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RELATIONSHIP BETWEEN HISTOMARKERS AND THE RISK OF RECURRENCE OF INTRACRANIAL MENINGIOMA AND REHABILITATION POTENTIAL

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ABSTRACT

The article presents an analysis of the influence of tumor proliferative activity Ki-67, microvascular density CD34, depth of invasion into brain tissue and radicality of surgical resection on the risk of recurrence of intracranial meningiomas, as well as their relationship with rehabilitation potential. Inclusion of these four parameters in postoperative risk stratification allows reasonable planning of adjuvant therapy and rehabilitation, as well as individualization of patient monitoring.

KEY WORDS: *Meningiomas, Tumor Activity, Angiogenesis, Invasion, Quantification, Prognosis, Relapse, Rehabilitation*

Meningiomas are primary intracranial tumors, accounting for 30 to 37% of all central nervous system neoplasms in adults aged 65 years and older [1,2]. Women are affected 2 to 3 times more often than men (ratio of approximately 2.3:1), which may reflect the role of hormonal factors such as estrogen and progesterone in the pathogenesis of the disease [3]. A classic risk factor is previous irradiation of the head and neck, especially in childhood, with even low doses of ionizing radiation associated with an increased likelihood of developing meningioma decades later [4]. Genetic predisposition is manifested predominantly in neurofibromatosis syndrome 2 (NF2), where the risk of meningioma increases by more than 50-fold [5]. Other putative factors, such as long-term use of hormone replacement therapy in women and some rare hereditary syndromes (e.g. Gardner syndrome), require further study. High prevalence and predominantly benign course (WHO Grade I) make meningiomas an important target for neuro-oncology and neurosurgery. However, up to 20-25% of tumors demonstrate atypical (Grade II) or anaplastic (Grade III) features with more aggressive behavior and high risk of recurrence [1,3]. Thus, a deep understanding of the epidemiological features of meningiomas is important for the development of screening strategies, assessment of the need for observation, and optimization of treatment tactics and rehabilitation of patients.

A central role in the risk stratification of intracranial meningiomas recurrence. Among them, the most important are the Ki-67 index , reflecting the proportion of cells in the cell cycle phase (mitosis); microvascular density (CD34), which allows for a quantitative assessment of the degree of angiogenesis in the tumor; microscopic invasion into the brain ≥ 3 mm, which serves as a marker of aggressive behavior and increases the risk of early recurrence by almost 4 times; the degree of resection (Simpson classification), which closely correlates with morphological signs of benignity and a reduced risk of recurrence. Complete resection reduces the likelihood of recurrence by 60-70% compared to Simpson III-V [4].
Integration of these markers into postoperative stratification allows for the identification of patients at «high risk» of recurrence for adjuvant therapy and more frequent surveillance.

THE AIM OF THE RESEARCH

The aim of the research is to evaluate the influence of independent histopathological predictors on the risk of relapse after surgical treatment and their informativeness in calculating the rehabilitation potential.

MATERIALS AND METHODS.

We examined 124 patients aged 32 to 75 years (average age 56 ± 12 years; 61% women) after surgery for single meningiomas stratified by grades I-III. The distribution by tumor grade was as follows: Grade I - 82 patients (66.1%), Grade II - 32 patients (25.8%), Grade III - 10 patients (8.1%) (Fig. 1 and Fig. 2).

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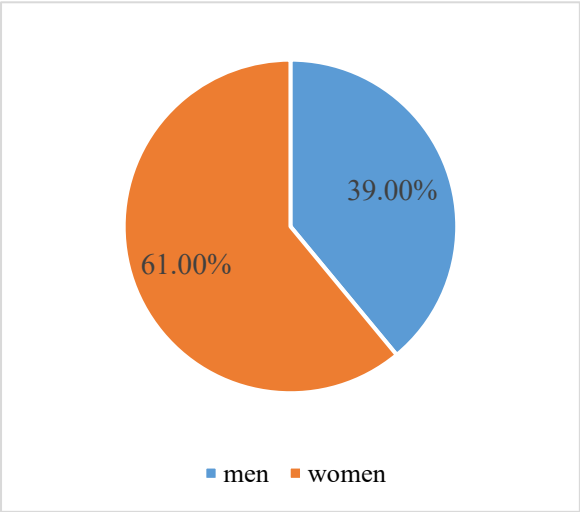


