Updates on the CNS classification of brain tumors

Eyas M Hattab, MD
Department of Pathology and Laboratory Medicine
ehattab@iupui.edu
Conflict of Interest

• Nothing to disclose
WHO classification of CNS tumors ("blue books")

- Diagnosis, classification and grading based solely on morphology
Since 2007....

- Explosion of molecular data
  - Better insight into biology of human disease (diagnostic, prognostic and/or predictive value)
  - How should clinically relevant molecular information be incorporated into nervous system tumor classification?
- Clinical applications lagging behind
  - Few translated into tangible medical advances
  - Most remain unused
- Higher healthcare costs but not better outcome!
Challenges to Future Classifications

• Focus on major conceptual issues:
  – How to incorporate molecular information optimally in tumor classification?
  – The right balance!

Latest Molecular Advances

Basic Diagnostic Needs
ISN-Haarlem (WHO’s Next?) 2014

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 Eberhart9; Dominique Figarella-Branger11; Gregory N. Fuller12; Felice Giangaspero13,14; Caterina Giannini15; Cynthia Hawkins16; Paul Kleihues17; Andrey Korshunov6,18; Johan M. Kros19; M. Beatriz Lopes20; Ho-Keung Ng21; Hiroko Ohgaki22; Werner Paulus23; Torsten Pietsch24; Marc Rosenblum25; Elisabeth Rushing26; Figen Soylemezoglu27; Otmar Wiestler28; Pieter Wesseling29,30

- 28 Neuropathologists, 10 countries
- Input from neuro-oncologists, medical oncologists, neurosurgeons, neuroradiologists, radiation-oncologists
Major Question:

“How can non-histological criteria (e.g. molecular, imaging, clinical, etc.) be used to enhance typing and grading of human brain tumors?”
1. Diagnostic entities should be defined as narrowly as possible to optimize interobserver reproducibility, clinicopathological predictions and therapeutic planning (avoid waste baskets!)

2. Diagnoses should be "layered" with histologic classification, WHO grade and molecular information as "integrated diagnosis"
3. Determinations should be made for each tumor entity as to whether molecular information is required, suggested or not needed for its definition

4. Some pediatric entities should be separated from their adult counterparts

5. Input for guiding decisions regarding tumor classification should be solicited from experts in complementary disciplines of neuro-oncology

6. Entity-specific molecular testing and reporting formats should be followed in diagnostic reports
Layer 1: Integrated diagnosis (incorporating all tissue-based information)

Layer 2: Histological classification

Layer 3: WHO grade (reflecting natural history)

Layer 4: Molecular information
The New WHO

- ISN-Haarlem set the stage for a major revision in the 2007 WHO
- WHO working group: 2016 CNS WHO Update
COMBINED MORPHOLOGY AND GENETICS
Major changes in 2016 CNS WHO

- Major restructuring and incorporation of genetically defined entities for:
  - Diffuse gliomas
  - Medulloblastomas
  - Embryonal tumors (including removal of the term “primitive neuroectodermal tumor (PNET)”)
- Incorporation of a genetically defined ependymoma variant
- Novel approach distinguishing pediatric look-alikes, including new entity of Diffuse Midline Glioma, H3 K27M
- Addition of other newly recognized entities:
  - Diffuse leptomeningeal glioneuronal tumor
  - Epithelioid glioblastoma
  - Others
- Addition of brain invasion as a criterion for atypical meningiomas
- Restructuring of solitary fibrous tumor/hemangiopericytoma, including soft tissue-type (non-CNS) grading system
Diffuse Glioma restructuring...
2007 WHO: Histogenesis

- Gliomas
  - Astrocytoma
  - Oligodendro-glioma
  - Mixed Oligoastro
  - Ependymoma
    - Diffuse
    - Localized
Gliomas

Localized

Potentially curable by complete resection

Diffuse

NOT curable by surgical resection
Diffuse Glioma (2016)

