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A.I. Cucu[1], Claudia Florida Costea[1,2], Mihaela Dana Turliuc[1,2], Cristina Gena Dascalu[2], Ioana Jitaru[1], R. Dinu[1], Gabriela Dumitrescu[1], Anca Sava[1,2], B. Dobrovat[1,2], Camelia Bogdanici[2], T. Andrei[1], I. Stirban[1], I. Poeata[1,2]

[1] "Prof. Dr. N. Oblu" Emergency Clinical Hospital Iasi, ROMANIA
[2] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA

Keywords
atypical meningiomas,
tumour volume,
progression-free survival

ABSTRACT

Objective: The objective of our study was to evaluate a possible relation between the volume of atypical meningiomas (AMs) and the risk of tumour recurrence, as well as progression-free survival (PFS).

Material and methods: We evaluated 81 patients diagnosed with AMs (WHO grade II meningioma) who have undergone surgery at the "Prof. Dr. N. Oblu" Emergency Clinical Hospital Iasi between January 1, 2010, and December 31, 2019. The recorded data were demographic and imagistic (MRI, contrast-enhanced T1WI). We calculated the tumour volume prior to the surgery and evaluated the tumour recurrence using MRI at 12, 24, 36, 48 and 60 months after the surgery.

Results: 50.6% of patients had meningioma volume < 26.4 cm3. Women had larger tumour volumes than men (52.6%). Patients of age ≤ 60 years old, had tumour volumes > 26.4 cm3 in 58.5% of cases and meningiomas with volumes > 26.4 cm3 recurred earlier (p=0.010). Also, patients who had tumour volumes > 26.4 cm3, had a shorter PFS (40.976 months), compared to patients with tumour volumes < 26.4 cm3, who had better PFS (53.4 months).

Conclusions: the tumour volume of AMs > 26.4 cm3 represents a negative prognostic factor for both early tumour recurrence and reduced PFS.

INTRODUCTION

Meningiomas are the most common primary intracranial tumors in adults and represent about one third of them (26). Out of the histopathological grades of meningiomas, AMs (WHO grade II meningiomas) represent approximately 20-30% of them (27, 28, 33), and their incidence has increased in the last years (10, 33).

Corresponding author:
Claudia Florida Costea

"Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

costea10@yahoo.com

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Regarding the multiple prognostic factors of tumor recurrence in case of AMs (8, 12, 13, 27, 30, 31), some studies have reported that the size and volume of the tumor would also represent a prognostic factor (16, 17, 22). Thus, some authors have proved that larger size of AMs (for example, over 4.5 cm) are associated with early tumor recurrence (16). Other authors have reached the conclusion that the size of the meningioma is not only a prognostic factor of tumor recurrence, but also of the survival of patients, both in the case of AMs, as well as in the case of anaplastic meningiomas (17).

This study is aimed to evaluate the influence of the tumor volume on early tumor recurrence, as well as on the survival period up to the tumor recurrence.

