Astrocytomas

Last updated: January 16, 2021

**ETIOLOGY**

1

**CLASSIFICATION, GRADING**

1

**GENETICS**

1

1. WHO 2016

2

MGMT methylation

4

Isocitrate dehydrogenase (IDH)-1/2 mutation

5

EGFR gene amplification

5

CdkN2A suppression

5

ATRX (alpha-thalassemia/mental retardation syndrome x-linked) gene

5

p53 gene mutations

5

BRAF V600E mutation

6

**PATHOLOGY**

6

**LOCATION**

7

**DIAGNOSTIC ENTITIES**

8

1. Pilocytic astrocytoma

8

2. Pilocytic astrocytoma

8

3. Pleomorphic xanthoastrocytoma (PXA)

10

4. Subependymal giant-cell astrocytoma (SEGA)

10

5. Diffuse Astrocytic Tumors

11

6. Diffuse astrocytoma (formerly - Low-grade astrocytoma)

11

7. Gemistocytic astrocytoma

12

8. Anaplastic astrocytoma

13

9. Glioblastoma (formerly - Glioblastoma multiforme)

14

10. Epithelioid glioblastoma

17

11. Giant cell glioblastoma

18

12. Gliosarcoma

18

13. Glioma with primitive neuronal component

18

14. Small cell glioblastoma/astrocytoma

18

15. Granular cell glioblastoma/astrocytoma

18

16. Diffuse midline glioma, H3 K27M-mutant

18

**CLINICAL FEATURES**

18

**DIAGNOSIS**

19

1. Pilocytic astrocytoma

19

2. Diffuse (Low-grade) astrocytoma

20

3. Anaplastic astrocytoma

21

4. Glioblastoma multiforme

22

5. Gliosarcoma

24

**TREATMENT**

24

1. Low-grade astrocytomas (GRADE I)

1. Low-grade gliomas (GRADE II)

24

2. Surgery

25

3. Biopsy

25

4. Extent of resection

25

5. Radiotherapy

26

6. Low-dose vs. high-dose radiotherapy

26

7. Early vs. delayed radiotherapy

26

8. Recurrent LGGs

26

9. Chemotherapy

27

10. Newly diagnosed LGGs

27

11. Recurrent LGGs

27

12. High-grade astrocytomas

27

13. Surgery

27

14. Extent of resection

27

15. Risk factors

28

16. LITT

29

17. Outcomes

29

18. Radiotherapy

30

19. Chemotherapy

30

20. Stupp protocol

31

21. Optuna® (Novocure)

31

22. Treatment of Recurrences

32

23. Surgery

33

24. LITT

33

25. Radiotherapy

33

26. Chemotherapy

33

27. Locoregional immunotherapy

34

28. FOLLOW-UP (AFTER SURGERY)

34

29. Low-grade astrocytomas

34

30. High-grade astrocytomas

34

31. Special Forms

34

32. Cerebellar Astrocytomas

34

33. Gliomas (Cerebri)

35

34. Brainstem Gliomas

37

35. Optic Pathway Glioma

39

**PROGNOSIS**

39

Most common (60%) primary CNS tumors in adults (second most common in children)!

- astrocytomas are one type of GLIOMAS (neoplastic transformation of neuraxis).

**ETIOLOGY**

- familial cases constitute only 1%

- associated with certain genetic syndromes:
  - neurofibromatosis type I ➔ LOW-GRADE ASTROCYTOMAS (esp. in optic nerve & chiasm)
  - tuberous sclerosis ➔ SUBPENETRAL GIANT-CELL Astrocytoma (SEGA)
  - Turcot’s syndrome ➔ GLIOMAS, MIDDLE-LOBE GLIOMAS
  - 90% GBMs are primary (i.e. arise de novo); 10% - secondary (i.e. arise from low grade astrocytomas).

