Meningioma – Standards of Care

Roland Goldbrunner
Disclosures

Advisory Board, Honorarium:

• AbbVie

• MagForce
Background - Meningioma

- Most common intracranial tumor, WHO grade I to III
- Mostly cured by surgery
- Radiosurgery frequently used
- Survival:

<table>
<thead>
<tr>
<th>5-year Local Freedom from Recurrence</th>
<th>5-year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade I</strong></td>
<td><strong>Grade I</strong></td>
</tr>
<tr>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Grade II</strong></td>
<td><strong>Grade II</strong></td>
</tr>
<tr>
<td>58%</td>
<td>73%</td>
</tr>
<tr>
<td><strong>Grade III</strong></td>
<td><strong>Grade III</strong></td>
</tr>
<tr>
<td>40%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>GTR</strong></td>
<td><strong>GTR</strong></td>
</tr>
<tr>
<td>81%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>STR</strong></td>
<td><strong>STR</strong></td>
</tr>
<tr>
<td>56%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Gennatas et al., PLOSone, 2018
Background - Meningioma

• Most common intracranial tumor, WHO grade I to III
• Mostly cured by surgery
• Radiosurgery frequently used
• Role of radiotherapy in different grades?
• (future) role of medical therapy?
• Molecular profiling meaningful?

➡ Evidence for diagnosis and therapy?

Imaging by E. Houdart,
In: Lancet Oncol 2016,17: e383-91
EANO guidelines for the diagnosis and treatment of meningiomas


Lancet Oncol 2016; 17: e383-91
Diagnosis – imaging

- Diagnosis of meningioma is made by MRI (T1+CM)
- CT effective in assessment of calcification and intraosseous growth
- No diagnostic role of angiography
- (Angiography in selected cases justified for embolization)
- Upcoming role of somatostatin receptor 2 specific PET imaging using dotatoc/dotatate tracers

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<th>PET tracers</th>
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</tbody>
</table>
## Diagnosis – molecular markers

### Table 2: Mutations in meningiomas

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AKT1</th>
<th>KLF4</th>
<th>TRAF7</th>
<th>NF2</th>
<th>SMO</th>
<th>TERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningothelial Meningioma WHO grade I</td>
<td>13%</td>
<td>-</td>
<td>8%</td>
<td>22%</td>
<td>16%</td>
<td>-</td>
</tr>
<tr>
<td>Transitional Meningioma WHO grade I</td>
<td>14%</td>
<td>-</td>
<td>5%</td>
<td>33%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fibroblastic Meningioma WHO grade I</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psammomatous M. WHO grade I Meningioma WHO grade I</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secretory Meningioma WHO grade I</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich Meningioma WHO grade I</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>Metaplastic Meningioma WHO grade I</td>
<td>25%</td>
<td>-</td>
<td>-</td>
<td>20%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Microcystic Meningioma WHO grade I</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Angiomatous Meningioma WHO grade I</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>10%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atypical Meningioma WHO grade II</td>
<td>4%</td>
<td>-</td>
<td>4%</td>
<td>70%</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Chordoid Meningioma WHO grade II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clear Cell Meningioma WHO grade II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anaplastic Meningioma WHO grade III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70%</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>Rhabdoid Meningioma WHO grade III</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>Papillary Meningioma WHO grade III</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
</tr>
</tbody>
</table>

Percentages, values <4% are given as "-"
Beyond the guideline – role of molecular genetics

DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis


Lancet Oncol 2017

• N=497 meningiomas

• N=309 other extra-axial intracranial/skull tumors

• Clear segregation of meningiomas from all other tumors by DNA methylation analysis

• Six clinically relevant methylation classes

• Methylation classes have a higher power in predicting recurrence and prognosis than WHO grades

• Validated in an independent cohort (n=140 meningiomas)
Methylation based classification and grading system
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Therapy of meningioma WHO grade I

