lower grade glioma: standards of care

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Disclosures

• none
Agenda

• Characteristics and risk factors of lower grade gliomas (LGG)
• Evidence für resection
  • Radicality?
• Evidence for radiation and chemotherapy
• Current standard of care
Lower grade glioma – WHO grade II

- WHO class. 2016, inclusion of molecular markers:
  - IDH-1-mutation
  - codeletion 1p/19q
  - ATRX loss
  - H3-K27M, Rela fusion, WHT, SHH...

- Diffuse Astrocytoma IDH-1 mut, 1p/19q non-codel, (ATRX lost)
- Oligodendroglioma IDH-1 mut, 1p/19q codel, (ATRX retained)

➔ No treatment decision based on imaging alone
➔ Histology + molecular genetics mandatory
➔ Surgery or stereotactic biopsy
Characterisation of „lower grade“ glioma

- Oligosymptomatic/asymptomatic
- High quality of life
- Slow growth

- Extremely heterogeneous
- Common malignisation
- Limited prognosis

Primum nihil nocere

aggressive therapy
Slow growth?

**Distribution** of growth rates

VDE = Velocity of diametric expansion, n = 407

Mean: $5.8 \pm 6.3$ mm/year

**Effect of growth on outcome:**

<table>
<thead>
<tr>
<th>Growth Rate</th>
<th>Malignant PFS</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 mm/year</td>
<td>103</td>
<td>249</td>
</tr>
<tr>
<td>&gt; 8 mm/year</td>
<td>35</td>
<td>91</td>
</tr>
</tbody>
</table>

Pallud et al., Neuro-Oncol, 2013
Prognostic factors

n = 322
- age < 40 y
- diameter < 6 cm
- no midline crossing
- oligo/mix. vs. astro
- no neurolog. deficit

n = 239
- age < 45 J \ p<0.01
- volume < 20 ml \ p<0.005
- KPS > 80 \ p<0.0001
- no CE \ p<0.05

Kreth et al., Cancer, 2006

Pignatti et al., JCO, 2002
Prognostic factor FET-PET

Diagnosis of metabolically active areas

- Identification of patients with early malignant progression and poor prognosis

Thon et al., Int J Cancer, 2015
Survival in real life

SEER database
n = 2825
Astrocytoma
mean survival
Astro 5.2 years

Claus et al., Neurosurg Focus, 2015
Survival in real life

SEER database

n = 2825

Oligodendroglioma

mean survival

Oligo 7.2 years

Claus et al., Neurosurg Focus, 2015
Growth, malignisation, limited survival

consequent therapy

maximal safe resection

early radiation

chemotherapy

radicality in gliomas (?)
Problem: Invasion of tumor cells

Image: Hyperintensity in MRI

Surgery

Solid tumor

Infiltration zone (cm)

Hyperintensity in MRI
Problem: Invasion of tumor cells

→ „complete removal“ not possible from biological point of view
Case report 1: „complete resection“
Case report 2. „complete resection“
Effect of resection on survival

Population based analysis: 2 norwegian hospitals: watchful waiting (WW) versus early resektion (ER)
Indication for surgery depends on living area retrospektive, only Astrocytoma °II

n = 117 fav. WW = 55 fav. ER = 62
OPs 12/55 51/62

OS: WW = 5.6 y vs. ER = 9.7 y
No difference in neurolog outcome p=0.843
No difference in surgical. complications p=0.914

Update 2017:
OS: WW = 5.8 y versus ER = 14.4 y p<0.01

Jakola et al., Ann Oncol, 2017

→ resection matters!
Effect of resection on survival

Shaw EG et al., J Neurosurg 2008:

Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low grade glioma: results of a prospective clinical trial
RTOG-Phase-II-Studie

Aim: Follow up of patients 18-29 years with LGG, who were operated intending GTR

Results: n=111
2-y-OS 99% 5-y-OS 93% 2-y-PFS 82% 5-y-PFS 48%

recurrency rate after 5 years

remnant tumor < 1 cm (59%) 26%
remnant tumor 1-2 cm (32%) 68%
remnant tumor > 2 cm (9%) 89%

