Astrocytomas

Last updated: August 8, 2020

ETIOLOGY

- familial cases constitute only 1%

- associated with certain genetic syndromes: 
  - neurofibromatosis type 1 \( \rightarrow \) low-grade astrocytomas (esp. in optic nerve & chiasm)
  - tuberous sclerosis \( \rightarrow \) SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA)
  - Turcot’s syndrome \( \rightarrow \) gliomas, medulloblastomas

- 90% GBMs are primary (i.e. arise de novo); 10% - secondary (i.e. arise from low grade astrocytomas).

CLASSIFICATION, GRADING

WHO 2016

- in WHO 2016 classification, the diffuse glioma category includes astrocytic and oligodendrogliogal tumors:
  1) grade II and III astrocytic tumors, i.e. diffuse astrocytoma and anaplastic astrocytoma
  2) grade II and III oligodendrogliomas
  3) grade II and III oligoastrocytomas
  4) grade IV glioblastomas
  5) related diffuse gliomas (e.g. those of childhood).

TREATMENT

- Primary surgery
- Radiotherapy
- Chemotherapy
- Targeted therapy
- Immunotherapy
- Gene therapy
- Stem cell therapy
- Pediatric treatment

CLINICAL FEATURES

- Presentation:
  - Neuropathic pain
  - Seizures
  - Hemiparesis
  - Cognitive dysfunction
  - Hydrocephalus
  - Endocrine dysfunction

- Prognosis:
  - Improve outcome
  - Increased survival
  - Reduced morbidity
  - Improved quality of life
Over many years, astrocytomas usually resemble a hierarchical system similar to the Ringertz system, the St. Anne/Mayo system, and the previously published WHO schemes.

- Tumors with cytological atypia alone (i.e. diffuse astrocytomas) are considered grade II, while those that also show anaplasia and mitotic activity (i.e. anaplastic astrocytomas) are considered WHO grade III, and tumors that additionally show microvascular proliferation and/or necrosis are grade IV.

N.B. necrosis is no longer a requirement for grade IV.

- Atypia is defined as variation in nuclear shape or size with accompanying hyperchromasia. Mitoses must be unequivocal, but no special significance is accorded to their morphology. The finding of a solitary mitosis in an ample specimen is not sufficient proof of WHO grade III behaviour, but the separation of grade II tumors from grade III tumors may be facilitated by determination of the Ki-67 proliferation index.

- Microvascular proliferation is defined as apparent multi-layering of endothelium (rather than simple hypervascularity) or glomeruloid vasculature.

- Necrosis may be of any type; pericentric psalading need not be present. Simple apposition of cellular zones with intervening pallor suggestive of incipient necrosis is insufficient.

- All WHO systems recognize that astrocytomas are graded using a three-tiered system similar to the Ringertz system, the St. Anne/Mayo system, and the previously published WHO schemes. Diffuse astrocytomas are graded using a three-tiered system similar to the Ringertz system, the St. Anne/Mayo system, and the previously published WHO schemes.

Historical Bailey and Cushing classification, based on embryologic development of astrocytoma:
- Pilocytic astrocytoma: glioma of childhood.
- Anaplastic astrocytoma: glioma of adolescence.
- Astrocytoma: glioma of adulthood.

WHO 2007 classification:

<table>
<thead>
<tr>
<th>WHO 2007 designation</th>
<th>WHO grade</th>
<th>Kernohan criteria</th>
<th>St. Anne/Mayo criteria**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade (s. benign)</td>
<td>I</td>
<td>1 criterion</td>
<td>1 criterion (usually nuclear atypia)</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>III</td>
<td>2 criteria</td>
<td>1 criterion (usually nuclear atypia and mitoses)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>II</td>
<td>no criteria</td>
<td>3 criteria - endothelial proliferation and/or necrosis</td>
</tr>
<tr>
<td>Multiforme</td>
<td>IV</td>
<td>3+4 criteria</td>
<td>4+4 criteria - endothelial proliferation and/or necrosis</td>
</tr>
</tbody>
</table>

**WHO and Kernohan systems are not criteria based (1).**

**Histologic criteria:**
1. Nuclear atypia
2. Mitoses – already grade III
3. Endothelial proliferation – already grade IV (tufts of piled-up vascular cells that bulge into vascular lumen, if proliferation is extreme, tuft forms ball-like structure - glomeruloid body) - vascular endothelial growth factor (VEGFR) produced by malignant astrocytes (in response to hypoxia) contributes to this vascular change; probably predisposes to necrosis.
4. Necrosis – already grade IV

**WHO 2016 diffuse gliomas**

- If tumor samples are obtained by stereotactic needle biopsy, high rate of error occurs (grades generally are underestimated by needle biopsy):
  - 4 biopsies → grading error rate ≈ 2%
  - 6 biopsies → grading error rate ≈ 25%.

- Multiforme glioblastoma: astrocytoma with microvascular proliferation and marked atypia; nevertheless, they are slow growing and well circumscribed (grade I).

- Grade II: diffuse astrocytoma is automatically ≥ grade II.

- Grade III: diffuse astrocytoma may have endothelial proliferation and marked atypia; nevertheless, they are slow growing and well circumscribed (grade I).

- Grade IV: diffuse astrocytoma has already grade III.

- WHO 2016 diffuse gliomas:

**GENETICS**

GBM is extraordinarily heterogeneous tumor with many, many pathways that are perturbed (overexpressed, deleted, mutant). GBM is not like chronic myelogenous leukemia, where 1 BCR-ABL translocation underlies the entire disease.

Over many years, astrocytomas undergo dedifferentiation into higher-grade lesions.

Progression in tumor grade is associated with ordered accumulation of specific mutations (genetic aberrations accumulate in fixed percentage of tumors at each stage of malignancy, some genetic aberrations are specific for early transformations, i.e. low grade tumors, while others represent late events):
Genes involved in gliomagenesis:

**I. Oncogenes:** EGF-R, PDGF, PDGF-R, p53, FGF-R

**II. Tumor suppressor genes:** CDKN2A [also known as p16INK4a], PTEN, RB1, TP53.

Most common genetic alterations in GBM:

1. LOH at 10q (69%)
2. CDKN2A (p16INK4a) deletion (50%)
3. EGF-R gene amplification
4. TP53 mutations
5. PTEN mutations
6. IDH1-12 mutations

Most frequently altered GBM cancer genes:


40% ANAPLASTIC ASTROCYTOMAS: (grade 3) in addition (to p53 mutation) show loss of heterozygosity on chromosome 19q, may also involve mutations in other tumor suppressor genes (e.g. retinoblastoma gene on 13q).>

70% Glioblastomas in addition have lost heterozygosity for chromosome 10 (most common deletion in malignant gliomas); 30-40% Glioblastomas have amplification of EGF-R gene (7p13-p11), which also may have gene rearrangement (→ tyrosine kinase activity↑ in absence of EGF → EGFR "turned on" in autocrine mode).

Virtually every growth factor known to stimulate cell division has been identified as aberrantly expressed in GBM cell lines! EGF-R gene is most frequently amplified oncogene in astrocytic tumors! CDKN2A gene is most frequently altered tumor suppressor gene in GBM!>

Molecular Signatures of Glioblastoma Multiforme:

Genetic subsets (variants of development) of glioblastoma multiforme:

6) progression from low-grade to high-grade tumors is much less common in pediatric patients (molecular genetic events that characterize adult process have not been described in children).

MGMT METHYLATION
O(6)-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation is predictor of good response to alkylating agents (e.g. temozolomide).

• assay is done routinely on surgical specimens
**Astrocytomas**

**METHYLATION OF MGMT PROMOTER**

- Grade II gliomas with MGMT promoter methylation have a shortened time to recurrence (in the absence of TMZ) and longer post-recurrence survival (in the presence of TMZ), ultimately producing similar overall survival to grade II gliomas without MGMT methylation.

**ISOCITRATE DEHYDROGENASE (IDH)-1/2 mutation**

- ≥ grade 2 tumor.
- First most common mutation to occur in gliomas.
- Mostly in young patients with secondary GBM (astrocytic tumor in ≥ 54 yo – only 1% chance to have IDH mutation).
- Thrombosed vessels in GBM – associated with IDH-wild type.
- IDH mutation is a must for oligodendrocyte lineage tumors.
- Significantly better prognosis (survival improved 3-fold).

**EGFR GENE AMPLIFICATION**

- GBM or tumor (even if otherwise looks like low grade) will behave as GBM.

**CDKN2A suppression**

- Loss of expression of the CDK2NA via either methylation or loss of chromosome 9p is associated with malignant progression of grade II gliomas.

