



Pathophysiological role and clinical applications of HER-2 expression in meningiomas: a systematic review

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Background: Although typically benign, malignant meningiomas represent 1–3% of cases and exhibit poor survival rates. Environmental and genetic risk factors, including neurofibromatosis type 2 (NF2), obesity, and hormone-related exposure, influence meningioma development.

Objective: This study investigated HER2 expression in meningiomas, exploring its potential as a therapeutic target and examining its role in tumor pathophysiology and grade progression.

Methods: A systematic review was conducted through a comprehensive search of the PubMed database, and 12 studies meeting the inclusion criteria were selected. Studies focusing on HER-2/neu expression in meningiomas, published in English, and demonstrating methodological consistency were included in our study.

Results: HER2 overexpression and gene amplification were identified in meningiomas, with higher expression correlating with tumor grade and recurrence rates. HER2-positive meningiomas exhibit enhanced invasion, migration, and proliferation via the HER2/PI3K/AKT pathway, implicating HER2 as a key player in tumor progression. Experimental studies have demonstrated that HER2 silencing reduces meningioma cell proliferation and angiogenesis by modulating vascular endothelial growth factor and CD34 expression. However, some studies have found no correlation between HER2 expression and meningioma characteristics.

Conclusion: HER2 expression is closely associated with meningioma pathogenesis and grade. This highlights HER2 as a potential biomarker and therapeutic target, warranting further clinical trials to explore HER2-targeted therapies, such as trastuzumab, for aggressive and non-resectable meningiomas.

Keywords: angiogenesis, HER2/neu, meningioma, therapeutic target, tumor grade, tumor progression

Introduction

Meningioma

Meningiomas account for approximately 37.6% of primary central nervous system (CNS) tumors and nearly 50% of benign brain tumors, making them the most prevalent primary CNS tumor^[1–3]. These tumors originate in the meninges, which are the protective layers surrounding the brain and spinal cord.

Although most meningiomas are benign, malignant transformation occurs in 1–3% of cases, with 5-year survival rates ranging from 32% to 64%^[2].

While most meningiomas arise sporadically, certain cases are associated with specific diseases and risk factors. Environmental factors, including obesity, alcohol consumption, exposure to ionizing radiation, radiotherapy, and hormonal factors (use of exogenous hormones, hormone replacement therapy, oral contraceptives, and a history of breast cancer), have been linked to an increased likelihood of meningioma development^[3–5]. Additionally, genetic predispositions, including a family history of meningiomas and conditions such

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as neurofibromatosis type 2 (NF2), significantly increase the risk of occurrence^[3].

The World Health Organization (WHO) grading system classifies meningiomas based on their histopathological characteristics^[6] (Table 1). Grade I meningiomas, accounting for over 80% of cases, include nine histological subtypes and lack the anaplastic features seen in higher-grade tumors. These subtypes include meningothelial, fibroblastic, transitional (or mixed), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacytic-rich, and metaplastic variants^[4,7]. More than 70% of these tumors exhibit progesterone receptor (PR) positivity^[4,8]. Histologically, meningiomas are characterized by meningothelial cell proliferation, which can mineralize to form psammomatous bodies. Hyperostosis of adjacent bone structures is occasionally observed.

Grade II or atypical meningiomas are defined by the presence of three or more of the following features: necrosis, sheet-like growth, prominent nucleoli, increased cellularity, or a high nucleus-to-cytoplasm (n:c) ratio. These tumors also demonstrate higher mitotic activity [4–19 mitoses per 10 high-power fields (HPF)]. Brain invasion, once identified, classifies meningiomas as Grade II, regardless of other histological features. Subtypes within this grade include atypical, clear cell, and choroid variants^[6,7].

Grade III anaplastic meningiomas are highly aggressive and have a propensity for distant metastasis. These tumors often mimic high-grade sarcomas, carcinomas, and melanomas. Histopathologically, they exhibit significant mitotic activity (≥ 20 mitoses per 10 high-power fields) and include papillary and rhabdoid subtypes^[7].

