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Predictor factors for recurrence in atypical meningiomas

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Abstract

Background and Objectives: Atypical meningiomas (AMs), *World Health Organization* (WHO) grade 2, are a group of tumors with uneven and unpredictable clinical behavior. Our aim was to analyze possible tumor recurrence predictors, and to identify factors that improve progression-free survival (PFS). *Patients, Materials and Methods*: Our retrospective study included 81 patients followed up in the Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania, between 1 January 2010 and 31 December 2020. The histopathological specimens were reviewed according to the *WHO* 2021 criteria. Analyses included clinical, imaging, pathological and surgical factors. *Results*: The tumor recurred in 53.1% of the 81 cases within 60 months of surgery. Tumor location (p<0.000), tumor volume (p<0.010), extent of surgical resection (p<0.000) and dural sinus invasion (p<0.001) were predictive factors of recurrence. Gross total resection (Simpson grade I and II) was achieved in 59.2% of patients. Patients with the tumors located in the brain convexity and volume <26.4 cm^3 had better survival rates up to recurrence. PFS showed a significant relationship between Simpson grade I–III and biopsy (p<0.000) and was statistically influenced by tumor volume and location, and dural sinus invasion. *Conclusions*: AMs are a heterogeneous group of tumors, and we identified posterior fossa location, volume ≥26.4 cm^3, Simpson grade III and IV resection and dural sinus invasion as predictive factors for relapse and a shorter PFS. Whereas certain characteristics provide some prognostic value, future molecular characterizations of AMs are necessary, which will support the clinical decision-making process.

Keywords: atypical meningioma, predictive factor, recurrence, progression-free survival.

Introduction

Meningiomas are the most common central nervous system (CNS) tumors, representing about one third of all primary brain tumors and generally being considered benign [1, 2]. Meningiomas subgroups with malignant and aggressive behaviors have been acknowledged as early as 1940 by Harvey Cushing, who also clarified the numerous confusions regarding histopathological (HP) names [3, 4], whereas the term 'atypical meningioma' (AM) was coined much later, in 1985 [5]. Based on HP criteria, the *World Health Organization* (WHO) performed several classifications of meningiomas, which were divided into three grades (1, 2, 3), the most recent such classification being conducted in 2021 [6]. According to the new reports, AMs account for about 20–30% of all meningiomas [7–9], and their incidence has increased in recent years [10, 11].

Compared to grade 1 meningiomas, AMs have a high risk of recurrence and shorter lengths of overall survival [12, 13]. They have a 7–8 times higher risk of recurrence [13] and the median time to progression is about 24 months [14–16], although some reports have shown tumor progression even within one year of surgery, despite total resection [17]. Regarding their ability to spread at a distance, most of the time, AMs do not metastasize, although such cases have been reported in the literature [18–20].

Clinical examinations of the head and face play an important role in the early detection of various pathologies that can be localized at this level, including intracranial, intraorbital, or cutaneous meningiomas. In some such cases, a multidisciplinary approach involving neurosurgeons, ophthalmologists, maxillofacial surgeons, dentists, dermatologists, and pathologists may even be considered.

Among possible prognostic factors of AMs recurrence, previous studies have reported age [21–24], HP factors [9, 24–27], tumor size [21, 28], tumor location [2, 27, 29–32], imaging features [22, 33–35] and the most important, extent of surgical resection [12, 21, 22, 36–39]. Nevertheless, some of these reports have not succeeded in predicting recurrence and justifying a more aggressive treatment against recurring tumors. Therefore, an appropriate management strategy in AMs has yet to be identified.

Aim

The paper aimed to analyze possible AMs recurrence predictors, and to identify factors that improve progression-free survival (PFS).

Patients, Materials and Methods

Patient selection

This retrospective study included 81 patients followed up in Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania, between 1 January 2010 and 31 December 2020. We included in our study group patients whose HP specimens were available for revision according to the current *WHO* 2021 criteria [6]. The study inclusion criteria were pathological diagnosis of AM (*WHO* grade 2) according to the *WHO* 2021 classification, age over 18 years, absence of any other genetic syndromes (neurofibromatosis, meningiomatosis, etc.) associated with AM and absence of any history of associated intracranial tumor or other neurosurgical condition. This retrospective study was approved by the Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy (Approval No. 25938), and by the Ethics Committee of Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania (Approval No. 19092) and was compliant with the Declaration of Helsinki (1964).