- Adult
- Pediatric
2016 WHO: Combined Morphology and Genetics

Gliomas
  - Diffuse
  - Localized
    - Oligo
    - Astro
    - ? Mixed OA
Diffuse Gliomas

IDH-mutant
- 1p/19q co-deletion
  - TERT
  - Oligo, WHO II/III
    - Good Prognosis
- 1p/19q intact
  - TP53
  - ATRX
  - D. Astro, WHO II-IV
    - Intermediate Prognosis

IDH-wild type
- EGFR
- PTEN
- CKDN2A
- D. Astro, WHO II-IV
  - Poor Prognosis
Molecular Genetics Refining Morphologic Classification

Hartmann et al, Acta Neuropathologica 2010
Gliomas

**Astrocytomas**
- Pilocytic astrocytoma
- PXA
- SEGA
- Diffuse astrocytoma
- Anaplastic astrocytoma
- GBM

**Oligodendrogliomas**
- Oligodendroglioma
- Anaplastic oligodendroglioma

**Other Astrocytomas**
- Pilocytic astrocytoma
- PXA
- SEGA

**Diffuse Gliomas**
- Diffuse astrocytoma
- Anaplastic astrocytoma
- GBM
- Oligodendrogioma
- Anaplastic oligodendrogioma
- Diffuse midline glioma, H3 K27M mutant

**Ependymomas**

NEW

OLD
Oligodendroglioma

- Diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires demonstration of an IDH mutation and 1p/19q co-deletion.

- Oligodendroglioma is now essentially defined by a particular genetic phenotype.
### Oligodendroglioma, WHO II

<table>
<thead>
<tr>
<th>Molecular Information</th>
<th>Integrative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH-mut, 1p/19q-nondel, ATRX loss</td>
<td>Diffuse astrocytoma, <em>IDH</em>-mutant, 1p/19q non-deleted, ATRX loss of expression, WHO grade II</td>
</tr>
<tr>
<td>IDH-mut, 1p/19q-codel, ATRX intact</td>
<td>Oligodendroglioma, <em>IDH</em>-mutant, 1p/19q-codeleted, WHO grade II</td>
</tr>
<tr>
<td>IDH wild type</td>
<td>Diffuse astrocytoma, <em>IDH</em> wild type, WHO grade II</td>
</tr>
<tr>
<td>Testing not performed</td>
<td>Diffuse glioma (oligodendroglioma phenotype), NOS, WHO grade II</td>
</tr>
</tbody>
</table>

Histologic classification: oligodendroglioma
WHO grade: grade II
2016: Diffuse astrocytoma, grades II and III

• 3 categories:
  – IDH-mutant
    • Majority of grade II and III diffuse astrocytomas
  – IDH-wildtype
  – NOS
    • If IDH testing is not available or cannot be fully performed

• WHO grading remains the same, even though IDH-mutant cases have a more favorable prognosis
# Diffuse Astrocytoma, WHO II

**Histologic classification:** diffuse astrocytoma  
**WHO grade:** grade II

<table>
<thead>
<tr>
<th>Molecular Information</th>
<th>Integrative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH-mut, 1p/19q-nondel, ATRX loss</td>
<td>Diffuse astrocytoma, <em>IDH</em>-mutant, ATRX loss, WHO grade II</td>
</tr>
<tr>
<td>IDH-mut, 1p/19q-codel, ATRX intact</td>
<td>Oligodendroglioma, <em>IDH</em>-mutant, 1p/19q-codeleted, WHO grade II</td>
</tr>
<tr>
<td>IDH wild type</td>
<td>Diffuse astrocytoma, <em>IDH</em> wild type, WHO grade II</td>
</tr>
<tr>
<td>Testing not performed</td>
<td>Diffuse glioma (astrocytoma phenotype), NOS, WHO grade II</td>
</tr>
</tbody>
</table>
The diagnosis of Oligoastrocytoma is strongly discouraged.