**CLASSIFICATION, GRADING**

WHO 2016

1. in WHO 2016 classification, the DIFFUSE GLIOMA category includes astrocytic and oligodendroglial 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).
WHO 2007 designation | WHO grade | Kernohan criteria | St. Anne/Mayo criteria**
---|---|---|---
**PILOCYTIC ASTROCYTOMA*** | I | ended | **WHO and Kernohan systems are not criteria based (1).**
**ANAPLASTIC ASTROCYTOMA** | III | 2 criteria fulfilled | **4 histologic criteria:**
---|---|---|---
1) nuclear atypia | | 1 criterion (usually nuclear atypia) |
2) mitoses – already grade III | | |
3) endothelial proliferation – already grade IV (tufts of piled-up vascular cells that bud into vascular lumen, if proliferation is extreme, tuft forms ball-like structure - glomeruloid body) | | |
4) necrosis (already grade IV) | | |
**GLIOBLASTOMA MULTIFORME** | IV | IV | 4 criteria - endothelial proliferation and/or necrosis |

WHO 2016 diffuse gliomas

Historical Bailey and Cushing classification - based on embryologic development of astrocytic spongioblast (PREGNANTGLIA) → astroblast (ASTROBLASTOMAS) → astrocyte (ASTROCYTOMA).

**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 and 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

II. Tumor suppressor genes: CDKN2A (also known as p16INK4a), PTEN, RB1, TP53.

- Frequent loss of heterozygosity (LOH) on chromosome arms 1p, 10p, 10q, and 19q suggests additional tumor suppressor genes.

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. IDH1/2 mutations

Most frequently altered GBM cancer genes:

- LOH at 10q (69%)
- CDKN2A (p16INK4a) deletion (50%)
- EGF-R gene amplification
- TP53 mutations
- PTEN mutations
- IDH1/2 mutations


> 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! EGFR 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:  
- see p. Onc3 >>

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**
O6)-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**

**ONCOLOGY**

**STROCYTOMAS**

Onc10 (5)

**Level I**

Recommendation: 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.

**Level II**

Recommendation: Grade II gliomas with IDH mutations have a shortened time to recurrence.

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

- mean ≥ 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)

**Level I**

Recommendation: Grade II gliomas with IDH mutations have a shortened time to recurrence.

**EGFR GENE AMPLIFICATION**

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

**CDKN2A** suppression

**Level III**

Recommendation: 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).
  - L-Fraszeni syndrome (inherited p53 mutations) – strong predisposition to astrocytomas
  - p53 mutation goes “hand to hand” with IDH mutation.

- globlastomas 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).

- Li-Fraumeni syndrome (inherited p53 mutation) – 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 mutations
  - BRAF is a serine/threonine kinase protein and is a downstream effector of the Ras-Raf-MEK extracellular signal-regulated kinase (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. ependymal glioblastoma (50%)
    4. astroblastoma (35%)
    5. ganglioglioma, dysplastic ependymal neuroepithelial tumor (DENTG)
    6. diffuse leptomeningeal glieneural 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 melanoblastoma.
  - 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-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.

**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:

- Gioma cells always reside outside of contrast enhancing margin and cannot be visualized
- Almost all recurrences local w/in 2 cm of resection cavity
- Need to better visualize tumor cells for maximal resection

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 astrocytoma).
- 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.

Plexiform xanthoastrocytoma – most common superficially in temporal lobe in teens and young adults.

Subependymal giant cell astrocytoma (almost exclusive in tuberous sclerosis) – most common in lateral wall at 3rd ventricle.

Astrocytomas – tend to occur in cerebral lobes (esp. frontal).

Malignant 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.
PILOCYTIC ASTROCYTOMA

(WHO grade I)

Genetics
- essentially all have various mutations affecting MAPK pathway:
  - most commonly (> 70%) tandem duplication of 7q34 involving BRAF gene → BRAF-KIAA1549 fusion – constitutively activates MAPK.
  - IDH-1 negative (vs. diffuse astrocytomas)
  - 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
- relatively well-circumscribed tumors but tumor cells typically permeate brain parenchyma up to several centimeters!!!
- frequently associated with cysts (with mural nodule of solid tumor).
- location – cerebellum and midline structures (brain stem*, optic pathways, hypothalamus).
- dorsal exophytic brain stem glioma (vs. diffuse astrocytoma of pons)
- may infiltrate leptomeninges; very occasionally seeds neuraxis but that does not mean further aggressive growth.
- may have regressive features - necrosis (but it is infarct-like and not pulsating), hyalinized vessels, calcifications (diff. from craniopharyngioma)
Astrocytomas

In the well-differentiated centrilobular astrocytoma, most of the cells bear numerous small, dark nuclei. The cells' cytoplasm is less distinct, and the arrangement is more rounded than in astrocytic processes in normal grey matter.

ASTROCYTOMAS

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

Imaging
- Intensely enhancing due to high vascularity.

PLEOMORPHIC XANTHOASTROCYTOMA (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.