**ATRX (Alpha-Thalassemia/mental Retardation Syndrome X-Linked) GENE**

- ATRX is present in every cell.
- Loss of ATRX = astrocytic lineage.
- Gene involved in chromatin regulation.
- Mutation in ATRX is frequently seen in grade II/III astrocytomas and secondary GBM.
**p53 gene mutations**

- astrocytic tumors (vs. oligo*)
  
  - may gain some p53 positivity in anaplastic stage
  
  - 33% low grade astrocytomas have mutations in p53 gene (17p).

  - 1p/19q codeletion syndrome (inherited p53 mutations) – strong predisposition to astrocytomas!

  - p53 mutation goes “hand to hand” with IDH mutation.

  - Glioblastomas which show p53 mutation are termed secondary glioblastomas (type 1) - occur in younger patients whose tumors have progressed from lower grade astrocytoma (vs. primary, or de novo, type 2 glioblastoma typically found in older patients with short clinical history; prognosis is worse).

- **BRAF V600E mutation**

  - BRAF is a serine/threonine kinase protein and is a downstream effector of the Ras-Raf-MEK-ERK signaling pathway, which is responsible for cell division and differentiation.

  - mutation of the BRAF gene in which valine (V) is substituted by glutamic acid (E) at amino acid 600.

  - BRAF V600E mutations are rarely found in adult gliomas with only 1-2% mutated samples in glioblastomas and 2-5% in low grade adult gliomas.

  - BRAF mutations are in most instances mutually exclusive to canonical IDH mutations.

  - clear prognostic difference could not be established yet.

  - BRAF-V600E mutations are most commonly found in the following primary brain tumors:

    1. papillary craniopharyngioma (81-95%)
    2. pleomorphic xanthoastrocytoma (12-60%)
    3. epithelioid glioblastoma (50%)
    4. astroblastoma (38%)
    5. ganglioglioma, dysembryoplastic neuroepithelial tumor (DNT)
    6. diffuse leptomeningeal glioneuronal tumor (DLGT)
    7. gliomas diagnosed at a younger age

  - it is a driver mutation in a proportion of certain diagnoses: melanoma*, hairy cell leukemia, papillary thyroid cancer, colorectal cancer, non-small-cell lung cancer, Langerhans cell histiocytosis, and ameloblastoma.

  - BRAF-KIAA1549 fusion is the most common BRAF alteration in pilocytic astrocytoma.

  - N.B. primary brain tumors with KIAA1549-BRAF fusion should not be treated with first-generation BRAFi due to paradoxical activation of the Ras-Raf-MEK-ERK pathway.

  - BRAF-PAK1 fusion is the most common BRAF alteration in pilocytic astrocytoma.

  - N.B. primary brain tumors with BRAF-PKA fusion should not be treated with first-generation BRAFi due to paradoxical activation of the Ras-Raf-MEK-ERK pathway.

  - N.B. only JUVENILE PILOCYTIC ASTROCYTOMAS are localized, all other tumors are infiltrative (invasive phenotype is acquired early in tumorigenesis!)

  - calcification occurs only in minority.

**PATHOLOGY**

N.B. only JUVENILE PILOCYTIC ASTROCYTOMAS are localized, all other tumors are infiltrative (invasive phenotype is acquired early in tumorigenesis!)

- calcification occurs only in minority.
Infiltration with tumor cells:

Glione in cerebral hemisphere - difficult to tell where margin is:

LOCATION

Any part of brain; LOW-GRADE ASTROCYTOMAS more common below tentorium, HIGH-GRADE ASTROCYTOMAS - above tentorium.

PILOCYTIC ASTROCYTOMAS - typically occur in children and young adults, usually in cerebellum.

- 70-80% cerebellar astrocytomas occur in children (most commonly - JUVENILE PILOCYTIC ASTROCYTOMAS).
- differential diagnosis is cerebellar HEMANGIOBLASTOMA.
- also common close to midline (3rd ventricle, hypothalamus, thalamus, optic chiasm, brain stem).
- occasionally in hemispheres (frontal, temporal, parietal lobes).
- pilocytic astrocytomas are slow-growing tumors even when their size, histologic appearance, clinical symptoms, or radiographic appearance suggests otherwise.

PLEOMORPHIC XANTHOASTROCYTOMA - most common superficially in temporal lobe in teens and young adults.

SUPREPENDYAL GIANT-CELL ASTROCYTOMA (almost exclusive in tuberous sclerosis) - most common in lateral wall of 3rd ventricle.

ASTROCYTOMAS - tend to occur in cerebral lobes (esp. frontal).

MALEIGANT ASTROCYTOMAS - anywhere (primarily in frontal lobes); spread across corpus callosum is common, also may spread through ventricular system or subarachnoid space.

- multicentric in 5% cases.

DIAGNOSTIC ENTITIES

PILOCYTIC ASTROCYTOMA

(Grade I)

Genetics
- essentially all have various mutations affecting MAPK pathway.

Figure 3A-3B: Diffuse astrocytoma. Expanded white matter of right posterior hemisphere and thinned corpus callosum (sagittal sect).
STROCYTOMAS

- most commonly (> 70%) tandem duplication of 7q14 involving BRAF gene → BRAF-KIAA1549 fusion – constitutively activates MAPK.
- IDH-1 negative (vs. diffuse astrocytomas)
- TP53 plays no role.
- pilocytic astrocytoma is hallmark of NF1 (esp. optic glioma) – neurofibromin protein acts in MAPK pathway.
  - 15% of NF1 patients develop pilocytic astrocytoma (esp. optic pathways); 1/3 of patients with optic glioma have NF1

Histology

- biphasic pattern – compacted bipolar cells with Rosenthal fibers + loose textured multipolar cells with microcysts and occasional granular bodies.
- tumor cells are mature-appearing astrocytes; microcystic changes*, fibrillary astrocytes (with long, thin “hairlike” processes) and stellate cells, characteristic Rosenthal's fibers (elongated eosinophilic mass composed of alpha-B-crystallin – modified process of astrocyte; also seen in reactive gliosis): *separates tumor from glial reaction
- piloid (hairlike) cells in 2 patterns: dense fascicles and loose arrangements.
- Ki67 < 1% - very slow growing and maintain grade I over years – can be cured surgically
- location – cerebellum and midline structures (brain stem*, optic pathways, hypothalamus).
  *dorsal exophytic brain stem glioma (vs. diffuse astrocytoma of pons)
- may have regressive features – necrosis (but it is infarct-like and not pulsating), hyalinized vessels, calcifications (diff. from craniopharyngioma)

http://www.pynology.com/
ASTROCYTOMAS

Epidemiology
- Most common glioma in children and adolescents
- 5.4% of all gliomas

Imaging
- Intensely enhancing due to high vascularity.

PILAMOID ASTROCYTOMA
(no WHO grade)
- Angiocentric arrangement of monomorphous bipolar cells in prominent myxoid background.
- CSF seeding more common, more rapid growth.
- Hypothalamic / chiasmatic region.
- Median patient age – 10 months.

PLEOMORPHIC XANTHOTHERCYTOMA (PXA)
(WHO grade II)
- High degree of astrocytic pleomorphism, lipidized giant cells (frequently multinucleated), abundant reticulin deposits, and chronic inflammatory cell infiltrates.
- BRAF V600E mutation (***) (plus, no IDH mutation).
- Median patient age – 22 years.
- Ki-67 < 1%; if ≥ 5 mitoses / 10 HPF, it is called anaplastic PXA (grade III) – significantly worse prognosis.
- Good prognosis (90% 5-year survival).
- Superficial location (esp. temporal lobe), cyst is frequent.
- Imaging - strong enhancement.

Large multinucleated xanthomatous cell (arrow) with foamy cytoplasm:

Salient diagnostic clue - large cell with foamy cytoplasm:

SUBEPENDYMAL GIANT-CELL ASTROCYTOMA (SEGA)
(WHO grade I)
Due to mixed glioneuronal phenotype, sometimes called subependymal giant-cell tumor.

- unique to tuberous sclerosis
- located in wall of lateral ventricle, near foramen of Monro
- histologically identical to subependymal nodules (so-called “candle-gutterings”) that line ventricles in tuberous sclerosis.
- often calcified.
- hyalized vessels and lymphocytic infiltration are consistent.
- treatment – surgery / mTOR inhibitors (everolimus).

**DIFFUSE ASTROCYTIC TUMORS**

- part of Diffuse Gliomas see above >>

**DIFFUSE ASTROCYTOMA (formerly - LOW-GRADE ASTROCYTOMA):**

( WHO grade II )

**Genetics**

- divided into IDH-mutant, IDH-wildtype and NOS categories:
  - great majority falls into the IDH-mutant category (more favorable prognosis than for IDH-wildtype – applies to both grade II and grade III tumors).
  - if immunohistochemistry for mutant R132H IDH1 protein and sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations are both negative, or if sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations alone is negative, then the lesion can be diagnosed as IDH-wildtype.
  - if IDH testing is not available or cannot be fully performed (e.g., negative immunohistochemistry without available sequencing), the resulting diagnosis would be NOS.