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<th>Grade</th>
<th>Definition</th>
<th>Extent of Resection (EOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Gross total resection of tumor, dural attachment and abnormal bone</td>
<td>GTR</td>
</tr>
<tr>
<td>II</td>
<td>Gross total resection of tumor, coagulation of dural attachment</td>
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<tr>
<td>III</td>
<td>Gross total resection of tumor without resection or coagulation of dural attachments, or extradural</td>
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</tr>
<tr>
<td></td>
<td>extensions (e.g. invaded or hyperostotic bone)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Partial resection of tumor</td>
<td>STR</td>
</tr>
<tr>
<td>V</td>
<td>Biopsy of tumor</td>
<td></td>
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- Simpson grade I resection should be intended (class II, rec level B)
- Extent of resection should be confirmed by MRI (good practice point)
- Preoperative embolization is reserved for rare, specialized cases (good practice point)
Therapy of meningioma WHO grade I

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- Extent of resection should be confirmed by MRI (good practice point)
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Therapy of meningioma WHO grade I

Stereotactic Radiosurgery (SRS):

- Alternative to surgery in small tumors (class III; rec. level B)
- Factors: condition of the patient, size and location of the tumor, (wish of the patient)
- Additional therapy after incomplete resection
- Technique: 14-16 Gy single fraction (Linac, Gamma Knife, Cyber Knife)

Fractionated Radiotherapy (RT):

- Option for large, inoperable or recurrent tumors (class III, rec level B)
- Techniques: intensity modulated radiotherapy (IMRT) and fractionated stereotactic radiotherapy (FSRT), 50-60 Gy

Pharmacotherapy: no role in meningiomas grade I (class III, rec. level B)
Therapy of meningioma WHO grade I
Therapy of meningioma WHO grade I

- Combining subtotal resection and radiosurgery or fractionated radiotherapy should be considered to allow comprehensive tumor treatment while reducing the risk of adverse effects from treatment in WHO grade I meningiomas (class IV, rec. level C)
Therapy of meningioma WHO grade I
Therapy of meningioma WHO grade II

- Surgery (Simpson I) is therapy of first choice (class III, rec. level B)

- **Role of RT after resection** is unclear: retrospective series led to differing results

- ROAM/EORTC 1308 study: newly diagnosed grade II meningioma, Simpson I-III resection, randomisation into RT (60 Gy in 30 fractions) or observation arm

- RT recommended
  - after incomplete resection (class III, rec. level C)
  - in case of progression (class III, rec. level C)

- **Pharmacotherapy** can be considered upon progression (class III, rec. level C)

- EORTC 1320 (NCT02234050) Trabectedin for recurrent grade II and grade III
Therapy of meningioma WHO grade III

- Strong tendency to recur and may metastasize systemically (rare!)
- Radical surgery (Simpson I) needed (class III, rec. level C)
- Resection should be followed by RT at least 54 Gy (class III, rec. level B)
- Pharmacotherapy: little data, differing class IV evidence, no recommendation possible

<table>
<thead>
<tr>
<th>Potential drug /drug class</th>
<th>Molecular target</th>
</tr>
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<tbody>
<tr>
<td>AKT inhibitor</td>
<td>AKT1 mutation</td>
</tr>
<tr>
<td>Hedgehog inhibitor</td>
<td>SMO mutation</td>
</tr>
<tr>
<td>FAK inhibitor</td>
<td>NF2/merlin loss</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor</td>
<td>PD-1/PD-L1</td>
</tr>
<tr>
<td>VEGF/VEGFR inhibitor</td>
<td>VEGF/VEGFR2</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>DNA, tumor associated macrophages, angiogenesis (Preusser, p.c., 2018)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>EGFR/Erb2 (Osorio, 2018)</td>
</tr>
</tbody>
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Follow up intervals

• No robust data about FU intervals, all recommendations are based on expert opinion (good practice point)

