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Evolving concepts in meningioma management in the era of genomics

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Abstract

Meningioma is the most common type of primary brain tumor. It was traditionally managed by surgical resection followed by surveillance due to its benign nature. However, recent advances in molecular sequencing, DNA methylation, proteomics, and single-cell sequencing provide insights into further characterizing this heterogeneous group of tumors with a wide range of prognoses. A subset of these tumors are highly aggressive and cause severe morbidity and mortality. Therefore, identifying those individuals with a poor prognosis and intervening is critical. This review aims to help the readers interpret the molecular profiling of meningiomas to identify patients with worse prognoses and to guide the management and strategy for surveillance.

Keywords

Meningioma; NF2; Methylation; Copy number alteration

In the era of prevalent cranial imaging for myriad causes, meningiomas, the most common primary brain tumor in adults, are increasingly diagnosed incidentally. Upon detection, the clinical decision for observation or treatment, most typically through surgery or radiation, or both, is driven by the association with symptoms, large size, steady growth, and potential risk of irreversible neurologic compromise. Appreciation for the natural history, evolving molecular characterization, and treatment options of meningiomas helps guide the increasingly nuanced management considerations.

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Epidemiology

Meningiomas affect approximately 30,000 people annually in the United States [1]. They are more common in women, especially benign ones, and exhibit increased incidence with age [1]. Malignant meningioma are associated with a higher proportion of males and blacks have a higher risk of developing malignant meningioma than Whites [1]. Cranial location predominates in meningioma, with ionizing radiation and long-term hormone intake being recognized risk factors [2–6]. Benign meningiomas exhibit stagnancy on serial imaging or an average growth rate of 1–1.5 mm per year when they do grow. Significant growth rate beyond this harbingers a more aggressive behavior and pathologic grade.

Grading

Meningiomas are classically subdivided based on histopathologic features into three grades by the World Health Organization (WHO), with progressive clinical aggressiveness [1, 7, 8]. WHO grade I meningioma encompasses nine histologic subtypes (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic) and has fewer than four mitoses per 10 high-power field (HPF). WHO grade II meningiomas include atypical, chordoid, and clear cell subtypes, with 4–19 mitoses in 10 HPF or three atypical histologic features (see Table 1). WHO grade III (anaplastic) meningioma previously included tumors with papillary and rhabdoid features, but more recently, it included molecularly defined meningiomas with CDKN2A/B homozygous loss or TERT promoter mutation. In the 2021 WHO classification, molecular signatures are officially incorporated into essential diagnostic criteria [9] (Table 1).

Genetics

Early signal into a genetic basis for meningioma emerged with observation of familial predisposition syndromes, including Neurofibromatosis type 2, schwannomatosis, Gorlin syndrome [10, 11], Cowden syndrome with PTEN mutations [12], multiple endocrine neoplasia type 1 (MEN1) [13], Rubinstein-Taybi syndrome [14] and Werner syndrome [15, 16]. The prevalence of meningioma in Neurofibromatosis type 2, with 40–60% of patients developing a meningioma in their lifetime, led to identifying the Neurofibromatosis type 2 gene [17]. Meningioma risk in schwannomatosis is attributed to perturbations in the SWI/SNF pathway, which have also been identified in aggressive sporadic meningiomas [18].

Increasingly next-generation genomic and epigenetic profiling have further elucidated a role for putative mutations, methylation signatures, and chromosomal copy number alterations in influencing meningioma prognosis and defining therapeutic avenues. Overall, increased genetic mutations and chromosomal alterations are associated with high-grade meningiomas. In addition, specific genetic mutations may indicate the type of meningiomas, such as SMARCE1 for clear cell meningioma and BAP1 for rhabdoid meningioma. DNA methylation classes and copy number alterations can assist in predicting meningioma prognosis.

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Somatic mutations

1. **NF2—**Neurofibromatosis 2 (NF2) was the first identified gene and familiar tumor syndrome associated with meningioma [19, 20]. *NF2* encodes protein Merlin on chromosome 22 [21]. Patients with NF2 present with bilateral vestibular schwannomas, multiple meningiomas and ependymoma [21, 22]. Inactivation of both alleles of NF2, commonly due to nonsense or frameshift mutations, leads to the development of this rare tumor syndrome [23, 24]. NF2 acts as a tumor suppressor gene via blocking the contact inhibition pathway, suppressing the YAP-mediated Hippo signaling pathway, and downregulating PI3K/AKT/mTOR pathway [25–30]. About 60% of sporadic meningiomas have *NF2* inactivation [31]. Mice harboring an arachnoid-specific deletion of *Nf2* grew meningiomas suggest that *NF2* is a genetic driver for meningiomas [32, 33]. The presence of *NF2* mutations in low-grade and high-grade meningiomas suggests its role in meningioma tumorigenesis [34, 35].

2. **Hedgehog pathway (SMO)—***Smoothened* encodes a G-protein-coupled receptor SMO downstream of the tumor-suppressor gene *Patched* in the hedgehog (Hh) signaling pathway [36, 37]. Binding to PTCH1 by Hh ligands or mutations that inactivate PTCH1 lead to the release of the transmembrane protein SMO to migrate to the tip of the primary cilium and activate the transcriptional factors Gli1/2 to promote tumorigenesis [36]. Genomic sequencing of meningiomas found *SMO* mutations occur in approximately 5% of non-*NF2* mutant meningiomas [38, 39]. *SMO*-mutated meningiomas are predominantly of the meningothelial subtypes and grade I tumors but can also present in high-grade and progressive tumors [38–40]. Interestingly, meningiomas harboring recurrent *SMO* L412F mutations tend to occur at the olfactory groove [38]. Furthermore, targeting SMO by Sonidegib inhibited the proliferation of *SmoM2*-induced cells [41].