**Histology**

- slight hypercellularity (more cellular than normal brain), uniform cells (closely resemble mature resting or reactive, nonanaplastic astrocytes), no nuclear pleomorphism (or very slight), no endothelial proliferation, no mitotic activity (or very rare):
  - Ki-67 proliferation index is usually < 4%.
  - major differential – reactive astrocytosis (H: look for Rl32H-mutant IDH1).

N.B. most of low grade astrocytomas are positive for IDH1 R132H mutant protein!
STROCYTOMAS

Onc10 (12)

Expanded white matter of left cerebral hemisphere and thickened corpus callosum and fornices:


FrONTAL tumor expanded flattened gyri (arrows):


Glioma demonstrates mass effect; note neoplasm variegation (areas of red, tan, white, and brown):

Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)

GEMISTOCYTIC ASTROCYTOMA - the only distinct variant of diffuse astrocytoma in WHO 2016 (protoplasmic and fibrillary variants have been eliminated).

- gemistocytic astrocytoma [Gr. plump] - greatly swollen, brightly eosinophilic normal reactive astrocyte (abundant glial fibrils and expanded cytoplasm) with eccentric nucleus [may have two nuclei]
  - usually appear during acute injury; after that, gradually shrink in size.
  - also found in some chronic diseases and in gemistocytic astrocytomas (gemistocytes are known to dedifferentiate to high grade gliomas at rapid pace, usually indicative of poor prognosis).
  - Presence of > 20% gemistocytes (in otherwise low-grade astrocytoma) suggests course similar to ANAPLASTIC ASTROCYTOMA.
  - “Gemistocytes are bad”
ANAPLASTIC ASTROCYTOMA

( WHO grade III)

Genetics
- divided into IDH-mutant, IDH-wildtype and NOS categories – see above >>

Histology
- moderate hypercellularity, anaplasia, nuclear pleomorphism, increased mitoses, endothelial proliferation:
**Glioblastoma (formerly – Glioblastoma Multiforme)**

(WHO grade IV)

**Genetics**

2016 CNS WHO:
1) glioblastoma, IDH-wildtype (about 90% of cases)
2) glioblastoma, IDH-mutant (about 10% of cases)
3) glioblastoma, NOS

- *Definition of full IDH evaluation can differ for glioblastomas in older patients relative to glioblastomas in younger adults and relative to WHO grade II and grade III diffuse gliomas: in the latter situations, IDH sequencing is highly recommended following negative R132H IDH1 immunohistochemistry, whereas the near absence of non-R132H IDH1 and IDH2 mutations in glioblastomas from patients over about 55 years of age suggests that sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry in such patients.*

<table>
<thead>
<tr>
<th>IDH-wildtype glioblastoma</th>
<th>IDH-mutant glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonym</td>
<td>Primary glioblastoma, IDH-wildtype</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Not identifiable; develops de novo</td>
</tr>
<tr>
<td>Proportion of glioblastomas</td>
<td>~90%</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>~62 years</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>1.42:1</td>
</tr>
<tr>
<td>Mean length of clinical history</td>
<td>4 months</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>Surgery + radiotherapy</td>
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<td></td>
<td>Surgery + chemotherapy</td>
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<tr>
<td>Location</td>
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<tr>
<td>Necrosis</td>
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<tr>
<td>TERT promoter mutations</td>
<td>72%</td>
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<td>TP53 mutations</td>
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<td>ATRX mutations</td>
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<td>EGFR amplification</td>
<td>35%</td>
</tr>
<tr>
<td>PTEN mutations</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Histology**

- marked cellularity, high proliferation indices, anaplasia, foci of tumor necrosis (!!!) accompanied by pseudopalisading (tumor cells crowded along edges of necrotic region)

N.B. necrosis distinguishes glioblastoma multiforme from anaplastic astrocytoma!
• poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells.
• infiltrates brain extensively (may become enormous before turning symptomatic); frequently involve and cross corpus callosum. **Gliomatosis Cerebri** – almost entire brain infiltrated with tumor cells (three lobes or more to both cerebral hemispheres with additional involvement of the deep gray matter structures, brain stem, cerebellum, and spinal cord); gliomatosis cerebri may be present also in grade II-III gliomas.

N.B. gliomatosis cerebri can be seen in any of the diffuse glioma subtypes, but is most common in anaplastic astrocytoma.

Marked cellularity with marked hyperchromatism and pleomorphism; prominent vascularity; necrosis (at left) with neoplastic cells palisading around it (pseudopalisading):

Foci of necrosis with pseudopalisading; endothelial cell proliferation leading to "glomeruloid" structure (arrows):

Necrotic, hemorrhagic, infiltrating mass:
ASTROCYTOMAS

Glioblastoma multiforme: Areas of necrosis (pale grey) and characteristic feature of this neoplasm are usually surrounded by the mantle of small, rounded cells. The term "multiforme" includes pleomorphic, and also includes multinucleated cells. Vascular endothelial proliferation is another characteristic histological feature.


Vascular neoplasm with prominent areas of necrosis and hemorrhage; note crossed midline.

Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" by Edward C. Klatt, MD

Figure 21. Vascular neoplasm with prominent areas of necrosis and hemorrhage; note crossed midline.
EPITHELIOID GLIOBLASTOMA

- variant of IDH-wildtype glioblastoma
- large epithelioid cells with abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli (often resembling melanoma cells), and variably present rhabdoid cells.
- predilection for children and younger adults.
- typically present as superficial cerebral or diencephalic masses.
- often harbor a BRAF V600E mutation.
- often lack other molecular features of conventional adult IDH-wildtype glioblastomas, such as EGFR amplification and chromosome 10 losses; instead, there are frequent hemizygous deletions of ODZ3.

Although the neuroimaging features are not specific, many cases show a superficial localization and sharp demarcation, as seen on this post-contrast T1-weighted MR image (a). Histologically, the Ep-GBM may also show a discrete border with adjacent brain, often suggestive of a metastasis (b). This mimicry is further complicated by the tumor cytology featuring large epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei, and large melanoma-like nucleoli (c). Not uncommonly, a subset of tumor cells display eccentric nuclei and paranuclear inclusions that overlap with rhabdoid neoplasms (arrows). Some Ep-GBMs show features of a lower grade precursor in adjacent tissue; in this particular example, there was focal evidence of pleomorphic xanthoastrocytoma, including bizarre giant cells despite lack of mitotic activity, numerous eosinophilic granular bodies, and xanthomatous appearing vacuolated astrocytes (d). GFAP expression is often limited (e) and may even be lacking entirely. In contrast, S100 protein is strongly expressed (f), whereas other melanoma markers are typically negative (not shown). Other glial markers, such as OLIG2 may also be positive (g), but many lack this protein as well. Roughly half of Ep-GBMs express BRAF V600E mutant protein as seen in this example (h):
**Giant Cell Glioblastoma**
- variant of IDH-wildtype glioblastoma

**Gliosarcoma**
- variant of IDH-wildtype glioblastoma

**Glioblastoma with primitive neuronal component**
(formerly - glioblastoma with PNET-like component)
- well-demarcated nodules containing primitive cells that display neuronal differentiation (e.g., Homer Wright rosettes, gain of synaptophysin positivity and loss of GFAP expression) and that sometimes has MYC or MYCN amplification.
- tendency for craniospinal fluid dissemination – image entire craniospinal axis.
- 25% develop in patients with a previously known lower grade glioma precursor, a subset of which shows R132H IDH1 immunoreactivity in both the glial and primitive neuronal components.

Glioblastomas with primitive neuronal components (GBMPNC; b and e–g show the astrocytic component on the left and the primitive neuronal component on the right). In this GBM-PNC, the imaging was essentially identical to that of conventional GBM, including a rim-enhancing mass; however, the markedly restricted diffusion on this DWI MR image highlights the more cellular primitive component (a). The primitive clone in this GBM-PNC is evident as a highly cellular nodule within an otherwise classic diffuse astrocytoma (b). Well-formed Homer Wright rosettes were seen in the primitive portion of this GBM-PNC (c). Large cell/anaplastic features (similar to those of medulloblastoma) are seen in a subset of GBM-PNC, note the increased cell size, vesicular chromatin, macronucleoli, and cell–cell wrapping (arrows) in this case (d). The primitive component typically displays loss of glial marker expression, including GFAP (not shown) and OLIG2 (e), along with gain of neuronal features, such as synaptophysin positivity (f; note also staining of Homer Wright rosettes).

