Histol Histopathol (2025) 40: 797-803

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW Open Access

The prognostic value of H3 K27me3 in meningiomas: A review on current evidence and methodological challenges

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Summary. Meningiomas are the most common primary intracranial neoplasms. Although they mostly exhibit a benign course, some cases recur after surgery and show high morbidity and mortality rates. In addition to currently established prognostic factors, such as the extent of surgical resection and tumor grade assessed according to World Health Organization (WHO) criteria, the prognostic significance of the immunohistochemical loss of Histone 3 trimethylation in Lysine 27 (H3 K27me3) has emerged in meningiomas. This review examined original studies that analyzed the immunohistochemical expression of H3 K27me3 in meningiomas and its correlation with various features, including overall survival (OS), recurrence-free survival (RFS), and WHO grade. A literature search was conducted in PubMed for English-language publications up to July 8, 2024. Sixteen studies were included in this review. In summary, current evidence indicates that H3 K27me3 loss is more frequent in tumors exhibiting higher biological aggressiveness, as reflected by a significant association with a higher WHO grade, proliferative index, and prognostically unfavorable methylation classes. In addition, published studies consistently indicate a negative prognostic significance for progression-recurrence-free survival (PFS/RFS) in WHO grade 2 meningiomas and OS in WHO grade 3 tumors. However, the lack of a standardized definition for H3 K27me3 loss significantly hampers the incorporation of the H3 K27me3 immunohistochemical assay into routine practice to establish the prognosis of meningiomas.

Key words: Meningioma, H3 K27me3, Prognosis, Recurrence, Precision medicine

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www.hh.um.es. DOI: 10.14670/HH-18-851

Introduction

Meningiomas represent approximately 38% of all primary intracranial tumors (Ostrom et al., 2022). According to the fifth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) (WHO CNS5), they are classified into fifteen histologically defined subtypes and three grades of malignancy (Sahm et al., 2021). The WHO grading criteria are based on morphological and molecular features. The former include mitotic index, spontaneous necrosis, patternless growth, hypercellularity, prominent nucleoli, small cells with a high nuclear/cytoplasmic ratio, brain invasion, and frank anaplasia; the latter include Telomerase Reverse Transcriptase (*TERT*) promoter (*pTERT*) mutation and homozygous deletion of Cyclin-Dependent Kinase inhibitor 2A/B (*CDKN2A/B*) (Sahm et al., 2021). The WHO grading is a major prognostic factor for meningiomas. Indeed, menin-giomas classified as WHO grade 1 exhibit a benign clinical course, whereas grade 2 meningiomas have an intermediate prognosis, and grade 3 meningiomas are malignant neoplasms with unfavorable outcomes (Sahm et al., 2021). Tumor location and the extent of surgical resection (Simpson grade; Simpson, 1957) are additional prognostic factors for these tumors. However, prediction of recurrence risk remains challenging, especially for tumors classified as WHO grade 2, and new markers are needed to improve patient stratification and identify cases that could benefit from post-surgical treatment (Aizer et al., 2015; Goldbrunner et al., 2016; Fioravanzo et al., 2020; Barresi et al., 2021).

Recent evidence suggests that the loss of Histone H3 trimethylation at lysine 27 (H3 K27me3) is associated with a higher recurrence risk in meningiomas (Katz et al., 2018; Behling et al., 2021; Nassiri et al., 2021; Ammendola et al., 2022). H3 K27me3 loss is a reversible, repressive, post-translational modification of histone H3, which is carried out by the H3 K27-specific

histone methyltransferase Enhancer of Zeste 2 (EZH2) as part of the Polycomb Repressive Complex 2 (PRC2) (Yang et al., 2022) and is associated with changes in chromatin structure, DNA methylation status, and gene expression (Yang et al., 2022). H3 K27me3 expression is routinely assessed using immunohistochemistry and a specific antibody in neuropathology laboratories for the diagnosis of diffuse midline glioma H3 K27-altered, and to identify a group of posterior fossa ependymomas characterized by an unfavorable prognosis (Bayliss et al., 2016; Bender et al., 2013). Therefore, the assessment of H3 K27me3 immunohistochemical expression is readily available in routine practice to identify meningiomas with a higher recurrence potential, which could benefit from adjuvant treatments after surgery (Katz et al., 2018; Behling et al., 2021; Nassiri et al., 2021; Ammendola et al., 2022).