3. **SWI/SNF (SMARCB1/SMARCE1)—**SWI/SNF (switch/sucrose nonfermenting) complex is an ATP-dependent chromatin remodeling complex frequently mutated in human cancer [42]. *SMARCB1(INI1)* of the SWI/SNF complex was found to be uniformly lost in malignant rhabdoid tumors [43, 44]. Mutations of SWI/SNF complex subunits were commonly found in meningiomas [38, 39, 45]. Non-NF2 meningiomas with clear-cell histological subtypes frequently harbor mutations in *SMARCE1* [46, 47]. Loss of *SMARCE1* in clear-cell meningioma attenuates canonical BAF (cBAF) complex and increases activity of noncanonical BAF (ncBAF) complex rendering sensitivity to ncBAF inhibition [48]. Among the subunits of the SWI/SNF complex, ARID1A is the most commonly mutated subunit in human cancers [42]. Recent extensive sequencing studies of high-grade and recurrent meningiomas observed prevalent *ARID1A* mutations across all grades and associated with a 7.4-fold increased hazard of death [49].

4. **PI3K-Akt-mTOR—**Phosphoinositide 3-kinase (PI3K)-Akt-mTOR is a major pathway of cell proliferation and growth in cancer downstream of receptor tyrosine kinases [50]. PI3K converts phosphatidylinositol-3, 4, 5-triphosphate (PIP3) from phosphatidylinositol-4, 5-bisphosphate (PIP2) while PTEN dephosphorylate PIP3 to PIP2 [50].]. PIP3 then activates protein kinase Akt. [50]. Akt inhibits tuberous sclerosis complex-2 (TSC2), which in turn activates the mammalian target of rapamycin (mTOR), a major regulator of cell

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growth [50]. Mutations of the PI3K-Akt-mTOR pathway frequently occur in meningiomas [38, 39, 51]. *AKT1* (E17K) mutations were most frequently observed in non-NF2 mutated tumors and are associated with skull base meningiomas [38, 39, 52].]. Furthermore, mutations in *PIK3CA* were detected in 7% of non-NF2-mutant meningiomas and were mutually exclusive from *AKT1* mutation [51]. A recent study analyzing outcome data from 469 meningiomas with known molecular subgroups identified that PI3K-activated tumors were associated with earlier recurrence [53].

5. **TRAF7/KLF4—**Tumor necrosis factor receptor (TNF-R)-associated factor (TRAF) proteins are signaling adaptors downstream of TNF-R [54]. TRAF7 interacts with MEKK3 to mediate TNFa-induced NF-kB activation and promotes ubiquitination of anti-apoptotic protein c-FLIP and tumor suppressor p53[54]. The association of TRAF7 in meningiomas was first discovered by *Clark et al.,* when 72/300 of the meningiomas carry mutations in *TRAF7* [38]. Interestingly, *TRAF7* mutations were mutually exclusive with *NF2* mutations and frequently co-occurred with *Kruppel-like factor 4 (KLF4)* K409Q or *AKT1* E17K mutations [38]. Mutations in both *TRAF7* and *KLF4* occurred exclusively in secretory meningiomas [38, 55]. Unlike KLF4 mutations that are primarily present in secretory meningiomas, TRAF7 mutations were also found in high-grade meningiomas [34]. A recent study has also shown $KLF4^{K409Q}$-mutated meningiomas upregulate hypoxia-associated genes and are susceptible to mTOR inhibitor both *in vitro* and *in vivo* [56].

6. **FOXM1/Wnt—**Forkhead Box M1 (FOXM1) is a transcription factor expressed in neural precursor cells and a pro-mitotic regulator [57]. FOXM1 interacts with β-catenin in the Wnt pathway to activate downstream genes, including *c-Myc* and *cyclin D1*, in glioma cells [57]. A comprehensive genomic, epigenomic and RNA sequencing analysis of 280 human meningiomas identified FOXM1 as a crucial transcription factor for meningioma cell proliferation and a biomarker for aggressive meningioma with poor survival [58]. Upregulation of FOXM1 expression secondary to the loss of the negative regulator NF2 is a likely mechanism [58]. Overexpressing FOXM1 was also found to upregulate the expression of vascular endothelial growth factor A (VEGFA), aryl hydrocarbon receptor (AHR) and cytochrome P450 family 1 subfamily A member 1(CYP1A1) in meningioma cell lines [59].

7. **TERT—**Telomere attrition during cell proliferation leads to DNA damage response and apoptosis; thus, maintaining telomere length by telomerase is crucial in cancer cells [60]. Telomerase reverse transcriptase (TERT), the catalytic component of telomerase, is frequently mutated and overexpressed in human cancers [60]. Mutations in *TERT* promoter can be found in all grades of meningiomas regardless of NF2 status but more frequently in high-grade meningiomas [61]. Recently, MRI with a low apparent diffusion coefficient (ADC) was found to be a useful imaging characteristic to predict TERT mutation in grade II meningiomas [62]. *TERT* gene alterations are associated with earlier recurrence and significantly shorter overall survival and thus have been incorporated in the revised 2021 WHO classification [9, 63, 64].

