Management of low grade glioma’s: update on recent trials

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Low grades...

- Female, born 1976
- 1st seizure 2005, poorly controlled partial seizures
- Febr 2012: growth
- No clear enhancement, rCBV 2.8.
- Gross total resection, 2 cm residual tumor left behind
- Histology: OD, 1p/19q loss, and IDH mutated

How To Treat?
LGG: Standard of Care

• Watch and wait approach in asymptomatic favorable prognosis patients

• Resection as extensive as safely possible
  – Unresolved debate on early resection

• Radiotherapy 45-50.4 Gy
  – Delayed RT outcome equal to early RT

• Role of chemotherapy up front or at PD
  – Improved outcome in 1p/19q co-deleted cases
  – Best timing?
ASCO 2014: RTOG 9802 and EORTC 22033

- Two RCT’s have further defined the role of chemotherapy in newly diagnosed LGG

- RTOG 9802
  - Radiotherapy and adjuvant PCV

- EORTC 22033
  - Radiotherapy
  - Temozolomide
LOW RISK
Age < 40 AND GROSS TOTAL RESECTION
Arm 1 = Observe

HIGH RISK
Age ≥ 40 OR SUBTOTAL RESECTION/BIOPSY
Stratify by:
Oligo-dominant vs. Astro-dominant;
KPS; Age; Enhancement

R A N D O M I Z E

Arm 2 = Radiation Therapy (54 Gy/30 fractions)

Arm 3 = Radiation Therapy →
PCV x 6 cycles
CCNU 110 mg/m² (day 1)
PCBZ 60 mg/m² (days 8-21)
VCR 1.4 mg/m² (days 8 & 29)
(2.0 mg cap)

Slide courtesy J Buckner
**EORTC 22033 Study Scheme**

- **Registration** → **Genetic Testing 1p** → **Random**

**Stratification:** *1p mutation*, contrast on MRI, age and PS, institute, contrast enhancement MRI, age: <40 vs ≥ 40 yrs, WHO PS 0 /1 versus 2

**Primary endpoint:** PFS

**Secondary endpoints:** OS, QoL, Neurocognitive function (specified centres)

- **Radiotherapy (standard arm):**
  - 50.4 Gy (28 x 1.8 Gy) conformal techniques

- **TMZ (experimental arm):**
  - 75 mg/m² daily x 21 days, q 28 days until progression or for max. 12 cycles

**PI:** Dr Baumert
Main Inclusion Criteria: poor risk patients

- Histologically proven WHO grade 2 glioma (astrocytoma, oligodendro and mixed glioma)
- Newly diagnosed or progressive disease
- Supratentorial tumor location
- No prior RT or chemotherapy

At least 1 criteria of the following (indication for initiating therapy):

- Radiographic progression
- New or worsening neurological deficit
- Intractable epilepsy = persistent seizures interfering with everyday life and failure of 3 lines of anti-epileptic drug regimen
- $\geq$ Age 40 years
Two phase III trials on chemotherapy in low grade glioma: similarities

- Both investigated
  - Newly diagnosed low grade glioma
  - Aiming at ‘high risk’ patients
Two phase III trials on chemotherapy in low grade glioma: differences

- RTOG 9802 more mature follow-up
  - EORTC reports on PFS only
- RTOG 9802: combined treatment
  - EORTC chemotherapy vs radiotherapy
- RTOG 9802 PCV
  - EORTC 22033 temozolomide
- RTOG 9802 still no molecular data available
  - EORTC 22033 emphasis on 1p status
ASCO 2014: adjuvant PCV improves outcome in low grade glioma (RTOG 9802)

PI: Dr E Shaw, presented by Dr J Buckner

- RTOG trial 9802 randomized trial on adjuvant PCV in LGG, started 1998
- In 2008 reported/published JCO 2012
  - PFS benefit but no OS benefit
- 2014 mature follow-up: major OS benefit of PCV in ITT population
- RT arm: of 126 pts 92 progressed, 72 (77%) received chemotherapy at PD
Follow-up data:
- Deaths: 138 (55%)  
- Median follow up: 11.9 yrs  

