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REVIEW

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Review of meningioma diagnosis and management

Chadwin Hanna Jr[1*], Matthew Willman[1], Dwayne Cole[1], Yusuf Mehkri[1], Sophie Liu[2], Jonathan Willman[1] and Brandon Lucke-Wold[1]

Abstract

Meningiomas are the most common intracranial tumors in adult patients. Although the majority of meningiomas are diagnosed as benign, approximately 20% of cases are high-grade tumors that require significant clinical treatment. The gold standard for grading central nervous system tumors comes from the World Health Organization Classification of Tumors of the central nervous system. Treatment options also depend on the location, imaging, and histopathological features of the tumor. This review will cover diagnostic strategies for meningiomas, including 2021 updates to the World Health Organization's grading of meningiomas. Meningioma treatment plans are variable and highly dependent on tumor grading. This review will also update the reader on developments in the treatment of meningiomas, including surgery, radiation therapy and monoclonal antibody treatment.

Keywords Meningioma, Tumor grade, WHO grade, Meningioma diagnosis, Meningioma treatment, Subtype, Intracranial tumor

Background

Accounting for approximately one-third of all primary central nervous system tumors in adult patients, meningiomas are the most prevalent primary brain tumor [1, 2]. With the median age of diagnosis being 65, 36.6% of all adult brain tumors are diagnosed as meningiomas, and as few as 3–5% of pediatric primary brain tumors are believed to be meningiomas [2, 3]. With the exception of rare high-grade variants and pediatric cases, primary brain meningiomas are more common in female patients at an incidence rate of 3:1 compared to males [4, 5]. Furthermore, the female to male ratio is approximately 9:1 for all primary meningiomas of the spine [4]. Neurofibromatosis type 2 (NF2), schwannomatosis, multiple endocrine neoplasia type 1 (MEN1), and numerous other familial syndromes are associated with an increased risk of meningioma occurrence [6]. This genetic predisposition is especially notable in NF2, with as many as 50% of patients presenting with meningiomas [6, 7].

Originating from meningothelial or arachnoid cap cells of dura tissue, meningiomas are commonly observed at the vault of the skull, the skull base, and locations of dural reflections (e.g., tentorium cerebelli, falx cerebri, and adjacent to dural venous sinuses) [8, 9]. In 12% of all cases, meningiomas occur as primary spinal lesions [10, 11]. Although less common, meningiomas can occur in the optic nerve sheath and the choroid plexus of ventricles [8, 12, 13]. Despite their benign nature in the vast majority of cases, meningiomas can cause symptoms due to mass effect displacement of surrounding tissue [14]. The presence of pre-operative seizures can be observed in a wide range of supratentorial intracranial meningiomas, while focal symptoms are often specific to the site of the lesion [15]. Some of the most common self-reported symptoms at the time of diagnosis include headache due to increased intracranial pressure, fatigue, vision changes, altered cognition, and extremity weakness or

*Correspondence:
Chadwin Hanna Jr
channa@ufl.edu
[1] Department of Neurosurgery, University of Florida, Gainesville, FL, USA
[2] Department of Neuroscience, Johns Hopkins University, Baltimore, MD, USA

numbness [16, 17]. While many meningiomas present with symptoms, a significant portion are asymptomatic when first diagnosed, representing one of the most common incidental brain tumor findings on imaging [18, 19].

Recent discoveries have identified genetic markers that have a high correlation with aggressive meningiomas. Telomerase reverse transcriptase (TERT) promoter gene alterations, which increase TERT expression and telomere length, conferring cell immortality, are linked to high-grade meningiomas with elevated rates of recurrence and poor clinical outcomes [20–24]. Similarly, homologous deletion of the CDKN2A/B tumor suppressor genes has been identified as a marker of aggressive meningioma clinical course [25, 26]. While uncommon (< 5%), loss of trimethylation expression of lysine 27 of histone H3 (H3K27me3) is believed to be correlated with an increased risk of meningioma tumor recurrence [27, 28].

