ICRO Lecture 09 July 2021:
LOW GRADE GLIOMAS- A COMPLETE GUIDE

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Outline

- Clinical presentation
- Classification
- Radiology
- Surgery
- Prognostic factors
- Radiotherapy
- Chemotherapy
- Future research
Introduction

- Annual incidence of gliomas: six cases per 100,000 individuals worldwide
- Men 1.6-fold more likely to be diagnosed with gliomas than women
- Majority sporadic
- Familial tumour syndromes associated with gliomagenesis: Neurofibromatosis type I, Tuberous sclerosis, Turcot syndrome, Li–Fraumeni syndrome and
Clinical Presentation

- New-onset epilepsy
- Focal deficits (such as pareses or sensory disturbances)
- Neurocognitive impairment
- Symptoms and signs of increased intracranial pressure
The Neurological Assessment in Neuro-Oncology (NANO) scale can be used to document some of the results of the neurological examination.

Neurocognitive assessment using a standardized test battery, beyond documenting performance status and performing a Mini Mental State Examination (MMSE).
WHO Grading of Brain Tumors

Based on four morphologic criteria: cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation), and necrosis

- **Grade I**: Do not meet any of the criteria. Slow growing, nonmalignant, long-term survival
- **Grade II**: Meet only one criterion, i.e., only cytological atypia. Slow growing but recur as higher-grade tumors. They can be malignant or nonmalignant
- **Grade III**: Meet two criteria, i.e., anaplasia and mitotic activity. Malignant and often recur as higher-grade tumors
- **Grade IV**: Meet three or four of the criteria, i.e., anaplasia, mitotic activity with microvascular proliferation, and/or necrosis. These tumors reproduce rapidly and are very aggressive malignant tumors
Histological Diagnosis

● LGG are separated into astrocytomas (those with nuclear irregularities with fibrillary processes) and oligodendrogliomas (Those with uniformly rounded nuclei and perinuclear halo (“fried egg”))

● A variant of diffuse astrocytic tumor is gemistocytic astrocytoma, characterized by abundant eccentrically placed cytoplasm. —rapid malignant progression
Incorporation of Molecular Markers

- The 2016 World Health Organization (WHO) classification integrates molecular markers in the routine histological diagnosis of CNS tumors. If molecular testing cannot be performed, the term “not otherwise specified (NOS)” is added.
- Treatment strategies changed drastically.
- Recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumour Taxonomy — Not Officially WHO (cIMPACT-NOW)
- Various practice-changing clinical trials
- Different Guidelines including the latest EANO 2020
# Molecular markers-Gliomas

<table>
<thead>
<tr>
<th>Molecular marker</th>
<th>Biological function of affected genes</th>
<th>Diagnostic roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1 R132 or IDH2 R172 mutation</td>
<td>Gain-of-function mutation</td>
<td>Distinguishes diffuse gliomas with IDH mutation from IDH-wild-type glioblastomas and other IDH-wild-type gliomas</td>
</tr>
<tr>
<td>1p/19q codeletion</td>
<td>Inactivation of putative tumour suppressor genes on 1p (such as \textit{FUBP1}) and 19q (such as \textit{CIC})</td>
<td>Distinguishes oligodendroglioma, IDH-mutant and 1p/19q-codeleted from astrocytoma, IDH-mutant</td>
</tr>
<tr>
<td>Loss of nuclear ATRX</td>
<td>Cell proliferation and promotion of cellular longevity by alternative lengthening of telomeres</td>
<td>Loss of nuclear ATRX in an IDH-mutant glioma is diagnostic for astrocytic lineage tumours</td>
</tr>
<tr>
<td>Histone H3 K27M mutation</td>
<td>Histone H3.3 (H3F3A) or histone H3.1 (\textit{HIST1H3B/C}) missense mutation affecting epigenetic regulation of gene expression</td>
<td>Defining molecular feature of diffuse midline glioma, H3 K27M-mutant</td>
</tr>
<tr>
<td>Histone H3.3 G34R/V mutation</td>
<td>Histone mutation affecting epigenetic regulation of gene expression</td>
<td>Defining molecular feature of diffuse hemispheric glioma, H3.3 G34-mutant</td>
</tr>
<tr>
<td>MGMT promoter methylation</td>
<td>DNA repair</td>
<td>None, but is a predictive biomarker of benefit from alkylating chemotherapy in patients with IDH-wild-type glioblastoma</td>
</tr>
<tr>
<td>Homozygous deletion of CDKN2A/CDKN2B</td>
<td>Encode cyclin-dependent kinase inhibitors 2A and 2B and tumour suppressor ARF, which function as regulators of Rb1 and p53-dependent signalling</td>
<td>A marker of poor outcome and WHO grade 4 disease in IDH-mutant astrocytomases</td>
</tr>
</tbody>
</table>
## Molecular markers-Gliomas

