

SELLAR AND PARASELLAR MENINGIOMAS - CLINICOPATHOLOGICAL FEATURES AND IMMUNOHISTOCHEMICAL PREDICTORS OF TUMOR GRADE

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SELLAR AND PARASELLAR MENINGIOMAS - CLINICOPATHOLOGICAL FEATURES AND IMMUNOHISTOCHEMICAL PREDICTORS OF TUMOR GRADE. INSIGHTS FROM A RETROSPECTIVE CASE SERIES (Abstract): Sellar and parasellar meningiomas (spMs) represent a rare but clinically challenging subgroup of intracranial tumors due to their proximity to critical neurovascular and endocrine structures. This study **aimed** to provide a comprehensive clinicopathological and statistical evaluation of spMs, with particular emphasis on biological markers associated with tumor aggressiveness. **Materials and methods:** We retrospectively analyzed 15 patients with histologically confirmed spMs treated surgically at Prof. Dr. N. Oblu Emergency Clinical Hospital, Iași, between 2021 and 2025. Demographical, clinical, radiological, surgical, and immunohistochemical data [Ki-67 labeling index (Ki67 LI), progesterone receptor (PR), and p53 expression] were evaluated. Statistical analysis included comparative tests and logistic regression modeling for predictors of WHO grade. **Results:** The cohort showed a marked female predominance (80%), with a mean age of 60.3 ± 13.2 years. Most tumors originated in the sellar region (66.7%). Gross total resection was achieved in 66.7% of cases. Histopathologically, WHO grade 1 spMs predominated (73.3%), while grade 2 spMs accounted for 26.7%. Ki-67 LI values were significantly higher in grade 2 tumors (12.0 ± 2.2 vs. 3.4 ± 1.3 ; $p=0.003$), whereas PR expression was significantly reduced (42.5 ± 18.9 vs. 81.4 ± 14.8 ; $p=0.010$). Logistic regression identified Ki-67 LI (OR=1.85) as an independent risk factor and PR (OR=0.92) as a protective factor for higher tumor grade. **Conclusions:** These findings highlight the central role of tumor biology in sellar and parasellar meningiomas. Ki-67 LI and PR expression represent complementary and clinically relevant biomarkers that improve risk stratification and may guide surgical and postoperative management. **Keywords:** SELLAR MENINGIOMA, KI-67, PROGESTERONE RECEPTOR, TUMOR GRADE, PREDICTIVE BIOMARKERS.

INTRODUCTION

Meningiomas are the most frequent primary intracranial tumors in adults, representing 36-41% of these (1, 2). Intracra-

nial meningiomas are currently classified according to the 2021 World Health Organization (WHO) Classification of Central Nervous System Tumors into grades 1–3,

based on histopathological criteria and selected molecular alterations (3). Although most meningiomas are WHO grade 1 tumor, a clinically relevant subset shows atypical or aggressive behavior, with increased recurrence risk and need for closer postoperative surveillance (3-5). Morphological grading of meningiomas does not always reflect the actual biological behavior, which is why immunohistochemical biomarkers become essential in prognostic stratification (6).

Ki-67/MIB-1 is widely used as a proliferation marker and has repeatedly been associated with higher grade, increased recurrence risk and more aggressive biological behavior (7-9).

Progesterone receptor (PR) expression, in contrast, is generally associated with more differentiated tumor biology and more favorable behavior, whereas reduced or absent PR expression is more frequently observed in higher-grade meningiomas (10).

One small group of intracranial meningiomas are the sellar and parasellar meningiomas (spMs) that may develop from arachnoid cap cell located on the level of the tuberculum sellae, planum sphenoidale, anterior or clinoid processes, sphenoid wing, cavernous sinuses, petroclival region, diaphragm sellae, or clivus (11).

SpMs represent a particularly challenging subgroup of skull base tumors because of their close anatomical relationship with the optic apparatus, pituitary region, cavernous sinus, internal carotid artery and anterior skull base structures (12). On the other hand, these tumors are quite rare, representing approximately 1%-2% of sellar lesions, but are the second most common sellar tumor after pituitary adenomas (13, 14).

In these locations, surgical management

must balance maximal tumor removal with preservation of visual, endocrine and neurovascular function (15-17).