This study aimed to review current knowledge regarding the significance of H3 K27me3 loss in meningiomas, highlighting the methodological issues that hinder its incorporation as a routine prognostic marker.

Materials and methods

This study was conducted in accordance with PRISMA guidelines for systematic reviews (Page et al., 2021). The combination of keywords "meningioma" AND "H3K27me3" was used to search all articles published until July 8 in PubMed (www.pubmed.gov).

Only articles meeting the following inclusion criteria were considered: (1) English language, (2) original studies assessing H3 K27me3 immunohistochemical loss in meningiomas. Case reports and articles that did not provide new data (letters to the editor, reviews, or editorials) were excluded.

Pertinent papers were read and reviewed for quality assessment. The Critical Appraisal Skills Programme (https://casp-uk.net/casp-tools-checklists/) and Joanna Briggs Institute (JBI) were used to conduct this systematic review (Critical Appraisal Skills Programme, 2022; Lockwood et al., 2015).

Results

The PubMed electronic database search yielded 30 articles. Subsequently, 14 papers were excluded because they did not meet the inclusion criteria. Finally, 16 papers were selected for this study, all published between 2018 and 2024 and including 3582 meningiomas in total (Katz et al., 2018; Gauchotte et al., 2020; Hua et al., 2020; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021; Ammendola et al., 2022; Maier et al., 2022; Zeng et al., 2022; Hua et al., 2023; Sharma et al., 2023; Singh et al., 2023, 2024; Vaubel et al., 2023; Tosefsky et al., 2024) (Table 1). However, 448 cases were subsequently excluded from the statistical analysis owing to insufficient tissue or absence of staining in the internal positive controls. Therefore, the prognostic significance of H3 K27me3 immuno-expression was analyzed in 3134 meningiomas across these studies.

All studies were retrospective and performed on formalin-fixed and paraffin-embedded (FFPE) specimens of meningioma, which were graded according to the WHO 2016 or 2021 criteria depending on the year of publication of the study.

Assessment of H3 K27me3 immunoexpression

H3 K27me3 immunostaining was carried out on whole slides of meningiomas in 11 studies (Gauchotte et al, 2020; Hua et al, 2020; Nassiri et al, 2021; Ammendola et al, 2022; Maier et al, 2022; Hua et al, 2023; Sharma et al, 2023; Singh et al, 2023, 2024; Vaubel et al, 2023; Tosefsky et al, 2024), on tissue microarrays (TMAs) in one study (Zeng et al, 2022), and on both whole slide sections and TMAs in the remaining four studies (Katz et al, 2018; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021).

All studies used the same antibody against H3 K27me3, namely the rabbit monoclonal antibody clone C36B11 (Cell Signaling, Danvers, MA, USA). The working dilutions varied between 1:50 and 1:700, with 1:100 and 1:200 being the most common. Nevertheless, the definition of H3 K27me3 loss of expression lacked uniformity across the studies. Specifically, in five studies (Katz et al., 2018; Behling et al., 2021; Nassiri et al., 2021; Hua et al., 2023; Singh et al., 2024), H3 K27me3 loss was defined as the complete absence of immunostaining in neoplastic cells (100% tumor cells negative) in the presence of positive internal controls. Nine studies (Gauchotte et al., 2020; Hua et al., 2020; Samal et al., 2020; Jung et al., 2021; Maier et al., 2022; Ammendola et al., 2022; Zeng et al., 2022; Sharma et al., 2023; Singh et al., 2023) used varying percentages of negative neoplastic cells as cut-off values, ranging from 50% to 95%, to define H3 K27me3 loss of expression. Finally, two studies (Vaubel et al., 2023; Tosefsky et al., 2024) did not provide a definition of H3 K27me3 loss of expression (Table 1).

Two studies described ambiguous immunostaining, consisting of areas of neoplastic cells with weaker staining intensity or patchy staining with alternating positive and negative neoplastic cells in 5-7% of meningiomas (Katz et al., 2018; Nassiri et al., 2021).

Five studies reported that, in a percentage of cases, H3 K27me3 immunostaining was inconclusive due to the absence of staining in the vessels that served as internal positive controls, presumably attributable to technical issues (Behling et al., 2021; Jung et al., 2021; Ammendola et al., 2022; Maier et al., 2022; Vaubel et al., 2023). It is noteworthy that the number of inconclusive cases was significantly associated with the increased age of paraffin blocks, and a maximum age of five years for the paraffin block was proposed as a threshold to ensure the quality of immunostaining (Jung et al., 2021).

