Meningioma: not always a benign tumor. A review of advances in the treatment of meningiomas

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Practice points

Background

• Meningioma is the most common tumor among primary CNS malignancies. Meningiomas originate from the arachnoid cells located on the inner surface of the dura. The diagnosis is often incidental.

Risk factors

• Recognized risk factors include ionizing radiation to the skull, while others are under investigation (e.g., sex hormones, smoking, diabetes mellitus, arterial hypertension and mobile phone use). Genetic syndromes have also been associated with meningiomas.

Clinical features

• Meningiomas are frequently asymptomatic. The main symptoms can be correlated with a mass effect (focal neurological symptoms, seizures, increased intracranial pressure).

Radiological features

• The cornerstone for the diagnosis of meningioma is MRI, with a typical presentation as a well circumscribed dural lesion with homogeneous enhancing. 68-gallium-labeled somatostatin receptor analog (68Ga-DOTATATE) could have a diagnostic role in detecting recurrence in irradiated meningiomas.

Histopathology

• The WHO 2016 classification distinguishes meningiomas in three different grades: grade I, grade II (atypical meningiomas) and grade III (anaplastic/malignant meningiomas).

Molecular alterations

• Genomic analysis identified four mutually exclusive pathways that could drive the development of meningiomas: increased hedgehog signaling, TRAF7, POLR2A mutations and other rarer mutations.

Surgery

• The treatment is usually surgical, with the aim to achieve complete resection. The extent of resection is measured by the Simpson grade.

Radiotherapy

• For meningiomas not suitable for surgery, irradiation represents a valid alternative for controlling local growth. Adjuvant radiotherapy is standard of care for grade III, is controversial for grade II and is not indicated for radically resected grade I meningiomas. Salvage radiotherapy alone or after surgical excision is a feasible option for recurrent disease.

Systemic treatments

• Systemic treatments have been associated with limited results in terms of activity and are usually indicated in cases of recurrent or progressive disease not amenable to surgery or radiotherapy. The most promising results have been obtained with antiangiogenic treatments and mTOR inhibitors.

Meningiomas are the most common primary intracranial tumors. The majority of meningiomas are benign, but they can present different grades of dedifferentiation from grade I to grade III (anaplastic/malignant) that are associated with different outcomes. Radiological surveillance is a valid option for low-grade asymptomatic meningiomas. In other cases, the treatment is usually surgical, aimed at achieving a complete resection. The use of adjuvant radiotherapy is the gold standard for grade III, is debated for grade II and is not generally indicated for radically resected grade I meningiomas. The use of systemic treatments is not standardized. Here we report a review of the literature on the clinical, radiological and molecular characteristics of meningiomas, available treatment strategies and ongoing clinical trials.
Meningiomas are the most common of all primary CNS tumors, accounting for about 36% of cases and for 53% of nonmalignant CNS tumors, with an incidence of 7.86 cases per 100,000 people per year [1,2]. Meningiomas are mostly considered to be benign and are often diagnosed incidentally [1].

Meningiomas originate from the arachnoid cells located on the inner surface of the dura. The latter originate from meningeal precursor cells derived from mesoderm and neuronal crest.

They can be located in any intracranial or spinal dural surface, but sometimes they can be found within the ventricles or in extracranial organs (e.g., the lungs).

The incidence of meningiomas increases significantly with older age, and there is a higher prevalence in the black population and a female predominance for nonmalignant meningiomas [3].

The diagnosis is radiological and, if imaging is strongly suggestive of meningioma, biopsy is not mandatory [4]. The tumor growth for asymptomatic meningiomas is linear with a growth rate of 2–4 mm/year [5], but in some cases it can present with no modification of volume or with exponential growth [6]. This factor underlines the importance of surveillance in untreated patients with asymptomatic meningioma. Patients with symptomatic meningiomas or a high growth pattern are generally resected [7].

Estimated 10-year overall survival for nonmalignant meningiomas is 81.4%, while for malignant ones is 57.1%; in particular, it is 53% for grade II and 0% for grade III tumors [2]. The rate of recurrence is approximately 50% for grade II and 90% for grade III [7]. Progression of disease is defined by the growth of the residual tumor or transformation into a higher-grade tumor.

We performed a review of the literature to summarize the current knowledge on meningiomas, the available therapeutic strategies and ongoing clinical trials.

Risk factors
A recognized risk factor for meningiomas is ionizing radiation to the skull, with reported risks from sixfold to tenfold greater [8–11]. Radiation-induced meningiomas are often multiple and tend to have an aggressive behavior [12]. Sex hormones have been proposed as other risk factors for developing meningiomas, due to the increased incidence of postpubertal disease in women (2:1 vs men), with a higher ratio (about 3:1) during the reproductive period. Despite different studies having been conducted to confirm this risk association, there is no definitive evidence on these putative risk factors [13–21].

Smoking, diabetes mellitus, arterial hypertension and mobile phone use have also been investigated as risk factors, but the results are inconclusive [21–23].

Li–Fraumeni, Gorlin, Cowden and von Hippel–Lindau syndromes, multiple endocrine neoplasia type 1 and especially neurofibromatosis type 2 (NF2) can determine the development of meningiomas; the tumors associated with these conditions are often multiple and occur mostly in children [5,24].

Clinical features
The majority of meningiomas are asymptomatic and are discovered incidentally. There is no pathognomonic clinical presentation and symptoms generally depend on the localization. Typically, these tumors have a slow growth rate and are rarely infiltrative. They can manifest with a mass effect with focal neurological symptoms (including cranial nerve), seizure (generalized or partial) and increased intracranial pressure, which can cause headache.

Radiological features
On computed tomography, intratumoral calcification with hyperostosis and remodeled skull can be present. The cornerstone for the diagnosis of meningiomas is MRI, where meningioma typically presents as a well-circumscribed dural lesion with homogeneous enhancing.

Benign meningiomas have a thickened, contrast-enhanced dural tail. This radiological feature can also be present in metastases, lymphoma or hemangiopericytomas, thus making the diagnosis challenging [25]. Other differential diagnoses include other neoplastic, inflammatory or infectious diseases that involve the dura or subdural space, such as metastases of other tumors, plasmacytoma, lymphoma, solitary fibrous tumor, gliosarcoma, sarcoïdosis,
granulomatosis and tuberculosis [26–29]. Peritumoral edema (seen by T2 and T2 fluid-attenuated inversion recovery [FLAIR] imaging) is not common but can be present in secretory meningiomas. Central necrosis (hypointense T1, nonenhancing) can be seen in both benign and malignant meningiomas.

Not only can MRI be useful in diagnosis and monitoring indolent meningiomas, but it can also allow clinicians to distinguish recurrence of surgically treated meningiomas from treatment-related radiological changes, such as dural thickening. Magnetic resonance spectroscopy typically shows decreased N-acetyl aspartate and creatinine peaks and increased choline and alanine peaks compared with normal brain tissue [30]. A lactate peak, typical of necrotic tissue, can be seen in atypical meningiomas [31].