However, spMs are increasingly understood as heterogeneous tumors due to their anatomical origin heterogeneity, clinical variability and sometimes coexistence with other tumors, such as pituitary adenoma (18) or sellar Rathke cleft cyst (19).

The aim of this study was to perform a comprehensive clinicopathological and statistical analysis of a consecutive institutional series of sellar and parasellar meningiomas, with particular focus on tumor biology, as there are only few data on this issue in literature as far as we know.

MATERIALS AND METHODS

We retrospectively identified 15 patients with histologically confirmed sellar and parasellar meningiomas that were surgically treated in Neurosurgical Clinics, Prof. Dr. N. Oblu Emergency Clinical Hospital, Iasi, Romania, in a period of 5 years (January 1, 2021 – December, 31, 2025).

The following demographic, clinical and radiological data were retrospectively extracted from the electronic observation sheets located in the hospital electronic archive: patients' age and gender, tumor localization, meningioma histological subtype, immunohistochemical assessment of Ki67 Labeling Index (Ki67 LI), p53 and Progesterone Receptor (PR) expression, grade of malignancy according to WHO Classification 2021, 5th Edition, type of surgical approach, and extent of tumor resection.

The data was analyzed using *SPSS Statistics version 27.0* (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). Descriptive statistics were calculated for all variables.

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The values were measured as median, mean, and SD according to the considered variables. Comparative analyses between WHO grade 1 and grade 2 tumors were performed using the Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Statistical significance set at $p < 0.05$. Logistic regression analysis was used to identify independent predictors of tumor grade.

RESULTS

The study cohort comprised 15 patients diagnosed with sellar and parasellar meningiomas (tab. I), with a marked predominance of female patients (80%), compared to males (20%), resulting in a female-to-male ratio of 4: 1. The mean age at diagno-

sis was 60.3 ± 13.2 years, with a median of 63 years (IQR: 52–71), and an age range spanning from 32 to 76 years. There was a clear predominance of lesions arising from the sellar region [tuberculum sellae (Fig. 1) and sellar diaphragm] (66.7% of all cases), while the remaining tumors (33.3%) were located in parasellar region (Fig. 2), including the anterior clinoid process of the sphenoid bone and cavernous sinus.

The most frequently used approaches were pteryonal and fronto-temporal (46.7%), followed by frontal and bifrontal (33.3%), and endoscopic endonasal approaches (20%). Complete resection was achieved in 66.7% of patients, subtotal resection in 20% of cases, and partial resection in only 13.3% of cases.

TABLE I.
Demographic, clinical, and surgical characteristics of patients with sellar and parasellar meningiomas (n=15).

Variable	No. of cases	Percentage
Age (years)		
mean \pm SD	60.3 ± 13.2	
median	63 (52-71)	
Gender		
Female	12	80%
Male	3	20%
Tumor location		
Sellar region (tuberculum sellae, sellar diaphragm)	10	66.7%
Parasellar (clinoidian, cavernous sinus)	5	33.3%
Surgical approach		
endonasal endoscopy	3	20%
pteryonal / frontotemporal	7	46,7%
frontal / bifrontal	5	33.3%
Tumor resection type		
total (macro-/microscopical)	10	66.7%
subtotal	3	20%
partial	2	13.3%
Total patients	15	100%

