Integrated Morphology-Molecular Glioma Diagnoses in the 2016 WHO Classification Scheme

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Disclosures

Dr. Perry has nothing to disclose
Challenge: balancing desires and needs

- Incorporate the latest molecular signatures
- Utilize the most accurate, cutting-edge techniques
- Do not disrupt current clinical diagnosis and patient management
- Weigh the availability and cost of novel diagnostic techniques
- Preserve the ability for long-term clinical, experimental and etiological correlations

Courtesy of Dr. David Louis

“Don’t throw the baby out with the bathwater”: “Das Kind mit dem Bade ausschütten”

Baby = roughly a century of clinicopathologic experience, tight correlations with outcome, and cost efficiency of light microscopy
Bathwater = subjectivity, diagnostic pitfalls, histologic mimicry, lack of sufficient reproducibility

A fool with a (molecular) tool is still a fool …

 Courtesy of Dr. Pieter Wesseling

World map by quartiles of Human Development Index in 2013

Courtesy of Dr. Pieter Wesseling
• Disease entities should be defined as narrowly as possible in order to establish highly biologically uniform groups (i.e., as previously undertaken by the hematopathology community)
• Molecular information will be incorporated into the definitions of some diagnostic entities
• For others, histology will remain the basis for definition and diagnosis

ISN-Haarlem conclusions (2)

• Molecular testing and reporting
  – Certain molecular tests will be required, recommended or suggested
  – Decisions to incorporate testing into definitions will be based on conclusive evidence from multiple investigators.
  – In settings in which molecular testing is recommended or suggested, a report should state if it was not done or ordered, along with a reason (e.g., TIFD)
  – Test methodology should be indicated in reports
  – Molecular testing must be based on histologically representative tissue in order to avoid false negatives.

ISN-Haarlem conclusions (4)

“Integrated Diagnoses”: a layered approach

ATTENTION
PARADIGM SHIFT

ISN-Haarlem format of “layered diagnoses”

• Integrated Diagnosis (incorporating all aspects of tissue diagnosis)
• Histological Classification
• WHO Grade (natural history)
• Molecular information (see parameters from previous slide)
BIOMARKER CONCEPTS

• Types
  – Diagnostic
  – Prognostic
  – Predictive
  – (Elucidate Biology)

• Practicality and regulatory issues
  – Cost and ease of implementation
  – IHC vs. FISH vs. PCR vs. genomics
  – Reimbursement and regulatory guidelines

OLIGODENDROGLIOMA 1p19q FISH

OLIGODENDROGLIOMA NGS SCATTER PLOT

GBM BIOMARKERS: EGFR/PTEN

Courtesy of Dr. Nancy Joseph, UCSF Molecular Pathology
GBM BIOMARKER: MGMT METHYLATION

Hegi ME et al., NEJM 352;10:997, 2005

Not Methylated

Methylated

Methylated

Sanger DNA Sequencing of Normal and Methylated MGMT Promoter from GBM Tumor Sections

Courtesy of Dr. Farid Chehab, UCSF Molecular Pathology

An Integrated Genomic Analysis of Human Glioblastoma Multiforme


321(5897):1807-12, 2008
**Example**

Should a histological glioblastoma with an IDH mutation be termed:

- Glioblastoma, grade IV, IDH mutant?
- Anaplastic astrocytoma?
- Glioblastoma, grade III?

_Hartmann et al., Acta Neuropathologica 2010_

_Courtesy of Dr. David Louis_
ATRX/H3.3 alteration $\rightarrow$ ALT


Killela et al. PNAS 2013; 110: 6021–6026
EXAMPLE CASE

- 46 yo man
- New onset seizures
- MRI: non-enhancing L fronto-temporal mass
- Resection performed

Modified from Dr. Dan Brat
POSSIBLE INITIAL REPORT

1. Integrated Diagnosis: pending
2. Histologic diagnosis: oligoastrocytoma (or ambiguous diffuse glioma) with scattered mitoses, but no MVP or necrosis
3. WHO grade: II
4. Molecular studies: pending

POSSIBLE FINAL REPORT

1. Integrated Diagnosis: Oligodendroglioma, WHO grade II, IDH1m, 1p19q codeleted
2. Histologic diagnosis: oligoastrocytoma (or ambiguous diffuse glioma) with scattered mitoses, but no MVP or necrosis
3. WHO grade: II
4. Molecular studies: IDH1 R132H mutant protein positive by IHC, 1p19q codeletion by FISH

FINAL REPORT

1. Integrated Diagnosis: Diffuse astrocytoma, IDH-mutant, WHO grade II
2. Histologic diagnosis: oligoastrocytoma (or ambiguous diffuse glioma) with scattered mitoses, but no MVP or necrosis
3. WHO grade: II
4. Molecular studies: 1p19q intact and EGFR non-amplified by FISH, MGMT methylated by ms-PCR, IDH1 R132H mutant on sequencing and IHC, ATRX loss of expression by IHC, p53 overexpression by IHC
EXAMPLE 2: POSSIBLE INITIAL REPORT

1. Integrated Diagnosis: pending
2. Histologic diagnosis: oligoastrocytoma (or ambiguous diffuse glioma) with atypia, mitoses, MVP, and necrosis
3. WHO grade: at least III
4. Molecular studies: pending

POSSIBLE FINAL REPORT

1. Integrated Diagnosis: AO, WHO III, IDHm, 1p19q codeleted, ATRX intact
2. Integrated Diagnosis: GBM (secondary type), WHO IV, IDHm, 1p19q intact, ATRX loss
3. Integrated Diagnosis: GBM (primary type), WHO IV, IDH intact, 1p19q intact, ATRX intact, +/- EGFR-AMP
4. Diagnosis: Diffuse glioma, NOS, at least WHO grade III (molecular studies not performed)
Performance of ‘Brain Tumor Rhapsody’ by Musaic (https://www.youtube.com/watch?v=FfP4HTuu6V)