Adult Diffuse Glioma

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Classification (WHO classification, 5th ed., 2021)

- Astrocytoma, IDH mutant
  - Astrocytoma, IDH-mutant, grade 2
  - Astrocytoma, IDH-mutant, grade 3
  - Astrocytoma, IDH-mutant, grade 4
- Oligodendroglioma, IDH-mutant & 1p/19q codeleted
  - Oligodendroglioma, IDH-mutant & 1p/19q codeleted, grade 2
  - Oligodendroglioma, IDH-mutant & 1p/19q codeleted, grade 3
- Glioblastoma, IDH-wildtype
  - Giant cell glioblastoma
  - Gliosarcoma
  - Epithelioid glioblastoma

Incidence

The most common primary intra-axial brain tumors

Risk factors for diffuse gliomas

- Syndromic (familial diseases like: NF 1 & 2, tuberous sclerosis, Li-Fraumeni syndrome)

- Radiation therapy to CNS

Neuroradiology

- Typically arise in white matter
- CT scan & MRI grading (imprecise & not applicable to Pilocytic astro)

WHO grade	Typical radiographic findings		Location
astrocytoma, IDH-mutant, grade 2	CT: low density MRI: abnormal signal on T2WI	no enhancement with little or no mass effect	temporal, posterior frontal & anterior parietal lobes
astrocytoma, IDH-mutant, grade 3	complex enhancement[a]		
astrocytoma, IDH-mutant, grade 4	solid enhancement[a]		frontal lobe predilection
glioblastoma, IDH-wildtype	central necrosis with ring enhancement[b]		temporal > parietal > frontal > occipital

MRS (MR spectroscopy)

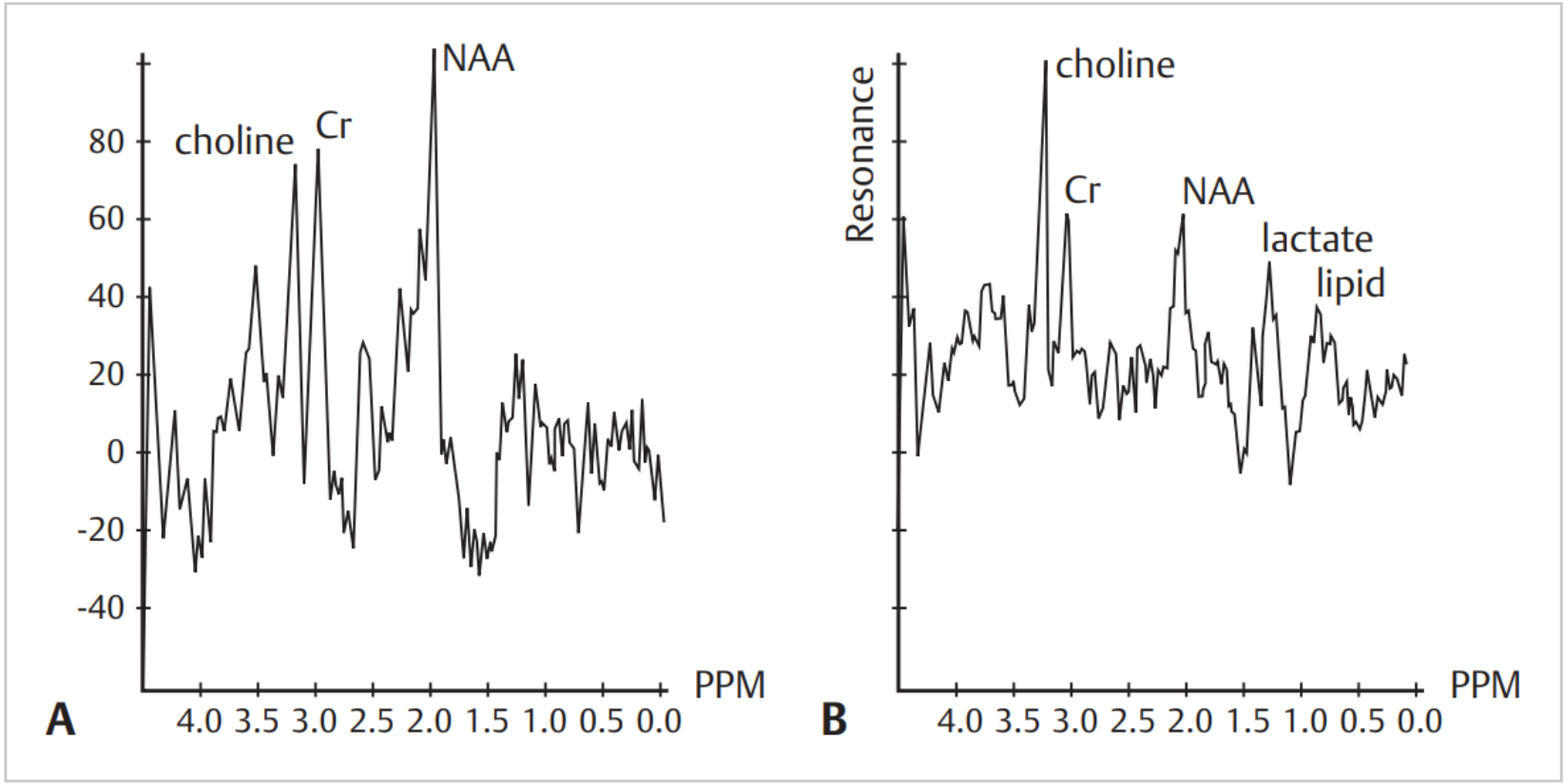


Fig. 13.1 Proton MRS. Image: A: normal brain, B: high grade glioma.

