Molecular diagnosis and treatment of meningiomas: an expert consensus (2022)

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Abstract

Meningiomas are the most common primary intracranial neoplasm with diverse pathological types and complicated clinical manifestations. The fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5), published in 2021, introduces major changes that advance the role of molecular diagnostics in meningiomas. To follow the revision of WHO CNS5, this expert consensus statement was formed jointly by the Group of Neuro-Oncology, Society of Neurosurgery, Chinese Medical Association together with neuropathologists and evidence-based experts. The consensus provides reference points to integrate key biomarkers into stratification and clinical decision making for meningioma patients.

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Introduction

Meningiomas are the most common primary tumors of the central nervous system with diverse pathological types and complicated clinical manifestations.[1] It is considered a single type in the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (WHO CNS5), with its broad morphological spectrum reflected in 15 subtypes.[2] Approximately 80% of cases are benign lesions and correspond to grade 1 according to the current WHO classification, whereas up to 20% of cases show signs of malignancy at histology and correspond to grade 2 or grade 3 meningiomas.[1] Most low-grade meningiomas can be cured by surgical resection and/or radiotherapy. However, meningiomas that are at surgically inaccessible locations, incompletely resected and/or with features of aggressive histology (WHO grade 2 and 3) tend to grow progressively or recur, and thereby pose a therapeutic challenge.[3,4] In the past few years, key genetic and epigenetic alterations that are strongly associated with clinicopathologic features, such as localization and prognosis, have been identified in meningiomas, and could represent targets for molecularly driven therapies.[1,5-8] However, some uncertainty still remains as to whether histopathological evaluation is the single best criterion for risk assessment in meningiomas. The inclusion of the newly identified frequent molecular alterations in the diagnostic assessment might further improve accuracy in the identification of meningioma patients who need close surveillance and more aggressive treatment.[1,5-8] Consistent with the updated WHO classification of brain tumors published in 2021, the present expert consensus aims to incorporate some molecular features, laying the foundation for improving future diagnosis and therapeutic efforts of meningiomas through the integration of essential molecular findings.

Advances in WHO Classification of Tumors of the Central Nervous System

Since 1979, the WHO has periodically published consensus classification and grading criteria of the central nervous system (CNS) tumors to ensure uniform histopathologic diagnostic criteria worldwide.[5-8] In 2016, the WHO published the fourth edition of the classification of CNS tumors that represents the consensus of 117 contributors and for the first time uses molecular parameters in addition to traditional histology to diagnose CNS tumors.[9] This results in major adjustment of the classification for many tumors, especially gliomas, ependymomas, and medulloblastomas.[9] In contrast to previous versions of the classification, the WHO CNS5 introduces major changes that advance the role of molecular diagnostics in meningioma for the first time.[2,10]

The WHO classification system describes 15 different meningioma subtypes, nine of which are WHO grade 1, three are WHO grade 2, and three are WHO grade 3 [Supplementary Table 1, http://links.lww.com/CM9/B285].[2,10] Besides histological features, secretory meningiomas (WHO grade 1) can also be diagnosed on the basis of detecting *KLF4*/tumor necrosis factor receptor associated factor 7 (*TRAF7*) mutations.[2,10,11] Among WHO grade 2 meningiomas, virtually all clear cell meningiomas harbor *SMARCE1* mutations (97%).[2,10,11] Likewise, regardless of the histological criteria of anaplasia, any meningioma with *TERT* promoter mutation and/or cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) homozygous deletion is allotted to WHO grade 3.[2,8,11]

Integrated Grading Scheme for Meningiomas

Genome-wide molecular-profiling studies have revealed the characteristic genetic alterations and epigenetic profiles associated with different types of meningiomas.[3,4,12,13] However, the development of prognosis relevant grading scheme with combined histologic and molecular features remains inchoate for meningioma.[3,4,14,15] In 2017, Sahm *et al*[14] demonstrated that unsupervised clustering of DNA methylation data divided meningiomas into two distinct subgroups associated with recurrence-free survival. After adjusting for clinical factors, such as WHO grade and Simpson grade, a statistically significant association between DNA methylation subclasses and tumor recurrence was found. Later, Maas *et al*[4]conducted a comprehensive investigation of 3031 meningiomas on multiple levels, from copy number through epigenomics to mutations. In 2021, Nassiri *et al*[3] defined four molecular groups of meningioma by combining somatic copy-number aberrations, somatic DNA point mutations, DNA methylation and messenger RNA abundance in a unified analysis. Each molecular group showed distinctive and prototypical biological characteristics (immunogenic type, MG1; benign neurofibromin 2 (*NF2*) wild-type, MG2; hypermetabolic type, MG3; and proliferative type, MG4). Importantly, these molecular groups more accurately predicted clinical outcomes compared with existing classification schemes. Besides, Driver *et al*[16] formulated a grading scheme that incorporates mitotic index and multiple high-risk copy number alterations (CNAs) to identify patients at risk for tumor recurrence.

On the basis of WHO CNS5, a consensus integrating molecular parameters with traditional histology to diagnose and manage meningioma might promote the development and clinical translation of novel pathogenesis-based therapeutic approaches, thereby paving the way towards precision medicine in meningiomas.

Consensus Development Process

The current consensus statements were formed jointly by the Group of Neuro-Oncology, Society of Neurosurgery, Chinese Medical Association together with neuropathologists and evidence-based experts. All clinical questions were developed using the Population, Intervention, Comparison, and Outcome format, which is beneficial for developing inclusion and exclusion criteria for retrieved literature and identifying relevant studies for inclusion. The consensus has been registered on the International Practice Guideline Registry Platform (Registration number: IPGRP-2022CN234). All statements were assessed and graded using the criteria for the recommendation grades of Chinese Society of Clinical Oncology clinical practice guidelines [Supplementary Tables 2 and 3, http://links.lww.com/CM9/B285].[17]

The consensus process was based on three rounds through online-meeting in 2021. Each member voted each statement according to the Delphi method.[18] Statements with agreement <75% (threshold value) were revised and entered in the subsequent round. The consensus document consists of 23 statements which benefited from expert discussion and fine-tuning, serving clinicians and researchers for the management of patients with meningioma.

Key Biomarkers Screening in Meningiomas

The consensus focuses on epigenomic and genomic features of sporadic meningiomas. Key biomarkers screening was performed by collecting available evidence on molecular landscape of meningiomas [Figure 1]. The following databases were queried for literature review: Medline (PubMed interface, www.pubmed.gov) and National Guidelines Clearinghouse (www.guideline.gov).

Key Molecular Alterations of Meningiomas Impacting on Clinical Management

Copy number alterations

Loss of chromosome 22q

Somatic CNAs play a critical role in meningiomagenesis by dysregulating oncogene and tumor suppressor activity.[1] The first cytogenetic study on meningiomas, published in 1967, showed loss of a G-group chromosome (either chromosome 21 or 22) in all tumor samples under investigation and multiple chromosomal aberrations in half of the samples.[1] Subsequent studies validated the increased incidence of monosomy 22 in meningiomas.[19] These landmark studies led to the critical insight that loss of chromosome 22 is pivotal in meningiomagenesis for a large subset of the tumors. Convexity and spinal meningiomas predominantly harbour 22q loss, whereas skull-base meningiomas are characterized by other frequent mutations.[20] Loss of heterozygosity (LOH) studies showed that chromosome 22q was lost in 60% to 70% of sporadic meningiomas.[21-24] The incidence of 22q LOH increases with WHO grade, with a 50% prevalence in WHO grade 1 tumors and 75% to 85% prevalence in WHO grades 2 and 3 tumors.[22-24] In 2004, Pfisterer *et al*[25] concluded the deletion of 22q was significantly associated with radiologically detected recurrence in 77 paraffin-embedded meningioma samples ($P < 0.05$). Hilton *et al*[26] investigated the expression and activation of epidermal growth factor receptor (EGFR) and downstream signalling pathways in 30 meningiomas. They found that the anti-EGFR based therapies may be less effective in meningiomas with 22q loss. Recently, Hong *et al*[27]reported a novel mutation concurrent with 1p/22q co-deletion in a patient with multiple recurrent meningiomas responding to sunitinib. The first identification of a specific genetic aetiology of meningiomas was the discovery of alterations in the tumor suppressor gene *NF2*, located on chromosome 22, which encodes the protein merlin.[28] A few clinical trials of drugs targeting *NF2* alterations have achieved promising results, and the details are presented in the following "Neurofibromin 2 (*NF2*) Mutations" section in this consensus.

Recommendation 1 22q testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with 22q loss could be done annually within 5 years (Evidence 3; Grade III recommendation).

Loss of chromosome 1p

Deletion of chromosome 1p is the second most common CNA identified after 22q loss and is mainly associated with higher WHO grade.[25,29] Besides, 1p loss is considered as an early event in the malignant progression of meningiomas.[25,29] 1p loss most frequently involves the 1p33–34 and 1p36 regions, which may cause methylation-mediated inactivation of *TP73* and *ALPL* genes.[30-33]

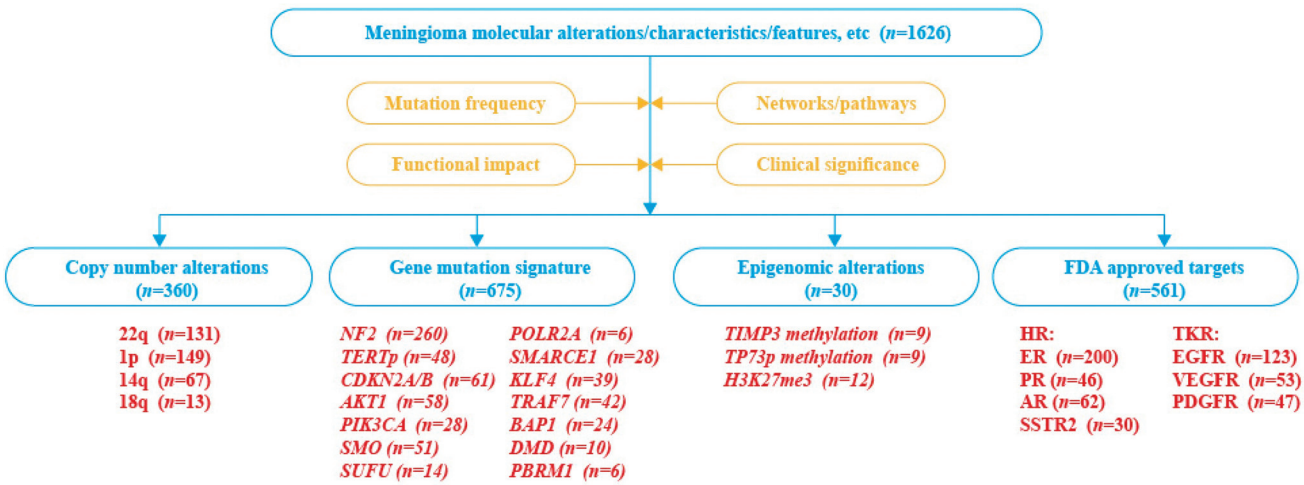

Figure 1: Work flow of biomarkers screening in meningiomas. *n*: Number of articles, AR: Andregen receptor, EGFR: Epidermal growth factor receptor, ER: Estrogen receptor, HR: Hormone receptor, PR: Progesterone Receptor, SSTR2: Somatostatin receptor 2, TKR: Tyrosine kinases receptors, VEGFR: Vascular endothelial growth factor receptor, PDGFR, Plateletderived growth factor receptor.

Linsler *et al*[31] performed a prospective study on 124 tumor samples from 105 meningioma patients. In WHO grade 1 meningiomas, loss of 1p36 was detectable in 27.4% (17/62), in grade 2 in 37.1% (13/35) and in anaplastic meningiomas in 87.5% (7/8) of cases. They thus concluded that the deletion of 1p36 emerged as a significant predictor of shorter overall survival in meningiomas (log-rank test, $P < 0.001$). Accumulated CNAs, such as the 1p/14q co-alteration, have been postulated to increase the risk of malignant behavior of sporadic meningiomas.[34] Combined 1p/14q deletions were encountered in 7% benign, 39% atypical, and 63% anaplastic meningiomas ($P < 0.001$). There was a trend for WHO grade 2 meningiomas with combined 1p/14q deletions to have poorer overall survival.[29] In 2007, Krayenbühl *et al* compared differences between *de novo* malignant meningiomas and meningiomas that progressed to malignancy. There was an increased monosomy or derivative chromosome 1 combined with monosomy of chromosome 14. These phenomena occurred mainly in patients with malignant transformation who had a worse outcome.[35,36]

Recommendation 2 1p testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with 1p loss could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

Loss of chromosome 14q

Loss of chromosome 14q is involved in the pathological progression of meningioma, but the specific mechanism remains unknown. Lusis *et al*[37] considered that 14q loss leads to low transcript expression of the tumor suppressor gene *NDRG2* at 14q11.2, thereby playing an essential role in meningioma progression. A few retrospective clinical studies showed that 14q loss is associated with higher tumor invasiveness and recurrence risk in meningiomas of all pathological grades.[38-41] In 2013, Balik *et al*[42] found that maternally expressed 3 (MEG3), a long non-coding RNA on 14q, suppressed meningioma growth to a certain degree, but further relevant clinical trials were needed. Gupta *et al*[43] published the results from 46 meningioma samples in a single-center retrospective clinical study conducted in 2016, reporting an association between 14q loss and a high mitotic index of tumors ($P < 0.05$).

Recommendation 3 14q testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with 14q loss could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

Loss of chromosome 18q

Loss of chromosome 18q in meningiomas was previously identified as indicators of poor outcome.[44] 18q loss is primarily located at the end of 18q22, but the specific mechanism of this CNA in tumor progression remains unclear. Weber *et al*[45] collected 90 meningioma samples to conduct a retrospective study in 1997, with 18q loss observed in up to 43% of WHO grade 2 meningiomas. In 2021, Barresi *et al*[46] reported a retrospective study enrolling 22 patients with atypical meningioma, which revealed a significant association between 18q loss and tumor recurrence (with recurrence-free survival shortened remarkably; $P = 0.008$). Limited by relevant studies, further research of 18q loss in meningiomas remains to be determined.

