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Atypical meningioma: Histopathological, genetic, and epigenetic features to predict recurrence risk

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Summary. Grading assessed according to World Health Organization (WHO) criteria is a major prognostic factor for determining the risk of recurrence in patients with meningiomas and establishing the most appropriate therapeutic strategy after surgery. However, the main issue is to predict the recurrence risk of WHO grade 2 meningioma and, more specifically, of the atypical subtype. Indeed, owing to a reported recurrence rate of 50%, either radiotherapy or observation is currently considered an option after gross total surgical resection of atypical meningiomas. These heterogeneous clinical outcomes are likely related to the broad histopathological diagnostic criteria for this subtype, and whether meningiomas with only brain invasion should be classified as atypical remains controversial.

Over the last few years, several studies have shown that DNA methylation profiling, next-generation sequencing, and transcriptomics can better stratify meningiomas for their recurrence risk than histology. The main limitations to the widespread use of these approaches to classify meningiomas are their high cost and the need for sophisticated technologies. However, all studies concurred that atypical meningiomas without chromosome 1p deletion display a low recurrence risk, suggesting that the assessment of this cytogenetic alteration could represent an easy and quick method to determine which patients could benefit from adjuvant treatment after surgery. In addition, prognostically unfavorable molecular groups can be distinguished using specific immunostainings, although further validation is required.

Key words: Meningioma, Atypical, Brain invasion, Recurrence, 1p, Methylation

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Introduction

Meningiomas represent approximately 40% of all primary tumors of the central nervous system (CNS) in adults (Ostrom et al., 2022).

According to the fifth edition of the World Health Organization (WHO 2021) classification of CNS tumors, meningiomas are classified into three CNS WHO grades and fifteen subtypes (Sahm et al., 2021). Along with the extent of surgical resection, the CNS WHO grade is currently considered the most significant predictor of the recurrence risk of meningiomas. Most of these tumors (approximately 80%) are CNS WHO grade 1 and have a favorable prognosis, whereas CNS WHO grades 2 and 3 meningiomas are associated with higher recurrence rates (Louis et al., 2016).

A major concern is the prediction of recurrence risk in patients with CNS WHO grade 2 meningioma. Indeed, these meningiomas demonstrated a wide range of clinical behavior and a recurrence rate of approximately 50% (Fioravanzo et al., 2020), which implies that, after surgical resection, around half recur, whereas the other half do not, and have a prognosis similar to that of CNS WHO grade 1 tumors. For this reason, the European Association of Neuro-oncology guidelines recommend either radiotherapy or observation as post-surgical options for patients with CNS WHO grade 2 meningioma who have undergone gross total resection (Goldbrunner et al., 2021).

CNS WHO grade 2 meningiomas account for approximately 18.3% of all meningiomas (Ostrom et al., 2022) and include three subtypes: chordoid, clear cell, and atypical. The latter is by far the most frequent, and, according to WHO 2021, its diagnosis is based on the following criteria: 1) a mitotic index ranging between 4 and 19 mitoses per 10 fields of 0.16 mm^2; and/or 2) brain invasion; and/or 3) at least three minor criteria (minor atypical criteria) among spontaneous necrosis, pattern-less architecture (sheeting), small cells with high nuclear/cytoplasmic ratio, macronucleoli and hypercellularity. The broad histopathological criteria for diagnosing atypical meningioma likely account for the diverse clinical outcomes of these tumors. These

include, at one end of the spectrum, meningiomas similar to CNS WHO grade 1 with a low risk of recurrence, and, at the other end, meningiomas closer to CNS WHO grade 3 exhibiting a high recurrence and progression risk.

This review outlines the histopathological, epigenetic, and genetic characteristics with demonstrated prognostic significance in the atypical meningioma subtype, with the goal of suggesting which information could be included in the histopathological reports of these tumors to guide post-surgical treatment. The histopathological, genetic, and epigenetic characteristics discussed below can be useful in categorizing patients with atypical meningiomas according to their risk of relapse, and in recognizing those who could benefit from adjuvant therapy to prevent disease recurrence.