In recent years the role of radiomics has been investigated in meningiomas. Radiomics consists of the correlation of quantitative radiological features with pathological and molecular characteristics of the tumor. This novel method has the potential to increase molecular knowledge of the tumor in a noninvasive manner, which is beneficial given the tumor’s hard-to-access location. Several studies showed a potential role of radiomics in predicting the pathological grade, subtypes, recurrence and brain invasion of meningiomas, [32–36] and could also be helpful for differential diagnosis [37–40]. For example, a study on 175 meningioma patients, of which 103 were low grade and 72 high grade, showed a strong association between 12 MRI radiographic features and histopathological grade [32]. Moreover, Laukamp et al. analyzed MRI data (T1-weighted/T2-weighted, T1-weighted contrast-enhanced, fluid-attenuated inversion recovery, diffusion-weighted imaging, apparent diffusion coefficient) of 46 grade I and 25 grade II meningiomas [34]. The results of this study evidenced that four radiomics features (roundness of FLAIR-shape, cluster shades of FLAIR/T1CE gray level, DWI/ADC gray level variability and FLAIR/T1CE gray level energy) have a strong predictive value for higher tumor grades. Furthermore, a multicenter study on 1728 patients with grade I, II and III meningiomas showed that 16 clinicoradiomic features present a high sensitivity for risk prediction of brain invasion in meningioma [40]. The development of radiomics in meningiomas can be of great relevance in clinical practice, considering the potential role of imaging-derived features in deepening the knowledge on tumor biology and pathology and the potential prognostic or predictive implication.

PET is not useful in clinical practice, but there is evidence that 68-gallium-labeled somatostatin receptor analog (68Ga-DOTATATE) could have a diagnostic role in detecting recurrence in irradiated meningiomas [41–43]. For skull base meningioma 18-fluoro-ethyl-tyrosine PET can help diagnosis, but it does not give information on histology [44]. Furthermore, tryptophan metabolism via α-[11C]-methyl-L-tryptophan PET has been evaluated to predict the meningioma grade [45].

Histopathology

The WHO 2016 classification distinguishes meningiomas in different grades, as shown in Table 1 [46]. Grade I meningiomas can present a range of different histological patterns that can mimic other tumors. These variants are: meningothelial and fibrous (which are the most frequent), transitional, psammomatous, angiomyomatous, microcystic, secretory, lymphoplasmacyte rich and metaphasic. Atypical meningiomas (grade II) can have a clear cell and choroid histology, while anaplastic/malignant meningiomas (grade III) can have papillary or rhabdoid histology.

| WHO grade | Frequency (%) | Description |
|-----------|--------------|-------------|
| Grade I  | 80–85        | Mitotic rate <4 per 10 HPFs or No brain invasion |
| Grade II atypical | 15–20 | Mitotic rate 4–19 per 10 HPFs or Brain invasion or ≥3 of 5 specific histological features: - spontaneous or geographic necrosis - patternless sheet-like growth - prominent nucleoli - high cellularity - small cells with high nuclear:cytoplasmic ratio |
| Grade III anaplastic malignant | 1–2 | Mitotic rate >20 per 10 HPFs or Papillary or rhabdoid histology |

HPF: High-power field.
Table 2. Molecular alterations in meningioma and their clinical significance.

| Gene   | Molecular alterations and pathway                                                                 | Frequent histological subtype               | Clinical significance                                                                 | Ref.       |
|--------|-------------------------------------------------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------|------------|
| SMO    | • Leu412Phe and Trp535Leu mutations                                                            | Multiple pathogenic variant                | • Relatively common                                                                   | [52,53]    |
|        | • Activation of PI3K-AKT-mTOR pathway                                                          |                                            | • Localization in the skull base                                                       |            |
|        | • Genomic stability                                                                             |                                            |                                                                                        |            |
| AKT1   | • p.Glu17Lys mutation                                                                           | Multiple pathogenic variant                | • Relatively common                                                                   | [52-54]    |
|        | • Activation of PI3K-AKT-mTOR pathway                                                          |                                            |                                                                                        |            |
|        | • Genomic stability                                                                             |                                            |                                                                                        |            |
| TRAF7  | • WD40 domain mutations                                                                        | Secretory meningiomas                      | • Up to 25% of grade I and II meningiomas                                              | [50,55-58] |
|        | • JUN N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling         |                                            | • Location in anterior and middle medial skull base                                    |            |
| KLF4   | • High rate of co-occurrence with TRAF7 mutations                                              | Secretory meningiomas                      | • Up to half of NF2-unmutated meningiomas                                              | [55,56,58-60] |
|        | • Oncogenic activation and tumor suppression                                                    |                                            |                                                                                        |            |
| POLR2A | • p.Gln403Lys mutation                                                                          | Meningothelial histology                   | • Location in the tuberculum sellae                                                   | [55]       |
|        | • p.Leu438His439del                                                                              |                                            |                                                                                        |            |
| NF2    | • 22q112 chromosome deletion                                                                    | Fibroblastic/transitional meningiomas      | • Location in the hemispheres                                                         | [52,55,61,62] |
|        | • Genomic instability                                                                           |                                            | • Frequently multiple                                                                 |            |
|        |                                                                                                 |                                            | • Greater risk of mortality                                                           |            |
| BAP1   | • Multiple mutations                                                                            | Rhabdoid grade III meningioma              | • Early tumor recurrence                                                              | [63]       |
| Epigenetic modifications | • Mutations in KDM5C, KDM6A, SMARC81, EZH2                                                                 | Multiple pathogenic variant                  | • 10% of non-NF2 meningiomas                                                          | [52,64-66] |
|        | • Multiple pathogenic variant                                                                   |                                            | • EZH2 mutation correlated with aggressiveness                                        |            |
| CDKN2A | • Somatic mutations and homozygous losses                                                        | Anaplastic meningiomas                     | • Higher risk of recurrence                                                           | [67-71]    |

Immunohistochemical markers to identify meningioma are epithelial membrane antigen, somatostatin receptor 2A, progesterone receptor (present in 70–80% of cases) and estrogen receptor (present in about 5–30% of cases) [47-49].

Molecular alterations

Genomic analysis has identified four mutually exclusive pathways that could drive the development of meningiomas [50,51]:

- Increased hedgehog signaling (through mutation of SMO, SUFU or PRKARIA)
- TRAF7 (through KLF4 mutation or PI3K pathway activation)
- POLR2A mutations
- Other rarer mutations

The main molecular alterations and their characteristics are summarized in Table 2 [52-71].

Recent research efforts have been made to identify prognostic markers of recurrence. Among these, TERT promoter mutations have never been observed in de novo atypical meningiomas, but they have been identified in secondary atypical meningiomas that have progressed from grade I primary tumors [72,73]. Moreover, overall copy number aberrations (e.g., monosomy 22, 1p loss, 6q loss, 18q loss and monosomy 14) have been associated with risk of recurrence in patients with resected atypical meningiomas, thus presenting as a tool to guide the use of adjuvant radiotherapy [54].

Sahm et al. identified six subclasses of meningiomas based on DNA methylation profiling, with distinct mutational, cytogenetic, histological and gene expression patterns and different risks of recurrence. Group A was composed of four methylation classes (MC) – MC benign-1 (n = 113), MC benign-2 (n = 118), MC benign-3 (n = 73) and MC intermediate-A (n = 105) – while group B was divided into MC intermediate-B (n = 47) and MC malignant (n = 41) [74]. Classification into these methylation subclasses proved superior to WHO grading in the prognosticication of progression-free survival (PFS). Patients in the WHO grade I MC intermediate group had a worse prognosis than patients classified in grade I only by histology and a similar prognosis to those with WHO grade II disease. Grade II MC benign patients had a better prognosis than patients classified in WHO grade II.

