Brain Tumors (GENERAL)

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EPIDEMIOLOGY

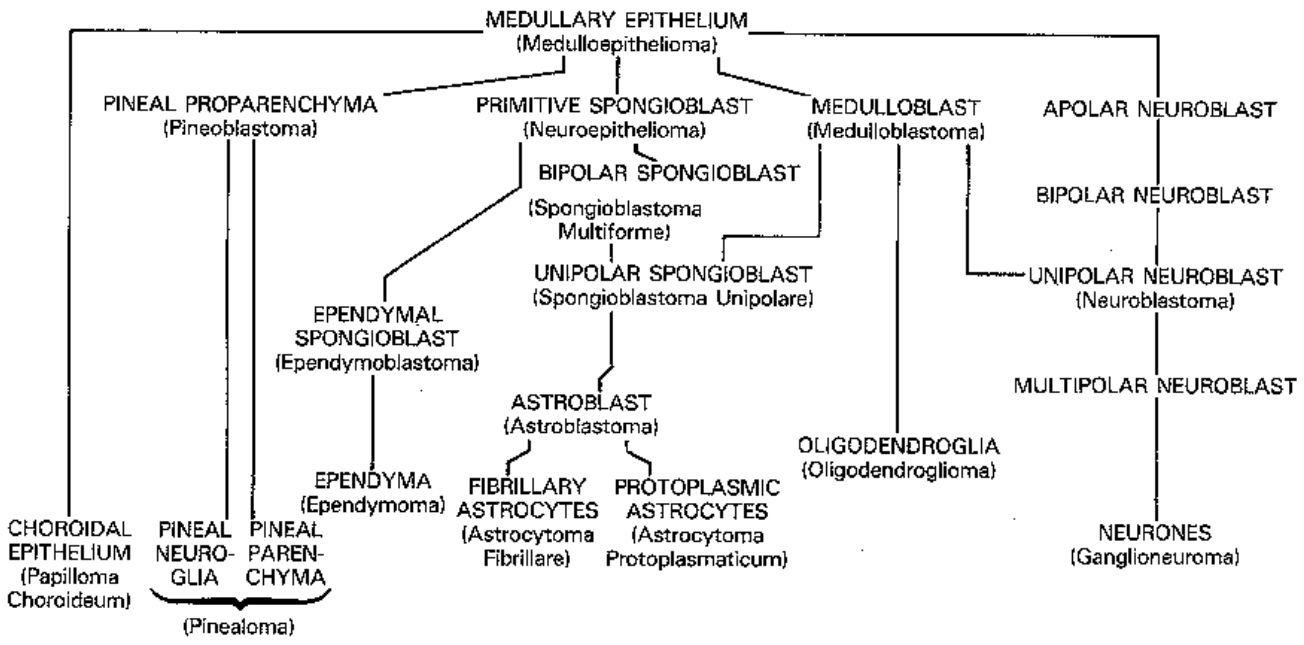
- ≈ 1.1-2% of all cancers.
- ≈ 13% of all cancer deaths.
- 20% of total yearly cost of cancer treatment in United States is for CNS cancers (primary or metastatic).
- median age-adjusted INCIDENCE (for primary brain tumors) ≈ 2-19 cases per 100,000 per year;
  - incidence of brain tumors continues to increase.
  - 6th most common cancer in adults.
- pediatric INCIDENCE (for primary brain tumors) ≈ 1-5 pediatric cases per 100,000 per year;
  - after leukemia, second most common cancer in children [20% pediatric tumors]!
- two peaks of incidence:
  small peak in childhood (predominance of *embryonal CNS neoplasms* and relative absence of gliomas) → drops slightly in adolescence → rises steadily → much higher peak in 60-80 years (predominance of supratentorial *gliomas*)
- men ≥ women (except meningiomas ← women : men = 2:1).
  - 4th leading cause of cancer-related deaths in males 35-54 yrs.

CELL OF ORIGIN

Neoplastic transformation can occur in:

1) **neuroglia** → gliomas - most commonly encountered (50-60%) and most feared brain tumors!
   astrocyte → astrocytoma (incl. glioblastoma multiforme)
   oligodendrocyte → oligodendroglioma
   ependymocyte → ependymoma, ependymoblastoma
2) **neurons** (almost exclusively postmitotic - not at risk for becoming tumor) or **neuroblast** → ganglioneuroma, neuroblastoma, retinoblastoma
3) **primitive neuroectoderm** → medulloblastoma
4) **choroid epithelial cell** → choroid plexus papilloma / carcinoma
5) **arachnoidal fibroblasts** → meningioma
6) **endothelial cell** or **"stromal" cell** → hemangioblastoma
7) **primitive notochord remnants** → chordoma
8) **pituitary cell** → adenoma
9) **pineal parenchymal cells** → pinealocytoma
10) **Schwann cell** → schwannoma (neurinoma)
11) **primary lymphocytes** → CNS lymphoma
12) **primitive germ cells** → germinoma, pinealoma, teratoma, cholesteatoma
13) **melanocyte** → melanotic carcinoma

BAILEY & CUSHING schema of normal developing cells and neuroepithelial tumors derived from them:



WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

First edition (1979)
Third edition (2000) – in addition to ***histological*** and ***immunohistochemical*** criteria is supplemented by ***genetic*** results (genetic profiling).
N.B. genetic basis represents definitive criterion for tumor classification!
Fourth edition (2007)
Fourth revised edition (2016)

WHO 2016

- CNS tumor diagnoses should consist of a histopathological name followed by the genetic features, with the genetic features following a comma and as adjectives, as in: *Diffuse astrocytoma, IDH-mutant* and *Medulloblastoma, WNT-activated*.
- for those entities with more than one genetic determinant, the multiple necessary molecular features are included in the name: *Oligodendroglioma, IDH-mutant and 1p/19q-codeleted*
- for a tumor lacking a genetic mutation, the term wildtype can be used if an official "wildtype" entity exists: *Glioblastoma, IDH-wildtype*; if formal wildtype diagnosis is not available, a tumor lacking a diagnostic mutation is given an *NOS* designation.

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
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	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {742A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone.*

<u>Summary of the major changes in the 2016 CNS WHO</u>

1. Formulating concept of how CNS tumor diagnoses are structured in the molecular era
2. Major restructuring of diffuse gliomas, with incorporation of genetically defined entities – see p. Onc10 >>
3. Major restructuring of medulloblastomas, with incorporation of genetically defined entities
4. Major restructuring of other embryonal tumors, with incorporation of genetically defined entities and removal of the term "primitive neuroectodermal tumor"*
5. Incorporation of a genetically defined ependymoma variant
6. Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity
7. Addition of newly recognized entities, variants and patterns:
    1) IDH-wildtype and IDH-mutant glioblastoma (entities)
    2) Diffuse midline glioma, H3 K27M–mutant (entity)
    3) Embryonal tumour with multilayered rosettes, C19MC-altered (entity)
    4) Ependymoma, RELA fusion–positive (entity)
    5) Diffuse leptomeningeal glioneuronal tumor (entity)
    6) Anaplastic PXA (entity)
    7) Epithelioid glioblastoma (variant)
    8) Glioblastoma with primitive neuronal component (pattern)
    9) Multinodular and vacuolated pattern of ganglion cell tumor (pattern)
8. Deletion of former entities, variants and terms:
    1) Gliomatosis cerebri
    2) Protoplasmic and fibrillary astrocytoma variants
    3) Cellular ependymoma variant
    4) "Primitive neuroectodermal tumor" terminology*
9. Addition of brain invasion as a criterion for atypical meningioma
10. Restructuring of solitary fibrous tumor and hemangiopericytoma (SFT/HPC) as one entity and adapting a grading system to accommodate this change
11. Expansion and clarification of entities included in nerve sheath tumors, with addition of hybrid nerve sheath tumors and separation of melanotic schwannoma from other schwannomas
12. Expansion of entities included in hematopoietic/lymphoid tumors of the CNS (lymphomas and histiocytic tumors)

*no more PNET!

WHO GRADES

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Gliomas are not divided sharply into BENIGN and MALIGNANT forms; rather, they represent **gradations on spectrum** from slowly growing to rapidly growing neoplasms. see p. Onc10 >>

- with time, as more aggressive cells replicate themselves to greater extent than do more indolent cells, gliomas may *shift from benign end of spectrum to malignant end* (i.e. propensity to transform into higher-grade glioma).

Quantitative measures of MITOTIC ACTIVITY (correlates with malignant clinical behavior):

a) **proliferation index** - measure of DNA synthesis - uptake of bromodeoxyuridine (thymidine analogue): BrdUrd IV prior to surgery → uptake into nuclei of tumor cells → uptake assessed in biopsy specimens (using BrdUrd-specific antibody).
b) immunohistochemical staining with **antibodies to proliferating cell nuclear antigen (PCNA)**.
c) immunohistochemical staining with **Ki-67 antibody** (recognizes histone protein expressed in proliferating but not quiescent cells).

Older WHO

NEUROEPITHELIAL tumors

1. **ASTROCYTIC** tumors:
    1) **(juvenile) pilocytic astrocytoma** (non-invasive, WHO grade I)
        a) *hemispheric*
        b) *diencephalic*
        c) *optic*
        d) *brain stem*
        e) *cerebellar*
    2) **subependymal giant cell astrocytoma** (non-invasive, WHO grade I)
    3) **pleomorphic xanthoastrocytoma** (non-invasive, WHO grade I)
    4) **astrocytoma** (WHO grade II)
        variants: *protoplasmic*, *gemistocytic*, *fibrillary*, *mixed*
    5) anaplastic (malignant) **astrocytoma** (WHO grade III)
        a) *hemispheric*
        b) *diencephalic*
        c) *optic*
        d) *brain stem*
        e) *cerebellar*
    6) **glioblastoma multiforme** (WHO grade IV) – most aggressive and most common of all CNS tumors!!!
        variants: *giant cell glioblastoma*, *gliosarcoma*
2. **OLIGODENDROGLIAL** tumors:
    1) **oligodendroglioma** (WHO grade II) ≈ 80%
    2) anaplastic (malignant) **oligodendroglioma** (WHO grade III) ≈ 20%
3. **EPENDYMAL CELL** tumors:
    1) **subependymoma** (WHO grade I)
    2) **ependymoma** (WHO grade II)
        variants: *cellular*, *papillary*, *epithelial*, *clear cell*, *mixed*
    3) **anaplastic ependymoma** (WHO grade III)
    4) **myxopapillary ependymoma**
4. **MIXED** gliomas:
    1) **mixed oligoastrocytoma** (WHO grade II)
    2) anaplastic (malignant) **oligoastrocytoma** (WHO grade III)
    3) others (e.g. **ependymoastrocytoma**)
5. Neuroepithelial tumors of **UNCERTAIN ORIGIN**:
    1) **polar spongioblastoma** (WHO grade IV)
    2) **astroblastoma** (WHO grade IV)
    3) **gliomatosis cerebri** (WHO grade IV)
6. Tumors of **CHOROID PLEXUS**:
    1) choroid plexus **papilloma** (66-90%)
    2) choroid plexus **carcinoma** (anaplastic choroid plexus papilloma) (10-33%)
7. **NEURONAL** and mixed **NEURONAL-GLIAL** tumors:
    1) **gangliocytoma** (s. **central ganglioneuroma**) – neuronal tumor; benign counterpart of neuroblastoma in CNS
    2) **dysplastic gangliocytoma of cerebellum** (Lhermitte-Duclos)
    3) **ganglioglioma** – gangliocytoma with glial component
    4) **anaplastic (malignant) ganglioglioma**
    5) **desmoplastic infantile ganglioglioma**

variant: *desmoplastic infantile astrocytoma*

6) **central neurocytoma** – tumor of well-differentiated neurons
7) **dysembryoplastic neuroepithelial tumor (DNET)** – benign mixed glial-neuronal tumor
8) **olfactory neuroblastoma** (**esthesioneuroblastoma**)
   variant: *olfactory neuroepithelioma*

8. **PINEAL PARENCHYMA** tumors:
   1) **pineocytoma** (WHO grade I)
   2) **pineoblastoma** (WHO grade IV)
   3) pineal parenchymal tumor of **intermediate differentiation** (WHO grade II-III)
   4) **papillary tumor** of pineal region (WHO grade II-III)

9. Tumors with **NEUROBLASTIC** or **GLIOBLASTIC** elements (s. EMBRYONAL TUMORS):
   1) **medulloepithelioma**
   2) primitive neuroectodermal tumors with multipotent differentiation:
      a) **medulloblastoma**
         variants: *melanocytic*, *desmoplastic*, *medullomyoblastoma*
      b) **primitive neuroectodermal tumor (PNET)**
   3) **neuroblastoma**
      benign counterparts: ganglioneuroblastoma, ganglioneuroma (s. ganglioma)
   4) **retinoblastoma**
   5) **ependymoblastoma**
   6) **atypical teratoid/rhabdoid tumor**

OTHER CNS tumors

1. Tumors of **SELLAR REGION**
   1) **pituitary adenoma**
   2) **pituitary carcinoma**
   3) **craniopharyngioma**

2. **HEMATOPOIETIC** tumors
   1) primary malignant **lymphomas**
   2) **plasmacytoma**
   3) **granulocytic sarcoma**