Designated as NOS categories—should only be rendered in absence of diagnostic molecular testing or in the very rare instance of a dual genotype Oligoastrocytoma.
Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma

Felix Sahm · David Reuss · Christian Koelsche · David Capper · Jens Schittenhelm · Stephanie Heim · David T. W. Jones · Stefan M. Pfister · Christel Herold-Mende · Wolfgang Wick · Wolf Mueller · Christian Hartmann · Werner Paulus · Andreas von Deimling

- 43 cases of oligoastrocytoma
- In all but one case, the combination of p53 mutation and ATRX loss was mutually exclusive with 1p/19q co-deletion
- 31/43 → oligo genotype (i.e. 1p/19q co-deletion and IDH mutation)
- 11/43 → astro genotype (i.e. p53 mutation, ATRX loss and IDH mutation)
- 1/43 → mixed genotype (p53 mutation, ATRX loss, IDH mutation and partial 1p/19q loss) [this pt had undergone radiotherapy prior to surgery]
<table>
<thead>
<tr>
<th>Molecular Information</th>
<th>Integrative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH-mut, 1p/19q-nondel, ATRX loss</td>
<td>Diffuse astrocytoma, <em>IDH</em>-mutant, ATRX loss, WHO grade II</td>
</tr>
<tr>
<td>IDH-mut, 1p/19q-codel, ATRX intact</td>
<td>Oligodendroglioma, <em>IDH</em>-mutant, 1p/19q-codeleted, WHO grade II</td>
</tr>
<tr>
<td>IDH wild type</td>
<td>Diffuse astrocytoma, <em>IDH</em> wild type, WHO grade II</td>
</tr>
<tr>
<td>Testing not performed</td>
<td>Diffuse glioma (ambiguous histology), NOS, WHO grade II</td>
</tr>
</tbody>
</table>
2016: Glioblastoma

- 3 categories:
  - Glioblastoma, IDH-wildtype
    - ~90% of cases
    - Most often corresponds to primary GBM
  - Glioblastoma, IDH-mutant
    - ~10% of cases
    - Most often corresponds to secondary GBM
  - Glioblastoma, NOS
    - Reserved for tumors for which a full IDH evaluation cannot be performed
2016: Glioblastoma

• Epithelioid GBM: new variant
  – Joins giant cell GBM and gliosarcoma
  – Large epithelioid cells with abundant eosinophilic cytoplasm, prominent nucleoli
  – ±Rhabdoid cells
  – Predilection for children and young adults
  – *BRAF V600E* mutation
  – Lacks typical IDH-wildtype GBM molecular features (EGFR and LOH 10)
  – Associated low-grade precursor (?)PXA
2016: Glioblastoma

- GBM with primitive neuronal component added as a pattern
  - Previously GBM with PNET-like component
  - Diffuse glioma (any grade) with well-demarcated nodules of primitive cells with neuronal differentiation (HW rosettes, synpa +, GFAP -)
  - MYC and MYCN amplification
  - CSF dissemination
  - ~25% origin from lower-grade glioma (IDHm)
2016: Diffuse Gliomas

• Variants deleted:
  – Protoplasmic astrocytoma
  – Fibrillary astrocytoma

• Entities deleted:
  – Gliomatosis cerebri
    • Now a *growth pattern* of any diffuse glioma
2016: Diffuse Midline Glioma, H3 K27M mutant

• Addition of this new entity
• Histology $\rightarrow$ Pediatric GBM = Adult GBM
• Molecular $\rightarrow$ Pediatric GBM $\neq$ Adult GBM
Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers

Andrey Korshunov · Marina Ryzhova · Volker Hovestadt · Sebastian Bender · Dominik Sturm · David Capper · Jochen Meyer · Daniel Schrimep · Marcel Kool · Paul A. Northcott · Olga Zheludkova · Till Milde · Olaf Witt · Andreas E. Kulozik · Guido Reifenberger · Nada Jabado · Arie Perry · Peter Lichter · Andreas von Deimling · Stefan M. Pfister · David T. W. Jones

