Gliomas in the 2016 WHO Classification of CNS Tumors

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Basic Considerations

• Why the need for a tumor classification system?
  – Classification (histogenesis vs. differentiation)
  – Prognosis (grade and stage)
  – Prediction of response to therapy

• History of CNS Tumor classification

• WHO classifications
Gliomas

• **Histopathological diagnosis is the gold standard** for classification and prognostication.
  – H&E, > 100 years: histological type and grade
  – EM: cell differentiation
  – IHC, ~30 years: cell differentiation
  – Molecular Tech., 10-20 years: diagnostic, prognostic and/or predictive

• **WHO 2016**: integration of histologic and molecular diagnoses.
WHO Classification of CNS Tumors

1st Ed. 1979
2nd Ed. 1993
3rd Ed. 2000
4th Ed. 2007

Classification solely based on morphologic features

Integration of morphologic & molecular features for Dx
Histological Dx of Glial and GN Tumors- Decision Tree WHO 2007

Perry & Wesseling. *Handbook of Clin Neurol.* 2016; 134:71-95
Histological Diagnosis of Glioms - Limitations

• Inadequate and limited tissue specimens
  – Tumor heterogeneity
• Mixed and overlapping features
• Imprecise diagnostic criteria.
• Confounding factors, e.g. necrosis in post therapy sample
• Inherent limitation of histology in representing the biology of tumor.
“WHO’s Next?:
A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading”

Brain Pathology 24 (2014) 429–435

MISCELLANEOUS

International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading

David N. Louis1; Arie Perry2; Peter Burger3; David W. Ellison4; Guido Reifenberger5,6; Andreas von Deimling6,7; Kenneth Aldape8; Daniel Brat9; V. Peter Collins10; Charles Eberhart3; Dominique Figarella-Branger11; Gregory N. Fuller12; Felice Giangaspero13,14; Caterina Giannini15; Cynthia Hawkins16; Paul Kleihues17; Andrey Korshunov18,19; Johan M. Kros16; M. Beatriz Lopes20; Ho-Keung Ng21; Hiroko Ohgaki22; Werner Paulus23; Torsten Pietsch24; Marc Rosenblum25; Elisabeth Rushing26; Figen Soylemezoglu27; Otmar Wiestler28; Pieter Wesseling29,30

Major Question:
How can non-histological criteria (eg, molecular, imaging, clinical, etc.) be used to enhance typing and grading of human brain tumors?
Adult DG Diagnosis - Paradigm Shift

*Perry & Wesseling. Handbook of Clin Neurol. 2016; 134:71-95*
WHO 2016

It is hoped that this phenotype-genotype integration will result in:

• More objectivity
• Narrowly defined entities
• More accuracy and reproducibility
• Improved patient management prognostication and prediction of response to therapy.

WHO 2016

Summary of Major Changes
WHO 2016-Diffuse Gliomas

• Restructuring of diffuse gliomas, with incorporation of genetically defined entities and the addition of newly recognized entities, variants and patterns
  – IDH-mutated and IDH-wild type DA and AA (entities)
  – IDH-mutated and 1p/19q –codeleted O and AO (entities)
  – IDH-wildtype and IDH-mutant glioblastoma (entities)
  – Epithelioid glioblastoma (variant)
  – Glioblastoma with primitive neuronal component (pattern)
WHO 2016-Diffuse Gliomas

- Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity
  - Diffuse midline glioma, H3 K27M–mutant (entity)
Diffuse Astrocytoma, IDH-mutant

• Young adults
• IDH1 codon 132 in 90% of cases (IHC)
• IDH2 codon 172 in 10% of cases
• Other alterations
  – P53: 94%
  – ATRX: 86% (IHC)
  – MGMT: 50%
  – 1p/19q co-deletion: 0% (regardless of morphology)
• Progression in 75% of cases (AA & GBM-IDH-m)
Diffuse Astrocytoma, IDH-wild type

• Rare
• Less favorable outcome
  – Especially with 7q+ and 10q-
Dx of DG - Decision Tree WHO 2016