3. **GERM CELL** tumors see Intro (various topics) 2.jpg >>
   1) **germinoma**
   2) **embryonal cell carcinoma**
   3) **yolk sac tumor** (**endodermal sinus tumor**)
   4) **choriocarcinoma**
   5) **teratoma**
   6) **mixed** germ cell tumor

4. Tumors of **MENINGES**
   1) **meningioma**
      variants: *meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, metaplastic subtypes*
   2) atypical **meningioma**
   3) anaplastic (malignant) **meningioma**

5. **NON-MENINGOTHELIAL** tumors of **MENINGES**
   1) benign mesenchymal
      a) **osteocartilaginous** tumors
      b) **lipoma**
      c) **fibrous histiocytoma**
   2) malignant mesenchymal
      a) **chondrosarcoma**
      b) **hemangiopericytoma**
      c) **rhabdomyosarcoma**
      d) **meningeal sarcomatosis**
   3) primary melanocytic lesions
      a) **diffuse melanosis**
      b) **melanocytoma**
      c) **malignant melanoma**
         variant: *meningeal melanomatosis*
   4) hemopoietic neoplasms
      a) **malignant lymphoma**
      b) **plasmacytoma**
      c) **granulocytic sarcoma**
      d) tumors of uncertain histogenesis - **hemangioblastoma** (**capillary hemangioblastoma**)

6. Tumors of **CRANIAL / SPINAL NERVES**
   1) **neurofibroma**
   2) **schwannoma** (**neurinoma**, **neurilemoma**)
      subtypes: *cellular*, *plexiform*, *melanotic*
   3) **malignant peripheral nerve sheath tumor**
      variants: *epithelioid*, *divergent mesenchymal or epithelial differentiation*, *melanotic*

7. **CYSTS** and **TUMOR-LIKE** lesions
   1) Rathke cleft cyst
   2) epidermoid cyst
   3) dermoid cyst
   4) colloid cyst of 3rd ventricle
   5) enterogenous cyst
   6) neuroglial cyst
   7) granular cell tumor (choristoma, pituicytoma)
   8) hypothalamic neuronal hamartoma
   9) nasal glial heterotopia
   10) plasma cell granuloma

8. **LOCAL EXTENSIONS** from regional tumors (i.e. secondary intracranial tumors)

1) **paraganglioma** (**chemodectoma**)
2) **chordoma**
3) **chondroma**
4) **chondrosarcoma**
5) **carcinoma**

9. **METASTATIC** tumors (i.e. secondary intracranial tumors as blood-borne metastases)
10. **UNCLASSIFIED** tumors

CONGENITAL NEOPLASMS

1) craniopharyngioma
2) chordoma
3) hemangioblastoma
4) colloid cysts
5) germ cell tumors (germinoma, teratoma, etc)
6) dermoid, epidermoid

FREQUENCY

Metastatic tumors are ≈ 5-10 times more common than **primary CNS tumors**!

– increased longevity of patients with cancer in other systems has resulted in higher incidence of metastatic CNS lesions!
– 15% patients with systemic cancer suffer neurological complications (*direct* or *paraneoplastic*).

	Children (< 14 yrs), %	**Adults**, %
INTRA-AXIAL		
Glioblastoma	20	50-60
Astrocytoma	21	10-25
Oligodendroglioma	1	3-5
Ependymoma	5-10	2-5
Medulloblastoma	10-30	1-6
Neuroblastoma	3	-
Primary CNS lymphoma		2.7
EXTRA-AXIAL		
Meningioma	5	15-22
Craniopharyngioma	4-10	1-3
Vestibular schwannoma	1	2-10
Pituitary adenoma	-	4-13
Pinealoma	0,5-2	1
Hemangioma	3	2
Sarcoma	1	0,1-1
Teratoma	2	-
Chordoma		0,1
Others	5	5

Three most common primary CNS tumors in **adults**:
1. Glioblastoma multiforme
2. Meningioma
3. Astrocytoma

N.B. 60% tumors in adults are astrocytomas! (50% glioblastoma multiforme!!!)

Three most common primary CNS tumors in **children**:
1. Medulloblastoma
2. Astrocytoma (esp. cerebellar pilocytic astrocytoma)
3. Glioblastoma multiforme

N.B. 1/4 tumors in children are medulloblastomas!

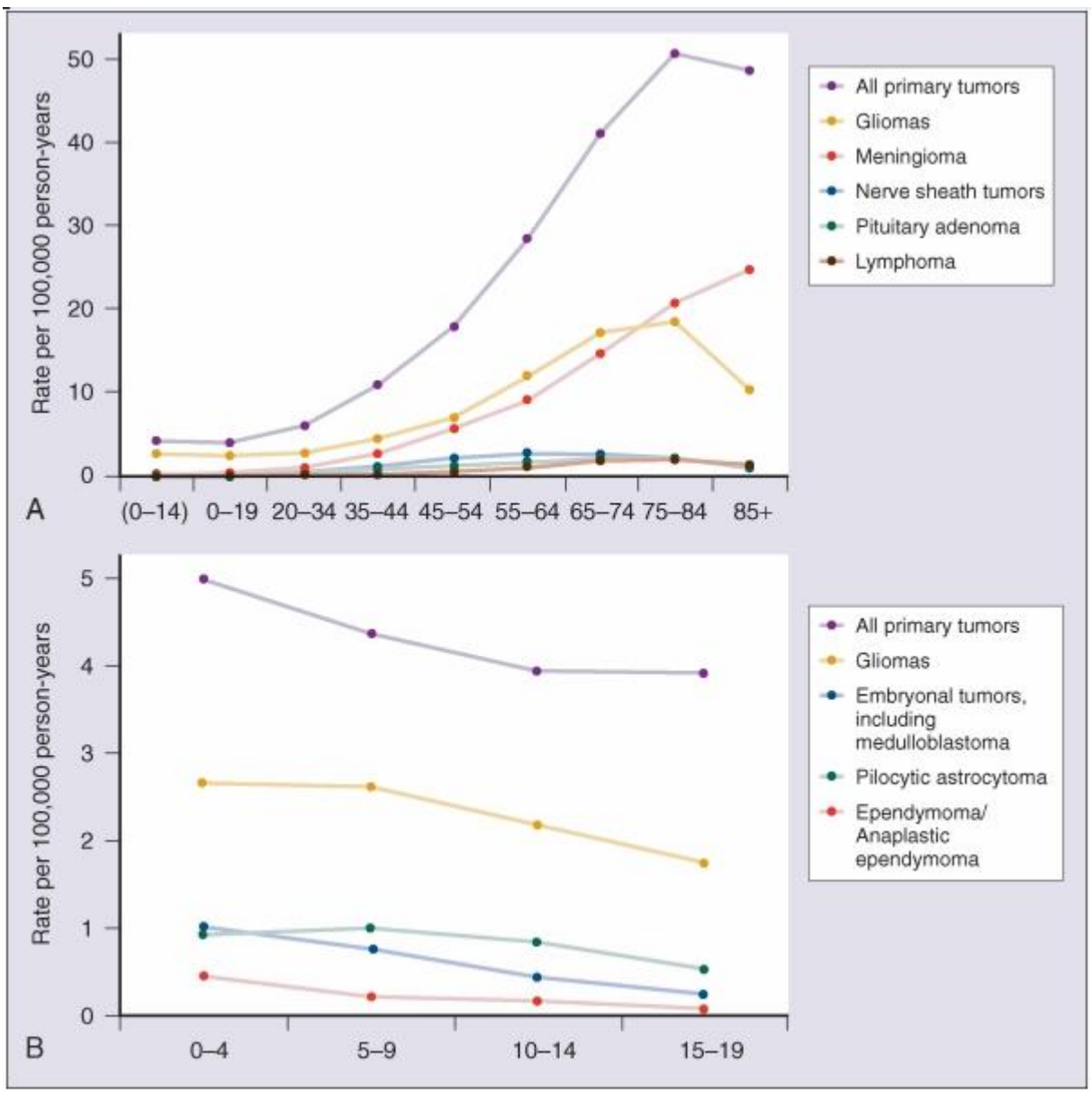
Three most common primary CNS tumors in **children (< 2 yrs)**:
1. Medulloblastoma
2. Ependymoma
3. Low-grade gliomas (esp. midline pilocytic astrocytomas)

Brain tumors (adults) with percentage incidence by category:

Primary intra-axial	**Primary extra-axial***	**Metastatic****
Glioblastoma (47)	Meningioma (80)	Lung (37-49)
Anaplastic astrocytoma (24)	Acoustic neuroma (10)	Breast (16-19)
Astrocytoma (15)	Pituitary adenoma (7)	Melanoma (16)
Oligodendroglioma (5)	Other (3)	Colorectum (9)
Lymphoma (2.7)		Kidney (8)
Other (7)		Other (11)

*in *childhood*, craniopharyngioma and pineal region tumors are most common.
**in *childhood*, most common metastatic tumors are neuroblastoma (usually epidural) and leukemia (meningeal).

Age-specific incidence of primary CNS tumors by histologic type:
A. Selected histologic types among all age groups.
B. Selected histologic tumor types in children.



PATHOLOGY

In most neoplasms, three zones may be identified:

1) **central** region of **necrosis**
2) densely **cellular ring** (area of CT/MRI contrast enhancement)
3) **peripheral edema** zone of lesser cellular density ("tumoral infiltration") with fingers extending peripherally from main mass.

Rosenthal fibers are characteristic feature of:

1) *JUVENILE PILOCYTIC ASTROCYTOMAS*
2) *CRANIOPHARYNGIOMAS*
3) around *EPENDYMOMAS*
4) *ALEXANDER DISEASE* (Rosenthal fibers radiate from vessels)

Rosenthal fibers in neuropil:

BENIGN vs. MALIGNANT

≈ 1/3 brain tumors can be called BENIGN (mainly extra-axial tumors - meningiomas, acoustic neuromas).

Concept of malignancy in CNS has different meaning from that which applies to systemic cancers;

- term "malignant" has nothing to do with metastasis out of CNS, which is extraordinarily rare.
- term "malignant" describes:
  1) ***histologic features***:
     BENIGN - grow slowly, low cellularity, few mitoses, no necrosis, no vascular proliferation.
     MALIGNANT – 1) rapid growth (frequent mitotic figures), 2) invasiveness, 3) vascular proliferation (endothelial hyperplasia), 4) necrosis.
  2) ***anatomic location*** - can have lethal consequences irrespective of histologic classification.
     e.g. benign meningioma, by compressing medulla, can cause cardiorespiratory arrest
  3) ***possibility of complete surgical removal*** - unless tumor can be completely excised to last cell, all intracranial neoplasms are potentially malignant in that they may recur, and often do.
     e.g. gliomas are rarely curable by surgical excision - fundamentally malignant!

Neuroectodermal tumors are never "benign"

N.B. because cranial vault allows no room for expansion, *even BENIGN tumors can be serious*! - not clearly separable into BENIGN and MALIGNANT forms.
e.g. histologically benign *PITUITARY ADENOMAS* may invade adjacent dura mater and bone and grow into cavernous or sphenoid sinus.
e.g. malignant *GLIOBLASTOMA MULTIFORME* invades brain locally but seldom spreads elsewhere.

Distinction between "benign" and "malignant" is less important than for systemic cancers

Tumor LOCATION & TYPES

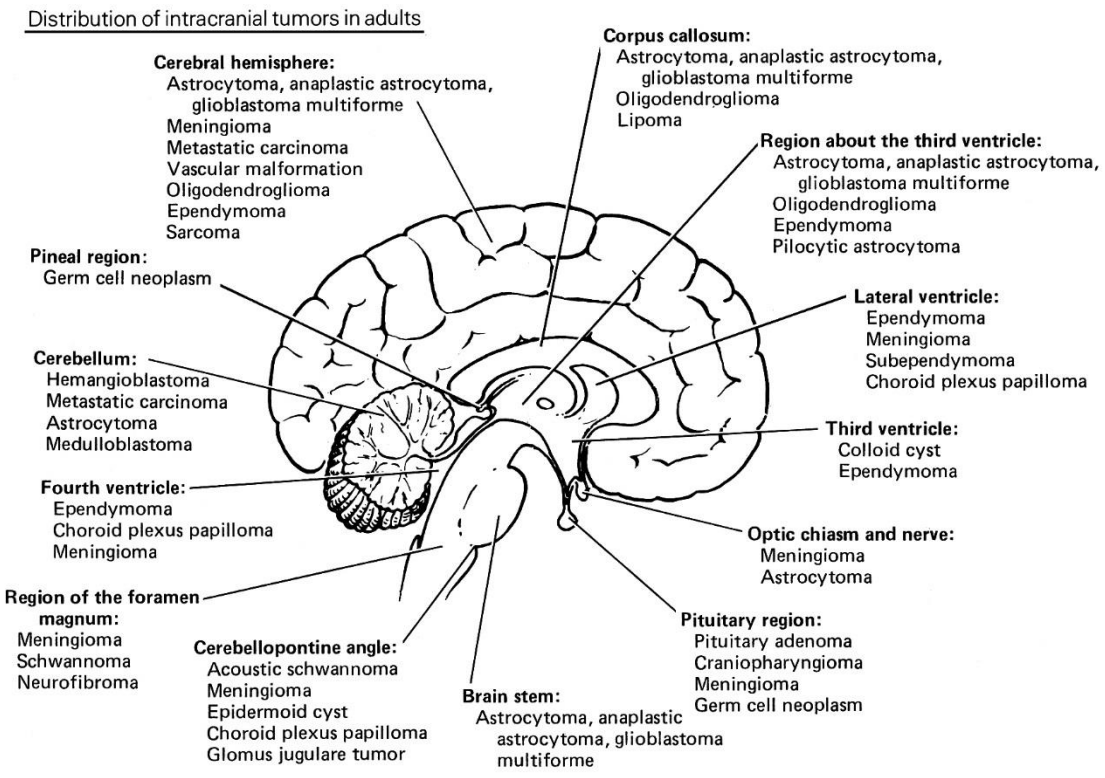
ADULTS - most commonly (70%) ***above tentorium***;
most common tumors ***above tentorium*** (intra-axial tumors predominate) – gliomas and metastases; meningiomas.
most common tumors ***below tentorium*** (extra-axial tumors predominate) – neuromas; metastases and hemangioblastomas.