- 202 pediatric GBMs
  - Genome-wide DNA methylation profiling
  - Known candidate genes were screened for alterations via direct sequencing or FISH
Pediatric GBM Molecular Subgroups

- PXA or pilocytic-like methylation profiles (20%)
  - Subset had BRAF V600E mutations
  - Good prognosis
- H3 K27M mutation (34%)
  - Midline location (including many diffuse intrinsic pontine gliomas)
  - Very poor prognosis
- H3 G34R mutation (12%)
- IDH mutation (5%)
  - Good prognosis
- H3/IDH wildtype (29%)
2016: Other Astrocytoma Grading Changes

- Anaplastic PXA, WHO grade III – *New entity*
  - ≥ 5 mitoses / 10hpf; ± necrosis
- Pilomyxoid astrocytoma – grading redacted
Evening view from the IU Health Pathology Laboratory
2016: Ependymoma, RELA fusion-positive

- New variant
- Accounts for the majority of supratentorial ependymomas in children
- Dismal prognosis
- Immunohistochemical expression of L1CAM – potential surrogate marker for this variant
- Cellular ependymoma variant deleted
Major changes in 2016 CNS WHO

- Major restructuring and incorporation of genetically defined entities for:
  - Diffuse gliomas
  - Medulloblastomas
  - Embryonal tumors (including removal of the term “primitive neuroectodermal tumor (PNET)”)
- Incorporation of a genetically defined ependymoma variant
- Novel approach distinguishing pediatric look-alikes, including new entity of Diffuse Midline Glioma, H3 K27M
- Additional of other newly recognized entities:
  - Diffuse leptomeningeal glioneuronal tumor
  - Epithelioid glioblastoma
  - Others
- Addition of brain invasion as a criterion for atypical meningiomas
- Restructuring of solitary fibrous tumor/hemangiopericytoma, including soft tissue-type (non-CNS) grading system

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary [not yet published, courtesy of Dr. Arie Perry]
Medulloblastoma: 4 histologic variants

- Classic
- Desmoplastic/nodular
- With extensive nodularity
- Large cell/anaplastic
## Medulloblastoma: 4 molecular subgroups

<table>
<thead>
<tr>
<th></th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at presentation</strong></td>
<td>Childhood</td>
<td>Infancy; adulthood</td>
<td>Childhood</td>
<td>Childhood</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Classic</td>
<td>Desmoplastic/nodular</td>
<td>Large cell/anaplastic; classic</td>
<td>Classic; Large cell anaplastic</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Very good &gt;90% long-term survival</td>
<td>Good to intermediate</td>
<td>Poor</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>CTNNB1 (β-catenin) mutations; monosomy 6; APC germline mutations (Turcot syndrome)</td>
<td>PTCH gene mutation (germline PTCH mutation=Gorlin syndrome); 9q deletion</td>
<td>MYC amplification</td>
<td>CDK6 amplification; isochromosome 17q; loss of X chromosome</td>
</tr>
<tr>
<td><strong>Immunos</strong></td>
<td>Nuclear β-catenin staining; DKK1 positive</td>
<td>GAB1 positive, SFRP1 positive</td>
<td></td>
<td>KCNA1</td>
</tr>
<tr>
<td><strong>% of all medullos</strong></td>
<td>7-8%</td>
<td>28-32%</td>
<td>26-27%</td>
<td>34-38%</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>? therapy de-escalation</td>
<td>Can treat with smoothened (SMO) inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medulloblastoma

- Both the histologic and molecular subgroups have prognostic and therapeutic value.

Outcome analyses among patients aged 3-16 years on the CNS9102/PNET3 trial. Progression-free survival curves.