Material and methods

We evaluated the tumor volume of 81 patients diagnosed with atypical meningioma (AM), who had undergone surgery at the Neurosurgery Department, "Prof. Dr. N. Oblu" Emergency Clinical Hospital Iasi, followed between January 1, 2010 and December 31, 2019. Each patient had the following recorded: demographic data regarding age and sex, and imaging studies (MRI). The tumor volume was calculated using the formula: volume = π /6 x legnth x wirdth x height (5, 18, 21, 29), and was analysed on magnetic resonance images prior to the surgery (contrast-enhanced T1WI). The mean tumor volume calculated was of 26.4 cm3, and depending on it, patients were grouped into two samples: (1) patients whose volume was < 24 cm3 and (2) patients whose volume was > 26.4 cm3. We also performed a qualitative evaluation of the AMs volume and evaluated the relation between the tumor volume, the rate of recurrence and PFS. The patients had an annual imaging examination (MRI), for a period of 5 years, and the tumor reccurence/tumor progression was defined as any contrast-enhancement at the level of the remaining tumor bed, or the increase in size of the the remnant tumor. In the cases of subtotal tumor resections, we named and classified the tumor progression as a tumor recurrence. Depending on its location in the intracranian space, the meningiomas were classified as: (1) skull base meningiomas, (2), convexity meningiomas, (3) parasagittal/falcine meningiomas, (4) posterior fossa meningiomas, and (5) intraventricular meningiomas. In the group of skull base meningiomas were included only those located at the level of the anterior and middle fossa. Posterior fossa meningiomas included all infratentorial meningiomas, including tentorium meningiomas or those located on the cerebellopontine angle or the petroclival junction. The statistical data processing was made in SPSS 24.0 (SPSS Inc., Chicago, IL). The data were characterized through descriptive statistics and frequency distributions. The data normality was checked using the Kolmogorov-Smironov fitting test; after this, we used t-Student and ANOVA tests to compare the samples of normally distributed data and Mann-Whitney and Kruskal-Wallis tests to compare the other samples. The qualitative data were characterized through frequency distributions and contingency tables, and the comparisons were made using the Chi-squared test. All p values were 2-tailed; a p value of 0.05 was considered significant. The actuarial data were represented with Kaplan-Meier plots, and the cumulative incidence curves were compared using the log-rank test. The study was approved by the Reasearch Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy of and by the Ethical Committee of the "Prof. Dr. N. Oblu" Emergency Clinical Hospital of Iași.

Results

Demography (age, sex)

The study group included 81 patients, of which most cases of AMs were in men, in a percentage of 53.1% (n = 43). The age of the patients in the total group ranged from 37 to 87 years, with a mean age of 61 years. When we evaluated the age of patients by sex, we noticed that women have a mean age of onset younger than men (58.42 years), compared to those who have a mean age of disease onset of 63.47 years (p=0.0052). 50.6% of patients had ages ≤ 60 years old (Figure 1). There were no statistically significant differences between the sexes in terms of age distribution. All patient characteristics can be seen in Table I.

Characteristics		n (%)
Gender	male	43 (53.1%)
	female	38 (46.9%)
Age	≤ 60 years	41 (50.6%)
	> 60 years	40 (49.4%)
Tumor localization	convexity	34 (42%)
	parasagittal/falcine	21 (25.9%)
	skull base	17 (21%)
	posterior fossa	6 (7.4%)

	intraventricular	3 (3.7%)
Tumor volume	< 26.4 cm^3	41 (50.6%)
	≥ 26.4 cm^3	40 (49.4%)

Table I. Characteristics of 81 patients with atypical meningiomas.

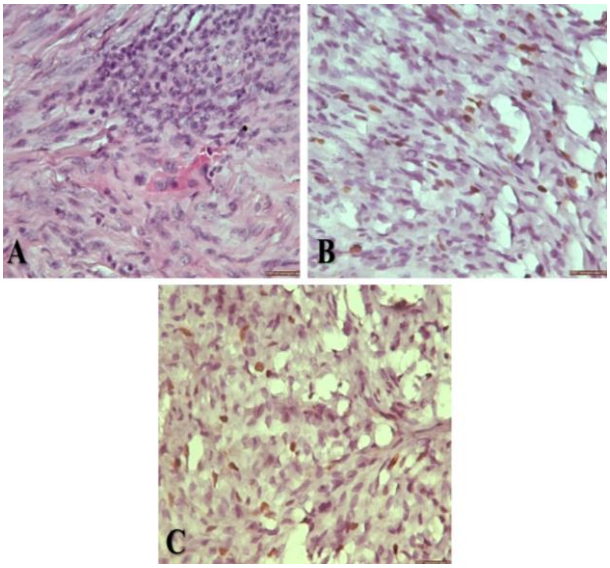

Figure 1. Female, 60 years-old with atypical meningioma. A. Well-cellularized tumor, infiltrative into adjacent dura mater, consisting of meningothelial cells arranged in syncytial pattern, with oval nuclei and fine granular chromatin (3 mitoses/10 high-power fields) (HE, x 400). B and C. two different fields of the same tumor showing high expression of Ki-67 LI (mean 12%) (immunohistochemical staining, x400).