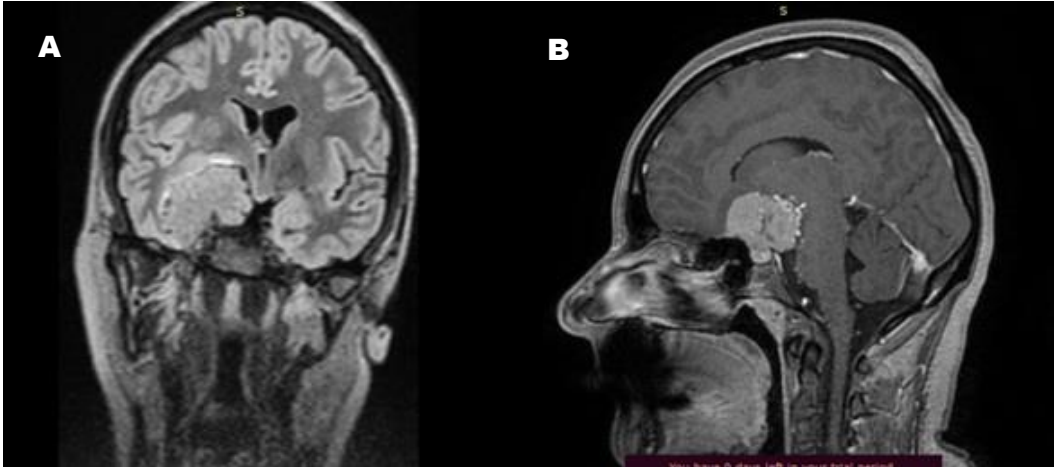


Fig. 1. Craniocerebral Magnetic Resonance Imaging (MRI) of a tuberculum sellae meningioma. (A) sagittal section.; (B) coronal section.

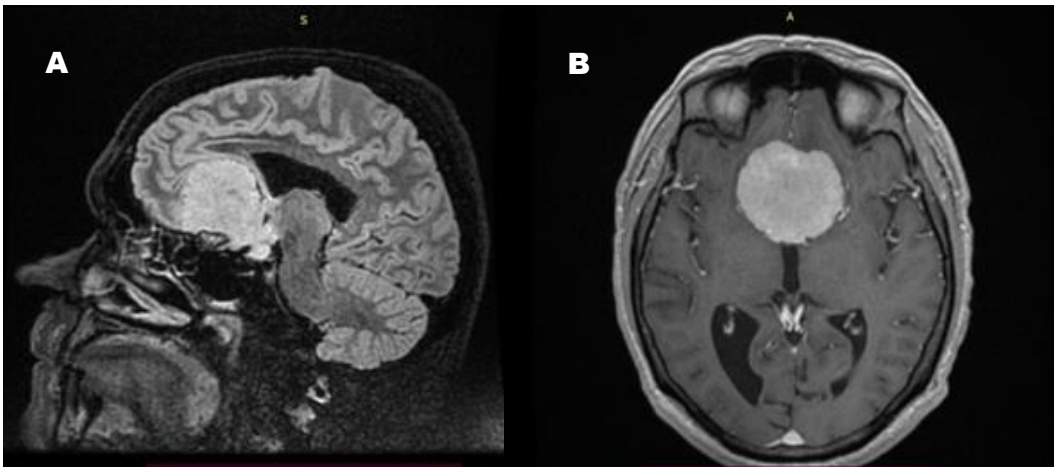


Fig. 2. Craniocerebral Magnetic Resonance Imaging (MRI) of a parasellar meningioma. (A) sagittal section.; (B) axial section.

Final histopathological analysis (tab. II) revealed a predominance of WHO grade 1 spMs (73.3%) (fig. 3), while WHO grade 2 spMs accounted for 26.7% of cases (fig. 4).

The meningothelial subtype was the most frequent (60%), followed by transitional (26.7%) (fig. 3) and secretory subtypes (6.7%). Atypical subtype represented 26.7% of all cases (fig. 4).

Dividing patients into two subgroups according to the degree of malignancy of spMs (tab. III), we found that grade 2 spM patients were younger than grade 1 spM patients (57.5 ± 18.5 years vs. 60.5 ± 12.5) but no statistical significance was found. 81.8% of cases with grade 1 spM and 75% of cases with grade 2 spM were female patients, but no statistical significance was found.

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TABLE II.

Pathological characteristics of patients with sellar and parasellar meningiomas (n=15).

Variable	No. of cases	Percentage
Tumor grade (WHO, 2021)		
Grade 1	11	73.3%
Grade 2	4	26.7%
Histological subtype		
meningothelial	9	60%
transitional	4	26.7%
secretory	1	6.7%
atypical	4	26.7%

Mean percentual value of Ki-67 LI was lower (3.4 ± 1.3) in WHO grade 1 spMs (fig. 3D) and markedly increased (12.0 ± 2.2) in WHO grade 2 spMs (fig. 4D) and these data had statistical significance ($p = 0.003$) (tab. III, fig. 5). Mean percentual value of PR was higher (81.4 ± 14.8) in WHO grade 1 spMs (fig. 3B) and markedly

decreased (42.5 ± 18.9) in WHO grade 2 spMs (fig. 4B), and these data had statistical significance ($p = 0.003$) (tab. III, fig. 5). Positivity of nuclear p53 was more frequently identified in WHO grade 2 sellar and parasellar meningiomas (Fig. 4C), but without statistical significance ($p = 0.077$) (tab. III).