Similarly, Olar et al. identified a 64-CpG loci methylation predictor associated with different recurrence risks and, in particular, patients were divided into two methylation subgroups: a clinically favorable subgroup with 98 hypermethylated CpG loci and a median recurrence-free survival (RFS) not reached (range 0.27–16.6 years) and
a clinically unfavorable subgroup with 185 hypermethylated CpG loci and a median RFS of 12.07 years (range 0.31–17.61) [75].

In a recent study, Nassiri et al. developed a nomogram that combined DNA methylation profiles with clinical factors to predict tumor recurrence and the consequent selection of patients who could benefit from adjuvant radiotherapy [76]. The nomogram used clinical factors such as histopathological grade, extent of resection and burden of copy number alterations. Patients were divided into lower- and higher-risk groups according to the 5-year methylome predictor profile in the three validation cohorts: higher-risk groups had median RFS of 2.1, 8.1 and 4.2 years, while lower-risk patients had median PFS unreached, unreached and 7.2 years in the three validation cohorts, respectively.

**Surgery**

While for incidental asymptomatic meningiomas radiological surveillance can an appropriate strategy [77,78], for growing and symptomatic tumors the standard of care remains a surgical approach. The localization of the tumor influences the surgical radicality, which can be limited in the case of brain tissue invasion or vascular involvement. When the tumor is resected, a patch is used to replace the dura. In the case of bone involvement, which can represent a site of recurrence, these parts have to be removed [79]. The extension of resection is measured with Simpson grade [80] and is classified in five grades:

1. Complete resection, with dural and bone resection
2. Gross total resection with dural coagulation
3. Macroscopic resection, without dural excision or coagulation
4. Subtotal resection
5. Biopsy

Five-year recurrence rates after gross total resection are 7–23% in grade I, 50–55% in grade II and 72–78% in grade III meningiomas [2,7,24]. When residual disease is present, the risk of recurrence is higher, and this can often happen when the localization of the meningioma limits a radical surgical approach.

Unfortunately, brain surgery could cause neurological, neurocognitive and functional consequences that limit the quality of life of these patients [81]. Another factor to consider is the localization of the tumor, because the resection is based on the removal of the bone to expose the tumor [82]. Novel surgical techniques include endoscopic approaches, image-guided surgery, neuromonitoring, or the use of intraoperative navigation and optical systems that allow a wider intraoperative visualization. Endoscopic approaches through the nasal cavity have been used to treat meningiomas localized at the olfactory groove, planum sphenoidale and tuberculum [83].

The visualization of tumor–vessel relationships has been enhanced with novel imaging techniques such as infrared technology, with the administration of intraoperative indocyanine green videoangiography [84,85]. High-definition exoscope systems are also notable among the technological advancements in neurosurgery. They consist of telescope-based visualization tools that allow clinicians to obtain high-quality video images with large focal distance and wide field of view and could be helpful in the treatment of spinal meningiomas [86].

**Radiotherapy**

For surgically untreatable meningiomas, irradiation represents a valid alternative to control local growth, but it is not as effective as surgery for symptom relief and it does not provide histological diagnosis. Different radiotherapy approaches can be used in the adjuvant setting after surgical resection or to treat disease recurrence: external beam radiotherapy (EBRT) and single-fraction stereotactic radiosurgery (SRS).

Single-fraction SRS is typically used in meningiomas of <30 mm diameter that are not adjacent to radiation-sensitive structures. The use of multiple-fraction SRS techniques in tumors of >10 mm³, with up to five fractions, is associated with decreased complication rates (especially edema and necrosis) [24], probably due to the possibility of repair of the normal tissue between treatments [87]. SRS has been associated with a 5-year PFS of 58–83% in the recurrent or adjuvant setting for grade II meningiomas [24]. For recurrent grade III meningiomas or in the adjuvant setting, the use of SRS at median dose of 14 Gy has been reported to confer a 5-year PFS of 57% [88].

For brain-invasive meningiomas, EBRT is beneficial to maintain a larger radiation field to prevent local recurrence. Currently, there is no consensus on doses, fractioning and timing of radiotherapy in meningiomas due to the lack of Phase III randomized controlled trials.
After surgery, adjuvant radiotherapy is aimed at decreasing the risk of recurrence and improving local control [4]. Adjuvant radiotherapy can be avoided in radically resected WHO grade I meningiomas, but can be proposed in cases of incomplete resection, for example in high-risk areas such as the cavernous sinus, or if subsequent salvage total resection is not possible, with a dose of approximately 50 Gy [24]. In grade II meningiomas the role of adjuvant radiotherapy is still controversial, but it can be considered in cases of incomplete resection. Grade III meningiomas are associated with higher risk of recurrence after resection, so postoperative high-dose radiotherapy is the standard of care and is correlated with improved local control [89]. In grade III meningiomas EBRT is associated with a 5-year PFS benefit of 15–80% in the adjuvant setting, but no benefit has been reported in recurrent disease [90,91]. In grade II–III meningiomas the dose of radiotherapy should be 54–60 Gy with daily fractions over 5–6 weeks [92].

The co-operative group trial NRG/RTOG 0539 (NCT00895622) has prospectively tested the role of adjuvant EBRT with the primary end point of 3-year PFS [92–94]. The patients enrolled were divided into three classes of risk based on tumor WHO grading and residual disease. The low-risk patients, including grade I meningioma with gross total resection (Simpson 1–3) or subtotal resection (grade 4–5), have been followed with observation only, with a preliminary RFS of 86%. Recurrence was higher in patients with subtotal resection (40%) compared with total resection (8.6% at 5 years) [93]. These data confirm that radiotherapy for gross totally resected grade I meningiomas can be avoided. Intermediate-risk patients included those with recurrent grade I or newly diagnosed gross totally resected grade II meningiomas. These patients were treated with salvage radiotherapy or adjuvant EBRT at the dose of 54 Gy, respectively. The radiation treatment was associated with a 3-year actuarial local failure rate of 4.1% and a 3-year overall survival rate of 96%, with no grade 3 toxicities [94]. Based on this benefit the use of EBRT is recommended in recurrent grade I meningiomas. The category of high-risk patients included those with newly diagnosed or recurrent grade III meningioma of any resection extent, recurrent grade II tumor of any resection extent, or newly diagnosed subtotally resected grade II meningioma. The treatment consisted of intensity-modulated radiotherapy (IMRT) with a simultaneous integrated boost technique (60 Gy high dose and 54 Gy low dose in 30 fractions). The treatment with IMRT (60 Gy/30) was associated with a 3-year PFS of 58.8%, with acute and late adverse events limited to grades 1–3, but with a single grade 5 event (necrosis-related event) [92]. These results support the use of postoperative IMRT for high-risk meningioma. In resected grade II meningiomas the prospective randomized trial (ROAM/EORTC-1308; ISRCTN71502099) is comparing the use of radiotherapy versus active monitoring after resection [95].

Brachytherapy with radioactive $^{125}$I seeds is no longer used in meningiomas [96].

In summary, for newly diagnosed radically resected grade I meningiomas adjuvant radiotherapy is not indicated, while it can be considered in cases of subtotal or partial resection, in particular in case of lesions adjacent to important structures [4]. SRS and EBRT have both been associated with improved and durable local control. SRS is preferred in the case of small meningiomas ($<3$ cm diameter or $<10$ cm$^3$ volume) with distinct margins and sufficiently distant from important CNS structures [24].

