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Meningioma in shape. Can the appearance of tumour margins be considered as a prognostic factor?

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ABSTRACT

Objective: The aim of this study was to evaluate the possible relationship between the appearance of tumour margins of atypical meningiomas and the risk of tumour recurrence, as well as progression-free survival. We also evaluated the correlations between the tumour margins and the neuroimaging characteristics (e.g. brain oedema and contrast enhancement) along with pathological features (e.g. brain invasion and mean value of Ki-67 LI).

Material and methods: In our study, we included 81 patients diagnosed with atypical meningioma (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. We followed the MRI imaging characteristics (e.g. tumour margins patterns, contrast enhancement, oedema grading and tumour volume), but also the pathological characteristics such as brain invasion and the mean value of the Ki-67 labelling index. The assessment of tumour recurrence was made using MRI imaging (T1+ contrast), over a follow-up period of 5 years after the surgery.

Results: In our study, we observed that 59.3% (*n=48*) of meningiomas had an irregular appearance. The irregular margins predominated in the male population (65.1%) and were statistically significantly correlated with brain oedema ($p<0.001$), contrast enhancement ($p<0.01$), anatomical location ($p<0.014$) and the mean value of the Ki-67 labelling index ($p<0.01$). The tumour margins were not correlated with brain invasion or volume of meningiomas.

Conclusion: In our series of patients we found that the irregular margin was not a prognostic factor for tumour recurrence over a period of 5 years or for progression-free survival.

Keywords
atypical meningioma, tumour shape, tumour margins, recurrence, prognostic factors

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Introduction

Meningiomas are the most frequent primary tumors of the central nervous system and represent about one third of all primary brain tumors (1). A preliminary study of ours has shown that in our region, the incidence of these tumors has increased in recent years (2, 3).

The World Health Organization (WHO) classification of central nervous system tumors, divides meningiomas into three major groups: WHO grade I meningiomas are typical or benign (88-94%), grade II meningiomas are atypical (5-7%), and grade III meningiomas that are anaplastic or malignant (1-2%) (4, 5). Although the vast majority of meningiomas are benign, these tumors are still a challenge for neurosurgeons and radiologists, especially in terms of neuroimaging features and the orientation of preoperative diagnosis. Regading this, various authors have reported certain "malignant" neuroimaging characteristics, such as: bony destruction, hyperostosis of the adjacent skull, extracranial tumor extension through the skull base, marked peritumoral brain edema, arterial encasement, absence of calcifications, presence of irregular margins or "mushrooming" (6–8). However, many of these studies have limitations, and no one can specify a clear predictive value for these characteristics. Moreover, there is no MRI or CT feature that can clearly distinguish between a benign and a malignant meningioma (9). Concerning the prognostic value of the appearance of tumor margins, previous studies have reported that the irregular margins of meningiomas and their lobulated appearance are associated with brain invasion and denote malignant behavior of the tumor (10–14).

The development of imaging techniques in recent years, especially MRI, allowed to perform a predictive analysis of malignancy degree. This was posible corroborated with clinical data, tumor morphology and also with imaging characteristics (study of perfusion, diffusion coefficient, spectroscopy - in MRI imaging) (15). It seems that these preoperative imaging studies can improve both the management strategy and the prognosis of these patients (16,17).

The aim of our article is to identify in a group of atypical meningiomas (AMs), the prognostic value of margins for recurrence and progression-free survival (PFS), but also to analyze the correlations between the tumor margins and other neuroimaging features (brain edema and contrast enhancement) and pathological characteristics such as brain invasion and the mean value of Ki-67 labeling index (LI).