Subependymal giant-cell astrocytoma (SEGA)
(WHO grade I)
- Salient diagnostic clue - large cell with foamy cytoplasm.
ASTROCYTOMAS

Due to mixed glioneuronal phenotype, sometimes called SUBEPENDYMAL GIANT-CELL TUMOR

- several types of cells, typically including small elongated cells as well as giant, multinucleated globoid cells (resemble gemistocytes).
  - unique to tuberous sclerosis!! (present in 5-15% TS patients) see p. Pha5 >>
  - located in wall of lateral ventricle, near foramen of Monro
  - histologically identical to subependymal nodules (so-called “candle-gutters”) that line ventricles in tuberous sclerosis.
  - often calcified.
  - hyalized vessels and lymphocytic infiltration are consistent.
  - Ki-67 3%
  - imaging – marked contrast enhancement.
  - 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, then the lesion can be diagnosed as IDH-wildtype.
  - N.B. diffuse astrocytoma, IDH-wildtype is an uncommon diagnosis – such cases need to be carefully evaluated to avoid misdiagnosis of lower grade lesions such as gangliogliomas; moreover, anaplastic astrocytoma, IDH-wildtype is also rare, and most such tumors will feature genetic findings highly characteristic of IDH-wildtype glioblastoma.
  - 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 R132H-mutant IDH1).
  - N.B. most of low grade astrocytomas are positive for IDH1 R132H mutant protein!

Normal astrocytes show no H&E-stainable cytoplasm that is distinct from the background neuropil. Reactive astrocytes are defined by enlarged nuclei and the presence of stainable, defined cytoplasm, culminating in the gemistocyte, which has a mass of eosinophilic cytoplasm, often an eccentric nucleus, and cytoplasm that extends into fine processes.

Glioma (at left) shows greater cellularity and pleomorphism than adjacent brain (at right), but margin is not distinct:
ASTROCYTOMAS

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 glioma 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:

![Histology images of anaplastic astrocytoma](image-url)
ASROCYTOMAS

Glioblastoma (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.

**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!

---

<table>
<thead>
<tr>
<th>IDH-wildtype glioblastoma</th>
<th>IDH-mutant glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonym</strong></td>
<td>Primary glioblastoma, IDH-wildtype</td>
</tr>
<tr>
<td><strong>Precursor lesion</strong></td>
<td>Not identifiable; develops de novo</td>
</tr>
<tr>
<td><strong>Proportion of glioblastomas</strong></td>
<td>~90%</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>~62 years</td>
</tr>
<tr>
<td><strong>Male-to-female ratio</strong></td>
<td>1.42:1</td>
</tr>
<tr>
<td><strong>Mean length of clinical history</strong></td>
<td>4 months</td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>Surgery + radiotherapy: 9.6 months</td>
</tr>
<tr>
<td></td>
<td>Surgery + radiotherapy + chemotherapy: 15 months</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Supratentorial</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>Extensive</td>
</tr>
<tr>
<td><strong>TERT promoter mutations</strong></td>
<td>72%</td>
</tr>
<tr>
<td><strong>TP53 mutations</strong></td>
<td>27%</td>
</tr>
<tr>
<td><strong>ATRX mutations</strong></td>
<td>Exceptional</td>
</tr>
<tr>
<td><strong>EGFR amplification</strong></td>
<td>35%</td>
</tr>
<tr>
<td><strong>PTEN mutations</strong></td>
<td>24%</td>
</tr>
</tbody>
</table>
• 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 grey 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:

Pseudopalisading (upper left), neovascularity, nuclear anaplasia, multinucleated giant cells (lower right): Cellular anaplasia, multinucleated cells, bizarre mitoses (upper left corner):
Figure 21-11. Microscopic detail of an astrocytoma, grade II. A mitotic figure (solid arrow), giant cell (dashed arrow) and a cluster of endothelial cells are evident.

Vascular neoplasm with prominent areas of necrosis and hemorrhage: note crossed midline.
EPIHELIOID 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).
ASTROCYTOMAS

GIANT CELL GLIOBLASTOMA
- variant of IDH-wildtype glioblastoma

GOLGIATUM
- variant of IDH-wildtype glioblastoma

Glioblastomas 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 (GBM-PNC; 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

Medium age of onset
LOW-GRADE ASTROCYTOMA = 35 years (JUVENILE PILOCYTIC ASTROCYTOMA 6.5-25 yrs).