**Histology**
- Astrocytoma
- Oligoastrocytoma
- Oligodendroglioma
- Glioblastoma

**IDH status**
- IDH mutant
- IDH wild-type

**1p/19q and other genetic parameters**
- ATRX loss
- TP53 mutation
- 1p/19q codeletion

**Diffuse astrocytoma, IDH mutant**

**Oligodendroglioma, IDH mutant and 1p/19q codeleted**

**After exclusion of other entities:**
- Diffuse astrocytoma, IDH wild-type
- Oligodendroglioma, NOS

**Glioblastoma, IDH mutant**

**Glioblastoma, IDH wild-type**

**Genetic testing not done or inconclusive**

**Diffuse astrocytoma, NOS**
**Oligodendroglioma, NOS**
**Oligoastrocytoma, NOS**
**Glioblastoma, NOS**

* = characteristic but not required for diagnosis
# WHO 2016 - Glioblastoma

<table>
<thead>
<tr>
<th></th>
<th>IDH-wildtype glioblastoma</th>
<th>IDH-mutant glioblastoma</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonym</strong></td>
<td>Primary glioblastoma, IDH-wildtype</td>
<td>Secondary glioblastoma, IDH-mutant</td>
<td>1830</td>
</tr>
<tr>
<td><strong>Precursor lesion</strong></td>
<td>Not identifiable; develops de novo</td>
<td>Diffuse astrocytoma, Anaplastic astrocytoma</td>
<td>1827</td>
</tr>
<tr>
<td><strong>Proportion of glioblastomas</strong></td>
<td>~90%</td>
<td>~10%</td>
<td>1797</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>~62 years</td>
<td>~44 years</td>
<td>214,1078,1797, 2103</td>
</tr>
<tr>
<td><strong>Male-to-female ratio</strong></td>
<td>1.42:1</td>
<td>1.05:1</td>
<td>214,1417,1797</td>
</tr>
<tr>
<td><strong>Mean length of clinical history</strong></td>
<td>4 months</td>
<td>15 months</td>
<td>1797</td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>Surgery + radiotherapy 9.9 months</td>
<td>Surgery + radiotherapy 24 months</td>
<td>1797</td>
</tr>
<tr>
<td></td>
<td>Surgery + radiotherapy + chemotherapy 15 months</td>
<td>Surgery + radiotherapy + chemotherapy 31 months</td>
<td>2810</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Supratentorial</td>
<td>Preferentially frontal</td>
<td>1417</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>Extensive</td>
<td>Limited</td>
<td>1417</td>
</tr>
<tr>
<td><strong>TERT promoter mutations</strong></td>
<td>72%</td>
<td>26%</td>
<td>1801,1830</td>
</tr>
<tr>
<td><strong>TP53 mutations</strong></td>
<td>27%</td>
<td>81%</td>
<td>1797</td>
</tr>
<tr>
<td><strong>ATRX mutations</strong></td>
<td>Exceptional</td>
<td>71%</td>
<td>1519</td>
</tr>
<tr>
<td><strong>EGFR amplification</strong></td>
<td>35%</td>
<td>Exceptional</td>
<td>1797</td>
</tr>
<tr>
<td><strong>PTEN mutations</strong></td>
<td>24%</td>
<td>Exceptional</td>
<td>1797</td>
</tr>
</tbody>
</table>
Pediatric Diffuse Gliomas

- Morphologically similar, but **genetically distinct** from adult-type counterparts
- Genetic alterations
  - MYB, BRAF V600E (IHC), FGFR1, KRAS, **H3 K27M (IHC)**
  - Lacks alterations in IDH1/2, p53 and ATRX
- Cerebral hemispheres and **thalami**
- Anaplastic transformation is rare
Pediatric High-Grade DA