Histopathological features

As specified above, the sole presence of brain invasion is sufficient to classify a meningioma as atypical, according to WHO 2021 (Sahm et al., 2021). Brain invasion is defined as the infiltration of tumor cells into the underlying brain parenchyma without intervening leptomeninges (Sahm et al., 2021) (Fig. 1). Although already included in the WHO 2016 classification of CNS tumors as a histopathological factor defining the atypical subtype (Louis et al., 2016), its association with a higher recurrence risk of meningiomas remains controversial. Indeed, several studies have suggested that meningiomas classified as CNS WHO grade 2 owing to the sole presence of brain invasion and lacking other criteria ("brain-invasive otherwise benign meningiomas"), have a recurrence rate similar to that of CNS WHO grade 1 meningiomas (Pizem et al., 2014; Baumgarten et al., 2016; Spille et al., 2016; Biczok et al., 2019). More specifically, 39 brain-invasive otherwise benign meningiomas from two different studies had a prognosis overlapping that of CNS WHO grade 1 meningiomas (Pizem et al., 2014; Spille et al., 2016), and brain invasion had no impact on early tumor recurrence in a series of 875 CNS WHO grade 1 meningiomas (Biczok et al., 2019). In a cohort of 61 brain-invasive but otherwise benign meningiomas, four cases recurred; however, they all showed other features typically associated with a higher risk of recurrence, such as a high Ki67 labeling index, incomplete surgical removal, or occurrence in the context of neurofibromatosis type 2, suggesting that tumor relapse was independent of brain invasion (Baumgarten et al., 2016).

After reviewing 177 meningiomas classified as atypical that had been treated with gross total resection in our hospital, we found 39 tumors that were brain-invasive otherwise benign meningiomas. Fifteen of these had recurrences over a follow-up period ranging between 3 and 194 months; however, compared with 138 atypical meningiomas with a mitotic index of ≥4 mitoses/1.6 mm^2 (brain-invasive or not), they had significantly longer recurrence-free survival (RFS) (Hazard ratio: 0.5; 95% confidence interval: 0.3-0.9) (*P*=0.0256) (Fig. 1) (unpublished data). These results further emphasize that brain-invasive otherwise benign meningiomas have a significantly lower probability of recurrence than mitotically active atypical meningiomas.

Few studies have explored whether other histopathological features can predict the likelihood of recurrence in patients diagnosed with atypical meningioma. As the mitotic indices for atypical meningiomas range from 4 to 19 mitoses per 1.6 mm^2, some studies have suggested that these tumors could be further classified based on their mitotic counts. However, there is still no consensus on the threshold for differentiating between "low-grade" and "high-grade" atypical meningiomas. In a meta-analysis of 25 studies involving 3560 atypical meningiomas, the progression

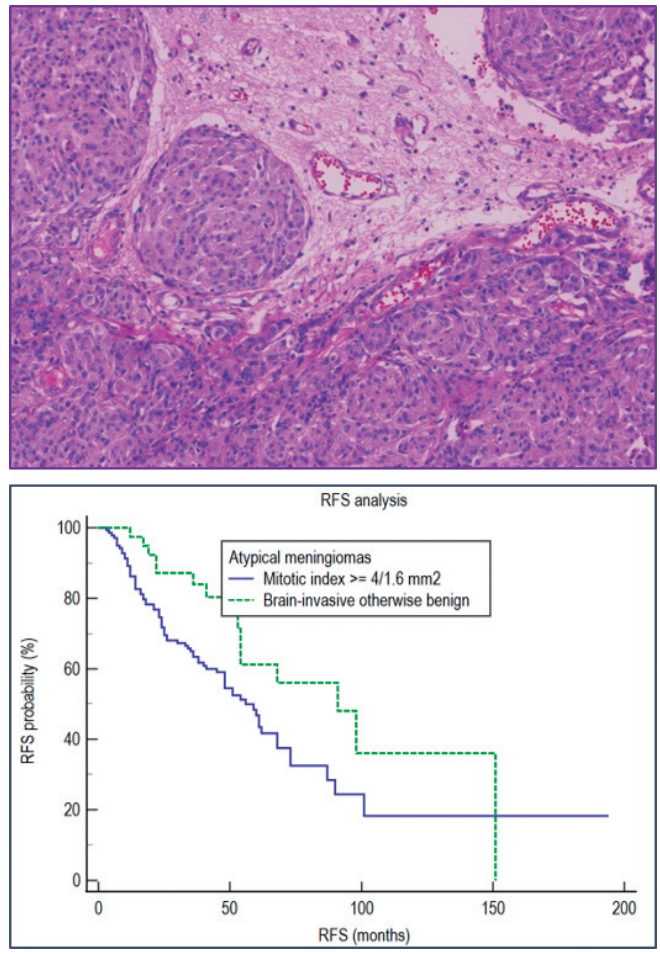

Fig. 1. Brain invasion in atypical meningioma (H&E stain; original magnification, x100) (upper image). Kaplan-Meier curves showing the comparison of RFS in brain-invasive otherwise benign and mitotically active meningiomas. RFS was significantly shorter in 138 patients with atypical meningiomas characterized by a mitotic index of ≥4 mitoses/1.6 mm^2 than in patients with brain-invasive otherwise benign atypical meningiomas (*P*=0.0256).

risk was not significantly different between tumors with a mitotic index of ≥4 mitoses per ten high-power fields (HPF) or below this cut-off (Kim et al., 2022). In contrast, a study that collected 200 atypical meningiomas from five different centers found that a cut-off of 6 mitoses/10 HPF had a high degree of sensitivity and specificity in identifying recurrent cases (Fioravanzo et al., 2020). However, other studies have suggested that a cut-off of 8 mitoses/10 HPF is a significant predictor of recurrence and progression in atypical meningiomas (Sun et al., 2014; Kwon et al., 2022).