For grade II meningiomas adjuvant radiotherapy still has an unclear role, but SRS could be employed after gross total resection as an alternative to observation – in particular for lesions in eloquent areas, after subtotal or partial resection, or for recurrent disease to achieve local control – while the role of EBRT is more controversial [4]. Some studies recommend EBRT irrespective of resection extent, especially when surgery cannot be radical [89,97]. Conversely, other studies did not reveal a survival benefit for adjuvant EBRT [98,99].

For grade III meningiomas, both EBRT and SRS are recommended following surgery irrespective of resection extent [24].

Salvage radiotherapy alone or after surgical excision is a feasible option for recurrent disease.

The NRG BN003 (NCT03180268) is testing the use of adjuvant radiotherapy with 54 Gy in newly diagnosed grade III meningiomas.

Ongoing clinical trials of radiotherapy approaches in meningiomas are listed in Table 3.

### Systemic treatments

The use of systemic treatments in meningiomas remains largely experimental considering the limited results in terms of response, and it is reserved for cases of recurrent/progressive disease not suitable for surgery or radiotherapy. At the present time there is no clear evidence on standard of care, and enrollment in clinical trials is recommended in case of disease progression, defined as a 15% increase in the sum of the products of perpendicular diameters of the lesion within 6 months with stable or increased steroid therapy, or when there is the development of a new lesion [100].
There has been a large debate about the best end point of treatment efficacy to use. A meta-analysis of 47 publications including various treatment options in surgery- and radiation-refractory meningioma identified the end point for medical therapy trials as 6-month PFS [101]. Another appropriate end point could be a combination of 6-month PFS and radiographic response [100].

Several compounds have been investigated in retrospective series and small prospective studies (summarized in Table 4), such as IFN-α [102–104], somatostatin analogs (pasireotide [105] and octreotide [106,107]), VEGF/VEGFR inhibitors [106–111], EGFR inhibitors (erlotinib and gefitinib) [112], imatinib [113], mifepristone [114] and chemotherapy (hydroxyurea [115–117], temozolomide [118], irinotecan [119] and trabectedin [120,121]). The use of cytotoxic chemotherapy has shown limited efficacy and it is not recommended. Meningioma is a highly vascular tumor with upregulated expression of VEGF [122], which has led to the investigation of antiangiogenic agents [123] such as bevacizumab (a monoclonal antibody against VEGF) [109–111,124–126], sunitinib (a tyrosine kinase inhibitor against VEGFR) [108] and vatalanib [127], which have been tested in Phase II trials (Table 4).

Considering the molecular alterations carried by meningiomas, several targeted agents have been tested. The inactivation of NF2 can be found in 50% of sporadic meningiomas [128,129]; this gene interacts with the mTOR pathway though a negative regulation of mTORC1 and a positive regulation of mTORC2. Consequently, NF2 inactivation results in mTORC1 being overexpressed [130]; thus mTOR inhibitors, like everolimus in combination with octreotide [131] or bevacizumab [109], have been investigated in the treatment of meningioma. Moreover, vistusertib (AZD2014), a dual inhibitor of mTORC1 and mTORC2, showed promising results in preclinical studies in recurrent and progressive meningiomas [132].
### Table 4. Studies of systemic therapies in meningiomas.

| Treatment | Type of study | Setting | N of patients | Outcome | Ref. |
|-----------|---------------|---------|---------------|---------|------|
| IFN-α     | Prospective Phase II trial | Recurrent grade I | 35 | PFS-6mo 54%; mOS 8 months | [103] |
| IFN-α     | Retrospective case series | Recurrent higher grade | 35 | PFS-6mo 17%; mOS 8 months | [104] |
| Mifepristone | Phase III prospective randomized trial (SWOG-S9005) | Primary or recurrent meningioma | 164 | No statistical difference between mifepristone and placebo in terms of failure-free and overall survival | [114] |
| Pasireotide long-acting release | Phase II trial | Recurrent grade I-II-III meningiomas | 34 | Grade I: PFS-6mo 50%; mOS 104 weeks Grade II-III: PFS-6mo 17%; mOS 26 weeks | [105] |
| Octreotide | Phase II trial | Recurrent high-grade meningioma | 9 | PFS-6mo 44%; mOS 18.7 months | [107] |
| Long-acting octreotide | Prospective pilot trial | Recurrent meningioma | 16 | PFS-6mo 44%; mOS 7.5 months | [106] |
| Peptide receptor radionuclide therapy | Phase II trial | Progressive unresectable meningioma | 34 | Stable disease 65.6%; mOS 8.6 years | [134] |
| Hydroxyurea | Retrospective study | Progressive grade I meningioma | 60 | PFS-6mo 10% | [115] |
| Hydroxyurea | Retrospective study | Progressive grade II/III meningioma | 35 | PFS-6mo 3%; mOS 8 months | [116] |
| Hydroxyurea plus imatinib | Phase II trial | Recurrent or progressive meningioma | 15 | Prematurely closed due to slow accrual rate Analysis on 15 patients: no activity | [117] |
| Temozolomide | Phase II trial | Recurrent grade I meningioma | 16 | PFS-6mo 0%; mOS 7.5 months | [118] |
| Irinotecan | Phase II trial | Recurrent grade I meningiomas | 16 | PFS-6mo 6%; mOS 7 months | [119] |
| Trabectedin | Randomized Phase II trial (EORTC-1320-BTG) | Grade II/III meningiomas progressed after maximal feasible surgery and radiotherapy | 90 | No improvement of mPFS or mOS | [121] |
| Everolimus plus octreotide | Phase II trial (CEVOREM trial) | Recurrent tumor progression ineligible for further surgery or radiotherapy | 20 | PFS-6mo 55%; OS-6mo 90% OS-12mo 75% Major decrease of growth rate of more than 50% in 78% of tumors | [131] |
| Everolimus plus bevacizumab | Phase II trial | Recurrent, progressive grade I-II-III meningioma after surgical resection and local radiotherapy | 17 | Stable disease 88% PFS-6mo 69%; mOS 23.8 months | [109] |
| Bevacizumab | Retrospective study | Recurrent or progressive meningioma | 14 | PFS-6mo 86%; mOS not reached | [110] |
| Bevacizumab | Retrospective study | Grade II or III meningiomas progressed after surgery and radiotherapy | 15 | PFS-6mo 44%; mOS 15 months | [111] |
| Bevacizumab | Phase II trial | Grade I-II-III recurrent meningioma | 40 | Grade I: PFS-6mo 87%; mOS 35.6 months Grade II: PFS-6mo 77%; mOS not reached Grade III: PFS-6mo 46%; mOS 12.4 months | [124] |
| Sunitinib | Phase II trial | Grade II-III refractory meningioma | 36 | PFS-6mo 42%; mPFS 5.2 months mOS 24.6 months | [108] |
| Vatalanib | Phase II trial | Recurrent high-grade meningioma | 22 | PFS-6mo 37.5%; mOS 23 months | [127] |
| Erlotinib or gefitinib | Phase II trial | Recurrent grade I-II-III meningiomas | 25 | Grade I: PFS-6mo 25%; 12mo OS 50% Grade II-II: PFS-6mo 29%; 12mo OS 65% | [112] |
| Imatinib | Phase II trial | Recurrent grade I-II-III meningiomas | 23 | Grade I: PFS-6mo 45%; Grade II-II: PFS-6mo 0% | [113] |

6mo: 6 months; 12mo: 12 months; m: Median; PFS: Progression-free survival; OS: Overall survival.
Table 5. Ongoing clinical trials of systemic treatments in meningiomas.