<table>
<thead>
<tr>
<th></th>
<th>RT Alone</th>
<th>RT + PCV</th>
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<tbody>
<tr>
<td>Median</td>
<td>7.8 years</td>
<td>13.3 years</td>
</tr>
<tr>
<td>5-year</td>
<td>63.1%</td>
<td>72.3%</td>
</tr>
<tr>
<td>10-year</td>
<td>40.1%</td>
<td>60.1%</td>
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</table>

HR: 0.59
Conclusions

• For patients with grade 2 glioma with less than gross total tumor resection or who are > 40 years of age, RT + PCV prolongs both progression-free and overall survival compared with RT alone

  – Median survival is increased by 5.5 years.
  – Five-year and 10-year survival are increased by 9% and 20%, respectively
Unanswered: does this apply to all LGG subtypes?

• No data on molecular subtypes
  – Probably only limited set of tumor specimen available

• Data on histological subtypes
  – Most benefit in oligodendroglial tumors
  – HR reduction in astrocytoma still 0.73, but with p value 0.30
  – Similar trend compared to anaplastic oligodendroglioma studies
### OS by Histology

<table>
<thead>
<tr>
<th></th>
<th>Median in years RT</th>
<th>Median in years RT + PCV</th>
<th>% at 5 years RT</th>
<th>% at 5 years RT + PCV</th>
<th>% at 10 Years RT</th>
<th>% at 10 Years RT + PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>10.8</td>
<td>NR (13.3+)</td>
<td>80</td>
<td>88</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>OA</td>
<td>5.9</td>
<td>11.4</td>
<td>55</td>
<td>66</td>
<td>25</td>
<td>51</td>
</tr>
<tr>
<td>A</td>
<td>4.4</td>
<td>7.7</td>
<td>41</td>
<td>57</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>7.8</td>
<td>13.3</td>
<td>63</td>
<td>72</td>
<td>40</td>
<td>60</td>
</tr>
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</table>
OS: Astrocytoma

\[
p = 0.60 \text{ (Wilcoxon)}
\]
\[
p = 0.31 \text{ (Log–rank)}
\]
\[
HR = 0.73
\]
Progression Free Survival

EORTC 22033 primary analysis: Progression-Free Survival in Intent to Treat Population

262 events/ 126 RT, 136 TMZ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>Median (95% CI) (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>46 (40, 55)</td>
<td></td>
</tr>
<tr>
<td>TMZ</td>
<td>1.2 (0.9, 1.5)</td>
<td>39 (34, 43)</td>
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P=0.22
EORTC 22033 on RT vs TMZ in low grade glioma: PFS in relation to 1p status

1p normal: 121 events/ 55 RT, 66 TMZ

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<th>Hazard Ratio (95% CI)</th>
<th>Median (95% CI) (Months)</th>
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</thead>
<tbody>
<tr>
<td>RT</td>
<td>1</td>
<td>41 (32, 55)</td>
</tr>
<tr>
<td>TMZ</td>
<td>1.4 (1.0, 2.0)</td>
<td>30 (24, 40)</td>
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1p deleted: 82 events/ 42 RT, 40 TMZ

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<tr>
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<th>Hazard Ratio (95% CI)</th>
<th>Median (95% CI) (Months)</th>
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<tbody>
<tr>
<td>RT</td>
<td>1</td>
<td>58 (41, 67)</td>
</tr>
<tr>
<td>TMZ</td>
<td>1.0 (0.7, 1.6)</td>
<td>76 (66, 83)</td>
</tr>
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P=0.06

P=0.95

ASCO 2015

ASCO 2013 slide courtesy Dr Baumert
Summary EORTC 22033

- Overall toxicity: mild
- Hematological toxicity $\geq$ grade 3: 9.4% of TMZ patients
- Primary endpoint: PFS not significantly different
- Secondary PFS analysis:
  - $1p$, $1p/19q$ no significant predictive value
  - $1p$, $1p/19q$ deletion significant positive prognostic factor irrespective of treatment
  - $1p$ intact improved PFS after radiotherapy?
- Median OS not yet reached – needs more mature data
In low grades: what are the big questions now?