Recommendation 4 18q testing could be considered for postoperative meningiomas (Evidence 2B; Grade III recommendation). Follow-up of meningiomas with 18q loss could be done annually within 5 years (Evidence 3; Grade III recommendation).

Gene mutation signatures

NF2 mutations

The *NF2* gene contains 17 exons and is located on chromosome 22q12.2. *NF2* produces a 69 kDa protein, merlin, that functions as a tumor suppressor by inhibiting cell growth through contact inhibition and resultant activation of multiple pathways.[28]*NF2* mutations are generally associated with convexity meningiomas rather than meningiomas of the anterior skull base.[12] In 2019, Youngblood *et al*[13] reported sequencing analysis of 3016 meningiomas. *NF2*-mutated meningiomas were commonly found in the spinal cord and non-skull base locations. Focal *NF2* inactivating mutations are found in 40% to 60% of sporadic meningiomas and identified in meningiomas of all 3 histopathological grades.[12,23,47,48] Wellenreuther *et al*[49] found *NF2* mutations mainly occur in fibrous (70%) and transitional (83%) subtypes after sequencing a cohort of 70 meningiomas. Yuzawa *et al*[50] reported a single-center retrospective study of 103 meningioma samples in 2016, which showed that the recurrence rate of *NF2*-mutated meningiomas was significantly increased compared with that of *NF2* wild-type meningiomas (Kaplan–Meier survival analysis: 48% *vs*. 25%, $P = 0.037$). Gupte *et al*[51] reviewed clinical and genomic sequencing data on 394 patients surgically treated for meningioma. While *NF2*-mutated tumors are significantly associated with preoperative seizures ($P = 0.012$), the association appears to be mediated through edema and atypical histology. In 2020, Deng *et al*[52] found that low merlin expression in meningiomas was associated with worse overall survival (OS, $P = 0.014$) and progression-free survival (PFS, $P = 0.024$) in a large patient series. In another single-center retrospective clinical study reported in 2021, Youngblood *et al*[53] also found that the 2-year recurrence rate of *NF2*-mutated meningiomas reached 16.8% (26/155), and the 5-year recurrence rate increased to 43.7%. Accordingly, the mutation status of the *NF2* gene in meningioma has a certain role in indicating patient survival, prognosis, and tumor recurrence risk.

The *NF2* mutation plays a crucial role in the pathogenesis of meningioma by activating the mammalian target of rapamycin (mTOR) biological pathway through modulation of the mTOR complex 1 (mTORC1).[54,55] In 2020, Williams *et al*[56] analyzed the genomic data from 850 patients with refractory meningioma, among which at least

three distinct patterns of biological invasion were observed. Of these, the *NF2*-mutated type was the most common ($n = 426$, 50%) and was associated with the male sex (64.4%). Moreover, additional mutations were often observed, such as those in *CDKN2A/B* (24%) and chromatin remodeling factor genes *ARID1A* (9%) and *KDM6A* (6%). Increasing chromosomal instability due to inactivation, homozygous loss, or point mutation in *NF2* together with *CDKN2A/B* can promote meningioma development in murine models.[56,57] The results of a preclinical study showed that everolimus, a selective inhibitor of mTOR, exhibited excellent tumor-suppressive effects in a meningioma mouse model.[58] Moreover, Shih *et al*[59] published a multi-center prospective phase II clinical study in 2016, which found no disease progression in ~35% of patients for >6 months following meningioma treatment with combined everolimus and bevacizumab. Combined everolimus and octreotide also effectively suppressed the growth of aggressive meningiomas in another multi-center phase II clinical trial (NCT02333565) reported by Graillon *et al* in 2020. Among the 20 samples included, a >50% reduction in tumor volume was observed in 78% of patients within 3 months following treatment, and the median tumor growth rate decreased from 16.6% to 0.02% over the 3-month period.[60] This combined therapeutic regimen showed similar effects in improving the PFS and OS of meningioma patients to the multi-targeted tyrosine kinase inhibitor sunitinib.[61] However, in 2021, Karajannis *et al* published a phase 0 pharmacokinetic study showing that the downstream effector protein phospho-S6 was inhibited incompletely by everolimus in *NF2*-mutated meningioma tissues, which may explain the limited therapeutic effect of everolimus on some *NF2*-mutated meningiomas.[62] Furthermore, an ongoing phase II clinical trial (NCT02523014) preliminarily indicated that a focal adhesion kinase (FAK) inhibitor (GSK2256098) improved the 6-month PFS of patients with *NF2*-mutant meningioma, but the specific research conclusions remain to be further reported.[63]

Recommendation 5 *NF2* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with *NF2* mutation could be done annually within 5 years (Evidence 3; Grade III recommendation).

TERT promoter (*TERT*p) mutations

Telomeres are conserved, repetitive (TTAGGG) DNA-protein complexes that are added to the ends of chromosomes by the enzyme telomerase to prevent DNA damage and maintain replicative potential.[64,65] Telomere attrition during DNA replication induces genomic instability that can result in tumorigenesis.[64,65] *TERT*p mutations were initially detected in melanoma and subsequently found in intracranial tumors, such as low-grade glioma, gliosarcoma, oligodendroglioma, and medulloblastoma.[64-68] *TERT*p mutations, occurring specifically in the hotspot regions C228T and C250T, are detected in 6.5% to 11.0% of meningiomas.[14,69,70] The presence of *TERT*p mutation is a potential biomarker for meningiomas with a higher likelihood of clinically aggressive behavior that exhibits higher rates of recurrence and shorter time to progression.[70-74] In 2016, Sahm *et al*[70] assessed the *TERT*p for mutations in the hotspot regions C228T and C250T in meningioma samples from 252 patients. Mutations were detected in 16 samples (6.4% across the cohort, 1.7%, 5.7%, and 20.0% of WHO grade 1, 2, and 3 cases, respectively). Besides, *TERT*p mutations were statistically significantly associated with shorter time to progression (mean time to progression [TTP]: 10.1 months *vs.* 179 months, $P < 0.001$). Goutagny *et al*[71] sequenced the *TERT*p in 73 meningiomas patients. They found a high incidence of *TERT*p mutations in patients with meningiomas undergoing malignant histological progression. In 2020, Mirian *et al*[72] compiled data from eight studies and allocated patients to *TERT*p alterations ($n = 59$) or *TERT*p wild-type ($n = 618$). *TERT*p alterations occurred in WHO 1 to 3 meningiomas, which is an important biomarker for significantly higher risk of recurrence and death in meningiomas. In 2021, Biczok *et al*[73] conducted Sanger sequencing of *TERT*p with samples obtained from 170 meningioma patients at a single center. Among patients with WHO grade 3 meningioma, both the recurrence rate and mortality were substantially higher in the *TERT*p-mutant group than in the *TERT*p wild-type group. Deng *et al*[74] found that *TERT* alterations were the predictor of tumor progression ($P = 0.003$) and were associated with decreased PFS ($P = 0.0114$) in *de novo* high-grade meningiomas after radiotherapy. The above findings suggest that *TERT*p mutations are associated with a high recurrence rate of meningiomas and high mortality of patients. Therefore, WHO CNS5 incorporated *TERT*p mutations in the molecular diagnostic criteria of WHO grade 3 meningioma for the first time.[2,70]

*TERT*p mutations provide a new target for targeted drug therapy in meningioma. However, the telomerase-based therapies that have been developed to date, mainly imetelstat and first-generation cancer vaccines, failed to achieve a satisfactory clinical efficacy.

Recommendation 6 *TERT*p mutation testing is recommended for postoperative meningiomas (Evidence 1A; Grade I recommendation). Follow-up of meningiomas with *TERT*p mutation could be done every 3 to 6 months indefinitely (Evidence 3; Grade III recommendation).

CDKN2A/B homozygous deletions

The *CDKN2A* gene, located at 9p21.3, regulates the cell cycle and acts as a tumor suppressor.[75] Homozygous losses of *CDKN2A* and *CDKN2B* have been shown to be associated with an increased frequency of meningioma in murine models inactivated for the *NF2* gene.[57] In 2019, Guyot *et al*[76] identified a *CDKN2A* SNV (NM_000077, exon2, c.G442A, p.Ala148Thr) in a 30 meningioma series. The presence of such *CDKN2A* alterations was strongly associated with recurrence ($P < 0.0001$) and a Ki-67 labeling index > 7% ($P = 0.004$). In 2020, Sievers *et al*[77] determine the overall prognostic role of the *CDKN2A/B* status in a cohort of 528 meningioma patients. They found meningiomas carrying *CDKN2A/B* homozygous deletions had a significantly worse outcome

and more rapid progression from the time of surgery ($P < 0.001$; median time to progression: 8 *vs.* 101 months). This observation combined with other groups demonstrating a strong association between homozygous deletion of *CDKN2A/B* mutations and aggressive clinical outcome led to a significant revision in the WHO CNS5 criteria.[2,4,11]

Recommendation 7 *CDKN2A/B* testing is recommended for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with *CDKN2A/B* homozygous deletion could be done every 6 months indefinitely (Evidence 3; Grade III recommendation).

AKT1 and *PIK3CA* mutations in the phosphatidylinositol-3 kinase (PI3K) pathway

Aberrant activation of PI3K pathway is one of the most frequent events in human cancer and serves to disconnect the control of cell growth, survival and metabolism from exogenous growth stimuli.[78] The relevance of PI3K pathway in meningiomas is underlined by the existence of several PI3K mutations.[79] $AKT1^{E17K}$, $PIK3CA^{E545K}$, and $PIK3CA^{H1047R}$ are the most common mutation sites in PI3K pathway-related driver genes.[12,80] Meningiomas with $AKT1^{E17K}$ mutation are almost exclusively observed in WHO grade 1 tumors and tend to have meningothelial and transitional histopathological morphology.[81] Besides, $AKT1^{E17K}$ mutant tumors are more commonly located in anterior and middle fossa skull base.[79-84] $AKT1^{E17K}$ mutation is found in 7% to 12% sporadic meningiomas, leading to abnormal activation of AKT1 and facilitating the proliferation of tumor cells.[79,85] *PIK3CA* is mutated in approximately 4% to 7% of meningiomas.[12] *PIK3CA* mutations are mutually exclusive of *NF2*, *SMO*, and *AKT1* and in few cases co-occur with *TRAF7* or *KLF4* mutations.[12] $PIK3CA^{H1047R}$ and $PIK3CA^{E545K}$, which are two of many mutations observed in *PIK3CA*, constitutively phosphorylate and activate AKT1.[86,87] Based on current evidence, PI3K-activated meningiomas exhibited a significantly shorter time to recurrence than other subgroups (mean time to recurrence: 14.3 months).[53]

Recommendation 8 *AKT1* and *PIK3CA* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with *AKT1* or *PIK3CA* mutation could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

In 2017, Weller *et al*[88,89] reported durable control of lung metastatic *AKT1* mutant WHO Grade 1 meningothelial meningioma by the AKT inhibitor, AZD5363 (capivasertib). The patient has been on that treatment for more than one year with ongoing clinical and radiographic response. As described in "*NF2* mutations" part, molecular analysis of meningiomas has identified numerous driver mutations involving PI3K pathway that can be targeted with everolimus, a small-molecule mTOR kinase inhibitor, or combined with other therapeutic strategies.[59-61] The combination of everolimus and bevacizumab has been promising, with a median PFS of 22 months in grade 2 and 3 meningiomas.[59] The phase II CEVOREM trial of 20 patients reported a median PFS of 6.6 months of the combination of octreotide and everolimus,[60] while a median PFS of 12.1 months was reported by Cardona *et al*[61] for their retrospective study of 14 patients treated with everolimus, octreotide, and sunitinib.

Recommendation 9 The combination therapy of everolimus with bevacizumab or octreotide could be considered for PI3K-activated meningiomas (Evidence 2B; Grade III recommendation).

SMO and *SUFU* mutations in the hedgehog pathway

The hedgehog pathway has also been implicated in the development of WHO grade 1 meningiomas, specifically via mutations in *SMO* and *SUFU* genes.[12,47] SMO^{L412F} and SMO^{W535L} mutations are found in 3% to 6% of meningiomas, mostly occurring in the anterior midline skull base.[13,53,79,83] Approximately 66% of meningioms with *SUFU* allele loss tend to have a long-term recurrence.[53] Additionally, *SUFU* mutated in less than 1% of sporadic meningiomas. However, familial cases of meningiomas are known to harbor germline mutations in *SUFU*.[48]

Recommendation 10 *SMO* and *SUFU* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of meningiomas with *SMO* or *SUFU* mutation could be done annually within 5 years (Evidence 3; Grade III recommendation).

TRAF7 mutations

TRAF7, located on chromosome 16p13, has been linked to modulation of Janus kinase and mitogen-activated protein kinase signaling pathways, and induction of apoptosis.[86,90] *TRAF7* mutations often lead to structural alterations in the protein *WD40*.[86,90] This mutation is found in 25% of meningiomas, which occur in 50% of *NF2* wild-types.[12,53] Tumors with mutations in *TRAF7* are often located at the sphenoid wing and floor of the middle fossa.[12] *TRAF7* mutations predominantly occur in WHO grade 1 meningiomas, whereas only 4% of high-grade meningioma samples have mutations in this gene.[91] It is currently considered that the coexistence of *TRAF7* and *PIK3CA* mutations indicates long-term recurrence of skull base meningiomas.[86,92] Youngblood *et al*[53] reported a multi-center retrospective clinical study with 469 meningioma samples in 2021, which found that meningiomas harboring *TRAF7* mutation were more prone to recurr within 2 years. Mutations in *TRAF7* are mutually exclusive of *NF2* mutations but often have a concomitant mutation in *AKT1* or *KLF4*.[12,48,86,93,94] According to WHO CNS5, besides histological features, secretory meningiomas can also be diagnosed on the basis of detecting *KLF4/TRAF7* mutations. [2]

Recommendation 11 *TRAF7* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation).

