2016 WHO CLASSIFICATION OF BRAIN TUMORS
STATE-OF-THE-ART IMAGING UPDATE

Suyash Mohan MD, PDCC

Assistant Professor of Radiology & Neurosurgery
Division of Neuroradiology
Department of Radiology
University of Pennsylvania
Philadelphia, PA
Disclosures

- Consultant: ACR Imaging Network (ACRIN) & ACR Image Metrix
  - GBM multi-institutional trial ABTC 0901
  - RANO Reader Eisai TM610-002 Study
  - Phase III RTOG 0825(4508)/ACRIN 6686

- Grant Support
  - PI - High Resolution MRI/MRS to Evaluate Therapeutic Response to Optune
  - PI: Galileo CDS Inc. – Clinical Diagnostic Decision Support in Radiology
  - Co-I: RSNA Education Scholar Grant: Development of a Novel Radiology Teaching Interface Using Bayesian Networks
  - Co-I: Guerbet 03277 Dose Finding Study in CNS MRI

- NovoCure Advisory board
Beginning of Modern Brain Tumor Classification

Published “A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis” in 1926

Based on cellular configuration, classification system of 13 categories. In 1927, reduced the number of categories to 10.
Following Cushing & Bailey, competing classification systems evolved

WHO classification is now the standard

- 2016 WHO update is not a true 5th edition, but a revision to the 4th edition, in light of new molecular & genetic information

- 3rd edition: 2000
# Molecular & genetic tumor definition

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Greater <strong>correlation</strong> with tumor behavior</td>
<td>• May potentially <strong>delay</strong> final diagnosis depending on availability of testing</td>
</tr>
<tr>
<td>• Useful for clinical care and research</td>
<td>• Some techniques (gene sequencing) may <strong>not be readily available</strong></td>
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<tr>
<td>• More <strong>objective</strong></td>
<td>• Changes may be a source of <strong>confusion</strong> for brain tumor clinicians &amp; <strong>radiologists</strong> 😊</td>
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<tr>
<td>• Provides insights into tumorigenesis</td>
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</tbody>
</table>
Outline

• **Five key updates** from the revised 4th edition of the 2016 WHO classification

• Multiparametric integration of conventional & advanced imaging techniques:
  • Improved diagnostic accuracy
  • Improved prognostication
  • Improved preoperative planning & functional mapping
45 Y/F with LOC following MVC. Several days of dysgeusia prior to the event.

Infiltrative abnormal FLAIR signal involving more than three lobes.

Gliomatosis Cerebri
Key Update # 1: Gliomatosis cerebri

• Gliomatosis cerebri is *no longer a distinct entity.*

• As of 2016, gliomatosis is a pattern of growth that can be displayed by any infiltrating glioma.
Infratentorial Neoplasms: *Intra-axial*

**Metastases**
- Most common intra-axial neoplasm

**Hemangioblastoma**
- Most common primary infratentorial intra-axial neoplasm in adults

**Glioma**

**Other**
- Medulloblastoma
Infratentorial Neoplasms: *Intra-axial*

- **Metastases**: Most common intra-axial neoplasm
- **Hemangioblastoma**: Most common primary infratentorial intra-axial neoplasm in adults
- **Glioma**
- **Other**: Medulloblastoma
Key Update # 2: Revised classification of Embryonal tumors

- Now with molecular/genetic subgroups
- Some entities eliminated
- New tumor designations added

Primitive Neuroectodermal Tumor (PNET)
No longer a part of the diagnostic lexicon
# Embryonal Tumors

## Genetically defined
1. Medulloblastoma
2. Embryonal Tumor with Multilayered Rosettes, C19MC altered
3. Atypical Teratoid/Rhabdoid tumor (ATRT)

## Not yet genetically defined
1. Medulloepithelioma
2. Neuroblastoma
3. Ganglioneuroblastoma
4. Embryonal tumor, NOS
**Medulloblastoma**

- **Most common** CNS embryonal, neuroepithelial tumor.
- Dominant population of undifferentiated cells.
- High nuclear-to-cytoplasmic ratio; Abundant mitotic figures.
- **All are WHO grade IV**, regardless of their histology/genetics.