Materials and methods

In this study we evaluated the imaging characteristics in 81 patients with AMs, who had undergone surgery in the Department of Neurosurgery, from Prof. Dr. N. Oblu Emergency Clinical Hospital, and the patients were followed between January 1, 2010 - December 31, 2019. The preoperative MRI factors assesed were: (1) tumor margins (regular vs. irregular), (2) the grade of peritumoral brain edema (absent, mild, moderate or severe), (3) contrast enhancement (homogeneous vs. heterogeneous), (4) anatomical location, (5) tumor volume and (6) recurrence. We also evaluated pathological characteristics such as brain invasion and the mean value of the Ki-67 LI. The tumor margins were delineated on preoperative MRI (contrast-enhanced T1WI) and were classified as regular or irregular. Brain edema was evaluated in the T2WI sequence, as hyperintense extension adjacent to the tumor and for grading, we used Hale scale: (0) no cerebral edema - absence of high T2WI signal around the meningioma, (1) mild edema - ring of high T2WI signal surrounding the meningioma, but without mass effect, (2) moderate edema - more extensive edema, but without mass effect, (3) severe edema - mass effect on neighboring structures or deep digitiform edema in the white matter (16,18). Regarding the anatomical classification, meningiomas were classified as follows: (1) skull base meningiomas, (2) convexity meningiomas, (3) parasagittal-falcine meningiomas, (4) posterior fossa meningiomas and (5) intraventricular meningiomas. Tumor volume was calculated according to the formula = π/6 x length x width x height (18–21), and mean tumor volume was 26.4 cm3. Patients underwent MRI imaging annually, for a period of 5 years, and tumor recurrence/progression was defined as any contrast-enhancement at the level of the remaining tumor bed, or the increase in volume of the remnant tumor (18).

The statistical data processing was made in SPSS 24.0 (SPSS Inc., Chicago, IL). The data were characterized through descriptive statistics and frequency distributions. We used the following tests: Kolmogorov-Smironov test, t-Student, ANOVA tests, Mann-Whitney and Kruskal-Wallis tests and Chi-squared test. 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.

Results

The study group included 81 patients of which 53.1% (n=43) were male. The mean age was 61 years (range 37-87 years). In the study group we observed that 59.3% (n=48) of meningiomas had irregular margins. This appearance of irregular margins was mainly in the male population, in a percentage of 65.1% (28 patients out of a total of 43 men male).

Results concerning preoperative imaging features

The appearance of the tumor margins were found to have a significant statistical influence on brain edema (p<0.001). In the study group, 73.3% (n=22) of patients with severe brain edema had irregular margins and 72.2% (n=13) of patients with moderate edema had irregular margins. Beside this, 86.7% of patients without brain edema had regular margins (Table 1). Between the appearance of tumor margins and contrast enhancement we identified a statistically significant correlation (p<0.01). Also, 72.7% of tumors with regular margins were homogeneous.

Between the tumor margins and the anatomical location of meningiomas, we observed a statistically significant difference (p<0.014). Thus, in the cases of parasagical-falcine meningiomas, 90.5% (n=9) had irregular margins, as well as 52.9% (n=9) of the skull base meningiomas. 50% (n=7) of all convexy meningiomas had irregular margins. There were no statistically significant differences between the tumor margins and tumor volume (p<0.221). We noticed instead that 65.9% (n=27) of patients with tumor volume > 26.4 cm3 had irregular margins (Table 1).

Results concerning pathological aspects

Of the 12 patients with brain invasion, 9 of them had irregular margins. However, we did not identify a statistically significant correlation between the tumor margins and brain invasion. Between the mean value of Ki-67 LI and the appearance of tumor margins we found a statistically significant correlation (p<0.01). 78.9% of patients with regular margins had Ki-67 LI <7% of the (Table 1). On the other hand, 15 patients with irregular marginis, out of 19, had Ki-67 LI > 8%.

Recurrence and progression-free survival

The tumor margins did not statistically significantly influenced the recurrence rate (p<0.111). However, of patients with irregular margins, 60.4% (n=29) relapsed in the 5-year follow-up period, in contrast to patients with regular margins, who relapsed less (42.4%; n=14). Although we did not identify statistically significant differences between the tumor margins and PFS (p<0.067), we observed that patients with regular margins had a better mean PFS (52 months), in contrast to patients with irregular margins, who had had a lower mean PFS (43.7 months). All the results are presented in Table 1.

