Brain Tumors (GENERAL)

Last updated: April 12, 2020

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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 per 100,000 (for primary brain tumors) = 2.15 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: men : women = 2:1).

• leading cause of cancer-related deaths in males 35-54 yrs.
BRAIN TUMORS (GENERAL)

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 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

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Genetic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma, IDH-mutant</td>
<td>IDH-mutant</td>
</tr>
<tr>
<td>Medulloblastoma, WNT-activated</td>
<td>WNT-activated</td>
</tr>
<tr>
<td>Oligodendroglioma, IDH-mutant and 1p/19q-codeleted</td>
<td>IDH-mutant and 1p/19q-codeleted</td>
</tr>
<tr>
<td>Glioblastoma, IDH-wildtype</td>
<td>IDH-wildtype</td>
</tr>
<tr>
<td>Other astrocytic tumours</td>
<td>Other astrocytic tumours</td>
</tr>
<tr>
<td>Medulloblastoma, MSLH-mutated</td>
<td>MSLH-mutated</td>
</tr>
<tr>
<td>Medulloblastoma, non-WNT-3A-SHMH</td>
<td>non-WNT-3A-SHMH</td>
</tr>
<tr>
<td>Medulloblastoma, group 3</td>
<td>Medulloblastoma, group 3</td>
</tr>
<tr>
<td>Medulloblastoma, histologically defined</td>
<td>Medulloblastoma, histologically defined</td>
</tr>
<tr>
<td>Metastatic glioblastoma, breast, colon, lung, prostate</td>
<td>Metastatic glioblastoma, breast, colon, lung, prostate</td>
</tr>
<tr>
<td>Metastatic glioblastoma, melanoma, sarcoma</td>
<td>Metastatic glioblastoma, melanoma, sarcoma</td>
</tr>
<tr>
<td>Medulloblastoma, astrocytic</td>
<td>Medulloblastoma, astrocytic</td>
</tr>
<tr>
<td>Medulloblastoma, ependymal</td>
<td>Medulloblastoma, ependymal</td>
</tr>
<tr>
<td>Medulloblastoma, melanocytic</td>
<td>Medulloblastoma, melanocytic</td>
</tr>
<tr>
<td>Medulloblastoma, rhabdoid</td>
<td>Medulloblastoma, rhabdoid</td>
</tr>
<tr>
<td>Medulloblastoma, xanthochromic</td>
<td>Medulloblastoma, xanthochromic</td>
</tr>
<tr>
<td>Medulloblastoma with mixed features</td>
<td>Medulloblastoma with mixed features</td>
</tr>
<tr>
<td>Choroid plexus tumours</td>
<td>Choroid plexus tumours</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>Choroid plexus papilloma</td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td>Choroid plexus carcinoma</td>
</tr>
<tr>
<td>Choroid plexus papilloma, low-grade</td>
<td>Choroid plexus papilloma, low-grade</td>
</tr>
<tr>
<td>Choroid plexus papilloma, high-grade</td>
<td>Choroid plexus papilloma, high-grade</td>
</tr>
<tr>
<td>Choroid plexus carcinoma, low-grade</td>
<td>Choroid plexus carcinoma, low-grade</td>
</tr>
<tr>
<td>Choroid plexus carcinoma, high-grade</td>
<td>Choroid plexus carcinoma, high-grade</td>
</tr>
<tr>
<td>Choroid plexus papilloma, NOS</td>
<td>Choroid plexus papilloma, NOS</td>
</tr>
<tr>
<td>Choroid plexus carcinoma, NOS</td>
<td>Choroid plexus carcinoma, NOS</td>
</tr>
</tbody>
</table>
Summary of the major changes in the 2016 CNS WHO

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

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 tumor with multilayered rosettes, C19MC–altered (entity)
   4) Ependymoma, RELA fusion–positive (entity)
   5) Diffuse leptomeningeal glioneuronal tumor (entity)
   6) Anaplastic PXA (entity)
   7) Epithelioid glial tumor (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 patterns:
   1) Gliomatosis cerebri
   2) Protoplasmic and fibrillary astrocytoma variants
   3) "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!
Gliomas are not divided sharply into benign and malignant forms, rather, they represent gradations on a spectrum from slowly growing to rapidly growing neoplasms.