• Include glioblastoma and anaplastic A in pts. <20 yrs old
• Almost all are de novo (“primary”)
• Midline: pons, thalamus – H3 K27M (IHC)
• Cerebral hemispheres (older pts.) – H3.3 G34R
• Genetic alterations:
  – p53, ATRX, SETD2, CDKN2A, PDGFRA
  – Rarely IDH1, TERT, EGFR
Diffuse midline glioma, H3 K27M-mutant

- Predominate in children
- Brain stem, thalamus and spinal cord
- WHO Grade IV: 2-yr survival <10%
  - In 10% no anaplastic features
  - In 25% mitosis only
  - Can have oligo-like morphology
Oligodendroglioma, IDH-mutated and 1p/19q codeleted

• By definition IDH1/2 mutation AND 1p/19q whole-arm codeletion
• Other genetic alterations
  – TERT promotor methylation
  – Lacks ATRX mutation
  – Other
Oligodendroglioma, NOS

- Small minority of oligodendrogliomas
- Diffusely infiltrating glioma
- Classic oligodendroglial morphology
- *Combined* IDH mutation and 1p/19q codeletion could not be completed or was inconclusive
- IDH+/ATRX retained IHC is supportive
- In adults, molecular workup to r/o GBM, IDH-wt
Pediatric-type Oligodendroglioma

- Lacks IDH mutation and 1p/19q codeletion
- Majority of oligos in children and adolescents; uncommon in adults
- Should rule out histologic mimics; unlikely with typical histology
- Overlaps genetically with other diffuse gliomas of childhood
“Oligoastrocytoma”

- Strongly discouraged in the WHO 2016
- Can be reclassified as astrocytoma or oligodendroglioma by molecular tests
- OA, NOS and AOA, NOS (provisional entities)
- True OA is rare
Diffuse Gliomas

**WHO 2007**

**Diffuse astrocytic and oligodendroglial tumors**
- Diffuse astrocytoma, *IDH* mutant
  - Gemistocytic astrocytoma, *IDH* mutant
  - Fibrillary astrocytoma
  - Protoplasmic astrocytoma
- Diffuse astrocytoma, *IDH* wild-type
- Diffuse astrocytoma, NOS

- Anaplastic astrocytoma, *IDH* mutant
- Anaplastic astrocytoma, *IDH* wild-type
- Anaplastic astrocytoma, NOS

- Glioblastoma, *IDH* wild-type
  - Giant cell glioblastoma
  - Gliosarcoma
  - Epithelioid glioblastoma
- Glioblastoma, *IDH* mutant
- Glioblastoma, NOS
- Gliomatosis cerebri

- Diffuse midline glioma, H3-K27M mutant

- Oligodendroglioma, *IDH* mutant and 1p/19q co-deleted
- Oligodendroglioma, NOS

- Anaplastic oligodendroglioma, *IDH* mutant and 1p/19q co-deleted
- Anaplastic oligodendroglioma, NOS

- Oligoastrocytoma, NOS
- Anaplastic oligoastrocytoma, NOS
WHO 2016- Other astrocytomas

• Addition of newly recognized entity
  – Anaplastic PXA (entity) replacing PXA with anaplastic features

• Pilomyxoid astrocytoma should not be graded; formerly automatically given WHO grade II
WHO 2016 - Ependymomas

• Incorporation of a genetically defined ependymoma variant
  – Ependymoma, RELA fusion–positive (entity)
    • Majority (70%) of supratentorial ependymomas in children; uncommon in adults
• Deletion of former entities, variants and terms
  – Cellular ependymoma variant
WHO 2016: Challenges

• Phenotype genotype discordance - rare
• Can we use genotype alone? – not in the near future.
  – Histology needed for diagnosing and grading DA
• Unavailability of molecular tests or their IHC surrogates in many labs around the world.
The category “Not Otherwise Specified”

A group of lesions that cannot be classified into any of the more narrowly defined groups

Insufficient information to assign a more specific code
  – Have not been fully tested for the relevant genetic parameter(s)
  – tested but do not show the diagnostic genetic alterations.

• The category “Not Otherwise Specified”
• WHO 2016: Work in progress
  5th edition coming soon
Thank You