8. **BAP1—**BRCA1-associated protein (BAP1) is a ubiquitin carboxy-terminal hydrolase and is involved in maintaining genome stability, transcription factors regulation, chromatin

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modification, and double-strand DNA repair [65]. The role of BAP1 as a tumor suppressor comes from the discovery of the familial BAP1 cancer syndrome, where the loss of BAP1 from 3p deletions leads to the development of uveal melanoma, mesothelioma, and clear cell renal carcinoma [65]. About 2.5% of $BAP1^{+/-}$ carriers developed meningioma [65]. Somatic BAP1 mutations are associated with the rhabdoid subtype of meningioma, particularly those with higher grades and poor prognosis, but not present in non-rhabdoid subtypes or low-grade meningiomas [66].

9. **POLR2A—***POLR2A* encodes the catalytic subunit of RNA polymerase II. Recurrent somatic mutations in *POLR2A* gene have been discovered in genomic analyses of 775 meningiomas [67]. Dysregulation of critical genes (*WNT6* and *ZIC1*/*ZIC4*) involved in meningeal cell development and differentiation were found to be associated in *POLR2A*-mutated tumor [67].

Copy number alteration

High-grade meningiomas have distinct genomic profiles compared with low-grade meningiomas [34]. Most single-gene mutations occurred in low-grade meningiomas and were thought to be possible drivers for tumorigenesis in those tumors. In contrast, loss of NF2 associated with chromosome 22 monosomy commonly occurs in high-grade meningiomas [34, 45]. Comprehensive cytogenetic studies revealed that chromosomal instability with copy number alterations (CNA) is more frequently observed in high-grade meningiomas with NF2 mutations but less common in atypical non-NF2 meningiomas [34, 45]. In addition to chromosome 22 deletion, losses of chromosomes 1p, 14q, 10p/10q and 6q were clustered in atypical meningiomas [34, 45].

Loss of 9p21, which includes CDKN2A and CDKN2B (CDKN2A/B) is an independent poor prognostic factor in meningiomas[68]. In mice, arachnoid-specific deletion of cdk (cdkn2ab) causes the development of grade II/III meningiomas [33]. *CDKN2A/B* is associated with early recurrence and shorter progression-free survival in patients with WHO grade II/III meningiomas [68]. While WHO 2021 classification recognizes and incorporates homozygous loss of CDKN2A/B as a grave prognostic marker for aggressive behavior in meningiomas, heterozygous loss of CDKN2A/B has been suggested to also be prognostic in meningioma [69]. However, its use to determine prognosis is limited by the rare occurrence of 9q21 losses in meningiomas.

Frequent alterations in genes of X-chromosome were detected in patients with progressive meningiomas, particularly at the locus of Duchenne muscular dystrophy (DMD) gene [70]. The deletion of DMD also predicted a worse outcome [70]. Other CNAs, including 1p/3p/4/6/10/14q/18/19 loss, can also help predict the behavior of meningiomas [69]. In addition, incorporating CNAs using a grading system may assist in identifying grade I/II tumors with early recurrence [69]. Unsupervised clustering analysis using gene expression profile corresponding with CNA further corroborated the value of incorporating CNA for prognosis prediction, where CNA alone was sufficient to predict recurrence [71].

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DNA methylation

Epigenetic regulations such as DNA methylation changes are highly sensitive markers for meningioma identity and biological behavior and appear relatively stable over recurrences [72–76]. At least three independent methylation classifiers currently exist, each with a prognostic association between distinct methylation groups [72–75]. Sahm et al. identified six distinct methylation classes (MC) from 479 meningiomas that predict clinical prognosis more accurately than the current WHO grading system [72]. There are 3 groups of benign MC (MC ben-1, MC ben-2, MC ben-3), 2 groups of intermediate MC (MC int-A, MC int-B) and malignant MC (MC mal) [69]. These methylation classes also represent unique molecular features [72]. For example, MC ben-1 has the majority of benign *NF2* mutated tumors with only chr22 loss; MC ben-2 has the tumors carrying *AKT1*, *SMO*, *KLF4*, and *TRAF7* mutations with no CAN; MC ben-3 has both *NF2* mutated and *PIK3CA* mutated tumors with mostly chromosomal gains, particularly chr5. MC int-A has 53% *NF2* mutated tumors with losses of both chr1p and 22q; MC int-B and MC mal both have *NF2* mutated tumors, *SUFU* mutations, occasional *TERT* mutations, and losses of chr1p, 10, and 22 with a higher frequency of *CDKN2A* deletion in MC mal group [72]. Pathways related to the immune system were also observed in MC ben-1, whereas checkpoint inhibition PD-1/PD-L1 pathway was more enriched in MC ben-2 and MC mal [73]. Choudhury et al. profiled 565 meningiomas and identified three epigenetic groups with distinct clinical outcomes [75]. These groups also have unique biological properties, including the Merlin-intact group, immune-enriched group, and hypermitotic group, providing insight into the underlying biology and guiding the therapeutic approach to these tumors [75].

The 2021 WHO classification for meningioma included methylome profiling for prognostic subtyping of meningiomas [9]. The importance of methylation status for grade II meningiomas was further demonstrated in a recent case-control study comparing 11 patients with more than two recurrences (Group Dismal) with matched 11 patients without any recurrence (Group Benign) [77]. Methylation profiling accurately separated Group Dismal from Group Benign and is independent of location and extent of resection [77]. Pathway analysis suggests the methylation changes in the Wnt pathway predicts poor outcome [77]. Notably, by comparing with the published data (Heidelberg classifier by *Sahm et al.* [72]), the majority of cases (77%) were categorized as an intermediate group, suggesting limited predictability and consistency between different studies on methylation status [77]. Despite the promising results of using methylation status to predict clinical outcomes of meningiomas, challenges that include availability, technical variation, and cost remain.