As an alternative to the mitotic index, the proliferation of meningiomas can also be evaluated by determining the Ki-67 labeling index. The potential prognostic value of this marker was explored in a cohort of 99 atypical meningiomas, where a Ki-67 labeling index >7.5%, assessed by two independent observers, was demonstrated to be a significant and independent predictor of shorter RFS (Lee et al., 2022). Nevertheless, Ki-67 assessment can be affected by inter-observer variability and no universally accepted threshold has been established to differentiate between high and low proliferation. It is probable that increasing the use of artificial intelligence tools to evaluate the Ki-67 labeling index will result in higher standardization and consensus on the definition of a cut-off value that is beneficial for recognizing atypical meningiomas with a greater risk of recurrence.

Regarding the minor atypical criteria, meningiomas classified as atypical due to the sole presence of these seem to have a significantly lower risk of recurrence (Barresi et al., 2018; Fioravanzo et al., 2020). Nevertheless, minor atypical criteria may still be relevant in atypical meningiomas with major criteria. In a multicenter study of 200 atypical meningiomas (Fioravanzo et al., 2020) and another study involving 79 atypical meningiomas (Bertero et al., 2019), sheeting, macronucleoli, and spontaneous necrosis were found to be the most reliable indicators of recurrence among the minor criteria. However, in a retrospective analysis of 262 atypical meningiomas and a meta-analysis of 25 studies, the only factor consistently found to be a significant predictor of progression across all pooled analyses was spontaneous necrosis (Kim et al., 2022).

Impact of the WHO 2021 classification on the prognostic stratification of atypical meningiomas

The WHO 2021 classification of CNS tumors did not modify the diagnostic criteria for atypical meningioma, nevertheless, it introduced, for the first time, the presence of particular genetic alterations as diagnostic criteria for CNS WHO grade 3 meningiomas. In more detail, meningiomas are classified as CNS WHO grade 3 not only when they have 20 or more mitoses in 10 HPF of 0.16 mm^2 and/or display evident histological anaplasia with morphology resembling a carcinoma, melanoma, or sarcoma, but also when they feature TERT promoter (*pTERT*) mutations and/or *CDKN2A/B* homozygous deletions (HD) (Sahm et al., 2021). This change with respect to the WHO 2016 classification (Louis et al., 2016) was introduced because these molecular alterations are strongly associated with meningioma recurrence and progression, regardless of the presence of worrisome histopathological features (Sahm et al., 2016; Mirian et al., 2020; Sievers et al., 2020; Khan et al., 2023). The use of these novel criteria for grading is expected to result in the re-classification of some atypical meningiomas as CNS WHO grade 3. However, it should be noted that both *pTERT* mutations and *CDKN2A/B* HD are infrequent in meningiomas histologically classified as CNS WHO grade 2. Indeed, *pTERT* mutations were found in only 29/365 (7.9%) of histologically CNS WHO grade 2 meningiomas in a meta-analysis including 677 patients, and in only one case (1.6%) from a recent analysis of 63 atypical meningiomas (Vaubel et al., 2023). Notably, Harmanci et al., found *pTERT* mutations only in secondary atypical meningiomas (i.e., representing the progression of grade 1 tumors), finding none in the 66 primary atypical meningiomas, suggesting that primary and secondary atypical meningiomas have different molecular pathways (Harmancı et al., 2017).

Likewise, *CDKN2A/B* HD was identified in only seven (4%) atypical meningiomas in a study analyzing 183 cases (Sievers et al., 2020).

Aside from their scarcity in CNS WHO grade 2 meningiomas, *pTERT* mutations and *CDKN2A/B* HD identify only some meningiomas that are prone to recurrence. Indeed, *pTERT* mutations were found only in 5/39 CNS WHO grade 2 recurring meningiomas in a study of 88 cases (Sahm et al., 2016). In addition, *CDKN2A/B* alterations were found in only 13.1% of recurring tumors in an analysis of 583 meningiomas (Khan et al., 2023) and in only one of the 12 recurring atypical meningiomas (classified according to WHO 2016) reported by our group (Barresi et al., 2021).

