Astrocytomas

Last updated: January 16, 2021

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

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

ETIOLOGY

- familial cases constitute only 1%.
- associated with certain genetic syndromes:
  neurofibromatosis type 1 → *LOW-GRADE ASTROCYTOMAS* (esp. in optic nerve & chiasm).
  tuberous sclerosis → *SUBEPENDYMAL GIANT-CELL ASTROCYTOMA*.
  Turcot's syndrome → *GLIOMAS*, *MEDULLOBLASTOMA*.
- *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 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).

- this approach more sharply separates **ASTROCYTOMAS THAT HAVE A MORE CIRCUMSCRIBED GROWTH PATTERN**, lack IDH gene alterations, and sometimes have BRAF mutations (i.e. pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma) from diffuse gliomas. In other words, diffuse astrocytoma and oligodendroglioma are now nosologically more similar than are diffuse astrocytoma and pilocytic astrocytoma.

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:

- tumors with cytological atypia alone (i.e. diffuse astrocytomas) are considered grade II , 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 number or 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 increased number of vessels) or glomeruloid vasculature.
- ***necrosis*** may be of any type; perinecrotic palisading need not be present. Simple apposition of cellular zones with intervening pallor suggestive of incipient necrosis is insufficient.
- aforementioned criteria make their appearance in a predictable sequence: atypia is followed in turn by mitotic activity, then increased cellularity, and finally microvascular proliferation and/or necrosis.

WHO 2007 designation	**WHO grade***	**Kernohan-Sayre grade***	**St. Anne/Mayo grade**	St. Anne/Mayo criteria**
Low-grade (s. benign) astrocytomas				
*PILOCYTIC ASTROCYTOMA****	I	I	excluded	-
ASTROCYTOMA	II	I-II	1	no criteria fulfilled
			2	1 criterion (usually nuclear atypia)
High-grade (s. malignant) astrocytomas				
ANAPLASTIC ASTROCYTOMA	III	II-III	3	2 criteria (usually nuclear atypia and mitoses)
GLIOBLASTOMA MULTIFORME	IV	III-IV	4	3-4 criteria - endothelial proliferation and/or necrosis

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

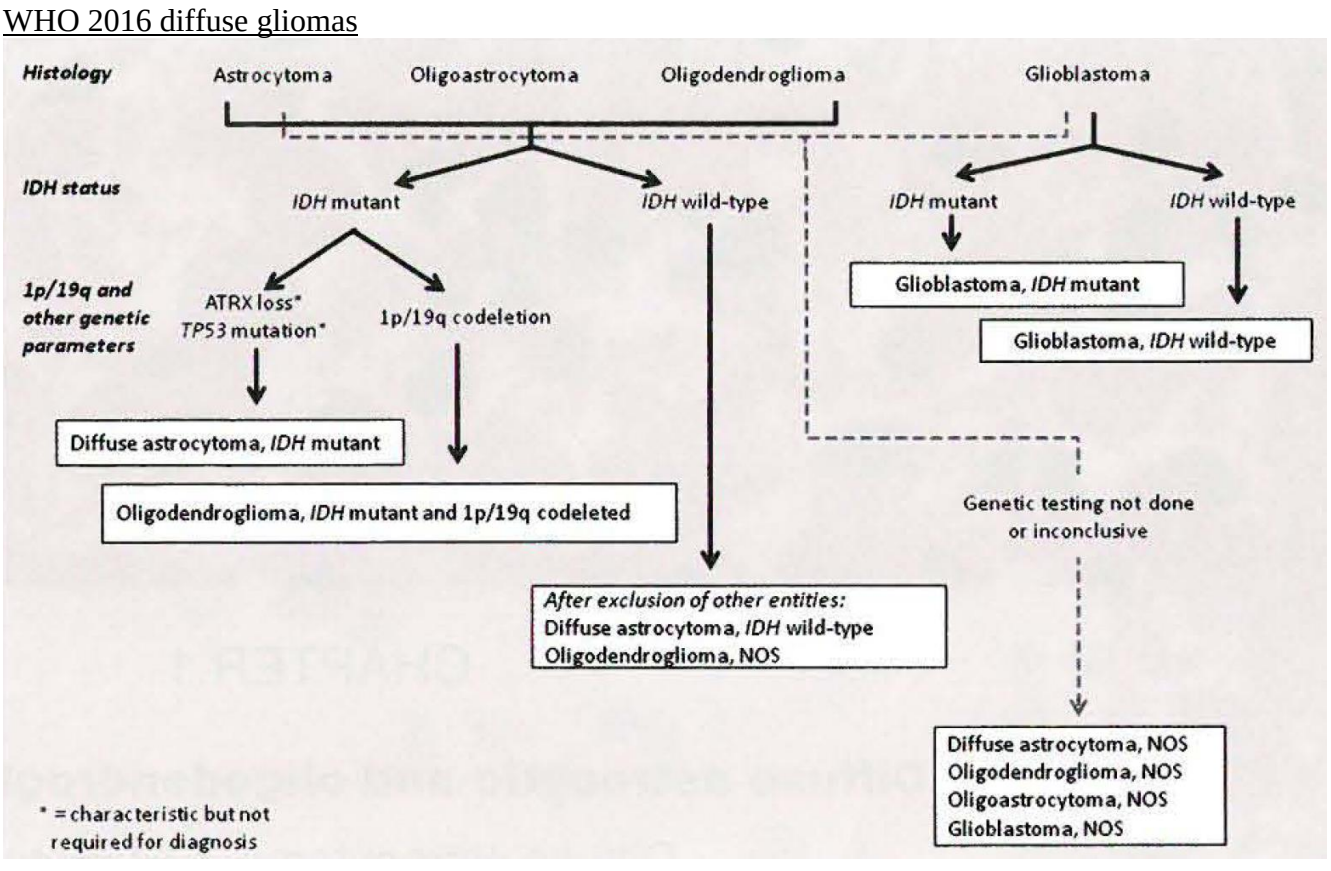
**4 histologic criteria:

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 (VEGF)*, produced by malignant astrocytes (in response to hypoxia) contributes to this vascular change; probably predisposes to necrosis.
4) necrosis – already grade IV

***grade I tumors - *PILOCYTIC ASTROCYTOMA*, *PLEOMORPHIC XANTHOASTROCYTOMA*, *SUBEPENDYMAL GIANT-CELL ASTROCYTOMA* - may have endothelial proliferation and marked atypia; nevertheless, they are slow growing and well circumscribed (grade I); i.e. diffuse astrocytoma is automatically ≥ grade II

- 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 ≈ 25%;
  6 biopsies → grading error rate ≈ 2%.
- necrosis loses its prognostic significance in *recurrent tumors after radiotherapy* because ***radiation necrosis*** is indistinguishable from ***tumor necrosis***.

WHO 2016 diffuse gliomas



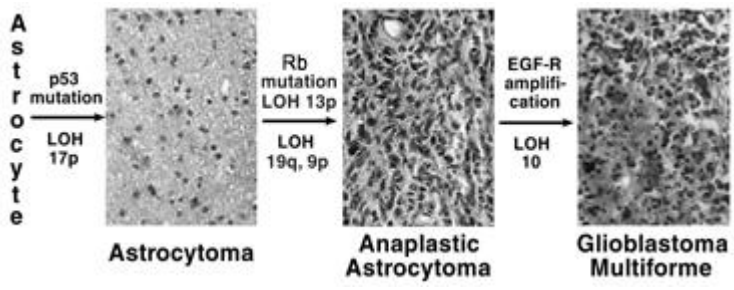
Historical **Bailey and Cushing** classification - based on *embryologic development of astroglia*:
spongioblast (*SPONGIOBLASTOMA*) → astroblast (*ASTROBLASTOMA*) → astrocyte (*ASTROCYTOMA*).

GENETICS

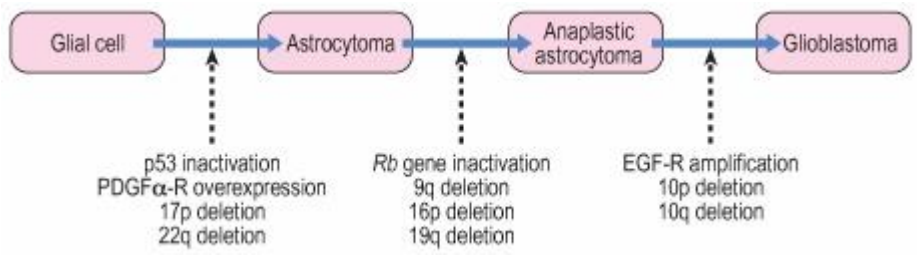
GBM is extraordinarily heterogenous tumor with many, many pathways that are perturbed (overexpressed, deleted, mutant); GBM is not like chronic myelogenous leukemia, where 1 BCR-ABL translocation underlies the entire disease.

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):



LOH = loss of heterozygosity, Rb = retinoblastoma gene, EGF-R = epidermal growth factor receptor.



Genes involved in gliomagenesis:

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

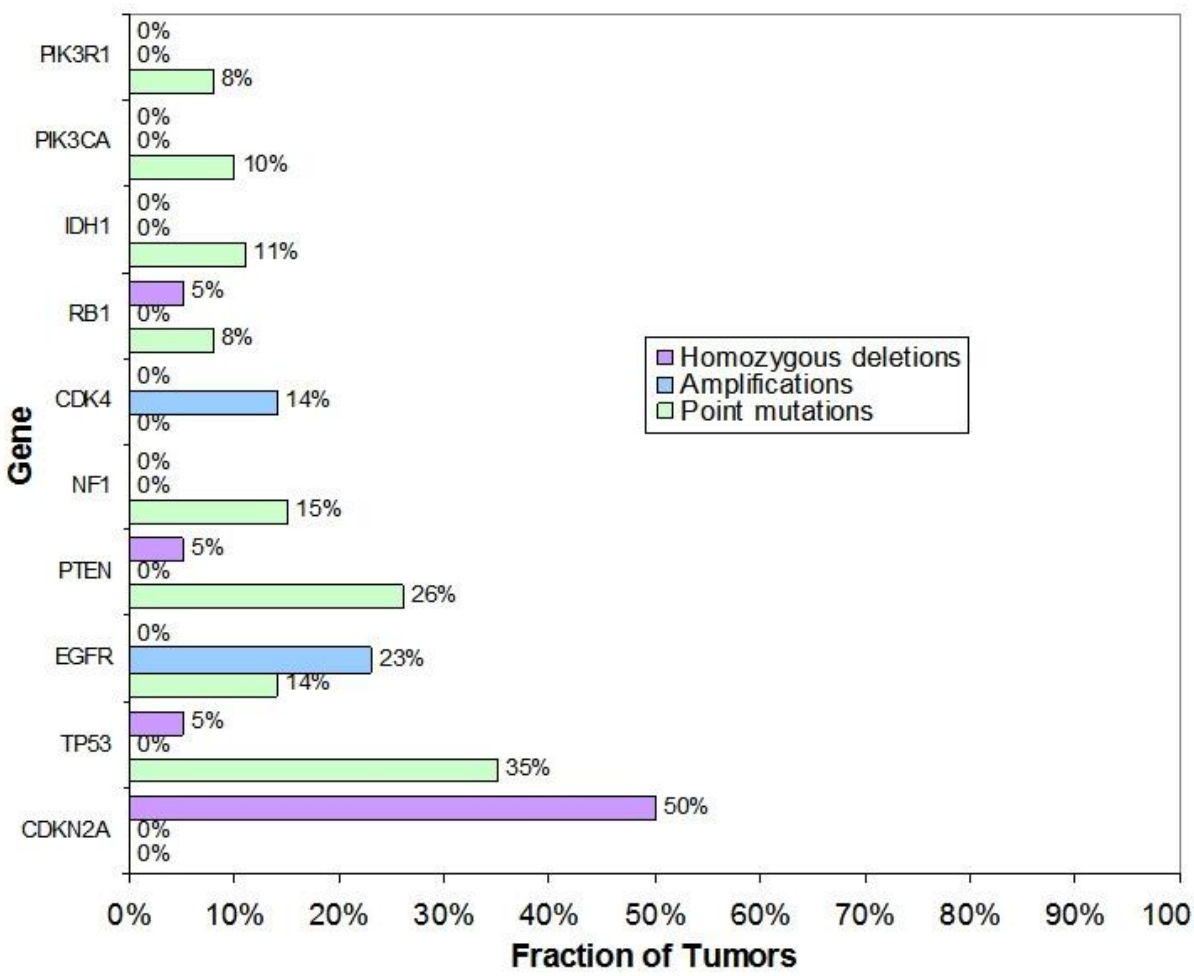
II. **Tumor suppressor genes**: CDKN2A [also known as p16INK4a], PTEN, RB1, TP53.

– frequent loss of heterozygosity (LOH) on chromosome arms 1p, 10p, 10q, 19q, and 22q 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. IDH-1/2 mutations

Most frequently altered GBM cancer genes:



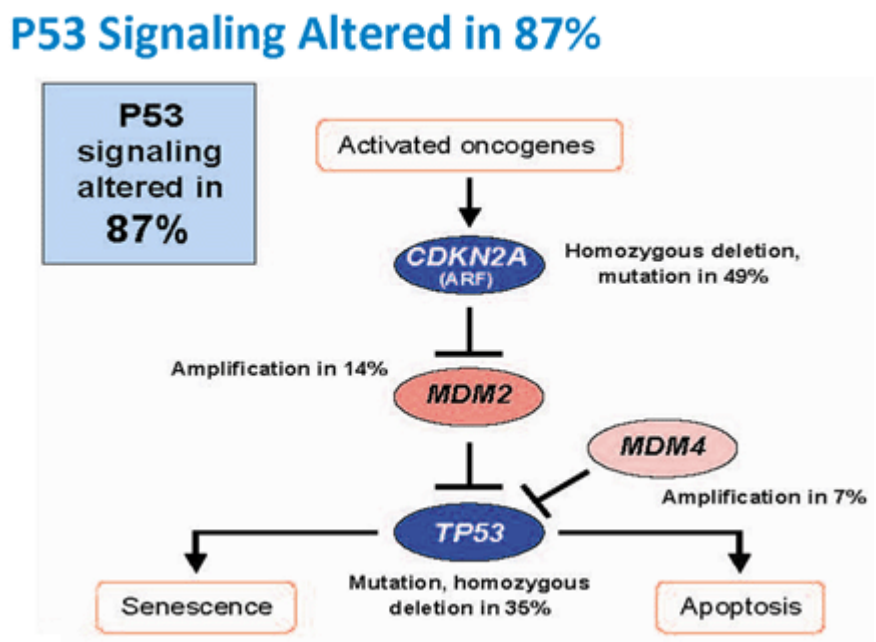
Medscape

Source of figure: Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321:1807-1812. >>

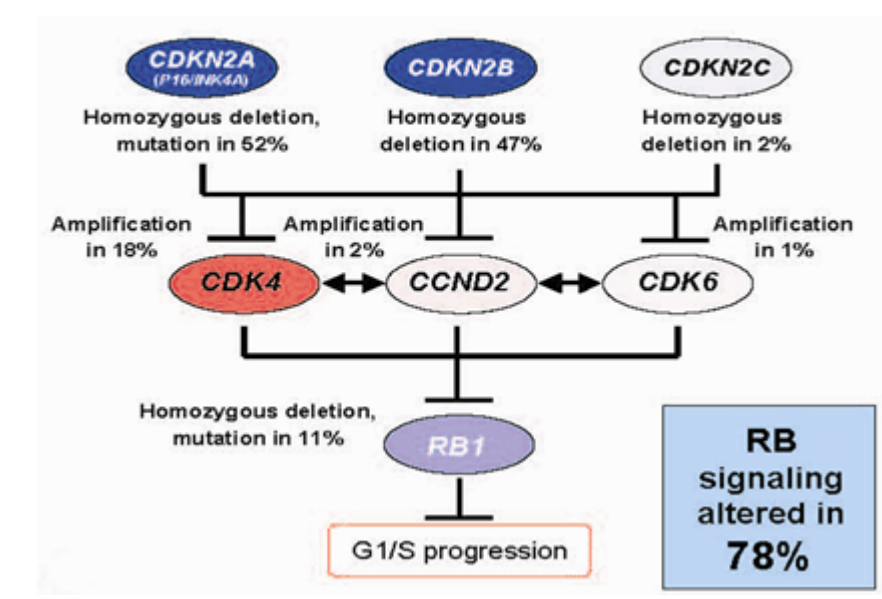
	Point mutations		Amplifications	
Gene	Number of tumors	Fraction of tumors	Number of tumors	Fraction of tumors
CDKN2A	0/22	0%	0/22	0%
TP53	37/105	35%	0/22	0%
EGFR	15/105	14%	5/22	23%
PTEN	27/105	26%	0/22	0%
NF1	16/105	15%	0/22	0%
CDK4	0/22	0%	3/22	14%
RB1	8/105	8%	0/22	0%
IDH1	12/105	11%	0/22	0%
PIK3CA	10/105	10%	0/22	0%
PIK3R1	8/105	8%	0/22	0%

Source of figure: Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321:1807-1812. >>

Source of figure: Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455:1061-1068 >>



Source of figure: Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455:1061-1068 >>



Source of figure: Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455:1061-1068 >>

> 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 13q14).

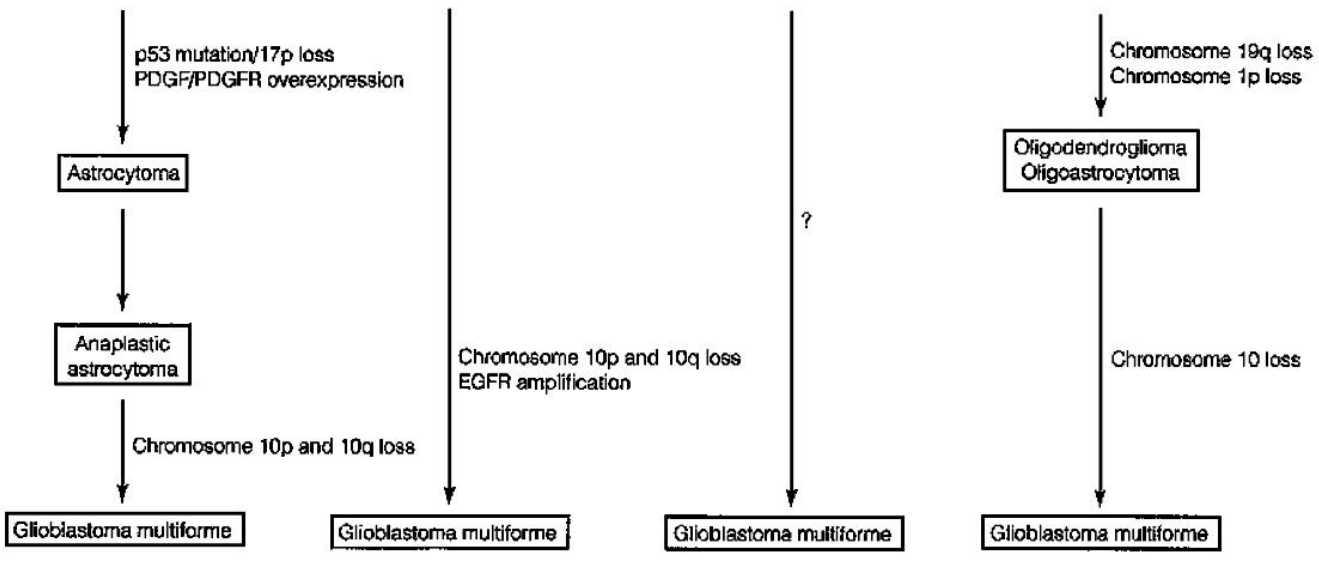
> 70% *GLIOBLASTOMAS* in addition have lost heterozygosity for chromosome 10 (most common deletion in malignant gliomas!);

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*:

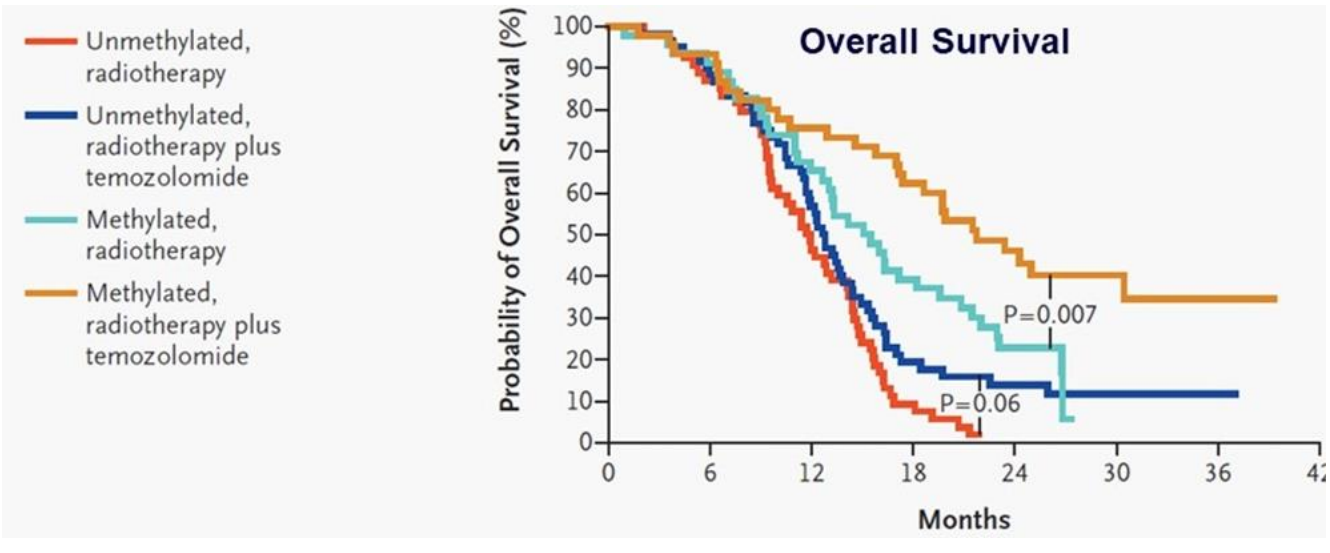


6) progression from low-grade to high-grade tumors is much less common in ***pediatric patients*** (molecular genetic events that characterize adult process have not been described in children).

MGMT METHYLATION

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



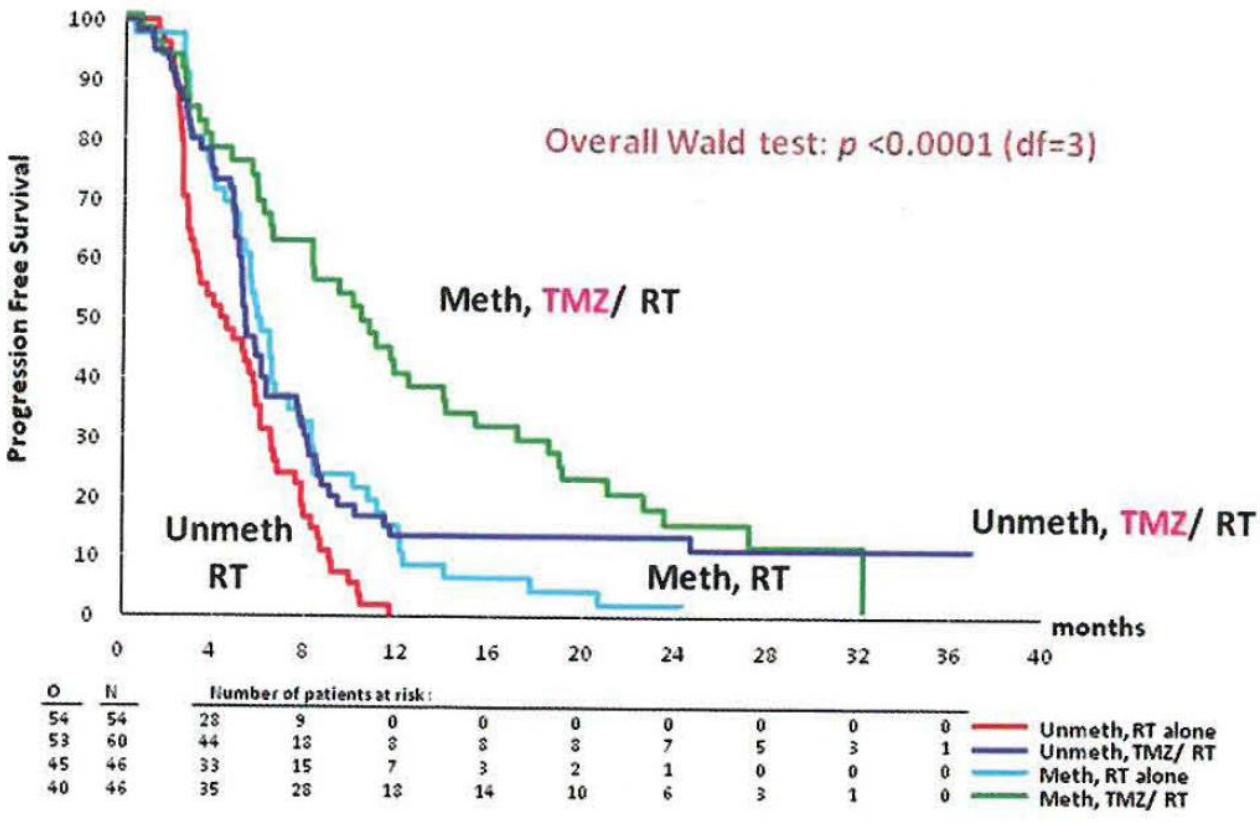
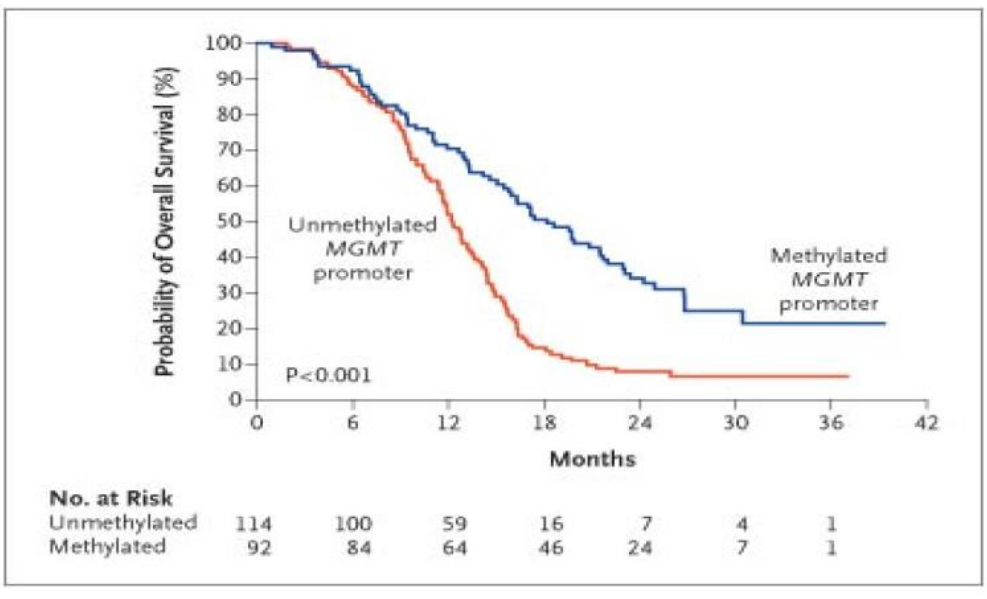


Fig. 1.38 *MGMT* promoter methylation (meth) and progression-free survival in glioblastoma patients randomized to treatment with radiotherapy (RT) alone or radiotherapy plus temozolomide (TMZ). Reprinted from Hegi ME et al. {982}.

Kaplan–Meier Estimates of Overall Survival according to *MGMT* Promoter Methylation Status



Cleveland Clinic Hegi M, et al. N Engl J Med 352:997-1003, 2005

	MGMT promoter?	2y OS
RT+TMZ	Methylated	46%
RT	Methylated	23%
RT+TMZ	Unmethylated	14%
RT	Unmethylated	2%

Cleveland Clinic Hegi M, et al. N Engl J Med 352:997-1003, 2005

Level III 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.

ISOCITRATE DEHYDROGENASE (IDH)-1/2 mutation

- means ≥ 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 III 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).

Li-Fraumeni syndrome (inherited p53 mutation) – strong predisposition to astrocytomas!

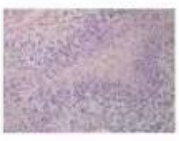
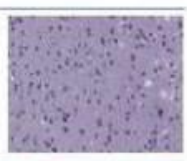
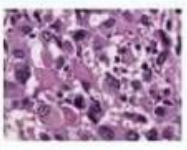
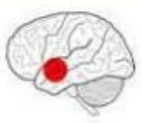
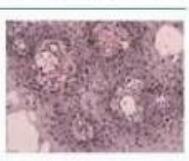
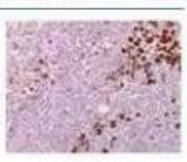
- p53 mutation goes "hand to hand" with IDH mutation.
- *GLIOBLASTOMAS* which show p53 mutation are termed *secondary glioblastomas* (type 1) - occur in younger patients whose tumors have progressed from lower grade astrocytoma (vs. *primary*, or *de novo*, type 2 *glioblastoma* typically found in older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

BRAF V600E mutation

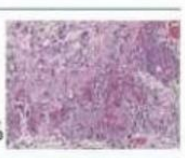
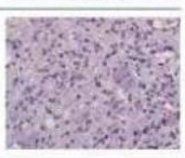
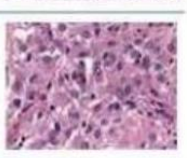
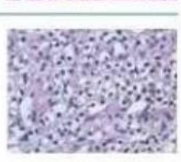
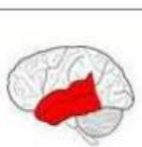
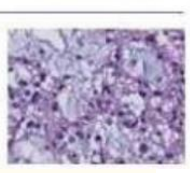
- BRAF is a serine/threonine kinase protein and is a downstream effector of the Ras-Raf-MEK extracellular signal-regulated kinase (ERK) signaling pathway, which is responsible for cell division and differentiation.
- mutation of the BRAF gene in which valine (V) is substituted by glutamic acid (E) at amino acid 600.
- BRAF V600E mutations are rarely found in adult gliomas with only 1-2 % mutated samples in glioblastomas and 2-% 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 carcinoma, 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.

Adult tumors

Diagnosis	Age	Typical Location	Prognosis	BRAF alteration / frequency	Histology
GBM	All ages Mainly 55-85y		poor	BRAF V600E: 1-2%	
Astrocytoma	All ages Mainly 35-45y		II°: variable III°: poor	BRAF V600E: 2-5%	
Astroblastoma	Children and young adults		variable	BRAF V600E: 38%	
PXA	Mainly children and young adults		variable	BRAF V600E: 12-60% Other MAPK fusion: rare	
Papillary Cranio-pharyngioma	Mean 40-55y		good	BRAF V600E: 81-95%	
Melanoma Metastasis	35-71y Mean 56y		poor	BRAF V600E: 42% NRAS: 18%	

Pediatric tumors

Diagnosis	Age	Typical Location	Prognosis	BRAF alteration / frequency	Histology
PA	5-20y		fusion: good V600E: poor	KIAA1549-BRAF: 70% BRAF V600E: 5% Other MAPK alteration: 5%	
GG	2m-70y Mean 10y		good	BRAF V600E: 20-60% BRAF Non-V600E: 12% KIAA1549-BRAF: rare	
DIA/DIG	Mainly infantile 0-24m		good	BRAF V600E/D: 45% Other BRAF : rare	
DLGT	Mainly children Median 5y		variable	KIAA1549-BRAF: 75% RAF1: rare BRAF V600E: rare	
DNT	3w-38y Mean 15y		good	BRAF V600E: frequent Germline FGFR1: rare FGFR1: some	

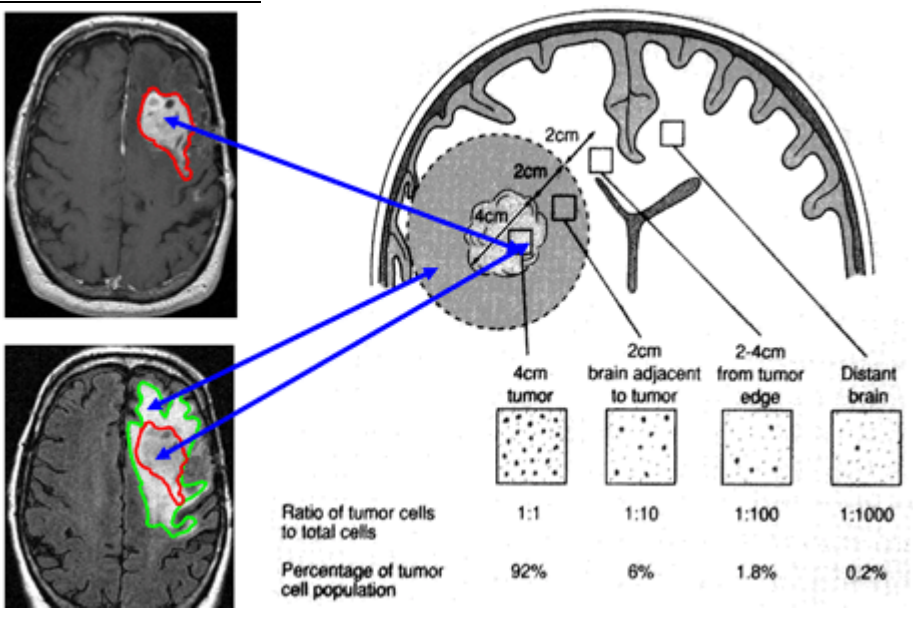
PA: pilocytic astrocytoma, GG: ganglioglioma, DIA/DIG: desmoplastic infantile astrocytoma/ganglioglioma, DLGT: diffuse leptomeningeal glioneuronal tumor, DNT: dysembryoplastic neuroepithelial tumor

PATHOLOGY

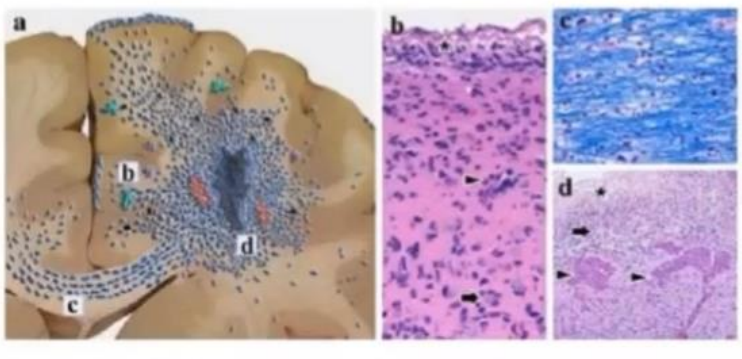
N.B. only *JUVENILE PILOCYTIC ASTROCYTOMAS* are **localized**, all other tumors are **infiltrative** (invasive phenotype is acquired early in tumorigenesis!)