• FU dependent on WHO grade, Simpson grade, SRS/RT, size and location of the tumor, condition and age of the patient

➢ Suspected WHO grade I meningioma, observation: first MRI after 6 mo, then annually

➢ WHO grade I (10-y recurrence rate 20-39%): annual MRI, after 5 years biannually. In elderly/ill patients controls may be omitted

➢ WHO grade II: MRI every 6 months, after 5 years annually

➢ WHO grade III: every three to six months, dependent on growth dynamics
Conclusions

➢ Surgery still most important treatment in WHO grade I-III
➢ Multimodal treatment (surgery + SRS) can be recommended
➢ Special challenge: molecular profiling, more valid classification systems
➢ Special challenge: development of medical treatment options
Outlook – role of molecular genetics

- Improved estimation of prognosis by (epi-)genetic analysis
- Predictive and prognostic power of molecular genetics better than classical histology (WHO grade)

➔ Tumor tissue provides much more information than before
➔ Molecular data are required for development of targeted therapies
➔ Please collect tissue!!!
➔ Impact on decision surgery versus radiosurgery
Thank you!

roland.goldbrunner@uk-koeln.de
European Association for Neurooncology (EANO) Task Force

Roland Goldbrunner, GER, Neurosurg
Giuseppe Minniti, ITA, Rad. Onc.
Matthias Preusser, AUT, Med. Onc.
Michael Jenkinson, UK, Neurosurg.
Kita Sallabanda, ESP, Radiosurg.
Emmanuel Houdart, FRA, Neurorad.
Andreas von Deimling, GER, Neuropath.
Pantelis Stavrinou, GRE, Neurosurg.
Florence Lefranc, BEL, Neurosurg.
Morten Lund-Johansen, NOR, Neurosurg.
Elizabeth Cohen-Jonathan Moyal, FRA, Rad. Onc.
Dieta Brandsma, NED, Neurooncol.
Roger Henriksson, SWE, Rad. Onc.
Riccardo Soffietti, ITA, Neurooncol.
Michael Weller, CH, Neurooncol.
Search algorithm

The authors searched the following databases:

- the Cochrane Library to date
- the Medline databases to date
- Embase-Ovid (January 1990 to date) Cancer Net
- Science Citation Index

Sensitive and specific keywords as well as combinations of keywords were used. Publications in all languages of the countries represented by this EANO task force were considered.
Evidence and recommendation levels

**Evidence:**

Class I  prospective randomized blinded trial or review of RCTs
Class II  prospective matched pair cohort studies
Class III any controlled trial (incl. retrospective controls)
Class IV  uncontrolled studies, case series, case reports, expert opinion

**Recommendation:**

Level A ("established")  one class I or at least two class II studies
Level B ("probably")    one class II or overwhelming class III evidence
Level C ("possibly")    at least two class III studies
"good practice point"    only class IV evidence

Brainin et al., Eur J Neurology, 2004
„targeted“ imaging

• Contrast enhanced MRI and high resolution T2 (CISS) mandatory
• Problems: complex skull base meningioma, intraosseus meningioma, recurrent tumor
• PET imaging helpful?

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➔ Somatostatin receptor 2 specific PET imaging
Targeting Somatostatin Receptor 2

- Tracers for diagnostics: $^{68}$Ga-DOTATATE or $^{68}$Ga-DOTATOC

- Tracers for radioimmunotherapy: coupling with the radionuclids $^{177}$Lu or $^{90}$Y

- Therapeutic use of $^{177}$Lu-DOTATATE or $^{90}$Y-DOTATOC
Radionuclid therapy for progressive meningiomas

- Use of $^{177}$Lu-DOTATATE or $^{90}$Y-DOTATOC therapy, n=20 (°I=5, °II=7, °III=8)
- Stable disease for a median of 17 months in n=10 pats., tumor reduction in n=4
- Higher PFS linked to high SSR2 expression

Seystahl et al., Neuro Oncol, 2016