**EANO Guidelines for the Diagnosis and Treatment of Meningiomas**

Roland Goldbrunner1, Giuseppe Minniti2, Matthias Preusser3, Michael D. Jenkinson4, Kita Sallabanda5, Emmanuel Houdart6, Andreas von Deimling7, Pantelis Stavrinou1, Florence Lefranc8, Morten Lund-Johansen9, Elizabeth Cohen-Jonathan Moyal10, Dieta Brandsma11, Roger Henriksson12, Riccardo Soffietti13, Michael Weller14

**Affiliations:**

1 Center of Neurosurgery, Department of General Neurosurgery, University of Cologne, Cologne, Germany

2 Radiation Oncology Unit, Sant’Andrea Hospital, University of Rome Sapienza, Roma, and IRCCS Neuromed, Pozzilli, Italy

3 Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Austria

4 Department of Neurosurgery, University of Liverpool and The Walton Centre, Liverpool, UK

5 Department of Neurosurgery, University Hospital San Carlos, Universidad Cumplutense and IMOncology Madrid Arturo Soria, Area de Oncologia Radioterapica Robotizada – Cyberknife, Madrid, Spain

6 Service de Neuroradiologie, Hôpital Lariboisière, Paris, France

7 Department of Neuropathology, Institute of Pathology, University of Heidelberg, and, CCU Neuropathology German Cancer Center (DKFZ), Heidelberg, Germany

8 Department of Neurosurgery, Hôpital Erasme, Université Libre de Bruxelles, Belgium

9 Department of Neurosurgery, Bergen University Hospital and Department of Clinical Medicine, Faculty of Medicine and Dentistry, University of Bergen, Norway

10 Department of Radiation Oncology, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France

11 Department of Neur-Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands

12 Regional Cancer Centre Stockholm, and Department of Radiation Science & Oncology, University of Umea, Sweden.

13 Department of Neuro-Oncology, University and City of Health and Science Hospital, Turin, Italy

14 Department of Neurology, University Hospital & University of Zurich, Frauenklinikstrasse 26, CH-0891 Zurich, Switzerland

Corresponding Author:

Prof. Dr. Roland Goldbrunner

Department for General Neurosurgery

Center of Neurosurgery

Unversity of Cologne

Kerpener Str. 72

50937 Cologne

phone: +49 221 478 82790

email: roland.goldbrunner@uk-koeln.de

**Summary**

This guideline provides background information and practical recommendations for the diagnosis and treatment of intracranial and spinal meningiomas. Although meningiomas represent the most common intracranial tumors, the level of evidence for recommendations that can be derived from the literature is low compared to other intracranial tumors. The meningioma task force of the European Association for Neuro-Oncology (EANO) assessed the literature available and composed a framework of best possible evidence-based recommendations for health professionals. The provisional diagnosis of meningioma is made by magnetic resonance imaging, in special cases supplemented by computed tomography. Definitive diagnosis including histological classification, grading, and molecular profiling requires a surgical procedure to obtain tumor tissue. In many elderly patients, observation is the best therapeutic option. If therapy of these usually benign tumors is deemed necessary, standard treatment is gross total surgical resection including the involved dura. As an alternative, radiosurgery can be performed for small tumors or fractionated radiotherapy in large or previously treated tumors. Treatment concepts combining surgery and radiosurgery or fractionated radiotherapy are evolving allowing treatment of the complete tumor volume with low morbidity. Pharmacotherapy for meningiomas has remained largely experimental. However, anti-angiogenic drugs, peptide receptor radionuclide therapy and increasingly targeted agents are promising candidates for future pharmacological approaches to refractory meningiomas across all WHO grades.

**Introduction**

Meningiomas are the most common primary intracranial tumors. Most meningiomas are WHO grade I lesions whereas a minority are classified as WHO grade II or even grade III lesions, based on local invasiveness and cellular features of atypia1. The vast majority of patients can be cured by surgery alone, notably patients with WHO grade I tumors at favorable locations. Beyond surgery, various approaches of radiotherapy are commonly used to increase local control, particularly if surgery alone seems not to be sufficient. In contrast, pharmacotherapy has so far assumed only a minor role in the management of meningiomas. Although management may appear to be fairly standardized across the globe, there are very few controlled clinical trials, resulting in a situation where standards of care are defined by local experience, long-standing traditional procedures, and experience-based practice. However, there are numerous situations where more than one approach appears feasible. For example, is there a need for intervention in case of incidental meningiomas of unclear growth kinetics? Furthermore, do all meningioma-suspect lesions require histological verification of the diagnosis? When is the right time and what is the right fractionation approach when radiotherapy is considered? How will medical therapy develop in the future and what is the role of molecular profiling? Defining standards of care and outlining answers to some of these difficult questions is the purpose of the present guideline prepared by a task force of EANO. The literature available was evaluated and the scientific evidence was sorted into classes I-IV and recommendations were rated at level A-C, according to EFNS guidelines2. When sufficient evidence for recommendations was not available, the task force offered advice as "good practice point".

**General recommendations**

Recommendations for the diagnostic and therapeutic management of meningioma patients in general, including epidemiology and clinical presentation, pathogenesis and risk factors, diagnostic procedures, therapeutic decision making, surgical and radiotherapeutic approaches as well as pharmacotherapy are summarized in the appendix. WHO grading is displayed in table 1.

**Specific recommendations**

Recommendations for diagnostic and therapeutic management of meningiomas of WHO grades I-III are outlined in figure 1.

**Meningioma WHO grade I**

Meningiomas can be diagnosed by magnetic resonance imaging (MRI) and additional computed tomography (CT) in most cases with high probability3. They usually present as solitary round tumors, with intense contact to the dura mater and strong enhancement after contrast injection. The typical appearance of meningioma is isointense on T1 weighted imaging, iso- or hyperintense on FLAIR and with high and homogenous enhancement following gadolinium injection. On T2 weighted imaging, the meningeal arteries can sometimes be seen as lines of low signal radiating from the center of the tumor (typical “sunburst” appearance). Thickening of the dura mater at the perimeter of the tumor (so-called dural tail) is displayed by T1 with gadolinium4. CT is valuable for the detection of calcification within the tumor, hyperostosis of adjacent bone and intraosseous tumor growth, particularly in skull base meningiomas. Conventional cerebral angiography is no longer used for the diagnosis of meningioma and is restricted to selected cases. Delineation of complex skull base meningiomas may be challenging. The expression of somatostatin receptor 2 of meningiomas can be used for discrimination from healthy tissue by using peptide ligands such as (68)Ga-Dotatate or (90)Y-Dotatoc as PET tracers5,6. Therefore, an improvement of diagnostic management of complex meningiomas can expected in the near future.

Beyond NF-2, several genes have been detected as frequently mutated in these tumors - for example KLF4 and TRAF7 are always mutated in secretory meningioma7. It is of interest that mutations in these genes are not randomly distributed in meningiomas but form groups with typical combinations of mutations and exclusion of other mutations. It is expected that a molecularly based classification will be developed and that this classification has the potential to direct individualized meningioma-specific therapy (table 2 & 4). More relevant, preliminary findings point to TERT mutations, irrespective of WHO grade, being an indicator for more aggressive growth in meningioma8,9. Molecular alterations associated with less favorable clinical courses are expected to develop as valuable adjuncts to tumor grading for identifying patients at higher risk for meningioma recurrence or progression. Additional work to correlate molecular signatures with tumor recurrence is needed to more reliably select and predict which patients will benefit from adjuvant therapy.

Most asymptomatic, incidentally discovered meningiomas can be managed by observation using annual clinical and MRI intervals, after an initial observation interval of 6 months10. There is no class I or II evidence to support guidelines for observational management of meningiomas, but there are numerous retrospective series and several reviews validating this concept11 (evidence level III, recommendation level C). If imaging is highly suggestive of meningioma, histological verification is not mandatory, but recommended to exclude rare differential diagnoses like metastasis (recommendation level: good practice point). The diagnostic and therapeutic role of molecular profiling, which makes the availability of tumor tissue necessary, still needs to be established. If therapy is needed because of radiologically confirmed growth or presence of clinical symptoms, surgery is the therapy of first choice (evidence level II, recommendation level B). The aim of microsurgery is complete tumor removal (gross total resection, GTR) including involved dura corresponding to Simpson grade I resection. Extent of resection (EOR) is defined by the Simpson Grade (table 3) and is an important prognostic factor for risk of tumor recurrence12. The Simpson classification pre-dates modern neuro-imaging and relies on the surgeon’s assessment at surgery. Today, the EOR should be confirmed by postoperative MRI that can be performed within 48 h after surgery or after 3 months to avoid artifacts. Preoperative embolisation is not generally recommended, however, it may facilitate surgery in selected cases (evidence level IV, recommendation level C). As an alternative to surgery in elderly patients, for tumors not safely accessible by surgery, or after incomplete surgical resection, stereotactic radiosurgery (SRS) or fractionated radiotherapy (RT) with 50-55 Gy given in 1·8-2.0 Gy per fraction can be offered evidence level (III, recommendation level B). After RT, control rates of 75 to 92 percent are described in various series13-17. When RT is added to subtotal resection (STR), control rates and survival similar to GTR are reported18,19. In order to spare tumor-surrounding sensitive neurovascular structures, intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT) are increasingly used offering similar control rates with conventional RT20,21. In selected cases of small meningiomas, SRS allows a single application of 14-16 Gy22-29. The use of planned combination therapies consisting of STR or partial resection followed by SRS or RT allows treating the complete tumor whereas reducing the risk of treatment26 (evidence level IV, recommendation level C). After therapy, annual MRI controls for 5 years are sufficient, followed by bi-annual controls. There are no data supporting the use of pharmacotherapy in meningiomas WHO grade I 30-33. Peptide receptor radionuclide therapy (PRRT) has shown some effect in small series and will be evaluated in clinical studies34-38.

**Meningioma WHO grade II**

There are no clear radiological criteria to distinguish grade I and grade II meningiomas. Exposure to ionizing radiation has been firmly linked to a higher risk for meningiomas and radiation-associated meningiomas are more likely to be atypical or malignant and multifocal39-43. The presence of type 2 neurofibromatosis (NF2) implies a risk of developing malignant or multiple meningiomas44. There are increasing data for a molecular genetic characterization of atypic and malignant meningiomas, e.g. PIK3CA mutations are associated with higher meningioma grades8,9.