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<tr>
<th>Molecular marker</th>
<th>Biological function of affected genes</th>
<th>Diagnostic roles</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>EGFR</em> amplification</td>
<td>Cell proliferation, invasion and resistance to induction of apoptosis</td>
<td><em>EGFR</em> amplification occurs in ~40–50% of glioblastoma, IDH wild type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Molecular marker of glioblastoma, IDH wild type, WHO grade 4 [REF.3]</td>
</tr>
<tr>
<td><em>TERT</em> promoter mutation</td>
<td>Cell proliferation; promotes cellular longevity by increasing <em>TERT</em> expression</td>
<td><em>TERT</em> promoter mutation occurs in ~70% of glioblastoma, IDH wild type and &gt;95% of oligodendrogloma, IDH-mutant and 1p/19q-codeleted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Molecular marker of glioblastoma, IDH wild type, WHO grade 4 [REF.3]</td>
</tr>
<tr>
<td>+7/−10 cytogenetic signature</td>
<td>Gain of chromosome 7 (harbouring genes encoding, among others, PDGFA and <em>EGFR</em>) combined with loss of chromosome 10 (harbouring genes including <em>PTEN</em> and <em>MGMT</em>)</td>
<td>Molecular marker of glioblastoma, IDH wild type, WHO grade 4 [REF.3]</td>
</tr>
<tr>
<td><em>BRAF</em>V600E mutation</td>
<td>Oncogenic driver mutation leading to MAPK pathway activation</td>
<td>Rare in adult diffuse gliomas but amenable to pharmacological intervention</td>
</tr>
</tbody>
</table>

Role of Molecular markers

- Diagnostic - for proper classification
- Prognostic Marker - Predicting biological behaviour
- Predictive marker - Predicting response to a particular therapy
- Therapeutic target - for treatment
Typical Genetic Signature in Gliomas

• **ODG**: 1p/19q codeletion, *IDH Mutation*, and mutation in *TERTp*

• **Grade 2 & 3 Astrocytic tumors**: *ATRX mutations*(loss) and *TP53* mutations

• **IDH-wildtype GBMs**: are characterized by the CNV of *EGFR*, *PTEN*, *CDKN2A/B*, *PDGFRA*, and *MET* genes, in addition to a lack of mutations in *IDH* and a codeletion in...
Radiology

- **CT**: LGG appear as iso or low attenuation, poorly delineated, often without contrast enhancement or perilesional edema.
- Calcifications (10–20% of cases) and may be related to oligodendroglial components.
- **Conventional MRI (cMRI)**
  - LGG are often homogeneous with low signal intensity on T1-weighted images and have high signal intensity on T2-weighted sequences. The high T2 signal is not related to cellularity or cellular atypia, but rather oedema, demyelination and other degenerative changes.
  - Cystic components are also encountered.
  - FluidAttenuated Inversion Recovery (FLAIR) sequence shows the best contrast between presumed infiltrating tumor margins and normal brain.
Advanced MRI (aMRI): Diffusion weighted imaging (DWI), MR Spectroscopy and Perfusion MRI:- complements, the anatomic information obtained from cMRI

- DWI quantifies tumor cellularity (Water diffusivity within the extracellular compartment is inversely related to the content of the intracellular space). LGGs present low cellularity and non-restricted diffusion.

