

  degree of their dedifferentiation

- St Anne/Mayo or Daumass- Duport system- 4 grades

  nuclear atypia, mitoses, endothelial proliferation, necrosis

GRADING

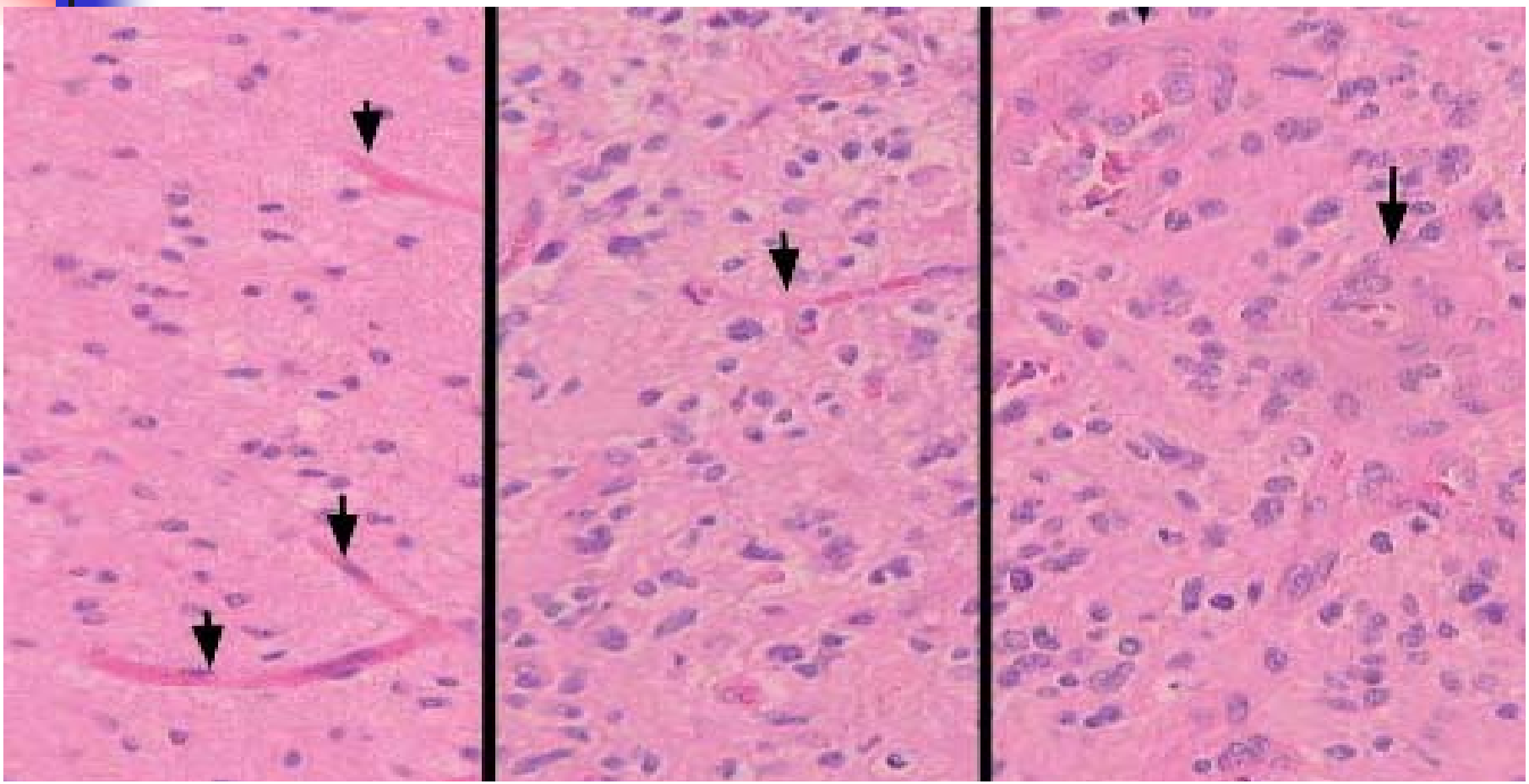
WHO classification of tumors of the nervous system

- includes a grading scheme - ‘malignancy scale’ across a wide variety of neoplasms
- rather than a strict histological grading system
- widely used, but not a requirement for the application of the WHO classification

WHO *Grading*

Grade I		• low proliferative potential	possibility of cure (surgical resection alone)	
Grade II	▪ + cytological atypia	• low-level proliferative activity • generally infiltrative in nature • often recur • tend to progress to higher grades of malignancy		Survive >5 yrs
Grade III	• + nuclear atypia/ anaplasia • + brisk mitotic activity		adjuvant radiation +/- chemotherapy	Survive 2-3 yrs
Grade IV	• + microvascular proliferation • + /- necrosis • cytologically malignant, • mitotically active, • necrosis-prone neoplasms	• rapid pre- and postoperative disease evolution • fatal outcome. • In some- • Widespread infiltration of surrounding tissue • craniospinal dissemination	adjuvant radiation +/- chemotherapy	Depends upon therapy, Survive <1 yr

WHO *Grading*



WHO GRADING OF BRAIN TUMORS, 4TH EDN, 2007

	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Pathophysiology of brain tumors...

W.H.O. 3

- Emphasizes molecular/cytogenetic factors
  - Identifies novel tumor suppressor gene mutations
  - Emphasizes how malignant tumors develop, disseminate
  - Looks at
    - Importance of angiogenesis
    - Possible importance of apoptosis vs. necrosis
    - Biological behavior
    - Imaging (standard MR, not newer techniques)
- Added new tumors
  - Chordoid glioma of third ventricle
  - Atypical teratoid/rhabdoid tumor
- Recognized familial tumor syndromes

Pathophysiology of brain tumors...

What's new in WHO , 4th edition, 2007

- New entities-
  angiocentric glioma
  papillary glioneuronal tumour
  rosette-forming glioneuronal tumour of the fourth ventricle
  papillary tumour of the pineal region
  pituicytoma
  spindle cell oncocytoma of the adenohypophysis

- histological variants added-
  any e/o different age distribution, location, genetic profile or clinical behaviour

- WHO grading scheme and the sections on genetic profile updated

- Rhabdoid tumour predisposition syndrome added to the familial tumour syndromes

Pathophysiology of brain tumors...

Classification-

The international classification of diseases for oncology (ICD-O)

ICD-O Coding

•Established more than 30 years ago

•An indispensable interface between pathologists and cancer registries.

•Assures histopathologically stratified population-based incidence and mortality data become available for epidemiological and oncological studies

•The histology (morphology) code is increasingly complemented by genetic characterization of human neoplasms.

•The ICD-O topography codes largely correspond to those of the tenth edition of the *International statistical classification of diseases, injuries and causes of death (ICD-10)* of the WHO.

Clinical presentations

1. Due to direct tissue destruction,
2. local brain infiltration or
3. secondary effect of increased ICP (Cushing's triad)

Depends upon location-

positive (headache/ seizure),
negative symptoms (loss of function)

Headache-

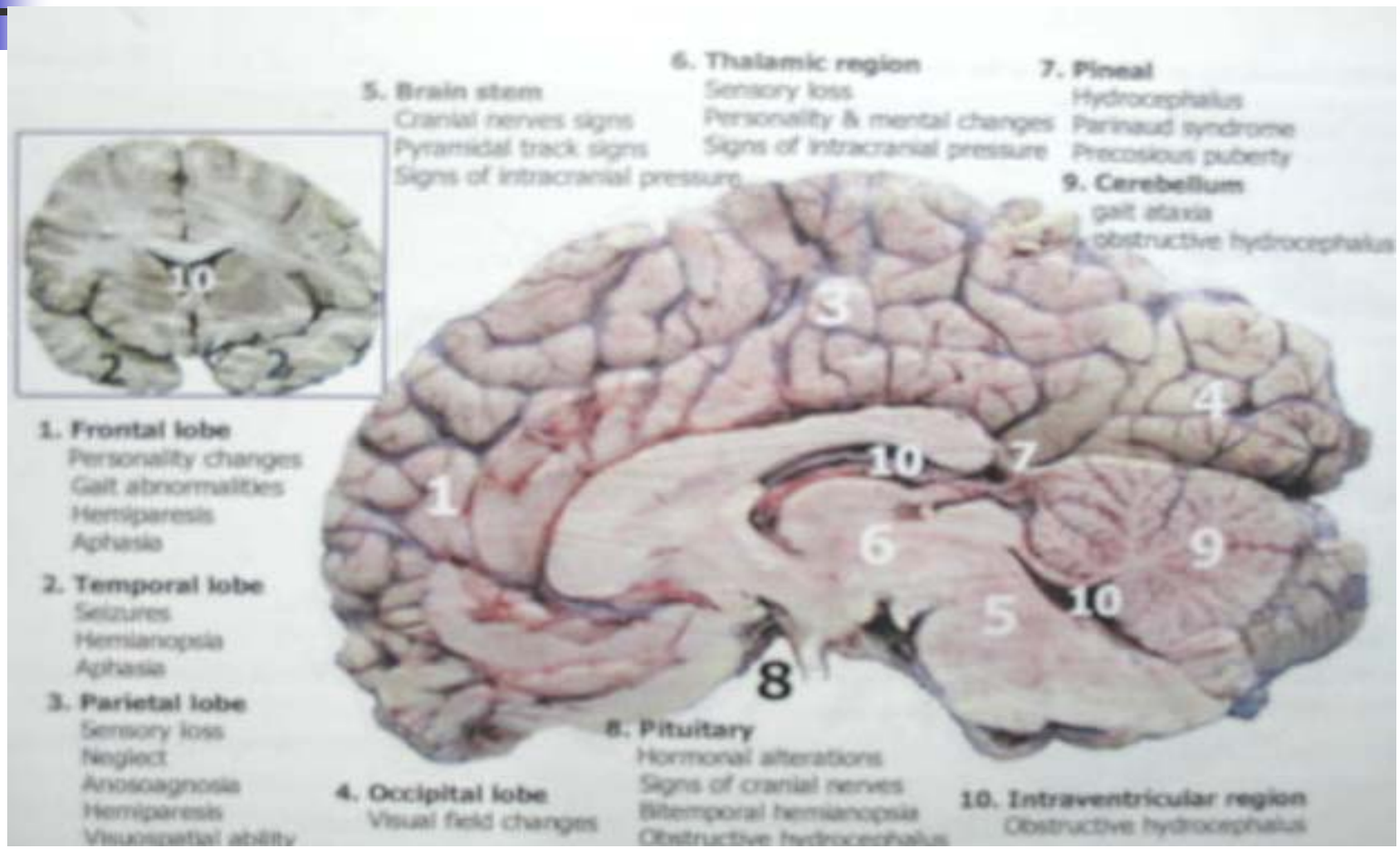
35% as first symptoms.
70% in growing tumor.
Associated with vomiting/ nausea, papilledema, focal cerebral signs

Facial pain- tumors at base of skull or nasopharynx

Seizure-

30% as first symptom.
98% in oligodendroglioma and 18% in mets

Pathophysiology of brain tumors...
Clinical presentations



Pathology of specific tumors

Metastatic (2^0 malignant) tumor

- 3 times more common than primary brain tumor
- Often lodge- gray- white junction of cerebral, cerebellar hemisphere
- Commonly from lung, breast, kidney
- 2 major forms:
    1. Single/ multiple well circumscribed deposits (commonest)
    2. Carcinomatous meningitis

        Leptomeningeal (breast, lung)
        dural metastasis (non CNS lymphoma)

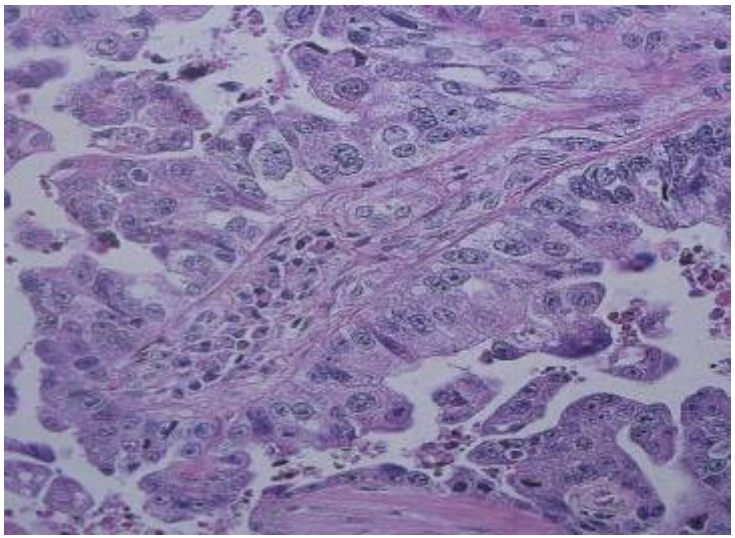
- Route- hematogenous/ direct/ CSF
- Abundant hemorrhage- melanoma, RCC, Chorioca
- Multiplicity common
- Retain primary characteristics

Metastatic (2^0 malignant) tumor

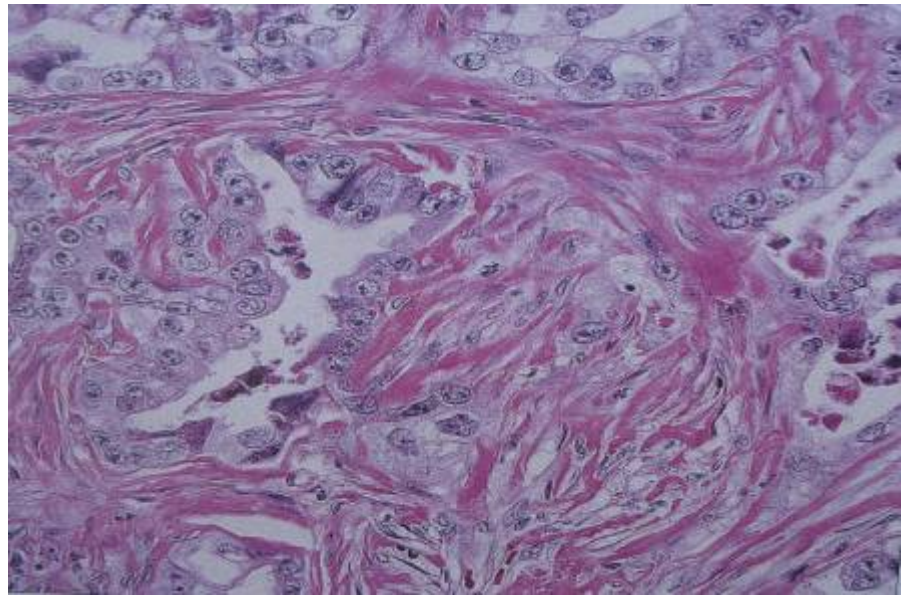
Well circumscribed glistening tumor in lateral lobe of cerebellum- adenoca colon

Heavily pigmented lesion in lateral aspect of cerebellum and brain stem- cutaneous melanoma (very hemorrhagic)

Metastatic (2^0 malignant) tumor



Papillary ca kidney/ colon/ thyroid-
exhibit papillary structure. Prominent nucleoli and irregular crowding of nuclei



Adenocarcinomatous mets-
Retain nuclei with prominent nucleoli, vacuolated cytoplasm, glands with mucinous secretion
Lung/ ovary/ breast/ colon

WHO CLASSIFICATION OF BRAIN TUMORS, 4TH EDN, 2007

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	*9390/1**
Choroid plexus carcinoma	9390/3
Other neuroepithelial tumours	
Astroblastoma	9430/3
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	*9431/1**
Neuronal and mixed neuronal-glial tumours	
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Extraventricular neurocytoma	*9506/1**
Cerebellar liponeurocytoma	*9506/1**
Papillary glioneuronal tumour	*9509/1**
Rosette-forming glioneuronal tumour of the fourth ventricle	*9509/1**
Paraganglioma	8680/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	*9395/3**
Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

TUMOURS OF CRANIAL AND PARASPINAL NERVES

Schwannoma (neurilemoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0

Astrocytoma

Classification by cell type

Ordinary-

- Fibrillary
- Gemistocytic
- protoplasmic

Special- favorable prognosis

- Pilocytic
- Microcystic cerebellar
- Subependymal giant cell

WHO GRADING OF BRAIN TUMORS, 4TH EDN, 2007

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Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
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Ependymoma		•		
Anaplastic ependymoma			•	
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Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
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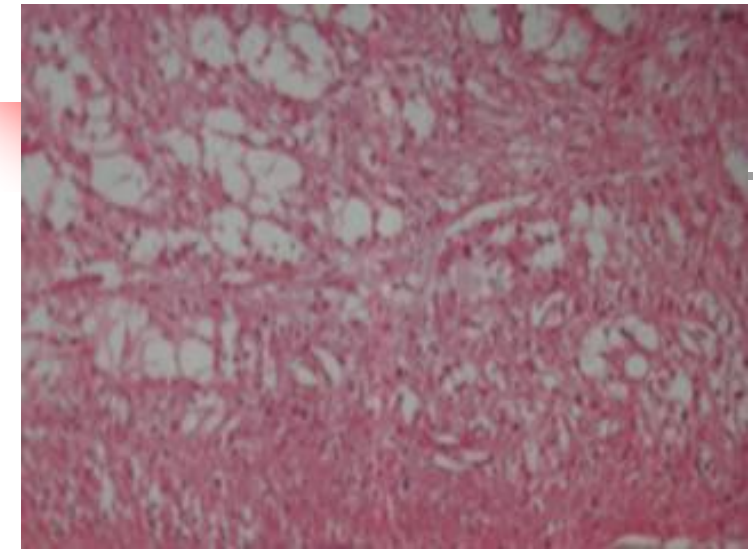
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			

	I	II	III	IV
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

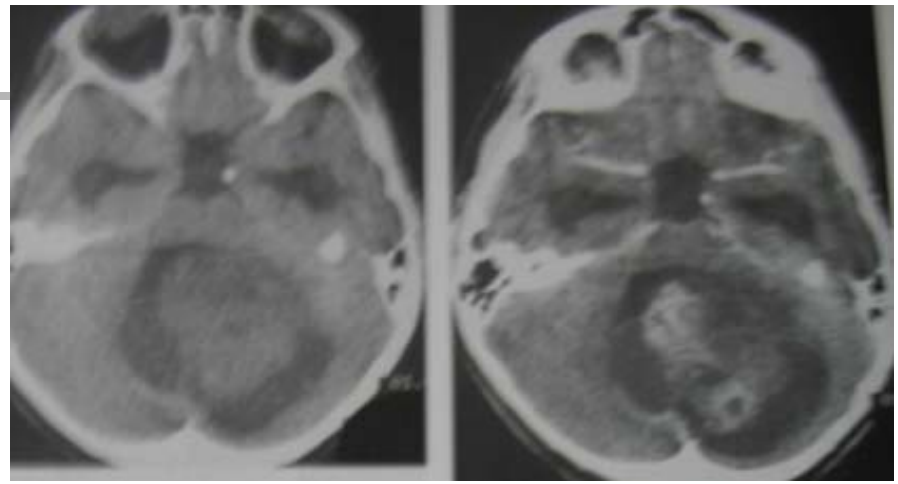
Pilocytic Astrocytoma

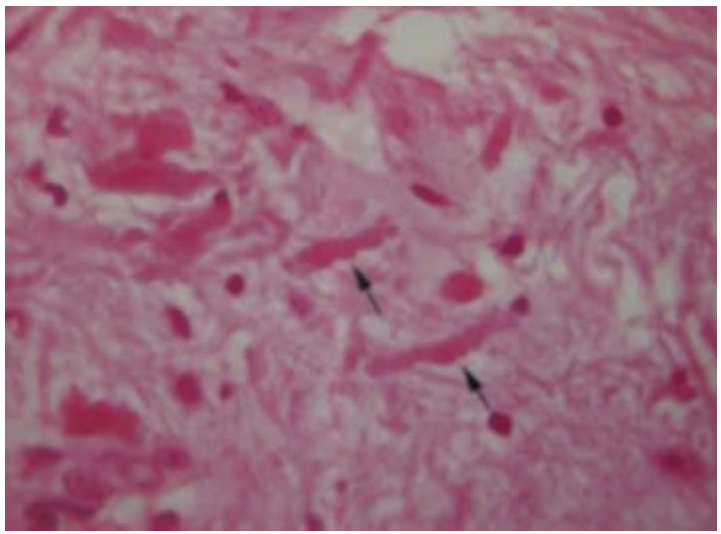
- Most common brain tumor in children
- Cerebellum> adj 3rd ventricle> brainstem
- Circumscribed cystic mass with mural nodule
- Genetics: sporadic/ syndromic
- Slow growing
- Histology:
  - Classic biphasic pattern
    - Compacted bipolar cells with rosenthal fibres
    - Loose textured mulitpolar cells
  - Leptomeningeal seeding