Surgery is the first choice of treatment and should aim at a Simpson I resection (evidence level III, recommendation level B). The diagnosis of WHO grade II meningioma implies an increased risk of recurrence requiring shorter control intervals (6 months instead of annual, see below)45. The question, if adjuvant therapy is mandatory, is still open. Retrospective series on adjuvant RT after GTR led to differing results and prospective data on adjuvant RT after GTR are missing46-52. The ROAM / EORTC 1308 trial is currently recruiting patients with newly diagnosed atypical meningioma (WHO grade II) who have undergone gross total resection (Simpson I-III) and will randomize between early adjuvant radiotherapy (60 Gy in 30 fractions) and observation to determine whether radiotherapy reduces the risk of tumor recurrence53. For incompletely resected tumors, adjuvant RT (54 to 60 Gy given in 1·8-2·0 Gy per fraction) should be considered (evidence level III, recommendation level C). In cases of progression, RT should be performed if not done following the initial surgery, with or without second surgery (evidence level III, recommendation level C). If the diagnosis of a WHO grade II or III is made, fractionated RT is preferred to stereotactic radiosurgery techniques54. There are no data about PRRT in meningioma WHO grade II. Retrospective studies and small prospective studies have evaluated a range of drugs including hydroxyurea, cycophosphamide/adriamycin/vincristine chemotherapy, interferon-alpha, megestrol acetate, medroxy-progesterone acetate, octreotide, sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib and bevacizumab in WHO grade II and III meningiomas31. PFS-6 rates ranged from 0% to 64% and median OS times from 6 to 33 months in patients progressing after surgical resection and radiotherapy. The most promising results have been reported for bevacizumab, vatalanib and sunitinib, all drugs with anti-angiogenic properties31,55-59. These results need to be confirmed in prospective controlled trials, before clinical use of these compounds in WHO grade II and III meningiomas can be recommended. An ongoing EORTC phase II trial (NCT02234050) explores the efficacy of trabectedin, a tetrahydroisoquinoline that has shown promising activity in recurrent grade II and grade III meningiomas60. Altogether, pharmacotherapy can be considered upon further progression in meningiomas WHO grade II (evidence level IV, recommendation level C).

**Meningioma WHO grade III**

Anaplastic meningiomas often are more irregularly shaped and display a higher relative cerebral blood volume compared to WHO grade I and II tumors3. Meningiomas WHO grade III have a strong tendency to recur and may metastasize systemically. There is a high proportion of NF2 mutations in WHO grade III meningiomas (table 2), diffuse growth and invasion of the cortex is often described61. Surgical resection should be as radical as possible (evidence level III, recommendation level C) and needs to be followed by fractionated RT with at least 54 Gy in 1.8-2 Gy fractions (evidence level III, recommendation level B). Current clinical trials address the question of dose: In the RTOG 0539 trial, WHO grade II meningiomas are treated by RT with 54 Gy in 30 fractions after GTR, while “high risk meningioma” (i.e. WHO grade II recurrent disease, WHO grade II after STR resection and all WHO grade III) receive up to 60 Gy. In the EORTC 22042-26042 trial, WHO grade II and grade III tumors post GTR are irradiated with 60 Gy in 30 fractions. After STR, 60 Gy plus a 10 Gy boost on the remaining tumor volume are delivered. Follow-up should be performed three months after initial therapy, then every 3 or 6 months, depending on initial growth kinetics. Pharmacotherapy options remain experimental (evidence level IV, recommendation level C) and only little data on the efficacy of antineoplastic drugs in WHO grade III meningiomas are available. No clinical trials have focussed on WHO grade III tumors, but small numbers of these neoplasms have been included in most studies together with WHO grade II tumors (see above). Consequently, no specific recommendations can be made for pharmacotherapy of grade III meningiomas and patients with this diagnosis should be enrolled into clinical trials whenever possible.

**Spinal meningiomas**

Surgical resection to remove the tumor and decompress the spinal cord is the therapy of choice in spinal meningiomas. The majority of data supports surgical strategies striving for completeness of excision. Recurrence rates of spinal meningiomas after surgical resection have been reported in the range of 1·3 – 14·7%62-65. There is consensus that incomplete resection is a risk factor for recurrence but it is unclear whether Simpson grade I resection achieves better long term outcome than Simpson grade II resection62,65-67. Most papers report lower recurrence rates after resection of the involved dura but at the cost of a higher complication rate, particularly for meningiomas located unfavorably or with severe calcification64. Therefore, Simpson grade I resection should be aimed for in all cases of spinal meningioma with a favorable location, but only if this can be achieved without compromising neurological function and if a safe and uncomplicated dural repair is feasible (recommendation level: good practice point). For patients with ventrally located meningiomas or with calcified dural attachment, excision of the dura should not be the goal – coagulation of the dural attachment is sufficient. For the rare cases where (i) surgical resection cannot be performed for any reason, (ii) stopping tumor growth is the only aim of treatment and (iii) decompression of the spinal cord does not seem necessary, SRS or hypofractionated RT is an alternative to surgical resection68 (recommendation level: good practice point). Adjuvant therapy is performed according to the WHO grade and resection status as stated above for cranial meningiomas.

**Surveillance and follow up**

There is no robust data on the best follow-up schedule for meningiomas, since most retrospective studies do not report on monitoring intervals and since prospective studies published so far had variable follow-up protocols, usually tailored to fit the treatment visits69,70. Therefore, the following recommendations are based more on expert consensus opinion rather than evidence (recommendation level: good practice point).

Our proposed approach on the management of small, asymptomatic meningiomas is to evaluate the dynamics of the tumor with MRI with contrast medium 6 months after initial diagnosis and then annually, as long as the patient remains asymptomatic. After five years this interval can be doubled. In patients with limited life expectancy due to high age or severe co-morbidities, controls may be omitted if the radiological diagnosis of a benign meningioma seems clear.

Monitoring after initial treatment depends on the degree of resection and grading of the tumor.

For WHO I meningiomas resected totally (GTR), the 10-year recurrence rates vary from 20-39%. Studies with long follow-up with MRI show that recurrence is more common than previously thought13,18,71. Therefore, it is advisable to perform a baseline MRI within 48 hours or after 3 months, in order to assess the radicality of resection. Thereafter, we propose annual MRI controls until five years post treatment, then every two years.

If resection is known to be incomplete, EOR should be documented by early postoperative MRI within 48 hours. For WHO grade I tumors after STR, the 10-year progression rates vary between 55 and 100%, suggesting a more vigilant long-term follow-up71,72. For those cases, MRI at 6 and 12 months is recommended, then annually.

The natural history of WHO grade II meningiomas is less clear, since the 2007 WHO criteria changed their definition and thus their identification rates. The 5-year recurrence rates may be as high as 30% and 40% after GTR and STR, respectively47,50. In these tumors, we suggest an early postoperative MRI within 48 hours. Follow up MRI should be done every 6 months for 5 years, then annually.

WHO grade III meningiomas are aggressive tumors with very poor local control, even after multimodal treatment. In the recent studies utilizing the WHO 2007 grading scheme, the 5-year-PFS ranged from 12 to 57%, even after resection and radiotherapy. Therefore, these tumors have to be followed up very closely73. After the initial, early post-treatment MRI, cranial imaging should be routinely done every 6 months, in rapidly growing cases every 3 months.

Table 1: WHO grading for meningiomas

|  |  |
| --- | --- |
| WHO Grade | Description |
| Grade I | Low mitotic rate (less than 4 per 10 high power fields (HPF)  Absence of brain invasion  9 subtypes |
| Grade II (atypical) | Mitotic rate: 4-19 per HPF, *or* brain invasion  *or* specific histologies:  clear cell or chordoid cell types |
| Grade III (anaplastic) | Mitotic rate: >20 per HPF  *or* specific histologies:  Papillary or rhabdoid meningioma |

Table 2: Mutations in meningiomas 27,28,30

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

Percentages, values <4% are given as "-"

Table 3: Simpson grades of resection and corresponding EORTC/RTOG definitions of extend of resection

|  |  |  |
| --- | --- | --- |
| Grade | Definition | Extent of Resection (EOR) |
| I | Gross total resection of tumor, dural attachment and abnormal bone | GTR |
| II | Gross total resection of tumor, coagulation of dural attachment | GTR |
| III | Gross total resection of tumor without resection or coagulation of dural attchments, or extradural extensions (e.g. invaded or hyperostotic bone) | GTR |
| IV | Partial resection of tumor | STR |
| V | Biopsy of tumor |  |

Table 4: Possible targets for future therapies

|  |  |
| --- | --- |
| **Potential drug / drug class** | **Molecular target / biomarker** |
| AKT inhibitor | AKT1 (p.Glu17Lys) mutation 27,28 |
| Hedgehog inhibitor | SMO (p.Trp535Leu) mutation 27,28 |
| FAK inhibitor | NF2/merlin loss 115,116 |
| Immune checkpoint inhibitor | PD1-/PD-L1 117 |
| VEGF or VEGFR inhibitor | VEGF/VEGFR2 105,118,119 |
| Trabectedin | DNA, tumor-associated macrophages, angiogenesis 109 |

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta neuropathologica* 2007; **114**(2): 97-109.

2. Brainin M, Barnes M, Baron JC, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces--revised recommendations 2004. *European journal of neurology* 2004; **11**(9): 577-81.

3. Zhang H, Rodiger LA, Shen T, Miao J, Oudkerk M. Preoperative subtyping of meningiomas by perfusion MR imaging. *Neuroradiology* 2008; **50**(10): 835-40.

4. Takeguchi T, Miki H, Shimizu T, et al. The dural tail of intracranial meningiomas on fluid-attenuated inversion-recovery images. *Neuroradiology* 2004; **46**(2): 130-5.

5. Collamati F, Pepe A, Bellini F, et al. Toward radioguided surgery with beta- decays: uptake of a somatostatin analogue, DOTATOC, in meningioma and high-grade glioma. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2015; **56**(1): 3-8.

6. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2015; **56**(3): 347-53.

7. Reuss DE, Piro RM, Jones DT, et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. *Acta neuropathologica* 2013; **125**(3): 351-8.

8. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. *Brain pathology (Zurich, Switzerland)* 2014; **24**(2): 184-9.

9. Sahm F, Schrimpf D, Olar A, et al. TERT Promoter Mutations and Risk of Recurrence in Meningioma. *Journal of the National Cancer Institute* 2016; **108**(5).

10. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *The New England journal of medicine* 2007; **357**(18): 1821-8.

11. Sughrue ME, Rutkowski MJ, Aranda D, Barani IJ, McDermott MW, Parsa AT. Treatment decision making based on the published natural history and growth rate of small meningiomas. *Journal of neurosurgery* 2010; **113**(5): 1036-42.

12. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *Journal of neurology, neurosurgery, and psychiatry* 1957; **20**(1): 22-39.

13. Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB, Jr., Rhoton AL. Benign meningiomas: primary treatment selection affects survival. *International journal of radiation oncology, biology, physics* 1997; **39**(2): 427-36.

14. Dufour H, Muracciole X, Metellus P, Regis J, Chinot O, Grisoli F. Long-term tumor control and functional outcome in patients with cavernous sinus meningiomas treated by radiotherapy with or without previous surgery: is there an alternative to aggressive tumor removal? *Neurosurgery* 2001; **48**(2): 285-94; discussion 94-6.

15. Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *Journal of neurosurgery* 1994; **80**(2): 195-201.

16. Mendenhall WM, Morris CG, Amdur RJ, Foote KD, Friedman WA. Radiotherapy alone or after subtotal resection for benign skull base meningiomas. *Cancer* 2003; **98**(7): 1473-82.

17. Nutting C, Brada M, Brazil L, et al. Radiotherapy in the treatment of benign meningioma of the skull base. *Journal of neurosurgery* 1999; **90**(5): 823-7.

18. Soyuer S, Chang EL, Selek U, Shi W, Maor MH, DeMonte F. Radiotherapy after surgery for benign cerebral meningioma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2004; **71**(1): 85-90.

19. Taylor BW, Jr., Marcus RB, Jr., Friedman WA, Ballinger WE, Jr., Million RR. The meningioma controversy: postoperative radiation therapy. *International journal of radiation oncology, biology, physics* 1988; **15**(2): 299-304.

20. Combs SE, Adeberg S, Dittmar JO, et al. Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2013; **106**(2): 186-91.

21. Solda F, Wharram B, De Ieso PB, Bonner J, Ashley S, Brada M. Long-term efficacy of fractionated radiotherapy for benign meningiomas. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2013; **109**(2): 330-4.

22. Colombo F, Casentini L, Cavedon C, Scalchi P, Cora S, Francescon P. Cyberknife radiosurgery for benign meningiomas: short-term results in 199 patients. *Neurosurgery* 2009; **64**(2 Suppl): A7-13.

23. Tuniz F, Soltys SG, Choi CY, et al. Multisession cyberknife stereotactic radiosurgery of large, benign cranial base tumors: preliminary study. *Neurosurgery* 2009; **65**(5): 898-907; discussion

24. Sallabanda K, Dos Santos MA, Salcedo JB, et al. Stereotactic radiosurgery as a salvage treatment option for atypical meningiomas previously submitted to surgical resection. *J Radiosurg BRT* 2011; **0**: 1-7.

25. Samblas J, Luis Lopez Guerra J, Bustos J, et al. Stereotactic radiosurgery in patients with multiple intracranial meningiomas. *Journal of BUON : official journal of the Balkan Union of Oncology* 2014; **19**(1): 250-5.

26. Jung HW, Yoo H, Paek SH, Choi KS. Long-term outcome and growth rate of subtotally resected petroclival meningiomas: experience with 38 cases. *Neurosurgery* 2000; **46**(3): 567-74; discussion 74-5.

27. Song CW, Kim MS, Cho LC, Dusenbery K, Sperduto PW. Radiobiological basis of SBRT and SRS. *International journal of clinical oncology* 2014; **19**(4): 570-8.

28. dos Santos MA, de Salcedo JB, Gutierrez Diaz JA, et al. Long-term outcomes of stereotactic radiosurgery for treatment of cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics* 2011; **81**(5): 1436-41.

29. Goldsmith B, McDermott MW. Meningioma. *Neurosurgery clinics of North America* 2006; **17**(2): 111-20, vi.

30. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology* 2015; **84**(3): 280-6.

31. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro-oncology* 2014; **16**(6): 829-40.

32. Ji Y, Rankin C, Grunberg S, et al. Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(34): 4093-8.

33. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology* 2004; **62**(7): 1210-2.

34. Bartolomei M, Bodei L, De Cicco C, et al. Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. *European journal of nuclear medicine and molecular imaging* 2009; **36**(9): 1407-16.

35. Kreissl MC, Hanscheid H, Lohr M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. *Radiation oncology (London, England)* 2012; **7**: 99.

36. Makis W, McCann K, McEwan AJ. Rhabdoid papillary meningioma treated with 177Lu DOTATATE PRRT. *Clinical nuclear medicine* 2015; **40**(3): 237-40.

37. Minutoli F, Amato E, Sindoni A, et al. Peptide receptor radionuclide therapy in patients with inoperable meningiomas: our experience and review of the literature. *Cancer biotherapy & radiopharmaceuticals* 2014; **29**(5): 193-9.

38. Seystahl K SV, Guillaume N, Schüller U, Rushing E, Schäfer N, Ilhan H, Weller M, Tonn JC, Sommerauer M, Jansen N. . Somatostatin receptor-targeted radionuclide therapy for progressive meningioma. *SNO 2015* 2015.

39. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. *Journal of neurosurgery* 2004; **100**(6): 1002-13.

40. Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer research* 1989; **49**(21): 6137-43.

41. Rubinstein AB, Shalit MN, Cohen ML, Zandbank U, Reichenthal E. Radiation-induced cerebral meningioma: a recognizable entity. *Journal of neurosurgery* 1984; **61**(5): 966-71.

42. Sadamori N, Shibata S, Mine M, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. *International journal of cancer Journal international du cancer* 1996; **67**(3): 318-22.

43. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiation research* 2005; **163**(4): 424-32.

44. Saraf S, McCarthy BJ, Villano JL. Update on meningiomas. *The oncologist* 2011; **16**(11): 1604-13.

45. Marosi C, Hassler M, Roessler K, et al. Meningioma. *Critical reviews in oncology/hematology* 2008; **67**(2): 153-71.

46. Park HJ, Kang HC, Kim IH, et al. The role of adjuvant radiotherapy in atypical meningioma. *Journal of neuro-oncology* 2013; **115**(2): 241-7.

47. Aghi MK, Carter BS, Cosgrove GR, et al. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. *Neurosurgery* 2009; **64**(1): 56-60; discussion

48. Komotar RJ, Iorgulescu JB, Raper DM, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. *Journal of neurosurgery* 2012; **117**(4): 679-86.

49. Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. *Journal of neurosurgery* 2011; **115**(4): 811-9.

50. Hammouche S, Clark S, Wong AH, Eldridge P, Farah JO. Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. *Acta neurochirurgica* 2014; **156**(8): 1475-81.

51. Stessin AM, Schwartz A, Judanin G, et al. Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)-based analysis. *Journal of neurosurgery* 2012; **117**(4): 669-75.

52. Yoon H, Mehta MP, Perumal K, et al. Atypical meningioma: randomized trials are required to resolve contradictory retrospective results regarding the role of adjuvant radiotherapy. *Journal of cancer research and therapeutics* 2015; **11**(1): 59-66.

53. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. *Trials* 2015; **16**: 519.

54. Mantle RE, Lach B, Delgado MR, Baeesa S, Belanger G. Predicting the probability of meningioma recurrence based on the quantity of peritumoral brain edema on computerized tomography scanning. *Journal of neurosurgery* 1999; **91**(3): 375-83.

55. Furtner J, Schopf V, Seystahl K, et al. Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma. *Neuro-oncology* 2015.

56. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro-oncology* 2015; **17**(1): 116-21.

57. Lou E, Sumrall AL, Turner S, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. *Journal of neuro-oncology* 2012; **109**(1): 63-70.

58. Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *Journal of neuro-oncology* 2012; **109**(1): 187-93.

59. Puchner MJ, Hans VH, Harati A, Lohmann F, Glas M, Herrlinger U. Bevacizumab-induced regression of anaplastic meningioma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**(12): 2445-6.

60. Preusser M, Spiegl-Kreinecker S, Lotsch D, et al. Trabectedin has promising antineoplastic activity in high-grade meningioma. *Cancer* 2012; **118**(20): 5038-49.

61. Lin BJ, Chou KN, Kao HW, et al. Correlation between magnetic resonance imaging grading and pathological grading in meningioma. *Journal of neurosurgery* 2014; **121**(5): 1201-8.

62. Gezen F, Kahraman S, Canakci Z, Beduk A. Review of 36 cases of spinal cord meningioma. *Spine* 2000; **25**(6): 727-31.

63. Gottfried ON, Gluf W, Quinones-Hinojosa A, Kan P, Schmidt MH. Spinal meningiomas: surgical management and outcome. *Neurosurgical focus* 2003; **14**(6): e2.

64. Kim CH, Chung CK, Lee SH, et al. Long-term recurrence rates after the removal of spinal meningiomas in relation to Simpson grades. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2015.

65. Klekamp J, Samii M. Surgical results for spinal meningiomas. *Surgical neurology* 1999; **52**(6): 552-62.

66. Nakamura M, Tsuji O, Fujiyoshi K, et al. Long-term surgical outcomes of spinal meningiomas. *Spine* 2012; **37**(10): E617-23.

67. Tsuda K, Akutsu H, Yamamoto T, Nakai K, Ishikawa E, Matsumura A. Is Simpson grade I removal necessary in all cases of spinal meningioma? Assessment of postoperative recurrence during long-term follow-up. *Neurologia medico-chirurgica* 2014; **54**(11): 907-13.

