WHO 2016 UPDATE OF CNS TUMORS

Arie Perry, M.D.
Director, Neuropathology

Sturm et al.,
Cancer Cell
2012;22:425-437

“WHO’s Next?”
A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading

Sponsored by the International Society of Neuropathology
Made possible through generous support from the STOPbraintumors Foundation

Organizers:
David Louis
Pieter Wesseling
Arie Perry

Program Committee:
Peter Burger
David Ellison
Guido Reifenberger
Andreas von Deimling
Challenge: balancing desires and needs

- 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

Incorporate the latest molecular signatures
Utilize the most accurate, cutting-edge techniques

**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

"Don’t throw the baby out with the bathwater": “Das Kind mit dem Bade ausschütten”
World map by quartiles of Human Development Index in 2013

ISN-Haarlem conclusions (1)

- 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)

“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

- **Practicality issues**
  - Cost and ease of implementation
  - IHC vs. FISH vs. PCR vs. genomics
  - Reimbursement
OLIGODENDROGLIOMA 1p19q FISH

School of Medicine

OLIGODENDROGLIOMA NGS SCATTER PLOT

UCSF 500 Gene Panel

OLIGODENDROGLIOMA 1p19q FISH

1p32
1q42
19p13
19q13

School of Medicine

Figure 2. Kaplan-Meier estimates of overall survival, according to MGMT Promoter Methylation Status.

The difference in survival between patients with a methylated MGMT promoter (52 patients, 36 of whom died) and those with an unmethylated MGMT promoter (62 patients, 26 of whom died) was highly significant (P < 0.001 by the log rank test), indicating that the MGMT methylation status has prognostic value. In the group of patients with a methylated MGMT promoter, there was a risk reduction of 53 percent (hazard ratio for death, 0.45; 95 percent confidence interval, 0.22 to 0.94), as compared with the group with an unmethylated MGMT promoter.

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

School of Medicine

GBM BIOMARKER: MGMT METHYLATION

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

School of Medicine

Courtesy of Dr. Nancy Joseph, UCSF Molecular Pathology

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

Not Methylated

Methylated

Methylated

Courtesy of Dr. Farid Chehab, UCSF Molecular Pathology

---

**An Integrated Genomic Analysis of Human Glioblastoma Multiforme**


321(5897):1807-12, 2008

---

**DIAGNOSTIC EXAMPLE OF HISTOLOGIC MIMICRY: “ELVIS IMPERSONATOR”**

- **AO (IDHm and 1p/19q codeletion)**
  - Average survival 15 years with 1p/19q loss if treated with combined PCV chemo and radiation
  - What about chemo alone up front?
- **SC-GBM (IDHwt, EGFR-AMP 70%, -10q 95%)**
  - Average survival 1 year
  - Typically treated with combined radiochemotherapy
  - Different set of clinical trials than the high-grade oligodendrogliomas
**CANCER CELLS ESCAPING SENESCENCE**

- Telomerase
- ATRX/H3.3 alterations
- Telomerase inhibitors
- Telomerase and ALT inhibitors
- ALT inhibitors
- ALT revertants
- Durable response
- Telomerase revertants


---

**ATRX/H3.3 alterations → ALT**

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

---


- TERT core promoter
- Transcription start site
- ATG coding region
- chromosome 5, minus strand
- 1,295,400 - 1,295,000 (hg19)

---

**Upstream signaling pathways (MAP kinase pathway?)**

---

**UCSF**
ALT FISH

ATRX IHC

ADULT GLIOMAS

ADULT TYPE ASTROCYTOMA

Killela et al. PNAS 2013; 110: 6021–6026
DIFFUSE MIDLINE GLIOMA (DIPG, THAL, SC)

- H3 K27M
- p53
- ATRX

DIFFUSE ASTROCYTOMA GRADING

- Atypia
- Mitoses
- Endothelial Proliferation (MVP, EH)
- Necrosis

WHO II=A; III=A+M; IV=A+M+(E or N)

IS IT VALID TO COMBINE TRADITIONAL GLIOMA GRADING CRITERIA WITH NEW MOLECULAR DEFINITIONS FOR CELL TYPE (e.g. IDHm)?