Correlation between H3 K27me3 loss and clinical-pathological and epigenetic features

The prevalence of meningiomas exhibiting immunohistochemical loss of H3 K27me3 ranged from 5% to 62% across various studies (Table 1), likely influenced by the proportion of grade 2 and 3 or recurrent cases and the threshold of negative neoplastic cells employed to define H3 K27me3 loss. Indeed, as demonstrated in seven studies, the loss of H3 K27me3 was significantly more frequent in grade 2 and 3 tumors than in grade 1 (Katz et al., 2018; Hua et al., 2020; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021; Singh et al., 2024) (Table 1).

Table 1. Data on H3 K27me3 immunohistochemical expression and correlations with clinicopatho-logical features in meningiomas analyzed in the sixteen studies included in this review.

Article	H3 K27me3 immunohistochemical loss				
	% of negative tumor cells for definition	N cases/analyzed cases	Inconclusive immunostain-ing (cases)	Association with other features	Significant association with survival times
Ammendola et al., 2022	>95%	7/34 (21%); 1/6 G1 (17%); 6/28 G2 (21%)	5 (13%)	None	- Shorter RFS after radio-surgery (UA); - OS NA
Behling et al., 2021	100%	60/1268 (4,7%); 31 G1 (3%); 26 G2 (10%); 14 G3 (18%)	64 (4.8%)	- Male sex - Intracranial location - Convexity/falx loca-tion - Higher WHO grade - Higher Ki-67 LI - Chordoid/rhabdoid,/ Atypical/anaplastic sub-type	-Shorter RFS in G2 (UA) - OS NA
Gauchotte et al., 2020	>50%	10/47 G3 (21%)	None	None	- RFS not different - Shorter OS (MA)
Hua et al., 2020	>50%	32/192 (17%); 6/131 G1 (5%); 7/40 G2 (18%); 19/21 G3 (91%)	None	Higher WHO grade	- Shorter RFS (MA) - OS not different
Hua et al., 2023	100%	83/164 (50%); 63/131 G1 (48%); 20/32 G2 (63%); All recurrent	None	None	- Shorter RFS in G1 (MA) - Shorter RFS in G2 (UA) - OS not different
Jung et al., 2021	>55%	48/141 (34%); 34/115 G2 (30%); 14/26 G3 (54%)	Most speci-mens before 2014	- Higher WHO grade - Higher mitotic index - Higher Ki-67 LI - Necrosis - Supratentorial location	- Shorter RFS in G2 (MA) - Shorter OS in G2 (MA)
Katz et al., 2018	100%	25/232 (11%); 1/49 G1 (2%); 18/155 G2 (12%); 6/28 G3 (21%)	None	- Higher WHO grade - Malignant/ intermediate MC - NF2 mutations	- Shorter RFS (MA) - OS NA
Maier et al., 2022	>50%	89/143 (62%); 16/36 G1 (44%); 13/27 G2 (48%); 60/80 G3 (75%)	9 (6.2%)	None	- RFS NA - OS not different
Nassiri et al., 2021	100%	21/151 (14%); 2/48 G1 (4%); 9/74 G2 (12%); 8/29 G3 (28%)	None	Higher WHO grade	- Shorter RFS in G2 (MA) - OS NA
Samal et al., 2020	>95%	6/147 (4%); 1/100 G1 (1%); 5/47 G2 (11%)	None	- Higher WHO grade - Higher Ki-67 LI	- Shorter RFS (UA) - OS NA
Sharma et al., 2023	>80%	8/18 (50%) grade unknown	NA	- Cavernous sinus extension - Brain edema	- RFS NA - OS NA
Singh et al., 2023	>80%	12/35 (34%); 5/15 G1 (33%); 2/14 G2 (14%); 5/6 G3 (83%)	None	- Malignant MC	- RFS NA - OS NA
Singh et al., 2024	100%	38/206 (18%); 12/108 G1 (11%); 20/89 G2 (23%); 6/9 G3 (67%)	None	WHO grade	- RFS: not different - OS NA
Tosefsky et al., 2024	Undefined	2/15 G3 (13%)	None	None	- Shorter RFS (UA*) - Shorter OS (UA*)
Vaubel et al., 2023	Undefined	4/62 G2 (67%)	1 (1.6%)	None	- RFS NA - OS NA
Zeng et al., 2022	>80%	39/276 (14%); 11/129 G1 (9%); 19/108 G2 (18%); 9/39 G3 (23%)	None	Lower infiltrating CD8+ lymphocytes	- Shorter RFS UA* - OS NA

LI: labelling index; MC: methylation class; RFS: recurrence-free survival; OS: overall survival; UA: univariate analysis (*multivariate analysis not performed); MU: multivariate analysis; NA: not assessed.