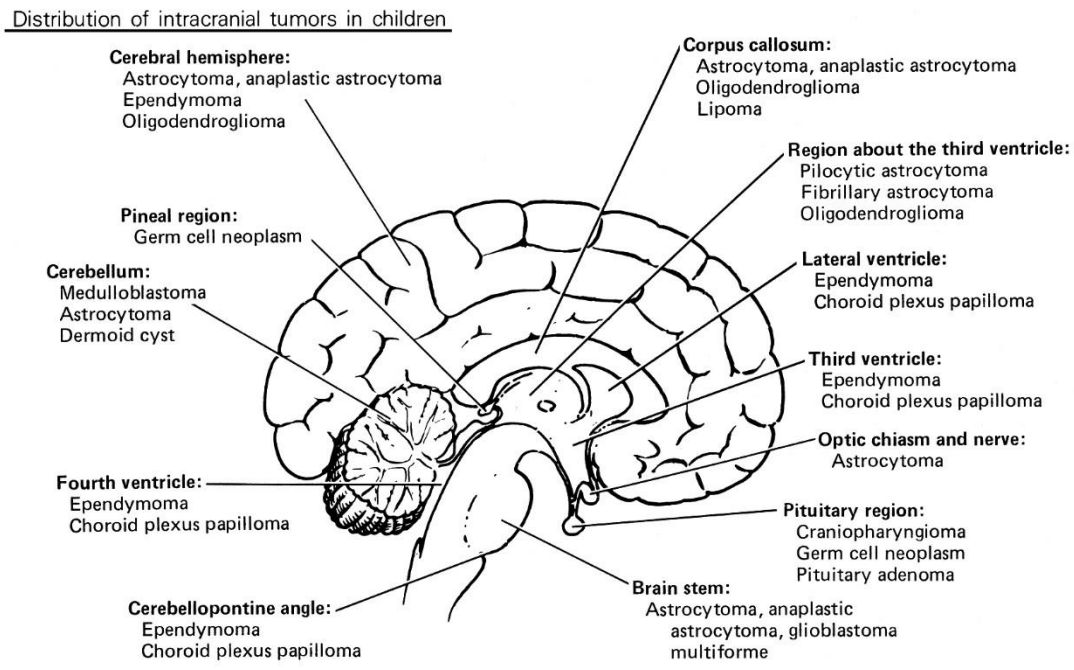
CHILDREN (2-12 yrs) - most commonly (70%) ***below tentorium*** (posterior cranial fossa, often in midline): medulloblastomas, cerebellar astrocytomas, ependymomas, brain stem or optic nerve gliomas, germinomas, congenital tumors.

ADOLESCENTS (> 12 yrs) and **INFANTS (< 2 yrs)** - equal frequencies ***below tentorium*** and ***above tentorium***.

- distribution of parenchymal tumors is directly related to mass of lobe or region.

Age	Hemispheres	Diencephalon	Posterior Fossa	Meninges	Spinal Cord
Adulthood	Astrocytoma, oligodendroglioma, metastases, lymphoma	Astrocytoma, colloid cyst, pituitary adenoma	Metastases, hemangioblastoma	Meningioma, CN8 schwannoma, metastases, lymphoma	Meningioma, nerve sheath tumors, astrocytoma, ependymoma
Childhood	Astrocytoma, ependymoma, choroid plexus tumor, primitive neuroectodermal tumor	Germ cell tumors, craniopharyngioma	Medulloblastoma!!!, ependymoma, cerebellar pilocytic astrocytomas, brain stem astrocytoma, choroid plexus tumor	Leukemia, lymphoma	Nerve sheath tumors, astrocytoma





INTRAVENTRICULAR TUMORS

Tumor	Typical site
COLLOID CYST	Foramen of Monro / 3rd ventricle
SEGA	Foramen of Monro
MENINGIOMA	Trigone of lateral ventricle
CHOROID PLEXUS PAPILLOMA	4th ventricle
EPENDYMOMA	Lateral ventricle (more common in children), 4th ventricle
*SUBEPENDYMOMA**	Lateral ventricle, 4th ventricle
*NEUROCYTOMA***	Lateral ventricles (involving septum pellucidum)
METASTASES	Lateral ventricles, ependyma and choroid plexus

*#1 differential of nonenhancing intraventricular mass
**most common lateral ventricle tumor in young adults

Differentials:
Neurocysticercosis

Tumor SPREAD

Tumors ordinarily grow **focally within one area** (but nevertheless they cannot be cured surgically):
1) intact BBB
2) brain lacks lymphatics

- even slow-growing gliomas can widely infiltrate brain.
  - glioma cells *spread preferentially along white matter tracts* (may cross corpus callosum into contralateral hemisphere) - brain function may be long preserved!

Some types may spread **via CSF** through ventricular / subarachnoid spaces:
HIGH-GRADE GLIOMAS (10-25%)
PRIMITIVE NEUROECTODERMAL TUMORS, incl. *MEDULLOBLASTOMAS* (10-20%)
EPENDYMOMAS (11%)
CHOROID PLEXUS CARCINOMAS
OLIGODENDROGLIOMAS (1%)
PINEAL GERMINOMAS (rare).

- spread down ventriculoperitoneal shunt → intra-abdominal metastases.

Metastasis **out of cranial cavity / spinal canal** is extraordinarily rare (≈ 1%) even for most malignant gliomas (unless operative procedure has interfered with normal meningeal barriers).

Brain tumors cause death by local growth!

Tumor BURDEN

- tumor mass of 30-60 g (3-6 × 10^{10} cells) usually produces ***neurologic symptoms***.
- brain cancer is ***lethal*** when tumor and its associated edema reaches **100 g** (vs. ≈ 1000 g in systemic cancers).
- immune system per se can suppress and eventually kill only ≈ 0.0001 g, or 1 × 10^{5} glioma cells.

CELLULAR HETEROGENEITY

While tumors are monoclonal in origin (i.e. they originate from single cell), as they grow they progress through ***series of genomic changes*** that permit evolution to more and more malignant stages.

- parental cell population is **genetically unstable** → *tumors are heterogeneous* in cellular content:
  a) genotypic (incl. chromosomal content [ranges from near diploid to hypo- or hypertetraploid] and molecular aberrations).
  b) phenotypic (cells that are immediately adjacent to one another may have very different histologic appearance).
- ***REGIONAL DIFFERENCES*** develop when tumor cells begin to invade surrounding normal brain - during migration, some cells develop additional abnormalities that confer selective advantage for growth → tumor is seeded with microfoci that are both genotypically and phenotypically different.

TUMOR MARKERS / IMMUNOHISTOCHEMISTRY, STAINS

Alcian blue – stain for mucin (e.g. myxopapillary ependymoma)

α-fetoprotein – embryonal carcinoma, endodermal sinus (yolk sac) tumor.

Anti-Leu 7 antibody – schwannomas.
N.B. uniformly negative in meningiomas

ATRX (alpha-thalassemia/mental retardation syndrome x-linked) gene
- ATRX is present in every cell!
- loss of ATRX = astrocytic lineage (grade II/III astrocytomas and secondary GBM).

Brachyury (protein encoded by the TBXT gene, transcription factor within the T-box family of genes**)**
- early mutational event in chordoma evolution (discriminates chordoma from chondrosarcoma).
- present in majority of hemangioblastomas (helps to differentiate from clear cell renal cell carcinoma metastases in von Hippel-Lindau syndrome).

CD68 (protein highly expressed by cells in the monocyte lineage: microglia, histiocytes) – differentiates histiocytosis from lymphoma.

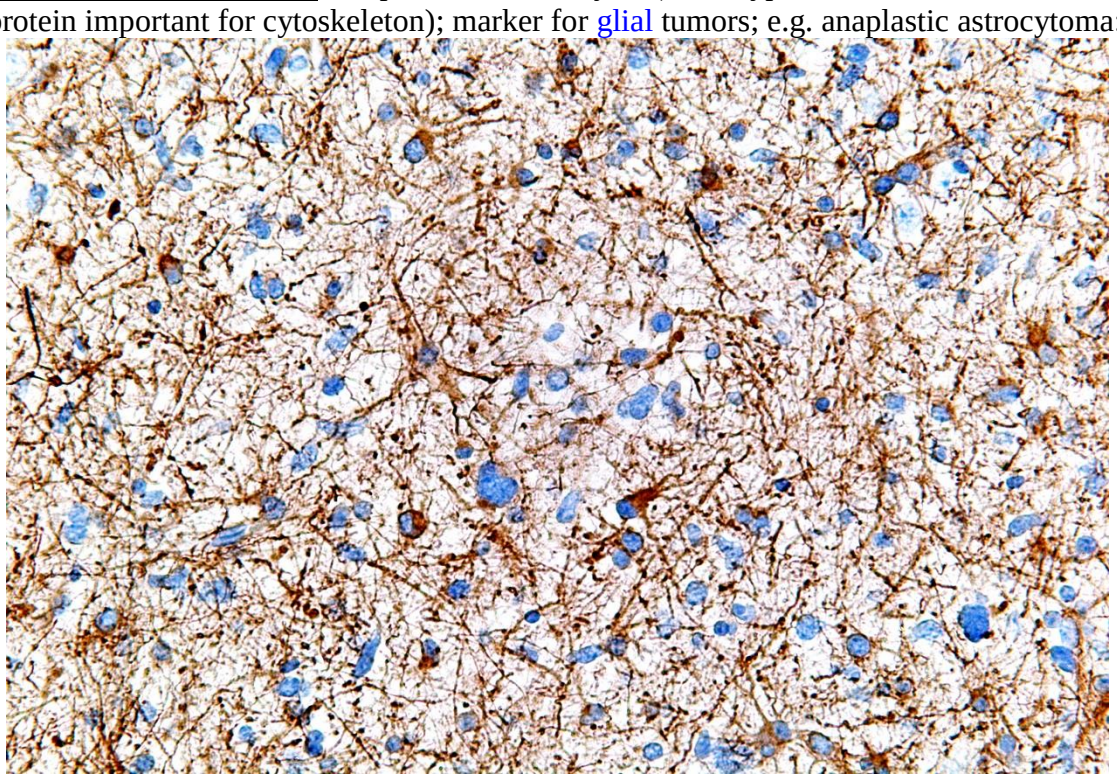
CD3 – T-cell lymphoma.

Desmin – tumors containing muscle (rhabdomyosarcoma, teratoma, etc), primitive neuroectodermal tumor.

EGFR (epidermal-derived growth factor receptor) – aberrantly expressed (usually amplified*) in many gliomas.
*poor prognostic factor!

EMA (epithelial membrane antigen) – epithelia marker (ependymoma, meningioma, epithelial areas of teratomas, rhabdoid tumor).
N.B. not present in melanoma!

GFAP (glial fibrillary acidic protein) – expressed in astrocytes (it is a type III intermediate filament (IF) protein important for cytoskeleton); marker for glial tumors; e.g. anaplastic astrocytoma:



Human chorionic gonadotropin – germinoma, choriocarcinoma

Luxol fast blue dye - myelin fibers appear blue, neuropil appears pink, and nerve cells appear purple.

Neuron-specific enolase – ***questionable utility*** - positive in normal and neoplastic cells of neural and non-neural origin.

p35 mutation = astrocytic tumors (vs. oligo*)
Li-Fraumeni syndrome (inherited p53 mutation) – strong predisposition to astrocytomas!
- p53 mutation goes "hand to hand" with IDH mutation.
- *GLIOBLASTOMAS* that show p53 mutation are termed *secondary glioblastomas* (type 1) - occur in younger patients whose tumors have progressed from lower grade astrocytoma.

Placental alkaline phosphatase – germ cell tumors

Retinal S-antigen – pineal parenchymal tumors, primitive neuroectodermal tumors, retinoblastoma.

S-100 – present in cells derived from the neural crest (Schwann cells, and melanocytes) - markers for certain melanomas, schwannomas (100%), neurofibromas (weaker than schwannomas), malignant peripheral nerve sheath tumors (50%, may be weak and/or focal).