Meningioma diagnostic strategies

With the identification of several high-risk mutations and molecular markers in higher grade meningiomas (Fig. 1), interest has grown for the use of molecular markers as a method of risk stratification [33]. Biopsy or resection, however, remains the only methods of definitive meningioma diagnosis [17]. Nevertheless, meningiomas are primarily first seen and diagnosed as a result of imaging [19]. In some cases, to rule out other types of tumors, a biopsy is taken and analyzed through histopathology [32].

The World Health Organization (WHO) grading is considered to be the "gold standard" in classifying histological and etiological meningioma factors [34]. 2016 WHO guidelines categorized meningiomas into 15 subtypes encompassed by 3 grades; benign (grade I), atypical (grade II), and anaplastic (grade III) (Fig. 2). The 2016 version of the WHO meningioma classifications was hallmark because it combined genetic/molecular alterations, along with tumor histopathology to categorize meningiomas [35]. This directly led to more detailed subtypes of meningiomas, which improved clinical estimation of recurrence and prognosis of meningioma patients. [36]. The number of subtypes increased specifically for grade II and grade III meningiomas. [37]

Grade I meningiomas make up approximately 80% of all meningioma cases [38]. Hence, meningiomas are regarded as being mostly benign and having a routine clinical course. The remaining approximately 20% (~ 17% grade II and ~ 3% grade III) of cases, however, tend to face more severe clinical challenges such as local recurrence, brain invasion, and/or progression to higher tumor grade [35].

The 2021 revision of the WHO guidelines further emphasizes the review of genomic alterations to support tumor classification and assist clinicians with meningioma management. However, this revision did change how meningiomas and other CNS tumors are graded. Within the 2016 guidelines, meningiomas were graded based on histopathological subtype. For example, an anaplastic subtype meningioma would automatically be classified

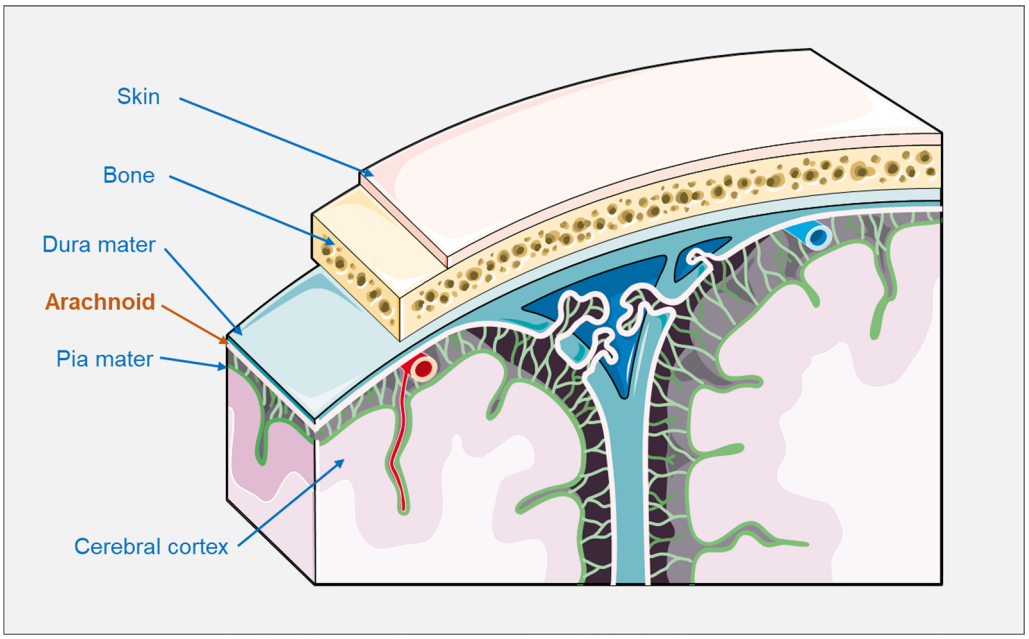

Fig. 1 Meningiomas arise from meningothelial and arachnoid cap cells of the leptomeninges and may progress to invade the dura mater [29–32]