Tumor localization

Regarding the localization of meningiomas at the skull level, most were located on the convexity level (42%, n=34), followed by parasagittal/falcine localization (25.9%) and at the level of the skull base (21%). Smaller percentages were located at the level of the posterior fossa (7.4%) or at the intraventricular level (3.7%) (Table I).

Following the qualitative analysis of the tumor volume, although there was no statistically significant difference between the tumor volume and the location of the meningioma at the level of the intracranial space, we found, however, that the largest tumors were located at the base of the skull, with a mean of 53.724 cm3 (ranging between 3.444-149.094 cm3). These were followed by intraventricular meningiomas (mean of 47.927 cm3), convexity meningiomas, (mean of 41.396 cm3), posterior fossa meningiomas (mean of 39.172 cm3) and those with parasagittal/falcine localization (mean of 36.596 cm3) (Figure 2).

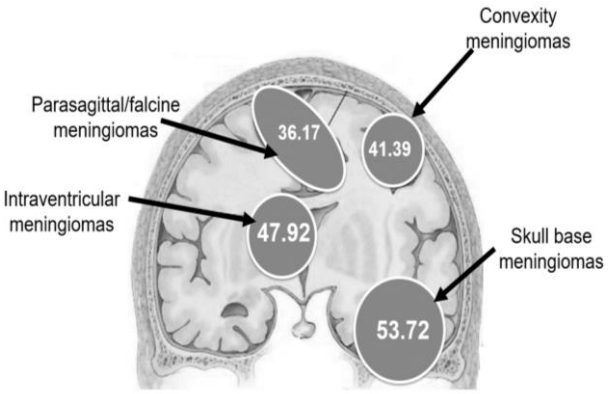

Figure 2. The mean tumor volume depending on location (personal collection of authors, public domain).

Tumor volume

The mean tumor volume was 26.4 cm3 and 50.6% of patients had meningioma volumes of < 26.4 cm3. Analyzing the differences between genres, although we did not identify any statistically significant values, we found that women had larger meningioma volumes than men (52.6%). Also, patients with ages ≤ 60 years old, had tumor volumes > 26.4 cm3 in 58.5% of cases.

We identified a statistically significant relation between the meningioma volume and the tumor recurrence (p=0.010). Tumors with volumes > 26.4 cm3 recurred earlier, and within this group the tumor recurrence rate was 17.1% at 12 months, 19.5% at 24 months and 41.5% at 60 months. On the other hand, tumors with volumes < 26.4 cm3 had no recurrence in the first 12 months, and the recurrence rate at 24 months was 5%. Moreover, 65% (n=26) of meningiomas with volumes < 26.4 cm3 had a slow recurrence, at 60 months. Also, recurrent meningiomas had a larger mean volume (49.438 ± 41.771) compared to meningiomas that did not recur (35.323 ± 35.524).

In regards to PFS, we identified a statistically significant relation between it and the tumor volume (p=0.030). Patients who had tumor volumes > 26.4 cm3 had shorter PFS (40.976 months). Patients who had tumor volumes < 26.4 cm3, had better PFS (53.4 months) (Figure 3).