KLF4 mutations

Recurrent mutations in *KLF4* (c.1225A>C, $KLF4^{K409Q}$) are potential candidate drivers of WHO grade 1 meningiomas.[12] *KLF4* mutant meningiomas occur in up to 28% of *NF2* wild-types,[95] which are usually found in the non-midline anterior and central skull base.[13] More severe brain edema is observed in *KLF4* mutant meningiomas than other subtypes, while such patients have a longer 5-year PFS.[13,53] According to WHO CNS5, *KLF4/TRAF7* mutations constitute the driver alteration in secretory meningiomas and can serve as alternative criterium, besides secretory granula, to identify this subtype.[2]

Recommendation 12 *KLF4* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation).

SMARCE1 mutations

Converging lines of evidence suggest an essential role for the switch/sucrose non- fermentable (SWI/SNF) chromatin-remodeling complex in meningioma formation and aggressiveness.[96,97] *SMARCE1*, also known as *BAF57*, encoding proteins of the SWI/SNF complex, has been implicated in hereditary meningiomatosis.[96,97] Spinal cord meningiomas show frequent *SMARCE1* mutations, whereas other frequent mutations are rare in this localization.[98] Loss-of-function mutations in *SMARCE1* are a molecular signature of the clear-cell subtype of meningiomas.[98-100] In 2021, Sievers *et al*[99] described a molecularly distinct subset of tumors among a cohort of 3093 meningiomas, identifying mutations in *SMARCE1* in 33 of the 34 clear cell cases (97%). Furthermore, there are no significant differences in tumor recurrence rates between clear cell meningiomas with *SMARCE1* mutation and other types in WHO grade 2 meningiomas.[99] Clear cell meningiomas harboring a *SMARCE1* mutation have been commonly described in children and young adults. This finding has important clinical implications because of the risk of the possibility of familial disease. Young patients presenting with multiple clear cell meningiomas could be referred for genetic testing.[100,101] How the *SMARCE1* mutation of meningioma affects potential treatment options is another question that needs to be addressed in future studies.

Recommendation 13 *SMARCE1* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation).

BRCA1-associated protein 1 (*BAP1*) mutations

BAP1 is a tumor suppressor gene that encodes a deubiquitylating enzyme which has been identified in a rare subset of aggressive meningiomas with rhabdoid morphology.[102] *BAP1* mutation in rhabdoid meningiomas was an important step towards the separation of rhabdoid-appearing meningiomas into aggressive and less-aggressive tumor types.[103] Identification of a germline *BAP1* mutation calls for increased vigilance in cancer surveillance in individuals who harbor this mutation.[104] Additionally, loss of BAP1 protein expression indicates early meningioma recurrence.[103,105] More importantly, BAP1 immunohistochemistry could be a promising tool for risk stratification in patients with rhabdoid meningiomas, and is associated with classification and grading of meningiomas in WHO CNS5.[2]

Recommendation 14 *BAP1* mutation testing should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Familial germline testing could be considered for *BAP1* inactivated meningiomas (Evidence 2B; Grade III recommendation).

Duchenne muscular dystrophy (*DMD*) mutations

The *DMD* gene encodes the protein dystrophin, and germline mutations in this gene are driving factors of DMD.[106] Inactivation of the *DMD* plays a vital role in the development and progression of various solid tumors.[107-110] In 2018, Juratli *et al*[111] reported a retrospective clinical study with 169 high-grade meningioma samples from 53 patients. *DMD* gene inactivation was found to be associated with shorter PFS and OS; it was an independent risk factor for poor prognosis in meningioma patients ($P = 0.033$, hazard ratio [HR] = 2.6, 95% confidence interval [CI] 1.0–6.6). In 2019, Paramasivam *et al*[112] reported that aberrations of *DMD* were found to be enriched in meningiomas with *NF2* mutations, and *DMD* was among the most differentially upregulated genes in *NF2* mutant compared to *NF2* wild-type cases. However, the specific role of *DMD* in meningiomas remains to be determined.

Recommendation 15 *DMD* mutation testing could be considered for postoperative meningiomas (Evidence 2B; Grade II recommendation).

Polybromo-1 (*PBRM1*) mutations

PBRM1 is a tumor suppressor gene encoding the BAF180 subunit of the SWI/SNF complex and is involved in the regulation of tumor cell proliferation and migration.[113] Alterations in the *PBRM1* gene are present in 40% of renal clear cell carcinomas, papillary renal carcinomas, and bladder carcinomas.[114,115] In 2020, Williams *et al*[116] reported the presence of high-frequency mutations in *PBRM1* in papillary meningiomas (WHO grade 3, with updated criteria of WHO CNS5). This conclusion was corroborated in a follow-up study with 850 meningioma samples, which found that 87.5% of *PBRM1* mutations occurred in WHO grade 2 and 3 meningiomas.[56] These studies have enhanced our understanding of the molecular biosignatures of high-grade meningiomas. However, further studies are still necessary to clarify whether *PBRM1* alterations are associated with clinical prognosis in patients with meningioma.

Recommendation 16 *PBRM1* mutation testing could be considered for postoperative meningiomas (Evidence 3; Grade III recommendation).

RNA polymerase II subunit A (*POLR2A*) mutations

POLR2A, the protein that mediates transcription of all protein-coding genes in eukaryotes, has been identified in

approximately 6% of grade 1 meningiomas. The recurrent somatic hotspot mutations include *POLR2A*^{L438H} and *POLR2A*^{Q403K}.[48] *POLR2A* mutant meningiomas are exclusively WHO grade 1 tumors that are most likely to be found in anterior skull base tumors, especially tuberculum sellae, and tend to harbor a meningothelial histopathological morphology.[12,48] In 2021, Youngblood *et al*[53] observed a longer time to recurrence in meningiomas with *POLR2A* mutation compared with that in other meningioma types ($P = 0.49$, HR 0.61, 95% CI 0.15–2.50). However, in this study, the meningioma samples with *POLR2A* mutation only constituted 4.9% ($n = 23$) of the total samples, and tumor recurrence was observed in 13% ($n = 3$) of patients during subsequent follow-up. Youngblood *et al*[53] also found an association between *POLR2A* mutations and female gender in another study. Furthermore, in a single-center clinical study enrolling 269 meningioma patients, Okano *et al*[21] observed tumor recurrence in 29.4% of meningioma patients harboring *POLR2A* mutation (5/17), with a mean time to recurrence of 45.6 months (range: 33.6–57.6 months). Moreover, *POLR2A* mutation was a risk factor for the tumor recurrence in WHO grade 1 skull base meningiomas.[117,118]

Recommendation 17 *POLR2A* mutation testing could be considered for postoperative meningiomas (Evidence 2B; Grade III recommendation).

Epigenomic alterations in meningioma

H3K27me3 alterations

Histones are highly conserved proteins composed of core proteins, which together with DNA constitute nucleosomes. Histone modification not only reversibly represses or facilitates gene transcription but also affects other processes, such as DNA repair, replication, stem cell formation, and cell state changes. The trimethylation of lysine 27 on histone 3 (H3K27me3) is a chromatin modification that is tightly linked to gene repression and plays an essential role in the development and progression of intracranial tumors.[119,120] An explicit association between H3K27me3 loss and meningioma recurrence has been shown in multiple retrospective clinical studies.[121,122] Based on the results from 232 meningioma studies, Katz *et al*[122] reported in 2018 that H3K27me3 loss increased the clinical recurrence risk of meningiomas and displayed a prominent effect on the clinical prognosis of WHO grade 1 and 2 cases. In another multi-center retrospective study, H3K27me3 immunohistochemical staining of paraffin sections and clinical variable analysis were conducted in 181 meningioma samples. The results showed that H3K27me3 loss increased the risk of tumor recurrence in WHO grade 1 and 2 meningiomas.[121]

Recommendation 18 H3K27me3 detection should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). Follow-up of H3K27me3 negative meningiomas could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

TIMP3 methylation

DNA methylation is one of the earliest discovered and most well-studied epigenetic regulatory mechanism. This process is catalyzed by the DNA methyltransferase family and involves the transfer of a methyl group to carbon 5' of cytosine in genomic CpG dinucleotides. DNA methylation controls gene expression by inducing changes in chromatin structure, DNA conformation, DNA stability, and DNA-protein interactions.[123] The hypermethylation of *TIMP3*, *CDKN2A*, and *TP73* occurs in 10% of meningiomas.[124] *TIMP3* hypermethylation causes a downregulation in transcription product and then loss of tumor suppressor activity.[125] Hypermethylated *TIMP3* is present in 40% to 60% of high-grade meningiomas, and these cases often experience rapid recurrence after therapy.[124,125] Furthermore, because *TIMP3* is located on chromosome 22 (22q12), almost all meningioma patients with *TIMP3* hypermethylation are accompanied by allelic loss of 22q.[125] Olar *et al*[44] reported the results from a multi-center retrospective clinical study conducted in 2017, which demonstrated for the first time that meningiomas could be divided into two distinct subtypes associated with PFS through clustering analysis of global DNA methylation data. Similarly, Sahm *et al*[14] divided meningiomas into two major classes and six subtypes based on clustering data of DNA methylation; these subtypes showed distinct genomic features and clinical manifestations. The expression profile and epigenomic feature in meningiomas highlight the value of molecular analysis both in prediction of tumor recurrence and in development of novel therapies.[126]

Recommendation 19 *TIMP3* methylation testing could be considered for postoperative meningiomas (Evidence 2B; Grade II recommendation). Follow-up of meningiomas with *TIMP3* methylation could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

TP73 promoter (*TP73*p) methylation

The human *TP73* gene on the short arm of chromosome 1 (1p36.32) is a *TP53* homologous family gene with a sequence highly similar to that of *TP53*. *TP73* is transcribed into two major functional subunits: TAp73 and DNp73. TAp73 is a tumor suppressor that plays a compensatory role in suppressing *p53*-mutated tumors, whereas DNp73 acts as a tumor promotor. *p53* is widely mutated in tumors, but its mutation rate in primary tumors is only 0.6%.[127] Allelic loss and promoter hypermethylation of *TP73* are the principal pathways that cause the aberrant expression of p73. Existing studies have confirmed that *TP73*p methylation is present in 70% to 80% of high-grade meningiomas; however, this phenomenon is not common in WHO grade 1 meningiomas,[128] indicating a certain specificity of *TP73*p methylation in high-grade meningiomas. Lomas *et al*[129] considered that *TP73*p methylation accounted for 20% of meningiomas and was not associated with tumor grade. Bello *et al*[124] found that the methylation rates of the *TP73*p in WHO grade 1 to 3 meningiomas were 13% (9/68), 19% (5/27), and 33% (1/3), respectively. However, these two studies

included only three WHO grade 3 meningioma samples and used different methylation primer sequences for polymerase chain reaction detection, which might cause biases in their results.[124,129] Hence, more research should be carried out to clarify the relationship between *TP73*p methylation and meningioma development and progression.

Recommendation 20 *TP73*p methylation testing could be considered for postoperative meningiomas (Evidence 2B; Grade II recommendation). Follow-up of meningiomas with *TP73*p methylation could be done every 6 months within 5 years (Evidence 3; Grade III recommendation).

Potential Targets for Individualized Management of Meningiomas

Hormone receptors: estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and somatostatin receptor 2 (SSTR2)

The expression of sex hormone receptors, including the ER, PR, and AR, has been reported in meningiomas by several retrospective clinical studies; however, their association with clinical prognosis in meningioma patients is still inconclusive.[130-133] In 2018, Hua *et al*[131] enrolled 87 WHO grade 3 meningiomas for a single-center retrospective study, which found that ER expression was associated with poor prognosis. However, survival benefits of tamoxifen, an ER inhibitor, were not observed for patients in several phase II clinical trials.[134,135] Similarly, the PR inhibitor mifepristone showed no benefit in meningioma patients in another phase III clinical trial (SWOG S9005).[136] Various studies have reported differences in PR expression in meningiomas.[137-141] Roser *et al*[142] conducted a single-center retrospective study with 588 meningioma samples in 2004, revealing an association of PR expression with a favorable clinical prognosis of patients. In 2006, Pravdenkova *et al*[143] conducted a retrospective study with 239 meningioma samples, which also found that PR expression was associated with a good clinical prognosis. To date, there have been no clinical trials of AR inhibitors for the treatment of meningioma.

Recommendation 21 ER (Evidence 2B; Grade III recommendation) and PR (Evidence 3; Grade III recommendation) detection should be considered for postoperative meningiomas.

SSTR2, which is specifically and highly expressed in meningioma, plays a major role in the pathological diagnosis of meningioma.[137-139] SSTR2 is associated with WHO grade and pathological subtype.[144] Fodi *et al*[145] analyzed the expression of SSTRs (SSTR1A, SSTR2A, SSTR3A, SSTR4A, and SSTR5A) in >700 meningioma samples in 2021, among which SSTR2A expression was found to be associated with poor clinical prognosis of patients ($P = 0.0143$). Owing to the wide expression of SSTR2 in meningioma, radiolabeled SSTR2 ligands (ie, octreotide) have been applied in the radiographic diagnosis of meningiomas.[146-161] This exploration, not yet available as standard practice, is helpful in distinguishing tumor from healthy tissue and postoperative tissue changes [Table 1].[162] Although somatostatin

Table 1: Clinical studies using radiolabeled SSTR2 ligands for meningioma diagnosis.