Fig. 1. Gender Distribution

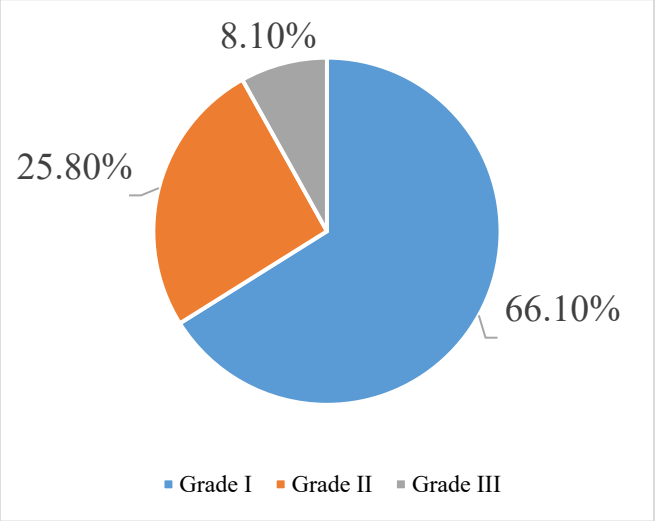


Fig. 1. Distribution of patients by grades

To all patients Histological analysis was performed in accordance with WHO recommendations 2021. The Ki-67 index was determined immunocytochemically according to the Baay protocol et al. (2018). The result was expressed as a percentage of positive cells. Microvascular density (CD34) was quantified: the average number of vessels in five fields ×400 (HPF) according to the Ribalta method et al . (2004). The depth of invasion was measured microscopically in millimeters (maximum penetration of tumor strands into the brain); invasion was considered ≥ 3 mm. Radicality of removal or assessment of the extent of resection were classified according to the Simpson IV scale based on intraoperative data and control MRI in the first 72 hours after surgery. Patients were followed clinically and by MRI every 6 months for a minimum of 24 months.

All obtained data were subject to statistical analysis using SPSS 13.0 software.

RESULTS OF THE RESEARCH

During the study, the assessment of histological markers of proliferation and angiogenesis revealed that the average values of the Ki-67 index and microvascular density (CD34) significantly differed between grades ($p < 0.001$) (Table 1).

Table 1
Histological markers of proliferation (Ki-67) and angiogenesis (CD34) in patients with meningiomas of different grades

Marker	Grade I (n=82)	Grade II (n=32)	Grade III (n=10)
Ki-67, %	2.15 ± 0.18%	7.65 ± 0.40%	18.73 ± 1.37%
CD34, vascular/HPF	8.06 ± 0.31	16.02 ± 0.68	21.55 ± 2.11

Note: Values are given as average ± standard error and range.

As can be seen from the table, there is a distinct gradation of the proliferative and angiogenic activity of meningiomas depending on their grade. The Ki-67 index increased from 2.15 ± 0.18% (range 0.20-5.46%) in Grade I to 7.65 ± 0.40% (4.07-15.88%) in Grade II and 18.73 ± 1.37% (13.36-25.54%) in Grade III. A more than 8.7-fold increase in Ki-67 from Grade I to Grade III reflects an increase in mitotic activity and serves as a reliable indicator of the biological aggressiveness of the tumor. Considering that the Ki-67 threshold > 8% is associated with high risks of relapse, in our data it is patients with Grade III who fall into this category, which confirms the need for their more intensive postoperative monitoring.

Microvascular density by CD34 also increased with increasing grades: 8.06 ± 0.31 vessels/HPF (2.07–11.70) for Grade I, 16.02 ± 0.68 (8.30–24.80) for Grade II, and 21.55 ± 2.11 (7.55–30.99) for Grade III. A two-fold or more increase in CD34 from Grade I to Grade II and almost a three-fold increase to Grade III indicates increased angiogenesis in more malignant meningiomas . Given that high vascular density promotes both tumor growth and microscopic tumor remnants after resection, the need for adjuvant therapy and close monitoring of patients with CD34> 12 vessels/HPF seems justified.

