Original article

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The prognostic role of Ki67, p53, Her2, and CyD1 immunohistochemical markers in recurrent parasagittal meningiomas

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Objective. Determine the role of Ki67, p53, Her2, and CyD1 immunohistochemical markers in predicting the recurrence of parasagittal meningiomas

Materials and Methods. The immunohistochemical (IHC) study was conducted in 26 parasagittal meningioma (PM) patients aged 36 to 72, who were treated in the Mechnikov Dnipropetrovsk Regional Clinical Hospital from 2000 to 2021 inclusive. 26 patients were divided into 2 equal groups with the most similar characteristics (patient's gender, age, and meningioma malignancy as of the time of primary surgery) using the balancing method (pairwise selection). The study group consisted of 13 (50%) patients with detected postoperative PM recurrence/prolonged growth, while the control group included the remaining 13 (50%) patients with no PM recurrence. To evaluate prospects of further studies, the expression of the following markers by the tumor was analyzed: cell proliferation (Ki67), genome stability (p53 protein), dysfunction of epidermal growth factor signaling pathways (ERBB2 or Her-2/neu (Her2)), and cell cycle regulators (cyclin D1 (CyD1)).

Results. An association between the PM's high proliferative activity and its recurrence was moderate (r_s=0.44, p=0.025). Median Ki-67 in the study PM group (with recurrence) was three times higher than that in the control group (no recurrence) — 6.0% (4.0%; 9.0%) vs. 2.0% (0.5%; 4.5%) (p=0.029). In the case of Ki67 expression > 4.5%, the risk of PM recurrence/prolonged growth increased by 7.5 times (OR=7.5; 95% CI (1.3–43.0)) (area under the ROC curve, AUC=0.751 (95% CI, 0.544–0.898), p=0.011). The comparative and correlation analysis found no significant association between the p53 protein mutation and the PM recurrence (r_s=0.23, p=0.254). Neither we found a significant association between the PM recurrence and the CyD1 expression (r_s=0.29, p=0.147) or severity (r_s=-0.08, p=0.696). The correlation between the Her2 expression in the PM cells and the PM recurrence was insignificant (r_s=0.23, p=0.251). The primary PM malignancy (Grade II–III) increases the risk of unfavorable prognosis by 5.3 times (95% CI, 1.0–29.4) (AUC= 0.722) (95% CI, 0.513–0.878); p=0.016, sensitivity= 61.5%, specificity= 76.9%.

Conclusions. The following can be considered probable predictors of the PM recurrence after the primary surgery (within 20 years of follow-up): Ki67 proliferation index > 4.5% and grade II–III tumor malignancy. The comparative and correlation analysis found no statistically significant association between the tumor recurrence and the p53, Her2, and CyD1 immunohistochemical markers. However, the detected significant correlation between the p53, Her2, and CyD1 markers expression and the Ki67 proliferative index and tumor malignancy requires further research with a larger number of clinical observations.

Key words: *parasagittal meningioma; parasagittal meningioma surgery; superior sagittal sinus; prolonged growth; recurrence; prognosis; risk factors; Ki67; p53; CyD1; Her2*

Introduction

Meningioma is the most common intracranial tumor, accounting for 18–34% of all primary brain neoplasms. More commonly, meningioma is a benign, slow-growing neoplasm that arises from meningothelial cells [1–3]. According to the WHO classification [3, 4], there are 3 grades of meningioma malignancy, which are distinguished by the histological subtype of the tumor. The predominant Grade I tumors are among meningiomas (about 80.5%) [1, 3], which have a benign clinical course, but recurrent at a rate of 7.0 to 20.0%, mainly in young patients and men [5]. Grade II and Grade III meningiomas occur in 17.7 and 1.7% of cases, respectively. They are characterized by greater mitotic activity, clinically aggressive behavior, and a significantly higher recurrence rate – 29–59 and

60–94%, respectively [1, 3, 6, 7]. The WHO classification does not assess the molecular genetic features of meningiomas, but according to recent studies [8,9] they may be reliable predictors of recurrence, more aggressive clinical behavior, and therefore useful for individualizing treatment tactics.