Pilocytic Astrocytoma

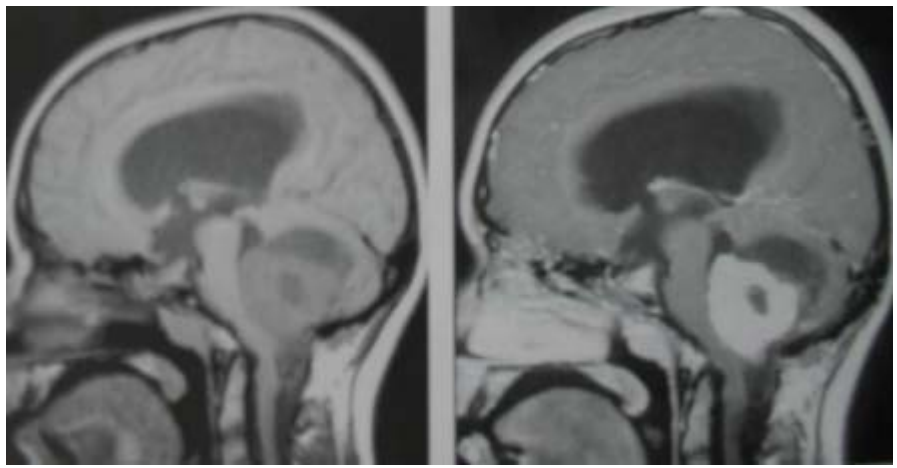


Combination of mildly cellular and loose areas with microcyst





Rosenthal fibres



Pathology of brain tumors
- Dr Amit Thapa

WHO GRADING OF BRAIN TUMORS, 4TH EDN, 2007

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Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
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Diffuse astrocytoma		•		
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Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
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Choroid plexus tumours				
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Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
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Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
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Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
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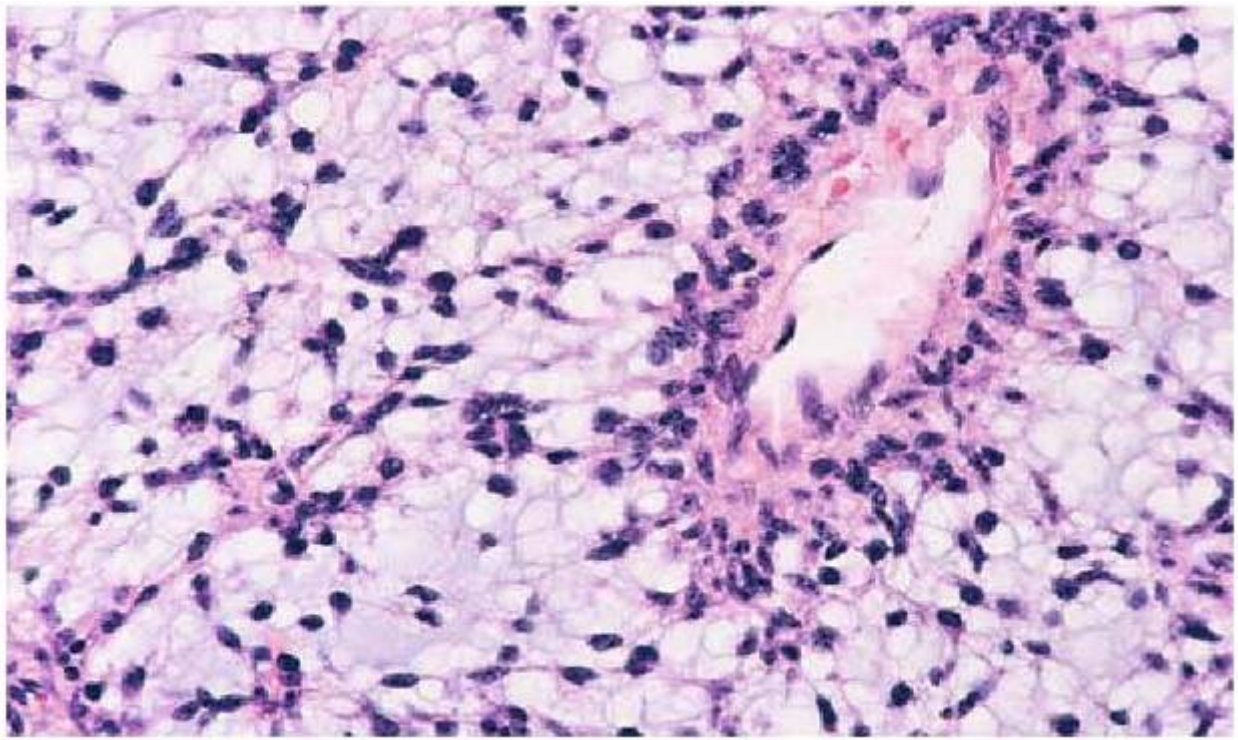
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Pilocytic Astrocytoma
Pilomyxoid astrocytoma

- WHO grade II
- Jänisch et al. in 1985 as
  'diencephalic pilocytic astrocytoma with clinical onset in infancy'
- hypothalamic/chiasmatic region,
  (sites also affected by classical pilocytic astrocytomas)
- Histologically- prominent myxoid matrix and angiocentric arrangement of monomorphous, bipolar tumour cells.
- Infants and children (median age, 10 months)
- Less favorable prognosis.
- Local recurrences and CSF spread are more likely

Pilocytic Astrocytoma

Pilomyxoid astrocytoma



Monomorphous population of tumor cells in a homogenously myxoid background with angiocentric accumulation

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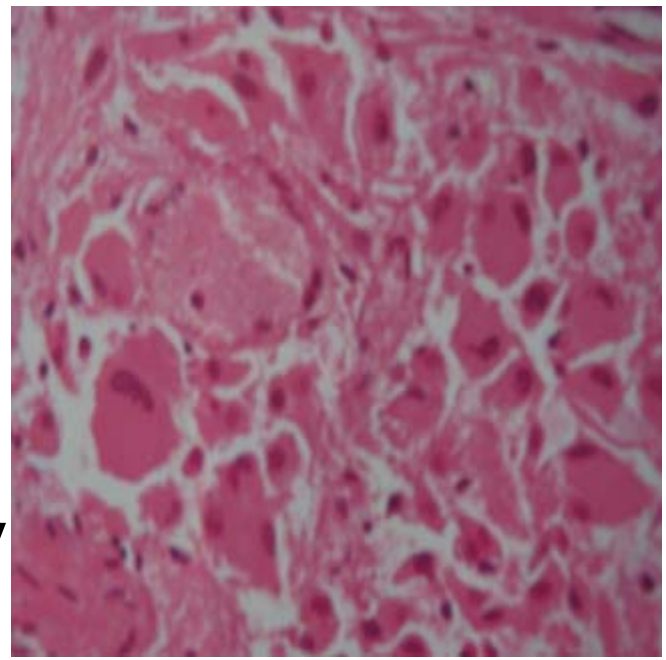
Subependymal giant cell astrocytoma

- Invariably with Tuberous sclerosis, 8-18yrs
- Near foramen of monro→ Hydrocephalus
- Histology: spindle to epithelioid large cells with abundant glassy eosinophilic cytoplasm, in perivascular pseudorosettes



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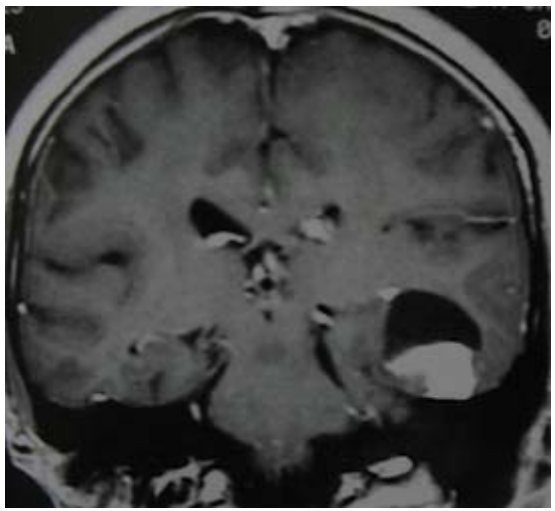
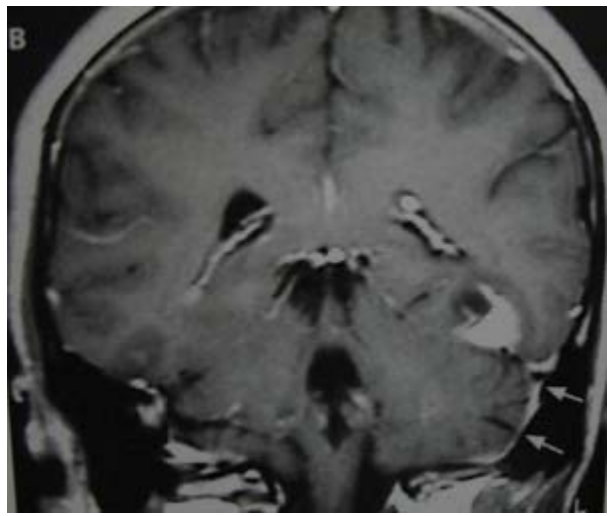
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

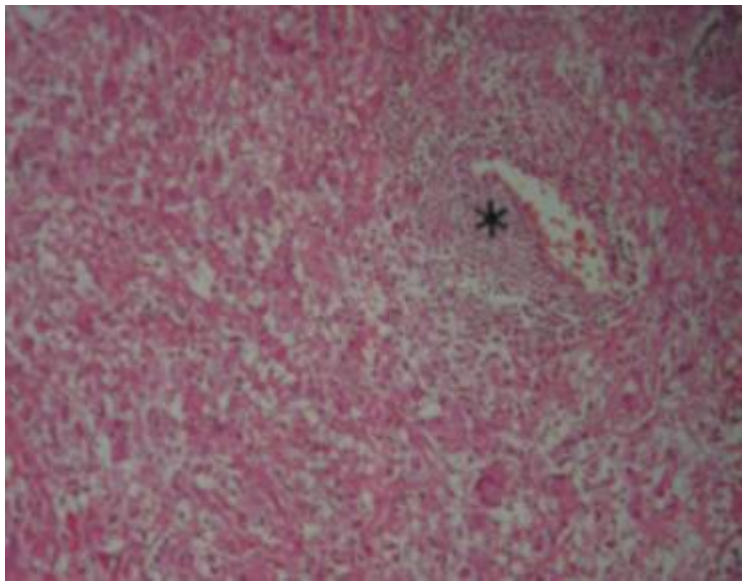
Pleomorphic xanthoastrocytoma

- Exclusive young adults
- Rare but important cause: TLE
- Supratentorial intracortical cystic mass with mural nodule abutting meninges with dural tail

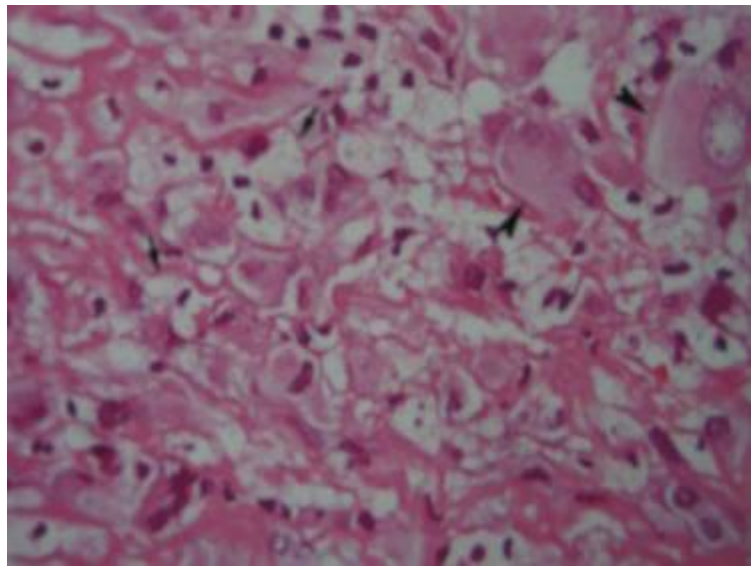




Pleomorphic xanthoastrocytoma



Cellular pleomorphic tumor with focus of perivascular lymphocytes



Large pleomorphic plump cells and cells filled with lipid droplets

D/D- glioblastoma

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Spindle cell oncocytoma of the adenohypophysis	•			

Diffuse astrocytoma

- 25% of all gliomas
- Supratentorial > brain stem (MC children)
- Mean age-34yrs , male >
- Gross: unencapsulated ill defined tumor with firm rubbery consistency, expanding involved cortex
- M/E:
  - hypercellularity with indistinct tumor border
  - Cellular differentiation
- Tendency to differentiate into higher grade with age

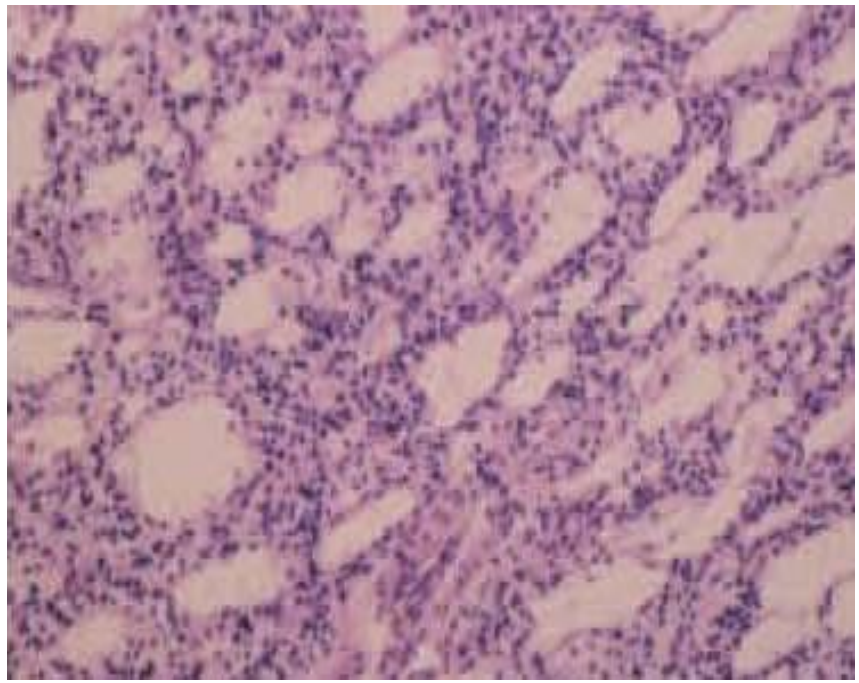
Diffuse astrocytoma Grading system

Kernohan	St A/M Current	WHO current	Ringertz	UCSF current	Bailey and Cushing 1926, 1930
1	2	II	Astrocytoma	MoAA	Astrocytoma
2	3	III	Anaplastic Astrocytoma	HAA	Astroblastoma
3	4	IV	GBM	GBM	Spongioblastoma multiforme
4					

Diffuse astrocytoma *subtypes*

protoplasmic astrocytoma

- homogenous, translucent, gelatinous appearance
- Composed- neoplastic astrocytes
  (small, round- oval nuclei, which are moderately rich in chromatin) surrounded by scanty cytoplasm with few processes.
- Microcytic and mucoid degenerations are common
- GFAP - sparse.

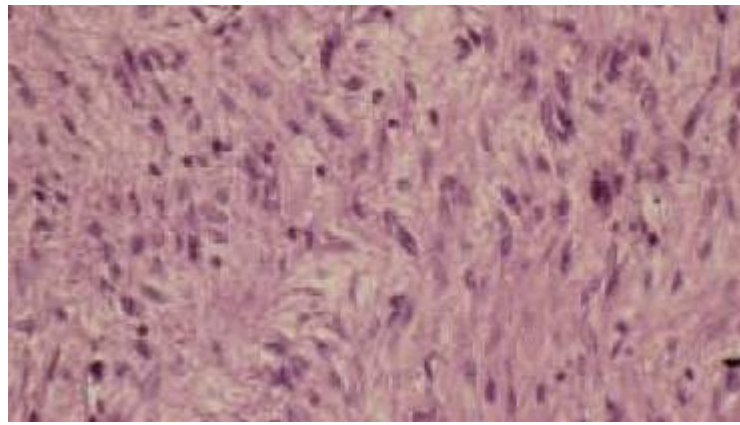


Microcystic degeneration

Diffuse astrocytoma *subtypes*

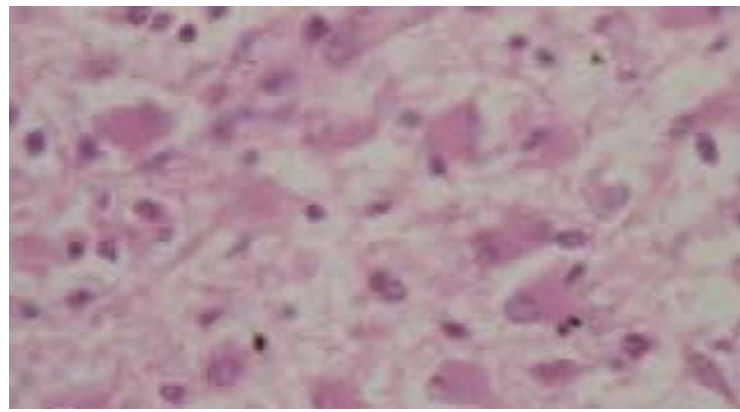
Fibrillary astrocytoma

- gross- firm rubbery, cut surfaces: whitish-gray.
- Composed: small stellate, elongated astrocytes fibrillary processes- fine in loose meshwork & bundles, leaving the pre-existing tissue relatively preserved.
- GFAP - variable.
- Microcystic degenerations +/-



Gemistocytic astrocytoma

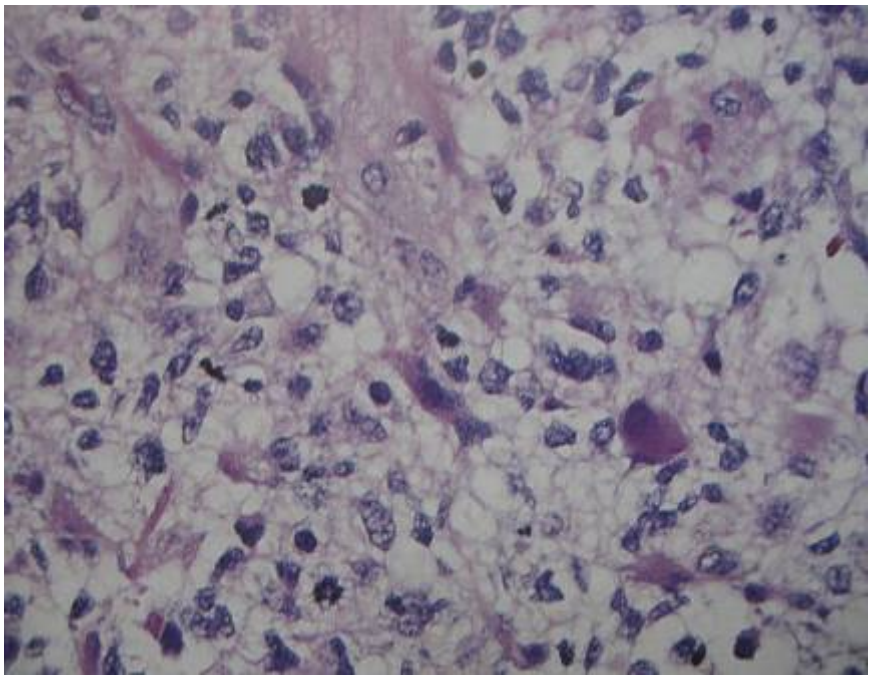
- soft & homogenous.
- Composed: large, plump neoplastic astrocytes with abundant glassy eosinophilic cytoplasms and peripherally displaced nuclei
- GFAP expression common