| Clinical.gov identifier name | Status | Setting | N | Phase | Arms(s) | Primary outcome |
|-----------------------------|--------|---------|---|-------|---------|----------------|
| NCT03071874                | Recruiting | Progressive or recurrent intracranial grade II–III meningioma | 30 | II | Vistusertib (AZD2014, mTORC1/mTORC2 inhibitor) | PFS |
| NCT02648997                | Recruiting | Progressive or recurrent grade II–III meningioma | 50 | II | Cohort 1: nivolumab monotherapy 240 mg every 2 weeks or 480 mg every 4 weeks  
Cohort 2: nivolumab in combination with ipilimumab:  
• External beam RT (IMRT, 3D-CRT, or proton-beam radiation therapy)  
• Followed by 4 cycles of nivolumab (3 mg/kg every 3 weeks) + ipilimumab (1 mg/kg every 3 weeks)  
• Followed by nivolumab monotherapy (480 mg every 4 weeks) | PFS-6mo |
| NCT03279692                | Recruiting | Treated or untreated recurrent or residual intracranial or metastatic meningioma or meningioma with extracranial spread | 26 | II | Pembrolizumab | PFS |
| NCT03971461                | Recruiting | Progressive grade I or progressive or residual grade II–III meningioma | 32 | II | Lutathera | PFS-6mo |
| NCT03631953                | Recruiting | Progressive grade I–III meningioma | 25 | I | A panel of three doses of alpelisib in combination with fixed dose of trametinib (1.5 mg every day) | Dose-limiting toxicity |
| NCT03267836                | Recruiting | Neoadjuvant | 12 | I | Avelumab for 3 months started concurrently with proton therapy 20 CGE, followed by surgery and adjuvant avelumab for 3 months  
If complete response after neoadjuvant therapy: no surgery, but adjuvant avelumab for 3 months | Immunogenicity as measured by changes of CD8+/CD4+ tumor infiltrating lymphocytes |
| NCT04501705                | Recruiting | Recurrent grade II–III meningioma | 29 | NA | Apatinib mesylate (anti-VEGFR2) | PFS-6mo |
| NCT03604978                | Recruiting | Progressive or recurrent grade II–III meningioma | 38 | I/II | Cohort A: nivolumab and radiosurgery  
Cohort B: nivolumab, ipilimumab and radiosurgery | Maximum tolerated combination of radiosurgery and nivolumab plus or minus ipilimumab  
Incidence of adverse event profile  
ORR: Objective response rate  
PFS: Progression-free survival  
PRRT: Peptide receptor radionuclide therapy |

6mo: 6 months; 12mo: 12 months; CGE: Cobalt gray equivalent; CRT: Conformal radiation therapy; CSF: Cerebrospinal fluid; IMRT: Intensity-modulated radiation therapy; NF: Neurofibromatosis; ORR: Objective response rate; PFS: Progression-free survival; PRRT: Peptide receptor radionuclide therapy.
### Table 5. Ongoing clinical trials of systemic treatments in meningiomas (cont.).

| Clinical.gov identifier name | Status | Setting | N  | Phase | Arm(s) | Primary outcome |
|-----------------------------|--------|---------|----|-------|--------|-----------------|
| NCT02933736                | Recruiting | Preoperative in Rb-positive grade II–III meningioma | 48 | I     | Ribociclib:  
  Cohort 1: last dose 2–4 h prior to craniotomy  
  Cohort 2: last dose 6–8 h prior to craniotomy  
  Cohort 3: last dose 23–25 h prior to craniotomy | Plasma exposure CSF penetration Brain accumulation of ribociclib |
| NCT03016091                | Recruiting | Recurrent surgically inaccessible grade II–III meningioma | 25 | II    | Pembrolizumab | PFS-6mo/12mo |
| NCT02831257                | Active, not recruiting | Progressive or symptomatic meningioma in NF2 syndrome | 18 | II    | AZD2014 (mTOR inhibitor) | Radiographic response rate |
| NCT04082520                | Recruiting | Previous treatment with fractionated radiotherapy or stereotactic radiosurgery, inoperable progressive meningioma of any grade | 41 | II    | Lutathera | PFS-6mo |
| NCT02847559                | Recruiting | Progressive or recurrent grade II–III meningioma | 27 | II    | Bevacizumab and electric field therapy | PFS-6mo |
| NCT02282917                | Active, not recruiting | 3 weeks prior to surgery of NF2 or sporadic meningioma | 5 | I     | AR-42 (histone deacetylase inhibitor) | Expression levels of phospho-Akt (p-AKT) and p16INKA |
| NCT03273712                | Recruiting | Meningioma not amenable to standard treatment | 46 | II    | 90Y-DOTATOC-PRRT | Treatment efficacy and renal, hematological and clinical toxicities |
| NCT04374305                | Recruiting | Progressive meningioma in NF2 syndrome | 80 | II    | Brigatinib | Radiographic response rate |
| NCT03173950                | Recruiting | Progressive grade II–III meningioma | 180 | II   | Nivolumab | ORR PFS |
| NCT03095248                | Recruiting | No prior medical treated meningioma in NF2 syndrome | 34 | II    | Selumetinib | ORR |
| NCT04541082                | Recruiting | No standard treatment options available for grade II–III meningioma | 102 | I    | ONC206 | Maximum tolerated dose |
| NCT03220646                | Recruiting | Recurrent meningioma | 78 | II    | Ribociclib | Radiographic response rate PFS-6mo |
| NCT02423525                | Active, not recruiting | Meningioma with no other option of standard therapy | 24 | I    | Afatinib | Rate of dose-limiting toxicities Maximum tolerated dose |

6mo: 6 months; 12mo: 12 months; CGE: Cobalt gray equivalent; CRT: Conformal radiation therapy; CSF: Cerebrospinal fluid; IMRT: Intensity-modulated radiation therapy; NF: Neurofibromatosis; ORR: Objective response rate; PFS: Progression-free survival; PRRT: Peptide receptor radionuclide therapy.
The identification of somatostatin receptor in meningiomas has led to the evaluation of somatostatin analogs in these tumors. Despite promising preliminary evidence of antitumor activity of these compounds in patients with recurrent, unresectable meningiomas, subsequent trials did not confirm a clear clinical benefit. Octreotide has an antiproliferative effect and does not induce apoptosis of meningioma cells, so its activity mostly results in reduced tumor growth and not in tumor shrinkage [133].

Peptide receptor radionuclide therapy, which links radioactive isotopes (such as ⁹⁰Y- and ¹⁷⁷Lu-DOTATOC) to analogs of the somatostatin receptor, has been tested in progressive meningioma in a Phase II trial, with disease stabilization in most patients [134].

Conclusion
Meningioma is a tumor difficult to diagnose in an early stage and which can be found incidentally, but not always it is a benign disease. Multiple types of treatments, including surgery and different radiotherapy approaches, are available depending on the grade and the extent of primary resection with no definite standard of care.

Future perspective
The management of meningioma still presents some unresolved issues. The expanding knowledge on the genetic alterations carried by this tumor is making possible to experiment with novel treatment strategies. The use of systemic therapies is not defined; some drugs have been investigated but with limited results in terms of response. Several clinical trials of radiotherapy and/or systemic therapies are ongoing to improve the management of this tumor, and inclusion in clinical trials is recommended.

Novel agents being tested in meningiomas include histone deacetylase inhibitors. Two trials are ongoing: NCT01324635 (panobinostat in association with RT) and NCT02282917 (AR-42).