Clinical presentation of intracranial meningiomas

Intracranial meningiomas most often arise supratentorially – in areas such as the parasagittal region, olfactory groove, convexity, sphenoid ridge, and parafalcine zones – but can also occur in the suprasellar space, posterior fossa (notably the cerebellopontine angle), intraventricular compartment, and orbit^[4,9]. Their presentation varies with location: cerebral tumors commonly cause upper motor neuron signs (hypertonia, clonus, hyperreflexia, and positive Babinski and Hoffmann) as well as anosmia, headache, dizziness, blurred vision, seizures, papilledema, or

Table 1
An overview of the WHO grading criteria for meningiomas, along with their respective frequencies^[6]

WHO Grade	Description	Frequency
Grade I	Low mitotic rate (<4 per 10 HPFs); absence of brain invasion; includes 9 histological subtypes	80–85%
Grade II (atypical)	Mitotic rate 4–19 per 10 HPFs OR brain invasion OR ≥ 3 specific histologies: • Spontaneous or geographic necrosis • Patternless, sheet-like growth • Prominent nucleoli • High cellularity • Small cells with a high n:c ratio	15–20%
Grade III (anaplastic)	Mitotic rate >20 per 10 HPFs OR papillary or rhabdoid histologies	1–2%

HPF, high-power field.

HIGHLIGHTS

- Various genetic markers have been associated with prognosis in malignant meningioma like HER-2/neu as a potential marker of interest.
- We investigate HER2 expression in meningiomas, exploring its potential as a therapeutic target and examining its role in tumor pathophysiology and grade progression.
- HER2 overexpression and gene amplification were identified in meningiomas, with higher expression correlating with tumor grade and recurrence.
- HER2-positive meningiomas exhibited enhanced invasion, migration, and proliferation via the HER2/PI3K/AKT pathway. HER2 expression appears to be closely associated with meningioma pathogenesis and grade.

behavioral changes. Frontal and suprasellar lesions often lead to cognitive and behavioral disturbances^[4], while posterior fossa or foramen magnum tumors present with neck pain, bulbar palsy, cerebellar signs, facial weakness, hearing loss, and lower cranial nerve deficits^[10,11]. Intraventricular meningiomas may obstruct cerebrospinal fluid (CSF) flow, resulting in hydrocephalus^[12], and tumors in the orbital, cavernous sinus, or parasellar regions frequently cause proptosis and visual impairment^[13].

HER-2

ErbB2/HER2/neu (hereafter referred to as HER2) is a member of the epidermal growth factor receptor (EGFR) family of tyrosine kinase receptors, notable for its lack of a specific ligand^[14,15]. HER2 is considered the primary ErbB dimerization partner because of its constitutively open conformation, which strongly predisposes it to heterodimer formation^[15,16]. In cancers that overexpress HER2, the receptor can form homodimers in the absence of ligand stimulation, leading to constitutive activation^[15].

Upon ligand activation, the extracellular domain of ErbB receptors reveals a “dimerization arm” that facilitates heterodimerization or homodimerization^[14,16]. These processes initiate a cascade of intracellular signaling through the phosphorylation and activation of the intracellular kinase domain, which also contains a transmembrane segment. This signaling influences several critical cellular processes, including apoptosis, proliferation, migration, adhesion, and differentiation^[14,15].

HER2 gene amplification and overexpression have been documented in various cancers, including gastric, endometrial, and urothelial bladder carcinomas^[17]. However, the strongest clinical evidence of HER2’s significance is found in breast cancer, where its role in tumor progression and treatment has been extensively studied^[17].

Meningiomas, whether benign or malignant, tend to recur. Repeated and aggressive resections are often associated with significant postoperative complications. Therefore, there is a need to explore alternative therapies to minimize the adverse effects of repeated surgeries. Molecular research has emerged to identify potential biomarkers involved in the pathogenesis of meningiomas. Our study explored HER2 as a potential therapeutic target

for malignant or otherwise intractable meningiomas. Additionally, this study sought to identify novel molecular pathways implicated in the pathophysiology of these tumors, offering new directions for treatment.