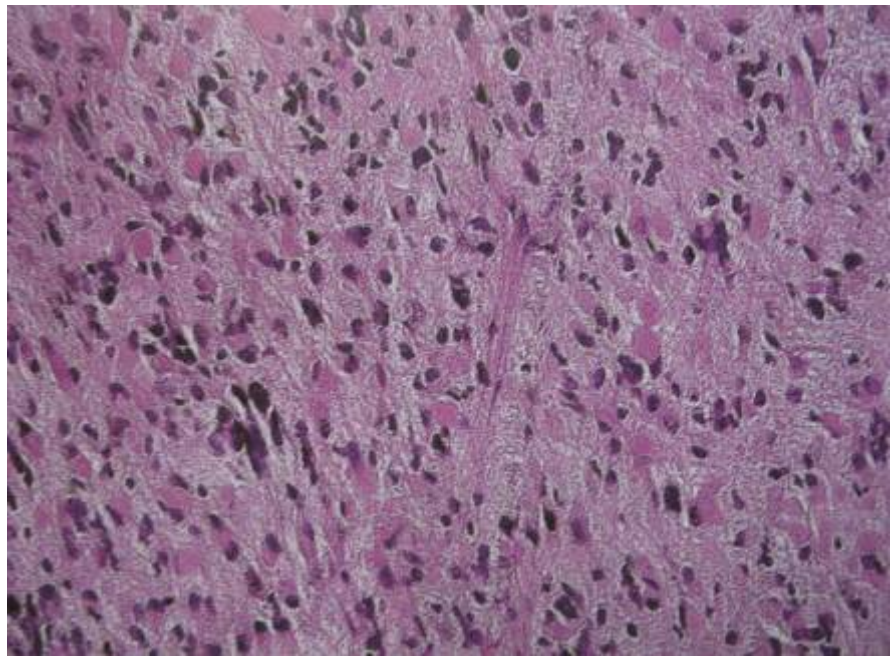
Anaplastic Astrocytoma (WHO grade III)

- Adults
- cerebral hemispheres.
- Grossly, it is somewhat better demarcated, soft, and grayish-pink.
- Histologically,
  - cellularity high, pleomorphism conspicuous
  - Hyperchromatic nuclei: small to large to multinucleated giant cells.
  - Mitoses frequent
  - Vascular proliferation not prominent, necrosis absent
- It may disseminate along the subarachnoid space

Anaplastic Astrocytoma (WHO grade III)

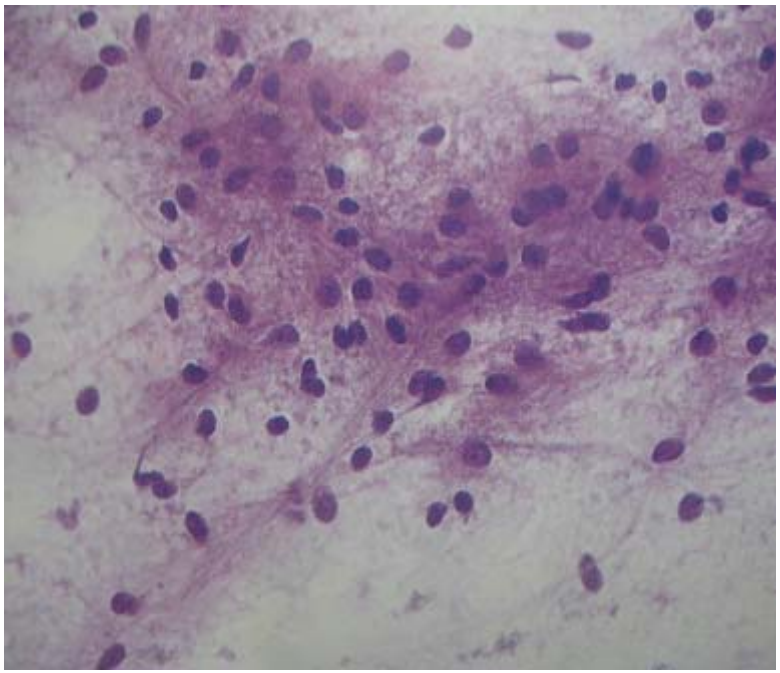


Significant nuclear pleomorphism and frequent mitotic figures but no necrosis

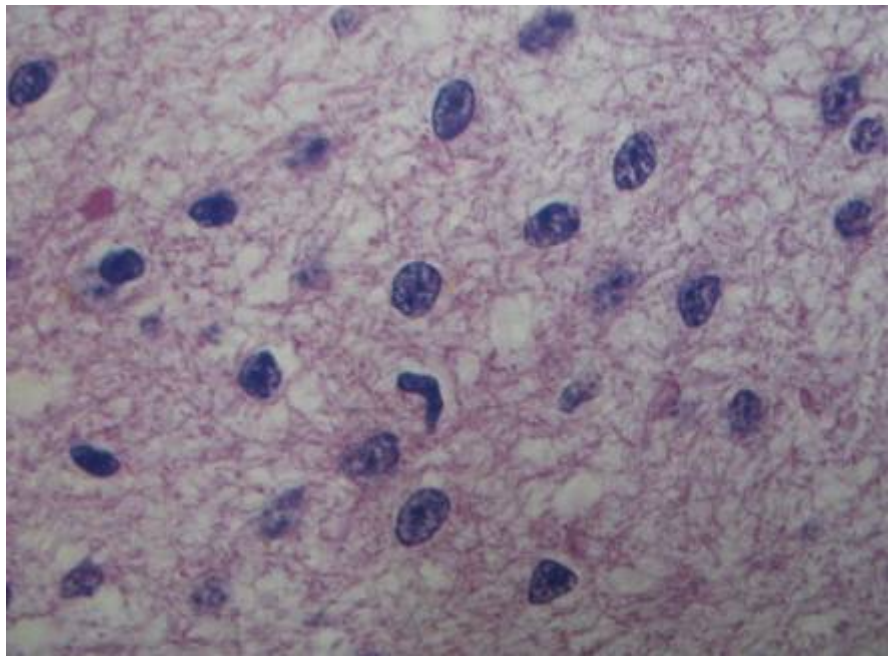


Hypercellularity urges one to see for mitotic figures to establish anaplasia by Dumas- Duport grading (H&H)

Anaplastic Astrocytoma (WHO grade III)

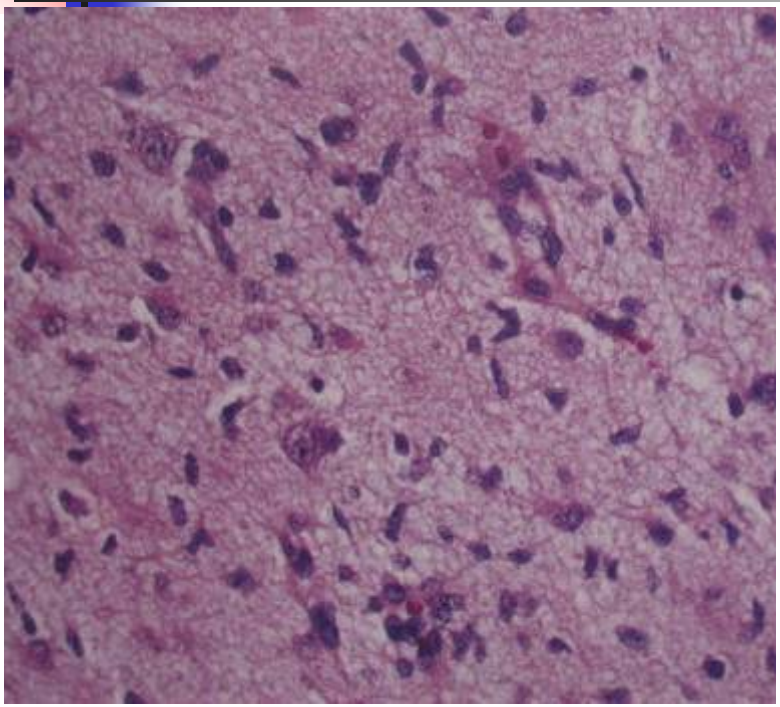


Touch smear- prominent fibrillar processes and moderate nuclear pleomorphism. Cytoplasm trailing away from a nucleus resulting in a unipolar appearance

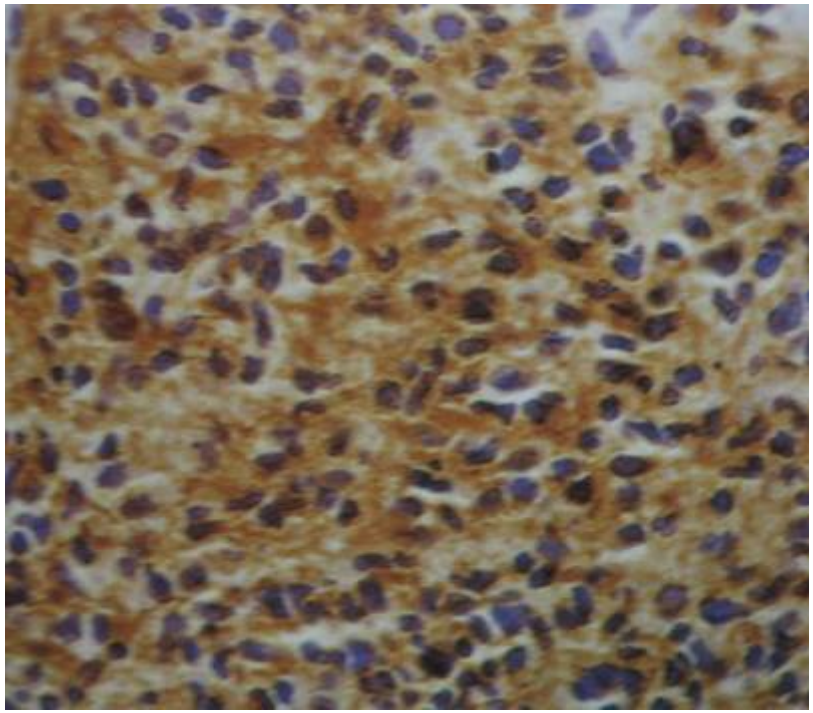


Nuclei showing typical smudgy or clumped chromatin pattern with nuclear pleomorphisk and elongated nuclear profile (H&H)

Anaplastic Astrocytoma (WHO grade III)

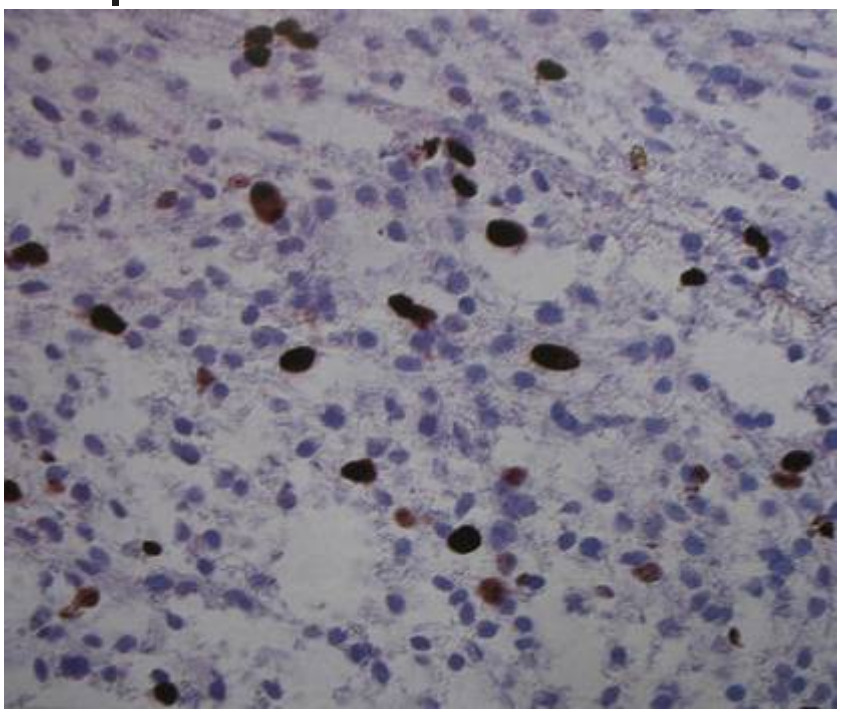


Lack of satellitosis more common as they infiltrate the cortex

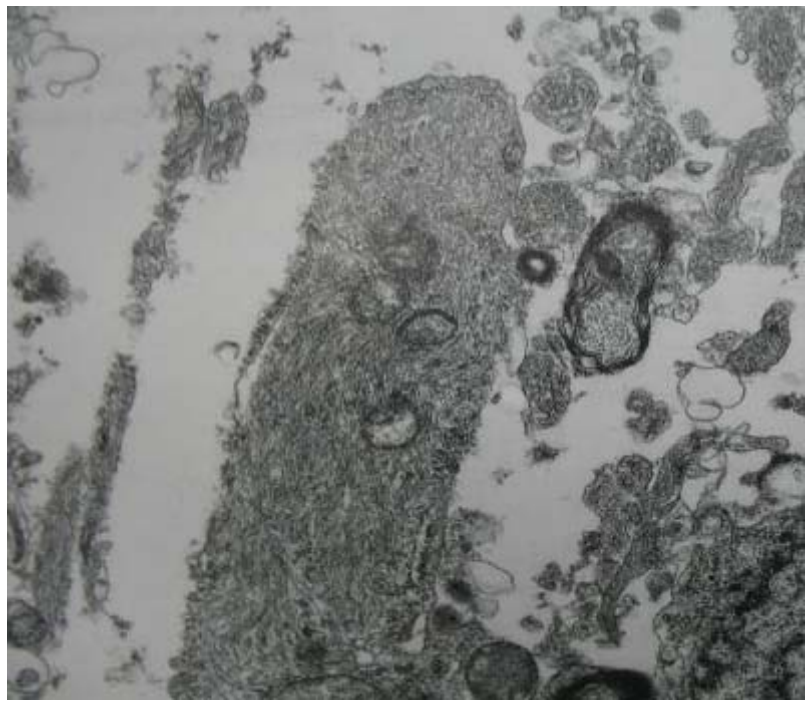


GFAP- diffuse smudgy appearance rather than the fibrillary appearance in higher grade where every cell is not reactive

Anaplastic Astrocytoma (WHO grade III)

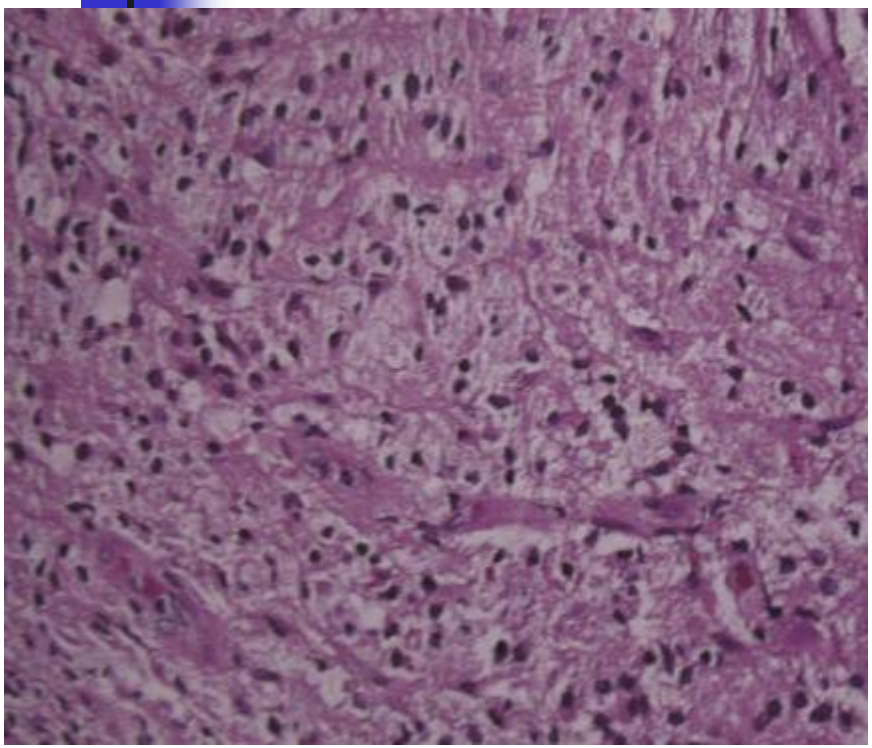


MIB-I reactive against Ki-67 antigen

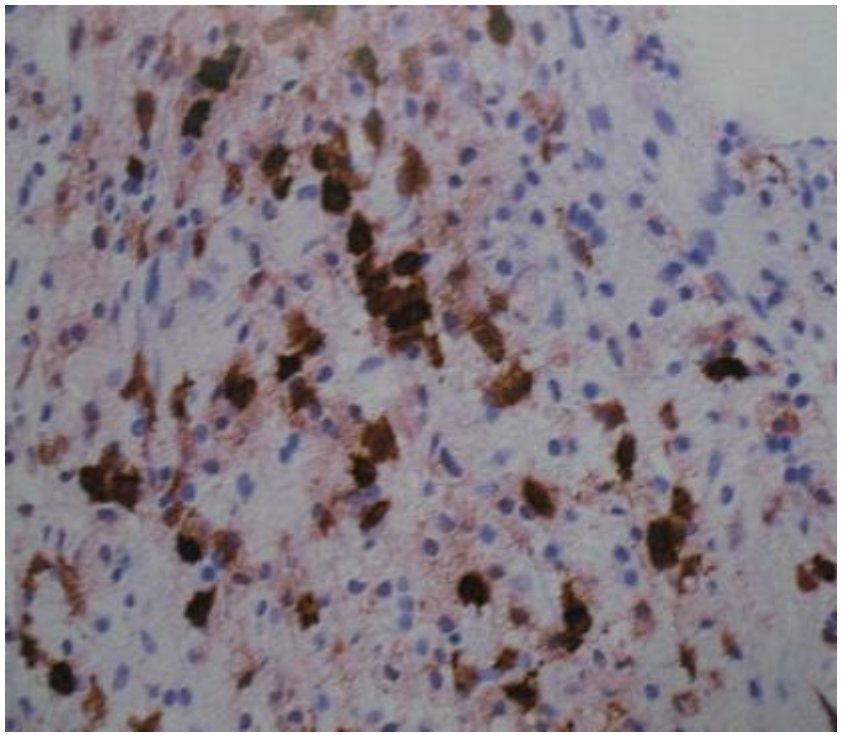


Abundant cytoplasmic intermediate filaments
(both within fibrillary process and around nucleus)

Recurrent glioma Vs Radiation necrosis



Dense cellular infiltrate associated with vascular prominence s/o recurrent high grade glioma



However, Macrophage related antibody MAC-387 reveals infiltrate to be of macrophage origin- Radiation effect

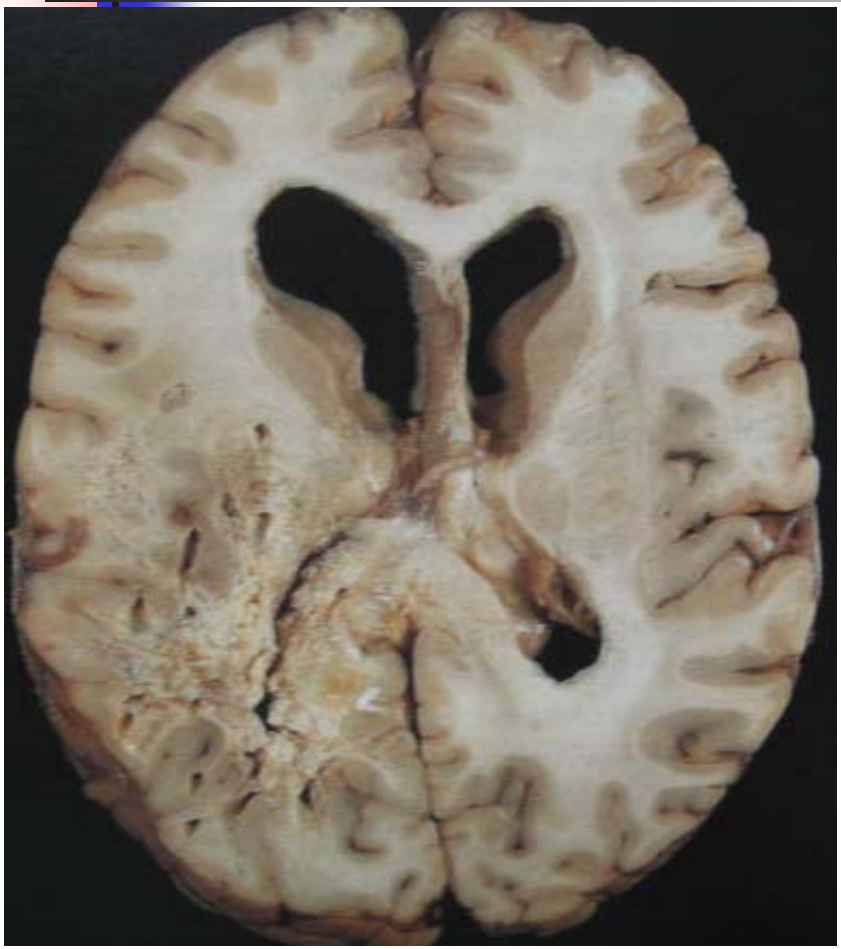
Glioblastoma (WHO grade IV)

	most frequent and most malignant
Location	**Hemispheric WM, frontal & temporal lobes**
Genetics	**Primary GBM-** • **Older patients, biologically more aggressive** • **Develops de novo (without pre-existing lower grade tumor)** • **Amplification, over-expression of EGFR, MDM2** • **PTEN mutation** • **Chromosome 10p LOH** **Secondary GBM** • **Younger patients, less aggressive than primary** • **Develops from lower grade astrocytoma** • **TP53 mutations** • **PDGFR amplification, overexpression** • **Chromosomes 10q, 17p LOH** • **Increased telomerase activity and hTERT expression**
Etiology **Pathogenesis** **pathophysiology**	**Occurs sporadically or as part of heritable tumor syndrome, NF-1 Turcot, Li- Graumeni syndromes** **Spreads by creating permissive environment** **Produces proteases** **Deposits extracellular matrix (ECM) molecules** **Expresses integrins (neoangiogenesis)**