Positron emission tomography (PET) scan

Tumor	Appearance
Astrocytoma, IDH-mutant, grade 2	hypometabolic “cold” spots
Grade 3 or 4	Hypermetabolic “hot” spots*

* This may distinguish the uncommon grade 3 or 4 tumors that do not enhance from grade 2

Spread

- Tracking through white matter
- CSF pathways
- Systemically (rare)

Cysts associated with Glioma

- Cystic central necrosis:
  - The enhancing ring is the cellular tumor; however, tumor cells also extend ≥ 15mm beyond the ring

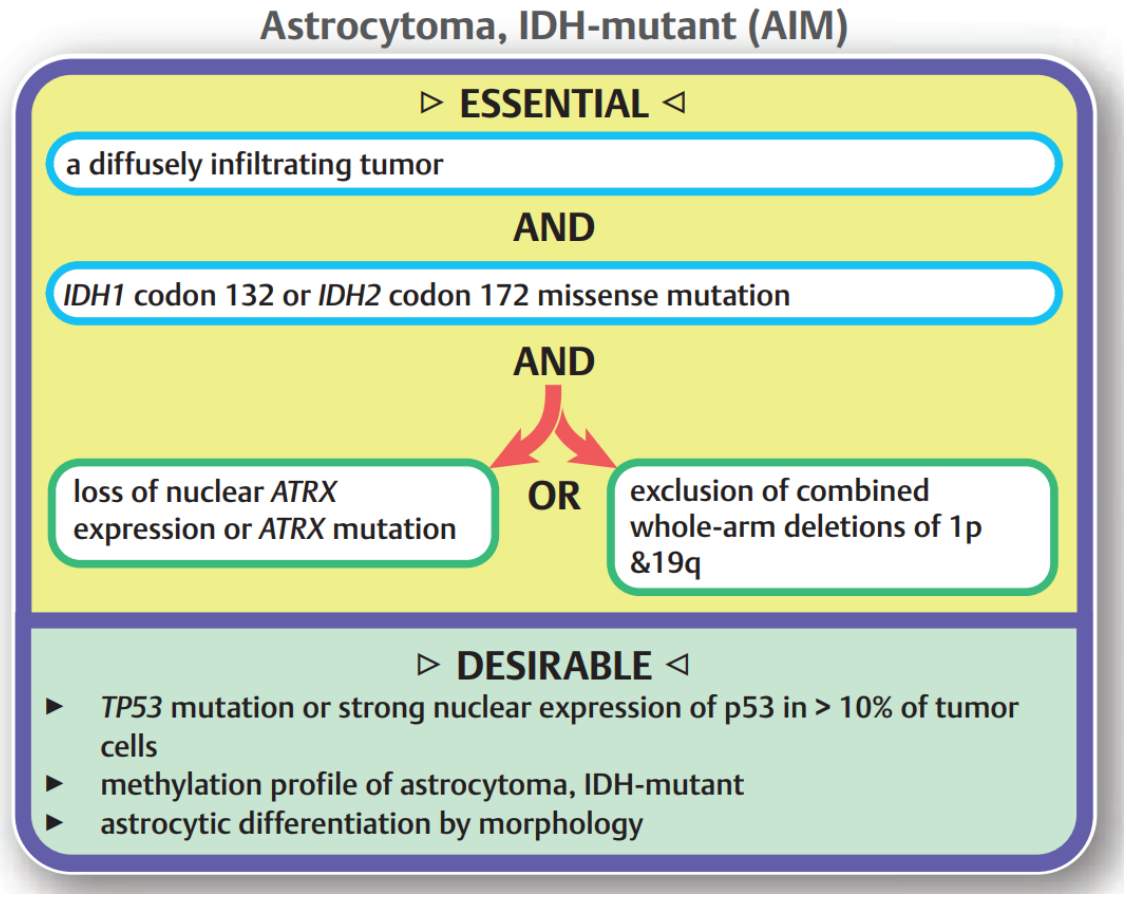
- Cyst without necrosis:
  - Fluid is usually xanthochromic and often clots once removed from the body

Astrocytoma, IDH-mutant (WHO grade 2, 3 or 4) (AIM grades 2-4) IDH = Isocitrate dehydrogenase

- A diffuse astrocytoma with mutation in either the IDH1 or IDH2 gene and absence of 1p/19q codeletion. ATRX and/or TP53 mutations are common
- Supratentorial (frontal)
- Seizures

- Grade 4 lesions has a slower growth of compared to glioblastoma (also larger at diagnosis with less area of necrosis & less edema)

Diagnostic criteria for astrocytoma, IDH-mutant



Astrocytoma, IDH-mutant subtypes (grades)