Image diagnostic methods	Radiolabeled SSTR2 ligand	Sample sizes	Major/novel functions	References
PET	68 Ga-DOTATATE	21 pts (81 MG)	Discriminating meningioma and tumor-free tissue even in recurrent tumors after previous therapy.	144
		64 MG	Selecting the time point for treatment initiation; predicting tumor growth rate.	145
		30 pts (49 MG)	Discriminating meningioma and post-treatment change; improving diagnosis and evaluation for the severity of disease.	146
	68 Ga-DOTATOC	3 pts (8 Ms)	Offering excellent imaging properties and a very high tumor-to-background ratio even in small meningiomas.	147
		21 pts	Showing higher specificity for meningioma diagnosis than FET PET.	148
PET/CT	68 Ga-DOTATATE	82 pts	Improving detection of the transosseous extension of intracranial meningiomas.	149
	68 Ga-DOTATOC	26 pts	Improving target volume delineation for IMRT, especially for skull base meningioma and recurrent disease after surgery.	150
		134 pts	Providing additional information in patients with uncertain or equivocal results on MRI; helping to confirm MRI-based diagnosis of meningiomas in cases of biopsy limitations.	151
PET/MRI	68 Ga-DOTATOC	10 pts	Sketching treatment target volume; benefiting radiosurgical treatment plan.	152
SPECT SRS	^{111} In-octreotide	27 pts	Discriminating meningioma and nonspecific hyper-perfusion; displaying remaining tumor tissue or relapse of meningioma in postsurgical follow-up.	153
		22 pts	Detecting MG with an extremely high sensitivity (100%).	154
		47 pts	Discriminating MG and other CNS tumors, combined with MRI.	155
		70 pts	Discriminating MG and other tumors, postoperative scar or radionecrosis at the skull base.	156
		95 pts	Discriminating MG and other CNS tumors.	157
		50 pts	Discriminating MG and other cranial dural-based lesions, combined with MRI.	158
SPECT/CT SRS	99m Tc-HYNIC-octreotide	30 pts	Showing high meningioma radioactivity accumulation with a sensitivity of 100%.	159

CNS: Central nervous system; CT: Computerized tomography; DOTATATE: DOTA-D-Phe1-Tyr3-octreotate; DOTATOC: DOTA-(Tyr3)-octreotide; FET: Fluoro-ethyl-tyrosine; HYNIC: Hydrazinonicotinamide; IMRT: Intensity modulated radiotherapy; ^{111}In: 111-Indium; MG: Meningiomas; MRI: Magnetic resonance imaging; PET: Positron emission tomography; pts: Patients; SPECT: Single-photon emission computed tomography; SRS: Somatostatin receptor scintigraphy; SSTR2: Somatostatin receptor 2.

receptors are expressed in meningiomas, the long-acting somatostatin analogue (octreotide or pasireotide) did not significantly increase PFS and OS in several small and uncontrolled studies or patient series.[163-165] A phase II clinical trial involving 34 subtotal resection meningioma samples showed that using Yttrium-90-DOTATOC and lutetium-DOTATOC for SSTR2-targeted radiotherapy achieved higher rates of radionuclide uptake and improved therapeutic effects.[166] Another ongoing phase I clinical study of 177Lu-DOTA-JR11 for the treatment of meningiomas (NCT04997317) is conducted by the Swiss Cancer League Dominic in Switzerland in 2021. Somatostatin analogs like octreotide and pasireotide have shown some effects on disease stabilization in meningiomas with SSTR2 expression, which has been described in "*NF2* mutations" part.[60,61]

Recommendation 22 SSTR2 detection should be considered for postoperative meningiomas (Evidence 2A; Grade I recommendation). SSTR2 directed radiological diagnosis could be considered for meningiomas (Evidence 2B; Grade II recommendation).

Tyrosine kinases receptors (TKRs): epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR)

TKRs are transmembrane proteins that facilitate interactions between tissue cells and their adjacent cells. In contrast to other cell surface receptors, TKRs exhibit specific enzymatic activity. When signaling molecules bind to TKRs to activate tyrosine kinases in the cytoplasmic tail of the receptor, a series of enzymatic reactions are initiated to transmit the signal to the nucleus, thereby altering the protein transcription pattern.[167] TKRs expressed in meningioma include EGFR, VEGFR, and PDGFR.[167] An experimental study indicated that TKR inhibitors improve the clinical prognosis of patients through different mechanisms, such as suppressing tumor cell proliferation, reducing tumor volume, and alleviating peritumoral edema.[168]

EGFR is expressed at different levels in meningioma. Notably, The expression of EGFR seems higher in low-grade meningiomas, but their association with the clinical prognosis of patients remains unclear.[169-171] In a phase II clinical trial reported by Norden *et al*[172] in 2010, no significant effects of gefitinib or erlotinib (EGFR inhibitor) were observed on PFS and OS improvements among meningioma patients. Later, Osorio *et al*[173] reported the results of a literature review in 2018, which found that lapatinib had a certain control effect on neurofibromatosis type 2-related meningioma, but further randomized controlled trials should be carried out for verification. Varied levels of VEGFR expression were observed in all meningiomas, and a higher expression was associated with a higher tumor grade and shorter PFS in most cases.[174-178] These findings suggest that VEGFR inhibitors may exhibit a certain therapeutic effect on refractory meningiomas. In a multi-center prospective phase II clinical trial reported in 2015, Kaley *et al*[179] enrolled 36 patients with high-grade meningioma who received sunitinib therapy. After treatment, the PFS rate at 6 months was 42%, and the median PFS reached 5.2 months (95% CI: 2.8–8.3 months), with a median OS of 24.6 months (95% CI: 16.5–38.4 months). However, certain adverse reactions to sunitinib were also observed, such as intratumoral hemorrhage, thrombotic microangiopathy and gastrointestinal perforation. Bevacizumab is a monoclonal antibody against recombinant humanized immunoglobulin G1 that inhibits VEGF-A and represses its binding to VEGF receptor-2. As a result, the biological functions of VEGF, including vascular permeability and proliferation, as well as endothelial cell migration and survival, are influenced, thereby achieving the suppression of tumor angiogenesis, growth, and metastasis.[180] To date, bevacizumab has been extensively used in the treatment of many tumors, such as colorectal carcinoma, pulmonary carcinoma, ovarian carcinoma, cervical carcinoma, and glioblastoma.[181-183] Presently, bevacizumab is considered to delay the postoperative growth of meningioma.[11,184] Shih *et al*[59] reported another prospective phase II clinical trial in 2016, demonstrating the therapeutic effects of bevacizumab combined with the mTORC1 inhibitor everolimus on recurrent and progressive meningiomas. Among all cases included in the trial ($n = 17$), the median tumor PFS was 10 months (range: 2–19 months), and the PFS of patients with WHO grade 2–3 meningioma was higher than that of patients with WHO grade 1 meningioma (PFS: 22 months *vs*. 17 months). Collectively, these results suggest that patients with refractory meningioma can benefit from this combined therapy with bevacizumab and everolimus. Additionally, three phase II clinical trials evaluating the therapeutic effects of bevacizumab (NCT01125046), bevacizumab coupled with electric field therapy (NCT02847559), and bevacizumab plus the programmed death-1 inhibitor pembrolizumab (NCT03279692) for recurrent and progressive meningiomas are still ongoing.

Platelet-derived growth factor and its receptors (PDGFR) are frequently co-expressed in meningiomas, potentially contributing to their pathogenesis.[185,186] Wen *et al*[187] published the results from a prospective phase II clinical trial that evaluated the therapeutic effects of the PDGFR inhibitor imatinib mesylate in 23 patients with different grades of meningioma. However, single-agent imatinib was well tolerated but had no significant activity in recurrent meningiomas (PFS: 2 months; range: 0.7–34.0 months).

Recommendation 23 Pharmacotherapy using bevacizumab targeting VEGER could only be considered if no further local treatment option exists (Evidence 2A; Grade II recommendation).

Limitations

Based on the update of WHO CNS5, this consensus mainly focuses on the application of key molecular biomarkers for meningioma in clinical diagnosis and treatment. Despite revisions according to expert opinions proposed on several revision meetings, the consensus still has the following limitations: (1) The consensus recommends expert opinions that can reach a consensus only

Table 2: A summary of recommended biomarkers for testing.

Biomarkers	Function	Tumor location	Clinical significance (evidence level)	Diagnosis (evidence level)	Adjuvant therapy (evidence level)		Follow-up (evidence level)	Test method	Recommendation grade
					Radiation therapy	Systemic therapy			
Copy number alterations									
22q	A critical role in meningiomagenesis by dysregulating oncogene and tumor suppressor activity	Convexity and spine	22q loss is significantly associated with worse clinical outcome (evidence 2B)	Unknown	Unknown	Sensitive to sunitinib (evidence 3)	Annually within 5 years (evidence 3)	Karyotyping, FISH, Array-CGH, NGS	Grade I
1p	Unknown	Unknown	1p loss is associated with worse clinical outcome (evidence 2A). 1p/14q loss increases the risk of tumor recurrence (evidence 2A)	Unknown	Unknown	Sensitive to sunitinib (evidence 3)	Every 6 months within 5 years (evidence 3)	Karyotyping, FISH, Array-CGH, NGS	Grade I
14q	Unknown	Unknown	1p/14q loss increases the risk of tumor recurrence (evidence 2A)	Unknown	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	Karyotyping, FISH, Array-CGH, NGS	Grade I
18q	Unknown	Unknown	18q loss increases the risk of tumor short-term recurrence (evidence 2B)	Unknown	Unknown	Unknown	Annually within 5 years (evidence 3)	Karyotyping, FISH, Array-CGH, NGS	Grade III
Gene mutation signatures									
NF2	*NF2* produces merlin that functions as a tumor suppressor by inhibiting cell growth	Convexity and spine	*NF2* mutation is associated with worse clinical outcome, increases the risk of tumor recurrence (evidence 2A)	Unknown	Unknown	Unknown	Annually within 5 years (evidence 3)	NGS, Sanger sequence, MLPA, FISH, IHC	Grade I
TERT promoter	*TERT*p regulates *TERT* gene expression and maintains normal cell mitosis	Unknown	*TERT*p mutation is associated with worse clinical outcome, and increases the risk of tumor recurrence (evidence 1A)	Histological criteria of WHO grade 3 (evidence 3)	*TERT*p alteration is associated with radiation sensitivity in *de novo* high-grade meningiomas (evidence 2B)	Unknown	Every 3–6 months indefinitely (evidence 3)	NGS, Sanger sequence	Grade I
CDKN2A/B	*CDKN2A/B* regulates cell cycle and inhibits tumor cell proliferation	Unknown	*CDKN2A/B* mutation is associated with worse clinical outcome, and increases the risk of tumor recurrence (evidence 2A)	Histological criteria of WHO grade 3 (evidence 3)	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	NGS, Sanger sequence	Grade I
AKT1, PIK3CA	PI3K pathway serves to disconnect the control of cell growth, survival and metabolism from exogenous growth stimuli	Middle fossa skull base	*AKT1* and *PIK3CA* mutation increases the risk of tumor recurrence (evidence 2A)	Unknown	Unknown	Everolimus-octreotide (evidence 2A); everolimus-bevacizumab (evidence 2A)	Every 6 months within 5 years (evidence 3)	*AKT1*: NGS, RT-PCR; *PIK3CA*: NGS, Sanger sequence, RT-PCR	Grade I
SMO, SUFU	Driver genes in Hedgehog pathway	Middle fossa skull base	*SMO* and *SUFU* mutation increases the risk of tumor recurrence (evidence 2A)	Unknown	Unknown	Unknown	Annually within 5 years (evidence 3)	*SMO*: NGS, Sanger sequence; *SUFU*: NGS, IHC	Grade I
TRAF7	Transduction molecules in TNFR mediated signaling pathway	Middle fossa skull base	*TRAF* mutation increases the risk of tumor short-term recurrence (evidence 2A)	Histological criteria of secretory subtype (evidence 3)	Unknown	Unknown	–	NGS, Sanger sequence	Grade I
KLF4	Zinc finger protein transcription factor, which involves in the regulation of cell proliferation, differentiation and embryonic development	Non-midline anterior and central skull base	*KLF4* mutation is associated with better 5-year progression-free survival and peritumoral brain edema (evidence 2A)	Histological criteria of secretory subtype (evidence 3)	Unknown	Unknown	–	NGS, Sanger sequence	Grade I
SMARCE1	Chromatin remodeling complex SWI/SNF involves in encoding part of ATP	Spine	Common mutation in clear cell subtype (evidence 2A)	Reference for diagnosis of secretory subtype (evidence 3)	Unknown	Unknown	–	NGS, IHC	Grade I
BAP1	A tumor suppressor gene that encodes a deubiquitylating enzyme, and inhibits tumor growth by	Unknown	*BAP1* mutation is associated with worse clinical outcome, and increases the risk of	Reference for diagnosis of rhabdoid	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	NGS, IHC	Grade I

(*continued*)

Table 2
(continued).