**Histologic subtypes**
- Classic
- Desmoplastic/Nodular
- Extensive nodularity
- Large cell / Anaplastic

**Genetic subtypes**
- WNT activated
- SHH activated, TP53 mutant
- SHH activated, TP53 wildtype
- Non-WNT, non-SHH
Medulloblastoma: **WNT (wingless)**

- ~10%
- Histology: Classic (90%)
- *Excellent prognosis*
- Older children
- Dorsal brain stem
- Centered on Foramen of Luschka
- Appear intraventricular
Medulloblastoma: *Sonic Hedgehog (SHH)*

- ~30%
- Histology: variable
  - TP53-wildtype; good prognosis
  - TP53-mutant (rare); poor prognosis
- Cerebellar granule neuron precursors
- Solid, avidly enhancing in *lateral cerebellar hemispheres* or vermis
- *Grape-like pattern*
Medulloblastoma: *Non WNT/Non SHH*

- **Group 3:** 20%
- **Histology:** Mostly classic
- **Intermediate/poor prognosis**
- **Infants & children**
- **Midline/fourth ventricle**
- **Very frequently metastatic**

**Diagnostic Pearl:**
Look for the point of origin!!
Roof of fourth ventricle
Medulloblastoma: Metastases

Courtesy: Karuna Shekdar MD CHOP
Embryonal tumor with multilayered rosettes, C19MC altered

- Formerly: Embryonal Tumor with Abundant Neuropil & True Rosettes (ETANTR)
- Most aggressive tumor of childhood (mean survival 9-12 months)

13 month boy, irritable, regression of motor function

Courtesy: Karuna Shekdar MD CHOP
Embryonal tumor with multilayered rosettes, C19MC altered

• ~ 50 cases reported
• 3 histologic patterns within a single entity, all with rosettes.
• New cases need to be reported to learn about its pathological & clinical behavior.

Rosettes have an elongated slit-like, or round lumen.
Cell-cell connections near the lumen form a circular zone.

Courtesy: Mariarita Santi MD, CHOP
Atypical Teratoid/Rhabdoid tumor (ATRT)

- Malignant, poorly differentiated G-IV embryonal tumor with rhabdoid cells.
- Supra or infratentorial
- < 3 years of age

- Heterogeneous lesion with **DWI restriction**, variable enhancement & cystic/necrotic regions
- Leptomeningeal spread ~ 25%

Diagnosis now defined by molecular feature of SMARCB1 (INI1) loss

33 Y/M from China, left hemiplegia, multiple left sided cranial nerve deficits, progressive gait ataxia, somnolence, hydrocephalus.
• Primary Neoplasms:
  • *Glial*: GBM—Most common primary glial tumor
  • *Non-glial*: Meningioma—Most common non-glial tumor
  • *Other non glial*: adenoma, lymphoma, PNET, etc

• Secondary Neoplasms:

• Non-neoplastic conditions:

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**TABLE 2. Distribution of All Primary Brain and CNS Gliomas by Histology Subtypes, CBTRUS 1998-2002 (N=25,539)*

<table>
<thead>
<tr>
<th>Histology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymomas</td>
<td>5.6</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>9.2</td>
</tr>
<tr>
<td>Pilocytic astrocytomas†</td>
<td>5.7</td>
</tr>
<tr>
<td>Diffuse astrocytomas</td>
<td>1.7</td>
</tr>
<tr>
<td>Anaplastic astrocytomas</td>
<td>7.9</td>
</tr>
<tr>
<td>All other astrocytomas</td>
<td>9.1</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>50.7</td>
</tr>
<tr>
<td>All other gliomas</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*CBTRUS = Central Brain Tumor Registry of the United States; CNS = central nervous system.
†Astrocytomas and glioblastomas account for 75% of all gliomas.

Key Update # 3: Glioblastoma & IDH mutation

- Formally subdivided by **presence or absence of mutation in the isocitrate dehydrogenase (IDH) gene**

- Vast majority of mutations occur in codon 132 of IDH1, (IDH2 rare)

WHO Grade IV
GBM
IDH Mutation

GBM
**IDH Mutant**

GBM
**IDH Wild-type**
<table>
<thead>
<tr>
<th>GBM, IDH Mutant</th>
<th>GBM, IDH wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ~10% of GBM</td>
<td>• ~90% of GBM</td>
</tr>
<tr>
<td>• Younger</td>
<td>• Older</td>
</tr>
<tr>
<td>• Better prognosis</td>
<td>• Poorer prognosis</td>
</tr>
<tr>
<td>• More likely MGMT methylated</td>
<td>• Most “primary” GBM</td>
</tr>
<tr>
<td>• Most “secondary” GBM</td>
<td>• Most “primary” GBM</td>
</tr>
<tr>
<td>• Targeted therapies</td>
<td></td>
</tr>
</tbody>
</table>
Relevance to Radiology

- IDH catalyzes oxidative decarboxylation of isocitrate to α-KG
- Mutant IDH causes accumulation of 2-HG (5-35 mM)
- **2HG can be detected by MRS**
- Knowledge of IDH status may influence surgical planning and subsequent therapy
- Response assessment
Non-invasive detection of 2-hydroxyglutarate in IDH-mutated gliomas using two-dimensional localized correlation spectroscopy (2D L-COSY) at 7 Tesla