Furthermore, two studies indicated that recurrent meningiomas exhibit a significantly higher frequency of H3 K27me3 loss compared with primary tumors (Behling et al., 2021; Hua et al., 2023).

Three studies highlighted a significant correlation between H3 K27me3 loss and an elevated mitotic or Ki-67 labeling index (LI) (Samal et al., 2020; Behling et al., 2021; Jung et al., 2021), while one study reported a lower number of CD8+ infiltrating lymphocytes in tumors characterized by H3 K27me3 loss (Zeng et al., 2022). Moreover, according to two distinct studies, H3 K27me3 loss was significantly more frequent in supratentorial (Jung et al., 2021) or falcine/convexity (Behling et al., 2021) meningiomas than in skull base tumors. Additionally, a study focusing on petroclival meningiomas reported a significant association between H3 K27me3 loss and extension within the cavernous sinus and cerebral edema (Sharma et al., 2023).

Notably, H3 K27me3 loss also varied according to the methylation class (MC) of meningiomas, as it was significantly more frequent in cases belonging to malignant and intermediate B MCs than meningiomas in Intermediate A and Benign MCs (Katz et al., 2018; Singh et al., 2023). Furthermore, cases with retained H3 K27me3 immuno-expression more frequently exhibited *NF2* mutations compared with meningiomas with H3 K27me3 loss (Katz et al., 2018).

Correlation between H3 K27me3 loss and patient survival

Twelve studies analyzed the correlation between H3 K27me3 loss and recurrence-free survival (RFS), and three of these additionally investigated the correlation with overall survival (OS) (Table 1).

One study focused on progression-recurrence-free survival (PFS/RFS) after stereotaxic radiosurgery and found that patients harboring meningiomas characterized by H3 K27me3 loss exhibited a significantly shorter PFS/RFS, although this was not an independent prognostic variable in the multivariate analysis (Ammendola et al., 2022). Another study demonstrated a significant correlation between H3 K27me3 loss and a shorter PFS/RFS in recurrent meningiomas (Hua et al., 2023).

Eight studies reported a significant association between H3 K27me3 loss and shorter RFS in univariate analyses (Katz et al., 2018; Hua et al., 2020; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021; Zeng et al., 2022; Tosefsky et al., 2024). All but one study (Samal et al., 2020) in which multivariate analysis was conducted demonstrated that H3 K27me3 loss was a negative and independent prognostic parameter for RFS (Katz et al., 2018; Hua et al., 2020, 2023; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021). Notably, in four studies, H3 K27me3 loss was identified as a negative prognostic factor within WHO grade 2 meningiomas (Katz et al., 2018; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021), but not throughout the entire cohort.

Three out of six studies demonstrated that H3 K27me3 loss was significantly associated with shorter OS (Table 1). Notably, in one of these studies, the prognostic significance of H3 K27me3 loss was observed only in WHO grade 2 meningiomas (Jung et al., 2021), whereas the remaining two studies included only WHO grade 3 meningiomas (Gauchotte et al., 2020; Tosefsky et al., 2024).

Discussion

In the CNS, immunohistochemical loss of H3 K27me3 is associated with a poorer prognosis in several tumor types and is routinely assessed in the diagnostic algorithm of diffuse midline gliomas and for prognostic subgrouping of posterior fossa ependymomas (Bender et al., 2013; Bayliss et al., 2016). Katz et al. initially reported that H3 K27me3 immunohistochemical loss was associated with shorter PFS in patients with meningiomas, suggesting the inclusion of this immunohistochemical assay in routine practice to identify cases characterized by a higher recurrence risk (Katz et al., 2018). As reviewed herein, the fifteen subsequent studies investigated H3 K27me3 immunoexpression in meningiomas. Overall, these studies consistently demonstrated that H3 K27me3 loss is more prevalent in meningiomas characterized by pathological and clinical features associated with biological aggressiveness. Indeed, tumors with H3 K27me3 loss more frequently exhibit a high proliferative index, as reflected by mitotic counts or Ki-67 LI (Samal et al., 2020; Behling et al., 2021; Jung et al., 2021), and a high WHO grade (Katz et al., 2018; Samal et al., 2020; Hua et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021; Singh et al., 2024). Furthermore, H3 K27me3 loss in meningiomas has been associated with male sex and a falcine location, both of which were considered negative prognostic indicators in a cohort of 200 WHO grade 2 meningiomas (Fioravanzo et al., 2020).