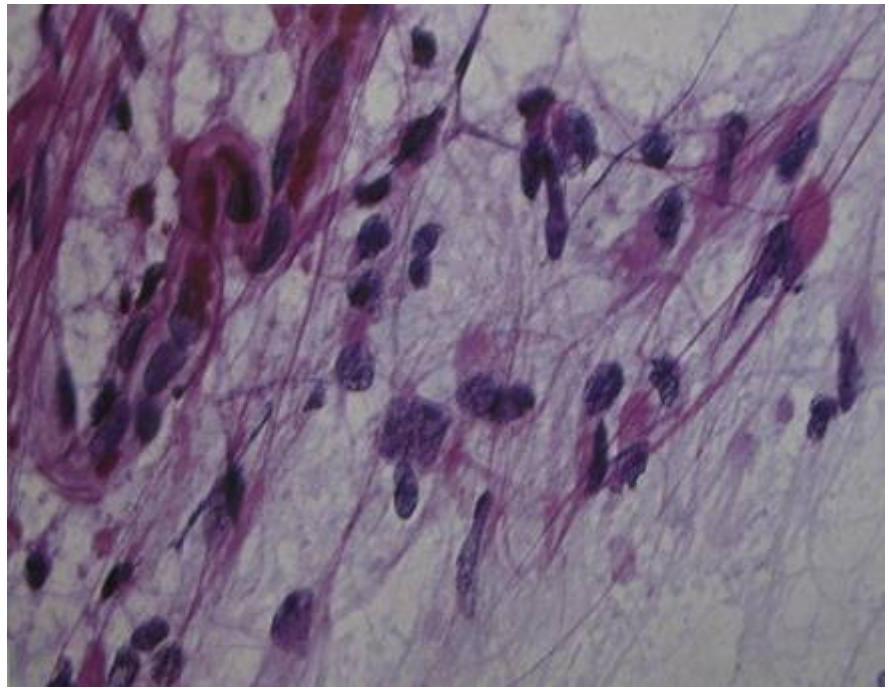
Glioblastoma (WHO grade IV)

Gross pathology	•Reddish gray 'rind' of tumor surrounds necrotic core •Infiltrating mass with poorly delineated margins •Often expands invaded structures •May appear discrete but tumor always infiltrates	uncommon- cysts, hemorrhage
Microscopic features	•Increased cellularity •Marked mitotic activity •Distinct nuclear atypia •High nuclear cytoplasmic ratio •Coarse nuclear chromatin •necrosis or microvacular proliferation •Histologic variant- Gemistocytic	
Immuno-pathology	•MIB-1 : 5-10% •GFAP + (multifocally reactive)	
Presentation	•Bimodal – small peak around 5yrs, Peak: 40- 50yrs •M:F= 1.8:1 •Seizures, focal neurological feficits •May have headache or raised ICP	
Natural history	•Progession to secondary GBM common •Commonly arises as recurrence after resection of Grade II tumor •Spreads along WM tracts •Other sites- ependymoma, leptomeninges, CSF	

Glioblastoma (WHO grade IV)

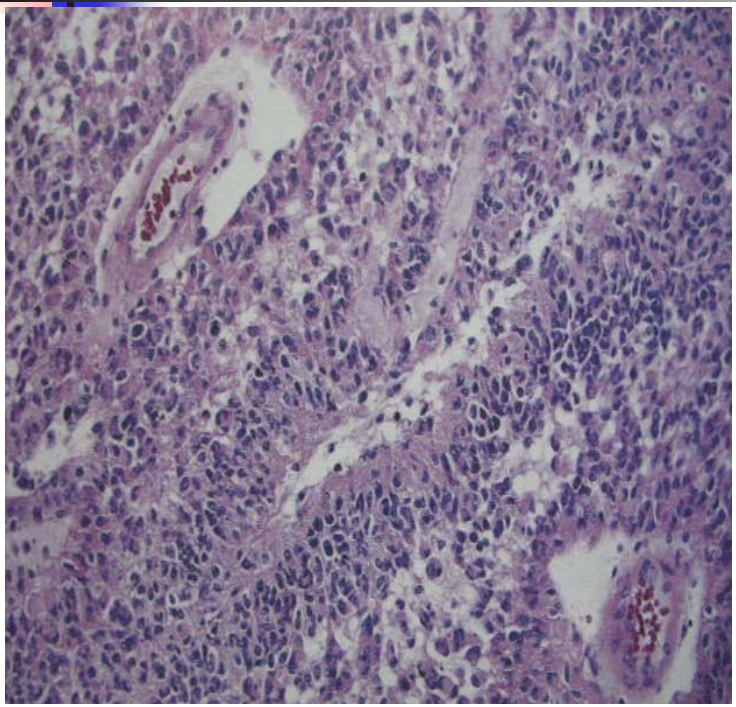


Irregular foci of hemorrhage indicative of glioblastomatous degeneration

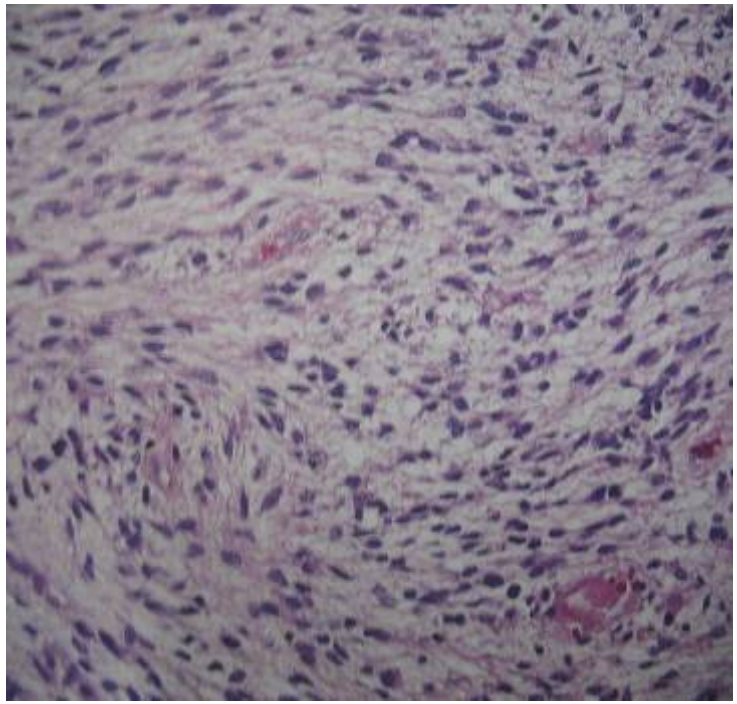


Smear preparation- nuclear pleomorphism, fibrillar processes with glial cells, proliferative vessel with very prominent endothelial cells

Glioblastoma (WHO grade IV)

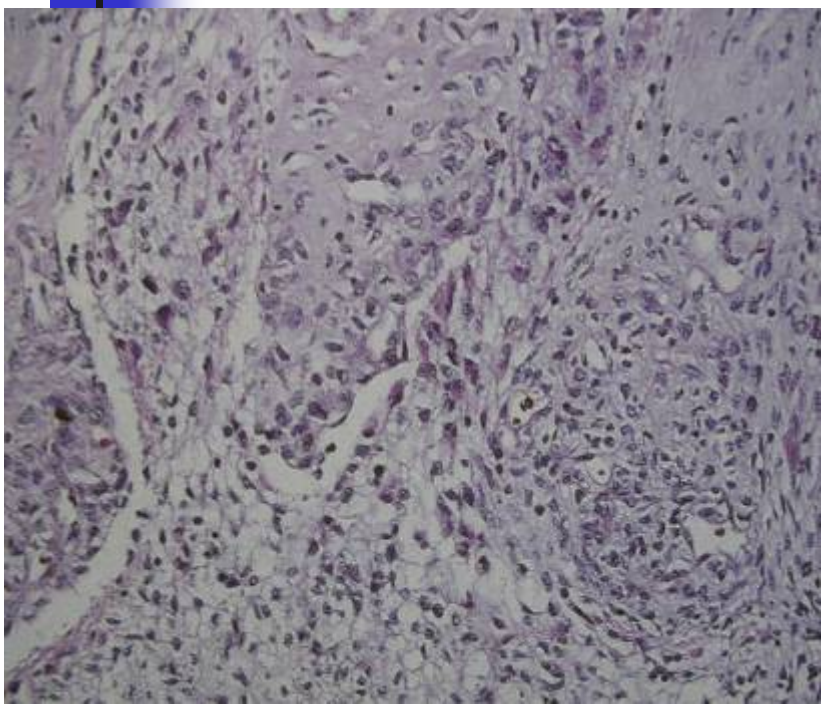


Pseudopalisading necrosis – hallmark of glioblastoma

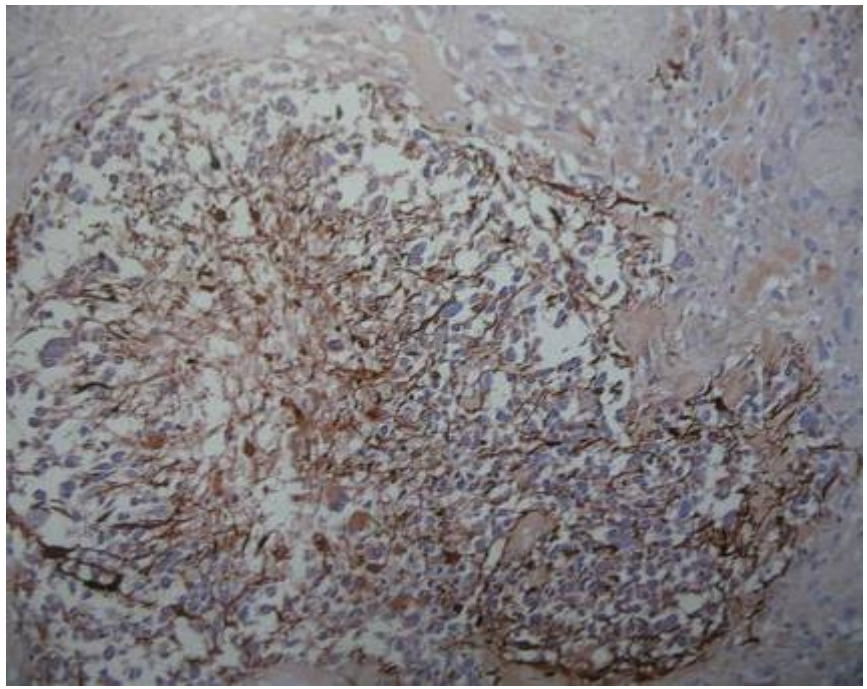


Spindle cell glioblastoma in irregular poorly woven fascicles mimicing herringbone pattern of fibrosarcoma

Glioblastoma (WHO grade IV)

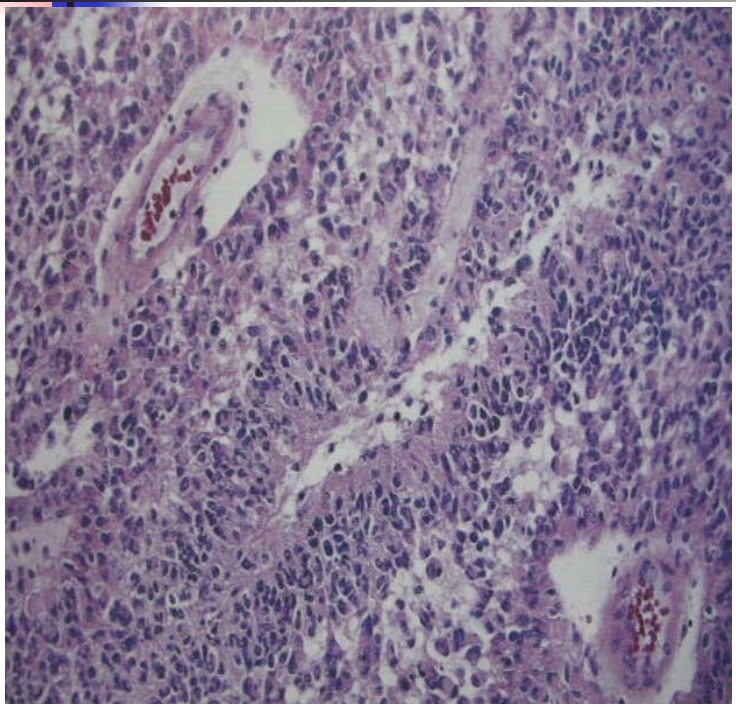


Occasionally exhibit exuberant stromal myxoid change with glomeruloid vascular proliferation

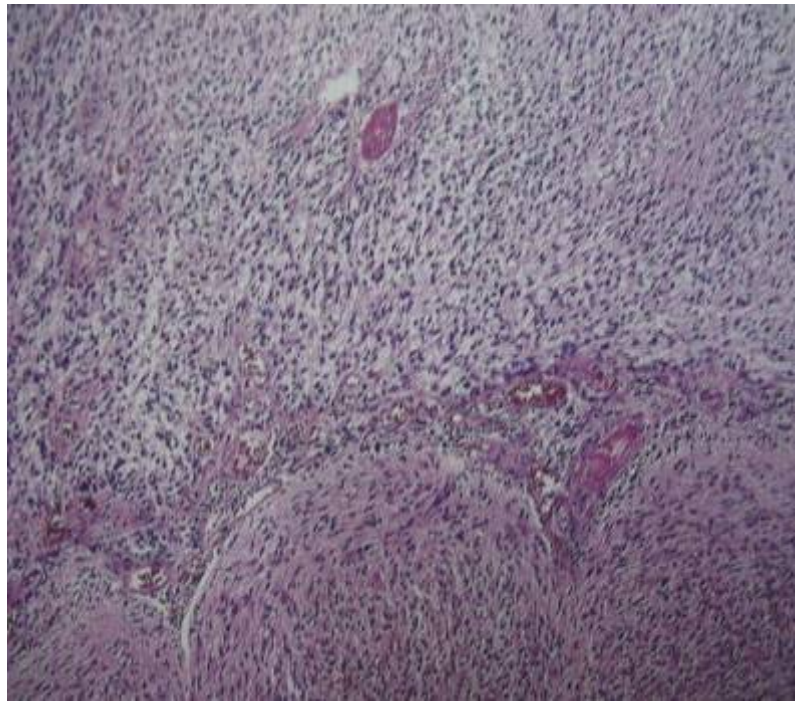


GFAP stain identifies nests of obvious glial cells amidst exuberantly proliferative non reactive cellular component. Sarcomatoid appearance in infact a metaplastic appearance

Glioblastoma (WHO grade IV)



Pseudopalisading necrosis – hallmark of glioblastoma



Superficial glioblastoma infiltrates into brain parenchyma, this differentiates it from malignant meningioma

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Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Oligodendroglial tumors

Oligodendroglioma

Partially calcified well differentiated slowly growing but infiltrating cortical mass in middle age adult

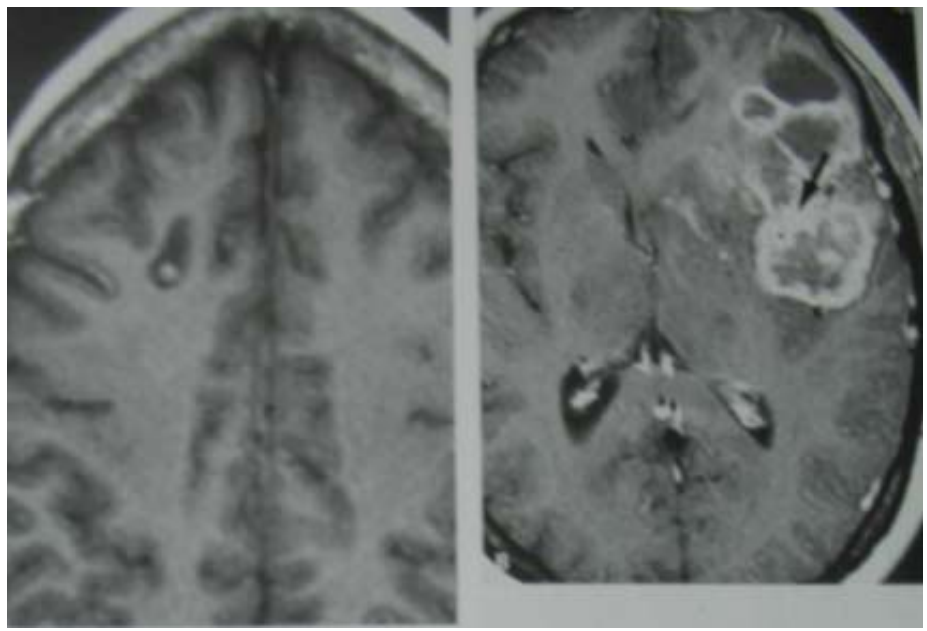
Calcification: 90% CT

Frontal > TPO lobe

Seizure: 50-80%

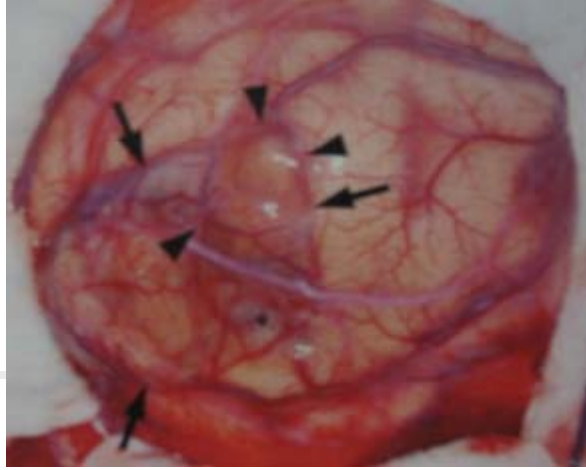
20-50% aggressive (anaplastic)

- high cell density
- **pleomorphism** + anaplastic nuclei
- Numerous **mitoses**
- Microvascular proliferation
- **Necrosis**+/-

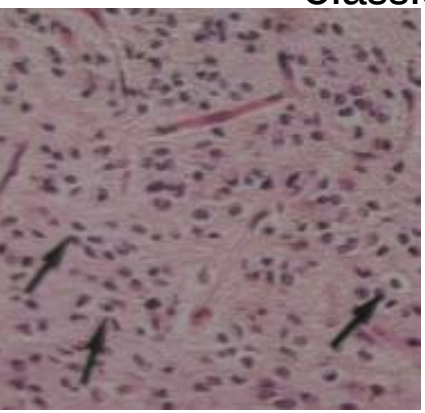


Oligodendroglial tumors

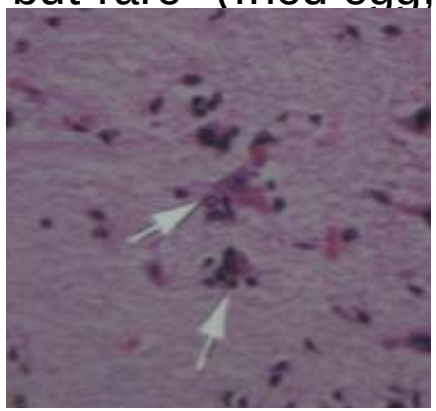
Oligodendroglioma



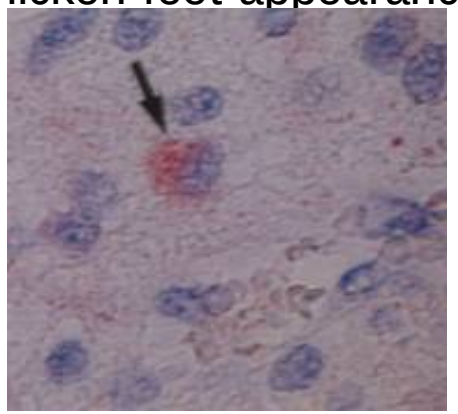
- Gross- unencap soft gelatinous gray to pink hue
- Histology
  - Moderately cellular with occasional mitoses
  - Monotonous round nuclei, eccentric rim of eosinophilic cytoplasm, lacking proceses
  - Classical but rare- (fried egg, chicken feet appearance)



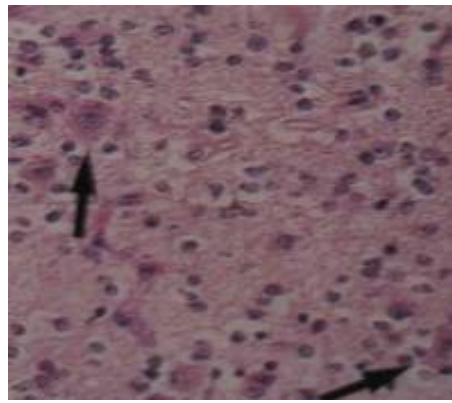
Classical- perinuclear halo and delicate capillary vascularity



Perinuclear satellitosis- sign of cortical invasion



Mini- gemistocytic astrocyte : GFAP + H&E



Malignant transformation

Oligodendroglial tumors

Grading

- Smith (AFIP) system
  - pleomorphism
  - necrosis
  - N/C ratio
  - endothelial proliferation
  - Cell density

Grade	Median survival (month)
A	94
B	51
C	45
D	17

Oligodendroglioma *variants*

Microgemistocytic oligodendroglioma

- displays small cells with round eosinophilic cytoplasm & eccentric nucleus
- GFAP +

Anaplastic oligodendroglioma (grade 3)

- Increased cellularity, nuclear pleomorphism, mitotic activity
- Vascular proliferation, hemorrhages, & micronecroses.
- Leptomeningeal spread & subarachnoid dissemination.