Variables

Each patient's demographic data (age at diagnosis, gender), clinical data (motor deficit, increased intracranial pressure syndrome), pathological reports, intraoperative protocols, pre- and postoperative imaging findings [head magnetic resonance imaging (MRI) scan findings] and time to recurrence/progression were analyzed. PFS was established as the period of time elapsed between surgery and tumor recurrence or progression.

The neuroimaging factors were tumor volume, tumor margins appearance (regular/irregular), peritumoral brain edema (PBE), contrast enhancement (heterogeneous/homogeneous) and tumor recurrence/progression. Tumor volume of meningiomas was assessed using the following formula: volume = $\pi/6 \times$ length $\times$ width $\times$ height [40–42] and was analyzed on preoperative MRI images [contrast-enhanced T1-weighted image (T1WI)]. The mean tumor volume was 26.4 cm^3, and, according to it, the group was divided into tumors <26.4 cm^3 in volume and tumors ≥26.4 cm^3 in volume. PBE was assessed as the hyperintense extension adjacent to the tumor in the T2-weighted image (T2WI) sequence, being assessed using the Hale scale: (0) no PBE – absence of high T2WI signal around the meningioma, (1) mild PBE – ring of high T2WI signal surrounding the tumor, but without mass effect, (2) moderate PBE – more extensive edema, but without mass effect, (3) severe PBE – mass effect on neighboring structures or deep digitiform edema [32].

Tumor recurrence or progression was defined as any contrast enhancement in the tumor remnant bed or increase in size of the tumor remnant. These aspects were assessed in the contrast enhanced T1WI sequence in serial head MRI imaging 12, 24, 36, 48 and 60 months after surgery. In the cases of Simpson III and IV resection, we classified tumor progression as tumor recurrence.

Depending on their location, the tumors were classified as follows: (*i*) skull base, (*ii*) convexity, (*iii*) parasagittal-falcine, (*iv*) posterior fossa, and (*v*) intraventricular meningiomas. Skull base tumors included meningiomas located in the anterior and middle fossa. Posterior fossa tumors included all infratentorial meningiomas, including tentorium or petroclival meningiomas.

The extent of tumor resection was assessed according to Simpson's grading system [43] and was evaluated based on intraoperative protocols and postoperative MRI imaging (contrast enhancement). The pathological diagnosis of AMs was set according to the *WHO* 2021 classification, after reviewing the HP specimens.

The assessed HP and immunohistochemical (IHC) factors were brain invasion by the tumor and IHC expression of Ki-67 labeling index (LI).

Cerebral invasion was assessed as present or absent in the pathological specimens in which its evaluation was possible. Thus, we were able to assess brain invasion aspects in 17 of the 81 patients. Brain infiltration was defined as irregular, digitiform protrusion of the tumor in the cerebral parenchyma, without leptomeninges interposed between the tumor and the brain.

We reviewed the value of the IHC expression of Ki-67 LI in 45 patients out of the whole group. Following the immunohistochemistry protocol used in our previous studies, representative specimens were fixed in 10% neutral buffered formalin, embedded in paraffin and then 4 μm sections were stained with Hematoxylin–Eosin. Furthermore, representative 4 μm sections were processed according to a two-step method (non-Avidin-Biotin, EnVision+, DAKO Corporation) [25] (Table 1).

Table 1 – ***Antibody used in our case series (n=45)***

Antibody	Clone	Manufacturer	Dilution*	Antigen retrieval	Control
Ki-67	Mouse monoclonal MIB-1	DAKO	1/75	Citrate, pH 6	Amygdala

*DAKO Antibody Diluent.

Ki-67 LI was defined as the percent of positive cells counting among 100 tumor cells in the fields with the largest number of positive cells [25]. The Ki-67 LI was analyzed as a variable, and the threshold for interpretation was set as follows: <7%, between 8–10%, and >10%, in accordance with some studies in the literature [44–47], as well as personal experience regarding tumor recurrence. These Ki-67 LI values were established in our attempt to achieve a subclassification of AMs.