- 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 thymidine analogues: 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) brainstem
   e) cerebellar
2) subependymal giant cell astrocytoma (non-invasive, WHO grade I)
3) pleomorphic xanthoastrocytoma (non-invasive, WHO grade I)
4) anaplastic (malignant) astrocytoma (WHO grade III)
   a) hemispheric
   b) diencephalic
   c) optic
   d) brainstem
   e) cerebellar
5) glioblastoma multiforme (WHO grade IV) – most aggressive and most common of all CNS tumors!!!
   variants: giant cell glioblastoma, gliosarcoma

2. OLIGODENDROGIAL 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: protoplasmic, gemistocytic, fibrillary, mixed
3) anaplastic ependymoma (WHO grade III)
4) myxopapillary ependymoma

4. MIXED GLIOMA

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) gliomatosi 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. NEUROEPITHELIAL AND MIXED NEURAL-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
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) medulloblastoma
2) primitive neuroectodermal tumors with multipotent differentiation:
   a) medulloblastoma
   b) primitive neuroectodermal tumor (PNET)
3) neuroblastoma
4) retinoblastoma
5) ependymoblastoma
6) atypical teratoid/rhabdoid tumor

OTHER CNS TUMORS

1. Tumors of SELAR 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) germ celloma
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, angiomyxomatous, microcystic, clear cell, chordoid, lymphoplasmacytoid, histiocytic
2) atypical meningioma
3) anaplastic (malignant) meningioma

5. NON-NEUROEPITHELIAL tumors of MENINGES

1) benign mesenchymal
   a) osteocartilaginous tumors
   b) lipoma
   c) fibrous histiocytoma
2) malignant mesenchymal
   a) chondrosarcoma
   b) hemangiopericytoma
   c) rhabdomyosarcoma
   d) meningial sarcomatosis
3) primary melanocytic lesions
   a) diffuse melanosis
   b) melanocytoma
   c) malignant melanoma
   - variant: meningofacial melanocytoma
4) hematopoietic neoplasm
   a) malignant lymphoma
   b) plasmacytoma
   c) granulocytic sarcoma
   d) tumors of uncertain histogenesis - hemangioblastoma (capillary hemangioendothelioma)

6. Tumors of CRANIAL/SPINAL NERVES

1) neurofibroma
2) schwannoma (neurinoma, neurilemoma)
   - subtypes: cellular, plexiform, melanotic
3) malignant peripheral nerve sheath tumor
   - variants: epithelial, discohesive neurenmymal 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) neuroepithelial cyst
7) granular cell tumor (choristoma, pilomatrixoma)
8) hypothyroidic neuronal hamartoma
9) nasal gland 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) solitaire 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).

Brain tumors (adults) with percentage incidence by category:

<table>
<thead>
<tr>
<th>Primary intra-axial</th>
<th>Primary extra-axial</th>
<th>Metastatic**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma (47)</td>
<td>Meningioma (80)</td>
<td>Lang (37-49)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma (24)</td>
<td>Acoustic neuroma (10)</td>
<td>Breast (16-19)</td>
</tr>
<tr>
<td>Astrocytoma (15)</td>
<td>Pituitary adenoma (7)</td>
<td>Melanoma (16)</td>
</tr>
<tr>
<td>Oligodendroglioma (5)</td>
<td>Other (3)</td>
<td>Colorectum (9)</td>
</tr>
<tr>
<td>Lymphoma (2.7)</td>
<td></td>
<td>Kidney (8)</td>
</tr>
<tr>
<td>Other (7)</td>
<td></td>
<td>Other (11)</td>
</tr>
</tbody>
</table>

*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.
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. ALEXANDER DISEASE (Rosenthal fibers radiate from vessels)
4. BLOOD VESSEL WALLS

Rosenthal fibres in neuropil:

BENIGN vs. MALIGNANT

BENIGN tumors can be called TUMORS (mainly extra-axial tumors - meningiomas, acoustic neuromas). The concept of malignancy in CNS has different meanings from that which applies to systemic cancers;

- The term “malignant” has no thing to do with metastasis out of CNS, which is extraordinarily rare.
- The 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.
  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.