Parasagittal meningiomas (PM) occur in 24.3–38.6% of cases. According to foreign authors [5, 10, 11], compared to meningiomas of other localization, PMs are more prone to recurrence (from 18 to 40%). This is explained not only by the topographic and anatomical location of the tumor in relation to intracranial structures, which complicates radical and safe surgical intervention [11, 12]. The frequency of detection of Grade II and III meningiomas is also higher among tumors of parasagittal localization. Most authors [10, 12–14] point to the dependence of meningioma recurrence on the patient's gender, the nature of the superior sagittal sinus (SSS) lesion and the radicality of tumor removal. According to other authors [15], the risk of PM recurrence/continued growth increases: 1) by 7.04 times if the initial size is >54 mm; 2) 5.57 times for non-radical tumor removal during primary intervention (Simpson II-V); 3) in 10.1 times with type I-II invasion of PM in the SSS and incomplete removal of the tumor (Simpson II-V); 4) 3.25 times in male patients; 5) in 3.33 times with IV type of invasion in SSS (according to M.P. Sindou and J.E. Alvernia). However, even under favorable conditions, cases of tumor recurrence are observed. Meningiomas of other localization, such as those of the cerebellopontine angle, the location of which in relation to intracranial structures also significantly complicates surgical intervention, are less likely to recur/continue growing than meningiomas of the SSS [16]. Some authors [17–23] attribute such an aggressive clinical course with immunohistochemical and molecular-biological features of SSS meningiomas.

According to the literature, Ki67 is the most significant marker for predicting meningioma recurrence. Ki67 is a nuclear protein expressed in the G1, S, G2, and M phases of the cell cycle, but is absent in the G0 and early G1 phases [21, 24]. It is a marker of cell proliferation, which is statistically significantly correlated with unfavorable clinical prognosis for solid tumors of many locations [22, 23]. According to research data, this protein is effective in determining the proliferation index in meningiomas. It is used in clinical practice because it is associated with mitotic index and histopathological grading in meningiomas [17].

Among other markers, the nuclear phosphoprotein p53 is distinguished, which is a crucial element in the tumor growth suppression signaling pathway due to the cell cycle arrest and the activation of apoptosis. An increase in its expression, as a result of a violation of these processes, is detected in about half of malignant tumors [22].

CyD1 is a proto-oncogene that is a mitogenic sensor, as its role is to regulate the cell transition from the G1 phase of the cell cycle to the S phase [25], after which cell division occurs. Some researchers have reported the presence of a directly proportional relationship between its expression and the degree of meningioma malignancy [26].

Her-2/neu (Her2) is a tyrosine kinase receptor of the epidermal growth factor family (ERBB2). Its overexpression has been detected in a number of malignant human tumors (endometrial adenocarcinoma, breast, stomach, and bladder cancer) [18–20]. According to studies, it correlates inversely proportionally with progesterone receptor expression and directly proportionally with Ki67 [27].

Therefore, the study of the potential role of these immunohistochemical markers in predicting PM recurrence may be useful for choosing the most optimal treatment tactics and postoperative follow-up.

Objective: Determine the role of Ki67, p53, Her2, and CyD1 immunohistochemical markers in predicting the recurrence of parasagittal meningiomas.

Materials and methods

Study participants

The immunohistochemical study was carried out in 26 patients with PM aged 36 to 72 years were treated in the Mechnikov Dnipropetrovsk Regional Clinical Hospital in the period from 2000 to 2021.

Written informed consent was obtained from all patients for conducting the study in accordance with the World Medical Association Declaration of Helsinki on the Ethical Principles of Scientific Medical Research Involving Human Subjects (1964–2008), European Society Directive 86/609 on the Participation of Humans in Medical and Biological Research, as well as by the order of the Ministry of Health of Ukraine, as amended, № 690 dated September 23, 2009.

The study was approved by the committee on ethics and bioethics of Dnipro State Medical University (Minutes № 1 dated February 10, 2020). The work is part of the research work of the Department of Nervous Diseases and Neurosurgery, Faculty of Postgraduate Education, Dnipro State Medical University (state registration number 2 dated February 18, 2020).

Inclusion criteria

Age of patients ≥18 years, parasagittal localization of extracerebral tumor according to the results of computer (CT) and magnetic resonance (MRI) imaging, histological verification of the diagnosis of meningioma.

Characteristics of groups

Two samples with the most similar characteristics (gender and age of the patient, degree of meningioma malignancy at the time of primary surgery) were formed from 26 patients using the balancing method (pairwise selection). The study subgroup was formed by 13 (50%) patients with detected recurrence/continued growth of PM after surgery, the control group consisted of 13 (50%) patients without PM recurrence. There were 8 (62%) female patients and 5 (38%) male patients in both subgroups (p=1.0). The average age was 59 (54; 65) and 58 (50; 65) years (p=0.738).

The duration of the interrelapse period in the study subgroup ranged from 1 to 13 years (median - 3 years (interquartile range - 2-6 years)).