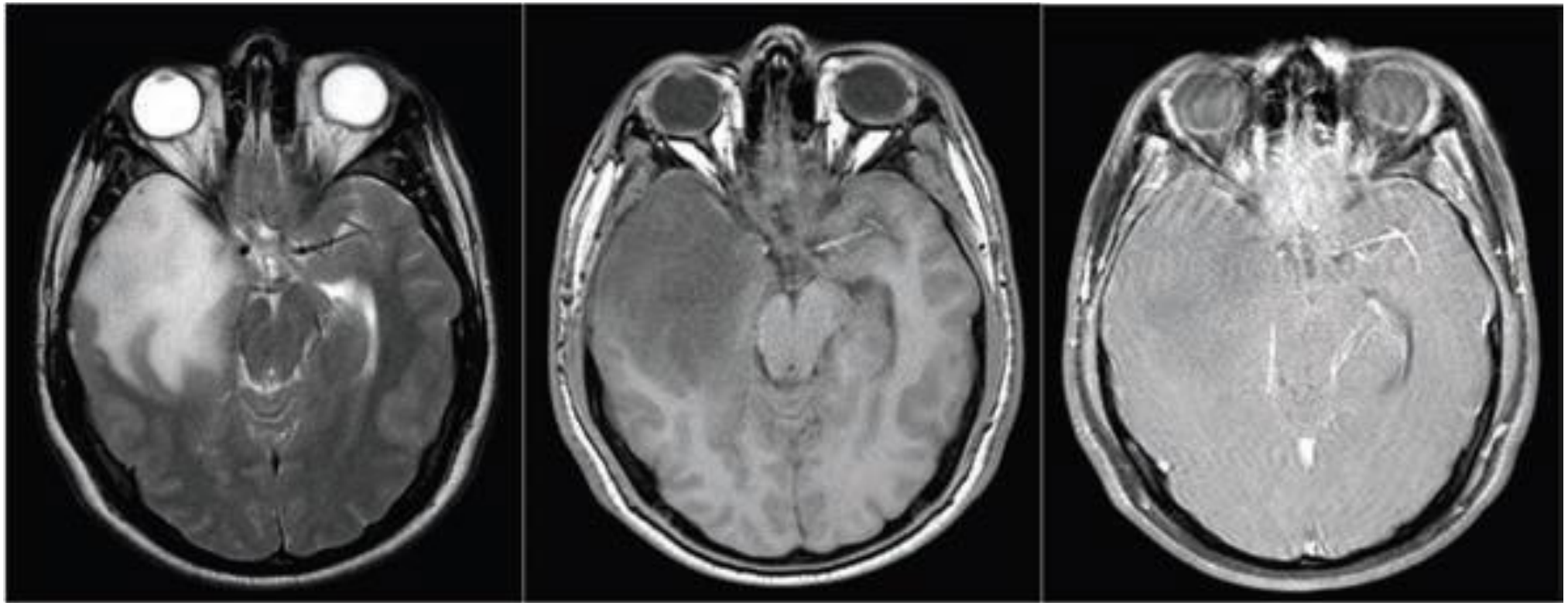
AIM grade 2	AIM grade 3	AIM grade 4
• Well differentiated • No features of anaplasia • Low or undetectable mitotic activity • No microvascular proliferation • No necrosis • No homozygous deletions of CDKN2A* or CDKN2B*	• Focal or dispersed anaplasia • Significant mitotic activity • No microvascular proliferation • No necrosis • No homozygous deletions of CDKN2A* or CDKN2B*	<u>Any combination of:</u> • Microvascular proliferation • Necrosis • Homozygous deletions of CDKN2A* and/or CDKN2B*

Ki-67 (MIB-1) index

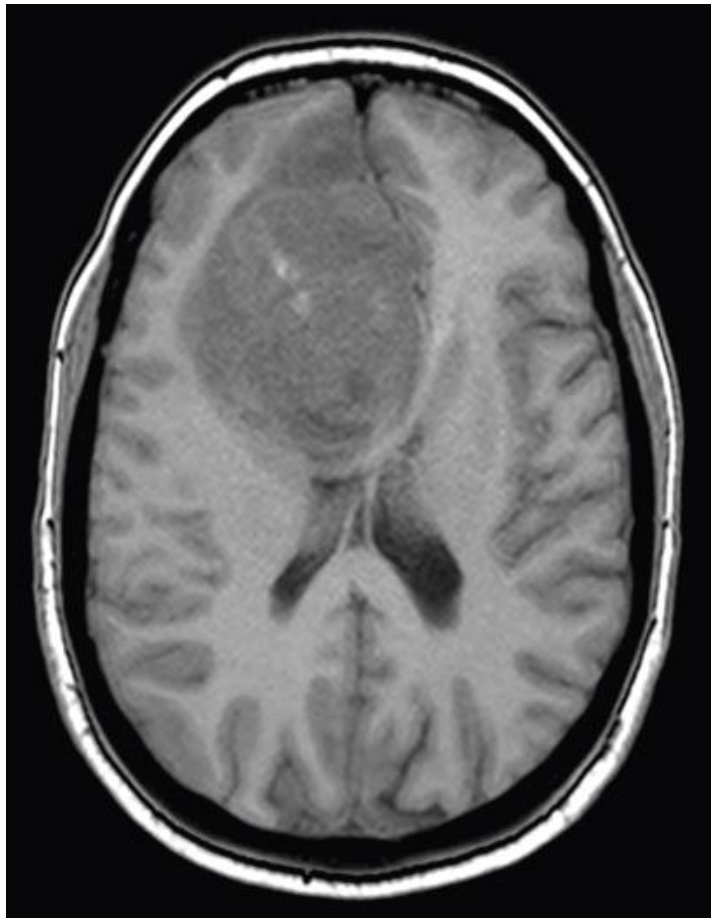
- It has been suggested that a MIB-1 index ≥ 7–9% is indicative of a high-grade tumor (not accurate!)

