PATHOLOGY OF BRAIN TUMORS

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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

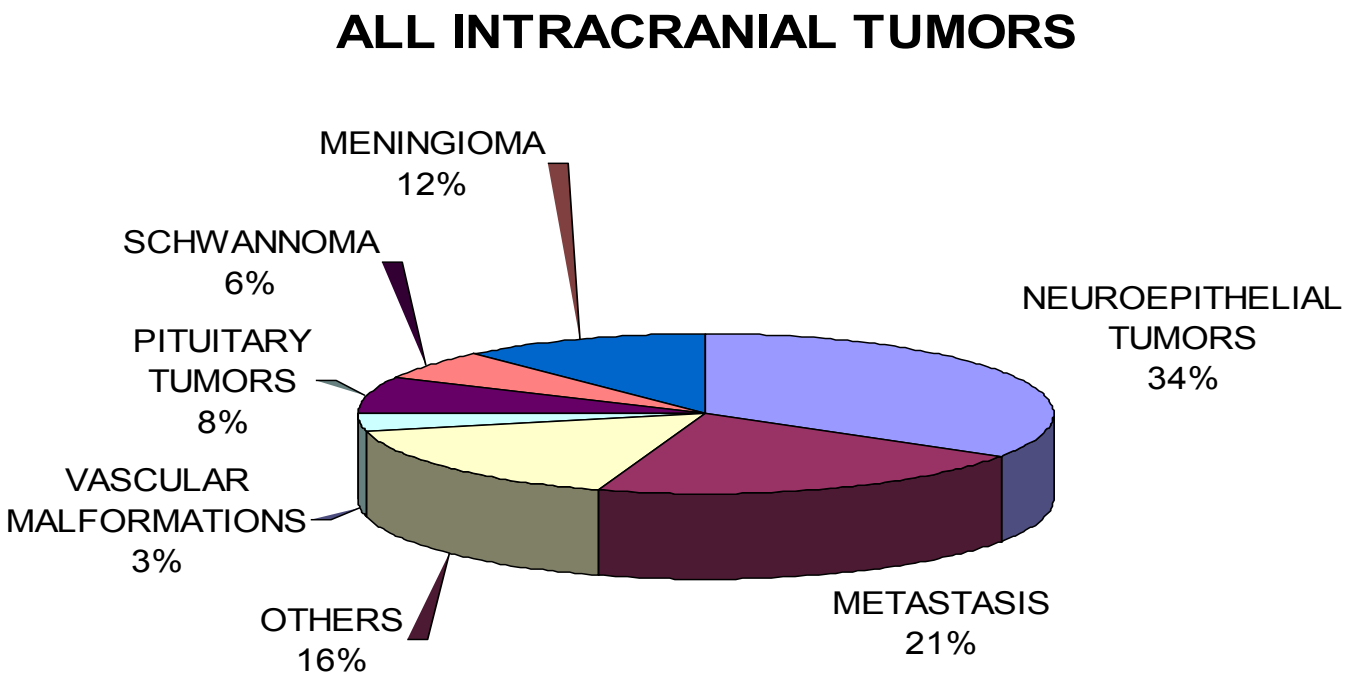
20% of all cancers in children <15 yrs