This manuscript has been prepared in line with TITAN guidelines^[18].

Methods

A comprehensive literature search was conducted in the PubMed database, covering the period from 1945 to 2022, following the PRISMA guidelines. The search terms included: “PI3K/AKT,” “HER-2/neu,” “Human epidermal growth factor receptor 2,” “Meningioma,” “HER-2 expression in brain tumors,” “HER-2/neu in meningioma,” and “HER2 receptor in meningioma pathology.” The search utilized subject-specific and free-text keywords combined with Boolean operators to refine the search results. References cited in the selected studies were manually reviewed to identify additional relevant articles. Articles were also retrieved from other sources such as bibliographic references and citation tracking. A total of 33 records were identified, of which 30 were retrieved from the PubMed database and 3 from other sources. After removing two duplicates, 31 records were screened based on their titles and abstracts. Following this initial screening, 20 studies were

selected for a full-text review (Table 2). Of these, 12 studies met the inclusion criteria and were ultimately included in this review. The PRISMA flowchart representing the steps described earlier is shown in Figure 1.

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) Guidelines (Supplemental Digital Content File S1, available at: <http://links.lww.com/MS9/A939> and File S2, available at: <http://links.lww.com/MS9/A940>, respectively).

Inclusion criteria

Studies were included if they were published between 1945 and 2024, written in English, focused on the expression of HER-2/neu in meningiomas or brain tumors, and provided full-text availability with consistent methodology.

Exclusion criteria

Studies were excluded if they were unrelated to HER-2/neu or meningiomas, published in languages other than English, or classified as narrative reviews, editorials, or isolated case reports.

Table 2
Summary of findings from reviewed studies

Study	Sample size	Type of study	Tumor type	HER-2 expression	Key findings
Eman Abdelzaher <i>et al</i>	60 patients	Retrospective	Benign meningiomas	Positive HER-2 associated with higher PI	Significant correlations with p53, BCL2; factors linked to recurrence
Bruce S. Chozick <i>et al</i>	60 patients	Retrospective	Benign and atypical meningiomas	Membrane staining in benign, weaker in atypical	Inverse correlation between erbB-2 and p53; no gene amplification found
Delphine Loussouarn <i>et al</i>	35 meningiomas	Retrospective	Atypical/classic meningiomas	28.5% positive, higher in atypical	No significant difference in MIB-1 index between groups
Parvin Mahzouni and Movahedipour	72 patients	Retrospective	Various grades meningiomas	31 positive cases identified	No significant difference between primary and recurrent tumors
B.R. Ongaratti <i>et al</i>	60 patients	Retrospective	Grade 1 and higher meningiomas	ERBB2 detected in 88.3% of cases	No significant association with tumor grade or recurrence
Jurgen Schlege <i>et al</i>	59 meningiomas	Prospective	Various types	Homogeneous gp185 expression in all tumors	No correlation with histological subtype or patient demographics
Sverre Helge Torp <i>et al</i>	84 patients	Retrospective	Meningiomas and other tumors	Positive in benign (11/16) and anaplastic (1/3) meningiomas	High reproducibility; normal brain tissue did not express HER2
Weijia Wang <i>et al</i>	Human malignant meningioma cells	N/A	Malignant meningiomas	HER-2 overexpression linked to increased proliferation and invasion	HER-2 downregulation decreased proliferation and invasion significantly
Özge Özer <i>et al</i>	55 sporadic meningiomas	Retrospective	Various grades meningiomas	Increased HER-2/neu gene copy number in some cases	Confirmed hybridization with chromosome probe for some patients
Shanshan Wang <i>et al</i>	IOMM-Lee cells study	Observational lab study	Malignant meningiomas (<i>in vitro</i>)	Significant reduction of HER2 protein with shRNA silencing	Inhibition of proliferation and angiogenesis assessed through immunohistochemistry
Magnus B. Arnli <i>et al</i>	186 patients	Observational lab study	Various grades meningiomas	Upregulated HER-2 expression noted across samples, clinical relevance identified for survival outcomes	Increased expression of specific antibodies linked to survival; biological heterogeneity noted
Ramesh Babu Telugu <i>et al</i>	Prospective and retrospective studies on multiple cases	Prospective	Grade II/III tumors and recurrences	Overexpression detected in 30–43% of cases, higher in aggressive tumors	HER-2 plays a central role; targeting the HER-2/PI3K/AKT pathway suggested for therapies

