WHO CLASSIFICATION OF BRAIN TUMORS AND APPROACH TO LOWER GRADE GLIOMAS

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Disclosures

- Honoraria from Celgene, Bayer, Boehringer, Agios, BMS, Carthera

Learning objectives:

- Understand the molecular basis of the 2016 WHO glioma classification
- Understand prognostic factors in IDH mutated glioma
- Understanding of the role of adjuvant chemotherapy in glioma
A 40 year old male with headache and difficulty walking

• 40 year old male with a short history headache and difficulty walking
• MRI: left frontal enhancing tumor; June 2016: partial resection
• Histopathology: glioblastoma
• Sequencing: IDH2 mutation, combined 1p/19q loss and deletion of chromosome 9
• Molecular diagnosis: anaplastic oligodendroglioma?
• Treated with RT/TMZ, 2 years later still doing well
• Diagnosis?
WHO 2007 – diffuse glioma (histology based)

Glial progenitor cells

- IDH mutation (>85%)
- CIMP (>85%)

Common precursor cells

- TP53 mutations (>65%)
- ATRX mutations (70%)

Diffuse astrocytoma

- Loss 1p/19q (>70%)
- TERT mutations (80%)

Oligodendroglioma

Anaplastic astrocytoma

- Loss 9p/CDKN2A
- Loss 10q (>60%)

(anaplastic) oligoastrocytoma

Anaplastic oligodendroglioma

Primary glioblastoma

Secondary glioblastoma

EGFR amplification (40-45%)
- TP53 mutations (30%)
- PTEN mutations (35%)
- NF1 alterations 20%
- LOH 10 (70%)
- trisomy 7 (75%)
- TERT mutations (80%)
- CDKN2A deletions 45%
- CDKN2B deletions (45%)
Shortcomings of the classical histopathological classification of gliomas

- Poor reproducibility of diagnosis in grade II and grade III tumors\(^1\)
  - Both with respect to lineage and grade
  - 25-33% of cases
- Based on morphological resemblance and clinical outcome (prognosis)
  - Not a functional approach
  - Not correlated to outcome to specific treatments
- Data from studies conducted in 2013-2016 showed improved classification of diffuse glioma and demonstrated improved prognostication using few molecular markers:
  - IDH 1,2 mutations, codeletion 1p/19, TERT promoter mutations, combined trisomy 7/LOH10q

\(^1\)van den Bent Acta Neuropathol (2010) 120:297–304
WHO 2016: Molecular diagnostics with NGS improves the classification of brain tumors

**Overall Survival**

**Classical histopathology**

- Probability of survival (%)
- *p*<0.001 (df=2)

**NGS Molecular diagnostics**

- Probability of survival (%)
- *p*<0.0001 (df=2)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Molecular characteristics</th>
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</thead>
<tbody>
<tr>
<td>Oligodendroglioma</td>
<td>IDH mutated, 1p/19q loss</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>IDH mutated</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>LOH10q &amp; trisomy 7, or TERT mutated but no 1p/19q loss</td>
</tr>
</tbody>
</table>

A modified WHO 2016 for diffuse glioma

IDH mutated glial precursor

- IDH mutated 1p/19q intact
  - low grade astrocytoma
  - anaplastic astrocytoma
  - grade IV astrocytoma?

- IDH mutated 1p/19q codeleted
  - low grade oligodendroglioma
  - anaplastic oligodendroglioma

1p/19q codel

TP53 mut
ATRX loss

IDH wt glioblastoma

grading

- grade 2
- grade 3
- grade 4

IDH wt glioblastoma

7+/10q- glial precursor

- TERT prom mt

IDH wt glioblastoma

diffuse astrocytic glioma, with molecular features of glioblastoma
Key Points from the 2016 WHO Glioma Classifications and cIMPACT-NOW revisions

- Key role in the classification for IDH and 1p/19q
- Not Otherwise Specified (NOS): intended for use for cases that could not be tested or in which testing was not successful
- Oligoastrocytoma is only classified if NOS
  - No clear molecular correlate: either 1p/19q co-deleted, IDH mt or only IDH mt
- Gliomatosis cerebri has disappeared as an entity
- IDHwt low grade astrocytoma with molecular features of glioblastoma: perception of grade IV
- Changing name for glioblastoma, IDHmt?

IDH mutation: a tumor driving mutation through altered enzym substrate affinity?