Subgroup-Specific Prognostic Implications of TP53 Mutation in Medulloblastoma


- p53 mutations are enriched in WNT (16%) and SHH (21%) subgroups, but not in groups 3 and 4
- WNT→p53 mutation has no prognostic implication (5 yr OS 90% and 97% for p53 mutant and wild type, respectively [p=.21])
- SHH→
  - p53 mutation: older children, poor prognosis (5 yr OS 41%)
  - p53 wild type: infants & adults, better prognosis (5 yr OS 81%) [p<.001]
2016 WHO: Medulloblastoma

• Integrated diagnosis that includes both the genotype and histological phenotype

• For the SHH group, the presence or absence of a p53 mutation should be reported
# Medulloblastoma: Surrogate IHC

<table>
<thead>
<tr>
<th></th>
<th>WNT</th>
<th>SHH</th>
<th>non-WNT/non-SHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-catenin (nuclear)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GAB-1</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>YAP-1</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>p53</td>
<td></td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>INI-1</td>
<td>retained</td>
<td>retained</td>
<td>retained</td>
</tr>
</tbody>
</table>
Indianapolis Motor Speedway
Other Embryonal Tumors

• **2007 WHO**: PNET is an umbrella term, under which fall multiple histologic variants
  – Cerebral neuroblastoma/gangioneuroblastoma
  – Embryonal tumor with abundant neuropil and true rosettes (ETANTR)
  – Ependymoblastoma
  – Medulloepithelioma

• **2016 WHO**: The term “primitive neuroectodermal tumor (PNET)” has been completely removed from the diagnostic lexicon
Other Embryonal Tumors

• **2007 WHO**: PNET is an umbrella term, under which fall multiple histologic variants
  − Cerebral neuroblastoma/gangioneuroblastoma
  − Embryonal tumor with abundant neuropil and true rosettes (ETANTR)
  − Ependymoblastoma
  − Medulloepithelioma

• **2016 WHO**: The term “primitive neuroectodermal tumor (PNET)” has been completely removed from the diagnostic lexicon
Embryonal tumor with multilayered rosettes, C19MC altered

- Clinical: usually patients less than 4 years of age; highly aggressive with avg survival of 12 months
- Immunostain for LIN28A
- FISH analysis for 19q13.42 (C19MC amplification)
Ependymoblastoma

Medulloepithelioma

LIN28A
Other Embryonal Tumors: AT/RT

• 2016 WHO
  – Atypical teratoid/rhabdoid tumor (AT/RT) is defined by alterations in \textit{INI1} (i.e. \textit{SMARCB1}) or very rarely \textit{BRG1}
### AT/RT morphology and INI1 lost

<table>
<thead>
<tr>
<th>Integrated diagnosis</th>
<th>Atypical teratoid/rhabdoid tumor, WHO grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological classification</td>
<td>Embryonal tumor with rhabdoid features</td>
</tr>
<tr>
<td>WHO grade</td>
<td>IV</td>
</tr>
<tr>
<td>Molecular information</td>
<td>INI1 loss of protein expression/mutation or BRG1 loss of protein expression/mutation</td>
</tr>
<tr>
<td>Integrated diagnosis</td>
<td>Embryonal tumor with rhabdoid features, WHO grade IV</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Histological classification</td>
<td>Embryonal tumor with rhabdoid features</td>
</tr>
<tr>
<td>WHO grade</td>
<td>IV</td>
</tr>
<tr>
<td>Molecular information</td>
<td>INI1 and BRG1 expression retained/not mutated or molecular/IHC testing not performed</td>
</tr>
</tbody>
</table>
Meningiomas

• Brain invasion now a WHO grade II (atypical) criterion
  – Previously a “staging feature”
Solitary Fibrous Tumor/HPC

- Both share inversions at 12q13 (fusing NAB2 and STAT6 genes)
- STAT6 nuclear expression (IHC)
- Combined SFT/HPC:
  - WHO I: previously SFT
  - WHO II: previously HPC
  - WHO III: previously anaplastic HPC
Unresolved issues/challenges

- **WHO grading**
  - Determinations are still made on the basis of histologic criteria
  - WHO grade (natural progression) vs “therapy” grade (based on response to adjuvant therapy)
  - Should grade be altered based on molecular findings?