- DTI and further application using fiber-tracking techniques (tractography) can reveal relationship between the tumor and adjacent white matter tracts: LGG tend to deviate, rather than destruct or infiltrate the adjacent white matter

- MRS noninvasively measure the brain metabolites in vivo. LGG present decreased N-Acetyl-Aspartate (NAA) peak, medium choline peaks, absence of lactate peak and increased myo-inositol.

- Perfusion-weighted MRI generates a series of parameters, including relative cerebral blood volume (rCBV), referring to volume of blood in a given region of brain tissue...estimation of tumor microvascular density. LGGs usually show no increase in tumor rCBV: LGG have rCBV values of range between 1.11 and 2.14
Surgery in LGG

- LGG predilection for eloquent regions, the risk of inducing new neurological deficits had tempered enthusiasm for radical resection.

- However resection of low-grade glioma improves overall survival and importantly delays the time to malignant progression.

- Early surgery and the widespread adoption of awake craniotomy with intra-operative functional mapping have revolutionised low-grade glioma management.

- Permanent Neurological deficit in experienced centres: 1.4%–3.4%; Temporary deficit: 17%–26%. Most patients improve within 3 months.

- Duffau et al found that neurological deficit reduced from 17% to 6.5% using
Median survival of 5.8 years (95% CI, 3.0-8.7) at hospital A, while median survival was not reached at hospital B ($P < .001$).

Jakola AS et al. JAMA 2012; 308(18):1881-8
Preoperative management

- Corticosteroids to decrease mass effect and vasogenic edema
- Anti convulsants for those having seizures
- Baseline motor, language and neurocognitive assessment
- cMRI and aMRI: Perfusion, Tactography, MRS, fMRI—Neuronavigation and functional Neuronavigation
Why surgery in LGG?

- Better survival with more EOR.
- Histological diagnosis and molecular analysis.
- Ameliorated mass effect and intracranial tension.
- Ease control of seizures (LGG with seizures would have seizure-free in 67–70% and improvement in another 20–25%).
Surgery

- GTR/NTR
- STR
- Decompression
- Biopsy only (deep lesions including brainstem, diffuse and/or multicentric tumor. Stereotactic/open)
Tactography, Functional MRI

Preoperative Neuronavigation and functional Neuronavigation

fMRI and DTI tractography of axial (A), coronal (B), and sagittal (C) FLAIR sequences in a patient with a WHO grade II infiltrative astrocytoma. Note displacement of corticospinal tract (yellow) in addition to language (green) and motor (purple). Hervey-Jumper SL et al. J Neurooncol 2016;DOI 10.1007/s11060-016-
Awake Craniotomy

- Indication: a supratentorial intrinsic brain tumor located within or adjacent to regions presumed to have language or sensorimotor function on preoperative imaging.

- Contraindications: uncontrolled persistent cough, hemiplegia with less than antigravity motor function, patients with severe dysphasia, greater than 25% naming errors despite a trial of corticosteroids and diuresis, and large tumors with mass effect with >2 cm of midline shift.

- Large tumors, obese patients, patients with a psychiatric history and/or severe anxiety, intraoperative seizures, chronic smokers, a chronic cough, reoperation with extensive dural scarring, and severely impaired preoperative function all potential risk factors.

- Intraoperative mapping gold standard technique: Stimulation is delivered using a bipolar electrode until somatosensory, language, or motor function is established, or...
## Literature on EOR in LGG