A subset of cases demonstrates features of secondary glioblastoma, including IDH1 R132H mutant protein expression (g). FISH revealed MYCN gene amplification limited to the primitive foci of this GBM-PNC (h; centromere 2 signals in red and MYCN signals in green):

**Small Cell Glioblastoma/Astrocytoma**
- uniform, deceptively bland small neoplastic cells often resembling oligodendroglioma and frequently demonstrating EGFR amplification.
- particularly poor prognosis even in the absence of microvascular proliferation or necrosis.

**Granular Cell Glioblastoma/Astrocytoma**
- markedly granular to macrophage-like, lysosome-rich tumor cells.
- particularly poor prognosis even in the absence of microvascular proliferation or necrosis.

**Diffuse Midline Glioma, H3 K27M-Mutant**

**Clinical Features**

**Low-grade astrocytoma = 35 years (juvenile pilocytic astrocytoma 6.5-25 yrs).**
**ASTROCYTOMAS**

- **Onc10**

**ANAPLASTIC ASTROCYTOMAS**: 40-50 yrs.

**GlioBLASTOMA MULTIFORME**: 50-70 yrs.

Most common complaints: seizure and headache → gradual onset of focal neurologic deficits.

- Some **LOW GRADE ASTROCYTOMAS** are extremely indolent in their growth (do not progress to malignancy); seizures are principal and initial symptom; duration of symptoms at time of diagnosis averages 3 years.
- Some **LOW GRADE ASTROCYTOMAS** transform to **GlioBLASTOMA** within few years.

**DIAGNOSIS**

**STROCYTOMAS**: Onc10 (19)

- Astrocytoma in patient > 45 yrs most likely represents poor sampling of heterogeneous tumor - should be treated aggressively as high-grade astrocytoma.

- Most investigators doubt that there are any **LOW GRADE ASTROCYTOMAS** after age 45.

**NAPLASTIC ASTROCYTOMA**: ≈ 40-50 yrs.

**GlioBLASTOMA MULTIFORME**: 50-70 yrs.

Most common complaints: seizure and headache → gradual onset of focal neurologic deficits.

- Some **LOW GRADE ASTROCYTOMAS** are extremely indolent in their growth (do not progress to malignancy); seizures are principal and initial symptom; duration of symptoms at time of diagnosis averages 3 years.
- Some **LOW GRADE ASTROCYTOMAS** transform to **GlioBLASTOMA** within few years.

**DIAGNOSIS**

Also see p. Onc1 p. >>

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>MRI with gadolinium</th>
<th>Contrast CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PILOCYTIC ASTROCYTOMA</td>
<td>enhance!, associated cysts particularly prominent on T2</td>
<td>enhance!</td>
</tr>
<tr>
<td>PXIEROPHILIC XANTHOSASTROCYTOMA</td>
<td>may enhance strongly, little or no edema</td>
<td></td>
</tr>
<tr>
<td>LOW GRADE ASTROCYTOMAS</td>
<td>T1 signal, (↑ on T2), do not enhance!, minimal mass effect</td>
<td>do not enhance! - avascular (or vague low density)</td>
</tr>
<tr>
<td>ANAPLASTIC ASTROCYTOMA</td>
<td>solidly bright or patchy (30-50% do not enhance)</td>
<td></td>
</tr>
<tr>
<td>GlioBLASTOMA</td>
<td>T1 signal, (↑ on T2); enhance heterogeneously in irregular ring configuration* (4-10% do not enhance)</td>
<td>inhomogeneous hypodense or isodense</td>
</tr>
</tbody>
</table>

*central lucency represents area of necrosis; in addition may represent hemorrhages

Contrast enhancement is sign of malignancy!

33% astrocytomas show no mass effect.

Advanced MRI techniques (1H-MRS, DW-MRI, PW-MRI) can be useful in establishing prognosis in GBM - marked BBB breakdown (necrosis), large regions with abnormal metabolism, areas with restricted diffusion → poor prognosis

MRI - large glioma impinging upon ventricular system:

- usually can be diagnosed accurately by MRI!
DIFFUSE (LOW-GRADE) ASTROCYTOMA

Best MRI sequence – FLAIR

Typical MRI characteristics: nonenhancing, T1 hypointense, T2 hyperintense, no hemorrhage, no necrosis; FLAIR signal (also look for diffusion restriction).

T1-MRI (signal): tumor does not enhance

T2-MRI (signal): 

T1-MRI: infiltrating tumor invades basal ganglia and causes mass effect with midline shift.

Noncontrast CT (hypodense tumor):
Astrocytomas

Contrast-enhanced MRI - T1 (A) and T2 (B) - faint contrast enhancement; site of stereotactic biopsy is visible (arrow):

A. T1-MRI - nonenhancing, low-density region (arrow); no significant mass effect, but edges of lesion are not well circumscribed, indicating infiltration.
B. T2-MRI - same region appears hypodense.

A. Contrast-enhanced CT fails to demonstrate medial left temporal lobe neoplasm; small mass effect associated with uncus can be appreciated (arrow).
B. T2-MRIs clearly indicate high-signal-intensity neoplasm (arrows).

ANAPLASTIC ASTROCYTOMA

T2-MRI - less well-circumscribed white signal in posterior temporal lobe; non-enhancing with contrast.
Contrast-enhanced T1-MRI and T2-MRI - large right frontal mass resulting in compression of corpus callosum and subfalcine herniation; small amount of surrounding edema.

**GLOBLASTOMA MULTIFORME**

A. T1 gadolinium demonstrates mixed solid and cystic components; irregular circular enhancement is necrosis
B. T2-FLAIR demonstrates surrounding edema

Source of picture: Medscape from WebMD >>

Contrast T1-MRI - heterogeneously enhancing mass (arrows) compresses cerebral peduncle and midbrain (white arrow):

“Butterfly” glioma (because of its shape):

T2-MRI (left) - large, bilateral white signal.
T1-MRI (right) - contrast outlines tumor edge (ring enhancement)

Extremely rapidly recurring glioblastoma (contrast CT) - dramatic tumor size increase from A to B (8 weeks later):
Astrocytomas

Unenhanced CT: white matter low density extends around but spares basal ganglia (important differentiation from stroke).

A. Unenhanced CT - white matter low density extends around but spares basal ganglia (important differentiation from stroke).
B. T1-MRI post-gadolinium - marked, irregular peripheral enhancement and central low signal.

Contrast-enhanced T1-MRI - large necrotic mass.

Contrast-enhanced T1-MRI - large necrotic mass.

T2-MRI - high signal intensity (neoplasm and adjacent edema); heterogeneous areas of lower signal intensity centrally indicate microhemorrhage and calcification.

T1-MRI - typical ring enhancement with central necrosis and marked mass effect:

T1-MRI - typically ring enhancing mass with central necrosis and significant mass effect; tumor is extending up to corpus callosum.

Contrast CT - ring enhancement with pronounced peritumoral edema.

Proton density-weighted MRI - heterogeneous mass (arrows) compressing third and lateral ventricles; area of hypointense signal (double arrows) indicate either hemorrhage or calcification.

T1-MRI: gadolinium - typical ring enhancement with central necrosis and marked mass effect.

T1-MRI: gadolinium - heterogenous mass (arrows) compressing third and lateral ventricles; area of hypointense signal (double arrows) indicate either hemorrhage or calcification.

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B. T1-MRI post-gadolinium - marked, irregular peripheral enhancement and central low signal.

Contrast-enhanced T1-MRI - large necrotic mass.
57 yo F who presented with seizures; pathology – gliosarcoma.

TREATMENT

Cornerstone of therapy is surgery! (patients who undergo gross total resection have longest survivals).

- depending on tumor appearance, gross total resection, subtotal resection, or only biopsy may be possible.
- if resection subtotal & tumor regrows → radiotherapy.

LOW- GRADE ASTROCYTOMAS (GRADE I)

Pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant-cell astrocytoma are curable with gross total resection and do not need further therapy;

- if resection subtotal & tumor regrows → radiotherapy.

LOW- GRADE GLIOMAS (GRADE II)

Oligodendroglioma, diffuse astrocytoma, oligo-astrocytoma are mostly incurable!

Initial management options for presumed LGG:

a) maximum possible early resection → radiotherapy (irrespective of extent of resection)
   — recurrence → tumor resection → chemotherapy.
   — recurrent tumors may have more aggressive behavior (also reflected histologically).

b) surgery not feasible: stereotactic biopsy → radiotherapy.

c) little or no mass effect + well controlled seizures: "wait and see" (serial neuroimaging to establish growth characteristics – may lead to misdiagnosis in up to 50% cases; if starts enhancing → surgery).