TABLE III.

Comparison of demographic and surgical features, as well as immunohistochemical markers of sellar and parasellar meningiomas (n=15) according to their WHO grade.

Variable	Who Grade 1 (N = 11)	Who Grade 2 (N = 4)	p-Value
Age, years, mean \pm SD	60.5 \pm 12.5	57.5 \pm 18.5	0.743
Age, median (IQR)	63 (56–69)	61 (52.3–66.3)	-
Female	9/11 (81.8%)	3/4 (75%)	1.000
Male	2/11 (18.2%)	1/4 (25%)	-
Ki-67, %, mean \pm SD	3.4 \pm 1.3	12.0 \pm 2.2	0.003
Ki-67, median (IQR)	3 (3–3.5)	12.5 (11.3–13.3)	-
PR, %, mean \pm SD	81.4 \pm 14.8	42.5 \pm 18.9	0.010
PR, median (IQR)	90 (75–90)	35 (30–47.5)	-
p53 positive	2/11 (18.2%)	3/4 (75%)	0.077
Complete resection	7/10	2/4 (50%)	0.580

We performed a logistic regression analysis for the prediction of WHO Grade 2 meningioma for the present cohort ($n = 15$) using tumor grade as the dependent variable (0 = Grade 1; 1 = Grade 2) and as independent variables we chose the biological variables Ki-67 LI (%), PR (%), and p53 (positive vs. negative).

Table IV shows that for every 1% increase in Ki-67 LI, the risk of diagnosing a grade 2 spM will increase by 85% and that a

1% increase in PR will decrease the risk of identifying a grade 2 spM by 8%. Regarding p53, an increased OR (≈ 4.5) was identified, but without statistical significance.

The model combining Ki-67, progesterone receptor expression, and p53 status demonstrated excellent discriminative ability (AUC = 1.00) for prediction of WHO grade 2 meningiomas (fig. 2), although the small sample size may lead to overestimation of performance.