⇒ Extent of resection matters!
## Effect of resection on survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>n</th>
<th>Approach</th>
<th>Parameter</th>
<th>Effect on OS</th>
<th>Effect on PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGirt, 2008</td>
<td>Neurosurgery</td>
<td>170</td>
<td>retro</td>
<td>GTR vs STR</td>
<td>p=0.017</td>
<td>p=0.043</td>
</tr>
<tr>
<td>Shaw, 2008</td>
<td>J Neurosurg</td>
<td>111</td>
<td>pro</td>
<td>EOR</td>
<td>n.d.</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Smith, 2008</td>
<td>J Clin Oncol</td>
<td>216</td>
<td>retro</td>
<td>EOR</td>
<td>p=0.001</td>
<td>p=0.035</td>
</tr>
<tr>
<td>Ahmadi, 2009</td>
<td>Acta Neurochir</td>
<td>130</td>
<td>retro</td>
<td>EOR</td>
<td>p=0.024</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ius, 2012</td>
<td>J Neurosurg</td>
<td>190</td>
<td>retro</td>
<td>EOR</td>
<td>p=0.001</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>Youland, 2013</td>
<td>Neuro Oncol</td>
<td>852</td>
<td>retro</td>
<td>EOR</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Coburger, 2015</td>
<td>Neurosurgery</td>
<td>288</td>
<td>retro</td>
<td>GTR vs STR</td>
<td>n.d.</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Patel, 2017</td>
<td>Neurosurgery</td>
<td>74</td>
<td>retro</td>
<td>EOR / IDH</td>
<td>P&lt;0.05 IDHwt</td>
<td>P&lt;0.05 IDHwt</td>
</tr>
<tr>
<td>Eseonu, 2017</td>
<td>J Neurosurg</td>
<td>109</td>
<td>retro</td>
<td>EOR</td>
<td>p=0.029</td>
<td>P=0.018</td>
</tr>
</tbody>
</table>

Only evidence class IIb-III, but uniform results
What about adjuvant therapy?

• Role of radiation?
• Role of chemotherapy?
Effect of radiation on survival

- **EORTC 22845**
- Effect of radiotherapy on OS and TTP (PFS)
- N=311, 2 arms: early RT (54 Gy) vs. RT at progression
- Median FU 5 years
- **Time to progression:**
  - 5-y-TTP: 44% vs. 37%
  - improved by early RT

Karim et al., Int J Rad Oncol, 2002
Effect of radiation on survival

- **EORTC 22845**

- Overall survival:

  5-\text{y-OS} 63\% vs 67\%

  ➔ No difference

Karim et al., Int J Rad Oncol, 2002
Effect of radiation on survival

- EORTC 22845
- Long term evaluation (FU 7.8 years)

Van den Bent et al., Lancet, 2005
Evidence for radiotherapy

- Radiotherapy is recommended to **improve PFS** of patients with diffuse LGG (evidence class I, recommendation **level A**)

- Radiotherapy is recommended to prolong OS in patients with subtotal resection (level C)

- Radiotherapy is recommended to improve seizure control in patients with epilepsy and subtotal resection (level C)

- Radiotherapy is recommended as an equivalent alternative to observation in preserving cognitive function (level B)

Ryken et al., J. Neurooncol, 2015
Radiotherapy or chemotherapy?

- EORTC 22033/26033 (Baumert et al., Lancet Oncol, 2016)
- Objective: radiotherapy versus TMZ chemotherapy in LGG (WHO °II)
- N=477 patients, median FU 48 months, any LGG, at least 1 negative prognostic factor, primary endpoint PFS
- Conformal RT 50.4 Gy/28 fractions versus dose dense Temozolomide (75 mg/m2 daily x 21 days, q28 days, max. 12 cycles)

- Median PFS RT: 46 mo
- Median PFS TMZ: 39 mo
- No sign. difference
Radiotherapy or chemotherapy?

- EORTC 22033/26033 (Baumert et al., Lancet Oncol, 2016)

- No difference in patients with 1p/19q codeleted tumors

- RT better in patients with 1p/19q non-codel tumors (astrocytomas)
Radiotherapy AND chemotherapy?