LOW-GRADE ASTROCYTOMA
≈ 35 years (JUVENILE PILOCYTIC ASTROCYTOMA 6.5-25 yrs).
• 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.

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>EMBRYONIC</td>
<td>may enhance strongly, little or no edema</td>
<td></td>
</tr>
<tr>
<td>LOW-GRDAE 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 homogeneously 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;

PILOCYTIC ASTROCYTOMA - 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): infiltrating tumor invades basal ganglia and causes mass effect with midline shift.
- Non-contrast CT (hypodense tumor):
STROCYTOMAS

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 hyperdense.

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

ANAPLASTIC ASTROCYTOMA

T2-MRI - less well-circumscribed white signal in posterior temporal lobe; non-enhancing with contrast.
Astrocytomas

Onc10 (22)

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.

Glioblastoma 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

Onc10

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

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 - irregularly ring enhancing mass with central necrosis and significant mass effect; tumor is extending up to corpus callosum (arrow):

Contrast CT - ring enhancement with pronounced peritumoral edema:

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:

A. Unenhanced T1-MRI - large necrotic mass (arrow):

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

Contrast-enhanced T1-MRI - large necrotic mass (arrow):

201Tl SPECT - typical high uptake:
Low-grade astrocytomas

57 yo F who presented with seizures; pathology – gliosarcoma.

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.

TREATMENT

Also see p. Onc3 >>

Glioma Algorithm

Low-grade astrocytomas (grade I)

Pilocytic astrocytomas, pleomorphic xanthoastrocytomas, subependymal giant-cell astrocytomas 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, and anaplastic 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 historically)
- 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 no negative 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.

- 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 critical tissue diagnosis needed for targeted treatment planning for patients with low-grade gliomas.

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

Level III Recommendation: For oligodendrogial 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 RESSECTION

Greater extent of resection improves outcome and should be safely attempted when not limited by eloquent cortex.

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).
RADIOTHERAPY

- radiation field margin of normal tissue:
  a) by CT: add 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 (vs. prolong overall survival in subtotal resection - Level II Recommendation).

Level II Recommendation: Radiotherapy is recommended in the management of newly diagnosed LGG to improve survival in patients with epilepsy and subtotal resection.

Level III Recommendation: Limited-field 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.

Non-surgical prognostic factors for overall survival after XRT (Level II Recommendation):
1) age > 40 years.
2) astrocytic pathology (vs. oligodendrogliat histological component and 1p19q 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

NCCTG-RTOG-ECOG: ‘US total’ - low-dose (50.4 Gy) vs. high-dose (64.8 Gy) radiotherapy

EORTC I: ‘Believers trial’

<table>
<thead>
<tr>
<th>Low-dose DXT</th>
<th>High-dose DXT</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Year survival</td>
<td>58%</td>
<td>59%</td>
</tr>
<tr>
<td>Progression (5-year PFS)</td>
<td>47%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- 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 Gy vs. 59.4–64.8 Gy) for newly diagnosed LGG with reduced toxicity.

EARLY VS. DELAYED RADIOTHERAPY

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


Early DXT
| 5 Year survival | 63% | 60% | None | p = 0.02 |
| 5-Year PFS | 46% | 37% | None | p = 0.02 |

- 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. Patient with residual tumor > 1 cm on post-operative 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 LGGs!

**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 1p/19q 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 7.8 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.

**HIGH-GRADE ASTROCYTOMAS**

**SURGERY**

**EXTENT OF RESECTION**

Maximal* possible resection / debulking (aim for supra-tot al resection – beyond contrast enhancement!)

*framework stereotactic neuronavigation, electrical stimulation mapping, high-field intraoperative MRI, 5-aminolevulinic acid (5-ALA) fluorescence guiding are helpful here

Why it matters? No clear answer (cytoreduction is unlikely effect) – probably removing necrotic hypoxic tissues improves postop XRT results

**The effect of extent of GBM resection**


- class II evidence
- inclusion: adults with KPS > 70 and GBM in a cerebral hemisphere.
  - Extent of resection
    - <25%
      - 25-49%
        - 50-74%
          - 75-99%
            - 100%
  - Median TTP (weeks)
    - 14.1
      - 24.1
        - 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).