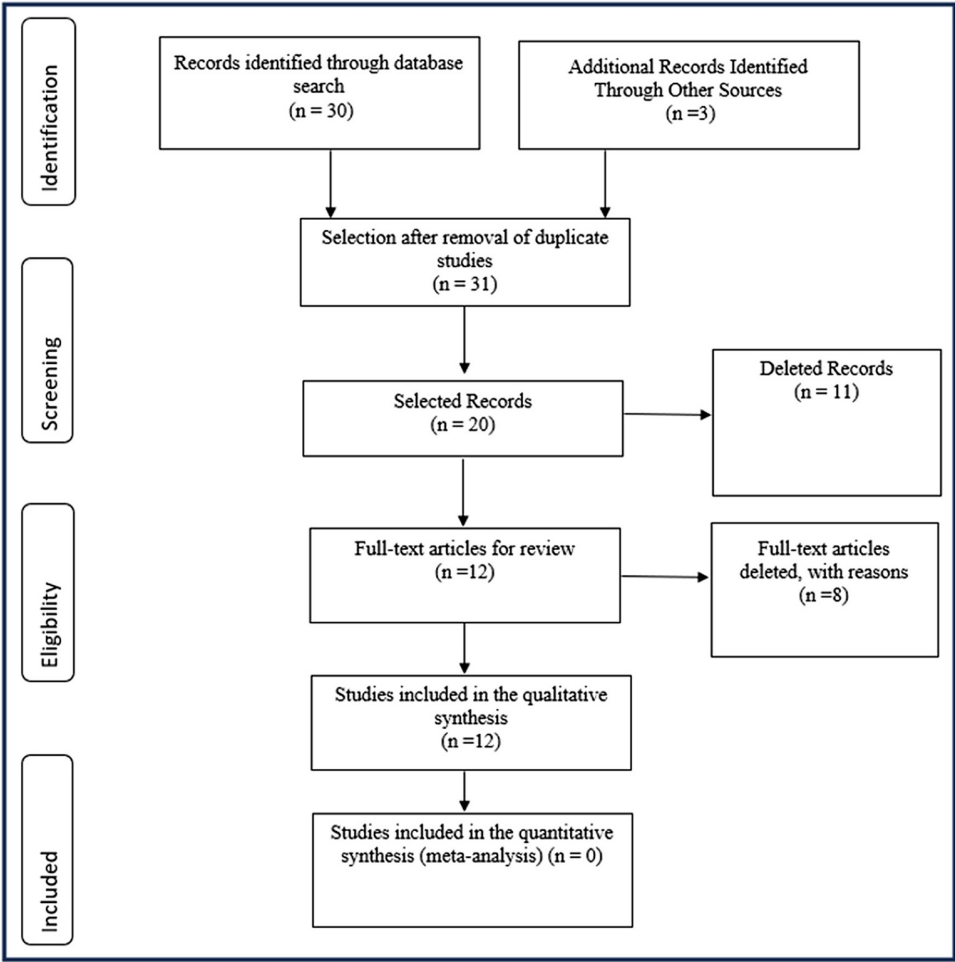


Figure 1. Flowchart representing the identification, screening, eligibility, and inclusion and exclusion criteria of this systematic review.