Characteristics	Tumor margins		*p* -Value
	Irregular n (%)	Regular n (%)	
Brain edema			p<0.001
Absent	2 (13.3%)	13 (86.7%)	
Mild	11 (61.1%)	7 (38.9%)	
Moderate	13 (72.2%)	5 (27.8%)	
Severe	22 (73.3%)	8 (26.7%)	
Enhancement			p<0.01
Homogeneous	27 (56.3%)	9 (27.3%)	
Heterogeneous	21 (43.8%)	24 (72.7%)	
Tumor location			p<0.0014
Parasagital-falcine	9 (90.5%)		
Skull base	9 (52.9%)		
Convexity	17 (50%)		
Posterior fossa	2	4	
Volume			
> 26.4 cm^3	27 (65.9%)		
< 26.4 cm^3	21 (52.5%)	19 (47.5%)	
Pathological aspects			
Brain invasion present (*n=12*)	9 of 12 (75%)	3	
Ki-67 LI >8% (*n=45*)	15	4	p<0.01
Recurrence (*5 years*)	29 (60.4%)	14 (42.4%)	
Progression-free survival (*months*)	43.7	52	

Table 1. Imaging and pathological characteristics in relation to tumor margins.

Discussions

In this retrospective study from a single-institution case series of AMs, we analyzed the usefulness of evaluating the appearance of tumor margins for tumor recurrence and PFS, but also the correlations between the tumor margins and other radiological

features (brain edema and contrast enhancement) and pathological findings (brain invasion and the mean value of Ki-67 LI).

Correlations between the tumor margins and brain edema

Analyzing the correlation between tumor margins and the degree of peritumoral cerebral edema, we observed statistically significant differences (p<0.001). Thus, almost half of the patients with irregular margins (45.8%) had severe brain edema, while 39.4% of patients with regular margins have no cerebral edema, or it was minimal (21.2%). Thus, we can consider that the irregular margins of a meningioma may be a predictor of the occurrence of brain edema (Figure 1).

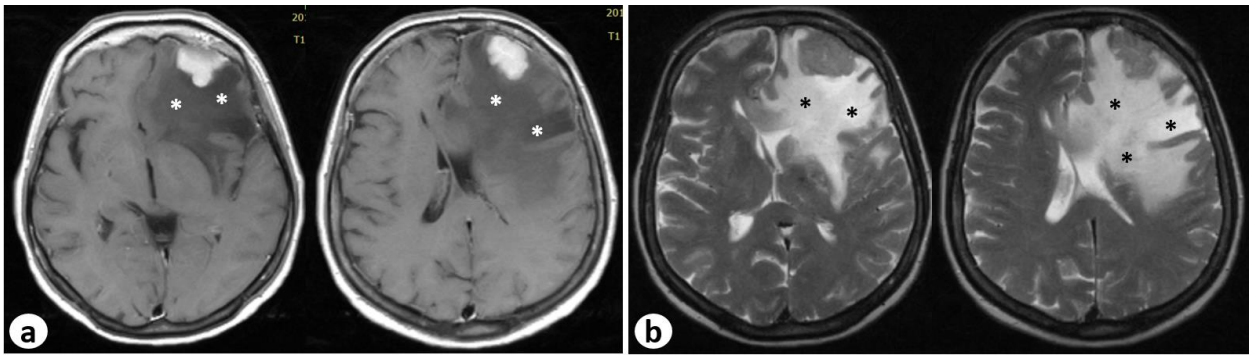

Figure 1. Illustrative examples of the analysed MRI variables: (a) axial T1-weighted MRI shows an irregular tumor shape with mushroom-like growth and peritumoral edema (white asterisk). (b) T2-weighted MRI shows the same tumor, with severe peritumoral edema which compresses the lateral ventricles (Hale 3 grade) (*black asterisk*).