Histone-specific modifications are associated with high-grade meningioma [75]. Loss of H3K27 trimethylation (H3K27me3) is associated with a shorter progression interval and overall survival [78, 79]. In a recent study, approximately 13.9 % of meningiomas (21/151) demonstrated complete loss of H3K27me3 [80]. Consistent with prior studies, loss of H3K27me3 correlates with faster recurrence, particularly in WHO grade II meningiomas [80]. However, multivariable Cox regression analysis did not demonstrate an independent prognostic value of H3K27me3 loss [80].

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Integration of genetic information for meningioma management

Access to genetic information about meningiomas creates new challenges for physicians. With improved quality and quantity of genomic analysis on meningiomas with associated clinical outcomes, we perhaps can predict patients' prognoses based on the tumors' genetic information. In general, NF2 from loss of chr22 is likely a major driver of low-grade and high-grade meningiomas. Non-NF2 mutations are potential drivers for primarily low-grade and skull base tumors. *TERT* mutations and *CDKN2A/B* codeletions link to high-grade meningiomas with poor clinical outcomes. Copy number alterations correlate with high-grade meningiomas, with losses of chr22 and 1p being the most common. DNA methylation profiling and gene expression sequencing can help to identify groups with worse survival and early recurrence. However, in a resource-scarce setting, losses of both chr22 and chr1p alone can help identify those aggressive meningiomas as they correlate with the worse groups characterized by DNA methylation profiling and RNA sequencing [71, 72]. We proposed a conceptual diagram for prognostic stratification based on currently available data in Figure 1.

Compared with traditional WHO classifications, integrated molecular classifications can better predict clinical outcomes in meningioma patients [69, 73, 74]. Maas et al. analyzed 3031 meningiomas and incorporated WHO grading, methylation classes, and CNAs (1p, 6q, and 14q losses) into three integrated model score (low, intermediate, high), which has a lower prediction error compared with WHO grades, copy number variation (CNV-lasso) model or methylation families alone [73]. In their datasets, 1p loss remains the most important prognostic predictor in all grades after the loss of chr22 [73]. Driver et al. developed a 3-tiered grading scheme (integrated grade 1–3) that incorporated mitotic counts, CNAs, and CDKN2A loss [69]. These integrated grades better predict the risk of recurrence and have a lower Brier score than WHO grades [69]. Nassiri et al. performed whole-exome sequencing, methylome analysis, and transcriptome analysis in 124 meningiomas and identified four molecular groups of meningiomas with distinct recurrent-free survival that are more accurate than WHO classifications or CNA/methylation/mRNA alone [74]. Transcriptome analysis of these meningiomas further categorizes molecular group 1 as immunogenic, whereas molecular group 3 is hypermetabolic and molecular group 4 is proliferative [74]. Different molecular groups' transcriptome signatures also effectively predict their susceptibility to the histone deacetylase inhibitor vorinostat [74]. Proteogenomic analysis of these meningiomas revealed unique histology markers for each molecular group, S100B, SCGN, ACADL, and MCM2 for molecular groups 1 to 4, respectively [74]. Further single-cell RNA sequencing of 8 tumors and two healthy meninges revealed significant heterogeneity between patients and samples [74].

Therapeutic options

Surgery

Meningiomas are primarily managed by surgery, followed by surveillance [81]. Surgical resections relieve symptoms and establish histological and molecular diagnosis [81]. However, the indication and timing of surgery, particularly for asymptomatic meningiomas, is controversial. Current recommendations for patients with asymptomatic meningiomas

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are imaging surveillance [82, 83]. At this time, although genetic information may predict prognosis, the value of biopsy in asymptomatic patients is still unclear.

The extent of resection determined by the Simpson grades remains one of the most reliable factors in predicting clinical outcomes [84]. However, not all tumors are amenable to gross total resection (GTR), and some studies have shown that Simpson grading predicts progression only in convexity meningiomas [85, 86]. In the past, molecular mutations of the meningiomas have not affected the rate of GTR [53]. Further studies are needed to determine whether STR is non-inferior in meningiomas with molecular mutations associated with a low risk of recurrence.

Modern neurosurgery techniques have significantly improved the complete resection rate and neurological outcomes after the surgery [87–89]. Intraoperative fluorescence-guided surgery utilizing 5-aminolevulinic acid (5-ALA), indocyanine green (ICG), or fluorescein has been used to differentiate meningioma from normal brain tissue. Emerging evidence of the effectiveness of 5-ALA in high-grade glioma is encouraging [90]. The role of 5-ALA in assisting intro-operative visualization for meningiomas is currently being evaluated in a phase 3 open-label single-arm trial (NCT04305470). A combination of microscopy and endoscopy, the supraorbital keyhole approach, the transorbital endoscopic eyelid approach, and the endoscopic endonasal approach are all promising surgical techniques[91–95]. However, developing an algorithm to determine surgical approaches according to the tumor location and preoperative neurological deficits will be helpful [96].

Radiation therapy

Radiation therapy is used as adjuvant therapy for partially resected, recurrent or high-grade meningiomas [97]. Radiation alone may achieve local control in nonresectable tumors such as cavernous sinus meningioma and optic nerve sheath tumors [97]. However, radiation therapy can be associated with complications, including radiation-induced meningioma, necrosis, and cognitive impairments [97].