This article contains some figures that are displayed in color online but in black and white in the print edition

To search for promising markers of prognosis and PM recurrence, tumor expression of Ki67, genome stability (p53), dysfunction of signaling pathways (ERBB2, or Hep2) and cell cycle regulators (cyclin D1 (CyD1)) were studied.

The expression severity was assessed for each marker individually:

- to characterize the expression of Ki-67 and p53, the proportion of cells with stained nuclei (percentage of the total number of tumor cells) was calculated - from 0 to 100%;

- immunohistochemical reactions with the CyD1 marker were assessed by a semi-quantitative method with the following levels: 0 – no expression (0%), 1 – weak (<25%), 2 – moderate (25–50%), 3 – distinct (>50%);

- the reaction with the Her2 marker was assessed by a semi-quantitative method: 0 – no staining or in less than 10% of cells, 1 – weak staining of part of membranes in more than 10% of cells, 2 – weak or moderate staining of the whole membrane in more than 10% of cells, 3 - distinct staining of the whole membrane in more than 30% of cells.

Study design

A single-centre retroprospective comparative study.

Pathohistological method

Paraffin blocks of the selected cases were obtained from the archive of the Dnipropetrovsk Regional Pathological Bureau. Sections with a thickness of 4.0 μm were made from them using a Misrom HM340E rotary microtome (Thermo Scientific, Germany). Deparaffinized and rehydrated sections were stained with hematoxylin and eosin, processed immunohistochemically, and studied using an Axio Imager 2 microscope (Zeiss, Germany) at 200, 400, and 630 magnification.

The grade of meningioma malignancy was determined according to the WHO classification [4]: Grade I – benign meningioma, Grade II – atypical meningioma, Grade III – anaplastic meningioma.

Immunohistochemical method

Microtome-derived 4.0 μm thick sections were placed on Superfrost Plus adhesive slides (Thermo Scientific, Germany), deparaffinized, and rehydrated in decreasing concentrations of alcohol. Antigens retrieval was performed by processing sections in a citrate buffer (pH=6.0) for 20 min at a temperature of 100°C using a PT Module (Thermo Scientific, Germany). After cooling and washing in phosphate buffered saline (PBS), endogenous peroxidase was blocked for 10 min at room temperature. Antibodies against CyD1, p53, Ki67 and Her2 (diluted at a ratio 1:1000–1:400, all produced by Abcam (Great Britain)) were used as primary antibodies. Sections with primary antibodies were incubated in a humid chamber at a temperature of 40°C overnight. Subsequent processing was performed using the UltraVision Quanto imaging system (Thermo Scientific, USA) according to the user manual. To differentiate tissue structures, sections were additionally stained with Gill's hematoxylin for 30 seconds.

Statistical processing of results

Data were processed and analazed using Statistica 10 (StatSoft® Inc., USA, license № STA862D175437Q) and MedCalc V.20.218 free trial version (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org/ download.php, 2023). Due to the small sample size and inconsistency with normal law of the distribution of quantitative data (according to the Shapiro–Wilk test), non-parametric characteristics and methods of comparison were used: median (Me), interquartile range (25%; 75%), for pairwise comparisons – the Mann–Whitney test (U), in the case of multiple - Dunn's test (Q). Statistical significance of categorical data differences was assessed by Pearson's chi-square test without Yates correction. Determining the prognostic significance of factors for assessing the probability of tumor recurrence process after surgery was carried out by ROC analysis by determining the point of differentiation of the values of indicator in the groups with and without recurrence while calculating the area under the ROC curve (AUC) and operational characteristics (sensitivity and specificity). ROC analysis was considered adequate at AUC values >0.5 [28]. The risk of recurrence was assessed by odds ratio (OR) with a 95% confidence interval (CI). The critical level of statistical significance (p) when testing all hypotheses was considered to be ≤0.05, a trend was seen at p<0.1.

Results and discussion

According to results of the morphological study of neoplasm specimens removed during the first surgical intervention, it was established that in each subgroup 10 (77%) PMs were benign (Grade I), 2 (15%) corresponded to Grade II criteria ***(Fig. 1)***, 1 (8%) – Grade III (p=1.0). During the second intervention for tumor recurrence in patients of the study subgroup, Grade I was found in 5 (38%) cases, Grade II – in 2 (16%), Grade III – in 6 (46%) (p=0.047, p=1 .0 and p=0.027, respectively, between subgroups (according to the χ^2 criterion).

Ki67 expression in the studied PMs (ranging from 0.5 to 17%) was detected in 23 (88%) cases ***(Fig. 2A)***. A moderate association between high PM proliferative activity and recurrence was found (r_s=0.44, p=0.025). The median Ki-67 level in the study PM subgroup was three times higher than the similar indicator in the control subgroup (p=0.029) ***(Table 1)***.