Biomarkers	Function	Tumor location	Clinical significance (evidence level)	Diagnosis (evidence level)	Adjuvant therapy (evidence level)		Follow-up (evidence level)	Test method	Recommendation grade
					Radiation therapy	Systemic therapy			
	binding to the ring finger domain of BRCA1		tumor recurrence (evidence 2A)	subtype (evidence 3)					
DMD	*DMD* locates at Xp21.1-p21.3, encoding dystrophin	Unknown	*DMD* mutation is associated with worse clinical outcome, and increases the risk of tumor recurrence (evidence 2B)	Unknown	Unknown	Unknown	Annually within 5 years (evidence 3)	NGS, IHC	Grade I
PBRM1	A tumor suppressor gene encoding the BAF180 subunit of the SWI/SNF complex, and involving in the regulation of tumor cell proliferation and migration	Unknown	Common mutation in papillary subtype (evidence 2B)	Unknown	Unknown	Unknown	–	NGS	Grade III
POLR2A	The protein that mediates transcription of all protein-coding genes in eukaryotes	Anterior skull base, especially tuberculum sellae	*POLR2A* mutation is associated with better clinical outcome (evidence 2B)	Unknown	Unknown	Unknown	–	NGS, Sanger sequence	Grade III
Epigenomic alterations									
H3K27me3	A chromatin modification that is tightly linked to gene repression and plays an essential role in the development and progression of intracranial tumors	Unknown	H3K27me3 loss increases the risk of tumor short-term recurrence (evidence 2A)	Unknown	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	IHC	Grade I
TIMP3 methylation	*TIMP3* methylation causes a down-regulation in transcription product and then loss of tumor suppressor activity	Unknown	*TIMP3* methylation increases the risk of tumor short-term recurrence (evidence 2B)	Unknown	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	Pyrosequencing	Grade II
TP73 promoter methylation	TP73 promoter methylation regulates downstream transcripts and inhibits tumor growth	Unknown	*TP73* promoter methylation increases the risk of tumor short-term recurrence (evidence 2B)	Unknown	Unknown	Unknown	Every 6 months within 5 years (evidence 3)	Pyrosequencing	Grade II
Hormone receptors									
ER	ER participates in regulation of multiple hormones, inhibits cell proliferation and promotes cell apoptosis	Unknown	High expression of ER is associated with worse clinical outcome (evidence 2B)	Unknown	Unknown	Unknown	–	IHC	Grade III
PR	PR participates in regulation of multiple hormones, inhibits cell proliferation and promotes cell apoptosis	Unknown	High expression of PR is associated with worse clinical outcome (evidence 2B)	Unknown	Unknown	Unknown	–	IHC	Grade III
SSTR2	SSTR2 participates in regulation of multiple hormones, inhibits cell proliferation and promotes cell apoptosis	Unknown	*SSTR2* alterations increase the risk of tumor recurrence (evidence 2B)	Octreotide-scanning (evidence 2B)	Unknown	Everolimus-octreotide (evidence 2B)	–	IHC	Grade I
Tyrosine kinases receptors									
VEGFR	VEGFR involves in regulation of lymphatic endothelial cells and vascular endothelial cells, and promotes the formation of lymphatic vessels and blood vessels	Unknown	Expressien of VEGFR is associated with higher WHO grade and shorter progression-free survival (evidence 2B)	Unknown	Unknown	Bevacizumab (evidence 2A)	–	IHC	Grade II

AKT1: Protein kinase B; Array-CGH: Array-comparative genomic hybridization; ATP: Adenosine triphosphate; BAF: BRM-associated factor; *BAP1*: BRCA1 associated protein 1; BRCA1: Breast cancer 1; *CDKN2A/B*: Cyclin-dependent kinase inhibitor 2A/B; *DMD*: Duchenne muscular dystrophy; ER: Estrogen receptor; FISH: Fluorescence *in situ* hybridization; H3K27me3: Trimethylation of lysine 27 on histone 3; IHC: Immunohistochemistry; *KLF4*: Krüppel-like factor 4; MLPA: Multiple ligation-dependent probe amplification; *NF2*: Neurofibromin 2; NGS: Next generation sequencing; *PBRM1*: Polybromo-1; *PI3K*: Phosphosphatidylinositol-3-kinase; *PIK3CA*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; *POLR2A*: RNA polymerase II; PR: Progesterone Receptor; RT-PCR: Reverse transcription-polymerase chain reaction; *SMARCE1*: SWI/SNF Related, matrix associated, actin dependent regulator of chromatin, subfamily E, member 1; *SMO*: Smoothened; SSTR2: Somatostatin receptor 2; *SUFU*: Suppressor of fused homolog; SWI/SNF: Switching defective/sucrose non-fermenting; *TERT*: Telomerase reverse tranase; TERTp: Telomerase reverse transcriptase promoter; *TIMP3*: Tissue inhibitor of matrix metalloproteinase 3; TNFR: Tumor necrosis factor receptor; *TP73*: Tumor protein p73; *TRAF7*: Tumor necrosis factor receptor associated factor 7; VEGFR: Vascular endothelial growth factor receptor; WHO: World Health Organization; -: Not available.

Table 3: Biomarkers of meningiomas with different locations and WHO grades.

Tumor location	WHO grade	Recommendation grade I	Recommendation grade II	Recommendation grade III	Adjuvant therapy
Midline anterior and central skull base	Grade 1	*AKT1, PIK3CA, SMO, SUFU, TRAF7,* H3K27me3, SSTR2	VEGFR	*POLR2A*	Everolimus-octreotide (SSTR2, *AKT1*, PI3K), bevacizumab (VEGFR)
	Grade 2	*AKT1, PIK3CA, SMO, SUFU, TRAF7, BAP1,* H3K27me3, SSTR2	VEGFR	–	Everolimus-octreotide (SSTR2, *AKT1*, PI3K), bevacizumab (VEGFR)
	Grade 3	*TERT*p, *CDKN2A/B, AKT1, PIK3CA, SMO, SUFU, TRAF7, BAP1,* H3K27me3, SSTR2	VEGFR	–	Everolimus-octreotide (SSTR2, *AKT1*, PI3K), bevacizumab (VEGFR)
Non-midline anterior and central skull base	Grade 1	*KLF4*, H3K27me3, SSTR2	VEGFR	–	Everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 2	*KLF4, BAP1*, H3K27me3, SSTR2	VEGFR	–	Everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 3	*TERT*p, *CDKN2A/B, KLF4, BAP1*, H3K27me3, SSTR2	VEGFR	–	Everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
Convexity	Grade 1	22q, *NF2,* H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 2	22q, *NF2, BAP1*, H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 3	22q, *NF2, TERT*p, *CDKN2A/B, BAP1*, H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
Spine	Grade 1	22q, *NF2, SMARCE1*, H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 2	22q, *NF2, BAP1, SMARCE1*, H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)
	Grade 3	22q, *NF2, TERT*p, *CDKN2A/B, BAP1, SMARCE1*, H3K27me3, SSTR2	VEGFR	–	Sunitinib (22q), everolimus-octreotide (SSTR2), bevacizumab (VEGFR)

AKT1: Protein kinase B; *BAP1*: BRCA1 associated protein 1; *CDKN2A/B*: cyclin-dependent kinase inhibitor 2A/B; H3K27me3: Trimethylation of lysine 27 on histone 3; *KLF4*: Krüppel-like factor 4; *NF2*: Neurofibromin 2; PI3K: Phosphosphatidylinositol-3-kinase; *PIK3CA:* Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; POLR2A: RNA polymerase II; *SMARCE1*: SWI/SNF Related, matrix associated, actin dependent regulator of chromatin, subfamily E, member 1; *SMO*: Smoothened; *SUFU*: Suppressor of fused homolog; SSTR2: Somatostatin receptor 2; *TERT*: Telomerase reverse transcriptase; TERTp: Telomerase reverse transcriptase promoter; *TRAF7*: Tumor necrosis factor receptor associated factor 7; VEGFR: Vascular endothelial growth factor receptor; -: Not available.

based on evidence that can be retrieved at the current stage. Consequently, it cannot completely cover or solve all questions in the clinical diagnosis and treatment of meningioma patients, including preoperative diagnosis, postoperative radiotherapy and chemotherapy decisions, prognosis evaluation, and disease monitoring. (2) Other molecular markers not listed for recommendation in this consensus have also been reported in previous studies of meningiomas. However, the association of such biomarkers with the clinical prognosis has not yet been clarified; therefore, they are not currently included in the recommendations. (3) In recent years, there has been rapid progress in molecular underpinnings of meningiomas, and updated studies have been reported continuously. Therefore, the recommendations presented in this consensus are time-limited and need to be updated regularly.

These limitations will be gradually addressed in our further work according to the advances in this field.

Conclusions

In recognition of the value of molecular features in meningioma subtyping in WHO CNS5, the present expert consensus aims to incorporate some of these molecular features, setting the stage for the improvement of future diagnosis and therapeutic efforts through the integration of key molecular findings in meningiomas [Tables 2 and 3]. It is hoped that our work could provide practical guidance to specialists and pathologists in meningiomas, and benefit the patients who are affected by meningiomas.

Conflicts of interest

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References

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol 2021;23:iii1–iii105. doi: 10.1093/neuonc/noab200.
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, *et al*. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 2021;23:1231–1251. doi: 10.1093/neuonc/noab106.
3. Nassiri F, Liu J, Patil V, Mamatjan Y, Wang JZ, Hugh-White R, *et al*. A clinically applicable integrative molecular classification of meningiomas. Nature 2021;597:119–125. doi: 10.1038/s41586-021-03850-3.
4. Maas S, Stichel D, Hielscher T, Sievers P, Berghoff AS, Schrimpf D, *et al*. Integrated molecular-morphologic meningioma classification: a multicenter retrospective analysis, retrospectively and prospectively validated. J Clin Oncol 2021;39:3839–3852. doi: 10.1200/JCO.21.00784.
5. Zulch KJ. Histological Typing of Tumours of the Central Nervous System. Geneva, Switzerland: World Health Organization; 1979.

6. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993;3:255–268. doi: 10.1111/j.1750-3639.1993.tb00752.x.
7. Cancer IAFR, Kleihues P, CWE. World Health Organization classification of tumours. Pathology and Genetics of Tumours of the Nervous System. Lyon, France: IARC Press; 2000.
8. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, *et al*. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109. doi: 10.1007/s00401-007-0243-4.
9. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–820. doi: 10.1007/s00401-016-1545-1.
10. WHO Classification of Tumours Editorial Board. World Health Organization Classification of Tumours of the Central Nervous System. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
11. Goldbrunner R, Stavrinou P, Jenkinson MD, Sahm F, Mawrin C, Weber DC, *et al*. EANO guideline on the diagnosis and management of meningiomas. Neuro Oncol 2021;23:1821–1834. doi: 10.1093/neuonc/noab150.
12. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Ozduman K, *et al*. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 2013;339:1077–1080. doi: 10.1126/science.1233009.
13. Youngblood MW, Duran D, Montejo JD, Li C, Omay SB, Özduman K, *et al*. Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. J Neurosurg 2019;1–10. doi: 10.3171/2019.8.JNS191266.
14. Sahm F, Schrimpf D, Stichel D, Jones D, Hielscher T, Schefzyk S, *et al*. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 2017;18:682–694. doi: 10.1016/S1470-2045(17)30155-9.
15. Patel AJ, Wan YW, Al-Ouran R, Revelli JP, Cardenas MF, Oneissi M, *et al*. Molecular profiling predicts meningioma recurrence and reveals loss of DREAM complex repression in aggressive tumors. Proc Natl Acad Sci U S A 2019;116:21715–21726. doi: 10.1073/pnas.1912858116.
16. Driver J, Hoffman SE, Tavakol S, Woodward E, Maury EA, Bhave V, *et al*. A molecularly integrated grade for meningioma. Neuro Oncol 2022;24:796–808. doi: 10.1093/neuonc/noab213.
17. Chen YP, Ismaila N, Chua M, Colevas AD, Haddad R, Huang SH, *et al*. Chemotherapy in combination with radiotherapy for definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma: CSCO and ASCO guideline. J Clin Oncol 2021;39:840–859. doi: 10.1200/JCO.20.03237.
18. Michael A, Erio Z. Gazing into the Oracle: The Delphi Method And its Application to Social Policy and Public Health. London: Kingsley Publishers; 1996.
19. Seizinger BR, de la Monte S, Atkins L, Gusella JF, Martuza RL. Molecular genetic approach to human meningioma: loss of genes on chromosome 22. Proc Natl Acad Sci U S A 1987;84:5419–5423. doi: 10.1073/pnas.84.15.5419.
20. Daoud EV, Zhu K, Mickey B, Mohamed H, Wen M, Delorenzo M, *et al*. Epigenetic and genomic profiling of chordoid meningioma: implications for clinical management. Acta Neuropathol Commun 2022;10:56. doi: 10.1186/s40478-022-01362-3.
21. Okano A, Miyawaki S, Hongo H, Dofuku S, Teranishi Y, Mitsui J, *et al*. Associations of pathological diagnosis and genetic abnormalities in meningiomas with the embryological origins of the meninges. Sci Rep 2021;11:6987. doi: 10.1038/s41598-021-86298-9.
22. Ruttledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, *et al*. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat Genet 1994;6:180–184. doi: 10.1038/ng0294-180.
23. Suppiah S, Nassiri F, Bi WL, Dunn IF, Hanemann CO, Horbinski CM, *et al*. Molecular and translational advances in meningiomas. Neuro Oncol 2019;21:i4–i17. doi: 10.1093/neuonc/noy178.
24. Bi WL, Greenwald NF, Abedalthagafi M, Wala J, Gibson WJ, Agarwalla PK, *et al*. Genomic landscape of high-grade meningiomas. NPJ Genom Med 2017;2:15. doi: 10.1038/s41525-017-0014-7.
25. Pfisterer WK, Hank NC, Preul MC, Hendricks WP, Pueschel J, Coons SW, *et al*. Diagnostic and prognostic significance of genetic regional heterogeneity in meningiomas. Neuro Oncol 2004;6:290–299. doi: 10.1215/S1152851704000158.
26. Hilton DA, Shivane A, Kirk L, Bassiri K, Enki DG, Hanemann CO. Activation of multiple growth factor signalling pathways is frequent in meningiomas. Neuropathology 2016;36:250–261. doi: 10.1111/neup.12266.
27. Hong W, Shan C, Ye M, Yang Y, Wang H, Du F, *et al*. Case report: identification of a novel GNAS mutation and 1p/22q co-deletion in a patient with multiple recurrent meningiomas sensitive to sunitinib. Front Oncol 2021;11:737523. doi: 10.3389/fonc.2021.737523.
28. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, *et al*. Neurofibromatosis type 2. Lancet 2009;373:1974–1986. doi: 10.1016/S0140-6736(09)60259-2.
29. Cai DX, Banerjee R, Scheithauer BW, Lohse CM, Kleinschmidt-Demasters BK, Perry A. Chromosome 1p and 14q FISH analysis in clinicopathologic subsets of meningioma: diagnostic and prognostic implications. J Neuropathol Exp Neurol 2001;60:628–636. doi: 10.1093/jnen/60.6.628.
30. Kakkar A, Kumar A, Das A, Pathak P, Sharma MC, Singh M, *et al*. 1p/14q co-deletion: a determinant of recurrence in histologically benign meningiomas. Indian J Pathol Microbiol 2015;58:433–438. doi: 10.4103/0377-4929.168852.
31. Linsler S, Kraemer D, Driess C, Oertel J, Kammers K, Rahnenführer J, *et al*. Molecular biological determinations of meningioma progression and recurrence. PLoS One 2014;9:e94987. doi: 10.1371/journal.pone.0094987.
32. Nagasaka T, Gunji M, Hosokai N, Hayashi K, Fujino M, Ikeda H, *et al*. Fluorescent in situ hybridization 1p/19q deletion/imbalance analysis of low-grade and atypical meningiomas. Neurol Med Chir (Tokyo) 2010;50:27–32; discussion 32. doi: 10.2176/nmc.50.27.
33. Sayagués JM, Tabernero MD, Maíllo A. Cytogenetic alterations in meningioma tumors and their impact on disease outcome (in Spanish). Med Clin (Barc) 2007;128:226–232. doi: 10.1016/s0025-7753(07)72543-5.
34. Och W, Szmuda T, Sikorska B, Springer J, Jaskólski D, Zakrzewska M, *et al*. Recurrence-associated chromosomal anomalies in meningiomas: single-institution study and a systematic review with meta-analysis. Neurol Neurochir Pol 2016;50:439–448. doi: 10.1016/j.pjnns.2016.08.003.
35. Lamszus K, Kluwe L, Matschke J, Meissner H, Laas R, Westphal M. Allelic losses at 1p, 9q, 10q, 14q, and 22q in the progression of aggressive meningiomas and undifferentiated meningeal sarcomas. Cancer Genet Cytogenet 1999;110:103–110. doi: 10.1016/s0165-4608(98)00209-x.
36. Krayenbühl N, Pravdenkova S, Al-Mefty O. De novo versus transformed atypical and anaplastic meningiomas: comparisons of clinical course, cytogenetics, cytokinetics, and outcome. Neurosurgery 2007;61:495–503; discussion 503-504. doi: 10.1227/01.NEU.0000290895.92695.22.
37. Lusis EA, Watson MA, Chicoine MR, Lyman M, Roerig P, Reifenberger G, *et al*. Integrative genomic analysis identifies NDRG2 as a candidate tumor suppressor gene frequently inactivated in clinically aggressive meningioma. Cancer Res 2005;65:7121–7126. doi: 10.1158/0008-5472.CAN-05-0043.
38. Rogers CL, Won M, Vogelbaum MA, Perry A, Ashby LS, Modi JM, *et al*. High-risk Meningioma: Initial Outcomes From NRG Oncology/RTOG 0539. Int J Radiat Oncol Biol Phys 2020;106:790–799. doi: 10.1016/j.ijrobp.2019.11.028.
39. Barbera S, San Miguel T, Gil-Benso R, Muñoz-Hidalgo L, Roldan P, Gonzalez-Darder J, *et al*. Genetic changes with prognostic value in histologically benign meningiomas. Clin Neuropathol 2013;32:311–317. doi: 10.5414/NP300580.
40. Pfisterer WK, Hendricks WP, Scheck AC, Nieman RA, Birkner TH, Krampla WW, *et al*. Fluorescent in situ hybridization and ex vivo 1H magnetic resonance spectroscopic examinations of meningioma tumor tissue: is it possible to identify a clinically-aggressive subset of benign meningiomas? Neurosurgery 2007;61:1048–1059; discussion 1060-1061. doi: 10. 1227/01.neu. 0000303201. 62123. 5c.
41. Lopez-Gines C, Cerda-Nicolas M, Gil-Benso R, Callaghan R, Collado M, Roldan P, *et al*. Association of loss of 1p and