1. **External beam radiation therapy (EBRT)—**The role of adjuvant EBRT was historically controversial because meningiomas were once considered radioresistant [97]. However, two prospective collaborative observation trials RTOG 0539 and EORTC 22042–26042 showed superior 3-year PFS over historical controls in grade II meningiomas with GTR [98–100]. The first randomized control trial ROAM/EORTC-1308, comparing early adjuvant radiotherapy versus active monitoring, is ongoing. The result will help to determine the benefit of adjuvant radiation in atypical meningiomas (ISRCTN71502099) [101].

2. **Stereotactic Radiosurgery (SRS)—**SRS has been proven effective in treating nonresectable WHO grade I meningiomas [102]. Rogers et al. summarized 35 retrospective studies of SRS in treating WHO or presumed grade I meningiomas and showed a 5-year PFS from 86 to 99.4% [97]. Typically, SRS is used to treat smaller meningiomas measuring less than 3 cm in diameter or 10 cc in volume, but a recent retrospective study of 273 patients suggested that single-session SRS can be safely used for meningiomas larger than 10 cc with a PFS at 5 and 10 years of 96% and 81% [97, 103]. Most recently, the international multicenter matched cohort analysis of incidental meningioma progression during active

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surveillance or after stereotactic radiosurgery (IMPASSE) reported superior tumor control from SRS versus active surveillance (99.4% and 62.1%), suggesting a benefit of SRS even in asymptomatic meningiomas [104]. While SRS appears to be an effective treatment for WHO grade I meningiomas, more data is needed to determine long-term tumor control for WHO grade II/III meningiomas [105–107].

3. **Particle therapy—**Proton therapy differs from photon therapy with its dose distribution and narrow dose delivery known as the Bragg peak [108]. The superior dose conformality, lower total radiation dose, and critical healthy tissue sparing make proton therapy a desirable approach for larger, irregularly shaped meningiomas with nearby critical structures. Direct comparison between proton and photon therapy is lacking, and the usage of proton therapy is still case-dependent. Retrospective studies showed that proton therapy achieves local control of 85–99% in 3 to 10 years for grade I meningiomas and 38–71% in 4–5 years for grade II/III meningiomas [109]. Two non-randomized, early-phase trials assessing the safety and efficacy of proton therapy in treating meningiomas are ongoing (NCT01117844, NCT02693990).

4. **Brachytherapy—**Brachytherapy uses interstitial intracranial radiotherapy implants near the surgical cavity to prevent tumor recurrence and can be used to achieve local control for recurrent high-grade meningiomas [110].]. Currently, both Iodine-125 (I-125) and cesium 131 (Cs-131) were used for meningiomas [110, 111]. Surgeons have shifted the usage from I-125 to Cs-131, given the shorter half-life, which reduces the risk of radiation necrosis [110]. The limitation of brachytherapy is that the residual tumor should not be thicker than a few millimeters. Magill et al. reported that the UCSF experience with 42 patients with I-125 brachytherapy implantations and median PFS and OS after brachytherapy was 20.9 months and 3.5 years for atypical meningioma and 11.4 months and 2.3 years for malignant meningioma [112]. The most common complications after I-125 brachytherapy include radiation necrosis, wound breakdown, hydrocephalus, and infection [112]. Koch et al. published 15 high-grade, recurrent meningioma patients treated with either I-125 or Cs-131 brachytherapy [113]. Median PFS and OS after brachytherapy were 8.5 and 13 months for grade II and 4.5 and 12 months for grade III meningiomas [113]. Reoperations due to infection or wound dehiscence and symptomatic radiation necrosis also occurred in 40% of patients [113]. Overall, brachytherapy is a reasonable treatment option for recurrent meningiomas but is associated with a high complication rate post-treatment.

5. **Radiation-induced meningioma—**The most feared complication of cranial radiation is radiation-induced meningioma (RIM), which is more aggressive than spontaneous meningiomas, with a median absolute growth rate of 0.62 cm^3 per year [114, 115]. RIMs are often WHO grade 2 with a median PFS of 28 months [115]. NF2 gene inactivation was uncommon in RIMs [116]. A retrospective study in Slovenia reported that the risk of developing meningiomas after high-dose cranial irradiation was 0.53% at 10 years and 8.18% at 25 years [114]. In children with acute lymphoblastic leukemia who received cranial radiation therapy, about 21.4% developed meningiomas with regular screening brain MRI, but 8.5% were diagnosed with meningioma in the unscreened group suggesting the risk of RIM may be underestimated [117]. SRS, with its considerably smaller

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radiation field, the secondary tumor risk is less than 0.1% [118]. Surgical resection has been the primary treatment for RIMs, but SRS has demonstrated durable local control with an acceptable complication profile [119].

6. **Radionucleotide—**For recurrent, treatment-refractory meningiomas, radionuclide therapy can be an alternative treatment. For example, ^{177}Lu-DOTATE, the somatostatin receptor type IIA (SSTR) ligand widely expressed in meningiomas, was approved for SSTR-positive gastroenteropancreatic neuroendocrine tumors in 2018 [120, 121]. Currently, there are two phase II trials utilizing ^{177}Lu-DOTATE for progressive meningiomas (NCT04082520 and NCT03971461). In addition, another somatostatin-targeted radionucleotide ^{64}Cu-SARTATE, was also tested in a clinical trial and was shown to be well-tolerated and safe (NCT03936426).