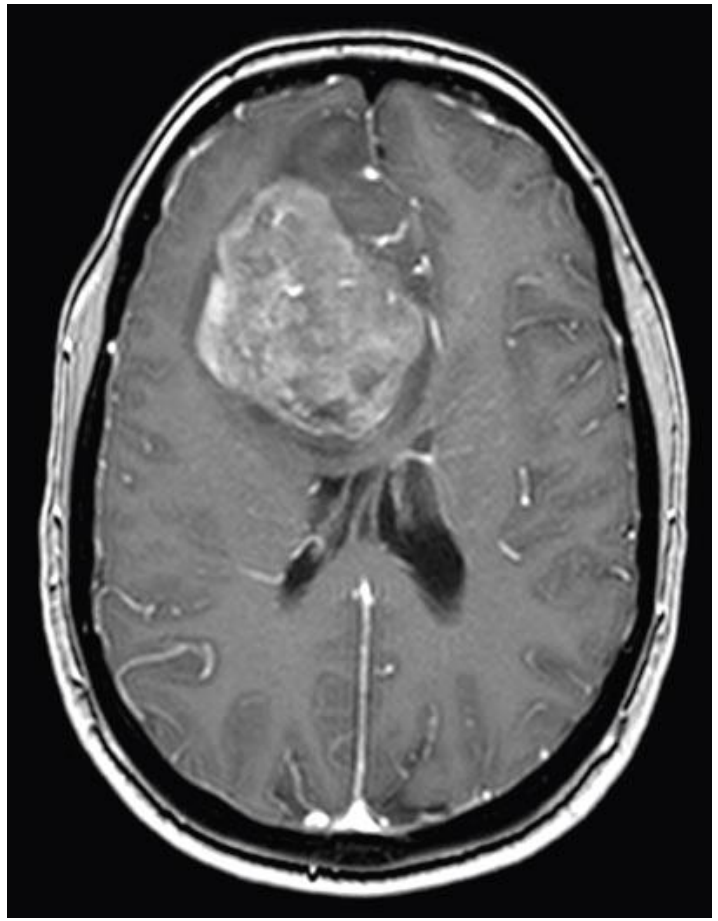
- Ki-67 index can’t be used as a sole discriminant between grade 2 & 3 or between grade 3 & 4 AIM

Astrocytoma, IDH-mutant, grade 2 of the right temporal lobe



Astrocytoma, IDH-mutant, grade 4 of the right frontal lobe





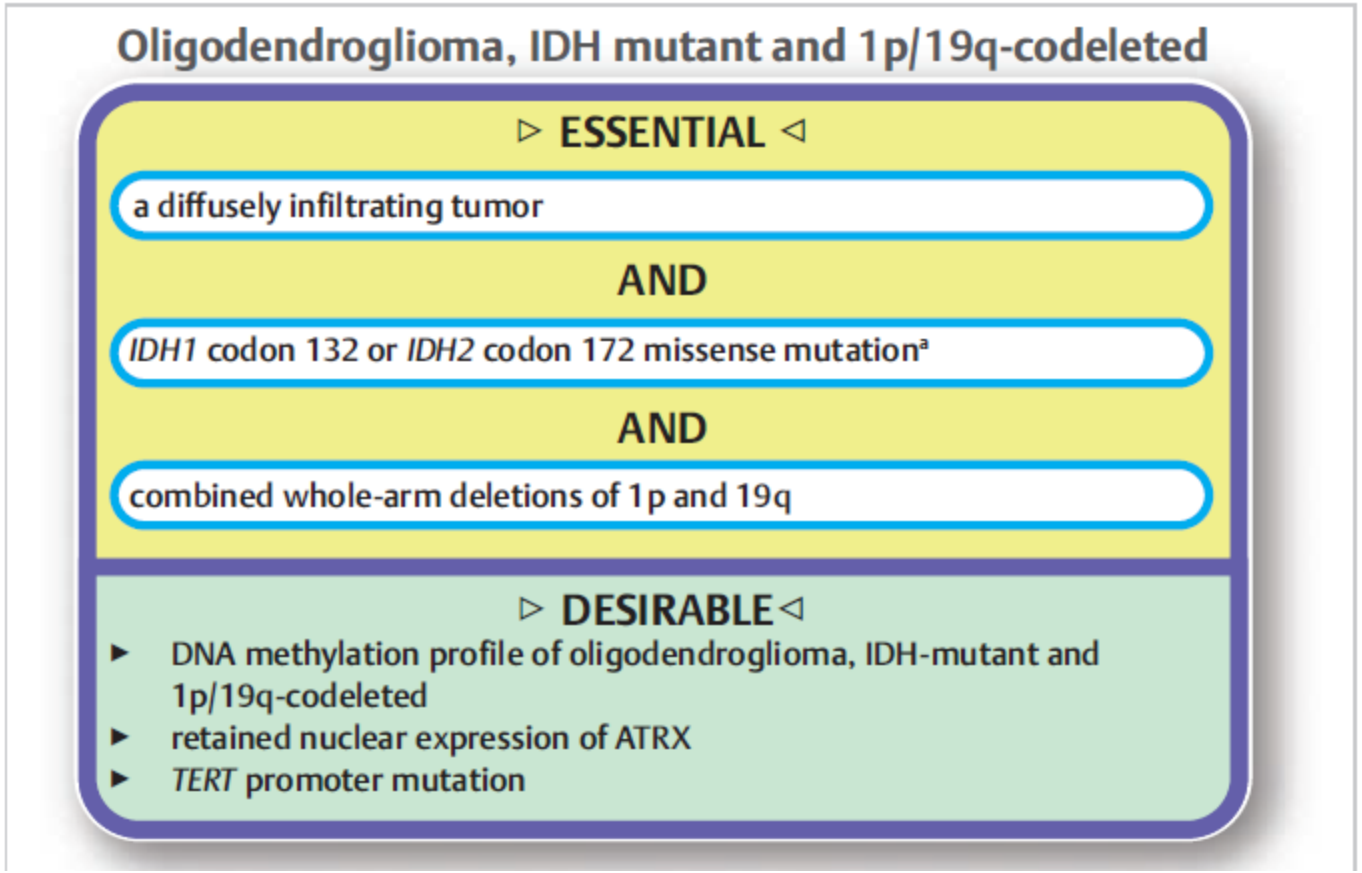
AIM Prognosis (Pre-IDH era)