Consistent with our results, Lobato *et al.* reported a statistically significant difference between the tumor margins and brain edema. He found that patients who had meningiomas with an irregular margins, had a 2.9 times higher risk for brain edema (10). Although cerebral edema can also occur as a result of brain invasion, there are additional biological mechanisms involved in the occurrence of this phenomenon, such as ischaemia from tumor mass effect or venous congestion (5, 22). Also, Nakano observed with his collaborators a statistically significant correlation between brain edema and meningioma margins, both in univariate analysis and in multivariate analysis (23). The conclusion of his study was that the incidence of brain edema was significantly higher in the group of tumors with irregular margins (23).

Correlations between the tumor margins and contrast enhancement

In our study, we identified a statistically significant correlation (p<0.010) between the tumor margins and contrast enhancement. Thus, 72.7% of tumors with regular margins was homogeneous (Figure 2). The heterogeneous aspect of meningiomas can also be given by the presence of intratumoral necrosis (24), and this can also indicate a malignant histology of the tumor (10, 25). The most common mechanism of necrosis in meningiomas is due to hypoxia (26), and in turn, this occurs due to high metabolic demands, and may be related to a more aggressive tumor progression (27).

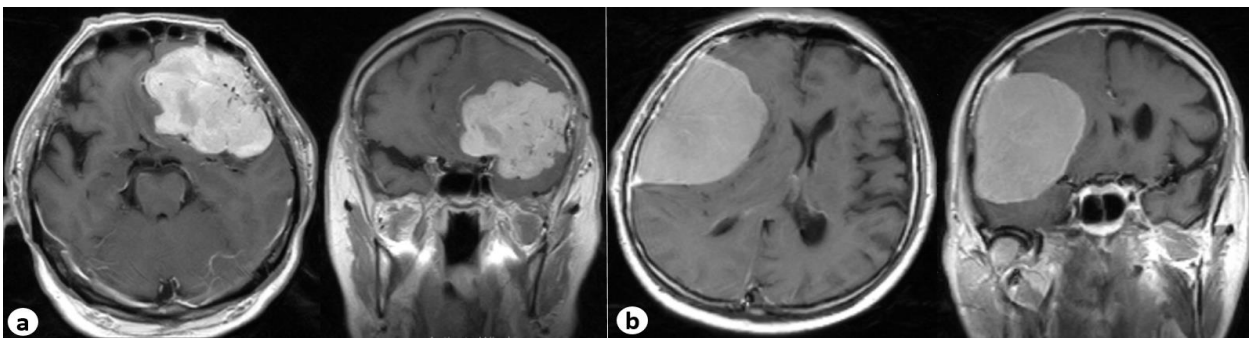

Figure 2. Illustrative examples of the analyzed MRI variables: (**a**) Axial and coronal contrast enhanced T1- weighted MRI showing a sphenoid wing meningioma with irregular margins and heterogeneous enhancement. (**b**) Axial and coronal contrast enhanced T1-weighted MRI showing another sphenoid wing meningioma with regular margins and homogeneous enhancement.

Correlations between the tumor margins and brain invasion

Analyzing the correlation between the margins and brain invasion, although there was no statistically significant difference between the two variables, we found that of the 12 patients with brain invasion, 9 of them had irregular margins (Figure 3, Figure 4.b.).