Level III Recommendation: surgical resection is recommended over observation to improve overall survival for diffuse low-grade gliomas.
Level II Recommendation: Observation has a non-impact on cognitive performance and quality of life.

Level II Recommendation: Radiotherapy is recommended for newly diagnosed LGG as an equivalent alternative to observation in preserving cognitive function, irrespective of extent of resection.

**MRI concerning for LGG**

**Maximal safe surgical resection**

- GTR
- STR

<table>
<thead>
<tr>
<th>Age &lt; 40 years</th>
<th>Age &gt; 40 years</th>
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<th>Age &gt; 40 years</th>
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</thead>
<tbody>
<tr>
<td>MRI surveillance</td>
<td>Chemotherapy</td>
<td>MRI surveillance</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Radiation and chemotherapy</td>
<td>Radiation and chemotherapy</td>
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</table>

Gross total resection and patient < 40 yo -> 52% recurrence within 5 years of surgery, thus, regular MRI surveillance is good option (no tumor than annually – recurrence is universal).

N.R. grade 2 astrocytoma that is IDH-wild type has a poor prognosis - observation may not be prudent, and, in these cases, immediate radiation + concomitant chemotherapy may be used.

Subtotal resection or patient > 40 yo – radiotherapy + chemotherapy – see below RTOG 9802 trial

- low grade oligodendroglioma that is co-deleted - by nature it is indolent, and can continue observation (resection and adjuvant treatment upon recurrence).

**SURGERY**

**BIOPSY**

Level III Recommendation: Stereotactic biopsy is recommended when definitive surgical resection is limited (lesions that are deep-seated, not resectable, and/or located within eloquent cortex or in patients unable to undergo craniotomy due to medical co-morbidities) to obtain the clinical tissue diagnosis needed for targeted treatment planning for patients with low-grade gliomas.

Level II Recommendation: IDH mutation assessment (IDH R132H antibody and/or IDH1/2 mutation hotspot sequencing), is recommended as highly-specific for low-grade diffuse glioma.

Level III Recommendation: For oligodendroglioma tumors, 1p/19q loss-of-heterozygosity testing is recommended.

There is insufficient evidence to recommend MGMT promoter methylation testing as a routine for low-grade diffuse gliomas.

- Consider advanced imaging techniques (e.g., perfusion, spectroscopy, metabolic studies) to target specific regions of interest to potentially improve diagnostic accuracy (based on class III evidence).

**EXTENT OF RESECTION**

Level II Recommendation: GTR or STR is recommended instead of biopsy alone when safe and feasible so as to decrease the frequency of tumor progression recognizing that the rate of progression after GTR is fairly high.

Level III Recommendation: Greater extent of resection can improve overall survival in LGG patients.

Level III Recommendation: The intraoperative MRI should be considered as a method of increasing the extent of resection of LGGs.

Level III Recommendation: gross total resection is recommended to achieve more favorable seizure control and to maximize the chance of accurate diagnosis.

Level III Recommendation: preoperative (MRI) and DTI should be utilized to improve functional outcome. Intraoperative mapping is recommended for diffuse LGGs in eloquent locations as a way of preserving function.

- Surgical resection is also a first choice for incidental (asymptomatic) LGGs (based on class III evidence).
- Insufficient evidence to make recommendations for surgery at LGG recurrence (level III recommendation).
- Continuous negative effects on survival with increasing amounts of residual disease, even in small remnants < 5 ml, subtotal resections with large remnants are reported to be equally effective as biopsy only.

**Extent of surgical resection**


**Extent of surgical resection**


**Gross total resection**

- OS - 45.9 years
- MFS - 12.5 years
- PFS - 7.0 years

**Sub-total resection**

- OS - 20.9 years
- MFS - 5.6 years
- PFS - 3.5 years

**Statistical significance**

- OS: *p* = 0.017
- MFS: *p* = 0.005
- PFS: *p* = 0.043

**MFS** (malignant-free survival) – survival without malignant progression of the tumor
**RADIOTHERAPY**

- radiation field margin of normal tissue: 
  a) by CT - add margin of 2-2.5 cm margin.
  b) by T2-MRI (abnormality tends to be larger than in CT) - add margin of 1-2 cm.

**Level I Recommendation**
- Radiotherapy is recommended in the management of newly diagnosed LGG to prolong progression free survival, irrespective of extent of resection (+ to prolong overall survival in subtotal resection - Level III Recommendation).

**Level III Recommendation**
- Radiotherapy is recommended in the management of newly diagnosed LGG to improve seizure control in patients with epilepsy and subtotal resection.

**Level I Recommendation**
- Radiotherapy is recommended over whole brain radiotherapy for LGG. Either SRS or brachytherapy are acceptable alternatives to external radiotherapy in selected patients with a reasonable expectation of response coupled with acceptable toxicity.

**Negative prognostic factors for overall survival after XRT (Level I Recommendation):**
1. age > 40 years
2. astrocytic pathology (vs. oligodendrogial histological component and 1p/19q deletion)
3. diameter > 6 cm
4. tumor crossing the midline
5. preoperative neurological deficit (vs. seizures at presentation – positive prognostic factor)
6. lower mini-mental status
7. subtotal resection

**LOW-DOSE VS. HIGH-DOSE RADIOTHERAPY**

**EORTC I: ‘Believers trial’, low-dose (45 Gy) vs. high-dose (59.4 Gy) radiotherapy**


**NCCRTG-RT0G-ECOG: ‘US trial’, low-dose (50.4 Gy) vs. high-dose (64.8 Gy) radiotherapy**


- no improvement in survival with higher-dose radiotherapy!
- combination of histology and age was the most powerful prognostic indicator of 5-year survival: patients ≤ 40 years with oligodendroglioma (82%) vs. patients ≥ 40 years with astrocytoma (32%).

**Level I Recommendation**: Lower dose immediate postoperative radiotherapy is recommended as an equivalent alternative to higher dose radiotherapy (45–50.4 Gy vs. 59.4 Gy) for newly diagnosed LGG with reduced toxicity.

**TABLE 1: VS. DELAYED RADIOTHERAPY**

**EORTC II: ‘Non-believers trial’ - early (< 8 weeks from surgery) vs. delayed radiotherapy (at the time of disease progression)**


- no significant difference in the median survival for the early-DXT group (7.2 years) vs. delayed-DXT group (7.4 years).
- early radiotherapy does not improve overall survival, but it does lengthen progression-free survival.

**Level III Recommendation**: Delaying radiotherapy until recurrence or progression is recommended as an equivalent alternative to immediate postoperative radiotherapy for newly diagnosed LGG but may result in shorter time to progression.

**CHEMOTHERAPY**

**NEWLY DIAGNOSED LGGs**

**Level III Recommendation**: The addition of chemotherapy to radiotherapy is not recommended over whole brain radiotherapy alone for LGG, as it provides no additional survival benefit.
Level III Recommendation: Chemotherapy is recommended as a treatment option to postpone the use of radiotherapy, to slow tumor growth and to improve progression-free survival (PFS), overall survival (OS) and clinical symptoms in newly diagnosed LGG.

Level III Recommendation: Chemotherapy is recommended as an optional component alone or in combination with radiation as the initial adjuvant therapy for all patients who cannot undergo gross total resection (GTR) of a newly diagnosed LGG. Patients with residual tumor >1 cm on postoperative MRI, presenting diameter of >4 cm or older than 40 years should be considered for adjuvant therapy as well.

Agent: insufficient evidence to make a recommendation.
- temozolomide use is controversial.
- temozolomide-treated recurrent tumors exhibited hypermutated phenotypes (likely caused by propensity of temozolomide to mutate and compromise DNA mismatch repair pathways) - suggest that temozolomide may contribute to malignant transformation of LGG.

Timing of starting chemotherapy (after surgical/pathological diagnosis of LGG has been made) - insufficient evidence to make a recommendation.
- 12 weeks mark as the latest timeframe to start adjuvant chemotherapy is suggested.

Tumor markers that can predict the benefit from chemotherapy

Level III Recommendation: The addition of chemotherapy to standard RT is recommended in LGG with IDH mutation. In addition, temozolomide is recommended as a treatment option to slow tumor growth in ip19q co-deletion.

RTOG 9802 - radiotherapy vs. radiotherapy + PCV (procarbazine + nitrosourea [lomustine] + vincristine)
- patients with high-risk low-grade glioma (patients > 40 years or subtotal resection)
- PCV = procarbazine + nitrosourea CCNU (lomustine) + vincristine.
- improvement in progression-free survival in patients treated with both radiation and chemotherapy, with no significant improvement in overall survival at 5 years of follow-up.
- longer follow-up (median of 11.9 years) - significant benefit in overall survival in patients treated with both radiation and chemotherapy compared with radiation alone (overall survival of 7.9 years in radiation alone vs. 13.3 years in radiation + chemotherapy; progression-free survival at 10 years was 21% in radiation alone, vs. 51% in radiation + chemotherapy) - the benefit of radiation and chemotherapy was seen in all histologic subgroups but did not reach significance in patients with astrocytoma.