IDHmt onco-protein: decreased levels of $\alpha$-ketoglutarate, accumulation of 2-HG

- 2HG inhibits a wide range of $\alpha$-KG dependent dioxygenases
- Epigenetic dysregulation via inhibition of $\alpha$KG-dependent histone and DNA demethylases, resulting in CIMP, MGMT methylation
- Block of cellular differentiation
- Pathological self renewal of stem like progenitor cells?
- Upregulation of PI3K/mTOR signaling
- Contributes to the immosuppressive landscape of gliomas

Other molecular entities in the WHO classification

- Partial introduction of histone 3 mutations as a separate entity\(^1\)
  - Limited to H3F3A-mutated only\(^1\)
  - Diffuse midline glioma with K27M mutation: very poor prognosis, MGMT not methylated (diffuse pontine glioma, thalamus glioma)
- Molecular subgroups of medulloblastoma with different outcome
- Ependymoma subclassification: RELA fusion hemispheric ependymoma
cIMPACT-NOW update 3

- Criteria for diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma:
  - Histologically grade II, III astrocytoma, IDHwt, with
    - EGFR amplification (high level)
    - or
    - Combined whole chr 7 gain and whole chr 10 loss (+7/-10)
    - or
    - TERT promoter mutation

- Erasmus MC series:
  - 74 IDHwt: 39 7+/10q- (38 TERTp mt), 14 only
  - Prognosis even worse in TERTp mt only

### OS in molecularly defined anaplastic glioma as reported in large phase III trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>Molecular Subtype</th>
<th>Treatment</th>
<th>N</th>
<th>Median OS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9802</td>
<td>Low grade glioma</td>
<td>IDH mutated (all) IDHwt</td>
<td>RT/PCV or RT RT/PCV or RT</td>
<td>71</td>
<td>13.1 yrs</td>
<td>5.1 years</td>
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<tr>
<td>EORTC 26951</td>
<td>Anaplastic oligodendroglioma</td>
<td>1p/19q codeleted IDHmt 1p/19q intact 7+/10q-/TERTpmt</td>
<td>RT/PCV RT/PCV RT or RT/PCV</td>
<td>43</td>
<td>NR (&gt;14 yrs)</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.3 yrs</td>
<td>4.2 yrs NS</td>
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<td></td>
<td></td>
<td>23</td>
<td>1.13 yrs</td>
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<td></td>
<td>55</td>
<td></td>
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<tr>
<td>RTOG 9402</td>
<td>Anaplastic oligodendroglioma</td>
<td>1p/19q IDHmt (all)</td>
<td>RT/PCV</td>
<td>59</td>
<td>14.7 yrs</td>
<td>8.4 yrs</td>
</tr>
<tr>
<td>RTOG 9804</td>
<td>Anaplastic astrocytoma</td>
<td>IDH mt (IHC) IDHwt</td>
<td>RT/chemo</td>
<td>49</td>
<td>7.9 yrs</td>
<td>83</td>
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<td>2.8 yrs</td>
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<td></td>
<td></td>
<td>54</td>
<td></td>
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<tr>
<td>NOA4</td>
<td>Grade III</td>
<td>1p/19q codeleted IDHmt 1p/19q intact IDHwt</td>
<td>RT or chemo</td>
<td>66</td>
<td>NR</td>
<td>7.0-7.3 yrs</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>83</td>
<td>3.1 – 4.7 yrs</td>
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<td></td>
<td>58</td>
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### Anaplastic glioma

<table>
<thead>
<tr>
<th></th>
<th>Reported survival after RT/chemo</th>
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<tbody>
<tr>
<td>Oligodendroglioma, IDHmut &amp; 1p/19q codeleted</td>
<td>&gt; 14 years</td>
</tr>
<tr>
<td>Astrocytoma, IDH mutated</td>
<td>7 - 8 years</td>
</tr>
<tr>
<td>Astrocytoma IDH wt</td>
<td>1 – 4.7 yrs</td>
</tr>
</tbody>
</table>
Extent of resection in IDHmt Astrocytoma

- Series on low grades, anaplastic IDHmt astrocytoma\(^1,\)\(^2\)
- Both show early and significant effect from less than total resection on OS
- 2nd look surgery in case of less than complete resection?