Ki67 indicator for Grade I meningiomas ranged from 0 to 5%, for Grade II - from 6 to 9%, for Grade III anaplastic meningiomas - from 5 to 17% ***(see Table 1)***.

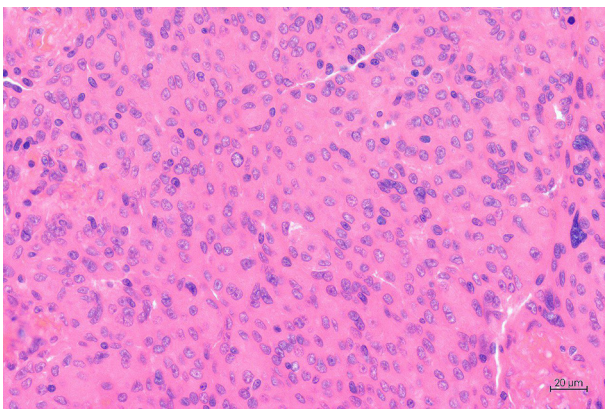

Fig. 1. Atypical meningioma, Grade II, stained with hematoxylin and eosin. ×400

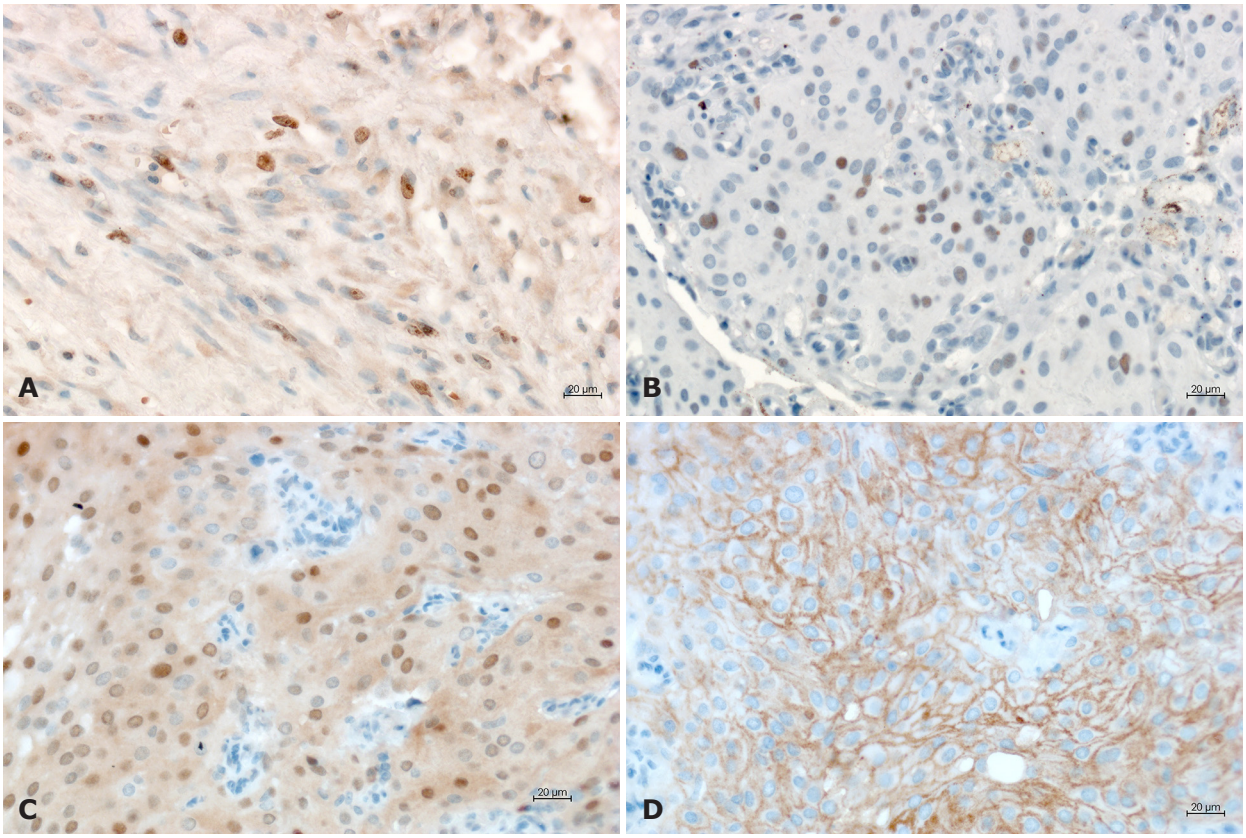

Fig. 2. Immunolocalization of tumor markers in PM (×400): A – nuclear expression of Ki67 in tumor cells outside G0 phase (proliferation index – 6%); B – expression of p53 in the nuclei of tumor cells (positive in 5% of cells); C – nuclear and weak cytoplasmic expression of CyD1 in tumor cells (positive nuclear reaction in 43% of cells); D – membrane expression of Her2 in tumor cells (reaction in more than 10% of cells)

