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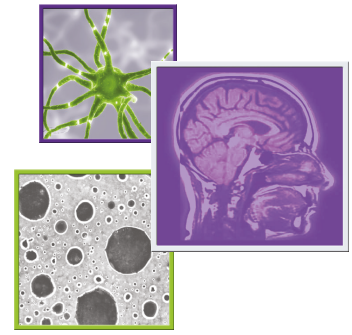

Meningioma: not always a benign tumor. A review of advances in the treatment of meningiomas

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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 (^{68}Ga-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.

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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, sarcoidosis,

Table 1. Meningioma frequency and WHO grading criteria.

WHO grade	Frequency (%)	Description
Grade I	80–85	Mitotic rate <4 per 10 HPFs 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.

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 (^{68}Ga-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-[(11)C]-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, angiomatous, microcystic, secretory, lymphoplasmacyte rich and metaplastic. Atypical meningiomas (grade II) can have a clear cell and choroid histology, while anaplastic/malignant meningiomas (grade III) can have papillary or rhabdoid histology.

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 • Activation of PI3K–AKT–mTOR pathway • Genomic stability	Multiple pathogenic variant	• Relatively common • Localization in the skull base	[52,53]
AKT1	• p.Glu17Lys mutation • Activation of PI3K–AKT–mTOR pathway • Genomic stability	Multiple pathogenic variant	• Relatively common • Grade I meningothelial meningiomas of the spine and skull base	[52–54]
TRAF7	• WD40 domain mutations • JUN N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling	Secretory meningiomas	• Up to 25% of grade I and II meningiomas • Location in anterior and middle medial skull base	[50,55–58]
KLF4	• High rate of co-occurrence with *TRAF7* mutations • Oncogenic activation and tumor suppression	Secretory meningiomas	• Up to half of *NF2*-unmutated meningiomas • Middle and lateral skull base	[55,56,58–60]
POLR2A	• p.Gln403Lys mutation • p.Leu438_His439del	Meningothelial histology	• Location in the tuberculum sellae	[55]
NF2	• 22q12 chromosome deletion • Genomic instability	Fibroblastic/transitional meningiomas	• Location in the hemispheres • Frequently multiple • Greater risk of mortality	[52,55,61,62]
BAP1	• Multiple mutations	Rhabdoid grade III meningioma	• Early tumor recurrence	[63]
Epigenetic modifications	• Mutations in *KDM5C*, *KDM6A*, *SMARCB1*, *EZH2*	• Multiple pathogenic variant • High-grade meningiomas (*EZH2*)	• 10% of non-NF2 meningiomas • *EZH2* mutation correlated with aggressiveness	[52,64–66]
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 *PRKAR1A*)
- *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 prognostication 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 mm^3, 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.

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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].

Table 3. Ongoing clinical trials of radiotherapy in meningiomas.

Clinical.gov identifier name	Status	Setting	N	Phase	Arm(s)	Primary outcome
NCT01166321 Carbon ion radiotherapy for atypical meningiomas (MARCIE)	Recruiting	Atypical meningioma macroscopic tumor after biopsy or subtotal resection (Simpson grade 4 or 5)	40	II	Carbon ion boost 18 Gy in single fractions of 3 Gy	PFS
NCT02974127 Multisession radiosurgery in large meningiomas (MuRaLM)	Active, not recruiting	Large and/or near to critical structures, intracranial benign meningiomas in exclusive or postoperative setting	170	II	Multisession radiosurgery	Radiation-related toxicities Local control evaluation assessed on MRI-based volumetric lesion measurements
NCT03180268 Phase III trial of observation versus irradiation for a gross totally resected grade II meningioma	Recruiting	Adjuvant in unifocal intracranial, gross totally resected grade II meningioma	148	III	**Arm I:** clinical observation **Arm II:** radiotherapy 5 days a week over 6.5–7 weeks for a total of 33 fractions	PFS
NCT0269399 A Phase I/II trial of increased dose intensity-modulated proton therapy for high-grade meningiomas	Recruiting	Grade II, Simpson grade 4–5 or unresected grade III meningioma	60	I/II	Intensity-modulated proton therapy	Dose-limiting toxicity
NCT01117844 Feasibility and Phase II study using proton radiation for WHO grade I–III meningiomas and hemangiopericytomas	Active, not recruiting	Untreated or incompletely excised grade I meningioma Recurrent, incompletely or completely excised grade II meningioma Recurrent, incompletely or completely excised grade III meningioma	52	I/II	Proton radiation	Feasibility and safety
NCT00895622 Phase II trial of observation for low-risk meningiomas and of radiotherapy for intermediate- and high-risk meningiomas	Active, not recruiting	Grade I–III meningioma, newly diagnosed or recurrent, and of any resection extent	244	II	Low risk: observation Intermediate risk: 54-Gy radiotherapy High risk: 60-Gy radiotherapy	3-year PFS
NCT04278118 HiPPI: A Phase II trial of hypofractionated pencil beam scanning proton therapy for benign intracranial tumors	Recruiting	Grade I–III meningioma	70		Hypofractionated radiotherapy	Local tumor control Incidence of adverse events

PFS: Progression-free survival.

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].