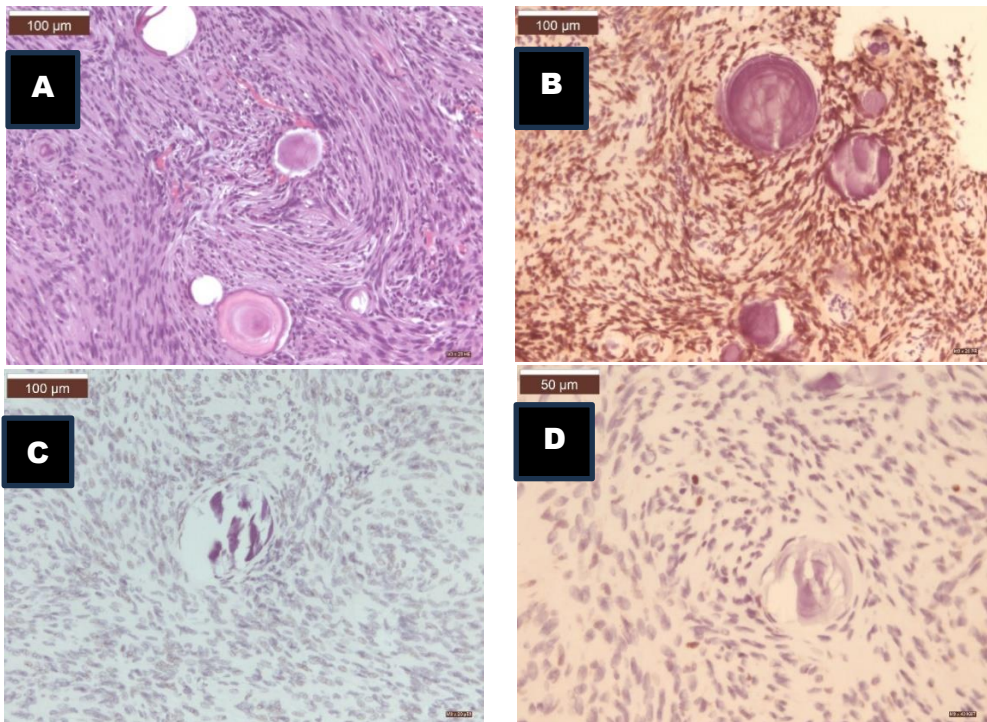


Fig. 3. Microphotographs of a grade 1 parasellar meningioma, transitional subtype.

(A). Meningothelial tumor cells with fibroblastic appearance formed syncytial structures and were disposed in fascicles or whorls. The tumor cells presented indistinguishable cell membranes and bland nuclear features. Numerous psammomatous bodies were randomly scattered throughout the tumor mass. (HE, x200). (B). Almost all cells showed intense nuclear immunopositivity for Progesterone Receptor (Immunohistochemistry, x200); (C) Tumor cells did not demonstrate nuclear immunostaining for p53 (Immunohistochemistry, x200); (D). Ki67 LI exhibited low values ($\leq 4\%$) (Immunohistochemistry, x400).

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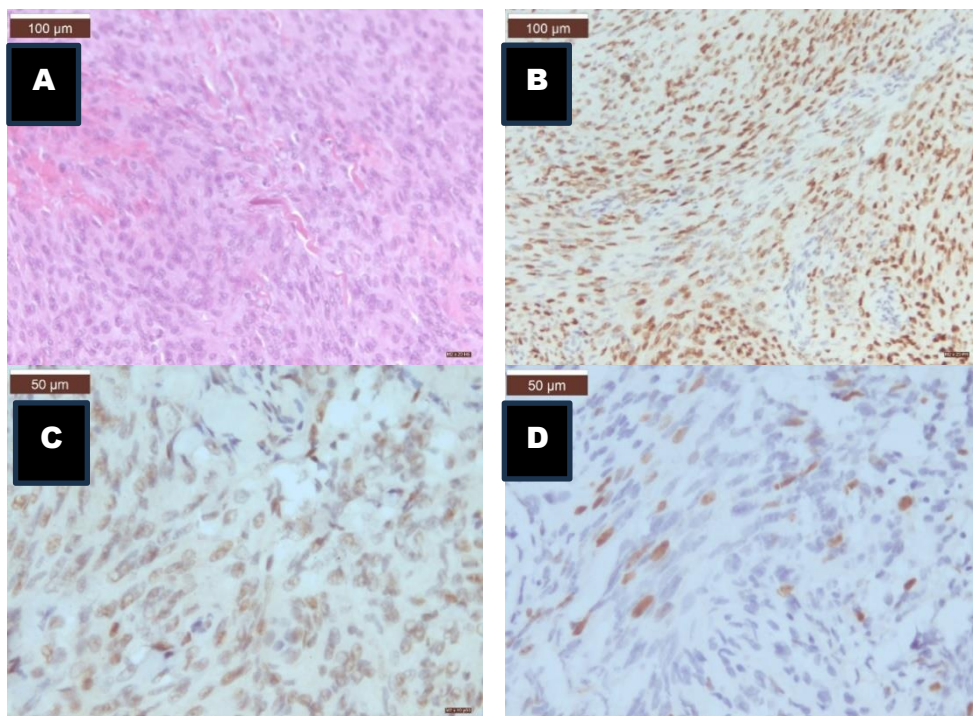


Fig. 4. WHO Grade II meningioma, atypical subtype. (A). Meningothelial tumor showing sheeting architecture, increased cellularity, and macro nucleoli (HE, x200); (B) The tumor showed nuclear immunopositivity for Progesterone Receptor varying from one area to another, with some areas having immunopositivity in 100% of the nuclei, others having it in 50% of the nuclei (Immunohistochemistry, x200); (C) Tumor cells demonstrated moderate nuclear immunostaining for p53 in almost all tumor cells (Immunohistochemistry, x400); (D). Ki67 LI exhibited higher values (Immunohistochemistry, x400).