Hence, there is a close correlation between proliferative activity and the grade of malignancy of PM (r_s =0.84, p<0.001).

Expression of p53 in meningiomas was found in 96% of cases (25 of 26), but in 2 (8%) cases it did not exceed 1%. The maximum value of its expression (38%) was recorded in recurrent PM. Overall, the mean level of p53 expression in PM was 5.0 (2.0; 8.0)% ***(Fig. 2B)***.

A statistically significant correlation of p53 expression with the grade of PM malignancy (r_s =0.50, p=0.010) and tumor proliferative activity (r_s=0.58, p=0.002) was revealed. The p53 expression rate ranged from 0 to 16% in Grade I, from 5 to 38 in Grade II (p=0.050 according to Dunn's criterion), from 2 to 18 in Grade III (p=0.124 and p=1.0 compared to Grade I and Grade II, respectively) ***(Table 2)***. According to comparative and correlational analysis, no statistically significant relationship between p53 protein overexpression and PM recurrence was found (r_s =0.23, p=0.254).

Pronounced expression of CyD1 (>50%) was detected in 7 (27%) PM, moderate (25–50%) in 4 (15%) ***(Fig. 2C)***, weak (<25%) in 10 (39%). No expression was detected in 5 (19%) cases, mainly in the nonrecurrent subgroup (31 and 8%, p=0.135 according to the χ^2 criterion). No statistically significant relationship was found between the recurrence of PM and the presence of CyD1 expression (r_s=0.29, p=0.147) or its severity (r_s =–0.08, p=0.696). The expression of this cell cycle marker was directly proportionally correlated with Ki67 expression (r_s=0.52, p=0.007), the grade of tumor malignancy (r_s =0.40, p=0.041), Her2 expression (r_s =0.41, p=0.038). In the absence of CyD1 expression on PM cells, the proliferation index did not exceed 2% and averaged 0.5 (0.5; 2.0) %, whereas the proliferative activity of tumor cells with CyD1 expression ranged from 0 to 17% (5.0 (3.0; 8.0) %, p=0.010 according to the U-criterion) ***(Fig. 3A)***.

Evaluation of CyD1 expression depending on the grade of PM malignancy demonstrated the absence of expression only in Grade I tumor cells. CyD1-expressing cells were detected in all Grade II-III tumors and 67% of Grade I tumors (p=0.033 according to the χ^2 criterion) ***(Fig. 3B)***.

The study of Her2 expression on PM cells showed its absence in 15 (58%) tumors (9 (69%) primary and 6 (46%) recurrent, p=0.234). In the remaining recurrent tumors (7 (54%)), Her2 expression was weak. Hyperexpression of Her2 (pronounced entire membrane staining >30% of cells) was detected in only one case of a non-recurrent tumor, in another case the reaction with this marker was moderate (in more than 10% of cells). Therefore, the correlation relationship between the severity of Her2 expression on PM cells and their recurrence was statistically insignificant (r_s =0.23, p=0.251).

Analysis of Her2 marker expression in relation to clinical and morphological characteristics of PM and other biomolecular markers of cell growth revealed the

Table 1. Ki67 marker expression rates in primary and recurrent parasagittal meningiomas

Indicator	Number of observations	Me (25%;75%)	p*	Correlation coefficient
PM group	26	4,3 (2,0;6,0)	–	–
Study subgroup	13	6,0 (4,0;9,0)	0,029	0,44 (p=0,025)
Control subgroup	13	2,0 (0,5;4,5)		
Grade of malignancy:				
Grade I	15	2,0 (0,5;4,0)	p_{G1-G2}=0,015 p_{G1-G3}<0,001 p_{G2-G3}=1,0	0,84 (p<0,001)
Grade II	4	7,0 (6,0;8,5)		
Grade III	7	9,0 (6,0;16,0)		

* – The difference between the study and control subgroups was evaluated using Mann-Whitney test, between subgroups by the grade of malignancy - using Dunn test.