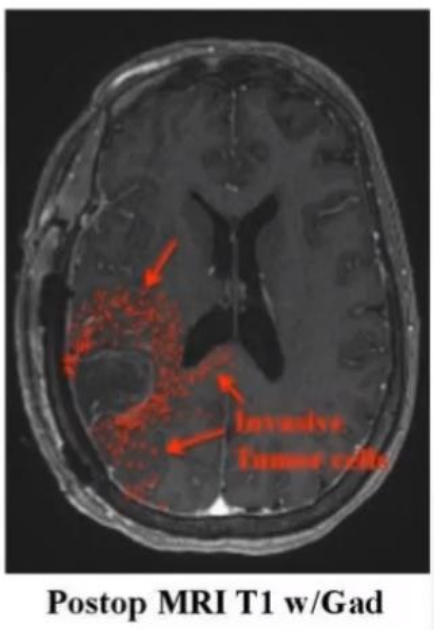
- **calcification** occurs only in minority.

Infiltration with tumor cells:



- Glioma 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**

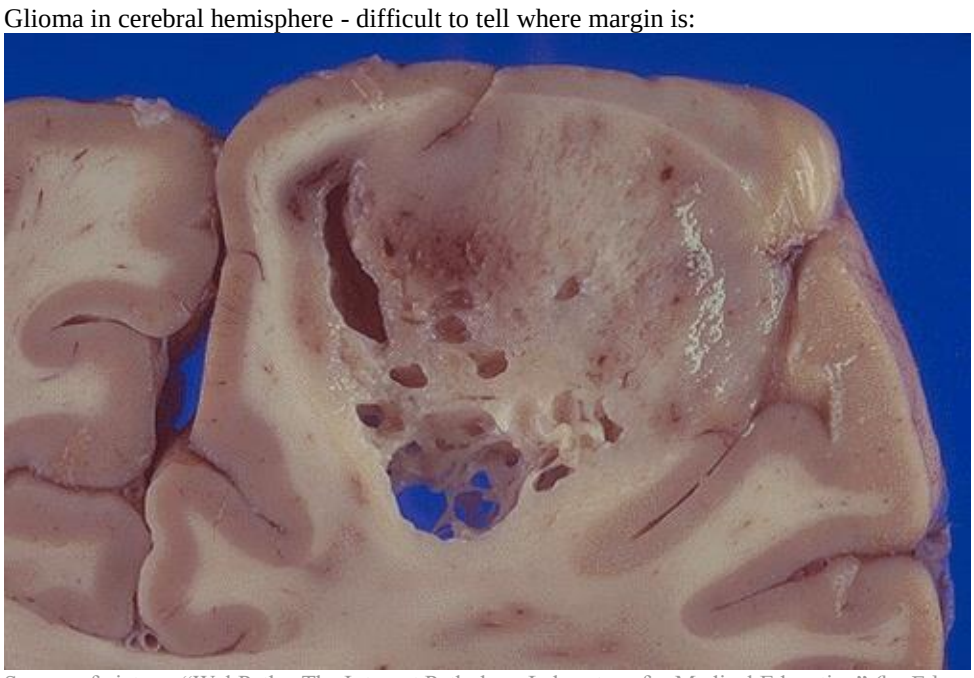




Postop MRI T1 w/Gad

Claes A et al. *Acta Neuropathol* 2007; Kelly PJ et al. *J Neurosurg* 1987.

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



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

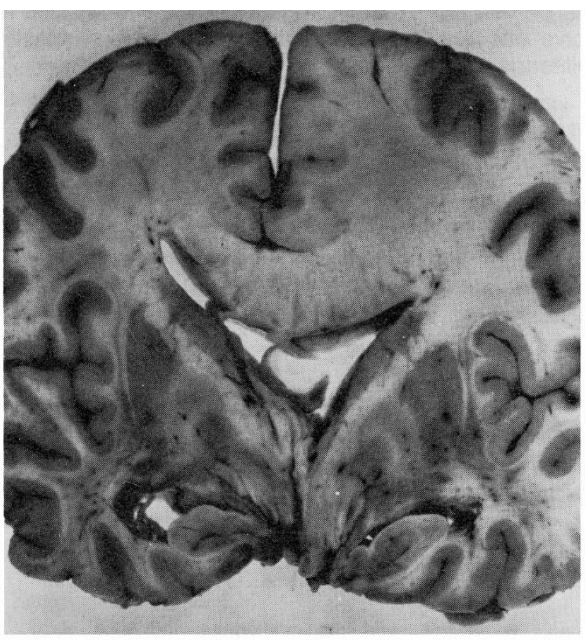


Figure 29–24. Diffuse astrocytoma. Expanded white matter of right cerebral hemisphere and thickened corpus callosum (coronal section).

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.

PLEOMORPHIC 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 of 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.

DIAGNOSTIC ENTITIES

PILOCYTIC ASTROCYTOMA

(WHO grade I)

Genetics

- essentially all have various mutations affecting **MAPK pathway**:

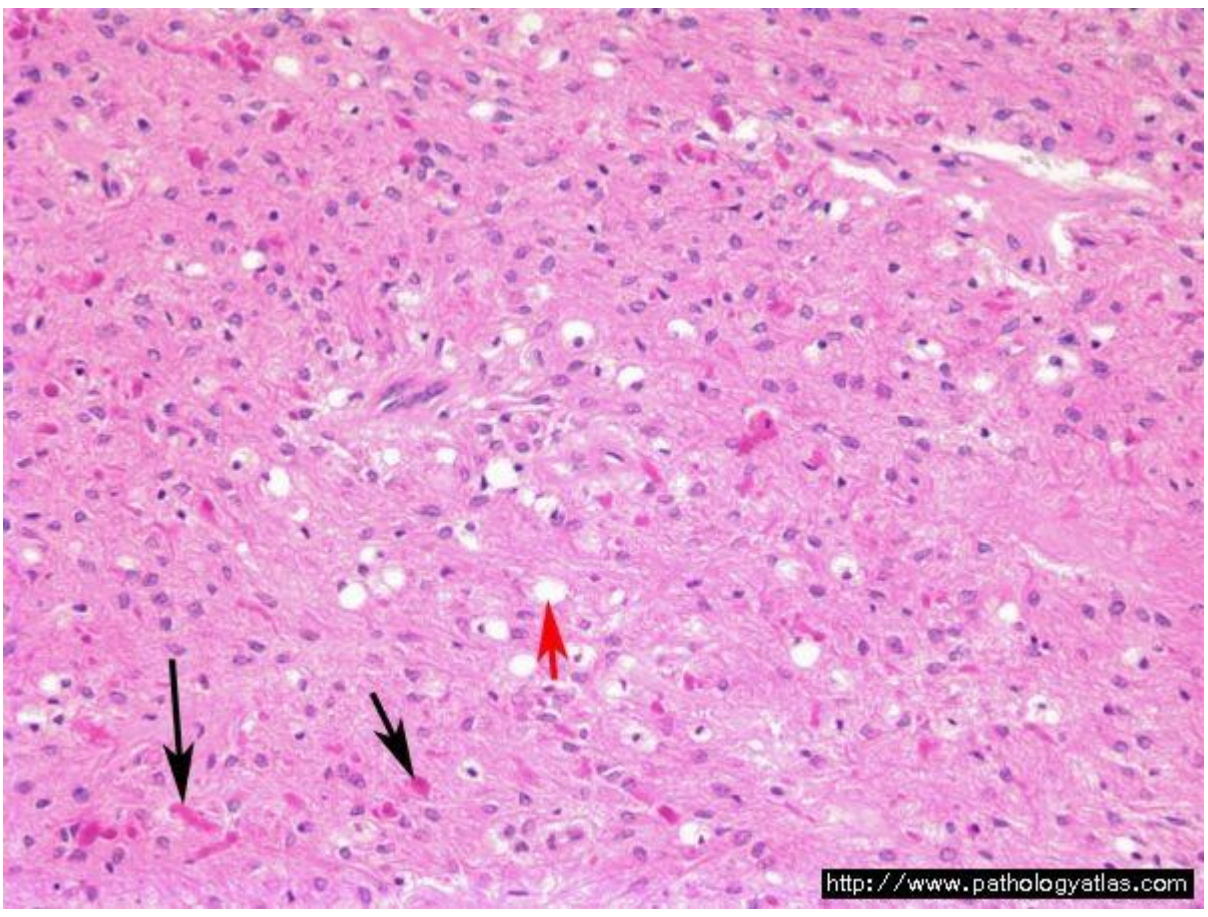
Table 2.01 Genetic alterations affecting the MAPK pathway in pilocytic astrocytomas and their diagnostic utility; adapted from Collins VP et al. (482)

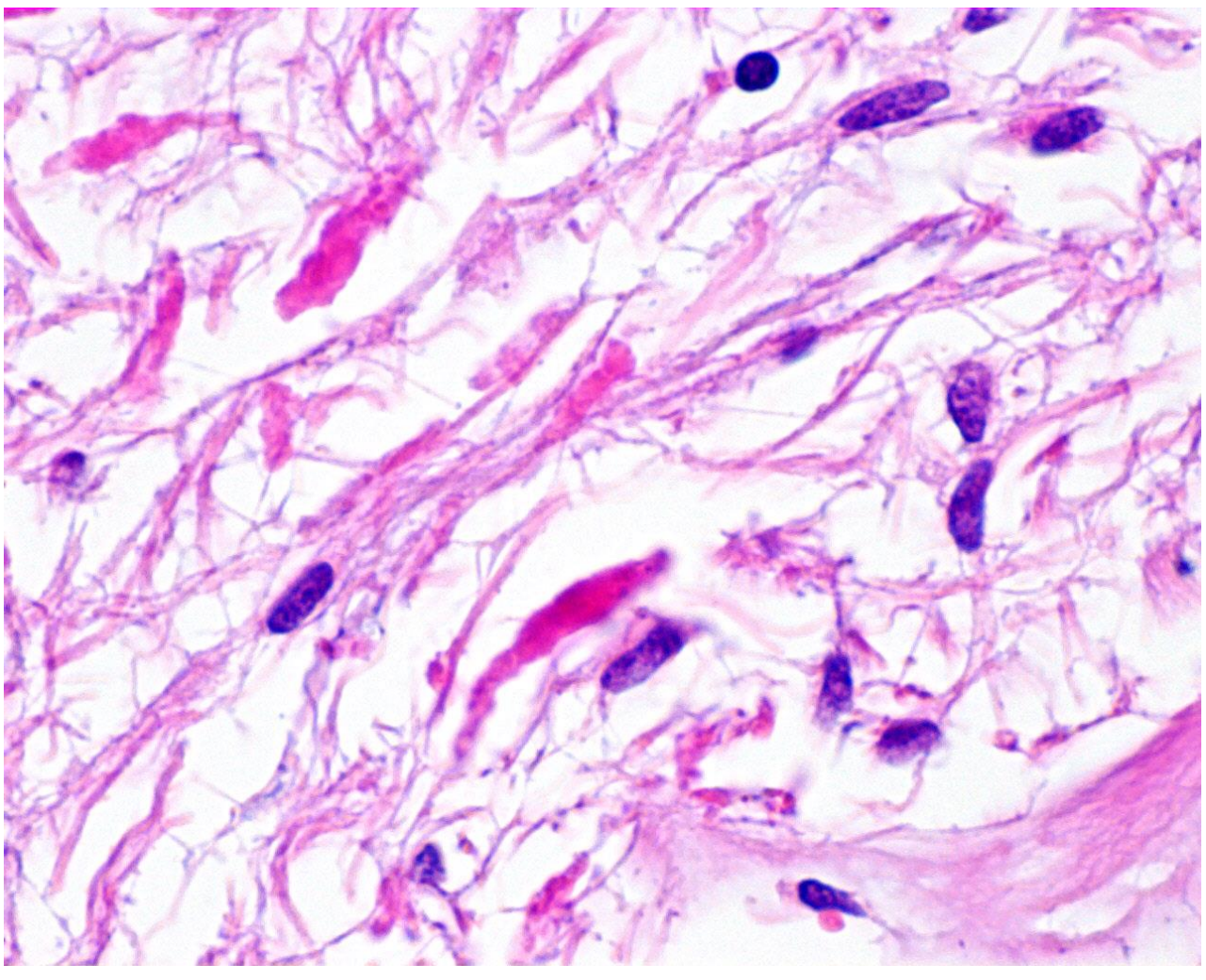
Gene	Change	% of tumours	Diagnostic utility
BRAF and *KIAA1549*	Tandem duplications resulting in KIAA1549-BRAF fusion proteins, all having the BRAF kinase domain and with the BRAF N-terminal regulatory domain replaced by the N-terminal end of KIAA1549	> 70%	Common in pilocytic astrocytomas, particularly cerebellar; rare in other tumour forms
BRAF and various other genes	Deletions or translocations resulting in BRAF fusion proteins, all having the BRAF kinase domain and with the BRAF regulatory domain replaced by the N-terminal part of another gene	~5%	Occur in pilocytic astrocytomas; extremely rare in other entities
BRAF	V600E mutation	~5%	Occurs mainly in supratentorial pilocytic astrocytomas; also in gangliogliomas, pleomorphic xanthoastrocytomas, and dysembryoplastic neuroepithelial tumours
NF1	Loss of wild type and retained inherited mutation	~8%	Typically germline; closely associated with optic pathway pilocytic astrocytoma
FGFR1	Mutation	< 5%	Found mainly in midline pilocytic astrocytomas; frequency not established in other entities
FGFR1	Fusions / internal tandem duplication	< 5%	Rare in pilocytic astrocytoma; also observed in other low-grade gliomas
NTRK family	Fusions	~2%	Rare in pilocytic astrocytoma; frequency not established in other entities
KRAS	Mutation	Single cases	Rare in pilocytic astrocytoma; frequency not established in other entities
RAF1	Fusions with consequences similar to those of BRAF fusions, i.e. the loss of the regulatory domain and its replacement by the N-terminal end of SGRAP3	Single cases	Rare in pilocytic astrocytoma; frequency not established in other entities

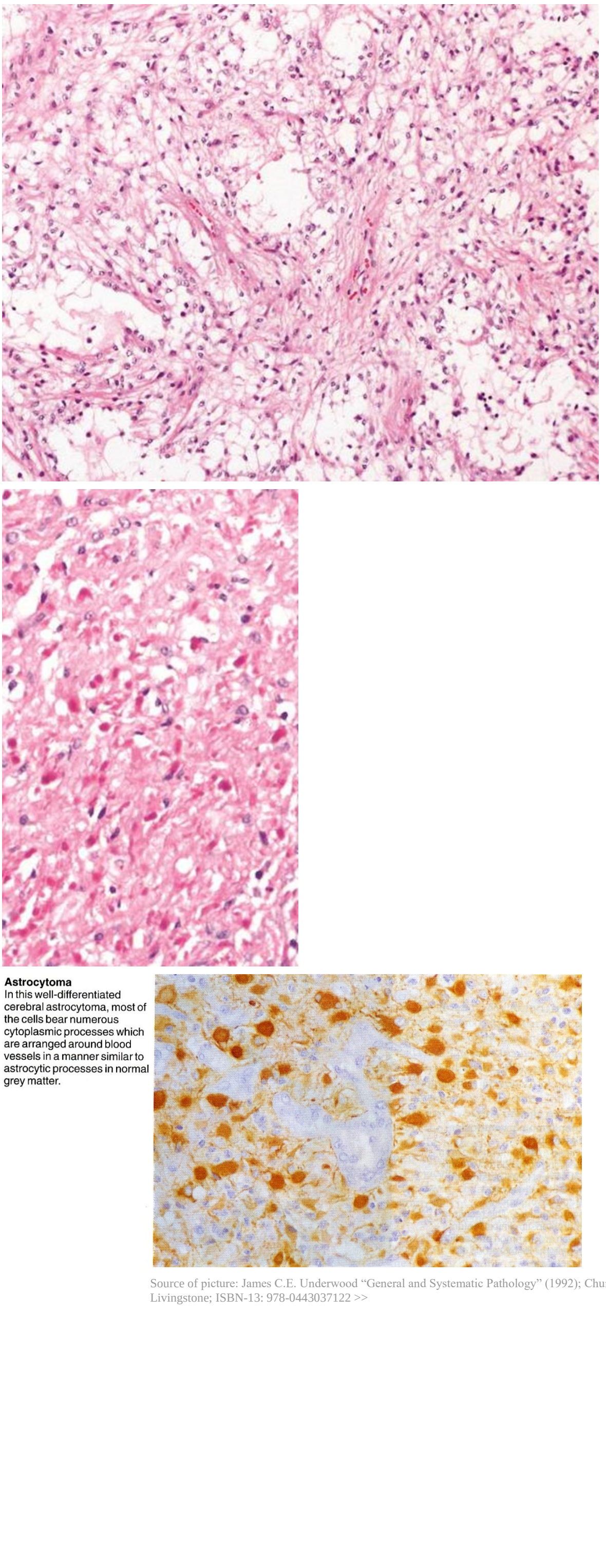
- most commonly (> 70%) tandem duplication of 7q34 involving BRAF gene → BRAF-KIAA1549 fusion – constitutively activates MAPK.
- IDH-1 negative (vs. diffuse astrocytomas)
- TP53 plays no role.
- pilocytic astrocytoma is **hallmark of NF1** (esp. optic glioma) – *neurofibromin protein acts in MAPK pathway*.
  15% of NF1 patients develop pilocytic astrocytoma (esp. optic pathways); 1/3 of patients with optic glioma have NF1
- **Noonan syndrome** (neuro-cardio-facial-cutaneous) – germline mutations of MAPK pathway genes → associated pilocytic astrocytomas.

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 palisading), hyalinized vessels, *calcifications* (dif. from craniopharyngioma)

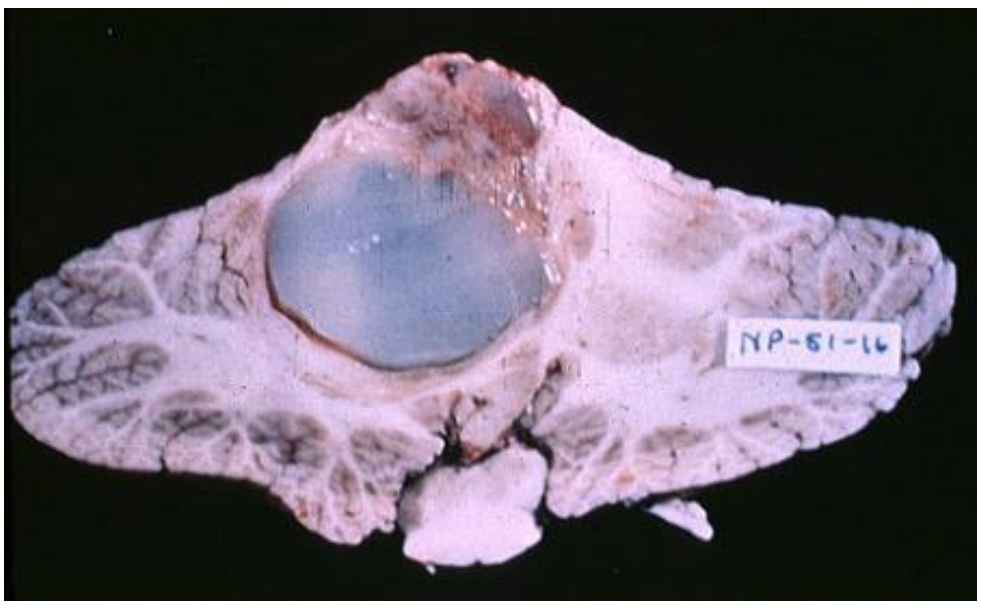






Astrocytoma
In this well-differentiated cerebral astrocytoma, most of the cells bear numerous cytoplasmic processes which are arranged around blood vessels in a manner similar to astrocytic processes in normal grey matter.

Source of picture: James C.E. Underwood "General and Systematic Pathology" (1992); Churchill Livingstone; ISBN-13: 978-0443037122 >>



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

Imaging
- intensely enhancing due to high vascularity.

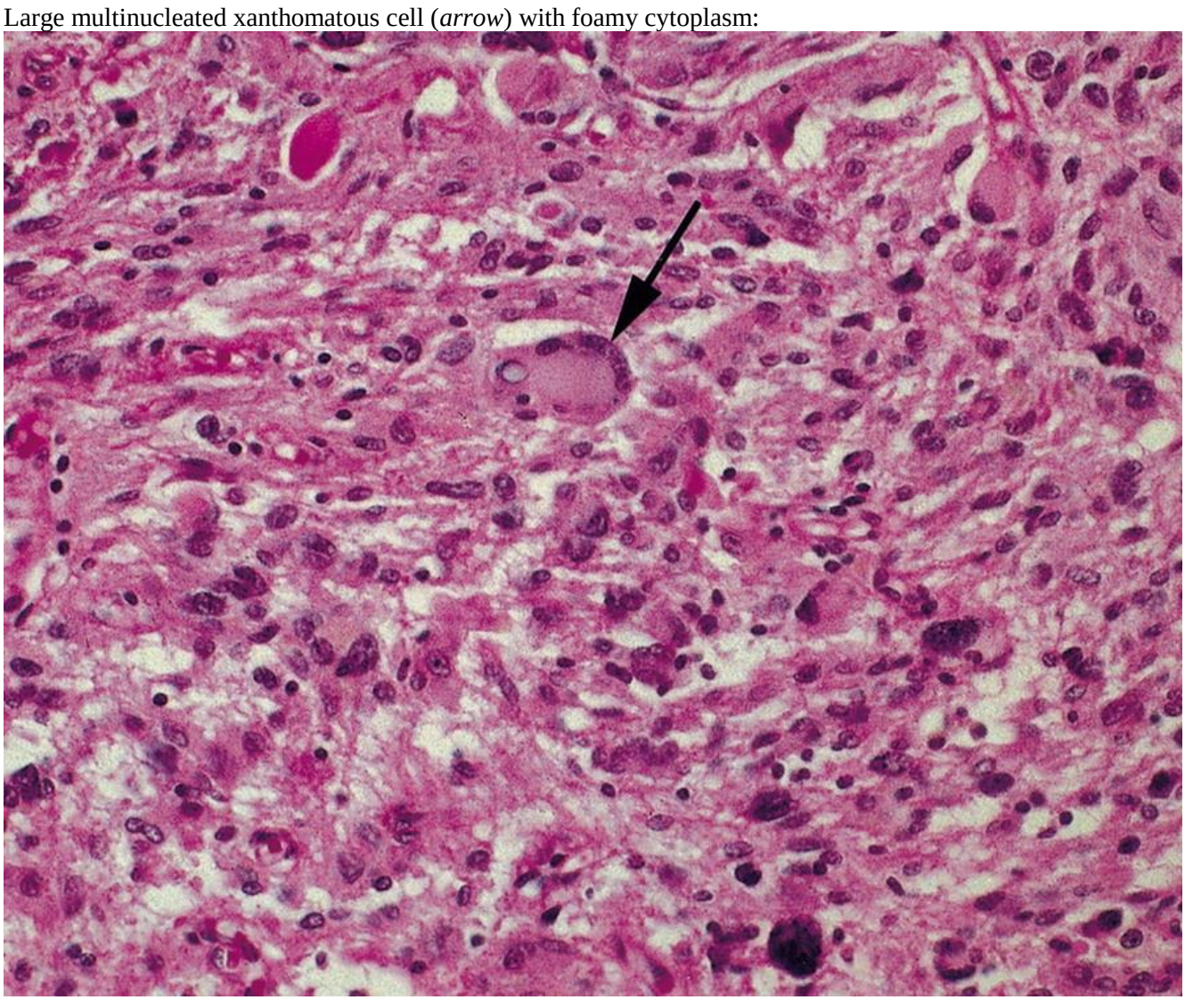
PILOMYXOID ASTROCYTOMA

(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.

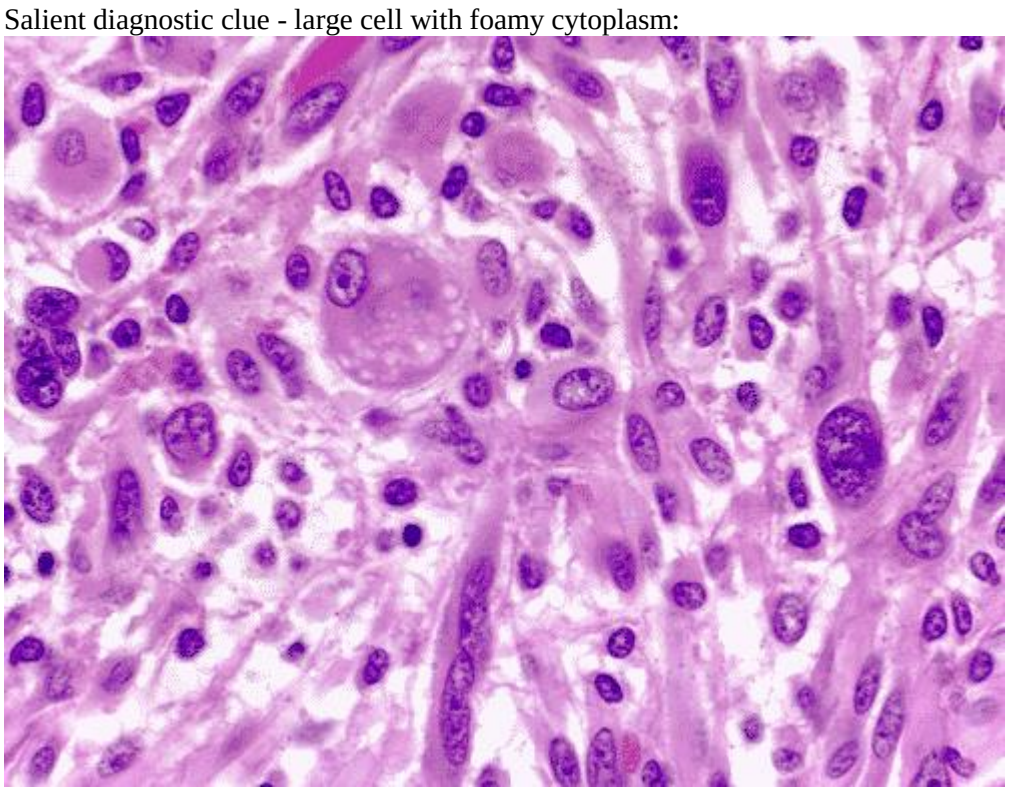
PLEOMORPHIC XANTHOASTROCYTOMA (PXA)

(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.

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**

- 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-gutterings") that line ventricles in tuberous sclerosis.
  - often calcified.
  - hyalinized 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)

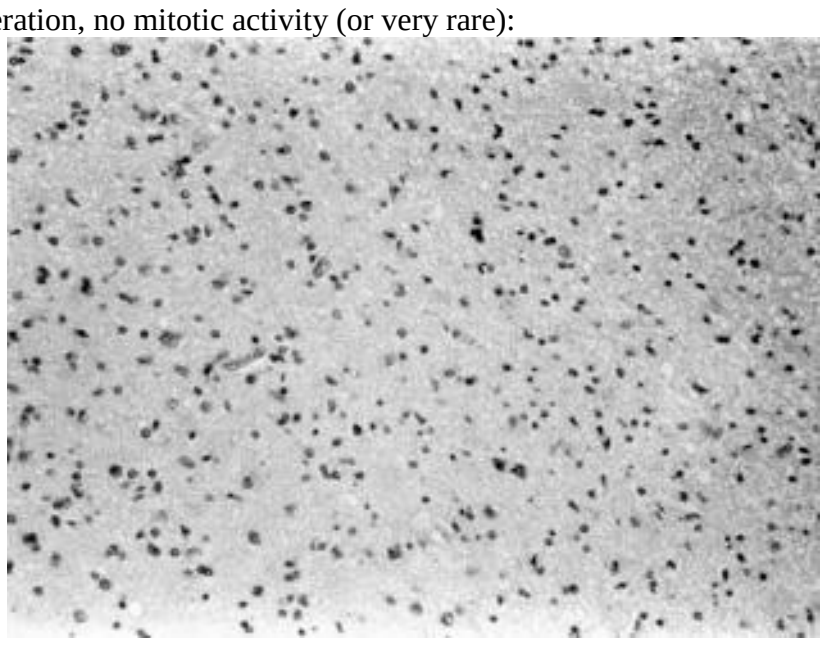
Genetics

- 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, 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**.
  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

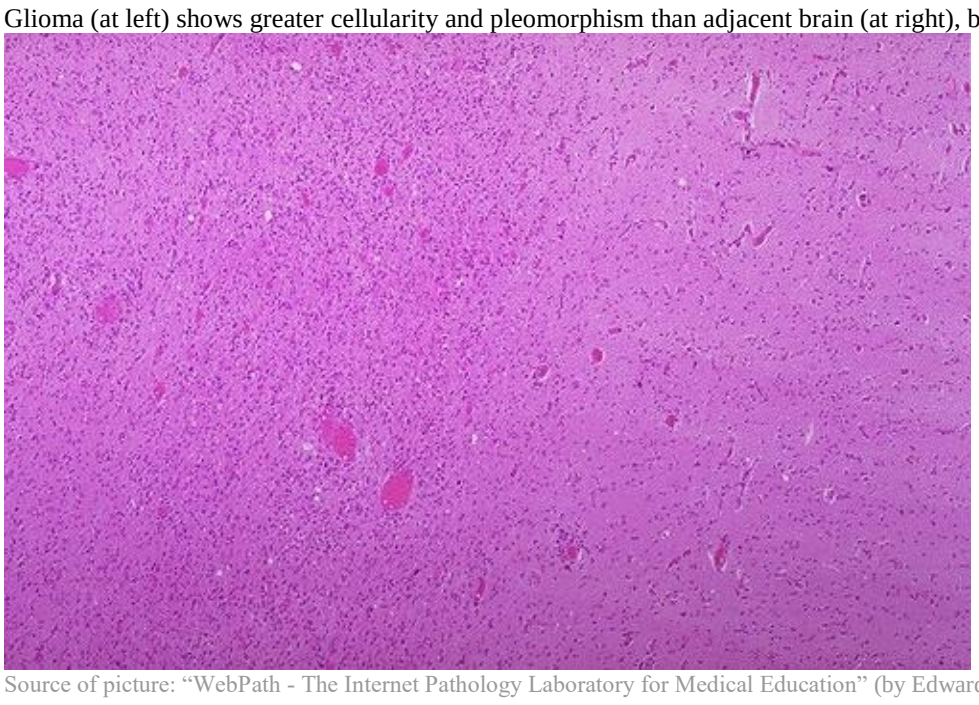
- slight hypercellularity (more cellular than normal brain), uniform cells (closely resemble mature resting or reactive, nonanaplastic astrocytes), no nuclear pleomorphism (or very slight), no endothelial proliferation, no mitotic activity (or very rare):



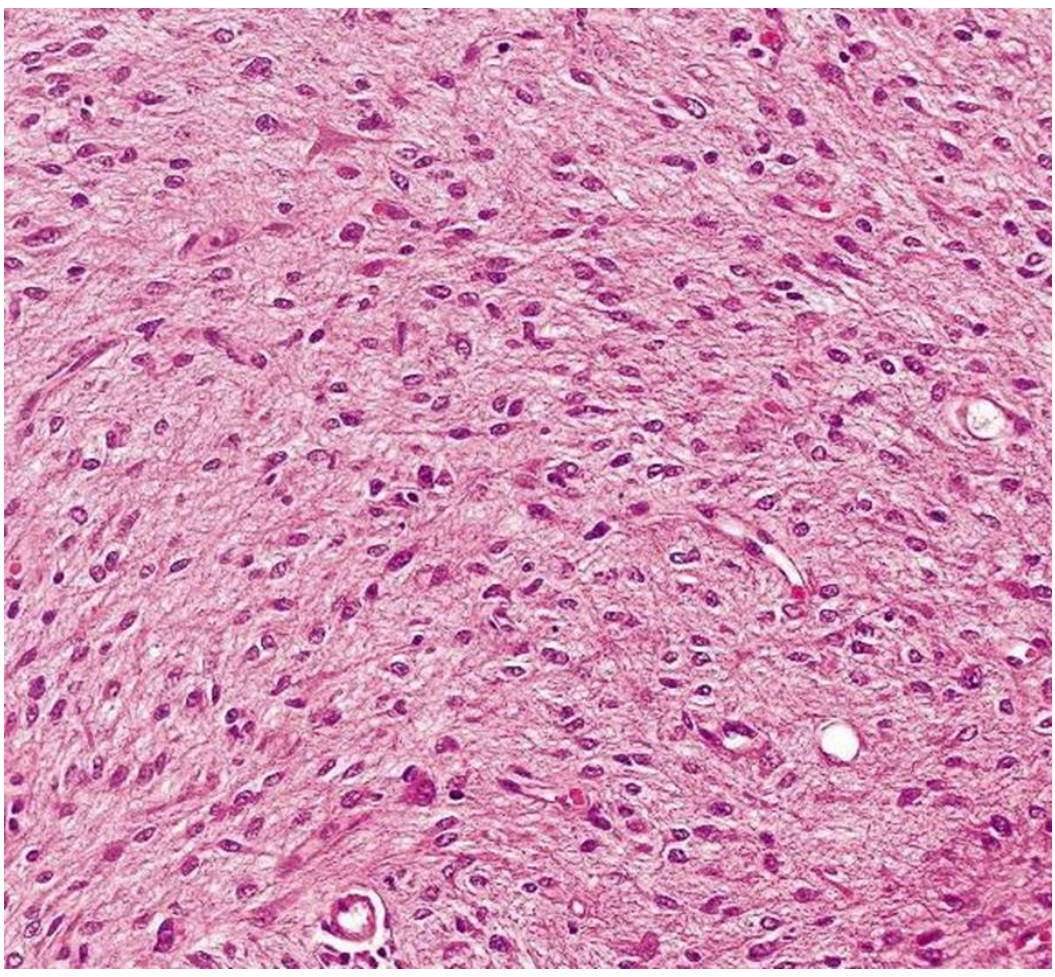
- Ki-67 proliferation index is usually < 4%.
- major differential – reactive astrocytosis (H: look for Rl32H-mutant IDH1).
  N.B. most of low grade astrocytomas are positive for IDH1 R132H mutant protein!