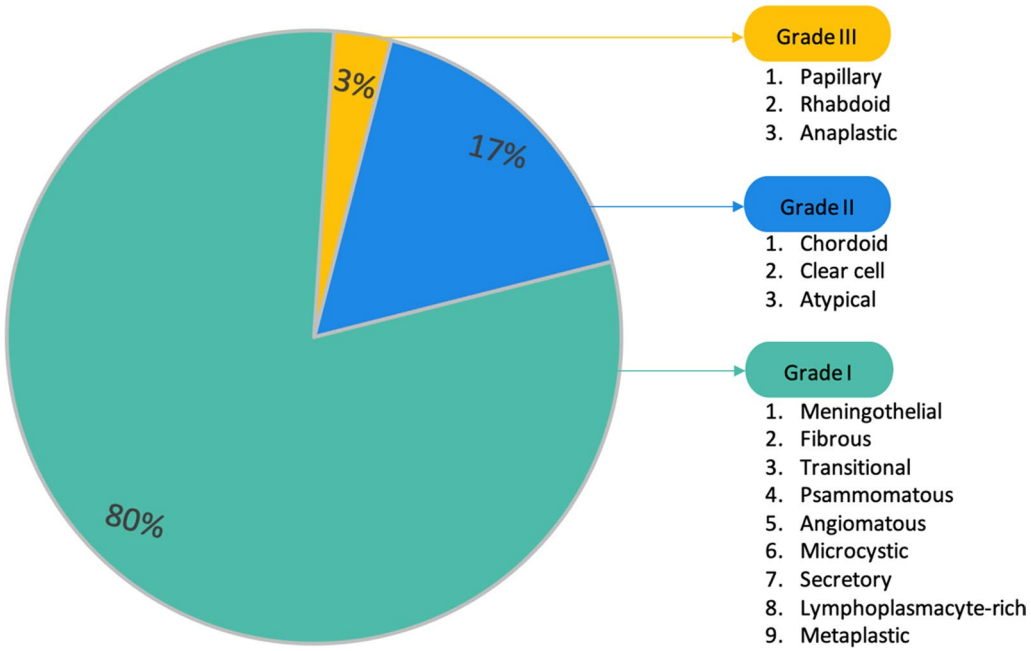

Fig. 2 2016 WHO Subtypes and Grades [35, 38]

as a grade III meningioma. Anaplastic lesions of other CNS tumor types would also be classified as grade III [35, 36, 38, 39]. This method of grading attempted to classify different categories of CNS tumors by expected clinical course. The problem with the clinical approach to grading was that it assumed different tumor types with similar histological findings behaved relatively the same. This was, however, not always true and did not conform to grading used for other non-CNS tumors [39]. 2021 WHO guidelines retained the 15 subtypes of meningioma, but shifted to within-tumor-type grading, allowing for the criteria of grade 2 or 3 to be applied to tumors regardless of subtype. This change gives clinicians more flexibility with tumor classification and puts further emphasis on the biological similarities between tumor types [38, 39]. The grading also changed from the use of Roman numerals to Arabic numerals to align CNS tumors with other systems. The use of Roman numerals throughout this paper refers to 2016 WHO grading.

The clinicopathological relevance of genetic alterations in meningiomas is still being studied, but certain alterations are seen more frequently in varying subtypes and locations of meningioma [38]. It has also been observed that higher grade meningiomas contain a higher frequency of abnormalities [40]. Alteration of the NF2 gene is the most common and is seen in approximately 60% of all sporadic meningiomas, along with other additional modifications [41] For example, meningiomas that occur on the surface of the brain (convexity meningiomas) are found to have abnormalities in NF2 as well as SMARCB1 (SWItch/Sucrose Non-Fermentable Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1), TERT and CDKN2A. Convexity meningiomas are predominantly of the fibrous and transitional subtypes and are more commonly grade 2 and 3 [42–45]. Contrastingly, meningiomas that occur along the base of the skull (skull base meningiomas) are predominantly of the meningothelial, microcystic and secretory subtypes [40]. Meningiomas located on the spinal cord are frequently associated with rhabdoid and clear cell subtypes [46]. Table 1 outlines common molecular biomarkers utilized in meningioma diagnosis per the 2021 WHO guidelines.