68. Kufeld M, Wowra B, Muacevic A, Zausinger S, Tonn JC. Radiosurgery of spinal meningiomas and schwannomas. *Technology in cancer research & treatment* 2012; **11**(1): 27-34.

69. Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *Journal of neuro-oncology* 2010; **96**(2): 211-7.

70. Raizer JJ, Grimm SA, Rademaker A, et al. A phase II trial of PTK787/ZK 222584 in recurrent or progressive radiation and surgery refractory meningiomas. *Journal of neuro-oncology* 2014; **117**(1): 93-101.

71. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL. Meningioma: analysis of recurrence and progression following neurosurgical resection. *Journal of neurosurgery* 1985; **62**(1): 18-24.

72. Barbaro NM, Gutin PH, Wilson CB, Sheline GE, Boldrey EB, Wara WM. Radiation therapy in the treatment of partially resected meningiomas. *Neurosurgery* 1987; **20**(4): 525-8.

73. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *Journal of neurosurgery* 2010; **113**(2): 202-9.

**Appendix:**

**Epidemiology and clinical presentation**

Meningiomas have the highest incidence rate among all intracranial and intraspinal tumors. In European countries the annual incidence rate of meningiomas is 4·2 per 100·000 individuals 1,2. The median age at diagnosis is 65 years and incidence increases with age 3. The majority of intracranial meningiomas are found in the supratentorial compartment, most commonly at the cerebral convexity, along the dural venous sinuses, along the falx or intraventricularly. Skull base meningiomas grow at the sphenoid wing, olfactory groove, clinoid process or petroclival regions. Additional sites include the cerebellopontine angle, the foramen magnum or – less commonly – the optic nerve sheath. Moreover, meningiomas represent 25-45% of intradural spinal tumors 4. Eighty percent of spinal meningiomas are located in the thoracic spine 5. Many meningiomas are asymptomatic and diagnosed incidentally. There is no clear critical size for the development of symptoms, however, meningiomas that do not exceed 2.5 cm in diameter rarely cause symptoms within 5 years of being discovered 6. The most common symptoms are epilepsy, or headache for weeks to months, or location-specific symptoms or signs such as unilateral weakness, visual field loss, changes in personality or speech problems. Meningioma patients have diminished neurocognitive function as compared with healthy controls except for intelligence and visuoconstructive skills 7-11. Neurocognitive functions in patients with meningiomas in the dominant hemisphere (usually left-side) are more compromised than in patients with meningiomas in the non-dominant hemisphere (usually right-side). Furthermore, neuro-cognition in patients with skull base meningiomas is worse than in patients with convexity meningiomas9. Meningioma patients do not differ from healthy controls with respect to anxiety or depression 12. In spinal meningiomas, pain, paraparesis and spinal ataxia are the typical presenting signs and symptoms reflecting spinal cord compression 5.

.

**Pathogenesis and risk factors**

Meningiomas are assumed to derive from arachnoid cap cells. The arachnoid mater is the middle part of the meninges whose origin is best described as mesenchymal. Meningiomas exhibit epithelial features such as multiple intercellular gap junctions and expression of the epithelial membrane antigen. They usually occur where meninges are present. However, intraventricular meningioma is an important differential diagnosis for tumors of the lateral ventricles. These tumors are believed to arise from arachnoid cells entrapped in the choroid plexus during organogenesis. Although rare, distant metastases of meningioma to the lung and other sites have been described, not only with anaplastic (WHO grade III) meningiomas. Multiplicity of meningioma is observed and clonality has been demonstrated in approximately half of the patients with two spatially separated meningioma manifestations, and in all patients with three or more meningioma manifestations 13.

Exposure to ionizing radiation has been firmly linked to a higher risk for meningiomas and radiation-associated meningiomas are more likely to be atypical or malignant and multifocal 14-18. Type 2 neurofibromatosis (NF2) is the most common genetic condition associated with an elevated risk for developing meningiomas. Patients with NF2 also may be more likely to develop malignant or multiple meningiomas. Based on the observations of (i) higher incidences in women of reproductive age, (ii) tumor expression of hormone receptors, (iii) an association with breast cancer and (iv) changes in meningioma size during pregnancy, the menstrual cycle and menopause, a number of studies have sought to link endogenous and exogenous hormone exposure to meningioma growth, without significant correlations 3,19.

**Diagnostic procedures**

**Imaging**

Cerebral magnetic resonance imaging (MRI) and computed tomography (CT) scans, when used in combination, allow the diagnosis of intracranial meningioma with high probability in most cases20. MRI should comprise the sequences T1, T2 spin echo, T2 gradient echo, fluid-attenuated inversion recovery (FLAIR), 3D time-of-flight (TOF) and T1 with gadolinium (figure 2). When the meningioma is located close to a major dural sinus vein, venous MRI angiography should be included to verify its patency. CT may be valuable in conjunction with MRI and should comprise bone window settings. Typically, meningiomas present as solitary round tumors, with intense contact to the dura mater and strong enhancement after contrast injection. The typical signal of meningioma is isointense on T1, iso- or hyperintense on FLAIR and with high and homogenous enhancement following gadolinium injection. On T2, the meningeal arteries can sometimes be seen as lines of low signal radiating from the center of the tumor (typical “sunburst” appearance). Thickening of the dura mater at the perimeter of the tumor (so-called dural tail) is displayed by T1 with gadolinium 21. Extra-axial growth can be verified on T2 MRI by CSF interposed between the tumor and the parenchyma 22. FLAIR and T2 sequences depict edema of the surrounding cerebral parenchyma. CT is valuable for the detection of calcification of varying degrees within the tumor, hyperostosis of adjacent bone and intraosseous tumor growth. Conventional cerebral angiography is no longer used for the diagnosis of meningioma and is restricted to selected cases. If cerebral angiography is performed, it shows a typical tumoral blush in most cases fed by the middle meningeal artery within the aspect of sunburst. Differential diagnoses of meningioma include vestibular schwannoma, if located in the cerebellopontine angle, meningeal metastasis, and hemangiopericytoma, if hypervascularity is seen. Meningiomas may express somatostatin receptor 2 and can be delineated from healthy tissue by using peptide ligands such as (68)Ga-Dotatate or (90)Y-Dotatoc as PET tracers 23,24.

**Histopathology**

The current WHO classification system recognizes 15 different meningioma entities, 9 of which are allotted WHO grade I, 3 WHO grade II and 3 WHO grade III (Table 1). Some of these subtypes are associated with distinct clinical features: For example, secretory meningioma is frequently accompanied by pronounced peritumoral edema, or psammomatous meningioma is predominantly seen in the spinal meninges. Over all, the distinction between the 9 WHO grade I meningioma variants is of limited clinical relevance. On the other hand, grading of meningioma is of major clinical importance, because patients with WHO grade II and grade III meningiomas are considered candidates for postsurgical radiotherapy as discussed below. Grading of meningioma depends on mitotic rate, presence of brain invasion or presence of some specific histological features. The currently applied parameters for defining the borders between the grades are not entirely satisfactory. While patient cohorts with WHO grade II meningioma generally exhibit shorter intervals to tumor recurrence, there is a considerable number of individual patients with meningioma WHO grade I with unexpected early tumor relapse. Conversely, some patients with WHO grade II meningioma, especially when a complete resection can be achieved, experience a very prolonged indolent clinical course even without adjuvant radiotherapy.

**Molecular pathology**

The current dynamics in the analysis of human tumors with massive parallel sequencing have provided novel insights into molecular mechanisms involved in the formation and progression of meningiomas. Several genes beyond NF2 have been detected as frequently mutated in these tumors - for example KLF4 and TRAF7 are always mutated in secretory meningioma 25. NF2 mutations predominate in meningiomas with some spindle cell morphology encompassing fibroblastic, transitional and psammomatous meningioma. AKT1 exhibits the E17K hotspot mutation in a fraction of meningiomas of basal localization and potentially these tumors have actionable targets using specific inhibitors 26. Another gene with recurrent mutations is SMO 27,28. It is of interest that mutations in these genes are not randomly distributed in meningiomas but form groups with typical combinations of mutations and exclusion of other mutations. It is expected that a molecularly based classification will be developed and that this classification has the potential to direct individualized meningioma-specific therapy (tables 2 & 4). More relevant, preliminary findings point to TERT mutations, irrespective of WHO grade, being an indicator for more aggressive growth in meningioma 29,30. Likewise, PIK3CA mutations are associated with higher meningioma grades. Molecular alterations associated with less favorable clinical courses are expected to develop as valuable adjuncts to tumor grading for identifying patients at higher risk for meningioma recurrence or progression. Additional work to correlate molecular signatures with tumor recurrence is needed to more reliably select and predict which patients will benefit from adjuvant therapy.

**Therapeutic strategies**

**Observation and decision making**

Meningiomas are a common finding on cranial MRI, and are often discovered incidentally 31. If a meningioma is diagnosed provisionally by neuroimaging, it must be ascertained if (1) the finding has a clinical correlate, (2) the symptoms, if any, may be relieved by treating the tumor, and if (3) the potential benefits from treatment outweigh the associated risks. If the answer is no to any of these three questions, observation may be the best strategy unless there is diagnostic doubt, necessitating early verification of the diagnosis. Observation is a preferred strategy in many cases of suspected meningioma, especially in small, incidentally discovered tumors. There is no class I or II evidence to support guidelines for observational management of meningiomas, but there are numerous retrospective series and several reviews validating this concept 6 (evidence level III). The most important determinant for symptom development is tumor size at diagnosis. A diameter of 2 cm or less is associated with a higher risk of growth, but very few of these tumors become symptomatic within a period of 5 years. Another important parameter for symptom development is a growth rate of more than 10% per year 6. A meta-analysis of 22 retrospective studies identified calcification and absence of peri-tumoural signal change, specifically edema, as factors associated with slower meningioma growth. Such tumors may be managed by active surveillance using MRI, and treatment should be offered only if they become symptomatic or show growth.