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

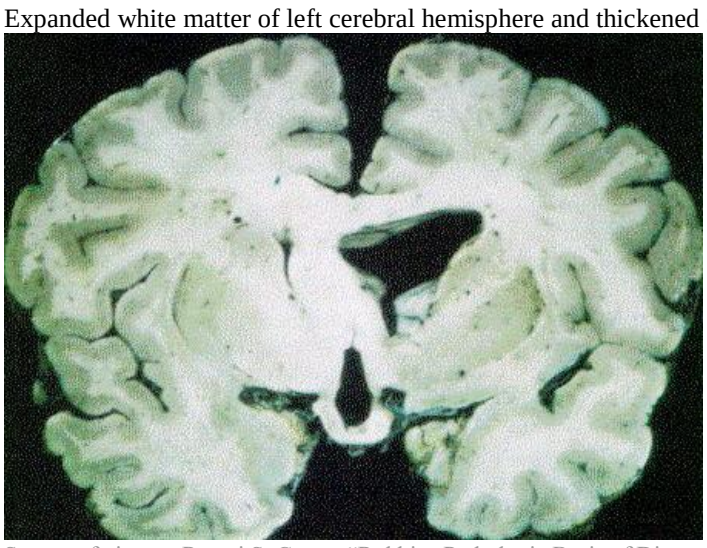
Glioma (at left) shows greater cellularity and pleomorphism than adjacent brain (at right), but margin is not distinct:



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

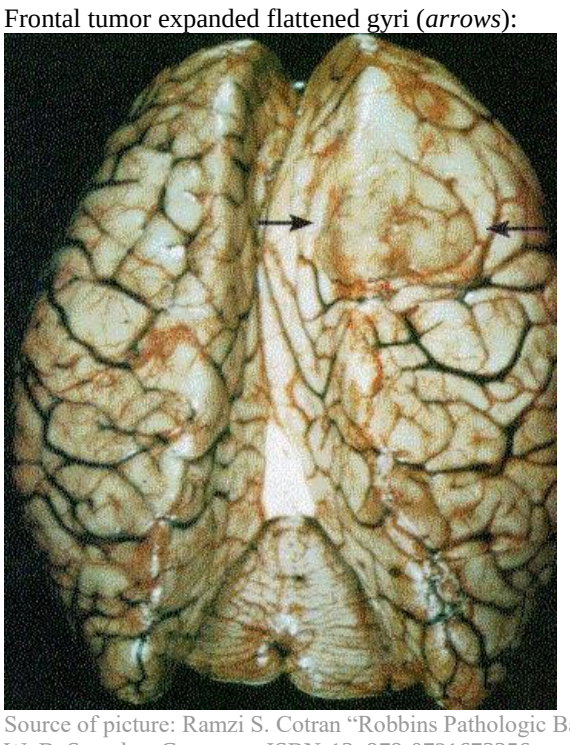


Expanded white matter of left cerebral hemisphere and thickened corpus callosum and fornices:



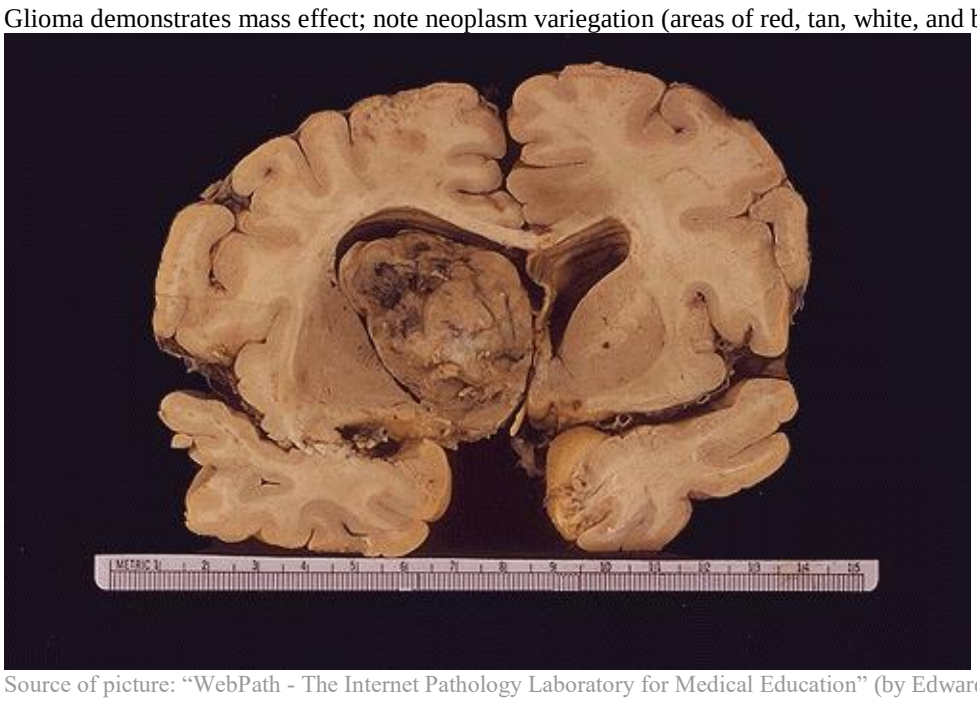
Source of picture: Ramzi S. Cotran "Robbins Pathologic Basis of Disease", 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>

Frontal tumor expanded flattened gyri (*arrows*):



Source of picture: Ramzi S. Cotran "Robbins Pathologic Basis of Disease", 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>

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 astrocyte** [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"

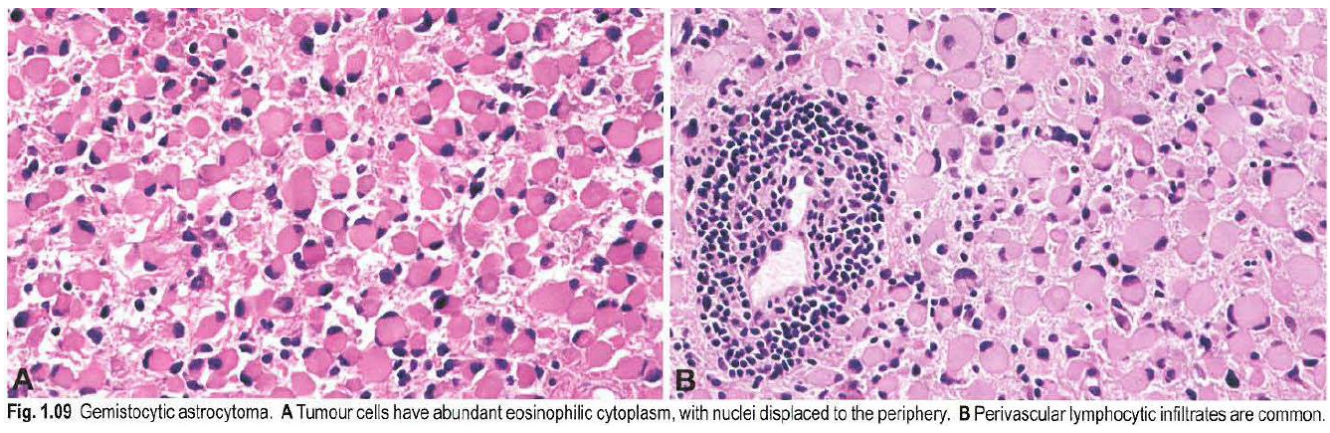
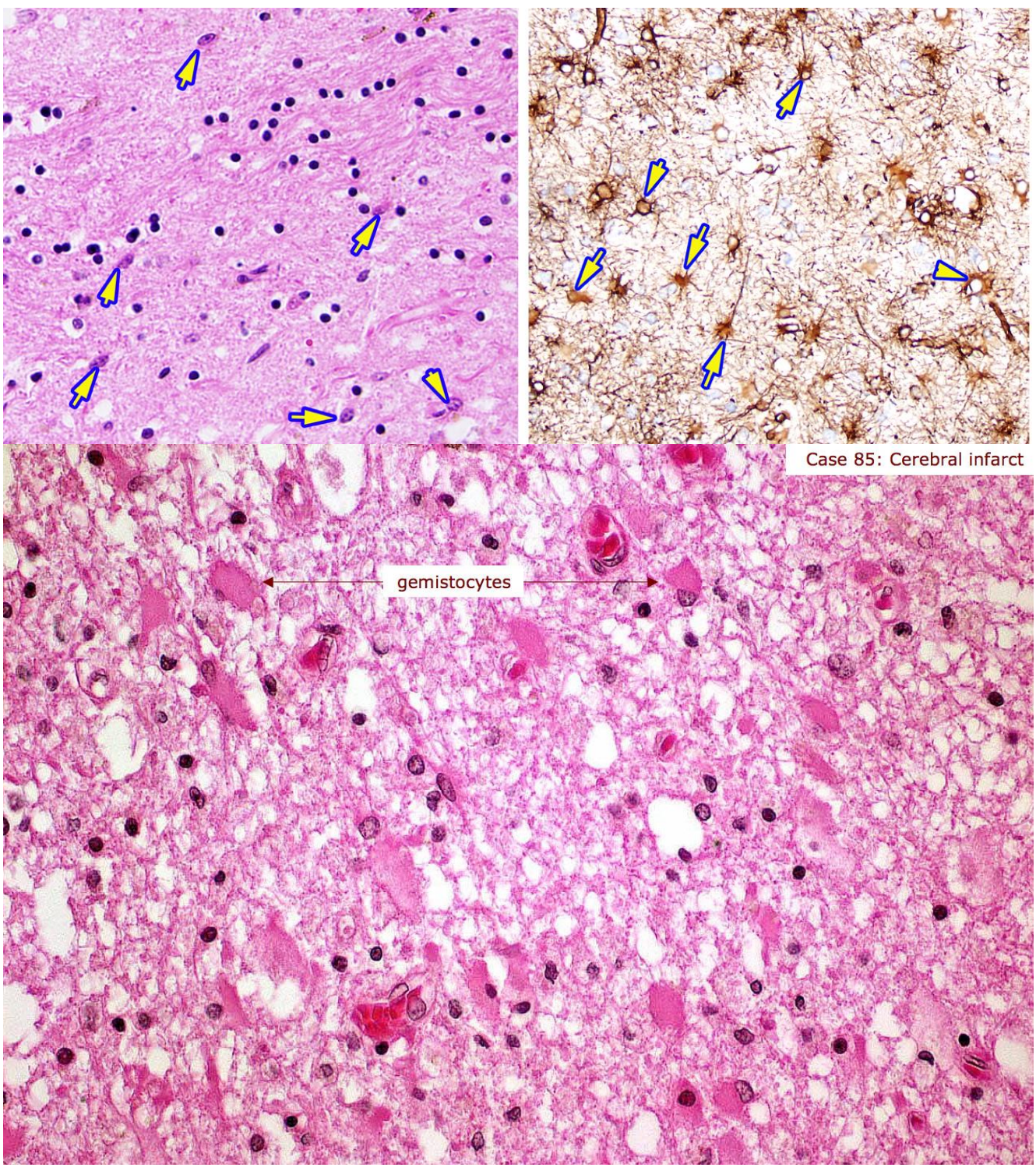


Fig. 1.09 Gemistocytic astrocytoma. **A** Tumour cells have abundant eosinophilic cytoplasm, with nuclei displaced to the periphery. **B** Perivascular lymphocytic infiltrates are common.



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:

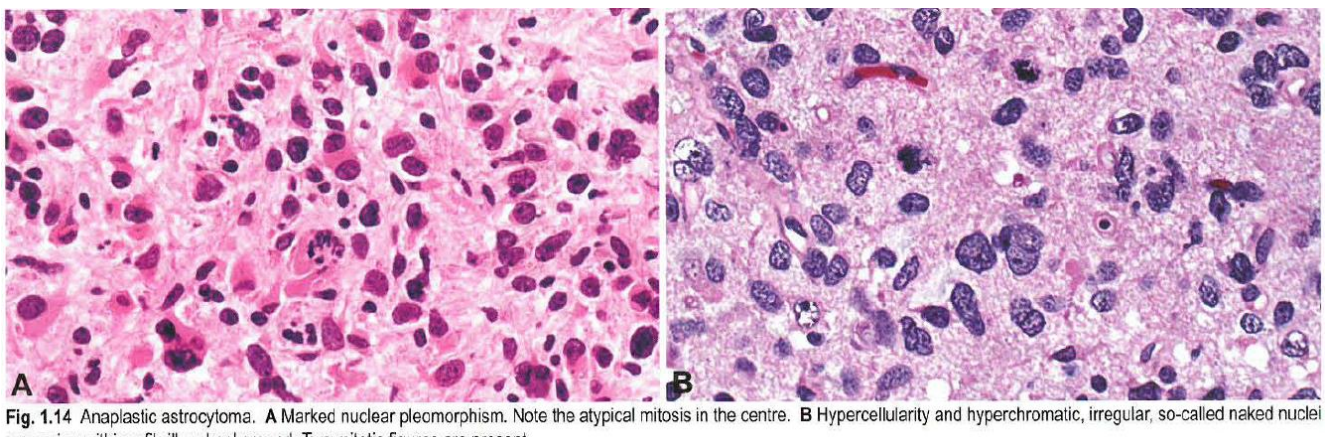
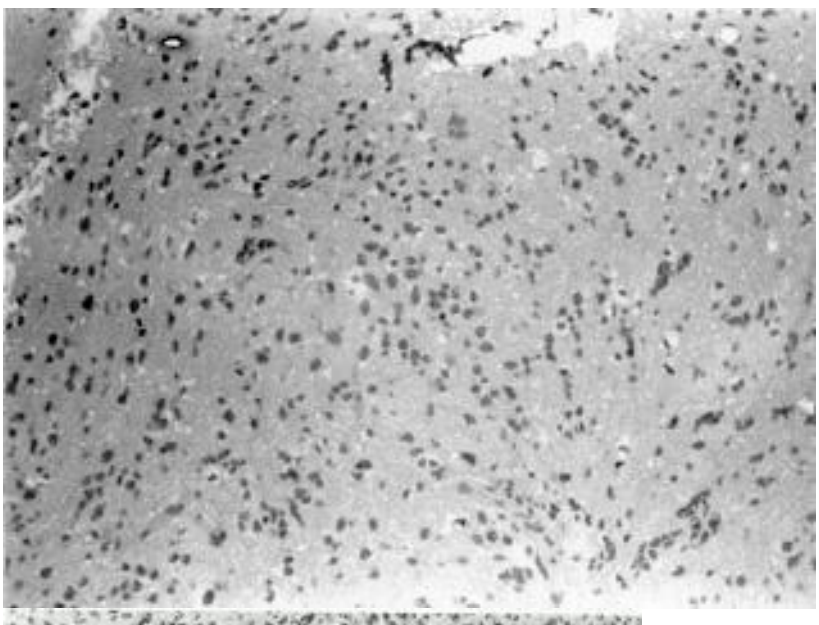
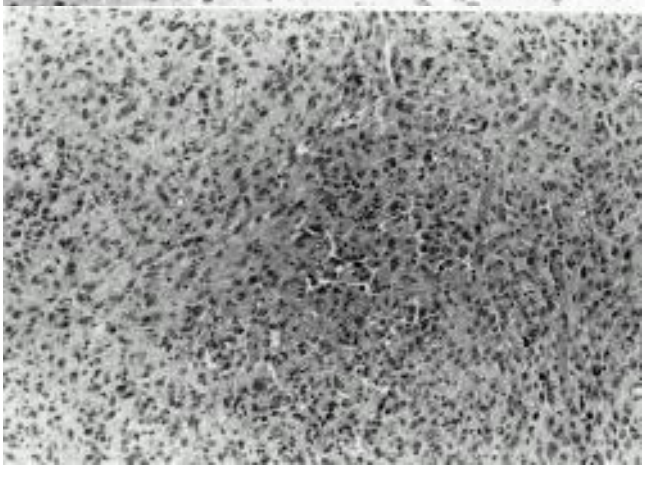
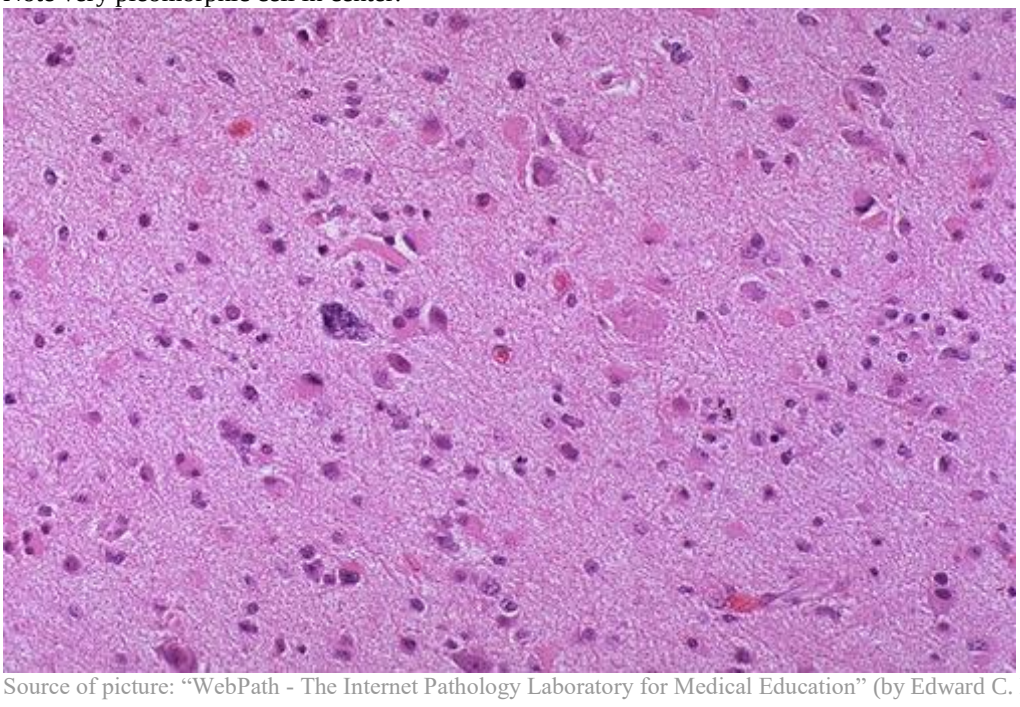


Fig. 1.14 Anaplastic astrocytoma. **A** Marked nuclear pleomorphism. Note the atypical mitosis in the centre. **B** Hypercellularity and hyperchromatic, irregular, so-called naked nuclei appearing within a fibrillary background. Two mitotic figures are present.





Note very pleomorphic cell in center:



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

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.

	IDH-wildtype glioblastoma	IDH-mutant glioblastoma
Synonym	Primary glioblastoma, IDH-wildtype	Secondary glioblastoma, IDH-mutant
Precursor lesion	Not identifiable; develops de novo	Diffuse astrocytoma Anaplastic astrocytoma
Proportion of glioblastomas	~90%	~10%
Median age at diagnosis	~62 years	~44 years
Male-to-female ratio	1.42:1	1.05:1
Mean length of clinical history	4 months	15 months
Median overall survival		
Surgery + radiotherapy	9.9 months	24 months
Surgery + radiotherapy + chemotherapy	15 months	31 months
Location	Supratentorial	Preferentially frontal
Necrosis	Extensive	Limited
TERT promoter mutations	72%	26%
TP53 mutations	27%	81%
ATRX mutations	Exceptional	71%
EGFR amplification	35%	Exceptional
PTEN mutations	24%	Exceptional

Histology

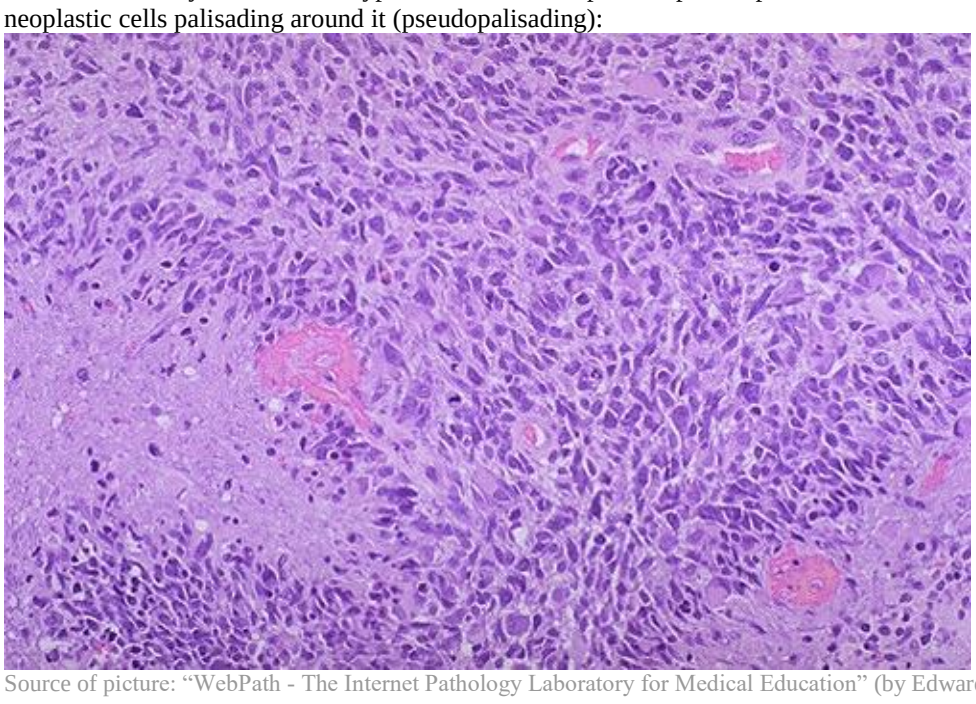
- marked cellularity, high proliferation indices, anaplasia, foci of tumor necrosis (!!!) accompanied by pseudopalisading (tumor cells crowded along edges of necrotic region):

N.B. necrosis distinguishes glioblastoma multiforme from anaplastic astrocytoma!

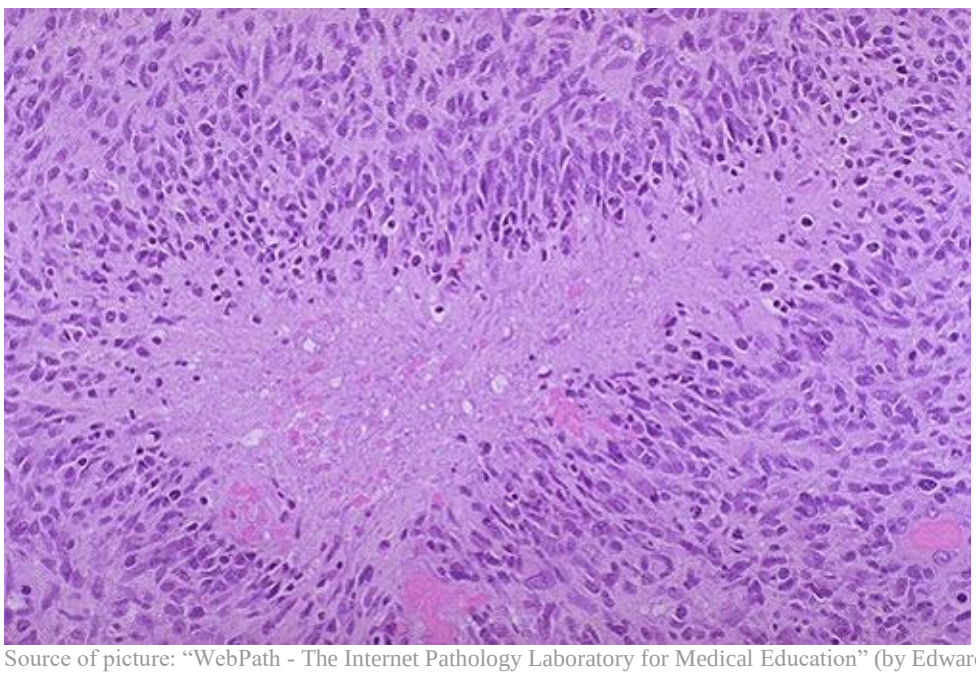
- poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells.
- infiltrates brain extensively (may become enormous before turning symptomatic); frequently involve and cross corpus callosum; **GLIOMATOSIS CEREBRI** – almost entire brain infiltrated with tumor cells (three lobes or more to both cerebral hemispheres with additional involvement of the deep 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.

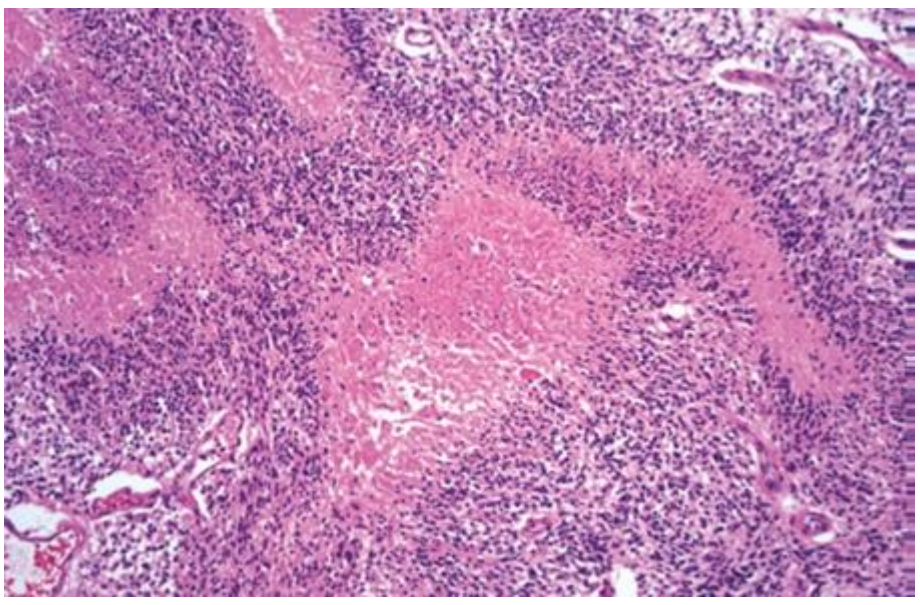
Marked cellularity with marked hyperchromatism and pleomorphism; prominent vascularity; necrosis (at left) with neoplastic cells palisading around it (pseudopalisading):



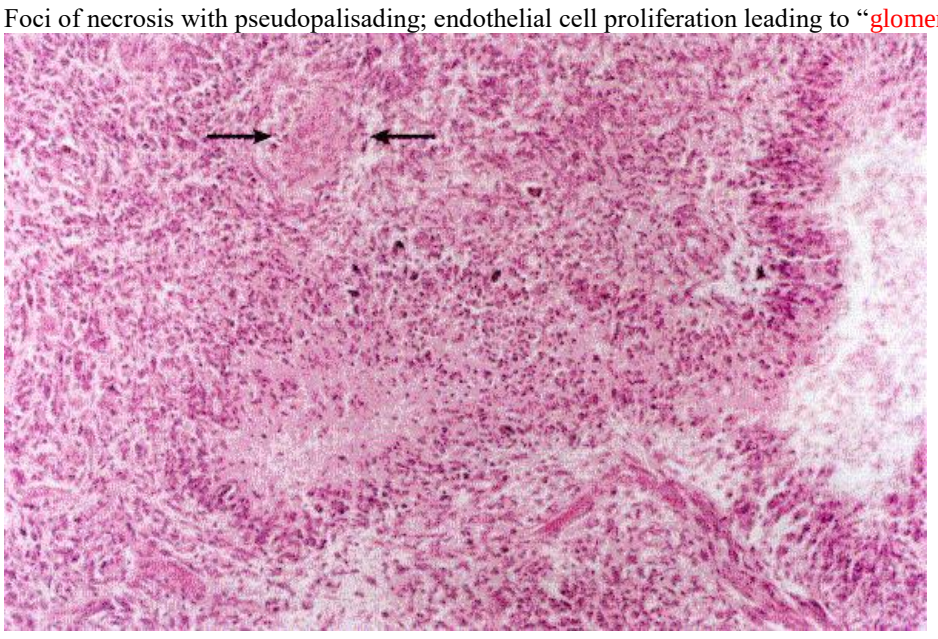
Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



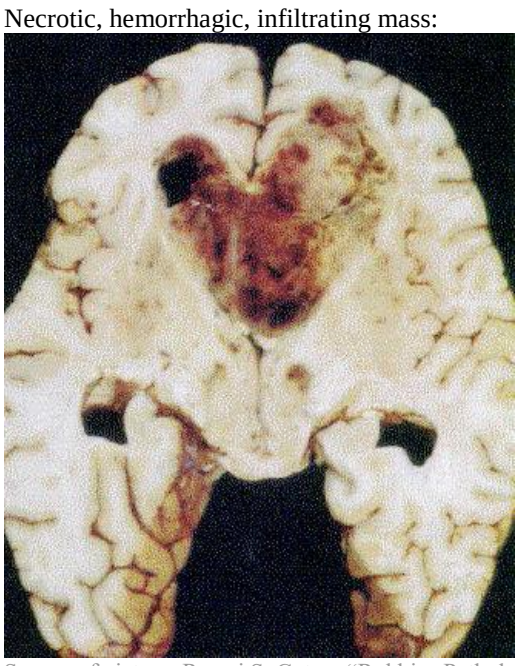
Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



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



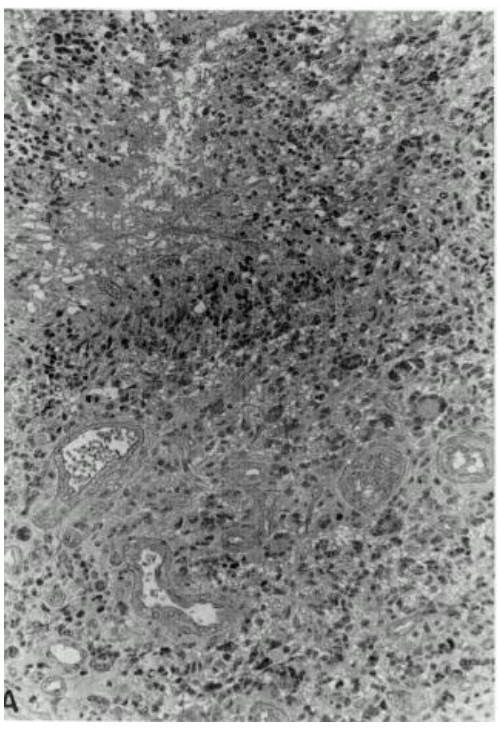
Necrotic, hemorrhagic, infiltrating mass:

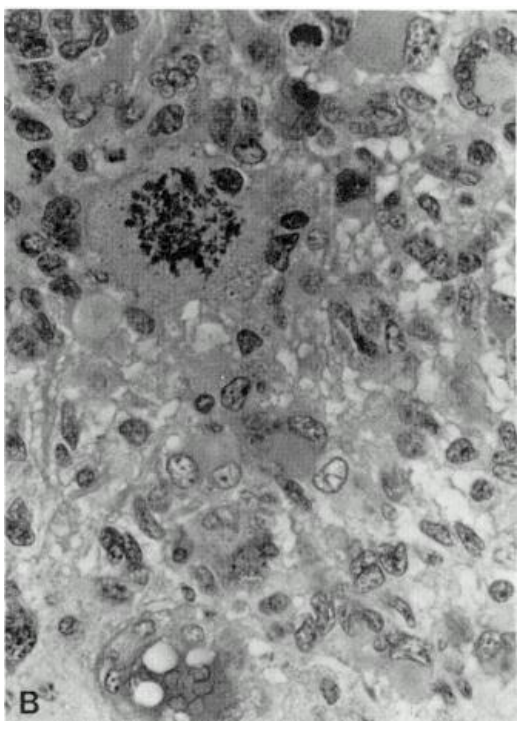


Source of picture: Ramzi S. Cotran "Robbins Pathologic Basis of Disease", 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>

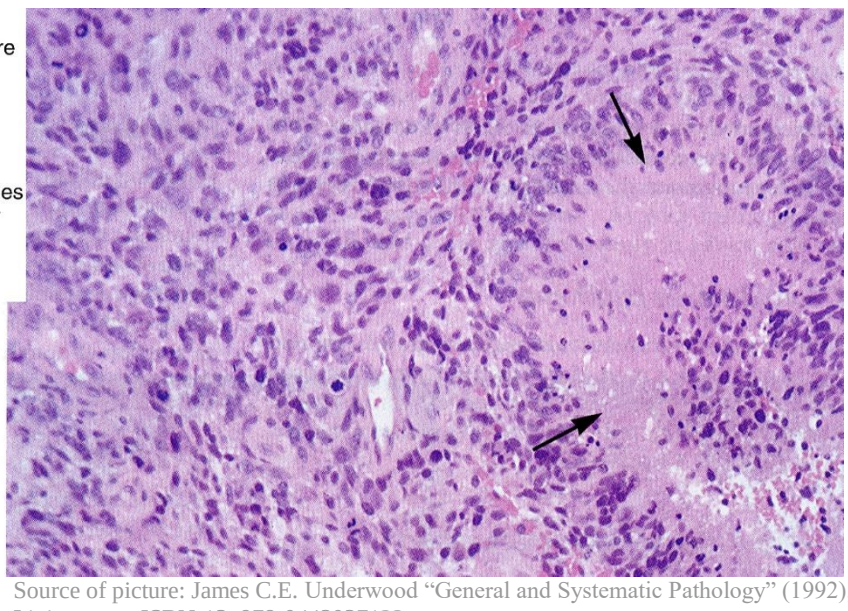
Pseudopalisading (*upper left*), neovascularity, nuclear anaplasia, multinucleated giant cells (*lower right*):

Cellular anaplasia, multinucleated cells, bizarre mitosis (*upper left corner*):



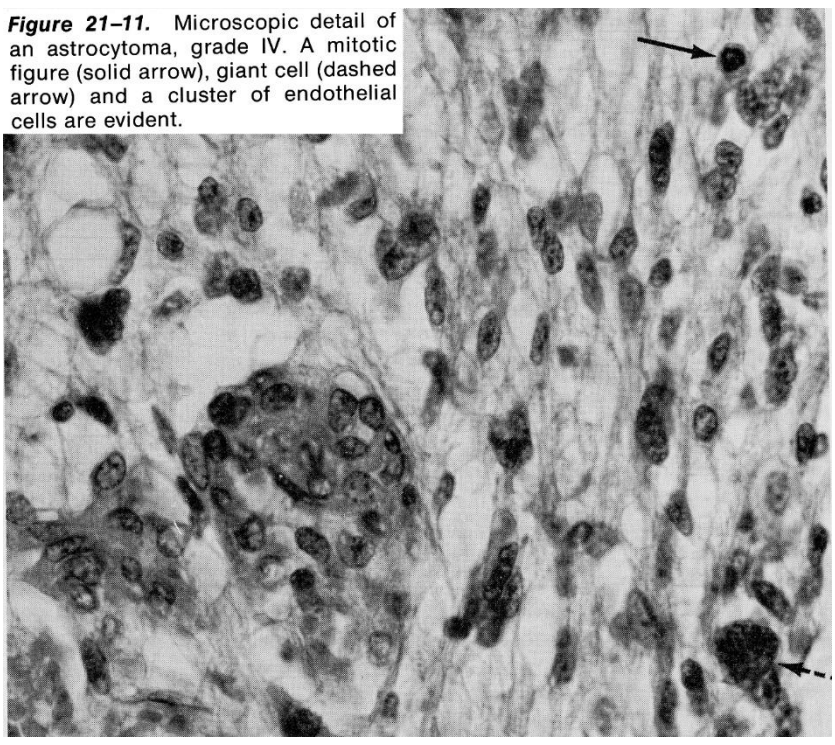


Glioblastoma multiforme
Areas of necrosis (arrows) are characteristic feature of this neoplasm, and are usually surrounded by the nuclei of small malignant cells. The neoplastic cell population is pleomorphic, and also includes multinucleate cells. Vascular endothelial proliferation is another characteristic histological feature.