Meningioma imaging modalities

While contrast-enhanced computed tomography (CT) may offer advantages in the identification of characteristic meningioma lesion calcification (15–20% of cases) and hyperostosis (25–49% of cases), magnetic resonance imaging (MRI) offers significant advantages in tumor tissue and edema analysis [55–57]. Compared to the cerebral cortex, meningiomas appear hypointense to isointense on T1-weighted MRI sequences and isointense to hyperintense on T2-weighted sequences [58]. Fig. 3 displays T2-weighted MRI images of a meningioma with an encasement partial occluding the superior sagittal sinus. The left is without contrast, while the right images are with contrast. The addition of gadolinium contrast

Table 1 Common genetic alteration in meningiomas [42–54]

Meningioma location	Meningioma subtype	Common genetic alterations
Convexity Meningioma	Fibrous	NF2, SMARCB1, TERT, CDKN2A
	Transitional	NF2, SMARCB1, TERT, CDKN2A
Skull Base Meningioma	Meningothelial	AKT1, SMO, POLR2A, PIK3CA
	Microcystic	AKT1, KLF4, TRAF7, SMO, POLR2A, PIK3CA
	Secretory	KLF4, TRAF7
Spinal Cord Meningioma	Clear Cell	SMARCE1
	Rhabdoid	BAP1

AKT1 AKT serine/threonine kinase 1, *SMO* smoothened, frizzled class receptor, *POLR2A* RNA polymerase II subunit A, *PIK3CA* Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha, *KLF4* Krüppel-like factor 4, *TRAF7* TNF Receptor Associated Factor 7, *BAP1* BRCA1 Associated Protein 1

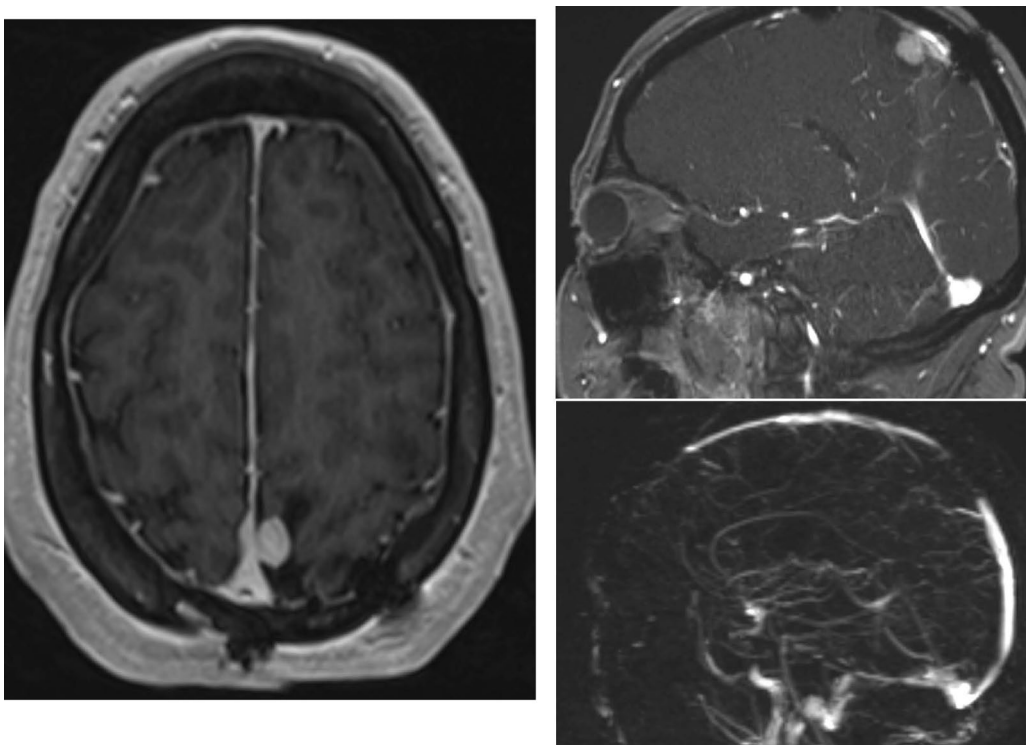

Fig. 3 Representative images of meningioma with encasement and partial occlusion of superior sagittal sinus. Recommended treatment is surgical resection given location