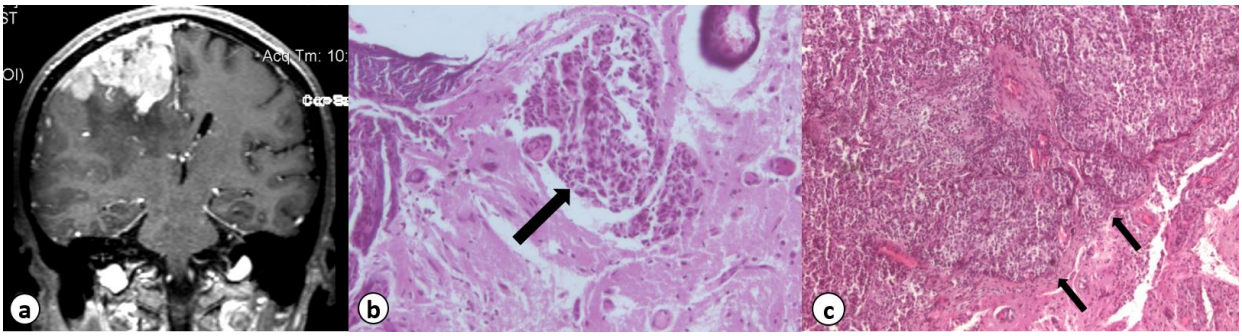

Figure 3. (**a**) Illustrative examples of the analyzed MRI variables: axial T1-weighted MRI shows an irregular tumor shape with mushroom-like growth. (**b**) Brain invasion revealed as small "islands" of tumor cells (*black arrow*) into adjacent nervous tissue, which also shows astrocytic gliosis (*HE, x200*). (**c**) Brain invasion as irregular projections of the tumor into adjacent nervous tissue without an intervening layer of leptomeninges at the tumor to brain interphase (*black arrows*). The adjacent brain parenchyma also exhibited astrocytic gliosis (*HE, x100*).

Some authors consider that the presence of irregular margins, as well as their lobulated appearance with fringed extensions to the brain parenchyma is associated with brain infiltration and denotes malignant tumor behavior (10–14,28). Among these authors, Adeli *et al.* observed a statistically significant correlation between irregular margins and brain invasion in 4% of 617 grade I, II and III meningiomas (28). In relation to brain invasion, in the evaluation of imaging factors, some authors observed that the absence of a cerebrospinal fluid rim separating the meningioma from brain, would suggest a higher histological degree of the tumor, due to the possibility of invasion of the adjacent brain tissue.

Correlations between the tumor margins and the mean value of the Ki-67 LI

Correlating the tumor margins with the value of the marker Ki-67 LI, we identified a statistically significant difference ($p<0.01$). Thus, 78.9% of patients with regular margins had Ki-67 LI <7% On the other hand, out of 19 patients with Ki 67 LI> 8%, 15 of them had meningiomas with irregular margins. Statistical significant differences were also reported by Beculic *et al.* between the two variables, noting that irregular margins were associated with higher Ki-67 LI values (30). Moreover, immunohistochemical detection of Ki-67 LI remins an important tool in addition to routine histopathological evaluation that can be used to predict tumor behavior of AM (31,32) (Figure 4).

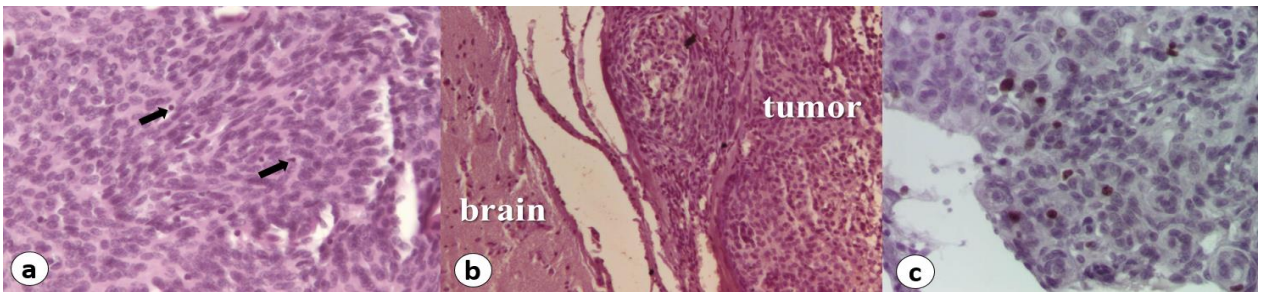

Figure 4. (**a**) Meningothelial tumor with sheet-like growth, increased cellularity and two mitotic figures/ high power field (*black*

arrows) (*HE, x400*). (**b**) Leptomeningeal tumoral invasion with a thin intervening layer of pia mater at the tumor (*black arrow*) to brain interphase (*white arrow*) (*IHC, anti-Ki67 antibody, x200*). (**c**) Nuclear immunoreactivity (8%) for Ki-67 LI in atypical meningioma, grade II of malignancy (*IHC, anti Ki-67- antibody, x200*)

The influence of tumormarginson recurrence

Until now, several authors have shown that grade of lobulation of a meningioma increases with the malignancy (33,34), so implicitly the irregular appearance of the tumor margins.