Patients should be counseled about the finding and given advice accordingly. If a patient refuses observation as a management strategy even after thorough information, treatment may be justified. If one decides to manage a suspected meningioma by observation alone, it has to be agreed who is responsible for patient follow-up. In an ideal setting, this is done by an experienced neurosurgeon or neurooncologist. The patient should receive written information about the need for follow-up, and the potential consequences of not adhering to the follow-up regimen. Annual MRI scans and clinical outpatient consultations are recommended for an initial period assigning the first scan as a reference.

It is uncertain for how long the follow-up of a meningioma should be continued if there is no sign of growth. If a tumor shows significant growth, and in particular if growth leads to new symptoms, treatment is usually indicated. In these cases, surgery is advocated if feasible 32. In addition or as alternatives, various schedules of radiotherapy, radiosurgery or combination therapies may be treatment options33. It is strongly recommended that these patients are discussed in a multidisciplinary panel of neurosurgeons, radiation oncologists and neuro-oncologists. The patient should be informed about the treatment alternatives and the pros and cons of the options should be presented in an unbiased way so as to allow the patient an informed decision about the choice of treatment.

**Surgery**

Surgery is the treatment of choice for the majority of symptomatic and enlarging meningiomas, serving the dual role of relieving symptoms and mass effect and providing tissue for distinguishing histological type and WHO grade of malignancy (evidence level II, recommendation level B). Surgical risks should be fully discussed with the patients prior to surgery including location-specific risks. There is no evidence that prophylactic antiepileptic drugs (AEDs) reduce the incidence of peri- or post-operative epilepsy. However, certain locations are more prone to seizures e.g. frontal, temporal, and parietal meningiomas have a higher risk than occipital tumors, and convexity and parasagittal/falx meningiomas have a higher risk than tumors of the skull base 34,35.

Careful pre-operative planning reduces the risk of post-operative deficits. Attention to venous anatomy is a key factor in successful surgery, particularly for meningiomas involving the venous sinuses. Whilst it is generally safe to divide the anterior third of the sagittal sinus, inadvertent damage to cortical veins and intra-diploic venous drainage can lead to post-operative venous infarction with devastating consequences. Image guidance is now routinely used to position the craniotomy and allows image fusion of multiple data sets that provide information about critical neurovascular structures. Meningiomas that involve the skull base may result in holes in the frontal, sphenoid and ethmoid air sinuses - these holes must be sealed off to prevent post-operative cerebrospinal fluid leaks. Care should also be taken when resecting meningiomas near to the optic apparatus so as not to disrupt blood supply which could result in visual loss. Intra-operative neurophysiological monitoring, e.g. facial nerve and brainstem-evoked potentials, may help to minimize neurological deficits.

The general principles of meningioma surgery are dividing the tumor from its blood supply and internal debulking followed by peripheral dissection. The aim is gross total resection including involved dura and bone, but this is determined by tumor location and size. Radical surgical procedures have gone out of vogue and surgeons will tend towards maximum safe resection, often electing to leave tumor remnant that can be monitored with MRI or treated with post-operative conformal or stereotactic fractionated radiotherapy or radiosurgery, depending on location, size and proximity to critical structures, e.g., cavernous sinus.

Extent of resection (EOR) is defined by the Simpson Grade (table 3) and is an important prognostic factor for risk of tumor recurrence 36. The Simpson classification pre-dates modern neuro-imaging and relies on the surgeon’s assessment at surgery. Today, the EOR should be confirmed by postoperative MRI that can be performed within 48 h after surgery or after 3 months to avoid artifacts. In case of incomplete resection or suspected grade II or III meningioma, early MRI within 48 hours should be performed to plan further therapy. In modern neurosurgery, the potential benefit of radical surgical resection must be balanced against the risks of complications and causing neurological deficit. In grade I meningioma, defining EOR as either gross total resection , i.e. no residual solid tumor, or subtotal resection (STR) is an equally good prognostic factor for tumor recurrence 37. Several clinical research consortia including the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) have adopted these definitions for use in prospective clinical trials 38.

Regarding spinal meningiomas, the majority of data supports surgical strategies striving for completeness of excision. Recurrence rates of spinal meningiomas after surgical resection have been reported in the range of 1·3 – 14·7% 39-42. There is consensus that incomplete resection is a risk factor for recurrence but it is unclear whether Simpson grade I resection achieves better long term outcome than Simpson grade II resection 39,42-44. Most papers report lower recurrence rates after resection of the involved dura but at the cost of a higher complication rate, particularly for meningiomas located unfavorably or with severe calcification 41. Therefore, Simpson grade I resection should be aimed for in all cases of spinal meningioma with a favorable location, but only if this can be achieved without compromising neurological function and if a safe and uncomplicated dural repair is feasible. For patients with ventrally located meningiomas or with calcified dural attachment, excision of the dura should not be the goal – coagulation of the dural attachment is sufficient.

**Radiotherapy**

External beam radiation therapy (RT) has been used extensively in patients with meningioma for the following indications: (i) in tumor locations not amenable to surgery, (ii) in tumors that are not completely resected, (iii) in atypical and malignant tumors and (iv) in recurrent tumors. No randomized or prospectively controlled studies have evaluated the survival and tumor control after conventional RT. Nevertheless, retrospective studies of patients with residual or recurrent WHO grade I meningiomas report a local control rate of 75-90% at 10 years 45-49. In a series of 82 patients with skull base meningiomas treated with conventional RT, Nutting et al. reported 5-year and 10-year local tumor control rates of 92% and 83%, respectively 48. In another series of 101 patients treated with 3-dimensional (3D) conformal RT, Mendenhall et al. reported a local control of 95% at 5 years and 92% at 10 and 15 years, respectively, and cause-specific survival rates of 97% and 92%, respectively 47. The reported control and survival after subtotal resection and RT are similar to those observed after complete resection, and better than that achieved with incomplete resection alone 50,51(evidence level III, recommendation level B)

Large skull base meningiomas may present a therapeutical challenge. Also in these tumors, RT has been suggested as an effective treatment. A 5-year tumor control in the range of 90 to 97% has been reported for skull base meningiomas up to 5 cm in greatest dimension 49,52,53; however, meningiomas larger than 5 cm in size seem to be associated with worse local control 54,55. There is little evidence that timing of RT is important, as local control and survival rates are similar whether the treatment is given as a part of the primary treatment or at the time of recurrence 47-49,56. In most series, the administered dose ranged between 50 and 57 Gy delivered in daily fractions of 1.8-2 Gy. The tumor control rates were similar for doses of 50-55 Gy or > 55 Gy 47,49,53,55-60. Doses below 50 Gy were associated with higher, mostly local recurrence rates 47,56.

In order to spare tumor-surrounding sensitive neurovascular structures, technical advances have enabled administration of fractionated RT by the use of intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT). FSRT has shown to improve symptoms within 1-3 months after treatment 61. Using FSRT with median doses of 57 Gy, Milker-Zabel et al. reported a 10-year local control of 89% in 317 patients with either skull base or intracranial meningiomas, and similar tumor control rates have been observed in other series of FSRT 55,59,62,63. Combs et al. evaluated the outcomes of 506 patients with skull base meningiomas who received FSRT (n =376) or IMRT (n=131), reporting a similar local control of 91% at 10 years for patients with WHO grade I meningiomas 62. Thus, both techniques are probably effective as primary and salvage treatment for meningiomas, with a local control at 5 and 10 years similar to that reported with conformal RT. Particle therapies like proton and carbon ion irradiation allow a high dose deposition on the tumor providing very low doses to the surrounding adjacent tissues via the “Bragg Peak”. Irradiation and re-irradiation of meningioma using protons or carbon ions as stand-alone therapies or in combination with photon therapy have been reported to be well tolerated and to allow dose escalation, particularly in WHO grade II and III meningioma, showing good local control rates 58,64-66. There is some evidence that dose escalation >60 Gy or even 65 Gy could lead to a better cause specific survival in patients with atypical and malignant meningioma 64. However, proton therapy has yet to be evaluated in prospective clinical trials.

The role of RT for WHO grade II meningiomas remains unclear. In a series of 83 patients of whom 66% had undergone GTR, Park et al. reported a 5-year tumor control of 59% versus 44% with and without postoperative RT, respectively 67. Improved progression-free survival rates after postoperative RT have been observed in comparative retrospective series 68-70.On the contrary, other studies showed no advantages in terms of progression-free survival for adjuvant RT 71-73. For WHO grade III meningiomas, postoperative RT using doses of 55-60 Gy in 1.8-2.0 Gy daily fractions is an established treatment. There is a trend toward longer survival for patients who had received adjuvant RT after surgery compared to those treated with surgery alone 74,75.

Current clinical trials address the question of dose: In the RTOG 0539 trial, WHO grade II meningiomas are treated by RT with 54 Gy in 30 fractions after GTR, while “high risk meningioma” (i.e. WHO grade II recurrent disease, WHO grade II after STR and all WHO grade III) receive up to 60 Gy. In the EORTC 22042-26042 trial, WHO grade II and grade III tumors post GTR are irradiated with 60 Gy in 30 fractions. After STR, 60 Gy plus a 10 Gy boost on the remaining tumor volume are delivered. The ROAM / EORTC 1308 trial is currently recruiting patients with newly diagnosed atypical meningioma (WHO grade II) who have undergone gross total resection (Simpson I-III) and will randomize between early adjuvant radiotherapy (60 Gy in 30 fractions) and observation to determine whether radiotherapy reduces the risk of tumor recurrence 76.