- Neuroectodermal tumors are never “benign”!
  - 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.
**Brain Tumors (General)**

### Age

#### Adulthood
- Astrocytoma, oligodendroglioma, metastases, lymphoma
- Astrocytoma, colloid cyst, primary adenoma
- Metastases, meningioblastoma
- Metastases, CNS 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 astrocytoma, brain stem astrocytoma, choroid plexus tumor
- Leukemia, lymphoma
- Nerve sheath tumors, astrocytoma

### Intraventricular Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Typical site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colloid Cyst</strong></td>
<td>Foramen of Monro / 3rd ventricle</td>
</tr>
<tr>
<td><strong>SEGA</strong></td>
<td>Foramen of Monro</td>
</tr>
<tr>
<td><strong>Meningioma</strong></td>
<td>Trigone of lateral ventricle</td>
</tr>
<tr>
<td><strong>Choroid Plexus Papilloma</strong></td>
<td>4th ventricle</td>
</tr>
<tr>
<td><strong>Ependymoma</strong></td>
<td>Lateral ventricle (more common in children), 4th ventricle</td>
</tr>
<tr>
<td><strong>Subependymoma</strong>*</td>
<td>Lateral ventricle, 4th ventricle</td>
</tr>
<tr>
<td><strong>Neurocytoma</strong>*</td>
<td>Lateral ventricles (involving septum pellucidum)</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>Lateral ventricles, ependyma and choroid plexus</td>
</tr>
</tbody>
</table>

- **SEGA** is a rare tumor that may spread via CSF through ventricular / subarachnoid spaces.

### 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.

### Metastasis

**Spread through CSF** → **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).

### Tumor Burden

- Tumor mass of 30-60 g (3-6 x 10^10 cells) usually produces neuropsychic 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 x 10^5 glioma cells.

### Brain Tumors Cause Death by Local Growth
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.

**CELLULAR HETEROGENEITY**

- 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 mutagenesis, 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)
- Brachury (protein encoded by the TBXBT gene, transcription factor within the T-box family of genes)
  - early mutational event in astrocytomas (discriminates chondroma from chondrosarcoma).
  - present in majority of hemangioablastomas (helps to differentiate from clear cell renal carcinoma metastases in von Hippel-Lindau syndrome).
- CDM8 (protein highly expressed by cells in the monocyte lineage: macrophia, histiocytes) – differentiates histiocytosis from lymphoma.
- Desmin → tumors containing muscle (schwannomas, teratoma, etc.), primitive neuroectodermal tumor.
- EGFR (epidermal-derived growth factor receptor) – abreactly expressed (usually amplified*) in many gliomas.
  - *poor prognostic factor!
- EMA (epithelial membrane antigen) → epithelia marker (endodermal and epithelial areas of teratoma, chordoid tumours).
  - 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. unaplastic astrocytoma.
- Human chorionic gonadotropin – germ cell, choriocarcinoma
- Luxol fast blue dye → myelin appears blue, neurit appears pink, and nerve cells appear purple.
- p53 mutation = astrocytic tumors (vs. oligo*)
  - 1) Fraumeni syndrome (inherited p53 mutation) → strong predisposition to astrocytoma!!
  - p53 mutation goes “hand in hand” with IDH mutation.
  - 2) Low expression that show p53 muts are termed secondary glialoblastomas (type I) occur in younger patients whose tumors have progressed from lower grade astrocytoma.
- Placental alkaline phosphatase – germ cell tumors