Systemic therapy

Recent advances in genomic sequencing have enabled deeper characterization of meningiomas, providing novel potential therapeutic opportunities. In the past, meningiomas were managed mainly by surgery, radiation, or both. Prior attempts to explore systemic therapies, including cytotoxic chemotherapy (temozolomide, hydroxyurea, irinotecan, cyclophosphamide/doxorubicin/vincristine), tyrosine kinase inhibitors (sunitinib, vatalanib), antiangiogenic (bevacizumab), molecular target therapy (everolimus, erlotinib), hormone therapy (mifepristone, somatostatin analogs) have had minimal success but largely limited by underpowered studies and lack of control [87, 122]. Trabectedin, an alkylating agent approved for treating sarcoma, failed to show PFS and OS benefits in the first prospective randomized trial performed in recurrent grade II/III meningiomas [123]. Recently, an Alliance National Cancer Institute sponsored cooperative group trial began to enroll patients based on the genetic alteration of their meningiomas (NCT02523014). Current ongoing trials of systemic therapy are summarized in Table 2.

1. ***NF2* meningioma—**Targeting NF2 is attractive since it is the most common molecular alteration in meningiomas. NF2 inhibited meningioma growth by directly suppressing mTOR complex 1 [30, 124]. A phase II study of mTORC1/mTORC2 Inhibitor Vistusertib is ongoing for high-grade meningiomas. The preliminary result was encouraging, with 51.5% PFS in 6 months, exceeding the RANO target of 35% for recurrent high-grade meningiomas [125]. Vistusertib was also studied in NF2 patients with progressive or symptomatic meningiomas (NCT02831257). Mitogen-activated protein kinase (MAPK) pathway (Ras/Raf/MEK/ERK) is one of the major cell proliferative pathways inhibited by NF2 and is an attractive pathway to target [126]. Selumetinib, a MEK inhibitor, is tested in patients with NF2-related tumors, including meningiomas (NCT03095248). Targeting ALK fusion oncogene using brigatinib, upstream of MAPK pathway, is also under investigation in NF2-related meningiomas (NCT04374305). Evaluating concurrent MEK inhibitor trametinib and PI3K inhibitor alpelisib in patients with progressive refractory meningiomas (NCT03631953) is also ongoing. Focal adhesion kinase (FAK) is an essential molecule affecting cell migration and invasion, and its phosphorylation can be suppressed by overexpression of *NF2* [127]. Excitingly, inhibiting FAK in the Alliance genomically-guided

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trial (NCT02523014) resulted in an improved 6-month PFS of 83% in grade I *NF2*-mutated and 33% in grade II/III *NF2*-mutated meningioma [128, 129].

2. *AKT* meningiomas—*AKT1*** (E17K) mutations were enriched in non-*NF2* mutated skull base meningiomas [38, 39, 52]. Capivasertib (AZD5363), a selective AKT inhibitor, was effective for a patient with multiple intracranial tumors harboring *AKT E17K* mutations [130]. Capivasertib is currently being evaluated in the Alliance trial to treat AKT-mutated meningiomas. A histone deacetylase inhibitor AR-42 with known activity suppressing phospho-AKT is also ongoing in *NF2*-altered meningiomas (NCT02282917).

3. *SMO* meningiomas—Targeting the hedgehog pathway using smoothened inhibitors in *Smoothened (SMO)*-mutated meningiomas is promising, given the existence of two FDA-approved SMO inhibitors vismodegib and sonidegib. In the Alliance trial (NCT02523014), SMO inhibition to treat *SMO*-mutated meningiomas is being evaluated. If SMO inhibitors were proven to be efficacious, they could potentially spare patients from the morbidities of high-risk surgeries since *SMO*-mutated meningiomas are frequently located near many critical structures in the anterior skull base.

4. *CDKN2A/CDKN2B* loss meningiomas—The 2021 WHO classification includes *CDKN2A/CDKN2B* loss as an independent determinant for grade III meningiomas, given its association with early recurrence and shorter PFS [68]. *CDKN2A* and *CDKN2B* encode the CDK4/6 inhibitor $p16^{ink4a}$ and $p15^{ink4b}$, respectively [131]. Loss of *CDKN2A/CDKN2B* leads to increased activity of CDK4/6 that drives tumor proliferation [131]. CDK4/6 inhibitors are thus an attractive anti-tumor strategy. Currently, there are several clinical trials using CDK4/6 inhibitors in treating meningiomas, including ribociclib (NCT02933736), palbociclib (NCT02255461), and abemaciclib (NCT03220646; NCT02523014) (Table 2).

5. Immunotherapy—Immune checkpoint blockade is a successful approach to treating many cancers [132]. The expression of PD-1/PD-L1 checkpoints was observed in high-grade meningioma and was thought to represent tumor-induced immune suppression [133–135]. Karimi et al. reported PD-L1 positivity in 43% (40/93) of their meningioma cases across different grades, 27% in grade I, 47% in grade II, and 67% in grade III [133]. Nivolumab was shown to achieve treatment success in a mismatch repair deficiency patient with recurrent high-grade meningioma [136]. However, nivolumab failed to improve 6-month PFS in patients with recurrent high-grade meningiomas [137]. Pembrolizumab, in contrast, showed promising efficacy and has met its primary endpoint in a recent phase II study in patients with recurrent and residual high-grade meningiomas [138]. Currently, there are also other trials across the country investigating the efficacy of immunotherapy in recurrent meningiomas, with or without SRS (Table 2).

Different genetic mutations alter the expression of immune checkpoints. PD-L2 and B7-H3 expressions were associated in meningiomas with mutations involving *PI3K/AKT/mTOR* pathway, while CTLA-4 expressing T lymphocytes were observed in meningiomas harboring *PIK3CA* or *SMO* mutations [139]. Meningiomas with TRAF7 mutations have higher PD-L1 expressions [140]. Implementing genetic mutations into immunotherapy trial design may be informative.