Note: no oligoastro!
NEW WHO Glioma Entities, Variants, and Patterns

- Diffuse midline glioma, H3 K27M mutant (entity)
- Diffuse leptomeningeal glioneuronal tumor (entity)
- Epithelioid glioblastoma (provisional variant)
- Glioblastoma with primitive neuronal component (pattern)
- Anaplastic PXA (entity)
Epithelioid Versus Rhabdoid Glioblastomas Are Distinguished by Monosomy 22 and Immunohistochemical Expression of INI-1 but not Claudin 6

Bette Kay Kleinschmidt-DeMasters, MD,⁎ † Ali H. Al-Assiri, MD,§ Diane K. Birks, MS,¶ Kathy L. Newell, MD, GR,§ Wayne Moore, MD,§ and Kevin O. Lillicrap, MD,§

Epithelioid GBMs Show a High Percentage of BRAF V600E Mutation

Bette Kay Kleinschmidt-DeMasters, MD,⁎ † Dana L. Aisor, MD, PhD,⁎ Diane K. Birks, MS,§ and Nicholas K. Foreman, MD,§

Clinical, radiological, histological and molecular characteristics of paediatric epithelioid glioblastoma

A. Brunner⁎, R. G. Tateson-Cranton, N. D. Sabir, P. Kilmo Jr⁎⁎, J. Dautort, R. Leel, A. Gajjar⁎ and D. W. Elston

Departments of *Neurology, †Pathology and ‡Radiological Sciences, St. Jude Children's Research Hospital, Department of †Pediatrics and ‡Neurosurgery, University of Tennessee Health Science Center, and **Stamford-Myerburg Neurologic and Spine Institute, Memphis, TN, USA.
EMBRYONAL CNS TUMORS

WHO 2016 SCHEME

- Medulloblastomas
  - WNT-activated
  - SHH-activated and TP53-mutant
  - SHH-activated and TP53-wildtype
  - Non-WNT/non-SHH
  - Classic
  - Desmoplastic/nodular
  - MB c extensive nodularity
- Large cell / anaplastic
- ET c multilayered rosettes, C19MC-altered
- Medulloepithelioma
- CNS Neuroblastoma / Ganglieneuroblastoma
- CNS ET, NOS
- Atypical teratoid / rhabdoid tumor (no ‘PNET’s')

---

Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups


Received: 13 December 2010 / Revised: 12 January 2011 / Accepted: 13 January 2011 / Published online: 26 January 2011

Abstract: Medulloblastoma is heterogeneous, being characterized by molecular subgroups that demonstrate distinct gene expression profiles. Activation of the WNT or SHH signaling pathway characterizes two of these molecular subgroups, the former associated with low-risk disease and the latter potentially targeted by novel SHH pathway inhibitors. This manuscript reports the validation of a novel diagnostic immunohistochemical method to distinguish SHH, WNT, and non-SHH/WNT tumors and details their associations with clinical, pathological and cytogenetic variables. A cohort (n = 235) of medulloblastomas from patients aged 0.4–52 years was studied for expression of four immunohistochemical markers (GABA, β-catenin, filamin A, and YAP1). Immunoreactivity (IR) for GABA characterizes only SHH tumors and nuclear IR for β-catenin only WNT tumors. IRs for filamin A and YAP1 identify SHH and WNT tumors. SHH, WNT, and non-SHH/WNT tumors comprised 31, 14, and 55% of the series. All desmoplastic/nodular (DN) medulloblastomas were SHH tumors, while most WNT tumors (94%) had a classic phenotype. Monosomy 6 was strongly associated with WNT tumors, while PTPNB loss occurred almost exclusively among SHH tumors. ACG and MLLA rearrangements and...
p53 expression predicts dismal outcome for medulloblastoma patients with metastatic disease

Mario Grad - Audel B. van Rooij - Irina V. Kulikarskaja - Vincenzo Peralesi

Abstract. Medulloblastomas (MBs) is the most common malignant primary brain tumor in childhood. Molecular features of MB (MBF) is diagnostic of the most significant subtype, immunohistochemistry and molecular techniques may be used to confirm the diagnosis.

Keywords: p53; Medulloblastoma; Molecular characterization; Prognostic; Immunohistochemistry; Outcome.

Introduction. Medulloblastomas (MBs) is the most common malignant primary brain tumor in childhood. Recent progress in understanding MB biology has indicated that the tumor is a heterogeneous disease characterized by well-defined molecular subsets with distinct histological and molecular features.[1]. A combination of clinical, pathologic, and molecular data can assist in the characterization of patients into risk groups. The current tumor classification includes four distinct subtypes: WNT, SHH, Group 3, and Group 4.[1] Prognostic biomarkers are important to patient risk assessment in clinical practice. This study further explored the role of p53 expression in the clinical outcome of MB patients with metastatic disease.

Methods. The study included 100 patients with metastatic MB from a single institution. Tumor specimens were analyzed using immunohistochemistry for p53 expression. The association of p53 expression with clinicopathological features was assessed using Fisher's exact test.

Results. In univariate analysis, p53 expression was significantly associated with shorter overall survival (OS) (p = 0.03) and shorter event-free survival (EFS) (p = 0.008) in patients with metastatic MB. No other clinicopathological variable was significantly associated with OS or EFS.

Conclusions. Our results suggest that p53 expression may be a useful predictor of outcome in patients with metastatic MB.

AT/RT

Examples

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

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)