**RETINAL S-ANTIGEN** → panretinal 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).
- SNT2 (somatostatin receptor type 2):
  - most sensitive marker for meningiomas (present in 100%).
- STAT3 – hemangiopericytoma.
- Synaptophysin → integral membrane protein localized to synaptic vesicles (specific and sensitive marker for synaptic terminal); gliosarcomas (primary primitive neuroectodermal tumor, ganglioglioma, ganglioneuroblastoma, central neurocytoma, neuroendocrine tumors)
  - diagnostically, it is often used in combination with chromogranin A.
- Vascular proliferation:
  - a) astrocytic lineage = GBM

N.B. Anti-α-smooth muscle actin (α-ASMA) – characteristic of leiomyomas (weaker than schwannomas), appear in majority of melanomas.
ETIOLOGY, RISK FACTORS

SEIZURES

Seizures may herald development of cerebral tumors by several years:

- British study (Journal of Neurology, Neuurosurgery 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 (Helzeli tumor inaming radiation (e.g. given treatment of tina 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).
- immuno-suppession (transplant recipients, AIDS patients, Wiskott-Aldrich syndrome, axiatal-telangiectasia) substantially increases risks for primary CNS lymphoma but not gliomas.
- role of onoma is unproven.

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

TUMORIGENESIS

- mutistep 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 tumor:

1) EGFR (ex-17) - encodes epidermal-derived growth factor receptor, aberrantly expressed (usually amplified) in many gliomas!
2) c-sis - encodes platelet-derived growth factor
3) c-ros
4) B-ros
5) H-ros
6) glutamine
7) 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 (TGF-
  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).
- normal brain cell is genetically quiescent (neurons are incapable of division after birth, glial cells are minimally proliferative in reactive or reparative gliosis)
- cardiac 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. 299-300 >>

TUMOR SUPPRESSOR GENES

Tumor suppressor genes associated with nervous system tumors:

NF1 (17p13) - loss predisposes to astrocytoma and neurofibromatosis.

- progression from low-grade astrocytoma to glioblastoma strongly correlates with loss of BP1 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 BP1 allele.
  - sporadic (randomal) forms of cancers associated with Li-Fraumeni syndrome also show BP1 inactivation.

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

HEREDITARY SYNDROMES associated with brain tumors

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

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Nervous Tumor</th>
<th>Other tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis</td>
<td>NFT (17q11)</td>
<td>Neurofibroma, malignant peripheral nerve sheath tumor (MPNST), meningioma, optic nerve glioma, (low-grade) astrocytoma, iris hamartomas, bosseous lesions, phacochromocytoma, leukemia, lymphoma.</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2 (22q13)</td>
<td>Bilateral vestibular schwannoma, peripheral schwannoma, Fornier’s lump, nodular retinal hamartoma.</td>
</tr>
</tbody>
</table>
extravasation of red blood cells (blood from tumor enters extravascular space)

**PATHOPHYSIOLOGY**

**BBB, BLOOD FLOW & BRAIN EDEMA**

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

- water-soluble, ionized molecules, macromolecules can enter tumor.
- *entry of some water
- *free white matter.
- *autonomous dominant combination of sebaceous gland tumors
- *at least one visceral cancer
- *malignancies characterized by microsatellite instability.

**PATHOGENESIS OF CLINICAL FEATURES**

- intra-axial tumors
- *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 do not improve after treatment.

- *Vascular endothelial growth factor (VEGF)
- *enormous edema surrounding small neoplasm suggests rapidely growing malignant tumor (exception – meningioma - benign slow-growing tumor that can produce profound edema and contrast enhancement).

- *is not unusual for 20 g tumor to produce 100 ml edema because of associated edema.
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. leuкоemic or carcinomatos 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 fronto 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) LOCAL 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!

XARKOFSKY 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 Definitions
0 Fully active, able to carry on all pre-disease performance without restriction.
1 Restricted in physically strenuous activities 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 any 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 these three syndromes:
   a) multifocal 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 sequelae, occurs in:
     50-60% primary brain tumors, 35-50% metastatic tumors.
   • rare as initial symptom in brainstem tumors, cerebellotopontine angle tumors, pituitary tumors, cranioopharyngiomas.
   • about features of "classic" brain tumor headache → see p. S30 >>
   • 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 unrelenting that patient seeks medical attention.