**Radiosurgery**

In cases that are associated with increased surgical risk, radiosurgery by gamma knife, cyber knife or other types of linear accelerator can be regarded as an effective alternative for radiologically diagnosed meningiomas. The dose used for radiosurgery in meningiomas is highly dependent upon the technique applied, the prescribed isodose, the proximity of neurovascular structures at risk, as well as the size and configuration of the tumor. Generally, a single coverage dose of 14 to 16 Gy is recommended 77. Besides direct cellular and toxic effects on tumor cells, the impact of a single high dose irradiation on nutritive microvessels seems to be relevant 78. Radiosurgery may be indicated in particular situations like tumor location in the cavernous sinus or the clivus, multiple meningiomas, partially resected tumors, recurrent meningioma, or in cases where comorbidities preclude open surgery. In these situations, radiosurgery can be used as an exclusive therapeutic option based on neuroimaging alone or as part of a combination therapy together with a planned partial surgical resection. A series analyzing the outcome of 79 patients with cavernous sinus meningiomas treated by radiosurgery alone revealed a tumor control rate of 89.8% at 10 years 79. A similar excellent clinical outcome and low toxicity have been reported in a few series with the use of multi-session radiosurgery at doses of 18-25 Gy delivered in 2 to 5 daily fractions in patients with meningiomas larger than 2·5-3·0 cm in size and/or situated close to critical structures 80,81. Although promising, the limited numbers of patients and follow-up time does not allow drawing definitive conclusions on the use of hypofractionated regimens in routine clinical practice as an alternative to conventionally fractionated radiotherapy. Petroclival meningiomas or sphenoid meningiomas are potential candidates for treatment strategies combining surgery and radiosurgery 45,82. In the latter tumors, combination therapy allows surgical decompression of the optic apparatus and irradiation of tumor remnants in the cavernous sinus. Radiosurgery has also been selected for treatment of recurrent atypical meningiomas. The overall survival of these patients was 87% after 5 years and 75% after 10 years 83. Multiple meningiomas and intracranial meningiomatosis might be an indication for radiosurgery, if there is no more treatment potential for surgery or fractionated radiotherapy 84.

There are no prospective randomized data comparing fractionated RT and radiosurgery. The control rates 5 and 10 years after RT or radiosurgery for WHO grade I meningiomas are very similar. 10 year PFS after RT using FSRT or IMRT was reported as 91% whereas 83 to 97% are documented for radiosurgery 62,85. Radiosurgery allows treatment of a circumscribed volume using a single dose, therefore achieving a high patient comfort. On the other hand, the use of radiosurgery is limited to small and non-infiltrative disease and locations distant from sensitive critical structures such as visual pathways because of the radiosensitivity of late reacting normal tissue to dose per fraction. In these indications, fractionated RT that sometimes can be performed using the same machines is preferred to radiosurgery. In case of infiltrative meningioma growth or WHO grade II or III meningiomas, which have a high recurrence rate, fractionated techniques seem superior 86.

**Peptide Receptor Radionuclide Therapy (PRRT)**

Some meningiomas show prominent expression of somatostatin receptors and peptide receptor radionuclide therapy (PRRT) using radiopeptides targeting somatostatin receptors such as 90Y-DOTATOC ([90Y-DOTA0, Tyr3]-octreotide), 177Lu-DOTATATE ([177Lu-DOTA0,Tyr3]-octreotate) and 111ln-Pentreotide has been evaluated in small series or singular cases of somatostatin receptor-positive meningiomas. PRRT was well tolerated and some disease stabilizations and few partial responses were reported. However, the available evidence is anecdotal and well designed studies are needed to evaluate the role of PRRT in meningiomas. In the meantime, PRRT should preferentially be offered in the framework of clinical studies 87-91.

**Embolization**

Preoperative embolisation of meningiomas aims to reduce blood loss during surgical resection 92-94. Unlike some hypervascular tumors, such as hemangioblastomas, for which embolisation is almost always carried out prior to surgery, indications for embolisation of meningiomas vary substantially depending on the neurosurgical team 95. There is no controlled study that shows better clinical outcomes of surgery if it has been preceded by pre-operative embolisation. Consequently, there is no general indication for embolisation of meningioma; individual indications are assessed on a case by case basis by each team. The principle is to first and foremost occlude the afferent arteries that cannot be reached by the surgeon when accessing the tumor. This is performed by free flow particle injection or coil embolisation within 24 hours of surgery. Complications may arise when the neuroradiologist tries to distally guide the embolus in the capillary bed of the tumor. This can result in tumor hemorrhage, erratic embolisation through anastomosis or cranial nerves palsy 96,97. Four different anatomical scenarios can be discussed: (i) In the very common convexity meningiomas, there is infrequently an indication for preoperative embolisation. If an embolisation is indicated, 100 to 300 µm particles are injected into the middle meningeal artery. These small particles allow a more distal penetration into the tumor bed. This results in a more substantial necrotic effect on the tumor, but their use also entails a higher risk of intra-tumoral hemorrhage 97,98. A controlled study indicated that preoperative embolisation resulted in a significant reduction of perioperative blood loss 92. Reported complications are tumor hemorrhage and ischemia due to erratic movement of the emboli. The incidence of complications varies from 0 to 9 %. (ii) Olfactory meningiomas are generally vascularized by ethmoidal arteries. Since these are branches of the ophthalmic artery implicating a risk of jeopardizing vision by embolisation, these tumors should never be embolized. (iii) Meningiomas of the cavernous sinus can be subjected to preoperative embolisation. However, the afferent arteries are small-sized dural arteries emanating from the carotid siphon which, aside from rare cases, are not amenable to selective catherization. Therefore, if an indication for embolisation of a cavernous sinus meningioma is made, the internal carotid artery needs to be occluded after testing patency of the Circle of Willis. (iv) Petroclival meningiomas can be embolized via the meningeal trunk of the ascending pharyngeal artery. This artery cannot be controlled by the neurosurgeon during lateral approaches to the clivus, the petrous bone or the cerebellopontine angle 99.

**Pharmacotherapy and experimental therapies**

Pharmacotherapy of meningiomas is typically considered in the following main patient populations: (i) patients with recurrent or progressive meningiomas of all tumor grades in whom surgical resection or radiotherapy are no longer feasible, and (ii) patients with metastatic meningioma. Principally, systemic therapy appears to be able to inhibit meningioma growth to some extent 100. A variety of drugs have been studied in meningiomas. However, the interpretation of most of the available studies is limited by several factors, in particular small patient numbers, the retrospective design of most studies, the heterogeneity of patient populations with regard to tumor type and prior therapies, the lack of comparator treatment arms or reliable historical benchmark activity parameters and the lack of standardized response criteria. Thus, pharmacotherapy of meningioma has so far an unclear benefit and has to be considered experimental. Overall, inclusion of patients with meningiomas in clinical trials evaluating novel treatment approaches is recommended. Depending on ongoing molecular classification of meningiomas, targeted therapies are evolving (table 4).

WHO grade I meningiomas

Hydroxyurea, temozolomide, irinotecan, interferon-alpha, sandostatin LAR, pasireotide LAR, imatinib, erlotinib and gefitinib have been studied in retrospective and single-arm phase II studies in WHO grade I meningiomas that have failed surgical resection and radiotherapy 101,102. Mifepristone was studied in a randomized phase III trial but failed to show any advantage over placebo 103. The PFS-6 rates in these studies ranged from 0% to 67%, while median OS times were only inconsistently reported and ranged from 7 to 13 months 102. The lack of clear data on the natural course and the uncontrolled character of these studies preclude definite conclusions. Based on the available data, none of the evaluated drugs showed clear signs of clinically relevant activity sufficient to recommend them for clinical use. Temozolomide is not active in meningioma 104.

WHO grade II and III meningiomas

Retrospective studies and small prospective studies have evaluated a range of drugs including hydroxyurea, cycophosphamide/adriamycin/vincristine chemotherapy, interferon-alpha, megestrol acetate, medroxy-progesterone acetate, octreotide, sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib and bavacizumab in WHO grade II and III meningiomas 102. PFS-6 rates ranged from 0% to 64% and median OS times from 6 to 33 months in patients progressing after surgical resection and radiotherapy 102. The most promising results have been reported for bevacizumab, vatalanib and sunitinib, all drugs with anti-angiogenic properties 100,102,105-108. These results need to be confirmed in prospective controlled trials, before clinical use of these compounds in WHO grade II and III meningiomas can be recommended. An ongoing EORTC phase II trial (NCT02234050) explores the efficacy of trabectedin, a tetrahydroisoquinoline that has shown promising activity in recurrent grade II and grade III meningiomas 109.

**Surveillance and follow up of meningiomas**

There is no robust data on the best follow-up schedule for meningiomas, since most retrospective studies do not report on monitoring intervals and since prospective studies published so far had variable follow-up protocols, usually tailored to fit the treatment visits 110,111. Therefore, the following recommendations are based more on expert consensus opinion rather than evidence.

Our proposed approach on the management of small, asymptomatic meningiomas is to evaluate the dynamics of the tumor with MRI with contrast medium 6 months after initial diagnosis and then annually, as long as the patient remains asymptomatic. After five years this interval can be doubled. In patients with limited life expectancy due to high age or severe co-morbidities, controls may be omitted if the radiological diagnosis of a benign meningioma seems clear.

Monitoring after initial treatment should depend on the degree of resection and grading of the tumor.

For WHO I meningiomas resected totally, the 10-year recurrence rates vary from 20-39%. Studies with long follow-up with MRI show that recurrence is more common than previously thought. Therefore, it is advisable to perform a baseline MRI within 48 hours or after 3 months, in order to assess the radicality of resection. Thereafter, we propose annual MRI controls until five years post treatment, then every two years.

If resection is incomplete, EOR should be documented by early postoperative MRI within 48 hours. For WHO grade I tumors after STR, the 10-year progression rates vary between 55 and 100% suggesting a more vigilant long-term follow-up 112,113. For those cases, MRI at 6 and 12 months is recommended, then annually.

The natural history of WHO grade II meningiomas is less clear, since the 2007 WHO criteria changed their definition and thus their identification rates. The 5-year recurrence rates may be as high as 30% and 40% after GTR and STR, respectively 68,71. In these tumors, we suggest an early postoperative MRI within 48 hours. Follow up MRI should be done every 6 months for 5 years, then annually.

WHO grade III meningiomas are aggressive tumors with very poor local control, even after multimodal treatment. In the recent studies utilizing the WHO 2007 grading scheme, the 5-year-PFS ranged from 12 to 57%, even after resection and radiotherapy. Therefore, these tumors have to be followed up very closely 114. After the initial, early post-treatment MRI, cranial imaging should be routinely done every 6 months, in rapidly growing cases every 3 months.

1. Woehrer A, Hackl M, Waldhor T, et al. Relative survival of patients with non-malignant central nervous system tumours: a descriptive study by the Austrian Brain Tumour Registry. *British journal of cancer* 2014; **110**(2): 286-96.