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, 0.82; 95% CI, 0.86-0.99; P < 0.01; number needed to treat [NNT] = 9) and after 2 years (RR, 0.84; 95% CI, 0.79-0.95; 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, 0.95-95% 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, 0.72; 95% CI, 0.51-1.00; P = .05; NNT = 21); however, these differences were not significant at 1 year (RR, 0.96; 95% CI, 0.79-1.17; P = .69).

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 = 21); 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 significantly affect survival:
1. Age
2. Preoperative Karnofsky Performance Status
3. Postoperative 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)

Factors that significantly affect 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).

A STROCYTOMAS Onc10 (28)
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 chemoradiation without any “direct” cytoreductive treatment).

1. 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
- median estimate of OS and PFS in LITT cohort was 14.4 and 4.3 mo compared to 15.8 mo and 5.9 mo for biopsy only cohort.
- the extent of tumor coverage by hyperthermic lines (TDT-lines) was independent predictor of survival (analog to extent of surgical tumor resection).

LITT for New vs. Recurrent GBM - Washington University, St. Louis, Missouri
- 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

A
B
C
D

LITT for New vs. Recurrent GBM - Washington University, St. Louis, Missouri


- median estimate of OS and PFS in LITT cohort was 14.4 and 4.3 mo compared to 15.8 mo and 5.9 mo for biopsy only cohort.
- the extent of tumor coverage by hyperthermic lines (TDT-lines) was independent predictor of survival (analog to extent of surgical tumor resection).

LITT for New vs. Recurrent GBM - Washington University, St. Louis, Missouri


- 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 9.1 mo*, in recurrent GBM treatment – 11.8 mo**, median progression free survival - 6.6 mo. *Stupp et al. data on chemoradiation alone (no surgery) gives median OS 9.4 mo, however, groups are different (our study frontline patients has poor prognostic factors). **adds 2 extra months (compared to historical data using only Avastin + Temodar)

**RADIOTHERAPY**

NB: SRS is not recommended for newly diagnosed GBM (based on the results of RTOG 9305 trial) vs. recurrent GBM (SRS is an option)

- 54-60 Gy in single daily fractions of 1.8-2.0 Gy; 5 times per week or frontline GBM treatment, median OS was 9.1 mo and 11.8 mo respectively; PFS was 3.6 and 4.3 mo respectively. There were no statistically significant differences.

**CHEMOTHERAPY**

- GBM is considered chemoresistant tumor - molecular subgroups have significant barrier to improving therapy
- only ≤ 10% malignant astrocytomas have meaningful and durable responses to chemotherapy.

FDA-approved chemotherapeutic regimens: see p. Onc10 >>

1. Oral TEMOZOLOMIDE - standard of care for newly diagnosed GBM (FDA approved in 2005; for recurrent anaplastic astrocytoma FDA approved in 1999)
   - given during and for 6 months following radiotherapy
   - see Stupp protocol >>
   - majority of GBMs demonstrate primary (inherent) resistance.
   - subpopulation of GBM patients with methylated (i.e. inactivated) MGMT gene promotor are more likely to respond. see p. Onc11
   - reports that metronomic chemotherapy with TMZ has improved efficacy. *90% doses of are given on a continuous or frequent, regular schedule (such as daily or weekly), usually over a long time.

2. Intravenous CARMUSTINE - (FDA approved in 1977)
   - implantable Gluide® wafers (FDA approved in 2003 for new and in 1996 for recurrent HGGs) - when surgical cavity is not contiguous with ventricular system.

3. Oral LOMUSTINE

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.

1. tumor resection cavity may shrink, resulting in reduced tissue susceptible to radiation injury.
2. 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 and could have negative impact on effect.)

**RTOG guidelines for treatment fields**

<table>
<thead>
<tr>
<th>GTV</th>
<th>CTV</th>
<th>PTV</th>
<th>OAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0/LITT post-op changes</td>
<td>+ 2 cm expansion</td>
<td>+3.0 cm expansion</td>
<td>44 Gy/23 Fr</td>
</tr>
<tr>
<td>T1 without enhancement</td>
<td>+ 2 cm expansion</td>
<td>+3.0 cm expansion</td>
<td>44 Gy/23 Fr</td>
</tr>
<tr>
<td>T1 with/contrast enhancement</td>
<td>+ 2 cm expansion</td>
<td>+3.0 cm expansion</td>
<td>44 Gy/23 Fr</td>
</tr>
<tr>
<td>14 Gy/7 Fr (i.e. = sequential boost/tezodown)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTV margins may be reduced to 0.5 cm around normal barriers to tumor growth: skull, ventricles, falk.