Results

Twelve articles were reviewed regarding the expression and relationship of HER-2 with meningiomas and their pathophysiology.

Abdelzaher and colleagues^[19] analyzed 60 patients with benign meningiomas, including 7 cases with tumor recurrence. The proliferation index (PI) ranged from 0.1% to 10% (mean $\pm$ SD: 2.37% $\pm$ 1.86). PR-negative and HER-2-positive cases showed a significantly higher mean PI ($P = 0.007$) than PR-positive and HER-2-negative cases. Additionally, positive expression of p53, BCL2, and HER-2 was associated with recurrence ($P < 0.05$). Correlation analysis revealed a significant inverse correlation between HER-2 expression and PR expression, and a significant direct correlation between HER-2 and PI. These findings underscore that factors such as tissue invasion, atypical histological features, and HER-2 expression are associated with higher recurrence rates in benign meningiomas. HER-2 positivity, in particular, correlates with elevated PI, suggesting its role in cellular proliferation and potential prognostic value. Therefore, patients with these findings require close follow-up to detect possible recurrences at an early stage.

Loussouarn and colleagues^[20] analyzed 35 meningiomas, where they concluded that HER2 was detected in 10 (28.5%) of the meningiomas, with marked expression in the cytoplasmic membrane. Of these, five were atypical/anaplastic meningiomas (26.6%) and five were classic (29.4%). The recurrence rate was higher in HER2-positive meningiomas (50%) than in HER2-negative meningiomas (20%, $P = 0.038$). In addition, there was no significant difference in the MIB-1 index between HER2-positive (average: 4.3%) and HER2-negative meningiomas (average: 5.1%).

Mahzouni and Movahedipour^[21] included 72 patients diagnosed with meningiomas, of which 52 were grade 1 and the remaining 20 were grades 2 and 3, predominantly located in the cerebral convexity and parasagittal areas. Additionally, 62 were primary tumors and 10 were recurrent. HER-2 expression was identified in 31 patients (9 men and 22 women), with no significant difference between the sexes. Furthermore, 26 of the 62 primary tumors and 5 of the 10 recurrent tumors were HER-2-positive, with no significant difference between these groups.

Torp and colleagues^[22], through a staining method for immunohistochemical analysis, evaluated meningioma samples from 84 patients. HER2 expression was predominantly localized to the membrane in metastatic adenocarcinomas and granular in

the cytoplasm of other tumors. More than 50% of the tumor cells were positive in most cases. In meningiomas, HER2 was positive in 11 of 16 benign and 1 of 3 anaplastic tumors, whereas in gliomas, only 1 of 44 glioblastomas and 1 medulloblastoma showed positivity. In brain metastatic tumors, HER2 was positive in 2 squamous cell carcinomas of the lung and 8 of 10 adenocarcinomas (lung, colon, uterus, and unknown origin), but absent in 1 renal carcinoma, 1 colon carcinoma, and 4 metastases of malignant melanomas. Normal brain tissue, meninges, and reactive astrocytes did not express HER2. Specificity was confirmed in the negative controls, with high intra-observer reproducibility ($\kappa = 0.89$; $SE = 0.11$).

Wang *et al*^[23] demonstrated in their study that HER-2 overexpression in human malignant meningioma cells led to a significant increase in cell proliferation, migration, and invasion by promoting cell cycle progression from the G1 to S phase and reducing apoptosis. Conversely, HER-2 downregulation results in decreased proliferative and invasive capacities, causing cell cycle arrest in the G0/G1 phase and increased apoptosis. Furthermore, variations in HER-2 expression affected phosphoinositide 3-kinase (PI3K) and AKT protein levels, suggesting a functional link between HER-2 signaling and PI3K/AKT pathway activity in cellular invasion.