Therefore, additional factors that can stratify CNS WHO grade 2 meningiomas based on their recurrence risk are required.

Cytogenetic alterations

Since the late 1990s, several cytogenetic studies have shown that meningioma progression is characterized by the progressive accumulation of chromosomal losses and gains (Weber et al., 1997; Zang, 2001; Williams et al., 2020).

Monosomy of chromosome 22q is the most common genetic abnormality observed in meningiomas of all histological grades and is thought to be an early event in the pathogenesis of these tumors (Weber et al., 1997; Zang, 2001; Williams et al., 2020). CNS WHO grade 2 meningiomas display additional chromosomal copy number aberrations (CNAs), including losses of 1p, 14q, 18q, 10, and 6q, as well as gains of 20q, 12q, 15q, 1q,

9q, and 17q (Weber et al., 1997). Grade 3 meningiomas have an increased frequency of 6q, 10, and 14q losses, and the loss of 9p, where the *CDKN2A/B* genes are located (Weber et al., 1997; Cai et al., 2001; Aizer et al., 2016; Harmancı et al., 2017; Olar et al., 2017; Harmanci et al., 2018; McNulty et al., 2018; Patel et al., 2019; Ma et al., 2020).

As early as the 2000s, the cytogenetic abnormalities associated with grades 2 and 3 were also demonstrated in histologically grade 1 meningiomas prior to their recurrence and progression (Cai et al., 2001; Al-Mefty et al., 2004), implying that CNA evaluation may be used to identify histologically low-grade meningiomas that will later recur and progress. Combined 1p and 14q deletions, assessed using dual-color fluorescence *in situ* hybridization with DNA probes localized to 1p32, 1p36, 14q13, and 14q32, were more frequent in a cohort of 74 atypical meningiomas than in grade 1 meningiomas; they were associated with shorter overall survival, however, statistical significance was not reached (Cai et al., 2001). Thereafter, the analysis of whole genome CNAs using comparative genomic hybridization in 32 atypical meningiomas, treated with gross total resection and no adjuvant therapies, showed that the presence of at least 3.5 CNAs was significantly linked to the development of recurrence (Aizer et al., 2016). Nevertheless, the evaluation of whole-genome CNAs may not be accessible in all medical facilities, which restricts the potential use of these findings in everyday clinical practice.

Subsequent studies explored the potential prognostic implications of specific chromosomal CNAs in atypical meningiomas. The loss of 10q was detected in four out of five anaplastic meningiomas and in none of 14 atypical meningiomas using next-generation sequencing (NGS), suggesting that this alteration was exclusive to CNS WHO grade 3 meningiomas (McNulty et al., 2018). However, a subsequent NGS study showed 10q loss in 3 out of 22 atypical meningiomas, all of which recurred (Barresi et al., 2021), implying that this chromosomal CNA is indicative of more aggressive meningiomas, regardless of their histopathological characteristics. The negative prognostic value of 10q loss, examined using a methylation array, was confirmed in 217 CNS WHO grade 2 meningiomas (Maas et al., 2021). Moreover, other chromosomal CNAs, such as 1p, 6q, and 14q losses, were significantly associated with shorter RFS, and among these, 1p loss was the most significant (Maas et al., 2021). Based on these results, a molecular model for risk stratification of meningiomas was proposed. In detail, cases with histology different from psammomatous, angiomatous, secretory, or clear cell should be initially assessed for 1p deletion. Cases lacking this CNA are considered at low risk of progression, whereas those harboring a 1p deletion should be further analyzed for 6q and 14q losses; cases with one or no additional losses will be considered intermediate risk, whereas those with two losses will be considered high risk (Maas et al., 2021) (Fig. 2). In a subsequent study, this risk stratification model was found to be effective in categorizing the recurrence risk of 98 CNS WHO grade 2 meningiomas, including 91 cases histologically classified as atypical (Zeng et al., 2022).