Immune checkpoint inhibitors are also being evaluated in meningioma. In particular, nivolumab (NCT02648997), pembrolizumab (NCT03279692 and NCT03016091) and avelumab in combination with proton radiotherapy (NCT03267836) are under investigation. Other studies are also analyzing the efficacy of the MEK inhibitor selumetinib (NCT03095248) and the CDK-p16-Rb inhibitor ribociclib (NCT02933736). Considering the promising preclinical results, the dual inhibitor of mTORC1 and mTORC2 vistusertib is currently under evaluation in two Phase II clinical trials (NCT03071874: recruiting; NCT02831257: active, not recruiting). Furthermore, several ongoing trials are testing the use of peptide receptor radionuclide therapy in meningiomas (NCT03971461, NCT04082520, NCT03273712).

Ongoing clinical trials of systemic therapies in meningiomas are shown in Table 5.

Author contributions
A Brandes and E Franceschi were responsible for conceptualization. A Brandes, E Franceschi and I Maggio were responsible for data curation. A Brandes, E Franceschi, I Maggio, A Tosoni, V Di Nunno, L Gatto and R Lodi undertook the investigation. A Brandes and E Franceschi were responsible for the methodology and A Brandes for supervision. A Brandes, E Franceschi and I Maggio wrote the original manuscript draft, and A Brandes, A Tosoni, V Di Nunno, L Gatto and R Lodi were responsible for review and editing.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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References
Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Gittleman HR, Ostrom QT, Rouse CD et al. Trends in central nervous system tumor incidence relative to other common cancers in adults, adolescents, and children in the United States, 2000 to 2010. Cancer 121(1), 102–112 (2015).

2. Ostrom QT, Gittleman H, Liao P et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol. 19(Suppl. 5), v1–v88 (2017).
3. Achey RL, Gittleman H, Schroer J, Khanna V, Kruchko C, Barnholtz-Sloan JS. Nonmalignant and malignant meningioma incidence and survival in the elderly, 2005–2015, using the Central Brain Tumor Registry of the United States. *Neuro Oncol.* 21(3), 380–391 (2019).

4. Goldbrunner R, Minniti G, Preusser M *et al.* EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 17(9), e383–391 (2016).

**European Association of Neuro-Oncology guidelines for meningiomas.**

5. Chamberlain MC. Meningiomas. In: *Primary Central Nervous System Tumors: Pathogenesis and Therapy.* Norden AD, Reardon DA, Wen PCY (Eds). 355–375 Humana Press, NJ, USA (2011).

6. Hashiba T, Hashimoto N, Izumoto S *et al.* Serial volumetric assessment of the natural history and growth pattern of incidentally discovered meningiomas. *J. Neurosurg.* 110(4), 675–684 (2009).

7. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. *Future Oncol.* 14(21), 2161–2177 (2018).

8. Hijiya N, Hudson MM, Lensing S *et al.* Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA* 297, 1207–1215 (2007).

9. Preston DL, Ron E, Yonehara S *et al.* Tumors of the nervous and pituitary gland associated with atomic bomb radiation exposure. *J. Natl Cancer Inst.* 94, 1555–1563 (2002).

10. Ron E, Modan B, Boice JD Jr *et al.* Tumors of the brain and nervous system after radiotherapy in childhood. *N. Engl. J. Med.* 319, 1033–1039 (1988).

11. Saderzki S, Flint-Richter P, Starinsky S *et al.* Genotyping of patients with sporadic and radiation-associated meningiomas. *Cancer Epidemiol. Biomarkers Prev.* 14, 969–976 (2005).

12. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. *J. Neurosurg.* 100(6), 1002–1013 (2004).

13. Claus EB, Black PM, Bondy ML *et al.* Exogenous hormone use and meningioma risk: what do we tell our patients? *Cancer* 110, 471–476 (2007).

14. Vadivelu S, Sharer L, Schulder M. Regression of multiple intracranial meningiomas after cessation of long-term progesterone agonist therapy. *J. Neurosurg.* 112, 920–924 (2010).

15. Blishteyn S, Crook JE, Jaeckle KA. Is there an association between meningioma and hormone replacement therapy? *J. Natl Cancer Inst.* 103, 4–23 (2015).

16. Wigertz A, Lonn S, Hall P *et al.* Reproductive factors and risk of meningioma and glioma. *Cancer Epidemiol. Biomarkers Prev.* 17, 2663–2670 (2008).

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

18. Claus EB, Park PJ, Carroll R, Chan J, Black PM. Specific genes expressed in association with progesterone receptors in meningioma. *Cancer Res.* 68, 314–322 (2008).

19. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *Epidemiol. Biomarkers Prev.* 19, 1588 (2017).

20. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. *J. Neurosurg.* 100(6), 1002–1013 (2004).

21. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. *Future Oncol.* 14(21), 2161–2177 (2018).

22. Flint-Richter P, Mandelzweig L, Oberman B, Sadetzki S. Possible interaction between ionizing radiation, smoking, and gender in the causation of meningioma. *Hum. Pathol.* 33, 1211 (2002).

23. Benson VS, Pirie K, Schüz J, Reeves GK, Beral V, Green J. Million Women Study Collaborators. Mobile phone use and risk of brain neoplasms and other cancers: prospective study. *Int. J. Epidemiol.* 42, 792–802 (2013).

24. Rogers L, Barani I, Chamberlain MC *et al.* Meningiomas: knowledge base, treatment outcomes, and uncertainties. a RANO review. *J. Neurosurg.* 122(1), 4–23 (2015).

25. Johnson MD, Powell SZ, Boyer PJ *et al.* Dural lesions mimicking meningiomas. *Hum. Pathol.* 33, 1211 (2002).

26. Nowosielski M, Galldiks N, Iglseder S *et al.* Diagnostic challenges in meningioma. *Neuro Oncol.* 19, 1588 (2017).

27. Johnson MD, Powell SZ, Boyer PJ *et al.* Dural lesions mimicking meningiomas. *Hum. Pathol.* 33, 1211 (2002).

28. Tu PH, Giannini C, Judkins AR *et al.* Clinicopathologic and genetic profile of intracranial marginal zone lymphoma: a primary low-grade CNS lymphoma that mimics meningioma. *J. Clin. Oncol.* 23, 5718 (2005).

29. Tan LA, Kasiwil MK, Wewel J *et al.* Neurosarcooidosis mimicking bilateral posterior fossa tentorial meningiomas. *J. Neurooncol.* 125, 435 (2015).
30. Haring I, Hartmann M, Sommer C, Sartor K. Characterization of necrotic meningioma using diffusion MRI, perfusion MRI, and MR spectroscopy: case report and review of the literature. *Neuroradiology* 46(3), 189–193 (2004).

31. Buhl R, Nabavi A, Wolff S et al. MR spectroscopy in patients with intracranial meningiomas. *Neurol. Rev.* 29(1), 43–46 (2007).

32. Coroller TP, Bi WL, Huynh E et al. Radiographic prediction of meningioma grade by semantic and radiomic features. *PloS ONE* 12(11), e187908 (2017).

33. Yan PF, Yan L, Hu TT et al. The potential value of preoperative MRI texture and shape analysis in grading meningiomas: a preliminary investigation. *Transl. Oncol.* 10(4), 570–577 (2017).

34. Laukamp KR, Shakirin G, Baessler B et al. Radiomics for the prediction of meningioma grade by perfusion CT and PET/MRI hybrid imaging. *World J. Surgical Oncol.* 15(1), 1–14 (2017).