Meningiomas can be categorized into six prognostically relevant groups based on their DNA methylation profile: three Benign, two Intermediate, and one Malignant MC (Sham et al., 2017). These MCs exhibit greater prognostic value than WHO grading (Sahm et al., 2024). The predominant distribution of meningiomas exhibiting H3 K27me3 loss in Malignant and Intermediate MCs (Katz et al., 2018; Singh et al., 2023) further suggests that the determination of H3 K27me3 may serve as an indicator to identify cases with a higher propensity for recurrence.

Studies analyzing the correlations between H3 K27me3 loss and RFS/PFS consistently demonstrated that H3 K27me3 loss is associated with a higher recurrence risk and shorter time to recurrence after surgery (Hua et al., 2020, 2023; Samal et al., 2020; Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021; Tosefsky et al., 2024) or stereotactic radiosurgery

(Ammendola et al., 2022). However, it is important to note that when the cases were stratified by WHO grade, H3 K27me3 immunoexpression emerged as a prognostic factor for RFS/PFS in the grade 2 meningioma subset, but not in grade 1 or 3 (Behling et al., 2021; Jung et al., 2021; Nassiri et al., 2021), and for OS in WHO grade 3 tumors (Gauchotte et al., 2020; Tosefsky et al., 2024).

Although H3 K27me3 could be a promising and readily assessable prognostic factor in meningiomas, the published studies indicate that a primary issue limiting its application in routine practice is difficulty in interpreting this immunostaining. While cases exhibiting complete loss of H3 K27me3 in all neoplastic cells are readily classified as "negative" (Fig. 1) and cases with retention of H3 K27me3 in all neoplastic cells as "positive" (Fig. 1), it remains unclear how cases with patchy loss or ambiguous immunostaining should be categorized (Fig. 1). Nassiri et al. subdivided meningiomas into three subgroups according to H3 K27me3 immunostaining and did not find any significant difference in terms of RFS/PFS between cases with partial or complete retention of H3 K27me3, suggesting that H3 K27me3 immunostaining should be classified as retained regardless of the percentage of positive neoplastic cells (Nassiri et al., 2021). However, whether patchy loss indicates biologically aggressive subclones remains to be investigated. The heterogeneity in the definition of H3 K27me3 loss across different studies presents a substantial obstacle to comparing their findings and to the incorporation of H3 K27me3 immunostaining in diagnostic practice. A further challenge in investigating H3 K27me3 loss in retrospective studies is the frequent inconclusiveness of H3 K27me3 immunostaining (Fig. 1) when evaluated in