Oligoastrocytoma

- well-differentiated neoplastic astrocytes (>25%) and oligodendrocytes
- either diffusely intermingled or separated
- Origin: GFOC

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Giant cell glioblastoma				•
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Spindle cell oncocytoma of the adenohypophysis	•			

Ependymal tumors

Ependymoma

- Ependymal lining of ventricular wall, projects into the ventricular lumen or invades the parenchyma
- Predominant children and adolescents.
- Fourth ventricle
- Accounting for 6% to 12% of intracranial childhood
- Drop mets: 11%

Ependymal tumors

Ependymoma

- Variants
  - Non anaplastic (low grade)
    - Clear cell
    - Cellular
    - tanycytic
    - Papillary- classic lesion, 30% metastatise, dark small nuclei. 2 cytoplasmic patterns
      - Differentiation along glial lines forms perivascular pseudorosettes
      - Cuboidal cells form ependymal tubules around a central bv (true rosettes)
    - Myxopapillary ependymoma- filum terminale. Papillary with microcystic vacuoles and mucosubstance
    - Subependymoma
  - Anaplastic : pleomorphism, multinucleation, giant cells, mitotic figures, vascular changes, necrosis (ependymoblastoma)

Ependymal tumors

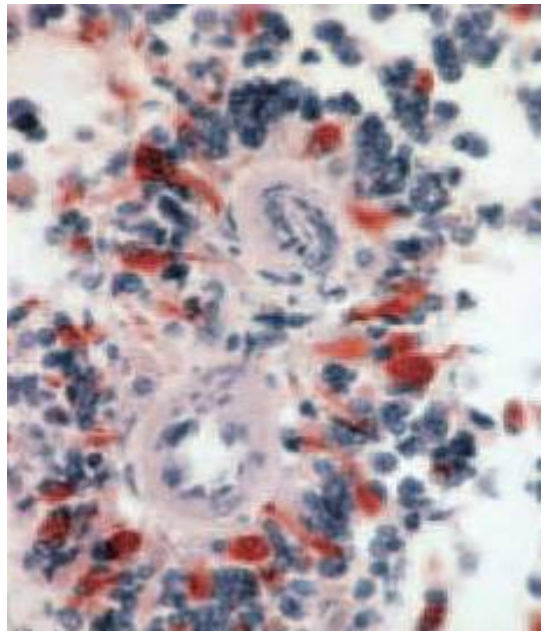
Ependymoma

	Ependymoma	**medulloblastoma**
Mass in 4th ventricle	Floor	Roof (fastigium), 4th ventricle drapes around tumor (banana sign)
Calcifications	Common	<10%
T1WI	Inhomogenous	Homogenous
T2WI	High intensity exophytic component	Mildly hyperintense

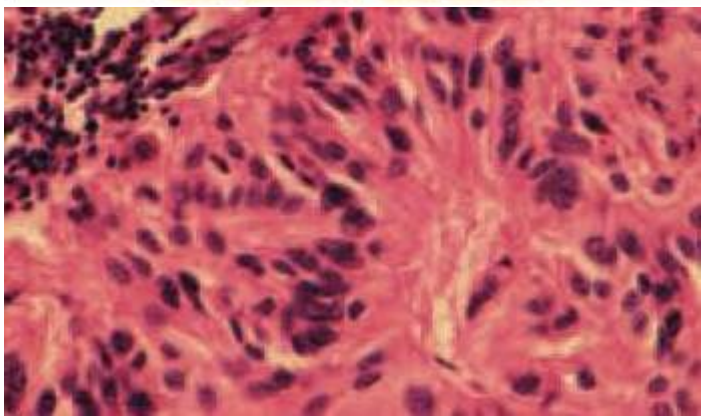
Ependymal tumors

Ependymoma

Circumscribed cherry sized firm, lobulated tumor filling lumen of fourth ventricle



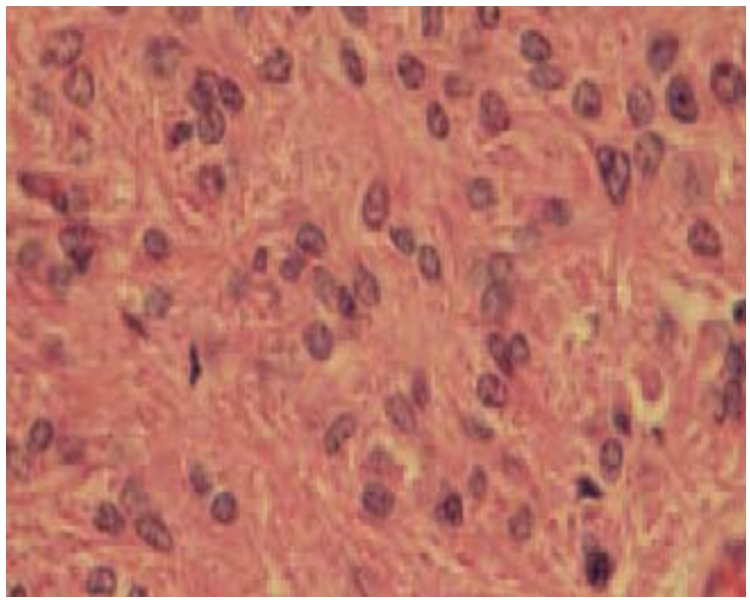
Perivascular rosette



H&E papillary pattern

Ependymal tumors
Subependymoma

- Subependymal glial cells
- Anterior lateral ventricles or posterior fourth ventricle



Nests of tumor cells in a fibrillary matrix

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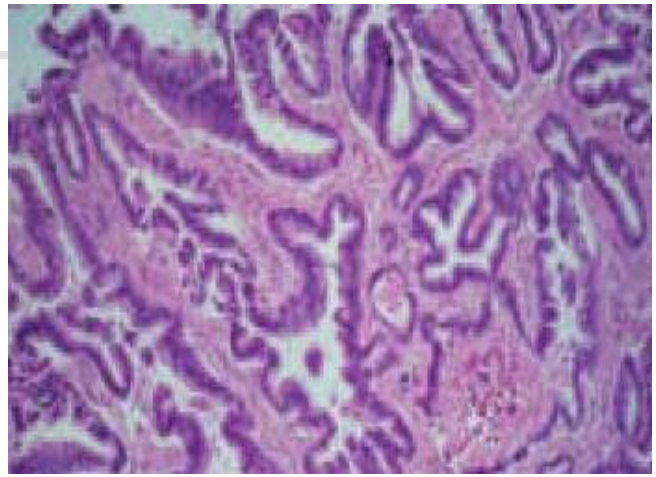
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Choroid Plexus tumors

- 0.4- 1% all intracranial tumors
- 70% patients are <2yrs
- Adults: infratentorial
- Children: lateral ventricle
- Clinical: raised ICP, Seizures, SAH

Choroid Plexus tumors

Choroid Plexus Papilloma



- intraventricular papillary neoplasms
- derived from choroid plexus epithelium
- benign in nature, cured by surgery
- Gross: circumscribed moderately firm, cut surface: cauliflower- like appearance.
- Histology: tumor resembles a normal choroid plexus, but is more cellular,with cuboidal and columnar epithelial cells resting on a fine fibrovascular stroma.
- Hemorrhages and calcifications: common

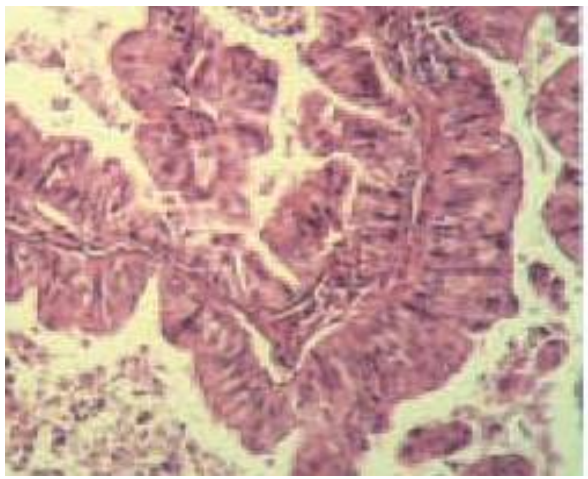
Choroid Plexus tumors
Atypical Choroid Plexus Papilloma

- WHO grade II
- Intraventricular papillary neoplasms (from choroid plexus epithelium)
- intermediate features
- distinguished from the choroid plexus papilloma by increased mitotic activity
- Curative surgery is still possible
- but the probability of recurrence significantly higher

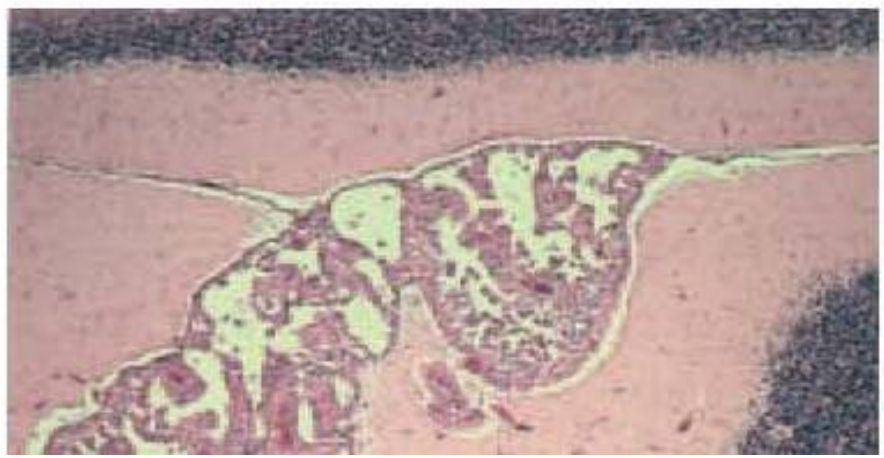
Choroid Plexus tumors

Choroid Plexus Carcinoma

- frank signs of malignancy,
  - brisk mitotic activity,
  - increased cellularity,
  - blurring of the papillary pattern,
  - necrosis and frequent invasion of brain parenchyma.



Highly cellular tumor of pleomorphic columnar epithelial cels in multiple rows on fibrovascular cores



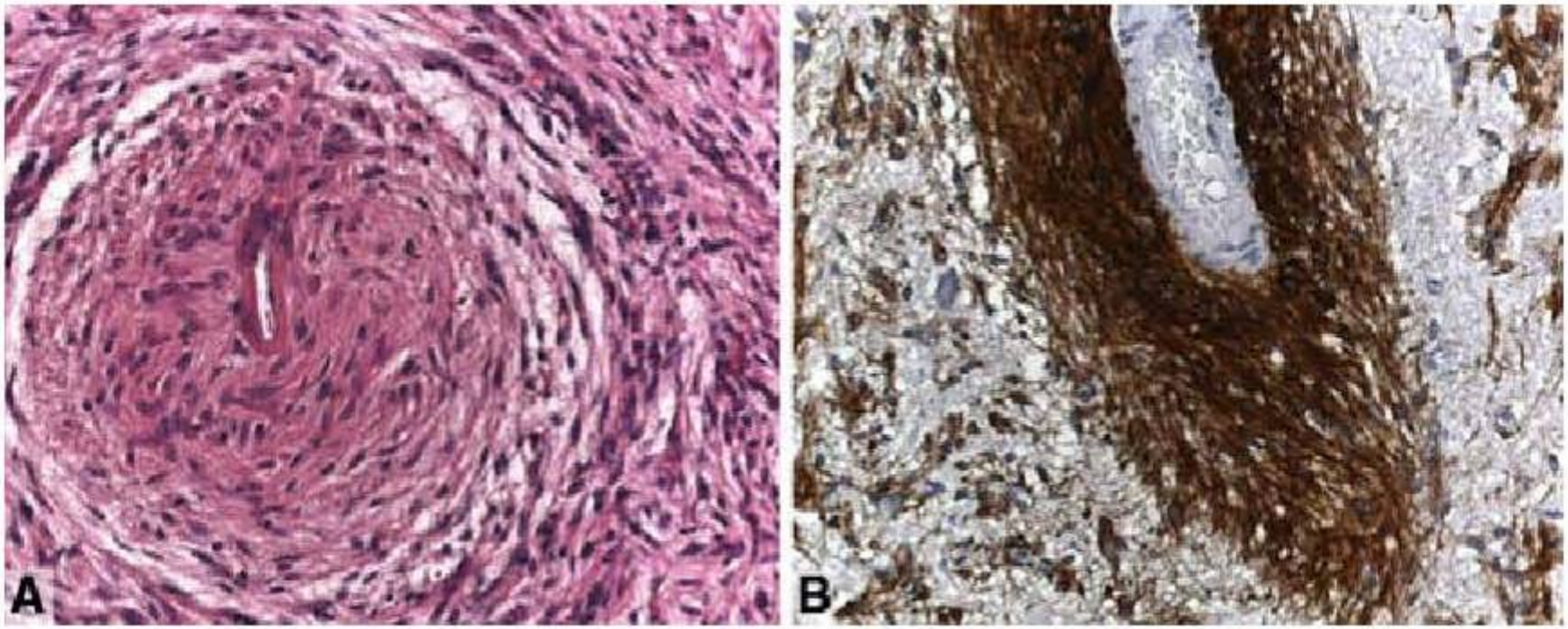
Tumorous infitration of cerebellum

Other Neuroepithelial tumors
Angiocentric glioma

- WHO grade 1
- Predominantly children and young adults (17yrs)
- Refractory epilepsy- leading symptom
- Total – 28 cases
- located superficially- fronto-parietal, temporal, hippocampal region.
- FLAIR - well delineated, hyperintense, non-enhancing cortical lesions, often with a stalk-like extension to the subjacent ventricle
- Stable or slowly growing
- Histopathology-
  - monomorphous bipolar cells,
  - an angiocentric growth pattern
- Immunoreactivity- EMA, GFAP, S-100 protein and vimentin,
  - Not for neuronal antigens.
- D/D- ependymal variant- Frequent extension of angiocentric glioma to the ventricular wall, M/E ependymal differentiation

Other Neuroepithelial tumors

Angiocentric glioma



Elongated tumor cells with concentric perivascular arrangement

Perivascular tumor cells strongly express GFAP

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Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
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Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
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Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
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Pineal parenchymal tumour of intermediate differentiation		•	•	
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Papillary tumour of the pineal region		•	•	
Embryonal tumours				
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CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
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Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
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Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Neuronal and mixed neuronal-glial tumors
Gangliocytoma & Ganglioglioma

- Temporal and frontal lobes.
- Gross: gray, firm, and often cystic.
- Gangliocytomas - atypical neoplastic neurons within fibrillary matrix
- Gangliogliomas- mixture of neoplastic neurons & glial cells, mostly astrocytes.
- Immunoreact for synaptophysin and neurofilament proteins.
- Calcifications, eosinophilic globules, and perivascular lymphocytic infiltrations common.
- Mitoses are rare, necrosis is absent.

Neuronal and mixed neuronal-glial tumors
Central neurocytoma

- Lateral or third ventricle at the Foramen Monro
- well-demarcated soft tumor
- Uniformly small neurocytes
- Several architectural patterns resembling oligodendroglial and ependymal tumors
- Calcifications- common, hemorrhages may occur.

Neuronal and mixed neuronal-glial tumors

Dysembryoplastic neuroepithelial tumor (DNET)

- Often temporal lobe, less cerebellum & pons.
- mucinous or gelatinous appearance.
- Neoplastic neurons, astrocytes, and oligodendrocytes in a nodular pattern.
- Pools of mucin, calcifications, abnormal blood vessels

Neuronal and mixed neuronal-glial tumors
Extraventricular neurocytoma

- WHO grade II
- Neuronal tumour with pathological features distinct from cerebral neuroblastoma,
- Young adults
- Preferential location- lateral ventricles in region of the foramen of Monro
- Favourable prognosis
- Central neurocytomas- uniform round cells
- Additional features - Fibrillary areas mimicking neuropil, & low proliferation rate
- Immunohistochemical and ultrastructural e/o neuronal differentiation

Neuronal and mixed neuronal-glial tumors

Papillary glioneuronal tumor (PGNT)

- WHO grade I
- Komori et al.- 1998
- wide age range (mean 27 years)
- Location- temporal lobe.
- CT & MRI- contrast-enhancing, well delineated mass, occasionally showing a cyst-mural nodule pattern.
- Histologically-
  - single or pseudostratified layer of flat to cuboidal GFAP-positive astrocytes surrounding hyalinized vascular pseudopapillae
  - synaptophysin-positive interpapillary sheets of neurocytes, large neurons and intermediate size “ganglioid” cells.