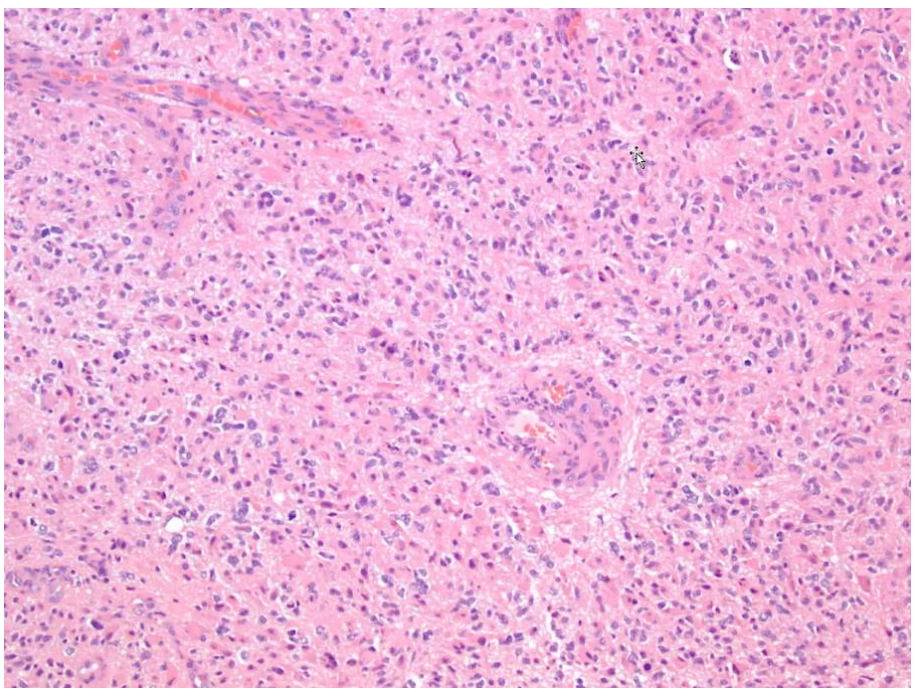
SSTR2 (somatostatin receptor type 2)
- most sensitive marker for meningiomas (present in 100%).

STAT6 – hemangiopericytoma.

Synaptophysin –integral membrane protein localized to synaptic vesicles (specific and sensitive marker for synaptic terminals); glioneuronal tumors (primitive neuroectodermal tumor, ganglioglioma, gangliocytoma, central neurocytoma, neuroendocrine tumors)
- diagnostically, it is often used in combination with chromogranin A.[

Vascular proliferation:
a) astrocytic lineage = GBM (grade IV)

b) 1p/19q co-deletion = anaplastic oligo (grade III)



Vimentin – type III intermediate filament (IF) protein, major cytoskeletal component of mesenchymal cells (significant role in supporting and anchoring the position of the organelles in the cytosol); staining may confirm mesenchymal origin (e.g. sarcomas, meningioma, lymphoma, chordoma) but numerous exceptions so ***relatively nonspecific***.

ETIOLOGY, RISK FACTORS

SEIZURES

Seizures may herald development of cerebral tumors by several years!

- British study (Journal of Neurology, Neurosurgery and Psychiatry, online March 28, 2011):
  - risk for any cerebral tumor after first admission for epilepsy is increased 20-fold (risk for malignant tumors is more than twice that for benign tumors).
  - risk is still elevated several years after first admission for epilepsy → need for *continued surveillance of patients with new-onset seizures*.

ENVIRONMENTAL EXPOSURE

Numerous epidemiologic studies* suggest statistically significant increased incidence of astrocytomas in people exposed to petrochemicals (e.g. in rubber industry) or electromagnetic radiation.

*equally impressive studies, however, have not confirmed association.

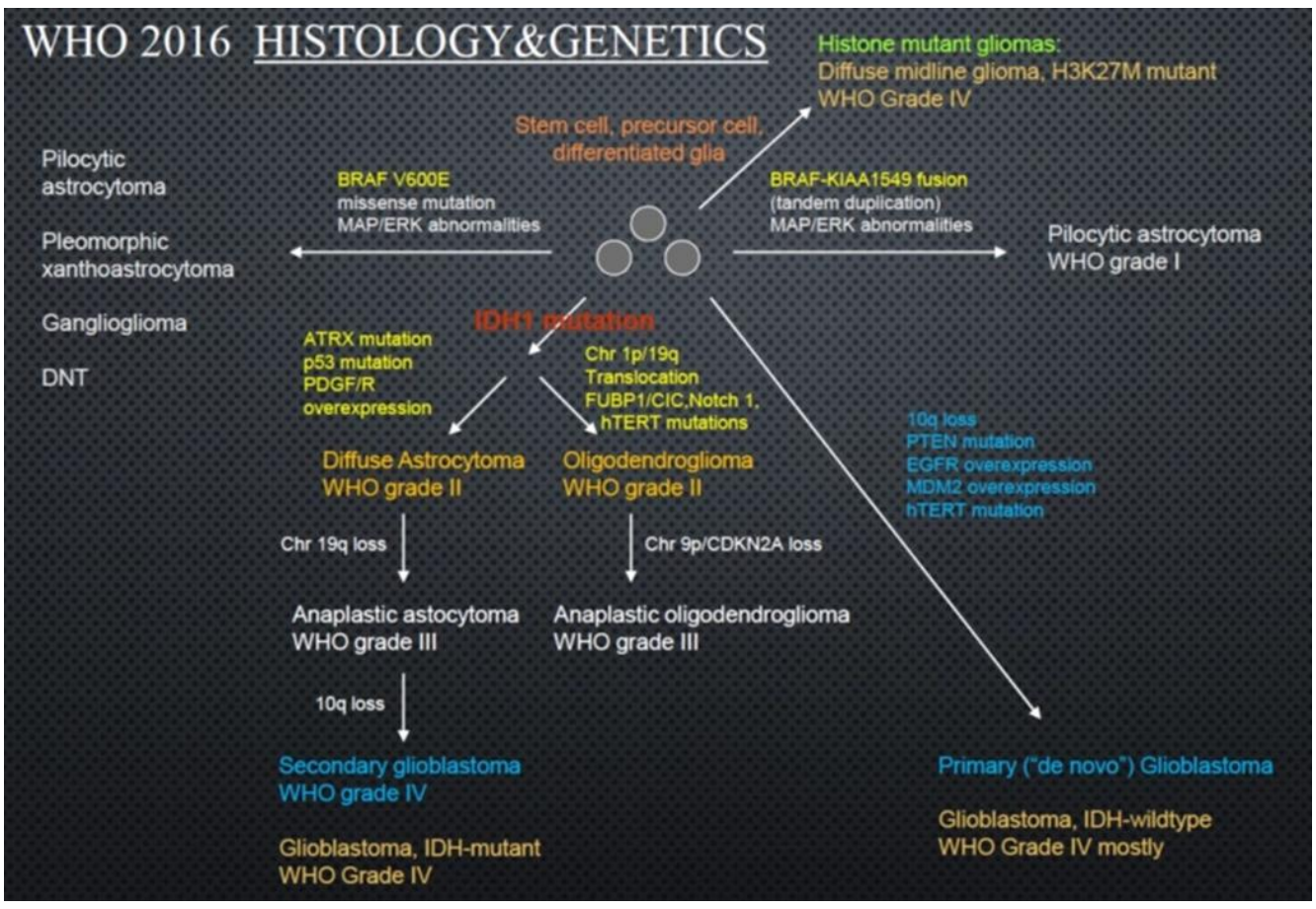
- well-documented environmental risk factor (Israeli study) - **ionizing radiation** (e.g. given for treatment of tinea capitis) - increases risk for meningiomas almost 10 times and for gliomas 2.5 times.
- insufficient epidemiologic evidence to support or refute claims, that *hand-held cellular telephones* generate electromagnetic radiation and cause brain tumors.
- both RNA and DNA *viruses* can induce animal brain tumors, but few viruses have been found to account for specific human tumor (e.g. ***Epstein-Barr virus*** evidence in primary CNS lymphoma tissue).
- immunosuppression (***transplant recipients***, ***AIDS patients***, Wiskott-Aldrich syndrome, ataxia-telangiectasia) substantially increases risks for primary CNS lymphoma but not gliomas.
- role of *trauma* is unproven.

> The only proven environmental risk factor for brain tumor is previous exposure to **high-dose ionizing radiation**

TUMORIGENESIS

- multistep process (probably at least 4-6 separate steps - multiple local mutations and clonal expansion). see p. 3781-3788 >>

Most important genetic markers – *see above >>*



PROTO-ONCOGENES

Proto-oncogenes mutated / overexpressed in brain tumors:

1) *EGFR (erb-B)* - encodes *epidermal-derived growth factor receptor*; aberrantly expressed (usually amplified) in many gliomas!
2) *c-sis* - encodes *platelet-derived growth factor*
3) *c-myc*
4) *ros1*
5) *H-ras*
6) *gli*

- medulloblastomas, 50% glioblastomas have *homogeneously staining regions* and *double minute chromosomes* - may contain amplified proto-oncogenes.

GROWTH FACTORS

- have potent growth stimulatory effects on glioma cells in culture:
    1) *platelet-derived growth factor* (PDGF)
    2) *epidermal-derived growth factor* (EGF)
    3) *transforming growth factor-α* (TGF-α) - 50% homology with EGF; secreted by numerous tumors (incl. high-grade malignant gliomas).
    4) *fibroblast growth factor* (FGF)
    5) *insulin-like growth factor* (IGF).

- many glioma cells produce growth factors and express appropriate growth factor receptor on their surface membranes - constantly stimulate own growth and division (AUTOCRINE GROWTH).
  N.B. *normal brain cells are kinetically quiescent* (**neurons** are incapable of division after birth; **glial cells** are minimally proliferative in reactive or reparative gliosis)
- cardinal histopathologic features that define malignant glioma - *cellular atypia, cellularity, mitoses, endothelial hyperplasia, necrosis*;
  - all (with exception of *necrosis* - attributed to growth beyond capacity of blood supply) are subject to modulation by growth factors.
- > 60% gliomas have **TELOMERASE activity** (correlates with tumor grading, being lowest in low-grade tumors). see p. 599-600 >>

TUMOR SUPPRESSOR GENES

Tumor suppressor genes associated with nervous system tumors:

p53 (17p13) – loss predisposes to *astrocytoma* and *neurofibrosarcoma*.

- *progression from low-grade astrocytoma to glioblastoma* strongly correlates with loss of *p53* gene.
- **Li-Fraumeni syndrome** - familial cancer syndrome in young adults (< 45 yrs) - breast cancer, soft tissue sarcomas, brain tumor (esp. astrocytoma), osteosarcoma, leukemia, adrenocortical carcinoma.
  - affected people inherit one mutant *p53* allele.
  - sporadic (nonfamilial) forms of cancers associated with Li-Fraumeni syndrome also show *p53* inactivation.

NF1 (17q11.2), **NF2** (22q12) - loss predispose to *neurofibromatosis*.

HEREDITARY SYNDROMES associated with brain tumors

- make only < 5% of all primary CNS tumors cases:

Syndrome	Gene	Nervous Tumor	Other tumors
Neurofibromatosis type 1 (von Recklinghausen's disease)	NF1 (17q11)	Neurofibroma, malignant peripheral nerve sheath tumor (MPNST), meningioma, **optic nerve glioma**, (low-grade) astrocytoma	Iris hamartomas, osseous lesions, pheochromocytoma, leukemia
Neurofibromatosis type 2	NF2 (22q12)	**Bilateral vestibular schwannoma**, peripheral schwannoma, meningiomas, astrocytoma, meningioangiomatosis, spinal ependymoma, glial hamartias, cerebral calcification	Posterior lens opacities, retinal hamartoma
von Hippel–Lindau syndrome	VHL (3p25)	**Hemangioblastoma**	Retinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, visceral cysts
Tuberous sclerosis	TSC1 (9q34), TSC2 (16p13)	**Subependymal giant cell astrocytoma (SEGA), cortical tubers**	Cardiac rhabdomyoma, adenomatous polyps of small intestine, cysts of lung and kidney, renal angiomyolipoma, lymphangioleiomyomatosis, cutaneous angiofibroma, subungual fibroma
Li-Fraumeni syndrome	p53 (17p13)	various malignant **gliomas**, PNET (**medulloblastoma**)	Breast carcinoma, bone and soft tissue sarcoma, adrenocortical carcinoma, leukemia
Multiple endocrine neoplasia 1	not known	**pituitary** adenomas, malignant **schwannoma**	
Retinoblastoma	Rb (13q14)	retinoblastoma, **pinealoblastoma**	
Turcot syndrome	APC (5q21), hMLH1 (3p21), hPSM2 (7p22)	**GBM**, **medulloblastoma**	Colorectal polyps
Werner's syndrome	WRN (8p12)	**meningioma**	
Cowden disease (multiple hamartoma syndrome)	PTEN (10q23)*	Dysplastic gangliocytoma of cerebellum (**Lhermitte-Duclos**), megalencephaly	Hamartomas of skin, GI tract, gingival fibromatosis, multiple trichilemmoma, thyroid neoplasms, breast carcinoma
GORLIN syndrome (nevoid basal cell carcinoma syndrome)	PTCH (9q31)**	**Medulloblastoma** (in ≈ 5% mutation carriers)	• autosomal dominant - nevoid basal cell carcinoma, jaw keratocysts, skeletal abnormalities, ovarian fibromas, ectopic calcifications, palmar and plantar pits
MUIR-TORRE syndrome	MSH2, MLH1 – DNA mismatch repair genes (subtype of Lynch Type II hereditary nonpolyposis colon cancer (HNPCC))	• autosomal dominant - combination of sebaceous gland tumors + at least one visceral cancer. • malignancies characterized by microsatellite instability.	
Goldenhar syndrome (oculoauriculovertebral dysplasia)		intracranial **dermoids**, **lipomas** of corpus callosum	
Rhabdoid tumor predisposition syndrome	INI1 (22q11.2)	**AT/RT**	Bilateral renal malignant rhabdoid tumors

*s. MMAC1 (mutated in multiple advanced cancers 1)
** human analog of "patched" gene of *Drosophila*

Most common scenario - *patient inherits one mutant (inactive) copy of tumor-suppressor gene* and thus carries so-called germline mutation in every cell, which is unveiled when second copy of tumor-suppressor gene is inactivated (either by mutation or by loss of portion of chromosome).