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**

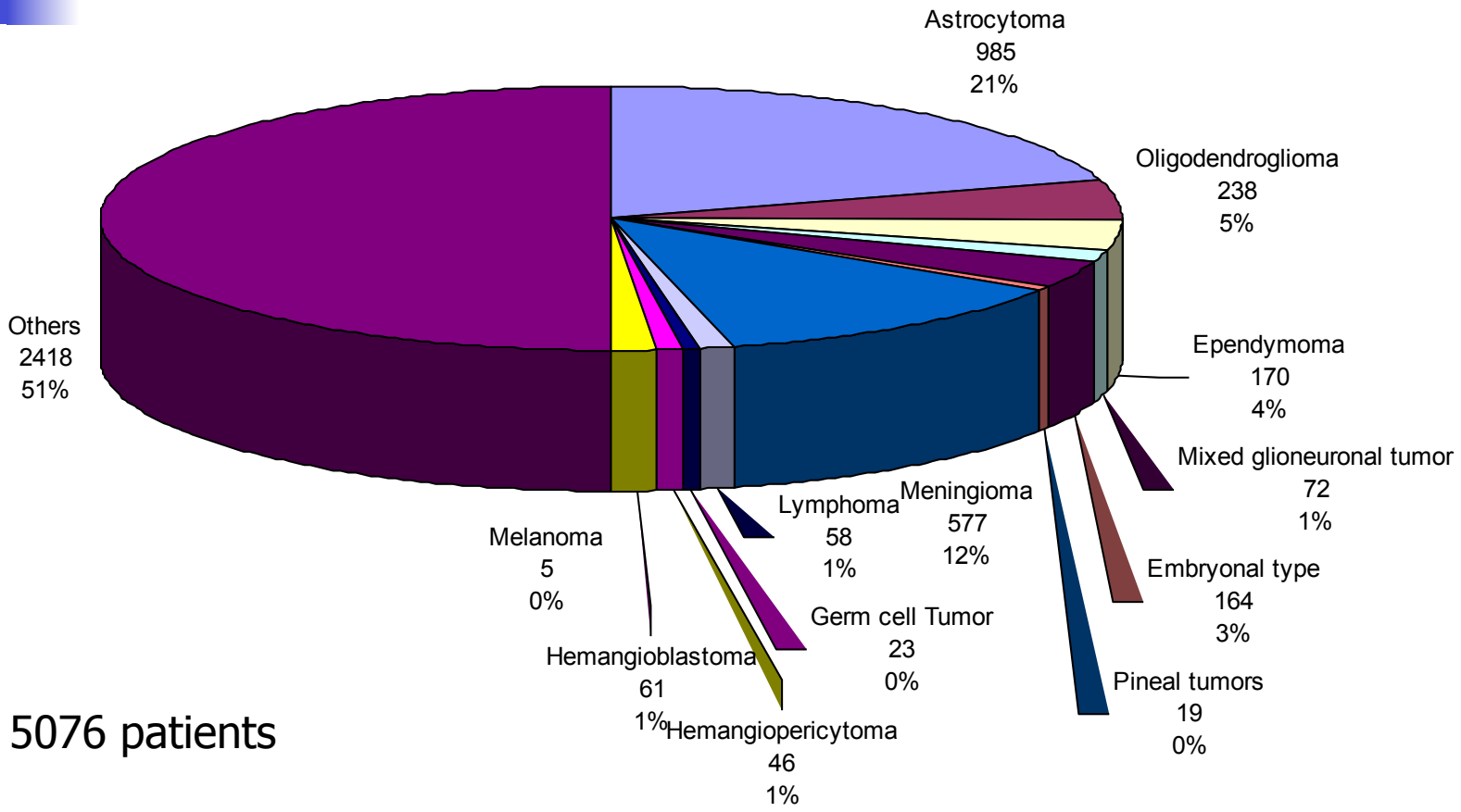
Parkin, 1997

Epidemiology
comparative incidence



Epidemiology

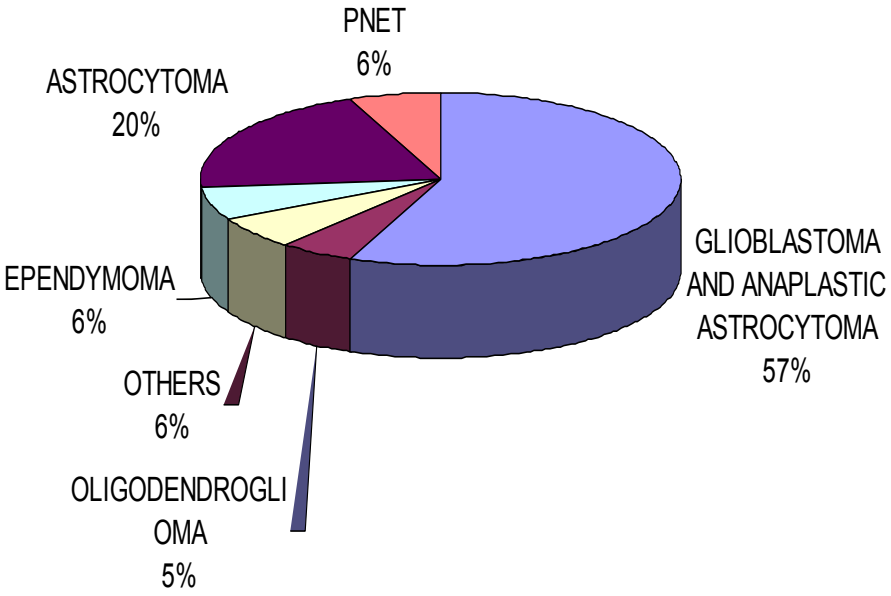
Relative incidence at AIIMS (2002-2007)