When studying The depth of tumor invasion and the frequency of deep invasion revealed a clear relationship between the depth of meningioma invasion into the brain tissue and the risk of its recurrence (Table 2). The average depth of tumor penetration into the brain increased from 0.92 ± 0.07 mm in Grade I to 2.50 ± 0.14 mm in Grade II and 4.51 ± 0.18 mm in Grade III. This progression reflects the increasing aggressiveness of tumors with increasing grade. The frequency of deep invasion (≥ 3 mm) increased from 4% in Grade I to 47% in Grade II and 80% in Grade III. The presence of invasion ≥ 3 mm was associated with a 3.8-fold increase in the odds of early recurrence (OR = 3.8; 95% CI 1.8-7.9; $p < 0.001$). This highlights the clinical significance of the morphological marker “depth of invasion” for risk stratification of patients.

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Table 2
Tumor invasion depth, deep invasion rate (≥ 3 mm), and 5-year recurrence rates by grade meningiomas

Grade	Depth of invasion, mm (M ± SE)	Invasion ≥ 3 mm, %	Five-year relapse, %
Grade I	0.92 ± 0.07	4%	9.8%
Grade II	2.50 ± 0.14	47%	28.1%
Grade III	4.51 ± 0.18	80%	60%

Notes: Differences in five-year relapse rates are significant (log-rank test, $p < 0.001$).

Five-year recurrence rates also correlated with the depth of invasion: Grade I - 9.8%, Grade II - 28.1%, Grade III - 60% (log-rank test, $p < 0.001$). Thus, patients with deep infiltrative growth (≥ 3 mm) require more aggressive postoperative monitoring and consideration of adjuvant treatment methods (radiotherapy, targeted therapy), even with macroscopically radical resection. From a neurosurgeon's point of view, these data allow predicting difficulties in achieving a clean ("barrier") resection margin and justifying a decision on extended adjuvant therapy or more frequent MRI controls. Taken together, the depth of invasion acts as an independent and pragmatic marker of meningioma aggressiveness , which is of direct importance for planning individual treatment tactics.

Analysis of the data presented in Figure 3 confirms the key role of radical surgical removal in the prevention of meningioma recurrence.

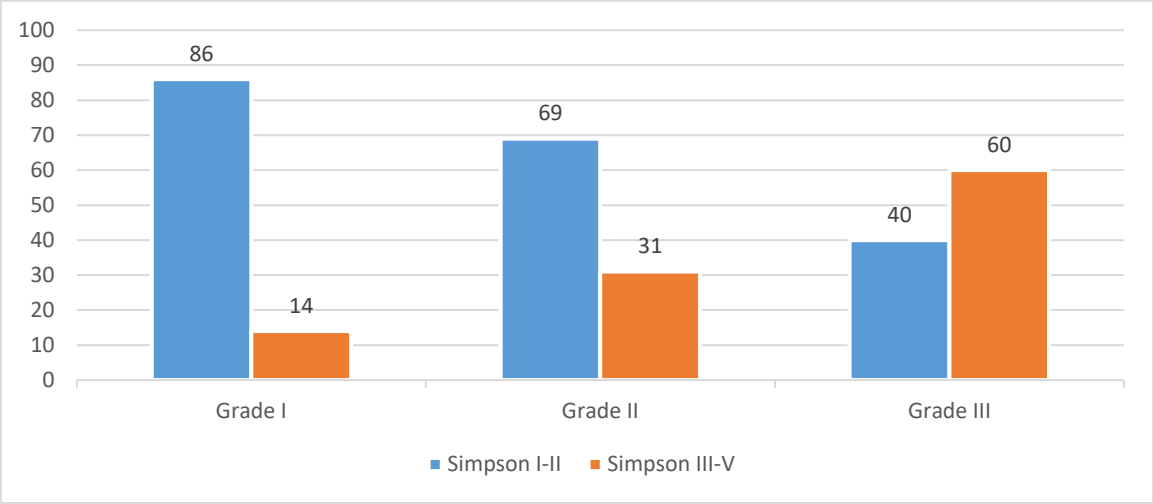


Fig. 3. Degree of radicality of resection according to grades meningiomas

Radical resection of Simpson I-II was achieved in 86% of Grade I tumors, 69% of Grade II tumors, and only 40% of Grade III tumors ($\chi^2 = 17.8$; $p < 0.001$**).** A decrease in the proportion of Simpson I–II resections with increasing tumor aggressiveness reflects both the more pronounced invasiveness and vascularization of high-grade tumors and their proximity to critical neuronal structures, which limits the possibilities of extirpation without the risk of neurological complications. Less radical interventions (Simpson III-V) were associated with a 2.6-fold increase in the odds of recurrence (OR = 2.6; 95% CI 1.3-5.4; $p = 0.007$**).** From a clinical point of view, this means that patients who fail a Simpson I-II resection for anatomical or functional reasons are automatically placed in a high-risk group for recurrence.