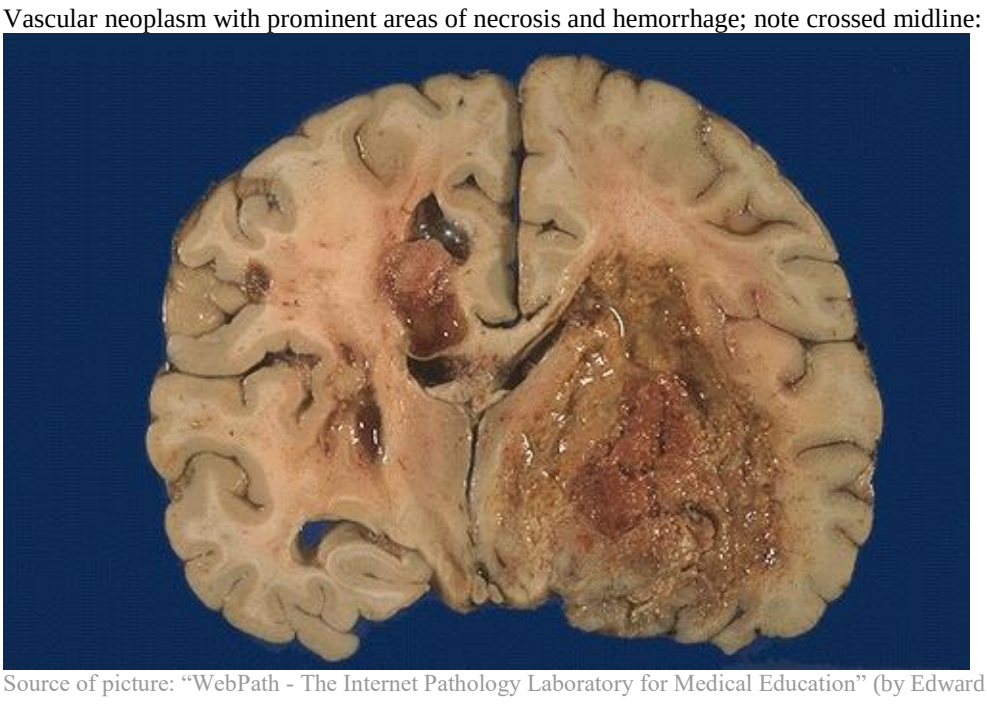


Source of picture: James C.E. Underwood "General and Systematic Pathology" (1992); Churchill Livingstone; ISBN-13: 978-0443037122 >>

Figure 21–11. Microscopic detail of an astrocytoma, grade IV. 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:



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

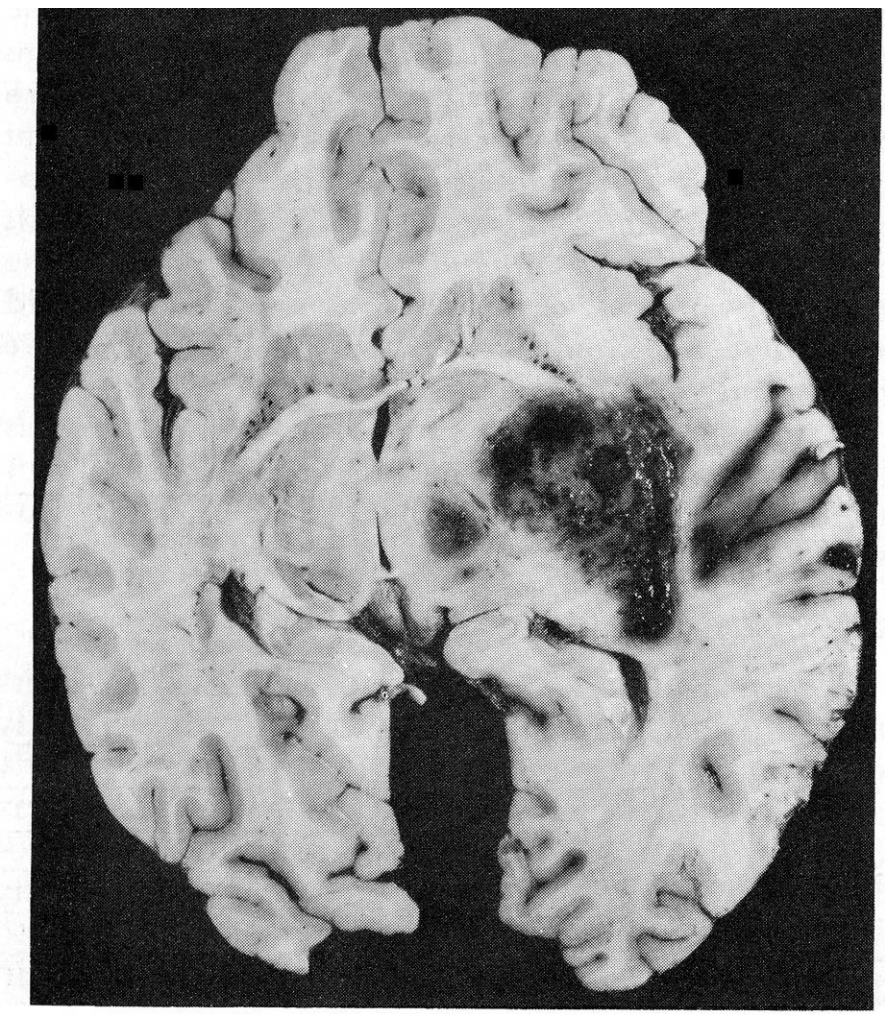
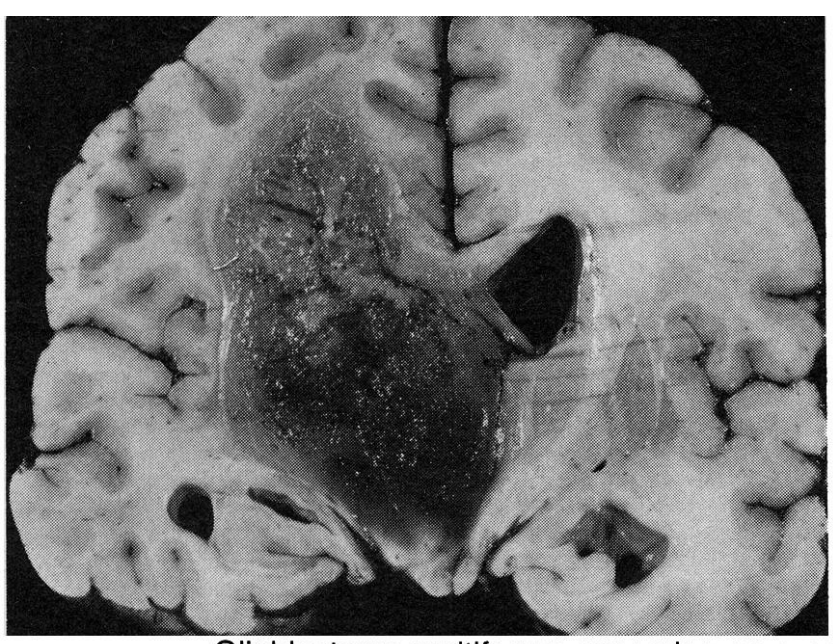
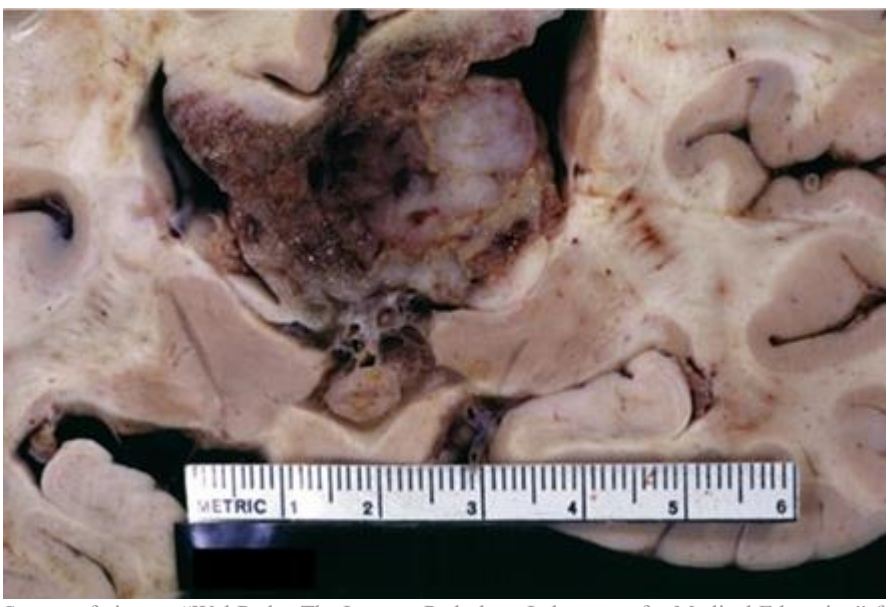


Figure 21–12. Astrocytoma, grade IV (glioblastoma multiforme), showing prominent hemorrhage and areas of cystic softening. The neoplasm and the surrounding edema have produced considerable expansion of the hemisphere.



Glioblastoma multiforme appearing as a necrotic hemorrhagic infiltrating mass.



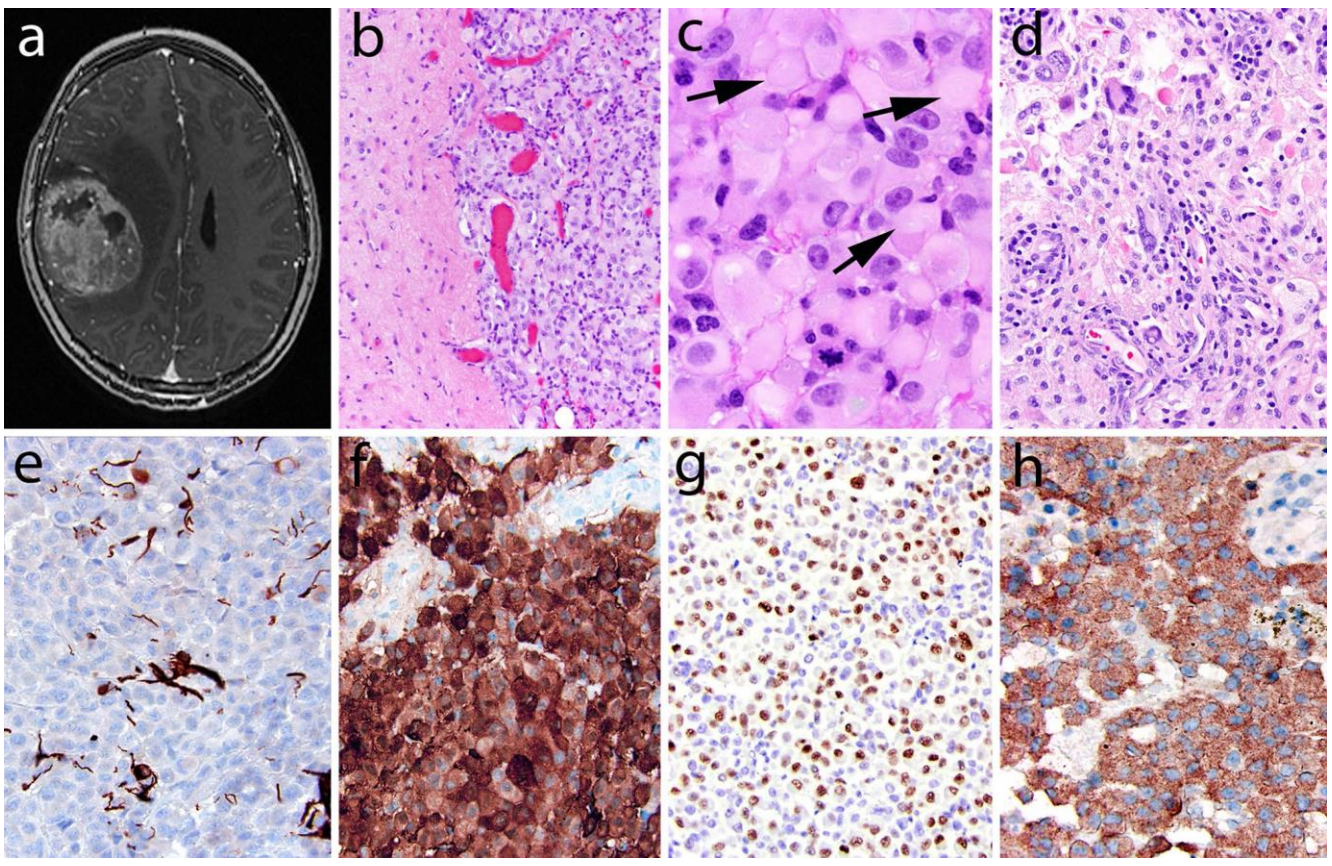
Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

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

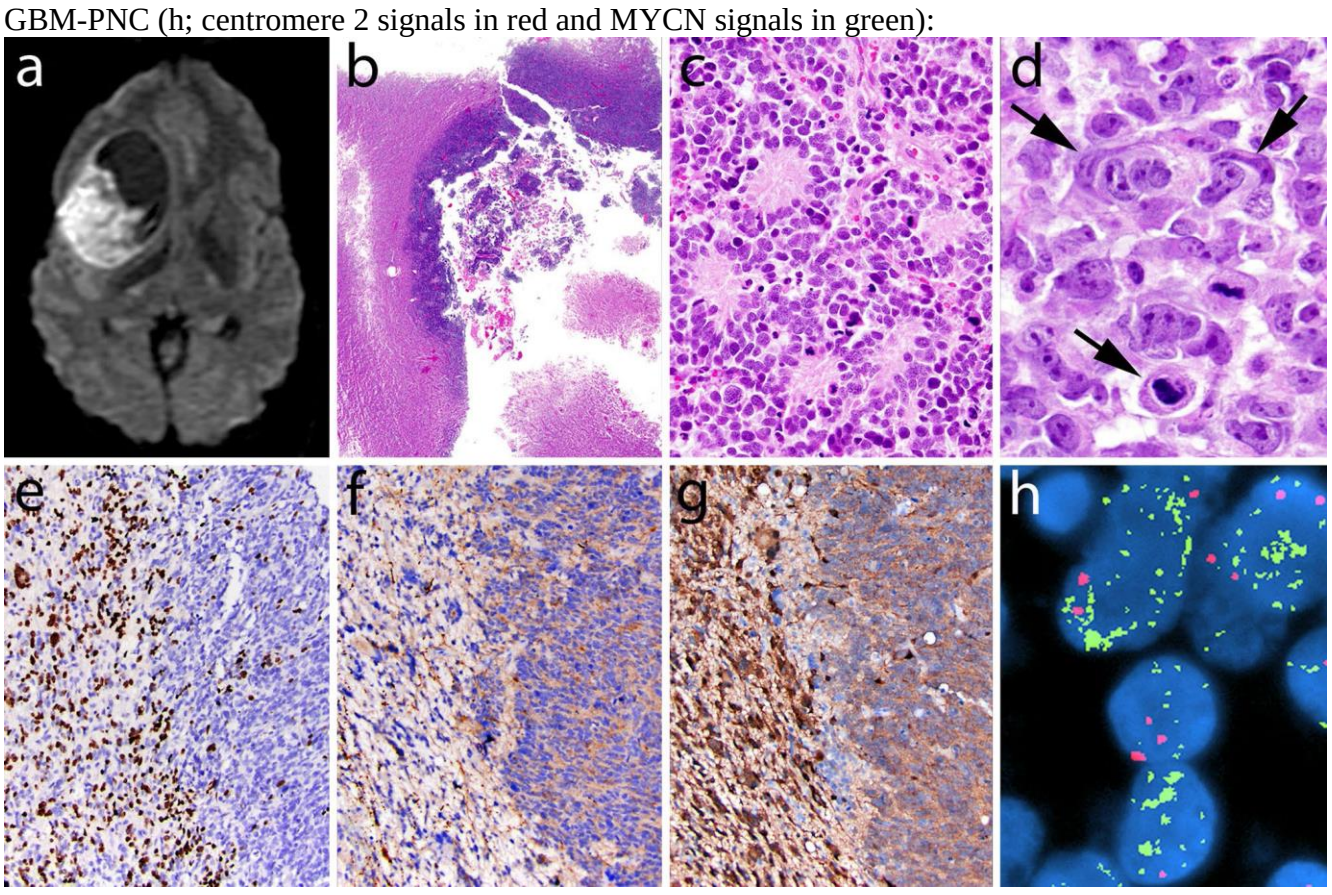
- variant of IDH-wildtype glioblastoma

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

Median age of onset:

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.

ANAPLASTIC 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. >>

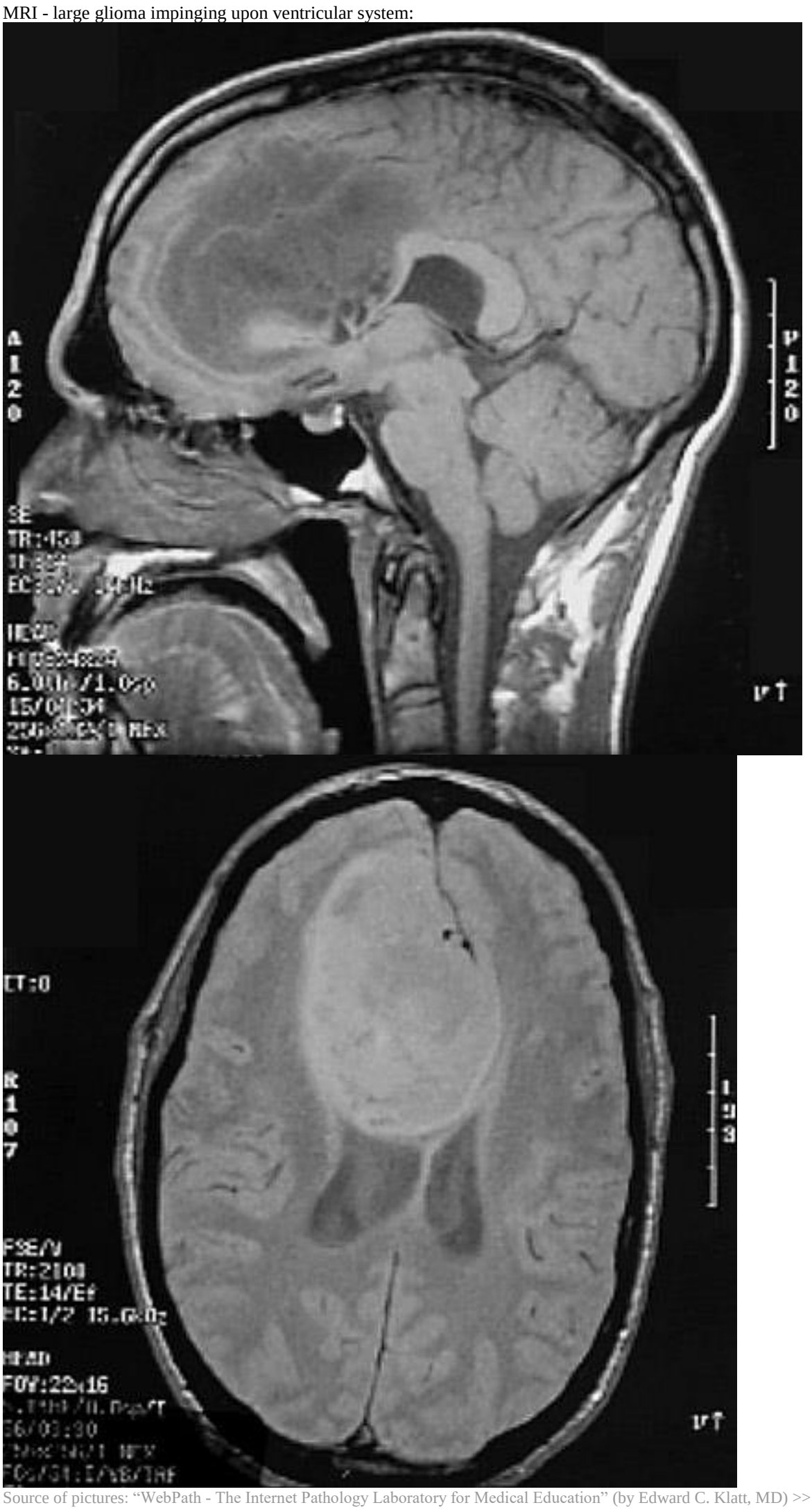
Tumor type	MRI with gadolinium	Contrast CT
PILOCYTIC ASTROCYTOMA	enhance!; associated cysts particularly prominent on T2	enhance!
PLEOMORPHIC XANTHOASTROCYTOMA	may enhance strongly; little or no edema	
LOW-GRADE ASTROCYTOMAS	T1 signal↓ (↑ on T2); do not enhance!; minimal mass effect	do not enhance! - invisible (or vague low density)
ANAPLASTIC ASTROCYTOMAS	solidly bright or patchy (30-50% do not enhance)	
GLIOBLASTOMA	T1 signal↓ (↑ on T2); enhance heterogeneously in irregular ring configuration* (4-10% do not enhance)	inhomogeneous hypodense or isodense

*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 (^{1}H-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:

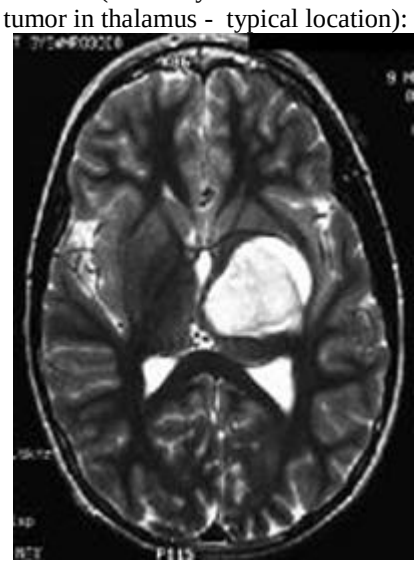


Source of pictures: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

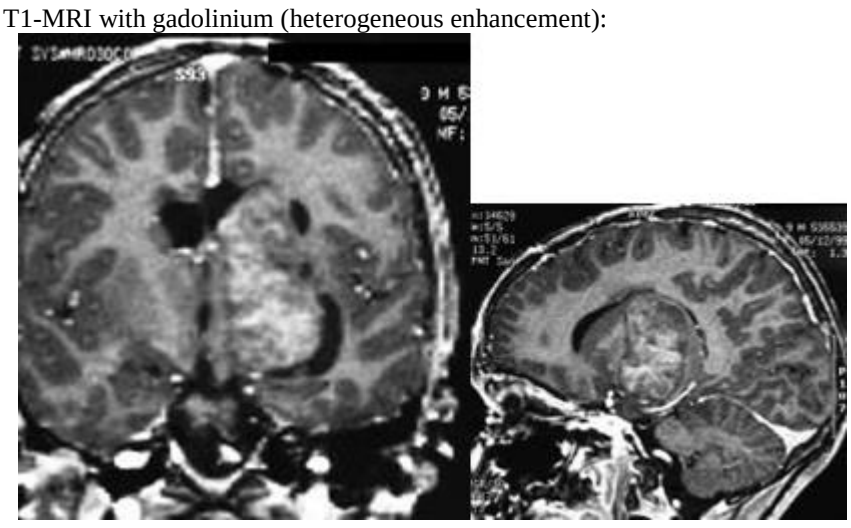
PILOCYTIC ASTROCYTOMA

- usually can be diagnosed accurately by MRI!

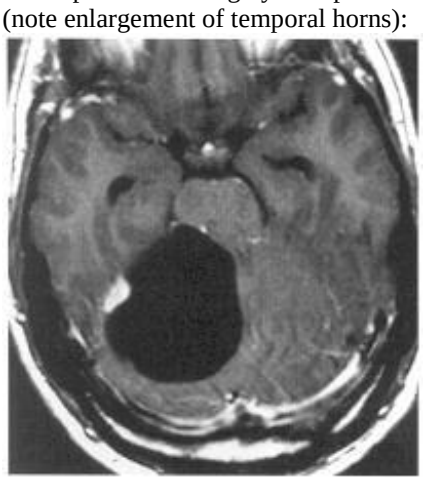
T2-MRI (relatively well-circumscribed tumor in thalamus - typical location):



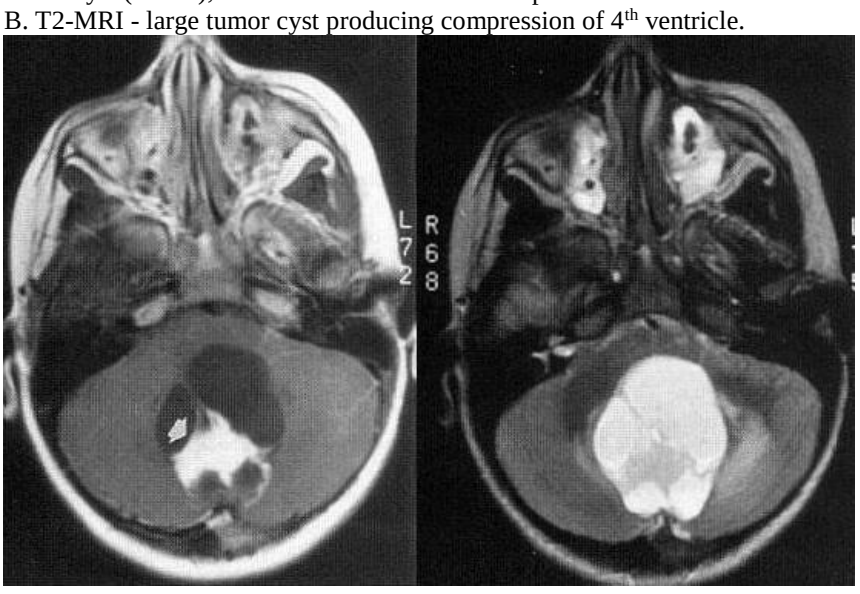
T1-MRI with gadolinium (heterogeneous enhancement):

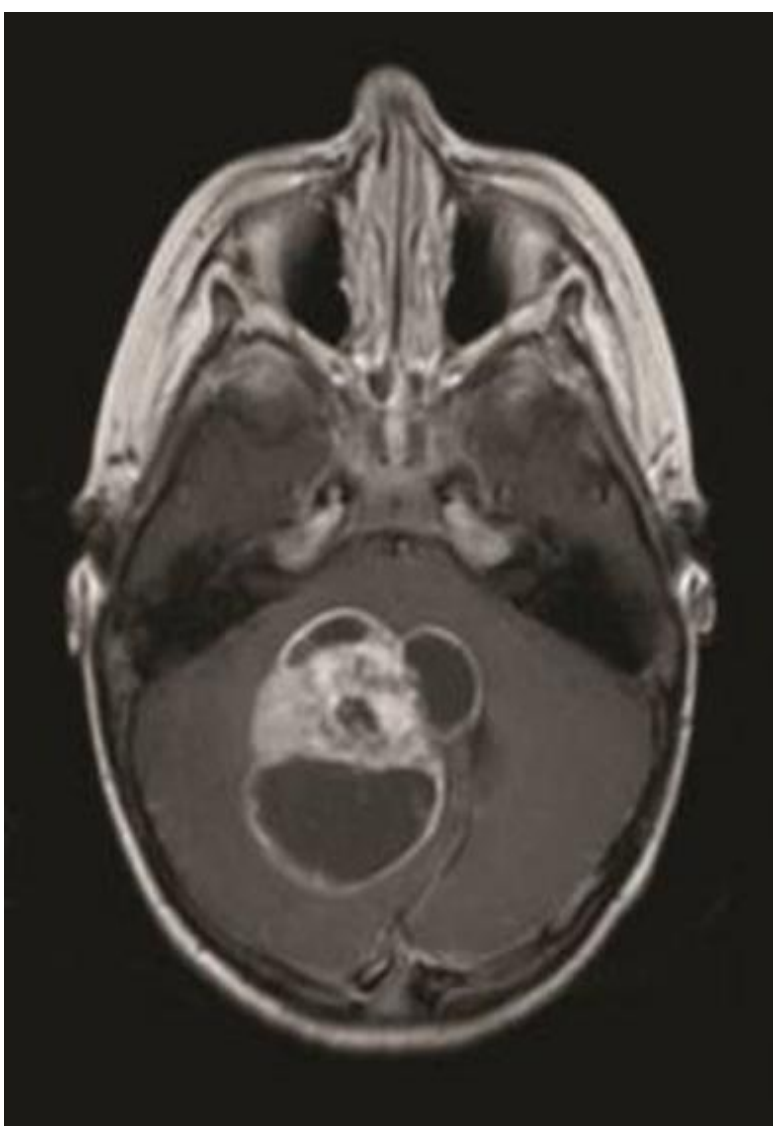


T1-MRI (post-gadolinium) - cystic lesion in cerebellum with small, *enhancing mural nodule* but otherwise non-enhancing cyst wall; 4th ventricle is compressed causing hydrocephalus (note enlargement of temporal horns):



A. T1-MRI with contrast - irregularly shaped nodule along posterior aspect of tumor cyst (*arrow*); nodule connects to several septations.
B. T2-MRI - large tumor cyst producing compression of 4th ventricle.