Significant overlap between brain tumor headache and migraine or tension-type headache

In series of 111 patients, headache had clinical features similar to migraine in 9% and tension-type headache in 77%, while "classic" brain tumor headache occurred in only 1%.

Intense paroxysmal headaches may develop abruptly (within seconds); last only few minutes and terminate as quickly as they come.
3. **Vomiting**
- associated with nausea and headache.
- direct compression of vomition 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 – preceedes appearance of headache by weeks).

3. **Deterioration in mental status** (psychomotor retardation, sleep / cognitive / social disturbances, confusion, lethargy)
- 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. 550 \*

5. **Brain mass shifts** (may manifest as false-localizing signs) - CN6 palsy, CN3 palsy, ipsilateral hemianopia (compression of opposite cerebral peduncle against Kornshaut’s notch), ipsilateral visual field defects (compression of opposite PCA), midclauddial & tectochills (herination of cerebellar tonsils), etc.


**SYMPTOMS due to TUMOR ITSELF (FOCAL BRAIN DYSFUNCTION)**

- may be absent in tumors growing in silent areas.
- result from compression of nervous 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! (FOCAL BRAIN DYSFUNCTION)

- suggestive features: status epilepticus at onset, prolonged postictal paralysis*, resistance to medical control, focal symptoms.

A 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 x 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**
- primary / pituital tumors → hormone overproduction.
- choroid-plexus papilloma → CSF overproduction.

**REGIONAL FEATURES**

**SLOTTEN’S SIGN**
- progressive focal neurologic signs and seizures predominate:

<table>
<thead>
<tr>
<th>Frontal lobe</th>
<th>Temporal lobe</th>
<th>Occipital lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures - may preceed other symptoms by months or years.</td>
<td>Personality change (bizarre thinking, trance-like states, mood symptoms, immature emotional behavior; bilateral amygdaloid lesions → Kihler-Bucy syndrome).</td>
<td>- contralateral quadrantopia or hemianopia with sparing of macula, visual misperceptions &amp; hallucinations; bilateral lesions – cortical blindness.</td>
</tr>
<tr>
<td>2. Intellectual impairment (esp. with bilateral tumors, e.g. butterfly glioma)</td>
<td>Sensory aphasia, anosmia.</td>
<td>Bilateral hydrocephalus.</td>
</tr>
<tr>
<td>b) orbital prefrontal lesions → apathy, depression &amp; euphoria (pseudopsychopathic).</td>
<td>5. Impairment of recent memory (bilateral hippocampal lesions → Korsakov amnesia)</td>
<td>- contralateral quadrantopia or hemianopia with sparing of macula, visual misperceptions &amp; hallucinations; bilateral lesions – cortical blindness.</td>
</tr>
<tr>
<td>6. Aphasias.</td>
<td>7. Anosmia (e.g. meningioma of olfactory groove).</td>
<td>- contralateral homonymous hemianopia (or inferior quadrantopia).</td>
</tr>
<tr>
<td>Personality changes: see also p. 550</td>
<td>5. Impairment of recent memory (bilateral hippocampal lesions → Korsakov amnesia)</td>
<td>- contralateral quadrantopia or hemianopia with sparing of macula, visual misperceptions &amp; hallucinations; bilateral lesions – cortical blindness.</td>
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*torcicallis also may be due to CN4 palsy

**BRAIN TUMORS (GENERAL)**

- ommunicating 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).

- Enlarging fossa tumors may be absent in tumors growing in silent areas.
- Hydrocephalus
  - Contralateral sensory abnormality, neuropathic pain, intermittent pareseshes.
  - Involvement of basal ganglia → contralateral intention tremor, hemiballistic movement.
  - Involvement of hypothalamus → eating disorders, precocious puberty.

- Impaired cortical sensory modalities (position sense, two-point discrimination, stereognosis).
- Contralateral homonymous hemianopia (or inferior quadrantopia).
- Mixed expressive-receptive aphasia, anosognosia.
- Dominant hemisphere – Gerstmann’s syndrome (agraphia, acalculia, finger agnosia).
- Nondominant hemisphere – apraxia, contralateral hemineglect.