Radiotherapy vs. radiotherapy + bevacizumab

- no benefit of adjuvant LOMUSTINE.

Level IIb Recommendation

Temozolomide is recommended as it may improve clinical symptoms.
Oligodendrogliomas and tumors with Ip19q co-deletion may derive the most benefit.

Level III Recommendation: PCV is recommended as it may improve clinical symptoms with the strongest evidence being for oligodendrogliomas.

Level III Recommendation: Carboplatin is not recommended - no significant benefit as single agent.

HIGH-GRADE ASTROCYTOMAS

Multidisciplinary team - resection / debulking / local field irradiation (± additional focal radiation boost) + chemotherapy

Reurrence → tumor resection → chemotherapy.

SURGERY

EXTENT OF RESECTION

Maximal* possible resection / debulking
*frailmeasures stereotactic neuronavigation, electrical stimulation mapping, high-field intraoperative MRI, 5-aminolevulinic acid (5-ALA) fluorescence guiding are helpful here.

The effect of extent of GBM resection
- class II evidence
- inclusion: adults with KPS > 70 and GBM in a cerebral hemisphere.
- Extent of resection
  - Median TIP (weeks) 14.1 24 31.9 45.8 53.1
  - Median survival (weeks) 31.8 56.6 62.9 88.5 93

- extent of resection also showed a correlation with post-operative KPS (p < 0.05).

Biopsy vs. resection of high-grade glioma

- class I evidence.
- all patients > 65 yo.
- all patients received XRT.
- survival advantage of > 2 months for craniotomy and surgical resection (p < 0.05).

GTR vs. STR vs. biopsy of GBM

- meta-analysis of 37 studies (41 117 unique patients).

- significantly improved overall survival (OS) after gross total resection (GTR) compared with subtotal resection (STR) at 1 year (RR, 0.62; 95% CI [0.56–0.69]; P < 0.01; number needed to treat [NNT] = 9) and after 2 years (RR, 0.84; 95% CI [0.79–0.90]; P < 0.01; NNT = 17). STR was superior to biopsy only in terms of 1-year OS (RR, 0.85; 95% CI 0.80-0.91; P < 0.01).

- However, no significant difference in OS was observed between STR and biopsy after 2 years (RR, 0.99; 95% CI, 0.97-1.00; P = 0.09).
At 6 months, GTR was better than STR in terms of progression-free survival (PFS), but the differences were not statistically significant (RR, 0.72; 95% CI, 0.48-1.09; P = .12) but became significant at 1 year (RR, 0.66; 95% CI, 0.43-0.99; P < .01; NNT = 26).

Risk for progression was also significantly reduced by STR compared with biopsy alone at 6 months (RR, 0.72; 95% CI, 0.51-1.00; P = .05; NNT = 321); however, these differences were not significant at 1 year (RR, 0.96; 95% CI, 0.79-1.17; P = .69).

**N.B.** there are studies that failed to show any benefit from aggressive surgery! – those studies either used nonvolumetric analysis or neurosurgeon’s description in operative report

**Factors that have significant effect on time to tumor progression (TTP):**
1. Preoperative Karnofsky Performance Status (KPS)
2. Chemotherapy
3. Percent of resection (POR)
4. Volume of residual disease (VRD)

- TTP ranged 4-170 weeks (53 weeks if total resection with no residual disease).
- POR and VRD effects much less significant in cases of re-resections (effect insignificant for third and fourth operations).

**Factors that significantly affect survival:**
1. Age
2. Preoperative KPS (Karnofsky Performance Status)
3. Postoperative KPS (Karnofsky Performance Status)
4. Percent of resection (POR)
5. Volume of residual disease (VRD)

- it has been speculated that extensive tumor resection may increase neurological morbidity. N.B. this study shows that greater resections did not compromise quality of life, and patients without any residual disease had a better postoperative KPS.
- survival ranged 6-188 weeks (total resection without any residual disease - median survival of 93 weeks)
**LITT**

- direct cytoreductive technique that is minimally invasive, effective, and less morbid than open craniotomy and, thus, can be repeated. see p. Op 345 >>

**Rationale**
- many patients with recurrence reach a point where repeat craniotomies are no longer feasible (advancing age, comorbidity, chronic steroids, thinned scalp, and inevitable decline in functional status).
- some new patients are not good candidates for traditional surgery at the time of initial diagnosis (typically undergo biopsy followed by chemotherapy without any "direct" cytoreductive treatment).
- if a tissue diagnosis had not yet been obtained, stereotactic needle biopsy is performed through the same trajectory prior to placement of the laser probe.

**OUTCOMES**

**LITT vs. biopsy-only for new GBM**

- retrospective study of 54 patients with 58 LITT (Monteris) treatments for GBM (41 were recurrent tumors while 17 were frontline treatments; 40 GBMs were lobar in location, while 18 were in deep structures; 3 patients underwent repeat ablation for recurrence and 1 was the second stage of a planned two-stage procedure).
- median overall survival after LITT for the total cohort - 11.5 mo (for frontline GBM treatment, median OS was 9.4 mos*, in recurrent GBM treatment – 11.8 mos**); median progression free survival - 6.6 mo.

*Stupp et al. data on chemoradiation alone (no surgery) gives median OS 9.4 mos, however, groups are different (in our study frontline patients has poor prognostic factors) **adds 2 extra months (compared to historical data using only Avastin ± Temodar)”
When should begin is controversial - early radiotherapy may maximize efficacy but may cause brain damage earlier, studies show the best time to begin is in early as surgical incisions healed, i.e. 3-4 weeks postop.

Window of 30-35 days after surgery - chemoradiation with temozolomide seems to have greatest efficacy:
- tumor resection cavity may shrink, resulting in reduction of tissue susceptible to radiation injury.
- local hypoxia in surgical bed might decrease efficacy or radiation (if treatment is too early, hypoxia might blunt cytotoxic effect of radiation; if treatment is beyond window, tumor repopulation occurs which would have negative impact on radiation).
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- local hypoxia in surgical bed might decrease efficacy or radiation (if treatment is too early, hypoxia might blunt cytotoxic effect of radiation; if treatment is beyond window, tumor repopulation occurs which would have negative impact on radiation).

Stupp protocol:
- first 4 weeks of adjuvant chemoradiation for GBM.
- 54-60 Gy in single daily fractions of 1.8-2.0 Gy, 5 times per week.
- 2-3 cm margin on T2-MRI (T2 + 2 cm region) (e.g. 46 Gy to larger field with 2-3 cm margin encompassing contrast-enhancing tumor + additional 20 Gy boost to reduced field encompassing only contrast-enhancing tumor).
- 80% malignant gliomas recur within 2 cm of their original margins.

RTOG guidelines for treatment fields

CHEMOTHERAPY

GBM is considered chemoresistant tumor - molecular subgroups is significant barrier to improving therapy:
- only ≤ 10% malignant astrocytomas have meaningful and durable responses to chemotherapy.
- most active chemotherapeutic regimens: see p. Onc10 >>
- oral Temozolomide - standard of care for newly diagnosed GBM.
- during and for 6 months following radiotherapy.
- majority of GBMs demonstrate primary (inherent) resistance.
- subpopulation of GBM patients with methylated (i.e. inactivated) MGMT gene promoter are more likely to respond; see Stupp protocol.>>
- intravenous BCNU/Carmustine (i.e. inactivated)
- Lomustine + Procarbazine + Vincristine (LCV).

N.B. delay in initiation of chemoradiation to > 28 days after surgery is associated with increased survival!!

STUPP PROTOCOL

Stupp protocol - standard of care (see Rx11 >>)
- 6 weeks of combination treatment.
- Radiotherapy 60 Gy in 30 fractions are delivered for a total of 6 weeks, to target volume defined as 2-3 cm margin of tissue surrounding perimeter of contrast-enhancing lesion.
- Temozolomide (75 mg / m² of body-surface area / day, 7 days per week from first to last day of radiotherapy, i.e. for 42 days in N.B. common mistake – give 75 mg 5 days/week.
- 6 months of 6 cycles of adjuvant Temozolomide (150–200 mg / m² of body-surface area / day for 5 days each during each 28-day cycle

- some oncologists prefer longer chemotherapy – 12 cycles (12 months).
- if patient* wishes shorter course, 40 Gy in 5 x 15 Gy or 30 Gy in 10 x is also reasonable.

*for older patients shorter courses of radiotherapy are more common; adding temozolomide to it is beneficial, esp. in oldest patients with MGMT methylation >>

Published: 28 October 2017

Large Hospital Database.