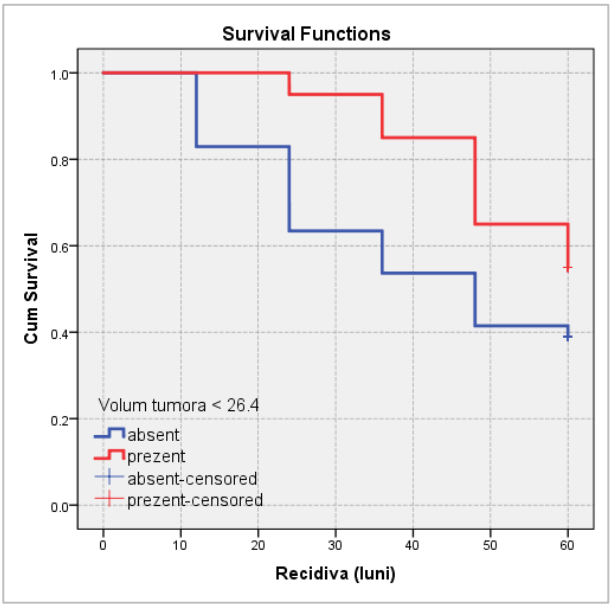

Figure 3. PFS depending on the tumor volume. It is notable that patients with tumor volume < 26.4 cm3 had better PFS.

Discussions

The influence of tumor volume on the tumor recurrence risk

In our study we observed a predominance of convexity meningiomas, in agreement with our previous studies (9, 11). We also noticed that a higher tumor volume has a negative influence on the rate of recurrence. Thus, in cases of meningiomas with tumor volumes > 26.4 cm3, the recurrence rate was higher than in the case of tumors with volumes below this value. This correlation between a larger size of the meningioma and the existence of the risk of tumor recurrence has also been observed by other authors in previous studies (16, 17, 19).

Fernandez et al. reported that the size of over 4.5 cm of AM is associated with a risk of early recurrence (16). Moreover, Garzon-Muvdi et al. also observed in his study that the size of the tumor can be considered an important factor not only for PFS, but also for overall survival. Nakasu et al. also reported the mean size of 4.4 ± 1.4 cm to influence tumor recurrence compared to non recurrent tumors which had a diameter of 3.5 ± 1.5 cm (25). Moreover, various authors reported that smaller sized AMs can represent a protective factor against tumor recurrence (4, 14, 16).

This relation between the larger tumor volume and the risk of tumor recurrence may be explained by the fact that a larger size meningioma makes a complete tumor resection more difficult due to the potential invasion of adjacent structures (3, 15, 20, 23).

Another interesting aspect was observed by Magill et al., who proved in a study conducted on 1113 meningiomas (905 grade I meningiomas and 208 grade II meningiomas) that the larger the size of the tumor, the higher the risks that it would be a grade II meningioma (24). In order to explain this, Magill et al. considered that there would be two possibilities: one would be that the grade II meningiomas grow faster than grade I meningiomas, and a second that once the slow growth tumor reaches a larger size, it develops a microenvironment due to hypoxia, which leads to the phenotype of this tumor becoming more aggressive (24).

In recent years, progress has been made in establishing the genetic factors that govern the growth of meningiomas or leading to their transformation into a more malignant histological grade, and in this sense, in addition to NF2, mutations in SMO, PI3K, TRAF7, KLF4 and AKTI have been identified (1, 6, 7). In the case of recurrent meningiomas, mutations in POLR2A have also been identified (7).

The influence of tumor volume on PFS

We found that the tumor volume of the meningioma influences the survival period until the tumor recurrence (p=0.030). Thus, tumor volumes > 26.4 cm3 had a shorter PFS. This can be explained by the fact that larger sized tumors invade more neuro-vascular structures, which make complete tumor resection more difficult, leaving a remnant tumor sometimes. In this sense, Wang et al. also found that tumors with dimensions > 41.5 mm are associated with a higher risk of tumor recurrence (32). Similarly, Nakasu et al. 1999 also reported that meningiomas with a mean diameter > 44 ± 14 mm have a significantly shorter PFS, consistent with other authors who consider that the tumor size is significantly associated with tumor recurrence in the case of patients diagnosed with AMs (2, 14, 17).

Conclusions

Our patients' series demonstrated that the tumor volume of AMs > 26.4 cm3 increases the tumor recurrence rate and decreases PFS. Moreover, mean tumor volumes had bigger values in case of recurrent AMs. We consider the tumor volume

represents a prognostic factor not only for tumor volume, but also for PFS.

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