Statistical analysis

Statistical data processing was made using Statistical Package for the Social Sciences (SPSS) 24.0 software (SPSS, Inc., Chicago, IL, USA) for Windows. The parameters of descriptive statistics were calculated for numerical data and the frequency distributions were calculated for categorial data. All the data were analyzed as risk factors of recurrence after one, three and five years, using the χ^2 (*chi*-squared) test, and the binary logistic model, as well as predictive factors of PFS, using the Kaplan–Meier method (the Mantel–Cox *log* rank test) and the Cox proportional hazards model. A *p*-value ≤0.05 was considered significant.

Results

Population

Forty-three (53.1%) of the 81 patients included in the study were men, and the patient age range was 34 to 87 years. Female patients were younger (mean age 58.4 years) than male patients (63.4 years), and the difference was statistically significant ($p<0.05$). When it comes to tumor recurrence based on age, we observed that, out of the 40 patients aged over 60, the tumor recurred in 22 patients. As for tumor recurrence based on gender, we did not observe statistically significant differences, as the tumor recurred in over half of both women and men (Table 2).

Location and volume of meningiomas

The most common tumor location was on the convexity (42%, *n*=34), followed by the parasagittal-falx area (25.9%, *n*=21), skull base (21%, *n*=17), and posterior fossa (7.4%, *n*=6). Tumor location statistically influenced tumor recurrence ($p<0.000$), patients with skull base meningiomas (including posterior fossa) being the most exposed (Table 3). Tumors located on the convexity showed better PFS (54.7 months) compared to the posterior fossa, with the shortest PFS (30 months) ($p<0.001$).

Table 2 – ***Demographic characteristics of the patients in our study group (n=81)***

Characteristics	*n* (%)	Recurrence		Recurrence		PFS	
				Univariate analysis	*Multivariate analysis*	*Univariate analysis*	*Multivariate analysis*
		No	*Yes*	*p-value*		*p-value*	
Age [years]				0.733		0.693	
≤60	41 (50.6%)	20	21				
>60	40 (49.4%)	18	22				
Sex				0.415		0.348	
Male	43 (53.1%)	22	21				
Female	38 (46.9%)	16	22				

n: No. of cases; PFS: Progression-free survival.

Table 3 – ***Neuroimaging characteristics of the patients in our study group (n=81), adapted from Cucu et al. (2020) [28]***

Characteristics	*n* (%)	Recurrence		Recurrence		PFS	
				Univariate analysis	*Multivariate analysis*	*Univariate analysis*	*Multivariate analysis*
		No	*Yes*	*p-value*		*p-value*	
Tumor location				**0.000**		**0.000**	
Convexity	34 (42%)	25	9			**0.000**	
Skull base	17 (21%)	3	14		**0.017**	**0.014**	
Parasagittal/falcine	21 (25.9%)	8	13			0.234	
Posterior fossa	6 (7.4%)	0	6			**0.001**	
Intraventricular	3 (3.7%)	2	1			0.597	
Tumor volume [cm^3]				**0.010**		**0.030**	
<26.4	41 (50.6%)	22	18				
≥26.4	40 (49.4%)	16	25				

n: No. of cases; PFS: Progression-free survival.

A significant percentage of 50.6% (*n*=41) had the volume of the meningioma <26.4 cm^3, this statistically influenced the rate of tumor recurrence ($p<0.010$). Therefore, out of the 43 meningiomas that recurred after a 5-year follow-up period, 25 had a volume ≥26.4 cm^3, while 18 tumors had a volume <26.4 cm^3 (Table 3). Detailed information about these correlations between tumor volume, anatomical localization, and tumor recurrence has been extensively published in a previous study [28]. Additionally, we also observed that patients under the age of 60 had tumor volumes greater than 26.4 cm^3 in 58.5% of cases.

The symptoms were unspecific and depended on tumor location. Intracranial hypertension syndrome occurred in 75.3% (*n*=61) of the patients, and 37 (45.7%) patients had motor deficit on admission. Out of the 37 patients with motor deficits upon admission, 23 experienced tumor recurrence over a 5-year follow-up period. Additionally, among the 61 patients with intracranial hypertension syndrome upon admission, 32 presented tumor recurrences during the same 5-year follow-up period. No statistical correlation was observed between tumor location or symptoms and recurrence, although we noted that patients with motor deficit on admission had PFS shorter by 7.9 months.