alterations of chromosome 14 in meningioma progression. Cancer Genet Cytogenet 2004;148:123–128. doi: 10.1016/s0165-4608(03)00279-6.
42. Balik V, Srovnal J, Sulla I, Kalita O, Foltanova T, Vaverka M, *et al*. MEG3: a novel long noncoding potentially tumour-suppressing RNA in meningiomas. J Neurooncol 2013;112:1–8. doi: 10.1007/s11060-012 -1038-6.
43. Gupta N, Chacko G, Chacko AG, Rajshekhar V, Jayprakash M. Fluorescence in situ hybridization for chromosome 14q deletion in subsets of meningioma segregated by MIB-1 labelling index. Neurol India 2016;64:1256–1263. doi: 10.4103/0028-3886.193768.
44. Olar A, Wani KM, Wilson CD, Zadeh G, DeMonte F, Jones DT, *et al*. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta Neuropathol 2017;133:431–444. doi: 10.1007/s00401-017-1678-x.
45. Weber RG, Boström J, Wolter M, Baudis M, Collins VP, Reifenberger G, *et al*. Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. Proc Natl Acad Sci U S A 1997;94:14719–14724. doi: 10.1073/pnas.94.26.14719.
46. Barresi V, Simbolo M, Fioravanzo A, Piredda ML, Caffo M, Ghimenton C, *et al*. Molecular profiling of 22 primary atypical meningiomas shows the prognostic significance of 18q heterozygous loss and CDKN2A/B homozygous deletion on recurrence-free survival. Cancers (Basel) 2021;13:903. doi: 10.3390/cancers13040903.
47. Brastianos PK, Horowitz PM, Santagata S, Jones RT, McKenna A, Getz G, *et al*. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet 2013;45:285–289. doi: 10.1038/ng.2526.
48. Clark VE, Harmancı AS, Bai H, Youngblood MW, Lee TI, Baranoski JF, *et al*. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. Nat Genet 2016;48:1253–1259. doi: 10.1038/ng.3651.
49. Wellenreuther R, Kraus JA, Lenartz D, Menon AG, Schramm J, Louis DN, *et al*. Analysis of the neurofibromatosis 2 gene reveals molecular variants of meningioma. Am J Pathol 1995;146:827–832.
50. Yuzawa S, Nishihara H, Yamaguchi S, Mohri H, Wang L, Kimura T, *et al*. Clinical impact of targeted amplicon sequencing for meningioma as a practical clinical-sequencing system. Mod Pathol 2016;29:708–716. doi: 10.1038/modpathol.2016.81.
51. Gupte TP, Li C, Jin L, Yalcin K, Youngblood MW, Miyagishima DF, *et al*. Clinical and genomic factors associated with seizures in meningiomas. J Neurosurg 2020;1–10. doi: 10.3171/2020.7.JNS201042.
52. Deng J, Hua L, Han T, Tian M, Wang D, Tang H, *et al*. The CREB-binding protein inhibitor ICG-001: a promising therapeutic strategy in sporadic meningioma with NF2 mutations. Neurooncol Adv 2020;2:vdz55. doi: 10.1093/noajnl/vdz055.
53. Youngblood MW, Miyagishima DF, Jin L, Gupte T, Li C, Duran D, *et al*. Associations of meningioma molecular subgroup and tumor recurrence. Neuro Oncol 2021;23:783–794. doi: 10.1093/neuonc/noaa226.
54. López-Lago MA, Okada T, Murillo MM, Socci N, Giancotti FG. Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling. Mol Cell Biol 2009;29:4235–4249. doi: 10.1128/MCB.01578-08.
55. James MF, Han S, Polizzano C, Plotkin SR, Manning BD, Stemmer-Rachamimov AO, *et al*. NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. Mol Cell Biol 2009;29:4250–4261. doi: 10.1128/MCB.01581-08.
56. Williams EA, Santagata S, Wakimoto H, Shankar GM, Barker FN 2nd, Sharaf R, *et al*. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. Acta Neuropathol Commun 2020;8:171. doi: 10.1186/s40478-020-01040-2.
57. Peyre M, Stemmer-Rachamimov A, Clermont-Taranchon E, Quentin S, El-Taraya N, Walczak C, *et al*. Meningioma progression in mice triggered by Nf2 and Cdkn2ab inactivation. Oncogene 2013;32:4264–4272. doi: 10.1038/onc.2012.436.
58. Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, *et al*. mTORC1 inhibitors suppress meningioma growth in mouse models. Clin Cancer Res 2013;19:1180–1189. doi: 10.1158/1078-0432.CCR-12 -1904.
59. Shih KC, Chowdhary S, Rosenblatt P, Weir AR, Shepard GC, Williams JT, *et al*. A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. J Neurooncol 2016;129:281–288. doi: 10.1007/s11060-016-2172-3.
60. Graillon T, Sanson M, Campello C, Idbaih A, Peyre M, Peyrière H, *et al*. Everolimus and octreotide for patients with recurrent meningioma: results from the phase II CEVOREM trial. Clin Cancer Res 2020;26:552–557. doi: 10.1158/1078-0432.CCR-19-2109.
61. Cardona AF, Ruiz-Patiño A, Zatarain-Barrón ZL, Hakim F, Jiménez E, Mejía JA, *et al*. Systemic management of malignant meningiomas: a comparative survival and molecular marker analysis between Octreotide in combination with Everolimus and Sunitinib. PLoS One 2019;14:e0217340. doi: 10.1371/journal.pone.0217340.
62. Karajannis MA, Mauguen A, Maloku E, Xu Q, Dunbar EM, Plotkin SR, *et al*. Phase 0 clinical trial of everolimus in patients with vestibular schwannoma or meningioma. Mol Cancer Ther 2021;20:1584–1591. doi: 10.1158/1535-7163.MCT-21-0143.
63. Brastianos PK, Twohy E, Gerstner ER, Kaufmann TJ, Iafrate AJ, Jeyapalan SA, *et al*. Alliance A071401: phase II trial of FAK inhibition in meningiomas with somatic NF2 mutations. J Clin Oncol 2020;38:2502–12502.
64. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT promoter mutations in human melanoma. Science 2013;339:957–959. doi: 10.1126/science.1229259.
65. Maillo A, Orfao A, Sayagues JM, Diaz P, Gómez-Moreta JA, Caballero M, *et al*. New classification scheme for the prognostic stratification of meningioma on the basis of chromosome 14 abnormalities, patient age, and tumor histopathology. J Clin Oncol 2003;21:3285–3295. doi: 10.1200/JCO.2003.07.156.
66. Koelsche C, Sahm F, Capper D, Reuss D, Sturm D, Jones DT, *et al*. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol 2013;126:907–915. doi: 10.1007/s00401-013-1195-5.
67. Remke M, Ramaswamy V, Peacock J, Shih DJ, Koelsche C, Northcott PA, *et al*. TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma. Acta Neuropathol 2013;126:917–929. doi: 10.1007/s00401-013-1198-2.
68. Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, Cooper LA, *et al*. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015;372:2481–2498. doi: 10.1056/NEJMoa1402121.
69. Holleczek B, Zampella D, Urbschat S, Sahm F, von Deimling A, Oertel J, *et al*. Incidence, mortality and outcome of meningiomas: a population-based study from Germany. Cancer Epidemiol 2019;62:101562. doi: 10.1016/j.canep.2019.07.001.
70. Sahm F, Schrimpf D, Olar A, Koelsche C, Reuss D, Bissel J, *et al*. TERT promoter mutations and risk of recurrence in meningioma. J Natl Cancer Inst 2016;108:djv377. doi: 10.1093/jnci/djv377.
71. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. Brain Pathol 2014;24:184–189. doi: 10.1111/bpa.12110.
72. Mirian C, Duun-Henriksen AK, Juratli T, Sahm F, Spiegl-Kreinecker S, Peyre M, *et al*. Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: an individual patient data meta-analysis. J Neurol Neurosurg Psychiatry 2020;91:378–387. doi: 10.1136/jnnp-2019- 322257.
73. Biczok A, Kraus T, Suchorska B, Terpolilli NA, Thorsteinsdottir J, Giese A, *et al*. TERT promoter mutation is associated with worse prognosis in WHO grade II and III meningiomas. J Neurooncol 2018;139:671–678. doi: 10.1007/s11060-018 -2912- 7.
74. Deng J, Sun S, Chen J, Wang D, Cheng H, Chen H, *et al*. TERT alterations predict tumor progression in de novo high-grade meningiomas following adjuvant radiotherapy. Front Oncol 2021;11:747592. doi: 10.3389/fonc.2021.747592.
75. Deng MY, Sturm D, Pfaff E, Sill M, Stichel D, Balasubramanian GP, *et al*. Radiation-induced gliomas represent H3-/IDH-wild type pediatric gliomas with recurrent PDGFRA amplification and