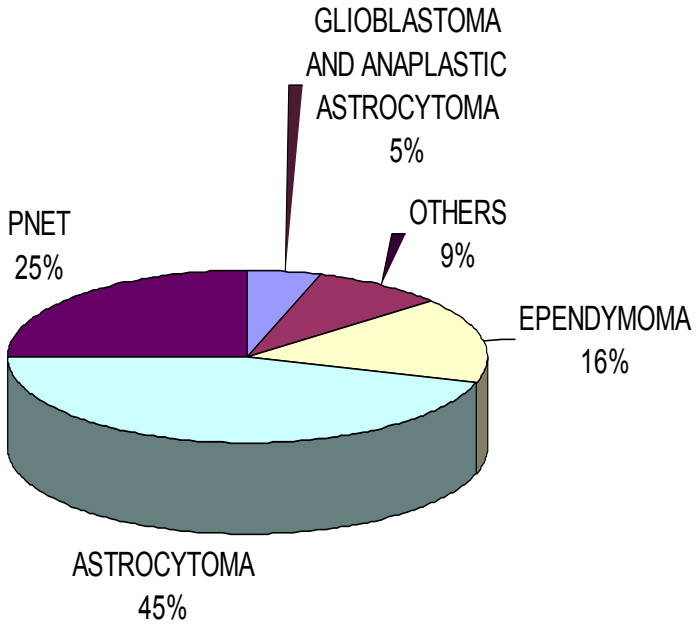
n= 5076 patients

Epidemiology
comparative incidence

INTRACRANIAL NEUROEPITHELIAL TUMORS, ALL AGES

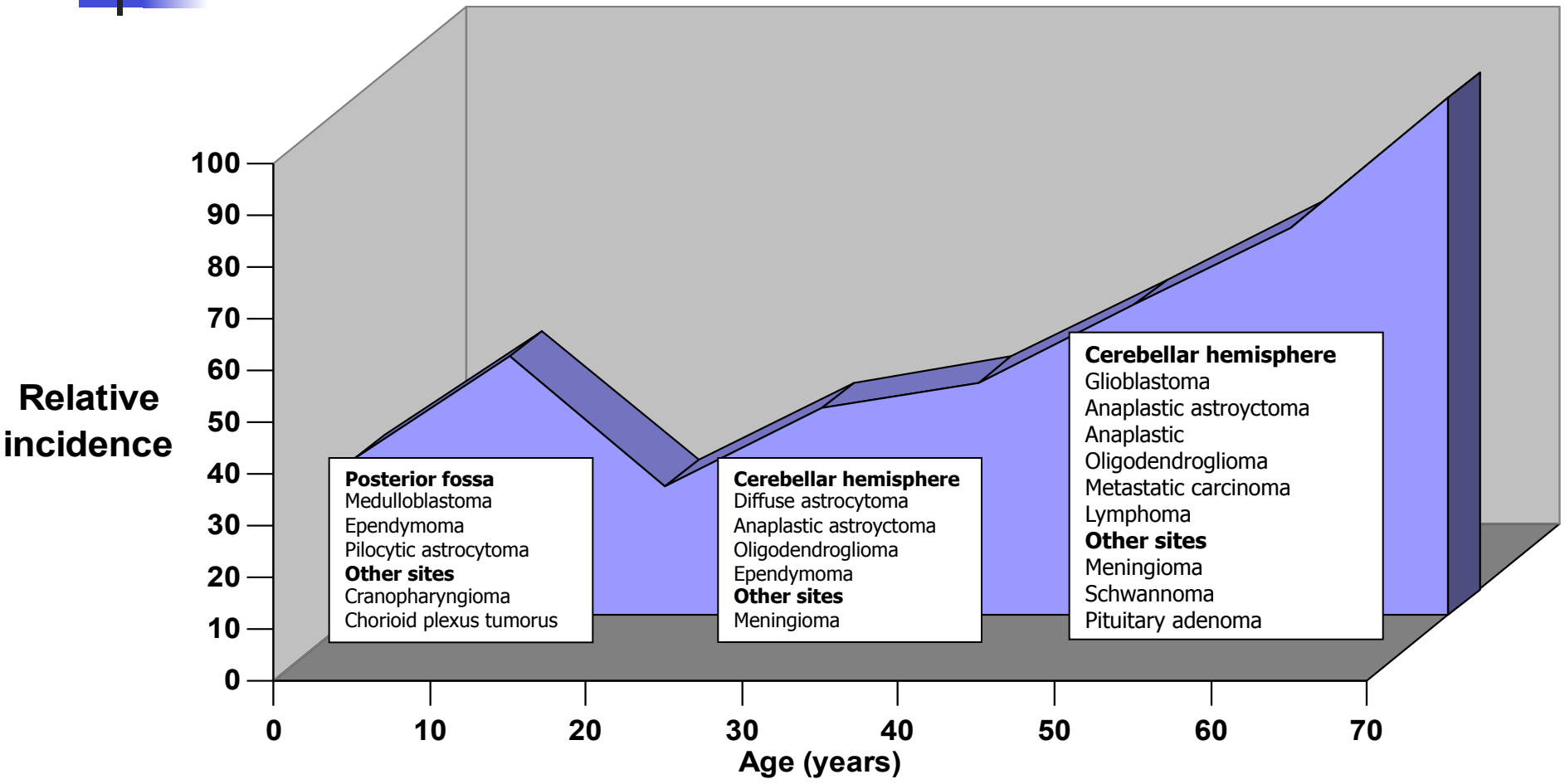


PRIMARY NEUROEPITHELIAL TUMORS OF CHILDHOOD



Epidemiological profile…

age wise distribution