2. Zouaoui S, Darlix A, Rigau V, et al. Descriptive epidemiology of 13,038 newly diagnosed and histologically confirmed meningiomas in France: 2006-2010. *Neuro-Chirurgie* 2015.

3. Saraf S, McCarthy BJ, Villano JL. Update on meningiomas. *The oncologist* 2011; **16**(11): 1604-13.

4. Sun SQ, Cai C, Ravindra VM, et al. Simpson Grade I-III Resection of Spinal Atypical (World Health Organization Grade II) Meningiomas is Associated With Symptom Resolution and Low Recurrence. *Neurosurgery* 2015; **76**(6): 739-46.

5. Goldbrunner R. Intradural extramedullary tumors. In: Tonn J, ed. Neuro-oncology of CNS tumors: Springer; 2006: 635-45.

6. Sughrue ME, Rutkowski MJ, Aranda D, Barani IJ, McDermott MW, Parsa AT. Treatment decision making based on the published natural history and growth rate of small meningiomas. *Journal of neurosurgery* 2010; **113**(5): 1036-42.

7. Tucha O, Smely C, Lange KW. Effects of surgery on cognitive functioning of elderly patients with intracranial meningioma. *British journal of neurosurgery* 2001; **15**(2): 184-8.

8. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *Journal of neurosurgery* 2003; **98**(1): 21-31.

9. Dijkstra M, van Nieuwenhuizen D, Stalpers LJ, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. *Journal of neurology, neurosurgery, and psychiatry* 2009; **80**(8): 910-5.

10. van Nieuwenhuizen D, Klein M, Stalpers LJ, Leenstra S, Heimans JJ, Reijneveld JC. Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. *Journal of neuro-oncology* 2007; **84**(3): 271-8.

11. Waagemans ML, van Nieuwenhuizen D, Dijkstra M, et al. Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. *Neurosurgery* 2011; **69**(1): 72-8; discussion 8-9.

12. Pringle AM, Taylor R, Whittle IR. Anxiety and depression in patients with an intracranial neoplasm before and after tumour surgery. *British journal of neurosurgery* 1999; **13**(1): 46-51.

13. Stangl AP, Wellenreuther R, Lenartz D, et al. Clonality of multiple meningiomas. *Journal of neurosurgery* 1997; **86**(5): 853-8.

14. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. *Journal of neurosurgery* 2004; **100**(6): 1002-13.

15. Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer research* 1989; **49**(21): 6137-43.

16. Rubinstein AB, Shalit MN, Cohen ML, Zandbank U, Reichenthal E. Radiation-induced cerebral meningioma: a recognizable entity. *Journal of neurosurgery* 1984; **61**(5): 966-71.

17. Sadamori N, Shibata S, Mine M, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. *International journal of cancer Journal international du cancer* 1996; **67**(3): 318-22.

18. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiation research* 2005; **163**(4): 424-32.

19. Custer B, Longstreth WT, Jr., Phillips LE, Koepsell TD, Van Belle G. Hormonal exposures and the risk of intracranial meningioma in women: a population-based case-control study. *BMC cancer* 2006; **6**: 152.

20. Zhang H, Rodiger LA, Shen T, Miao J, Oudkerk M. Preoperative subtyping of meningiomas by perfusion MR imaging. *Neuroradiology* 2008; **50**(10): 835-40.

21. Takeguchi T, Miki H, Shimizu T, et al. The dural tail of intracranial meningiomas on fluid-attenuated inversion-recovery images. *Neuroradiology* 2004; **46**(2): 130-5.

22. Alvernia JE, Sindou MP. Preoperative neuroimaging findings as a predictor of the surgical plane of cleavage: prospective study of 100 consecutive cases of intracranial meningioma. *Journal of neurosurgery* 2004; **100**(3): 422-30.

23. Collamati F, Pepe A, Bellini F, et al. Toward radioguided surgery with beta- decays: uptake of a somatostatin analogue, DOTATOC, in meningioma and high-grade glioma. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2015; **56**(1): 3-8.

24. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2015; **56**(3): 347-53.

25. Reuss DE, Piro RM, Jones DT, et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. *Acta neuropathologica* 2013; **125**(3): 351-8.

26. Sahm F, Bissel J, Koelsche C, et al. AKT1E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. *Acta neuropathologica* 2013; **126**(5): 757-62.

27. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nature genetics* 2013; **45**(3): 285-9.

28. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science (New York, NY)* 2013; **339**(6123): 1077-80.

29. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. *Brain pathology (Zurich, Switzerland)* 2014; **24**(2): 184-9.

30. Sahm F, Schrimpf D, Olar A, et al. TERT Promoter Mutations and Risk of Recurrence in Meningioma. *Journal of the National Cancer Institute* 2016; **108**(5).

31. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *The New England journal of medicine* 2007; **357**(18): 1821-8.

32. Rogers L, Barani I, Chamberlain M, et al. Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. *Journal of neurosurgery* 2014: 1-20.

33. Seifert V. Clinical management of petroclival meningiomas and the eternal quest for preservation of quality of life: personal experiences over a period of 20 years. *Acta neurochirurgica* 2010; **152**(7): 1099-116.

34. Chaichana KL, Pendleton C, Zaidi H, et al. Seizure control for patients undergoing meningioma surgery. *World neurosurgery* 2013; **79**(3-4): 515-24.

35. Weston J, Greenhalgh J, Marson AG. Antiepileptic drugs as prophylaxis for post-craniotomy seizures. *The Cochrane database of systematic reviews* 2015; **3**: CD007286.

36. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *Journal of neurology, neurosurgery, and psychiatry* 1957; **20**(1): 22-39.

37. Sughrue ME, Kane AJ, Shangari G, et al. The relevance of Simpson Grade I and II resection in modern neurosurgical treatment of World Health Organization Grade I meningiomas. *Journal of neurosurgery* 2010; **113**(5): 1029-35.

38. Vogelbaum MA, Leland Rogers C, Linskey MA, Mehta MP. Opportunities for clinical research in meningioma. *Journal of neuro-oncology* 2010; **99**(3): 417-22.

39. Gezen F, Kahraman S, Canakci Z, Beduk A. Review of 36 cases of spinal cord meningioma. *Spine* 2000; **25**(6): 727-31.

40. Gottfried ON, Gluf W, Quinones-Hinojosa A, Kan P, Schmidt MH. Spinal meningiomas: surgical management and outcome. *Neurosurgical focus* 2003; **14**(6): e2.

41. Kim CH, Chung CK, Lee SH, et al. Long-term recurrence rates after the removal of spinal meningiomas in relation to Simpson grades. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2015.

42. Klekamp J, Samii M. Surgical results for spinal meningiomas. *Surgical neurology* 1999; **52**(6): 552-62.

43. Nakamura M, Tsuji O, Fujiyoshi K, et al. Long-term surgical outcomes of spinal meningiomas. *Spine* 2012; **37**(10): E617-23.

44. Tsuda K, Akutsu H, Yamamoto T, Nakai K, Ishikawa E, Matsumura A. Is Simpson grade I removal necessary in all cases of spinal meningioma? Assessment of postoperative recurrence during long-term follow-up. *Neurologia medico-chirurgica* 2014; **54**(11): 907-13.

45. Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB, Jr., Rhoton AL. Benign meningiomas: primary treatment selection affects survival. *International journal of radiation oncology, biology, physics* 1997; **39**(2): 427-36.

46. Dufour H, Muracciole X, Metellus P, Regis J, Chinot O, Grisoli F. Long-term tumor control and functional outcome in patients with cavernous sinus meningiomas treated by radiotherapy with or without previous surgery: is there an alternative to aggressive tumor removal? *Neurosurgery* 2001; **48**(2): 285-94; discussion 94-6.

47. Mendenhall WM, Morris CG, Amdur RJ, Foote KD, Friedman WA. Radiotherapy alone or after subtotal resection for benign skull base meningiomas. *Cancer* 2003; **98**(7): 1473-82.

48. Nutting C, Brada M, Brazil L, et al. Radiotherapy in the treatment of benign meningioma of the skull base. *Journal of neurosurgery* 1999; **90**(5): 823-7.

49. Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *Journal of neurosurgery* 1994; **80**(2): 195-201.

50. Soyuer S, Chang EL, Selek U, Shi W, Maor MH, DeMonte F. Radiotherapy after surgery for benign cerebral meningioma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2004; **71**(1): 85-90.

51. Taylor BW, Jr., Marcus RB, Jr., Friedman WA, Ballinger WE, Jr., Million RR. The meningioma controversy: postoperative radiation therapy. *International journal of radiation oncology, biology, physics* 1988; **15**(2): 299-304.

52. Maire JP, Caudry M, Guerin J, et al. Fractionated radiation therapy in the treatment of intracranial meningiomas: local control, functional efficacy, and tolerance in 91 patients. *International journal of radiation oncology, biology, physics* 1995; **33**(2): 315-21.

53. Minniti G, Clarke E, Cavallo L, et al. Fractionated stereotactic conformal radiotherapy for large benign skull base meningiomas. *Radiation oncology (London, England)* 2011; **6**: 36.

54. Connell PP, Macdonald RL, Mansur DB, Nicholas MK, Mundt AJ. Tumor size predicts control of benign meningiomas treated with radiotherapy. *Neurosurgery* 1999; **44**(6): 1194-9; discussion 9-200.

55. Milker-Zabel S, Zabel A, Schulz-Ertner D, Schlegel W, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy in patients with benign or atypical intracranial meningioma: long-term experience and prognostic factors. *International journal of radiation oncology, biology, physics* 2005; **61**(3): 809-16.

56. Vendrely V, Maire JP, Darrouzet V, et al. [Fractionated radiotherapy of intracranial meningiomas: 15 years' experience at the Bordeaux University Hospital Center]. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique* 1999; **3**(4): 311-7.

57. Tanzler E, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM. Outcomes of WHO Grade I meningiomas receiving definitive or postoperative radiotherapy. *International journal of radiation oncology, biology, physics* 2011; **79**(2): 508-13.