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Non-volumetric studies</th>
<th>No. patients</th>
<th>Volumetric studies</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit</td>
<td>North et al. [16]</td>
<td>77</td>
<td>van Veelen et al. [25]</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Philippon et al. [18]</td>
<td>179</td>
<td>Claus et al. [9]</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Rajan et al. [19]</td>
<td>82</td>
<td>Smith et al. [23]</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>Yeh et al. [27]</td>
<td>93</td>
<td>Hollon et al. [10]</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>McGirt et al. [53]</td>
<td>170</td>
<td>Snyder et al. [24]</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Ahmadi et al. [155]</td>
<td>130</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chaichana et al. [156]</td>
<td>191</td>
<td></td>
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<tr>
<td></td>
<td>Jakola et al. [28]</td>
<td>153</td>
<td></td>
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<tr>
<td></td>
<td>Lote et al. [3]</td>
<td>379</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Nicolato et al. [5]</td>
<td>76</td>
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<td></td>
<td>Scerrati et al. [6]</td>
<td>131</td>
<td></td>
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<tr>
<td></td>
<td>Ito et al. [12]</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Karim et al. [14]</td>
<td>311</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peraud et al. [17]</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shaw et al. [21]</td>
<td>203</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shibamoto et al. [22]</td>
<td>178</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No benefit</td>
<td>Whitton and Bloom [26]</td>
<td>88</td>
<td>None to date</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bauman et al. [8]</td>
<td>401</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Johannesen et al. [13]</td>
<td>993</td>
<td></td>
<td></td>
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</tbody>
</table>
Orange fluorescence (Asterisk) is seen at the base of the resection cavity, indicating residual disease.

Adjuvant Treatment

- Surgery alone is not curative in patients with low-grade gliomas, and additional therapy (radiation and/or chemotherapy) is ultimately required.
- However, the optimal timing of additional therapy is uncertain and the decision to proceed with immediate versus delayed postoperative therapy must be individualized.
## LGG Prognostic scores

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0/1</td>
<td>Age &gt;50 years</td>
<td>Age ≥40 years</td>
</tr>
<tr>
<td>0/1</td>
<td>Karnofsky Performance Status</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>0/1</td>
<td>≤80</td>
<td>Maximum diameter ≥6 cm</td>
</tr>
<tr>
<td>0/1</td>
<td>Eloquent location</td>
<td>Tumour crossing midline</td>
</tr>
<tr>
<td>0/1</td>
<td>Maximum diameter &gt;4 cm</td>
<td>Neurological deficit</td>
</tr>
</tbody>
</table>

The Pignatti score: low risk (score 0–2) and high risk (score 3–5), with median survival of 7.8 years in the low-risk group and 3.7 years in the high-risk group.

Hayhurst C. Pract Neurol 2017;0:1–8.
High risk factors in RTOG 9802

- >/=40 yrs; Subtotal resection or biopsy
  
  - For <40 yrs and GTR (Low risk) (RTOG 111 pts)- Factors associated with a poorer prognosis for progression-free survival (PFS):
    1. Preoperative tumor diameter ≥ 4 cm;
    2. Astrocytoma/oligoastrocytoma histological type
    3. Residual tumor ≥ 1 cm


Factors to decide adjuvant therapy

- > 40 years
- Large preoperative tumour size > 4 cm
- Incomplete resection
- Astrocytic histology
- Tumor crossing midline
- Neurological deficits
- Absence of 1p/19q-codeletion
- IDH mutation status

- It is important to recognize, however, that individual risk factors are relative (including the age cut-off of 40 years and exist on a biological continuum. In addition, there is no single agreed-upon definition of low versus high risk, and risk has been variably defined across trials.
‘Wait and see’ approach for low risk

- A “wait and see” approach following initial surgery may be followed in young patients < 40 years) with a favorable prognosis who have undergone an extensive resection for an IDH-mutant low-grade glioma, especially if molecular studies show the presence of a 1p/ 19q-codeletion
- It is expected that these patients will eventually recur and require additional therapy at the time of progression

111 patients
Overall survival rates at 2 and 5 years were 99 and 93%, respectively.
PFS rates at 2 and 5 years were 82 and 48%, respectively
### Leading studies of RT in LGG