- Grade 2: M. survival 10 years (75% undergo anaplastic progression)
- Grade 3&4: M. survival 2-3 years
- Dedifferentiation is quicker after age 45 years
- Prognosticators of worse prognosis:
  - Age > 40 years
  - *Largest tumor diameter ≥ 6cm*
  - Tumor crossing the midline
  - Neurologic deficit prior to surgery
  - *Subtotal resection*

Oligodendroglioma, IDH mutant and 1p/19q-codeleted (WHO grade 2 or 3) (ODG grade 2 or 3)

- Slow growing tumor
- Frequently presents with seizures (in 2/3 of patients)
- Other symptoms are nonspecific (focal deficit > high ICP)
- Occur primarily in adults
- Frontal lobes > temporal lobe
- “fried egg” cytoplasm (on permanent pathology) and “chicken wire” vasculature are unreliable.
- Calcifications are common

Diagnostic criteria for oligodendroglioma, IDH mutant and 1p/19q-codeleted



ODG grade 2 or 3

- WHO grade 2 has a more favorable prognosis
- Grade 3 ODGs usually have several of the following features:
  - High cellularity
  - Marked cytological atypia
  - Brisk mitotic activity (alone is not enough)
  - Pathological microvascular proliferation
  - Necrosis with or without palisading
  - High Ki-67 (MIB1) index
  - Clinical or radiologic evidence of rapid symptomatic growth and contrast enhancement.

ODG Imaging

- Calcifications: in 28–60% on plain radiographs & 90% of CTs.
- CT: hypodense to iso-dense.
- MRI: poorly demarcated, hypointense on T1 and hyperintense on T2.
- Fewer than 20% of grade 2 ODG and over 70% of grade 3 ODG enhance with gadolinium

ODG Histology

- Round nuclei
- Moderate cellularity
- Microscopic calcifications in 73%
- “fried egg”: artifact of formalin fixation. “chickenwire” pattern.
- Grade 2: Nuclear atypia and an occasional mitotic figure
- Grade 3: Extensive mitotic activity, prominent microvascular proliferation and spontaneous necrosis
- 16% of hemispheric ODGs are cystic (from microhemorrhages)
- ODGs usually do not stain for GFAP