loss of CDKN2A/B. Nat Commun 2021;12:5530. doi: 10.1038/s41467-021-25708-y.
76. Guyot A, Duchesne M, Robert S, Lia AS, Derouault P, Scaon E, *et al*. Analysis of CDKN2A gene alterations in recurrent and non-recurrent meningioma. J Neurooncol 2019;145:449–459. doi: 10.1007/s11060-019-03333-6.
77. Sievers P, Hielscher T, Schrimpf D, Stichel D, Reuss DE, Berghoff AS, *et al*. CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. Acta Neuropathol 2020;140:409–413. doi: 10.1007/s00401-020-02188-w.
78. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer 2020;20:74–88. doi: 10.1038/s41568-019-0216-7.
79. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. Brain Tumor Pathol 2016;33:237–247. doi: 10.1007/s10014-016-0271-7.
80. Jungwirth G, Warta R, Beynon C, Sahm F, von Deimling A, Unterberg A, *et al*. Intraventricular meningiomas frequently harbor NF2 mutations but lack common genetic alterations in TRAF7, AKT1, SMO, KLF4, PIK3CA, and TERT. Acta Neuropathol Commun 2019;7:140. doi: 10.1186/s40478-019-0793-4.
81. Lee YS, Lee YS. Molecular characteristics of meningiomas. J Pathol Transl Med 2020;54:45–63. doi: 10.4132/jptm.2019.11.05.
82. Williams SR, Juratli TA, Castro BA, Lazaro TT, Gill CM, Nayyar N, *et al*. Genomic analysis of posterior fossa meningioma demonstrates frequent AKT1 E17K mutations in foramen magnum meningiomas. J Neurol Surg B Skull Base 2019;80:562–567. doi: 10.1055/s-0038-1676821.
83. Sahm F, Bissel J, Koelsche C, Schweizer L, Capper D, Reuss D, *et al*. AKT1E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. Acta Neuropathol 2013;126:757–762. doi: 10.1007/s00401-013-1187-5.
84. Karsy M, Azab MA, Abou-Al-Shaar H, Guan J, Eli I, Jensen RL, *et al*. Clinical potential of meningioma genomic insights: a practical review for neurosurgeons. Neurosurg Focus 2018;44:E10. doi: 10.3171/2018.2.FOCUS1849.
85. Bleeker FE, Felicioni L, Buttitta F, Lamba S, Cardone L, Rodolfo M, *et al*. AKT1(E17K) in human solid tumours. Oncogene 2008;27:5648–5650. doi: 10.1038/onc.2008.170.
86. Abedalthagafi M, Bi WL, Aizer AA, Merrill PH, Brewster R, Agarwalla PK, *et al*. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. Neuro Oncol 2016;18:649–655. doi: 10.1093/neuonc/nov316.
87. AlSahlawi A, Aljelaify R, Magrashi A, AlSaeed M, Almutairi A, Alqubaishi F, *et al*. New insights into the genomic landscape of meningiomas identified FGFR3 in a subset of patients with favorable prognoses. Oncotarget 2019;10:5549–5559. doi: 10.18632/oncotarget.27178.
88. Weller M, Roth P, Sahm F, Burghardt I, Schuknecht B, Rushing EJ, *et al*. Durable control of metastatic AKT1-mutant WHO Grade 1 meningothelial meningioma by the AKT inhibitor, AZD5363. J Natl Cancer Inst 2017;109:1–4. doi: 10.1093/jnci/djw320.
89. John P, Waldt N, Liebich J, Kesseler C, Schnabel S, Angenstein F, *et al*. AKT1 -mutated meningioma cell lines respond to treatment with the AKT inhibitor AZD5363. Neuropathol Appl Neurobiol 2022;48:e12780. doi:10.1111/nan.12780.
90. Najm P, Zhao P, Steklov M, Sewduth RN, Baietti MF, Pandolfi S, *et al*. Loss-of-function mutations in TRAF7 and KLF4 cooperatively activate RAS-Like GTPase signaling and promote meningioma development. Cancer Res 2021;81:4218–4229. doi: 10.1158/0008-5472.CAN-20-3669.
91. Bi WL, Prabhu VC, Dunn IF. High-grade meningiomas: biology and implications. Neurosurg Focus 2018;44:E2. doi: 10.3171/2017.12.FOCUS17756.
92. Toland A, Huntoon K, Dahiya SM. Meningioma: a pathology perspective. Neurosurgery 2021;89:11–21. doi: 10.1093/neuros/nyab001.
93. Aizer AA, Abedalthagafi M, Bi WL, Horvath MC, Arvold ND, Al-Mefty O, *et al*. A prognostic cytogenetic scoring system to guide the adjuvant management of patients with atypical meningioma. Neuro Oncol 2016;18:269–274. doi: 10.1093/neuonc/nov177.
94. Reuss DE, Piro RM, Jones DT, Simon M, Ketter R, Kool M, *et al*. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. Acta Neuropathol 2013;125:351–358. doi: 10.1007/s00401-013 -1093- x.
95. Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, *et al*. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol 2016;17:e383–391. doi: 10.1016/S1470-2045(16)30321-7.
96. Mittal P, Roberts C. The SWI/SNF complex in cancer - biology, biomarkers and therapy. Nat Rev Clin Oncol 2020;17:435–448. doi: 10.1038/s41571-020-0357-3.
97. Collord G, Tarpey P, Kurbatova N, Martincorena I, Moran S, Castro M, *et al*. An integrated genomic analysis of anaplastic meningioma identifies prognostic molecular signatures. Sci Rep 2018;8:13537. doi: 10.1038/s41598-018-31659-0.
98. Smith MJ, O'Sullivan J, Bhaskar SS, Hadfield KD, Poke G, Caird J, *et al*. Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. Nat Genet 2013;45:295–298. doi: 10.1038/ng.2552.
99. Sievers P, Sill M, Blume C, Tauziede-Espariat A, Schrimpf D, Stichel D, *et al*. Clear cell meningiomas are defined by a highly distinct DNA methylation profile and mutations in SMARCE1. Acta Neuropathol 2021;141:281–290. doi: 10.1007/s00401-020-02247-2.
100. Smith MJ, Wallace AJ, Bennett C, Hasselblatt M, Elert-Dobkowska E, Evans LT, *et al*. Germline SMARCE1 mutations predispose to both spinal and cranial clear cell meningiomas. J Pathol 2014;234:436–440. doi: 10.1002/path.4427.
101. Lu JQ, Reddy K. Letter: familial syndromes involving meningiomas provide mechanistic insight into sporadic disease. Neurosurgery 2019;85:E396. doi: 10.1093/neuros/nyz135.
102. Carbone M, Harbour JW, Brugarolas J, Bononi A, Pagano I, Dey A, *et al*. Biological mechanisms and clinical significance of BAP1 mutations in human cancer. Cancer Discov 2020;10:1103–1120. doi: 10.1158/2159-8290.CD-19-1220.
103. Shankar GM, Abedalthagafi M, Vaubel RA, Merrill PH, Nayyar N, Gill CM, *et al*. Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. Neuro Oncol 2017;19:535–545. doi: 10.1093/neuonc/now235.
104. Chau C, van Doorn R, van Poppelen NM, van der Stoep N, Mensenkamp AR, Sijmons RH, *et al*. Families with BAP1-tumor predisposition syndrome in the netherlands: path to identification and a proposal for genetic screening guidelines. Cancers (Basel) 2019;11:1114. doi: 10.3390/cancers11081114.
105. Shankar GM, Santagata S. BAP1 mutations in high-grade meningioma: implications for patient care. Neuro Oncol 2017;19:1447–1456. doi: 10.1093/neuonc/nox094.
106. Kunkel LM, Hejtmancik JF, Caskey CT, Speer A, Monaco AP, Middlesworth W, *et al*. Analysis of deletions in DNA from patients with Becker and Duchenne muscular dystrophy. Nature 1986;322:73–77. doi: 10.1038/322073a0.
107. Arbajian E, Puls F, Antonescu CR, Amary F, Sciot R, Debiec-Rychter M, *et al*. In-depth genetic analysis of sclerosing epithelioid fibrosarcoma reveals recurrent genomic alterations and potential treatment targets. Clin Cancer Res 2017;23:7426–7434. doi: 10.1158/1078-0432.CCR-17-1856.
108. Cheng J, Demeulemeester J, Wedge DC, Vollan H, Pitt JJ, Russnes HG, *et al*. Pan-cancer analysis of homozygous deletions in primary tumours uncovers rare tumour suppressors. Nat Commun 2017;8:1221. doi: 10.1038/s41467-017-01355-0.
109. Körner H, Epanchintsev A, Berking C, Schuler-Thurner B, Speicher MR, Menssen A, *et al*. Digital karyotyping reveals frequent inactivation of the dystrophin/DMD gene in malignant melanoma. Cell Cycle 2007;6:189–198. doi: 10.4161/cc.6.2.3733.
110. Wang Y, Marino-Enriquez A, Bennett RR, Zhu M, Shen Y, Eilers G, *et al*. Dystrophin is a tumor suppressor in human cancers with myogenic programs. Nat Genet 2014;46:601–606. doi: 10.1038/ng.2974.
111. Juratli TA, McCabe D, Nayyar N, Williams EA, Silverman IM, Tummala SS, *et al*. DMD genomic deletions characterize a subset of progressive/higher-grade meningiomas with poor outcome. Acta Neuropathol 2018;136:779–792. doi: 10.1007/s00401-018-1899-7.
112. Paramasivam N, Hübschmann D, Toprak UH, Ishaque N, Neidert M, Schrimpf D, *et al*. Mutational patterns and

regulatory networks in epigenetic subgroups of meningioma. Acta Neuropathol 2019;138:295–308. doi: 10.1007/s00401-019-02008-w.
113. Chabanon RM, Morel D, Eychenne T, Colmet-Daage L, Bajrami I, Dorvault N, *et al*. PBRM1 deficiency confers synthetic lethality to DNA repair inhibitors in cancer. Cancer Res 2021;81:2888–2902. doi: 10.1158/0008-5472.CAN-21-0628.
114. Masliah-Planchon J, Bièche I, Guinebretière JM, Bourdeaut F, Delattre O. SWI/SNF chromatin remodeling and human malignancies. Annu Rev Pathol 2015;10:145–171. doi: 10.1146/annurev-pathol-012414-040445.
115. Varela I, Tarpey P, Raine K, Huang D, Ong CK, Stephens P, *et al*. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. Nature 2011;469:539–542. doi: 10.1038/nature09639.
116. Williams EA, Wakimoto H, Shankar GM, Barker FN, Brastianos PK, Santagata S, *et al*. Frequent inactivating mutations of the PBAF complex gene PBRM1 in meningioma with papillary features. Acta Neuropathol 2020;140:89–93. doi: 10.1007/s00401-020-02161-7.
117. Meng TG, Zhou Q, Ma XS, Liu XY, Meng QR, Huang XJ, *et al*. PRC2 and EHMT1 regulate H3K27me2 and H3K27me3 establishment across the zygote genome. Nat Commun 2020;11:6354. doi: 10.1038/s41467-020-20242-9.
118. Inoue A, Jiang L, Lu F, Suzuki T, Zhang Y. Maternal H3K27me3 controls DNA methylation-independent imprinting. Nature 2017;547:419–424. doi: 10.1038/nature23262.
119. Krug B, De Jay N, Harutyunyan AS, Deshmukh S, Marchione DM, Guilhamon P, *et al*. Pervasive H3K27 acetylation leads to ERV expression and a therapeutic vulnerability in H3K27M Gliomas. Cancer Cell 2019;35:782–797. e8. doi: 10.1016/j.ccell.2019.04.004.
120. Larson JD, Kasper LH, Paugh BS, Jin H, Wu G, Kwon CH, *et al*. Histone H3.3 K27M accelerates spontaneous brainstem glioma and drives restricted changes in bivalent gene expression. Cancer Cell 2019;35:140–155. e7. doi: 10.1016/j.ccell.2018.11.015.
121. Nassiri F, Wang JZ, Singh O, Karimi S, Dalcourt T, Ijad N, *et al*. Loss of H3K27me3 in meningiomas. Neuro Oncol 2021;23:1282–1291. doi: 10.1093/neuonc/noab036.
122. Katz LM, Hielscher T, Liechty B, Silverman J, Zagzag D, Sen R, *et al*. Loss of histone H3K27me3 identifies a subset of meningiomas with increased risk of recurrence. Acta Neuropathol 2018;135:955–963. doi: 10.1007/s00401-018-1844-9.
123. Capper D, Jones D, Sill M, Hovestadt V, Schrimpf D, Sturm D, *et al*. DNA methylation-based classification of central nervous system tumours. Nature 2018;555:469–474. doi: 10.1038/nature26000.
124. Bello MJ, Amiñoso C, Lopez-Marin I, Arjona D, Gonzalez-Gomez P, Alonso ME, *et al*. DNA methylation of multiple promoter-associated CpG islands in meningiomas: relationship with the allelic status at 1p and 22q. Acta Neuropathol 2004;108:413–421. doi: 10.1007/s00401-004-0911-6.
125. Barski D, Wolter M, Reifenberger G, Riemenschneider MJ. Hypermethylation and transcriptional downregulation of the TIMP3 gene is associated with allelic loss on 22q12.3 and malignancy in meningiomas. Brain Pathol 2010;20:623–631. doi: 10.1111/j.1750-3639.2009.00340.x.
126. Gonzalez-Gomez P, Bello MJ, Arjona D, Alonso ME, Lomas J, Amiñoso C, *et al*. CpG island methylation of tumor-related genes in three primary central nervous system lymphomas in immunocompetent patients. Cancer Genet Cytogenet 2003;142:21–24. doi: 10.1016/s0165-4608(02)00799-9.
127. Liu Y, Chen C, Xu Z, Scuoppo C, Rillahan CD, Gao J, *et al*. Deletions linked to TP53 loss drive cancer through p53-independent mechanisms. Nature 2016;531:471–475. doi: 10.1038/nature17157.
128. Nakane Y, Natsume A, Wakabayashi T, Oi S, Ito M, Inao S, *et al*. Malignant transformation-related genes in meningiomas: allelic loss on 1p36 and methylation status of p73 and RASSF1A. J Neurosurg 2007;107:398–404. doi: 10.3171/JNS-07/08/0398.
129. Lomas J, Amiñoso C, Gonzalez-Gomez P, Eva Alonso M, Arjona D, Lopez-Marin I, *et al*. Methylation status of TP73 in meningiomas. Cancer Genet Cytogenet 2004;148:148–151. doi: 10.1016/s0165-4608(03)00244-9.
130. Claus EB, Park PJ, Carroll R, Chan J, Black PM. Specific genes expressed in association with progesterone receptors in meningioma. Cancer Res 2008;68:314–322. doi: 10.1158/0008-5472.CAN-07-1796.
131. Hua L, Zhu H, Li J, Tang H, Kuang D, Wang Y, *et al*. Prognostic value of estrogen receptor in WHO Grade III meningioma: a long-term follow-up study from a single institution. J Neurosurg 2018;128:1698–1706. doi: 10.3171/2017.2.JNS162566.
132. Iplikcioglu AC, Hatiboglu MA, Ozek E, Ozcan D. Is progesteron receptor status really a prognostic factor for intracranial meningiomas? Clin Neurol Neurosurg 2014;124:119–122. doi: 10.1016/j.clineuro.2014.06.015.
133. Guevara P, Escobar-Arriaga E, Saavedra-Perez D, Martinez-Rumayor A, Flores-Estrada D, Rembao D, *et al*. Angiogenesis and expression of estrogen and progesterone receptors as predictive factors for recurrence of meningioma. J Neurooncol 2010;98:379–384. doi: 10.1007/s11060-009-0086-z.
134. Moazzam AA, Wagle N, Zada G. Recent developments in chemotherapy for meningiomas: a review. Neurosurg Focus 2013;35:E18. doi: 10.3171/2013.10.FOCUS13341.
135. Goodwin JW, Crowley J, Eyre HJ, Stafford B, Jaeckle KA, Townsend JJ. A phase II evaluation of tamoxifen in unresectable or refractory meningiomas: a Southwest Oncology Group study. J Neurooncol 1993;15:75–77. doi: 10.1007/BF01050266.
136. Ji Y, Rankin C, Grunberg S, Sherrod AE, Ahmadi J, Townsend JJ, *et al*. Double-blind phase III randomized trial of the antiprogestin agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. J Clin Oncol 2015;33:4093–4098. doi: 10.1200/JCO.2015.61.6490.
137. Telugu RB, Chowhan AK, Rukmangadha N, Patnayak R, Phaneendra BV, Mowliswara Prasad BC, *et al*. Estrogen and progesterone receptor in meningiomas: an immunohistochemical analysis. J Cancer Res Ther 2020;16:1482–1487. doi: 10.4103/jcrt.JCRT_1075_16.
138. Fakhrjou A, Meshkini A, Shadrvan S. Status of Ki-67, estrogen and progesterone receptors in various subtypes of intracranial meningiomas. Pak J Biol Sci 2012;15:530–535. doi: 10.3923/pjbs.2012.530.535.
139. Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H. Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. J Neurooncol 2006;80:1–7. doi: 10.1007/s11060-006-9146-9.
140. Mnango L, Mwakimonga A, Ngaiza AI, Yahaya JJ, Vuhahula E, Mwakigonja AR. Expression of progesterone receptor and its association with clinicopathological characteristics in meningiomas: a cross-sectional study. World Neurosurg X 2021;12:100111. doi: 10.1016/j.wnsx.2021.100111.
141. Maiuri F, Mariniello G, de Divitiis O, Esposito F, Guadagno E, Teodonno G, *et al*. Progesterone Receptor Expression in Meningiomas: Pathological and Prognostic Implications. Front Oncol 2021;11:611218. doi: 10.3389/fonc.2021.611218.
142. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol 2004;57:1033–1037. doi: 10.1136/jcp.2004.018333.
143. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. J Neurosurg 2006;105:163–173. doi: 10.3171/jns.2006.105.2.163.
144. Silva CB, Ongaratti BR, Trott G, Haag T, Ferreira NP, Leães CG, *et al*. Expression of somatostatin receptors (SSTR1-SSTR5) in meningiomas and its clinicopathological significance. Int J Clin Exp Pathol 2015;8:13185–13192.
145. Fodi C, Skardelly M, Hempel JM, Hoffmann E, Castaneda S, Tabatabai G, *et al*. The immunohistochemical expression of SSTR2A is an independent prognostic factor in meningioma. Neurosurg Rev 2022;45:2671–2679. doi: 10.1007/s10143-021-01651-w.
146. Rachinger W, Stoecklein VM, Terpolilli NA, Haug AR, Ertl L, Pöschl J, *et al*. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. J Nucl Med 2015;56:347–353. doi: 10.2967/jnumed.114.149120.
147. Sommerauer M, Burkhardt JK, Frontzek K, Rushing E, Buck A, Krayenbuehl N, *et al*. 68Gallium-DOTATATE PET in meningioma: a reliable predictor of tumor growth rate. Neuro Oncol 2016;18:1021–1027. doi: 10.1093/neuonc/now001.