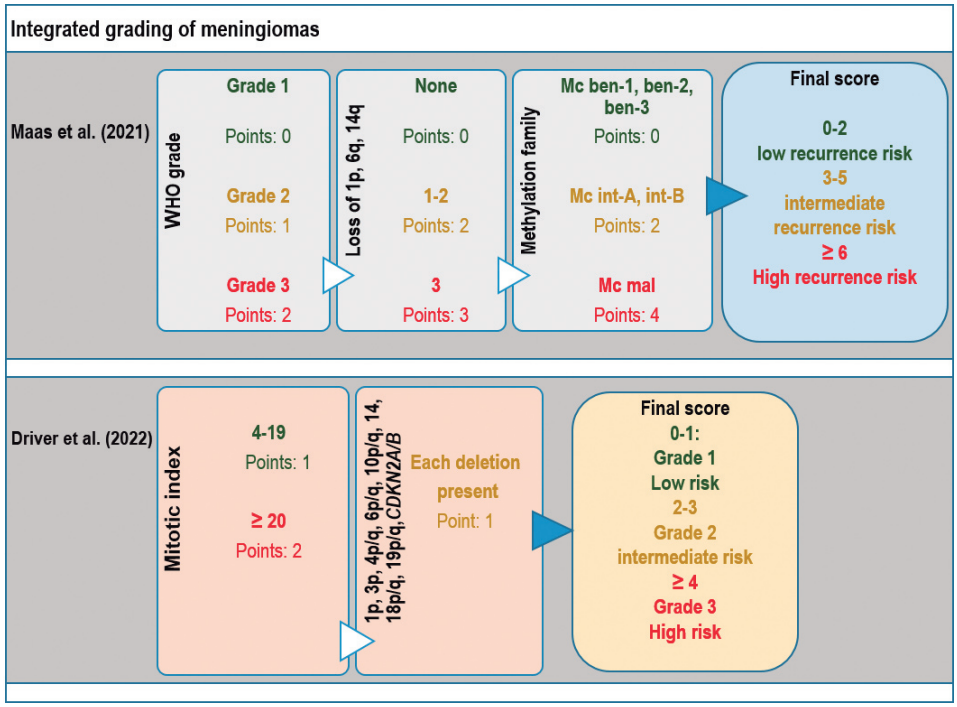

Fig. 2. Systems for integrated grading proposed by Maas et al., 2021; Driver et al., 2022.

The association between 1p and 10q loss and shorter RFS was additionally confirmed in a recent study that utilized a molecular inversion probe array to analyze copy number variations in 63 atypical meningiomas (Vaubel et al., 2023). In this cohort, 7p and 18 losses were additional negative prognostic markers, whereas 6q and 14q losses were not associated with RFS (Vaubel et al., 2023). Given its high frequency, independent prognostic value, and accessibility in routine practice, it has been suggested that the presence or absence of 1p deletions can be used to stratify atypical meningiomas according to their risk of recurrence, and cases without this genetic alteration can be managed conservatively (Maas et al., 2021; Vaubel et al., 2023).

Notably, two different studies demonstrated that heterozygous deletion of *CDKN2A/B* was associated with a shorter time to recurrence in meningiomas (Khan et al., 2023; Wang et al., 2023). In addition, this genetic alteration was significantly correlated with shorter RFS in 55 surgically resected atypical meningiomas analyzed using fluorescent *in situ* hybridization (Barresi et al., 2023).

Gene mutations

NF2 is the gene most commonly mutated in atypical meningiomas, with mutations occurring in 51-75% of these tumors (Harmancı et al., 2017, Barresi et al., 2021, Vaubel et al., 2023). *NF2* mutations are also present in benign meningiomas, however, it was estimated that meningiomas with *NF2* mutations have a 3.78-times higher risk of being atypical than those without *NF2* alterations (Harmancı et al., 2017). In a cohort of 63 atypical meningiomas, a tendency towards shorter RFS was observed in cases with *NF2* mutations but the difference was not statistically significant (Vaubel et al., 2023). Mutations in other genes, including *AKT1*, *SMARCB1*, and *SMO*, are uncommon in atypical meningiomas (Clark et al., 2013; Harmancı et al., 2017; Barresi et al., 2018; Vaubel et al., 2023). Based on the observation that *KLF4* and *TRAF7* mutations are mainly found in meningiomas characterized by indolent clinical behavior (Sahm et al., 2017; Patel et al., 2019; Nassiri et al., 2021b; Berghoff et al., 2022), it was recently proposed that tumors harboring mutations in these genes are considered at low risk of progression (Maas et al., 2021).

DNA methylation profile

In the past decade, it has been widely demonstrated that tumors can be categorized and stratified based on their DNA methylation patterns. Different tumors have distinct methylation profiles, depending on their cell of origin and the molecular changes they undergo during progression (Capper et al., 2018). Based on genome-wide DNA methylation profiling and clinical outcomes, 497 meningiomas of all three histological grades were subdivided into six combined methylation classes (MC): three featuring a benign clinical course (MC ben-1, MC ben-2, and MC ben-3), two with intermediate clinical behavior (MC int-A and MC int-B), and one that was aggressive (MC mal) (Sahm et al., 2017).