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

- Hyperactive function
  - primary / pituital tumors – hormone overproduction.
  - choroid-plexus papilloma – CSF overproduction.

- Hyperactive function
  - primary / pituital tumors – hormone overproduction.
  - choroid-plexus papilloma → CSF overproduction.
### DIAGNOSIS

#### BODY 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.

- **Polythemia** associated with cerebellar tumor - presumptive evidence of MENINGIOMATOSIS.

- 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).

#### OPHTHALMOSCOPIC

1. Papilledema - most reliable sign of ICP↑ (but present in only ≤ 20% patients)
   - see p. Eyelid >>
   - more common with supratentorial tumors than supraventricular tumors (rapidly worsening mental status)
2. Other signs of ICP↑
   - see p. Sinus >>
   - thorough ophthalmologic examination (incl. visual field testing) is important in pre- and postoperative evaluation of tumors adjacent to visual / olfactory pathways.

#### SKULL X-RAY

- only rare indications:
  1. screening skull for metastatic disease
  2. assessing integrity of various sinuses
  - may show signs of raised ICP, see p. Sinus >>

#### CSF

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

- does not provide significant diagnostic information: raised opening pressure, protein?, mild lymphocytic pleocytosis.

  - **ASTROCYTOMA** that extend to ventricular surface, or **EPENDYMOMA** rapture, can produce intense CSF inflammation simulating infections 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, CHORDOMA PLEURIC CARCINOMA, some ENDOCRINE PINEAL and SPARGANUM 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 anticovulsant 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 EXAE

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

#### NEUROIMAGING

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

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

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

- better definition (than MRI) of calcification – suggests more indolent growth,
tumors that tend to calcify, oligodendrogliomas (90%), meningiomas, craniohypophyseoma, teratoma, chordoma, chordoid plexus tumors, ependymoma, central neurocytoma.

- CT preferable (over MRI) for evaluating bones, intramural 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 (a submass effect).

- on nonenhanced CT
  - tumors can be hypo-hypo- 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 enhance strongly
- meningiomas, neurtomas, 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), epidermidis

MRI RECOMMENDATIONS

- Most sensitive test of choice for detection of brain tumors (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 intraxial 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.

- corticosteroids use can significantly diminish contrast enhancement!!!
- postoperative enhancement and radiosclerosis 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).

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...
**Tumor type** | **TI with gadolinium** | **Contrast CT**
--- | --- | ---
**Aneurysmal subarachnoid hemorrhage** | Ring configuration | 
Anaplastic astrocytoma | Solidly bright or patchy or do not enhance. | Invisible (or vague low density).
Low-grade astrocytoma | Do not enhance (except pilocytic astrocytoma). | Invisible (unless anaplastic).
Oligodendroglioma | Do not enhance (unless anaplastic). | Invisible (unless calcified).
Primitive neuroectodermal tumor | Always enhance less than normal primitive gland. | CT is inferior in every way.
Metastases | Variable: some enhance brightly and solidly; others are in ring configuration (central necrosis & cavitation). | Many are avascular.
Histiocytic neuroblastoma, meningioblastoma | Intensely contrasted (non-homogenously) | Contrast.
Primary CNS lymphoma | Smoothly rounded homogenous 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!

**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 (PWI-MRI):**
Markedly increased CBV - excess vascularity (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)

**Diffusion Tensor Imaging (DTI):**
- Shows tracts in peritumoral area – guides safer tumor resection.

**Generalized Q-Sampling Imaging:**
- Can visualize tracts in peritumoral edema even better than DTI.

**MR:**
- Presurgical evaluation of eloquent cortex. See also p. D66 >
- Alternative – intraoperative electrical cortical mapping.