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

Cells of origin for most brain tumors – debatable

Molecular enquiries-

most likely cells of origin are multipotential stem cells

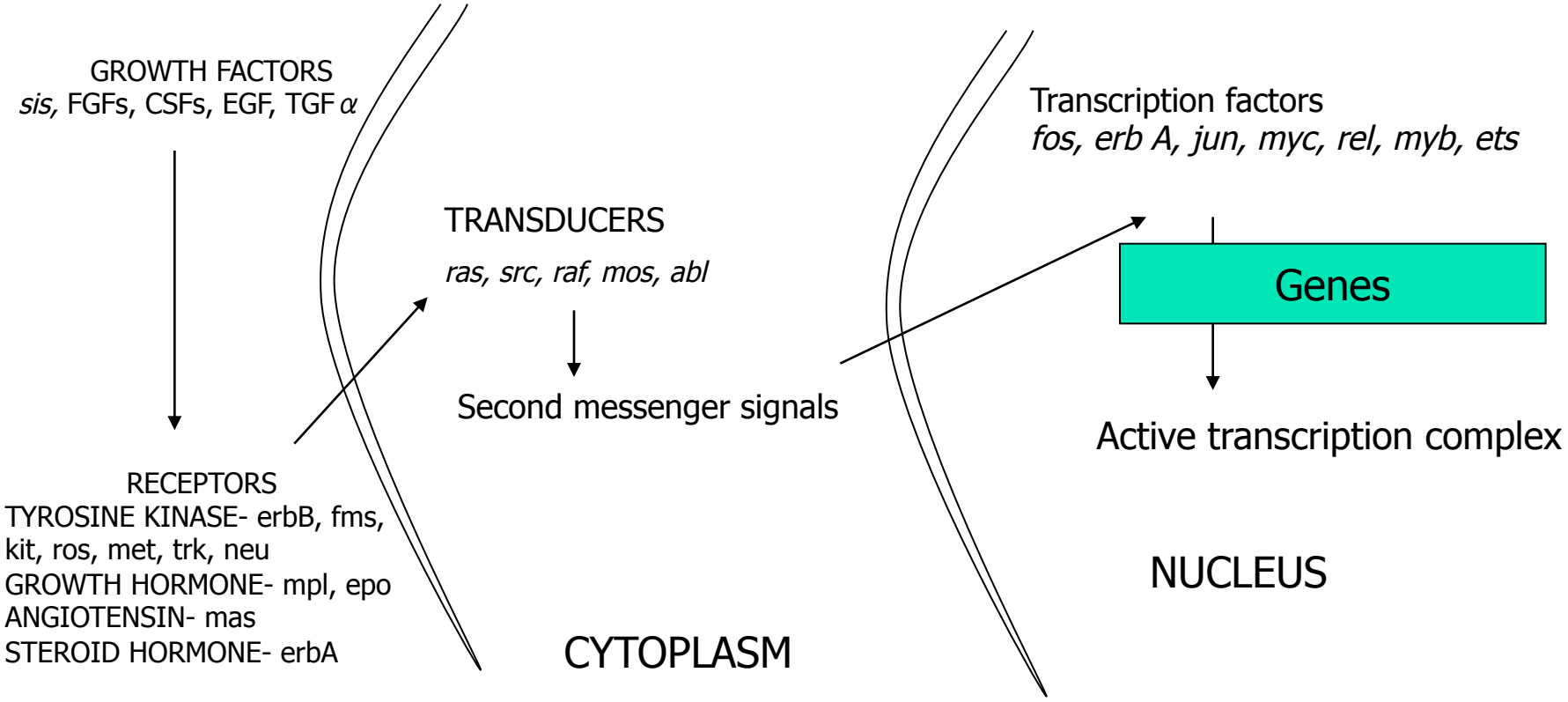
reside in both the developing and adult brain.