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6. **Tumor-treating fields—**FDA approved TTF in 2017 for treating glioblastoma based on a randomized trial showing survival benefits [141]. Its alternating electric fields interfere with mitotic spindles, leading to an antiproliferative effect [142]. Currently, one trial investigates the effect of TTF with bevacizumab for recurrent/progressive high-grade meningiomas (NCT02847559).

Conclusions and future directions

Genomic and epigenomic characterization of meningiomas has yielded improved understanding of their biological behavior. Incorporation of such information to guide the diagnosis, prognostication, and treatment of meningiomas ultimately aims to improve patient outcomes. Classical tools, including surgery and radiation, serve a vital role in treatment of meningiomas, while emerging therapeutic modalities based on genomic drivers or tumor microenvironment-directed targets pose intriguing potential in the coming era. While enthusiasm for development of targeted therapies motivates advances in the field, greater attention must also be paid to dissecting the mechanisms of meningioma tumorigenesis and potential treatment resistance. Molecularly-based clinical trials will be invaluable in understanding critical biological pathways in meningiomas and improving the signal of experimental treatments. Lastly, prudence in the timing of treatment and better appreciation of how to maximize durability of control in aggressive meningioma remain areas for further exploration.

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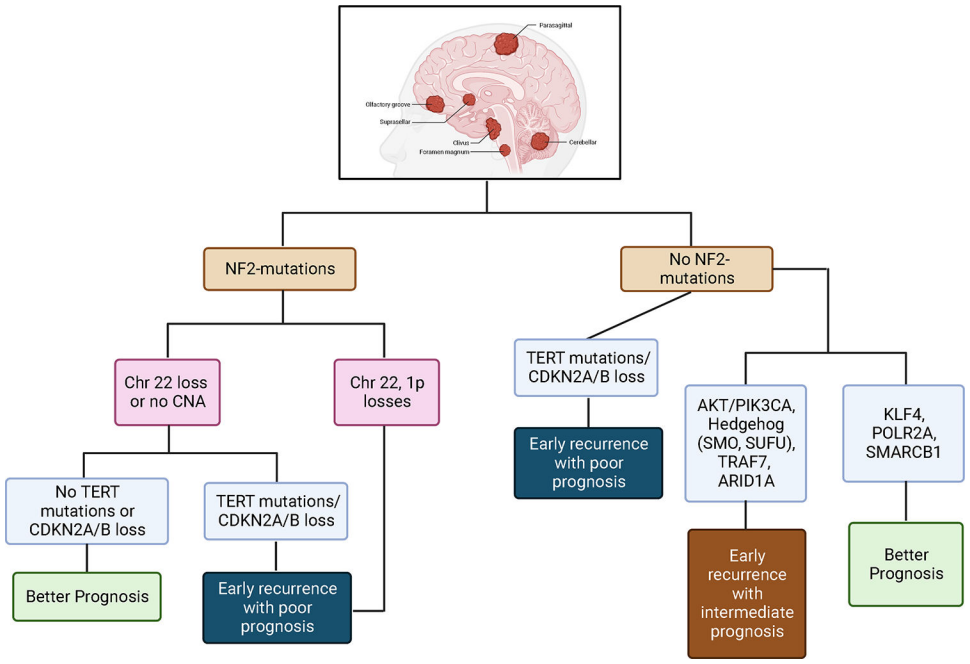

Figure 1. Schematic diagram of meningioma prognostic stratification.

NF2 mutations can stratify meningiomas into two groups: NF2-mutated tumors are either low-grade or high-grade meningiomas and non-NF2 mutated meningiomas are mostly low-grade and skull-base tumors. NF2-mutated tumors can be further categorized into two groups: meningiomas with chromosome 22 (Chr 22) and 1p losses usually are associated with early recurrence and poor prognosis; meningiomas with only Chr 22 loss or no copy number alterations (CNA) are usually associated with favorable prognosis unless they harbor TERT promoter mutations or CDKN2A/B loss. Non-NF2 mutated tumors can be further categorized into three groups: KLF4/POLR2A/SMARCB1 mutated meningiomas are usually associated with better prognosis, whereas AKT/PIK3CA/SMO/SUFU/TRAF7/ARID1A mutated meningiomas are associated with early recurrence with intermediate prognosis. If non-NF2 mutated tumors harbor TERT promoter mutations or CDKN2A/B loss, they likely have an early recurrence with poor prognosis. NF2: Neurofibromatosis 2; TERT: Telomerase reverse transcriptase; KLF4: Kruppel-like factor 4; TRAF7: Tumor necrosis factor receptor-associated factor 7.

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Table 1:

The WHO classification of meningiomas in 2021

	WHO grade I	WHO grade II	WHO grade III
WHO diagnostic criteria	1–3 mitosis in 10 HPF[#]	4–19 mitosis in 10 HPF Unequivocal brain invasion [*] At least three of the following: increased cellularity, small cells with high nuclear-to-cytoplasmic ratio, prominent nucleoli, sheeting (uninterrupted patternless or sheet-like growth), and foci of spontaneous (non-iatrogenic) necrosis [*]	>19 mitosis in 10 HPF Frank anaplasia (sarcoma-, carcinoma-, or melanoma-like appearance) [*]
WHO histological subtypes	Meningiothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic	Chordoid, clear cell, and atypical [*]	Papillary, rhabdoid, anaplastic. (high proliferation index (Ki67> 20%) was removed in 2021)
Genetic mutations			TERT promoter mutation [*] Homozygous deletion of CDKN2A/B [*]

[*] Represents changes from WHO 2016 criteria.