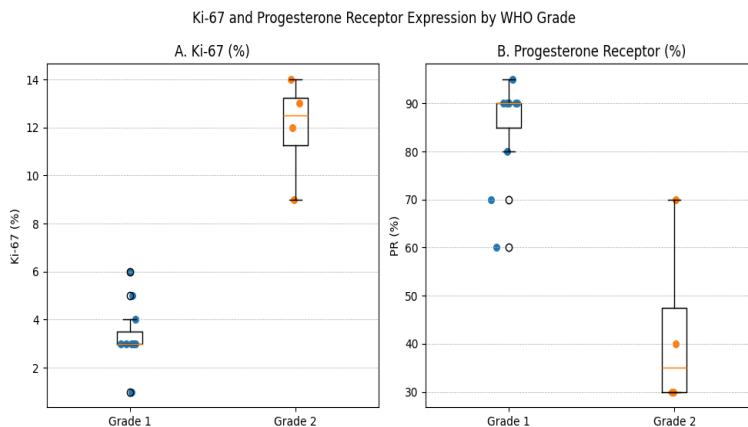


Fig. 5. Distribution of Ki-67 LI values (A) and progesterone receptor (PR) expression (B) in sellar and parasellar meningiomas according to their WHO grade.

TABLE IV.
Logistic regression analysis of immunohistochemical predictors of WHO grade 2 sellar and parasellar meningiomas in the present study

Variable	Odds Ratio (OR)	C.I. 95%	p-Value
Ki-67 (%)	1.85	1.20 – 3.90	0.01
PR (%)	0.92	0.86 – 0.98	0.02
Positive p53	4.50	0.70-35.0	0.11

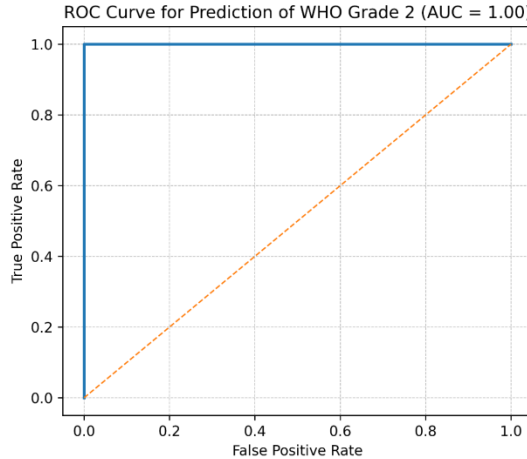


Fig. 5. Receiver operating characteristic (ROC) curve for the prediction of WHO grade 2 sellar and parasellar meningiomas in the present study.

DISCUSSION

The present study provides a comprehensive clinicopathological and statistical evaluation of sellar and parasellar meningiomas. The majority of cases in our study were clustered in the sixth and seventh decades of life, which represent a decade (20) or even two decades later (21) than previous studies realized on spMs thus reflecting a particularity for the present cohort.

The majority of the patients in the present study were females, and this result was similar to the gender ratios in studies realized on meningiomas in general who found out a F: M ratio=3.8: 1 (22). But studies focusing on spMs revealed an even higher ratio. Kwancharoen *et al.* (20) highlighted

the fact that spM are common in females, with F: M ratio of 6: 1.

In our study, tumor anatomical distribution highlights the predilection of spMs for development in close proximity to the optic apparatus and pituitary region, i.e. tuberculum sellae and sellar diaphragm, explaining the frequent visual and endocrinological symptoms observed in clinical practice (23, 24).

Our study also revealed a heterogeneous but anatomically tailored surgical strategy, and these data are similar to those reported by other authors (25). The fronto-temporal approach was the most used approach, and the same data was reported by some other authors in order to reduce post-surgical

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morbidity (26). Our findings reflect both the technical feasibility of surgery in this region and the anatomical constraints imposed by critical neurovascular structures, particularly in parasellar tumors. SpM resection can vary, depending mostly on the tumor extension, and the pattern of growth (25, 27). In our study, a high rate of complete resection was identified and was associated with grade 1 spMs. Subtotal and partial resections were more frequently encountered in grade 2 spMs, indicating a tendency toward more complex surgical management due to infiltration of the surrounding structures.