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…
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 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

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

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 tumor 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

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

Astrocytoma

Classification by cell type

Ordinary-

- Fibrillary
- Gemistocytic
- protoplasmic

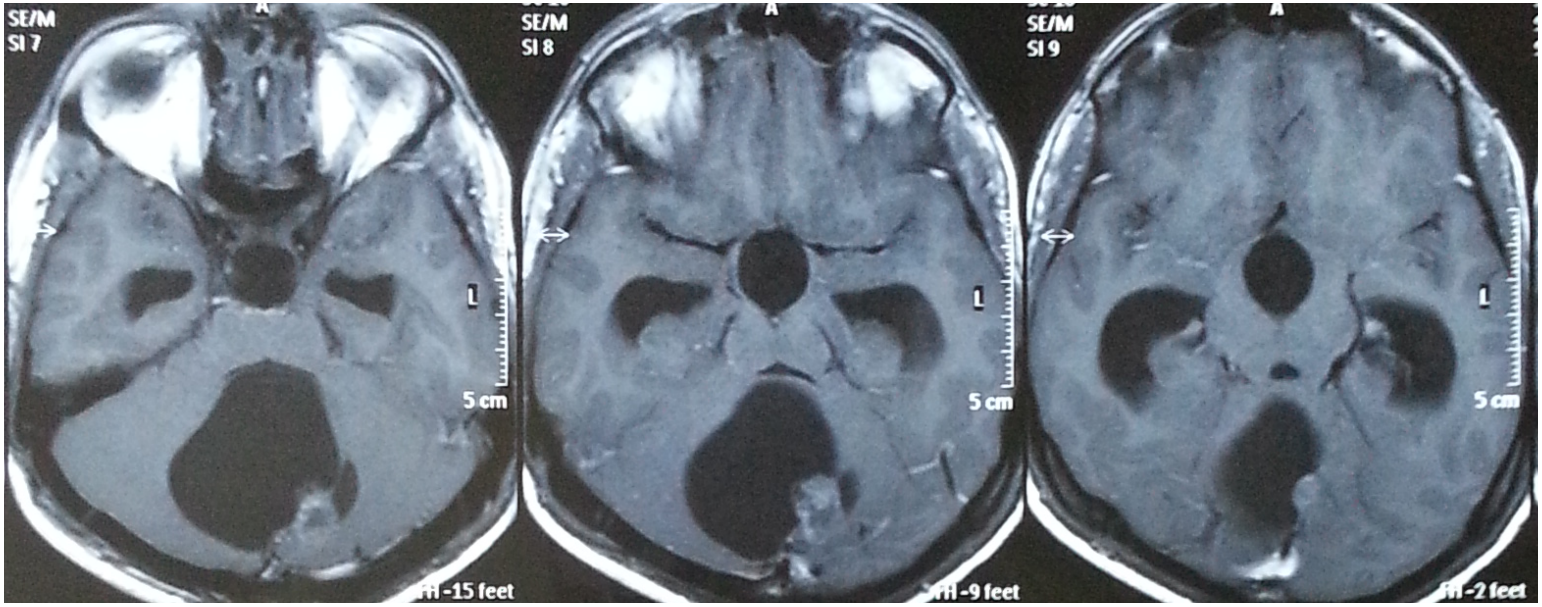
Special- favorable prognosis

- Pilocytic
- Microcystic cerebellar
- Subependymal giant cell

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



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

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

Pleomorphic xanthoastrocytoma

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

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.

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

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- Fraumeni 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**	

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)

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

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

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.

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

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

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
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

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

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

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

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 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*

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

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

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

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

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

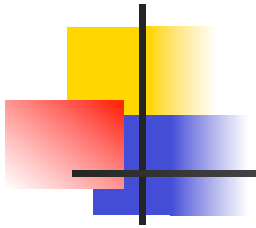
Spindle cell oncocytoma *of adenohypophysis*

- 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

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 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

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

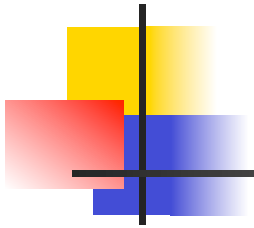
- **(Comparative genomic hybridization) CGH:**

  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