ODG Prognosis

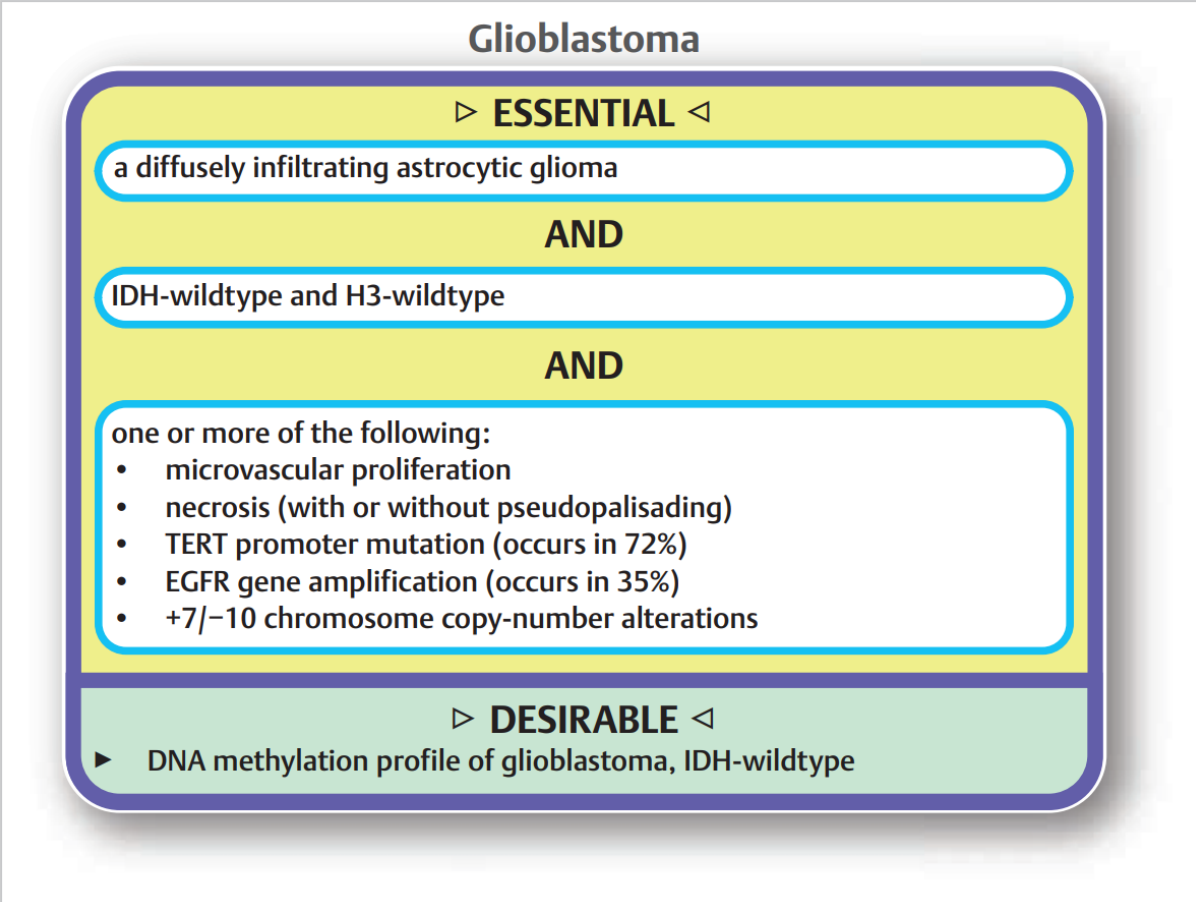
- Median survival 8 years
- Codeletion of 1p/19q by itself is associated with longer median survival (8 years vs. 6.4 years for astrocytoma)
- ODG grade 2 is an independent favorable prognosticator compared to ODG grade 3

- CSF metastases (drop mets) ≈ 1% (Symptomatic is less)

Glioblastoma, IDH-wildtype (WHO grade 4) (GBM)

- The term “glioblastoma multiforme” is obsolete, although the abbreviation “GBM” persists.
- Arises de novo (formerly called “primary glioblastoma)
- All GBM are now, by definition, IDH-wildtype
- 14% of primary brain tumors
- The most common adult malignant primary brain tumor (comprising 49% of them)
- Mean age at diagnosis ≈ 62 years. Male predominance of 1.6:1
- Rare in pediatric. Rarely infratentorial (if so, CSF seeding)