Radiology

MRI scan showed homogeneous enhancement in 45 (55.6%) tumors and irregular tumor margins in 59% of the cases. Between homogeneous enhancement and recurrence, we noted no statistical correlation. Out of the 45 patients with homogeneous meningiomas, 22 experienced recurrences,

while among the 36 patients with heterogeneous meningiomas, 21 had recurrences. Regarding the appearance of PBE, most patients (37%) had severe edema, followed by moderate (22.2%) and mild edema (22.2%). PBE was absent in 18% of the cases. We noted no statistical correlation between imaging findings and tumor recurrence or PFS.

Most patients (59.3%, *n*=48) had meningiomas with an irregular appearance, and among these, 60.41% relapsed over a 5-year follow-up period. Furthermore, out of the 33 meningiomas with a regular appearance, 19 did not recur after five years. Although the appearance of the tumor margin did not significantly influence the rate of tumor recurrence (p=0.111) or PFS (p=0.067) from a statistical point of view, it is worth mentioning that patients with regular-appearing meningiomas had a better average PFS (52 months) compared to patients with irregular-appearing meningiomas, who had a shorter average PFS (43.7 months). All neuroimaging characteristics of the meningiomas are shown in Table 4.

Table 4 – ***Neuroimaging characteristics of the meningiomas in our study group (n=81)***

Characteristics	*n* (%)	Recurrence		Recurrence		PFS	
				Univariate analysis	*Multivariate analysis*	*Univariate analysis*	*Multivariate analysis*
		No	*Yes*	*p-value*		*p-value*	
Tumor margins				0.111		0.067	
Regular	33 (40.7%)	19	14				
Irregular	48 (59.3%)	19	29				
Peritumoral edema				0.811		0.794	
Absent	15 (18.5%)	8	7				
Mild	18 (22.2%)	9	9				
Moderate	18 (22.2%)	9	9				
Severe	30 (37%)	12	18				
Enhancement				0.397		0.265	
Homogeneous	45 (55.6%)	23	22				
Heterogeneous	36 (44.4%)	15	21				

n: No. of cases; PFS: Progression-free survival.

Correlations between the appearance of tumor margins (irregular *versus* regular) and the appearance of peritumoral cerebral edema, enhancement, tumor location, tumor volume, recurrence, and PFS have been studied and previously published in a separate study [48].

Pathological data

Given that, as indicated by Brokinkel *et al.* [49], the brain parenchyma is not often included in the sample examined by the pathologist, in our study, brain invasion could be evaluated only in 17 patients, occurring in 12 (70.6%) of them. Out of the 12 cases, the majority of meningiomas (*n*=7) were located on the cerebral convexities. Although we did not identify a statistically significant relationship between brain invasion and tumor recurrence, we observed that when brain invasion was present, meningiomas recurred earlier, within the first 12 months following surgery. Furthermore, in cases where there was no brain invasion, tumors recurred later, at 48 months. Although we did not identify any statistically significant correlation, patients with brain invasion had lower PFS (43 months) than patients without invasion (55 months).

Ki-67 LI was performed in 45 cases (55.5% of all meningiomas). Tumors with Ki-67 LI >10% expression had the highest mean volume (54.7 cm^3), unlike meningiomas with Ki-67 LI <7% expression, which had a mean volume of 45.4 cm^3. Even though we did not observe any statistically significant relationship between the Ki-67 LI value and the tumor recurrence, meningiomas with average Ki-67 LI values <7% had lower recurrence rates in the first 36 months. On the other hand, meningiomas with average Ki-67 LI values between 8–10% and >10% recurred earlier, after 12 months, with percentages of 22.2% and 20%, respectively. We did not find any statistical correlation between HP characteristics and tumor recurrence or PFS. All pathological characteristics of the patients are shown in Table 5.

Table 5 – ***Pathological characteristics of the patients in our study group (n=81)***

Characteristics	*n* (%)	Recurrence		Recurrence		PFS	
				Univariate analysis	*Multivariate analysis*	*Univariate analysis*	*Multivariate analysis*
		No	*Yes*	*p-value*		*p-value*	
Brain invasion	17/81			0.563		0.487	
Present	12 (70.6%)	6	6				
Absent	5 (29.4%)	3	2				
Ki-67 LI	45/81			0.663		0.709	
<7%	26 (57.8%)						
8–10%	9 (20%)						
>10%	10 (22.2%)						

LI: Labeling index; *n*: No. of cases; PFS: Progression-free survival.