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatments</th>
<th>Number of Patients</th>
<th>Median Overall Survival (Years)</th>
<th>Median PFS</th>
<th>5-Year OS (%)</th>
<th>5-Year PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karim et al. EORTC 22844 [101]</td>
<td>45 Gy in 25 ff 59.4 Gy in 33 ff</td>
<td>171 172</td>
<td>NA</td>
<td>NA</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>Van den Bent et al.</td>
<td>54 Gy in 30 ff</td>
<td>157</td>
<td>7.4</td>
<td>5.3</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>EORTC 22845 [102]</td>
<td>Observation</td>
<td>157</td>
<td>7.2</td>
<td>3.4</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Shaw et al. NCCT/ RTOG/ECOG [103]</td>
<td>50.4 Gy in 33 ff 64.8 Gy in 36 ff</td>
<td>101 102</td>
<td>NA</td>
<td>NA</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>Buckner et al. RTOG 9802 [104]</td>
<td>54 Gy in 30 ff 54 Gy in 30 ff + PCV × 6</td>
<td>126 125</td>
<td>7.8</td>
<td>4.0 Years</td>
<td>63</td>
<td>44</td>
</tr>
<tr>
<td>Baumert et al. EORTC 22033-26033 [105]</td>
<td>TMZ × 12 cycles 50.4 Gy in 28 ff</td>
<td>237 240</td>
<td>NR</td>
<td>39 months</td>
<td>NA</td>
<td>29</td>
</tr>
</tbody>
</table>

Timing of Radiotherapy?
Early Vs Delayed RT in LGG: EORTC 22845

RT Dose: 54 Gy in 1.8 Gy fr

In the control, 65% received RT at progression.

Seizures were better controlled in the early RT treatment group.

Early Vs Delayed: EORTC 22845/MRC BR04

- Phase III (n = 290)
- Early RT (54 Gy) versus No postoperative RT

- Early RT showed an improvement in TTP (4.8 versus 3.4 years; p = 0.02). HR = 0.68 (95% CI 0.50–0.94).
- No differences in OS: HR = 1.15 (95% CI 0.67–1.74). The 5-year OS rate were: 63 versus 66% (p = 0.49).

Dose of RT?
N=379.
At a median follow-up of six years, OS was 58% and 59% in the 45 Gy and the 59.4 Gy arms,

Survival at 2 and 5 years is nonsignificantly better with low-dose RT; survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64%, respectively, with high-dose RT (log rank $P = .48$).

RT dose contd..

- RTOG 9802
  - 54 Gy/28 Fractions

- RTOG 0424
  - 54 Gy in 30 fractions

- EORTC 22033-26033
  - 50.4 Gy/28 Fractions
Chemotherapy in LGG
## Studies of Chemotherapy in LGG

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Phase</th>
<th>Patients</th>
<th>Arm(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9802 [104]</td>
<td>III</td>
<td>≥40 years or subtotal resection or biopsy</td>
<td>RT versus RT-PCV</td>
<td>RT-PCV &gt; RT for OS and PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;40 years or progressive disease</td>
<td></td>
<td>No difference for PFS (all patients) Subgroup analyses:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or tumor &gt; 5 cm or crossing midline or neurological symptoms</td>
<td></td>
<td><em>IDHm/non-codel</em>: RT &gt; TMZ for PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 or more: ≥40 years, astrocytoma, bumphemispherical tumor, preoperative</td>
<td></td>
<td><em>IDHm/codel and IDHiot</em>: no difference</td>
</tr>
<tr>
<td>EORTC 22033-26033 [105]</td>
<td>III</td>
<td>tumor size ≥ 6 cm, preoperative neurological function status &gt; 1</td>
<td>RT versus TMZ</td>
<td>5-year OS rate: 60.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median OS: 8.2 years (95%CI: 5.6–9.1)</td>
</tr>
<tr>
<td>RTOG 0424 [112]</td>
<td>II</td>
<td>Incomplete surgical resection</td>
<td>RT-TMZ</td>
<td>No difference between treatment arms</td>
</tr>
<tr>
<td>Eyre et al. [115]</td>
<td>II</td>
<td>Incomplete surgical resection</td>
<td>RT versus RT-CCNU</td>
<td>Median OS (all patients): Median PFS: 4.45 years</td>
</tr>
<tr>
<td>Ruda et al. [116]</td>
<td>II</td>
<td>Incomplete surgical resection or biopsy or progressive disease</td>
<td>TMZ alone</td>
<td>Median PFS: 3.4 years (95%CI: 2.2–4.3) Median OS: 9.2 years (95%CI: 8.2–11.9)</td>
</tr>
<tr>
<td>Wahl et al. [117]</td>
<td>II</td>
<td>Gross residual disease after resection</td>
<td>TMZ alone</td>
<td>Median PFS: 4.2 years (95%CI: 3.0-5.0) Median OS: 9.7 years (95%CI: 7.2-11.3)</td>
</tr>
<tr>
<td>Kaloshi et al. [118]</td>
<td>II</td>
<td>Progressive disease, refractory epilepsy, neurological deficit</td>
<td>CCNU alone</td>
<td>Median PFS: 27.8 months (95%CI: 21.2–59.6) 5-year OS rate: 71%</td>
</tr>
<tr>
<td>Kesari et al. [119]</td>
<td>II</td>
<td>Oligodendroglioma and oligoastrocytoma with a MIB-1 index &gt; 5% or</td>
<td>TMZ alone</td>
<td>5-year OS rate: 73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recurrent LGG</td>
<td></td>
<td>5-year PFS rate: 34%</td>
</tr>
</tbody>
</table>
PCV X 6 Cycles