Thus, the degree of radicality of removal remains one of the most controllable prognostic factors. Its increase even by a few percent in Grade II and III patients can significantly reduce the risk of recurrence and improve long-term outcomes.

Multivariate analysis of relapse factors revealed that Cox proportional hazards models independently increased the risk of early relapse (Table 3) . Multivariate Cox analysis identified four independent factors that significantly increased the risk of early meningioma recurrence: 1. Ki-67> 8% (HR = 5.2; 95% CI 2.1–12.8; $p < 0.001$). Patients with a proliferation index above 8% have a more than fivefold risk of recurrence. 2. CD34> 15 vessels/HPF (HR = 3.7; 95% CI 1.5–9.0; $p = 0.004$). High microvascular density increases the risk of recurrence almost fourfold. 3. Invasion ≥ 3 mm (HR = 3.8; 95% CI 1.8–7.9; $p < 0.001$). Deep invasion is a strong prognostic marker. Even with Simpson I–II resection, residual “microfoci” in the brain tissue may remain, which requires more aggressive postoperative monitoring and discussion of extended therapy, including radiation intervention. 4. Simpson resection III - V (HR = 2.6; 95% CI 1.3–5.4; $p = 0.007$). Incomplete resection increases the risk of relapse by 2.6 times. This confirms the need for maximum radicality of surgical intervention while preserving neurological function.

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Table 3
Multivariate analysis of risk factors for early relapse using the Cox proportional hazard model

Factor	HR	95% CI
Ki-67> 8%	5.2	2.1-12.8
CD34> 15 vessels/HPF	3.7	1.5-9.0
Invasion ≥ 3 mm	3.8	1.8-7.9
Simpson III-V resection	2.6	1.3-5.4

DFS curves obtained from the Kaplan-Meier analysis of relapse-free survival demonstrated significant differences between groups for each marker (log-rank test, $p < 0.001$). The most favorable curve was noted with Ki-67 < 4%, CD34 < 12, no invasion and Simpson I-II resection.

Table 4
Kaplan-Meier analysis of relapse-free survival (DFS) according to marker values

Marker	Favorable group	Log-rank test (p)
Ki-67	<4%	<0.001
CD34	<12 vessels/HPF	<0.001
Invasion	<3 mm	<0.001
Resection	Simpson I–II	<0.001

Note: *the differences between the compared groups are statistically significant (log-rank test, p < 0.001).*

Disease-free survival (DFS) curves confirmed the prognostic significance of all four markers (Table 6). Patients with Ki-67 index below 4% demonstrated 5-year DFS of about 90%**,** while in the group with Ki-67 ≥ 4% this figure decreased to 55% (log-rank test, $p < 0.001$**).** This once again emphasizes that low proliferative activity is a key favorable factor. According to CD34 microvascular density: in patients with CD34 < 12 vessels/HPF 5-year DFS exceeded 85%**,** while with CD34 ≥ 12 it dropped to 60% ($p < 0.001$). Moderate angiogenesis is associated with better controllability of residual tumor. Invasion depth <3 mm provided 5-year DFS of 92% versus 55% for invasion ≥3 mm ($p < 0.001$). It is clearly seen that microscopic brain infiltration is one of the strongest predictors of recurrence. Finally, Simpson I-II radical resections provided 5-year DFS of about 88% **,** while Simpson III-V - only 50% ($p < 0.001$).

Taken together, these results demonstrate that the combination of four markers allows for clear stratification of patients into low and high risk of relapse and justifies an individualized approach to adjuvant therapy and surveillance schedule.

CONCLUSIONS

Comparison with international studies demonstrates the consistency of our data: proliferative (Ki-67), angiogenic (CD34), invasive (depth of infiltration) and surgical (Simpson) factors remain reliable predictors of recurrence. Implementation of these markers into standardized protocols will allow neurosurgeons around the world to develop personalized plans for the management of patients with meningiomas . Taken together, these data confirm that a high Ki-67 index, pronounced angiogenesis (CD34), deep invasion and less radical resection are independent risk factors for both early and long-term recurrence of intracranial meningiomas.

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