Table 2. Marker p53 expression patterns in primary and recurrent parasagittal meningiomas

Indicator	Number of observations	Me (25%;75%)	p*	Correlation coefficient
PM group	26	5,0 (2,0;8,0)	–	–
Study subgroup	13	5,0 (2,0;9,0)	0,246	0,23 (p=0,254)
Control subgroup	13	4,0 (1,0;5,0)		
Grade of malignancy:				
Grade I	15	2,0 (1,0;5,0)	p_{G1-G2}=0,050 p_{G1-G3}=0,124 p_{G2-G3}=1,0	0,50 (p=0,010)
Grade II	4	12,5 (5,0;29,0)		
Grade III	7	7,0 (3,0;9,0)		

* – The difference between the study and control subgroups was assessed using Mann-Whitney test, between subgroups by the grade of malignancy - using the Dunn test.

presence of a direct proportional statistically significant association with Ki67 (r_s =0.59, p=0.001), tumor grade (r_s =0.49, p=0.010) and the presence of cells expressing CyD1 (r_s=0.42, p=0.034). Tumor cells expressing Her2 had a higher proliferative index - 6.0 (5.0; 9.0) and 2.0 (0.5; 4.5) % in the absence of Her2 response with PM cells (p=0.003 by U-criterion) ***(Fig. 4A)***.

The assessment of Her2 expression depending on the grade of malignancy of PM demonstrated no response (no staining or less than 10% of cells) of the specified marker on the cells of Grade I tumors in 80% of cases, whereas Her2-expressing cells were found in 75 and 71% of Grade II-III tumors ***(Fig. 2D)*** and only in 20% of Grade I tumors (p=0.027 according to the χ^2 criterion) ***(Fig. 4B)***.

In 11 (42%) cases, the expression of Her2 and SyD1 was detected, in 5 (19%) – no expression, in 10 (39%) – increasing number of cells expressing CyD1, against a slight background (no staining or in less than 10 % cells) of Her2 expression.

According to the literature, p53 expression in meningiomas is observed in 10–88% of cases. Some studies have found a directly proportional relationship between the presence of p53 expression and the grade of malignancy of meningiomas [29], while other authors did not record the presence of any relationship [30].

The results of studying the effect of Her2 overexpression on meningioma invasiveness, recurrence rate and grade of malignancy of tumors according to the WHO classification are contradictory. Its

expression ranges from 2 to 100%. Her2 is reported to be more frequently detected in benign meningiomas, namely meningothelial and secretory ones [17–19]. According to some early studies, there is an inversely proportional relationship between increased Her2 expression and the tumor malignancy grade, but other sources refute this association[31]. Recent studies have found that Her2 does not correlate with meningioma malignancy grade, which was confirmed by us on the example of PM [18].

It has been established that in some cases, overexpression of CyD1 may be induced by Her2 [25], but there are no studies confirming this association in meningiomas. CyD1 expression in intracranial meningiomas is directly proportional to the Ki67 proliferative index and tumor malignancy grade [26]. Some authors consider the association between the meningioma malignancy grade and CyD1 expression to be questionable. However, a number of studies have demonstrated that a quantitative increase in its expression indicates a high probability of recurrence, whereas an induced decrease in its synthesis promotes clinical remission [26].

Some authors have found a correlation between the presence of progesterone receptors and meningioma recurrence. The majority of cases (66.7%) of meningiomas had progesterone receptors. Among typical meningiomas (Grade I), the progesterone receptors content was 78%, among atypical (Grade II) - 62.4%, among anaplastic (Grade III) - 29.5%. In the absence of progesterone receptors, Ki67 levels were found to be significantly higher than in meningiomas that had such receptors [24].

We did not study progesterone receptors expression, but according to the results of comparative and correlational analysis of primary and recurrent PMs, no statistically significant association was found between tumor recurrence and most of the studied immunohistochemical cell cycle markers (p53, Her2, CyD1), which may be explained by a small number observations, but confirms the results of most previous studies. An exception is the indicator of proliferative activity of the tumor. According to many studies, Ki67 is a predictor of worse prognosis for meningiomas. Its expression >3% indicates a greater tendency of meningiomas to recur [22, 23]. A meta-analysis of 53 articles (6,498 patients with meningiomas) demonstrated the existence of a correlation between Ki67 and the degree of malignancy. The average rate of Ki67 for Grade I meningioma corresponded to 3% (1–16%), for Grade II – 8% (2–20%), for Grade III – 17% (7–32%), for primary meningiomas – >2% , for recurrent – >4%.