Intracranial meningiomas, regardless of their location, are more common of the meningothelial (6) or transitional type (22, 28). Posterior fossa meningiomas are mostly of fibrous subtype (29). In the present series, which included only spMs, we identified a preponderance of the meningothelial subtype as found by other studies focused on parasellar meningiomas (17, 30).

Grade 1 spMs from the present study represented the majority of cases, followed by grade 2 spMs that represented a quarter of all analyzed cases. This proportion of higher-grade tumors is slightly elevated compared to other studies based on intracranial meningiomas in general (1, 31, 32). Thus, our results can suggest either referral bias toward complex cases or a true enrichment of biologically aggressive lesions in this anatomical region.

When comparing the subgroup of grade 1 and grade 2 spMs, we did not identify significant differences for age, sex, or extent of resection in the present cohort. Ki-67 LI showed significantly higher values in grade 2 spMs compared to grade 1 spMs, supporting the role of Ki-67 as a proliferative marker associated with histological

aggressiveness. PR expression showed the opposite pattern, with higher values in grade 1 spMs and significantly reduced expression in grade 2 spMs. p53 expression was more frequent in grade 2 spMs but did not reach a statistical significance. Thus, the present study highlights the importance of integrating immunohistochemical markers into the evaluation of spMs. However, Ki-67 is a well-established marker of proliferative activity and has been consistently associated with tumor grade and recurrence (2, 33). Guresci *et al.* (34) found that the median survival of patients with meningiomas harboring Ki-67 $\leq 13.2\%$ was 122 months and of those with meningioma revealing Ki67 LI $> 13.2\%$ was only 60 months ($p = 0.004$). Also, the prediction of recurrence based on Ki-67 LI had an acceptable discrimination (AUC = 0.74).

For the present cohort, Ki-67 Li was also shown to be an independent predictor for spMs. Ki-67 LI is not just a descriptive marker, but a major biological determinant of tumor aggressiveness. On the other hand, the results of the present study also showed that PR has an independent protective role for spMs, an aspect also confirmed by Aung *et al.* (35), who showed that high values of PR in meningiomas were associated with longer recurrence-free survival.

We found an inverse correlation between PR expression and malignancy grade of spMs and this fact is also clinically relevant being of interest in predicting tumor aggressiveness and guiding postoperative management. Loss of PR expression may indicate dedifferentiation and increased proliferative potential, i.e. tumor aggressiveness. Similar findings were reported in large cohorts and meta-analyses (35-38).

In the present study, although p53 was

more frequently positive in grade 2 spMs, it did not reach statistical significance in the adjusted model. Therefore, in our cohort, p53 acted as an auxiliary marker, not as a primary determinant. Also, in the literature, p53 is considered a marker of genomic instability, an aspect previously observed by some of the authors of the present study in other types of brain tumors (39), and not an independent predictor for tumor aggressiveness (2, 33). Its role is more evident in grade 3 meningiomas or recurrent tumors (40, 41).

In the present research, using logistic regression analysis, we identified Ki-67 LI and PR expression as independent predictors of WHO grade 2 spMs. The same results were obtained by Akca and Gökçe for intracranial meningiomas (37).

Our predictive model provides a practical clinical tool for estimating the probability of higher-grade spMs based on routinely available parameters.

Combining histology, immunohistochemistry, and statistical methods, these findings align with the broader trend in neuro-oncology (42) toward integrative predictive models to improve clinical decision-making.

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CONCLUSIONS

The present cohort of sellar and parasellar meningiomas demonstrated a typical epidemiological and anatomical profile, combined with a relatively high proportion of grade 2 tumors, and a biologically meaningful immunohistochemical pattern. The present study demonstrates that the behavior of sellar and parasellar meningiomas is primarily driven by tumor biology rather than age, gender or anatomical location. Ki-67 Labeling Index and Progesterone Receptor expression are complementary and independent predictors of tumor grade in sellar and parasellar meningiomas. Their combined assessment provides valuable insights into tumor biology and may improve clinical decision-making. The integration of these two immunohistochemical markers into routine evaluation supports a more personalized approach to meningioma management.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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