- Procarbazine 60 mg per square meter of body-surface area orally per day on days 8 through 21 of each cycle
- CCNU 110 mg per square meter orally on day 1 of each cycle
- Vincristine 1.4 mg per square meter [maximum dose, 2.0 mg] administered intravenously on days 8 and 29 of each cycle

**TMZ Chemoradiation**

The cycle length was 8 weeks

- Concurrent TMZ 75 mg/m² daily with radiation
- Adjuvant TMZ 150-200 mg/m² every 28 days x 6-12 cycles, starting one month after RT
RTOG 9802: RT 54Gy/28Fr +/- PCV

- High-risk LGG:
  - Age >/= 40 years and/or
  - Subtotal resection

A. Progression-free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Failure</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>64</td>
<td>125</td>
</tr>
<tr>
<td>RT Alone</td>
<td>104</td>
<td>126</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.50 (95% CI, 0.36–0.68) P<0.001

No. at Risk
- RT+PCV: 125
- RT alone: 126

Years after Randomization

B. Progression-free Survival, Grade 2 Oligodendroglioma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Failure</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>RT Alone</td>
<td>43</td>
<td>57</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.36 (95% CI, 0.21–0.62) P<0.001

No. at Risk
- RT+PCV: 50
- RT alone: 57

Years after Randomization

C. Progression-free Survival, Grade 2 Oligoastrocytoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Failure</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>RT Alone</td>
<td>36</td>
<td>40</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.52 (95% CI, 0.30–0.89) P=0.02

No. at Risk
- RT+PCV: 39
- RT alone: 40

Years after Randomization

D. Progression-free Survival, Grade 2 Astrocytoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Failure</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>RT Alone</td>
<td>25</td>
<td>29</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.58 (95% CI, 0.33–1.03) P=0.06

No. at Risk
- RT+PCV: 36
- RT alone: 29

Years after Randomization
IDHmut has longer survival than wt, regardless of treatment

RTOG 9802; IDHmut/Codel

Significantly improved PFS & OS by adding PCV

Significantly improved PFS & OS by adding PCV

No Significant PFS / OS advantage by adding PCV

Can TMZ replace PCV?
RTOG 0424-single arm phase 2

High-risk LGG with \( \geq 3 \) risk factors as defined by Pignatti

RT (54 Gy in 30 fractions) with Conc & adjuvant TMZ up to 12 cycles.

The MST was 8.2 years (95% CI, 5.6-9.1).

The 3-year OS rate was 73.5% (95% CI, 65.8%-81.1%). Five year OS rates were 60.9% (95% CI, 52.4-69.4). 10-year OS rates were 34.6% (95% CI, 25.1-44.1),

TMZ or PCV??