Surgery

Simpson grade I resection was performed on 12.3% of the patients (eight cases with convexity and two with intraventricular meningiomas), while Simpson grade II resection was on 46.9% of the patients (of these 38 cases,

19 tumors were located in the convexity and 10 in the parasagittal-falcine area). Subtotal resection was performed for 33 patients: Simpson grade III resection in 19.8% (of these 16 cases, four tumors were located in the parasagittal-falcine area and four in the skull base) and Simpson grade IV resection in 21% (of these 17 cases, seven tumors were located in the parasagittal-falcine area). Tumor bed hemorrhage was the most common complication after surgery (10 patients out of 15), but it required surgical removal in a single case. An important statistical correlation was noted between surgical resection and tumor recurrence (p<0.000).

Multivariate analysis confirmed the prognostic significance of Simpson grade III or IV resection [p<0.000; hazard ratio (HR) 0.206; confidence interval (CI) 0.082–0.516]. The extent of resection also significantly improved PFS, and we noticed an important statistical significance between them (p<0.000). Thus, the PFS of patients with Simpson grade I, II, III and IV resections were 56.4, 55.5, 44.2 and 25.4 months, respectively.

Twenty-six of the 81 tumors were located in the proximity of the venous sinuses, and 15 of them showed tumor invasion. Dural sinuses invasion had a strong statistically significant influence on tumor recurrence (p<0.001), as all tumors with sinus invasion recurred during the 5-year follow-up period. The PFS of patients with sinus invasion was 27.2 months compared to patients with no invasion (55.6 months) (p<0.001). The size of the meningiomas also influenced sinus invasion (p<0.047). 66.7% (n=10) of the 15 meningiomas invading the dural sinuses had a tumor volume >26.4 cm^3, and most tumors that invaded the dural sinuses were meningiomas of the superior sagittal sinus (n=9). On the other hand, multivariate analysis has shown that skull base meningiomas and Simpson grade III and IV resection are prognostic factors of recurrence. All the patient characteristics are shown in Table 6.

Table 6 – *Surgical characteristics of the patients in our study group (n=81)*

Characteristics	*n* (%)	Recurrence		Recurrence		PFS	
				Univariate analysis	*Multivariate analysis*	*Univariate analysis*	*Multivariate analysis*
		No	*Yes*	*p-value*		*p-value*	
Extent of surgical resection				**0.000**		**0.000**	
Simpson grade I	10 (12.3%)	9	1				
Simpson grade II	38 (46.9%)	25	13				
Simpson grade III	16 (19.8%)	4	12		**0.000**		**0.001**
Simpson grade IV	17 (21%)	0	17		**0.000**		**0.001**
Dural sinuses vicinity	26/81			**0.001**		**0.000**	
Invasion	15 (57.7%)	0	15				
No invasion	11 (42.3%)	7	4				
Complications	15/81	5	10	0.243		0.549	
Hematoma	10						
Hydrocephalus	1						
Convulsions	2						
Neurological deficit	2						

n: No. of cases; PFS: Progression-free survival.

Recurrence

53.1% (n=43) of the patients had tumor recurrences during the 5-year follow-up period (Figure 1). The recurrence rates 12, 24, 36, 48 and 60 months after surgery were 8.6% (n=7), 12.3% (n=10), 9.9% (n=8), 16% (n=13) and 6.2% (n=5) (Figure 1).

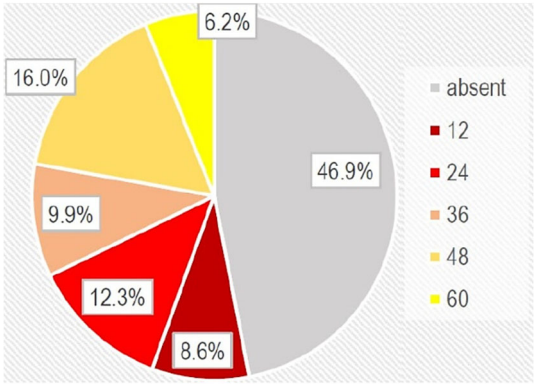

Figure 1 – *The distribution of tumor recurrence rates over a 60-month period (n=81).*

In our study, we observed that tumor recurrence was more prevalent in patients over 60 years old (55%, n=22), and it was more frequent among females (57.9%). Analyzing the risk factors, we found that after one year, Simpson grade I–II resections were protective factors against tumor recurrence, while Simpson grade III–IV resections were risk factors for recurrence. Practically, patients with Simpson grade IV resections had a 10-fold higher risk of tumor recurrence after one year compared to other patients (CI 1.193–91.408).