Atypical meningiomas mostly fell into MC int-A and MC-int B, yet a relevant percentage (23%; 31 cases) fell into MC ben-1 (Sahm et al., 2017). These findings demonstrate that DNA methylation profiling can stratify atypical meningiomas into groups characterized by distinct recurrence risks (Sahm et al., 2017). Notably, the MCs displayed particular genetic alterations. More specifically, regarding the three MCs into which atypical meningiomas were predominantly distributed, MC ben-1 had isolated *NF2* mutations, MC int-A had *NF2* mutations and concurrent 22q and 1p losses, whereas MC int-B had additional *pTERT* mutations and/or *CDKN2A* HD (Sahm et al., 2017). According to the WHO 2021 criteria for meningioma grading, cases in MC int-B would now be reclassified into the anaplastic subtype owing to the presence of *pTERT* mutations and/or *CDKN2A* HD. While showing that atypical meningiomas with or without 1p and 22q losses are epigenetically different, DNA methylation profiling confirms that the former has a higher recurrence risk than the latter.

H3K27me3 immunohistochemical loss

Among the epigenetic modifications of DNA, the immunohistochemical loss of histone H3 trimethylation at lysine 27 (H3K27me3) was found to be a predictor of prognosis in meningiomas (Katz et al., 2018; Behling et al., 2021; Nassiri et al., 2021a). A complete loss of H3K27me3 immuno-expression was found in 10.4%-12.1% of grade 2 meningiomas in association with MC int-B, MC-mal, and a significantly shorter RFS (Katz et al., 2018; Behling et al., 2021; Nassiri et al., 2021a). Therefore, the assessment of H3K27me3 immuno-expression may represent a possible tool to identify patients at increased risk of recurrence after surgery who could benefit from adjuvant treatments. In addition to its prognostic significance, H3K27me3 loss was significantly associated with shorter RFS of atypical meningiomas after stereotactic radiosurgery, suggesting that tumors harboring this epigenetic modification may be more resistant to radiation treatment (Ammendola et al., 2022).

Despite the promising role of H3K27me3 immuno-expression in predicting the risk of recurrence in atypical meningiomas, approximately 5.6-7.3% of tumors analyzed in the aforementioned studies presented an ambiguous staining pattern, with positive and negative areas, which can be complex to evaluate in clinical practice (Katz et al., 2018; Nassiri et al., 2021a; Hua et al., 2023). In a recent analysis of 62 primary atypical meningiomas, only four tumors showed unequivocal loss of H3K27me3 (Vaubel et al., 2023). Thirty-six (58%) meningiomas exhibited unequivocal retained expression of H3K27me3, whereas 22 (35%) had a heterogeneous

staining pattern (Vaubel et al., 2023). This ambiguous staining pattern has been considered "retained expression" in other studies (Katz et al., 2018; Nassiri et al., 2021a; Hua et al., 2023); nevertheless, the number of cases with unequivocal loss of H3K27me3 was insufficient to establish its prognostic value in this cohort.

Based on these findings, further investigation is perhaps necessary to clarify the distinct frequencies and prognostic value of H3K27me3 loss in primary and secondary atypical meningiomas. In two studies (Behling et al., 2021; Nassiri et al., 2021a), H3K27me3 loss was more frequent in secondary than in primary meningiomas (8% vs. 17% and 4% vs. 11%, respectively). Furthermore, in Nassiri et al. when the RFS analysis was restricted to 76 patients with primary, untreated tumors, only seven meningiomas had complete loss of H3K27me3; although these tended to have a shorter time to recurrence, statistical significance was not achieved (Nassiri et al., 2021a).

Notably, a recent analysis of paired samples of primary and relapsed meningiomas showed that H3K27me3 is lost at the time of relapse in 35% of cases and after radiotherapy in 25% (Hua et al., 2023), suggesting that this epigenetic modification may be linked to tumor recurrence or adjuvant treatments (Ammendola et al., 2022).

Integrated molecular-morphological grading

Because of the demonstrated prognostic significance of DNA methylation patterns, chromosomal CNAs, and WHO grade, Maas et al. created an integrated molecular-morphological grading of meningiomas by combining all these features (Maas et al., 2021). Specifically, each meningioma was scored by attributing 0-2 points to the WHO grade, 0-4 points to the methylation class, and 0-3 points to each chromosomal loss among 1p, 14q, and 6q. Cases with a final score of 0-2 are classified as low risk, those with a score of 3-5 as intermediate risk, and meningiomas with a score of 6-9 as high risk (Fig. 3). In their cohort of 514 meningiomas and a validation set of 471 meningiomas, this integrated grade was more effective than the WHO grade for determining the risk of recurrence. Most CNS WHO grade 2 meningiomas were categorized as intermediate risk, however, a significant number of cases were classified as either low risk or high risk (Maas et al., 2021). Therefore, the integrated grade of Maas et al., differentiated CNS WHO grade 2 meningiomas into prognostically significant groups. Moreover, it proved to be more accurate in predicting recurrence risk than the assessment of 1p deletion alone. A later study from the same research team showed that, with the use of this combined grade, there is no need to evaluate *pTERT* and/or *CDKN2A/B* HD, as required by the WHO 2021 criteria, to estimate the recurrence risk in meningioma patients (Hielscher et al., 2023). However, a major obstacle to the widespread use of this scoring system for meningiomas is its high cost and the necessity of sophisticated instruments for performing methylation analysis.