Gaurav Verma¹, Suyash Mohan¹, MacLean P. Nasrallah², Steven Brem³, John Y. K. Lee³, Sanjeev Chawla¹, Sumei Wang¹, Rajakumar Nagarajan⁴, M. Albert Thomas⁴ and Harish Poptani⁵
MR Spectroscopy at 7 Tesla

18 Y/M after a grand mal seizure

7T 2D L-COSY Spectrum

IDH Mutant Astrocytoma (G-II)
Chemical Shift Imaging (CSI) at 3.0 T

- 2D CSI
  - TE/TR = 97/1700 ms
  - 1.5 ml voxels
  - 6:53 min
  - *Optimized for 2HG*

- LCModel Fitting

IDH Mutant Grade III AA
Wild-Type Glioblastoma

No detectable 2HG

Voxel [10,6]
2HG
48 % CRLB
1. Multinodular and vacuolating neuronal tumor

2. Diffuse Midline Glioma, H3-K27M mutant (DIPG variant)

3. Diffuse Leptomeningeal Glioneuronal Tumor
Multinodular & Vacuolating Neuronal Tumor

- Uncertain class assignment
  (Provisional classification)
- Seizure
- Incidental finding

**DDx**
1. DNET
2. Ganglioglioma

MNVT at high power showing vacuolation.
Diffuse Leptomeningeal Glioneuronal Tumor

- New in WHO 2016
- Rare glioneuronal neoplasm in children
- Cystic/nodular T2 hyperintense subpial lesions
- Formerly Disseminated Oligodendroglial-like Leptomeningeal Tumor of childhood.
Diffuse Leptomeningeal Glioneuronal Tumor

- Obstructive hydrocephalus, ataxia, CN involvement or cord compression
- Majority exhibit minimal proliferative activity, prognosis unpredictable
- Genetic profile: Distinct from oligodendroglioma & neurocytoma (KIAA1549-BRAF fusion, 1p deletion & some 1p/19q codeletion)

Cystic/nodular hyperintense subpial lesions

Diffuse, plaque-like enhancement

Mimics chronic inflammatory meningitis
Diffuse Midline Glioma, H3-K27M mutant

Former: Diffuse Intrinsic Pontine Glioma

- Large, expansile brainstem mass
- CN deficits, long tract signs, ataxia
- More likely enhancement, edema, hemorrhage or necrosis

- Infiltrative HG midline glioma
- H3-K27M ~ H3 Histone mutation
- Cannot differentiate from wildtype DIPG
- Worse prognosis
Diagnostic Pearls:

- **Location:** Pons, Thalamus, Vermis/fourth ventricle, Spinal cord.
- **Imaging:** Diverse imaging appearance without distinguishing features from histone H3 WT diffuse gliomas.
Key Update #5: Gr II/III infiltrating gliomas defined by IDH & 1p/19q status

Oligodendroglioma

IDH Mutant

YES

1p/19q Codeleted

YES

Oligodendroglioma

NO

1p/19q Codeleted

NO

Astrocytoma

Astrocytoma like expression

Note: “Oligoastrocytoma” is discouraged
Will be used when IDH & 1p/19q information is not available.

Prognostic markers of overall survival & predictive of response to chemotherapy

IDH Mutant

YES

NO

Better prognosis

Worse prognosis

1p/19q codeleted

ATRX Loss

TP53 mutation

Gr II/III infiltrating gliomas defined by IDH & 1p 19q status

Prognostic markers of overall survival & predictive of response to chemotherapy
Relevance to Radiology

1p/19q codeletion can be predicted by MRI

- Oligodendroglioma (WHO 2016)
- 1p/19q codeletion & IDH mutant
- *Poorly defined borders*
- Heterogeneous. Fontal or parietal

- Non-codeleted, morphologic oligo
- Now astrocytoma, IDH mutant
- *Well-defined borders*
- Homogenous, Insular

Classic teaching that oligodendroglioma tends to be well-defined is *no longer applicable!!*
• **Five key updates**

- Key Update # 1: Gliomatosis cerebri no longer a distinct entity
- Key Update # 2: Revised classification of Embryonal tumors
- Key Update # 3: GBM & IDH mutation
- Key Update # 4: Addition of new tumors!
- Key Update # 5: Gr II/III infiltrating gliomas defined by IDH & 1p 19q status
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Thank you for your attention!

Acknowledgements: MacLean Nasrallah MD, PhD; Aivi Nguyen MD (Neuropathology)