- Whether temozolomide should replace PCV is not clear.
- However, temozolomide may not be as efficacious as PCV in low-grade gliomas. For example, median survival in RTOG 0424 has not been reached, but early results demonstrated median PFS of 4.5 years and a 3-year PFS rate of 59%. These results with temozolomide appear inferior to those with PCV from RTOG 9802 in which median PFS was 10.4 years and the 3-year PFS rate was 75–80%, although cross-trial comparisons are fraught with difficulty because of differences in entry criteria and study populations.
TMZ alone as initial adjuvant therapy?
(deferring RT)
EORTC 22033-26033: TMZ Vs RT Phase 3 in High risk LGG

Neurological symptoms); 50.4Gy/28Fr Vs. TMZ 75 mg/m2/day, 21/28 x 12 cycles

Initial TMZ for LGG; AINO (Italian Association for Neuro-Oncology)

Phase 2

# TMZ in LGG

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients</th>
<th>Median F/U</th>
<th>Response Rate (CR + PR)</th>
<th>3y PFS</th>
<th>3y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brada et al  -</td>
<td>30</td>
<td>3 y</td>
<td>10%</td>
<td>66%</td>
<td>82%</td>
</tr>
<tr>
<td>Quinn et al  -</td>
<td>46</td>
<td>&lt;1 y</td>
<td>61%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hoang-Xuan et al -</td>
<td>60</td>
<td>1.2 y</td>
<td>17%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kesari et al -</td>
<td>44</td>
<td>3 y</td>
<td>20%</td>
<td>57%</td>
<td>81%</td>
</tr>
<tr>
<td>UCSF Wahl</td>
<td>120</td>
<td>7.5 y</td>
<td>6%</td>
<td>58%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Table 4. Comparison to recent cooperative group studies utilizing adjuvant radiation

<table>
<thead>
<tr>
<th></th>
<th>RTOG 9802 RT⁷</th>
<th>RTOG 9802 RT+PCV⁷</th>
<th>RTOG 0424 RT+TMZ²³</th>
<th>UCSF TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>40</td>
<td>41</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>45%</td>
<td>40%</td>
<td>23%</td>
<td>48%</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>31%</td>
<td>31%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>23%</td>
<td>29%</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>Extent of resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTR</td>
<td>9%</td>
<td>11%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>STR</td>
<td>45%</td>
<td>41%</td>
<td>61%</td>
<td>77%</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>47%</td>
<td>48%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>Median PFS (y)</td>
<td>4.0</td>
<td>10.4</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Median OS (y)</td>
<td>7.8</td>
<td>13.3</td>
<td>NR (&gt;5 y)</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Wahl M et al. Neuro Oncol 2017 Feb 1;19(2):242-251
IDHwt LGG

- Significantly worse prognosis compared with IDHmut
- Relatively small proportion and underrepresented in trials
- Some bear molecular similarity to glioblastoma (e.g., TERT mutations, loss of heterozygosity of chromosome 10). In such cases treat with immediate postoperative radiation and chemotherapy, regardless of extent of resection or other prognostic factors.
- The rational to use the same regimen as in glioblastoma, the Stupp regimen, is the fact that IDH-wt astrocytoma has the same biology and natural history is very similar to primary GBM.
Diffuse LGG treatment algorithm

**Post-surgical Diffuse Low-Grade Glioma**

**Low risk**
- All of the following:
  - Age ≤ 40 years
  - Preoperative tumour size ≤ 4 cm
  - Gross total resection surgery
  - IDH mutation and 1p19q codeleted

**High Risk**
- Any of the following:
  - Age > 40 years
  - Preoperative tumour size > 4 cm
  - Partial resection surgery or biopsy
  - IDHwt
  - 1p19q non-codeleted tumor

**IDH mutation**
- 1p19q codeleted
- 1p19q Non-codeleted

**Observation (Level II-B)**

**RT + PCV > RT (Level I-A)**
RT + TMZ > RT (Level III-C)
RT = TMZ (Level II-B)

**RT + PCV > RT (Level I-A)**
RT-TMZ > TMZ (Level III-C)
RT > TMZ (Level II-B)

**RT + PCV > RT ? RT-TMZ > RT ? (Level III)**
RT= TMZ (Level II-B)
Thank You