Neuronal and mixed neuronal-glial tumors

Papillary glioneuronal tumor (PGNT)

Histologically-

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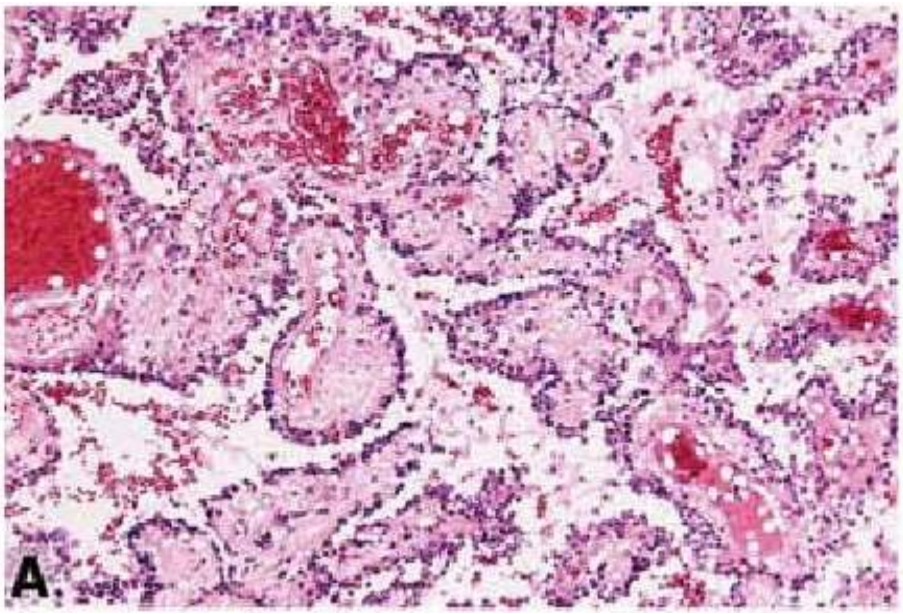
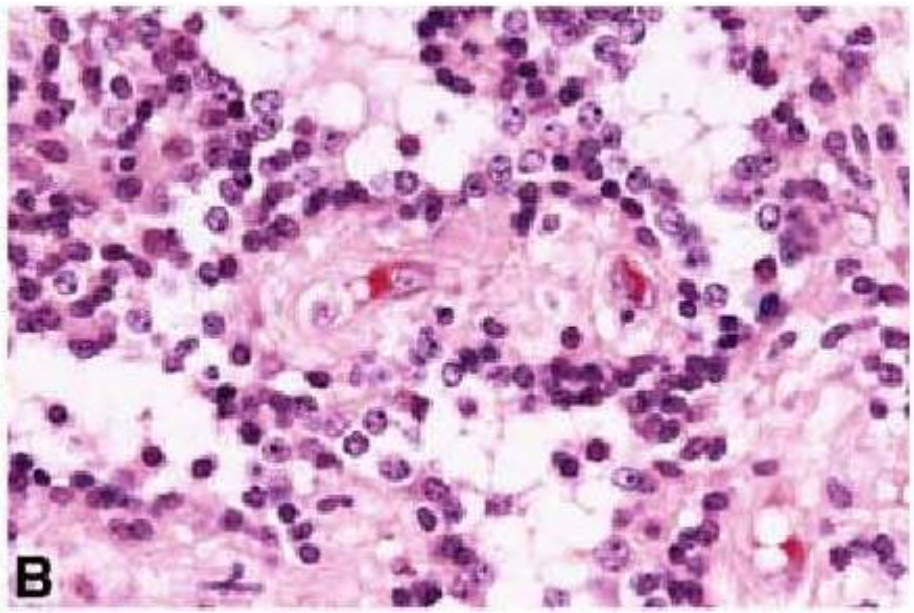




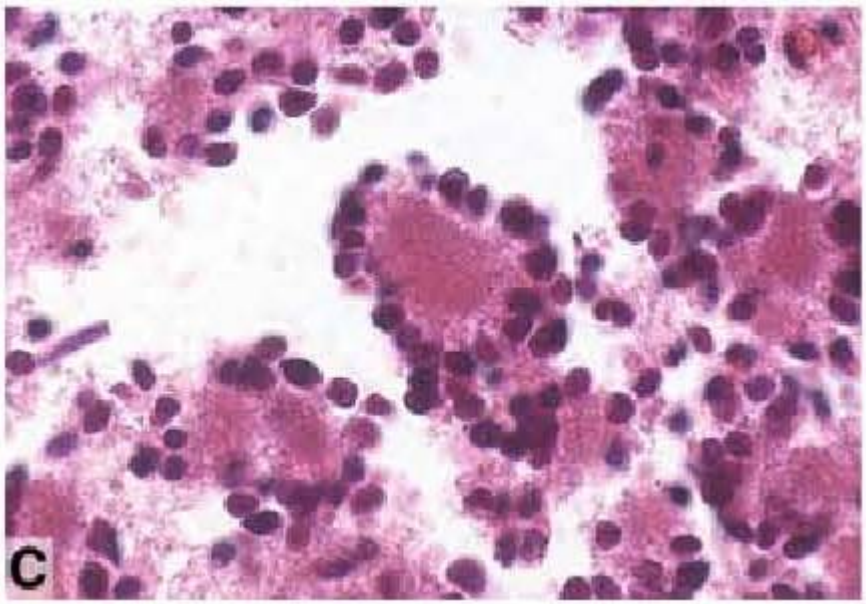
Neuronal and mixed neuronal-glial tumors

Rosette forming glioneuronal tumor of the fourth ventricle

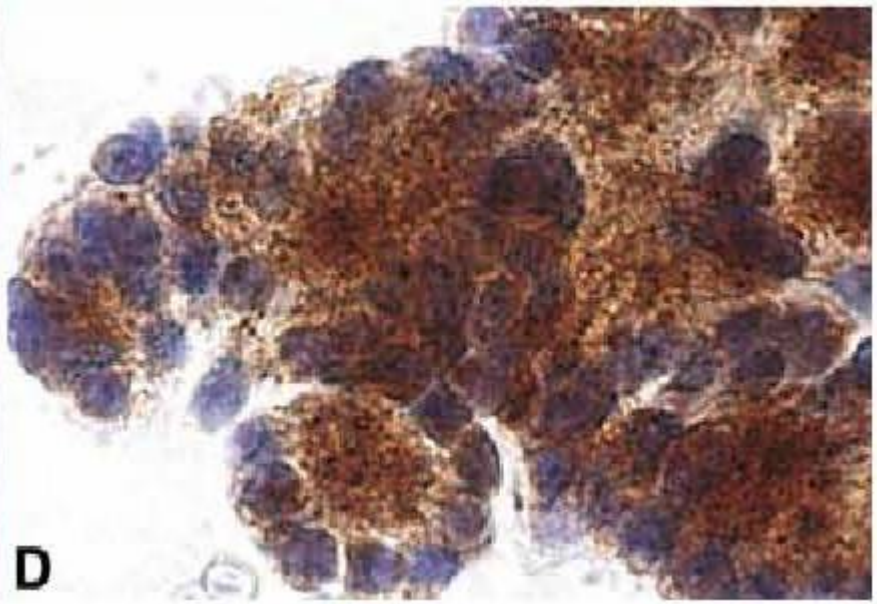
- WHO grade I
- Initially described as dysembryoplastic neuroepithelial tumour (DNT) of the cerebellum
- Komori et al. in 2002 , total of 17 cases
- Rare slowly growing tumour of the fourth ventriclular region
- Young adults (mean age 33 years)
- Ostructive hydrocephalus, ataxia- most common clinical manifestation.
- Typically midline, involves the cerebellum and wall or floor of the fourth ventricle.
- T2WI- well delineated, hyperintense tumour.
- Histopathologically- a biphasic neurocytic and glial architecture
  - Neuronal component consists of neurocytes that form neurocytic rosettes with eosinophilic, synaptophysin-positive cores and/or perivascular pseudorosettes.
  - Glial component dominates and typically exhibits features of pilocytic astrocytoma.
- Benign clinical behaviour with the possibility of surgical cure

Neuronal and mixed neuronal-glial tumors

Rosette forming glioneuronal tumor of the fourth ventricle



Pseudorosette with ring like arrangement of neurocytic tumor cell nuclei around an eosinophilic neuropil core



Neuropil core show strong immunoreactivity to synaptophysin

Neuronal and mixed neuronal-glial tumors

Paraganglioma

- Chemodectoma or glomus tumors
- Slow growing (<2cm in 5 yrs)
- Histologically benign, <10% LN or distant mets
- Most secretory granules (Epinephrine/ NE)
- Site: carotid bifurcation, superior vagal ganglion, auricular branch of vagus, inferior vagal (nodose) ganglion
- GJ from glomus body in area of jugular bulb, and track along vessels
- May have finger like extensions

Tumors of the pineal region

Pineal region: bounded dorsally by splenium of corpus callosum and tela choroidea, ventrally by quadrigeminal plate and midbrain tectum, rostrally by posterior aspect of 3rd ventricle and caudally by cerebellar vermis

3-8% of paediatric brain tumors, <1% adults

Substrate	Tumor
Pineal glandular tissue	Pineocytomas, pineoblastomas
Glial cells	Astrocytomas, oligodendroglioma, cyst
Arachnoid cells	Meningiomas, cyst
Ependymal lining	Ependymomas
Sympathetic nerves	Chemodectomas
Rests of germ cells	Choriocarcinoma, germinoma, embryonal ca, endodermal sinus tumor, teratoma
No BBB	Hematogenous mets

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Tumors of the pineal region

Pineocytoma

Well differentiated

CSF mets

radiosensitive

Tumors of the pineal region
Pineoblastoma

Malignant tumor – a PNET

Metastasize through CSF

Radiosensitive

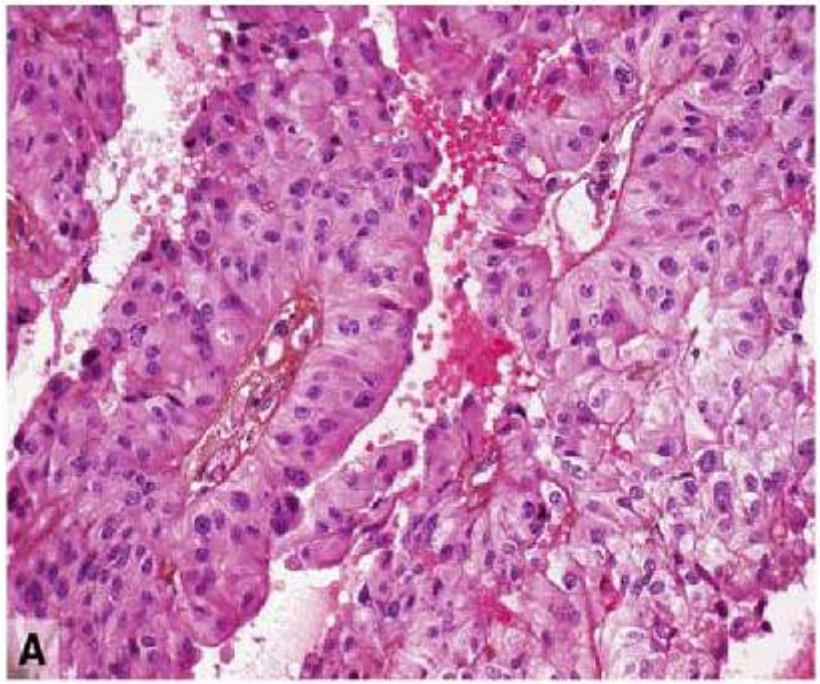
Tumors of the pineal region

Papillary tumor of the pineal region (PTPR)

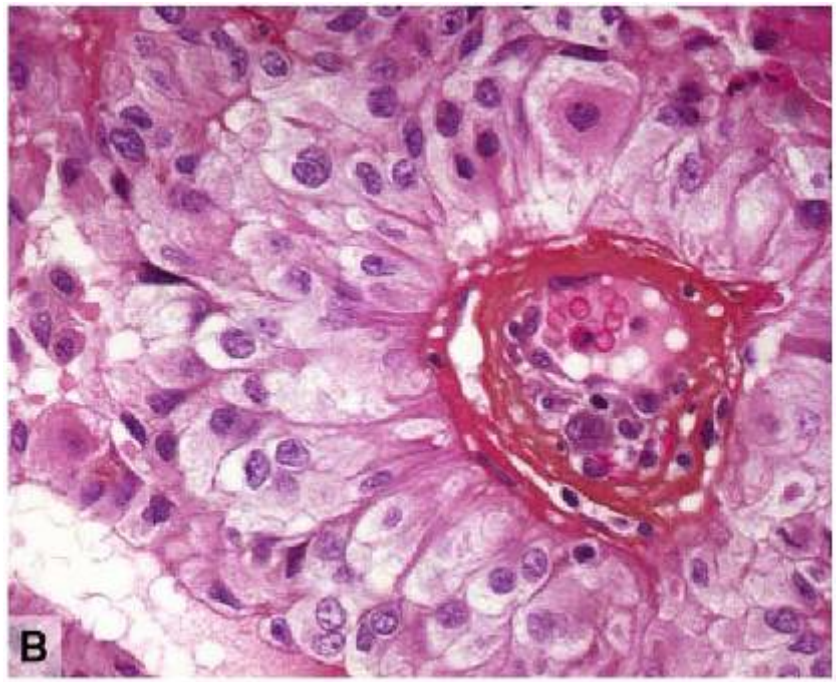
- WHO grade II/III
- children and adults (mean age 32 years)
- Relatively large (2.5–4 cm), and well-circumscribed,
- MRI- low T1 and increased T2 signal , contrast enhancement.
- 2003, Jouvet et al.- total of 38 cases
- Histologically, papillary architecture and epithelial cytology
- immunoreactivity for cytokeratin and, focally, GFAP.
- Macroscopically indistinguishable from pineocytoma
- Ultrastructural features s/o ependymal differentiation and a possible origin from specialized ependymal cells of the subcommissural organ
- Biological behaviour- variable

Tumors of the pineal region

Papillary tumor of the pineal region (PTPR)



typical papillary architecture and epithelial cytology



tumour cells are large with columnar or cuboidal shape.

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Spindle cell oncocytoma of the adenohypophysis	•			

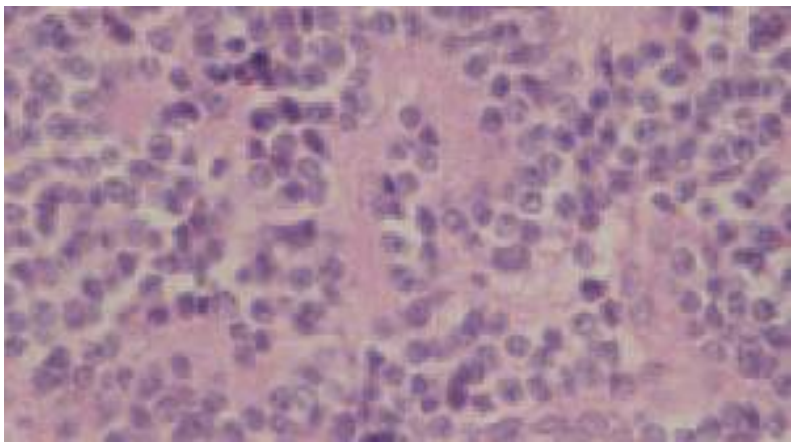
Embryonal tumors

Medulloblastoma

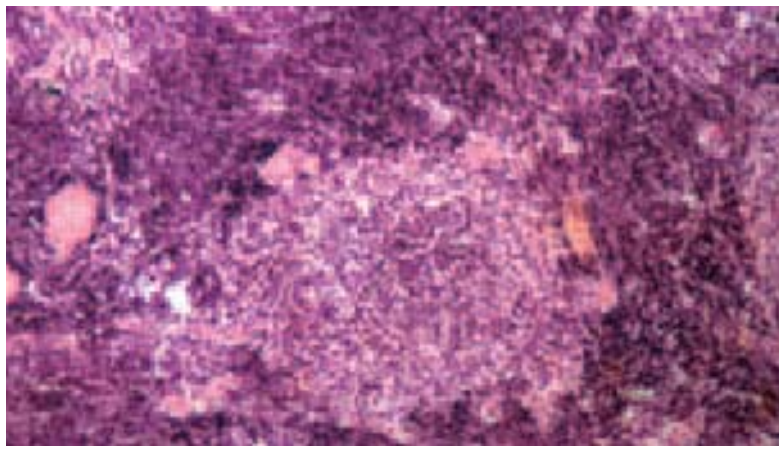
- Most common malignant paediatric Ca
- 1st decade of life
- Male: Female= 2:1
- Cerebellar vermis, apex of 4th ventricle roof (fastigium)
- Cl: early hydrocephalus, cerebellar signs
- Solid midline contrast enhancing
- Highly radiosensitive and moderately chemosensitive
- Recurrence: 10-35%, extraneural mets: 5%
- Poorly demarcated, pinkish-gray and soft.
- Histology-
  - densely cellular & small cells with round, oval, or carrot- shaped hyperchromatic nuclei surrounded by scanty cytoplasm (blue cell tumor).

Embryonal tumors
Medulloblastoma

- Medulloblasts may differentiate into neurons and glial cells.
- Neuronal differentiation – NSE+ & synaptophysin+
- Glial differentiation- GFAP-positive
- Disseminate via CSF pathway- small nodules & diffuse infiltrates in the ventricular wall and subarachnoid space



Highly cellular tumor – anaplastic cells with small round to oval hyperchromatic nuclei surrounded by scanty cytoplasm (HE).



Pale island in nodular variant (HE)

Embryonal tumors

Medulloblastoma

Histological Variants

Nodular medulloblastoma –

- "pale islands," of tumor cells with small nuclei, abundant cytoplasm, and a tendency to differentiate along neuronal line.
- Less aggressive, longer survival.

Large cell/anaplastic medulloblastomas

- cells with large vesicular nuclei and pleomorphic anaplastic cells.
- Mitoses and apoptotic bodies are numerous.
- more aggressive, shorter survival.

Desmoplastic medulloblastoma

- Cerebellar hemispheres of children and young adults.
- clusters of tumor cells are separated by a rich reticulin and collagenous network

Medullomyoblastoma, lipomatous, and *melanotic medulloblastomas*

- striated muscle fibers, lipid cells, and melanotic cells, respectively.

Embryonal tumors

Medulloblastoma

Anaplastic medulloblastoma

- WHO grade IV
- Characterized by
  - marked nuclear pleomorphism,
  - nuclear moulding,
  - cell–cell wrapping
  - high mitotic activity, often with atypical forms.
- Atypia- particularly pronounced and widespread
- Histological progression from classic to anaplastic medulloblastomas
- The highly malignant large cell medulloblastomas and anaplastic medulloblastomas have considerable cytological overlap
- The large cell variant features often spherical cells with round nuclei, open chromatin and prominent central nucleoli
- combined **large cell/anaplastic category** has been used.

Embryonal tumors

CNS primitive neuroectodermal tumor

- Wide variety with common pathologic features
- Originate from primitive neuroectodermal cells
- May disseminate through CSF

Embryonal tumors

CNS primitive neuroectodermal tumor

Ependymoblastoma

Highly cellular embryonal form of ependymal tumor

Age <5rs

Prognosis poor with median survival 12-20 months

100% mortality at 3 yrs

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Tumors of Cranial Nerves and Paraspinal Nv

Schwannoma

Misnomer- acoustic neuroma

Arise form superior vestibular division of CN VIII

Loss of suppressor gene on 22q (NF)

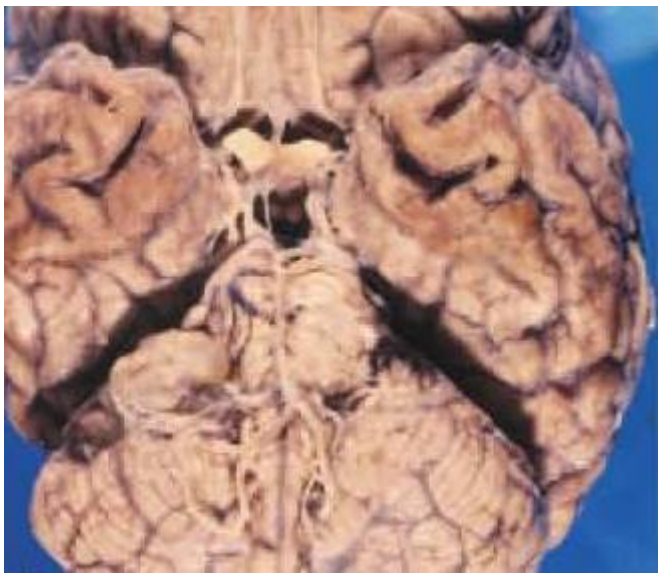
Cl: hearing loss, tinnitus, dysequilibrium

Histology:

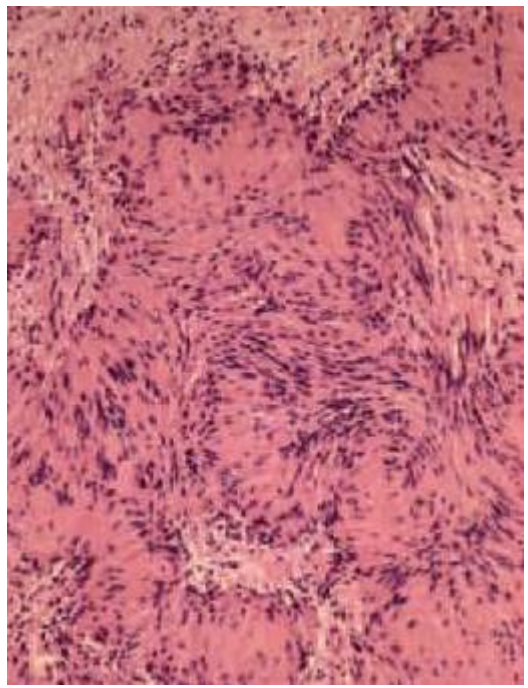
- Antoni A – narrow elongated bipolar cells
- Antoni B- loose reticulated

Tumors of Cranial Nerves and Paraspinal Nv

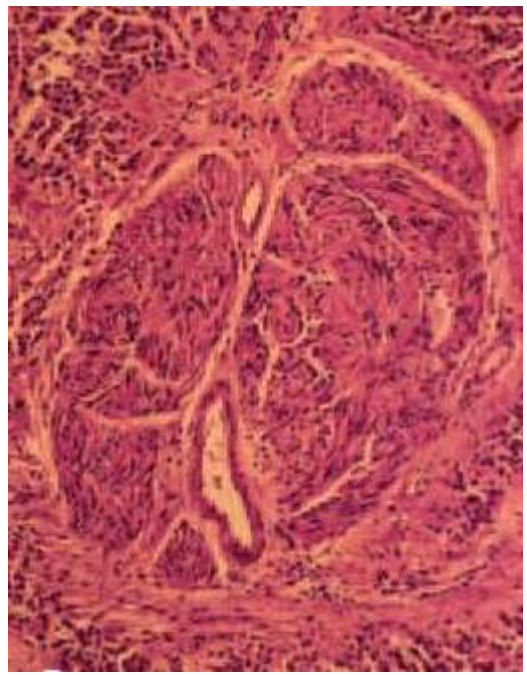
Schwannoma



Cherry sized encapsulated tumor in R CP angle



Spindle shaped bipolar cells forming fascicles and palisading with alternating zones of nuclei and processes