Seunggu Han, MD, a neurosurgery resident at UCSF, at CNS 2014 Annual Meeting
Final results of a five-year phase 3 trial - extends overall survival of patients with newly diagnosed GBM by nearly 5 months – effect as of temozolomide!

2-year survival increased from 30 to 43% for patients treated with the device in combination with chemotherapy; 5-year survival rate increased from 5 to 13%.

Trail weakness: median number of TMZ cycles was six for the experimental TTF/TMZ arm and five for the TMZ-alone control arm. Dr Stupp countered that the higher median number of adjuvant TMZ cycles in the TTF/TMZ group was easily explained. "They progressed earlier. You treat until progression," he said. "Duration of the chemo doesn't matter," he further said, and referenced the RTOG-0525 trial, in which intensified-dose TMZ was no better than standard-dose TMZ in the treatment of glioblastoma. "More temozolomide is not that helpful," he argued.

- produces alternating electrical fields called tumor treatment fields ("TTFields") within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp.
- frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM).
- TTFields have not been shown to have an effect on cells that are not undergoing division.
- patient should use Optune for at least 18 hours a day to get the best response to treatment.
- generator and battery pack (2.7 lb, with 3 to 4 hours per charge) that are carried in a shoulder bag with a cord that extends to a cap with electrodes that connect with the skull. The treatment, once begun, is permanent, although some patients disconnect the device during sleep.
- not covered currently by Medicare, which may hurt its uptake. Some private insurers cover TTF, which costs more than $20,000.

Indications

- Optune® with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.
- For the treatment of recurrent GBM, Optune® is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region after receiving chemotherapy.
- The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Pivotal Clinical Study in Recurrent GBM
TREATMENT OF RECURRENCES

GBM recurrence (after surgery + chemotherapy + radiation) → surgery + chemotherapy (repeat radiation has no clear role).

Management patterns in Switzerland:

- BEV, bevacizumab
- BSC, best supportive care
- rGBM, recurrent glioblastoma multiforme
- TMZ, temozolomide

SURGERY

Indications for reoperation:
1) new focal neurological deficits
2) seizure frequency↑
3) radiographic evidence of tumor progression, tumor mass effect, signs of elevated intracranial pressure, headaches

Important predictors of benefit from reoperation:
1) time interval of at least 6 months between operations
2) Karnofsky Performance Status score ≥ 70
3) ↑ extent of resection (even in patients with subtotal resection at initial operation)

Contraindications:
1) poor performance status
2) bevacizumab within 4 weeks of surgery.

- additional reoperations (beyond first reoperation) may add to overall survival and should be considered in patients with favorable KPS score at the time of recurrence, regardless of symptomatology

– repeat resection confers a small but significant benefit in survival since recurrence (10.8 months vs 6.9 months) and quality of life over non-operative treatment
– best prognosis is associated with: younger age, KPS ≥ 80, late recurrence (> 9 months), MGMT promoter methylation, and extent of resection (EOR) > 80 %
– surgery is followed by chemotherapy (either temozolomide or bevacizumab); currently, adjuvant radiotherapy has no clear role is patient was irradiated after the first operation.

LITT
- Dr. Danish – prefers LITT first and then SRS for LITT failure (vs. metastases - do not use LITT upfront, always do SRS first).
**RADIOThERApy**

- radiotherapy (e.g. SRS) maybe used as an option if patient is not a candidate for reoperation.
- adjuvant radiotherapy has no clear role in patient was irradiated after the first operation.

**SURGICAL RESECTION**

- Recurrent disease is seen in nearly all patients with GBM.
- Bevacizumab (anti-VEGF monoclonal antibody — see p. Onc3 >>) - FDA approved for recurrent GBM.

- anti-VEGF therapy is de facto standard of care for recurrent GBM.

  N.B. addition of bevacizumab to TMZ does not increase overall survival in patients with newly diagnosed glioblastoma (GBM); current research suggests that anti-VEGF therapy may even promote more aggressive phenotype.

- frequently combined with **BEVACIZUMAB**.

- Population-based analysis of 5607 adult patients with glioblastoma in the SEER (Surveillance Epidemiology and End Results) database found that bevacizumab therapy may improve survival. In study, GBM patients who died in 2010 (after FDA approved bevacizumab for this condition) survived significantly longer than those who died of disease in 2008. Median survival was 8 months for patients who died in 2006, 7 months in 2008, and 9 months in 2010. This difference in survival was highly significant between 2008 (pre-bevacizumab) and 2010 (post-bevacizumab). This survival difference was unlikely due to improvements in supportive care during this time interval, because there was no significant difference between those who died in 2006 and patients who died 2 years later, in 2008.

- AVASTIN and [**VEGF**] **0853 trial** - although both studies found a benefit in progression-free survival following treatment with bevacizumab, there was no overall survival benefit.

- Patients with progressive glioblastoma do not benefit (no survival benefit) from bevacizumab addition to LOMUSTINE.

**LOCOREGIONAL IMMUNOTHERAPY**

- see p. Onc3 >>

**FOLLOW-UP (AFTER SURGERY)**

**GENERAL PRINCIPLES**

- First year post-surgery: 2–4 scans.
- Second year post-surgery: 1–2 scans.

- Annually thereafter for the duration of follow-up.

**LOW-GRADE ASTROCYTOMAS**

- Serial MRRs: at 3 mos postop -> q6 mos x 2 — annually.
- Second year post-surgery: 1–2 scans.

**MD Anderson protocol**

- During chemotherapy - MRRs q2 months.
- After completion of chemotherapy - MRRs q2 months for 1 yr → q3 months for 1 year → q4 months for 1 year → q6 months indefinitely.

- N.B. look for pseudoprogression vs. true progression (pMRI, TRAM, MRS, and other protocols)

**HIGH-GRADE ASTROCYTOMAS**

**SPECIAL FORMS**

- **Pilocytic astrocytoma:** post-tumor fissa cranietomia; cyst is located with ultrasound, then excised through osteotomy of temporal bone, either with decompression of the temporal bone or with opening the dura mater. The cyst is then removed; the surrounding brain tissue is healthy.

- **SUTURE**
  a) cystic astrocytoma: posterior fossa craniectomy; cyst is located with ultrasound, then excised through osteotomy of temporal bone, either with decompression of the temporal bone or with opening the dura mater. The cyst is then removed; the surrounding brain tissue is healthy.
  b) solid astrocytomas: separated carefully from surrounding cerebellar white matter tissue; with opening the dura mater, cyst is examined; vascular, firm mural nodule is removed; nonneoplastic cyst wall is not excised.
  c) infiltrating astrocytomas: infiltrating astrocytomas do not require radiation therapy; for others → 50-60 Gy.

- **High-grade astrocytomas** are uncommon in cerebellum.!!!

- Clinically: cerebellar dysfunction → obstructive hydrocephalus.

- MRI of cystic tumor: mural nodule enhances in T2 images; cystic wall may or may not enhance; displacement of 4th ventricle, hydrocephalic changes.

- Surgery:
  a) cystic astrocytoma → posterior fossa cranietomia; cyst is located with ultrasound, then excised through osteotomy of temporal bone, either with decompression of the temporal bone or with opening the dura mater. The cyst is then removed; the surrounding brain tissue is healthy.
  b) solid astrocytomas: separated carefully from surrounding cerebellar white matter tissue; with opening the dura mater, cyst is examined; vascular, firm mural nodule is removed; nonneoplastic cyst wall is not excised.

- **HIGH GRADE ASTROCYTOMAS**

- Cystic astrocytoma of cerebellum in child.
Microcystic area is seen on one side; surrounding astrocytes have round and ovoid small nuclei; other part of tumor shows denser architecture with more prominent pilocytic elements.

MRI - low-signal cyst outline denser tumor; cerebellar tonsil has herniated below foramen magnum.

**Gliomatosis Cerebri**
- Diffuse white matter spread of glioma (by degrading extracellular matrix with secreting proteases) - involving ≥ 3 cerebral lobes; frequent bilateral growth and regular extension to infratentorial structures.
  - it is no longer a separate entity in WHO 2016, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendrogial tumors as well as IDH-wild-type glioblastomas.
  - clinical syndrome - dominated by dementia, personality change, or seizures.
  - course may be slowly progressive or rapidly downhill.
  - MRI - increased FLAIR/T2 signal in diffuse areas of white matter and cortex; tumor is infiltrative (no enhancing mass!); contrast enhancement is later phenomenon.
  - biopsy - tumor from low grade to glioblastoma.
  - treatment - whole-brain radiotherapy (50 Gy) + chemotherapy (TMZ).
  - very poor prognosis.