- **RTOG 9802**
  
  Shaw et al., J Clin Oncol, 2012
  Prabhu et al., J Clin Oncol, 2014
  Van den Bent et al., Neuro Oncol, 2014

- **Objective:** radiotherapy versus radiotherapy plus PCV in LGG

- N=251, any LGG WHO °II (old WHO), at least 1 risk factor, 1998-2002

- <40 y old with subtotal resection or
  
  >= 40 with any extent of resection

- RT with 54 Gy, 6 cycles of PCV=Procarbazin+CCNU +Vincristin

- median FU 5.9 y (Shaw et al., 2012)
Radiotherapy AND chemotherapy?

- **RTOG 9802**
  
  Shaw et al., J Clin Oncol, 2012  
  Prabhu et al., J Clin Oncol, 2014  
  Van den Bent et al., Neuro Oncol, 2014

**Results 2012:**

- Median OS  
  - RT 7.5 years  
  - RT+PCV not reached
- OS-5y  
  - RT 63%  
  - RT+PCV 72%  
  \((p=0.33)\)
- Median PFS  
  - RT 4.4 years  
  - RT+PCV not reached
- PFS-5y  
  - RT 46%  
  - RT+PCV 63%  
  \((p=0.005)\)

**Conclusions**

- PFS but not OS was significantly improved by adding PCV to RT

**Results 2014:**

- Median OS  
  - RT 7.7 years  
  - RT+PCV 13.3 years
Radiotherapy AND chemotherapy?

- Buckner et al., NEJM, 2016
- median FU 11.9 years, 55% of patients died
Radiotherapy AND chemotherapy?

**PFS 10 years:**
- 51% in RT + PCV
- 21% in RT alone

**OS 10 years:**
- 60% in RT + PCV
- 40% in RT alone
- Median OS: 13.3 versus 7.7 years
Radiotherapy AND chemotherapy?

- Significant differences in PFS and OS for all histologies except astrocytoma!!
Radiotherapy AND chemotherapy!

**Conclusion:**

- Chemotherapy should be added to radiotherapy in LGG patients with risk factors (age > 40, no GTR)
- Evidence class I, recommendation level A

**Open questions:**

- Valid for new WHO (codel)?
- What about non-codel tumors / astrocytomas?
- PCV versus temozolomide

Buckner et al., NEJM, 2016
Conclusion – standard of care

- Histology incl. molecular genetic markers needed (tissue!!!)
- GTR should be intended if safe resection seems possible
- Young patients (<40y) without residual tumor maybe observed
- In patients with risk factors adjuvant therapy is needed
- Radiotherapy plus PCV chemotherapy recommended (level A)
- Open question PCV versus TMZ
- Supportive care: seizures, cognition and psychooncology
- No one man show ➞ specialised neurooncology center w. tumorboard

Current Glioma Guideline: Weller et al., Lancet Oncol, 2017
Thank you!

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Evidence and recommendations:

- Surgical resection is recommended over observation to improve overall survival for patients with diffuse LGG (evidence class III, recommendation level C)
- GTR or STR should be performed instead of biopsy alone, when it is safe and feasible (level B)
- Greater extent of resection can improve OS (level C)
- GTR should be employed to improve seizure control (level C)
- Use of intraoperative MR imaging (level C)
- Use of intraoperative mapping in eloquently located gliomas (level C)

Aghi et al., J Neurooncol, 2015
Malignisation of LGG – does surgery help?

- IDH-1- mutated astrocytoma °II after malignant progression, n=56
- Histo: °III: n=42
  °IV: n=14
- Median OS 123 months
- Med. OS after MP 33 months
- Prognostic factors:
  GTR, KPS post-surgical, CTX

Grau et al., J Neurooncol, 2017
GTR not possible – what to do?