PATHOPHYSIOLOGY

BBB, BLOOD FLOW & BRAIN EDEMA

BBB is *substantially altered* (tight endothelial cell junctions are disrupted, fenestrations appear within endothelium, and pinocytotic vesicles increase), but is not completely broken in brain tumor*.

- water-soluble, ionized molecules, macromolecules can enter tumor.

*entry of some water-soluble chemotherapeutic agents is still impeded

Tumor blood flow is about same as in tumor-free white matter.

Causes of BRAIN EDEMA:

1) disrupted BBB
2) leaky capillaries (permeability varies over range of 1 to 100 times normal brain values)

Brain edema type in tumors is VASOGENIC

N.B. *brain tumor increases capillary permeability* not only in **tumor itself**, but also in **adjacent** capillaries (probably through action of soluble "vascular permeability factor"*).

– formerly, it was thought that edema in adjacent white matter is result of diffusion of fluid from tumor.

*e.g. vascular endothelial growth factor (VEGF)

- enormous edema surrounding small neoplasm suggests rapidly growing malignant tumor (exception – MENINGIOMA - benign slow-growing tumor that can produce profound edema and contrast enhancement).

it is not unusual for 20 g tumor to produce 100 ml mass because of associated edema.

PATHOPHYSIOLOGY of CLINICAL FEATURES

Intra-axial tumors produce symptoms by three mechanisms:

A. Tumor cells infiltrate among nerve cells and along nerve fiber tracts, producing little or no damage to these structures (*low-grade astrocytomas*, *oligodendrogliomas*) - first manifestation is often single **seizure**.
B. Tumor cells grow as mass, displacing surrounding brain tissue, but not destroying it (*metastatic brain tumors*) → **generalized** and **focal** symptoms, which return to normal if tumor can be resected.
C. Tumor cells infiltrate, grow as mass, *and* destroy surrounding neuropil (*malignant gliomas*) → **generalized** and **focal** symptoms, which not improve after treatment.

Extra-axial tumors compress adjacent brain - may present only as **mass** (without focal symptoms), or may induce **seizure** focus; tumor resection often restores patient to normal neurologic state.

- as tumor grows, signs of **brain damage** become evident.

How intracranial neoplasms increase ICP:

1) tumor mass
2) cerebral edema adjacent to neoplasm
3) obstruction of CSF pathways (producing hydrocephalus):
   a. intraventricular (at Monro foramen, aqueduct, 4th ventricle)
   b. leukemic or carcinomatous involvement of meninges
4) obstruction of venous pathways.

- 75% infants < 6 months of age have tumor volumes > 1/3 of their intracranial volume - plasticity of cranial vault allows asymptomatic growth.

CLINICAL FEATURES

Characteristic feature of all intracranial neoplasms is that they produce *progressive* symptoms!

Clinical presentation depends primarily on:

1. **Age** of patient (ability of skull bones to adjust to growing intracranial mass).
   N.B. symptoms in young children and infants are nonspecific and are frequently mistaken for non-CNS problems - diagnosis of *pediatric brain tumor* can be extremely difficult to make without very high index of suspicion!
2. Primary **histology** – determines *rate* of symptom evolution.
   e.g. ***benign tumors*** may achieve considerable size before producing symptoms (grow slowly, cerebral edema occurs infrequently).
3. Tumor **location**
   e.g. ***extra-axial tumors*** - usually *well circumscribed* with *benign histology* - clinical presentation is directly related to CNS structures immediately adjacent to lesion.
   e.g. ***posterior fossa tumors*** or ***tumors near foramen of Monro*** tend to obstruct CSF pathways early.

Symptoms do not differ much by tumor *histology* but rather relate to *area of brain affected*

Asymptomatic cases:

1) *silent areas* (tumors may grow large): parietal or frontal association cortices, nondominant temporal lobe.
2) *slow growth* (brain can accommodate to slowly growing mass).

Manifestations can be divided (but it may not be possible to differentiate these except in retrospect):

a) FOCAL SYMPTOMS due to ***tumor itself*** (direct compression or infiltration)
b) GENERALIZED SYMPTOMS due to ***secondary consequences**** (mass effect causing ICP↑) – tumor volume, peritumoral edema, hydrocephalus, shift of critical structures.

*these may cause *false-localizing signs*!

Systemic symptoms (malaise, weight loss, anorexia, fever) suggests metastatic rather than primary brain tumor!

KARNOFSKY performance scale - objective measurement of ***functional ability*** (useful in assessing and following patients with CNS neoplasm):

100 – Normal (no evidence of disease)
90 – Minor symptoms (able to carry on normal activity)
80 – Some symptoms (normal activity with effort)
70 – Unable to carry on normal activity (cares for self) - level of function justifying aggressive therapy!
60 – Cares for most needs (requires occasional assistance)
50 – Requires considerable assistance
40 – Disabled
30 – Severely disabled

20 – Active supportive treatment needed (very sick)
10 – Moribund

WHO performance scale

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out ay work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Brain tumors usually present with one of three syndromes:
a) nonfocal neurologic disorder (due to ICP↑).
b) subacute progression of focal neurologic deficit (rarely stroke-like onset)
c) seizure

ICP↑

1. Headache – chief complaint in 30% patients (most common in large tumors with midline shift).
- with most brain tumors, headache is relatively late sequela; occurs in:
  50-60% primary brain tumors;
  35-50% metastatic tumors.
- rare as initial symptom in brainstem tumors, cerebellopontine angle tumors, pituitary tumors, craniopharyngiomas.
- about features of "classic" brain tumor headache → see p. S50 >>
- typically ***semilocalized*** in vicinity of tumor (e.g. worse on side of tumor); posterior fossa tumors may present with pain referred to occipital region.
- with time, plateau waves of increased ICP are replaced with sustained elevated ICP - headache *gradually increases in intensity or duration* → becomes so unremitting that patient seeks medical attention.

Significant overlap between brain tumor headache and **migraine** or **tension-type headache**.
No pattern is diagnostic of brain tumor!

In series of 111 patients, headache had characteristics similar to migraine in 9% and to tension-type headache in 77%, while "classic" brain tumor headache occurred in only 17%.

Intense paroxysmal headaches may develop abruptly (within seconds); last only few minutes and terminate as quickly as they come.
– ominous sign of markedly increased ICP (ICP monitoring shows that peak pressure coincides with *plateau waves*).
– during episode, patient may vomit, lose vision, consciousness↓, fall.
– possible mechanism - acute hydrocephalus (ball-valve obstruction of CSF outflow with tumor in ventricular system).

2. Vomiting
- *associated with nausea and headache*.
- ***direct compression of vomiting center*** → ***projectile vomiting*** - highly characteristic of posterior fossa tumors!
  N.B. "projectile" is misnomer - nothing pathognomonic about forcefulness of ejection; term "projectile" more appropriately refers to vomiting without antecedent nausea or headache (precedes appearance of headache by weeks).

3. Deterioration in mental status (psychomotor retardation, sleep / cognitive / social disturbances, confusion, lethargy). see p. S50 >>
- frequent clinical manifestation of intracranial tumor!
- often subtle in presentation and onset and may not attract attention of friends and family members until patient begins to behave unusually.
  N.B. it is not unusual for patient to seek psychiatric help (up to 20% of all patients)

4. Cushing reflex signals life-threatening ICP↑↑↑. see p. S50 >>

5. Brain mass shifts (may manifest as *false-localizing signs*) - CN6 palsy, CN3 palsy, ipsilateral hemiplegia (compression of opposite cerebral peduncle against Kernohan's notch), ipsilateral visual field defects (compression of opposite PCA), nuchal rigidity & torticollis* (herniation of cerebellar tonsils), etc.

*torticollis also may be due to CN4 palsy

6. Enlarging head (tense fontanelle, 'sun set' eyes, dilated scalp veins) in young children.

SYMPTOMS due to TUMOR ITSELF (FOCAL BRAIN DYSFUNCTION)

- may be absent in tumors growing in silent areas.
- result from compression of *neurons* and *white matter tracts* by expanding tumor and accompanying edema.
- *vascular* compression may produce focal brain ischemia.

1. Seizures - occur in 20-71% patients (as presenting symptom in 18-50% cases);
- **focal** or **generalized**.
- most common with *SLOWLY GROWING* tumors affecting *cortex* (esp. meningiomas, oligodendrogliomas, low-grade gliomas).
  Even small meningiomas that compress adjacent cerebral cortex may present with seizures!
  Epilepsy rates range 60-100% in low-grade gliomas and 25-60% in high-grade gliomas
- suggestive features: status epilepticus at onset, prolonged postictal paralysis*, resistance to medical control, focal symptoms.

*brain tumor patients have higher incidence of postictal neurologic deficit!

2. Negative signs - hemiparesis, sensory loss, aphasia, cranial nerve palsies, visual deficits, hearing impairment, anosmia, personality changes, etc.
- ***multiple metastases*** or ***diffuse brain infiltration*** (by glioma or lymphoma) may present as dementia or decline in level of alertness.
- hand preference in child < 3-5 yrs may signify hemiparesis.

3. Hyperactive function:
- pituitary / pineal tumors → hormone overproduction.
- choroid plexus papilloma → CSF overproduction.

REGIONAL FEATURES

SUPRATENTORIAL TUMORS

- progressive **focal neurologic signs** and **seizures** predominate:

Frontal lobe

1. Seizures - may precede other symptoms by months or years.
2. Intellectual impairment (esp. with bilateral tumors, e.g. butterfly glioma)
3. Impairment of initiative and spontaneity: abulia → akinetic mutism.
4. Personality changes: see also p. Psy5 >>
   a) dorsolateral prefrontal lesions → apathetic & indifferent (pseudodepressed)
   b) orbital prefrontal lesions → loss of inhibition & euphoric (pseudopsychopathic).
5. Motor disturbances – hemiparesis, precipitate urination (tumor of medial surfaces of frontal lobe).
6. Motor aphasia.
7. Anosmia (e.g. meningioma of olfactory groove).

Temporal lobe

1. Personality change (bizarre thinking, trance-like states, mood symptoms, immature emotional behavior; bilateral amygdaloid lesions → Klüver-Bucy syndrome).
2. Sensory aphasia, anomia.
3. Seizures - complex partial (psychomotor).
4. Contralateral hemianopia (or superior quadrantanopia).
5. Impairment of recent memory (bilateral hippocampal lesions → Korsakoff amnesia)

N.B. temporal tumors (esp. in nondominant hemisphere) are often relatively "silent"!

Parietal lobe

1. Seizures - generalized or sensory focal seizures.
2. Impaired contralateral cortical sensory modalities (position sense, two-point discrimination, stereognosis)
3. Contralateral homonymous hemianopia (or inferior quadrantanopia).
4. Mixed expressive-receptive aphasia, anosognosia.
5. Dominant hemisphere – Gerstmann's syndrome (agraphia, acalculia, finger agnosia).
6. Nondominant hemisphere – apraxia, contralateral hemineglect.

Occipital lobe

- contralateral quadrantanopia or hemianopia with sparing of macula; visual misperceptions & hallucinations; bilateral lesions – cortical blindness.

Thalamus

1. Hydrocephalus.
2. Contralateral sensory abnormality, neuropathic pain, intermittent paresthesias.
3. Involvement of ***basal ganglia*** → contralateral intention tremor, hemiballistic movement.
4. Involvement of ***hypothalamus*** → eating disorders, precocious puberty.

POSTERIOR FOSSA

- more devastating than supraventricular tumors (limited space + vital brain stem nuclei)

1) early CSF flow obstruction → hydrocephalus (rapidly worsening mental status)
2) projectile vomiting
3) common symptoms – cranial nerve dysfunction (CN6, CN7), nystagmus, ataxia, long tract signs.

- commonest tumor of brain stem is astrocytoma.

DIAGNOSIS

BLOOD TESTS

Primary* brain tumors typically do not produce blood abnormalities (anemia, ESR↑ or tumor-specific antigens).

*vs. CNS metastases, depending on primary tumor, may be associated with systemic features of malignancy.