T2-MRI - widespread areas of increased signal in both cerebral hemispheres.

FLAIR MRI - tumor infiltration involving both temporal lobes (Short arrows), and substantia nigra (Long arrows).
FLAIR MRI - tumor-related infiltration involving lenticular nuclei (Arrow):

Type I – classic
Differentials:
1. Paraneoplastic syndrome
2. Herpes encephalitis
3. Status epilepticus
4. Neurosarcoidosis

Diffuse cerebral neurosarcoidosis mimicking gliomatosis cerebri:

**Brainstem Gliomas**
- Highly aggressive brain tumors (but prognosis is highly variable):
  1. Focal (most commonly **low-grade astrocytomas**; best prognosis (median survival > 50 months))
2. **Diffuse intrinsic pontine** – most common (80% of all brain stem tumors); worst prognosis (median survival < 12 months) – most commonly **ANAPLASTIC ASTROCYTOMAS** producing diffuse infiltration in pons → extending throughout brainstem → spinal cord and cerebellum; exophytic growth is seen in 2/3 cases.

3. **Focal cervicomedullary** – most commonly **LOW-GR ADE ASTROCYTOMAS**; arise in upper cervical spinal cord and grow rostrally; axial growth is limited by decussations at junction of cervical cord and medulla → tumor grows posteriorly, causing bulge of medulla.

- **special subtype** - *dorsal exophytic tumors* - arise from floor of 4th ventricle and fill it; large, well circumscribed, and uniformly enhancing.

**Epidemiology:** 2.4% of all intracranial tumors in adults; 9.4% - in children (20-25% of primary brain tumors in children).

- ¾ patients are < 20 years (some are < 1 yr).
- Predominantly tumors of childhood!

**Pathology:**

More likely to be low grade (more indolent course) in adults than in children, vs. hemispheric gliomas - children typically fare better than older patients.

**Clinically:**
1) cranial nerve lesions (esp. CN6 and CN7)
2) long tract signs
3) ataxia, nystagmus
4) failure to thrive
5) hydrocephalus (most common in tectal tumors)
6) signs of ICP↑ - rare as presenting feature (vs. other CNS tumors)

**Diagnosis:**

- **MRI** - expansile, infiltrative process (enlarged brainstem).
- **tissue confirmation** is frequently not feasible (unless exophytic component exists - even then, biopsy cannot always be obtained);
- biopsy is not required for **diffuse intrinsic pontine gliomas** (diagnosis can be made by MRI alone; histologic findings do not influence treatment).

**T1-MRI** - cystic astrocytoma involving pons; note small mural nodule.

**Pontine glioma (T2 - and T1 - postgadolinium MRI); no abnormal contrast enhancement:**
A. T1-MRI without contrast - marked expansion of pons, basilar artery has been enveloped by neoplasm; small amount of hemorrhage (arrow); compressed 4th ventricle.

B. T2-MRI confirms marked expansion of brainstem.

Low-grade astrocytomas of medulla (T1-MRI) - marked enlarged medulla (arrow); exophytic component was biopsied.

Treatment - focal radiotherapy under DEXAMETHASONE coverage:
- a) standard treatment - conventional radiotherapy 54 Gy.
- b) investigational treatment - hyperfractionated radiotherapy 72 Gy.
- surgery is most appropriate for benign focal, dorsal exophytic, cystic tumors; most suitable locations - cervicomedullary and rectal; in these cases, radiotherapy is reserved for:
  - a) unexpectedly high-grade lesions
  - b) early progressive disease
  - c) inoperable recurrence

N.B. surgery has no role in diffuse intrinsic pontine tumors!
- chemotheraphy efficacy has not been proved - cannot be recommended! (may benefit in some recurrences).
- some adults with rectal or cervicomedullary tumor, or with mild symptoms of long duration, may be candidates for observation alone.

1. Benign optic glioma (PILOCYTIC ASTROCYTOMA) – most often in children (median age 5 yrs).
- 10-38% pediatric patients have neurofibromatosis type 1 (15-20% children with NF-1 have optic nerve glioma) or, in some cases, hybrid phakomatosis.
- development occurs in stages: from generalized hyperplasia of glial cells* to complete disorganization with loss of neural landmarks (reactive meningeal hyperplasia may be incited - difficult to distinguish from perioptic meningioma).
- it is unclear which glial cells give rise to benign optic glioma
- grows relatively slowly, if at all, over extended periods.
- malignant degeneration is rare (but 20% demonstrate more aggressive course - extend to optic chiasm, optic radiations).

2. Aggressive optic glioma (ANAPLASTIC ASTROCYTOMA OR GLOBLASTOMA MULTIFORME) – rare; most common in adults (mean age 52 years [22-79]).
- almost uniformly fatal, even with aggressive treatment!

Location - various portions of retrobulbar visual pathway (up to optic radiations).

*Optic nerve glioma formed by elongated, swirling piloid processes of astrocytes, nuclei of which are inconspicuous; note plump Rosenthal fiber (upper center, arrow):
• in 66% NF-1 patients, glioma involves intraorbital optic nerve (80-90% such cases extend to intracranial compartment).
• in absence of NF-1, optic chiasm is most commonly involved.

Clinically:
1) painless proptosis (with intraorbital tumors, also with 20% of intracranial tumors).
2) slow and progressive visual acuity ↓, optic atrophy (in adults – bilateral – because most lesions involve optic chiasm).
   - intraorbital tumors - central vision loss.
   - chiasmatic tumors - bitemporal hemianopic loss.
   - use visual evoked responses for young children (in whom clinical evaluation is difficult).
3) strabismus and nystagmus in involved eye.
4) large lesion may compress hypothalamus (e.g. diencephalic syndrome - hyperalert and euphoric but anorectic and emaciated child), 3rd ventricle (hydrocephalus).

Diagnosis:
Funduscopy: normal optic disks ÷ venous engorgement ÷ disk atrophy.
CT - can detect subtle erosion or expansion of optic canal.
• marked, diffuse isodense enlargement (tubular, fusiform, or excrescent) of optic nerve, with characteristic kinking or bending.
• areas of lucency (mucinous or cystic changes).
• contrast enhancement – all optic nerve tumors, but only 50% chiasmal tumors and their projections along visual pathways
• fine calcification means MENINGIOMA rather than glioma.
MRI (preferred) - high degree of confidence when lesion involves optic chiasm and retrochiasmatic optic pathways (in intraorbital disease, some differential entities exist).
• T1 - isointense to cortex and hypointense to white matter; hypointense to orbital fat.
• T2 - mixed appearance (isointense ÷ hyperintense) relative to white matter and cortex.
• intense enhancement is common.

Biopsy - only way to confirm diagnosis (but may further compromise vision in 75% patients!!); biopsy rarely influences treatment; reserved for unusual clinical or radiographic circumstances.

T1 MRI – large intraorbital mass (arrow) centered on optic nerve.

The same patient with postgadolinium T1 MRI with fat saturation:

Postgadolinium T1 MRI with fat saturation - enhancement of intracranial optic nerve (arrow), which is slightly expanded:

Noncontrast T1 MRI - bilateral optic nerve gliomas - fusiform enlargement of optic nerves (arrows) in NF-1:

Noncontrast T1 MRI - enlargement of both optic tracts (arrowheads) and optic chiasm (arrow):

T2 MRI - mass in thalamic lateral geniculate nucleus resulting from extension of optic nerve glioma.
Marked expansion of right optic nerve (NF-1): 

Lateral skull radiograph - J-shaped sella secondary to optic chiasm glioma:

Differential diagnosis – meningioma (‘tram-track’ sign - enhancement of nerve-optic sheath periphery).

Treatment

- optic nerve gliomas
  a) no severe progressive symptoms → observation
  b) proptosis, progressing visual decline → radiotherapy
  c) if eye is already blind (unilateral tumor of optic nerve) → resection (prevents recurrence or extension through chiasm).
  - transcranial approach.
  - complete resection of tumor-infiltrated nerve from chiasm to globe (spare globe for cosmetic effect).
  N.B. resection of chiasm with resultant blindness is never indicated!

- chiasmatic/hypothalamic gliomas → radiotherapy (45-55 Gy in daily 1.8-Gy fractions).

- chemotherapy is alternative to radiotherapy in progressive disease (e.g. may delay initiation of radiation therapy in young children):
  a) CARBOPLATIN
  b) CARBOPLATIN + alkylating agent (CYCLOPHOSPHAMIDE, nitrosourea) + VINCRISTINE

Prognosis

In general, optic nerve gliomas have better prognosis than those involving chiasm.

- in NF patients, prognosis is similar (or better) to non-NF patients (but NF patients have greater risk of developing other tumors).

BIBLIOGRAPHY for ch. “Neuro-Oncology” – follow this LINK >>