Özer and colleagues^[24] studied 55 samples of sporadic meningiomas, with 83.65% of the tumors being grade 1, 14.54% grade 2 (atypical), and 1.81% grade III (anaplastic). An increase in HER-2/neu gene copy number was observed in seven patients, including one with grade 2 and another with grade 3 tumors. Additionally, two patients exhibited a single signal for the HER-2/neu gene region, confirmed by hybridization with the chromosome 17p13.1 (p53) probe.

Arnli and colleagues^[25] evaluated 186 patients, of whom 129 tumors were benign (grade I), 56 were atypical (grade II), and 1 was anaplastic (grade III). High expression of the 6B12 antibody was significantly associated with survival, whereas no other HER-2 antibodies demonstrated a significant association with survival outcomes. Thus, HER-2 expression is generally upregulated in human meningiomas, and the expression of the active receptor is clinically relevant.

Telugu *et al*^[26] evaluated HER-2 expression in prospective and retrospective studies, detecting its overexpression in 30–43% of cases, with higher prevalence in grade II/III tumors and tumor recurrences. This overexpression was associated with cell proliferation, tumor invasion, and reduced apoptosis mediated by the PI3K/AKT pathway, whereas HER-2 silencing significantly reduced proliferation and angiogenesis. An inverse correlation between HER-2 and PRs, absent in more aggressive tumors, was also identified, along with associations with c-MYC and chromosomal deletions, which are linked to higher aggressiveness and recurrence. Distinct immunohistochemical HER-2 staining patterns reflect biological heterogeneity. Thus, HER-2 plays a central role in the biology of meningiomas, and the HER-2/PI3K/AKT pathway emerges as a promising target for targeted therapy.

Ongaratti *et al*^[27] evaluated 60 patients with meningioma, of which 48 were grade 1 and 12 were grades 2 and 3, and showed the expression of markers such as merlin, NDRG2, ERBB2, and c-MYC. Merlin was expressed in all samples, while NDRG2 was positive in 93.3%, ERBB2 was detected in 88.3% of cases, and c-MYC was positive in 38.3%. However, there was no significant association between

tumor grade and the expression of merlin, NDRG2, or ERBB2, or between these expressions and sex, age, recurrence, or tumor regrowth.

Schlege *et al*^[28] conducted an immunohistochemical study that demonstrated homogeneous immunoreactivity to the gp185 oncoprotein encoded by c-erbB-2 in all tumor cells of 59 meningiomas; however, there was no significant correlation between gp185 expression and the histological subtype, degree of anaplasia, sex, or age of the patients. Western blot analysis revealed that all meningiomas expressed gp185. Southern blot analysis revealed the presence of a single copy of the c-erbB-2 gene in meningiomas and normal brain tissue, in contrast to the marked amplification observed in the SK-BR-3 breast cancer cell line.

Wang *et al*^[29] used IOMM-Lee cells transfected with three lentiviral shRNA vectors for HER2 to evaluate HER2 protein expression, finding that shRNA2 had the highest efficiency in reducing HER2 protein and mRNA levels. HER2 gene silencing significantly reduced cell proliferation (*in vitro*), with an inhibition rate of 68.05% after 96 h ($P < 0.01$), and decreased Ki-67 and vascular endothelial growth factor (VEGF) levels ($P < 0.05$ and $P < 0.01$, respectively). *In vivo* studies showed smaller tumor volumes in the Her2-sh group, with a growth inhibition rate of $56.58 \pm 9.34\%$ ($P < 0.05$). After 34 days, the tumor weight in the Her2-sh group was 0.70 ± 0.23 g, which was significantly lower than that in the control group (1.65 ± 0.30 g, $P = 0.005$), with an inhibition rate of $58.34 \pm 6.37\%$. Immunohistochemistry confirmed a significant reduction in HER2, Ki-67, VEGF, and CD34 expressions ($P < 0.05$). These results indicate that HER2 silencing inhibits meningioma cell proliferation and angiogenesis.