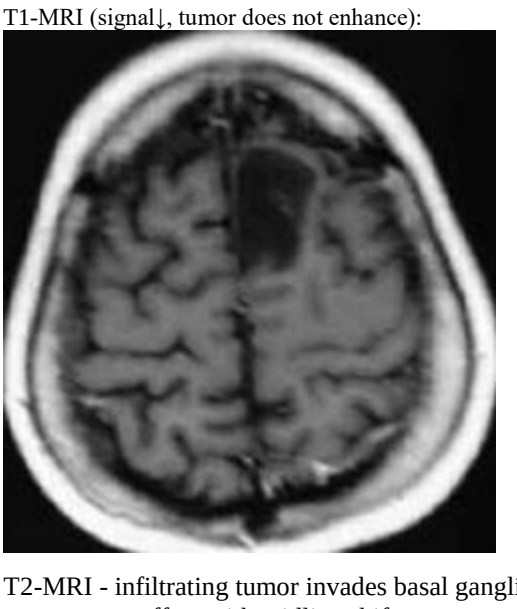


DIFFUSE (LOW-GRADE) ASTROCYTOMA

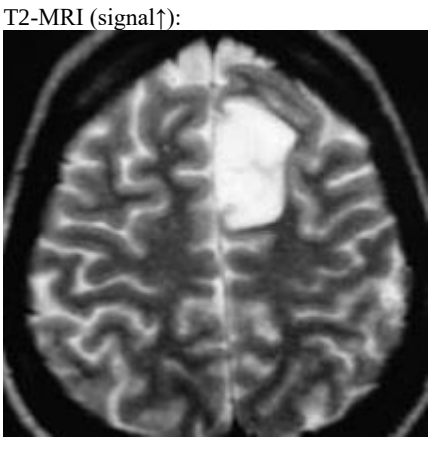
Best MRI sequence – **FLAIR**

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):

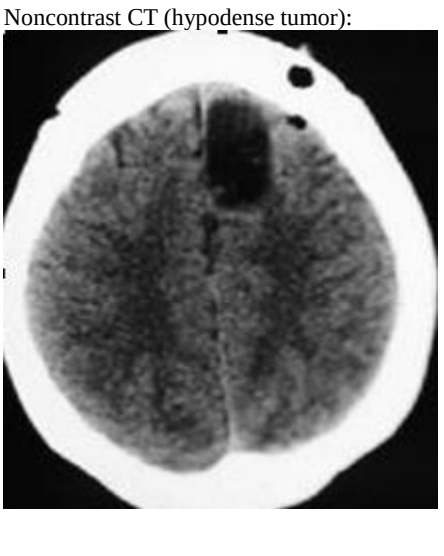


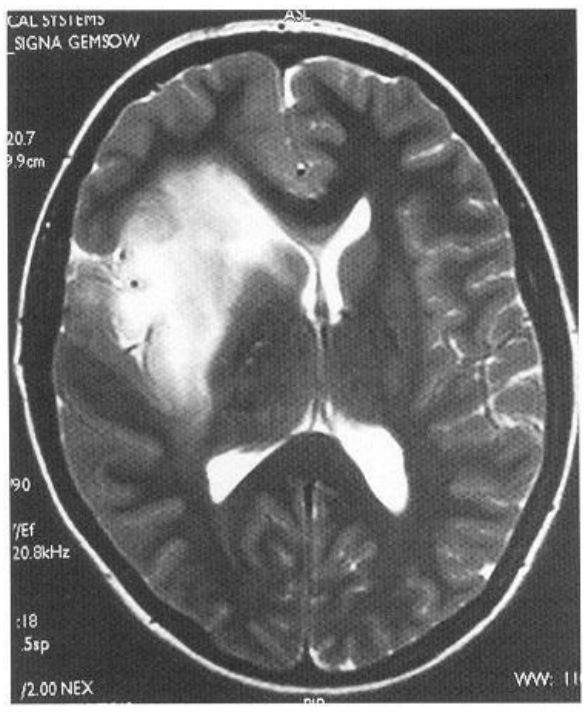
T2-MRI (signal↑):



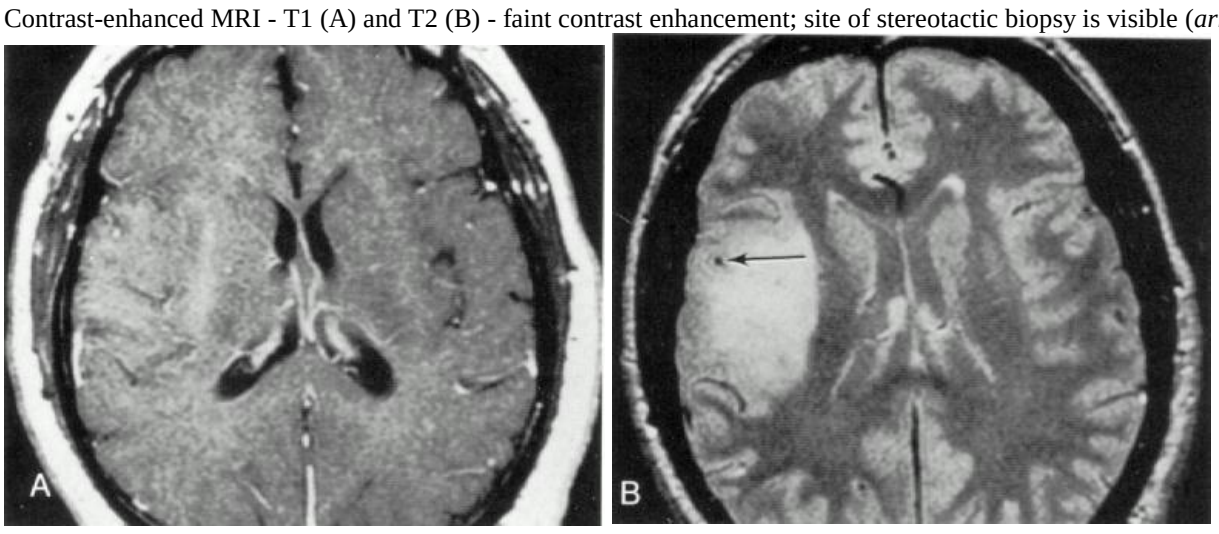
T2-MRI - infiltrating tumor invades basal ganglia and causes mass effect with midline shift:

Noncontrast CT (hypodense tumor):

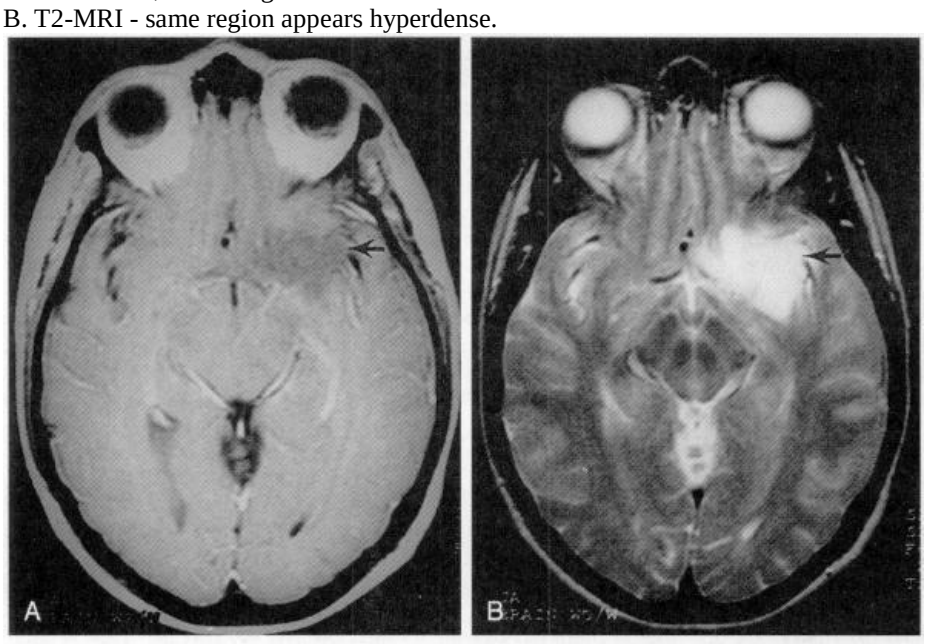




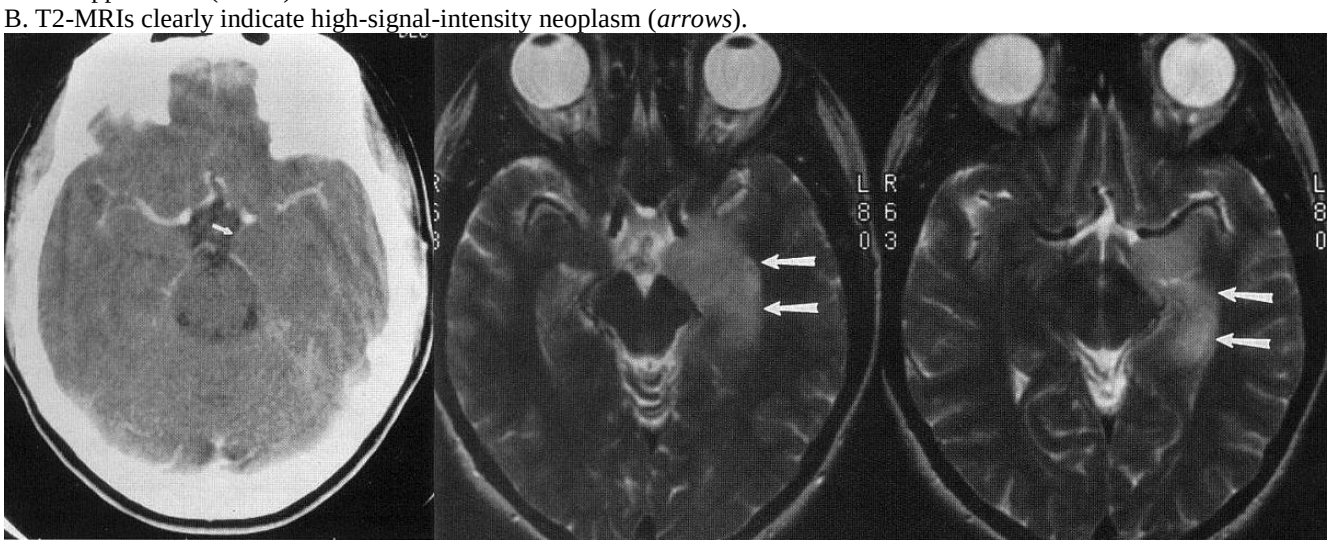
Contrast-enhanced MRI - T1 (A) and T2 (B) - faint contrast enhancement; site of stereotactic biopsy is visible (*arrow*):

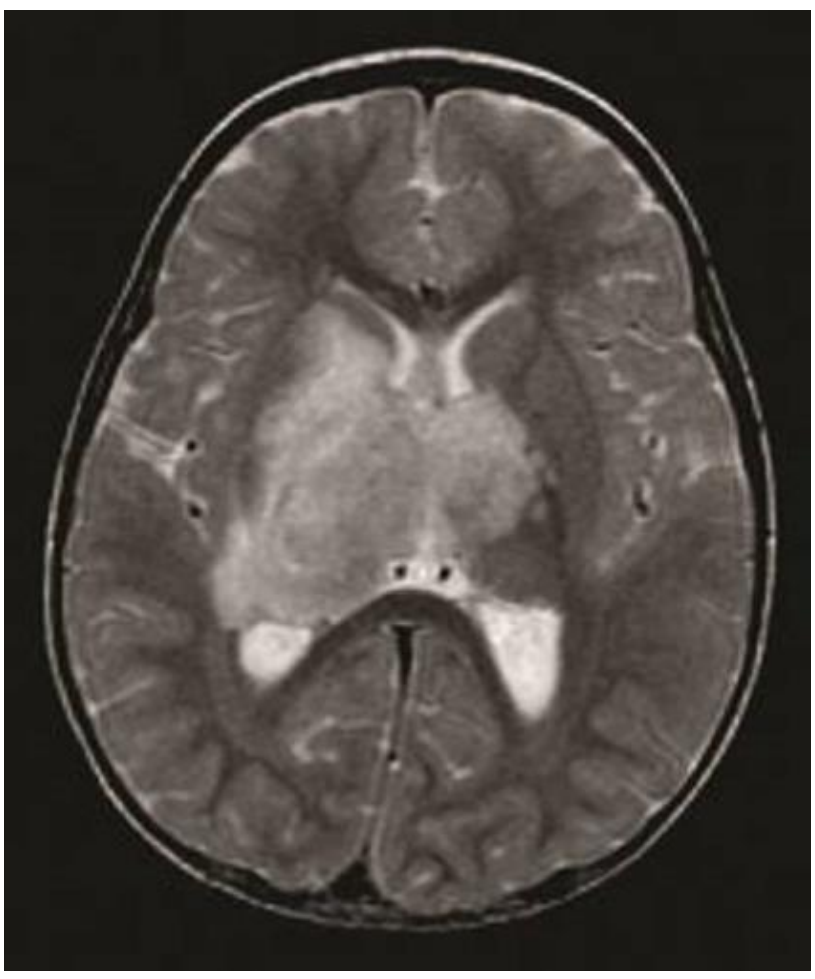


A. T1-MRI - nonenhancing, low-density region (*arrow*); no significant mass effect, but edges of lesion are not well circumscribed, indicating infiltration.
B. T2-MRI - same region appears hyperdense.



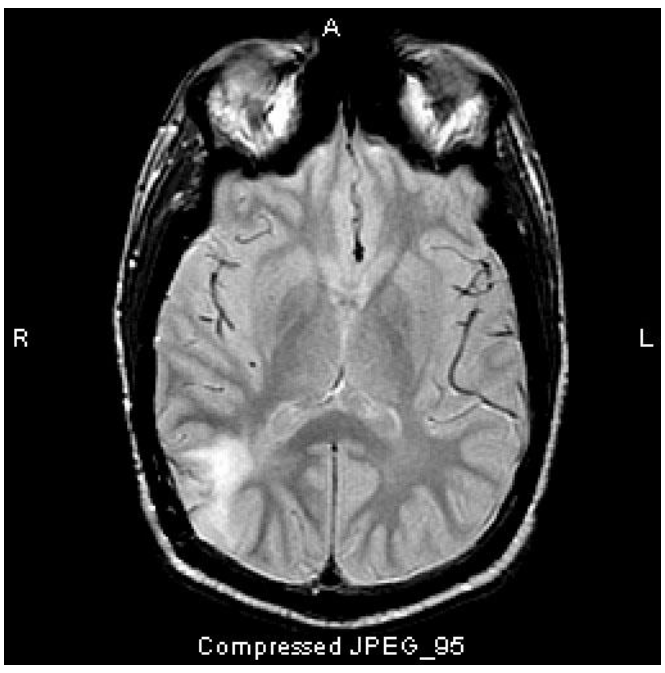
A. Contrast-enhanced CT fails to demonstrate medial left temporal lobe neoplasm; small mass effect associated with uncus can be appreciated (*arrow*).
B. T2-MRIs clearly indicate high-signal-intensity neoplasm (*arrows*).



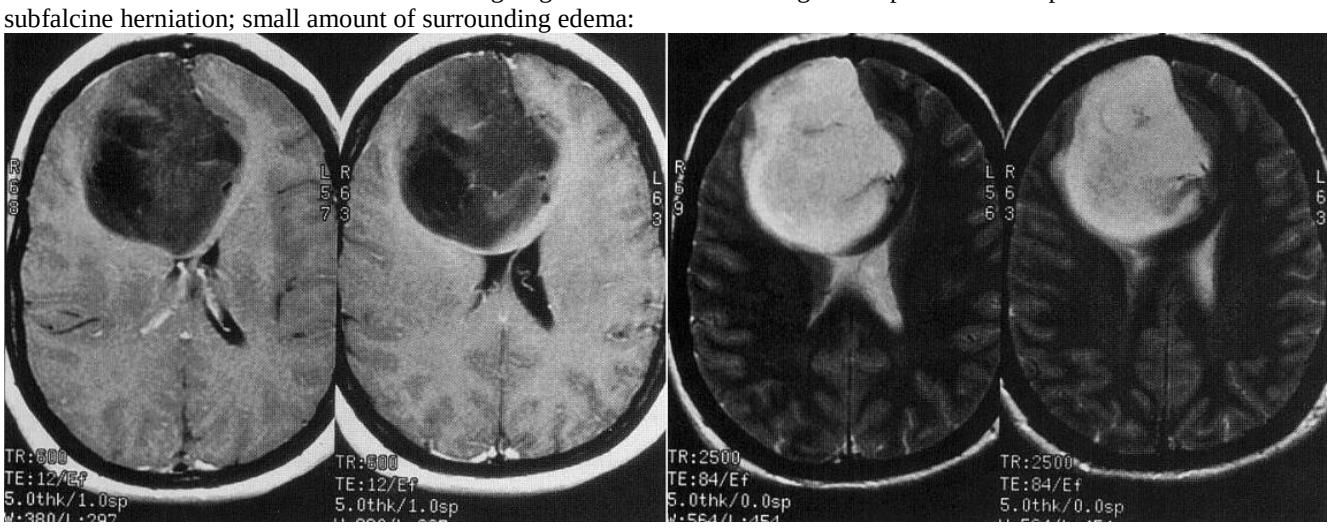


ANAPLASTIC ASTROCYTOMA

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

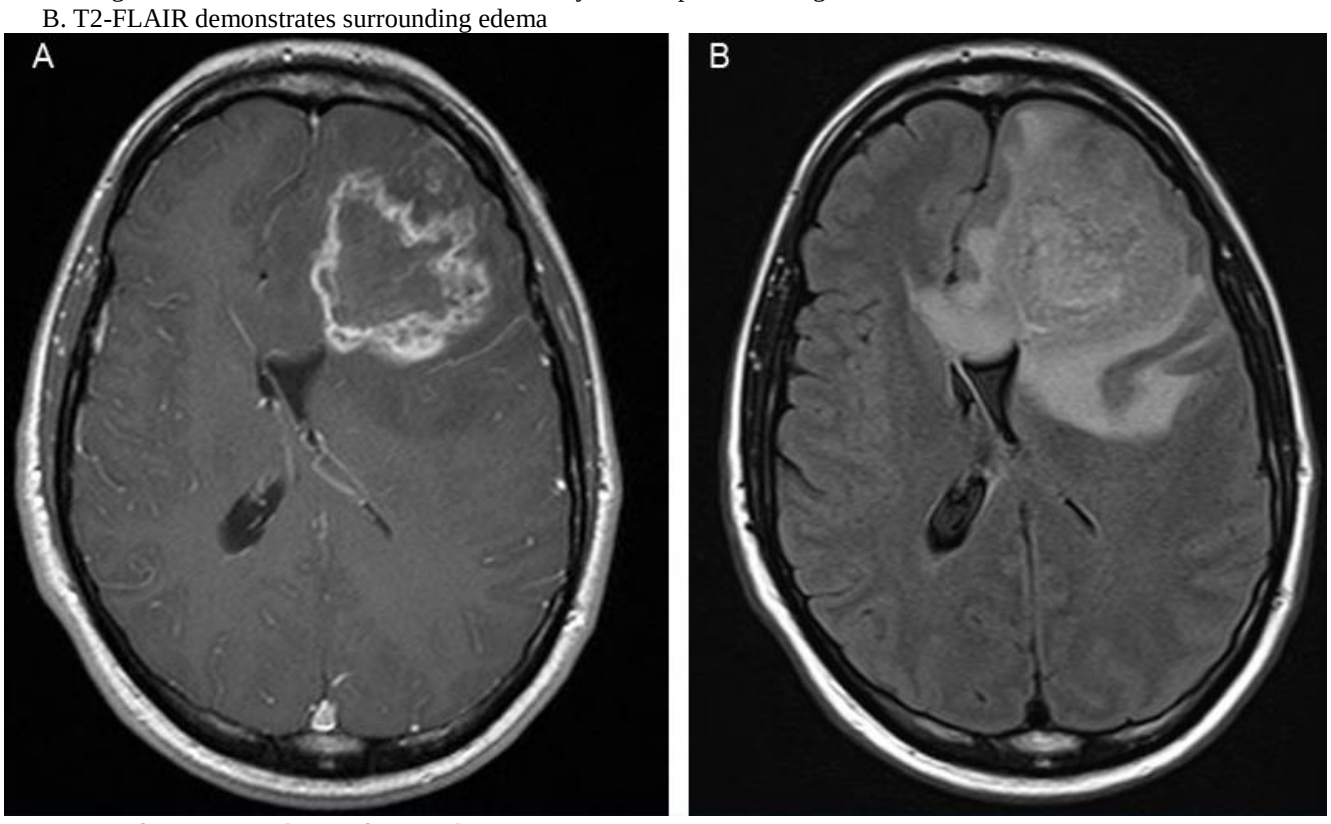


Contrast-enhanced T1-MRI and T2-MRI - large right frontal mass resulting in compression of corpus callosum and subfalcine herniation; small amount of surrounding edema:



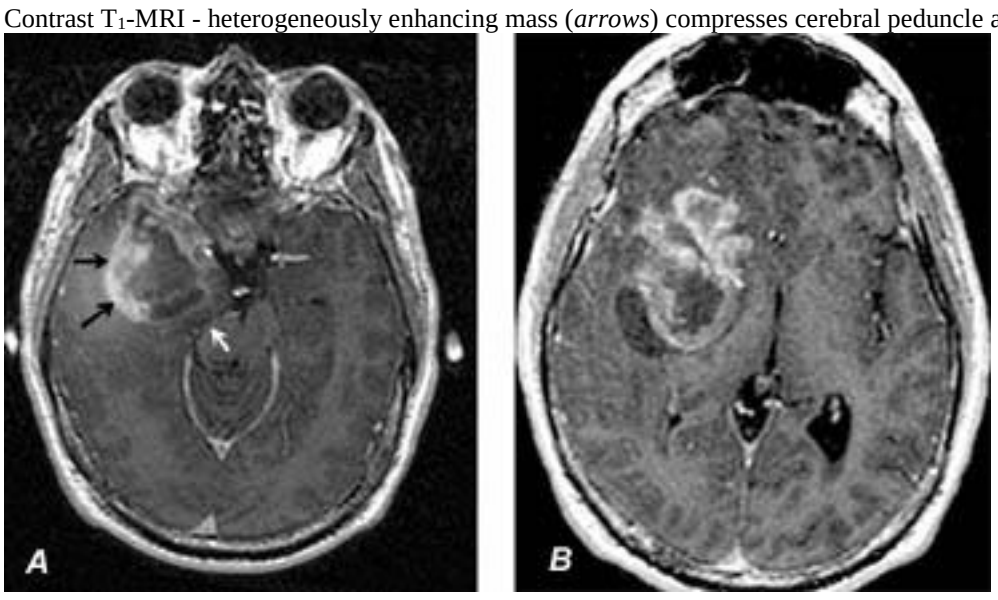
GLIOBLASTOMA MULTIFORME

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



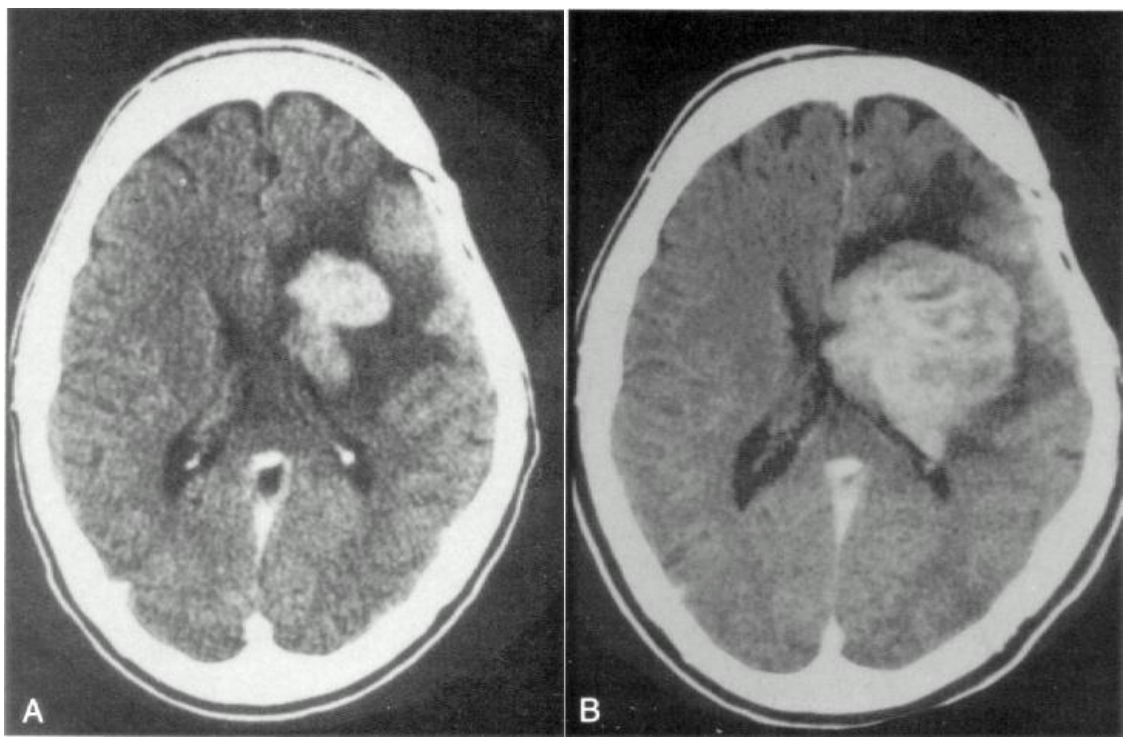
Source of picture: **Medscape** from WebMD >>

Contrast T_1-MRI - heterogeneously enhancing mass (*arrows*) compresses cerebral peduncle and midbrain (*white arrow*):

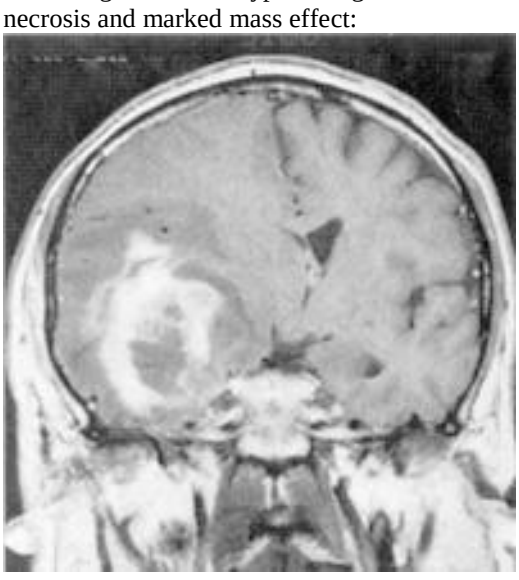


"Butterfly" glioma (because of its shape):
T2-MRI (left) - large, bilateral white signal.
T1-MRI (right) - contrast outlines tumor edge (ring enhancement).

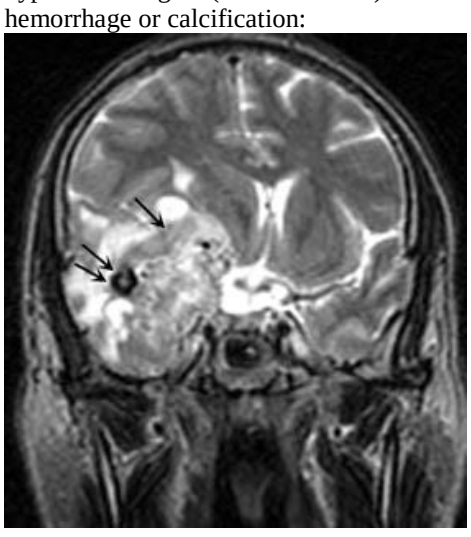
Extremely rapidly recurring glioblastoma (contrast CT) - dramatic tumor size increase from A to B (8 weeks later):



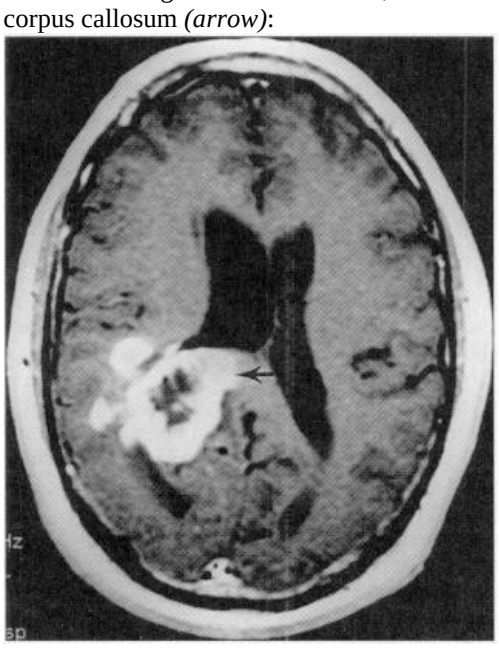
T1-MRI gadolinium - typical ring enhancement with central necrosis and marked mass effect:



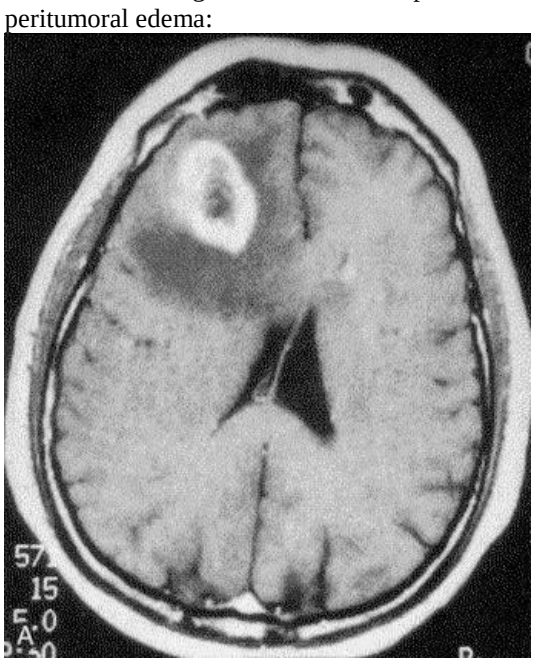
Proton density-weighted MRI - heterogeneous mass (*arrows*) compressing third and lateral ventricles; area of hypointense signal (*double arrows*) indicate either hemorrhage or calcification:



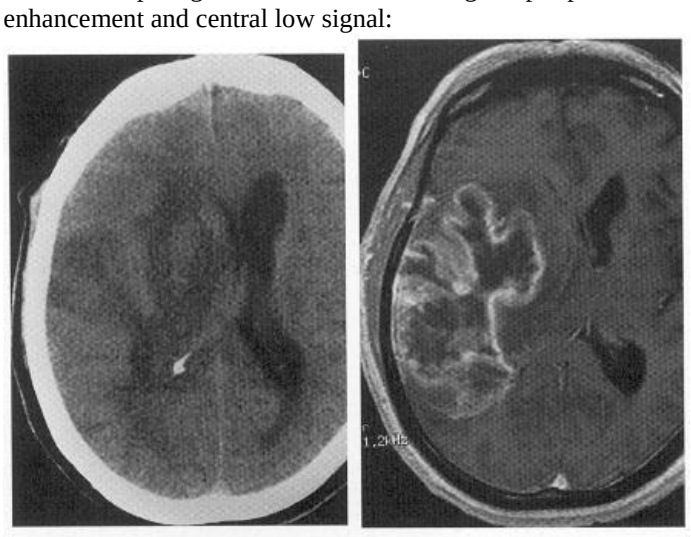
T1-MRI - irregularly ring enhancing mass with central necrosis and significant mass effect; tumor is extending up to corpus callosum *(arrow)*:



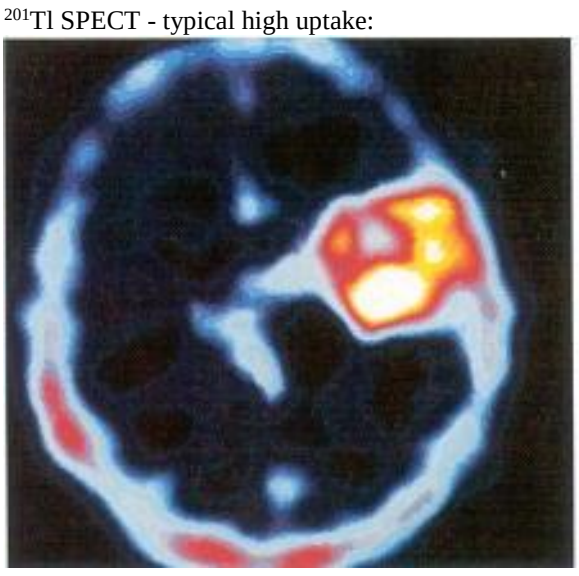
Contrast CT – ring enhancement with pronounced peritumoral edema:



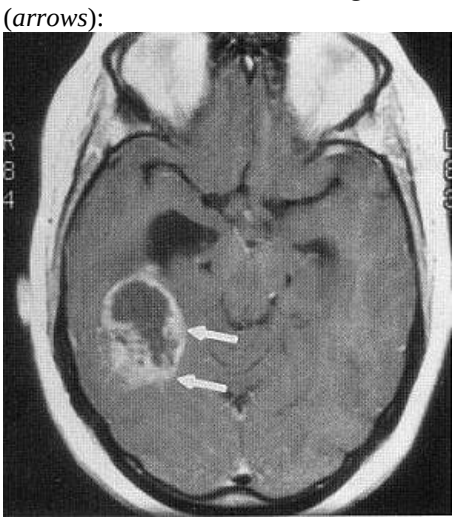
A. Unenhanced CT - white matter low density extends around but spares basal ganglia (important differentiation from stroke!).
B. T1- MRI post-gadolinium - marked, irregular peripheral enhancement and central low signal:



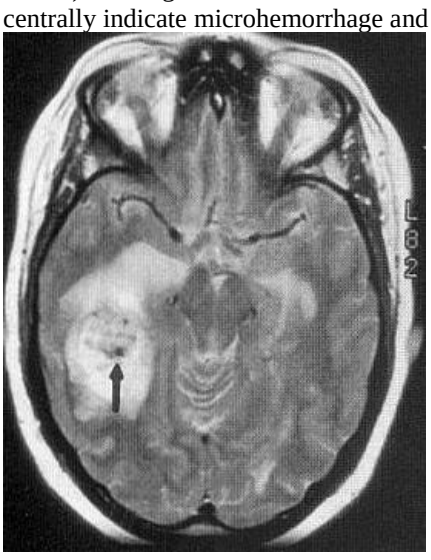
^{201}Tl SPECT - typical high uptake:

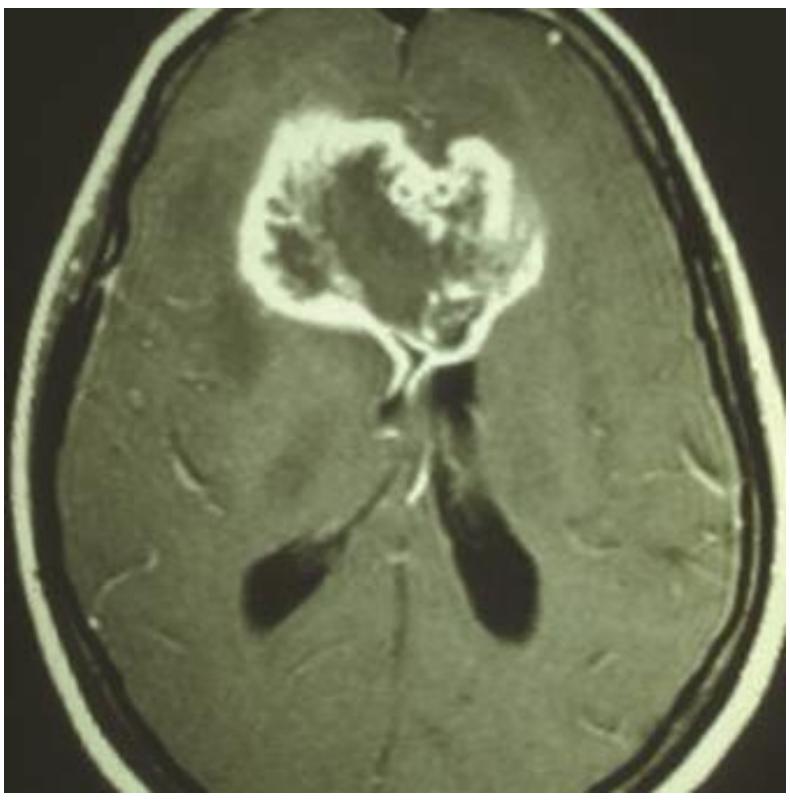


Contrast-enhanced T1-MRI - large necrotic mass (*arrows*):



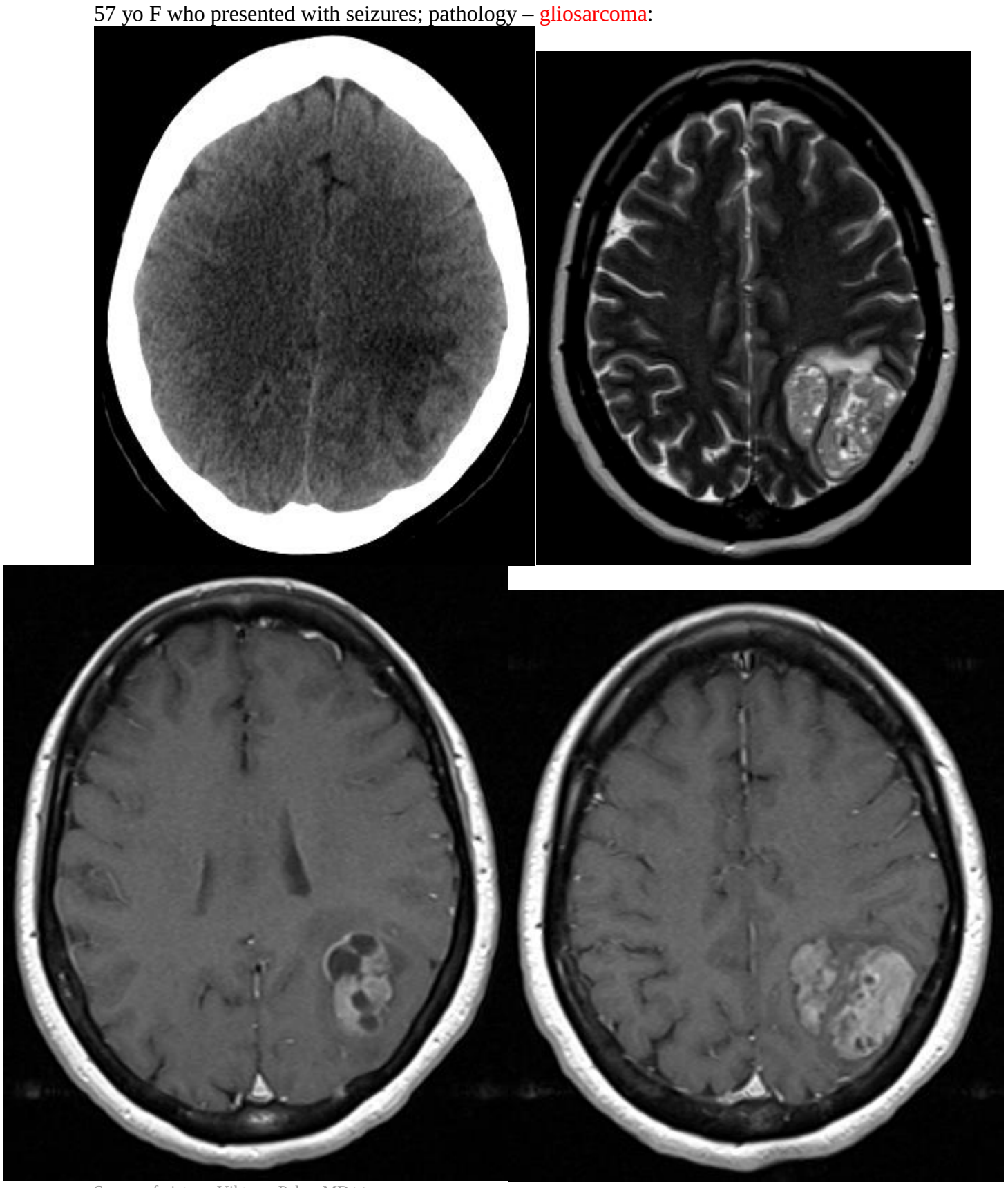
T2-MRI - high signal intensity (neoplasm and adjacent edema); heterogeneous areas of lower signal intensity centrally indicate microhemorrhage and calcification (*arrow*).