Driver et al. suggested an alternative integrated grading system for meningiomas using mitotic counts, *CDKN2A/B* deletion, and chromosomal CNAs (Fig. 3).

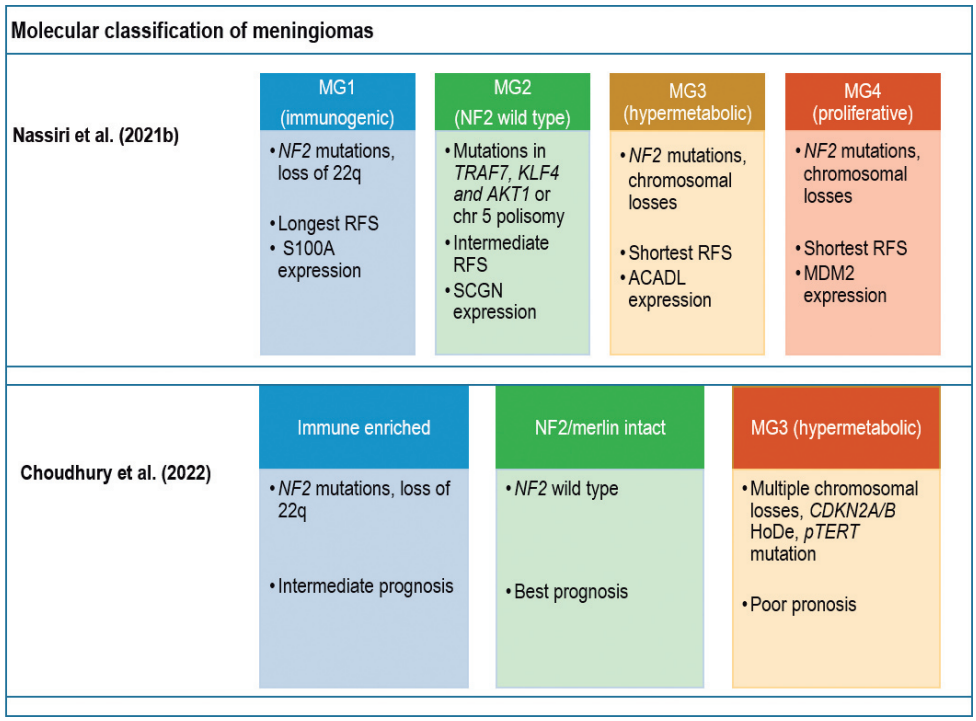

Fig. 3. Molecular classification of meningiomas according to Nassiri et al., 2021b; Choudhury et al., 2022.

Specifically, this grading is determined by assigning one point to each CNA among 1p, 3p, 4p/q, 6p/q, 10p/q, 14q, 18p/q, and 19p/q deletions, and *CDKN2A/B* homozygous or heterozygous deletions; one point to a mitotic index of 4 to 19 mitoses/1.6 mm^2; and two points to a mitotic index of ≥20 mitoses/1.6 mm^2 (Driver et al., 2022). Meningiomas with 0-1 points are classified as grade 1, those with 2-3 points as grade 2, and those with 4 or more points as grade 3. In their study, only 31% of CNS WHO grade 2 meningiomas were classified as integrated grade 2, while one-third were classified as integrated grade 1, and another third as integrated grade 3. These findings demonstrate that CNS WHO grade 2 meningiomas can be further divided into prognostically significant categories using this integrated grading system, which could be used to decide adjuvant treatments (Driver et al., 2022).