- **polycythemia** associated with cerebellar tumor - presumptive evidence of *HEMANGIOBLASTOMA*.

Tumor Markers – see above >>
With MRI ability to image tumors clearly, role of tumor markers is more limited than in other parts of body!

URINE TESTS

Two **markers in urine** can be effective, noninvasive way of detecting presence / recurrence of brain tumors:

1) matrix metalloproteinase-2 (MMP-2)
2) vascular endothelial growth factor (VEGF)

- both are secreted by tumor tissue (have role in tumor angiogenesis).

OPHTHALMOSCOPY

1. **Papilledema** - most reliable sign of ICP↑ (but present in only ≈ 20% patients) see p. Eye62 >>
   - more common with *tumors that occlude CSF ways* – infratentorial, pineal, thalamic, 3rd ventricle tumors.
2. Other signs of ICP↑ see p. S50 >>

- thorough ophthalmologic examination (incl. visual field testing) is important in pre- and postoperative evaluation of tumors adjacent to visual / oculomotor pathways.

SKULL X-RAY

- only rare indications:

1) screening skull for *metastatic disease*
2) assessing integrity of various *shunts*

- may show *signs of raised ICP*. see p. S50 >>
- tumor *calcification*.
- *MENINGIOMAS*: hyperostotic bone reaction, enlargement of middle meningeal artery grooves.
- *DERMOID CYSTS*, *SCHWANNOMAS*: bone thinning → enlargement of middle cranial fossa or internal auditory meatus.

PNEUMOENCEPHALOGRAPHY

- historical method for diagnosing brain tumors.

CSF

LP should not be performed if intracranial mass is suspected!!!

- does not provide significant diagnostic information: raised opening pressure, protein↑, mild lymphocytic pleocytosis.
  - *ASTROCYTOMAS* that extend to ventricular surface, or *EPIDERMOID CYST* rupture, can produce intense CSF inflammation simulating infectious meningitis.
- positive **CSF cytology** postoperatively is common, but seeding and new growth may not occur.

Indications - diagnosing:

1) ***neoplastic meningitis*** (malignant cells in CSF) – LP indicated only if:
   a) symptoms suggest meningeal involvement.
   b) parenchymal tumor has propensity to seed (e.g. *MEDULLOBLASTOMA*, *EPENDYMOMA*, *CHOROID PLEXUS CARCINOMA*, some *EMBRYONAL PINEAL* and *SUPRASELLAR TUMORS*) – combine with spinal MRI (CSF is negative in ≈ 50% MRI-positive cases!)

      N.B. routine CSF examination in all patients with tumors, searching for malignant cells, is discouraged.
2) ***benign intracranial hypertension*** (***pseudotumor cerebri***)

N.B. both conditions are not emergency - wait until tumor (if present) has been brought under control by surgical decompression, corticosteroids, radiation, or chemotherapy.

e.g. LP is safe about 10-21 days after intracranial decompression.

EEG

- no role in diagnosis of brain tumors, does not assist in choice of anticonvulsant drugs.

- *seizure focus* or *slow wave focus* over hemisphere tumor.
- *generalized slowing* suggests either involvement of deep midline centers or metabolic problems.
- unresponsive patient often requires EEG to rule out *subclinical seizures*.

OTOLOGIC EXAM

(audiometry, auditory evoked potential testing, electronystagmography) - for tumors of cerebellopontine angle or posterior skull base.

NEUROIMAGING

- indispensable component of modern diagnosis - confirms presence, but not type, of brain tumor!

One type of tumor can look like another or even resemble non-neoplastic mass lesion, such as brain abscess, fungal infection, parasitic invasion, demyelinating disease, or stroke.

- because human brain possesses remarkable capacity to make room for growing tumor, patient usually appears better clinically than might be expected from degree of abnormality seen on imaging!

CT WITH CONTRAST

- most common screening examination (but MRI is test of choice!)

CT without contrast enhancement is of little value in diagnosis of brain tumors or other mass lesions!

although hemorrhage, calcifications, hydrocephalus, shifts can be well seen on non-contrast CT, underlying causative structural abnormality can be missed.

- better definition (than MRI) of *calcification* – suggests more indolent growth;
  tumors that tend to calcify: oligodendrogliomas (90%), meningiomas, craniopharyngioma, teratoma, chordoma, choroid plexus tumors, ependymoma, central neurocytoma.
- CT preferable (over MRI) for evaluating *bones*, intratumoral *hemorrhage*.
- CT-guided localization (in stereotactic biopsies) is more precise than MRI (because of "MRI distortion").
- on enhanced CT – most commonly as *ring-like hyperdense region* around central radiolucent area.
  - enhancement is stronger with more malignant tumors.
  - enhanced CT may be completely normal (± subtle mass effect).
- on nonenhanced CT:
  - **tumors** can be hypo-, iso- or hyperdense (depends on histological tumor type and presence of calcification or necrosis) relative to surrounding structures.
  - associated **vasogenic edema** (low attenuation in white matter).
- contrast enhancement is sign of malignancy / high-grade! (exceptions exist)

Tumors that **enhanced strongly**: meningiomas, neuromas, pilocytic astrocytoma, malignant tumors (high-grade gliomas, metastases, CNS lymphoma)

Pituitary adenomas always enhance less than normal pituitary gland!

Tumors that show **no enhancement**: low-grade gliomas (astro, oligo), epidermoids

- in presence of leaky tumor vessels there is some *risk of precipitating seizure* by iodinated contrast material used for CT scanning;

  H: pretreatment with 10 mg IV DIAZEPAM or 4 mg LORAZEPAM 10 min before contrast administration.

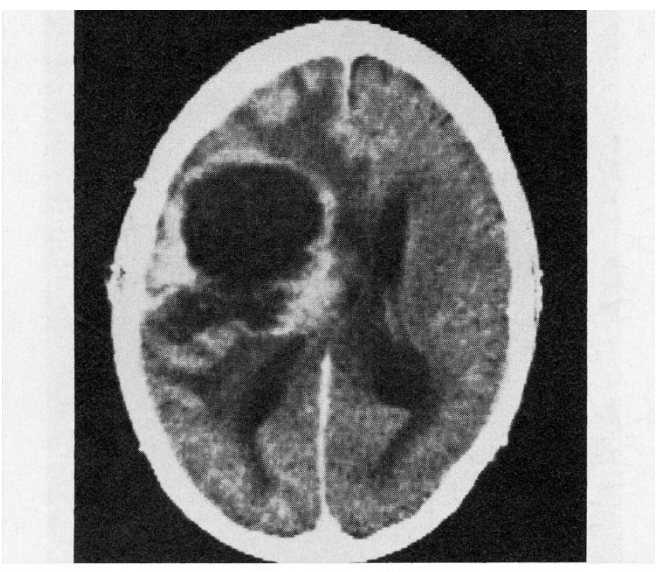


Figure 29–23. Large tumor in cerebral hemisphere showing ring enhancement with contrast material and pronounced peritumor edema.

MRI WITH CONTRAST

- most sensitive test of choice for detection of brain tumor (MRI reveals greater extent of tumor than does CT!!!; MRI may detect additional tumors not suspected with CT), esp.:
  1) ***posterior fossa tumors*** – no bony artefacts as in CT.
  2) ***low-grade gliomas*** – MRI shows extensive brain infiltration when CT fails to produce any image abnormality.

- most protocols include T1, proton density, and T2 images.

Many brain tumors will not be seen unless contrast medium is used (small lesions that lack mass effect and edema may only be detectable on contrast-enhanced MRI)

- delineates tumor in all three planes without requiring patient to change position.
- important application - use of sagittal MRI image in planning radiation treatment.
- MRI has supplanted CT as ***preferred test of choice in follow-up*** of patients undergoing active therapy.

Features of tumors:

1) *signal alteration* – depends on MRI type. *see below*
   - irregular tumor borders suggest invasiveness (histologic malignancy).

   Feature that most affects MRI appearance is *increased water content*

2) *mass effect* (volume of neoplastic tissue + surrounding vasogenic edema*)
   *malignant tumors are associated with considerable edema
   - MRI is more accurate (than CT) in defining extent of infiltrating tumor.
   - features of extra-axial mass (differentiation from intra-axial mass):
     – 'buckling' and medial displacement of grey–white matter interface;
     – CSF cleft separating base of mass from adjacent brain.

3) *contrast enhancement* (reflects BBB breakdown in neovascular structures)
   N.B. volume of enhancement represent major tumor mass, but tumor cells typically extend beyond this boundary (important in planning therapy for *MALIGNANT GLIOMAS*).
   - contrast enhancement is sign of malignancy! (exceptions exist). *see above >>*
   - ***degree of enhancement homogeneity*** varies - more benign lesions tend to be more homogeneous.
   - border between tumor and edema may not be clear (important when planning biopsy); neoplastic infiltration frequently extends some distance into zone of edema.
   - *corticosteroid use* can significantly diminish contrast enhancement!!!
   - postoperative enhancement and radionecrosis may be difficult to distinguish from residual or recurrent tumor; consider TRAM protocol – see p. Rx11 >>

4) *necrotic* core
   - ***how to distinguish from cystic tumor*** – DWI (diffusion restriction in necrosis), GRE (old hemorrhagic cavity).

5) peritumor *edema* – more pronounced in metastases, less in primary CNS tumors.

T1 - well-demarcated area of ***low density***.

T1 with gadolinium - most precise way to image brain tumor!

- patients can be followed up during and after treatment with T1 alone.

T2 - ***bright whiteness*** in more extensive region (signal of *surrounding brain edema*);

FLAIR - most precise way to spot brain tumor!

- better contrast between normal and abnormal tissue than in T1.
- T2 may miss some brain metastases!!!
- tumors that are ***hypointense*** on T2:

  METASTATIC MELANOMA (paramagnetic properties of melanin)
  DERMOID (due to fat)
  COLLOID CYSTS
  INTRATUMORAL HEMORRHAGE

- T2 also delineates *demyelinating effects* of radiation (FLAIR, variant of T2, is even better for this).

MENINGIOMAS are usually ***isointense*** on all image sequences!!!

Tumor type	T1 with gadolinium	Contrast CT
GLIOBLASTOMA	ring configuration	
ANAPLASTIC ASTROCYTOMAS	solidly bright or patchy or do not enhance.	
LOW-GRADE ASTROCYTOMAS	do not enhance (except pilocytic astrocytoma)	invisible (or vague low density)
OLIGODENDROGLIOMAS	do not enhance (unless anaplastic)	invisible (unless calcified)
PITUITARY ADENOMAS	always enhance less than normal pituitary gland.	CT is inferior in every way
METASTASES	variable: some enhance brightly and solidly, others are in ring configuration (central necrosis & cavitation)	many are invisible
ACOUSTIC NEUROMAS, MENINGIOMAS	intensely contrasted (≈ homogeneously)	contrasted
PRIMARY CNS LYMPHOMA	smoothly rounded homogeneous enhancement; periventricular location is common; multiple in 25% cases (easily mistaken for metastases)	hyperdense even without contrast (due to hypercellularity)

N.B. for tumors with *propensity for leptomeningeal spread* (*MEDULLOBLASTOMAS*, *EPENDYMOMAS*, *CHOROID PLEXUS CARCINOMAS*, malignant *PINEAL REGION TUMORS*), spinal MRI must be done!

Any child found to have **posterior fossa tumor** (that is not obviously benign) → contrast MRI of entire spinal axis; vice versa - detection of **extramedullary, intradural spinal tumor** → immediate brain MRI.

Cyst + mural nodule:

1) pilocytic astrocytoma
2) pleomorphic xanthoastrocytoma (PXA)
3) hemangioblastoma
4) ganglioglioma, esp. desmoplastic infantile ganglioglioma / astrocytoma (DIG/DIA)
5) metastasis
6) neurocysticercosis

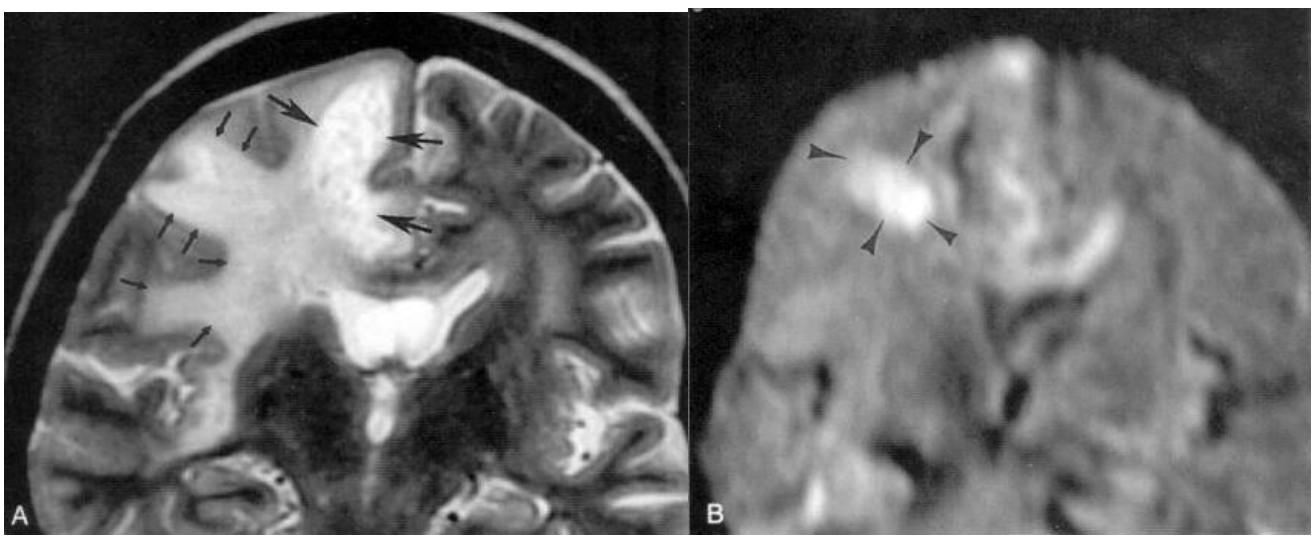
PERFUSION-WEIGHTED MRI (PW-MRI)

markedly increased rCBV - excess vascularization (growth of high-grade tumors);
increased rCBV - low-grade tumors;
decreased rCBV - vasogenic edema or radiation necrosis.