GLIOSARCOMA

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



Source of picture: Viktoras Palys, MD >>

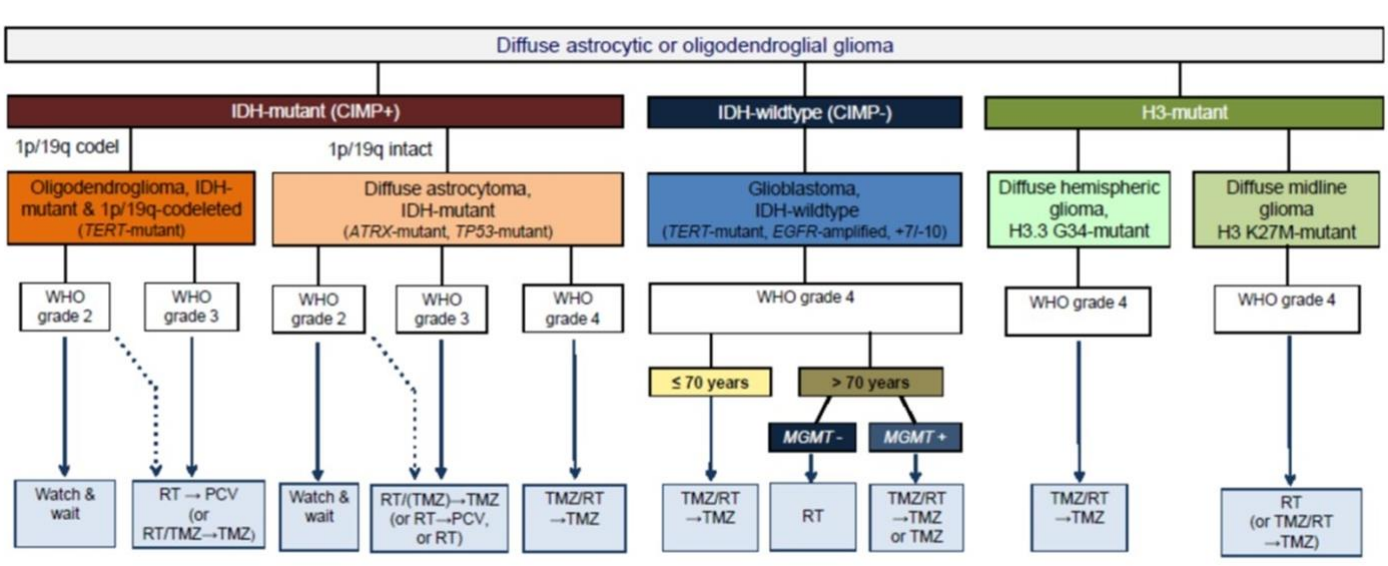
TREATMENT

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.

Also see p. Onc3 >>

GLIOMA ALGORITHM



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).

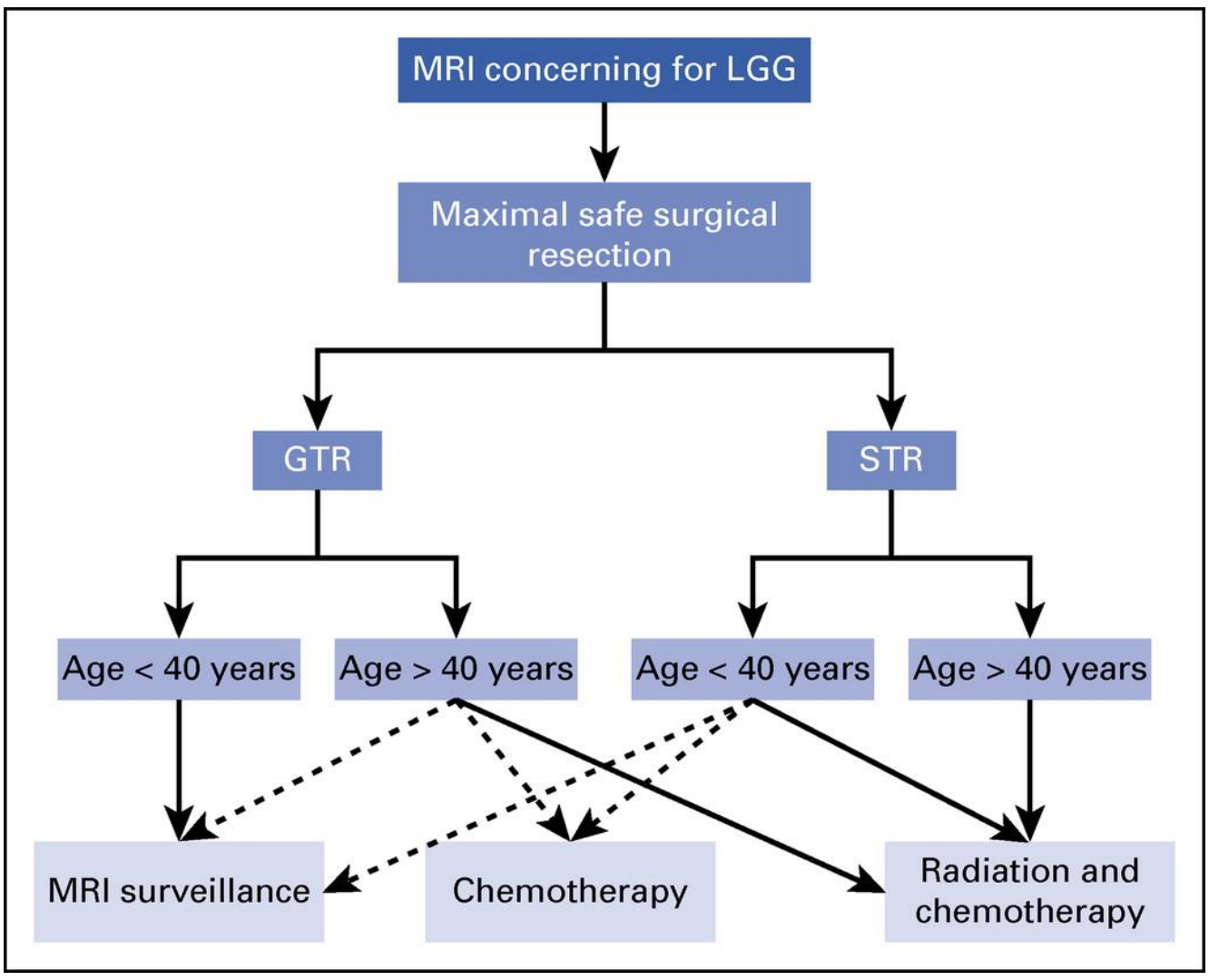
b) surgery not feasible: stereotactic **biopsy** → **radiotherapy**.

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 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.



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

N.B. 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 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 hotspot sequencing), is recommended as highly-specific for low-grade diffuse glioma.

Level III Recommendation: For oligodendroglial tumors, 1p/19q loss-of-heterozygosity testing ir 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

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 fMRI 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

McGirt MJ et al. Extent of surgical resection is independently associated with survival in patients with hemispheric low-grade glioma. Neurosurgery 2008; 63 : 700 – 708

	Gross total resection	Sub-total resection	Statistical significance
OS	15 years	9.9 years	$p = 0.017$
MFS	12.5 years	7.0 years	$p > 0.05$
PFS	7.0 years	3.5 years	$p = 0.043$

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

Extent of surgical resection

Smith JS et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008; 10 : 1338 – 1345 .

	5-year survival		8-year survival	
	>90% resection	<90% resection	>90% resection	90% resection
OS	97%	76%	91%	60%
MFS	93%	72%	76%	48%
PFS	75%	40%	43%	21%

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

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 (+ 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 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.

Negative prognostic factors for overall survival after XRT (***Level II Recommendation***):
1) age > 40 years
2) astrocytic pathology (vs. oligodendroglial 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

Karim AB et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma. European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Rad Oncol Biol Phys 1996 ; 36 : 549 – 556

NCCTG-RTOG-ECOG: 'US trial' - low-dose (50.4 Gy) vs. high-dose (64.8 Gy) radiotherapy

Shaw E et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study. J Clin Oncol 2002 ; 20 : 2267 – 2276

	EORTC I 'Believers trial'			NCCTG-RTOG-ECOG 'US trial'		
	Low-dose DXT	High-dose DXT	Statistical significance	Low-dose DXT	High-dose DXT	Statistical significance
5-Year survival	58%	59%	None	72%	65%	None
Progression (5-year PFS)	47%	50%	None	52%	50%	None

- 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 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)

Karim AB et al. Randomised trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22844 with the Medical Research Council study BRO4: an interim analysis. Int J Rad Oncol Biol Phys 2002; 52: 316 – 324

van den Bent MJ et al. EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005; 366: 985 – 990

	Early DXT	Delayed DXT	Statistical significance
5-Year survival	63%	66%	None
5-Year PFS	44%	37%	$p = 0.02$

- 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.

RECURRENT LGGS

Level III Recommendation: *Radiation* is recommended if there was no previous radiation treatment.

Level III Recommendation: *Re-irradiation* is to be considered as it may provide benefit in disease control.

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 + lomustine

Eyre HJ et al. A randomised trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study. J Neurosurg 1993; 78: 909 – 914

- no benefit of adjuvant LOMUSTINE.

RECURRENT LGGS

Level III Recommendation: TEMOZOLOMIDE is recommended as it may improve clinical symptoms. Oligodendrogliomas and tumors with 1p/19q 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**.
Recurrence → tumor resection → chemotherapy.

SURGERY

EXTENT OF RESECTION

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

*frameless 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

Keles GE et al. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. Cancer 1999;74:1784 – 1791

- 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	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

Vuorinen V et al. Debulking or biopsy of malignant glioma in elderly people – a randomized study. Acta Neurochir (Wein) 2003 ; 145 : 5 – 10

- class I evidence.
- all patients > 65 yo.
- all patients received XRT.

- survival advantage of > 2 months for craniotomy and surgical resection ($p < 0.05$).

	Craniotomy and resection	Biopsy	Statistical significance
Median survival (days)	171	85	$p = 0.03$
PFS (6 months)	41%	21%	$p = 0.0003$

GTR vs. STR vs. biopsy of GBM

Khan, Muhammad B. "Gross Total Resection of Glioblastoma Improves Overall Survival and Progression-Free Survival Compared to Subtotal Resection or Biopsy Alone" Neurosurgery: December 2016 - Volume 79 - Issue 6 - p N12–N13

- 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, 0.79-0.89; P < .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).

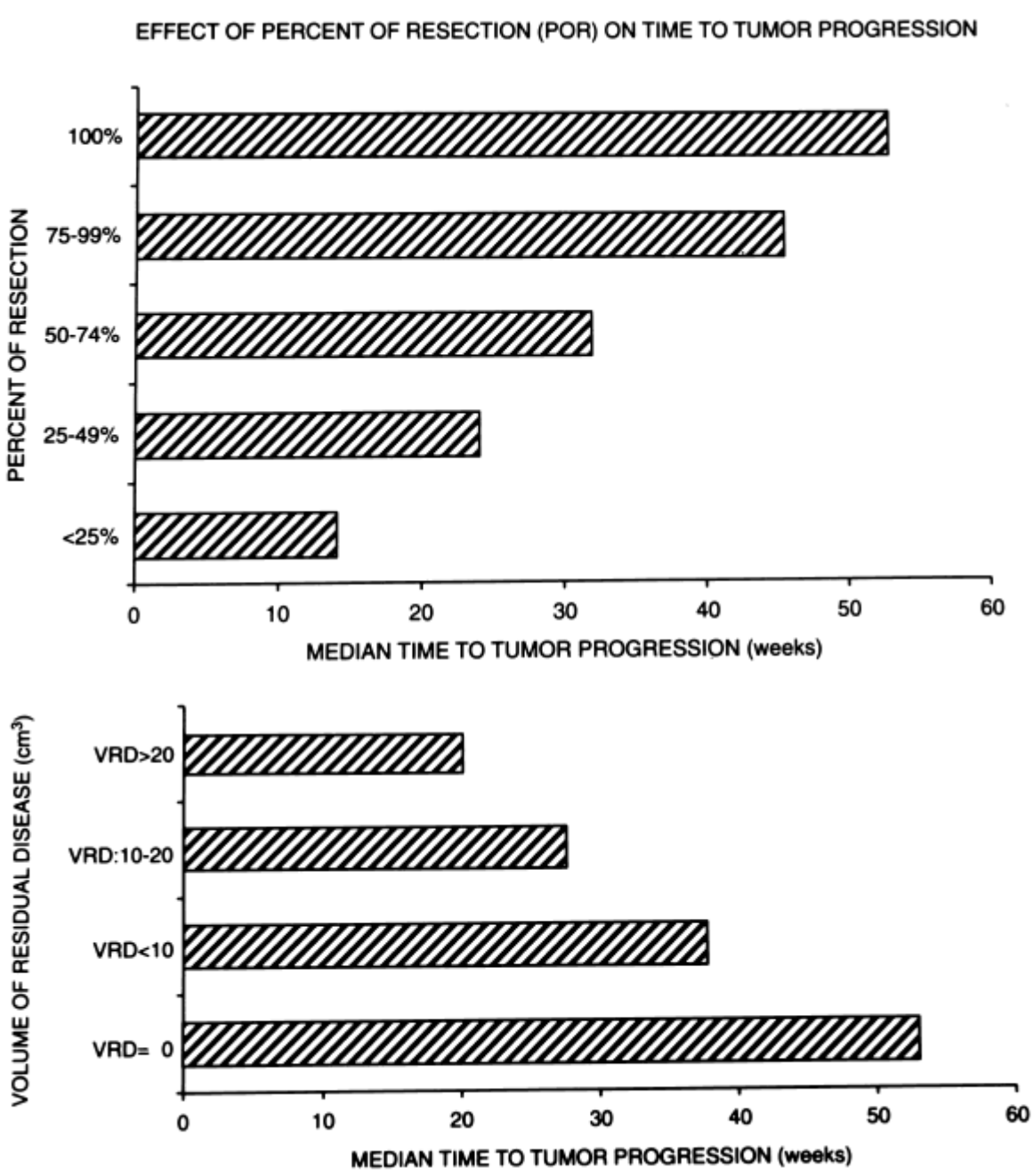
N.B. there are studies that failed to show any benefit from aggressive surgery! – those studies either used nonvolumetric analysis or neurosurgeon's description in operative report

RISK FACTORS

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)**

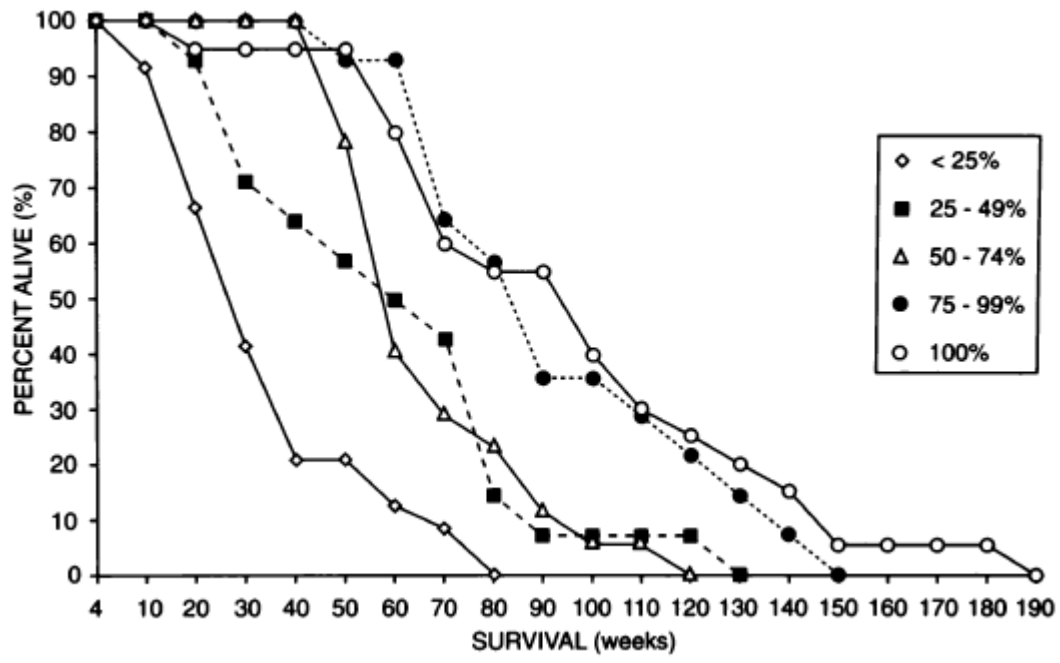
- TTP ranged 4-170 weeks (53 weeks if total resection with no residual disease).
- POR and VRD effects much less significant in cases of re-resections (effect insignificant for third and fourth operations).

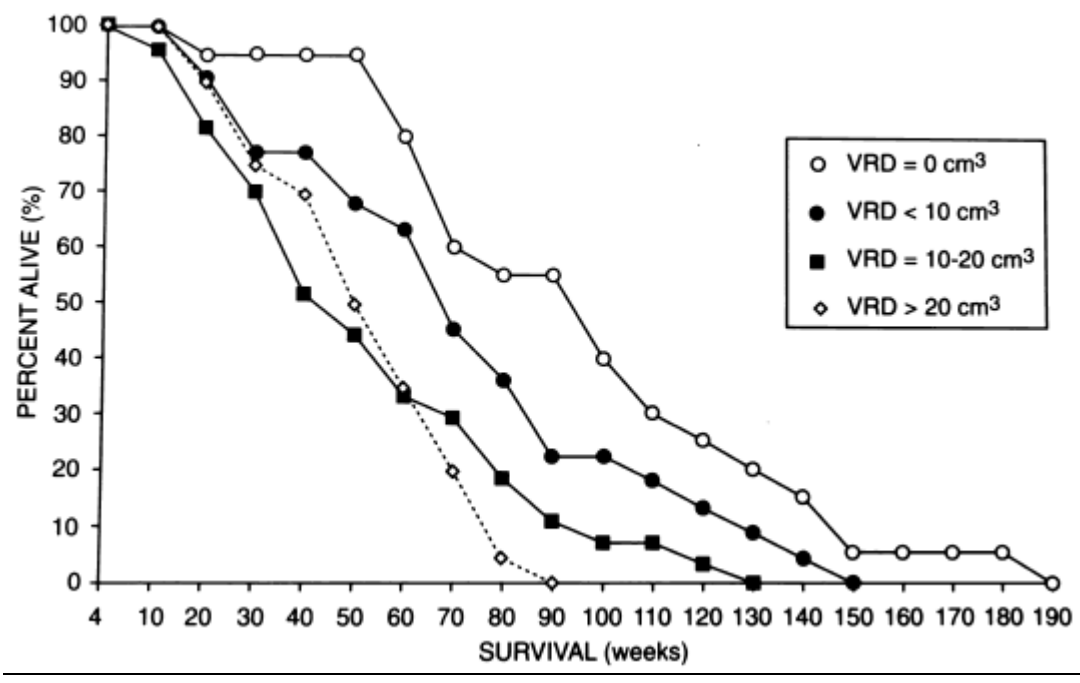


Factors that significantly affect survival:

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. Op345 >>

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).

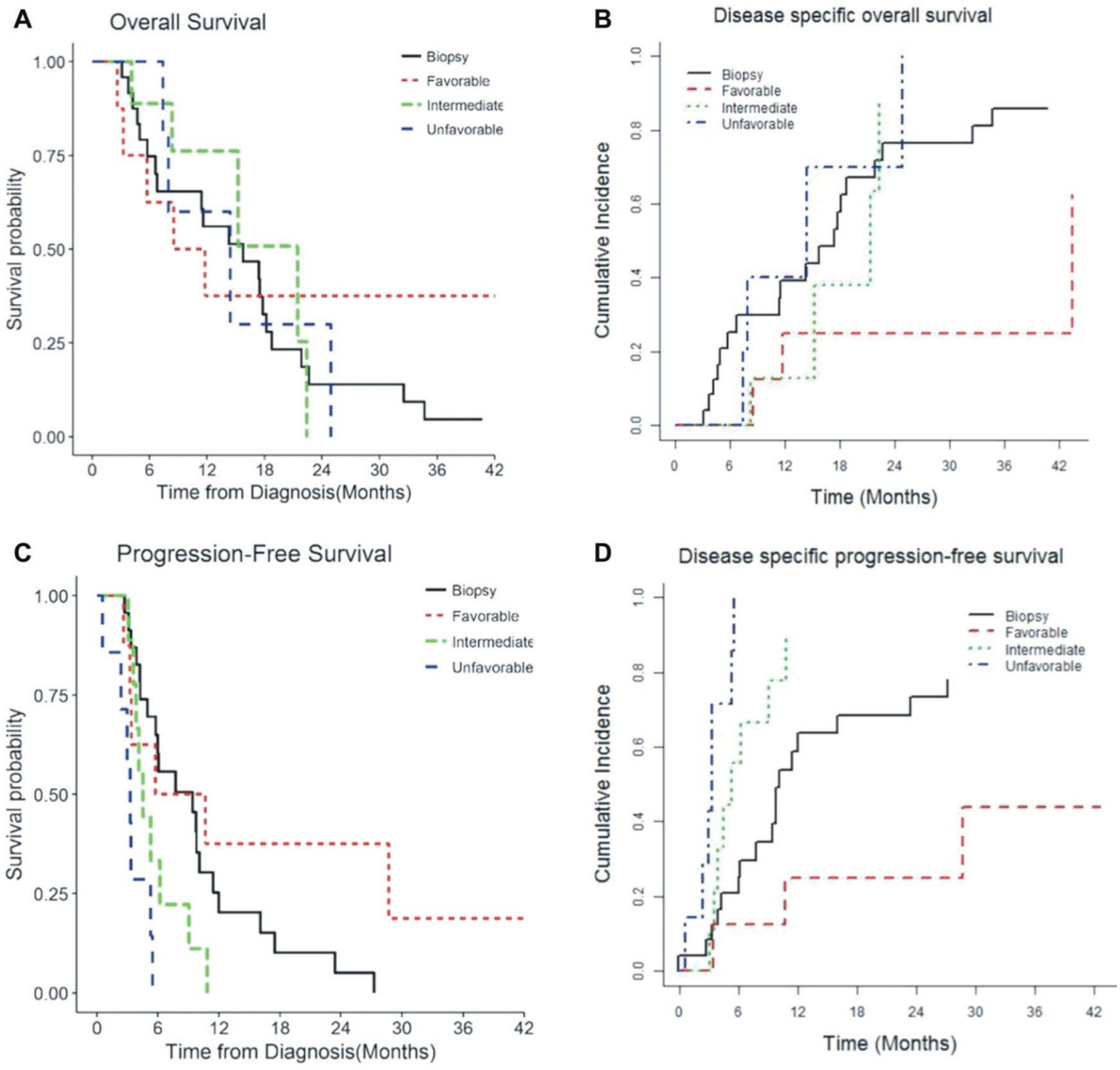
1. if a tissue diagnosis had not yet been obtained, stereotactic needle biopsy is performed through the same trajectory prior to placement of the laser probe.

OUTCOMES

LITT vs. biopsy-only for new GBM

Alireza M Mohammadi et al. Upfront Magnetic Resonance Imaging-Guided Stereotactic Laser-Ablation in Newly Diagnosed Glioblastoma: A Multicenter Review of Survival Outcomes Compared to a Matched Cohort of Biopsy-Only Patients. Neurosurgery, Volume 85, Issue 6, December 2019, Pages 762–772

- 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 (analogy to extent of surgical tumor resection):



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

Ashwin A. Kamath et al. Glioblastoma Treated With Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy: Safety, Efficacy, and Outcomes. Neurosurgery 84:836–843, 2019 DOI:10.1093/neuros/nyy375

- 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*

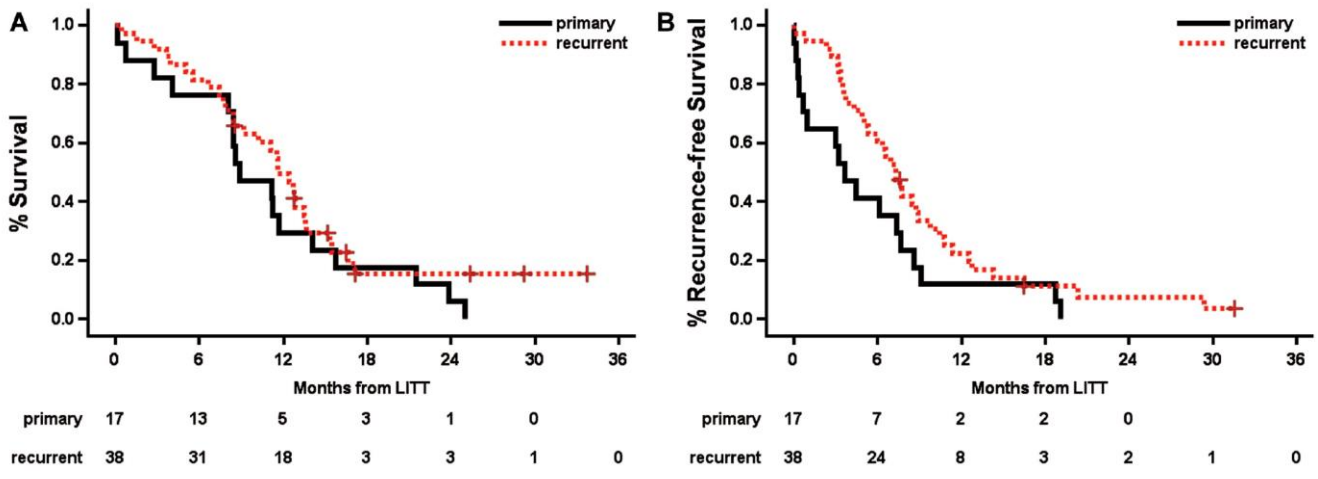
structures; 3 patients underwent *repeat* ablation for recurrence and 1 was the second stage of a planned two-stage procedure).

- median **overall survival** after LITT for the total cohort - 11.5 mo (for frontline GBM treatment, median OS was 9.1 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)

A, *Overall and* **B**, *PFS in primarily treated vs recurrent GBM after LITT. OS for primarily treated vs recurrent GBM was 9.1 and 11.8 mo, respectively; PFS was 3.6 and 7.3 mo, respectively. There were no statistically significant differences.*



RADIOTHERAPY

N.B. 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 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

GTV	CTV	PTV	Dosage
T2/FLAIR post-op changes	+ 2 cm expansion	+0.3-0.5 cm expansion	46 Gy / 23 fx
T1 w/contrast enhancement	+ 2 cm expansion	+0.3-0.5 cm expansion	14 Gy / 7 fx (i.e. – sequential boost/conedown)

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

About volumes – see p. Rx11 >>

When should begin is controversial - early radiotherapy may maximize efficacy but may cause brain damage earlier; studies show the best time to begin is as 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 reduction of 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 which would have negative impact on radiation)

Seunggu Han, 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 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 31 to 37 d** (HR 0.93, 95% CI 0.88-0.99, P = 0.02).

Virginia W Osborn et al. Impact of Timing of Adjuvant Chemoradiation for Glioblastoma in a Large Hospital Database. Neurosurgery, nyx487, https://doi.org/10.1093/neuros/nyx497 Published: 28 October 2017

- recurrence after **conventional (external beam)** radiotherapy → repeat resection and **stereotactic radiosurgery**.
- **boron neutron capture therapy** - still investigational.
- radioenhancers are still being investigated; MOTEXAFIN GADOLINIUM (MGD) is putative radiation enhancer.

GAMMATILE® 131Cs radiation emitting seeds in a resorbable collagen-based carrier tile.

- FDA-cleared (2019) for new and recurrent HGGs - surgically targeted highly conformal radiation therapy.

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.

FDA-approved chemotherapeutic regimens: see p. Onc3 >>

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 promoter** are more likely to respond. see p. Onc3 >>
   - reports that ***metronomic**** chemotherapy with TMZ has improved efficacy.

     *low 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 **Gliadel® 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

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

PLUS

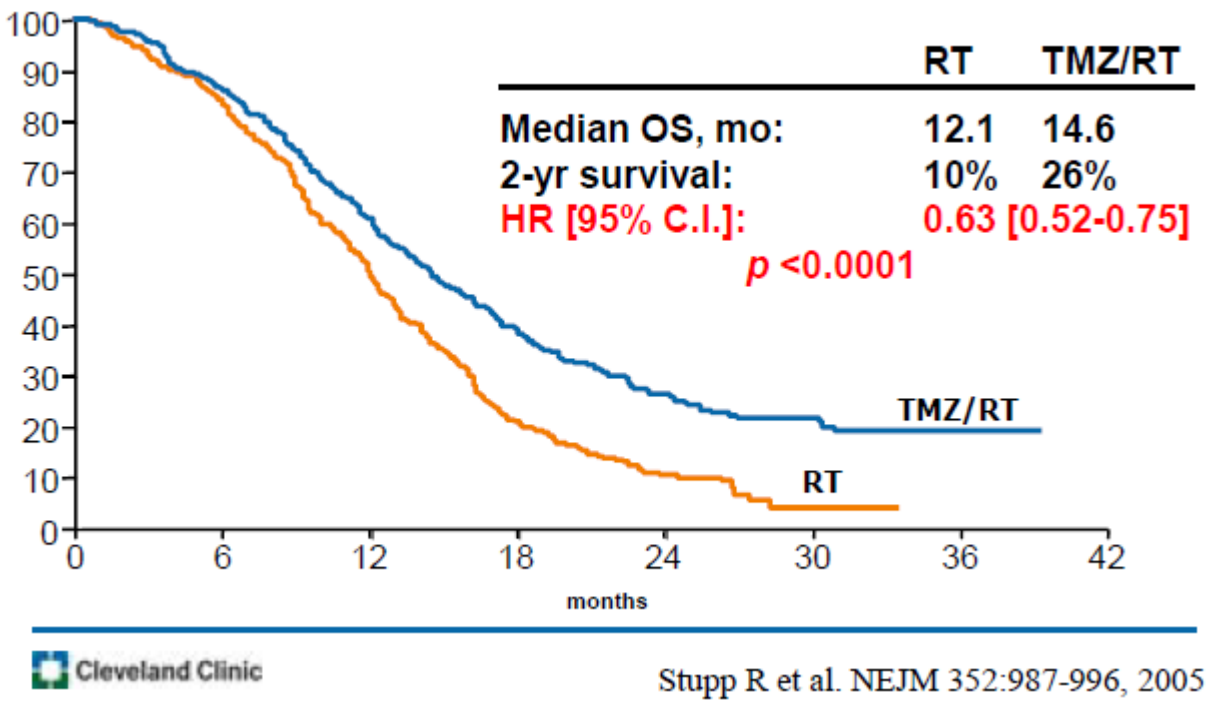
TEMOZOLOMIDE (75 mg / m^2 of body-surface area / day, 7 days per week from first to last day of radiotherapy, i.e. for 42 days N.B. common mistake – give 75 mg 5 days/week

↓

6 months of 6 cycles of adjuvant TEMOZOLOMIDE (150–200 mg / m^2 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!

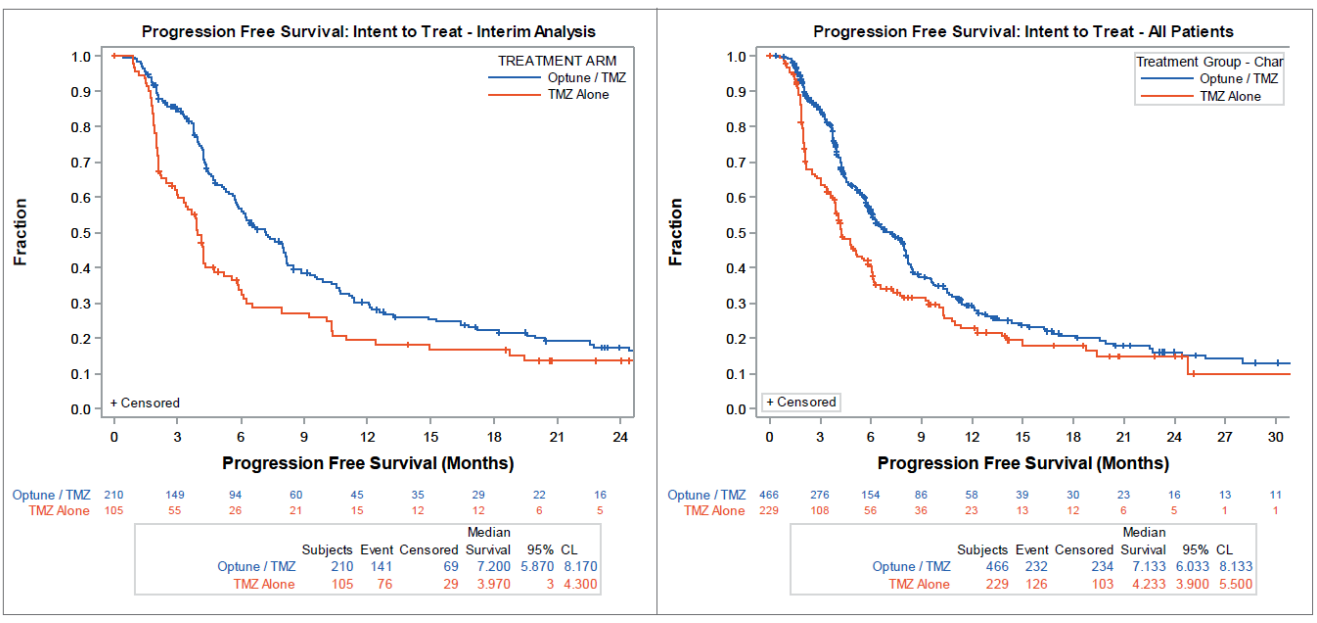
2-year survival increased from 30 to 43% for patients treated with the device in combination with chemotherapy; 5-year survival rate increased from 5 to 13%.

