Alphabet Soup:
Making sense of the new WHO CNS glioma classifications and the growing importance of molecular markers

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Glioma

- Most common primary intraaxial tumor
- Occur anywhere in the CNS, but most commonly arise from brain glial tissue

- **Incidence** (per 100,000) in US
  - All glioma: ~4.7-5.7
  - All astrocytoma: ~4.5
  - **Glioblastoma**: 3.2
  - Anaplastic Astrocytoma: 0.4
  - Oligodendroglioma: 0.3
  - Anaplastic oligodendroglioma: 0.1

George Gershwin, American composer – Cause of death: glioma
Glioma

- 5-year survival (US)
  - All astrocytoma:
    • Grade I-IV: 47%
  - Glioblastoma:
    • Grade IV: 4.7%
  - Anaplastic Astrocytoma:
    • Grade III: 27%
  - Oligodendroglioma:
    • Grade II-III: 79%
  - Anaplastic oligodendroglioma:
    • Grade III: 51%

Charles Whitman, Responsible for 1966 U of Texas massacre - Glioma found at autopsy
Astrocytoma
- WHO grade II or III (anaplastic)
- Ill-defined T2/FLAIR hyperintense expansile white matter lesion
- Two thirds are supratentorial, most frontal/temporal
- Grade II, more homogenous, unlikely to enhance
- Grade III, more heterogeneous, can enhance
- Low cerebral blood volume = low grade, low to high blood volume = high grade
Radiologic Refresher on Diffuse Glioma

• Oligodendroglioma
  – WHO grade II or III (anaplastic)
  – T2/FLAIR hyperintense expansile white matter lesion
  – >80% supratentorial, most frontal
  – Heterogenous, can **calcify**, have cysts, and enhance (50%)
  – Low cerebral blood volume = low grade, low to high blood volume = high grade
  – Prominent enhancement, hemorrhage or necrosis? Think anaplastic/high grade

Pathology: Grade III
Anaplastic oligodendroglioma
Radiologic Refresher on Diffuse Glioma

Glioblastoma
- WHO grade IV
- Ill-defined T2/FLAIR hyperintense expansile white matter lesion + vasogenic edema
- Most supratentorial, rarely occipital
- Variable enhancement pattern: thick rim, solid, patchy nodular
- Heterogenous, can have cysts, necrosis, hemorrhage, calcium rare
- High cerebral blood volume on perfusion
- Hypercellular elements T2 hypointense, restrict diffusion

Pathology: Grade IV glioma (Glioblastoma)
Though imaging can occasionally predict the pathology, it is not a replacement for surgical pathology.
The Old Paradigm

- Until 2016, gliomas (and all CNS tumors) classified solely by HISTOLOGY

- Assumed histology could predict cell of origin and level of differentiation. Considered:
  - Ultrastructure
  - Cellular features
  - Staining for cellular lineage-related proteins
The Old Paradigm

• Can histologic appearance dependably predict prognosis and tumor behavior?
• Sometimes, but…
  – Some grade II astrocytomas act like grade II astrocytomas
  – Some grade II astrocytomas act like glioblastoma
  – Not all glioblastomas are created equal

These problems and advances in technology drove the current paradigm shift.
Developing a New Paradigm

- 2007 WHO guidelines: genetic markers were applied to *preexisting* categories to aid in prognosis
- 2014 International Society of Neuropathology Meeting – set groundwork for new classification scheme
- Finalized 2016 CNS WHO subsequently released
- Notably, molecular parameters are now used for tumor *classification*, not just *prognosis*
Where to Start

• The more circumscribed gliomas and childhood gliomas (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) are now considered pathologically and clinically dissimilar from diffuse astrocytoma than oligodendroglioma.