Chozick and colleagues^[30], using immunohistochemistry for erbB-2, identified that all benign meningiomas exhibited membrane staining, while atypical tumors displayed weaker diffuse cytoplasmic staining, with median scores of 5.0 for benign and 1.0 for atypical tumors ($P < 0.0001$). Regarding p53, benign meningiomas showed rare positive cells, whereas atypical tumors exhibited a higher number of positive cells, with median scores of 1.0 and 4.0, respectively ($P < 0.0001$). A significant inverse correlation between erbB-2 and p53 expression was observed ($P < 0.0001$). Southern blot analysis revealed no erbB-2 gene amplification, and point mutation analysis of the transmembrane domain in 29 meningiomas showed normal sequences in all the samples.

Table 3 shows the bias assessment of studies.

Discussion

The expression of HER2 in meningiomas was first reported in 1993, when multiple studies confirmed the presence of HER2 protein in these tumors^[22,28]. Given the well-established association between breast cancer and meningiomas, as well as their shared risk factors, Chozik *et al* hypothesized that dysregulated HER2 expression might represent a common pathogenic mechanism underlying both conditions. Their study revealed a notable difference in HER2 expression between normal and atypical meningiomas^[21].

Subsequent investigations using fluorescence *in situ* hybridization have demonstrated HER2 gene amplification in

Table 3
Bias assessment of studies

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Overall risk of bias
Abdelzaher <i>et al</i> ^[19]	Low – Clear recruitment and inclusion strategy.	Low – Standardized procedures used.	Low – Appropriate tools and blinded outcome assessment.	Low – No loss to follow-up reported.	Low – All prespecified outcomes reported.	Low
Chozick <i>et al</i> ^[30]	Low – Recruitment well-documented.	Low – Intervention clearly described.	Low – Pathological confirmation.	Low – No missing data evident.	Low – Transparent results section.	Low
Loussouarn <i>et al</i> ^[20]	Low – Retrospective study but patient selection appears justified.	Low – Data collected using consistent protocols.	Low – Diagnosis confirmed pathologically.	Low – Full dataset analyzed.	Low – No selective outcome reporting.	Low
Mahzouni and Movahedipour ^[21]	Low – Recruitment appears systematic.	Low – Consistent methods.	Low – Pathological diagnoses validated.	Low – No attrition bias noted.	Low – All outcomes discussed.	Low
Ongaratti <i>et al</i> ^[27]	Low – Consecutive patients included.	Low – Imaging and pathology reviewed systematically.	Low – Clear histopathology.	Low – Full cohort analyzed.	Low – Predefined objectives met.	Low
Schlegel <i>et al</i> ^[28]	Low – Inclusion criteria were explicit.	Low – Uniform workup and surgical technique.	Low – Diagnosis confirmed microscopically.	Low – Data complete.	Low – Findings match objectives.	Low
Torp <i>et al</i> ^[22]	Low – Early study, but methodologically sound.	Low – Consistent data acquisition.	Low – Neuropathology confirmed.	Low – Follow-up complete.	Low – No obvious selective reporting.	Low
Wang <i>et al</i> ^[23]	Low – Adequate case series methodology.	Low – Uniform diagnostic approach.	Low – Pathological review undertaken.	Low – All patients accounted for.	Low – Transparent reporting.	Low
Ozer <i>et al</i> ^[24]	Low – Systematic inclusion.	Low – Standard imaging and histopathology.	Low – Pathology used as gold standard.	Low – Minimal to no missing data.	Low – Matches stated objectives.	Low
Wang <i>et al</i> ^[29]	Low – Study well designed with low selection risk.	Low – Procedures clearly defined.	Low – Blinded pathology interpretation possible.	Low – Attrition not an issue.	Low – All outcomes reported.	Low

Joanna Briggs Institute. (2017). JBI critical appraisal tools. The University of Adelaide. Retrieved from <https://jbi.global/critical-appraisal-tools>.

meningiomas, further implicating HER2 in their pathogenesis. Additionally, several studies have proposed that HER2 expression may influence prognosis, as HER2-positive meningiomas are associated with higher recurrence rates than HER2-negative tumors^[19,20,31].