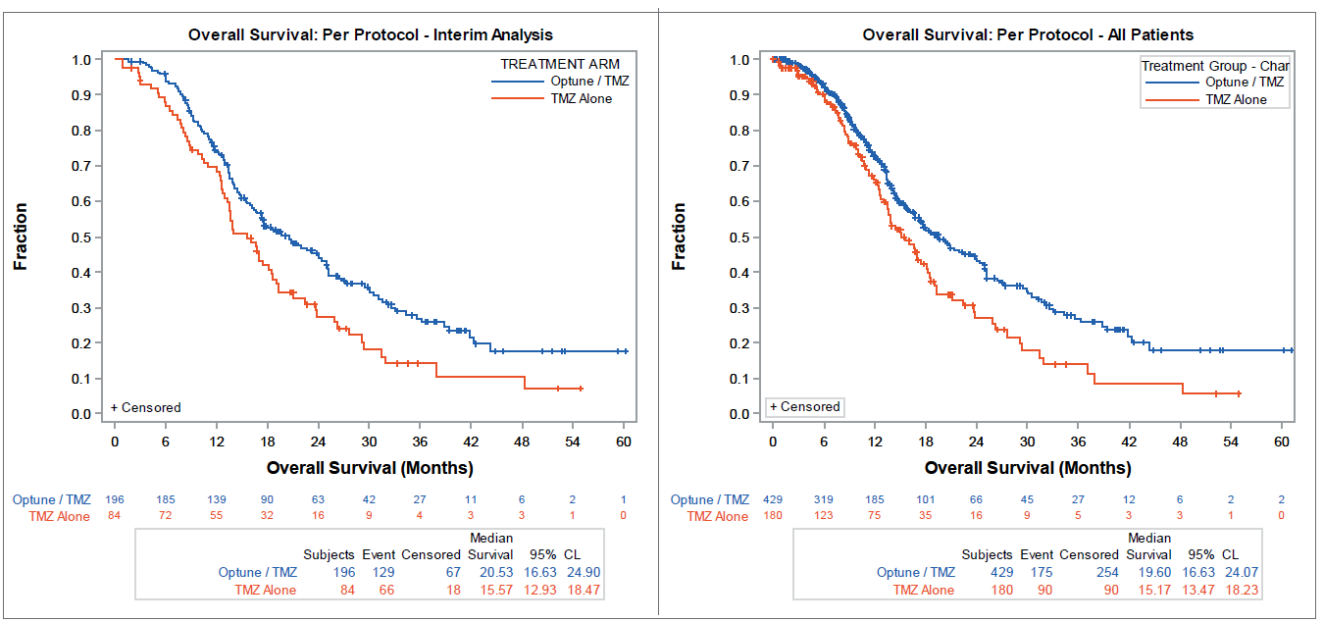
Trail weakness: median number of TMZ cycles was six for the experimental TTF/TMZ arm and five for the TMZ-alone control arm.
Dr Stupp countered that the higher median number of adjuvant TMZ cycles in the TTF/TMZ group was easily explained. "They progressed earlier. You treat until progression," he said. "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 glioblastoma. "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

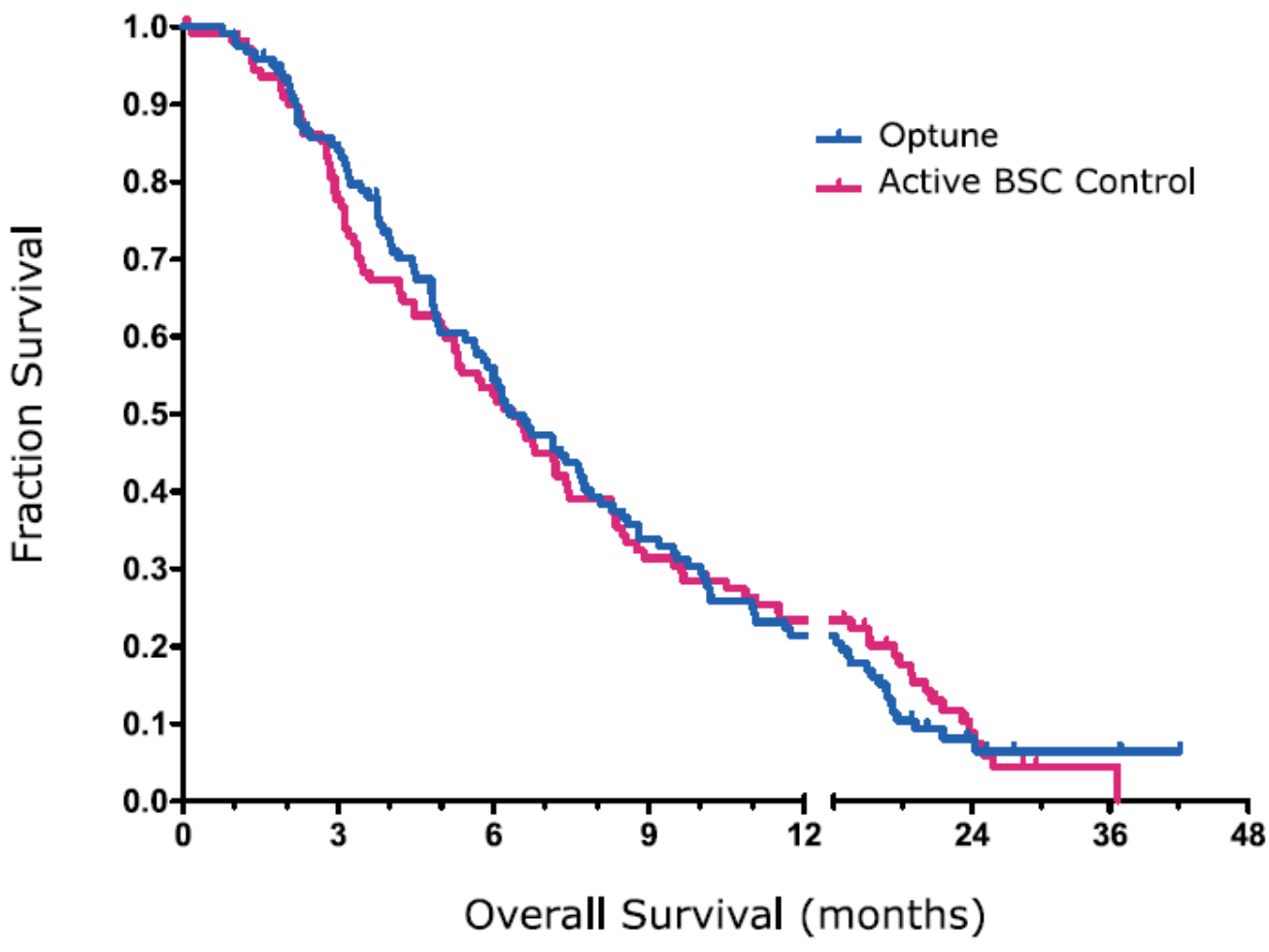
- Optune® with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.
- For the treatment of recurrent GBM, Optune® 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

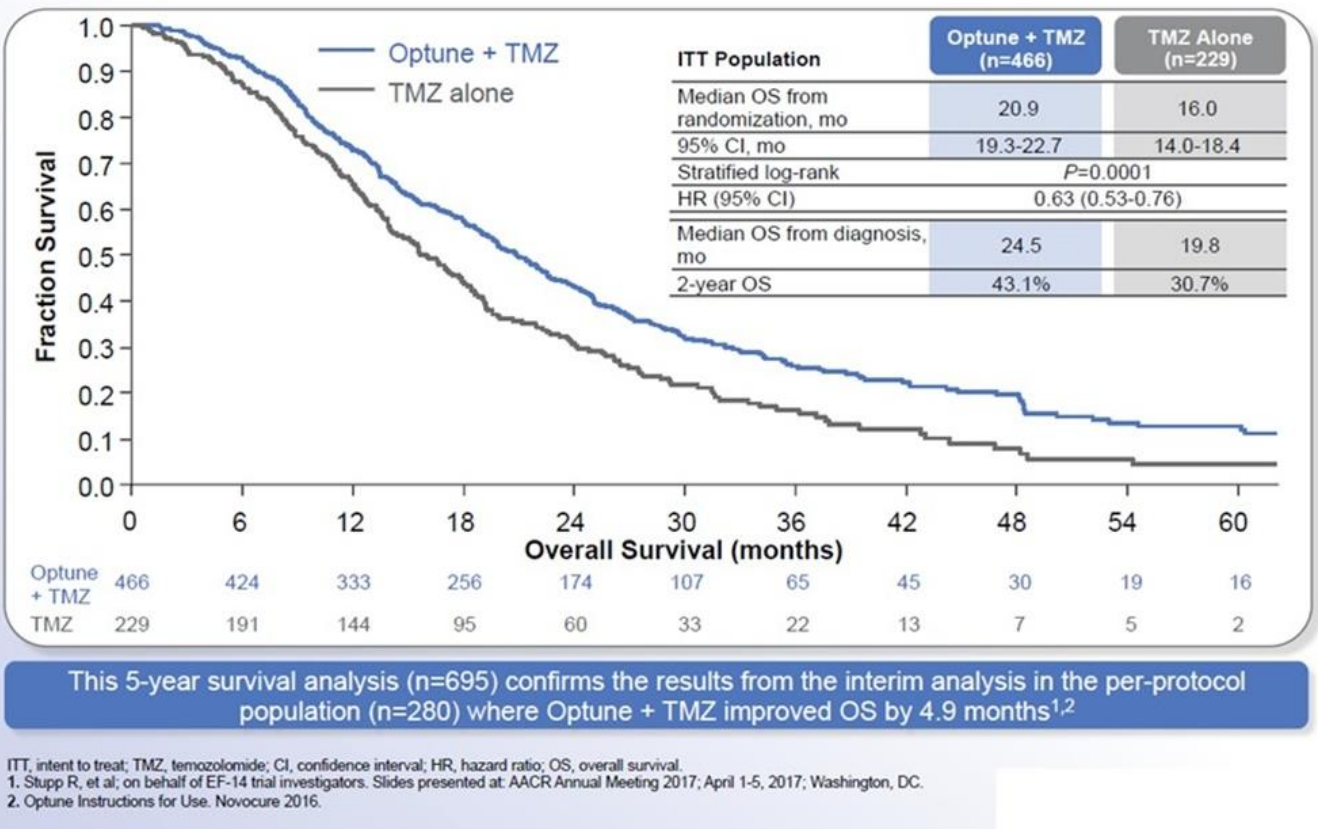




Pivotal Clinical Study in Recurrent GBM

Stupp, R., et al., (2012). "NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality." Eur J Cancer 48(14): 2192-202

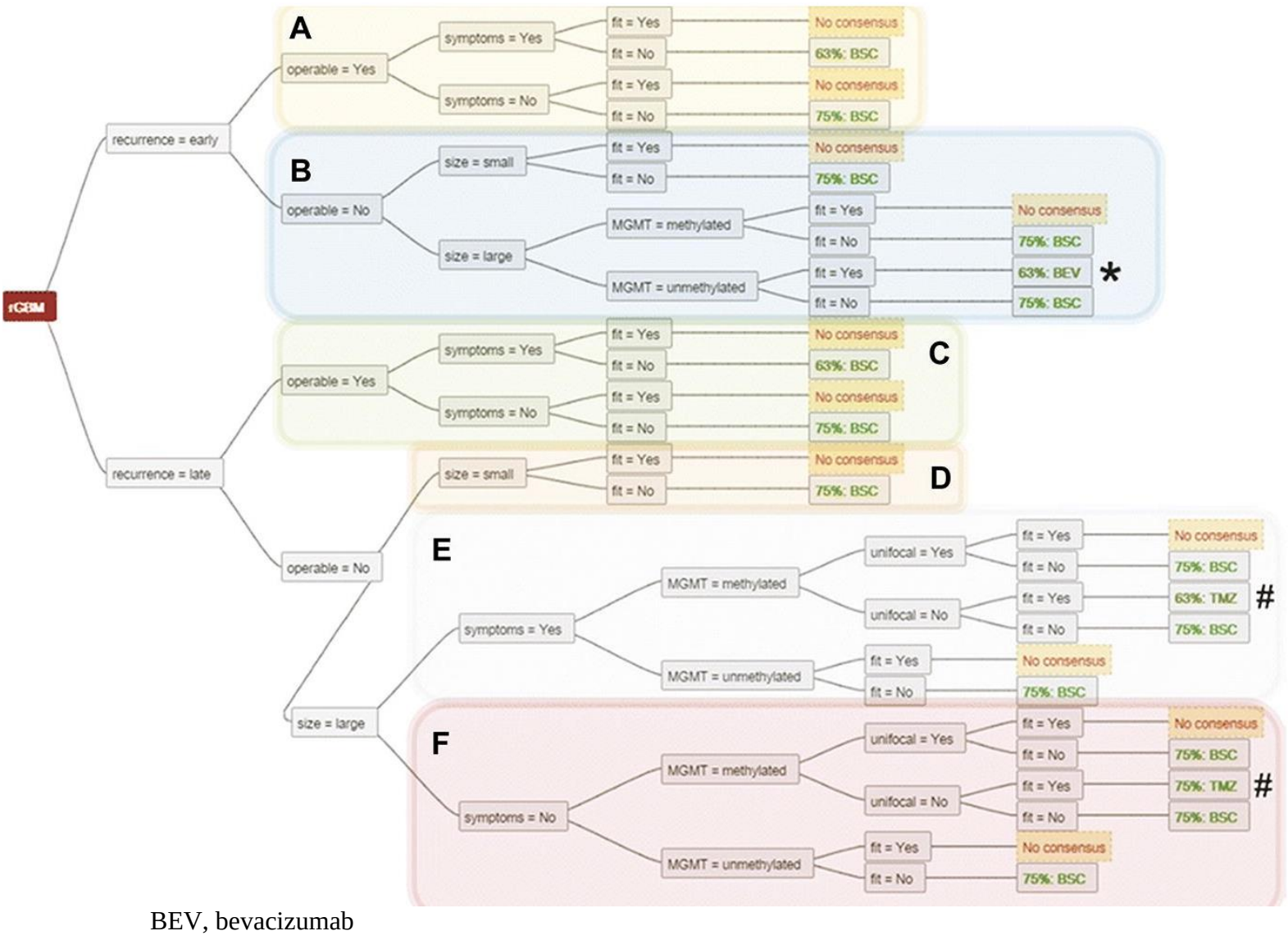




TREATMENT OF RECURRENCES

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.

  Craniotomy for recurrent glioblastoma: Is it justified? A comparative cohort study with outcomes over 10 years. Soumya Mukherjee, Joseph Wood, Imran Liaquat, Simon R Stapleton, Andrew J Martin. Clinical Neurology and Neurosurgery 2019 October 24, 188: 105568

  – 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 is patient was irradiated after the first operation

CHEMOTHERAPY

Recurrent disease is seen in nearly all patients with GBM

BEVACIZUMAB (anti-VEGF monoclonal antibody – see p. Onc3 >>) - FDA approved (2009) 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 IRINOTECAN.
- patients with progressive glioblastoma do not benefit (no survival benefit) from BEVACIZUMAB addition to LOMUSTINE.

  Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med. 2017;377:1954-1963.

BEVACIZUMAB-BVZR (Zirabev®, Pfizer Inc) – FDA approved (6/28/2019) for recurrent glioblastoma; biosimilar to Avastin.

Studies

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.

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.

Simon P. Stevens et al. The utility of routine surveillance screening with magnetic resonance imaging (MRI) to detect tumour recurrence in children with low-grade central nervous system (CNS) tumours: a systematic review. J Neurooncol. 2018; 139(3): 507–522.

- 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.

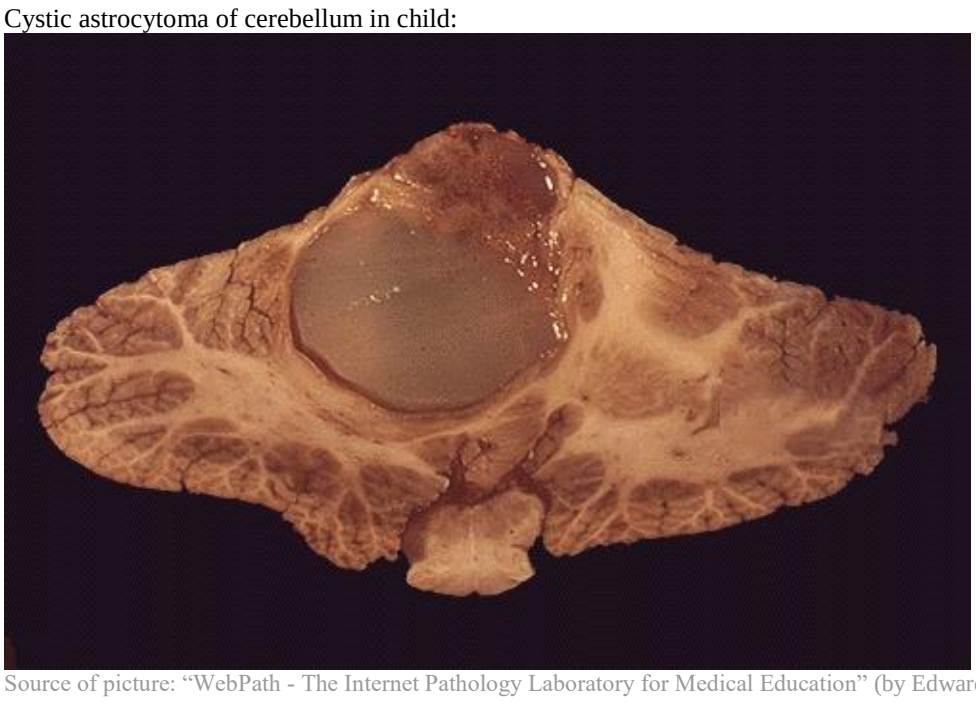
N.B. look for pseudoprogression vs. true progression (pMRI, TRAM, MRS, and other protocols)

SPECIAL FORMS

CEREBELLAR ASTROCYTOMAS

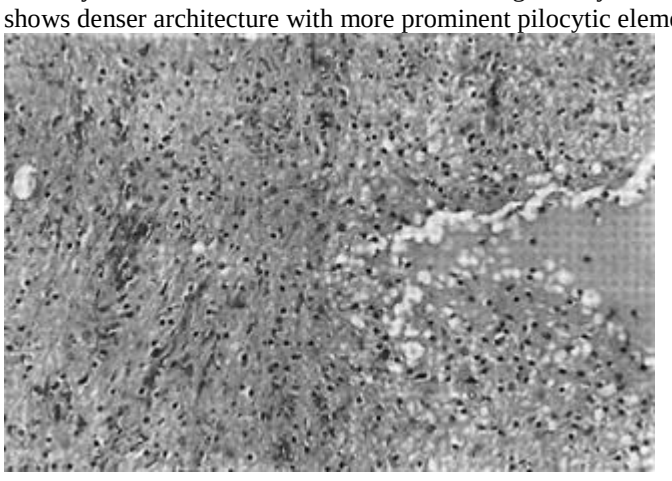
- *prognosis is consistently better* than astrocytomas arising elsewhere!
- occur almost exclusively during first two decades of life.
- usually well circumscribed, low grade (61-85% are *PILOCYTIC ASTROCYTOMAS*; other 15-28% are *DIFFUSE* or *FIBRILLARY ASTROCYTOMAS*).
  - frequently **cystic**!
  - 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:

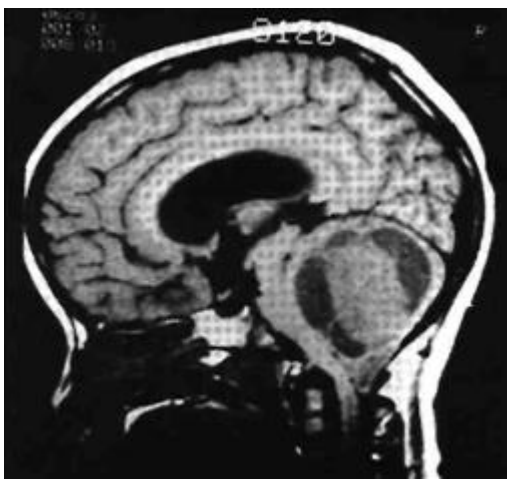


Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

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 cysts outline denser tumor; cerebellar tonsil has herniated below foramen magnum:

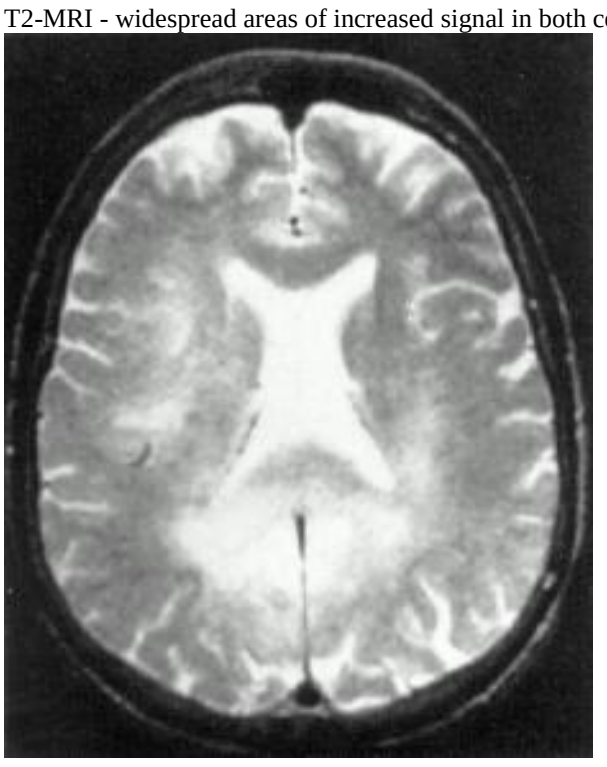


GLIOMATOSIS CEREBRI

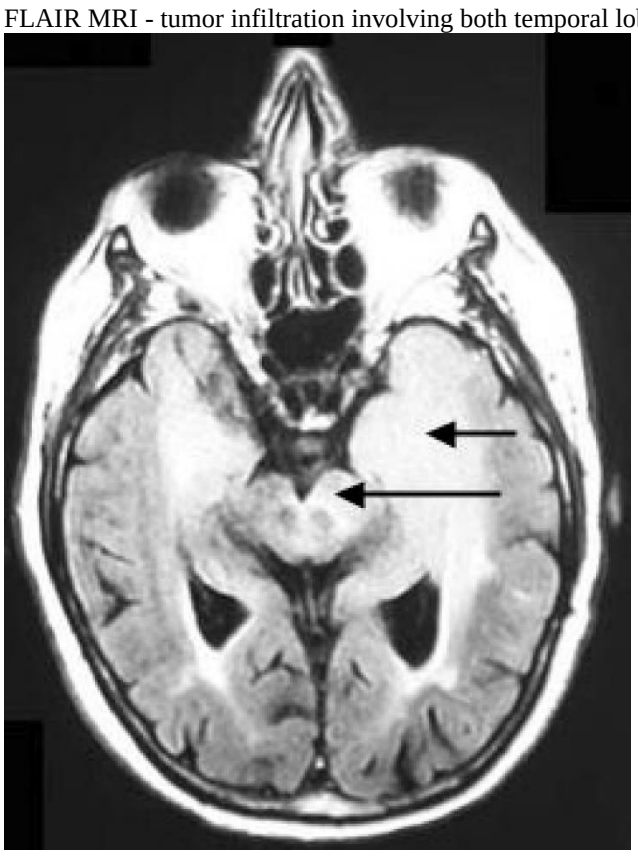
- diffuse white matter spread of glioma (by degrading extracellular matrix with secreting proteases) - involving ≥ 3 cerebral lobes, frequent bilateral growth and regular extension to infratentorial structures.

- 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 oligodendroglial 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/T_2 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.

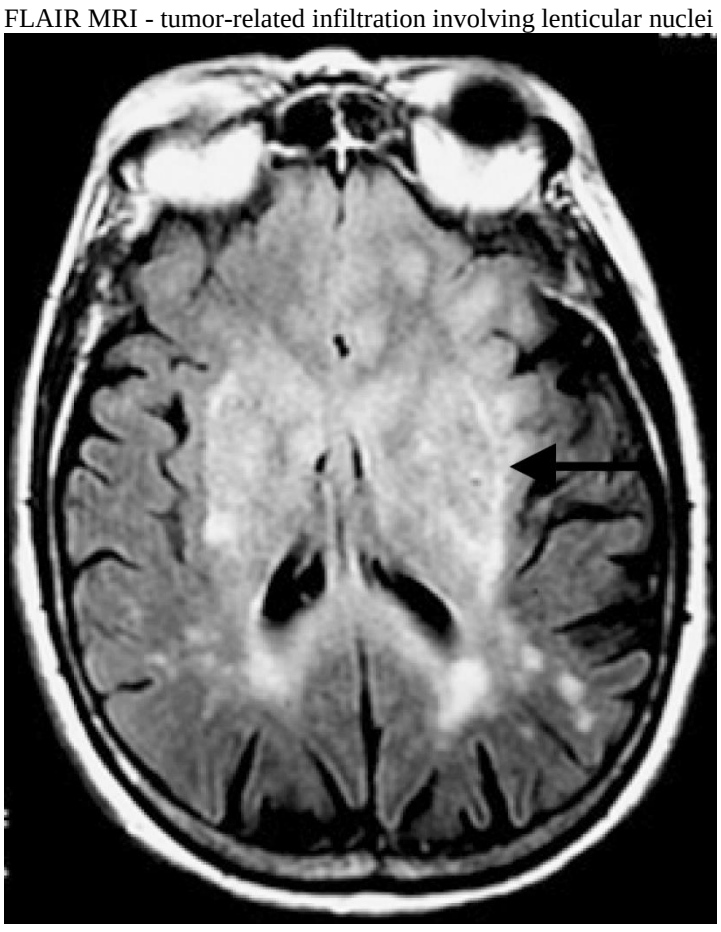
T2-MRI - widespread areas of increased signal in both cerebral hemispheres:



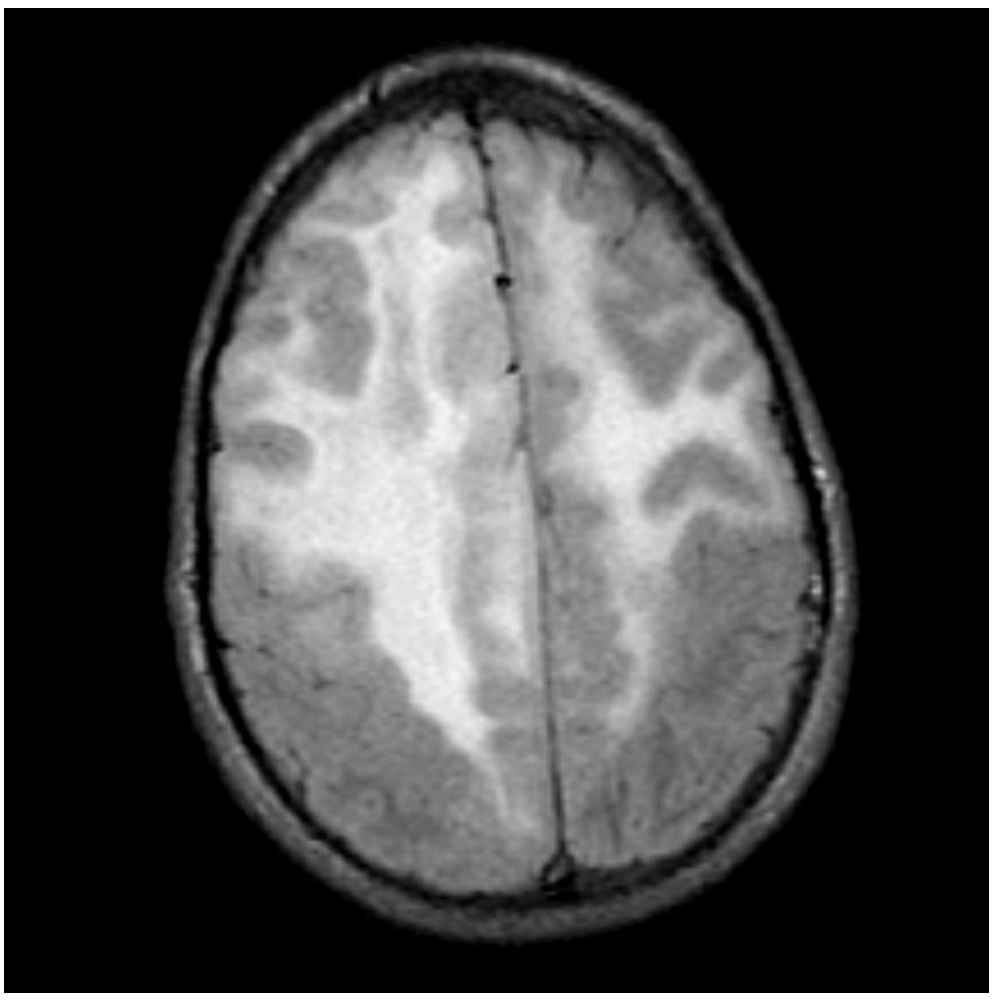
FLAIR MRI - tumor infiltration involving both temporal lobes (*Short arrow*), and substantia nigra (*Long arrow*):



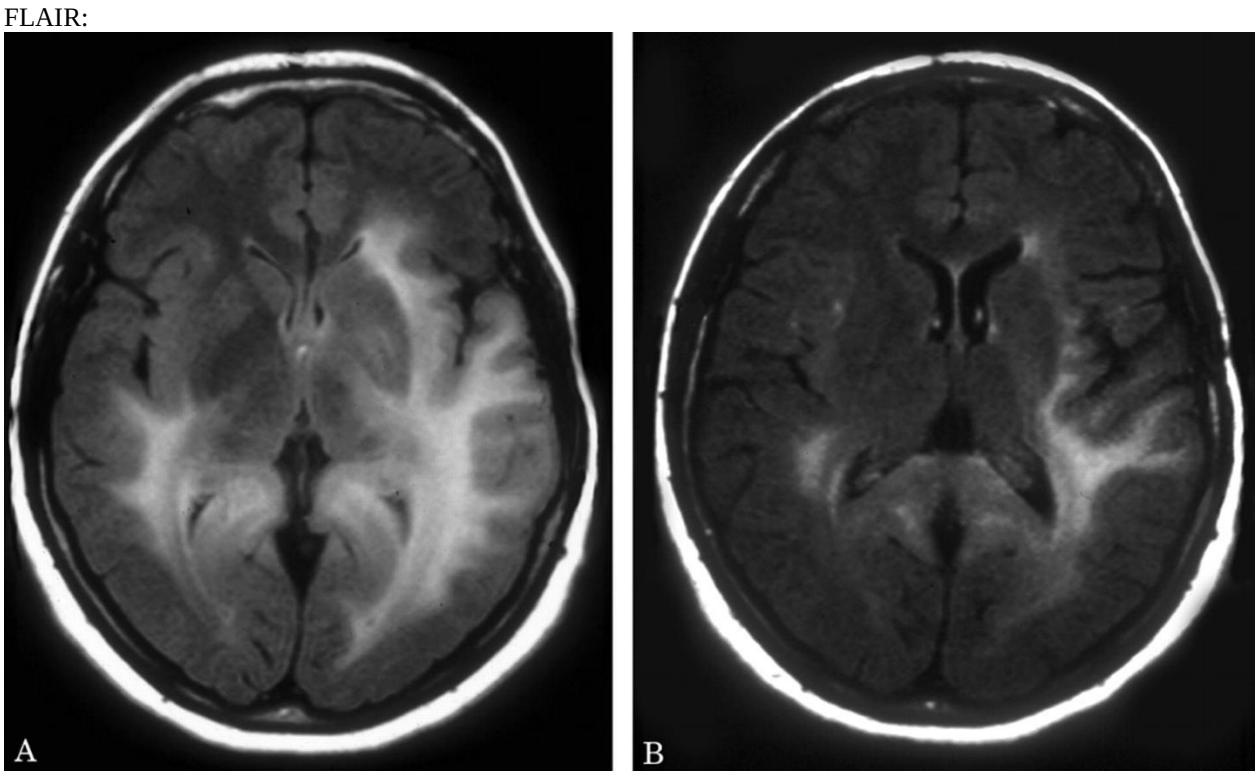
FLAIR MRI - tumor-related infiltration involving lenticular nuclei (*Arrow*):



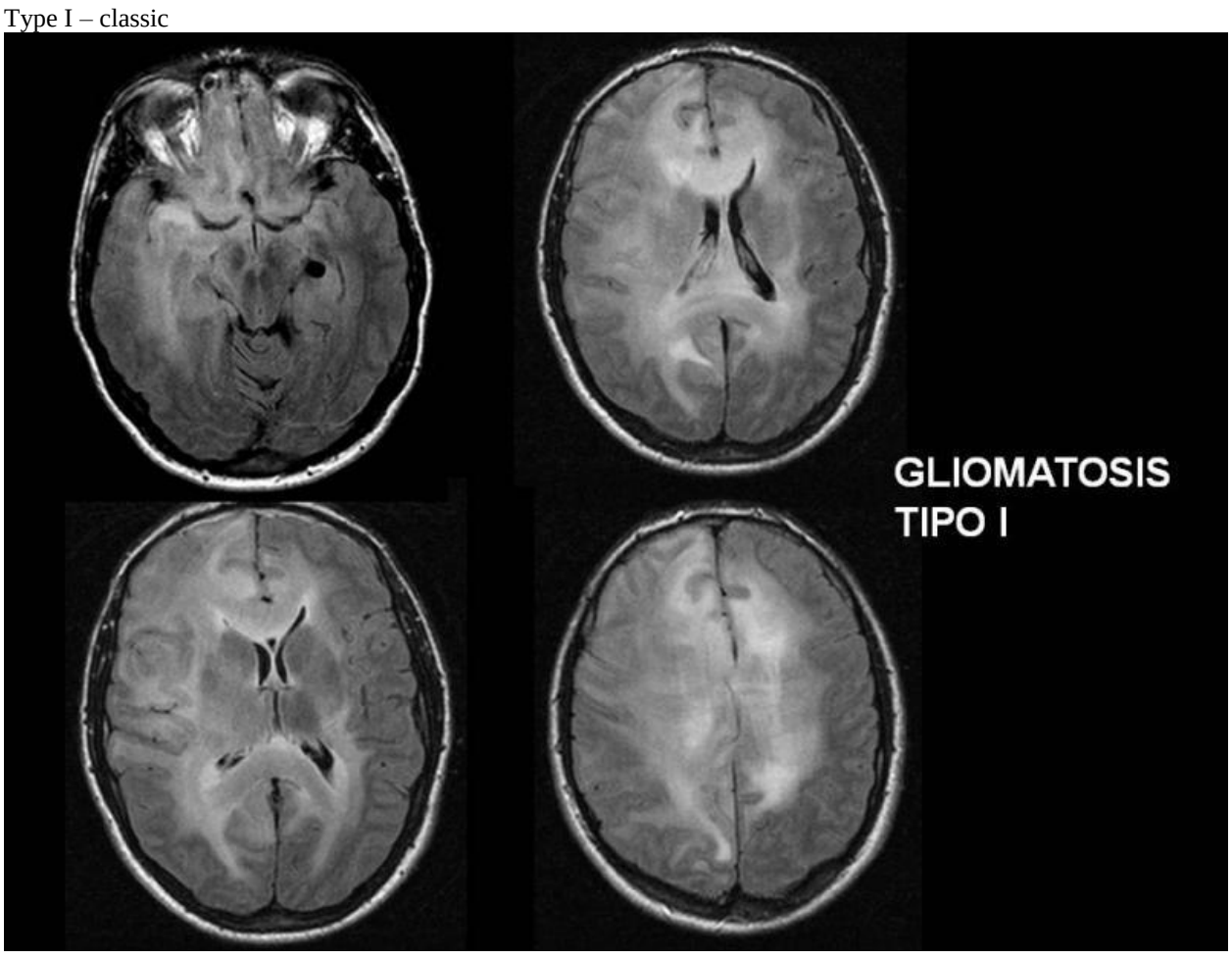
FLAIR:



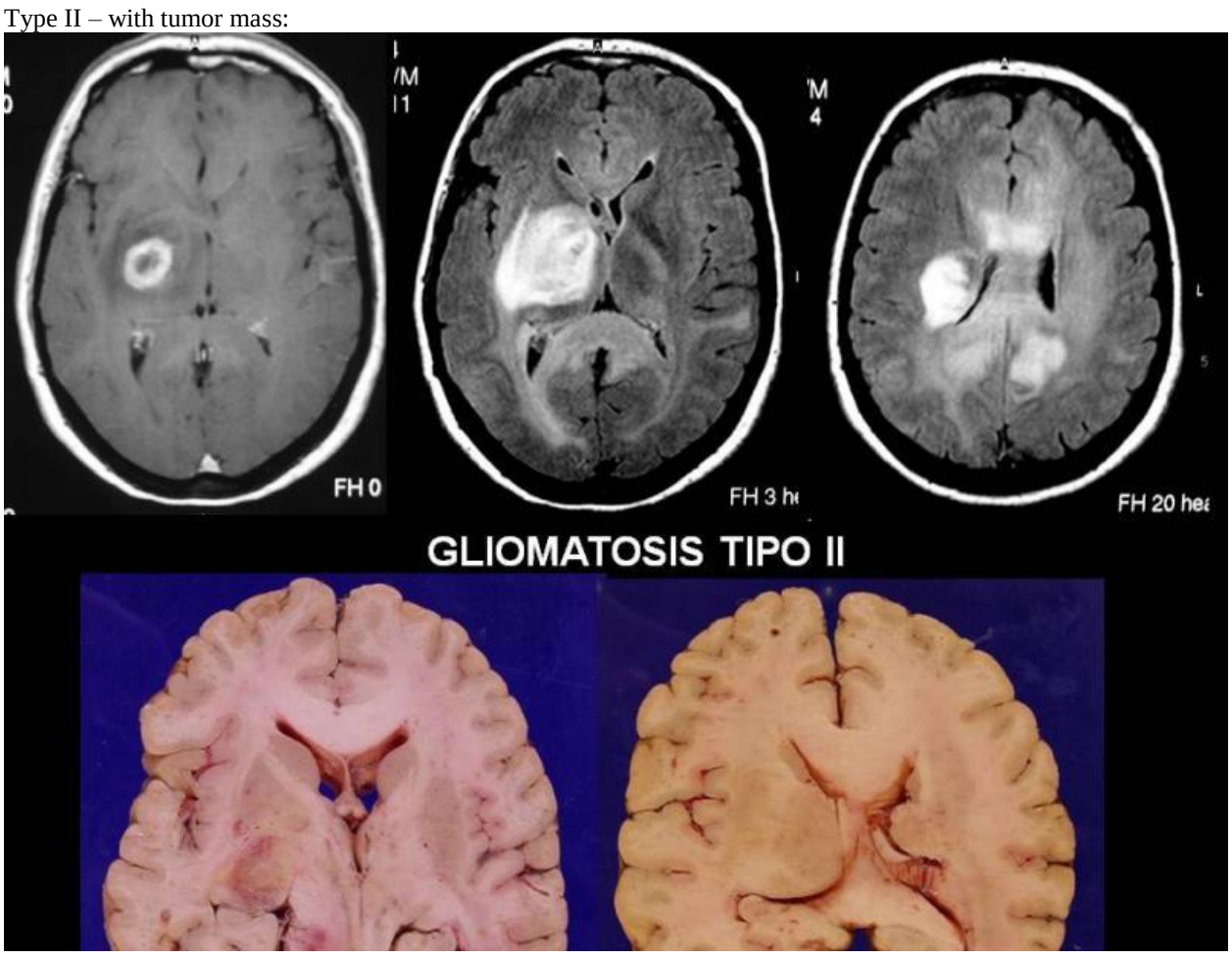
FLAIR:



Type I – classic



Type II – with tumor mass:

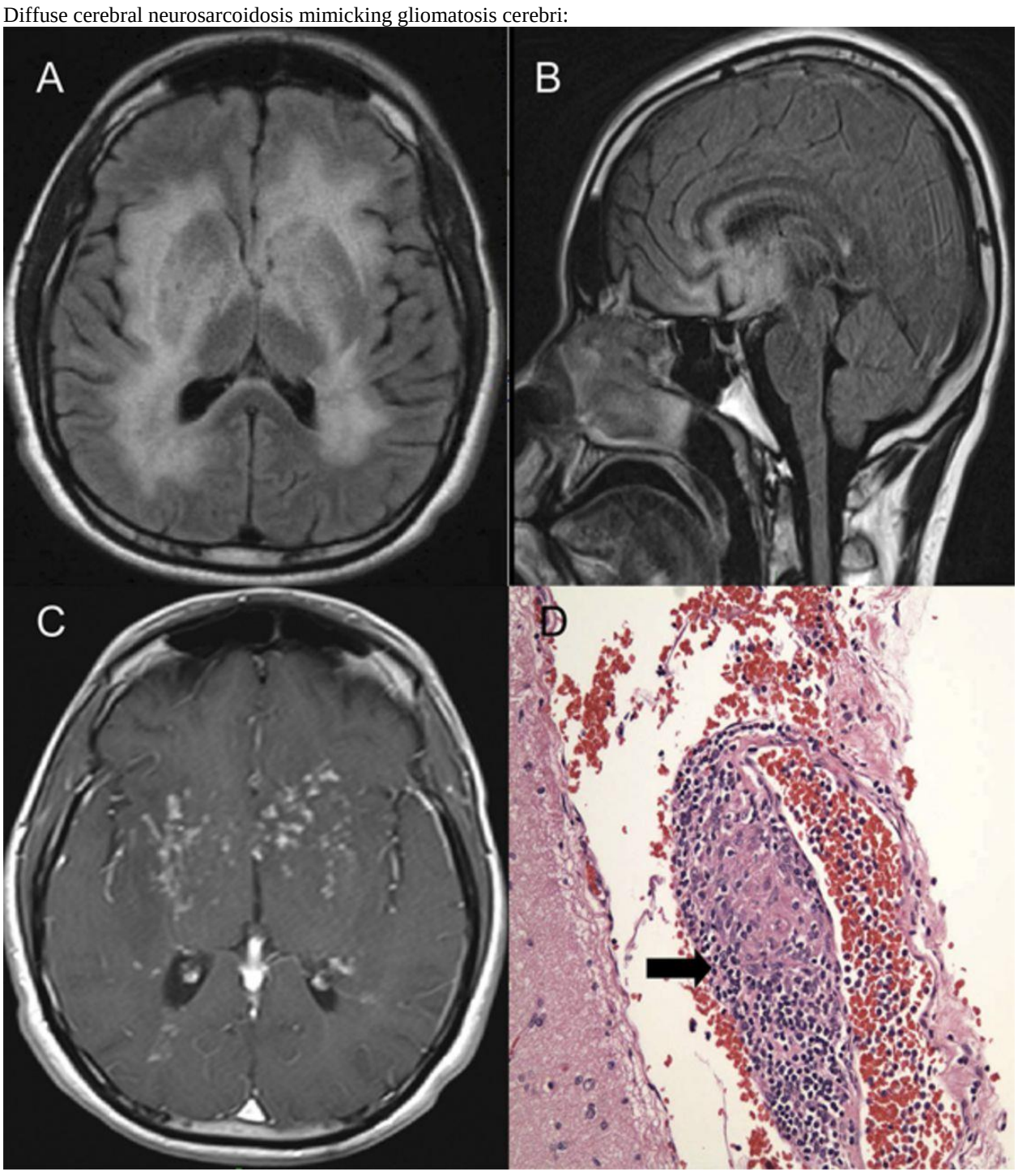


<u>Differentials</u>

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 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.

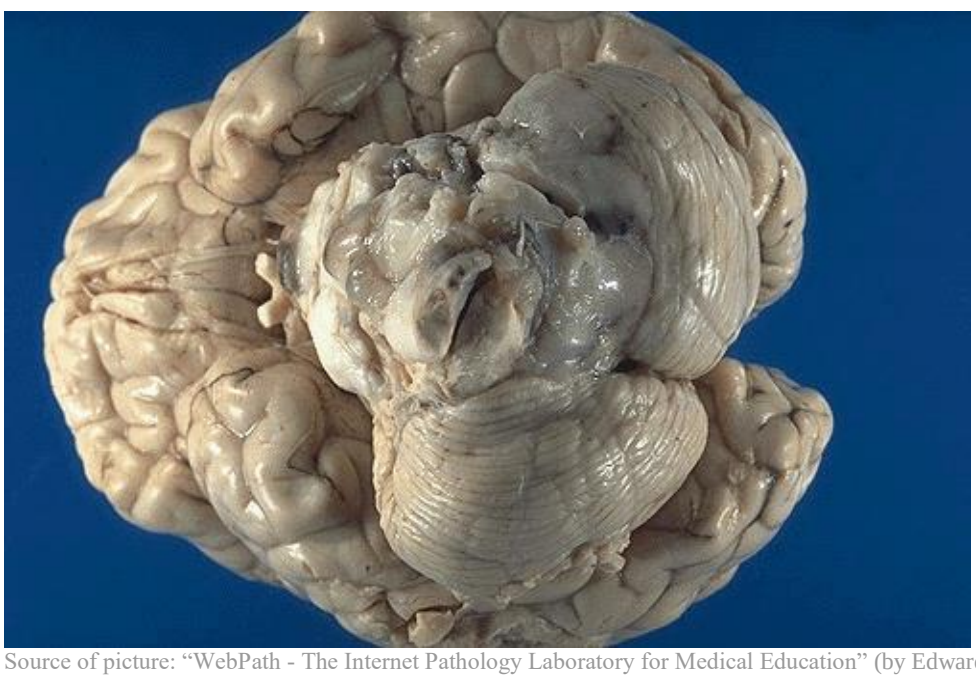
- special subtype - dorsal exophytic tumors - arise from floor of 4th ventricle and fill it; large, well circumscribed, and uniformly enhancing.

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

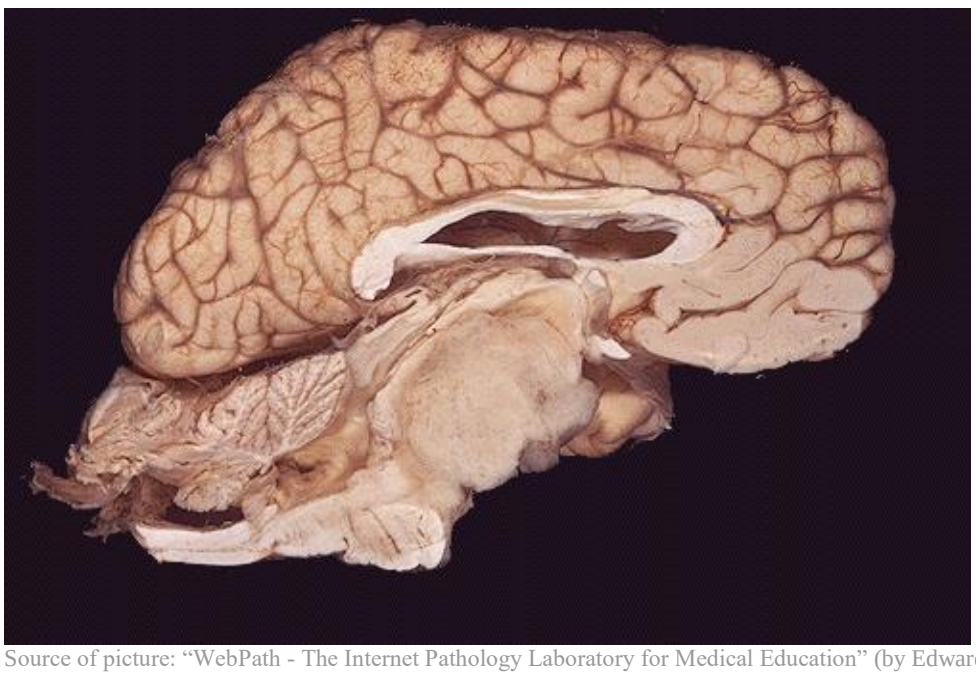
- ¾ patients are < 20 years (some are < 1 yr).
  Predominantly tumors of childhood!
- risk factor – ***neurofibromatosis***.

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*.



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



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

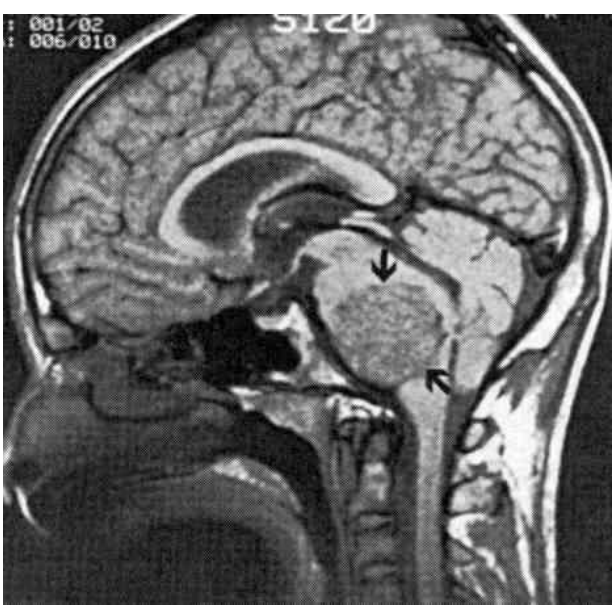
Clinically:

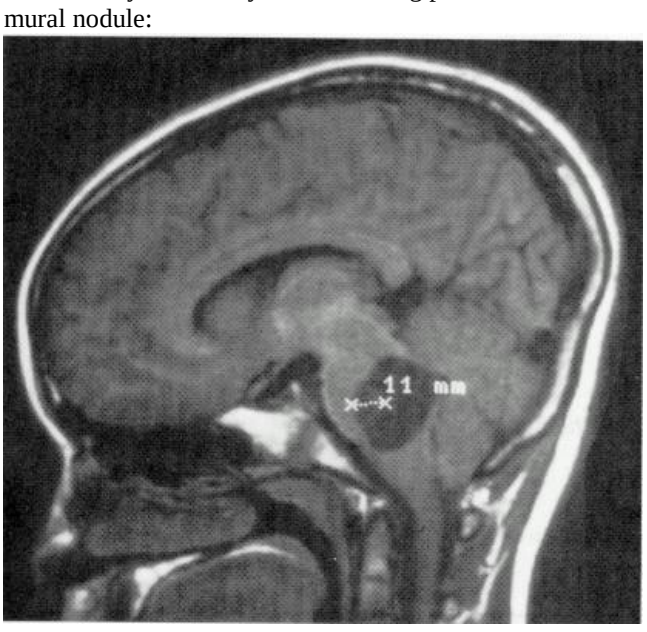
1) cranial nerve lesions (esp. CN6 and CN7)
2) long tract signs
3) ataxia, nystagmus
4) failure to thrive
5) hydrocephalus (most common in tectal tumors)
6) signs of ICP↑ - rare as presenting feature (vs. other CNS tumors)

Diagnosis:

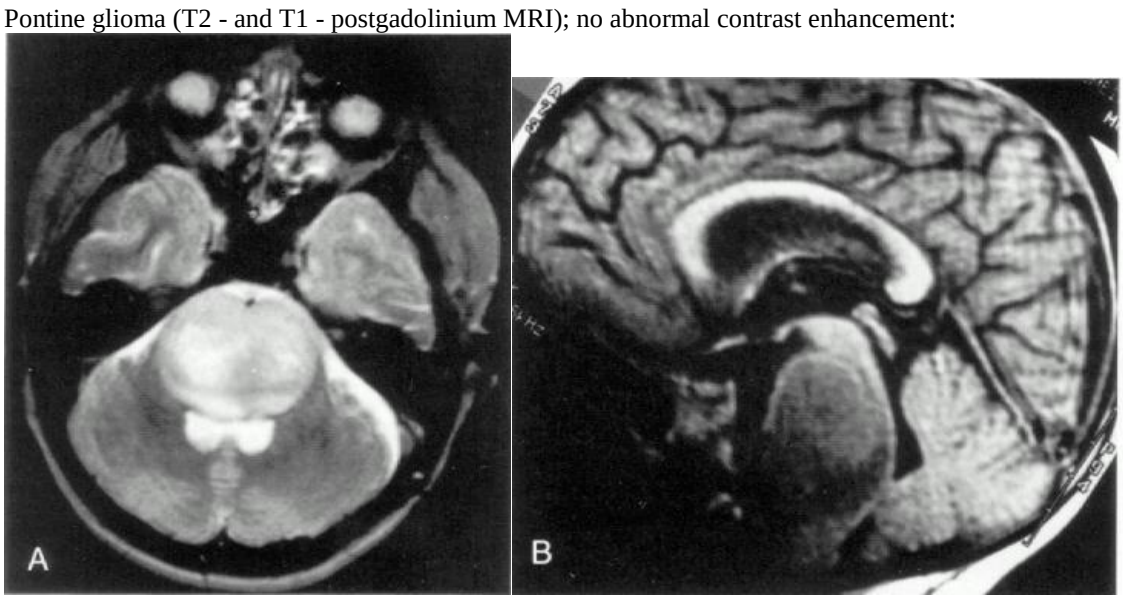
- **MRI** - expansile, infiltrative process (enlarged brainstem).
- **tissue confirmation** is frequently not feasible (unless exophytic component exists - even then, biopsy cannot always be obtained);
  - biopsy is not required for diffuse intrinsic pontine gliomas (diagnosis can be made by MRI alone;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

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

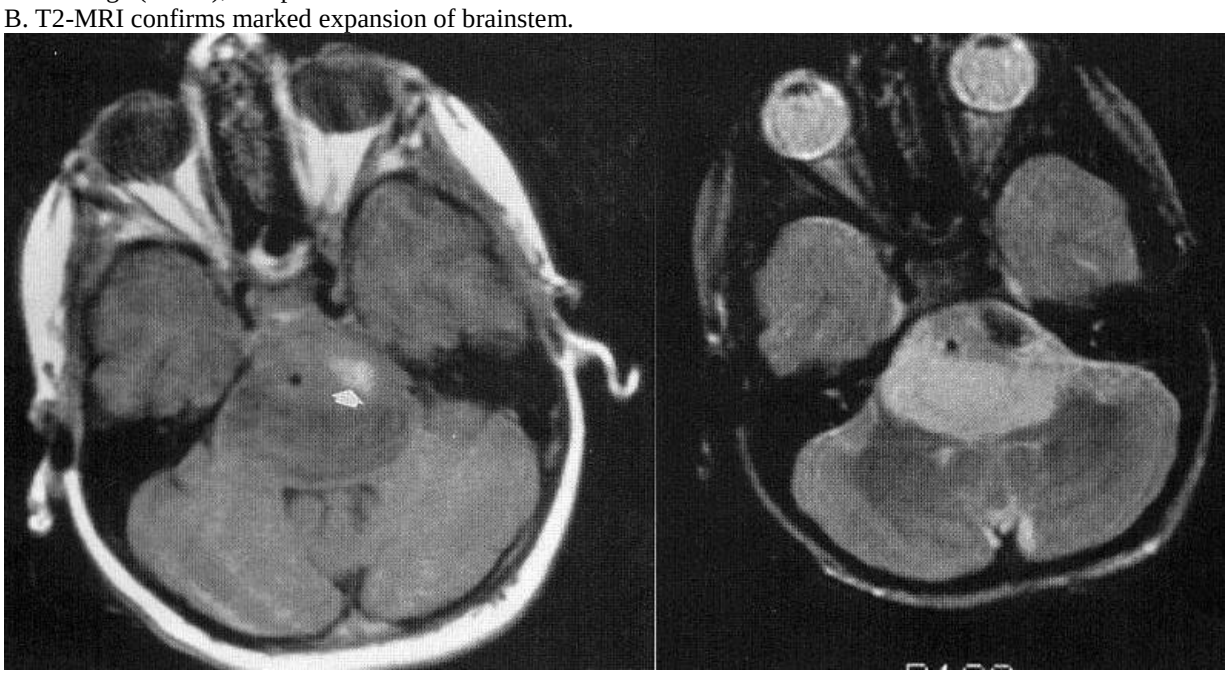




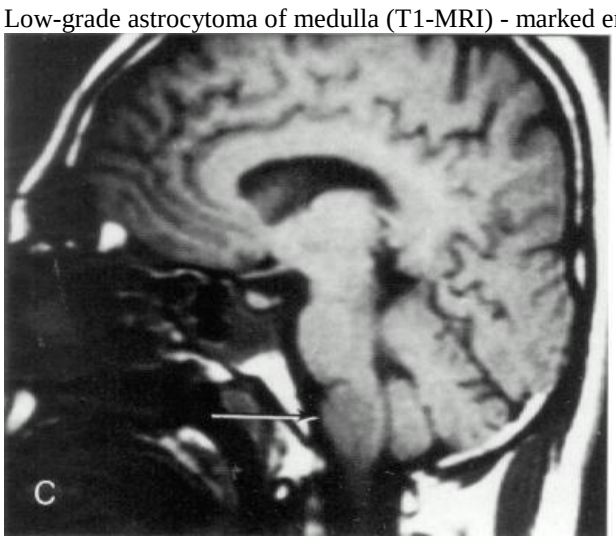
Pontine glioma (T2 - and T1 - postgadolinium MRI); no abnormal contrast enhancement:



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 astrocytoma 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 tectal; 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!
- chemotherapy efficacy has not been proved - cannot be recommended! (may benefit in some recurrences).
- some ***adults*** with tectal or cervicomedullary tumor, or with *mild symptoms of long duration*, may be candidates for observation alone.

OPTIC PATHWAY GLIOMA

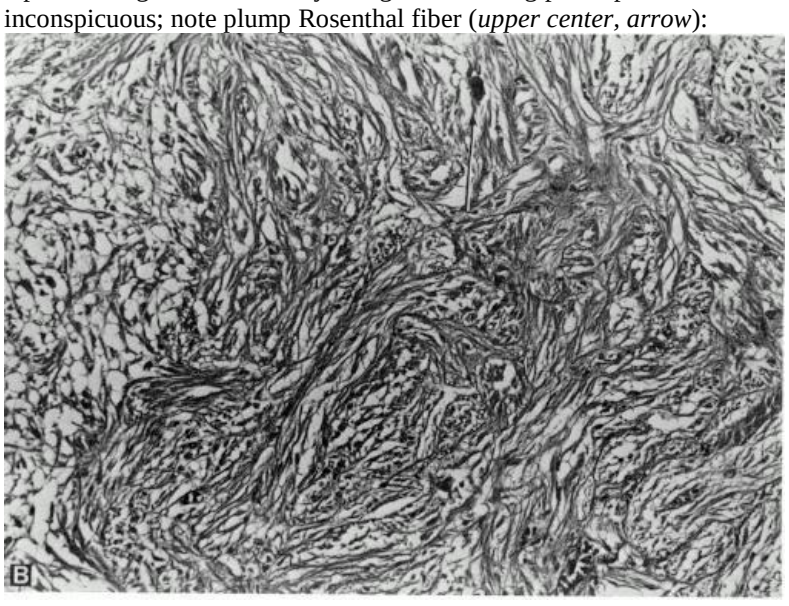
1. **Benign optic glioma** (*PILOCYTIC ASTROCYTOMA*) – most often in ***children*** (median age 5 yrs).

- 10-38% pediatric patients have **neurofibromatosis type 1** (15-20% children with NF-1 have optic nerve glioma) or, in some cases, **hybrid phakomatosis**.

  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 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).

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



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).
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.

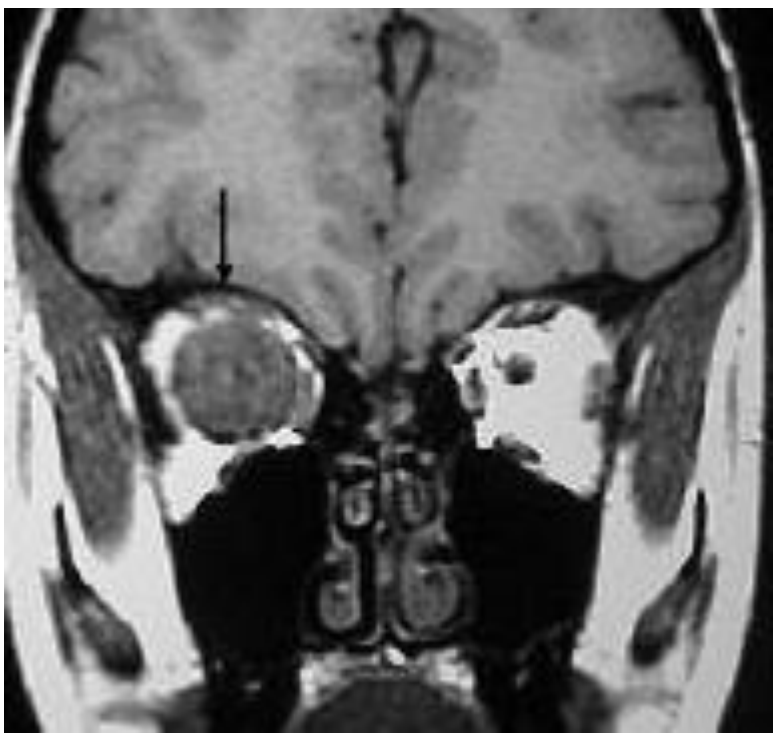
- marked, diffuse isodense enlargement (tubular, fusiform, or excrescent) of optic nerve, with characteristic kinking or bending.
- areas of lucency (mucinous or cystic changes).
- contrast enhancement – all **optic nerve** tumors, but only 50% **chiasmal** tumors and their projections along visual pathways
- *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).

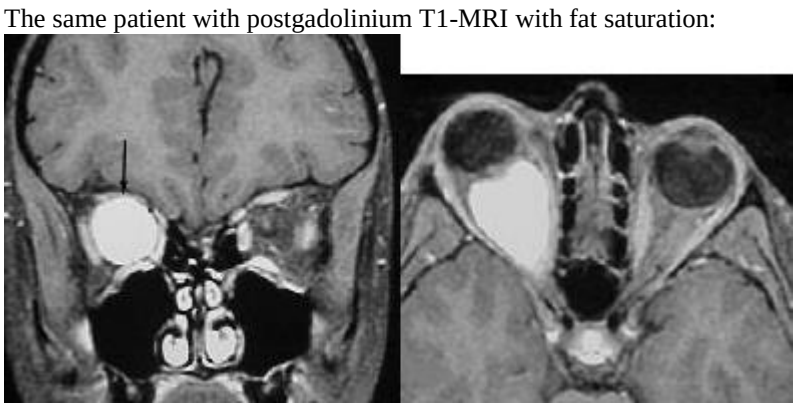
- T1 - isointense to cortex and hypointense to white matter; hypointense to orbital fat.
- T2 - mixed appearance (isointense ÷ hyperintense) relative to white matter and cortex.
- intense enhancement is common.

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.

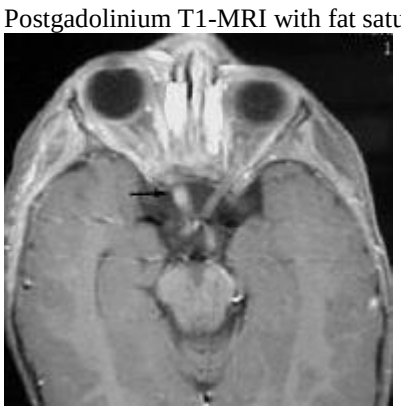
T1-MRI - large intraorbital mass (*arrow*) centered on optic nerve:



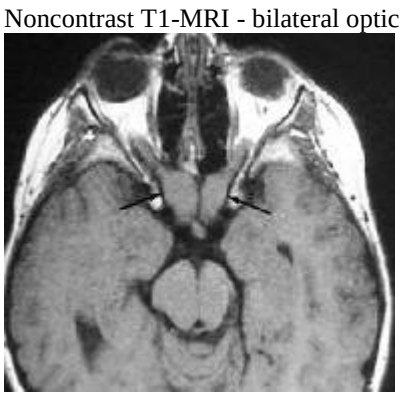
The same patient with postgadolinium T1-MRI with fat saturation:



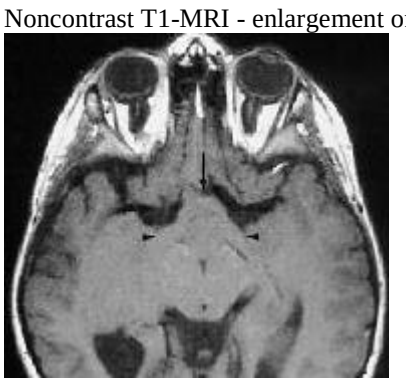
Postgadolinium T1-MRI with fat saturation - enhancement of intracranial optic nerve (*arrow*), which is slightly expanded:



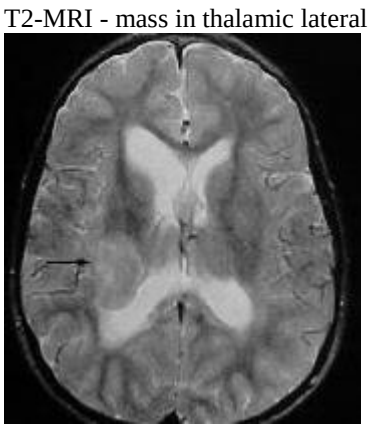
Noncontrast T1-MRI - bilateral optic nerve gliomas - fusiform enlargement of optic nerves (*arrows*) in NF-1:



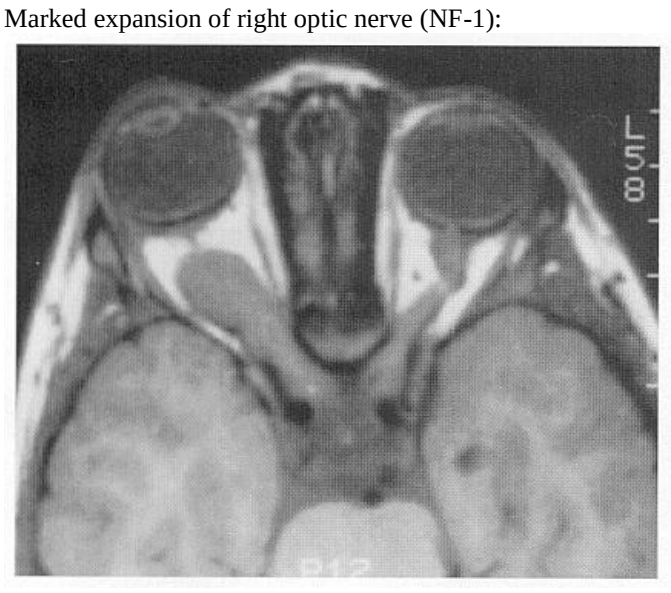
Noncontrast T1-MRI - enlargement of both optic tracts (*arrowheads*) and optic chiasm (*arrow*):



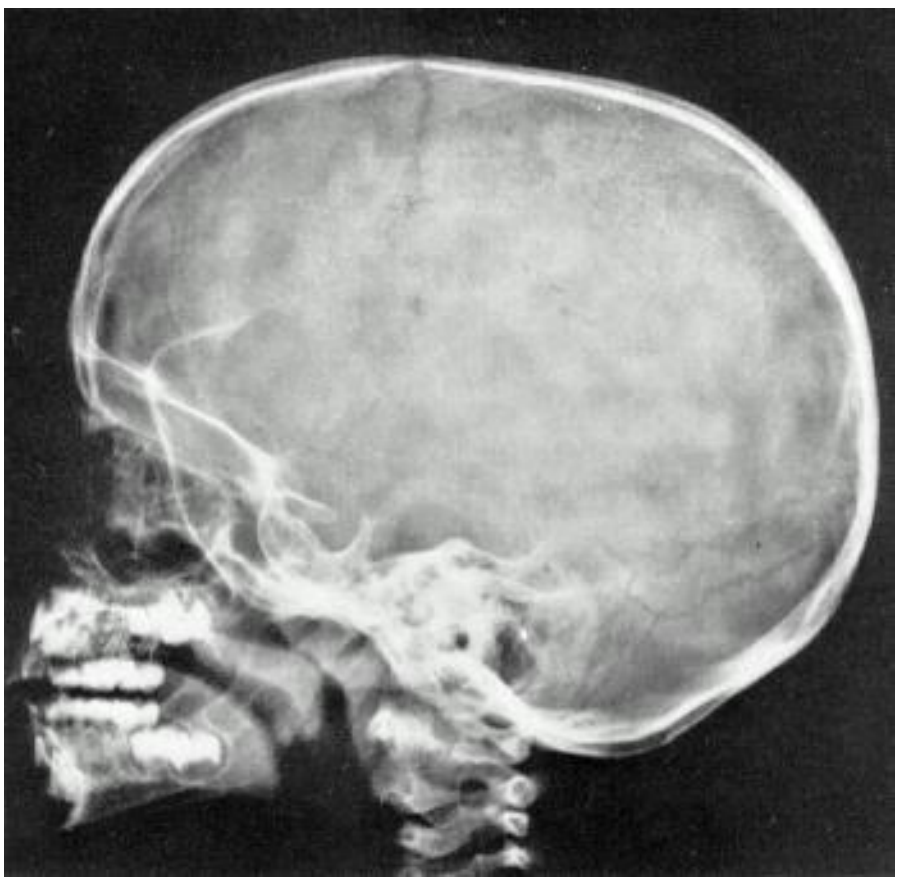
T2-MRI - mass in thalamic lateral geniculate nucleus resulting from extension of optic nerve glioma:



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 (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 >>