58. Combs SE, Kalbe A, Nikoghosyan A, et al. Carbon ion radiotherapy performed as re-irradiation using active beam delivery in patients with tumors of the brain, skull base and sacral region. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2011; **98**(1): 63-7.

59. Fokas E, Henzel M, Surber G, Hamm K, Engenhart-Cabillic R. Stereotactic radiation therapy for benign meningioma: long-term outcome in 318 patients. *International journal of radiation oncology, biology, physics* 2014; **89**(3): 569-75.

60. Henzel M, Gross MW, Hamm K, et al. Significant tumor volume reduction of meningiomas after stereotactic radiotherapy: results of a prospective multicenter study. *Neurosurgery* 2006; **59**(6): 1188-94; discussion 94.

61. Metellus P, Kapoor S, Kharkar S, et al. Fractionated conformal radiotherapy for management of optic nerve sheath meningiomas: long-term outcomes of tumor control and visual function at a single institution. *International journal of radiation oncology, biology, physics* 2011; **80**(1): 185-92.

62. Combs SE, Adeberg S, Dittmar JO, et al. Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2013; **106**(2): 186-91.

63. Solda F, Wharram B, De Ieso PB, Bonner J, Ashley S, Brada M. Long-term efficacy of fractionated radiotherapy for benign meningiomas. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2013; **109**(2): 330-4.

64. Boskos C, Feuvret L, Noel G, et al. Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *International journal of radiation oncology, biology, physics* 2009; **75**(2): 399-406.

65. Chan AW, Bernstein KD, Adams JA, Parambi RJ, Loeffler JS. Dose escalation with proton radiation therapy for high-grade meningiomas. *Technology in cancer research & treatment* 2012; **11**(6): 607-14.

66. Weber DC, Schneider R, Goitein G, et al. Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. *International journal of radiation oncology, biology, physics* 2012; **83**(3): 865-71.

67. Park HJ, Kang HC, Kim IH, et al. The role of adjuvant radiotherapy in atypical meningioma. *Journal of neuro-oncology* 2013; **115**(2): 241-7.

68. Aghi MK, Carter BS, Cosgrove GR, et al. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. *Neurosurgery* 2009; **64**(1): 56-60; discussion

69. Komotar RJ, Iorgulescu JB, Raper DM, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. *Journal of neurosurgery* 2012; **117**(4): 679-86.

70. Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. *Journal of neurosurgery* 2011; **115**(4): 811-9.

71. Hammouche S, Clark S, Wong AH, Eldridge P, Farah JO. Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. *Acta neurochirurgica* 2014; **156**(8): 1475-81.

72. Stessin AM, Schwartz A, Judanin G, et al. Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)-based analysis. *Journal of neurosurgery* 2012; **117**(4): 669-75.

73. Yoon H, Mehta MP, Perumal K, et al. Atypical meningioma: randomized trials are required to resolve contradictory retrospective results regarding the role of adjuvant radiotherapy. *Journal of cancer research and therapeutics* 2015; **11**(1): 59-66.

74. Dziuk TW, Woo S, Butler EB, et al. Malignant meningioma: an indication for initial aggressive surgery and adjuvant radiotherapy. *Journal of neuro-oncology* 1998; **37**(2): 177-88.

75. Rosenberg LA, Prayson RA, Lee J, et al. Long-term experience with World Health Organization grade III (malignant) meningiomas at a single institution. *International journal of radiation oncology, biology, physics* 2009; **74**(2): 427-32.

76. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. *Trials* 2015; **16**: 519.

77. Goldsmith B, McDermott MW. Meningioma. *Neurosurgery clinics of North America* 2006; **17**(2): 111-20, vi.

78. Song CW, Kim MS, Cho LC, Dusenbery K, Sperduto PW. Radiobiological basis of SBRT and SRS. *International journal of clinical oncology* 2014; **19**(4): 570-8.

79. dos Santos MA, de Salcedo JB, Gutierrez Diaz JA, et al. Long-term outcomes of stereotactic radiosurgery for treatment of cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics* 2011; **81**(5): 1436-41.

80. Colombo F, Casentini L, Cavedon C, Scalchi P, Cora S, Francescon P. Cyberknife radiosurgery for benign meningiomas: short-term results in 199 patients. *Neurosurgery* 2009; **64**(2 Suppl): A7-13.

81. Tuniz F, Soltys SG, Choi CY, et al. Multisession cyberknife stereotactic radiosurgery of large, benign cranial base tumors: preliminary study. *Neurosurgery* 2009; **65**(5): 898-907; discussion

82. Jung HW, Yoo H, Paek SH, Choi KS. Long-term outcome and growth rate of subtotally resected petroclival meningiomas: experience with 38 cases. *Neurosurgery* 2000; **46**(3): 567-74; discussion 74-5.

83. Sallabanda K, Dos Santos MA, Salcedo JB, et al. Stereotactic radiosurgery as a salvage treatment option for atypical meningiomas previously submitted to surgical resection. *J Radiosurg BRT* 2011; **0**: 1-7.

84. Samblas J, Luis Lopez Guerra J, Bustos J, et al. Stereotactic radiosurgery in patients with multiple intracranial meningiomas. *Journal of BUON : official journal of the Balkan Union of Oncology* 2014; **19**(1): 250-5.

85. Bloch O, Kaur G, Jian BJ, Parsa AT, Barani IJ. Stereotactic radiosurgery for benign meningiomas. *Journal of neuro-oncology* 2012; **107**(1): 13-20.

86. Mantle RE, Lach B, Delgado MR, Baeesa S, Belanger G. Predicting the probability of meningioma recurrence based on the quantity of peritumoral brain edema on computerized tomography scanning. *Journal of neurosurgery* 1999; **91**(3): 375-83.

87. Bartolomei M, Bodei L, De Cicco C, et al. Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. *European journal of nuclear medicine and molecular imaging* 2009; **36**(9): 1407-16.

88. Kreissl MC, Hanscheid H, Lohr M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. *Radiation oncology (London, England)* 2012; **7**: 99.

89. Makis W, McCann K, McEwan AJ. Rhabdoid papillary meningioma treated with 177Lu DOTATATE PRRT. *Clinical nuclear medicine* 2015; **40**(3): 237-40.

90. Minutoli F, Amato E, Sindoni A, et al. Peptide receptor radionuclide therapy in patients with inoperable meningiomas: our experience and review of the literature. *Cancer biotherapy & radiopharmaceuticals* 2014; **29**(5): 193-9.

91. Seystahl K SV, Guillaume N, Schüller U, Rushing E, Schäfer N, Ilhan H, Weller M, Tonn JC, Sommerauer M, Jansen N. . Somatostatin receptor-targeted radionuclide therapy for progressive meningioma. *SNO 2015* 2015.

92. Bendszus M, Rao G, Burger R, et al. Is there a benefit of preoperative meningioma embolization? *Neurosurgery* 2000; **47**(6): 1306-11; discussion 11-2.

93. Dean BL, Flom RA, Wallace RC, et al. Efficacy of endovascular treatment of meningiomas: evaluation with matched samples. *AJNR American journal of neuroradiology* 1994; **15**(9): 1675-80.

94. Macpherson P. The value of pre-operative embolisation of meningioma estimated subjectively and objectively. *Neuroradiology* 1991; **33**(4): 334-7.

95. Sakamoto N, Ishikawa E, Nakai Y, et al. Preoperative endovascular embolization for hemangioblastoma in the posterior fossa. *Neurologia medico-chirurgica* 2012; **52**(12): 878-84.

96. Shah A, Choudhri O, Jung H, Li G. Preoperative endovascular embolization of meningiomas: update on therapeutic options. *Neurosurgical focus* 2015; **38**(3): E7.

97. Carli DF, Sluzewski M, Beute GN, van Rooij WJ. Complications of particle embolization of meningiomas: frequency, risk factors, and outcome. *AJNR American journal of neuroradiology* 2010; **31**(1): 152-4.

98. Sluzewski M, van Rooij WJ, Lohle PN, Beute GN, Peluso JP. Embolization of meningiomas: comparison of safety between calibrated microspheres and polyvinyl-alcohol particles as embolic agents. *AJNR American journal of neuroradiology* 2013; **34**(4): 727-9.

99. Sawlani V, Browing S, Sawhney IM, Redfern R. Posterior circulation stroke following embolization of glomus tympanicum?relevance of anatomy and anastomoses of ascending pharyngeal artery. A case report. *Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences* 2009; **15**(2): 229-36.

100. Furtner J, Schopf V, Seystahl K, et al. Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma. *Neuro-oncology* 2015.

101. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology* 2015; **84**(3): 280-6.

102. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro-oncology* 2014; **16**(6): 829-40.

103. Ji Y, Rankin C, Grunberg S, et al. Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(34): 4093-8.

104. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology* 2004; **62**(7): 1210-2.

105. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro-oncology* 2015; **17**(1): 116-21.

106. Lou E, Sumrall AL, Turner S, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. *Journal of neuro-oncology* 2012; **109**(1): 63-70.

107. Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *Journal of neuro-oncology* 2012; **109**(1): 187-93.

108. Puchner MJ, Hans VH, Harati A, Lohmann F, Glas M, Herrlinger U. Bevacizumab-induced regression of anaplastic meningioma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**(12): 2445-6.

109. Preusser M, Spiegl-Kreinecker S, Lotsch D, et al. Trabectedin has promising antineoplastic activity in high-grade meningioma. *Cancer* 2012; **118**(20): 5038-49.

110. Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *Journal of neuro-oncology* 2010; **96**(2): 211-7.

111. Raizer JJ, Grimm SA, Rademaker A, et al. A phase II trial of PTK787/ZK 222584 in recurrent or progressive radiation and surgery refractory meningiomas. *Journal of neuro-oncology* 2014; **117**(1): 93-101.

112. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL. Meningioma: analysis of recurrence and progression following neurosurgical resection. *Journal of neurosurgery* 1985; **62**(1): 18-24.

113. Barbaro NM, Gutin PH, Wilson CB, Sheline GE, Boldrey EB, Wara WM. Radiation therapy in the treatment of partially resected meningiomas. *Neurosurgery* 1987; **20**(4): 525-8.

114. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *Journal of neurosurgery* 2010; **113**(2): 202-9.