About volumes – see p. Rx11 >>

*Published: 28 October 2017
Large Hospital Database.
Virginia W. Osborn, MD, a neurosurgery resident at UCSF, at CNS 2014 Annual Meeting

11 652 patients diagnosed with GBM, treated with surgery followed by chemoradiation. The time from surgery to initiation of radiotherapy was divided into 4 equal quartiles of ≤ 24, 25 to 30, 31 to 37, and > 37 d. There were no significant differences when comparing start within 24 d to 25 to 30, 31 to 37, and > 37 d (HR 0.96, 95% CI 0.90-1.01, P = 0.13) or > 37 d (HR 0.97, 95% CI 0.91-1.03, P = 0.26), although a small overall survival improvement was seen if initiated within ≤ 37 d (HR 0.93, 95% CI 0.88-0.99, P = 0.02)

*Stupp et al. data on chemoradiation alone (no surgery) gives median OS 9.4 mos

*vs. frontline GBM treatment, median OS was 9.1 mo and 11.8 mo respectively; PFS was 3.6 and 4.3 mo respectively.

SurgeneX Blan, MD, a neurosurgery resident at UCSF, at CNS 2014 Annual Meeting

reoccurrence after LITT for the total cohort

surgical cavity is not contiguous with ventricular system

We observed a consistent correlation between an event occurring within 35 days after surgery and overall survival (HR 0.97, 95% CI 0.91-1.03, P = 0.26), although a small overall survival improvement was seen if initiated within ≤ 37 d (HR 0.93, 95% CI 0.88-0.99, P = 0.02)

*Stupp et al. data on chemoradiation alone (no surgery) gives median OS 9.4 mos

*vs. frontline GBM treatment, median OS was 9.1 mo and 11.8 mo respectively; PFS was 3.6 and 4.3 mo respectively.

SurgeneX Blan, MD, a neurosurgery resident at UCSF, at CNS 2014 Annual Meeting

reoccurrence after LITT for the total cohort
A

STROCYTOMAS

Onc10 (31)

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

STUPP PROTOCOL

Stupp protocol – standard of care (Stupp R et al. NEJM 352:987-996, 2005):

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 ring 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)

6 months of 6 cycles of adjuvant TEMOZOLOMIDE (150–200 mg/m² of body-surface area/day for 5 days during each 28-day cycle)

- some oncologists prefer longer chemotherapy – 12 cycles (12 months).

- if patient wishes shorter course, 40 Gy in 15 fx or 30 Gy in 10 fx 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

OPTUNE® (NOVOCURE)

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 glioblastomas. “More temozolomide is not that helpful,” he argued.

- approved for new (2015) and recurrent (2011) HGGs.

- 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 supra-tentorial 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


Management patterns in Switzerland:

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

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

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 in patient was irradiated after the first operation.

De Dambis – prefers LITT first and then SRS for LITT failure (vs. metastases) – do not use LITT upfront, always do SRS first.

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.

Recent disease is seen in nearly all patients with GBM.

anti-VEGF monoclonal antibody – see p. Onc3 – FDA approved (2009) 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 BENEDICT.

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


Clinical Neurology and Neurosurgery 2019 October 24, 188: 105568

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.

AVAGlio and RTOG 0825 trials – although both studies found a benefit in progression-free survival following treatment with bevacizumab, there was no overall survival benefit.
LOCOREGIONAL IMMUNOTHERAPY

→ see p. Onc3

FOLLOW-UP (AFTER SURGERY)

General principles – see p. Onc3

LOW-GRADE ASTROCYTOMAS

Serial MRIs: at 3 mos postop → q6 mos x 2 → annually.

Alternative

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

Annually thereafter for the duration of follow-up.


• may do MRI without contrast (e.g. if patient is allergic to gadolinium) – if see recurrence (FLAIR signal, diffusion restriction), then add gadolinium.