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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–III: 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–III: 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	Arm(s)	Primary outcome
NCT03071874 Single-arm Phase II study of the dual mTORC1/mTORC2 inhibitor vistusertib (AZD2014) provided on an intermittent schedule for sporadic patients with grade II–III meningiomas that recur or progress after surgery and radiation	Recruiting	Progressive or recurrent intracranial grade II–III meningioma	30	II	Vistusertib (AZD2014, mTORC1/mTORC2 inhibitor)	PFS
NCT02648997 Open-label Phase II study of nivolumab in adult participants with recurrent high-grade meningioma	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 Phase II trial of pembrolizumab in recurrent or residual high grade meningioma	Recruiting	Treated or untreated recurrent or residual intracranial or metastatic meningioma or meningioma with extracranial spread	26	II	Pembrolizumab	PFS
NCT03971461 Single-arm, open-label, multicenter Phase II study of ^{177}Lu-DOTATATE radionuclide in adults with progressive or high-risk meningioma	Recruiting	Progressive grade I or progressive or residual grade II–III meningioma	32	II	Lutathera	PFS-6mo
NCT03631953 Combination of alpelisib and trametinib in progressive refractory meningiomas: Phase I study	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 Phase Ib study of neoadjuvant avelumab and hypofractionated proton radiation therapy followed by surgery for recurrent radiation-refractory meningioma	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 Clinical study of apatinib in the treatment of recurrent atypical/malignant meningioma in adults	Recruiting	Recurrent grade II–III meningioma	29	NA	Apatinib mesylate (anti-VEGFR2)	PFS-6mo
NCT03604978 Phase I/II study of nivolumab plus or minus ipilimumab in combination with multi-fraction stereotactic radiosurgery for recurrent high-grade radiation-relapsed meningioma	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 radiological response

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.

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Table 5. Ongoing clinical trials of systemic treatments in meningiomas (cont.).

Clinical.gov identifier name	Status	Setting	N	Phase	Arm(s)	Primary outcome
NCT02933736 Phase 0/II study of ribociclib (LEE011) in preoperative Rb-positive recurrent high-grade glioma and meningioma patients scheduled for resection to evaluate central nervous system (CNS) penetration	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 Phase II, open-label, single-arm trial of pembrolizumab for refractory atypical and anaplastic meningioma	Recruiting	Recurrent surgically inaccessible grade II–III meningioma	25	II	Pembrolizumab	PFS-6mo/12mo
NCT02831257 Single-arm Phase II study of the dual mTORC1/mTORC2 inhibitor AZD2014 provided on an intermittent schedule for neurofibromatosis 2 patients with progressive or symptomatic meningiomas	Active, not recruiting	Progressive or symptomatic meningioma in NF2 syndrome	18	II	AZD2014 (mTOR inhibitor)	Radiographic response rate
NCT04082520 Prospective, Phase II study of lutetium Lu 177 DOTATATE (LUTATHERA) in patients with inoperable, progressive meningioma after external beam radiation therapy	Recruiting	Previous treatment with fractionated radiotherapy or stereotactic radiosurgery, inoperable progressive meningioma of any grade	41	II	Lutathera	PFS-6mo
NCT02847559 Phase II, single-arm, multi-center, open label trial combining optune with concurrent bevacizumab in the setting of recurrent or progressive meningioma	Recruiting	Progressive or recurrent grade II–III meningioma	27	II	Bevacizumab and electric field therapy	PFS-6mo
NCT02282917 Exploratory evaluation of AR-42 histone deacetylase inhibitor in the treatment of vestibular schwannoma and meningioma	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 Phase II, dosimetry guided, peptide receptor radiotherapy (PRRT) using 90Y-DOTA tyr3-octreotide (90Y-DOTATOC) in children and adults with neuroendocrine and other somatostatin receptor positive tumors	Recruiting	Meningioma not amenable to standard treatment	46	II	90Y-DOTATOC-PRRT	Treatment efficacy and renal, hematological and clinical toxicities
NCT04374305 Innovative trial for understanding the impact of targeted therapies in NF2 (INTUITT-NF2)	Recruiting	Progressive meningioma in NF2 syndrome	80	II	Brigatinib	Radiographic response rate
NCT03173950 Phase II trial of the immune checkpoint inhibitor nivolumab in patients with select rare CNS cancers	Recruiting	Progressive grade II–III meningioma	180	II	Nivolumab	ORR PFS
NCT03095248 Phase II trial of selumetinib in patients with neurofibromatosis type II related tumors	Recruiting	No prior medical treated meningioma in NF2 syndrome	34	II	Selumetinib	ORR
NCT04541082 A first-in-human Phase I single-agent dose-escalation, food effect and dose expansion study of oral ONC206 in recurrent and rare primary central nervous system neoplasms	Recruiting	No standard treatment options available for grade II–III meningioma	102	I	ONC206	Maximum tolerated dose
NCT03220646 Phase II study of abemaciclib in patients with recurrent brain tumors	Recruiting	Recurrent meningioma	78	II	Ribociclib	Radiographic response rate PFS-6mo
NCT02423525 Phase I dose escalation and central nervous system (CNS) pharmacokinetic study of the ErbB family inhibitor afatinib in patients with recurrent or progressive brain cancer	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 ^{90}Y- and ^{177}Lu-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.

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