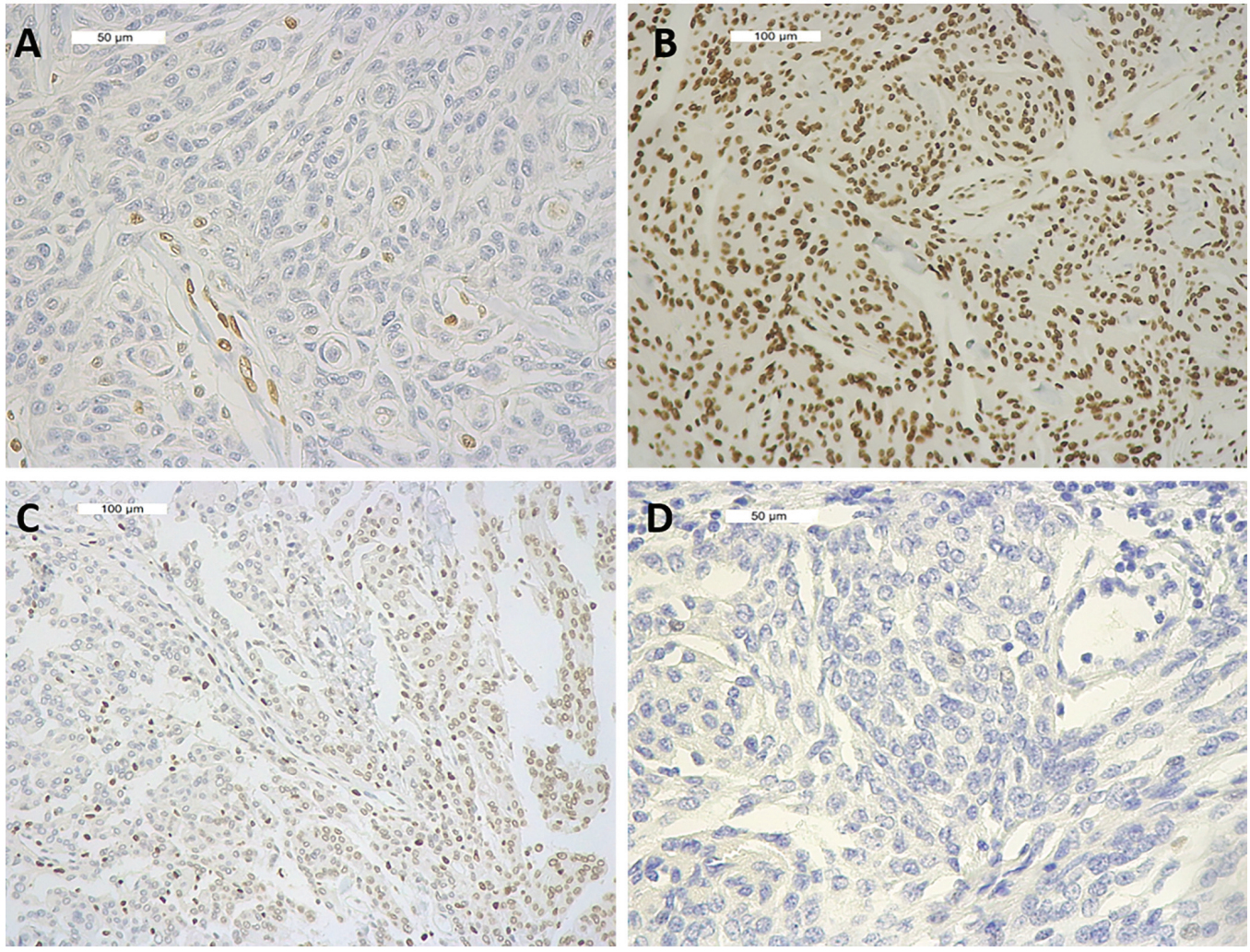

Fig. 1. H3 K27me3 immunostaining in meningiomas. **A.** Complete loss of H3 K27me3 immunostaining in neoplastic cells and positive staining in endothelial cells. **B.** Retention of H3 K27me3 immunostaining in neoplastic cells. **C.** Ambiguous staining with alternation of positive and negative cells. **D.** Inconclusive staining: both neoplastic and endothelial cells serving as internal positive controls are negative for H3 K27me3.

older paraffin blocks (Behling et al., 2021; Ammendola et al., 2022; Maier et al., 2022; Vaubel et al., 2023). In one study, the proportion of cases with inconclusive staining reached 13%, significantly reducing the number of specimens available for statistical analyses (Ammendola et al., 2022).

An additional confounding factor when evaluating the potential of H3 K27me3 as a valid and robust prognostic indicator was the inclusion of both primary and secondary (recurrent) meningiomas in the same study. Indeed, secondary meningiomas exhibit a higher frequency of H3 K27me3 loss (Behling et al., 2021; Hua et al., 2023), and H3 K27me3 loss in these cases may not have the same prognostic significance as in primary tumors (Ammendola and Barresi, 2022) but may instead be a consequence of adjuvant treatments.

In conclusion, the literature demonstrates a strong association between H3 K27me3 loss and the biological aggressiveness of meningiomas, and consistently suggests that H3 K27me3 loss may be used to predict the recurrence risk of WHO grade 2 meningiomas and as a prognostic factor for WHO grade 3 tumors. Nonetheless, the absence of a standardized definition of H3 K27me3 loss constitutes a significant limitation for the incorporation of this test into routine diagnostics. In accordance, the recent Update 8 published by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) states that available data on H3 K27me3 immunoexpression in meningiomas are still insufficient for recommendations on its use in routine practice (Sahm et al., 2024).

Further studies comparing different cut-off values of negative tumor cells to define H3 K27me3 loss in homogeneous cohorts of primary, untreated meningiomas are necessary to definitively assess the prognostic relevance of this marker and standardize its evaluation.

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Accepted November 21, 2024