Diagnostic criteria for glioblastoma, IDH-wildtype



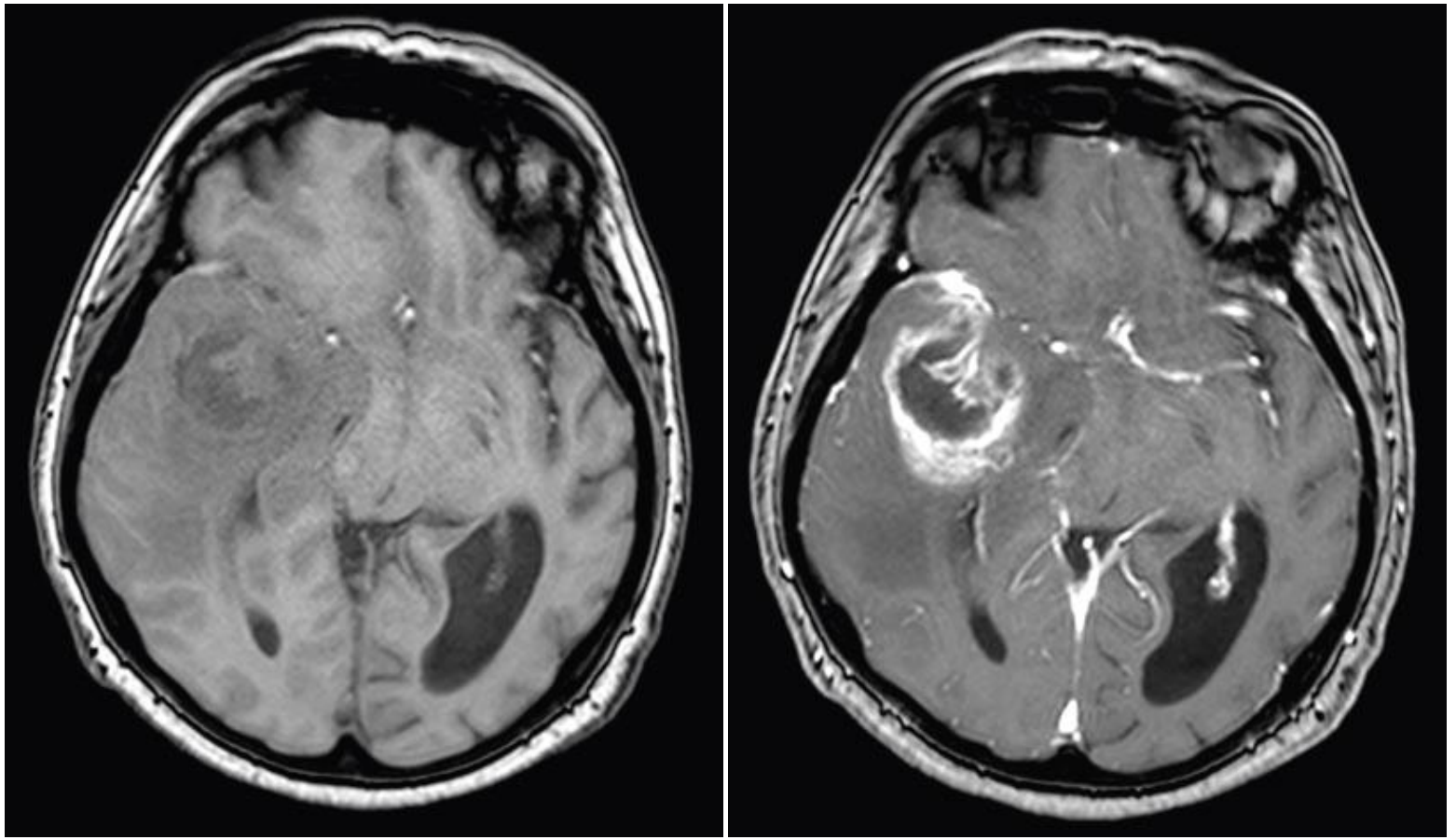
Histopathology

- Infiltrating, highly cellular
- Poorly differentiated, nuclear atypia, cellular pleomorphism
- Marked mitotic activity
- Microvascular proliferation
- Necrosis

Subtypes

Giant cell glioblastoma	Gliosarcoma	Epithelioid glioblastoma
• < 1% of glioblastomas • Multinucleated giant cells • Younger patients (mean age = 51 years)	• 2–8% of GBMs • Biphasic tissue (glial & mesenchymal)	• Epithelioid cells • Rhabdoid cells • Affects young adults and children • Predilection for the cerebellum and diencephalon

Glioblastoma, IDH-wildtype of the right temporal lobe



Prognosis for high grade diffuse gliomas (WHO grades 3 & 4)

Improved prognosis with:

- KPS ≥ 80
- Patients < 45 years
- IDH1 mutation
- Methylation of MGMT promoter gene

Survival with GBM based on MGMT promotor gene status

	MGMT promoter gene	
	Unmethylated	Methylated (in 75 % of AIM gr 4 & only 36% of GBM)
Median OS (months)	12.2	18.2
2-year survival	7.8%	34.1%
Survival benefit between RT & (RT + Temozolomide)	No difference	MS with RT alone: 15.3 mths MS with RT+ TMZ: 21.7 mths

Multiple gliomas

- Also called: “multicentric” & “multifocal”
- It is not the same as “infiltrative extension”
- Occurrence 2-4%
- Commonly associated with neurofibromatosis and tuberous sclerosis
- Meningeal gliomatosis (in 20%) → Cranial neuropathy, HCP
- Biopsy is generally required
- Radio/chemo
- Surgery is impractical & limited to debulk a tumor that threatens herniation

Treatment
Steroid use in brain tumors

- More effective in metastatic tumors than primary infiltrating gliomas

- For patients not previously on steroids:
  - Adult: 10mg IVP loading, then 6mg PO/IVP q 6 hrs.
  - In cases with severe vasogenic edema, 10mg q 4 hrs (< 48-72 hours)
  - Peds: 0.5–1 mg/kg IVP loading, then 0.25–0.5 mg/kg/d PO/IVP divided q 6 hrs. NB: avoid prolonged treatment because of growth suppressant effect
- For patients already on steroids:
  - For acute deterioration, double the usual dose
- Prophylaxis against Cushing ulcers

Treatment
Prophylactic antiseizure medications (ASMs)

- Prophylactic ASMs do not provide substantial benefit & carry significant risks (so, should not be used routinely)
- Prophylactic ASMs are not indicated for isolated posterior fossa tumors
- ASMs are indicated in these patients who have had a seizure
- In patients with brain tumors undergoing craniotomy, prophylactic ASMs may be used, and if there has been no seizure, it is appropriate to taper off ASMs starting 1 week post-op

Treatment
Surgery (cytoreduction or biopsy)

- Indicated for almost all suspected diffuse gliomas
- Never curative alone
- The objective for cytoreduction is maximal safe resection (Goal: GTR)
- When maximal safe resection is severely limited → Biopsy

- Note: the onset of a new postoperative motor or speech deficit reduces OS

Treatment
Definition of (GTR) for diffuse gliomas

- Lesions that enhance on pre-op imaging: (most high-grade): complete removal of enhancing portions of the tumor and any nonenhacing portion contained within, as verified by post-operative contrast imaging within 48 hours of surgery