markedly enhances the visibility of meningiomas on MRI [58]. Characteristics typical of more benign meningiomas include a dural tail, calcification, homogenous enhancement, and a uniform border. While not pathognomonic for meningiomas, dural tails are a common feature found in 72% of meningiomas [59]. MRI radiographic features that correlate with more aggressive and higher-grade meningiomas include intra-tumoral necrosis, cortex invasion, intertumoral cystic changes, edema volume, and tumor extension across skull base foramina [56, 60–65]. Additional radiographic features are detailed in Table 2.

Table 2 Typical MRI radiographic features of meningioma

Low-grade meningioma	High grade meningioma
Dural tail	Intra-tumoral necrosis
Calcification	Cortex invasion
Homogenous enhancement	Intertumoral cystic changes
Uniform border	Elevated Edema volume
	Tumor extension across skull base foramina
	Reduced apparent diffusion coefficient (ADC)
	Lower intertumoral rCBV
	Higher peritumoral edema rCBV

Another useful tool in the risk stratification of meningiomas is MRI diffusion-weighted imaging (DWI), which quantifies water diffusion levels in tissue through a reported apparent diffusion coefficient (ADC) value [66]. A lower intertumoral ADC may correlate with higher Ki-67 levels, increased cell proliferation, and higher-grade meningiomas [67–72]. Relative cerebral blood volume (rCBV), a measure generated through MR perfusion analysis, is an estimate of blood volume in a given space and is elevated with increased vasculature [73]. Studies have demonstrated that lower intertumoral rCBV and a higher peritumoral edema rCBV correlate with higher-grade meningiomas and may be effective in distinguishing meningiomas from schwannomas [74–79].

Meningioma treatment

Most meningiomas are routinely treated as a neurosurgical disease. Despite its reputation as a commonly benign disease, the associated clinical symptoms, risk of recurrence, and unfavorable course of outcomes are far from indolent [80]. Fortunately, since Harvey Cushing first coined the term "meningioma" in 1922, there have been significant advances made in systemic treatment and monitoring [81].

The current treatment strategies can be determined based on two main types of meningiomas, asymptomatic and symptomatic [17]. For small, asymptomatic meningiomas, a watchful waiting strategy is usually recommended. Clinical observation and MRI screening are performed every 6 months following initial diagnosis [17]. Patients that remain asymptomatic after 5 years are then seen for annual observation-only [17].

In contrast, symptomatic meningiomas are treated with surgical intervention. Surgical resection remains the first line of treatment. Symptomatic meningiomas are classified according to the WHO grading system [82]. Recurrence risk, survival rates, and morbidity all correlate with WHO grades, holding major consideration into the choice of treatment [82]. However, patients who are not fit for surgery, including elderly or disabled individuals, have the option to choose either stereotactic radiotherapy/radiosurgery (SRT/SRS) or chemotherapy as a primary treatment [83].

Patients with grade I meningiomas typically undergo gross total resection (GTR) with routine follow-ups or subtotal resection (STR) followed by rounds of SRT/SRS therapy [82]. Patients with grade II meningiomas also either undergo GTR or STR. For those patients, intimate follow-up is recommended after GTR, and SRT/SRS follow-up is recommended after STR. Grade III meningiomas require adjuvant radiotherapy following surgical resection, regardless of the degree of resection [82]. There is debate on how long after diagnosis radiotherapy should start [83].