Verocay body, Anntony B

WHO GRADING OF BRAIN TUMORS, 4TH EDN, 2007

	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Tumors of the meninges

Tumor of the meningothelial cells

Meningioma

- Slow growing extra-axial
- Arising from arachnoid not dura
- Falx> convexity> sphenoid bone
- Head injury and therapeutic radiation – predispose meningioma.
- Solitary or multiple - NF2
- Hyperostosis of adjacent bone
- Frequently calcified
- Grossly- extra-axial, encapsulated,round, oval, or lobulated; firm or moderately soft.
- Blood supply- meningeal branches of ECA
- Cut surfaces- pinkish-gray, granular, or gritty.
- Histology:
  - Classical- psammoma bodies
- EMA+, Vimetin+, inconsistently for S-100 protein

Tumors of the meninges

Tumor of the meningothelial cells

Meningioma

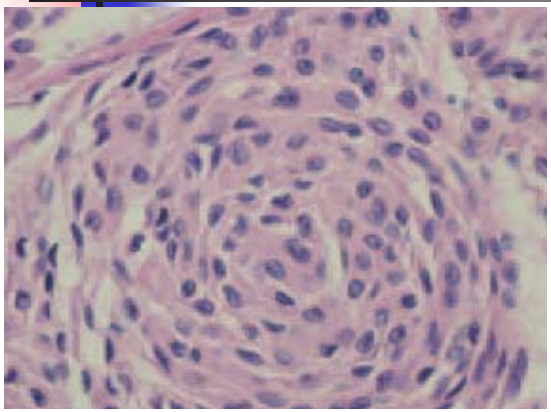
- Classic meningioms
  - Meningotheliomatous
  - Fibrous or fibroblastic
  - Transitional

  Other variants- microcystic/ psammomatous/ myxomatous/ xanthomatous/ lipomatous/ granular/ secretory/ chondroblastic/ osteoblastic/ melanotic
- Angioblastic- *hemangiopericytoma*
- Atypical
- Malignant meningiomas

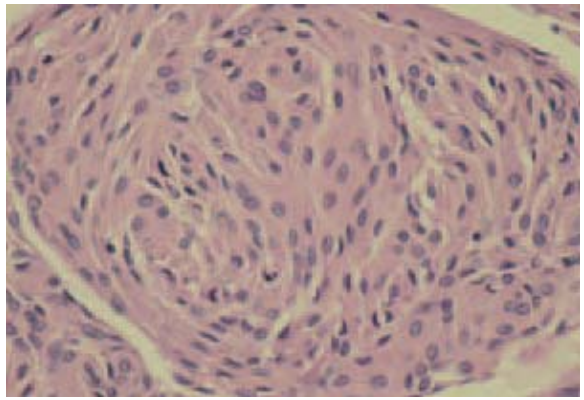
Tumors of the meninges

Tumor of the meningothelial cells

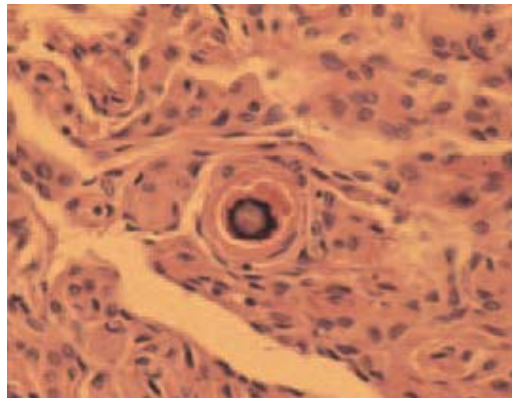
Meningioma



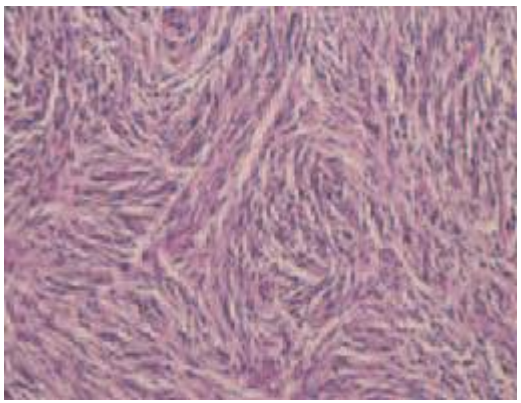
SYNCYTIAL TYPE:
moderately large, oval nuclei



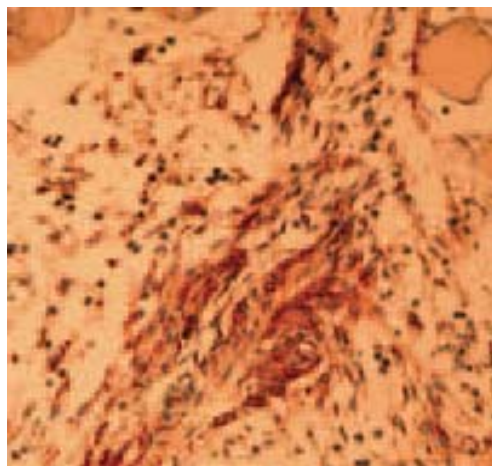
SYNCYTIAL TYPE: arranged
in whorls



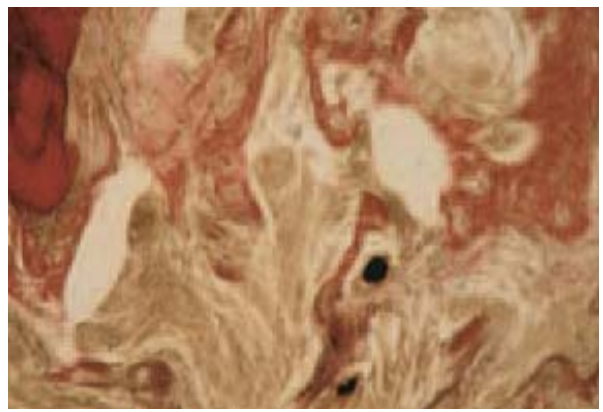
Psammoma bodies



Fibrous: fibrillated spindle
cells in interlacing bundles



Vimentin positivity



Bony invasion by meningioma

Tumors of the meninges

Tumor of the meningothelial cells *Meningioma*

Simpson etal, 1957

GRADE	DEGREE OF REMOVAL
I	Macroscopically complete removal with excision of dural attachment and abnormal bone
II	Macroscopically complete with endothermy coagulation of dural attachment
III	Macroscopically complete without resection or coagulation of dural attachment/ extradural extensions
IV	Partial removal leaving tumor in situ
V	Simple decompression +/- biopsy

Tumors of the meninges

Mesenchymal tumors

Chondroma

- Primary malignant tumor of spine or clivus with high recurrence rate
- Physaliphorous cells with mucin
- Slow growing
- Radioresistant

Tumors of the meninges

other related neoplasms

Haemangioblastoma

Benign WHO grade1

1% all intracranial, 7% posterior fossa (adults)

80% solitary, occassionally with VHL

Adults: 30-65yrs

Location: cerebellum (83-86%)

Spinal cord (3-13%)

Medulla (2-5%)

Cerebrum (1.5%)

Cl: occipital headache

Lab: polycythemia (erythropoietin)-20%

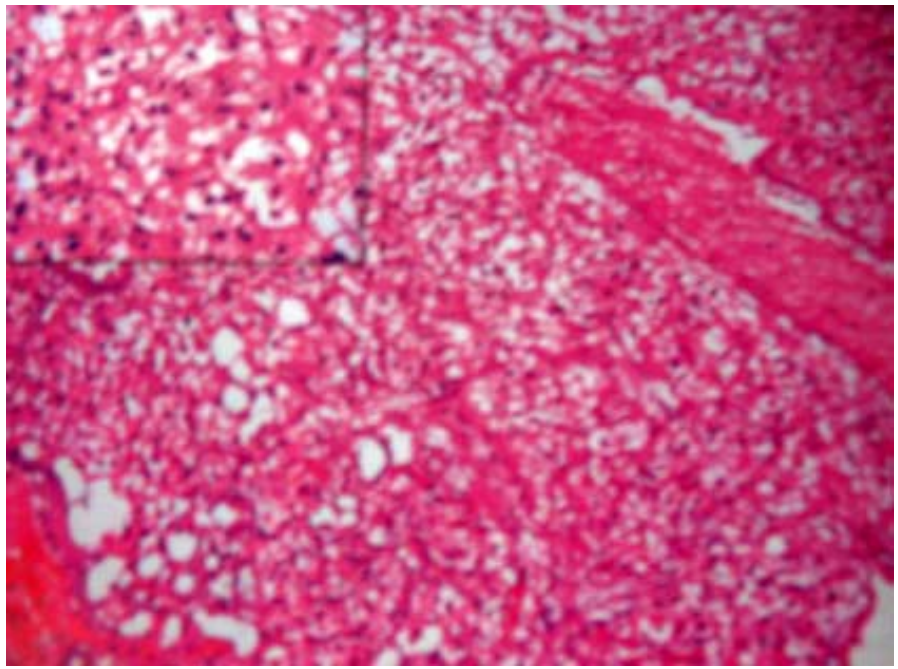
Prognosis: 5-20yr survival following Sx

Tumors of the meninges

other related neoplasms

Haemangioblastoma

Cystic hemangioblastoma
(60%) with Small mural nodule



Char: network of capillary like channels separated by trabeculae or islands of stromal cells with lipid droplets

Tumors of the meninges

other related neoplasms

Haemangioblastoma

Histology:

- Stromal cells- vimentin & neuron specific enolase.
- GFAP and S100 protein positivity in some cells

NCCT: thin walled well marginated cystic lesion (hypodense) with a mural nodule (isodense) abutting the pial surface.

Nodule- strong homogenous enhancement

MRI: cystic – iso/ hyper on T1, hyper on T2

DWI- cystic portion is hypo (increased diffusion)

Tumors of the meninges

other related neoplasms

Haemangioblastoma

VHL

- AD
- Multiple hemangioblastomas + retinal tumors+ pancreatic or renal cysts + renal carcinoma + phaeochromocytoma
- chromosome 3
- 29 yrs

Germ cell tumors

Midline tumors (suprasellar & pineal)

Except benign teratoma, all are malignant

Metastasize through CSF

1. Germinoma
2. Non germinoma-
    1. Embryonal carcinoma
    2. Choriocarcinoma
    3. Teratoma

Tumors of the sellar region

Pituitary adenomas

- 10% of all intracranial tumors, common 3rd & 4th decades
- Arise from adenohypophysis;
- neurohypophysis – rare (glioma, granular cell tumor)
- Classification
  Size- Microadenoma <1cm diameter
  Endocrine function- 2/3 secretory
  Anatomical- Modified Hardy system
  Histological- chromophobe/ acidophil/ basophil
  Electron microscopic appearance

WHO GRADING OF BRAIN TUMORS, 4TH EDN, 2007

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Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

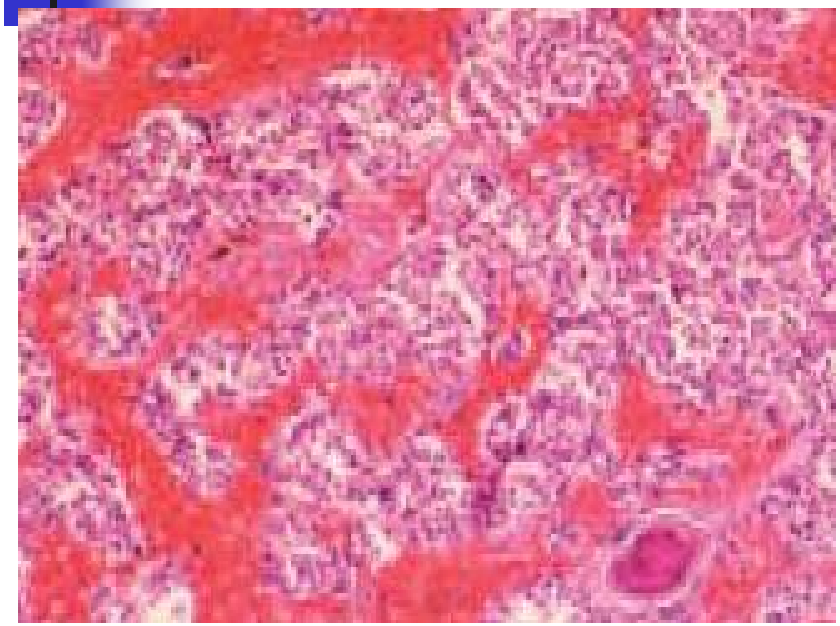
Tumors of the sellar region

Pituitary adenomas

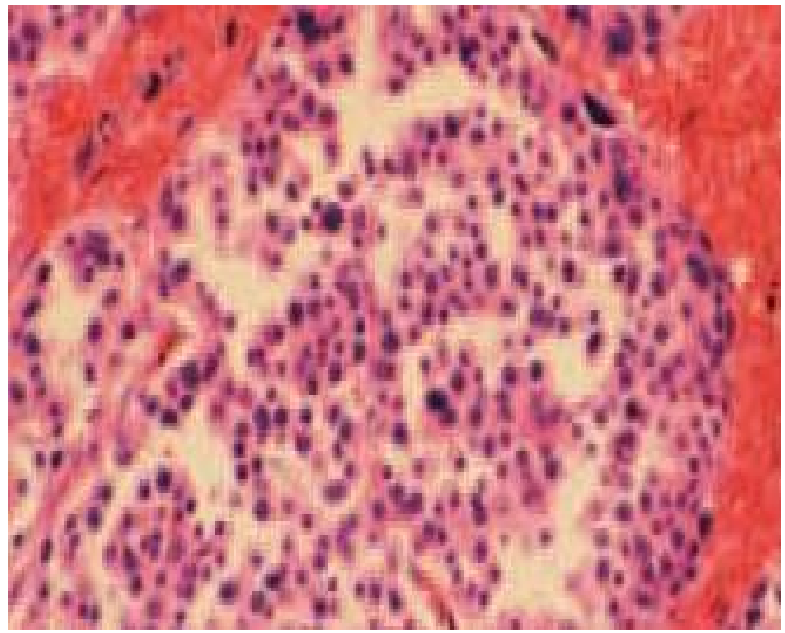
- Cl:
  - visual disturbance
  - Endocrine abnormalities
  - Pituitary apoplexy- 1 to 2%
- Gross: discrete grayish yellow, soft mass <1 cm dia
- Histology:
  - small round or oval nuclei with stippled chromatin
  - Aggressive: mitoses, pleomorphism
- Hormone IHC identify specific hormone

Tumors of the sellar region

Pituitary adenomas



Pituitary chromophobe (null cell): Cells separated into groups by sinusoidal trabeculae



Small nucleus with variable amount of cytoplasm and slight pleomorphism

Tumors of the sellar region

TABLE 11.8.

Nonpituitary Tumors in the Sellar Region

Meningioma	Epidermoid, dermoid cysts
Craniopharyngioma	Teratoma
Germinoma	Lipoma
Glioma	Chordoma
Hamartoma	Metastasis

Tumors of the sellar region

Craniopharyngioma

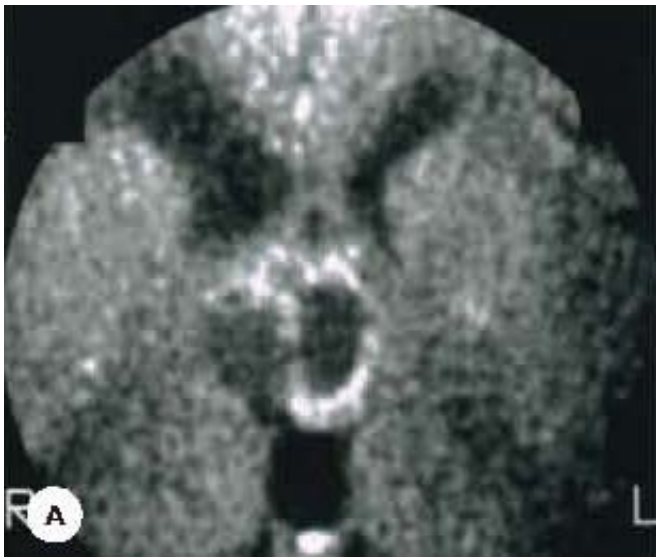
- More often children
- slowly growing
- originates from remnant epithelial cells of craniopharyngeal duct
- Mixed signal intensity with enhancing solid component; calcification
- Grossly: cystic with thick machine oil like contents
- Histlogy: multistratified squamous epithelial cells.

Two types:

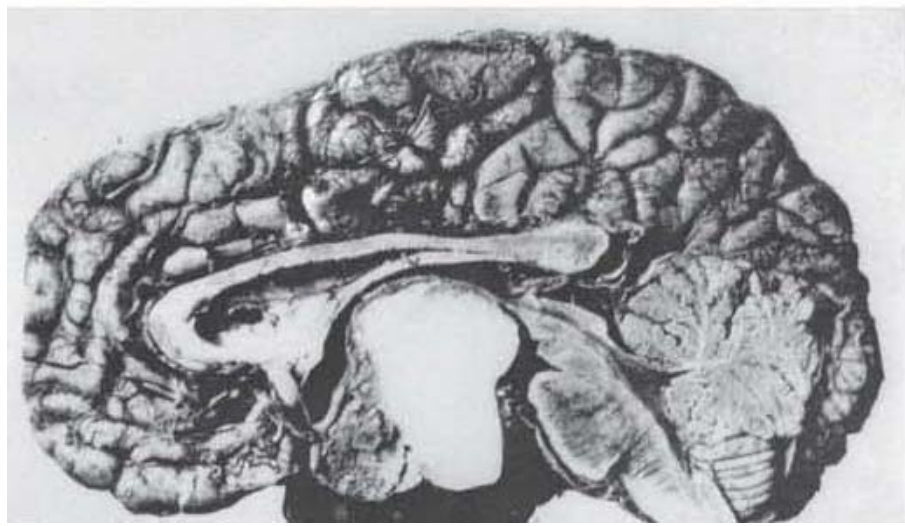
- The adamantinomatous type- cells form strands and cords
  calcifications, amorphous masses of keratin (wet keratin)
  cholesterol clefts characteristic
- The papillary type- cells rest on a fibrovascular stoma.
  lacks calcifications and cholesterol crystals
  Glial reaction and Rosenthal fibers round the tumor

Tumors of the sellar region

Craniopharyngioma



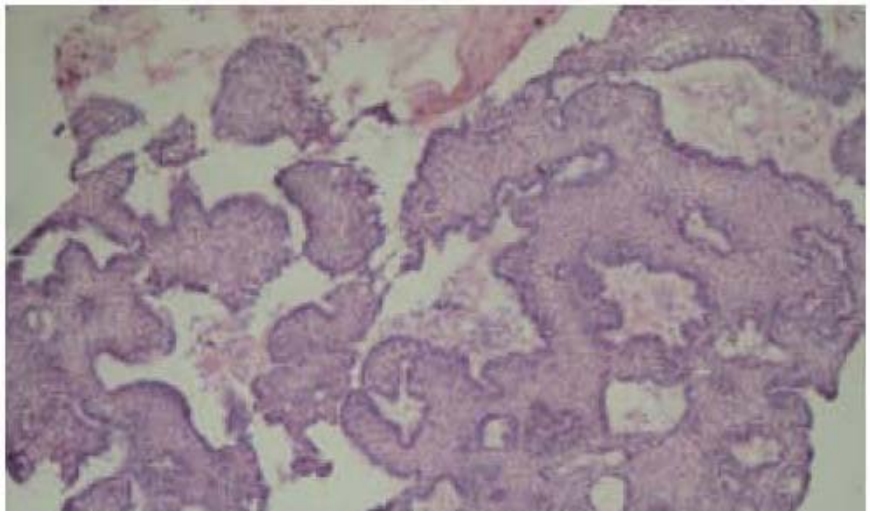
CECT showing large cystic mass within third ventricle



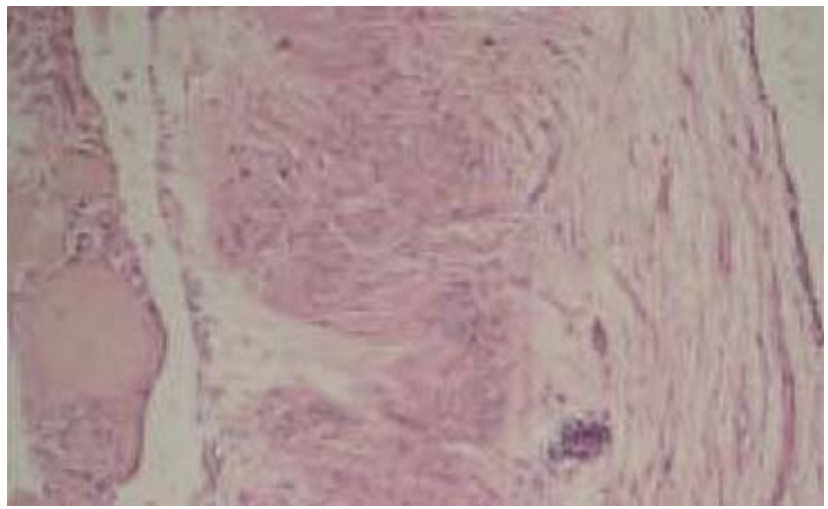
Large cyst with small tumorous mural nodules