• The following slides will subsequently detail diffusely infiltrating gliomas.
The Key Flowchart

Pathology

Astrocytoma
- ATRX loss, P53 mutation
  - Astrocytoma

Oligoastrocytoma
- 1p/19q codeletion
  - IDH-Wild Type
  - Oligodendroglioma

Oligodendroglioma
- IDH-Mutant

Glioblastoma
- IDH-Mutant
- IDH-Wild Type
  - MGMT methylation status

Oligodendroglioma NOS
- IDH-Mutant

Astrocytoma NOS, Oligodendroglioma, NOS
- IDH-Wild Type

Oligoastrocytoma, NOS
- IDH-Wild type Astrocytoma, Oligodendroglioma NOS

Glioblastoma, IDH-Mutant

Glioblastoma, IDH-Wild Type
First Branch Point: IDH mutation status
IDH (Isocitrate dehydrogenase 1 and 2)

- Tumor status is either wild-type (functional IDH enzyme) or mutated
- Mutation results in production of 2-hydroxyglutarate (2-HG) which can effect methylation profile of multiple genes and can alter telomere length
- Mutation also results in a reduction of alpha-ketoglutarate and NADPH, which can facilitate cellular proliferation
IDH mutation has been implied in initial tumorigenesis, followed by further molecular pathway changes which push either astrocytic or oligodendroglial differentiation.

**Normal glial precursor**

- IDH MUTATION
- 1p/19q codeletion plus other mutations

**Precancerous glial cell**

- ATRX, P53, and other mutations

**Oligodendroglialoma**

**Astrocytoma**
Unclear if overall function of IDH mutation is oncogenic or if mutation results in loss of tumor suppression.

What is clear, is that IDH wild-type and mutated tumors are clinically distinct entities.

IDH mutated tumors have a relatively favorable outcome – less aggressive, better progression-free and overall survival.

The minority of GBM (12%), majority of grade II-III infiltrating gliomas are IDH mutated – and that said: **IDH wild-type low grade gliomas ACT like glioblastoma**
Pathology: Diffuse infiltrating astrocytoma, grade II

Would knowing IDH status change your reporting?

Conceivably, as the threshold for calling progression should be lower in an IDH wild-type glioma.
A Word on IDH in Glioblastoma

- IDH is an important prognostic indicator in GBM - IDH mutant GBMs have an improved survival (~30 mos) over wild-type (~15 mos)
- Additionally, presence of IDH mutation (~10% of GBM), implies tumor arose from degeneration of initial lower grade glioma
- Wild-type GBM (~90%) implies a de novo tumor which did not develop from a low grade precursor

An example of a heterogeneously enhancing, diffusion restricting grade IV glioma
Second branch point: For grade II & III gliomas, differentiating between astrocytoma and oligodendroglioma.
ATRX loss

- Alpha-thalassemia/mental retardation syndrome x-linked gene
- Function: telomere maintenance enzyme
- Mutation/loss of function almost never occurs in the setting 1p/19q codeletion
- Loss of function almost always occurs in the setting of IDH mutation – thus making thea a powerful marker for astrocytoma
- Presence of ATRX function loss correlates with a favorable prognosis in astrocytoma

Grade II astrocytoma, positive for ATRX loss
p53 mutation

• p53 is a powerful tumor suppressor gene, known as the “guardian of the genome”

• Acts to promote DNA repair, arrest the cell cycle, and promote apoptosis in the setting of DNA damage

• p53 mutation occurs in the setting of numerous different cancers, not just glioma
  – Think Li-Fraumeni syndrome: congenital p53 mutation leads to development of multiple malignancies

• p53 when mutated/non-functional promotes cell proliferation, invasion, and immortalization
p53 mutation

• p53 status acts as a clear division between oligodendroglioma and astrocytoma – one study (Wang YY, AJNR 2015) showed that all low-grade gliomas were either p53 mutated or 1p/19q codeleted

• Unclear what the effect of mutation is on prognosis

• Curiously, some data suggests p53 mutated tumors in specific locations (left medial and right anterior temporal lobes) have shorter progression free survival