HIGH-GRADE ASTROCYTOMAS

MD Anderson protocol:

During chemotherapy - MRIs q2 months.
After completion of chemotherapy - MRIs 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)

SPECIAL FORMS

CEREBELLAR ASTROCYTOMAS

• prognosis is consistently better than astrocytomas arising elsewhere!
• occur almost exclusively during first two decades of life
• usually well circumscribed, low grade (61-85% are pilocytic astrocytomas; other 15-28% are diffuse or fibrillary astrocytomas).
  - frequently cystic!
  - 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 astrocytomas - posterior fossa craniectomy; cyst is located with ultrasound, cannulated, and then exposed by incision through cerebellar folia; self-retaining retractors; with operating microscope cyst is examined; vascular, firm mural nodule is removed; nonneoplastic cyst wall is not excised.
  b) solid astrocytomas - separated carefully from surrounding cerebellar white matter (usually not difficult; only barrier to complete resection becomes deep tumor penetration into dentate nucleus, cerebellar peduncles, or brainstem).
• completely resected astrocytomas do not require radiotherapy; for others → 50-60 Gy.
• nitrosourea-based chemotherapy is limited to recurrences or for highly anaplastic tumors.
• most consistent prognostic factor is presence of brain stem involvement (poor prognosis independent of tumor histology or size).

Cystic astrocytoma of cerebellum in child:

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

Microcystic area is seen to 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 cystic outline denser tumor; cerebellar tonsil has herniated below foramen magnum:
Diffuse cerebral gliomatosis (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.

FLAIR MRI - widespread areas of increased signal in both cerebral hemispheres:

FLAIR MRI - tumor infiltration involving both temporal lobes (Short arrow), and substantia nigra (Long arrow):

FLAIR MRI - tumor cranial infiltration involving lentiform nuclei (Arrow):
Differentials
1. Paraneoplastic syndrome
2. Herpes encephalitis
3. Status epilepticus
4. Neurosarcoïdosis

Astrocytomas

Diffuse cerebellar neurosarcoïdosis mimicking gliomatosis cerebri.

Brainstem Gliomas
- Highly aggressive brain tumors (but prognosis is highly variable):

1. Focal tectal – 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-grade 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.
**Astrocytomas**

Onc10 (38)

**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).

**Histology:**
- Low-grade astrocytomas of medulla (T1-MRI) - marked enlargement medulla (arrow); exophytic component was biopsied.
Treatment: focal radiotherapy under DEXAMETHASONE coverage:
- standard treatment - conventional radiotherapy 54 Gy.
- investigational treatment - hyperfractionated radiotherapy 72 Gy.

- surgery is most appropriate for benign focal, dorsal exophytic, cystic tumors; most suitable locations - cervicomedullary and frontal; in these cases, radiotherapy is reserved for:
  - unexpectedly high-grade lesions
  - early progressive disease
  - inoperable recurrence

N.B.: surgery has no role in diffuse intrinsic poutine tumors!

- chemotherapy efficacy has not been proved - cannot be recommended! (may benefit in some recurrences).

- some adults with focal or cervicomedullary tumor, or with mild symptoms of long duration, may be candidates for observation alone.

**Optic Pathway Glioma**

1. Benign optic glioma (*PLIOCTIC 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.

- Bilateral optic nerve gliomas are almost pathognomonic for NF-1!

- development occurs in stages: from generalized hyperplasia of glial cells* to complete disorganization with loss of neural landmarks (reactive meningeval hyperplasia may be incurred - difficult to distinguish from perioptic meningioma).

- 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 GLIOBLASTOMA 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).
- 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).
  - strabismus and nystagmus in involved eye.
  - large lesion may compress hypothalamus (e.g. diencephalic syndrome - hypotalamic and suprachiasmatic nuclei, or with anorectic and emaciated child), 3rd ventricle (hydrocephalus).

- **Diagnosis:**
  - Fundoscopy: normal optic disks & venous engorgement & disk atrophy.
  - CT - can detect subtle erosion or expansion of optic canal.
  - marked, diffuse sioedem enlargement (tubular, fusiform, or ex cresc ent) 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.

* Optic nerve glioma formed by elongated, swirling piloid processes of astrocytes, nuclei of which are inconspicuous; nontumoral Rosenthal fiber (upper center, arrow).

Optic nerve glioma formed by elongated, swirling piloid processes of astrocytes, nuclei of which are inconspicuous; nontumoral Rosenthal fiber (upper center, arrow).

Optic nerve glioma formed by elongated, swirling piloid processes of astrocytes, nuclei of which are inconspicuous; nontumoral Rosenthal fiber (upper center, arrow).

**T1-MRI** - large intraorbital mass (arrows) centered on optic nerve.
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 (sparing 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] >>

---

**Viktor’s Notes℠ for the Neurosurgery Resident**
Please visit website at www.NeurosurgeryResident.net