148. Ivanidze J, Roytman M, Lin E, Magge RS, Pisapia DJ, Liechty B, *et al*. Gallium-68 DOTATATE PET in the evaluation of intracranial meningiomas. J Neuroimaging 2019;29:650–656. doi: 10.1111/jon.12632.
149. Henze M, Schuhmacher J, Hipp P, Kowalski J, Becker DW, Doll J, *et al*. PET imaging of somatostatin receptors using [68GA] DOTA-D-Phe1-Tyr3-octreotide: first results in patients with meningiomas. J Nucl Med 2001;42:1053–1056.
150. Dittmar JO, Kratochwil C, Dittmar A, Welzel T, Habermehl D, Rieken S, *et al*. First intraindividual comparison of contrast-enhanced MRI, FET- and DOTATOC- PET in patients with intracranial meningiomas. Radiat Oncol 2017;12:169. doi: 10.1186/s13014-017-0913-x.
151. Kunz WG, Jungblut LM, Kazmierczak PM, Vettermann FJ, Bollenbacher A, Tonn JC, *et al*. Improved detection of transosseous meningiomas using ^{68}Ga-DOTATATE PET/CT compared with contrast-enhanced MRI. J Nucl Med 2017;58:1580–1587. doi: 10.2967/jnumed.117.191932.
152. Gehler B, Paulsen F, Oksüz MO, Hauser TK, Eschmann SM, Bares R, *et al*. [68Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. Radiat Oncol 2009;4:56. doi: 10.1186/1748-717X-4-56.
153. Afshar-Oromieh A, Giesel FL, Linhart HG, Haberkorn U, Haufe S, Combs SE, *et al*. Detection of cranial meningiomas: comparison of 68Ga-DOTATOC PET/CT and contrast-enhanced MRI. Eur J Nucl Med Mol Imaging 2012;39:1409–1415. doi: 10.1007/s00259-012-2155-3.
154. Acker G, Kluge A, Lukas M, Conti A, Pasemann D, Meinert F, *et al*. Impact of 68Ga-DOTATOC PET/MRI on robotic radiosurgery treatment planning in meningioma patients: first experiences in a single institution. Neurosurg Focus 2019;46:E9. doi: 10.3171/2019.3.FOCUS1925.
155. Klutmann S, Bohuslavizki KH, Brenner W, Behnke A, Tietje N, Kröger S, *et al*. Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma. J Nucl Med 1998;39:1913–1917.
156. Hildebrandt G, Scheidhauer K, Luyken C, Schicha H, Klug N, Dahms P, *et al*. High sensitivity of the in vivo detection of somatostatin receptors by 111indium (DTPA-octreotide)-scintigraphy in meningioma patients. Acta Neurochir (Wien) 1994;126:63–71. doi: 10.1007/BF01476412.
157. Bohuslavizki KH, Brenner W, Braunsdorf WE, Behnke A, Tinnemeyer S, Hugo HH, *et al*. Somatostatin receptor scintigraphy in the differential diagnosis of meningioma. Nucl Med Commun 1996;17:302–310. doi: 10.1097/00006231-199604000-00157.
158. Luyken C, Hildebrandt G, Krisch B, Scheidhauer K, Klug N. Clinical relevance of somatostatin receptor scintigraphy in patients with skull base tumours. Acta Neurochir Suppl 1996;65:102–104. doi: 10.1007/978-3-7091-9450-8_28.
159. Maini CL, Sciuto R, Tofani A, Ferraironi A, Carapella CM, Occhipinti E, *et al*. Somatostatin receptor imaging in CNS tumours using 111In-octreotide. Nucl Med Commun 1995;16:756–766. doi: 10.1097/00006231-199509000-00006.
160. Nathoo N, Ugokwe K, Chang AS, Li L, Ross J, Suh JH, *et al*. The role of 111indium-octreotide brain scintigraphy in the diagnosis of cranial, dural-based meningiomas. J Neurooncol 2007;81:167–174. doi: 10.1007/s11060-006-9210-5.
161. Wang S, Yang W, Deng J, Zhang J, Ma F, Wang J. Correlation between 99mTc-HYNIC-octreotide SPECT/CT somatostatin receptor scintigraphy and pathological grading of meningioma. J Neurooncol 2013;113:519–526. doi: 10.1007/s11060-013-1146-y.
162. Wu W, Zhou Y, Wang Y, Liu L, Lou J, Deng Y, *et al*. Clinical Significance of Somatostatin Receptor (SSTR) 2 in Meningioma. Front Oncol 2020;10:1633. doi: 10.3389/fonc.2020.01633.
163. Johnson DR, Kimmel DW, Burch PA, Cascino TL, Giannini C, Wu W, *et al*. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. Neuro Oncol 2011;13:530–535. doi: 10.1093/neuonc/nor044.
164. Schulz C, Mathieu R, Kunz U, Mauer UM. Treatment of unresectable skull base meningiomas with somatostatin analogs. Neurosurg Focus 2011;30:E11. doi: 10.3171/2011.1.FOCUS111.
165. Norden AD, Ligon KL, Hammond SN, Muzikansky A, Reardon DA, Kaley TJ, *et al*. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. Neurology 2015;84:280–286. doi: 10.1212/WNL.0000000000001153.
166. Marincek N, Radojewski P, Dumont RA, Brunner P, Müller-Brand J, Maecke HR, *et al*. Somatostatin receptor-targeted radiopeptide therapy with 90Y-DOTATOC and 177Lu-DOTATOC in progressive meningioma: long-term results of a phase II clinical trial. J Nucl Med 2015;56:171–176. doi: 10.2967/jnumed.114.147256.
167. Cuneo MJ, Mittag T. Oncogenic signaling of RTK fusions becomes more granular. Mol Cell 2021;81:2504–2506. doi: 10.1016/j.molcel.2021.05.029.
168. Mongre RK, Mishra CB, Shukla AK, Prakash A, Jung S, Ashraf-Uz-Zaman M, *et al*. Emerging importance of tyrosine kinase inhibitors against cancer: quo vadis to cure. Int J Mol Sci 2021;22:11659. doi: 10.3390/ijms222111659.
169. Caltabiano R, Barbagallo GM, Castaing M, Cassenti A, Senetta R, Cassoni P, *et al*. Prognostic value of EGFR expression in de novo and progressed atypical and anaplastic meningiomas: an immunohistochemical and fluorescence in situ hybridization pilot study. J Neurosurg Sci 2013;57:139–151.
170. Baxter DS, Orrego A, Rosenfeld JV, Mathiesen T. An audit of immunohistochemical marker patterns in meningioma. J Clin Neurosci 2014;21:421–426. doi: 10.1016/j.jocn.2013.06.008.
171. Guillaudeau A, Durand K, Bessette B, Chaunavel A, Pommepuy I, Projetti F, *et al*. EGFR soluble isoforms and their transcripts are expressed in meningiomas. PLoS One 2012;7:e37204. doi: 10.1371/journal.pone.0037204.
172. Norden AD, Raizer JJ, Abrey LE, Lamborn KR, Lassman AB, Chang SM, *et al*. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. J Neurooncol 2010;96:211–217. doi: 10.1007/s11060-009-9948-7.
173. Osorio DS, Hu J, Mitchell C, Allen JC, Stanek J, Hagiwara M, *et al*. Effect of lapatinib on meningioma growth in adults with neurofibromatosis type 2. J Neurooncol 2018;139:749–755. doi: 10.1007/s11060-018-2922-5.
174. Lamszus K, Lengler U, Schmidt NO, Stavrou D, Ergun S, Westphal M. Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. Neurosurgery 2000;46:938–947. doi: 10.1097/00006123-200004000-00033.
175. Nakada S, Sasagawa Y, Tachibana O, Iizuka H, Kurose N, Shioya A, *et al*. The clinicopathological analysis of receptor tyrosine kinases in meningiomas: the expression of VEGFR-2 in meningioma was associated with a higher WHO grade and shorter progression-free survival. Brain Tumor Pathol 2019;36:7–13. doi: 10.1007/s10014-018-0332-1.
176. Baumgarten P, Brokinkel B, Zinke J, Zachskorn C, Ebel H, Albert FK, *et al*. Expression of vascular endothelial growth factor (VEGF) and its receptors VEGFR1 and VEGFR2 in primary and recurrent WHO grade III meningiomas. Histol Histopathol 2013;28:1157–1166. doi: 10.14670/HH-28.1157.
177. Preusser M, Hassler M, Birner P, Rudas M, Acker T, Plate KH, *et al*. Microvascularization and expression of VEGF and its receptors in recurring meningiomas: pathobiological data in favor of anti-angiogenic therapy approaches. Clin Neuropathol 2012;31:352–360. doi: 10.5414/NP300488.
178. Maiuri F, De Caro MB, Esposito F, Cappabianca P, Strazzullo V, Pettinato G, *et al*. Recurrences of meningiomas: predictive value of pathological features and hormonal and growth factors. J Neurooncol 2007;82:63–68. doi: 10.1007/s11060-005-9078-9.
179. Kaley TJ, Wen P, Schiff D, Ligon K, Haidar S, Karimi S, *et al*. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. Neuro Oncol 2015;17:116–121. doi: 10.1093/neuonc/nou148.
180. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391–400. doi: 10.1038/nrd1381.
181. Weiss J. Bevacizumab in adjuvant treatment of non-small-cell lung cancer. Lancet Oncol 2017;18:1558–1560. doi: 10.1016/S1470-2045(17)30843-4.
182. Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, *et al*. Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediatric patients with newly

diagnosed high-grade glioma. J Clin Oncol 2018;36:951–958. doi: 10.1200/JCO.2017.76.0611.
183. Bertucci F, Fekih M, Autret A, Petit T, Dalenc F, Levy C, *et al*. Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. Lancet Oncol 2016;17:600–611. doi: 10.1016/S1470-2045(16)00011-5.
184. Lou E, Sumrall AL, Turner S, Peters KB, Desjardins A, Vredenburgh JJ, *et al*. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. J Neurooncol 2012;109:63–70. doi: 10.1007/s11060-012- 0861-0.
185. Nagashima G, Asai J, Suzuki R, Fujimoto T. Different distribution of c-myc and MIB-1 positive cells in malignant meningiomas with reference to TGFs, PDGF, and PgR expression. Brain Tumor Pathol 2001;18:1–5. doi: 10.1007/BF02478918.
186. Johnson MD, Woodard A, Kim P, Frexes-Steed M. Evidence for mitogen-associated protein kinase activation and transduction of mitogenic signals by platelet-derived growth factor in human meningioma cells. J Neurosurg 2001;94:293–300. doi: 10.3171/jns.2001.94.2.0293.
187. Wen PY, Yung WK, Lamborn KR, Norden AD, Cloughesy TF, Abrey LE, *et al*. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). Neuro Oncol 2009;11:853–860. doi: 10.1215/15228517-2009-010.

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