Advancements in operating techniques including surgical microscopy, neuronavigation, intraoperative monitoring, imaging, and endovascular approaches have allowed for more radical resections [84]. However, depending on factors like surgical approach, tumor location, the extent of dural attachment, and the proximity to neurovascular structures, total tumor resection is not always possible [81]. In 1957, Donald Simpson classified the extent of surgical tumor resection into Simpson Grades I–V [84]. Typically, Simpson Grades I-III are designated as GTR, whereas Simpson Grades IV-V are designated as STR. Simpson Grading remains a reliable tool for classifying the extent of surgical tumor resections [82]. The characterization of recurrence rates of meningiomas has a high correlation with the Simpson Grading. Studies show the recurrence rate of Simpson grade I surgery patients is 9%, grade II is 19%, and grade III is 29% [85]. Similar to other neoplastic entities, meningiomas make up a range of marked variation; therefore, the different grading criteria discussed remains broad.

For total surgical resection, the tumor and its dural base are removed. Resection of the dura was found to be important for the prevention of recurrence [86]. The dura is replaced with a dural patch or graft. When the tumor includes the involvement of the skull, that portion of the bone is removed, and replaced post-surgically through cranioplasty [87]. Aside from these general techniques, the surgical approach differs depending on the location and extent of the tumor [87]. For example, for tumors that invade and obstruct the superior sagittal sinus, attempts are made to remove the entire tumor along with that portion of the sinus. This is followed by venous reconstruction [88]. Contrastingly, for parasellar meningiomas, a conservative approach is taken due to the anatomical complexity of the area. The preference is STR followed by irradiation to reduce the chance of neurological injury or deficit [89]. Meningiomas comprise a spectrum of disease types, so treatment plans should be individualized for each patient, especially when predicting risk stratifications [80].

Current treatment developments for meningioma

With the development of monoclonal antibody-based pharmacotherapies that effectively treat other oncologic conditions, there have been a host of new cell cycle regulators and antibody-based drugs which are currently in clinical trials for the treatment and management of varying severities of meningioma [90–92]. Palbociclib is a CDK4/6 inhibitor that blocks the cell cycle and prevents rapid cell replication [90, 91]. Palbociclib, in combination with radiation, has been shown to diminish cell growth

in vivo using mouse models with anaplastic and radiation-induced meningioma cells [90].

Another monoclonal antibody, Nivolumab, a programmed cell death protein 1 (PD-1) blocker, underwent Phase II clinical trials but was not shown to bolster six-month progression-free survival in patients with recurrent atypical/anaplastic meningioma [92]. Positively, however, Nivolumab treatments did not show significant side effects and were generally well tolerated by patients [92]. The ability to attack specific tumor cells without causing significant harm to healthy cells is essential in cancer treatment. Further research and clinical trials of these drugs can revolutionize how we treat and manage meningioma. Some current clinical trials involving cell cycle inhibitors and antibody therapy in the treatment of various forms/grades of meningioma are listed in Fig. 4.

Currently, MRI is the standard of care for the thorough assessment of meningiomas from an imaging standpoint. With further advancement in artificial intelligence, radiomics could play a role in the diagnosis of and classification of meningioma [94]. Radiomics is the use of MRI, CT, or PET/CT to produce mathematical models which allow for a more detailed analysis of bodily structures based on the texture, shape, and intensity of lesions provided by basic imaging [95–97]. When radiomics was applied to basic MRI, it was shown to distinguish between Grade I, II, and III meningiomas between 76 and 93% based on the features of the lesion [98–101]. This accuracy can be further increased when radiomics is applied to diffusion-weighted imaging (advanced MRI) [102]. Radiomics, therefore, presents a new way to assess and diagnose meningiomas [94].

Abbreviations

AKT1	AKT serine/threonine kinase 1
ADC	Apparent diffusion coefficient
BAP1	BRCA1 associated protein 1
CT	Contrast-enhanced computed tomography
DWI	Diffusion-weighted imaging
GTR	Gross total resection
KLF4	Krüppel-like factor 4