In our study, Ki67 was moderately associated both with worse prognosis (r_s = 0.44, p=0.025) and with other studied markers (r_s=0.52, r_s =0.59, p<0.01). All immunohistochemical markers were statistically significantly correlated with the degree of PM malignancy: for Ki67 – r_s =0.84 (p<0.001), for p53 – r_s =0.50 (p=0.010), for CyD1 – r_s =0.40 (p=0.041), for Her2 – r_s =0.49 (p=0.010). This gives reason to consider indicators of proliferative activity and degree of tumor malignancy as predictors of PM recurrence after primary surgical treatment. Their prognostic potential was assessed by ROC analysis. It was found that Ki67 expression >4.5% increased the risk of recurrence/continued growth of PM by 7.5 times (OR – 7.5, 95% CI – 1.3–43.0, AUC – 0.751 (95% CI – 0.544–0.898), p=0.011). This criterion has good characteristics of sensitivity (69.2%) and specificity (76.9%) ***(Fig. 5A)***.

The grade of malignancy of primary PM (Grade II-III) increased the risk of an unfavorable prognosis by 5.3 times (95% CI – 1.0–29.4), AUC – 0.722 (95% CI – 0.513–0.878), p=0.016, sensitivity – 61.5%, specificity – 76.9%) ***(Fig. 5B)***.

Therefore, an increase in the Ki67 proliferation index >4.5% and II-III tumor malignancy grade can be considered statistically significant predictors of PM recurrence after primary surgical intervention (within 20 years of follow-up). The role of p53, Her2, and CyD1 markers in predicting PM recurrence is the subject of further research. The statistically significant correlation of the expression of p53, Her2 and CyD1 markers with the Ki67 proliferative index and tumor grade malignancy that we found, as well as the statistically significant correlation of these markers with each other, requires further study involving a larger number of clinical observations.

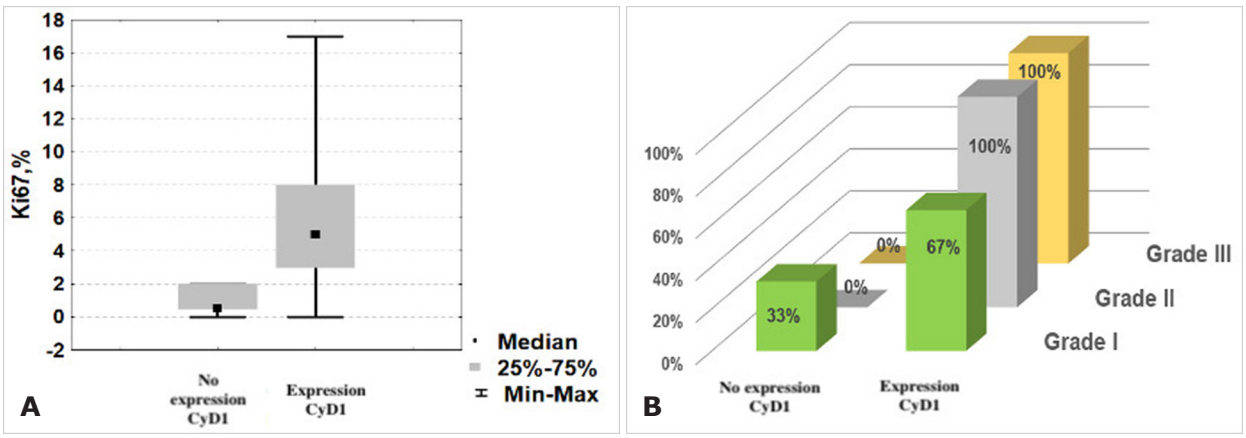

Fig. 3. Expression of CyD1: A – depending on the expression of Ki67 in meningiomas; B – in PM with different degrees of malignancy