35. Hamerla G, Meyer HJ, Schob S et al. Radiomic characterization of meningiomas using multiparametric MRI and MR spectroscopy: case report and review of the literature. *Neuroradiology* 36(3), 221–228 (1997).

36. Gu H, Zhang X, di Russo P, Zhao X, Xu T. The current state of radiomics for meningiomas: promises and challenges. *Front. Oncol.* 10, 577736 (2020).

37. Niu L, Zhou X, Duan C et al. Differentiation researches on the meningioma subtypes by radiomics from contrast-enhanced magnetic resonance imaging: a preliminary study. *World J. Neurosurg.* 126, e646–e652 (2019).

38. Li X, Lu Y, Xiong J et al. Presurgical differentiation between malignant haemangiopericytoma and angiomatous meningioma by a radiomics approach based on texture analysis. *J. Neuroradiol.* 46(5), 281–287 (2019).

39. Zhang Y, Chen JH, Chen TY et al. Radiomics approach for prediction of recurrence in skull base meningiomas. *Neuroradiology* 61(12), 1355–1364 (2019).

40. Zhao J, Yao K, Liu P et al. A radiomics model for preoperative prediction of brain invasion in meningioma non-invasively based on MRI: a multicentre study. *EBioMedicine* 58, 102908 (2020).

41. Rachinger W, Stockeitg VM, Terpolilli NA et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *J. Nucl. Med.* 56(3), 347–353 (2015).

42. Afshar-Oromieh A, Wolf MB, Kratochwil C et al. Comparison of 68Ga-DOTATOC-PET/CT and PET/MRI hybrid systems in patients with cranial meningioma: initial results. *Neuro Oncol.* 17(12), 1576–1587 (2015).

43. Galldiks N, Albert NL, Sommerrauer M et al. PET imaging in patients with meningioma-report of the RANO/PET Group. *Neuro Oncol.* 19(12), 1576–1587 (2017).

44. Rutten I, Cabay J-E, Wintgens N et al. PET/CT of skull base meningiomas using 2–18F-fluoro-L-tyrosine: initial report. *J. Nucl. Med.* 48(5), 720–725 (2007).

45. Bosnyak E, Kamson DO, Guastella A et al. Molecular imaging correlates of tryptophan metabolism via the kynurenine pathway in human meningiomas. *Neuro Oncol.* 17(9), 1284–1292 (2015).

46. Louis DN, Perry A, Reifenberger G et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 131(6), 803–820 (2016).

**Pivotal work of the World Health Organization that describes histological classification of CNS tumors, including meningioma.**

47. Menke JR, Raleigh DR, Gown AM, Thomas S, Perry A, Tihan T. Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen. *Acta Neuropathol.* 130(3), 441–443 (2015).

48. Hsu DW, Efird JT, Hedley-Whyte ET. Progesterone and estrogen receptors in meningiomas: prognostic considerations. *J. Neurosurg.* 86(1), 113–120 (1997).

49. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. *J. Neurosurg.* 105(2), 163–173 (2006).

50. Abedalthagafi M, Bi WL, Aizer AA et al. Oncogenic PI3K mutations are as common as *AKT1* and *SMO* mutations in meningioma. *Neuro Oncol.* 18(5), 649–655 (2016).

51. Clark VE, Harmancı AS, Bai H et al. Recurrent somatic mutations in *POLD2A* define a distinct subset of meningiomas. *Nat. Genet.* 48(10), 1253–1259 (2016).

52. Brastianos PK, Horowitz PM, Santagata S et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat. Genet.* 45(3), 285–289 (2013).

53. Boetto J, Bielle F, Sanson M, Peyre M, Kalamarides M. *SMO* mutation status defines a distinct and frequent molecular subgroup in olfactory groove meningiomas. *Neuro Oncol.* 19, 345–351 (2017).

54. Aizer AA, Abedalthagafi M, Bi WL et al. A prognostic cytogenetic scoring system to guide the adjuvant management of patients with atypical meningioma. *Neuro Oncol.* 18(2), 269–274 (2016).

55. Clark VE, Erson-Onay EZ, Serin A et al. Genomic analysis of non-NF2 meningiomas reveals mutations in *TRAF7, KLF4, AKT1*, and *SMO*. *Science* 339, 1077–1080 (2013).

56. Yuzawa S, Nishihara H, Yamaguchi S et al. Clinical impact of targeted amplicon sequencing for meningioma as a practical clinical sequencing system. *Modern Pathol.* 29, 708–716 (2016).
57. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

58. Reuss DE, Piro RM, Jones DT et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. Acta Neuropathol. 125, 351–358 (2013).

59. McConnell BB, Yang VW. Mammalian Kruppel-like factors in health and diseases. J. Biol. Chem. 215(4), 827–832 (1995).

60. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

61. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

62. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

63. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

64. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

65. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

66. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

67. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

68. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

69. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

70. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

71. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

72. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

73. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

74. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

75. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

76. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

77. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

78. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

79. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

80. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

81. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

82. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

83. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).

84. Xu LG, Li LY, Shu HB. TRAF7 potentiates MEKK3-induced AP1 and CHOP activation and induces apoptosis. J. Biol. Chem. 279, 17278–17282 (2004).
d’Avella E, Volpin F, Manara R. Indocyanine green videoangiography (ICGV)-guided surgery of parasagittal meningiomas occluding the superior sagittal sinus (SSS). *Acta Neurochir. (Wien)* 155, 415–420 (2013).

De Divitiis O, D’avella E, Denaro L, Somma T, Sacco M et al. Vitom 3D: preliminary experience with intradural extramedullary spinal tumors. *J. Neurosurg. Sci.* doi: 10.23736/S0390-5616.19.04666-6 (2019) (Epub ahead of print).

Kirkpatrick JP, Solty S G, Lo SS, Beal K, Shrieve DC, Brown PD. The radiosurgery fractionation quandary: single fraction or hypofractionation? *Neuro Oncol* 19(Suppl. 2), i38–i49 (2017).

El-Khair M, Majdoub E, Hoevels M et al. Stereotactic LINAC radiosurgery for incompletely resected or recurrent atypical and anaplastic meningiomas. *Acta Neurochirurgica* 153(9), 1761–1767 (2011).

Hug EB, Devries A, Thornton AF et al. Management of atypical and malignant meningiomas: role of high-dose, 3D–conformal radiation therapy. *J. Neurooncol* 48, 151–160 (2000).

Fatima N, Meola A, Ding YY et al. The Stanford stereotactic radiosurgery experience on 7000 patients over 2 decades (1999-2018): looking far beyond the scalpel. *J. Neurosurg.* 1–17 (2021). doi:10.3171/2020.9.JNS201484

Dziuk TW, Woo S, Butler EB et al. Malignant meningioma: an indication for initial aggressive surgery and adjuvant radiotherapy. *J. Neurooncol* 37, 177–188 (1998).

Rogers CL, Won M, Vogelbaum MA et al. High-risk meningioma: initial outcomes from NRG Oncology/RTOG 0539. *Int. J. Radiat. Oncol. Biol. Phys.* 106(4), 790–799 (2020).

**Phase II study that supports postoperative radiotherapy for high-risk meningioma.**

Rogers L, Zhang P, Vogelbaum MA et al. Low-risk meningioma: initial outcomes from NRG oncology/RTOG 0539. *Int. J. Radiat. Oncol. Biol. Phys.* 96(5), 939–440 (2016).