- **Testing:**
  - What about centers that don’t have access to molecular techniques or surrogate immunostains? (NOS)
  - How much testing?

- **Reporting:** format and timing

- **Wastebaskets** (NOS designations)—these groups of tumors should be the subject of future studies to further improve classification
Molecular Genetics Refining Morphologic Classification

(a) Overall Survival
(b) Progression-free Survival

Hartmann et al, Acta Neuropathologica 2010
IDH-Wildtype Diffuse Glioma Grading

Diffuse Glioma, IDH-w

Histologically low-grade?
- Localized glioma with a “diffuse” pattern?
  - BRAF?
- DG, IDH-w, WHO II

Histologically high-grade?
- GBM?
- DG, IDH-w, WHO III
When to do IDH1/2 sequencing?

• All R132H IDH1 IHC negative diffuse gliomas?
• Limit to “lower-grade” diffuse gliomas? (exclude GBMs)
• Stratify GBMs according to age?
  – GBM < 50 years: yes
  – GBM > 50 years: no
• Oligo, astro, both phenotypes?
Why not genotyping alone?

• Histology guides molecular testing (e.g. diffuse gliomas)
• Histology still needed for WHO grading
• Histology needed to deal with entities that are not yet narrowly defined by molecular parameters (e.g. IDH-wild type diffuse gliomas)
Take-home points

• Molecular alterations are helping to further refine the diagnosis and classification of CNS tumors

• Updated 2016 WHO will feature an integrated diagnosis concept, including histology, grade and molecular features

• Diffuse gliomas: 3 molecular groups
  – IDH mut, 1p/19 co-deleted → good prognosis
  – IDH mut, 1p/19q intact → intermediate prognosis
  – IDH wt → poor prognosis

• Medulloblastoma: combination of both molecular and histologic subgroups have prognostic and therapeutic significance
Thank you!
References


Other Questions:

- How does one formulate diagnoses if some institutions use molecular tests and others do not?
- If one uses molecular parameters to classify tumors, what does one call tumors that have the histological appearance but not the defining molecular feature?
- What does one do with a tumor that has the defining molecular features of one tumor type, but the histologic appearance of another?
- In the era of broad sequencing/profiling, how does one classify a tumor with an unexpected but diagnostic mutation/profile?
The Evolution of WHO Classification

• 1st Edition: very simple format (list of diagnostic terms, ICD-O morphology codes, short descriptions)
• 2nd Edition: histologic features + IHC markers, color images
• 3rd Edition: transformation in content and layout (richly illustrated, genetic diagnostic criteria, epidemiological and clinical data)
• 4th Edition: revision and update of 3rd, highlights the increasing importance of genetic information including tumor-defining genetic alterations (not incorporated in classification)
Pediatric GBM – overall survival based on molecular subgroup

**OS by Molecular Class**
- LGG-like
- PXA-like

**OS by GBM Subgroup**
- IDH
- G34
- WT

Statistical significance:
- $p = 3.69 \times 10^{-8}$
- $p = 5.0 \times 10^{-13}$
Major changes in 2016 CNS WHO

• Major restructuring and incorporation of genetically defined entities for:
  – Diffuse gliomas
  – Medulloblastomas
  – Embryonal tumors (including removal of the term “primitive neuroectodermal tumor (PNET)”)

• Incorporation of a genetically defined ependymoma variant

• Novel approach distinguishing pediatric look-alikes, including new entity of Diffuse Midline Glioma, H3 K27M

• Additional of other newly recognized entities:
  – Diffuse leptomeningeal glioneuronal tumor
  – Epithelioid glioblastoma
  – Others

• Addition of brain invasion as a criterion for atypical meningiomas

• Restructuring of solitary fibrous tumor/hemangiopericytoma, including soft tissue-type (non-CNS) grading system

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary [not yet published, courtesy of Dr. Arie Perry]
Ependymoma molecular subgroups