Analyzing the risk factors in terms of predicting tumor recurrence within three years, we identified five associated risk factors: (*i*) symptom onset between 6–12 months, (*ii*) tumor location in the posterior fossa, (*iii*) Simpson grade III–IV surgical resection, (*iv*) tumor volume ≥26.4 cm^3, and (*v*) invasion of the dural sinuses. Within five years, tumor recurrence is also influenced by meningioma location at the base of the skull (Figure 2) and by Simpson grade III or IV resection.

Analyzing the overall time of recurrence, we observed a median PFS of 47.1 months, with a range between 43.4 and 50.7 months. PFS was significantly influenced by (*i*) the anatomical location of the meningioma, (*ii*) tumor volume ≥26.4 cm^3, (*iii*) the extent of surgical resection (Simpson grade resection), and (*iv*) invasion of the dural sinuses. The univariate Cox regression showed that tumor location, tumor volume, extent of surgical resection, and dural sinus invasion were associated with the risk of recurrence (Figure 3).

When analyzing the factors that influenced the survival of patients until tumor recurrence, we introduced them into a Forward Stepwise Cox regression model to observe their hierarchy and the way they influence one another when acting simultaneously. We excluded cases with invasion of the dural sinuses as they were few and would significantly reduce the sample size. Among the factors used, the Cox regression model identified a single important factor, surgical resection with Simpson grade III or IV (HR 0.206, CI 0.082–0.515).

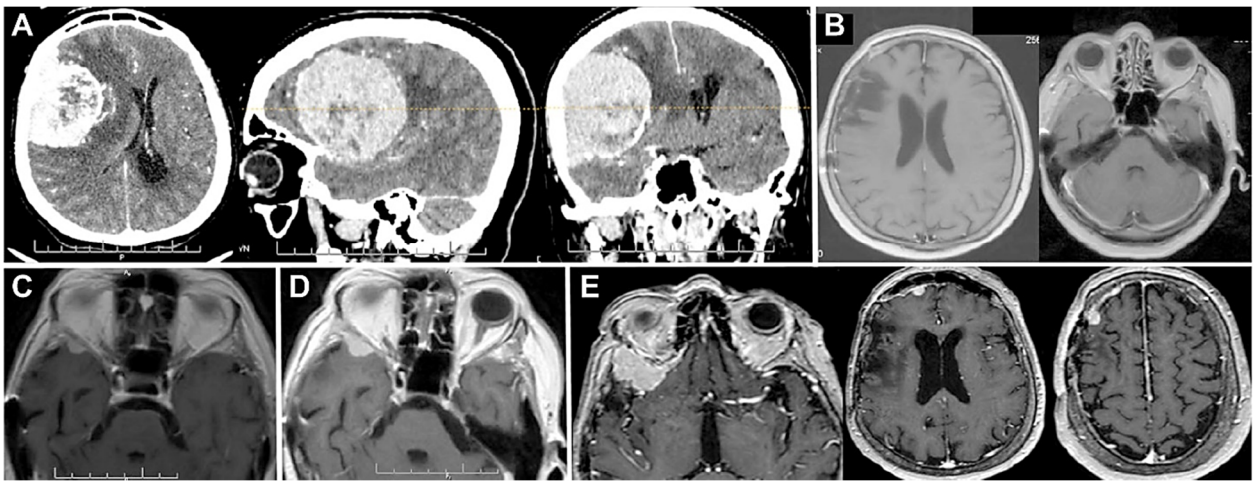

Figure 2 – ***Recurrence of atypical meningioma: (A) Axial sagittal coronal contrast-enhanced CT showing a right pterional meningioma with strong and heterogeneous enhancement in a 58-year-old man; (B) Postoperative axial contrast-enhanced T1W MRI at 12 months showing absence of recurrence; (C) Axial contrast enhanced T1W MRI showing recurrence at 36 months, (D) at 48 months, and (E) at 60 months. Also, in the image (E) it can be observed the appearance of distant tumor nodules at 60 months after surgery. CT: Computed tomography; MRI: Magnetic resonance imaging; T1W: T1-weighted.***