**MR:**
- Non-invasive in vivo method of analyzing tissue chemical spectrum. See p. D53 >
  - Commonest abnormalities in gliomas (vs. necrosis):
    - Increased: choline (membrane metabolism) / N-acetyl aspartate (living neurologic tissue)
    - Decreased: - NAA/creatine.
    - Tumor – lots of membranes (choline≤), no normal neurons (NAA≤), metabolism anaerobic (lactate≥ and creatine≥).
  - Commonest abnormalities in radiation necrosis:
    - Increased – lipid/fat (large peak)
    - Decreased - choline, N-acetyl aspartate, creatine.

**Necrosis – only tumors:**
no normal neurons (NAA↓), no normal membranes (choline↓), no metabolism (creatine↓, lactate↓)

As comparison – infarction (stroke) region:
- 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 (1.01 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 H215O.
  - tumors that respond to therapy become hypometabolic (before they shrink in size on MRI).
  - recurrent symptoms after radiation therapy:
    - recurrent / residual tumor (glycolytic activity↑)
    - 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.
**BRAIN TUMORS (GENERAL)**

**Onc**

**H215O 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.**

- **201Tl 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.

- **123I 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 falk 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. 544 >>

**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;
- GIZZONIX and, particularly, METASTASES - dural supply is well documented.

<table>
<thead>
<tr>
<th>Type</th>
<th>Increased vascularity</th>
<th>Tumor vessels</th>
<th>Blush</th>
<th>Venous filling</th>
<th>Meningeal supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRA-AXIAL</td>
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</table>
BIOPSY
- definitive tissue diagnosis necessary for adequate treatment planning.
  - most primary brain tumors are verified histologically, but 80% metastatic tumors are diagnosed clinically.
  - biopsy is not indicated in CHORDOMA, GIOMAS, and DURASENSTMEDULLAR GIOMAS - 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.
- any tumor causes most effect on neurologic symptoms in relatively nonmobile area of brain should be removed (as 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).
- *Tumors are of heterogeneous nature - areas of low-grade histology are commonly noted in many high-grade tumors.
- stereotactic biopsy is reserved for non-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. Paraneoplastic infections (such as cysctercisosis)
5. Vascular malformations (esp. without AV shunts)
6. Solitary large MS plaque, concentric sclerosis of BaLo (but T2-MRI usually reveals additional asymptomatic lesions)
7. Progressive strokes (rare)
  *usually cannot be distinguished from tumors by CT or MRI alone - reliably management may demand biopsy

N.B. immunosuppressed patients are at risk for both primary CNS lymphomas and CNS infections* (such as toxoplasmosis and 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
- 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 cmH2O).
  - 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) glioblastoma/malignant glioma, 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 - osmetic agents and glucocorticoids & surgical decompression.

<table>
<thead>
<tr>
<th>Type</th>
<th>Increased</th>
<th>Tumor vessels</th>
<th>Blush</th>
<th>Venous filling</th>
<th>Meningeal supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliona (low grade)</td>
<td>rare</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Glioblastoma (50%)</td>
<td>increased</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Metastases (50%)</td>
<td>increased</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>normal</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>++</td>
<td>++ to +++</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

INTRA-VENTRICULAR

Chordoid pl. papilloma
- increased
- early (−)

Menigienia
- increased
- early (−)

Colloid cyst
- no

EXTRA-AXIAL

Menigienia
- increased (75%)
- (angioblastic)

Neuramias
- normal/increased (+)
- can be increased (+)

Pitutar adenoma
- can be increased (−)
- normal (−)

Craniopharyngioma
- normal
- no
- normal

Choroid pl
- normal
- increased

Hemangioblastoma
- normal/increased
- (−)

Venous plaque
- (−)

Intraventricular tumors:
- should do gross total resection.
- Open biopsies - should be strongly considered.
- if depressed consciousness persists despite steroid administration, CSF diversion procedure should be strongly considered.
- CHOROID PAPILLOMA:
  - increased
- early (−)

- MENINGIOMA:
  - increased
- early (−)

- CHORDOMA:
  - normal/increased
- early (−)

*Note: The table above shows the increased or decreased characteristics of various tumors and their relation to different parameters such as tumor vessels, blush, and meningeal supply.