Irregular margins of meningiomas have been attributed to different growth rates in certain regions of the tumor (35) and are associated with increased cell proliferation (33) and an increased risk of tumor recurrence (7). In this regard, Zhang *et al.* demonstrated in a study of 33 AMs that tumors with irregular margins are more prone to malignant progression compared with AMs with regular margins (36). Also, Gobran *et al*. observed in its series of 138 intracranial meningiomas (all grades), that lobed-looking meningiomas had a recurrence rate of 23.5%, and mushroom meningiomas had a recurrence rate of 62.5% over a five-year period, observing a statistically significant correlation (37).

When we evaluated the relationship between the tumor margins and the recurrence, although we did not find any statistical corellation between tumor margins and recurrence, according to other studies (6, 38). However, we observed that the majority of meningiomas that recurred had irregular margins (60.4%). Moreover, 57.6% of regular-margin tumors did not recur over a 5-year follow-up period.

In the literature, the existence of irregular margins or "mushrooming" is considered to be an important prognostic factors for recurrence, as it could reflect the high proliferative potential of the tumor (7). Also, Nakasu *et al.* noted that tumors "mushrooming" tumors had the highest recurrence rate, followed by lobulated tumors and then tumors with smooth and irregular margins (7). Also Ildan *et al.* observed in 137 patients with grade I-III meningiomas, that mushroom - shaped meningiomas was associated with a significantly higher risk of recurrence than those with smooth margins (39). However, this atypical imaging feature of irregular margins cannot be considered as an indicator of a higher-grade behavior, and cannot be reliable and specific in differentiating benign and malignant meningiomas (40).

The influence of tumor margins on the progression-free survival

In our study, we observed that patients who had meningiomas with irregular margins had a lower rate of survival than those with regular margins (43.75 months vs. 52 months) (Figure 5). As we did not identify a statistically significant difference between the two variables in agreement with other authors (6), we can consider that the irregular appearance of meningiomas did not influence the PFS. However, other authors such as Nakasu *et al.* observed that irregular margins correlates with PFS (7, 41).

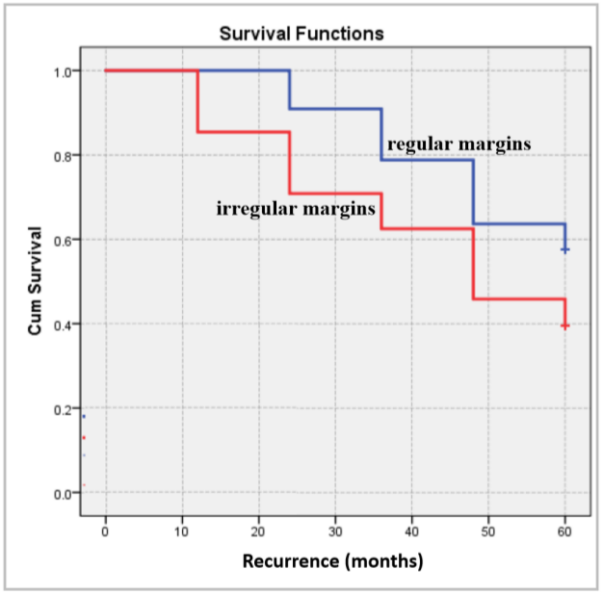

Figure 5. Progression-free survival depending on the appearance of meningioma margins. It is notable that patients with regular margins (blue line) had a better progression-free survival (52 months vs. 43.75 months).

Conclusions

We found that in our series of patients, that irregular margins has no prognostic value for tumor recurrence over a period of 5 years follow up and also for PFS, but instead correlates statistically with grade of brain edema, contrast enhancement and the mean value of Ki-67 LI. Even so, the appearance of tumor margins must be a factor to consider when evaluating neuroimaging of meningiomas and such studies should be extended to other types of intracranial tumors.

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