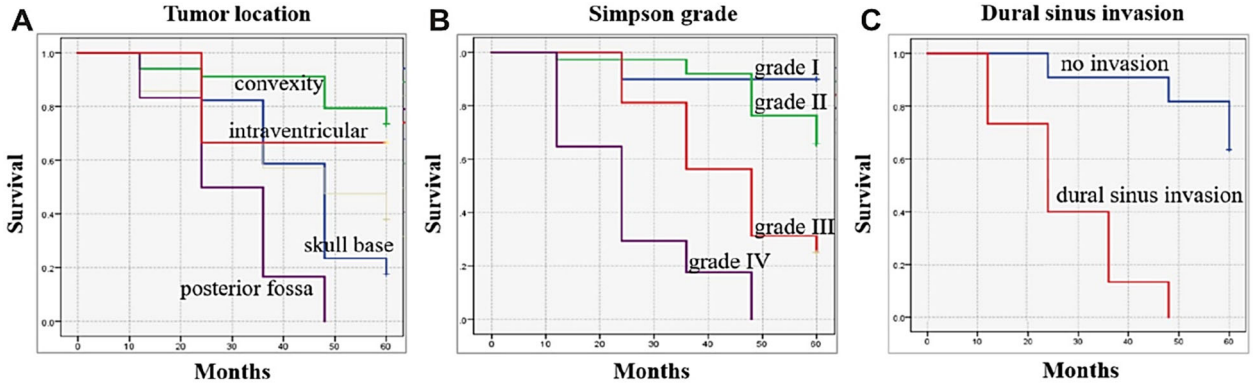

Figure 3 – ***Kaplan–Meier recurrence-free survival curves for tumor location, Simpson grade resection and status of dural sinus invasion.***

Discussions

In this retrospective study of prognostic factors of recurrence from single-institution cases of AMs, we analyzed the benefit and utility of clinical, radiological, pathological, and surgical findings in predicting tumor recurrence and improving PFS.

Tumor location

Regarding concerns the anatomical location of tumors in intracranial space, previous studies have suggested that there may be a relationship between the location and recurrence rate of meningiomas [29–31, 50, 51]. Thus, some authors argued that parasagittal [2, 31, 32], skull base [30] or posterior fossa locations were risk factors of recurrence [31, 52].

Tumor location on the convexity is most frequently cited in literature as being associated with good outcome, both in terms of recurrence and PFS, this being explained by the high rate of complete resections at this level [23, 52–54]. Thus, some authors have reported that tumor location on the brain convexity is associated with better survival rates compared to other locations, such as the parasagittal-falcine area or skull base [55], and especially the posterior fossa [23, 53]. We noted the same in patients with AMs on the convexity, who had the lowest recurrence rate of all anatomical locations and the longest PFS (Figure 3).

The highest tumor recurrence rate (100%) was experienced by patients with posterior fossa meningiomas, who relapsed early, *i.e.*, within the first 12 months after surgery, and who also had the lowest PFS. These findings support those of other authors who also reported the posterior fossa as a negative prognostic factor of recurrence [31, 52]. This may be related to the high rate of incomplete resection due to the ample representation of the dural sinuses at this level [56]. Moreover, recent studies have shown that meningiomas occurring in the midline and posterior fossa have tumor necrosis factor receptor-associated factor 7 (TRAF7) receptors and Krüppel-like factor 4 (*KLF4*) mutations, which are associated with a more aggressive biological behavior [57].

Tumor volume

Previous studies have linked tumor size to tumor recurrence and poor patient survival rates. Thus, Fernandez *et al*. argued that large meningiomas, such as those >45 mm, are associated with early tumor recurrence [58], whereas Garzon-Muvdi *et al*. concluded in their research that it is not only a prognostic factor for relapse, but also of PFS and overall survival [52]. Nakasu *et al.* also pointed out that the mean size of 44±14 mm influenced tumor recurrence, unlike non-recurring meningiomas whose diameters were 35±15 mm [59]. Moreover, various studies have shown that small AM size is a protective factor against tumor recurrence [21, 58, 60]. In line with these previous studies, we also noted that >26.4 cm^3 meningiomas had higher recurrence rates. The results have been previously published in one of our earlier studies [28].