- Bias remains: smaller tumors more likely to get extensively resected

- Less impact tumor residu in oligodendroglioma

\(^1\)Wijnenga et al Neurooncol 2017  doi:10.1093/neuonc/nox176
\(^2\)Kawaguchi et al, J Neurooncol 2016;129:505-14
Prognosis in grade II, III glioma

- Depends on a combination of clinical and molecular factors
- Some clinical factors known
- Molecular factors within the WHO 2016 classification still to be unravelled
Contrast enhancement and outcome in IDHmt grade II and III tumors

- Series on 301 grade II and III glioma
  - 208 IDHmt

- Grade III tumors more likely to present with CE (60.8%) than WHO II tumors (26.5%, p<0.001).

- CE on initial MR imaging prognostic for survival in IDH mt tumors
  - No impact in IDHwt tumors

- With dependence on volume (p<0.05)
  - IDHmt: HR 0.31 (0.14 -0.69)
  - IDHmt 1p/19q codel: HR 0.08 (0.01 – 0.69)

Methylation, CIMP, IDH

- Most IDHmt tumors show CpG Island Methylated Phenotype (CIMP)
- In 95% includes MGMT promoter
- In astrocytoma, IDHmt reported worse outcome in
  - G-CIMP low
  - Necrosis and homozygous deletion CDKN2A/B
  - 7 hypomethylated CpG sites
  - Total CNA

Multi-faceted computational assessment of risk and progression in oligodendroglialoma implicates NOTCH and PI3K pathways

- CE+ tumors, high proliferation markers worse outcome
- Notch pathway inactivation and PI3K pathway activation associated with MRI and pathology findings of advanced disease and poor clinical outcome.
- However: NOTCH, PI3KC mutations in univariate analysis not informative

Halani et al, NPJ Precis Oncol 2018;2:24
And chemo for all grade II and III glioma!
Four trials that changed the standard of care

Low grade glioma: RTOG 9802

- 10 year survival
  - PCV+RT: 60%
  - RT alone: 40%

Anaplastic oligodendroglioma
RTOG 9402

- Median Survival
  - PCV+RT: 4.6 years
  - RT alone: 4.7 years

1p/19q codeleted anaplastic oligodendroglioma: EORTC 26951

- Median Survival
  - PCV+RT: >14 yrs
  - RT alone: 11 years

1p/19q intact anaplastic astrocytoma: the EORTC CATNON trial

- 5 year survival
  - RT / adj TMZ: 56%
  - RT no adj TMZ: 44%
The CATNON trial: Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

- IDH wild type
  - Overall Survival
  - IDH 1/2 wt
  - Adjuvant TMZ
  - Median OS 19.4 mo
  - No adjuvant TMZ
  - Median OS 17.5 mo
  - HR: 1.03 (0.73, 1.44)

- IDH mutant
  - Overall Survival
  - IDH 1
  - Adjuvant TMZ
  - 5 yr OS 83%
  - Median OS 19.4 mo
  - No adjuvant TMZ
  - 5 yr OS 60%
  - Median OS 17.5 mo
  - HR: 0.46, 95% CI: 0.32, 0.67

- Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma
EORTC 26951: Quality of Survival in a cohort with long term follow-up

Evaluation of cognitive functioning:
- Progression-free patients (n=27): highly variable
  - 44% no cognitive impairments
  - 30% severe cognitive impairments
- Treatment (small subgroups): additional PCV not associated with worse cognition
- 41% were employed and 81% could live independently
- Progressive disease (n=5): more cognitive impairments

Does this warrant postponement of RT?

Habets et al, J Neurooncol 2014;116:161-8
EORTC IDHmut grade II/III Study:  
**Wait Or Treat?**

Primary endpoint: Next Intervention Free Survival  
Secondary endpoints:  
- OS, QoL, Neurocognitive function  
- Radiogenomics, 2nd surgery question  
- Tissue collection  

**Stratification:** *center, age*

- IDH mutated  
- Absence of 1p/19q co-deletion  
- No indication for immediate RT/CTX  

**Random**

- **Radiotherapy**  
  50.4 Gy (28 x 1.8 Gy)  
  Then: 12 cycles Temozolomide  
  200 mg/m² day 1-5/28 days

- **Wait and See**  
  Further treatment at PD  
  (2nd Surgery, RT/TMZ)

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**EORTC**  
*The future of cancer therapy*
Some conclusions

- The WHO 2016 molecular based classification is more robust in terms of specificity and sensitivity, with improved prognostication
  - Histology deceives…
- Currently based on mutational analysis and copy number alterations
- For all diffuse grade II, III astrocytoma, oligodendroglioma: standard of care radiotherapy with chemotherapy
  - Benefit in particular in IDHmt tumors
- Low grade tumors with molecular features of glioblastoma: to be considered as glioblastoma