Wang *et al* provided evidence of HER2’s dual role in meningiomas: while HER2 expression inhibited neoplastic cell motility and proliferation by inducing apoptosis and arresting the cell cycle in the G0/G1 phase, overexpression of HER2 was associated with enhanced invasion, migration, and proliferation of tumor cells^[23]. Furthermore, high-grade meningiomas (grades II and III) exhibit greater HER2 expression than low-grade tumors (Grade I)^[20,27]. Nevertheless, conflicting evidence exists, with some studies reporting no significant association between HER2 expression and meningioma characteristics^[21].

Ozer *et al* identified HER2/neu gene amplification in five patients with Grade I meningiomas and in one patient each with Grade II and Grade III meningiomas. The authors hypothesized that HER2/neu gene amplification might influence different stages of tumor oncogenesis^[24]. Notably, HER2/neu-positive meningiomas demonstrated significantly higher recurrence rates than their HER2/neu-negative counterparts, suggesting that HER2/neu could serve as an independent prognostic biomarker for predicting recurrence^[20].

However, our findings diverge from this hypothesis, as the two patients in our study who experienced tumor recurrence did not exhibit HER2/neu gene amplification. This highlights the complex genetic and molecular pathways underlying meningioma progression, particularly the transformation of

benign meningiomas into atypical (Grade II) and anaplastic (Grade III) forms, which comprise approximately 15–20% and 1–3% of all meningiomas, respectively^[32].

HER2 and angiogenesis as a therapeutic target

Wang and colleagues demonstrated that silencing the HER2 gene in human meningioma cells inhibited their ability to proliferate and form new blood vessels. The study suggested that HER2 may play a critical role in regulating the expression of VEGF and CD34. These findings provide a theoretical foundation for considering HER2 as a potential therapeutic target for the treatment of human meningiomas^[23].

HER2/PI3K/AKT pathway and therapeutic strategies

In a related study, Wang and colleagues reported that HER2 overexpression significantly enhanced the invasion and proliferation of human meningioma cells, potentially driving tumor progression and metastasis. This overexpression is clinically associated with a poor prognosis and greater metastatic potential. This study further identified a functional link between HER2 signaling and the PI3K/AKT pathway in promoting cell invasion. Specifically, changes in HER2 expression directly affected the protein levels of PI3K and AKT in IOMM-Lee cells, indicating that the HER2/PI3K/AKT signaling axis may be a viable therapeutic target. These findings underscore the potential for developing novel therapeutic strategies to inhibit cell invasion and metastasis in meningiomas by targeting this pathway^[33–35].

Conclusion

This review highlights the role of HER2 expression in the pathogenesis of meningiomas and potential correlation with tumor grade, suggesting its potential as a biomarker of tumor aggressiveness and a prospective therapeutic target. However, the complexity of HER2's involvement in tumor behavior necessitates further research to fully establish its impact on meningioma progression and recurrence. Validation of this association could lead the way for innovative treatments, including clinical trials exploring trastuzumab (Herceptin) as a targeted therapy, particularly in metastatic and non-resectable cases. To move forward, large cohort prospective studies, standardized HER2-testing protocols for meningioma specimens and clinical trials showing the efficacy of HER-2 targeted therapy are essential. Such advancements may offer improved outcomes for patients with aggressive or refractory meningiomas, aligning with the growing emphasis on precision medicine in neuro-oncology.

Ethical approval

Ethics approval was not required for this review.

Consent

Informed consent was not required for this review article.

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Author contributions

Writing the paper – R.J. and B.C. Study concept or design, data collection, data analysis, or interpretation: I.B., M.G.d.S.B., V.O.d.S., I.I.O., M.K., K.P.P., G.E.U., M.M.K., M.F., E.G.F., N.A., B.C.

Conflicts of interest disclosure

The authors have no conflict of interest to declare.

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Provenance and peer review

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Data availability statement

None.

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