Extent of surgical resection

Concerning AMs treatment, surgical resection should be the first treatment option. In this regard, most literature studies have shown that total tumor removal is associated with better local tumor control than subtotal tumor removal [23, 38, 61–63].

Total tumor removal (Simpson I–II) was accomplished in 59.2% of the patients in our study, which was in line with data reported by other authors. In literature, Simpson I–II resection grade ranges from 36.4% to 100%, whereas the Simpson III–IV resection grade varies within the 18–60% range [22, 32, 34, 35, 57, 62–64]. We noted an important statistically significant correlation between the extent of surgical removal and recurrence (p<0.000). Thus, we may conclude that the extent of surgical resection is an important prognostic factor for relapse, in agreement with most previous studies [23, 29, 37, 65–68]. Also, the tumor recurrence rate over a 5-year period in Simpson I, II, III and IV grade resections, respectively, was 10%, 34.2%, 75% and 100%, in line with literature studies, which have reported recurrence rates for grade II and III meningiomas of 9–50% after total resections [22, 26, 27, 38, 69–73] and of 36–83% after subtotal surgical resections [38, 74].

In our series, the extent of surgical resection (Simpson grade) statistically significantly influenced PFS, in agreement with other authors [31, 64, 75]. Thus, a statistically significant relationship was noted between PFS and the Simpson I (p<0.012), Simpson I–II (p<0.000) or even Simpson I–III (p<0.000) resection grades (Figure 3). The mean PFS was 56.4 months, 55.5 months, 44.2 months, and 25.4 months after Simpson I, II, III and IV surgical resections, respectively.

We may say that a more extensive surgical resection will be associated with better PFS, which was also claimed by other literature studies, which recommend total resection as much as possible to improve PFS [53, 74].

Dural sinus invasion

Invasion of the dural sinuses significantly statistically influenced the extent of surgical removal (p<0.001). Most of the tumors that invaded the venous sinuses (73.3%) were resected Simpson grade IV, followed by Simpson III resection in 20% of these cases. This fact influenced the relapse of meningiomas, in agreement with other studies that have depicted that recurrence is related to the extension of surgery [76–79].

In accordance with Murata *et al.* [80] and Marks *et al.* [81], we noted statistically significant differences between venous sinus invasion and tumor recurrence rates. AMs that had infiltrated the dural sinuses recurred faster, this being since the invasion of the dural sinuses makes it difficult to remove the tumor fully and safely [82]. In another study of 328 patients with meningiomas infiltrating the superior sagittal sinus, Caroli *et al*. noticed that the extent of tumor resection significantly influenced the recurrence rate, with a mean recurrence of 6.8 years for grade 1 meningiomas and 4.7 years for grade 2 and 3 meningiomas [83].

The presence of invasion of the dural sinuses strongly influenced the statistical significance of PFS (p<0.000), in agreement with other authors [82]. Patients with venous sinus infiltration had the lowest mean PFS (27.2 months), in contrast to patients without dural sinus invasion, who had a better mean PFS (55.6 months) (Figure 3). In a study carried out on a group of patients with grade 1, 2 and 3 parasagittal meningiomas, Colli *et al*. (2006) showed that malignant meningiomas had the lowest PFS, followed by grade 2 and grade 1 meningiomas. Moreover, they noted a significant difference between grade 1 and 2 meningiomas, but not between grade 2 and 3 meningiomas [84].

Study limitations

Our study has a few limitations, the most important being due to its retrospective design and small number of patients. Also, our follow-up period was only five years, which is short in our opinion. Therefore, we advise extending the duration of follow-up periods to be able to identify delayed recurrences in patients in a more effective manner.

Conclusions

We identified a group of prognostic factors of tumor recurrence with strong statistical significance: the extent of surgical resection, the anatomical location of meningiomas, tumor volume ≥26.4 cm^3, and invasion of the dural sinuses. Among them, complete surgical resection (Simpson I and II) is the main prognostic factor in AMs. To avoid possible tumor recurrence, we recommend total resection, but this should be adapted for each patient, depending on the existing risks. Prospective studies are likely to better delineate the aggressiveness of treatment strategies for these tumors, to prevent tumor recurrence.

Conflict of interests

The authors declare that they have no conflict of interests.

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