Molecular classification

Combining the findings of DNA somatic CNAs, DNA somatic point mutations, DNA methylation, and messenger RNA abundance in 201 meningiomas of different WHO grades, Nassiri et al., identified four consensus molecular groups (MG) showing distinctive genetic alterations and proteomes: immunogenic (MG1); benign *NF2*-wild type (MG2); hypermetabolic (MG3); and proliferative (MG4) (Nassiri et al., 2021b). MG1 meningiomas had the longest RFS, featured *NF2* biallelic inactivation consequent to co-occurring *NF2* mutation and 22q loss, and lacked other chromosomal alterations. Meningiomas in MG2 were *NF2* wild type and had *KLF4*, *TRAF7*, or *AKT1* mutations, or, alternatively, polysomy of chromosomes 5, 12, 13, and 20. MG3 and MG4 meningiomas had the worst prognosis, were enriched in mutations in chromatin remodeling and tumor suppressor genes, and had high aneuploidy with frequent losses in 1p, 6q, 14q, 18q, and 22q (Fig. 3). Of the 43 CNS WHO grade 2 meningiomas that were studied, two were MG1, nine were MG2, 18 were MG3, and 14 were MG4. MG3 and MG4 Grade 2 meningiomas had significantly shorter RFS, indicating that the evaluation of molecular groups can be used to stratify atypical meningiomas according to their risk of recurrence (Nassiri et al., 2021b).

It may be challenging to use this molecular classification of meningiomas in everyday practice, however, the MG can be identified by surrogate immunohistochemical markers, namely MG1 by S100A immuno-expression, MG2 by SCGN, MG3 by ACADL, and MG4 by MCM2 (Nassiri et al., 2021b). A recent study of 55 atypical meningiomas revealed that cases with immuno-expression of ACADL and MCM2, surrogates for MG3 and MG4, had a significantly higher mitotic index, 1p and 18q losses, and shorter RFS (Barresi et al., 2023).

By combining DNA methylation profiling, genetic, transcriptomic, biochemical, proteomic, and single-cell analyses, Choudhury et al., (Choudhury et al., 2022) obtained similar results to those reported by Nassiri et al., (Nassiri et al., 2021b). In a separate cohort of 565 meningiomas of all WHO grades, three MGs with distinct clinical outcomes and biological drivers were identified (Choudhury et al., 2022). The NF2/merlin intact group, which likely corresponds to the MG2 (*NF2* wild-type) group described by Nassiri et al., had the most favorable prognosis. The immune-enriched group, overlapping MG1 (immunogenic), showed *NF2* inactivation and an intermediate outcome. Finally, the hypermitotic group, corresponding to MG3 and MG4, showed high aneuploidy with frequent chromosomal losses (1p, 6q, 9p, 14q, and 22q), *CDKN2A/B* HD, hypermethylation, and the worst prognosis (Choudhury et al., 2022) (Fig. 4). Using this approach, approximately half of 142 grade 2 meningiomas were in the hypermitotic group; however, 28% were classified as immune-enriched and 22% as NF2/merlin intact, confirming that CNS WHO grade 2 meningiomas are widely heterogeneous molecularly and clinically (Choudhury et al., 2022). In a subsequent study, Choudhury et al., showed that the hypermitotic group can be further subdivided into two subgroups: proliferative, enriched in the expression of genes driving cell proliferation and corresponding to MG4, and hypermetabolic, enriched in the expression of genes driving macrometabolism and corresponding to MG3.

Conclusions

Several studies published over the last decade have demonstrated that meningioma classification can be refined using genome-wide DNA methylation profiling, transcriptomics, and assessment of CNAs and gene mutations. However, the findings of these analyses have not yet resulted in significant changes in the WHO grading of meningiomas, except for the inclusion of *CDKN2A/B* HD and *pTERT* mutations as additional criteria for CNS WHO grade 3. The assessment of these genetic alterations certainly improves the prognostic stratification of meningiomas histologically classified as atypical, however, their scarcity leaves the issue of predicting the recurrence risk of these tumors mostly unsolved. In addition, an open question is whether it makes sense, in a cost-benefit balance, to analyze these genetic alterations in all cases of atypical meningioma to detect only a modest proportion of aggressive cases.

Based on the growing evidence that meningiomas classified as atypical owing to the sole presence of brain invasion have a recurrence risk overlapping that of benign meningiomas, we propose that this should be acknowledged in histopathological reports. In addition, although it is likely a rare event, the unequivocal immunohistochemical loss of H3K27me3 in atypical meningiomas may represent a cheap and easy method to detect cases more prone to recurrence and which could benefit from adjuvant treatments.

DNA methylation- and transcriptomic-based approaches may be challenging to apply in routine

practice, nevertheless, different studies have unanimously demonstrated that the presence of 1p deletions is useful for stratifying atypical meningiomas for their recurrence risk. Several methods are widely available in routine practice to assess 1p deletions, including chromosomal microarray, fluorescence *in situ* hybridization, and next-generation sequencing, thus the evaluation of 1p deletions in atypical meningiomas can be easily incorporated into routine assessment.

Although this requires further validation, the use of immunostainings as a surrogate for molecular groups of meningiomas could be useful in predicting the recurrence risk of atypical meningiomas with the aim of establishing the most appropriate post-surgical treatment for patients with these tumors.

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