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Kristian W. Pajtler,1,2,37 Hendrik Witt,1,3,4,37 Martin Sill,5,37 David T.W. Jones,1 Volker Hovestadt,6 Fabian Kratochwil,1 Khalida Wani,7 Ruth Tatevossian,8 Chandanamali Punchihewa,8 Pascal Johann,1 Jüri Reimand,9 Hans-Jörg Wamatz,10 Marina Ryzhova,11 Steve Mack,12 Vijay Ramaswamy,12,13 David Capper,14,15 Leonille Schweizer,14,15 Laura Sieber,1 Andrea Wittmann,1 Zhiqin Huang,6 Peter van Sluis,16 Richard Volckmann,16 Jan Koster,16 Rogier Versteeg,16 Daniel Fults,17 Helen Toledano,18 Smadar Avigad,19 Lindsey M. Hoffman,20 Andrew M. Donson,20 Nicholas Foreman,20 Ekkehard Hewer,21 Karel Zitterbart,22,23 Mark Gilbert,24 Terri S. Armstrong,24,25 Nalin Gupta,26 Jeffrey C. Allen,27 Matthias A. Karajannis,28 David Zagzag,29 Martin Hasselblatt,30 Andreas E. Kulozik,3 Olaf Witt,31 V. Peter Collins,32 Katja von Hoff,33 Stefan Rutkowski,33 Torsten Pietsch,34 Gary Bader,9 Marie-Laure Yasplo,10 Andreas von Deimling,14,15 Peter Lichter,4,6 Michael D. Taylor,12 Richard Gilbertson,35 David W. Ellison,8 Kenneth Aldape,36 Andrey Korshunov,14,15,38 Marcel Kool,1,38,* and Stefan M. Pfister1,3,4,38,*

Cancer Cell 27, 728–743, May 11, 2015

• Classified 500 ependymal tumors using DNA methylation profiling into nine molecular subgroups

• This molecular classification outperforms the current histopathological grading in the risk stratification of patients
<table>
<thead>
<tr>
<th>Location</th>
<th>Tumor Type</th>
<th>WHO Grade</th>
<th>Age Group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial (ST-)</td>
<td>ST-SE Subependymoma Balanced Genome</td>
<td>I</td>
<td></td>
<td><img src="green" alt="Green" /></td>
</tr>
<tr>
<td>ST-EPN-YAP1 (Anaplastic Ependymoma YAP1-fusion)</td>
<td>II / III</td>
<td><img src="green" alt="Green" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-EPN-RELA (Anaplastic Ependymoma Chromothripsis, RELA-fusion)</td>
<td>II / III</td>
<td><img src="red" alt="Red" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Fossa (PF-)</td>
<td>PF-SE Subependymoma Balanced Genome</td>
<td>I</td>
<td></td>
<td><img src="green" alt="Green" /></td>
</tr>
<tr>
<td>PF-EPN-A (Anaplastic Ependymoma Balanced Genome)</td>
<td>II / III</td>
<td><img src="red" alt="Red" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-EPN-B (Anaplastic Ependymoma Chromosomal Instability)</td>
<td>II / III</td>
<td><img src="green" alt="Green" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine (SP-)</td>
<td>SP-SE Subependymoma 6q deletion</td>
<td>I</td>
<td></td>
<td><img src="green" alt="Green" /></td>
</tr>
<tr>
<td>SP-MPE Myxopapillary Ependymoma Chromosomal Instability</td>
<td>I</td>
<td></td>
<td><img src="green" alt="Green" /></td>
<td></td>
</tr>
<tr>
<td>SP-EPN (Anaplastic Ependymoma NF2 mutation)</td>
<td>II / III</td>
<td><img src="green" alt="Green" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Medulloblastoma: The 2016 WHO