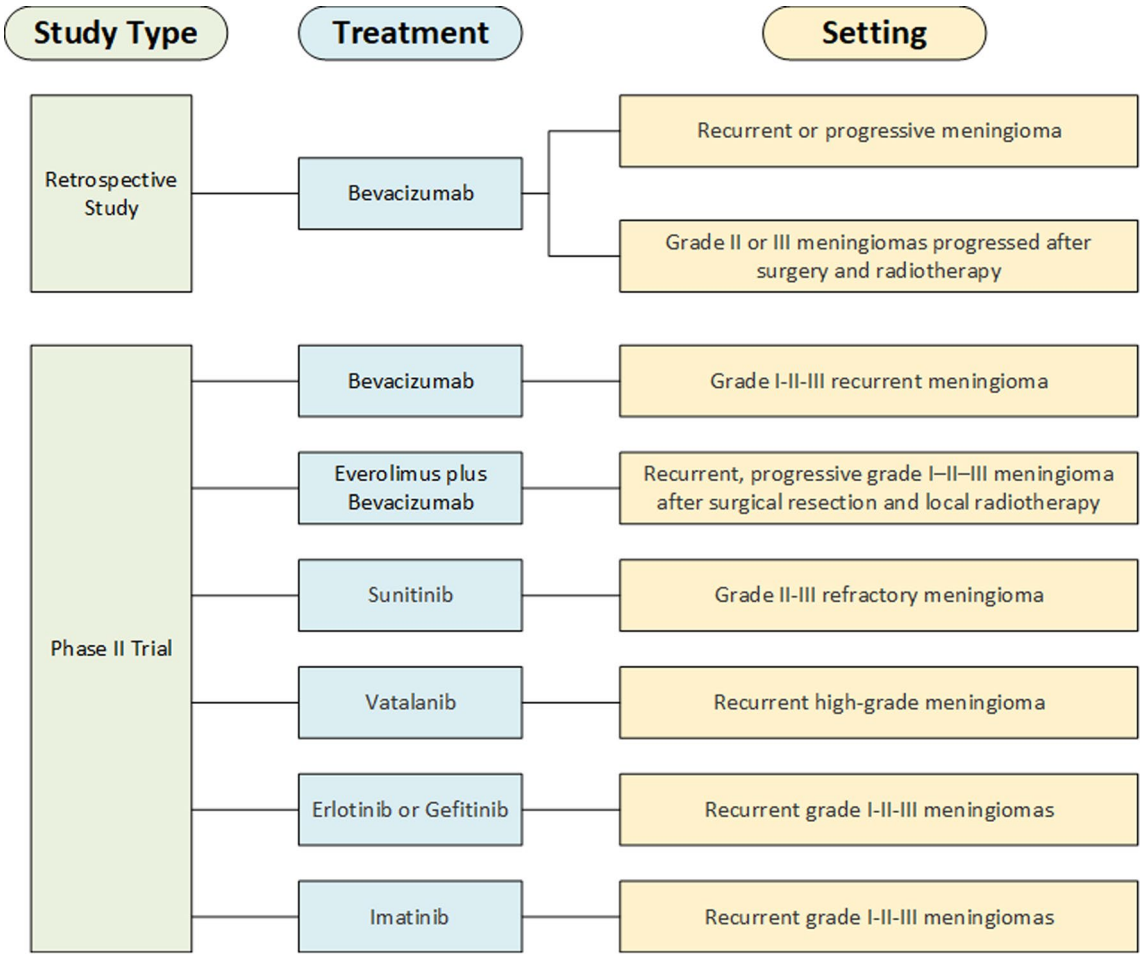

Fig. 4 Monoclonal Antibody Studies for Meningioma [93]

MRI	Magnetic resonance imaging
MEN1	Multiple endocrine neoplasia type 1
NF2	Neurofibromatosis type 2
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase catalytic subunit alpha
rCBV	Relative cerebral blood volume
POLR2A	RNA polymerase II subunit A
SMO	Smoothened, frizzled class receptor
SRT/SRS	Stereotactic radiotherapy/radiosurgery
STR	Subtotal resection
SMARCB1	SWItch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
TERT	Telomerase reverse transcriptase
TRAF7	TNF receptor associated factor 7
WHO	World Health Organization

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C.H. Jr. contributed to diagnostic strategies. M.W. contributed to background. D.C. contributed to current developments in treatment. J.W. contributed to imaging. Y.M. contributed to treatment approaches. S.L. contributed to treatment approaches. B.L.-W. is the senior author. All authors read and approved the final manuscript.

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