DIFFUSION-WEIGHTED MRI (DW-MRI)

Tumors show **diffusion restriction**! (due to hypercellularity and proteinaceous stroma)

Glioblastoma multiforme:
A. T2-MRI shows only necrotic part of tumor (*large arrows*) and peritumoral edema (*small arrows*).
B. Diffusion-weighted MRI - solid parts of tumor (*arrowheads*) are well demonstrated:



DIFFUSION TENSOR IMAGING (DTI) MRI

- shows tracts in peritumoral area – guides safer tumor resection.

GENERALIZED Q-SAMPLING IMAGING

- can visualize tracts in peritumoral edema even better than DTI.

fMRI

- presurgical evaluation of eloquent cortex. see also p. D66 >>

Alternative – intraoperative electrical cortical mapping.

MRS

- noninvasive in vivo method of analyzing tissue chemical spectrogram. see p. D53 >>

- commonest abnormalities in *gliomas* (vs. necrosis)
  - increased:
    - choline (membrane metabolism) / *N*-acetyl aspartate (living neurologic tissue)
    - choline / creatine (cellular bioenergetics).
    - lactate
  - decreased – NAA/creatine.

Tumor – lots of MEMBRANES (choline↑), no normal neurons (NAA↓),
metabolism ANAEROBIC (lactate↑ and creatine↓)

- commonest abnormalities in *radiation necrosis*:
  - increased – lipid/lactate (large peak)
  - decreased - choline, *N*-acetyl aspartate, creatine.

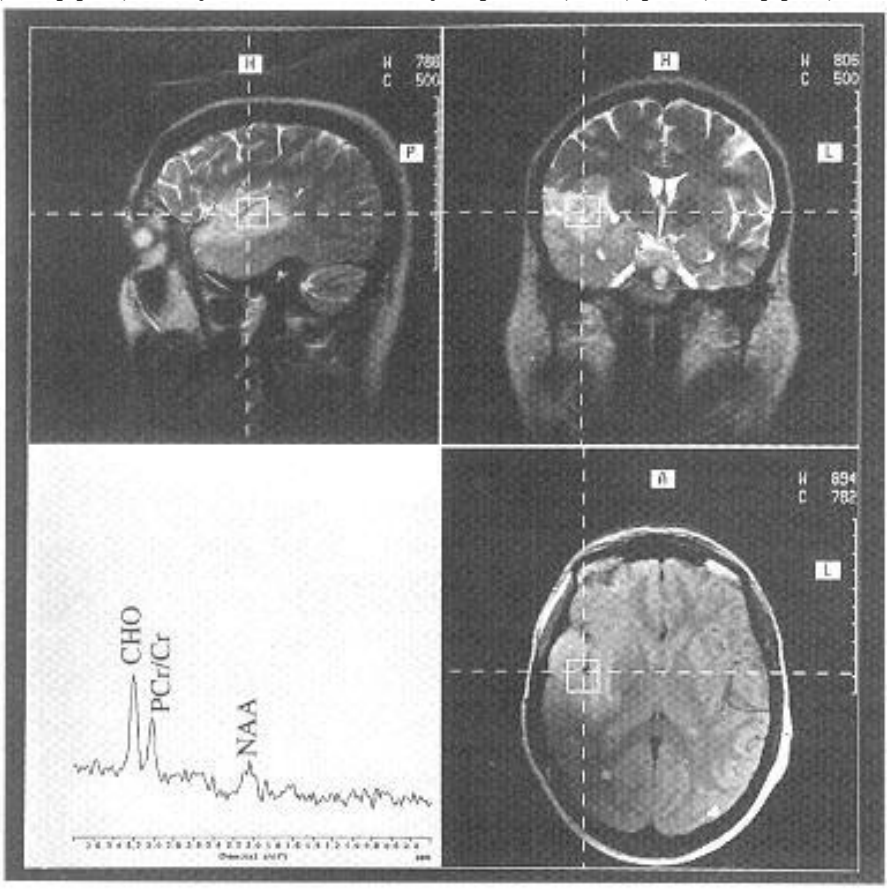
Necrosis – only LIPIDS;
no normal neurons (NAA↓), no normal membranes (choline↓),
no metabolism (creatine↓, lactate↓)

As comparison – *infarction (stroke)* region:
lactate↑
N-acetylaspartate (NAA)↓, creatine↓, choline↓*

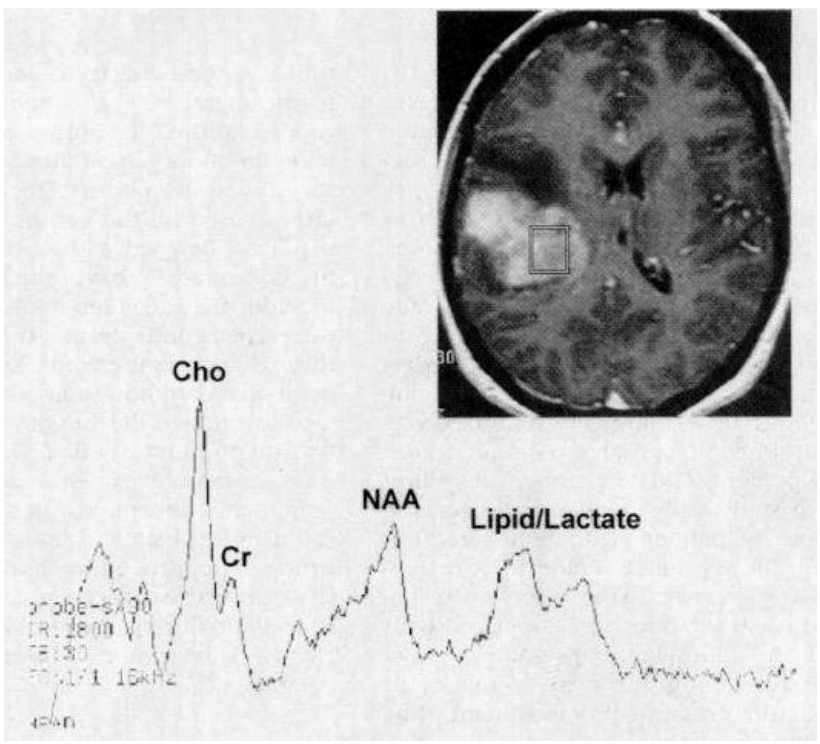
*choline is only difference from tumor

Tumor – lots of membranes (choline) and anaerobic metabolism (lactate)
Stroke – everything is down except anaerobic metabolism (lactate)↑
Necrosis – everything is down except dead lipids↑

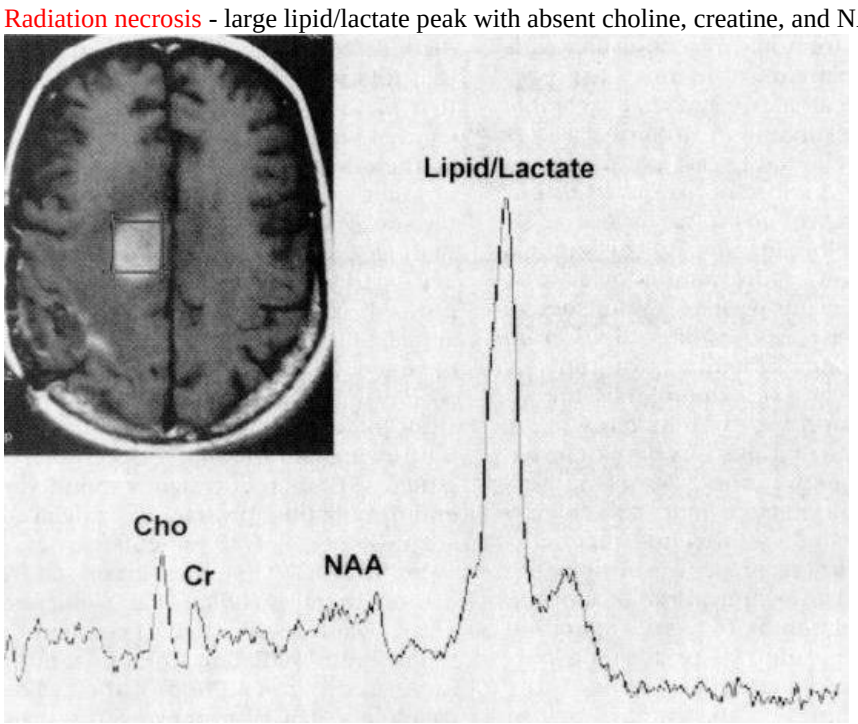
Characteristic spectroscopic appearance of glioma - elevated choline (CHO) peak (3.22 p.p.m.), low creatine (PCr/Cr) peak (3.03 p.p.m.), nearly undetectable *N*-acetyl aspartate (NAA) peak (2.01 p.p.m.):



Glioblastoma multiforme - elevated choline/creatine (Cho/Cr), persistent N-acetylaspartate (NAA) and lipid/lactate peaks:



Radiation necrosis - large lipid/lactate peak with absent choline, creatine, and NAA:



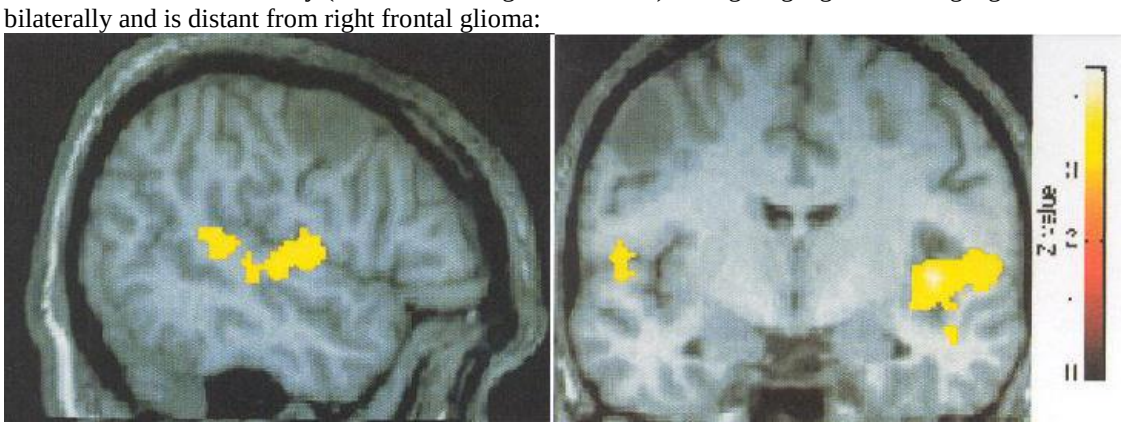
PET

- tumor localization & specification:
  - characteristic of rapidly growing tumor is increased anaerobic glycolysis (FDG PET - high glucose utilization but low oxygen extraction).
  - tumor metabolic activity correlates with biologic aggressiveness - *HIGH-GRADE GLIOMAS* show more glycolytic activity than *LOW-GRADE GLIOMAS*.
- preoperative PET localization of eloquent cortex - activation studies with $H_2{}^{15}O$.
- tumors that respond to therapy become hypometabolic (before they shrink in size on MRI).
- recurrent symptoms after radiation therapy:
  a) recurrent / residual tumor (glycolytic activity↑)
  b) radiation necrosis (glycolytic activity↓)
  - often appear identical on MRI / CT (contrast enhancement, mass effect, edema).