<table>
<thead>
<tr>
<th>Molecular Group</th>
<th>Histological Group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WNT</td>
<td>Classic</td>
<td>Low-risk tumor; almost all WNT tumors have classic morphology</td>
</tr>
<tr>
<td></td>
<td>LC/A</td>
<td>Very rare tumor, uncertain clinicopathologic significance</td>
</tr>
<tr>
<td>SHH, p53 mutant</td>
<td>Classic</td>
<td>Uncommon high-risk tumor</td>
</tr>
<tr>
<td></td>
<td>LC/A</td>
<td>High-risk tumor; children aged 7-17 years</td>
</tr>
<tr>
<td></td>
<td>DN</td>
<td>Very rare tumor, uncertain clinicopathologic significance</td>
</tr>
<tr>
<td>SHH, p53 wildtype</td>
<td>Classic</td>
<td>Standard-risk tumor</td>
</tr>
<tr>
<td></td>
<td>LC/A</td>
<td>High-risk tumor; prevalent in adults</td>
</tr>
<tr>
<td></td>
<td>DN</td>
<td>Low-risk tumor in infants; prevalent in infants and adults</td>
</tr>
<tr>
<td></td>
<td>MBEN</td>
<td>Low-risk tumor of infancy</td>
</tr>
<tr>
<td>non-WNT/non-SHH (Group 3)</td>
<td>Classic</td>
<td>Standard-risk tumor</td>
</tr>
<tr>
<td></td>
<td>LC/A</td>
<td>High-risk tumor</td>
</tr>
<tr>
<td>non-WNT/non-SHH (Group 4)</td>
<td>Classic</td>
<td>Standard-risk tumor</td>
</tr>
<tr>
<td></td>
<td>LC/A</td>
<td>Very rare tumor, uncertain clinicopathologic significance</td>
</tr>
</tbody>
</table>
WHAT IS YOUR DIAGNOSIS?
Oligo morphology, IDHm, 1p/19q intact, ATRX retained

a. Oligodendroglioma, IDHm, 1p/19q intact, ATRX retained
b. Oligoastrocytoma, IDHm, 1p/19q intact, ATRX retained
c. Astrocytoma, IDHm, 1p/19q intact, ATRX retained
d. Oligodendroglioma, NOS
e. Diffuse glioma, NOS
Special thanks to Dr. Arie Perry for providing the as of yet unpublished manuscript summarizing the changes to be made in the 2016 WHO
Questions?
**Diffuse gliomas: histology, IDH status, other genetic parameters → WHO diagnosis**

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

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

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

- **Diffuse astrocytoma, IDH mutant**
- **Oligodendroglioma, IDH mutant and 1p/19q codeleted**
- **Glioblastoma, IDH mutant**
- **Glioblastoma, IDH wild-type**

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

* = characteristic but not required for diagnosis

Genetic testing not done or inconclusive

Diffuse astrocytoma, NOS
Oligodendroglioma, NOS
Oligoastrocytoma, NOS
Glioblastoma, NOS
Traditional classification and grading scheme → Morphology

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Astrocytoma</th>
<th>Oligodendrogliaoma</th>
<th>Mixed oligoastrocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Diffuse astrocytoma</td>
<td>Oligodendrogliaoma</td>
<td>Oligoastrocytoma</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>Anaplastic oligodendrogliaoma</td>
<td>Anaplastic oligoastrocytoma</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma</td>
<td>N/A</td>
<td>GBM with oligodendrogliial features</td>
</tr>
</tbody>
</table>
Major changes in the diagnosis and classification of Diffuse Gliomas

1. Overall restructuring
2. Diffuse astrocytoma, grades II and III
3. Oligodendroglioma
4. Oligoastrocytoma
5. Glioblastoma
6. Diffuse midline glioma, H3 K27M mutant
1. Overall restructuring

- In the past all astrocytic tumors had been grouped together, but now all diffuse gliomas (whether astrocytic or oligodendroglial) are grouped together.

- *Diffuse astrocytoma is more similar to oligodendroglioma than it is to pilocytic astrocytoma*
Fig. 2 Two examples of primary ETANTR (a, c) with further tumor transformation in either EBL (b) or MEPL (d) histology as it has been identified during analysis of the recurrence samples.