Only GTR (maximum safe resection) offers effect on OS/PFS (class III evidence)

Options:

• Not to operate
• Partial resection and hope for a wonder
• Treatment of the whole tumor volume by combination therapy
Combination STR/PR plus brachytherapy

Aim: complete therapy of whole tumor volume

Requirement: Expertise in both techniques

Principle: resect all areas with low risk +
implant Jodine125-Seed in eloquent areas

⇒ addition of therapeutic effects with minimised risk
Combination STR/PR plus brachytherapy
Combination STR/PR plus brachytherapy

Results (Schnell et al., 2008)

- 31 Patients (de novo n = 18, recurrent n = 13), median FU 37 months
- Age 38 ± 12 y
- Histology: 26 Astrozytoma °II, 4 Oligodendroglioma °II, 1 mixed glioma
- Complications:
  - temporary: OP 17.8% SBT 6.4%
  - permanent: 0% 0%
  - median KPS end of follow up: 80
- Response after brachytherapy:
  - CR: 8 Pat.
  - PR: 9 Pat.
  - SD: 14 Pat.
  - 5-y-PFS: 72% (de novo) 62% (recurrent)
  - 5-y-OS: 93%
Darstellung von Funktion - nTMS
Darstellung von Funktion - nTMS

Weiß et al., 2012
Krieg et al., 2012
Picht et al., 2015
Weiß Lucas et al., 2016
N=364, N\textsubscript{incid}=35, all surgically managed

Potts et al., 2012
EANS – EANO Guideline for LGG

Recommendation for resection:

- Positive effect of resection (maximum safe resection) on seizure control, PFS und OS (class II und III)
- Resection reduces risk of malignisation (class III)
- Positive effect of intraoperative techniques (awake surgery, funct. mapping) on extent of resection (class II)

seizure control
- Ruda et al., Neuro-Oncol, 2013
- Pallud et al., Brain, 2014
- Koekkoek et al., JNNP, 2015
- Avila et al., Neuro-Oncol, 2017
- Xu et al., J Neurosurg, 2017

Growth kinetics

Fig 2. Mean tumor diameter (MTD) evolution after time adjustment before temozolomide (TMZ) treatment. For each patient, the MTD is plotted against its size-adjusted time. (A) Patients without 1p-19q codeleted tumors are plotted in black, and patients with codeleted 1p-19q tumors are plotted in white. (B) Patients with p53 overexpression are plotted in black, and patients with undetectable levels of p53 are plotted in white. By eliminating the lead-time bias, this procedure demonstrates that the spontaneous evolution of the MTD is influenced by the tumor molecular status as 1p-19q deleted tumors display a growth rate of 3.4 versus 5.9 mm/year ($p = 0.0016$) and tumors that overexpress p53 display a growth rate of 6.3 versus 4.2 mm/year ($p = 0.05$). Histograms show the MTD growth rate distributions under each condition.

1p/19q Codel: 3.4 mm/a
non-Codel: 5.9 mm/a

Ricard et al., 2007
Extent of resection

„maximal“ resection

Anatomically defined
Image guided resection (iMRT, iUS, landmarks)

„supramaximal“ resection

electrophysiologically defined
Awake craniotomy with IOM
Resection of invasion zone until electrophys./clin. deficits occur

Rest of the world

Kelly PJ, Neurosurgery, 2004:
„someone once defined madness as doing the same thing over and over again, expecting a different result“

Hugues Duffau, Montpellier
„The goal of supracomplete resection is to delay the anaplastic transformation even if it does not (yet) enable a cure“
J Neurosurg, 2011
Radiotherapy AND chemotherapy!
Malignisation – myth or reality?

Malignant PFS

N=364, N_{\text{incid}}=35
„surgically managed“

⇒ Median 9 years

Potts et al., J Neurosurg., 2012
Malignisation

\[ \text{age} \geq 35 \text{ yrs.} + \text{tumor} > 20\text{mL} \]

\[ \text{age} \geq 35 \text{ yrs.} \text{ or tumor} > 20\text{mL} \]

\[ \text{age} \leq 35 \text{ yrs.} + \text{tumor} \leq 20\text{mL} \]

\[ \text{N=239} \]

Kreth et al., 2006

⇒ All LGG turn malignant, question of time and prognostic factors