1. Adjuvant chemotherapy only for tumors that are incompletely resected or in patients > 40 years?
2. And always? Or is a watch and wait policy still justified in selected patients?
3. PCV? Or temozolomide?
4. Is RT/chemotherapy in all LGG indicated? Or can RT be postponed in chemotherapy sensitive tumors?
1. LGG: patient selection for adjuvant PCV

- RTOG used high risk definition: incomplete resection and/or >40 yrs
- EORTC 22033 trial used other but similar definition
- Well accepted risk factors for OS:
  - Max tumor diameter, age, KPS, astrocytic histology, extent of resection, 1p/19q status
- Why should high risk tumors benefit more from adjuvant chemotherapy??
More logical approach

• Decide whether adjuvant treatment is indicated
  – Focal deficits, cognitive deficits, growing lesions, mass effect, age, uncontrolled seizures
  – That decision is taken regardless of decision for surgery
  – So: not the well controlled seizures only patient
• If so: 1st consideration is RT/chemotherapy
2. Watch and wait policy: still an option?

• Accepted policy in young LGG patients presenting with seizures only or with incidental findings
• This still applies in incompletely resected patients
• Patients should be carefully monitored for growth
  – And further treatment when radiologically progressive
3. PCV or temozolomide?

• All three positive RT + chemo trials in grade II and III have been conducted with PCV
  – no similar data on temozolomide

• PCV: associated with cumulative bone marrow suppression, nausea, malaise
  – TMZ has largely replaced PCV

• NOA4*: so far no difference in PFS between patients treated with PCV versus TMZ

4. Can we withhold RT and give chemotherapy only?

- Rationale: concern about delayed cognitive deficits after early RT
- Question: if RT/PCV is superior to RT, and RT is equivalent to chemotherapy, will postponing RT be detrimental for OS?
- Will salvage RT with or without chemotherapy at the time of PD bring the same OS benefit?
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
Can we safely delay RT?

- RT + PCV trials were positive despite significant cross over in RT arm (> 70%)
- 2nd line chemotherapy is of limited efficacy in grade II and III
- Can we use PFS to analyse this?
  - So far changes in PFS predicted changes in OS in the phase III trials on diffuse glioma
  - OS data from several trials not yet mature
LGG & chemo vs RT: how effective is chemo only? A PFS analysis

<table>
<thead>
<tr>
<th>Wait and see</th>
<th>chemo</th>
<th>RT</th>
<th>RT/CTX</th>
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<tbody>
<tr>
<td>EORTC 22085</td>
<td>41</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>EORTC 22033</td>
<td>40</td>
<td>47</td>
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</tr>
<tr>
<td>1p deleted</td>
<td>76</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>1p intact</td>
<td>30</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Kaloshi et al (TMZ)</td>
<td>28</td>
<td>?</td>
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<tr>
<td>1p/19q deleted</td>
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<tr>
<td>1p/19q intact</td>
<td>20</td>
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<tr>
<td>RTOG 9802</td>
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<td>48</td>
<td>125</td>
</tr>
<tr>
<td>high risk</td>
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<tr>
<td>low risk</td>
<td>±60</td>
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PFS in months
Delaying RT in diffuse grade II and III glioma

- This considers completely different events
  - Cognition vs overall survival

- With very limited real data

- RT delay in non-1p/19 co-deleted is quite limited

- Delaying RT in more favorable (1p/19q del) patients has potential trade off: decreased survival

- Despite the limited data: this needs to be discussed with the patient
Diffusae grade II and III glioma: now what?

• RT with adjuvant chemotherapy improves OS compared to RT with chemotherapy at PD in most patients

• Still a need for optimal patient selection for both grade II and III (IDH, 1p/19q, MGMT)

• Effects of radiotherapy and chemotherapy unlikely to be further improved

• We need new drugs to improve outcome…

Suggested reading: van den Bent, Neuro Oncol. 2014;16:1570-4