**Phase II study showing that adjuvant radiotherapy can be avoided in gross totally resected grade I meningiomas.**

Rogers L, Zhang P, Vogelbaum MA et al. Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. *J. Neurosurg.* 129(1), 35–47 (2018).

**The results of this Phase II trial support the use of postoperative radiotherapy for newly diagnosed gross-total resected grade II or recurrent WHO grade I meningioma.**

Jenkinson MD, Weber DC, Haylock BJ, Mullucci CL, Zakaria R, Javadpour M. Radiotherapy versus observation following surgical resection of atypical meningioma (the ROAM trial). *Neuro Oncol* 16(11), 1560–1561 (2014).

Walcott BP, Nahed BV, Brastianos PK, Loeffler JS. Radiation treatment for WHO grade II and III meningiomas. *Acta Neurochirurgica* (Wien) 153(9), 1761–1767 (2011).

Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. *J. Neurosurg.* 115(4), 811–819 (2011).

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. *J. Neurosurg.* 117(4), 669–675 (2012).

Huang RY, Bi WL, Weller M et al. Proposed response assessment and endpoints for meningioma clinical trials: report from the Response Assessment in Neuro-Oncology Working Group. *Neuro Oncol* 21(1), 26–36 (2019).

Kaley TJ, Barani I, Chamberlain M et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neurol Oncol* 16, 829–840 (2014).

Koper JW, Zwarthoff EC, Hagemeijer A et al. Inhibition of the growth of cultured human meningioma cells by recombinant interferon-alpha. *Eur. J. Cancer* 27(4), 416–419 (1991).

Chamberlain MC, Glantz MJ. Interferon-alpha for recurrent World Health Organization grade 1 intracranial meningiomas. *Cancer* 113(8), 2146–2151 (2008).

Chamberlain MC. IFN-α for recurrent surgery- and radiation-refractory high-grade meningioma: a retrospective case series. *CNS Oncol* 2(3), 227–235 (2013).

Norden AD, Ligon KL, Hammond SN et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology* 84(3), 280–286 (2015).

Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 69(10), 969–973 (2007).

Simó M, Argirio AA, Macià M et al. Recurrent high-grade meningioma: a Phase II trial with somatostatin analogue therapy. *Cancer Chemother. Pharmacol.* 73(5), 919–923 (2014).

Kaley TJ, Wen P, Schiff D et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neurol Oncol* 17(1), 116–121 (2015).

**This Phase II study showed that sunitinib is active in recurrent atypical/malignant meningioma.**

Shih KC, Chowdhary S, Rosenblatt P et al. A Phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. *J. Neurosurg.* 129(2), 281–288 (2016).
Phase II trial that evaluated the efficacy of everolimus plus bevacizumab in patients with recurrent, progressive meningioma following surgical resection and local radiotherapy.

110. Lou E, Sumrall AL, Turner S et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. J. Neurooncol. 109(1), 63–70 (2012).

111. Nayak I, Iwamoto FM, Rudnick JD et al. Atypical and anaplastic meningiomas treated with bevacizumab. J. Neurooncol. 109(1), 187–193 (2012).

112. Norden AD, Raizer JJ, Abrey LE et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. J. Neurooncol. 96(2), 211–217 (2009).

113. Wen PY, Yung WKA, Lammorn KR et al. Phase II study of imatinib mesylate for recurrent meningioma (North American Brain Tumor Consortium study 01–08). J. Neurooncol. 11(6), 853–860 (2009).

114. Ji Y, Rankin C, Grunberg S et al. Temozolomide for treatment-resistant recurrent meningioma. J. Neurooncol. 104(3), 765–771 (2011).

115. Chamberlain MC, Johnston SK. Hydroxyurea for recurrent surgery and radiation refractory meningioma: a retrospective case series. J. Neurooncol. 107(2), 315–321 (2012).

116. Chamberlain MC. Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma. J. Neurooncol. 78(3), 271–276 (2006).

117. Mazza E, Brandes A, Zanon S et al. Hydroxyurea with or without imatinib in the treatment of recurrent or progressive meningiomas: a randomized Phase II trial by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). Cancer Chemother. Pharmacol. 77(1), 115–120 (2016).

118. Chamberlain MC, Tsao-Wei DD, Groschen S. Temozolomide for treatment-resistant recurrent meningioma. Neurology 62(7), 1210–1212 (2004).

119. Chamberlain MC, Tsao-Wei DD, Groschen S. Salvage chemotherapy with CPT-11 for recurrent meningioma. J. Neurooncol. 78(3), 271–276 (2006).

120. Preusser M, Spiegl-Kreinecker S, L¨otsch D et al. Trabectedin has promising antineoplastic activity in high-grade meningioma. Cancer 118(20), 5038–5049 (2012).

121. Preusser M, Sivani A, Le Rhun E et al. Trabectedin for recurrent WHO grade II or III meningioma: a randomized Phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG). J. Clin. Oncol. 37(Suppl. 15), 2007–2007 (2019).

122. Le Rhun E, Taillibert S, Chamberlain MC. Systemic therapy for recurrent meningioma. Expert Rev. Neurother. 16(8), 889–901 (2016).

123. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Central Nervous System Cancers. Version 3.2020. September 11, 2020.

124. Grimm S, Kumthekar P, Chamberlain MC et al. MNGO-04 Phase II trial of bevacizumab in patients with surgery and radiation refractory progressive meningioma. Neuro Oncol. 17(Suppl. 5), v130 (2015).

125. Dasanu CA, Alvarez-Arge J, Limonadi FM, Codreanu I. Bevacizumab in refractory higher-grade and atypical meningioma: the current state of affairs. Exp. Op. Biol. Ther, 19(2), 99–104 (2019).

126. Goutagny S, Raymond E, Sterkers O, Colombani JM, Kalamarides M. Radiographic regression of cranial meningioma in a NF2 patient treated by bevacizumab. Ann. Radiol. 22(4), 990–991 (2011).

127. 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. J. Neurooncol. 117(1), 93–101 (2014).

128. Lekanne Deprez RH, Bianchi AB, Groen NA et al. Frequent NF2 gene transcript mutations in sporadic meningiomas and vestibular schwannomas. Am. J. Hum. Genet. 54(6), 1022–1029 (1994).

129. Rutledge MH, Sarrazin J, Rangaratnam S et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat. Genet. 6(2), 180–184 (1994).

130. Pachow D, Andrae N, Kiese N et al. mTORC1 inhibitors suppress meningioma growth in mouse models. Clin. Cancer Res. 19(5), 1180–1189 (2013).

131. Graillon T, Sanson M, Campello C et al. Everolimus and octreotide for patients with recurrent meningioma: results from the Phase II CEVOREM trial. Clin. Cancer Res. 26(3), 552–557 (2020).

132. Beauchamp RL, James MF, DeSouza PA et al. A high-throughput kinase screen reveals serum/glucocorticoid-regulated kinase 1 as a therapeutic target for NF2-deficient meningiomas. Oncotarget 6(19), 16981–16997 (2015).

133. Graillon T, Romano D, Defilles C et al. Octreotide therapy in meningiomas: in vitro study, clinical correlation, and literature review. J. Neurosurg. 127(3), 660–669 (2017).

134. Marincek N, Radojewski P, Dumont RA et al. Somatostatin receptor-targeted radiolpeptide therapy with 90Y-DOTATOC and 177Lu-DOTATOC in progressive meningioma: long-term results of a Phase II clinical trial. J. Nucl. Med. 56(2), 171–176 (2015).