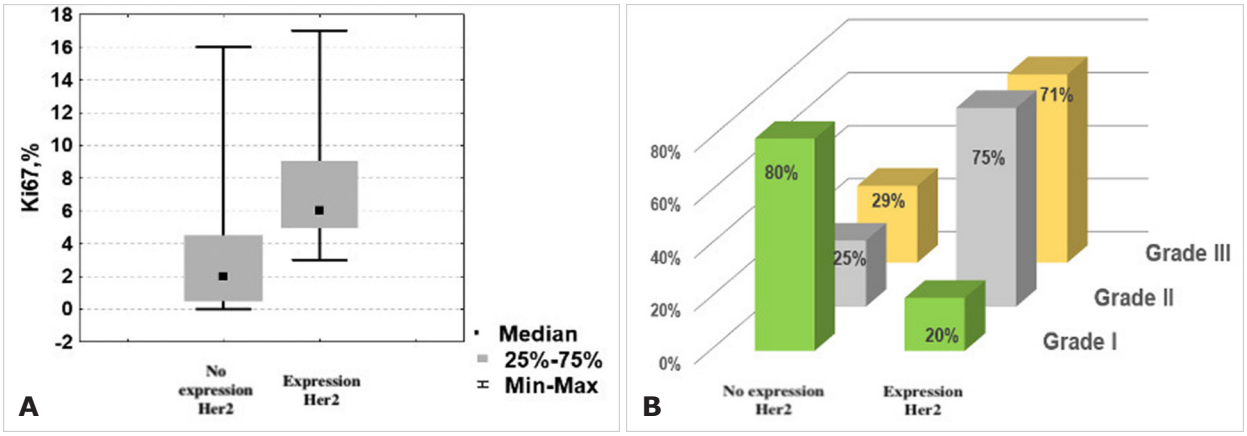

Fig. 4. Her2 expression: A – depending on Ki67 expression in meningiomas; B – in PM with different grades of malignancy

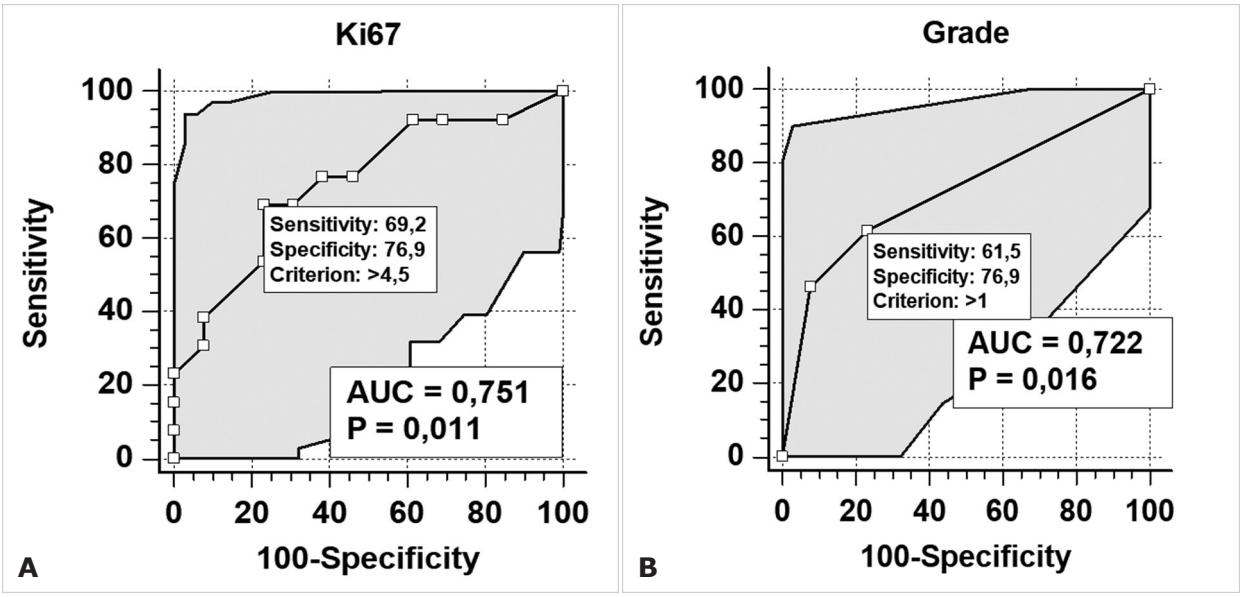

Fig. 5. ROC curves of Ki67 expression indicators (A) and PM malignancy grade (B) in determining the risk of PM recurrence during 20 years of follow-up

Conclusions:

1. Examination of tumor material (PM) must necessarily include not only a pathohistological examination, but also immunohistochemical one, irrespective of the degree of meningioma malignancy.

2. Immunohistochemical examination of tumor material should include analysis of the Ki67 marker as a significant predictor of PM recurrence.

3. In case of detection of Ki67 >4.5% and/or II-III grade of PM malignancy, the patient should be given increased attention during postoperative follow-up, as the risk of recurrence increases by 7.5 and 5.3 times, respectively.

4. Adequate analysis of these findings will help the neurosurgeon to plan the optimal postoperative management, which will contribute to improving the outcomes of treatment of patients with PM.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients during the study comply with ethical standards of institutional and national ethics committees, and the Declaration of Helsinki (1964) and its amendments or similar ethical standards.

Informed consent

Informed and voluntary written consent to participate in the study was obtained from each patient.

Funding

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