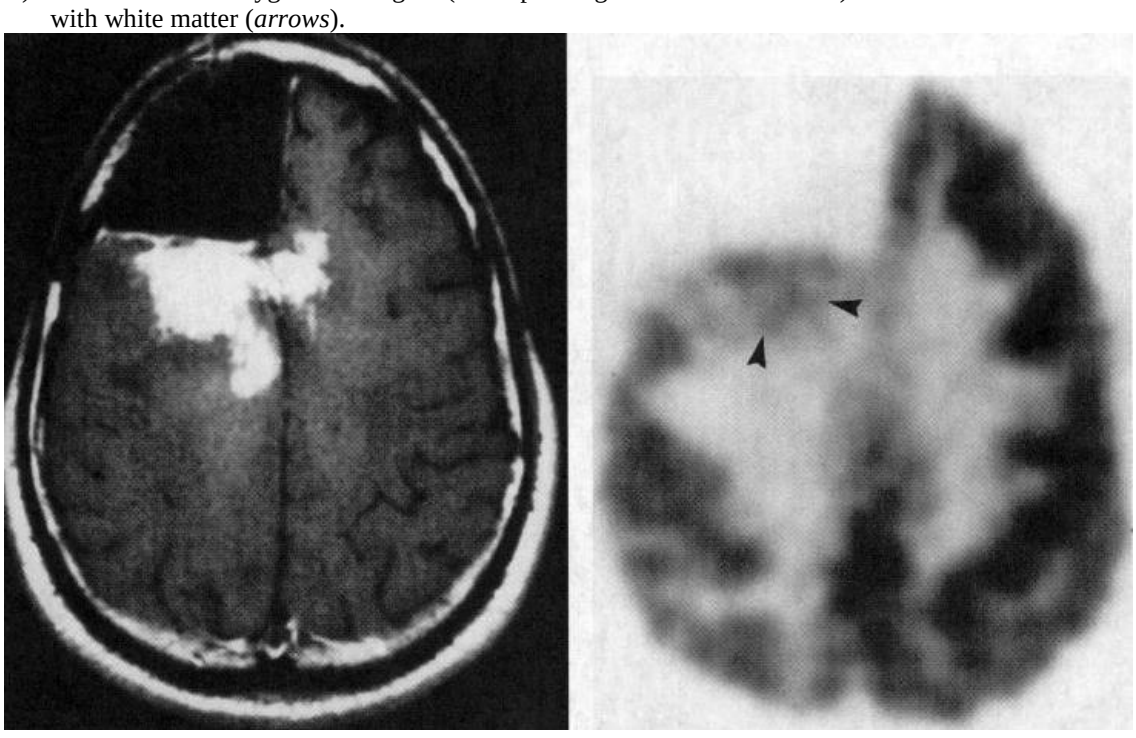
PET has great value in distinguishing **tumor recurrence** from **radiation necrosis**.

- ***false-positives***: inflammatory cells in areas of radiation necrosis may show increased metabolic activity.
- ***false-negatives***: tumor cells also may be present in areas of low glucose activity.

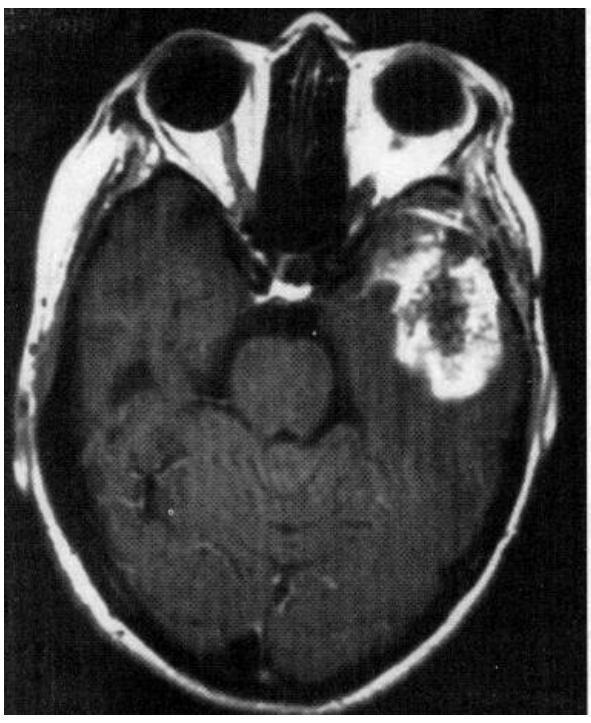
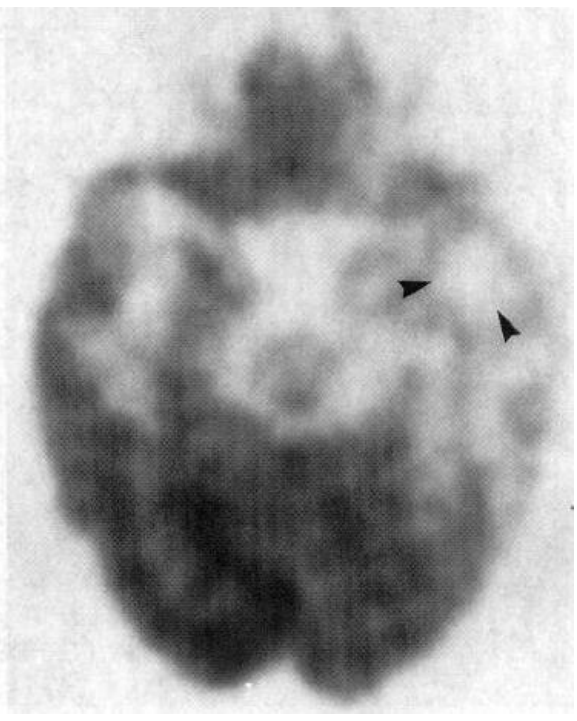
$H_2{}^{15}O$ PET activation study (before neurosurgical resection) during language task - language activation is seen bilaterally and is distant from right frontal glioma:



Recurrent malignant glioma (after surgical resection, radiation therapy, and chemotherapy):
A) gadolinium-enhanced MRI - area of contrast enhancement.
B) PET with 18 F-deoxyglucose - region (corresponding to MRI enhancement) has *increased* metabolism compared with white matter (*arrows*).



Radiation necrosis (after surgical resection, radiation therapy, and chemotherapy):
A) gadolinium-enhanced MRI - area of contrast enhancement.
B) PET with 18 F-deoxyglucose - region (corresponding to MRI enhancement) has *reduced* metabolism compared with white matter (*arrows*).

SPECT

Principal value - distinguishing ***tumor recurrence*** from ***radiation necrosis***.

- ^{201}Tl chloride SPECT can distinguish between *HIGH-GRADE GLIOMAS* (show increased uptake compared with normal brain parenchyma) and *LOW-GRADE GLIOMAS* (no increased uptake);
  can also distinguish CNS lymphoma (increased activity) from toxoplasmosis (decreased activity) in immunocompromised patients
- ^{123}I α-methyl tyrosine SPECT shows uptake at sites of increased protein synthesis - used to distinguish *LOW-GRADE GLIOMAS* from *benign lesions*.

ANGIOGRAPHY

- historical method for diagnosing brain tumors (for many cases MRA suffices).

Current indications:

1. Preoperative assessment of **tumour vascularity**, **mapping of major vessels** before biopsy:
   a) tumors that may ***encircle critical vessels*** (e.g. basal *MENINGIOMAS*)
   b) tumors that can be ***extremely vascular*** (e.g. *HEMANGIOBLASTOMAS*, *MENINGIOMAS*, *GLOMUS* tumors).
2. **Embolization** to reduce intraoperative bleeding (e.g. bulky highly vascular *MENINGIOMAS*) - done in temporal proximity (24-96 hours) to planned surgery.
3. **Differentiation** of *intra-axial* and *extra-axial* tumors (if cross-sectional imaging is equivocal).

Angiographic abnormalities:

1. *Increased vascularity*:
   1) increased number of ***normal vessels*** (or accentuated capillary blush)
   2) ***actual tumor vessels*** - irregular and tortuous (bizarre), may bear microaneurysms or show AV shunting; may be seen as *blush* (diffuse stain) during late arterial or capillary phase.
      Most hypervascular tumors - *CHOROID PLEXUS PAPILLOMAS*, *HEMANGIOBLASTOMAS*
2. *Avascular areas* - necrosis or cyst formation.
3. *Vascular displacement*;
   – may indicate ***tumor position relative to neuraxis***: superficial brain mass will compress vessels against cranial vault or falx cerebri, whereas one outside brain will separate them from these structures; mass within temporal lobe elevates MCA (MCA draped over expanded lobe).
   – may indicate ***herniation***. see p. S54 >>

- *feeding vessels are clue to tumour origin*: cerebral tumors are fed by cerebral vessels, choroid plexus tumors - by choroidal vessels, extracerebral tumors - by meningeal vessels.
  Exceptions:
  MENINGIOMAS - not infrequently acquire pial supply;
  GLIOMAS and, particularly, *METASTASES* - dural supply is well documented.

Type	Increased vascularity	Tumor vessels	Blush	Venous filling	Meningeal supply
INTRA-AXIAL					
Glioma (low grade)	rare	(+)	(+)	normal	v. rare
Glioblastoma	increased (50%)	++	+	early	rare
Metastases	increased (50%)	+++	++	early	(+)
Lymphoma	normal	(+)	rare	normal	rare
Hemangioblastoma	++	++ to +++	++	rapid	(+)
INTRA-VENTRICULAR					
Choroid pl. papilloma	increased	+	+	early	no
Meningioma	increased	+	+ to ++	early	no
Colloid cyst	no	no	no	normal	no
EXTRA-AXIAL					
Meningioma	increased (75%)	+ (angioblastic)	++	early/normal	typical
Neuromas	normal/increased	(+)	(+)	can be early	+
Pituitary adenoma	can be increased	no	(+)	normal	from ICA
Craniopharyngioma	normal	no	no	normal	no
Chemodectoma	+++	+++	++	rapid	++
Chordoma	normal/increased	+ to ++	+ to ++	early	+

BIOPSY

- definitive tissue diagnosis necessary for adequate treatment planning. see p. D34 >>

- most **primary brain tumors** are verified histologically (either resection surgery or biopsy for unresectable cases), but 80% **metastatic tumors** are diagnosed & treated empirically (if biopsy is available from extra-CNS locations)
- biopsy is not indicated in *CHIASMAL GLIOMAS* and *DIFFUSE BRAIN STEM GLIOMAS** - characteristic MRI features and uniform histology - biopsy rarely influences treatment (prognosis is dismal in diffuse brain stem tumors regardless of biopsy results + biopsy is hazardous).
  *unless brain stem glioma has exophytic component (which may be biopsied)

Open biopsies (without tumor removal) are not justifiable! - if skull and dura are to be opened, surgeon should do gross total resection; however, if tumor is unresectable (due to eloquent infiltration) but close to cortex, open biopsy gives more material!!! (Dr. Cohen-Gadol)

any tumor causing mass effect or neurologic symptoms in relatively noneloquent area of brain should be removed (so biopsy is part of surgical resection)

All brain regions may be approached by MR-guided stereotactic biopsy!

- stereotactic biopsy usually provides enough tissue to *make diagnosis* of glioma but may not provide enough to *grade tumor* (most informative specimen is one taken from ***area of contrast enhancement***).

  Gliomas are of heterogeneous nature - areas of low-grade histology are commonly noted in many high-grade tumors!

- stereotactic biopsy is reserved for poor-surgical risk patients* (but if tumor has *prominent blood vessels* or *hemorrhage within tumor*, open biopsy is preferable).

  *open excision may result in unacceptable functional impairment without positive influence on survival

There is no indication for craniotomy when purpose is merely to biopsy (and not resect) tumor

DIFFERENTIAL DIAGNOSIS

1. Hematomas (may be mistaken for acute bleeding into tumor)
2. Abscesses*
3. Granulomas*
4. Parasitic infections (such as cysticercosis)
5. Vascular malformations (esp. without AV shunts)
6. Solitary large MS plaque, concentric sclerosis of Balo (but T_2-MRI usually reveals additional asymptomatic lesions)
7. Progressive strokes (rare)

*usually cannot be distinguished from tumors by CT or MRI alone - reliable management may demand biopsy

N.B. immunosuppressed patients are at risk for both ***primary CNS lymphomas*** and ***CNS infections*** (such as *toxoplasmosis* or *cryptococcosis*) - patients treated empirically with antibiotics should undergo prompt biopsy of lesions that are not responding to therapy.

COMPLICATIONS

HYDROCEPHALUS

A. **Obstructive hydrocephalus** - obstruction at ventricular atrium → foramen of Monro → aqueduct → 4th ventricle.
   - tumor can act as valve (e.g. tumor in region of foramen of Monro) → sudden potentially life-threatening **hydrocephalus**.

B. **Communicating hydrocephalus**
   a) tumor seeding to meninges
   b) reaction to previous therapy

- if depressed consciousness persists despite steroid administration, CSF diversion procedure should be strongly considered.

  N.B. **posterior fossa tumors** can cause *reverse herniation* after ventricular shunt insertion (therefore, drain EVD at 15 cmH_2O)

- hydrocephalus requiring permanent shunt develops in 25-33% patients after posterior fossa tumor removal.

INTRATUMOR HEMORRHAGE

- tumors that most often cause hemorrhage (stroke-like onset of focal neurologic deficit):
  1) oligodendrogliomas, high-grade astrocytomas
  2) some metastatic tumors (melanoma!!!, renal cell carcinoma, choriocarcinoma*, testicular carcinomas).
  3) WNT among medulloblastomas

  *"menses in brain"
- may be provoked by ***iatrogenic thrombocytopenia*** (associated with chemotherapy).
- clinically: insignificant ÷ dramatic.
- treatment - osmotic agents and glucocorticoids ± surgical decompression.

BIBLIOGRAPHY for ch. "Neuro-Oncology" → follow this LINK >>