- For nonenhancing lesions (most astrocytoma, IDH-mutant grade 2): removal of high intensity lesion on T2 MRI or very low intensity on T1 MRI, if safe, as verified on post-operative imaging

Treatment

Relative contraindications to surgical debulking

- Extensive dominant lobe high grade glioma
- Significant bilateral involvement
- Elderly patients
- Karnofsky score < 70
- Multicentric gliomas
- Poor medical condition

Treatment
Surgical goals

- Obtain adequate tissue for histological and molecular study
- Cytoreduction
  - Facilitates adjuvant therapy
  - Reduce mass effect & ICP
  - May reduce peritumoral edema
  - May reduce seizure frequency
  - Prevent or delay malignant transformation in LGG
- The extent of tumor removal and (in an inverse relationship) the residual tumor volume on post-op imaging studies have a significant correlation with time to tumor progression and median survival.

Technical enhancements at surgery

- Image-guidance (stereotactic surgery): especially for deep tumors or in areas bordering on eloquent brain & for low-grade diffuse gliomas
- Intraoperative MRI, U/S
- Preoperative mapping (fMRI, DTI)
- Intraoperative mapping
  - The motor strip and primary sensory → Awake or GA
  - Speech area → awake craniotomy
- Intraoperative dyes (ICG, 5-ALA) → higher 6-month progression free survival, but no effect on OS (Indocyanine green, 5-Aminolevulinic acid)

Treatment of adult diffuse gliomas grade 2 (AIM grade 2, ODG grade 2)

Treatment options:

- Surveillance: has been controversial. Now early resection is better
- Radiation: as a post-op adjunct
- Chemotherapy
- Surgery
- Combinations of radiation and chemotherapy, with or without surgery

Treatment of adult diffuse gliomas grade 2

Management recommendations

- Maximal safe surgical resection (the initial step), then (if KPS ≥ 60):
  - In low-risk patients (age < 40 years & GTR):
    - Routine imaging surveillance Q 3-6 months
  - In high-risk patients (age > 40 or STR)
    - XRT + Chemotherapy

Treatment of diffuse gliomas, grades 3 & 4
(AIM grades 3 & 4, ODG grade 3, glioblastoma)

Maximal safe cytoreductive surgery followed by external beam radiation and concurrent temozolomide has become the standard against which other treatments are compared

Treatment of diffuse gliomas, grades 3 & 4
Adjuvant therapy

Stupp regimen

- Concomitant Chemoradiotherapy is started within six weeks after histological Diagnosis.
- XRT (focal with margin 2-3 cm): 2 Gy/d, 5d/ wk, over 6 wks
- TMZ: 75mg/m2/day, 7 days per week till the end of XRT
- 4 weeks later, start 6 cycles of adjuvant chemotherapy with each cycle consisting of 5 days of TMZ, repeated every 28 days
  - First cycle dosing: 150mg/m2/day
  - Subsequent cycles dosing: 200mg/m2/day

Treatment of diffuse gliomas, grades 3 & 4
Temozolomide

- Oral alkylating agent
- May cause myelosuppression. It should not be given unless the neutrophil count is ≥ 1.5 x 109/L and platelet count ≥ 100 x 109/L
- prophylaxis against Pneumocystis jirovecii (formerly P. carinii) pneumonia is required for the initial 6-week regimen (with oral Trimethoprim/sulfamethoxazole)
- Associated with malignant transformation in low grade diffuse gliomas

Treatment of diffuse gliomas, grades 3 & 4

Σ: Transcriptional silencing of MGMT synthesis

Finding	Comment
Hypermethylation (sometimes reported simply as "methylation") of the MGMT promoter gene	This naturally occurs on chromosome 10q26 of the DNA in 75% of grade 4 AIMs. It usually leads to reduced levels of MGMT activity (see the next row in this table) which becomes very significant at >30% methylation
Reduced (or undetectable) MGMT activity	MGMT is an enzyme that repairs the damage to DNA caused by alkylating chemotherapy drugs such as temozolomide (Temodar®). Tumors with reduced MGMT levels are more susceptible to cytotoxic effects of temozolomide than nontumor cells which have normal MGMT levels, and are better able to repair the DNA damage. This results in longer patient survival

Response to treatment
Pseudoprogression (radiation necrosis)

- Increase in contrast-enhancing areas on MRI
- Seen ≤ 3 months in 28–60% of patients after (XRT + temozolomide)
- More common with temozolomide treatment for tumors with methylated MGMT promoter genes
- No definitive diagnostic test
- Serial MRIs and clinical exams seems to be an effective strategy
- Rule of thumb: MRI S/O GBM recurrence within 6 months after XRT + temozolomide should be assumed to be pseudoprogression as long as it is within the radiation field.
- If symptomatic: Steroids, Bevacizumab (Avastin)

Response to treatment
Pseudoresponse

- Occurs when enhancement reduced after giving agents that stabilize the BBB (steroids, bevacizumab)

RANO (Response Assessment in Neuro-Oncology) criteria

Response can be assessed as:

- Complete response
- Partial response
- Stable disease
- Progression

Thanks



Any Questions?