• Can in theory be used to differentiate between “primary” GBM (p53 intact) and “secondary” GBM arising from dedifferentiated astrocytoma (p53 mutated)
1p/19q codeletion: The oligodendroglioma marker
1p/19q Codeletion

- Deletions involving the 1p and 19q chromosomal arms – detected by FISH analysis
- Codeletion effects multiple genes, notably resulting in CIC and FUBP1 inactivation (both transcription regulators)
- Considered to be an objective marker of oligodendroglioma cellular lineage, though notably, a small subset of glioblastomas can also be 1p/19q codeleted as well
1p/19q Codeletion

- Seen in up to 90% oligodendrogliomas when strict histopathologic correlation is employed.
- Most gliomas that are not 1p/19q codeleted have ATRX loss and P53 mutation, which are markers of astrocytoma.
- Codeleted tumors act more indolently and respond better to temozolomide and radiation, thus, codeletion status is correlated with improved survival.
Radiologic implications of 1p/19q codeletion status

Both tumors resected – pathology proven glioblastoma

15 MONTHS
1p/19q not deleted

120 MONTHS
1p/19q codeleted
A Word on Oligoastrocytoma

- Contentious diagnosis: tumor with features of both astrocytoma and oligodendrogliaoma

- Now, 1p/19q codeletion status and ATRX and p53 status allow for easier classification of previously ambiguous tumors

- Oligoastrocytoma still exists per WHO 2016:
  - cases where marker testing is unavailable
  - rare cases where markers contradict: 1p19q codeleted, ATRX loss tumor, for example
Q: How does oligoastrocytoma fit on the master flowchart?

A: Not cleanly, as molecular markers allow for more concise astrocytoma/oligodendroglioma differentiation.
MGMT Methylation Status:
Not a diagnostic marker, but instead a marker to predict response to therapy
MGMT methylation

- MGMT = O\textsuperscript{6}-methyl-guanine-DNA methyltransferase, a DNA repair enzyme
- Temozolomide methylates the O\textsuperscript{6} position of guanine leading to DNA breakage. The effect of temozolomide can be repaired/negated by a functional MGMT enzyme
• The MGMT gene itself can be methylated or “turned off” by promotor region methylation and epigenetic silencing

• Methylated MGMT means temozolomide can work better as MGMT is not produced, thus methylation is associated with increased survival

• MGMT methylation is detected in ~36% gliomas
MGMT methylation

- The MGMT gene itself can be methylated or “turned off” by promotor region methylation and epigenetic silencing
- Methylated-MGMT means temozolomide can work better, and is therefore associated with increased survival
- Methylation is encountered in ~36% gliomas
MGMT methylation

• The MGMT gene itself can be methylated or “turned off” by promotor region methylation and epigenetic silencing
• Methylated-MGMT means temozolomide can work better, and is therefore associated with increased survival
• Methylation is encountered in ~36% gliomas
An example of MGMT status in radiologic follow-up

MGMT NOT methylated

PROGRESSION: 12 MONTHS

MGMT methylated

PROGRESSION: 39 MONTHS
Summation

• New WHO 2016 guidelines assign more importance to molecular markers in the diagnosis, not just prognosis, of diffuse glioma

• IDH mutation – key mutation in development of low grade glioma
  – Improved prognosis when present

• 1p/19q codeletion = oligodendroglioma
  – Improved prognosis when present

• ATRX and p53 mutated = astrocytoma

• MGMT methylated = improved response to temozolomide, increased survival
The Key Flowchart

Astrocytoma

ATRX loss, P53 mutation

Oligoastrocytoma

MGMT methylation status

Oligodendroglioma

1p/19q codeletion

IDH-Mutant

IDH-Wild Type

Glioblastoma

IDH-Mutant

IDH-Wild Type

Astrocytoma NOS, Oligodendroglioma, NOS, Oligoastrocytoma, NOS

Glioblastoma, IDH-Mutant

Glioblastoma, IDH-Wild Type

Astrocytoma, Oligodendroglioma NOS

Oligodendroglioma, NOS