Tumors of the sellar region

Craniopharyngioma



Mural nodule contains squamous epithelial cells arranged in small islands

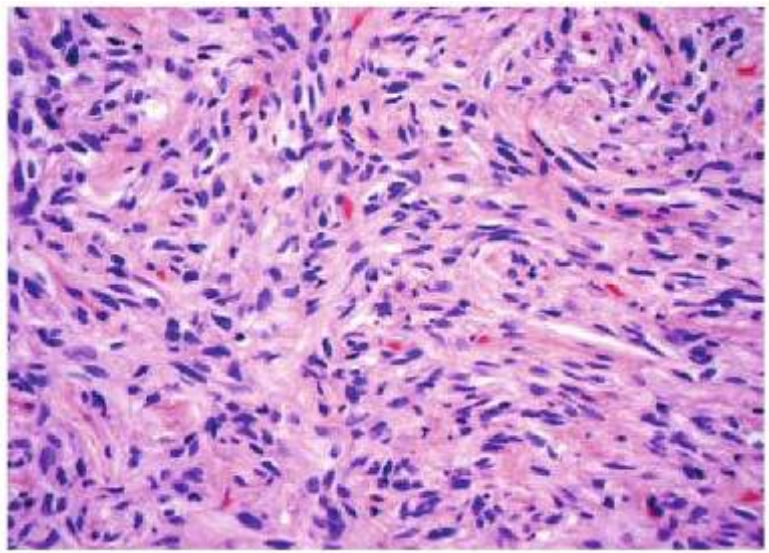


Cyst wall loosely attached to ventricular wall- contains astrocytic fibers and Rosenthal fibers

Tumors of the sellar region

Pituicytoma

- WHO grade I
- Rare, solid, low grade, spindle cell, glial neoplasm of adults
- Originates in the neurohypophysis or infundibulum
- < 30 cases reported
- Visual disturbance, headache, hypopituitarism
- Well-circumscribed, solid masses, can measure up to several centimetres.
- Histologically- compact architecture consisting of elongate, bipolar spindle cells arranged in interlacing fascicles or assuming a storiform pattern.
- Mitotic figures are absent or rare.
- Positive- vimentin, S-100 protein ,
- variable- GFAP.
- slow growth
- possibility of curative surgery



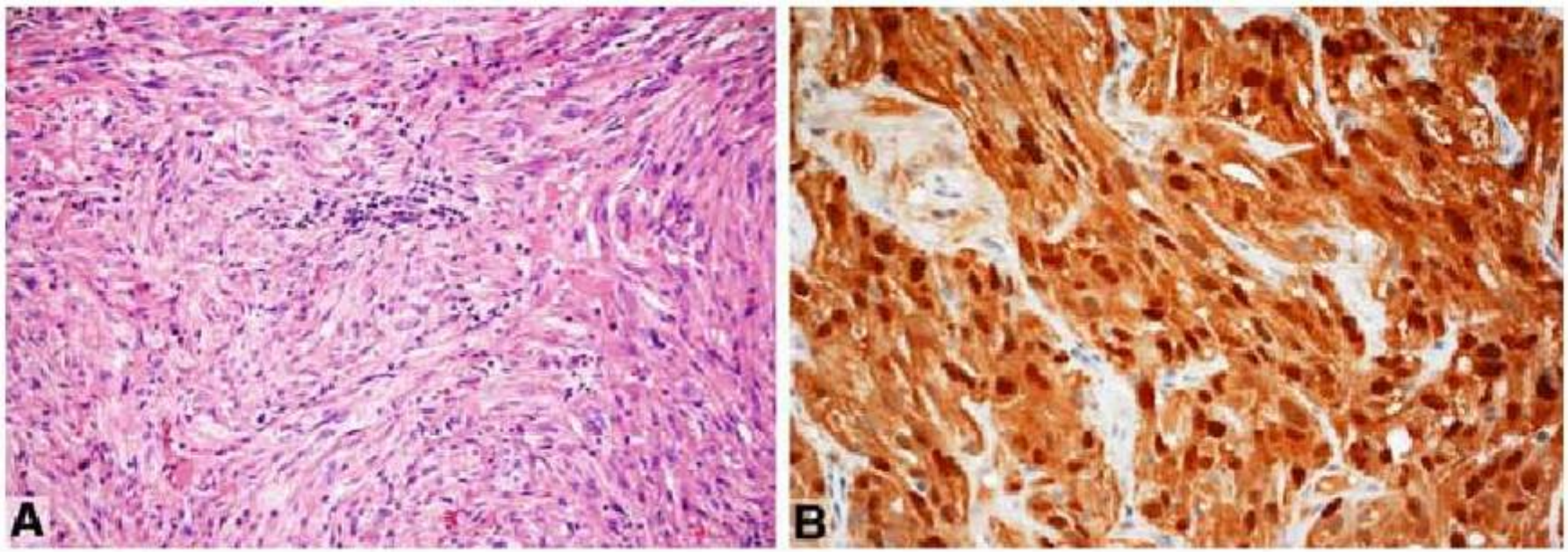
Tumors of the sellar region

Spindle cell oncocytoma *of adenohypophysis*

- WHO grade II
- 2002, Roncaroli et al. – till today 10 cases
- Oncocytic, non-endocrine neoplasm of the anterior pituitary
- Adults (mean age 56 years)
- Macroscopically be indistinguishable from a non-functioning pituitary adenoma and follow a benign clinical course
- The eosinophilic, variably oncocytic cytoplasm contains numerous mitochondria
- Immunoreactive for the anti-mitochondrial antibody 113-I, S-100 protein and EMA, but is negative for pituitary hormones

Tumors of the sellar region

Spindle cell oncocytoma *of adenohypophysis*



Spindle and somewhat epithelioid cells with abundance of variably granular cytoplasm, different degree of nuclear atypia and focal inflammatory reaction

Generalised staining for S-100 protein

Diagnostic approach
Radiology

- XRay Skull
- CT Scan- plain and Contrast enhanced
- MRI brain and spinal cord
- Angiography
- PET
- SPECT
- MRS
- Myelography

Diagnostic techniques in pathology
TUMOR MARKERS

Oncofetal proteins

Placental proteins

Ectopic hormones

Enzymatic markers

Polyamines

Desmosterol

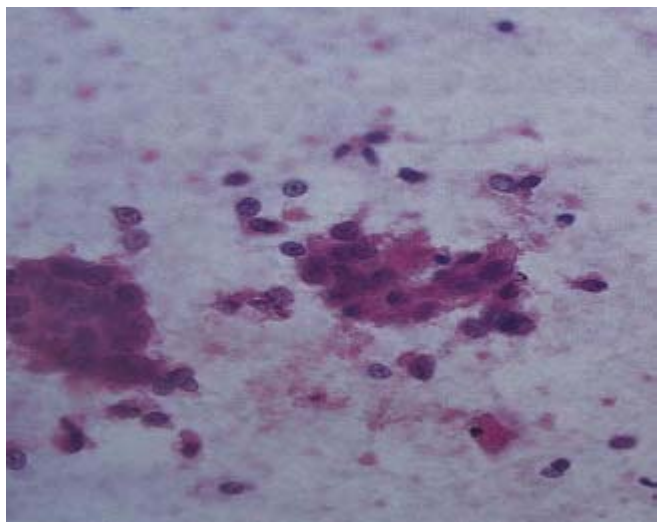
Beta-2-Microglobulin

Immunochemically Defined markers

Diagnostic techniques

Needle biopsy

Gliosis – confined to tumor/ brain interface
Inflammation and necrosis- within tumor

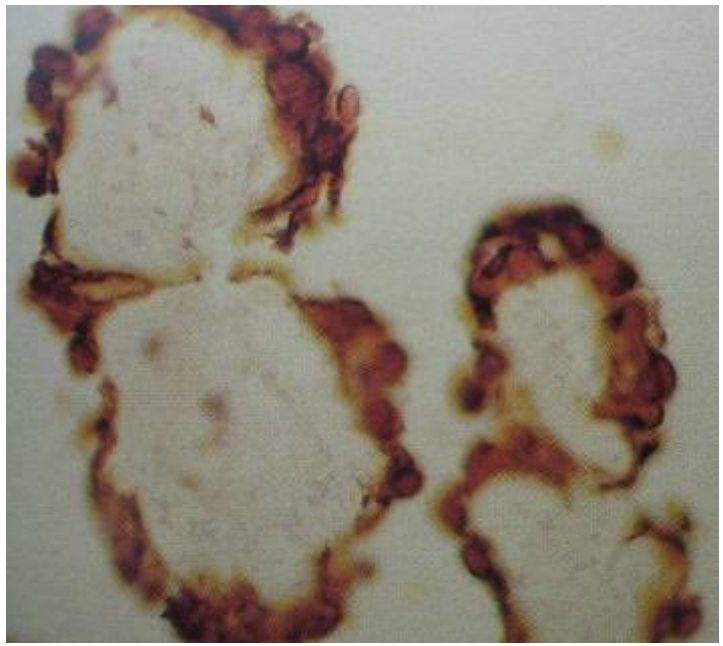


Touch smear-

clumps of tumor cells adherent to one other
metastatic epithelial neoplasm

Immunohistochemistry

Panel- LCA, GFAP, Cytokeratin, EMA
If non reactive- vimentin, S100, synaptophysin



Strong cytoplasmic reactivity to EMA s/o mets papillary adenoca and R/o Choroid plexus neoplasm as single layer of epithelium upon papillary frond raise suspicion

Diagnostic techniques in pathology
intra-operative diagnosis

When to ask

- Definitive neurosurgical management will be influenced

- When an unexpected lesion is encountered during surgery, or when the appearances of lesion visualized during surgery suggest an alternative diagnosis

- The main aim to obtain a tissue based diagnosis.

Diagnostic techniques in pathology

FROZEN SECTION

- In stereotactic biopsy- adequacy of the specimen

- Diagnosis and classification of a tumor - overall less reliable than diagnosis made on paraffin sections

Diagnostic techniques in pathology

Fluorescent imaging (Chemical probe)

- Cytoreductive surgery
- **Intravenous injection of fluorescein Na** (0.2 cc/kg body weight)
- the yellow-stained tumor is visible to the naked eye
- in an eloquent area- resect at the surface of the yellow-stained tumor or debul within the yellow-colored lesion until the resection surface becomes pale yellow.
- in non-eloquent regions- suction of peritumoral white matter
- no special equipment
- wide applicability in resection of malignant gliomas

No Shinkei Geka. 2007;35(6):557-62

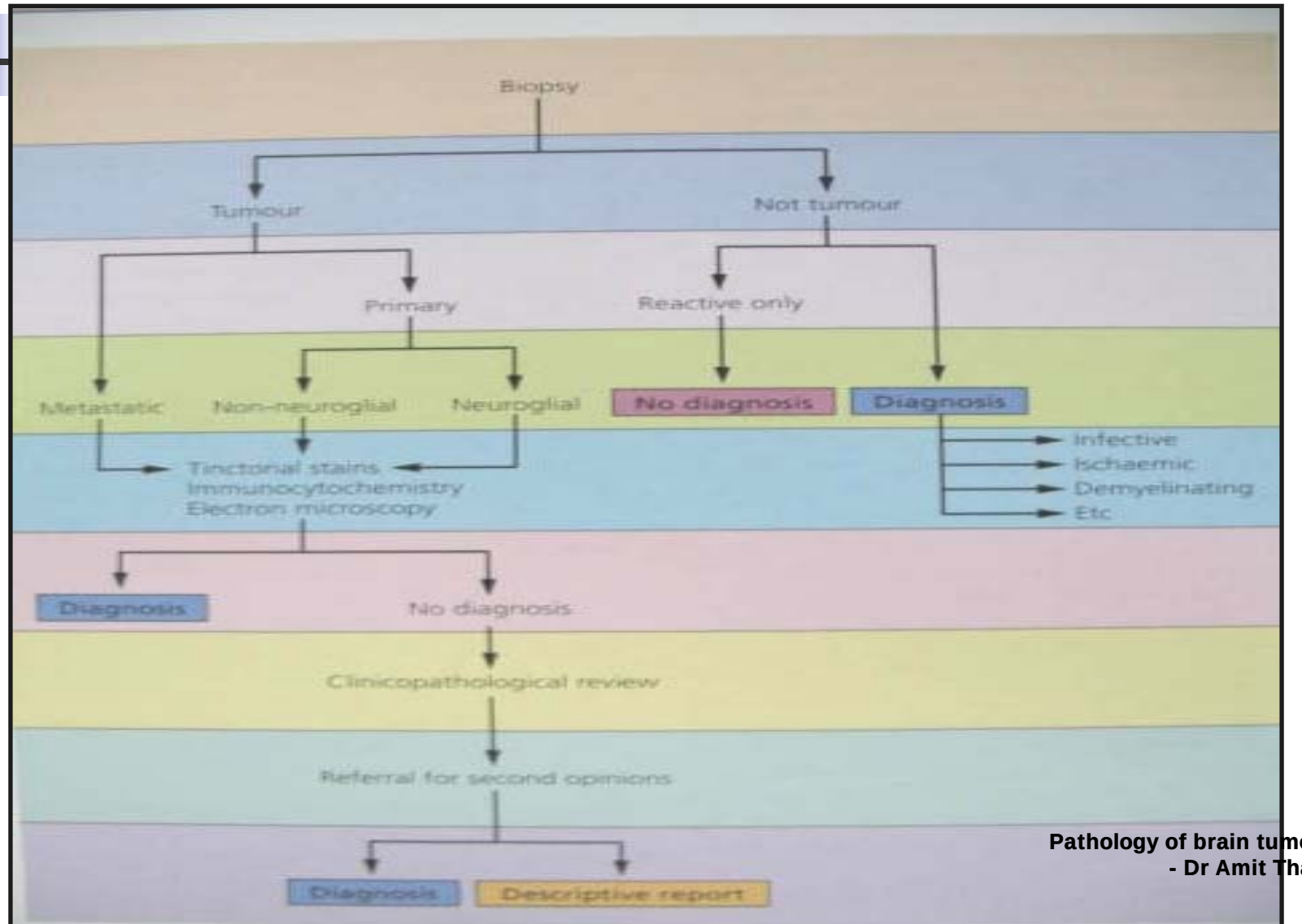
Diagnostic techniques in pathology
BIOPSY

Paraffin sections better-

- Greater amount of tissue
- Better cytology
- More time to assess the section

Diagnostic techniques in pathology

Approach to histological diagnosis of tumor biopsy



Pathology of brain tumors
- Dr Amit Thapa

Diagnostic techniques in pathology

Useful information to be provided by surgeons

- Relationship of the lesion to adjacent structures
- changes in the character and nature of the tissue
- calcifications (which can be missed by MRI)
- Any changes in the tissue specimen occurring due to surgery
- Preoperative embolisation
- Precise location of different portion of biopsy
- Record whether certain key areas were sampled
- Any apparent multiple lesions
- Extent of resection
- If lobectomy or larger resection- identify the resection margins
- Relationship to blood vessels, other associated lesions, reactive changes

Diagnostic techniques in pathology
BIOPSY

Tissue handling and sampling

- Specimen not to be fixed-
  - Allows tissue to be sampled
  - Stored for a number of techniques
  - Allow use of greater range of tissue fixatives
- Optimal fixation in glutaraldehyde for EM.
- Usually fixed in 10% formalin, buffered at neutral pH
- Then within 6-24hrs, sampling for paraffin section processing done depending upon size and volume of the specimens

Diagnostic techniques in pathology
BIOPSY

Protocol for handling a lobectomy specimen

- receive fresh and orient prior to dissection.
- describe carefully - tumor on the external surface, relationship to specialized structures (e.g. the hippocampus) and the resection margins.
- sample - microbiology, virology or molecular genetic studies.
- then fix overnight for further dissection or dissected fresh
- after fixation, section serially in the coronal plane at 5mm intervals
- the cut surfaces - inspected and photograph.
- the entire specimen should be blocked out on non adjacent faces
- all tissues should be processed for histology
- use of special stains and immuncytochemistry as appropriate.

Diagnostic techniques in pathology

Tinctorial stains used in CNS tumors

Haematoxylin and eosin	General histological features
Toluidine blue	Rapid staining of smears for intraop diagnosis
Reticulin	Reticulin framework around blood vessels in gliomas and lymphomas; soft tissue tumors
Van gieson	Dural infiltration in meningioma
Periodic acid Schiff	Glycogen (diastase sensitive) Mucins (intra and extracellular)
Alcian blue	Mucins (intra and extracellular)
Mucicarmine	Mucins (intra and extracellular)
Singh, Masson- Fontanna	Melanin
Luxol fast blue	Myelin
Solochrome cyanin	Myelin

Diagnostic techniques in pathology

Immunocytochemistry

Useful to define the neuroepithelial histogenesis using antibodies to cellular antigen

Gliofibrillary acidic protein (GFAP), synaptophysin, neurofilament protein	Astrocytic tumors
GFAP, Leu7	oligodendroglioma
Epithelial membrane antigen (EMA), vimentin, cytokeratins, progesterone receptors	meningioma
Leucocyte common antigen (LCA), CD3,20,45,68,79a immunoglobulins, EBV latent protein	lymphoma cells
S-100 protein, Neurofilament proteins (for axons)	Schwannoma
S-100 protein, GFAP, EMA	Ependymoma
Transthyretin, Carbonic anhydrase C, Cathepsin D, GFAP, EMA, Cytokeratins	Choroid plexus tumors
GFAP, Synaptophysin, Neuron specific enolase (NSE), Neurofilament protein	Medulloblastoma
Synaptophysin, NSE, Neurofilament protein, MAP-2, NeuN	Neuronal tumors
Placental alkaline phosphatase, alpha fetoprotein, Beta hCG, CEA	Germ cell tumors
S-100 protein, NSE, HMB45, MART-1	Melanoma
GH, PRL, ACTH, FSH, LH, TSH Alpha glycoprotein subunit	Pituitary tumors
Cytokeratins (Pan and Mono, e.g. CK7, CK20), EMA, Chromogranin, NSE Cell specific markers- ER, PSA, Thyroglobulin	Metastatic tumors

Diagnostic techniques in pathology
Prognostic indicators

- Nuclear hyperchromasia & nuclear: cytoplasmic
  - Large densely staining nuclei
  - Raised N: C ratio
  - Enlarged nuclei showing hyperchromasia and pleomorphism
  - Mitotic and proliferation indices
- Necrosis
- Blood vessels, blood- brain barrier and edema
- Invasion, spread and metastasis
- Cytoplasmic features of tumour cells
- Expression of proteins detectable by immunocytochemistry
- Organoid arrangements of the cells
- High P glycoprotein levels
- Amplification of the c-myc oncogene,
- Elevated levels of c-myc mRNA
- Ki-67/ MIB-1 labelling indices

Good prognosis
- high TrkC mRNA expression

Diagnostic techniques in pathology
Proliferative potentials

Histologically similar tumors may have different proliferative potentials

J Neurooncol 1989; 7: 137-143

- Mitotic figure counts- *M phase fraction*
- ^{3}H Thymidine- *S phase fraction*
- Bromodeoxyuridine and Iododeoxyuridine (BUdR, IUdR)
- AgNORs
- PCNA/ Cyclin
- DNA polymerase Alpha
- Ki-67/ MIB 1

Prognostic variables

For each tumour entity,

combinations of parameters

- WHO grade
- Clinical findings- age/ neurologic performance status
- Tumour location
- Radiological features - contrast enhancement
- Extent of surgical resection
- Proliferation indices
- Genetic alterations

RECENT ADVANCES

Modern techniques

- **Molecular techniques**
- **DNA analysis:**
  structural changes in genes and chromosomes
  - **Southern blot**
  - **PCR**
  - **FISH**
  - **SSCP**

RECENT ADVANCES

Modern techniques

- **LOH ANALYSIS:**

  Chromosomal loss- reflects inactivation of tumor suppressor genes

- **(Comparative genomic hybridization) CGH:**

  A screening technique – detect large genomic gains or losses

RECENT ADVANCES

Modern techniques

- **RNA analysis**: changes in levels of mRNA expression
  - **Northern blot**:
  - **In-situ hybridization (ISH):**
- **Protein analysis**: changes in levels of protein expression, structural and functional protein changes
  - **Western blot:**
  - **Immunohistochemistry:**

THANK YOU