[#] HPF: high power field

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Table 2:

Active and selected completed trials of systemic therapies for meningiomas registered on clinicaltrials.gov

Official Study Title	Study drug	Phase	Number of participants	Principle Investigator	Completion Date	Trial Registration Number
Trabectedin for Recurrent Grade II/III Meningioma	Trabectedin	2	90	Matthias Preusser	1/16/2019	NCT02234050
Vistusertib (AZD2014) For Recurrent Grade II-III Meningiomas	Vistusertib (AZD2014)	2	28	Scott Plotkin	July 25, 2024 *	NCT03071874
AZD2014 In NF2 Patients With Progressive or Symptomatic Meningiomas	Vistusertib (AZD2014)	2	18	Scott Plotkin	October 1, 2020	NCT02831257
Innovative Trial for Understanding the Impact of Targeted Therapies in NF2 (INTUITT-NF2)	Brigatinib	2	80	Scott Plotkin	December 1, 2030 *	NCT04374305
Trial of Selumetinib in Patients With Neurofibromatosis Type II Related Tumors (SEL-TH-1601)	Selumetinib	2	34	Trent Hummel	June, 2024 *	NCT03095248
Efficacy and Safety of REC-2282 in Patients With Progressive Neurofibromatosis Type 2 (NF2) Mutated Meningiomas (POPLAR-NF2)	REC-2282	2/3	89	Recursion Pharmaceuticals (contacts)	July 2027 *	NCT05130866
Vismodegib and FAK Inhibitor GSK2256098 in Treating Patients With Progressive Meningiomas	Vismodegib GSK2256098	2	69	Priscilla Brastianos	October 2024 *	NCT02523014
Combination of Alpelisib and Trametinib in Progressive Refractory Meningiomas (ALTREM)	Alpelisib Trametinib	1	25	Thomas Graillion	September 1, 2022 *	NCT03631953
Innovative Trial for Understanding the Impact of Targeted Therapies in NF2 (INTUITT-NF2)	Brigatinib	2	80	Scott Plotkin	December, 1, 2030 *	NCT04374305
Exploratory Evaluation of AR-42 Histone Deacetylase Inhibitor in the Treatment of Vestibular Schwannoma and Meningioma	AR-42	0/1	5	Brad Welling	October, 2023 *	NCT02282917
Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients	Ribociclib	1	48	Nader Sanai	November 2022 *	NCT02933736
Palbociclib Isethionate in Treating Younger Patients With Recurrent, Progressive, or Refractory Central Nervous System Tumors	Palbociclib	1	35	David Van Mater	February 25, 2019	NCT02255461
Abemaciclib (LY2835219) in Patients With Recurrent Primary Brain Tumors	Abemaciclib	2	78	Thomas Kaley	July 2023 *	NCT03220646
SJDAWN: St. Jude Children's Research Hospital Phase 1 Study Evaluating Molecularly-Driven Doublet Therapies for Children and Young Adults With Recurrent Brain Tumors	Gemcitabine Ribociclib Sonidegib Trametinib Filgrastim	1	108	Giles W. Robinson	March 2025 *	NCT03434262

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Official Study Title	Study drug	Phase	Number of participants	Principle Investigator	Completion Date	Trial Registration Number
Phase I Study of Oral ONC206 in Recurrent and Rare Primary Central Nervous System Neoplasms	ONC206	1	102	Mark Gilbert	February 2025 *	NCT04541082
Nivolumab and Multi-fraction Stereotactic Radiosurgery With or Without Ipilimumab in Treating Patients With Recurrent Grade II-III Meningioma	Ipilimumab Nivolumab	1/2	15	Jiayi Huang	December 2022 *	NCT03604978
Immune Checkpoint Inhibitor Nivolumab in People With Recurrent Select Rare CNS Cancers	Nivolumab	2	180	Marta Penas-Prado	May 21, 2024 *	NCT03173950
Stereotactic Radiosurgery and Immunotherapy (Pembrolizumab) for the Treatment of Recurrent Meningioma	Pembrolizumab	2	90	Nancy Ann Oberheim Bush	April 30, 2028 *	NCT04659811
An Open-Label Phase II Study of Nivolumab in Adult Participants With Recurrent High-Grade Meningioma	Nivolumab Ipilimumab	2	50	David Reardon	December, 2023 *	NCT02648997
Phase II Trial of Pembrolizumab in Recurrent or Residual High Grade Meningioma	Pembrolizumab	2	26	Priscilla Brastianos	September, 2025 *	NCT03279692
Neoadjuvant Avelumab and Hypofractionated Proton Radiation Therapy Followed by Surgery for Recurrent Radiationrefractory Meningioma	Avelumab	1	12	Jiayi Huang	September 30, 2025 *	NCT03267836
Exploratory Study of PD-1 Neoadjuvant Treatment of Recurrent Meningioma	Sintilimab	0	15	Feng Chen	June 1, 2025 *	NCT04728568
Apatinib in the Treatment of Recurrent Atypical/Malignant Meningioma in Adults	Apatinib Mesylate	0	29	Jun-ping Zhang	August 31, 2025 *	NCT04501705
Optune Delivered Electric Field Therapy and Bevacizumab in Treating Patients With Recurrent or Progressive Grade 2 or 3 Meningioma	Electric field therapy Bevacizumab	2	27	Priya Kumthekar	August 2024 *	NCT02847559

* Estimated completion date